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Haemoglobin concentration and survival of haemodialysis patients before and after experiencing cardiovascular disease: a cohort study from Japanese dialysis outcomes and practice pattern study (J-DOPPS)

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ABSTRACT

Objectives Differences in the association of haemoglobin concentration with mortality or adverse cardiovascular events in haemodialysis patients before and after experiencing cardiovascular disease are unclear. We aimed to assess the influence of cardiovascular-comorbid condition on the association between haemoglobin concentration and mortality.

Design A prospective cohort study.

Setting The Dialysis Outcomes and Practice Patterns Study Dialysis in phases 2 to 4 (2002 to 2011), including 80 randomly selected dialysis facilities in Japan (J-DOPPS).

Participants 5515 adult haemodialysis patients.

Primary and secondary outcome measures Primary outcome was all-cause mortality. Cardiovascular mortality and adverse cardiovascular events were also evaluated. The association of these outcomes with haemoglobin concentration, categorised into six classes by 1.0 g/dL units, and cardiovascular-comorbid condition, treated as a time-dependent variable updated every 4 months, was evaluated. Adjusted hazard ratios (aHRs) were computed using a time-dependent Cox model with interaction test for cardiovascular comorbidity.

Results Over a median 2.0 years, 847 all-cause and 326 cardiovascular deaths, and 1000 adverse cardiovascular events occurred. Compared with haemoglobin 11.0 to 11.9 g/dL, the aHRs of mortality at the lowest range (<9.0 g/dL) were 1.29 (95% CI 0.95 to 1.76) and 2.11 (95% CI 1.47 to 3.06) in cardiovascular-comorbid and non-cardiovascular-comorbid patients, respectively (p=0.04 for cardiovascular-comorbid interaction), with increased cardiovascular mortality in both groups. At the second-lowest range (9.0 to 9.9 g/dL), mortality was increased only in non-cardiovascular-comorbid patients. Respective risks for mortality and adverse cardiovascular events at the second-highest range (12.0 to 12.9 g/dL) were non-significant but increased in both groups, while adverse cardiovascular events were increased at the highest range (≥13.0 g/dL) in non-cardiovascular-comorbid patients.

Conclusions The association of low haemoglobin concentration with all-cause mortality differed between haemodialysis patients with and without cardiovascular comorbidity. Cardiovascular-comorbid condition should be considered when the association of haemoglobin concentration with mortality is addressed.

Strengths and limitations of this study

- ► While previous studies evaluated the association of haemoglobin level with mortality in haemodialysis patients with and without cardiovascular disease in combination, we evaluated them separately and tested interaction for cardiovascular comorbidity.
- ► We included a large number (>5000) of representative dialysis patients in Japan.
- ► We treated haemoglobin concentration and cardiovascular comorbidity as time-dependent variables, which might have helped reduce bias from misclassification associated with changes in haemoglobin concentration and the high incidence rate of cardiovascular disease.
- ► A limitation of this study is potential residual confounding due to unmeasured variables, which might have influenced the estimated values of the association.

INTRODUCTION

Because haemodialysis patients have higher mortality than the general population,[1] it is important to identify modifiable patient or dialysis factors or interventions that improve prognosis in these patients. Haemoglobin concentration is associated with mortality,[2–14] cardiovascular events,[15] health-related quality of life[16 17] and physical activity.[18 19] Appropriate target ranges for haemoglobin concentration should therefore be determined and suitable pharmacological management strategies identified to minimise the risk of adverse outcomes.

Previous observational studies indicate that promising outcomes can be expected with haemoglobin concentrations of 11.0 to 13.0 g/dL. Lower concentrations tend to increase the risk of death,[4–14] while the effects of concentrations above this range have been controversial, with conflicting findings reported from randomised trials.[2 20] The ideal target range of haemoglobin concentration is therefore still being explored.

Cardiovascular disease (CVD) is a frequent comorbidity in haemodialysis patients and the leading cause of death in this population.[21] Although cardiovascular comorbidity associated with increased mortality risk is a major prognostic factor in these patients,[22] few studies have addressed the differences in the association between haemoglobin concentration and mortality according to cardiovascular-comorbid condition.[2 4 5] A randomised trial in haemodialysis patients with CVD suggested that a haematocrit level approaching the normal range conferred no significant clinical benefit compared with moderate anaemia. This finding supports the clinical guideline recommendation to maintain haemoglobin concentrations at <12.0 g/dL.[2] However, the generalisability of these findings is limited by the fact that no study has yet confirmed details of the association of haemoglobin concentration with mortality or the incidence of adverse cardiovascular events in a real-world setting. Further, no study has addressed such associations in haemodialysis patients without CVD, who account for the majority of haemodialysis patients.[22]

Here, we explored the association between the haemoglobin concentration and all-cause mortality with an interaction test for cardiovascular comorbidity, and subsequent comparison by cardiovascular-comorbid condition. We also evaluated cardiovascular mortality and the incidence of adverse cardiovascular events.

