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Interdialytic Weight Gain Effects on Hemoglobin Concentration and Cardiovascular Events

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Introduction: Although predialysis hemoglobin concentration is affected by interdialytic weight gain (IDWG), the interaction between these parameters is not well understood.

Methods: Using data from the Japanese Dialysis Outcomes and Practice Pattern Study phases 1–5, we analyzed patients who underwent maintenance hemodialysis. The exposure variable was hemoglobin concentration, and the effect modifier was IDWG at baseline. These 2 categorical variables were then combined and analyzed. The primary outcome was major adverse cardiovascular events (MACEs). Hazard ratios were estimated using a Cox model for the association between exposure and MACEs after adjusting for potential confounders. We examined additive interactions between hemoglobin concentration and IDWG by calculating the relative excess risk due to interaction, which is defined as a departure from the additivity of effects.

Results: A total of 8234 patients were enrolled. During a median follow-up of 2.1 years, 1062 (12.9%) patients developed MACEs. In IDWG categories of $<$6%, adjusted hazard ratios for MACEs tended to be lower as hemoglobin concentration increased. In IDWG categories of $\geq$6%, point estimation of MACEs with hemoglobin concentration of $\geq$11.0 g/dl–$<$12.0 g/dl was higher than that with hemoglobin concentration of $\geq$10.0 g/dl–$<$11.0 g/dl. The relative excess risk due to interaction was 0.22 (95% confidence interval 0.02–0.42) between IDWG category of $\geq$6% and hemoglobin categories of $\geq$11.0 g/dl–$<$12.0 g/dl, indicating a synergistic interaction.

Conclusions: The association between hemoglobin concentration and MACEs differed across IDWG. Consideration should be given to the upper limit of hemoglobin concentration in patients with high IDWG.

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Anemia is a common complication in patients undergoing hemodialysis (HD). A low hemoglobin concentration is associated with a high mortality rate, cardiovascular events, fatigue, and negative health-related quality of life.[1–13] The introduction of erythropoiesis-stimulating agent has facilitated anemia management.

Nevertheless, studies have consistently reported more harms than benefits associated with higher hemoglobin targets in erythropoiesis-stimulating agent treatment.[14–19] Based on randomized controlled trial results, clinical guidelines in Europe and the United States have recommended avoiding intentional increases in hemoglobin concentrations to $\geq$13 g/dl.[20,21] In Japan, clinical practice guidelines also suggest a target hemoglobin concentration range of 10 g/dl–12 g/dl in the first session of the week based on study results in Japan and differences in sampling timing from that in other countries.[12,22]

Hemoglobin concentration varies dynamically depending on measurement timing because of body

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fluid volume changes.[23,24] Although predialysis hemoglobin concentration is mainly affected by IDWG,[25] the interaction between these parameters is not well understood.

A previous study reported a relationship between IDWG and hemoglobin concentrations and mortality.[26] However, the interaction of IDWG and hemoglobin concentrations could not be evaluated because the IDWG was divided into 2 groups, and each group was analyzed as a different group.

Therefore, to clarify the impact of IDWG on hemoglobin concentration and cardiovascular events, we conducted a longitudinal study using data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) in Japan. On the assumption that the measured predialysis hemoglobin concentration reflects the true hemoglobin concentration diluted with IDWG, we hypothesized that high IDWG as extracellular fluid and high levels of hemoglobin in blood vessels in the closed system of dialysis patients would synergistically promote a volume load, and as a consequence, have a synergistic interaction with the risk of cardiovascular events.

METHODS

Study Design and Population

The DOPPS was a prospective cohort study of patients enrolled randomly from a representative sample of dialysis facilities within each participating country. All participants in the DOPPS provided written informed consent before study enrollment. Detailed information on the design of DOPPS has been provided elsewhere.[27,28] 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 the Faculty of Medicine Kyoto University Hospital Ethics Committee (approval number R1301). Data for the current analysis were obtained from J-DOPPS 1 (1999–2001), J-DOPPS 2 (2002–2004), J-DOPPS 3 (2005–2008), J-DOPPS 4 (2009–2011), and J-DOPPS 5 (2012–2014). The study included patients undergoing maintenance HD for ≥6 months who were ≥18 years of age and had available data on hemoglobin concentration and predialysis and postdialysis body weights. We excluded patients with hemoglobin concentration ≥12.0 g/dl because we considered this group clinically heterogeneous, with a sample size that was too small to accurately estimate the association.[22]

Exposure and Effect Modifier

The exposure of interest was the hemoglobin concentration, and the effect modifier was IDWG. Hemoglobin concentration and IDWG were assessed in the first session of the week at enrollment into J-DOPPS. Interdialytic weight loss (IDWL) was used as an IDWG substitute, with the assumption that all the weight gained in the interdialytic interval was lost during the dialysis session, as defined in a previous study.[29]

We classified hemoglobin concentration into 4 categories by 1.0-g/dl increments (<9.0 g/dl, ≥9.0 g/dl–<10.0 g/dl, ≥10.0 g/dl–<11.0 g/dl, and ≥11.0 g/dl–<12.0 g/dl) and IDWG into 6 categories by 1% increments (<2%, ≥2%–<3%, ≥3%–<4%, ≥4%–<5%, ≥5%–<6%, and ≥6%). The 2 categorical variables were combined and used as exposure categories to evaluate the mechanistic interaction between hemoglobin concentration and IDWG.

