Table 3. Factors associated with the difference between office BP and ABP: Univariate analysis

	Difference in BP (mmHg)	*P* Value
Dichotomous variables		
Men (versus women)	0.79	0.26
Overweight (BMI ≥25)	0.55	0.48
Obesity (BMI ≥30)	0.34	0.83
Antihypertensive medicine use	3.35	0.01
Diuretic use	1.53	0.04
Diabetes	2.19	0.002
Proteinuria	2.30	0.03
Nocturia	0.89	0.30
Much difficulty in sleep	0.83	0.32
Winter (versus summer)	−0.17	0.83
CKD stage 4 (versus stage 3)	1.29	0.08
CKD stage 5 (versus stage 3)	2.79	0.01
Continuous variables		
Age (10 yr)	0.87	0.003
BMI (1 kg/m^2)	0.09	0.36
eGFR (10 ml/min per 1.73 m^2)	−0.82	0.003

Simple linear regression analysis was used for univariate evaluations to detect the factors associated with the difference between office BP and 24-hour average BP calculated from ABP data. Dependent variable is absolute value of 24-hour average BP minus office BP. ABP, ambulatory BP; BMI, body mass index; eGFR, estimated GFR.

Table 4. Factors associated with the difference between office BP and ABP: Multivariate analysis

Variables	Difference in BP (mmHg)	*P* Value
Men (versus women)	0.31	0.67
Age (10 yr)	0.56	0.07
eGFR (10 ml/min per 1.73 m^2)	−0.56	0.05
Diabetes	1.70	0.02
Antihypertensive medicine use	2.61	0.03
Much difficulty in sleep	0.86	0.31
Nocturia	−0.06	0.95
Winter (versus summer)	−0.52	0.50

Multiple regression analysis was performed for multivariate evaluations including sex, other variables with *P* value <10% explored in Table 3, and patients' questionnaire variables as independent variables. As for renal function, we adopted eGFR instead of CKD stages. We did not incorporate proteinuria into this model. ABP, ambulatory BP; BMI, body mass index; eGFR, estimated GFR.

24-hour average BP of <130/80 mmHg. MHT is the office BP of <140/90 mmHg and 24-hour average BP ≥130/80 mmHg. Persistent hypertension (PHT) is the office BP ≥140/90 mmHg and 24-hour average BP ≥130/80 mmHg.

Renal Function

Serum creatinine from single blood sampling at baseline was measured at a central laboratory and estimated GFR (eGFR) was calculated by the following equations (26):

$$\text{Men}: \text{eGFR} = 194 \times (\text{age}^{-0.287}) \times (\text{serum Cre}^{-1.094})$$
$$\text{Women}: \text{eGFR} = 0.739 \times 194 \times (\text{age}^{-0.287}) \times (\text{serum Cre}^{-1.094})$$

CKD stage was defined using eGFR (60 > eGFR ≥ 30 for stage 3, 30 > eGFR ≥ 15 for stage 4, and 15 > eGFR ≥ 10 for stage 5).

Statistical Analyses

Continuous variables from two groups were compared with *t* tests, and ANOVA was used for comparisons among ≥3 groups. For multiple comparisons, tendencies were explored by ANOVA with linear contrast. For categorical variables, chi-squared tests (2×2 contingency table), or Cochran-Mantel-Haenszel tests (m×n table) were performed when there were additional categories.

Simple linear regression analysis or the chi-squared test were used for univariate evaluations to investigate the relation between ABPM parameters and patient questionnaires (night urination times and sleep quality), season for ABPM, and baseline characteristics (sex, age, body mass index [BMI], overweight, eGFR, CKD stage, antihypertensive medicine use, diuretic use, and systolic and diastolic BP). Multiple regression analyses were used for multivariate evaluations including variables with *P* values <10% explored above. All statistical analyses were performed by using the SAS software program for Windows (version 9.2; SAS Institute Inc, Tokyo, Japan).

Results

Demographics

Table 1 summarizes the patient demographics, showing that 393 participants were women (mean age, 58.5 years) and 682 were men (mean age, 62.0 years). Our results showed that 19.9% of women and 26.7% of men had a BMI ≥25, and 32.6% of women and 37.1% of men had diabetes. Approximately 90% of all participants were receiving antihypertensive medications and 27% were treated with diuretics. In addition, 43.8% had stage 3 CKD, 41.8% had stage 4 CKD, 14.4% had stage 5 CKD.

Office BP and 24-Hour Average BP

Figure 1 shows the scatter plot of office and 24-hour average systolic BP (SBP). The coefficients of correlation were 0.50 for SBP ($P<0.001$) and 0.52 for diastolic BP (DBP) ($P<0.001$). Based on office BP, 31.6% of all participants were diagnosed as having hypertension. Based on the 24-hour average BP, 56.9% were diagnosed as having hypertension. Our results showed that 30.9% of patients

Table 5. Patterns of nocturnal BP change

	Extreme Dipper	Dipper	Nondipper	Riser	Total	*P* Value
CKD stage						
Total	105	395	408	167	1075	
3	54 (11.5)	181 (38.4)	173 (36.7)	63 (13.3)	471	
4	44 (9.8)	152 (33.9)	172 (38.3)	81 (18.0)	449	
5	7 (4.5)	62 (40.0)	63 (40.6)	23 (14.8)	155	
Much difficulty in sleep						
Total	104	394	403	166	1067	
No	89 (10.5)	325 (38.3)	314 (37.0)	121 (14.3)	849	
Yes	15 (6.9)	69 (31.7)	89 (40.8)	45 (20.6)	218	0.02
Nocturia						
Total	105	393	404	166	1068	
No	95 (11.0)	347 (40.2)	301 (34.8)	121 (14.0)	864	<0.001
Yes	10 (4.9)	46 (22.5)	103 (50.5)	45 (22.1)	204	
Season						
Total	105	395	408	167	1075	
Summer	21 (7.2)	90 (31.0)	114 (39.3)	65 (22.4)	290	<0.001
Winter	84 (10.7)	305 (38.9)	294 (37.5)	102 (13.0)	785	
Antihypertensive medicine use						
Total	105	395	408	167	1075	
No	13 (13.0)	39 (39.0)	40 (48.0)	8 (8.0)	100	0.14
Yes	92 (9.4)	356 (36.5)	368 (37.7)	159 (16.3)	975	
Diuretic use						
Total	105	395	408	167	1075	
No	82 (10.5)	298 (38.0)	294 (37.5)	111 (14.1)	785	0.10
Yes	23 (7.9)	97 (33.5)	114 (39.3)	56 (19.3)	290	
Overweight						
Total	105	395	408	167	1075	
No	79 (9.7)	294 (36.1)	318 (39.0)	124 (15.2)	815	0.65
Yes	26 (10.0)	101 (38.9)	90 (34.6)	43 (16.5)	260	
Diabetes						
Total	105	395	408	167	1075	
No	73 (10.5)	277 (39.9)	265 (38.2)	79 (11.4)	694	<0.001
Yes	32 (8.4)	118 (31.0)	143 (37.5)	88 (23.1)	381	
Proteinuria						
Total	99	383	402	161	1045	
No	20 (16.8)	43 (36.1)	41 (34.5)	15 (12.6)	119	0.03
Yes	79 (8.5)	340 (36.7)	361 (39.0)	146 (15.8)	926	

Data are *n* (%) unless otherwise indicated. Nocturnal BP change is classified into four patterns according to the level of nocturnal BP decrease. The patterns of nocturnal BP change and background factors such as CKD stage, quality of sleep, nocturia, season, antihypertensive medication use, diuretic use, obesity, and diabetes. *P* value for general association is general correlation between row and column, and it means a rough indication of correlation between background factors and these BP patterns.

had MHT, 5.6% had WCHT, and 26.0% had PHT, whereas 37.6% had well controlled BP. The median interval between the office BP measurement and ABPM was 41 days (25th percentile, 0 days; 75th percentile, 154 days). We divided the patients into two groups by the 75th percentile value, and analyzed for the patterns of hypertension. However, we did not observe any difference between them (data not shown).

