Intra-Dialytic Hemoglobin Changes and Cardiovascular Events: A Cohort Study on Dialysis Outcomes and Practice Patterns in Japan

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Keywords

Hemodialysis · Ultrafiltration · Plasma refilling · Hemoglobin · Cardiovascular events

Abstract

Background: Ultrafiltration during hemodialysis (HD) causes hemoconcentration. Little is known about the relationships between intra-dialytic changes in hemoglobin concentration and cardiovascular events. Thus, this study aimed to elucidate the relationships between intra-dialytic changes in hemoglobin concentration and cardiovascular events among HD patients. **Methods:** This prospective cohort study was based on the Japanese Dialysis Outcomes and Practice Pattern Study phases 4 and 5. The predictor was the ratio of post-dialysis hemoglobin concentration to pre-dialysis hemoglobin concentration (post-Hb/pre-Hb) at baseline. The primary outcome was major adverse cardiovascular events (MACEs). Hazard ratios (HRs) were estimated using a Cox model for the association between post-Hb/pre-Hb and MACEs, adjusting for potential confounders. **Results:** A total of 865 patients were enrolled. During a median follow-up of 2.6 years, 145 (16.8%) patients developed MACEs. Patients were divided into 4 categories according to baseline post-

Hb/pre-Hb (<1.0, ≥1.0 to <1.1, ≥1.1 to <1.2, and ≥1.2). The multivariable-adjusted HRs for MACEs were 1.69 (95% CI 1.36–2.10), 1.29 (95% CI 1.10–1.51), and 1.31 (95% CI 1.02–1.68) in patients with post-Hb/pre-Hb ratios of <1.0, ≥1.0 to <1.1, and ≥1.2, respectively, compared with the reference post-Hb/pre-Hb ratio of ≥1.1 to <1.2. Cubic spline analyses revealed a U-shaped association between post-Hb/pre-Hb and MACEs. **Conclusion:** High and low intra-dialytic changes in hemoglobin concentration are associated with a high risk of MACEs in patients undergoing HD.

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Introduction

The aim of hemodialysis (HD) is to remove waste, uremic toxins, and fluid from the blood by diffusion and ultrafiltration. Fluid removal is usually performed by ultrafiltration and the aim is to achieve a clinical “dry weight (DW)” [1]. Fluid removal for patients undergoing HD is one of the major challenges. Previous studies on fluid removal in HD patients have pointed to an association between an interdialytic weight loss

(IDWL) >5.7% of post-dialytic body weight and higher mortality [2]. Furthermore, a high ultrafiltration rate (>10 mL/kg/h) is associated with high mortality [3, 4]. In fact, a recent statement from the Chief Medical Officers of US dialysis providers suggests that appropriate fluid management is one of the most important unmet issues for contemporary HD patients globally; moreover, this statement promotes “volume first,” meaning that volume control should be the primary goal of dialysis care [5].

Fluid removal also results in hemoconcentration and increases hemoglobin concentration after HD [6]. The previous observational study showed that each 1 L of ultrafiltration led to an increase in hemoglobin concentration of approximately 0.4 g/dL. However, the correlation between IDWL and the hemoglobin increment was moderate (correlation coefficient: $r = 0.527$) [6]. Some patients show significant increased hemoglobin concentration and others show none at all after fluid removal. In the situation of increased hemoglobin concentration, the ultrafiltration volume exceeds the refill volume from the interstitial spaces into the vascular space. However, when the ultrafiltration volume exceeds the refill volume significantly, this results in intravascular volume depletion and causes potentially intradialytic morbid events, such as muscle cramping and intradialytic hypotension [7, 8]. These events are known risk factors for cardiovascular events [9]. On the other hand, no change in hemoglobin concentration during dialysis as measured with a continuous monitor such as CRIT-LINE, is interpreted as volume overload in accordance with the previous studies [10, 11]. A status of fluid overload is also a well-known risk factor for mortality and cardiovascular events [12, 13]. Intra-dialytic changes in hemoglobin concentration may reflect changes in intravascular fluid volume [14] and may provide an index for balance of ultrafiltration and fluid refilling when it assesses the ratio between post-dialysis hemoglobin concentration and pre-dialysis hemoglobin concentration (post-Hb/pre-Hb). Our hypothesis was that some increase in this index might be good practice but too much of an increase or no change at all may still carry high risk of cardiovascular events.