Outcomes

The primary outcome was MACEs, including acute myocardial infarction, stroke, and all-cause mortality.[30] We included all-cause mortality as a composite outcome because substantial causes of death among patients undergoing HD were related to cardiovascular events.[31] The secondary outcome was all-cause mortality.

Statistical Analysis

With regard to the baseline characteristics of patients categorized by hemoglobin concentration, continuous data with a normal distribution were summarized as means (SD), continuous variables with skewed data were presented as medians (interquartile range), and dichotomous data were presented as proportions. Unadjusted and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for MACEs according to the categories of exposure were calculated using a Cox proportional hazards model. The assumption of the proportional hazards was checked graphically using a log cumulative hazard plots for each outcome according to the categories. The reference category was hemoglobin concentration of ≥10.0 g/dl–<11.0 g/dl and IDWG of ≥3%–<4%, as reported in previous studies.[12,32] The multivariable model was adjusted for age, sex, physical function, body mass index, dialysis vintage, cause of end-stage renal disease, vascular access, smoking, systolic blood pressure, single pool Kt/V, normalized protein catabolism rate, serum albumin, calcium, phosphorus, intact parathyroid hormone, Fe, total iron binding capacity, ferritin, hypertension, coronary heart disease, congestive heart failure, dysrhythmia, other cardiovascular diseases, stroke/transient ischemic attack, peripheral vascular disease, lung disease, liver disease, cancer, gastrointestinal bleeding, neurologic disorder, psychiatric disorder, anticoagulant drug, antiplatelet drug, renin-angiotensin system inhibitor, iron use, and

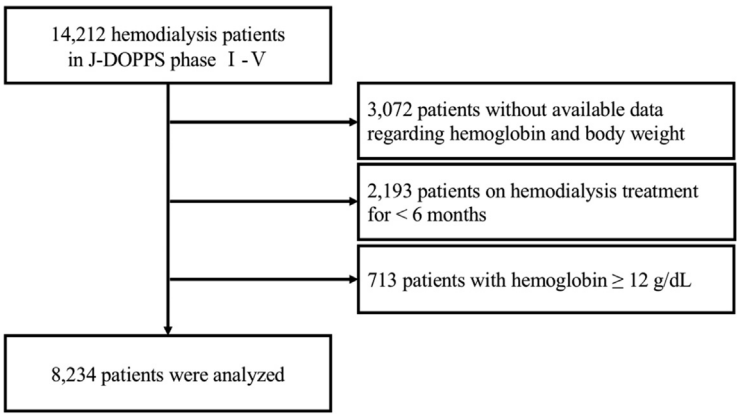

Figure 1. Selection process for study population. J-DOPPS, Japanese Dialysis Outcomes and Practice Pattern Study.

erythropoietin-stimulating agent resistance index (ERI). Physical function was assessed using the physical function subscale of the Medical Outcome Study 12-Item Short-Form with norm-based scoring. ERI was derived by dividing weekly erythropoiesis-stimulating agent dose by postdialysis body weight (in kg) and hemoglobin concentration (in g/dl).[33] Darbepoetin alfa and epoetin beta pegol doses were converted to erythropoiesis-stimulating agent dose (IU/week) using a dose conversion ratio (epoetin:darbepoetin alfa:epoetin beta pegol = 200:1:1). These variables were based on an *a priori* clinical judgment and existing studies.[2–4,34] We used robust variance estimates to consider cluster effects at the facility level.

We examined additive interactions between hemoglobin concentration and IDWG, as additive interactions more closely correspond to tests for mechanistic interaction rather than multiplicative interaction.[35] We estimated the relative excess risk due to interaction (RERI).[36] RERI between 2 factors (X and Z) is defined as departure from additivity of effects and is calculated as follows using adjusted HRs: RERI = ($HR_{X\&Z} - HR_X - HR_Z + 1$). RERI < 0, RERI $= 0$, and RERI > 0 indicates an antagonistic interaction, absence of interaction, and synergistic interaction, respectively.