We evaluated the relationship between hypertension patterns and background factors (Table 2). As for the CKD stage, prevalence of normal BP decreased from 42.3% to 29.0%, and that of PHT rose from 21.7% to 36.1% with advancing CKD stage. The prevalence of WCHT was little associated with factors of clinical interest excluding diabetes and the season. The prevalence of MHT and PHT was higher in men than women and in winter than in summer. Incidence of MHT and PHT was high in patients with diabetes or overweight.

We also evaluated the difference between office BP and ambulatory BP (ABP) as a continuous variable (Tables 3 and 4), and diabetes, antihypertensive medicine use, and low eGFR accounted for the difference between them. Proteinuria was not associated significantly with the difference between office BP and ABP in another multivariate model (Supplemental Table 1).

Characteristics of NBPC

NBPC patterns were analyzed (Table 5). Prevalence of nondippers and risers was lower at stage 3 than at stages 4 and 5. Prevalence of nondippers or risers was markedly high among the patients with much difficulty sleeping (P=0.02) and among the patients with nocturia

Table 6. Factors associated with nocturnal BP change: Univariate analysis

	Difference in Nocturnal BP Change (%)	*P* Value
Dichotomous variables		
Men (versus women)	0.22	0.70
Overweight (BMI ≥25)	−0.25	0.69
Obesity (BMI ≥30)	0.33	0.80
Antihypertensive medicine use	−1.88	0.04
Diuretic use	−1.75	0.004
Diabetes	−2.56	<0.001
Proteinuria	−1.88	0.03
Nocturia	−3.99	<0.001
Much difficulty in sleep	−1.82	0.007
Winter (versus summer)	2.55	<0.001
CKD stage 4 (versus stage 3)	−1.44	0.01
CKD stage 5 (versus stage 3)	−1.18	0.15
Continuous variables		
Age (10 yr)	−0.53	0.03
BMI (1 kg/m^2)	0.04	0.56
eGFR (10 ml/min per 1.73 m^2)	0.59	0.008

Simple linear regression analysis was used for univariate evaluations to detect the factors associated with nocturnal BP change. BMI, body mass index; eGFR, estimated GFR.

($P<0.001$). In general, there are two methods to separate the daytime period and night-time period: the patient diaries and the short-window setting. In this study, we adopted the former. We checked whether the ratio of NBPC patterns changed according to these two definitions; however, there was a slight difference (data not shown).

Our results showed that 290 patients underwent ABPM in summer, whereas there were 785 patients in winter. The 24-hour average BP was higher during winter than during summer. The prevalence of nondippers or risers was higher during summer than winter.

As for other baseline factors, diabetes was a significant variable on NBPC. The prevalence of nondippers or risers was higher among diabetic patients than among nondiabetic patients.

Univariate regression analyses were also performed in an attempt to identify factors associated with NBPC as a continuous variable. Table 6 shows that the significant factors were antihypertensive medication use, diuretic use, diabetes, proteinuria, nocturia, much difficulty in sleep, season, age, and renal function (eGFR and CKD stage).

We performed multivariate regression analyses with the NBPC as a dependent variable and the above-mentioned factors as independent variables, stratifying the participants according to nocturia (Figure 2). In the nocturia-negative group, CKD stage 4 (relative to stage 3), diabetes, and season (winter) were identified as significant, and CKD stage 5 relative to stage 3, much difficulty in sleep, and diuretic use also tended to reduce the NBPC. In the nocturia-positive group, neither CKD stage nor sleep quality was a significant independent variable. Only diabetes was significant. Proteinuria was not significantly associated with NBPC in a multivariate model (Supplemental Table 2).

MBPC

We performed univariate regression analyses to clarify which factors were associated with MBPC. Age, BMI, overweight, obesity, and season were found to be significant variables (Table 7). Next, we performed multivariate regression analyses with the above-mentioned factors as independent variables (Table 8). BMI was selected as representative of obesity-related variables and eGFR as representative renal function-related variables. MBPC became larger with advancing age and higher BMI. MBPC tended to become larger in winter than summer. For patients with diabetes, MBPC is smaller than in patients without diabetes.

Discussion

Office BP and 24-Hour Average BP

The majority of participants had hypertension and proteinuria but the mean BP was normal (132/76 mmHg) and >90% of participants were treated with angiotensin converting enzyme inhibitors/angiotensin receptor blockers (22). However, the large SD of mean office BP suggested the presence of patients with relatively poorly controlled BP.

In ABPM studies, the 24-hour average BP was the first parameter to be examined (27). WCHT accounted for 5.6% of all participants. Its prevalence has been reported to be 13% (10,28) or 18% (29) among the population in general. Bangash and Agarwal performed a meta-analysis of CKD patients (six trials, reported from 2005 to 2008) and reported that the prevalence was 18.3% (10.5%–31.7%) (30) and 15% among CKD cohort (31). Compared with these previous data, the prevalence of WCHT in this study was very low. There is no consensus on the prognosis of WCHT (32). Some investigators have reported that WCHT is likely to shift to PHT (33) or that the risk for stroke does not differ between WCHT and PHT, whereas other investigators have reported that the incidence of stroke is significantly lower among patients with WCHT (34).

In this study, about 30% of all participants had MHT. The prevalence of MHT varies considerably among different reports: Ohkubo *et al.* reported 17% among the population in general (10); Bogrie *et al.* and Mancia *et al.* reported 8% (28,29) among the population in hypertensives. As for the prevalence of MHT among CKD patients, a meta-analysis by Bangash and Agarwal reported 8.3% (4.7%–31.3%) (30); Kanno *et al.* estimated 15% from The Ohasama Study data (31); and Pogue *et al.* reported 42.9% from the African American Study of Kidney Disease and Hypertension trial data (35). The percentage of MHT in this study was relatively high compared with these previous reports except for the African American Study of Kidney Disease and Hypertension. The prognosis of MHT is poor according to many reports (10,28,36–38). If the diagnosis of