MATERIALS AND METHODS

Data source and study design

This study included participants from the Japanese Dialysis Outcomes and Practice Patterns Study (J-DOPPS) phase 2 (2002 to 2004; n=2 792), phase 3 (2005 to 2008; n=2 556) and phase 4 (2009 to 2011; n=2 742). The DOPPS is an international prospective cohort study of randomly-selected haemodialysis patients from a representative sample of dialysis facilities. Details of the study design, such as the sampling and data collection methods have been described previously.[23 24] Clinical outcomes, such as all-cause and cardiovascular mortality or hospitalisation, were recorded through each study phase. Participant demographics, causes of end-stage kidney disease and comorbid conditions were collected at study entry as baseline data. Dialysis-related or laboratory data and prescriptions were updated every 4 months, excluding prescriptions in DOPPS 2, which were updated every 12 months. These analysis data were obtained from patient records.

Study population

The target population of this study was maintenance haemodialysis patients. Among patients enrolled in J-DOPPS phases 2, 3 and 4 from 80 randomly-selected dialysis facilities, we excluded those who had not had any data measured after study entry or who had missing data on follow-up time (figure 1). We further excluded those who had missing baseline data on age, gender, duration of dialysis or haemoglobin concentration. Finally, a total of 5515 patients were enrolled in this study.

Outcomes, exposures and covariates

The primary outcome was all-cause mortality. We also evaluated cardiovascular mortality and the incidence of

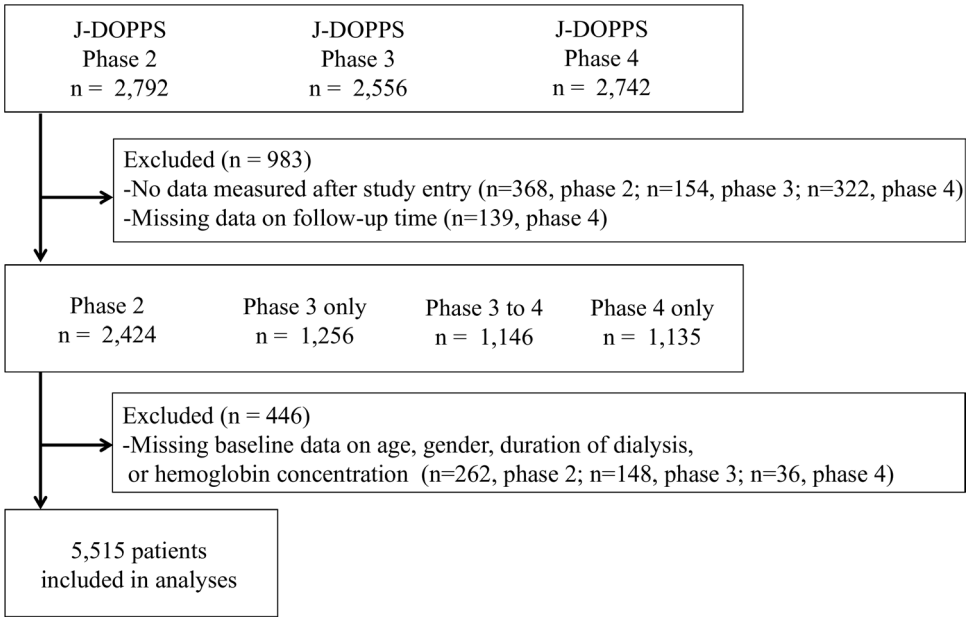

Figure 1 Flow chart of participants in this study. J-DOPPS, Japanese Dialysis Outcomes and Practice Patterns Study.

adverse cardiovascular events. Cardiovascular mortality was defined as follows: death due to cardiac arrest, fatal arrhythmia, myocardial infarction, ischaemic heart disease, congestive heart failure, cardiomyopathy, pericarditis, valvular disease, cerebral infarction or haemorrhage or aneurysmal rupture. Adverse cardiovascular event was defined as follows: cardiovascular mortality or hospitalisation due to CVD, such as cardiac arrest, arrhythmia, myocardial infarction, ischaemic heart disease, congestive heart failure, cerebral infarction or haemorrhage or transient ischaemic attack.

The exposure of interest was the haemoglobin concentration. The data were categorised into six classes by 1.0 g/dL units, with the lowest concentration category set at <9.0 g/dL and the highest at ≥13.0 g/dL. These data were handled as time-dependent variables updated every 4 months. The effect modification by cardiovascular comorbidity is also of interest. Cardiovascular comorbidity was defined as the experience of CVD, based on the same definition of adverse cardiovascular events described above. The status of cardiovascular comorbidity was also handled as a time-dependent variable that was updated according to the incidence of adverse cardiovascular events during the study period. Each of the six haemoglobin categories was further classified into two groups according to cardiovascular-comorbid condition on the date when haemoglobin concentration was measured within every 4 month study period.

