Kidney Medicine Original Research

Inflammation and Erythropoiesis-Stimulating Agent Response in Hemodialysis Patients: A Self-matched Longitudinal Study of Anemia Management in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Rationale & Objective: Previous studies of inflammation and anemia management in hemodialysis (HD) patients may be biased due to patient differences. We used a self-matched longitudinal design to test whether new inflammation, defined as an acute increase in C-reactive protein (CRP) level, reduces hemoglobin response to erythropoiesis-stimulating agent (ESA) treatment.

Study Design: Self-matched longitudinal design.

Setting & Participants: 3,568 new inflammation events, defined as CRP level > 10 mg/L following a 3-month period with CRP level ≤ 5 mg/L, were identified from 12,389 HD patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 4 to 6 (2009-2018) in 10 countries in which CRP is routinely measured.

Predictor: "After" (vs "before") observing a high CRP level.

Outcomes: Within-patient changes in hemoglobin level, ESA dose, and ESA hyporesponsiveness (hemoglobin < 10 g/dL and ESA dose > 6,000 [Japan] or >8,000 [Europe] U/wk).

Analytical Approach: Linear mixed models and modified Poisson regression.

Results: Comparing before with after periods, mean hemoglobin level decreased from 11.2 to 10.9 g/dL (adjusted mean change, −0.26 g/dL), while mean ESA dose increased from 6,320 to 6,960 U/wk (adjusted relative change, 8.4%). The prevalence of ESA hyporesponsiveness increased from 7.6% to 12.3%. Both the unadjusted and adjusted prevalence ratios of ESA hyporesponsiveness were 1.68 (95% CI, 1.48-1.91). These associations were consistent in sensitivity analyses varying CRP thresholds and were stronger when the CRP level increase was sustained over the 3-month after period.

Limitations: Residual confounding by unmeasured time-varying risk factors for ESA hyporesponsiveness.

Conclusions: In the 3 months after HD patients experienced an increase in CRP levels, hemoglobin levels declined quickly, ESA doses increased, and the prevalence of ESA hyporesponsiveness increased appreciably. Routine CRP measurement could identify inflammation as a cause of worsened anemia. In turn, these findings speak to a potentially important role for anemia therapies that are less susceptible to the effects of inflammation.

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Kidney Med. 2(3):286-296. Published online March 26, 2020.

doi: 10.1016/j.xkme.2020.01.007

Best practice guidelines for anemia management in hemodialysis (HD) patients, including use of erythropoiesis-stimulating agents (ESAs), have varied over time and by international region, with a lower hemoglobin level threshold of 10 g/dL frequently targeted.[1-6]

Editorial, p 245

Randomized trials have demonstrated the cardiovascular harm of targeting higher hemoglobin levels in anemic patients with chronic kidney disease,[7-10] but the mechanism remains unclear. ESA hyporesponse has been associated with worse survival, and this association is driven at least in part by poor outcomes in patients who require the highest doses.[11] The US Food and Drug Administration has recommended to use the lowest ESA dose needed to avoid transfusions in patients who have not demonstrated sufficient response to ESA therapy.[12] Financial incentives and clinical risk mitigation strategies to reduce ESA doses also motivate the need to distinguish between HD patients who may require higher ESA doses to achieve hemoglobin levels ≥ 10 g/dL and those who may be overtreated. ESA hyporesponsiveness is thought to be present in ∼10% of HD patients[13,14] and is commonly defined as one of the following: (1) a decrease in hemoglobin level at constant ESA dose, (2) an increase in ESA dose to preserve a similar hemoglobin level, or (3) a failure to increase hemoglobin level into the target range despite large ESA doses.[2]

Inflammation, easily identified clinically by a high C-reactive protein (CRP) level, is common in HD patients and associated with increased mortality.[15-18] Inflammation may also blunt the hematopoietic response of ESA therapy to produce hemoglobin by decreasing bone marrow response to ESAs, altering iron regulation through hepcidin, and/or causing hemolysis of red blood cells/erythrocytes.[13,16,19,20] Several cross-sectional analyses have shown a positive correlation between CRP level and ESA dose.[21-25] However, longitudinal

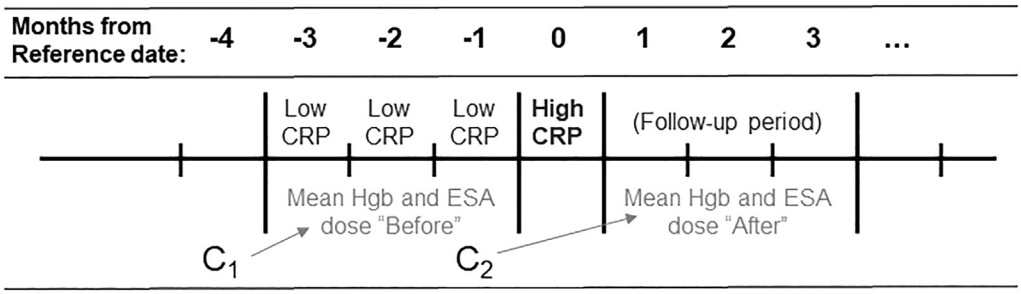

Figure 1. Illustration of before-after study design. For a given patient, average hemoglobin (Hgb) level and erythropoiesis-stimulating agent (ESA) dose were observed during the 3 months following an increase in C-reactive protein (CRP) level from low (≤5 mg/L) to high (>10 mg/L). Time-varying confounders were included during the month preceding the "before" period (C_1) and the month preceding the CRP level increase (C_2).

studies have been less frequent and have used a variety of analytic approaches.[26-28]

In this study, we focus on newly developed inflammation and aim to quantify the magnitude of within-patient changes in hemoglobin levels and ESA doses relative to preinflammation levels. We hypothesized that patients are more likely to be ESA hyporesponsive, with lower hemoglobin levels and/or larger ESA doses in the 3 months after an increase in CRP level (from ≤5 to >10 mg/L) compared with the 3 months before this increase.