To our knowledge, there is no study about the relationship between intra-dialytic changes in hemoglobin concentration – defined as the ratio between post-Hb/pre-Hb concentration and cardiovascular events.

Hence, to clarify this relationship, we conducted a cohort study using data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) in Japan.

Materials and Methods

Study Design and Population

DOPPS was a prospective cohort study of patients enrolled randomly from a representative sample of dialysis facilities within each participating country. All participants in DOPPS provided written informed consent prior to study enrollment. Detailed information on the design of DOPPS has been provided previously [15, 16]. Our cohort study used the Japanese DOPPS (J-DOPPS), which was approved by a central Ethics Committee. The current study design was approved by Kyoto University Graduate School and Faculty of Medicine Kyoto University Hospital Ethics Committee (approval number R1301). Data for the current analysis were obtained from J-DOPPS4 (2009–2011) and J-DOPPS5 (2012–2014). The study included patients undergoing maintenance HD who were older than 18 years and had available data on post-Hb/pre-Hb concentrations. We excluded patients with hemoglobin concentrations <7.0 g/dL because there was some possibility of the requirement for blood transfusion clinically.

Predictor

The predictor was the ratio of post-Hb/pre-Hb concentration, which was calculated as follows:

Post-Hb concentration/Pre-Hb concentration

(hereinafter called “post-Hb/pre-Hb”)

$= \text{post-Hb volume} / (\text{pre dialysis intravascular volume} - \text{ultrafiltration volume} + \text{refill volume}) / \text{pre-Hb volume} / \text{pre dialysis intravascular volume}$

$= \text{pre dialysis intravascular volume} / \text{pre dialysis intravascular volume} - \text{ultrafiltration volume} + \text{refill volume}$

$= \text{pre dialysis intravascular volume} / \text{post dialysis intravascular volume}$

This index shows the intra-dialytic change in intravascular fluid volume in a simple fashion. When pre-Hb/post-Hb volumes are nearly equal, they cancel each other out. For example, when the pre-Hb concentration is 10.0 g/dL and the post-Hb concentration is 11.0 g/dL, the index is 1.1. This means that intra-dialytic intravascular fluid loss led to a 1.1-fold hemoconcentration. Hemoglobin concentrations were assessed in the first session of the week at the beginning of the observation period. Patients were divided into 4 categories by 0.1 increments as follows: (1) <1.0, (2) ≥1.0 to <1.1, (3) ≥1.1 to <1.2, and (4) ≥1.2. The 0.1 increment was based on a 2.5 kg IDWL patient with a pre-Hb concentration of 10.7 g/dL. The 2.5 kg IDWL level was derived from the recommended interdialytic weight gain and the pre-Hb concentration of 10.7 g/dL was derived from the mean pre-Hb level based on exhaustive data for HD patients in Japan [17, 18]. According to a previous study [6], each 1 L of ultrafiltration led to an increase in hemoglobin concentration of approximately 0.4 g/dL. Therefore, based on this, the pre-Hb concentration was estimated to increase by 1.0 g/dL, whereas the post-Hb/pre-Hb was estimated to increase by approximately 0.1 g/dL. A post-Hb/pre-Hb = 1.0 meant that the ultrafiltration volume equaled the refill volume. A post-Hb/pre-Hb >1.0

meant that the ultrafiltration volume exceeded the refill volume. A post-Hb/pre-Hb = 1.1 was used as a reference in our model for continuous variable analysis and a post-Hb/pre-Hb ratio of ≥ 1.1 to < 1.2 was used as a reference in our model for categorical variable analysis.

Outcomes

The primary outcome was major adverse cardiovascular events (MACEs), including acute myocardial infarction, stroke, and all-cause mortality [19]. We have included all-cause death as a composite outcome because substance causes of death among HD patients were related to cardiovascular events [20, 21]. The secondary outcome was all-cause mortality and vascular access failure.