The covariates included baseline-fixed variables (demographics, cause of end-stage kidney disease and comorbid conditions excluding cardiovascular comorbidity; table 1) and time-dependent variables updated every 4 months (dialysis-related or laboratory data, and prescription of drugs; table 1), excluding prescription in DOPPS 2, which was updated every 12 months.

For missing variables, we performed multiple imputation using IVEware (Imputation and Variance Estimation Software, University of Michigan).[25] Each of five imputed data sets was constructed by repeating 10 iterations of sequential imputations for missing data based on a regression model according to the type of variable missing,[26] and used to compute the final estimates.

Statistical analyses

Differences in the distribution of patient characteristics at baseline (median and IQR or proportion) among different haemoglobin concentrations were assessed using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables.

The primary analysis estimated the adjusted hazard ratios (aHRs) and 95% CI using Cox regression models. The time-to-outcomes were compared among the 12 haemoglobin concentration categories according to cardiovascular-comorbid conditions as the main exposure while controlling for possible confounding by covariates, stratified by J-DOPPS phase. For each 4 month data collection period ending at visit t, the incidence of each clinical outcome was modelled based on the main exposure and covariates handled as time-dependent variables measured in the previous 4 month period (visit t-1). This time-lagged model was constructed to clarify the time relationship between the exposure and outcomes in the study period. Patients were deemed 'at risk' from study entry until death or first hospitalisation due to CVD, kidney transplantation, departure from the facility, loss to follow-up or the end of follow-up. Differences in the association of each haemoglobin concentration category with outcomes between cardiovascular-comorbid conditions were evaluated by a pointwise interaction test using the same analytical model as the primary analysis but with replacement of the main exposure with haemoglobin concentration categorised into six classes, cardiovascular comorbidity and their product term. The association among patients with the same cardiovascular-comorbid condition was also assessed using the same analytical model as the primary analysis.

Sensitivity analysis

To evaluate the consistency of our results regarding the association in the different analytical models, we used baseline-fixed Cox models in this population. The covariates used were the same as those in the primary analysis, while the time-dependent variables were fixed at baseline. To explore the effect of multiple imputation for covariates with large amounts of missing data, we evaluated the model excluding ferritin (35%), transferrin saturation (57%) and parathyroid hormone (28%) as covariates from the primary analysis model.

We then evaluated the consistency of our results regarding the association between haemoglobin concentration and outcomes in analyses of patients with specific characteristics, using the same model as the primary analysis. First, we evaluated the association in patients using erythropoietin-stimulating agents (ESAs) to estimate the effect of medically controlled haemoglobin concentration. We then analysed subjects who had received haemodialysis for ≥3 months to evaluate the association under maintenance haemodialysis conditions. Finally, we analysed subjects without cancer at entry to exclude the detrimental effects of cancer, such as anaemia, general fatigue and a shorter prognosis.

A two-sided p<0.05 indicated statistical significance. Data were analysed with SAS V.9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Patient and public involvement

There was no patient and public involvement.

RESULTS

Patient characteristics

The 5515 patients (median age: 64 years; 37.8% women) had a median haemodialysis duration of 2.9 years and diabetes mellitus rate of 34.9% (table 1). They also had a CVD comorbidity rate of 35.7% and cancer comorbidity rate of 8.1%.

Table 1 Baseline characteristics of participants enrolled in the study (n=5515) with stratification by haemoglobin concentration