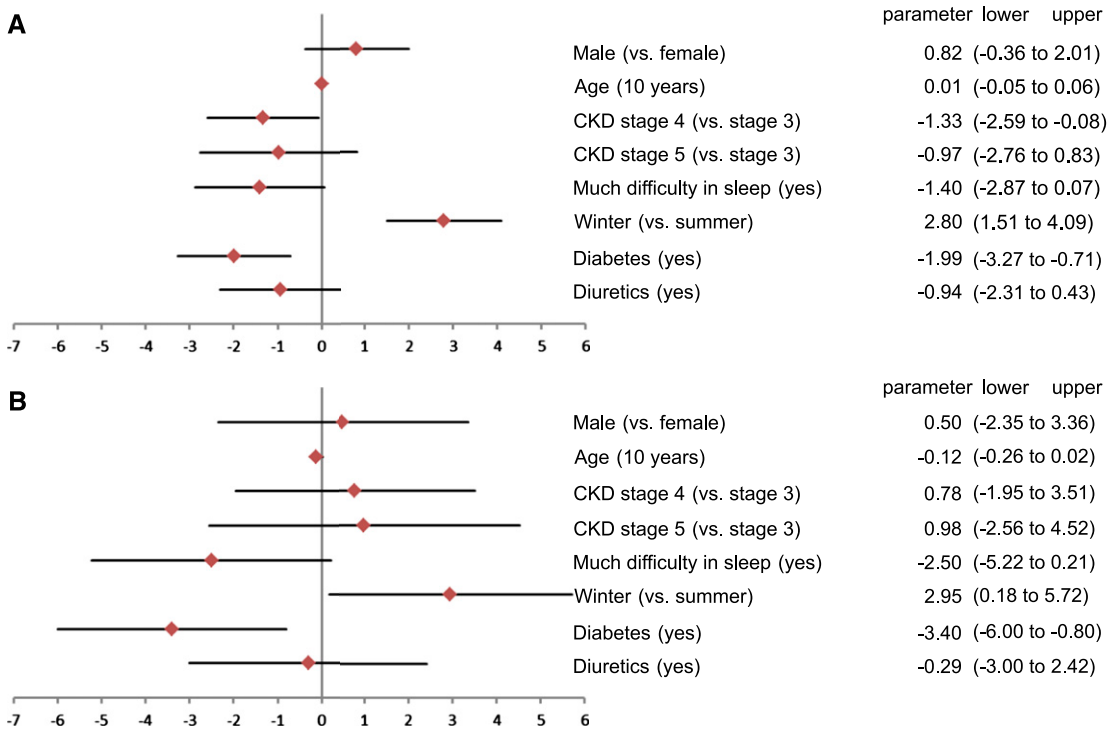

Figure 2. | Multiple regression model for the identification of factors associated with the degree of the nocturnal BP change. The degree of the nocturnal BP change was stratified according to presence/absence of nocturia. The parameter estimate (filled diamond) and its 95% confidence interval (95% CI) (solid line) are shown. The first column to the right shows the independent variables; the second column shows the parameter estimates; and the third shows the 95% CIs. The independent variables analyzed were sex (men), age (plus 10 years), CKD stage 4 (relative to stage 3), CKD stage 5 (relative to stage 3), sleep quality (poor sleep), and season (winter). (A) Linear multiple regression model for the nocturia-negative group, with the degree of the nocturnal BP change as a dependent variable. (B) Linear multiple regression model for the nocturia-positive group, with the degree of nocturnal BP change as a dependent variable.

hypertension relies only on office BP, many patients who require treatment may be overlooked. The factors that increased the difference between office BP and ABP were renal function, diabetes, and antihypertensive medicine use including diuretic use. This means that we are unable to control BP of patients with CKD, diabetes, and hypertension only by office BP. Quality of sleep, nocturia, and season did not have a large effect on the difference.

NBPC and CKD Stage

The findings of the relationship between NBPC and CKD stage were approximately equal to our predictions. The percentage of patients showing a nondipper or riser pattern was higher at stages 4 and 5 than at stage 3. However, there was no linear increase in the percentage of those two patterns with advancing CKD stages (data not shown). When evaluating NBPC as a continuous variable, we were not able to find the tendency that the degree of nocturnal fall became small with advancing CKD stage or eGFR decrease (Supplemental Table 3).

Factors Associated with NBPC

Quality of sleep has been suggested to affect the NBPC (39). Quality of sleep and the frequency of urination at night were evaluated in this study. Both appear to influence the pattern of the nocturnal BP decrease markedly. They can be collected by simple questionnaire and they are useful when interpreting NBPC and its patterns.

We also observed a seasonal effect on NBPC. The significantly higher percentage of patients showing an insufficient nocturnal BP decrease during summer than winter was contradictory to our anticipation. However, the MBPC was more marked during winter. This suggests that some of the patients who were classified as showing a sufficient nocturnal BP decrease had MBPC. The degree of MBPC was also greater during winter (19.5 mmHg in summer versus 24.0 mmHg in winter; $P<0.001$). If a goal is to achieve good BP control throughout the day, it seems essential to note the seasonal effect on diurnal BP variation.

From the multiple regression analysis with NBPC as a dependent variable and nocturia as a stratifying factor, CKD stage 4 (relative to stage 3), diabetes, and season (winter) were identified as significant variables in the nocturia-negative group, and CKD stage 5 (relative to stage 3), much difficulty in sleep, and diuretic use tended to have the same effect on NBPC (Figure 2A). However, the results differed considerably in the nocturia-positive group. Season and diabetes remained significant factors, but the influence of sleep status and CKD stage was not significant in this group (Figure 2B). When using eGFR as an independent variable instead of CKD stage, it remained significant in the nocturia-negative group (Supplemental Table 3). In this analysis, the nocturia was used as a stratifying factor rather than as an independent variable for the following reasons: the NBPC will inevitably decrease if the

Table 7. Morning BP change as a dependent variable: Univariate analysis

	Difference in BP (mmHg)	*P* Value
Dichotomous variable		
Men (versus women)	1.82	0.09
Overweight (BMI ≥25)	2.72	0.02
Obesity (BMI ≥30)	5.44	0.02
Antihypertensive medicine use	2.21	0.21
Diuretic use	0.03	0.98
Diabetes	−1.82	0.09
Proteinuria	−0.34	0.83
Nocturia	−0.98	0.45
Much difficulty in sleep	−1.91	0.13
Winter (versus summer)	4.58	<0.001
CKD stage 4 (versus CKD stage 3)	0.88	0.88
CKD stage 5 (versus CKD stage 3)	0.59	0.59
Continuous variables		
Age (10 yr)	2.07	<0.001
BMI (1 kg/m^2)	0.48	0.001
eGFR (10 ml/min per 1.73 m^2)	0.08	0.84

Morning BP change is defined as the difference between morning SBP (the average of SBPs during the first 2 hours) minus the lowest SBP (the average SBPs of three readings centered on the lowest night-time readings). Simple linear regression analysis was used for univariate evaluations to detect the factors associated with morning BP change. BMI, body mass index; eGFR, estimated GFR.

Table 8. Morning BP change as a dependent variable: Multivariate analysis

Variables	Difference in BP (mmHg)	*P* Value
Men (versus women)	0.63	0.57
Age (10 yr)	0.22	<0.001
Diabetes	−3.65	0.001
Winter (versus summer)	4.52	<0.001
BMI (1 kg/m^2)	0.56	<0.001
Much difficulty in sleep	−1.46	0.26
Nocturia	−2.29	0.10
Antihypertensive medicine use	1.76	0.34
eGFR (10 ml/min per 1.73 m^2)	0.35	0.44

Multiple regression analysis was performed for multivariate evaluations. Model includes variables with *P* value <10% explored in Table 7 and variables of clinical interest. BMI is selected as the representative of obesity-related variables such as overweight (BMI ≥25), obesity (BMI ≥30), and BMI. BMI, body mass index; eGFR, estimated GFR.

patient is getting up frequently during the night for urination, nocturia is likely to develop as CKD stages advance, and the quality of sleep is also associated with nocturia. These results suggest that this way of patient stratification was rational. The results also suggest that when interpreting the ABPM data, identifying nocturia is essential.

For reference, we evaluated multiple regression models with/without nocturia (Supplemental Table 4). In model 2, nocturia had a largest slope among independent variables. R^2 values were 0.05 (model 1) and 0.08 (model 2), that is, nocturia increased the R^2 value nearly 50%. The R^2 was very small due to wide variation of NBPC, but this result showed that nocturia was a very important variable when interpreting ABPM data.

MBPC

MBPC is smaller in patients with diabetes than in patients without diabetes. Renal function was not significant. This is probably due to various interventions to the lifestyle of patients with diabetes or advancing CKD, including drugs. In other words, a reversal of cause and effect might be happening here.

Summary

In this study, we confirmed that the prevalence of PHT was high in the CKD population and increased in association with progression of CKD. The difference in office BP and ABP was increased by diabetes, taking antihypertensive medications, and low eGFR. Various background factors such as eGFR, diabetes, antihypertensive medication use, BMI, and season accounted for abnormal BP patterns in CKD patients. A longitudinal study with use of CKD-JAC data will elucidate the relationship between nondippers, risers, MBPCs, and cardiovascular outcomes.