In previous studies, mortality and cardiovascular events tended to be lower as hemoglobin concentration increased between the range of 9 g/dl–12 g/dl.[11,12] Our hypothesis conjectured that hemoglobin concentration increments would promote a volume load for higher IDWG, and we expected HR of MACEs to start increasing at a certain hemoglobin concentration in the high IDWG category. Therefore, we evaluated RERI in the IDWG category when HR of MACEs increased along with hemoglobin concentration increments.

Missing covariates were replaced using the multiple imputations with chained equations method, assuming that analyzed data were missing at random.[37] These estimates from 20 imputation datasets were combined using Rubin rules.

All analyses were performed using Stata software (version 15.0; Stata Corp, College Station, Texas). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 8234 patients were enrolled in the study (Figure 1). The mean age was 62.5 years, 60.7% were male, 29.0% had end-stage renal disease caused by diabetes, and the median duration of dialysis therapy was 5.7 years (Table 1). Patients with lower hemoglobin concentrations were older and included a higher proportion of females, nonsmokers, those with IDWG ≥6%, dysrhythmia, stroke/transient ischemic attack, gastrointestinal bleeding, serum total calcium <8.4 mg/dl, and serum phosphorus <3.5 mg/dl. In contrast, patients with higher hemoglobin concentrations exhibited longer dialysis vintage, higher proportion of serum phosphorus ≥6.0 mg/dl and iron use, and lower ERI.

Association of Hemoglobin Concentration with MACEs and Mortality by IDWG Categories

During a median follow-up of 2.1 years, 1062 (12.9%) patients developed MACEs. The incidence rate of MACEs was 6.3 per 100 person-years. Incidence of MACEs by each category of IDWG and hemoglobin concentration are shown in Table 2. The details of MACEs are shown in Table 3. The associations between the 24 categories of IDWG, hemoglobin concentration, and MACEs are shown in Tables 4 and 5. Between IDWG categories of <2% and ≥5%–<6%, the adjusted HRs for MACEs tended to be lower as the hemoglobin concentration increased (Table 5). However, this tendency was not evident in the IDWG category of ≥6%. The point estimation with a hemoglobin concentration of ≥11.0 g/dl–<12.0 g/dl and IDWG of ≥6% was higher than that with a hemoglobin concentration of ≥10.0 g/dl–<11.0 g/dl and IDWG of ≥6%.