	Total		Haemoglobin concentration, g/dL						
Variable	Value	n	<9.0 (n=1096)	9.0 to 9.9 (n=1362)	10.0 to 10.9 (n=1608)	11.0 to 11.9 (n=1009)	12.0 to 12.9 (n=335)	≥13.0 (n=105)	P value
Demographics									
Age, yr	64 (55 to 72)	5515	66 (57 to 74)	65 (57 to 73)	63 (55 to 72)	62 (54 to 71)	62 (53 to 69)	58 (50 to 71)	<0.001
Sex, female, %	37.8	5515	43.2	40.0	37.6	33.0	29.3	27.6	<0.001
Duration of dialysis, yr	2.9 (0.5 to 8.0)	5515	0.7 (0.03 to 4.9)	3.3 (0.6 to 8.2)	3.5 (0.8 to 8.9)	3.7 (0.8 to 9.1)	3.4 (0.7 to 9.0)	2.0 (0.6 to 2.7)	<0.001
Past smoker, %	19.5	4414	18.8	19.2	19.8	19.9	19.7	21.4	0.69
Current smoker, %	19.3		19.3	18.4	19.1	19.1	22.4	27.4	
Married, %	71.0	5375	72.4	72.0	71.0	69.9	67.9	67.0	0.48
Living alone, %	11.6	5393	11.6	10.4	12.2	11.0	14.6	14.6	0.44
Employed, %	70.7	4932	76.2	73.0	70.1	66.2	62.8	64.5	<0.001
Cause of end-stage kidney disease, %									
Hypertension	5.1	4833	5.2	5.1	5.6	4.3	4.5	4.4	0.09
Glomerulonephritis	44.4		41.1	45.7	46.2	45.0	42.8	30.8	
Diabetic nephropathy	34.9		38.2	33.9	33.4	34.5	36.0	38.5	
Other disease	15.6		15.5	15.3	14.8	16.2	16.8	26.4	
Comorbid conditions, %									
Hypertension	71.5	5483	73.2	72.0	72.7	69.9	66.8	59.6	0.002
Diabetes mellitus	36.3	5499	38.8	36.2	34.7	36.3	35.5	39.1	0.37
Cardiovascular disease	35.7	5513	40.8	35.5	34.2	30.9	38.2	43.8	<0.001
Lung disease	2.1	5507	1.9	2.3	1.6	2.8	2.1	2.9	0.39
Liver disease	11.1	5512	11.8	10.2	11.6	11.0	11.9	9.5	0.76
Gastrointestinal bleeding	12.6	5496	14.4	13.0	12.2	10.7	12.6	13.5	0.22
Cancer	8.1	5475	8.2	8.7	7.8	7.9	7.5	6.7	0.94
Peripheral vascular disease	13.7	5513	13.5	13.0	13.8	14.5	14.3	12.4	0.93
Psychiatric disorder	2.0	5511	1.9	1.8	2.1	1.9	2.1	3.8	0.79
Neurological disease	11.7	5512	13.4	11.8	10.6	11.1	11.6	15.2	0.26
Joint and bone disease	12.0	5512	9.2	11.2	12.6	14.4	13.7	13.3	0.007
Dialysis									
BMI, kg/m^2	20.7 (18.9 to 22.9)	5268	20.7 (18.7 to 22.8)	20.6 (18.5 to 22.7)	20.9 (19.0 to 22.9)	20.6 (18.9 to 22.8)	21.2 (19.3 to 23.3)	21.7 (18.8 to 24.1)	<0.001
Systolic BP, mm Hg	150 (135 to 166)	5365	151 (132 to 167)	151 (138 to 167)	150 (136 to 167)	150 (134 to 165)	150 (130 to 162)	150 (130 to 161)	0.09
Diastolic BP, mm Hg	78 (70 to 87)	5359	74 (66 to 84)	78 (70 to 87)	79 (70 to 86)	80 (70 to 88)	80 (70 to 88)	82 (70 to 92)	<0.001
Kt/V, single pool	1.28 (1.09 to 1.48)	4415	1.20 (0.94 to 1.44)	1.29 (1.11 to 1.50)	1.30 (1.11 to 1.50)	1.30 (1.10 to 1.49)	1.26 (1.07 to 1.42)	1.31 (1.05 to 1.47)	<0.001
nPCR, g/kg/day	0.97 (0.83 to 1.12)	4353	0.91 (0.76 to 1.08)	0.98 (0.84 to 1.12)	0.99 (0.83 to 1.14)	1.00 (0.84 to 1.14)	0.98 (0.84 to 1.14)	0.97 (0.87 to 1.13)	<0.001