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References

1. Dawber TR, Moore FE, Mann GV: Coronary heart disease in the Framingham study. *Am J Public Health Nations Health* 47: 4–24, 1957
2. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 3rd: Factors of risk in the development of coronary heart disease—six year follow-up experience. The Framingham Study. *Ann Intern Med* 55: 33–50, 1961
3. Kannel WB, Wolf PA, Verter J, McNamara PM: Epidemiologic assessment of the role of blood pressure in stroke. The Framingham study. *JAMA* 214: 301–310, 1970
4. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D: The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: Design, recruitment, and initial examination. *Am J Epidemiol* 165: 1328–1335, 2007

5. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS; AIPRD Study Group: Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 139: 244–252, 2003
6. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 42: 1050–1065, 2003
7. Andersen MJ, Khawandi W, Agarwal R: Home blood pressure monitoring in CKD. *Am J Kidney Dis* 45: 994–1001, 2005
8. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH: How common is white coat hypertension? *JAMA* 259: 225–228, 1988
9. Pickering TG, Davidson K, Gerin W, Schwartz JE: Masked hypertension. *Hypertension* 40: 795–796, 2002
10. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y: Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 46: 508–515, 2005
11. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J; Systolic Hypertension in Europe Trial Investigators: Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 282: 539–546, 1999
12. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K: Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 38: 852–857, 2001
13. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y: Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: The Ohasama study. *J Hypertens* 20: 2183–2189, 2002
14. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K: Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension* 27: 130–135, 1996
15. Minutolo R, Agarwal R, Borrelli S, Chiodini P, Bellizzi V, Nappi F, Cianciaruso B, Zamboli P, Conte G, Gabbai FB, De Nicola L: Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med* 171: 1090–1098, 2011
16. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T: Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension* 16: 692–699, 1990
17. Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C: Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 81: 528–536, 1990
18. Bianchi S, Bigazzi R, Baldari G, Sgherri G, Campese VM: Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am J Hypertens* 7: 23–29, 1994
19. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A: Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 24: 793–801, 1994
20. Omboni S, Parati G, Palatini P, Vanasia A, Muiesan ML, Cuspidi C, Mancia G; Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation: Reproducibility and clinical value of nocturnal hypotension: Prospective evidence from the SAMPLE study. *J Hypertens* 16: 733–738, 1998
21. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, Iimuro S, Ohashi Y, Hishida A; CKD-JAC Study Group: Chronic Kidney Disease Japan Cohort (CKD-JAC) study: Design and methods. *Hypertens Res* 31: 1101–1107, 2008
22. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, Iimuro S, Ohashi Y, Hishida A: Chronic Kidney Disease Japan Cohort study: Baseline characteristics and factors associated with causative diseases and renal function. *Clin Exp Nephrol* 14: 558–570, 2010
23. van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, Jennum P, Johnson T, Lose G, Mattiasson A, Robertson G, Weiss J; Standardisation Sub-committee of the International Continence Society: The standardisation of terminology in nocturia: Report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 21: 179–183, 2002
24. JCS Joint Working Group: Guidelines for the clinical use of 24 hour ambulatory blood pressure monitoring (ABPM) (JCS 2010): – Digest version –. *Circ J* 76: 508–519, 2012
25. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H; Japanese Society of Hypertension Committee: The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 32: 3–107, 2009
26. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 53: 982–992, 2009
27. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G: Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens* 5: 93–98, 1987
28. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM: Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 291: 1342–1349, 2004
29. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R: Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 47: 846–853, 2006
30. Bangash F, Agarwal R: Masked hypertension and white-coat hypertension in chronic kidney disease: A meta-analysis. *Clin J Am Soc Nephrol* 4: 656–664, 2009
31. Kanno A, Metoki H, Kikuya M, Terawaki H, Hara A, Hashimoto T, Asayama K, Inoue R, Shishido Y, Nakayama M, Totsune K, Ohkubo T, Imai Y: Usefulness of assessing masked and white-coat hypertension by ambulatory blood pressure monitoring for determining prevalent risk of chronic kidney disease: The Ohasama study. *Hypertens Res* 33: 1192–1198, 2010
32. Kario K, Pickering TG: White-coat hypertension or white-coat hypertension syndrome: Which is accompanied by target organ damage? *Arch Intern Med* 160: 3497–3498, 2000
33. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Tsuji I, Imai Y: White-coat hypertension as a risk factor for the development of home hypertension: The Ohasama study. *Arch Intern Med* 165: 1541–1546, 2005
34. Kario K, Shimada K, Schwartz JE, Matsuo T, Hoshide S, Pickering TG: Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. *J Am Coll Cardiol* 38: 238–245, 2001
35. Pogue V, Rahman M, Lipkowitz M, Toto R, Miller E, Faulkner M, Rostand S, Hiremath L, Sika M, Kendrick C, Hu B, Greene T, Appel L, Phillips RA; African American Study of Kidney Disease and Hypertension Collaborative Research Group: Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension* 53: 20–27, 2009

36. Hänninen MR, Niiranen TJ, Puukka PJ, Johansson J, Jula AM: Prognostic significance of masked and white-coat hypertension in the general population: The Finn-Home Study. *J Hypertens* 30: 705–12, 2012
37. Shimbo D, Newman JD, Schwartz JE: Masked hypertension and prehypertension: Diagnostic overlap and interrelationships with left ventricular mass: The Masked Hypertension Study. *Am J Hypertens* 25: 664–671, 2012
38. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB: Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 131: 564–572, 1999
39. Kario K, Schwartz JE, Pickering TG: Ambulatory physical activity as a determinant of diurnal blood pressure variation. *Hypertension* 34: 685–691, 1999

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ORIGINAL ARTICLE

Efficacy and safety of darbepoetin alfa for anemia in children with chronic kidney disease: a multicenter prospective study in Japan

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Abstract
Background We evaluated the safety and efficacy of darbepoetin alfa (DA), an attractive alternative to recombinant human erythropoietin (rHuEPO) in managing renal anemia, in Japanese children with chronic kidney disease (CKD) on peritoneal dialysis (PD) and hemodialysis (HD), and not on dialysis (ND).
Methods A total of 31 pediatric CKD patients (13 PD, 2 HD, and 16 ND) were enrolled. DA was administered biweekly intravenously (IV) or subcutaneously (SC) for PD or ND patients, and weekly IV for HD patients for 24 weeks. The target Hb was defined as 11.0 to ≤13.0 g/dl. In patients receiving rHuEPO, the initial DA dose was calculated at 1 μg DA for 200 IU rHuEPO. The initial DA dose for naïve patients was determined by body weight, and intended not to exceed 0.5 μg/kg per administration. For some PD or ND patients, the dosing frequency was subsequently changed to once every 4 weeks.
Results Mean Hb values increased from 10.5 ± 1.1 to 11.1 ± 1.1 g/dl after 4 weeks of DA treatment. The target Hb was achieved in all patients, 64.5 % of whom maintained the value at completion of the study. Hb responses were similar between IV and SC. The dosing frequency

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was extended to once every 4 weeks in 37.9 % of PD or ND patients. Eighty-seven adverse events were noted in 27 (87.1 %) of 31 patients, none of which were associated with DA.

Conclusion These results suggest that IV or SC administration of DA is an effective and safe treatment for renal anemia in Japanese children with CKD.

Keywords Anemia · Chronic kidney disease · Darbepoetin alfa · Children

Introduction

Anemia is a common comorbidity in children with chronic kidney disease (CKD) [1, 2]. At all stages of CKD, low hemoglobin (Hb) is associated with increased risk of hospitalization and death, lower cognitive function, increased risk of cardiovascular disease and decreased quality of life [1, 2]. Recombinant human erythropoietin (rHuEPO) has become the standard for treatment of renal anemia in children [1]; however, conventional rHuEPO requires two to three injections per week to maintain target Hb levels (≥11 g/dl) [1]. In contrast, darbepoetin alfa (DA), which has an increased sialic acid carbohydrate content, shows decreased clearance and has a longer serum half-life than rHuEPO, allowing extended dosing intervals [3]. A number of clinical studies have proven DA to be effective and safe in the treatment of renal anemia in adults [4–7]. DA was also shown to be an attractive alternative to rHuEPO in managing anemia in pediatric patients with CKD because of its comparable efficacy and safety profile, as well as its potentially longer dosing intervals [8–11]. However, DA has yet to be approved for the indication of renal anemia in children in Japan. Since only one study describing its efficacy and safety profile in Japanese pediatric CKD patients undergoing peritoneal dialysis (PD) has been reported [12], more data for DA treatment are needed to better treat anemia in pediatric CKD patients in Japan.