METHODS

Data Source

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international multiphase prospective cohort study of patients 18 years and older treated with in-center HD in 21 countries. Maintenance HD patients were randomly selected from national samples of HD facilities in each country; detailed information is included in prior publications[29,30] and at http://www.dopps.org. Study approval and patient consent were obtained as required by national and local ethics committee regulations. Information for patient demographics and comorbid condition history was abstracted from medical records at DOPPS enrollment in each phase. Monthly data for measured laboratory values and medication prescriptions were abstracted from medical records at baseline and during follow-up.

This analysis included HD patients from 10 DOPPS countries for which monthly CRP data were widely available: Japan, Australia and New Zealand (ANZ), and 7 countries in Europe: Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom. No data from the United States or Canada were used because routine measurement of CRP in the HD setting remains rare in North America.[31] Countries were included only during phases when data for laboratory values and medications were collected monthly: all 10 countries in DOPPS phase 4 (2009-2011), all countries except Belgium and Sweden in phase 5 (2012-2015), and only Japan in phase 6 (2015-2018).

Study Design

Our goal was to assess whether newly developed inflammation led to increased ESA resistance. To operationalize this hypothesis, we considered CRP level to be a surrogate for inflammation and used a self-matched before-after study design as illustrated in Figure 1 to assess within-patient changes in hemoglobin levels, ESA doses, and ESA hyporesponsiveness from the "before" period (little or no inflammation) to the "after" period (following the onset of inflammation). This self-matched design prevents confounding due to fixed patient characteristics, for example, sex, baseline age, and comorbid condition history, as well as other unmeasured confounders such as genetic or environmental factors.

Because longitudinal ascertainment of CRP level was required, we excluded patients with fewer than 2 CRP measurements during DOPPS follow-up and facilities that did not routinely assess CRP, defined as CRP data available in >25% of patient-months (ie, measured at least once every 4 months on average). The remaining patients were potentially eligible for inclusion. We then identified instances of high CRP levels (>10 mg/L), considered "month 0." These instances needed to meet 4 additional criteria to be included in the matched analysis: (1) the patient was enrolled in DOPPS for 4 or more months before month 0, (2) CRP was measured at least once during the 3 months before month 0, (3) all available CRP values were low (≤5 mg/L) during the 3 months before month 0, and (4) the patient remained in DOPPS for 3 or more months following month 0. Detailed information on the number excluded for various reasons is shown in the flow diagram (Fig 2).

Statistical Analyses

We first summarized the distribution of CRP levels by country. After applying the inclusion/exclusion criteria above, we summarized both time-fixed and time-varying patient characteristics of the study sample used in the matched analysis. In descriptive analyses to illustrate trends in hemoglobin level, ESA dose, and ESA hyporesponsiveness over the 3 months before and after the CRP increase,

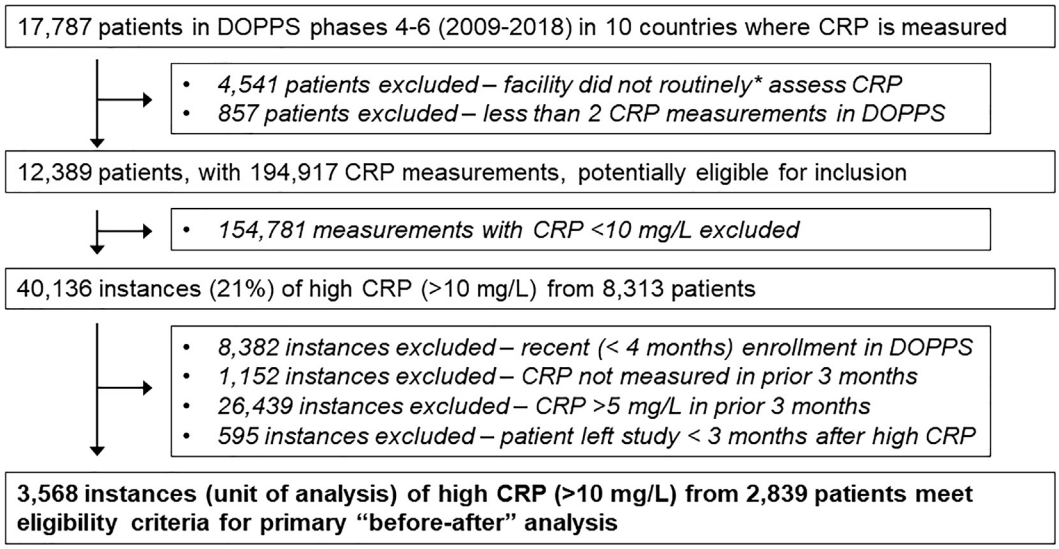

Figure 2. Flow chart illustrates inclusion/exclusion criteria. *Routine measurement of C-reactive protein (CRP) by a facility defined as ≥25% of patient-months with a CRP measurement, that is, CRP measured at least once every 4 months on average. Note that the 194,917 CRP measurements from 12,389 patients were used as the basis to report the distribution of CRP in Figure 3. Abbreviation: DOPPS, Dialysis Outcomes and Practice Patterns Study.

the mean and 95% confidence interval (CI) were calculated in each month. To convert ESA doses to units of intravenous (IV) epoetin, we used conversion factors of 250:1 for darbepoetin,[32] 208:1 (250/1.2) for pegylated epoetin beta,[33] and 1.15:1 for subcutaneous injections.[34]