Continued

Table 1 Continued

Variable	Total		Haemoglobin concentration, g/dL						P value
	Value	n	<9.0 (n=1096)	9.0 to 9.9 (n=1362)	10.0 to 10.9 (n=1608)	11.0 to 11.9 (n=1009)	12.0 to 12.9 (n=335)	≥13.0 (n=105)	
Residual KF, %‡	33.8	5286	45.4	31.9	30.8	29.4	30.7	30.2	<0.001
Laboratory data									
Serum albumin, g/dl	3.8 (3.5 to 4.0)	5167	3.5 (3.2 to 3.8)	3.7 (3.5 to 4.0)	3.8 (3.6 to 4.0)	3.9 (3.6 to 4.1)	3.9 (3.6 to 4.1)	3.8 (3.4 to 4.1)	<0.001
Ferritin, ng/ml	174 (72 to 410)	3568	237 (107 to 626)	175 (74 to 406)	168 (69 to 392)	151 (65 to 354)	134 (52 to 297)	88 (39 to 166)	<0.001
TSAT, %	23.6 (16.6 to 32.3)	2370	21.3 (14.3 to 31.2)	22.2 (18.5 to 22.7)	24.2 (17.6 to 32.6)	25.2 (18.3 to 33.1)	28.4 (20.0 to 35.4)	22.9 (17.4 to 29.9)	<0.001
Calcium, mg/dl†	9.2 (8.7 to 9.8)	5061	9.0 (8.5 to 9.6)	9.2 (8.7 to 9.8)	9.2 (8.7 to 9.8)	9.2 (8.7 to 9.8)	9.3 (8.8 to 10.0)	9.4 (8.9 to 10.0)	<0.001
Phosphorus, mg/dl	5.4 (4.5 to 6.4)	5463	5.1 (4.2 to 6.1)	5.3 (4.4 to 6.3)	5.4 (4.6 to 6.4)	5.5 (4.6 to 6.6)	5.6 (4.7 to 6.6)	5.7 (4.8 to 6.8)	<0.001
Intact PTH, pg/ml	142 (66 to 253)	3950	160 (72 to 280)	142 (63 to 251)	141 (69 to 241)	130 (63 to 245)	140 (63 to 243)	141 (69 to 270)	0.08
Prescription of drugs									
Calcium channel blocker, %	54.5	5280	60.2	57.6	53.0	50.5	49.2	37.0	<0.001
Beta blocker, %	15.1	5280	14.9	14.5	14.9	16.4	16.1	12.0	0.73
Diuretic, %	30.4	5280	36.3	29.5	28.1	30.7	30.0	18.0	<0.001
Statin, %	10.5	5280	10.1	9.9	11.1	10.3	11.8	11.0	0.86
ARB, %	36.1	5280	35.8	38.3	36.8	36.2	28.5	25.0	0.006
ACEI, %	10.6	5280	11.5	10.9	9.8	11.2	9.3	7.0	0.50
Antiplatelet drug, %	37.3	5280	37.1	36.8	38.6	34.7	37.8	47.0	0.15
Anticoagulant drug, %	4.0	5280	4.6	3.6	3.8	4.1	3.1	6.0	0.60
Benzodiazepine, %	17.2	5280	16.8	16.7	17.2	16.4	20.4	25.0	0.19
Intravenous iron use, %	30.0	5439	27.1	29.1	31.5	31.5	30.4	34.0	0.14
ESA use, %	82.6	5029	86.3	88.7	84.1	79.0	62.4	53.0	<0.001
ESA dose, unit/week	4500 (1500 to 6750)	5029	6000 (3000 to 9000)	4500 (2438 to 9000)	4000 (1500 to 6000)	3000 (1313 to 6000)	2000 (0 to 4500)	0 (0 to 3000)	<0.001

For continuous variables, median and IQR are shown.
*Albumin-corrected value; calcium + (4.0-albumin) if albumin is less than 4.0 g/dL.
†Urine volume ≥200 mL/day or daily urine collection volume of ≥1 cup.
ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II type one receptor blocker;BMI, body mass index; BP, blood pressure; ESA, erythropoietin-stimulating agents; KF, kidney function; nPCR, normalised protein catabolic rate; PTH, parathyroid hormone;TSAT, transferrin saturation; yr, year.

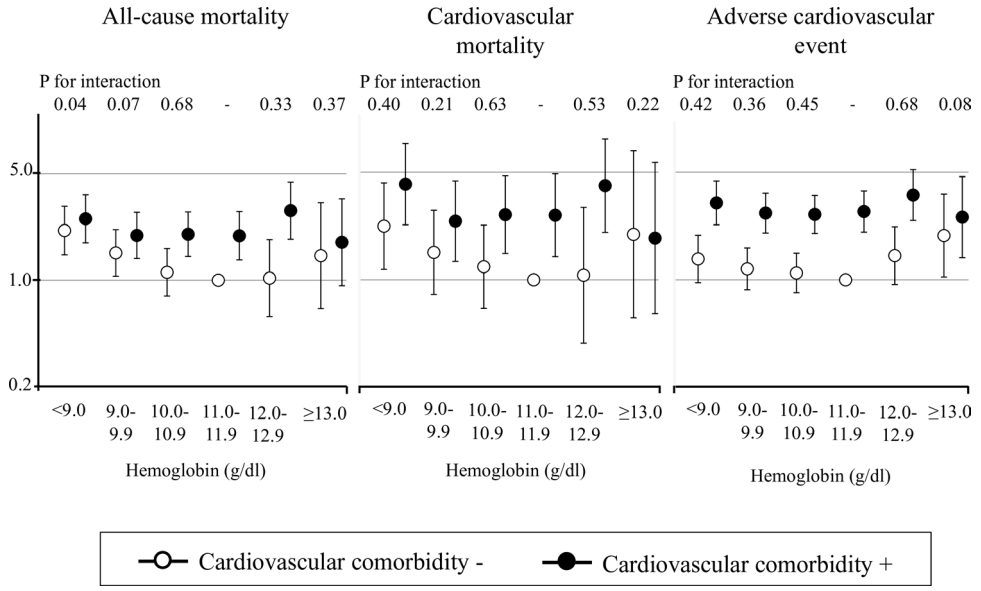

Figure 2 Association between the haemoglobin concentration and outcome with interaction testing for cardiovascular-comorbid condition. Values have been adjusted for possible confounding with Cox regression models. Bars denote 95% CI. The haemoglobin concentration category of 11.0 to 11.9 g/dL in non-cardiovascular-comorbid patients is provided as a reference for comparison.