Statistical Analysis

With respect to the baseline characteristics of patients categorized by post-Hb/pre-Hb ratio, continuous data with a normal distribution were summarized as means SD; continuous variables with skewed data, as medians (interquartile range); and dichotomous data, as proportions. The distribution of baseline data according to the categorized post-Hb/pre-Hb ratio was compared using trend analysis. The event-free survival rate for MACEs, all-cause mortality, and vascular access failure according to the categorized post-Hb/pre-Hb ratio was described by the Kaplan-Meier method and compared using the log-rank test. Unadjusted and multivariable-adjusted hazard ratios (HRs) with 95% CI for MACEs, all-cause mortality, and vascular access failure according to the post-Hb/pre-Hb ratio were calculated using a Cox proportional hazards model. The assumption of proportional hazards was graphically checked using a log cumulative hazard plots for each outcome according to the post-Hb/pre-Hb ratio. The multivariable-adjusted model was adjusted for age, sex, cause of end-stage renal disease (ESRD), history of heart disease, HD vintage, IDWL, treatment time, ultrafiltration rate, serum albumin, serum phosphorus, pre-Hb concentration, pre-dialysis systolic blood pressure (BP), changes in systolic BP before and after dialysis, and post-dialysis body weight. These variables were based on a priori clinical judgment and existing studies. We used robust variance estimates to consider cluster effects at the facility level. Furthermore, we analyzed the relationship nonlinearly by modeling the post-Hb/pre-Hb ratio as a continuous variable rather than a categorical value using a restricted cubic spline. We used 4 knots located at the 5th, 35th, 65th, and 95th percentiles of the post-Hb/pre-Hb ratio, as recommended [22].

Sensitivity Analysis

A multiple imputation approach was used to account for missing covariates. Twenty imputations were performed using the multiple imputations with chained equations methods, assuming that analyzed data were missing at random [23]. These estimates were combined using Rubin's rules. We analyzed imputed missing covariate data in the same way as for primary outcome (Sensitivity analysis 1). In addition, we analyzed imputed missing covariate data, including C-reactive protein (CRP) data, in the same way as for the primary outcome (Sensitivity analysis 2). Furthermore, we defined the predictor as mean baseline data and data after 4 months, and we conducted the same analysis as for the primary outcome (Sensitivity analysis 3). We performed a survival analysis after 4 months from study initiation.

All analyses were performed using Stata software version 15.0 (Stata Corp., College Station, TX, USA). *p* values < 0.05 were considered to indicate statistical significance.

Results

Baseline Characteristics

A total of 865 patients were enrolled in the study (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000502633). The mean age was 65.6 years, 61.4% were male, 36.3% had ESRD caused by diabetes, and the median duration of dialysis therapy was 3.6 years (Table 1). Patients with higher post-Hb/pre-Hb ratios showed longer dialysis vintage, longer treatment time, higher serum phosphorus, a higher proportion of IDWL $> 5.7\%$ of post-dialytic body weight, a higher proportion of ultrafiltration rate > 10 mL/kg/h, higher pre-dialysis systolic BP, and greater changes in systolic BP before and after dialysis. In contrast, patients with lower post-Hb/pre-Hb ratios were older, with a higher proportion of ESRD caused by diabetes. The missing data for each variable are shown in online supplementary Table 1.

Association between Post-Hb/Pre-Hb and Risk of MACEs, All-Cause Mortality, and Vascular Access Failure

Categorical Variable Analysis

During a median follow-up of 2.6 years, 145 (16.8%) patients developed MACEs. The details of MACEs are shown in online supplementary Table 2. Survival rates according to post-Hb/pre-Hb ratio are shown in Figure 1a. The Kaplan-Meier survival estimates of patients from varying post-Hb/pre-Hb categories differed among all 4 groups ($p < 0.001$). The unadjusted HRs for MACEs were 1.73 (95% CI 1.40–2.14), 1.33 (95% CI 1.10–1.61), and 1.17 (95% CI 0.95–1.43) in patients with post-Hb/pre-Hb ratios of < 1.0 , ≥ 1.0 to < 1.1 , and ≥ 1.2 respectively. Furthermore, after adjustment for potential confounders, adjusted HRs for MACEs were 1.69 (95% CI 1.36–2.10), 1.29 (95% CI 1.10–1.51), and 1.31 (95% CI 1.02–1.68) in patients with post-Hb/pre-Hb ratios of < 1.0 , ≥ 1.0 to < 1.1 , and ≥ 1.2 respectively (Table 2).