ESA hyporesponsiveness, the main binary outcome, was defined in each 3-month period as low hemoglobin level (<10 g/dL) plus high ESA dose, for which the threshold for high ESA dose was lower in Japan (>6,000 U/wk) than in Europe/ANZ (>8,000 U/wk) due to generally lower ESA doses in Japan. Hemoglobin levels and ESA doses were averaged over each 3-month period. To estimate the unadjusted prevalence ratio of ESA hyporesponsiveness in the after versus before period, we used Mantel-Haenszel methods for matched designs[35] to analyze the 2×2 table. To incorporate potential time-varying confounders, we used an extension of the modified Poisson regression approach for correlated binary data,[36] a valid alternative when log-binomial regression fails to converge.[37,38]

The 2 secondary outcomes were hemoglobin level and ESA dose, each averaged over the 3 months before and after the increase in CRP level. We used a natural log transformation of ESA dose due to skewness of the distribution, but we also modeled the untransformed ESA dose. For these continuous outcomes, we used mixed-effects linear regression with an indicator variable for after (vs before) as the exposure contrast of interest. Because multiple inflammation events per patient could be eligible, we used a random intercept to account for within-facility and within-patient clustering.

Factors that are constant within patients (eg, sex), change uniformly over time (eg, age), or are otherwise constant within each pre-post pair (eg, DOPPS phase/country) cannot be confounders in this analysis because they are "matched" perfectly within patients. Within-patient factors that changed between the before and after periods (eg, laboratory values and medications), potentially caused by disease progression, could plausibly confound the estimated effect of increasing CRP levels on each outcome. We adjusted for several of these potential confounders to exclude alternative sources of changes in hemoglobin level or ESA dose; we included a set of covariates measured at 2 time points: 4 months before the high CRP level and 1 month before the high CRP level (C_1 and C_2, as illustrated in Fig 1). By measuring potential confounders before the high CRP level was observed, the covariates cannot be affected by the new inflammation (thus avoiding controlling for a mediator on the causal pathway), whereas they may still plausibly affect hemoglobin level and ESA dose during the before (C_1) and after (C_2) periods. Our models thus included adjustment for DOPPS phase, country, age, sex, vintage (time since HD initiation), body mass index, and history of 13 comorbid conditions (listed in Table 1), plus the following time-dependent variables measured at 4 and 1 month before the observed high CRP level: serum albumin level, white blood cell count, serum phosphorus level, cinacalcet use, IV iron dose, hospitalization, and catheter use.

We performed subgroup analyses to assess heterogeneity between Japan and the other countries (due to population differences in CRP levels) and effect modification by patient characteristics. We also performed sensitivity analyses to assess the robustness of our results: (1) varying the number of CRP measurements during the 3-month before period, (2) restricting to patients' first instance of high CRP level, (3) varying the thresholds used to define "low" and "high" CRP levels, (4) varying the length of the outcome assessment period, (5) varying the

Table 1. Summary Statistics for Time-Fixed Patient Characteristics, by Region

	Europe/ANZ	Japan
No. of eligible instances of high CRP	1,530	2,038
No. of patients	1,293	1,546
Age, y	67.3 (14.5)	68.1 (11.5)
Sex, male	951 (62%)	1438 (71%)
Time on dialysis, y	3.5 [1.7, 6.9]	6.5 [3.0, 12.5]
Body mass index, kg/m^2		
<18	52 (4%)	300 (16%)
18-25	647 (45%)	1,364 (71%)
25-30	492 (34%)	223 (12%)
≥30	249 (17%)	40 (2%)
Comorbid conditions		
Coronary artery disease	578 (38%)	664 (33%)
Heart failure	323 (21%)	464 (23%)
Cerebrovascular disease	258 (17%)	313 (15%)
Other cardiovascular disease	500 (33%)	606 (30%)
Cancer (nonskin)	239 (16%)	266 (13%)
Diabetes	574 (38%)	899 (45%)
Gastrointestinal bleeding	72 (5%)	96 (5%)
Hypertension	1,329 (87%)	1,686 (84%)
Lung disease	204 (13%)	62 (3%)
Neurologic disease	200 (13%)	149 (7%)
Psychiatric disorder	289 (19%)	105 (5%)
Peripheral vascular disease	470 (31%)	345 (17%)
Recurrent cellulitis, gangrene	114 (7%)	108 (5%)

Note: Values expressed as mean (standard deviation), median [interquartile range], or number (percent). Age, time on dialysis, and body mass index were captured at the time of the CRP level increase (month 0, as defined in Fig 1); comorbid conditions were captured at DOPPS enrollment. Columns may not sum to 100% due to rounding.
Abbreviations: A/NZ, Australia/New Zealand; CRP, C-reactive protein; DOPPS, Dialysis Outcomes and Practice Patterns Study.

longevity of the CRP level increase as sustained (CRP > 10 mg/L throughout the 3-month after period) versus transient (CRP ≤ 5 mg/L throughout 3-month after period), and (6) varying the ESA dose threshold used to define ESA hyporesponsiveness.

We used multiple imputation, assuming that data were missing at random, to impute missing covariate values using the Sequential Regression Multiple Imputation Method by IVEware.[39] Results from 20 such imputed data sets were combined for the final analysis using Rubin's formula.[40] The proportion of missing data was <10% for all covariates in each region, with the exception of white blood cell count (12%). All analyses were conducted using SAS software, version 9.4 (SAS Institute).

RESULTS

Prevalence of High CRP by Country

As shown in Figure 2, a total of 12,389 patients potentially eligible for inclusion had a total of 194,917 CRP measurements; the median number of measurements was 13 (interquartile range [IQR], 6-24). The CRP distribution in this population is reported by country in Figure 3. The prevalence of high CRP levels (>10 mg/L) was greatest in the United Kingdom (43%) and 30% to 40% across other Europe/ANZ countries; median CRP level was 6 to 8 mg/L across Europe/ANZ. The prevalence of CRP level >10 mg/L was much lower in Japan (10%), where 57% of CRP measurements were ≤1 mg/L.