Therefore, a multicenter prospective study was conducted at 11 institutions in Japan in order to determine the efficacy and safety of DA in pediatric patients with CKD on PD and hemodialysis (HD), and not on dialysis (ND).

Patients and methods

Study design

This multicenter, open-label, prospective study was conducted at 11 institutions in Japan from October 2010 to March 2012. The study protocol complied with the Declaration of Helsinki and was approved by each local institutional review board (approval number at Tokyo Women's Medical University; 1654). Written informed consent was obtained from patients or their parents before the study-related procedures were performed.

Patients

Japanese pediatric PD, HD, and ND patients aged between 2 and 18 years were eligible for enrollment in this study. Patients with uncontrolled hypertension, cardiac failure, malignancy and/or hematological diseases, serious allergies, and known resistance to rHuEPO were excluded. Patients were also excluded if they were scheduled for living-related kidney transplantation or introduction of dialysis within 24 weeks or if they had been receiving DA therapy before this study. Patients were required to have a baseline Hb concentration of <11.0 g/dl for erythropoiesis-stimulating agent (ESA)-naïve patients (never treated with rHuEPO) and $9 \leq \text{Hb} < 12$ g/dl for patients switched from rHuEPO (previously treated with rHuEPO).

DA administration

The DA used in this study was an investigational new drug (KRN321: Kyowa Hakko Kirin, Co. Ltd.). DA was administered once every 2 weeks intravenously (IV) or subcutaneously (SC) for PD or ND patients, and once weekly IV for HD patients for a period of 24 weeks. The target Hb was determined as 11.0 to ≤13.0 g/dl based on the Japanese anemia therapy guideline [13]. The initial dose of DA for DA-naïve patients was determined by body weight, as shown in Table 1, in reference to the methods used in the previous studies for adult CKD patients [6, 7, 14–16]. An initial dose of DA for DA-naïve patients was intended not to exceed 0.5 μg/kg per dose. In patients switched from rHuEPO, the initial dose was calculated from the prior biweekly dose of rHuEPO according to the following conversion index: 1 μg DA for 200 IU rHuEPO, as previously reported [12]. To achieve and maintain the

Table 1 Initial dose of darbepoetin alpha for ESA-naïve patients

Weight	Dose	
	PD or ND (SC or IV) biweekly (μg)	HD (IV) weekly (μg)
<20 kg	5	5
≥20 to <30 kg	10	5
≥30 to <40 kg	15	10
≥40 to <60 kg	20	15
≥60 kg	30	20

ESA erythropoiesis-stimulating agent, *PD* peritoneal dialysis, *ND* not on dialysis, *HD* hemodialysis, *SC* subcutaneously, *IV* intravenously

target Hb level, the DA dosage was appropriately adjusted, ranging from 5 to 180 μg, not exceeding 3 μg/kg per injection. The dosing frequency was changed from once every 2 weeks to once every 4 weeks for some PD or ND patients whose Hb was controlled between 11.0 and 13.0 g/dl and, accordingly, the DA dosage was doubled in these patients.

Concomitant medication and treatment

Red blood cell transfusions, concomitant rHuEPO, and other anemia-correcting medications were prohibited during this study. Iron was appropriately supplemented to maintain a transferrin saturation (TSAT) of ≥20 % or a serum ferritin level of ≥100 ng/ml.

Evaluation

The efficacy of DA was evaluated by the Hb profiles of the patients, i.e. changes in Hb concentration, changes in DA doses per week, rate of increase in Hb concentration in naïve patients, changes in Hb concentration in patients switched from rHuEPO, and the percentage of patients who maintained the target Hb. Additionally, changes in Hb and changes in DA dose per week were analyzed in some patients whose dosing frequency was switched from once every 2 weeks to once every 4 weeks.

Safety was assessed by monitoring adverse events (both treatment-related and unrelated), laboratory parameters, and vital signs. For safety analysis, the number and percentage of patients who experienced adverse events or adverse drug reactions were tallied by event, coded by MedDRA/J 15.0.

Statistical analysis

For categorical variables, the descriptive statistics include the frequency and percentage. For continuous variables, the descriptive statistics include the number of observations, mean, standard deviation (SD), median, minimum and maximum. Safety parameters were summarized descriptively. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute).

Results

Patient allocation

A patient flowchart is shown in Fig. 1. Of the 34 patients who were enrolled in this study, 31 were eligible for DA therapy. The remaining three were judged to be ineligible because of lower baseline Hb values in two patients

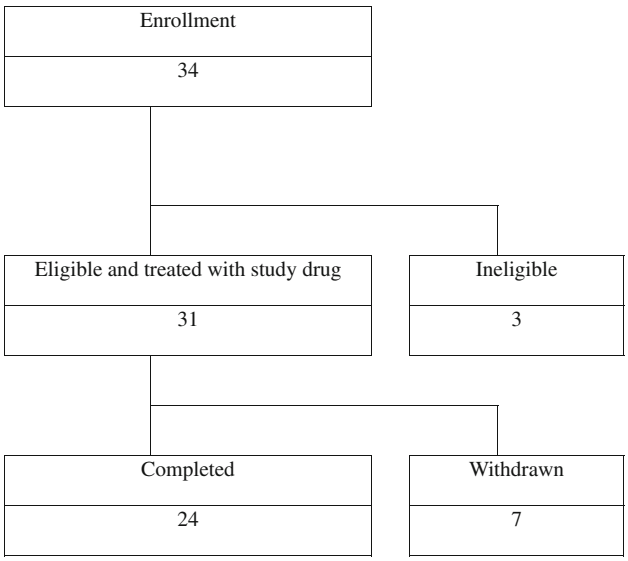

Fig. 1 Patient allocation

receiving rHuEPO and previous DA use in one patient. Of those who were treated with DA, 24 patients completed the study and seven patients withdrew. Of the seven patients who withdrew, three withdrew because of adverse events (sepsis, catheter site infection, and status epileptics), two ND patients withdrew due to initiation of PD, one withdrew due to deceased kidney transplantation, and one withdrew with his consent.

Patient demographics and baseline characteristics

The patients enrolled in the study included 13 PD, 16 ND, and 2HD patients. Patient demographics and baseline characteristics are summarized in Table 2. Males represented 58.1 % of the patient population, and the mean age and mean body weight at the start of DA therapy were 10.4 ± 4.7 years and 30.9 ± 16.8 kg, respectively. The most common underlying CKD disease among the study patients was hypoplastic/dysplastic kidneys (48.3 %). Of the 31 patients, 22 had been treated with rHuEPO, and the mean weekly rHuEPO dose (IU/kg per week) was 112.0 ± 70.0. The mean Hb concentration (g/dl) was 10.5 ± 1.1, and the mean values of ferritin (ng/ml) and TSAT (%) were 100.5 ± 85.9 ng/ml and 32.3 ± 14.5 %, respectively.

There were no differences in gender, age, body weight, underlying disease, Hb concentration, and values of ferritin and TSAT between PD and ND patients; however, all PD patients had been treated with rHuEPO and the weekly rHuEPO doses were lager in PD patients compared to those in ND patients. The mean estimated glomerular filtration rate (eGFR) of ND patients, which were calculated using the Schwarz formula [17], was 21.9 ± 12.8 ml/min/1.73 m^2.

