AJN
American Journal
of Nephrology

Novel Research Findings

Am J Nephrol
DOI: 10.1159/000534701

Received: August 30, 2023
Accepted: October 12, 2023
Published online: November 7, 2023

Proton Pump Inhibitors and Hyporesponsiveness to Erythropoiesis-Stimulating Agents in Hemodialysis Patients: Results from the Japan Dialysis Outcomes and Practice Patterns Study

Akio Nakashima[a] Yoshia Miyawaki[b] Hirotaka Komaba[c, d]
Noriaki Kurita[e, f, g] Yoshihiro Onishi[h] Takashi Yokoo[a] Masafumi Fukagawa[c]

[a]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [b]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Dentistry and Pharmaceutical Sciences, Okayama University Faculty of Medicine, Okayama, Japan; [c]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; [d]The Institute of Medical Sciences, Tokai University, Isehara, Japan; [e]Department of Clinical Epidemiology, Graduate School of Medicine, Fukushima Medical University, Fukushima, Japan; [f]Department of Innovative Research and Education for Clinicians and Trainees (DiRECT), Fukushima Medical University Hospital, Fukushima, Japan; [g]Center for Innovative Research for Communities and Clinical Excellence (CiRC2LE), Fukushima Medical University, Fukushima, Japan; [h]Institute for Health Outcomes and Process Evaluation Research (iHope International), Kyoto, Japan

Keywords
Proton pump inhibitor · Erythropoietin resistance index · Anemia · Hemodialysis iron deficiency · Erythropoietin-stimulating agents

Abstract

Introduction: Hyporesponsiveness to erythropoiesis stimulating agents (ESAs) is important problem in dialysis patients. While proton pump inhibitors (PPIs) may inhibit iron absorption, few studies have examined associations between PPIs and ESA-resistant anemia in hemodialysis patients. This study examined the associations between PPIs and ESA-resistant anemia in hemodialysis patients. ***Methods:*** The present study was a cross-sectional study using repeated 4-month observations, up to eight observations/patient, from the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS). The primary outcome was erythropoietin resistance index (ERI). ESA dose, hemoglobin, proportion of erythropoietin-resistant anemia, transferrin saturation (TSAT), and ferritin were also examined. Linear or risk-difference regression models were used with generalized estimating equations to account for repeated measurements. ***Results:*** Of 1,644 patients, 867 patients had PPI prescriptions (52.7%). Patients prescribed PPI had higher ERI, higher ESA dose, and lower TSAT levels. Multivariable analysis for 12,048 four-month observations showed significantly greater ERI in PPI users (adjusted difference 0.95 IU/week/kg/[g/dL] [95% CI: 0.40–1.50]). Significant differences were also found in ESA dose (336 IU/week [95% CI: 70–602]) and the prevalence of erythropoietin-resistant anemia (3.9% [2.0–5.8%]) even after adjusted for TSAT and ferritin. Among possible mediators between the association of PPIs and anemia, TSAT was significantly different between PPI users and non-users (adjusted difference, −0.82% [95% CI: −1.56 to −0.07]). ***Conclusions:*** This study showed the associations between PPI and ERI,

karger@karger.com
www.karger.com/ajn

Correspondence to:
Akio Nakashima, a-nakashima@jikei.ac.jp

ESA dose, and TSAT in hemodialysis patients; physicians should consider anemia's associations with PPIs in hemodialysis patients.

Introduction

Regardless of erythropoiesis-stimulating agent (ESA) use, renal anemia remains frequent among hemodialysis patients. Depending on the definition, about 5–15% of end-stage renal disease patients are ESA hyporesponsive [1–3]. Higher ESA dose is a risk factor for cardiovascular disease and mortality in dialysis patients, and causes increased medical costs as well, and ESA response to anemia also affects several outcomes [4, 5]. ESA hyporesponsiveness refers to the constant need for high doses of ESA to maintain target hemoglobin (Hb) levels [3]. There are several factors of ESA hyporesponsiveness, such as blood loss, iron deficiency, chronic inflammation, malnutrition, vitamin D deficiency, renin-angiotensin inhibitor (ACE-i), angiotensin-II receptor blocker (ARB), and severe secondary hyperthyroidism. On the other hand, the causes of ESA hyporesponsiveness remain as unresolved problems, and searches for new causes and approaches are required [6–8]. Proton pump inhibitors (PPIs) are widely prescribed throughout the world, including for patients with chronic kidney disease (CKD). Due to an increase in the number of patients taking PPIs, the risk of its use has been reported recently [9]. Gastric acid promotes absorption of non-heme iron by converting it from a non-absorbable ferric form to an absorbable ferrous one [10]. As chronic PPI use reduces gastric acid and keeps gastric pH high, it seems possible that iron deficiency and anemia result from taking PPIs chronically. Iron deficiency is a critical complication in dialysis patients because it is a risk factor for cardiovascular events and mortality regardless of anemia status. Iron deficiency occurs frequently among dialysis patients, with a prevalence of 10–30% [11, 12]. In Japan, its prevalence is as high as about 40% [13]. Several studies have reported iron deficiency anemia caused by PPI use [14–17]. In addition, earlier studies reported that PPIs also inhibit absorption of vitamin B12 and cause macrocytic anemia [18, 19]. Another study reported that PPIs have direct effects on erythrocytes and cause apoptosis of red blood cells and hemolysis [20]. Although the relationship of PPIs and anemia has recently been clarified, it is not clear whether PPIs cause ESA-resistant anemia in hemodialysis patients. The purpose of this study is to clarify how PPI use is associated with the erythropoietin resistance index (ERI), Hb level, ESA dosage, and iron status in hemodialysis patients.