Self-matched Analysis

Patient Characteristics

After applying the inclusion/exclusion criteria as shown in Figure 2, we identified 3,568 instances of high CRP levels (month 0) from 2,839 patients eligible for the primary analysis: 1,659 from phase 4 DOPPS, 1,316 from phase 5, and 593 from phase 6. More than half (54%) the eligible patients were from Japan. Baseline patient characteristics treated as time-fixed are shown in Table 1 for patients eligible for the before-after analysis, by region. Compared with Europe/ANZ, patients in Japan tended to have longer vintage, have lower body mass index, and were less likely to have several comorbid conditions.

Time-varying patient characteristics collected longitudinally are shown in Table 2. In the 3 months after versus before an increase in CRP level, patients in both regions tended to experience modest decreases in transferrin saturation and serum albumin level and modest increases in ferritin level and white blood cell count. The proportion of patients prescribed IV iron and their respective doses changed minimally. In Europe/ANZ, patients were more likely to receive a red blood cell transfusion (6% vs 3%) or experience inpatient hospitalization (26% vs 19%) in the 3 months after versus before an increase in CRP level, but differences were minimal in Japan. More granular month-level changes in characteristics are shown in Table S1, in which clear differences are observed concurrent with the increase in CRP level. Median CRP level was 19 (IQR, 14-37) in Europe/ANZ and 20 (IQR, 14-36) mg/L in Japan during the reference month, then decreased to 6 (IQR, 3-14) in Europe/ANZ and 3 (IQR, 1-7) in Japan during the after period, illustrating that in most cases the increase in CRP level to >10 mg/L was not sustained.

Descriptive Results

In Figure 4, we present unadjusted monthly: (1) mean hemoglobin levels, (2) mean ESA doses, and (3) proportions of ESA hyporesponsive during the 3 months before and after the high CRP level was observed (month 0), by region. In the 2 regions, hemoglobin level changes paralleled each other during the 7-month study period. In Europe/ANZ, mean hemoglobin level was 11.6 to 11.7 g/dL in the 3 months before the CRP level increase, decreased to 11.2 g/dL in month 0 (concurrent with the CRP increase), then rebounded to 11.5 g/dL 3 months later. In Japan, mean hemoglobin level was ~10.8 g/dL in the 3

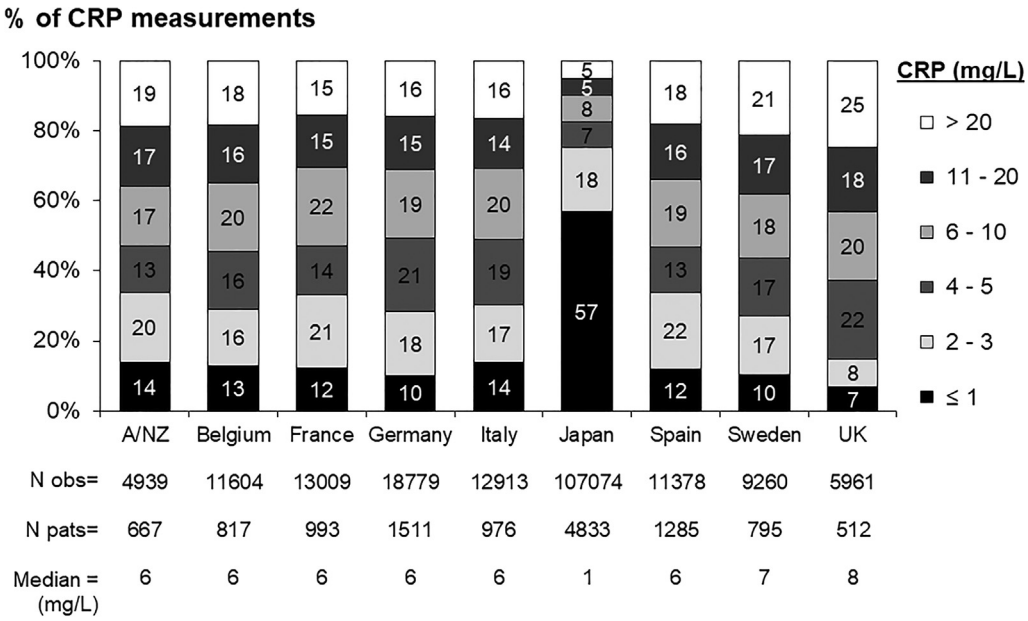

Figure 3. C-Reactive protein (CRP) level distribution, by country. Columns may not sum to 100% due to rounding. Abbreviations and Definitions: A/NZ, Australia/New Zealand; N obs, number of monthly CRP measurements available from these patients (denominators for the figure); N pats, number of patients with CRP measurements who are potentially eligible for inclusion (as described in Fig 2); UK, United Kingdom.

months before the CRP level increase, decreased to 10.6 g/dL in month 0, then rebounded to 10.8 g/dL 3 months later. Mean ESA dose in Europe/ANZ was about 7,800 U/wk in the 3 months before the CRP level increase, then steadily increased to ~8,500 U/wk, starting 1 month following the CRP level increase. In Japan, mean ESA dose was ~5,200 U/wk in the 3 months before the CRP level increase; in contrast to Europe/ANZ, ESA dose started to increase in month 0 (immediately following the CRP increase) and increased to >6,000 U/wk 2 months after the CRP level increase. ESA hyporesponsiveness in both regions increased in month 0, peaked in month 1, and then started to decline toward preinflammation levels by month 3.