Table 2 Patient characteristics

Demographic and other baseline characteristics	Total ($n = 31$)	PD ($n = 13$)	ND ($n = 16$)	HD ($n = 2$)
Gender, *n* (%)				
Male	18 (58.1)	8 (61.5)	8 (50.0)	2 (100)
Female	13 (41.9)	5 (38.5)	8 (50.0)	0
Age (years)				
Mean ± SD	10.4 ± 4.7	10.2 ± 5.4	10.9 ± 3.9	8.0 ± 8.5
Body weights (kg)				
Mean ± SD	30.9 ± 16.8	28.6 ± 15.3	31.3 ± 15.0	43.1 ± 44.1
Underlying disease, *n* (%)				
Hypoplastic/dysplastic kidney	15 (48.3)	7 (53.8)	7 (43.8)	1 (50.0)
Autosomal recessive polycystic kidney disease	2 (6.5)	1 (7.7)	1 (6.3)	0
Denys–Drash syndrome	2 (6.5)	2 (15.4)	0	0
Focal segmental glomerulosclerosis	2 (6.5)	1 (7.7)	1 (6.3)	0
Others	10 (32.3)	2 (15.4)	7 (43.8)	1 (50.0)
Previous use of rHuEPO				
No	9 (29.0)	0	9 (56.3)	0
Yes	22 (71.0)	13 (100)	7 (43.7)	2 (100)
Weekly rHuEPO (IU/kg/week), mean ± SD	112.0 ± 70.0	142.9 ± 74.1	75.4 ± 40.6	72.5 ± 72.8
Hb concentration (g/dl), mean ± SD	10.5 ± 1.1	10.5 ± 0.9	10.6 ± 1.2	9.5 ± 0.3
Ferritin (ng/ml), mean ± SD	100.5 ± 85.9	107.5 ± 83.2	95.3 ± 89.8	96.8 ± 127.6
TSAT (%), mean ± SD	32.3 ± 14.5	34.4 ± 15.2	31.2 ± 13.6	26.9 ± 25.2

PD peritoneal dialysis, *HD* hemodialysis, *ND* not on dialysis, *TSAT* transferrin saturation ratio, *rHuEPO* recombinant human erythropoietin

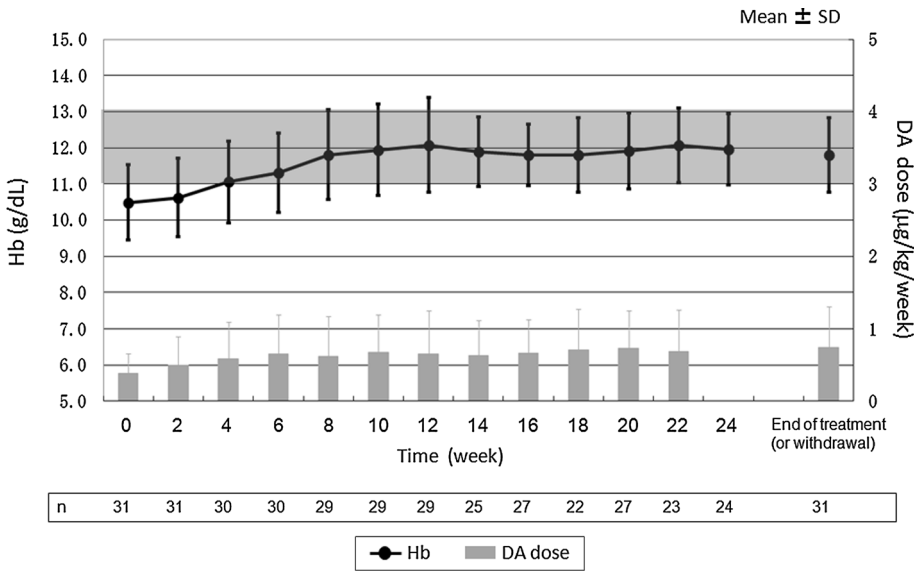

Fig. 2 Changes in hemoglobin (Hb) profiles and darbepoetin alpha (DA) doses in all enrolled patients. The *shaded area* shows the target Hb concentration. *Line* and *bars* indicate Hb levels (g/dl) and DA dose (μg/kg/week), respectively

Efficacy

The changes in Hb profile and DA dose for all patients are shown in Fig. 2. At the start of DA treatment, Hb was 10.5 ± 1.1 g/dl (mean ± SD), while at week 4 it was 11.1 ± 1.1 g/dl, which was above the lower limit of the target Hb (11.0 g/dl). Thereafter, the mean Hb increased further and remained at around 12.0 g/dl throughout the study period. The mean DA dose at final observation in this study was 0.74 ± 0.57 μg/kg per week.

The changes in Hb profile and DA dose were examined between some study sub-sets including PD vs ND, IV vs SC, and different age groups (age < 12 years, age ≥ 12 years). In this analysis, HD patients were excluded since the number of patients ($n = 2$) in this group was not sufficient for analysis, and HD patients received DA

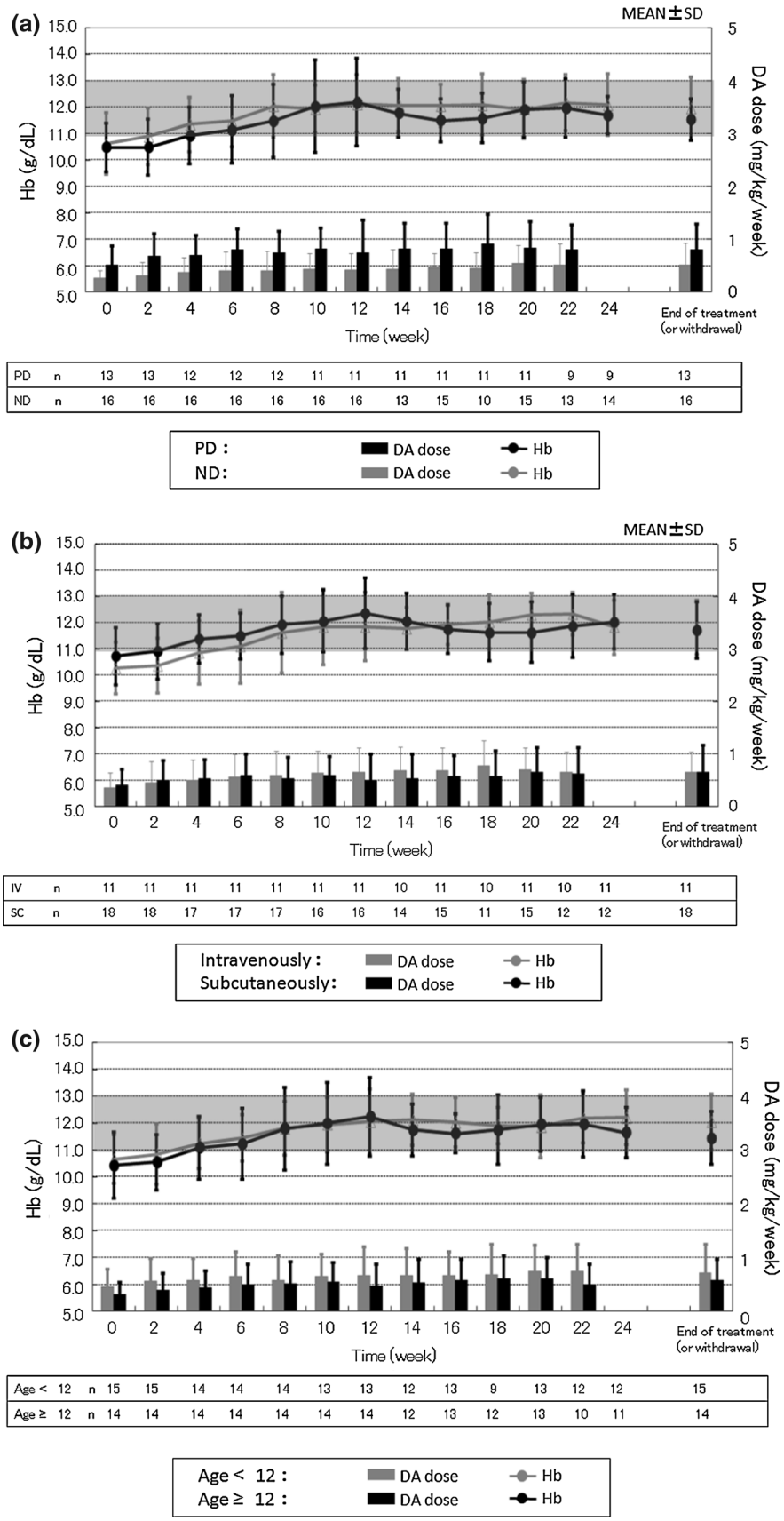

Fig. 3 Changes in hemoglobin (Hb) profiles and darbepoetin alpha (DA) doses in peritoneal dialysis (PD) and not on dialysis (ND) patients. **a** PD vs ND, **b** IV vs SC, **c** age < 12 years vs age ≥ 12 years. *Lines* and *bars* indicate Hb levels (g/dl) and DA dose (μg/kg/week), respectively

intravenously weekly that was different from the rest of the subjects (PD and ND).