Methods

Study Design and Data Source

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a world-wide cohort study in a random representative sample of selected dialysis which facilities within each participating country in more than 20 countries [21, 22]. The present study was a cross-sectional study using repeated 4-month observations, up to eight observations/patient, from Japan DOPPS (J-DOPPS) Phase 6 (2015–2018).

Study Population

The inclusion criteria were patients aged 20 years or older and at least 3 months' duration since the start of the hemodialysis. Patients were excluded if they had polycystic kidney disease because anemia management may differ considerably in these patients [23]. Other exclusion criteria were serious infections and hemorrhagic diseases at baseline. Patients taking histamine-2 blockers were excluded in order to evaluate the effects of PPIs only.

Exposure

The exposure of interest was the use of PPIs, defined as any prescription of PPIs including esomeprazole, lansoprazole, omeprazole, rabeprazole, and vonoprazan in each 4-month observation period.

Outcome Measures

We used the erythropoietin resistance index (ERI) as the primary outcome, defined as ERI (IU/week/kg/[g/dL]) = ESA dose (IU/week)/Hb (g/dL)/BW (kg) by references to previous reports [24–26], where ESA dose is the average weekly dose of an ESA, Hb is the average pre-dialysis blood Hb concentration, and body weight is the average pre-dialysis body weight, within each observation period. The ESA doses were converted into an erythropoietin alfa dose equivalent (erythropoietin alfa: darbepoietin alfa: epoetin beta pegol = 1: 200 [27]: 225 [28]).

We further examined five secondary outcomes: (1) Hb (g/dL), (2) ESA dose (IU/week), (3) transferrin saturation (TSAT) (%), (4), serum ferritin (ng/mL), and (5) the prevalence of erythropoietin-resistant anemia (being present if Hb <10 g/dL and ESA dose ≥6,000 IU/week).

Statistical Analysis

Baseline characteristics were expressed either as frequencies, means (standard deviation) or medians (interquartile range), for the total population and subpopulations taking or not taking PPIs. The outcome values were summarized in a box-whisker plot or a bar plot.

For the primary analysis, a linear regression model was used with generalized estimating equations accounting for the repeated measurements. The outcome variable was the ERI, and the exposure was the use of a PPI. The following variables were

Table 1. Baseline characteristics of the study patients

	Total	PPI(+)	PPI(−)
	N = 1,644	*N* = 867	*N* = 777
Age, years	66.1 (11.9)	67.4 (11.3)	64.7 (12.4)
Male sex, %	69	86	71
Dialysis vintage, years	7.1 (8.0)	7.3 (7.9)	6.9 (8.0)
Causes of ESRD, %			
Glomerulonephritis	32	32	30
Diabetic nephropathy	42	42	43
Others	25	26	27
Comorbid disease, %			
Cardiovascular diseases	60	67	52
Diabetes mellitus	47	48	46
Gastrointestinal bleeding	1.9	2.7	1.0
Single-pool Kt/V	1.5 (0.3)	1.5 (0.3)	1.5 (0.3)
Albumin, g/dL	3.6 (0.4)	3.6 (0.4)	3.7 (0.4)
CRP, mg/dL	3.5 (38.9)	1.8 (17.7)	5.7 (55.7)
Medications, %			
Antiplatelets	45	55	34
Anticoagulants	7	9	4
ACEIs or ARBs	48	49	46
Iron drugs*	56	56	56

Data are presented as the mean (standard deviation) for continuous variables or percentages for categorical variables. *Iron drugs include oral and intravenous irons and iron-based phosphate binders. PPI, proton pump inhibitor; PPI(+), taking a PPI; PPI(−), taking no PPI; ESRD, end-stage renal disease; CRP, C-reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker.

included as potential confounders: age, sex, hemodialysis vintage, comorbidities (cardiovascular disease, diabetes mellitus, and gastrointestinal bleeding), medications (antiplatelet agents, anticoagulants, non-steroidal anti-inflammatory drugs, and renin-angiotensin system inhibitors including angiotensin-converting enzyme inhibitors [ACE-Is] and angiotensin receptor blockers [ARBs]), and laboratory values (C-reactive protein (CRP), platelet counts, aspartate aminotransferase, serum albumin, creatinine, and parathyroid hormone) (model 1). Results were shown as point estimates and 95% confidence intervals (95% CIs).

Other outcomes, including Hb, ESA dose, TSAT, serum ferritin, and the prevalence of erythropoietin-resistant anemia were analyzed using the same models and covariates [29]. Missing data were imputed using multiple imputation by chained equations with 100 repetitions using predictive-mean matching [30, 31]. All available cases were included rather than performing a formal sample size calculation. All statistical analyses used Stata SE17 (StataCorp, College Station, TX, USA) and were two-sided with level of significance set at 0.05 without correction for multiple testing.

Subgroup Analysis

For the ERI, we did subgroup analyses stratified by each of eight predetermined variables: age category (<75, ≥75 years), sex, BMI (<25, ≥25), serum albumin (<3.8, ≥3.8 g/dL), normalized protein catabolism rate (<1.0, ≥1.0), single-pool Kt/V (<1.0, ≥1.0), history of gastrointestinal bleeding within 12 months before registration, and use of an antithrombotic drug, including antiplatelets and anticoagulants. Effect modifications were tested by assessment of the interaction term.

Sensitivity Analyses

We hypothesized that TSAT, serum ferritin, and iron drugs affect iron metabolism and may act as an intermediate. We therefore did not include them in our primary model (model 1). To assess intermediate effects of these factors, we performed two sensitivity analyses: as model 2, we included serum ferritin and TSAT as covariates in addition to model 1, and as model 3, the use of oral and/or intravenous iron drugs in addition to model 2, and assessed whether the direction or magnitude of the effect size was altered or not.