With regard to mortality, during a median follow-up of 2.6 years, 116 (13.4%) patients died (all-cause). The causes of death are shown in online supplementary Table 2. Event-free survival rates according to post-Hb/pre-Hb ratio are shown in Figure 1b. The association between the 4 categories of post-Hb/pre-Hb ratio and

Table 1. Baseline characteristics according to post-Hb/pre-Hb categories

	Total (n = 865)	<1.0 (n = 115)	≥1.0 to <1.1 (n = 348)	≥1.1 to <1.2 (n = 314)	≥1.2 (n = 88)	p for trend
Age, years	65.6 (12.5)	67.1 (12.0)	66.6 (12.1)	64.8 (12.6)	62.6 (14.1)	0.003
Gender, male	61.4	64.4	65.5	56.4	59.1	0.055
Hypertension	86.1	82.6	85.6	86.9	89.7	0.130
Diabetes	42.3	53.9	42.0	39.8	37.5	0.016
History of cerebrovascular disease	15.1	13.9	18.1	13.7	10.2	0.186
History of heart disease	45.9	42.6	44.3	47.1	52.3	0.128
Cause of ESRD: diabetes	36.3	46.1	36.2	34.7	29.6	0.019
Vascular access: arteriovenous fistula	89.3	90.7	89.6	89.7	84.7	0.277
Hemodialysis vintage, years	3.6 (0.6–8.3)	1.6 (0.2–7.1)	2.7 (0.5–7.1)	4.6 (1.4–10.5)	5.7 (1.3–11.7)	<0.001
IDWL >5.7% of post-dialytic body weight	9.6	1.7	8.3	10.5	21.6	<0.001
Ultrafiltration rate >10 mL/kg/h	43.1	21.7	36.8	51.0	68.2	<0.001
Treatment time, minutes	230.7 (29.3)	223.6 (30.6)	229.6 (28.6)	232.0 (28.2)	239.9 (32.2)	0.001
Pre-dialysis Hb, g/dL	10.4 (1.2)	10.4 (1.3)	10.4 (1.2)	10.4 (1.1)	10.6 (1.2)	0.174
Serum albumin, g/dL	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)	3.7 (0.3)	3.7 (0.4)	0.423
Serum total calcium, mg/dL	8.8 (0.8)	8.8 (0.8)	8.9 (0.8)	8.8 (0.7)	8.9 (0.7)	0.965
Serum phosphorus, mg/dL	5.3 (1.3)	5.1 (1.3)	5.3 (1.3)	5.4 (1.2)	5.7 (1.5)	0.006
Intact PTH, pg/mL	133.3 (74.1–215.0)	157.0 (99.0–227.0)	125.0 (72.0–208.0)	135.5 (74.1–216.5)	143.0 (74.6–194.0)	0.802
CRP, mg/dL	0.12 (0.05–0.41)	0.10 (0.05–0.30)	0.11 (0.05–0.32)	0.15 (0.07–0.49)	0.10 (0.05–0.42)	0.592
Pre-dialysis systolic BP, mm Hg	147.4 (23.8)	153.4 (25.6)	148.2 (23.6)	144.8 (22.1)	146.0 (26.6)	0.010
Changes in systolic BP before and after dialysis, mm Hg	7.8 (23.9)	2.1 (22.2)	5.3 (23.1)	9.5 (23.6)	19.4 (25.5)	<0.001
Post-dialysis body weight, kg	54.9 (12.0)	54.2 (11.0)	55.0 (12.4)	54.7 (11.4)	56.3 (13.6)	0.276

Values for categorical variables are given as percentages. Values for continuous variables are given as mean (SD) or median (interquartile range). Patients were divided into 4 categories (<1.0, ≥1.0 to <1.1, ≥1.1 to <1.2, and ≥1.2).