Among haemoglobin concentration categories, those in the lowest concentration category had the oldest median age of 66 years and the largest proportion of women (43.2%), while those in the highest concentration category had the youngest median age of 58 years and the smallest proportion of women (27.6%). Those in the lowest concentration category had the shortest median duration of dialysis (0.7 years) and lowest values of Fractional urea clearance (Kt/V), normalised protein-catabolic rate (nPCR) and serum albumin, as well as the largest proportion of residual kidney function, hypertensive patients (73.2%) and calcium channel blocker users. Subjects in the lowest and highest haemoglobin categories had higher proportions of cardiovascular comorbidity than those in the other categories.

Mortality, cardiovascular mortality and adverse cardiovascular events

During a median follow-up of 2.0 years (IQR 1.5 to 2.7 years), 847 patients experienced all-cause death. Of these deaths, 326 were due to CVD. Of the 1000 patients who experienced adverse cardiovascular events, 433 and 287 with and without cardiovascular comorbidities at baseline, respectively, were hospitalised for non-fatal CVD.

Association of haemoglobin concentration and outcomes with interaction test for cardiovascular-comorbid condition

Figure 2 shows the association of the haemoglobin concentration according to cardiovascular comorbidity with outcomes adjusted for possible confounding using Cox models. The follow-up time (person-years) in each haemoglobin category is shown in online supplementary table S1.

With a non-cardiovascular-comorbid (CV−) haemoglobin concentration of 11.0 to 11.9 g/dL as the reference, the associations of both cardiovascular-comorbid (CV+) and CV− haemoglobin concentrations with all-cause mortality appeared U-shaped, excluding the highest CV+ haemoglobin category, with higher estimated values of mortality risk observed across CV+ haemoglobin categories. Pointwise interaction testing for cardiovascular comorbidity showed p values of 0.04 in the lowest haemoglobin category. The results for cardiovascular mortality and adverse cardiovascular events appeared similar, while an interaction test showed no significance with any haemoglobin concentration.

Association of the haemoglobin concentration with outcomes by cardiovascular-comorbid condition

Figure 3 shows the association of haemoglobin concentration with outcomes by cardiovascular-comorbid condition. Compared with the haemoglobin category of 11.0 to 11.9 g/dL, the lowest CV− haemoglobin concentrations were associated with an increased all-cause mortality risk (aHR 2.11, 95% CI 1.47 to 3.06), while CV+ haemoglobin categories narrowly showed no association (aHR 1.29, 95% CI 0.95 to 1.76); a significantly increased cardiovascular mortality was observed in both groups. At the second-lowest range, mortality was increased only in the CV− haemoglobin category. Respective risks for mortality and adverse cardiovascular events at the second-highest range in CV+ and CV− patients were narrowly non-significant but increased, while adverse cardiovascular events were significantly increased in the highest CV− haemoglobin category.

Sensitivity analysis

Associations of haemoglobin concentration with all-cause or cardiovascular mortality appeared U-shaped in baseline-fixed Cox models, although that most haemoglobin