Results

Participants

The study included 1,644 patients after excluding 406 (20%) (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000534701). The total number of 4-month observations was 12,048. At the baseline, 867 patients (52.7%) received PPI prescriptions (PPI[+]); the remaining 777 patients did not (PPI[−]). Characteristics of patients at the baseline are shown in Table 1.

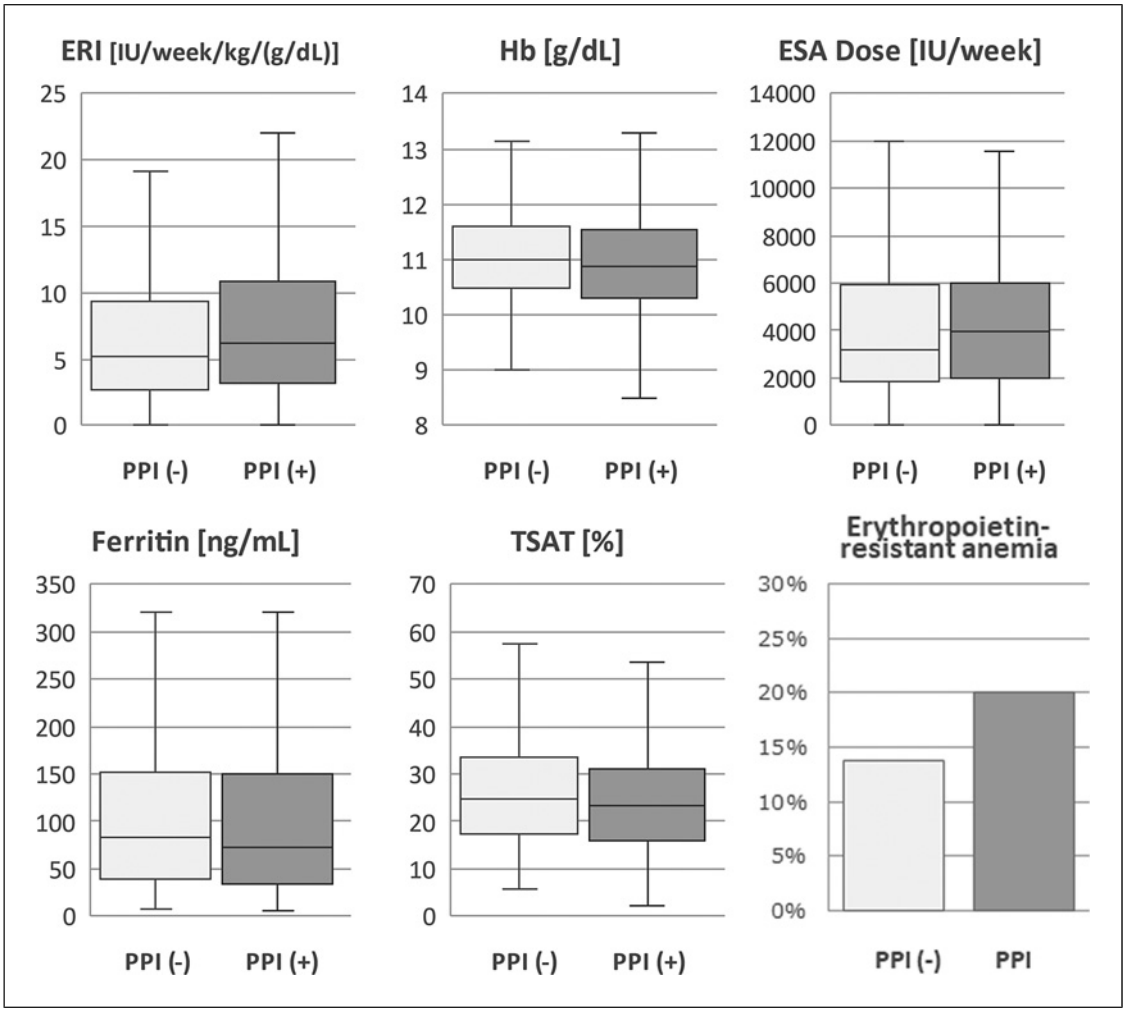

Fig. 1. Distribution of anemia-related indices at the start of the study stratified by non-use/use of proton pump inhibitors (PPI[−]/PPI[+]). Each box plot indicates median, 1st and 3rd quartiles, minimum, and maximum (omitting outliers that were greater than 1.5 times the IQR from the median). The bar chart indicates proportions. ERI, erythropoietin resistance index; Hb, blood hemoglobin; ESA, erythropoiesis stimulating agent; TSAT, transferrin saturation; IQR, interquartile range.

Data were complete for sex, dialysis vintage, comorbidities, cause of end-stage renal disease, and medications. For up to about 25% of the cohort, data for age, BMI, and laboratory values (CRP, platelet counts, aspartate aminotransferase, serum albumin, creatinine, and parathyroid hormone) were missing.

Distributions of the outcomes are shown in Figure 1. Means (standard deviations) in PPI(+) and PPI(−) patients were 7.1 (7.0) and 8.7 (9.9) for ERI, 11.0 (1.0) and 10.9 (1.1) for Hb, 4,140 (3,661) and 4,843 (4,809) for ESA dose, 122 (147) and 121.3 (151) for ferritin, and 26.5 (12.2) and 24.7 (12.1) for TSAT, respectively. Proportions of erythropoietin-resistant anemia in the two groups were 13.8% and 20.1%, respectively. When looking at the raw values, ESA dose and erythropoietin-resistant anemia were higher, and Hb, serum ferritin, and TSAT were lower in PPI(+) than in PPI(−) patients.