Model Results

The main findings of this self-matched analysis are shown in the top row of Table 3. The adjusted prevalence ratio of ESA hyporesponsiveness of 1.68 (95% CI, 1.48-1.91) indicates that patients were much more likely to be hyporesponsive during the 3 months after versus before the increase in CRP level. The unadjusted prevalence ratio was also 1.68 (95% CI, 1.48-1.91), providing strong evidence that our self-matched design adequately accounted for time-fixed and time-varying confounders. Results from the adjusted mixed-effects linear regression models showed that hemoglobin levels were on average 0.26 g/dL lower (95% CI, 0.22-0.30) in the 3 months after versus before the increase in CRP level. The average within-patient change in log(ESA dose) was 0.080 (95% CI, 0.057-0.104), which, after exponentiating, can be interpreted as an ~8.4% (95% CI, 5.8%-11.0%) increase in ESA dose. In absolute terms, the average within-patient increase in ESA dose was 588 (95% CI, 403-773) U/wk. Table 3 also shows that results from several subgroup analyses by region, catheter use, sex, and age were all directionally consistent with the primary analysis.

Table 4 illustrates the robustness of our results to several sensitivity analyses. Results were consistent when requiring 3 CRP measurements during the before period (Table 4[a]) and when restricting to patients' first instance of high CRP level (Table 4[b]). Increasing the contrast when defining low and high CRP levels (eg, from ≤3 to >20 mg/L; Table 4[c]) resulted in a similar decrease in hemoglobin level but a larger increase in ESA dose (14.7%). Reducing the length of the after period (eg, from 3 to 1 month) (Table 4[d]) resulted in a larger hemoglobin level decrease (0.42 g/dL) but smaller ESA dose increase (4.4%), as also reflected in the descriptive results (illustrated in Fig 4). We observed much larger changes among patients for whom the CRP level increase was sustained at >10 mg/L (0.70 g/dL decrease in hemoglobin and 14.2% increase in ESA dose) throughout the 3-month after period, compared with those with a transient CRP level increase (Table 4[e]). Finally, the adjusted prevalence ratio for ESA hyporesponsiveness was consistent (1.71 vs 1.68) when increasing the ESA dose thresholds from 6,000 to 7,500 U/wk in Japan and 8,000 to 10,000 U/wk in Europe/ANZ, and when using the same 8,000-U/wk threshold in both regions (Table 4[f]).

Table 2. Summary Statistics for Time-Varying Patient Characteristics Before and After the CRP Increase From ≤5 to >10 mg/L, by Region

	Europe/ANZ		Japan	
No. of eligible instances of high CRP	1,530		2,038	
No. of patients	1,293		1,546	
Time-Varying Characteristic	**3 mo "Before"**	**3 mo "After"**	**3 mo "Before"**	**3 mo "After"**
CRP, mg/L	3 [2, 4]	6 [3, 14]	2 [1, 3]	3 [1, 7]
TSAT, %	29.6 (12.3)	27.7 (11.9)	25.2 (11.1)	24.1 (11.1)
Serum ferritin, ng/mL	402 [223, 613]	452 [259, 689]	77 [37, 147]	83 [42, 172]
Serum albumin, g/dL	3.8 (0.4)	3.7 (0.5)	3.7 (0.4)	3.6 (0.4)
Serum phosphorus, mg/dL	4.9 (1.4)	4.9 (1.5)	5.2 (1.2)	5.1 (1.2)
Mean WBC count, 10^3 cells/μL	6.7 (1.9)	6.9 (2.1)	5.9 (1.8)	6.1 (1.9)
IV iron use (any during 3 mo)	1,120 (75%)	1,094 (74%)	622 (31%)	663 (33%)
IV iron dose, mg/mo	261 [145, 435]	272 [145, 435]	116 [58, 174]	116 [58, 174]
Cinacalcet use (any during 3 mo)	270 (18%)	282 (19%)	530 (26%)	538 (27%)
Catheter use (any during 3 mo)	361 (25%)	353 (25%)	11 (1%)	15 (1%)
Transfused (any during 3 mo)	29 (3%)	69 (6%)	27 (2%)	54 (3%)
Hospitalized (any during 3 mo)	280 (19%)	394 (26%)	316 (16%)	346 (17%)

Note: Values expressed as mean (standard deviation), median [interquartile range], or number (percent). Shown among all eligible instances of high CRP level. Monthly laboratory measures averaged over 3 months. IV iron dose averaged over 3 months among users.
Abbreviations: "after", 3 months after the C-reactive protein level increase; A/NZ, Australia/New Zealand; "before", 3 months before the C-reactive protein level increase; CRP, C-reactive protein; IV, intravenous; TSAT, transferrin saturation; WBC, white blood cell.

DISCUSSION

This self-matched longitudinal (before-after) design and analysis tracked real-world changes in anemia control and ESA dosing in an international sample of HD patients during the 3 months before and after detection of new inflammation by routine CRP measurement. The results supported our hypothesis of a hemoglobin level decrease, concurrent with the increase in CRP level, and ESA dose increase within 1 month, resulting in greater ESA resistance and exposing patients to the potential risks of larger ESA doses.[7-10] The associations were particularly strong among patients for whom the CRP level increase was sustained over the subsequent 3 months, further supporting a causal relation between inflammation and ESA hyporesponsiveness.

Despite major differences in the study design and analytic approach, our results were generally consistent with other longitudinal studies, thus strengthening the evidence for the link between inflammation and ESA hyporesponsiveness.[26-28] Bradbury et al[26] observed that elevated CRP levels led to larger ESA doses at the same hemoglobin levels. However, the authors acknowledged the potential for selection bias in their US HD sample because only ~1% of patients had CRP measured. These patients were likely selected for CRP measurement due to suspicion of inflammation because the median CRP level (20 mg/L) was much higher than reported in other HD populations.[17,24,25]

Gillespie et al[27] conducted a case-crossover study of ESA hyporesponsiveness defined as hemoglobin level < 10 g/dL and ESA dose greater than the median dose of 80 U/kg per week, which they observed in 672 European HD patients. Among the many exposures that Gillespie et al[27] examined, they found a positive association with CRP level (adjusted odds ratio for highest vs lowest quartile [no values provided], 2.02; 95% CI, 1.20-3.38).