Post-Hb/pre-Hb, post-dialysis hemoglobin concentration to pre-dialysis hemoglobin concentration; ESRD, end-stage renal disease; IDWL, interdialytic weight loss; Hb, hemoglobin; PTH, parathyroid hormone; CRP, C-reactive protein; BP, blood pressure.

mortality is shown in Table 2. Similarly, compared with the reference, the unadjusted HRs for all-cause mortality were 1.76 (95% CI 1.44–2.16), 1.32 (95% CI 1.10–1.59), and 1.15 (95% CI 0.95–1.39) in patients with post-Hb/pre-Hb ratios of <1.0, ≥1.0 to <1.1, and ≥1.2, respectively, compared with the reference (≥1.1 to <1.2). Furthermore, adjusted HRs for all-cause mortality were 1.71 (95% CI 1.37–2.12), 1.29 (95% CI 1.10–1.50), and 1.28 (95% CI 1.01–1.62) in patients with post-Hb/pre-Hb ratios of <1.0, ≥1.0 to <1.1, and ≥1.2 respectively.

With regard to vascular access failure, during a median follow-up of 2.3 years, 106 (12.3%) patients developed vascular access failure. Event-free survival rates according to post-Hb/pre-Hb ratio are shown in Figure 1c. Similarly, compared with the reference, the unadjusted HRs for vascular access failure were 1.78 (95% CI 1.44–2.20), 1.32 (95% CI 1.09–1.59), and 1.11 (95% CI 0.93–1.33) in patients with post-Hb/pre-Hb ratios of <1.0, ≥1.0 to <1.1, and ≥1.2, respectively, compared with the reference (≥1.1 to <1.2). Furthermore, adjusted HRs for vascular access failure were 1.69 (95% CI 1.37–2.09), 1.27 (95% CI 1.07–1.50), and 1.20 (95% CI 0.95–1.52) in patients with post-Hb/pre-Hb ratios of <1.0, ≥1.0 to <1.1, and ≥1.2 respectively.

Continuous Variable Analysis

Multivariable-adjusted restricted cubic spline analyses revealed a U-shaped association between post-Hb/pre-Hb ratio and MACEs, all-cause mortality and vascular access failure (Fig. 2).

Sensitivity Analysis

In the dataset, imputed missing covariate data, adjusted HRs for MACEs were 1.69 (95% CI 1.41–2.02), 1.28 (95% CI 1.08–1.52), and 1.35 (95% CI 1.07–1.71) in patients with post-Hb/pre-Hb ratios of <1.0, ≥1.0 to <1.1, and ≥1.2, respectively, compared with the reference (online suppl. Table 3).

In the dataset, imputed missing covariate data, including CRP, compared with the reference, the adjusted HRs for MACEs were 1.69 (95% CI 1.40–2.03), 1.27 (95% CI 1.08–1.51), and 1.33 (95% CI 1.05–1.68) in patients with post-Hb/pre-Hb ratios of <1.0, ≥1.0 to <1.1, and ≥1.2 respectively (online suppl. Table 3).

In the dataset in which the predictor was defined as the mean baseline and data after 4 months, a total of 831 patients were enrolled. During a median follow-up of 2.6 years, 136 (16.4%) patients developed MACEs. The adjusted HRs for MACEs were 1.77 (95% CI 1.33–2.36), 1.27 (95% CI 1.11–1.46), and 1.38 (95% CI 1.11–

Fig. 1. Event-free survival rate for (a) MACEs, (b) all-cause mortality and (c) vascular access failure by post-Hb/pre-Hb categories during the follow-up period. MACEs included acute myocardial

infarction, stroke, and all-cause mortality. MACEs, major adverse cardiovascular events; post-Hb/pre-Hb, post-dialysis hemoglobin concentration to pre-dialysis hemoglobin concentration.

1.72) in patients with post-Hb/pre-Hb ratios of <1.0, ≥ 1.0 to <1.1, and ≥ 1.2 respectively (online suppl. Table 3).

Similar results were obtained for the continuous associations between post-Hb/pre-Hb ratio and MACEs in all datasets (online suppl. Fig. 2).

Discussion

In this study, we found that both high and low intra-dialytic changes in hemoglobin concentration were associated with higher risk of MACEs in patients undergoing

HD. The continuous variable analysis revealed a U-shaped association between intra-dialytic changes in hemoglobin concentration and MACEs. Consistent associations were shown in both categorical and continuous analyses. Additionally, similar results regarding this association were also obtained in the sensitivity analysis.