Erythropoiesis Resistance Index (ERI)

Crude and adjusted differences in ERI are shown at the top of Table 2. PPI(+) patients had significantly greater ERI than PPI(−) patients (adjusted difference of 0.95 IU/week/kg/[g/dL] [95% CI: 0.40–1.50]). The results of subgroup analyses are shown in Figure 2. There was a significant interaction for gastrointestinal bleeding (p = 0.03), but not for other subgroups (p for interaction = 0.72

Table 2. Differences in anemia-related indices between use and no-use of proton pomp inhibitors

Variable	Unit for the difference	Difference (95% CI) between two groups					
		crude estimates			adjusted estimates		
ERI	IU/week/kg/g/dL	1.18	(0.62, 1.74)	$p < 0.01$	0.95	(0.40, 1.50)	$p < 0.01$
Hb	g/dL	−0.02	(−0.09, 0.04)	$p = 0.48$	0.02	(−0.05, 0.08)	$p = 0.62$
ESA dose	IU/week	410	(153, 668)	$p < 0.01$	336	(70, 602)	$p = 0.01$
ER anemia	Proportion	5.5%	(3.7%, 7.4%)	$p < 0.01$	3.9%	(2.0%, 5.8%)	$p < 0.01$
Ferritin	ng/mL	2.21	(−9.11, 13.54)	$p = 0.70$	1.69	(−9.80, 13.17)	$p = 0.77$
TSAT	%	−1.04	(−1.79, −0.30)	$p = 0.01$	−0.82	(−1.56, −0.07)	$p = 0.03$

The differences were estimated by separate regression models each other (rather than in a single model). ERI, erythropoietin resistance index; ESA, erythropoietin-stimulating agent; ER anemia, erythropoietin-resistant anemia; TSAT, transferrin saturation.

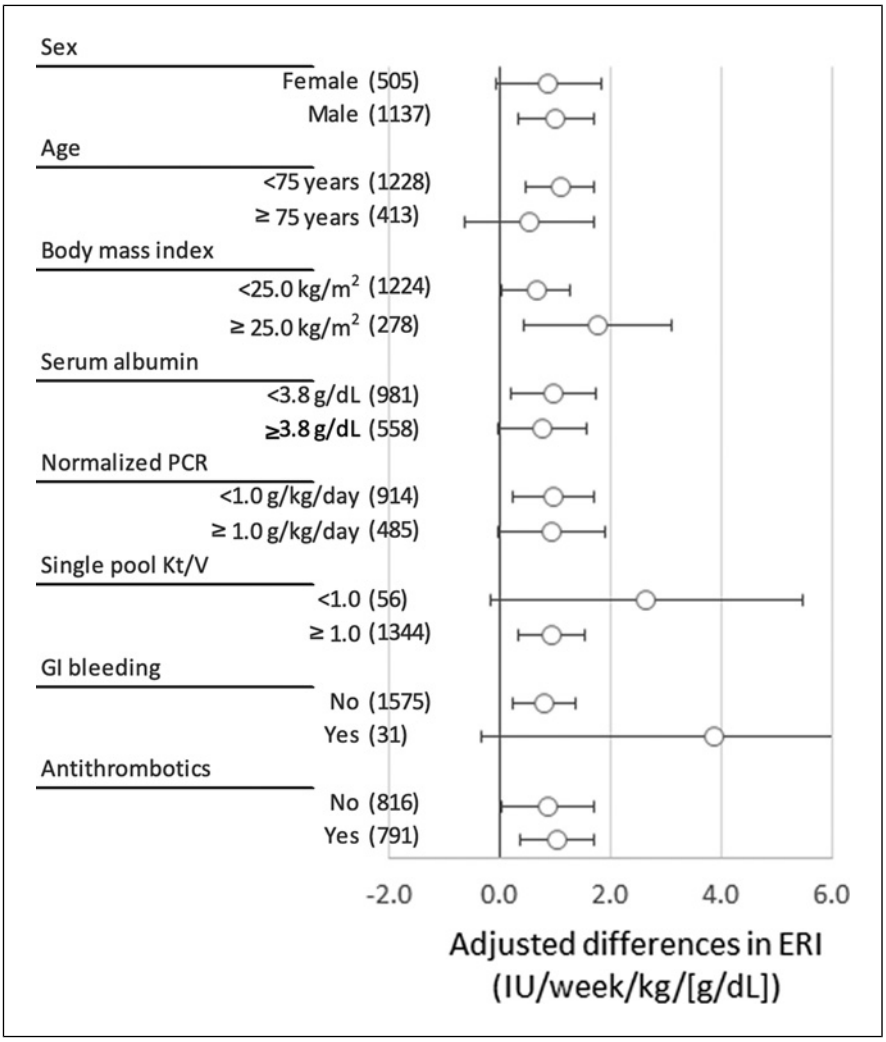

Fig. 2. Adjusted differences in erythropoietin resistance index (ERI) associated with the use of proton pump inhibitors (PPIs) in the subgroup analyses. Figures in parentheses are the number of patients at baseline in each subgroup.