Table 1. Baseline characteristics by hemoglobin concentration categories

		Hemoglobin concentration, g/dl			
	Total, $N = 8234$	<9.0, $n = 1384$	≥9.0-<10.0, $n = 2300$	≥10.0-<11.0, $n = 2822$	≥11.0-<12.0, $n = 1728$
Age, yr	62.5 (12.6)	63.2 (12.5)	63.0 (12.2)	62.2 (12.7)	61.7 (12.7)
Male	60.7	54.2	59.1	62.3	65.4
Physical function	29.2 (16.0–55.7)	29.2 (16.0–42.5)	29.2 (16.0–55.7)	42.5 (29.2–55.7)	42.5 (29.2–55.7)
BMI	20.5 (18.6–22.6)	20.0 (18.0–22.0)	20.4 (18.5–22.6)	20.7 (18.8–22.7)	20.7 (18.9–22.9)
Smoking					
Current smoker	21.6	20.3	21.2	21.9	22.8
Past smoker	17.9	15.7	16.4	19.1	20.1
Nonsmoker	60.5	64.0	62.4	59.0	57.1
Diabetes as primary cause of ESRD	29.0	29.2	28.5	28.7	30.0
Hemodialysis vintage, yr	5.7 (2.5–11.3)	5.4 (2.4–11.0)	5.5 (2.5–10.7)	5.9 (2.6–11.3)	5.9 (2.7–12.4)
Vascular access, AVF	91.2	88.2	91.8	91.8	92.2
IDWG, %					
<2	9.1	9.3	9.7	8.8	8.6
≥2–<3	13.9	12.6	13.7	14.7	13.7
≥3–<4	21.9	20.0	22.0	22.3	22.8
≥4–<5	23.4	22.5	22.7	23.2	25.2
≥5–<6	16.7	15.5	17.0	17.3	16.4
≥6	15.0	19.9	14.7	13.9	13.3
Coronary arterial disease	25.6	25.3	26.1	25.3	25.9
Congestive heart failure	15.0	16.9	14.8	14.1	14.9
Dysrhythmia	21.6	22.8	22.3	21.3	20.4
Other cardiovascular disease	11.5	11.6	10.7	11.2	13.0
Peripheral artery disease	15.2	16.2	14.8	14.8	15.6
Stroke/TIA	13.7	16.3	13.2	13.6	12.3
Gastrointestinal bleeding	4.5	7.4	4.3	4.0	3.2
Hypertension	70.2	67.6	70.3	71.9	69.3
Liver disease	12.5	14.9	12.4	11.8	11.9
Lung disease	2.6	2.8	2.7	2.3	2.6
Cancer	8.8	9.0	8.8	8.7	8.9
Psychiatric disorder	3.0	3.3	3.1	2.7	3.4
Neurologic disease	6.5	8.9	5.7	6.5	5.7
nPCR, g/kg/d	1.01 (0.21)	1.00 (0.23)	1.01 (0.22)	1.01 (0.20)	1.01 (0.20)
Single pool Kt/V	1.38 (0.27)	1.37 (0.29)	1.38 (0.27)	1.39 (0.27)	1.39 (0.27)
Serum albumin, g/dl	3.8 (0.4)	3.6 (0.5)	3.7 (0.4)	3.8 (0.4)	3.8 (0.4)
Serum total calcium, mg/dl					
<8.4	23.0	27.7	23.4	21.5	21.0
≥8.4–≤10.0	63.6	58.9	63.6	64.6	65.9
>10.0	13.4	13.4	13.0	13.9	13.1
Serum phosphorus, mg/dl					
<3.5	5.8	9.9	6.2	4.5	4.2
≥3.5–<6.0	59.1	58.0	60.3	59.6	57.6
≥6.0	35.1	32.2	33.6	35.9	38.2
Intact PTH, pg/ml					
<60	26.5	29.5	28.2	25.1	24.5
≥60–≤ 240	51.0	46.4	49.4	53.9	51.5
>240	22.5	24.1	22.3	21.1	24.0
Fe, μg/dl	58 (43–77)	52 (37–71)	56 (41–75)	60 (46–79)	61 (46–80)
Ferritin, ng/ml	120 (47–281)	138 (50–366)	120 (48–288)	117 (46–275)	108 (44–245)
TIBC, μg/dl	241 (207–280)	236 (195–282)	237 (204–282)	242 (209–278)	246 (214–282)
Predialysis systolic BP, mm Hg	150.9 (23.4)	151.3 (24.2)	151.5 (22.8)	150.9 (23.4)	149.8 (23.5)
Antiplatelet drug	44.3	43.0	42.6	45.9	45.0
Anticoagulant drug	6.0	5.4	5.0	6.3	7.4
RASI	51.4	47.2	51.6	52.7	52.3
Iron use	31.9	26.1	30.3	33.3	36.6
ERI, IU/week/kg/g/dl	5.7 (3.0–10.1)	8.3 (4.9–13.0)	5.8 (3.5–10.2)	5.3 (2.8–9.5)	4.3 (1.9–8.0)

AVF, arteriovenous fistula; BMI, body mass index; BP, blood pressure; ERI, erythropoietin-stimulating agents resistance index; ESRD, end-stage renal disease; IDWG, interdialytic weight gain; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; RASI, renin-angiotensin system inhibitor; TIA, transient ischemic attack; TIBC, total iron binding capacity. Values for categorical variables are given as percentages. Values for continuous variables are given as mean (SD) or median (IQR).

Table 2. Number of patients and incidence rate of MACEs and mortality by hemoglobin concentration and IDWG categories

		Interdialytic weight gain (%)					
	Hemoglobin concentration, g/dl	<2	≥2–<3	≥3–<4	≥4–<5	≥5–<6	≥6
No. of patients (incidence rate of MACEs/mortality per 100 person-years)	<9.0	129 (16.7/16.6)	175 (10.0/9.0)	277 (8.3/7.1)	312 (8.6/7.8)	215 (10.0/8.4)	276 (6.9/6.3)
	≥9.0–<10.0	224 (7.9/7.7)	316 (7.5/6.7)	507 (6.3/5.1)	523 (5.2/4.4)	391 (5.1/4.6)	339 (6.3/5.6)
	≥10.0–<11.0	247 (5.5/4.9)	415 (5.7/5.0)	628 (4.2/3.3)	654 (5.4/4.1)	487 (5.1/4.0)	391 (7.9/6.7)
	≥11.0–<12.0	149 (9.4/7.7)	237 (4.8/4.2)	394 (6.0/4.6)	435 (6.0/3.9)	283 (6.0/4.9)	230 (5.3/4.7)

MACE, major adverse cardiovascular event; IDWG, interdialytic weight gain.
MACEs included acute myocardial infarction, stroke, and all-cause mortality.