Figure 3a shows the changes in Hb profile and DA dose between PD and ND patients. There were no obvious differences in Hb profile and DA dose between the two groups, although the DA dose tended to be higher in PD patients compared to ND patients.

Figure 3b shows that the changes in Hb profile and DA dose between patients administered DA by IV or SC injection. No obvious differences in Hb profile and DA dose were seen between the two groups.

Figure 3c shows the changes in Hb profile and DA dose between different age groups (age $<$ 12 years, age $\geq$ 12 years). There were no obvious differences in Hb profile and DA dose between the two groups, although DA dose tended to be higher in younger pediatric patients.

Figure 4 shows the rate of increase or change in Hb concentration following DA therapy for each patient plotted by individual in some ND or PD patients. In ESA-naïve patients ($n = 9$), the rate of increase in Hb concentration during the 4 weeks following the initiation of DA treatment was 0.26 ± 0.18 g/dl per week. In patients switched from rHuEPO ($n = 15$), the mean change in Hb concentration during the 2 weeks after switching from rHuEPO to DA was 0.07 ± 0.25 g/dl per week.

Figure 5 shows the profiles of the percentage of patients who maintained the target Hb concentration. The proportion of patients whose Hb was within the target ranges gradually increased after commencement of DA treatment. Four weeks after the start of DA therapy, 66.7 % of the patients maintained the target Hb. At the end of treatment (or at withdrawal), 64.5 % of patients were within the target Hb range, 22.6 % were below it, and 12.9 % were above it.

In PD or ND patients, 11 patients (37.9 %) successfully changed their dosing intervals from once every 2 weeks to once every 4 weeks. Figure 6 shows the changes in Hb and DA dose in these 11 patients. The mean Hb value when treatment was changed to once every 4 weeks was 12.1 ± 0.3 g/dl. After the change, Hb remained within the target range and Hb value at the end of treatment was 11.4 ± 0.9 g/dl. The mean doses at the end of treatment (or withdrawal) were 0.35 ± 0.15 μg/kg per week.

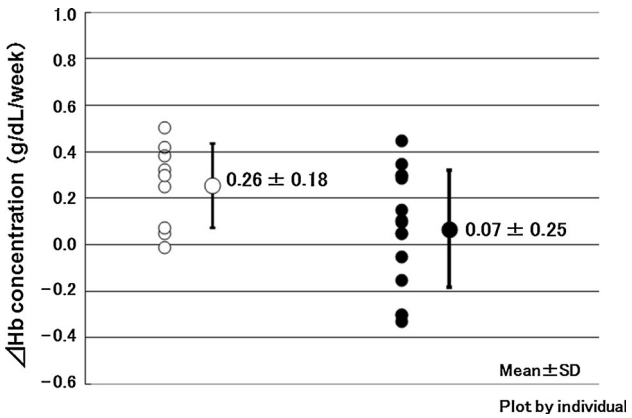

Fig. 4 Rate of increase or change in hemoglobin (Hb) concentration following darbepoetin alpha (DA) therapy. *Open circles* indicate the naïve patients ($n = 9$), and *closed circles* indicate the switched patients ($n = 15$), respectively

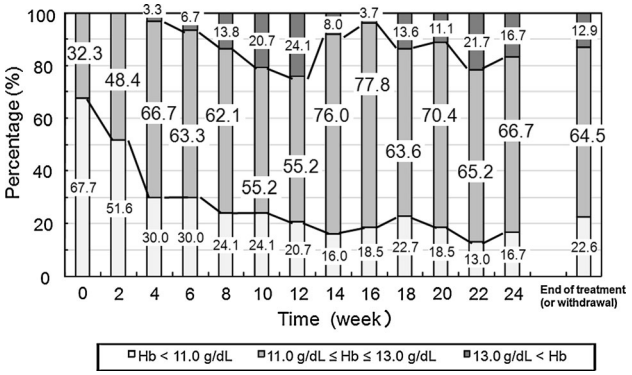

Fig. 5 Change in the percentage of patients who maintained the target hemoglobin (Hb) concentration

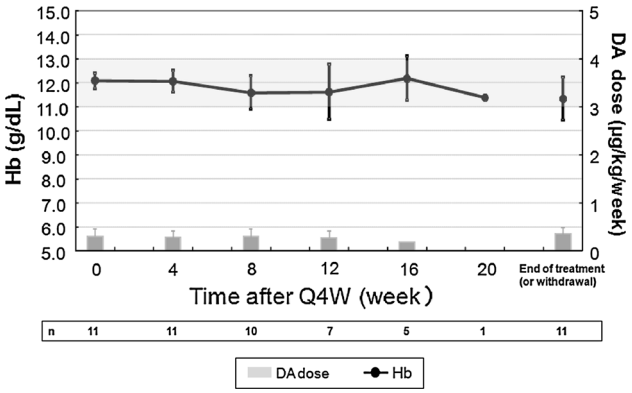

Fig. 6 Changes in hemoglobin (Hb) and darbepoetin alpha (DA) doses after the change to medication once every 4 weeks in peritoneal dialysis (PD) and not on dialysis (ND) patients. The *shaded area* shows the target Hb concentration. *Line* and *bars* indicate Hb levels (g/dl) and DA dose (μg/kg/week), respectively

Safety

Eighty-seven adverse events were noted in 27 (87.1 %) of 31 patients. Adverse events observed in 5 % or more of the patients are shown in Table 3. Among the adverse events, no adverse drug reactions indicating causality with DA treatment were observed. In addition, no clear correlation was found between the incidence of adverse events and Hb values at the time they occurred. No changes in laboratory findings were noted other than in parameters related to erythropoiesis.

Table 3 Adverse events which occurred in at least 5 % of the patients ($n = 31$)

System organ class	Preferred term	*n*	%
Infections and infestations	Nasopharyngitis	13	41.9
	Catheter site infection	4	12.9
	Bronchitis	3	9.7
	Pharyngitis	3	9.7
	Influenza	2	6.5
	Device related infection	2	6.5
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract inflammation	4	12.9
Gastrointestinal disorders	Diarrhea	3	9.7
	Constipation	2	6.5
Metabolism and nutrition disorders	Fluid retention	2	6.5
Renal and urinary disorders	Renal failure chronic	2	6.5

MedDRA/J Version 15.0

Discussion

Recently, it was reported that intravenous administration of DA for the switch from rHuEPO is an effective and safe treatment for renal anemia in Japanese children undergoing PD [12]. However, more data for DA treatment are needed to better treat anemia in pediatric CKD patients in Japan. Therefore, to further examine the efficacy and safety of DA in pediatric CKD patients in Japan, we conducted a multicenter prospective study at 11 institutions, in which eligibility of the study subjects was broadened to include HD or ND patients in addition to PD patients, and ESA-naïve patients were enrolled in addition to those who had been on rHuEPO. We also examined the efficacy and safety of DA administered SC in addition to IV. As a result, a total of 31 pediatric CKD patients, including 13 PD, 2 HD, and 16 ND patients, were enrolled in this study. Also, 9 of 31 patients were naïve to ESA, and 18 patients received DA subcutaneously.