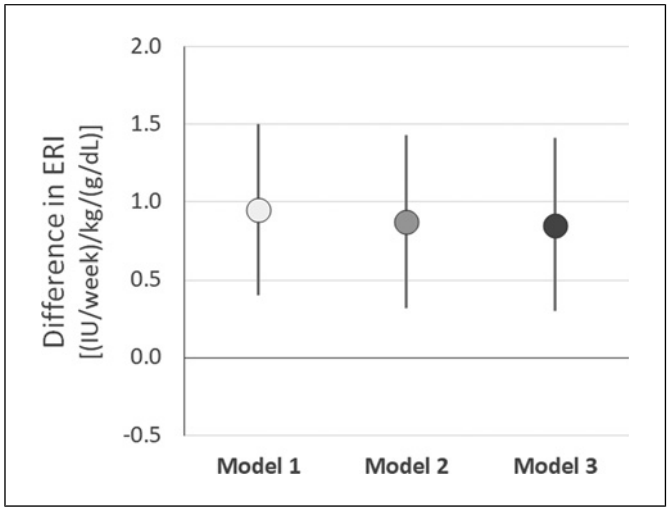

Fig. 3. Three regression model-estimated differences in erythropoietin resistance index (ERI) between the use and non-use of PPIs. Each plot indicates the point estimate and 95% CIs. Model 1 (the base model): adjusted for age, sex, hemodialysis vintage, comorbidities (cardiovascular disease, gastrointestinal bleeding, and diabetes mellitus), laboratory results (CRP, platelet counts, AST, albumin, creatinine and intact parathyroid hormone [iPTH]), and drug uses (antiplatelet, anticoagulant, non-steroidal anti-inflammatory drugs [NSAID], and renin-angiotensin system inhibitors [RASi]). Model 2: model 1 + TSAT and ferritin. Model 3: model 2 + iron drugs (intravenous or oral).

for sex, 0.96 for age, 0.45 for body mass index, 0.81 for normalized PCR, 0.72 for single-pool Kt/V, 0.03 for gastrointestinal bleeding, and 0.96 for antithrombotics.).

Secondary Outcomes

Crude and adjusted differences in secondary outcomes are shown after the second row of Table 2. Among other measures representing anemia, there were significant differences in ESA dose and the prevalence of erythropoietin-resistant anemia even after adjusting for potential confounders (336 IU/week [95% CI: 70–602] and a risk difference of 0.04 (0.02–0.06), respectively), but not in Hb. Among mediators of the association of PPIs and anemia, there was a significant difference in TSAT (−0.82% [95% CI: −1.56 to −0.07]), but not in serum ferritin.

Sensitivity Analyses

Adjusted differences derived from model 1, model 2, and model 3 are shown in Figure 3. The inclusion of TSAT and serum ferritin (model 2) (0.87, 95% CI: 0.32–1.43) among the covariates and the addition of iron drugs (model 3) (0.85, 95% CI: 0.30–1.41) gave estimates similar to model 1.

Discussion

This study examined whether PPIs play a harmful role in response to ESAs using J-DOPPS data collected from multiple centers in a real-world setting of Japanese dialysis patients. We found a significant association between PPI use and higher ERI. PPI use was also associated with higher ESA doses and lower TSAT levels, but not with serum Hb and ferritin levels. There were no interactions of clinical parameters examined, except for gastrointestinal bleeding, on the association of PPI use and ERI. Further adjustment using iron-related TSAT, ferritin, and use of iron drugs did not alter the association of PPI use and ERI.

The background of patients with hemodialysis makes them more likely to be prescribed PPIs. In this study, 53% of the patients were prescribed PPIs. Previous studies have also reported that more than 50% of dialysis patients are taking PPIs [32, 33]. Gastrointestinal disorders, such as gastrointestinal bleeding or GERD, are more frequently seen in dialysis patients [34]. In addition, as PPIs undergo extensive hepatic metabolism, there is no need for dose adjustment according to renal function, as there is, for example, with H2 receptor antagonists [35]. For that reason, although earlier studies have reported that overuse of PPIs is seen in hemodialysis patients, PPI prescriptions are rarely reviewed in clinical practice [36, 37]. Epidemiological studies have revealed that PPIs produce side effects, including pneumonia, diarrhea, *Clostridium difficile* colitis, bone fractures, hypomagnesemia, and interstitial nephritis [38–42]. Recent meta-analysis also reported that PPIs use in hemodialysis patients is independently associated with adverse reactions such as fractures and all-cause mortality. In this study, the relationship between PPI and ESA dose and ERI was clarified for the first time in hemodialysis patients.

Several former studies have been reported on PPI, anemia, and iron metabolism. Termanini et al.'s [43] cohort study of patients with Zollinger-Ellison syndrome concluded there is no association between long-term use of PPIs and iron malabsorption. On the other hand, Lam et al. [16] evaluated PPI use and iron deficiency in a community-based case-control study and showed longer use of PPIs was a risk factor for iron deficiency. Tran-Duy et al. [17] also found that chronic PPI use increases the risk of iron deficiency in a population-based case-control study. The study of Sarzynski et al. [14] reported that patients taking PPIs have lower Hb levels and lower mean corpuscular volume. Previous studies of PPIs and anemia have

reported controversial results [14–17, 43]. However, earlier studies that analyzed PPIs and anemia excluded CKD patients and did not evaluate ESA doses nor was information obtained in earlier studies on Hb, TSAT, or ferritin. Our study, which did include laboratory test values, did, however, show associations between PPIs and ERI and iron status.

Anemia is usually evaluated using Hb or hematocrit. It is possible, indeed likely, that no differences were found in Hb levels with or without PPI use in this study because clinicians routinely make adjustments to ESA doses to maintain stable Hb levels. In this study, as Hb levels were very similar in patients whether they took PPIs or not, most of the difference of ERI appears to result from differences in ESA dosage. Although various causes of ESA resistance have been reported, such as malnutrition [6], vitamin D deficiency [7], renin-angiotensin inhibitor (ACE-i) use, ARB use [8], and severe secondary hyperthyroidism, many of the causes have not yet been elucidated. Patients with hemodialysis using high-dose ESAs, may pose a clinical problems. This study showed that the use of PPIs may cause an increase in the ESA dose and cause ERA-resistance anemia.