Kimachi et al[28] used Japanese DOPPS data from phases 2 to 4 (2002-2011) to evaluate the cumulative incidence of ESA hyporesponsiveness (hemoglobin < 10 g/dL and >9,000 U/wk of ESA) by baseline CRP. Those authors found that the risk for ESA hyporesponsiveness was highest at CRP levels > 10 mg/L but also elevated at CRP levels of 3 to 10 mg/L (vs CRP < 1 mg/L).

The proportion of CRP measurements > 10 mg/L was much lower in Japan (10%) than in Europe/ANZ (34%), consistent with prior research.[17,24,28] Japanese HD practices may help explain this discrepancy, including the use of ultrapure dialysate fluid to keep endotoxins low and avoidance of central venous catheters, which can cause infections and inflammatory reactions.[31] However, CRP levels are also lower in Asians than in whites outside the HD setting,[41] suggesting dietary, environmental, and/or genetic factors as likely contributors to differences in CRP levels.[15]

In our analysis, hemoglobin levels began to decline in the same month that CRP levels increased. Elevated CRP level is generally considered a marker of inflammation, so new inflammation may alter hemoglobin levels roughly concurrent with its effect on CRP levels. In Japan the increase in ESA dose occurs in the same month that hemoglobin levels began to decline (ie, month 0), but in Europe/ANZ, the initial ESA dose increase lags by 1 month. Increases in CRP levels from ≤5 to >10 mg/L were also less likely to be sustained for 3-plus months in Japan (5%) than in Europe/ANZ (18%). These findings suggest either that clinicians in Japan respond more rapidly to a

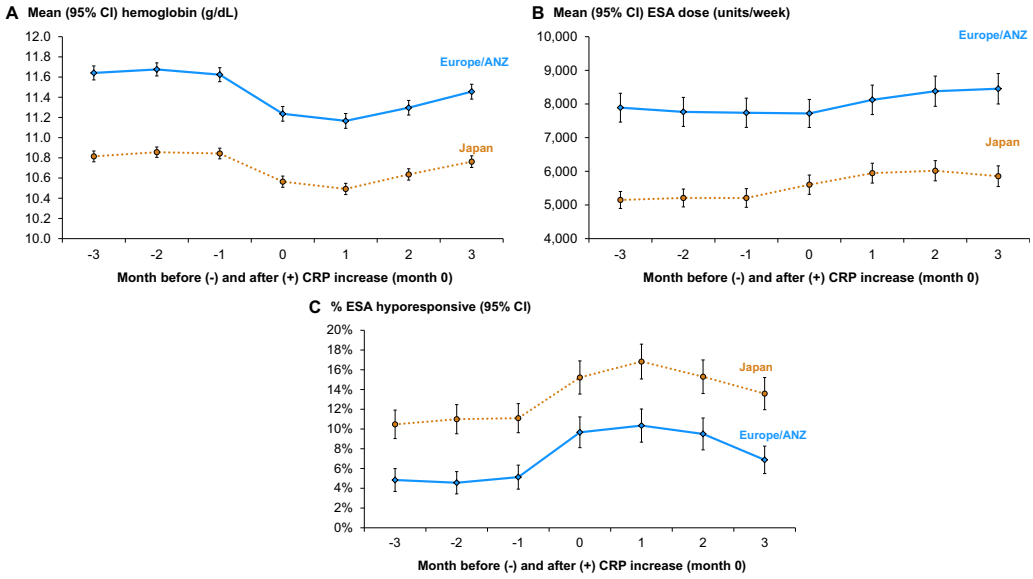

Figure 4. (A) Mean monthly hemoglobin level, (B) mean monthly erythropoiesis-stimulating agent (ESA) dose, and (C) percent ESA hyporesponsive in the 3 months before and after a C-reactive protein (CRP) level increase from ≤5 to >10 mg/L, by region. Mean hemoglobin level and ESA dose were calculated as the average across all patients at each time point. Months during which ESA was not prescribed are considered 0 U/wk. ESA hyporesponsive defined as hemoglobin level <10 g/dL and ESA dose > 6,000 (Japan) or >8,000 (Europe/ANZ) U/wk. Abbreviations: ANZ, Australia/New Zealand; CI, confidence interval.

decline in hemoglobin levels than in Europe/ANZ or that Japanese providers are reacting proactively to increases in CRP levels below the 10-mg/L threshold used in this analysis.

CRP is relatively inexpensive and convenient to routinely measure in the HD setting[42]; this is generally done in Europe and Japan, but not in North America. Routine measurement of CRP can potentially help better identify causes of and inform targeted strategies to reduce inflammation in HD patients. For example, an increase in CRP level may prompt examination for the source of infection (eg, dental and diabetic foot

Table 3. Within-Patient Changes (95% CI) in Hemoglobin, ESA Dose, and ESA Hyporesponsiveness From the 3 Months Before Versus After the CRP Increase From ≤5 to >10 mg/L, Overall and by Subgroup