The association between low intra-dialytic changes in hemoglobin concentration and high mortality risk is consistent with that reported in a previous study [24]. On the other hand, the associations between high intra-dialytic change in hemoglobin concentration and high cardiovascular events and mortality risk are new findings. The mechanisms may be explained as follows. Pre-

Table 2. HRs for MACEs, all-cause mortality and vascular access failure by post-Hb/pre-Hb categories

	<1.0	≥1.0 to <1.1	≥1.1 to <1.2	≥1.2
MACEs				
Unadjusted HR	1.73 (1.40–2.14)	1.33 (1.10–1.61)	Reference	1.17 (0.95–1.43)
Adjusted HR	1.69 (1.36–2.10)	1.29 (1.10–1.51)	Reference	1.31 (1.02–1.68)
All-cause mortality				
Unadjusted HR	1.76 (1.44–2.16)	1.32 (1.10–1.59)	Reference	1.15 (0.95–1.39)
Adjusted HR	1.71 (1.37–2.12)	1.29 (1.10–1.50)	Reference	1.28 (1.01–1.62)
Vascular access failure				
Unadjusted HR	1.78 (1.44–2.20)	1.32 (1.09–1.59)	Reference	1.11 (0.93–1.33)
Adjusted HR	1.69 (1.37–2.09)	1.27 (1.07–1.50)	Reference	1.20 (0.95–1.52)

Bold values statistically significant values. The multivariable-adjusted model was adjusted for age, sex, cause of end-stage renal disease, history of heart disease, hemodialysis vintage, IDWL, treatment time, ultrafiltration rate, serum albumin, serum phosphorus, pre-Hb concentration, pre-dialysis systolic BP, changes in systolic BP before and after dialysis, and post-dialysis body weight.

MACEs included acute myocardial infarction, stroke, and all-cause mortality.

HR, hazard ratio; MACEs, major adverse cardiovascular events; post-Hb/pre-Hb, post-dialysis hemoglobin concentration to pre-dialysis hemoglobin concentration; IDWL, interdialytic weight loss; BP, blood pressure.

vious studies have suggested that the change in hemodynamics during HD caused by the effects of ultrafiltration on hemoglobin concentration is a potential cause of intra-dialytic hypotension that results in decreased perfusion of important organs, such as the heart and brain [25, 26]. Decreased perfusion of vital organs results in damage in each HD session. We presume that the ultrafiltration condition that results in high changes in hemoglobin concentrations during HD may be not appropriate.

In addition, this index may be useful as a tool to decide whether the DW is appropriate. In 1967, DW was initially defined as “the reduction of BP to hypotensive levels during ultrafiltration and unassociated with other obvious causes” by Thomson et al. [27]. Since then, the definition has changed [28]. In 2009, Sinha and Agarwal [29] proposed this definition: “DW is defined as the lowest tolerated post-dialysis weight achieved via gradual change in post-dialysis weight at which there are minimal signs or symptoms of hypovolemia or hypervolemia.” Considering the latest DW definition, in some patients with low intra-dialytic changes in hemoglobin concentration, true DW would be lower. In contrast, in some patients with high intra-dialytic changes in hemoglobin concentration, true DW would be higher.

Finally, the association between intra-dialytic changes in hemoglobin concentration and MACEs remained even with adjustments for IDWL and ultrafiltration rate. Considering the index formula described in the Methods section, the association between intra-dialytic changes in hemoglobin concentration and cardiovascular events may

indicate the association between plasma refilling and cardiovascular events. Plasma refilling cannot be measured easily in the clinical setting [30]. Of course, this study did not directly measure plasma refilling. However, we presume that there is an association between plasma refilling and cardiovascular events due to the influence of injury to the endothelial glycocalyx, which plays a central role in the fluid movement [31].

The strengths of this study are as follows. First, this research was a prospective study with a relatively large sample size. Second, the sampling approach of J-DOPPS renders it representative of most Japanese dialysis settings. Third, this index is very easy to use clinically. Through this simple method, post-dialysis intravascular fluid balance can be evaluated by calculating the ratio of post-Hb/pre-Hb concentration.