Several mechanisms may be involved in an association between PPIs and anemia. First, PPIs could suppress iron absorption and cause iron deficiency anemia. Gastric acid promotes absorption of non-heme iron to an absorbable ferrous form, and this condition is dependent on pH in the stomach. Earlier, animal studies reported omeprazole inhibits iron absorption in rats that were fed an iron-deficient diet [44]. In addition, several clinical studies have reported an association between PPIs and iron deficiency anemia [14–16]. If dialysis patients are regularly receiving intravenous iron, the impact of decreased iron absorption due to changes in gastric pH by PPIs may be mitigated, lowering the ability to detect associations between PPI use, iron deficiency, and PPI-induced ESA resistance. Although the use of intravenous iron preparations is less common in Japanese hemodialysis patient [13], it is important in future studies to consider the extent to which intravenous iron is administered. Second, PPIs could inhibit vitamin B12 absorption and cause macrocytic anemia. Vitamin B12 in food is bound to protein and is released by gastric acid and pancreatic proteases. Vitamin B12 released from protein binds to the glycoprotein intrinsic factor secreted [18] by gastric parietal cells and is absorbed in the ileum. PPIs inhibit gastric acid secretion and decrease the absorption of vitamin B12 [19]. Vitamin B12 is essential for blood cell production and causes macrocytic anemia in vitamin B12 deficiency [45, 46]. Third, although the detailed mechanism of effects on the bone marrow is unknown, several reports have shown that cytopenia is induced by PPIs [47, 48].

Because PPI use was significantly associated with TSAT, suggesting an association between PPIs and iron metabolism, it is possible that the iron factor may be partially associated in the mechanism of PPIs' influence on anemia. On the other hand, there were no significant differences in ferritin levels between PPI use and PPI non-use. Although there was no difference between PPI(−) and PPI(+) groups in factors that lead to high ferritin levels, dialysis patients have many factors other than iron metabolism that affect ferritin; it is possible that there was no difference in this study. Because the results of this study showed that PPIs and the ERI were significantly associated even after the analysis included the iron factor, it is suggested that other mechanisms such as vitamin B12 or direct myelosuppression due to PPIs should also be considered. In the subgroup analysis of the ERI in this study, there were significant interactions affecting the ERI in cases with or without GI bleeding. Although the number of cases with a past history of GI bleeding is small, the effect of PPIs on the ERI may differ in patients depending on whether there was GI bleeding or not. A causal statement cannot be made in the current study because of the possibility that patients with active gastrointestinal bleeding who usually use PPIs were using high doses of ESA. However, since no interaction was observed in other subgroup analyses, the relationship between PPI and ERI is considered to be uniform regardless of patient background. In Japan, PPIs are commonly used when prescribing antiplatelet drugs and anticoagulants. Therefore, it is thought that there is a relationship between PPIs and these drugs. Prescription of anticoagulants or antithrombotic drugs may be a marker of potential bleeding. Adjusting for these two regimens in the analysis is thought to reduce the effect of potential bleeding, an unmeasured confounding.

The present study has one notable strength: patients in Japan, unlike other countries, cannot obtain PPIs without a physician's prescription [49]; we therefore had information about PPI therapy without missing data. In clinical practice in Japan, not only Hb but also TSAT and ferritin levels of dialysis patients are measured periodically (once every 1–3 months); this has the advantage that data on iron metabolism is more detailed than what is found in previous studies

using medical records or conducted in a local resident cohort. This study had several limitations. First, because this was an observational study, the association found between PPI exposure and anemia status could not establish causality. Most importantly, it was threatened by confounding by indication: the reasons for PPI prescription could be a gastric symptom, which was not captured in the data and may have caused occult hemorrhage, and anemia eventually. On the other hand, a previous study in which the upper gastrointestinal tract was examined using video capsule endoscopy for screening purposes in dialysis patients [16] reported that asymptomatic gastrointestinal bleeding was not observed. Therefore, the impact of such occult hemorrhage on the association observed in this study might not be critical. Second, the cross-sectional design may cause the reverse causality. However, this is less likely in this study because physicians do not change PPI prescriptions because of anemia in routine practice. Third, in this study, we used ERI as an indicator of ESA usage, but it is not a commonly used indicator in daily clinical practice. On the other hand, the results regarding ESA dosage were also lower in the PPI use group. In the future, we believe it is necessary to conduct more detailed studies that analyze PPI and ERI, as well as PPI and ESA doses. Fourth, chronic inflammation is an important factor involved in renal anemia and also plays a role in ESA dosage. One of the limitations of CRP is that there are many missing values, so we used multiple imputations as a countermeasure. Fifth, although the diagnosis of gastrointestinal bleeding was adjusted in the analysis model as a past history, it cannot be denied that latent and asymptomatic chronic bleeding was a confounding factor. The effects may be minimal as occult bleeding has been reported to be low in hemodialysis patients [50]. However, it cannot be said with certainty that there will be no impact.

In conclusion, the present study revealed associations between PPIs and the ERI, ESA dose, and TSAT in hemodialysis patients. The possible associations of anemia and PPI use should be considered in high ERI and high-dose ESA hemodialysis patients.

Practical Application

ESA-resistant anemia is a major problem in hemodialysis patients, and few studies have analyzed the association between PPIs and anemia or ESA in hemodialysis patients. Associations were found between PPIs and ERI, ESA dose, and TSAT in hemodialysis patients. In patients with high ERIs and high-dose ESAs, the possibility of anemia associated with PPIs should also be considered.

Acknowledgments

Christopher Holmes at the Institute for Health Outcomes & Process Evaluation Research (iHope International) provided comments, suggestions, and editorial advice on the manuscript.

Statement of Ethics

All participants provided written informed consent and the study protocol of J-DOPPS was approved by the Ethics Committee of Tokyo Women's Medical University (approval number: 2388-R4).

Conflict of Interest Statement

None declared.