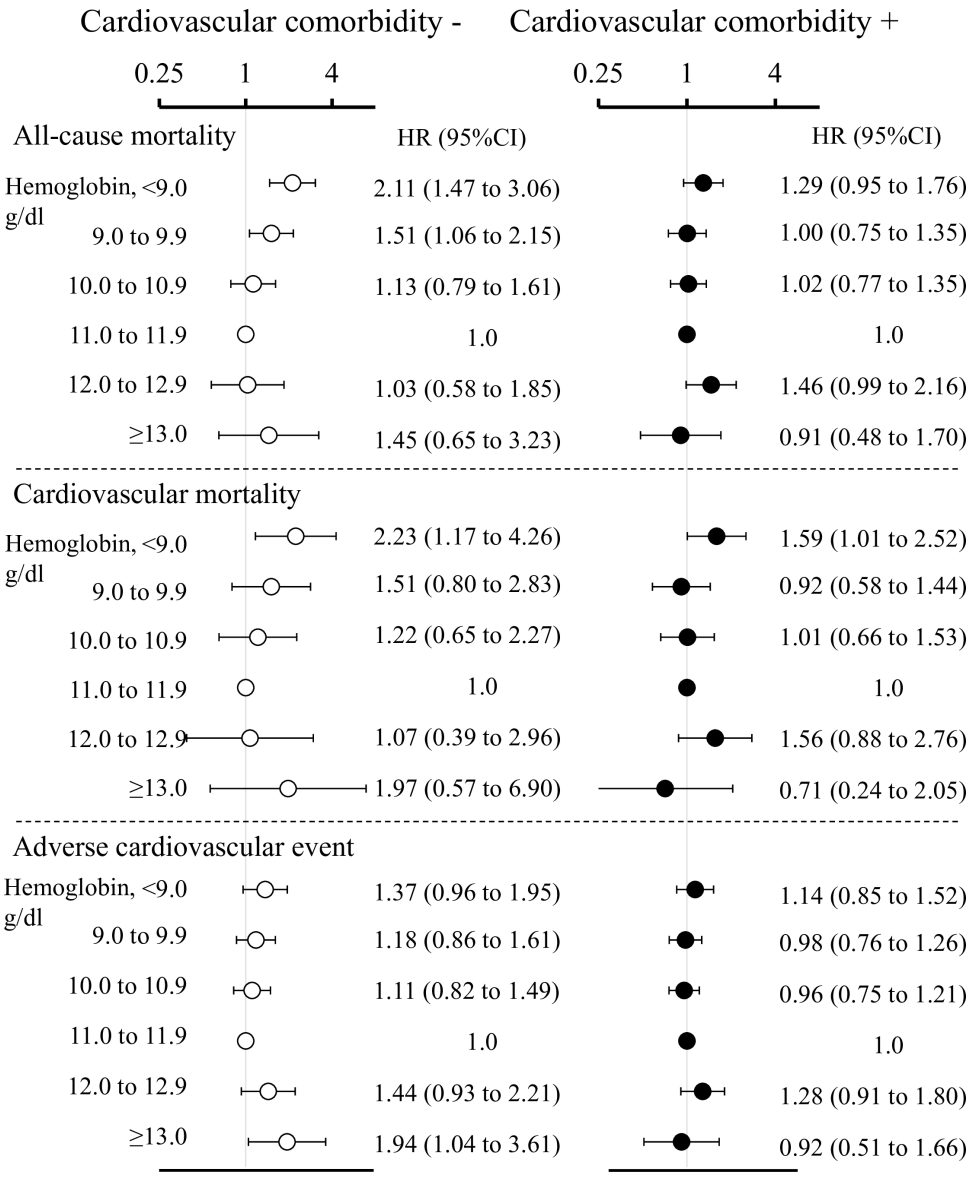

Figure 3 Association between the haemoglobin concentration and outcome by cardiovascular-comorbid condition. Values have been adjusted for possible confounding with Cox regression models. The haemoglobin concentration category of 11.0 to 11.9 g/dL is provided as a reference for comparison. Open and filled circles denote HRs. Bars denote 95% CI.

concentrations lacked significant differences, with smaller estimated risk values than in the primary analysis (online supplementary tables S2–S5). The association with adverse cardiovascular events lacked a U-shape for all CV– haemoglobin categories (online supplementary tables S6–S7). The interaction test showed no significance for any haemoglobin concentration. Results using a model which excluded covariates with large amounts of missing data at baseline before multiple imputation were similar to those of the primary analysis (online supplementary tables S2–S7).

Among other analyses, results using data under ESA use were similar to those of the primary analysis, while the interaction test reached significance in the highest and second-highest haemoglobin categories in the association with mortality (online supplementary table S8–S9). Results excluding patients who had received dialysis for less than 3 months or with cancer were also similar to those of the primary analysis (online supplementary table S10–S13).

DISCUSSION

In this study, the association of haemoglobin concentration with all-cause mortality differed between haemodialysis patients with and without cardiovascular comorbidity. Low haemoglobin concentrations (<10.0 g/dL) in CV– patients were associated with higher relative mortality risk than in CV+ patients, with higher thresholds of haemoglobin concentration for increasing mortality. Higher haemoglobin concentrations, ranging moderate anaemia to normal (≥11.0 to 11.9 g/dL), appeared to be associated with increasing mortality or risk of adverse cardiovascular events, significantly so in CV– patients. These findings suggest that CV– patients are more sensitive to

the detrimental effect of low haemoglobin concentration than CV+ patients. In turn, CV+ patients might tolerate low haemoglobin concentrations better than CV− patients. Meanwhile, haemoglobin concentrations near the normal range might give no additional survival advantage to either group. To our knowledge, this is the first study to address haemoglobin concentrations according to the cardiovascular-comorbid condition associated with not only mortality but also the incidence of adverse cardiovascular events.

One strength of this study is our use of representative data of haemodialysis patients in a real-world setting. Because mortality among haemodialysis patients is far lower in Japan than in Western countries with fewer semi-competing risks for death in Japan,[22] these data will be particularly useful for evaluating associations between haemoglobin concentrations and mortality. Second, this study included patients with varied characteristics. For example, those in the lowest haemoglobin category had the lowest values of Kt/V, nPCR and serum albumin, and the largest proportion of residual kidney function. This is likely due to the shorter duration of dialysis in these patients than in those in the other haemoglobin categories. In addition, the results were unchanged in sensitivity analyses limited to ESA users, those on haemodialysis for more than 3 months, and non-cancer patients, supporting the high generalisability of our results. Third, treating the haemoglobin concentrations and cardiovascular comorbidity as time-dependent variables might have helped reduce bias from misclassification, which could tend to attenuate the observed association between study variables. In this study, bias might have arisen due to the difficulty of maintaining haemoglobin concentrations in individual patients within a narrow range,[27] and changes in cardiovascular-comorbid condition during the study period due to the high incidence of CVD.[21] The difference in results between a sensitivity analysis using the baseline-fixed model and the primary analysis indicates that considerable bias is in fact present.