Regarding mortality, during a median follow-up of 2.1 years, 894 (10.9%) patients died, and the mortality rate was 5.3 per 100 person-years. The incidence rates of mortality by each category of IDWG and hemoglobin concentration are shown in Table 2. The associations between the 24 categories of IDWG, hemoglobin concentration, and mortality are shown in Tables 4 and 5. Similarly, between IDWG categories of <2% and ≥5%–<6%, the adjusted HRs for mortality tended to be lower as hemoglobin concentration increased (Table 5). This tendency was not observed in the IDWG category of ≥6%. Point estimation with hemoglobin concentration of ≥11.0 g/dl–<12.0 g/dl and IDWG of ≥6% was higher than that with hemoglobin concentration of ≥10.0 g/dl–<11.0 g/dl and IDWG of ≥6%.

Interaction Between Hemoglobin Concentration and IDWG on MACEs and Mortality

Figure 2a shows adjusted HRs for MACEs by hemoglobin categories of ≥10.0 g/dl–<11.0 g/dl and ≥11.0 g/dl–<12.0 g/dl and IDWG. The RERI was 0.22 (95% CI, 0.02–0.42) between IDWG category of ≥6% and hemoglobin categories of ≥11.0 g/dl–<12.0 g/dl with respect to MACEs, indicating a synergistic interaction.

Similarly, the RERI was 0.19 (95% CI, −0.004 to 0.39) between the IDWG category of ≥6% and hemoglobin category of ≥11.0 g/dl–<12.0 g/dl with respect to mortality, indicating a synergistic interaction (Figure 2b). However, we did not find this to be statistically significant.

DISCUSSION

In this study, we observed that the adjusted HRs for MACEs tended to be lower as hemoglobin concentration increased in IDWG categories of <6%. However, this tendency was not observed in IDWG categories of ≥6%. The point estimation of MACEs with a hemoglobin concentration of ≥11.0 g/dl–<12.0 g/dl and IDWG of ≥6% was higher than that with a hemoglobin concentration of ≥10.0 g/dl–<11.0 g/dl and IDWG of ≥6%. The RERI was 0.22 (95% CI, 0.02–0.42) between IDWG categories of ≥6% and hemoglobin categories of ≥11.0 g/dl–<12.0 g/dl with respect to MACEs, indicating a synergistic interaction. With respect to mortality, similar results were obtained.

As with previous studies, the present study also shown cardiovascular events risk decreased in IDWG categories of <6% as hemoglobin concentration increased between 9 g/dl–12 g/dl.[11,12] However, it was noteworthy that the association between hemoglobin concentration and MACEs differed across IDWG by stratification, especially in IDWG categories of ≥6%.

Table 3. Number of MACEs by hemoglobin concentration categories

		Hemoglobin concentration, g/dl			
	Total, $N = 8234$	<9.0, $n = 1384$	≥9.0–<10.0, $n = 2300$	≥10.0–<11.0, $n = 2822$	≥11.0–<12.0, $n = 1728$
AMI, *n*	71	9	16	23	23
Stroke, *n*	151	20	37	53	41
Death, *n*	840	200	228	253	159
AMI	48	8	13	17	10
Stroke	79	17	27	27	8
Other cardiac events	228	51	59	73	45
Other vascular events	26	6	8	7	5
Infections	152	49	43	35	25
Gastrointestinal diseases	4	1	0	2	1
Liver disease	8	2	1	2	3
Cancer	86	22	19	30	15
Others	89	23	29	19	18
Unknown	120	21	29	41	29

AMI, acute myocardial infarction; MACE, major adverse cardiovascular event.
MACEs included AMI, stroke, and all-cause mortality.

Table 4. Unadjusted HRs for MACEs and mortality by hemoglobin concentration and IDWG categories

		Interdialytic weight gain (%)					
	Hemoglobin concentration (g/dl)	<2	≥2–<3	≥3–<4	≥4–<5	≥5–<6	≥ 6
MACEs	<9.0	1.97 (1.56–2.48)[a]	1.58 (1.20–2.08)[a]	1.54 (1.27–1.86)[a]	1.78 (1.52–2.08)[a]	1.93 (1.54–2.43)[a]	1.94 (1.63–2.32)[a]
	≥9.0–<10.0	1.55 (1.30–1.85)[a]	1.22 (1.06–1.39)[a]	1.33 (1.18–1.49)[a]	1.41 (1.27–1.58)[a]	1.47 (1.30–1.67)[a]	1.48 (1.25–1.74)[a]
	≥10.0–<11.0	1.11 (0.98–1.25)	0.97 (0.86–1.09)	Reference	1.07 (0.97–1.18)	1.16 (1.01–1.32)[a]	1.29 (1.11–1.49)[a]
	≥11.0–<12.0	1.00 (0.80–1.26)	0.94 (0.84–1.07)	0.93 (0.82–1.06)	0.95 (0.85–1.07)	1.12 (0.94–1.34)	1.50 (1.29–1.75)[a]
Mortality	<9.0	1.93 (1.53–2.44)[a]	1.58 (1.20–2.08)[a]	1.55 (1.28–1.87)[a]	1.78 (1.53–2.07)[a]	1.97 (1.57–2.46)[a]	1.94 (1.62–2.32)[a]
	≥9.0–<10.0	1.53 (1.29–1.82)[a]	1.21 (1.06–1.38)[a]	1.34 (1.19–1.51)[a]	1.41 (1.26–1.57)[a]	1.46 (1.29–1.65)[a]	1.47 (1.26–1.72)[a]
	≥10.0–<11.0	1.10 (0.97–1.25)	0.97 (0.86–1.09)	Reference	1.08 (0.99–1.19)	1.16 (1.02–1.33)[a]	1.29 (1.11–1.49)[a]
	≥11.0–<12.0	1.02 (0.81–1.28)	0.94 (0.83–1.05)	0.94 (0.83–1.07)	0.98 (0.87–1.10)	1.13 (0.95–1.35)	1.50 (1.28–1.74)[a]