Funding Sources

This manuscript was directly supported by the Kidney Foundation, Japan. Global support for the ongoing DOPPS Program is provided without restriction on publications by a variety of funders (details in https://www.dopps.org/AboutUs/Support.aspx). All grants were made to Arbor Research Collaborative for Health and not to coauthors directly.

Author Contributions

A.N., Y.M., H.K., N.K., Y.O., T.Y., and M.F. contributed to the study design and coordinated the study. Y.M. conducted the statistical analysis. A.N., Y.M., and Y.O. wrote the first draft of the manuscript. All authors read, reviewed, edited, and finally approved the final manuscript.

Data Availability Statement

The data underlying this article were provided by Arbor Research Collaborative for Health under license and are not publicly available. However, data requests can be sent to Arbor Research via their website (http://www.arborresearch.org/AboutUs/ContactUs.aspx). Further inquiries can be directed to the corresponding author.

References

1 Luo J, Jensen DE, Maroni BJ, Brunelli SM. Spectrum and burden of erythropoiesis-stimulating agent hyporesponsiveness among contemporary hemodialysis patients. Am J Kidney Dis. 2016;68(5):763–71.
2 Gillespie IA, Macdougall IC, Richards S, Jones V, Marcelli D, Froissart M, et al. Factors precipitating erythropoiesis-stimulating agent responsiveness in a European haemodialysis cohort: case-crossover study. Pharmacoepidemiol Drug Saf. 2015;24(4):414–26.
3 Sibbel SP, Koro CE, Brunelli SM, Cobitz AR. Characterization of chronic and acute ESA hyporesponse: a retrospective cohort study of hemodialysis patients. BMC Nephrol. 2015;16:144.
4 Fukuma S, Yamaguchi T, Hashimoto S, Nakai S, Iseki K, Tsubakihara Y, et al. Erythropoiesis-stimulating agent responsiveness and mortality in hemodialysis patients: results from a cohort study from the dialysis registry in Japan. Am J Kidney Dis. 2012;59(1):108–16.
5 Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631–4.
6 Rattanasompattikul M, Molnar MZ, Zaritsky JJ, Hatamizadeh P, Jing J, Norris KC, et al. Association of malnutrition-inflammation complex and responsiveness to erythropoiesis-stimulating agents in long-term hemodialysis patients. Nephrology. 2013;28(7):1936–45.
7 Icardi A, Paoletti E, De Nicola L, Mazzaferro S, Russo R, Cozzolino M. Renal anaemia and EPO hyporesponsiveness associated with vitamin D deficiency: the potential role of inflammation. Nephrol Dial Transplant. 2013;28(7):1672–9.
8 Ajmal A, Gessert CE, Johnson BP, Renier CM, Palcher JA. Effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on hemoglobin levels. BMC Res Notes. 2013;6:443.
9 Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complications and risks. Nat Rev Gastroenterol Hepatol. 2017;14(12):697–710.
10 Bezwoda W, Charlton R, Bothwell T, Torrance J, Mayet F. The importance of gastric hydrochloric acid in the absorption of non-heme food iron. J Lab Clin Med. 1978;92(1):108–16.
11 Bazeley JW, Wish JB. Recent and emerging therapies for iron deficiency in anemia of CKD: a review. Am J Kidney Dis. 2022;79(6):868–76.
12 Batchelor EK, Kapitsinou P, Pergola PE, Kovesdy CP, Jalal DI. Iron deficiency in chronic kidney disease: updates on pathophysiology, diagnosis, and treatment. J Am Soc Nephrol. 2020;31(3):456–68.
13 Bailie GR, Larkina M, Goodkin DA, Li Y, Pisoni RL, Bieber B, et al. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. Kidney Int. 2015;87(1):162–8.
14 Sarzynski E, Puttarajappa C, Xie Y, Grover M, Laird-Fick H. Association between proton pump inhibitor use and anemia: a retrospective cohort study. Dig Dis Sci. 2011;56(8):2349–53.
15 Shikata T, Sasaki N, Ueda M, Kimura T, Itohara K, Sugahara M, et al. Use of proton pump inhibitors is associated with anemia in cardiovascular outpatients. Circ J. 2015;79(1):193–200.
16 Lam JR, Schneider JL, Quesenberry CP, Corley DA. Proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. Gastroenterology. 2017;152(4):821–9.e1.
17 Tran-Duy A, Connell NJ, Vanmolkot FH, Souverein PC, de Wit NJ, Stehouwer CDA, et al. Use of proton pump inhibitors and risk of iron deficiency: a population-based case-control study. J Intern Med. 2019;285(2):205–14.
18 Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 2013;310(22):2435–42.
19 Porter KM, Hoey L, Hughes CF, Ward M, Clements M, Strain J, et al. Associations of atrophic gastritis and proton-pump inhibitor drug use with vitamin B-12 status, and the impact of fortified foods, in older adults. Am J Clin Nutr. 2021;114(4):1286–94.
20 Naveed A, Jilani K, Siddique AB, Akbar M, Riaz M, Mushtaq Z, et al. Induction of erythrocyte shrinkage by omeprazole. Dose Response. 2020;18(3):1559325820946941.
21 Young EW, Goodkin DA, Mapes DL, Port FK, Keen ML, Chen K, et al. The dialysis outcomes and practice patterns study (DOPPS): an international hemodialysis study. Kidney Int. 2000;57:S74–S81.
22 Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA. The dialysis outcomes and practice patterns study (DOPPS): design, data elements, and methodology. Am J Kidney Dis. 2004;44(5 Suppl 2):7–15.
23 Brookhart MA, Freburger JK, Ellis AR, Winkelmayer WC, Wang L, Kshirsagar AV. Comparative short-term safety of sodium ferric gluconate versus iron sucrose in hemodialysis patients. Am J Kidney Dis. 2016;67(1):119–27.
24 Marcelli D, Bayh I, Merello JI, Ponce P, Heaton A, Kircelli F, et al. Dynamics of the erythropoiesis stimulating agent resistance index in incident hemodiafiltration and high-flux hemodialysis patients. Kidney Int. 2016;90(1):192–202.
25 Johnson DW, Pascoe EM, Badve SV, Dalziel K, Cass A, Clarke P, et al. A randomized, placebo-controlled trial of pentoxifylline on erythropoiesis-stimulating agent hyporesponsiveness in anemic patients with CKD: the Handling Erythropoietin Resistance with Oxpentifylline (HERO) trial. Am J Kidney Dis. 2015;65(1):49–57.
26 Mercadal L, Coudert M, Vassault A, Pieroni L, Debure A, Ouziala M, et al. L-carnitine treatment in incident hemodialysis patients: the multicenter, randomized, double-blinded, placebo-controlled CARNIDIAL trial. Clin J Am Soc Nephrol. 2012;7(11):1836–42.
27 Aljama P, Bommer J, Canaud B, Carrera F, Eckardt KU, Hörl WH, et al. Practical guidelines for the use of NESP in treating renal anaemia. Nephrol Dial Transplant. 2001;16(Suppl 3):22–8.
28 Vega A, Abad S, Verdalles U, Aragoncillo I, Velazquez K, Quiroga B, et al. Dose equivalence between continuous erythropoietin receptor activator (CERA), Darbepoetin and Epoetin in patients with advanced chronic kidney disease. Hippokratia. 2014;18(4):315–8.
29 Naimi AI, Whitcomb BW. Estimating risk ratios and risk differences using regression. Am J Epidemiol. 2020;189(6):508–10.
30 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med. 2011;30(4):377–99.
31 Von Hippel PT. 4. Regression with missing ys: an improved strategy for analyzing multiply imputed data. Socio Methodol. 2007;37(1):83–117.
32 Bailie GR, Mason NA, Elder SJ, Andreucci VE, Greenwood RN, Akiba T, et al. Large variations in prescriptions of gastrointestinal medications in hemodialysis patients on three continents: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Hemodial Int. 2006;10(2):180–8.
33 Fusaro M, D'Arrigo G, Pitino A, Iervasi G, Tentori F, Robinson B, et al. Increased risk of bone fractures in hemodialysis patients treated with proton pump inhibitors in real world: results from the dialysis outcomes and practice patterns study (DOPPS). J Bone Miner Res. 2019;34(12):2238–45.
34 Zuvela J, Trimingham C, Le Leu R, Faull R, Clayton P, Jesudason S, et al. Gastrointestinal symptoms in patients receiving dialysis: a systematic review. Nephrology. 2018;23(8):718–27.
35 Desbuissons G, Mercadal L. Use of proton pump inhibitors in dialysis patients: a double-edged sword? J Nephrol. 2021;34(3):661–72.
36 Strid H, Simrén M, Björnsson ES. Overuse of acid suppressant drugs in patients with chronic renal failure. Nephrol Dial. 2003;18(3):570–5.
37 Kawarazaki H, Nakashima A, Furusho M, Shimizu S, Nakata T. A questionnaire on prescription patterns of proton pump inhibitors for hemodialysis patients in Japan. Clin Exp Nephrol. 2020;24(6):565–72.