Our finding of an association between lower haemoglobin concentration and mortality is consistent with those of most previous reports in haemodialysis patients. Speculated mechanisms include reduced oxygen delivery causing damage to vital organs, in turn increasing myocardial oxygen consumption by necessitating a higher stroke volume and heart rate to maintain systemic oxygen delivery.[28 29] Why CV+ patients might be more tolerant of low haemoglobin concentrations than CV− patients is presently unclear. One potential explanation is that CV+ patients might have a lower quality of life or physical activity than CV− patients at that particular haemoglobin concentration due to the burden of impaired cardiac or vascular function, or to psychological impairment due to having CVD. These health conditions might lead to reduced oxygen consumption, and thereby permit reduced oxygen delivery. Meanwhile, our results suggesting that patients with a high haemoglobin concentration enjoy no additional survival advantage may be due to the higher oxygen consumption with greater quality of life or physical activity that the high haemoglobin concentration affords; or to reduced oxygen supply due to increased blood viscosity leading to increased microthrombosis and a subsequent decrease in flow volume due to the heightened resistance of vessel walls.[30]

Our results suggest no association of CV+ haemoglobin concentrations of ≥13 g/dL with the outcomes. Some errors in estimation associated with the small sample size might be present. Meanwhile, previous reports suggested that the best haemoglobin concentration range for survival in non-dialysis CV+ patients was 14.0 to 16.0 g/dL, with a U-shaped association.[31] CV+ haemodialysis patients at haemoglobin concentrations ≥13 g/dL might also enjoy beneficial effects due to sufficient supply of oxygen to vital organs, thereby attenuating the detrimental effect on the outcomes. Further, we included patients with naturally high haemoglobin concentrations, as this condition was recently reported not to increase mortality[32]; the inclusion of these patients might also have attenuated the detrimental effect on the outcomes. Indeed, our sensitivity analysis excluding data from patients not using ESAs with haemoglobin concentrations ≥13 g/dL suggested a non-significant but increased risk of mortality and adverse cardiovascular events, contrary to the primary analysis. These results should be confirmed by further studies.

Our results may be useful in developing strategies for the differentiated management of haemoglobin concentration in patients before and after experiencing CVD. CV+ patients may need to start using ESAs at haemoglobin concentrations of 9.0 to 10.0 g/dL to avoid a decrease below 9.0 g/dL, whereas CV− patients may need to start using ESAs at ≥10.0 g/dL to avoid a decrease below 10.0 g/dL, contrary to published guidelines.[33–35] Conversely, haemoglobin concentrations might be better controlled at <12.0 g/dL for both groups, with concentrations ≥13.0 g/dL particularly eschewed in CV− patients, consistent with the existing guidelines. Further studies, including controlled trials, are warranted to verify the causality of these associations.

Several limitations associated with the present study warrant mention. First, this was an observational study which examined real-world practices and therefore could not prove causal inferences. Second, because the DOPPS is an observational study, no additional or routine laboratory testing was performed. This prevented us from identifying any other variables as possible confounders, such as inflammation markers like C-reactive protein or interleukin-6, severity of CVD, compliance with treatments or diet restriction and physical activity. Third, the existence of other unmeasured confounders cannot be ruled out, including variables reflecting ESA responsiveness or undetermined variables that might explain the existence of ESA responsiveness.[36 37] Fourth, many facilities in Japan measure patient laboratory data in the supine position at the beginning of the week. Our findings should therefore be carefully applied to patients in facilities using different approaches. Finally, a subgroup analysis limited to non-ESA users was not performed because of the low

precision of the analysed results, likely due to the small number of patients remaining following stratification.

In conclusion, the association of the haemoglobin concentration with all-cause mortality differed between haemodialysis patients before and after experiencing CVD. Our results suggest the need for caution in CV– patients against low haemoglobin concentrations, like CV+ patients. Further, they suggest that cardiovascular-comorbid condition should be considered when the association of haemoglobin concentration with mortality is addressed. Further investigations will be required to confirm the causality of these associations using the latest real-world data of haemodialysis patients with a larger sample size, including controlled studies, to determine the optimum target range of haemoglobin concentration for individualised management.

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Ethics approval J-DOPPS was approved by a central ethics committee (Tokyo Women's Medical University, approval no. 678 and 1527 for phase 3 and 4, respectively). For phase 2, the steering committee of J-DOPPS decided not to be required ethical approval by a central ethics committee because no interventional study using anonymised data was performed after patient consent forms were obtained.

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