Subgroup	Instances of High CRP	Change in Hb, g/dL	Relative Change in ESA Dose	Prevalence Ratio of ESA Hyporesponsiveness
Overall	3,568	−0.26 (−0.30 to −0.22)	8.4% (5.8% to 11.0%)	1.68 (1.48 to 1.91)
By region				
Europe/ANZ	1,530	−0.34 (−0.41 to −0.27)	5.2% (1.5% to 9.0%)	2.09 (1.60 to 2.74)
Japan	2,038	−0.20 (−0.25 to −0.16)	10.8% (7.4% to 14.3%)	1.54 (1.34 to 1.78)
By catheter use during "before" period				
Any catheter use	372	−0.50 (−0.62 to −0.37)	9.8% (2.0% to 18.3%)	3.16 (1.74 to 5.76)
No catheter use	2,908	−0.23 (−0.27 to −0.19)	8.0% (5.4% to 10.8%)	1.54 (1.35 to 1.77)
By sex				
Male	2,389	−0.25 (−0.30 to −0.20)	7.2% (4.1% to 10.4%)	1.63 (1.40 to 1.90)
Female	1,177	−0.29 (−0.36 to −0.22)	10.8% (6.3% to 15.4%)	1.81 (1.45 to 2.27)
By age, y				
<60	874	−0.23 (−0.31 to −0.15)	9.2% (4.1% to 14.4%)	1.51 (1.14 to 1.98)
60-75	1,559	−0.27 (−0.33 to −0.21)	7.8% (3.9% to 11.8%)	1.79 (1.47 to 2.17)
>75	1,135	−0.28 (−0.35 to −0.21)	8.9% (4.7% to 13.3%)	1.66 (1.35 to 2.04)

Note: Linear mixed model with random facility and patient intercepts to calculate mean changes in Hb level and ESA dose, and modified Poisson regression to calculate prevalence ratio of ESA hyporesponsiveness. Baseline adjustment for DOPPS phase, country, age, sex, vintage, body mass index, and 13 comorbid conditions and adjustment for serum albumin level, white blood cell count, serum phosphorus level, cinacalcet use, intravenous iron dose, hospitalization, and catheter use at 4 and 1 month before the CRP level increase. ESA hyporesponsiveness defined as Hb level <10 g/dL and ESA dose >6,000 (Japan) or >8,000 (Europe/ANZ) U/wk. Primary analysis includes patients with CRP levels ≤ 5 mg/L during the 3-month "before" period, increased to >10 mg/L, then followed up during the 3-month "after" period.

Abbreviations: ANZ, Australia/New Zealand; CI, confidence interval; CRP, C-reactive protein; DOPPS, Dialysis Outcomes and Practice Patterns Study; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

Table 4. Within-Patient Changes (95% CI) in Hemoglobin, ESA Dose, and ESA Hyporesponsiveness From the 3 Months Before Versus After the CRP Increase: Sensitivity Analyses

Sensitivity Analysis	Instances of High CRP	Change in Hb, g/dL	Relative Change in ESA Dose	Prevalence Ratio of ESA Hyporesponsiveness
Primary analysis	3,568	−0.26 (−0.30 to −0.22)	8.4% (5.8% to 11.0%)	1.68 (1.48 to 1.91)
(a) CRP measurements during 3-mo "before" period				
CRP measured all 3 mo	2,312	−0.26 (−0.30 to −0.21)	9.9% (6.7% to 13.1%)	1.65 (1.42 to 1.93)
CRP measured in 1 or 2 of the 3 mo	1,256	−0.28 (−0.36 to −0.21)	5.9% (1.8% to 10.2%)	1.76 (1.41 to 2.20)
(b) Restricting to 1 record per patient				
First instance of high CRP during DOPPS enrollment	2,839	−0.27 (−0.31 to −0.22)	8.1% (5.5% to 10.8%)	1.74 (1.50 to 2.01)
(c) Varying thresholds for "low" and "high" CRP				
CRP increase from ≤10 to >20 mg/L	3,008	−0.27 (−0.32 to −0.23)	10.2% (7.4% to 13.1%)	1.56 (1.35 to 1.80)
CRP increase from ≤5 to >20 mg/L	1,703	−0.30 (−0.36 to −0.24)	11.7% (8.0% to 15.6%)	1.70 (1.39 to 2.07)
CRP increase from ≤3 to >20 mg/L	1,053	−0.27 (−0.34 to −0.19)	14.7% (9.7% to 19.8%)	1.66 (1.29 to 2.15)
CRP increase from ≤3 to >10 mg/L	2,178	−0.27 (−0.32 to −0.22)	11.1% (7.8% to 14.5%)	1.73 (1.46 to 2.05)
CRP increase from ≤3 to >5 mg/L	4,230	−0.18 (−0.22 to −0.15)	6.4% (4.2% to 8.7%)	1.43 (1.25 to 1.63)
CRP increase from ≤1 to >5 mg/L	1,624	−0.18 (−0.23 to −0.12)	10.9% (7.2% to 14.7%)	1.36 (1.10 to 1.68)
(d) Vary length of "after" period for assessing outcome				
1-mo "after" period	3,958	−0.42 (−0.46 to −0.37)	4.4% (1.9% to 6.9%)	1.91 (1.68 to 2.17)
2-mo "after" period	3,755	−0.34 (−0.39 to −0.30)	7.7% (5.3% to 10.2%)	1.82 (1.60 to 2.08)
(e) By longevity of CRP increase in "after" period				
Sustained: CRP > 10 mg/L in "after" period	352	−0.70 (−0.85 to −0.55)	14.2% (4.7% to 24.5%)	2.89 (1.97 to 4.24)
Transient: CRP ≤ 5 mg/L in "after" period	1,652	−0.14 (−0.19 to −0.09)	5.6% (2.1% to 9.1%)	1.22 (1.00 to 1.48)
(f) Vary thresholds for ESA hyporesponsiveness				
ESA dose >8,000 (Japan) or >8,000 (Europe/ANZ) U/wk	3,568	NA	NA	1.74 (1.51 to 2.00)
ESA dose >7,500 (Japan) or >10,000 (Europe/ANZ) U/wk	3,568	NA	NA	1.71 (1.49 to 1.96)