However, there were several limitations to this study. First, patients may have transferred into the different categories because baseline data were used to define exposure categories in this cohort. However, similar results were obtained when we defined the predictor as mean baseline data and data after 4 months and conducted the same analysis as for primary outcome.

Second, measurements were performed during the first dialysis session of the week when patients were at maximum volume overload and maximum hemodilution. The proportion of patients with high intra-dialytic changes in hemoglobin concentration was likely to decrease around the mid-week dialysis session, and this may have affected the results. However, in practice, when clinicians perform fluid removal, they attempt to

Fig. 2. HRs for MACEs, all-cause mortality, and vascular access failure by post-Hb/pre-Hb ratio. Multivariable-adjusted restricted cubic spline plots of the HR for (a) MACEs, (b) all-cause mortality, and (c) vascular access failure according to post-Hb/pre-Hb ratio. The solid line represents HR, and the dotted line represents 95% CI. The horizontal gray line corresponds to the normal reference HR of 1.0. Post-Hb/pre-Hb ratio = 1.1 was used as reference in this study. The multivariable-adjusted model was adjusted for

age, sex, cause of ESRD, history of heart disease, HD vintage, IDWL, treatment time, ultrafiltration rate, serum albumin, serum phosphorus, pre-Hb, pre-dialysis systolic BP, changes in systolic BP before and after dialysis, and post-dialysis body weight. MACEs included acute myocardial infarction, stroke, and all-cause mortality. MACEs, major adverse cardiovascular events; post-Hb/pre-Hb, post-dialysis hemoglobin concentration to pre-dialysis hemoglobin concentration; HR, hazard ratio.

achieve a clinical DW in all dialysis sessions. Further studies considering the timing of measurements are warranted.

Third, we lacked information on 2 major confounding factors, CRP and residual renal function (RRF), in our study. CRP, as an inflammatory factor, could not be adjusted for in our model of main analysis because about 41% of CRP data was missing from this dataset. However, similar results were obtained using imputed missing CRP data, assuming that analyzed data were missing at random (online suppl. Table 3). RRF would affect post-Hb/pre-Hb ratios through fluid removal. In practice, clinicians tend to aim for lower IDWL and lower ultrafiltration rates for patients with sufficient RRF, which might

result in low intra-dialytic changes in hemoglobin concentration. The presence of RRF is associated with a lower mortality risk [32]. Therefore, we might have underestimated the association between low intra-dialytic changes in hemoglobin concentration and higher mortality risk. Fourth, post-Hb was measured in only 20% of patients in the J-DOPPS 4–5. Therefore, there may be some characteristic differences in the analyzed patients compared with all patients in the J-DOPPS 4–5, which may have led to selection bias (online suppl. Table 1). Fifth, this study was observational, and therefore, it could not provide direct cause-and-effect associations.

In conclusion, our study revealed a U-shaped association between intra-dialytic changes in hemoglobin con-

centration and MACEs among patients undergoing maintenance HD. Our results may contribute to future recommendations regarding appropriate fluid removal conditions and appropriate DW.

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Statement of Ethics

All participants in J-DOPPS provided written informed consent prior to study enrollment. The study design was approved by the appropriate ethics review board.

Disclosure Statement

T.A. has been a scientific advisor or consultant for Astellas Pharma, JT Pharmaceuticals, Torii Pharmaceutical, Kyowa Hakko Kirin, Nipro Medical, Ono Pharmaceutical, Bayer HealthCare, Fuso Pharmaceutical, GlaxoSmithKline, and Kissei Pharmaceuti-

cal and has received lecture fees from Chugai Pharmaceutical, Kyowa Hakko Kirin, Bayer HealthCare, Torii Pharmaceutical, Kissei Pharmaceutical, and Ono Pharmaceutical. T.H., M.K., T.I., S.F., and Y.Y. have no conflicts of interest to declare.

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Author Contributions

T.H., M.K., T.I., and S.F.: research idea and study design. T.H. and M.K.: data acquisition. T.H., M.K., and Y.Y.: data analysis/interpretation. T.H., M.K., and Y.Y.: statistical analysis. T.A. and S.F.: supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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