38 Deshpande A, Pant C, Pasupuleti V, Rolston DD, Jain A, Deshpande N, et al. Association between proton pump inhibitor therapy and Clostridium difficile infection in a meta-analysis. Clin Gastroenterol Hepatol. 2012; 10(3):225–33.
39 Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. Jama. 2006;296(24): 2947–53.
40 MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. JAMA Intern Med. 2014;174(4):564–74.
41 Antoniou T, Macdonald EM, Hollands S, Gomes T, Mamdani MM, Garg AX, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open. 2015;3(2): E166–171.
42 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.
43 Stewart CA, Termanini B, Sutliff VE, Serrano J, Yu F, Gibril F, et al. Iron absorption in patients with Zollinger-Ellison syndrome treated with long-term gastric acid antisecretory therapy. Aliment Pharmacol Ther. 1998;12(1):83–98.
44 Golubov J, Flanagan P, Adams P. Inhibition of iron absorption by omeprazole in rat model. Dig Dis Sci. 1991;36(4):405–8.
45 Miller JW. Proton pump inhibitors, H2-receptor antagonists, metformin, and vitamin B-12 deficiency: clinical implications. Adv Nutr. 2018;9(4):511s–518s.
46 Swarnakari KM, Bai M, Manoharan MP, Raja R, Jamil A, Csendes D, et al. The effects of proton pump inhibitors in acid hypersecretion-induced vitamin B12 deficiency: a systematic review (2022). Cureus. 2022; 14(11):e31672.
47 Yu Z, Hu J, Hu Y. Neutropenia and thrombocytopenia induced by proton pump inhibitors: a case report. Drug Saf Case Rep. 2018;5(1):28.
48 Tao D, Wang H, Xia F, Ma W. Pancytopenia due to possible drug-drug interactions between low-dose methotrexate and proton pump inhibitors. Drug Healthc Patient Saf. 2022;14:75–8.
49 Tokunaga K, Suzuki C, Hasegawa M, Fujimori I. Cost analysis in Helicobacter pylori eradication therapy based on a database of Health insurance claims in Japan. Clinicoecon Outcomes Res. 2021;13:241–50.
50 Hosoe N, Matsukawa S, Kanno Y, Naganuma M, Imaeda H, Ida Y, et al. Cross-sectional small intestinal surveillance of maintenance hemodialysis patients using video capsule endoscopy: SCHEMA study. Endosc Int Open. 2016;4(5):E589–596.