Note: Linear mixed model with random facility and patient intercepts to calculate mean changes in Hb level and ESA dose, and modified Poisson regression to calculate prevalence ratio of ESA hyporesponsiveness. Baseline adjustment for DOPPS phase, country, age, sex, vintage, body mass index, and 13 comorbid conditions and adjustment for serum albumin level, white blood cell count, serum phosphorus level, cinacalcet use, intravenous iron dose, hospitalization, and catheter use at 4 and 1 month before the CRP increase. ESA hyporesponsiveness defined as Hb level < 10 g/dL and ESA dose > 6,000 (Japan) or >8,000 (Europe/ANZ) U/wk unless otherwise specified. Primary analysis includes patients with CRP levels ≤ 5 mg/L during the 3-month "before" period, increased to >10 mg/L, then followed up during the 3-month "after" period. Relative change in ESA dose based on models using log(ESA dose) as outcome.
Abbreviations: ANZ, Australia/New Zealand; CI, confidence interval; CRP, C-reactive protein; DOPPS, Dialysis Outcomes and Practice Patterns Study; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; NA, not applicable.

examinations) and timely initiation of antimicrobial therapy when indicated. Other longer-term strategies to limit or reduce inflammation include removing old nonfunctioning arteriovenous grafts,[43,44] transplant nephrectomy,[45] using ultrapure dialysate fluid,[13,15] and improving diet and exercise.[18] Specific to anemic patients, quicker recognition of new inflammation can help identify the cause of worsening anemia and guide reactive ESA and IV iron dosing decisions. Further, frequent assessment of inflammation can help identify patients who may be candidates for new alternative anemia therapies, such as hypoxia-inducible factor prolyl hydroxylase inhibitors, not yet approved in the United States or Europe, that may be less susceptible to the effects of inflammation than current ESA and IV iron-based treatment regimens.[46-48]

This study had some limitations. First, CRP levels can be highly variable over time within a patient,[49,50] likely due to infections causing acute increases. The resulting error in classifying CRP level is likely to be nondifferential with respect to the outcomes and covariates, thus probably resulting in bias toward the null (ie, underestimates). Further, subgroup analyses show that associations were stronger when CRP level increases were sustained over the 3-month after period.

Second, although the study would be strengthened by potentially better markers of inflammation such as interleukin 6, increasing CRP level was the best indicator of inflammation available through routine measurement.

Third, if patients excluded due to fewer than 3 months of data postinflammation were more likely to have experienced ESA hyporesponsiveness following their high CRP levels, the true effect may be underestimated. However, that bias is likely minimal because of the small proportion (14%) of excluded patients.

Fourth, although we adjusted for several time-varying confounders, it is possible that our estimates experienced residual confounding by unmeasured time-varying risk

factors for ESA hyporesponsiveness. However, because the extensive covariate adjustments in our models had little impact on our estimates in this self-matched study, the likelihood of bias due to unmeasured confounding is low.

Several strengths distinguish this analysis from other longitudinal studies of inflammation and ESA hyporesponsiveness.[26-28] First, the longitudinal study design focuses on incident inflammation to avoid the temporal ambiguity of cross-sectional designs. By matching patients to themselves and measuring outcomes before and after the detection of elevated CRP levels, this design does not require a comparison group of patients who did not experience an increase in CRP level. The self-matching seems to have controlled adequately for potential confounders, both fixed and time-varying factors, as evidenced by the unchanged estimates after additional adjustment. It is thus likely that residual bias by additional unmeasured time-varying confounders would be minimal. However, future studies could perform between-patient comparisons that we did not investigate.

Second, we used a large international sample of HD patients from facilities that routinely measured CRP, the best available marker of inflammation, to avoid bias in which a clinical indication for measuring CRP also affects the outcome (a phenomenon we call "measurement-by-indication bias").

Third, in addition to a single ESA hyporesponse outcome, we treated the 2 components of that outcome, hemoglobin level and ESA dose, as separate continuous outcomes, allowing us to better explore relative changes in ESA sensitivity without relying on the flawed erythropoietin resistance index.[51,52]

This study demonstrates that new inflammation, as detected by an increase in CRP level, is associated with the development of ESA resistance and reduction in hemoglobin levels under current anemia treatment paradigms. These findings speak to a potentially important role for anemia therapies that are less susceptible to the effects of inflammation.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Monthly summary statistics for time-varying patient characteristics before and after the CRP increase from ≤5 to >10 mg/L, by region

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Support: Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details, see https://www.dopps.org/AboutUs/Support.aspx. Part of this work has been supported by specific funding from AstraZeneca. All grants were made to Arbor Research Collaborative for Health and not to coauthors directly. None of the funders had any role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit this report for publication.

Financial Disclosure: Drs Karaboyas, Robinson, and Pisoni are employees of Arbor Research Collaborative for Health, which administers the DOPPS. Dr Akizawa has consulted for Astellas, Bayer Yakuhin Ltd, GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co Ltd, Kyowa Hakko Kirin, Ono Pharmaceutical Co Ltd, Fuso Pharmaceutical Industries, Ltd, and Nipro Corp and received lecture fees from Yakuhin Ltd, Kissei Pharmaceutical Co Ltd, Kyowa Hakko Kirin, Ono Pharmaceutical Co Ltd, Chugai Pharmaceutical Co Ltd, and Torii Pharmaceutical Co Ltd. Dr James is an employee of AstraZeneca and receives a salary from AstraZeneca. Ms Schaeffner received honoraria from Siemens, Fresenius Medical Care, and Fresenius Kabi for lectures. Dr Sinsakul is an employee of AstraZeneca and receives stock options as part of his compensation. Dr Dhalwani is an employee at Evidera. Evidera was contracted to work for AstraZeneca on this project. The remaining authors have no conflicts of interest to declare.

Acknowledgements: Jennifer McCready-Maynes, an employee of Arbor Research Collaborative for Health, provided editorial support for this manuscript.

Prior Presentation: The results presented in this report have not been published previously in whole or part, except in abstract form at the American Society of Nephrology: Kidney Week, October 25-28, 2018, San Diego, CA (Poster TH-PO252).

Peer Review: Received September 10, 2019. Evaluated by 2 external peer reviewers, with direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form January 6, 2020.

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