As a limitation of this study, the number of patients enrolled in this study was too small to draw definite conclusions. However, given the annual report from the Japanese Society for Dialysis Therapy indicating that the number of dialysis patients aged less than 15 years was 99 at the end of 2011 [18] and a nationwide survey in Japan indicating that the number of pre-dialysis CKD stage 4 and 5 patients aged less than 15 years was 132 on 1 April 2010 [19], our analysis of the efficacy and safety of DA treatment in Japanese pediatric CKD patients was deemed possible.

A number of clinical studies have proven DA to be effective and safe in the treatment of renal anemia in adults [4–7, 14–16]. Additionally, several publications on the administration of DA in children with CKD have found it to be effective in controlling renal anemia [8–11]. In this study, all pediatric CKD patients achieved the target Hb level, their mean Hb levels remained at approximately 12 g/dl during the study period, and approximately two-thirds of patients maintained the target Hb level at the completion of the study. Therefore, although the number of patients in the present study was limited, these data suggest that DA is effective in Japanese children with CKD.

In this study, efficacy of DA was examined in subgroups (PD vs ND and IV vs SC). Although there were no obvious differences in Hb profile between the PD and ND groups, pediatric PD patients tended to need larger doses of DA compared to pediatric ND patients, which may be associated with the differences in residual kidney functions between the two groups. Also, there were no obvious differences in Hb profile between the IV and SC groups. These results are in line with data from a study in adult patients [14]. Therefore, DA is equally effective regardless of route of administration in pediatric PD and ND patients.

It has been shown that younger children tend to require a higher dose of rHuEPO [2]. Therefore, in this study, changes in Hb profiles and DA doses were examined in PD and ND patients who were divided into two age groups (age < 12 years, age ≥ 12 years) according to the ICH 11 guideline [20]. A higher DA dose appeared to be required to maintain the target Hb levels in younger pediatric patients in this study. This is an important observation that needs clarification with further studies.

The dosing frequency was extended from once every 2 weeks to once every 4 weeks in 11 (37.9 %) out of 29 PD or ND patients. In the study comparing the efficacy of DA and rHuEPO for pediatric CKD patients, DA was administered once weekly in 80 % of patients and once every 2 weeks in 20 % of patients to maintain the targeted Hb levels [10]. The present study also suggested that DA might allow further reduction of injection frequency in pediatric PD or ND patients. Although further study is necessary to verify efficacy of the extended dosing interval, these findings are clinically important for reduced outpatient visits and fewer painful experiences by the affected children, leading to better treatment compliance.

The weekly rate of increase and change in Hb following DA therapy in naïve patients and patients switched from rHuEPO were 0.26 ± 0.18 g/dl per week and 0.07 ± 0.25 g/dl per week, respectively. This rate of increase meets the Japanese anemia therapy guideline [13], which recommends ESA therapy with a rate of Hb increase of 0.5 g/dl/week or less. Thus, an initial dose of DA (less than 0.5 μg/kg per dose) for ESA-naïve patients and the conversion index of 1 μg DA/200 IU rHuEPO for patients switched from rHuEPO appear to have been satisfactory in pediatric CKD patients.

Tolerance to DA was excellent in the present study. Eighty-seven adverse events were noted in the enrolled

patients during the study, but no clear correlation was found between incidence of the adverse events and Hb levels or DA administration at the time of the event occurrence.

Although hypertension is a common adverse event in adult patients [14], only two adverse events related to hypertension were observed in this study. Nonetheless, since hypertension can develop after a rapid rise in Hb concentration [13], it is essential that DA be administered carefully to prevent such a rapid increase.

In conclusion, the results of this study suggest that IV or SC administration of DA is an effective and safe treatment for renal anemia in Japanese children with CKD.

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References

1. Koshy SM, Geary DF. Anemia in children with chronic kidney disease. Pediatr Nephrol. 2008;23:209–19.
2. Atkinson MA, Furth SL. Anemia in children with chronic kidney disease. Nat Rev Nephrol. 2011;7:635–41.
3. Gary L, Kale AS, Warady BA, Jabs K, Bunchman TE, Heatherington A, et al. Pharmacokinetics of darbepoetin alfa in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2002;17:933–7.
4. Jadoul M, Vanrenterghem Y, Foret M, Walker R, Gray SJ. Darbepoetin alfa administered once monthly maintains hemoglobin levels in stable dialysis patients. Nephrol Dial Transplant. 2004;19:898–903.
5. Brunkhorst R, Bommer J, Braum J, Hagg-Weber M, Gill C, Wagner J, et al. Darbepoetin alfa effectively maintains hemoglobin concentrations at extended dose intervals relative to intravenous or subcutaneous recombinant human erythropoietin in dialysis patients. Nephrol Dial Transplant. 2004;19:1224–30.
6. Hiramatsu M, Kubota M, Iwasaki M, Akizawa T, Kosikawa S, the KRN321 A09 Study Group. Darbepoetin alfa (KRN321) administered intravenously once monthly maintains hemoglobin levels in peritoneal dialysis patients. Ther Apher Dial. 2008;12:19–27.
7. Kubota M, Hiramatsu M, Yamakawa M, Fukuhara S, Morita S, Iwasaki M, et al. Darbepoetin alfa (KRN321) is safe and effective when administered subcutaneously once every 2 or 4 weeks to patients on peritoneal dialysis in Japan. Clin Exp Nephrol. 2011;15:884–92.
8. De Palo T, Giordano M, Palumbo F, Bellantuono R, Messina G, Colella V, et al. Clinical experience with darbepoetin alfa (NESP) in children undergoing hemodialysis. Pediatr Nephrol. 2004;19:337–40.
9. Geary DF, Keating LE, Vigneux A, Stephens D, Hebert D, Harvey EA. Darbepoetin alfa (Aranesp^{TM}) in children with chronic renal failure. Kidney Int. 2005;68:1759–65.
10. Warady BA, Arar MY, Lerner G, Nakanishi AM, Stehman-Breen C. Darbepoetin alfa for the treatment of anemia in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2006;21:1144–52.
11. Andre JL, Deschenes G, Boudailliez B, Broux F, Fischbach M, Gagnadoux M-F, et al. Darbepoetin, effective treatment of anaemia in paediatric patients with chronic renal failure. Pediatr Nephrol. 2007;22:708–14.
12. Hattori M, Matsunaga A, Akioka Y, Fujinaga S, Nagai T, Uemura O, et al. Darbepoetin alfa for the treatment of anemia in children undergoing peritoneal dialysis: a multicenter prospective study in Japan. Clin Exp Nephrol. 2013;17:582–8.
13. 2008 Japanese Society for Dialysis Therapy guideline for renal anemia in chronic kidney disease. J Jpn Soc Dial Ther. 2008;41:661–716.
14. Akizawa T, Gejyo F, Suzuki M, Akiba T, Iino Y, Saito A, et al. Efficacy and safety of subcutaneous or intravenous administration of KRN321 (darbepoetin alfa) in patients with chronic kidney disease not on dialysis or those on peritoneal dialysis. Kidney Dial. 2011;71:887–98 (in Japanese).
15. Akizawa T, Ishida H, Matsui N, Iizuka T, Asano Y, Homma S, et al. Dose-evaluation study of intravenous KRN321 (darbepoetin alfa) in EPO-naïve hemodialysis patients in Japan. Kidney Dial. 2010;68:423–35 (in Japanese).
16. Nishi S, Gejyo F, Shigematsu T, Iino Y, Hosoya T, Shoji T et al. The validity of the transition from rHuEPO to KRN321 in chronic kidney disease (CKD) patients not on dialysis. Kidney Dial. 2010;68:284–94 (in Japanese).
17. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34:571–90.
18. An overview of dialysis treatment in Japan (as of Dec. 31, 2011). J Jpn Soc Dial Ther. 2013;46:1–76 (in Japanese).
19. Ishikura K, Uemura O, Ito S, Wada N, Hattori M, Ohashi Y et al. Pre-dialysis chronic kidney disease in children: results of a nationwide survey in Japan. Nephrol Dial Transplant. 2013 (in press).
20. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf. Accessed 14 June 2013.