MACEs included acute myocardial infarction, stroke, and all-cause mortality.
[a]Statistically significant. The reference was hemoglobin concentration of ≥10.0–<11.0 g/dl and IDWG of ≥3%–<4%.
HR, hazard ratio; IDWG, interdialytic weight gain; MACE, major adverse cardiovascular event.

Potential mechanisms of increased cardiovascular event risk with higher hemoglobin concentration are as follows: (i) effects of hemoglobin itself, (ii) effects of erythropoiesis-stimulating agent treatment, (iii) erythropoiesis-stimulating agent hyporesponsiveness, (iv) effects of iron treatment, (v) increased blood volume and pressure, and (iv) others.[34] This study may support the fifth mechanism listed above. In the present study, we presumed that predialysis hemoglobin concentration was in a state where unmeasured true hemoglobin concentration was diluted by IDWG, and it was possible that true hemoglobin concentration was higher than measured hemoglobin concentration for high IDWG. Therefore, in categories of hemoglobin concentration ranging from ≥11.0 g/dl–<12.0 g/dl and IDWG of ≥6%, true hemoglobin concentration may have been higher than the optimal hemoglobin concentration, promoting volume overload and increasing the risk of cardiovascular events.

True hemoglobin concentration cannot be measured in patients undergoing HD. Predialysis hemoglobin concentration is affected by IDWG, and postdialysis hemoglobin concentration is affected by the balance between ultrafiltration volume and refill volume.[23–25] In current predialysis measurement practices, consideration of IDWG in the interpretation of predialysis hemoglobin concentration may contribute to reduction of cardiovascular event risk even if true hemoglobin concentration in patients receiving HD is unknown. Considering the mechanism of volume load, a previous study reported that the risk of cardiovascular events increased as IDWG increased.[38] However, in our study, the risk of cardiovascular events was higher in the low IDWG and low hemoglobin concentration group. Previous studies have shown that inflammatory factors are associated with anemia, cardiovascular events, and prognosis.[39,40] In addition, it is well known that both inflammatory factors and IDWG are nutritional indicators that affect cardiovascular events and prognosis.[32,40] Therefore, we might have overestimated the synergistic association between both low hemoglobin concentration and low IDWG and higher cardiovascular risk because we could not adjust for the inflammatory factors. Although there were effects of residual confounders, in the stable population of hemoglobin concentration from 10 g/dl–12 g/dL, there was a trend toward increased cardiovascular event risk as IDWG increased. Therefore, we considered that the effects of

Table 5. Adjusted HRs for MACEs and mortality by hemoglobin concentration and IDWG categories

		Interdialytic weight gain (%)					
	Hemoglobin concentration (g/dl)	<2	≥2–<3	≥3–<4	≥4–<5	≥5–<6	≥ 6
MACEs	<9.0	1.79 (1.45–2.21)[a]	1.46 (1.13–1.90)[a]	1.41 (1.18–1.69)[a]	1.67 (1.44–1.94)[a]	1.71 (1.42–2.08)[a]	1.68 (1.42–1.99)[a]
	≥9.0–<10.0	1.38 (1.16–1.65)[a]	1.25 (1.09–1.44)[a]	1.23 (1.08–1.39)[a]	1.33 (1.19–1.50)[a]	1.37 (1.20–1.56)[a]	1.29 (1.08–1.55)[a]
	≥10.0–<11.0	1.03 (0.90–1.19)	0.93 (0.82–1.04)	Reference	1.01 (0.92–1.12)	1.07 (0.94–1.21)	1.15 (0.98–1.34)
	≥11.0–<12.0	0.89 (0.69–1.13)	0.98 (0.86–1.13)	0.96 (0.84–1.08)	0.93 (0.83–1.05)	1.04 (0.87–1.25)	1.32 (1.13–1.55)[a]
Mortality	<9.0	1.75 (1.41–2.16)[a]	1.45 (1.11–1.90)[a]	1.42 (1.18–1.70)[a]	1.67 (1.45–1.93)[a]	1.74 (1.44–2.10)[a]	1.67 (1.41–1.99)[a]
	≥9.0–<10.0	1.36 (1.14–1.63)[a]	1.25 (1.09–1.43)[a]	1.24 (1.10–1.40)[a]	1.33 (1.19–1.50)[a]	1.35 (1.19–1.54)[a]	1.29 (1.08–1.53)[a]
	≥10.0–<11.0	1.03 (0.89–1.18)	0.92 (0.82–1.04)	Reference	1.02 (0.93–1.13)	1.08 (0.95–1.23)	1.16 (0.99–1.34)
	≥11.0–<12.0	0.91 (0.71–1.16)	0.98 (0.86–1.13)	0.97 (0.86–1.10)	0.95 (0.84–1.07)	1.06 (0.88–1.26)	1.32 (1.13–1.55)[a]

HR, hazard ratio; IDWG, interdialytic weight gain; MACE, major adverse cardiovascular event.
[a]Statistically significant. The reference was hemoglobin concentration of ≥10.0–<11.0 g/dl and IDWG of ≥3%–<4%.
The multivariable-adjusted model was adjusted for age, gender, physical function, body mass index, vintage, cause of end-stage renal disease, vascular access, smoking, systolic blood pressure, single pool Kt/V, normalized protein catabolic rate, serum albumin, calcium, phosphorus, intact parathyroid hormone, Fe, total iron binding capacity, ferritin, hypertension, coronary heart disease, congestive heart failure, dysrhythmia, other cardiovascular disease, stroke/transient ischemic attack, peripheral vascular disease, lung disease, liver disease, cancer, gastrointestinal bleeding, neurologic disorder, psychiatric disorder, anticoagulant drug, antiplatelet drug, renin-angiotensin system inhibitor, iron use, and erythropoietin-stimulating agent resistance index. MACEs included acute myocardial infarction, stroke, and all-cause mortality.

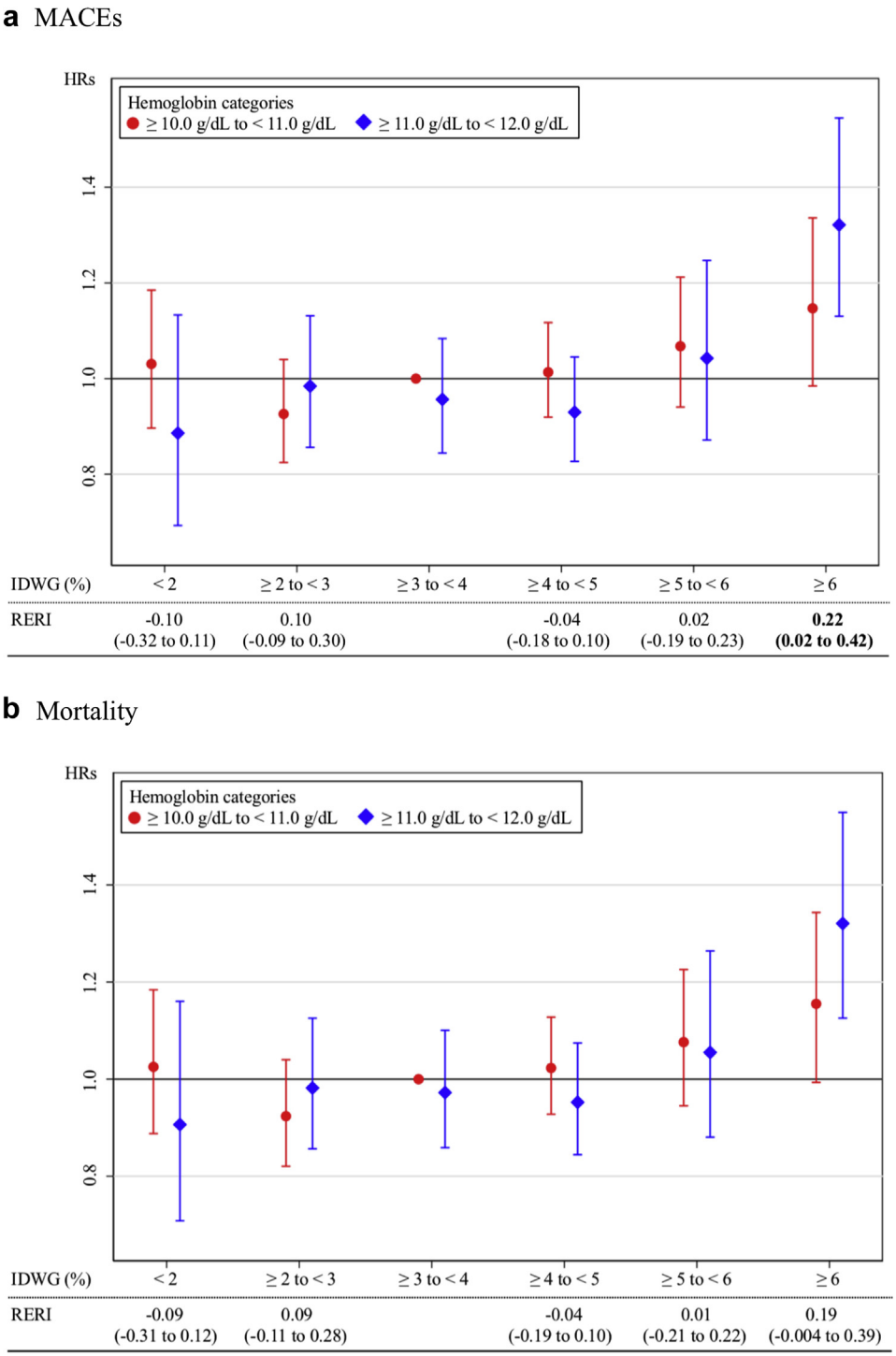

Figure 2. Effect of interdialytic weight gain (IDWG) on hazard ratios (HRs) for the association between hemoglobin concentration and (a) major adverse cardiovascular events (MACEs) and (b) mortality. HRs of hemoglobin concentration of ≥10.0 g/dl–<11.0 g/dl and of ≥11.0 g/dl–<12.0 g/dl on (a) MACEs and (b) mortality by IDWG. The reference was hemoglobin concentration of ≥10.0 g/dl–<11.0 g/dl and IDWG of ≥3%–<4%. Bold values are statistically significant. MACEs included acute myocardial infarction, stroke, and all-cause mortality. RERI, relative excess risk due to interaction.

residual confounders were likely to be small in the groups.

Furthermore, these results support the concept of "volume first," whereby volume control is considered the primary goal of dialysis care.[41] This study did not directly establish this priority between hemoglobin concentration and IDWG, but interpretation of hemoglobin concentration is facilitated under good fluid management. Hemoglobin concentration management is mainly performed by dialysis physicians, whereas IDWG management predominantly depends on patients. Although the RERI estimate was not large, it

would be undesirable for hemoglobin treatment by dialysis physicians' practices to lead to patient harm. Attention should be paid to IDWG before attempting to control hemoglobin concentration within guideline target ranges.

The major strengths of this study are as follows. This is the first study to evaluate the interaction between hemoglobin concentration and IDWG. Second, we defined exposure categories based on 2 categorical factors, which enabled us to examine the separate and combined effects of these components and their additive interaction by calculating the RERI. Third, this research was a prospective study with a large sample size, representative of most Japanese dialysis settings.

There were also several limitations to this study. First, patients may have transferred into different categories given that baseline data were used to define exposure categories in this cohort. Second, caution should be exercised when extrapolating our results because of the differences in sampling timing from that of other countries. Hemoglobin concentration is assessed in the midweek dialysis session in almost all countries. Weight gain in the midweek dialysis session is generally less than that in the first dialysis session. Therefore, the influence of weight gain on the interpretation of predialysis hemoglobin concentration may be attenuated. However, our results may be extrapolated to populations with high weight gain in the midweek dialysis session. Further studies considering the timing of measurements are warranted. Third, there were unmeasured confounding factors. In this study, we lacked information on residual renal function and inflammatory factors throughout all phases. However, we minimized the effects by excluding patients undergoing maintenance HD for <6 months and adjusting for related factors, such as dialysis vintage, ferritin, and albumin.

In conclusion, our study is the first to reveal that the association between hemoglobin concentration and MACEs differs across IDWG. Attention should be paid to hemoglobin concentration in patients with high IDWG even if it falls within the target ranges of the guidelines.

DISCLOSURE

TA has been a scientific advisor or consultant for Astellas, JT Pharmaceuticals, Torii Pharmaceutical, Kyowa Kirin, Nipro Medical, Ono Pharmaceutical, Bayer HealthCare, Fuso Pharmaceutical, GlaxoSmithKline, and Kissei Pharmaceutical and has received lecture fees from Chugai Pharmaceutical, Kyowa Kirin, Bayer HealthCare, Torii Pharmaceutical, Kissei Pharmaceutical, and Ono Pharmaceutical. All the other authors declared no competing interests.

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