Effects of Erythropoietin-Stimulating Agents on Blood Pressure in Patients with Non-Dialysis CKD and Renal Anemia

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Keywords

Blood pressure · Chronic kidney disease · Erythropoietin-stimulating agent · Renal anemia · Japanese patients

Abstract

Introduction: Erythropoietin-stimulating agents (ESAs) are used to treat renal anemia in patients with non-dialysis CKD, but this can lead to increases in blood pressure (BP). **Objective:** We investigated the effects of continuous erythropoietin receptor activator (CERA) and darbepoetin alfa (DA) on office/ambulatory BP in 36 patients with non-dialysis CKD and renal anemia who did not receive ESA treatment. **Methods:** Participants were randomly assigned to CERA or DA, and received ESA treatment for 24 weeks. ESA doses were adjusted to maintain hemoglobin (Hb) at 10–12 g/dL. Primary outcomes were office/ambulatory BP after 24 weeks of ESA treatment. Hb levels were within the target range at 24 weeks. **Results:** Office/ambulatory BP, renal function, and other parameters were not significantly different between groups. However, we could not exclude the possibility that differences may exist because our sample size was small. Therefore, we also performed analysis of all of the data that were compiled from the groups of per-protocol population.

Although office/ambulatory BP profiles had not worsened after 24 weeks of ESA treatment, more than half of the patients required an increase in the antihypertensive agent dose. **Conclusions:** CERA and DA may have similar effects on BP profiles in patients with non-dialysis CKD and renal anemia. ESA treatment often requires increases in the doses of antihypertensive agents.

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Introduction

Renal anemia is the primary complication of non-dialysis CKD. Renal anemia occurs because of a decrease in erythropoietin production associated with a decline in renal function and is a risk factor of cardiovascular disease (CVD) and death [1, 2]. The effects of therapeutic inter-

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The study was registered at the Clinical Trial Registry of University Hospital Information Network (UMIN Clinical Trials Registry: UMIN000008505).

Fig. 1. a Study design. **b** Patient populations and disposition. CERA, continuous erythropoietin receptor activator; DA, darbepoetin alfa; Hb, hemoglobin.

vention with erythropoietin-stimulating agents (ESAs) in patients with non-dialysis CKD and renal anemia on preventing progression of CKD and CVD events remain to be determined. However, ESAs are widely used in clinical practice to improve quality of life and avoid RBC transfusions [3–5].

Recently, the long-acting ESAs epoetin beta pegol (continuous erythropoietin receptor activator [CERA]) and darbepoetin alfa (DA) have been widely used for treating renal anemia in patients with non-dialysis CKD. However, an increase in blood pressure (BP) has been reported to be an adverse event of CERA and DA treatment [3, 6, 7]. Several mechanisms have been considered in the pathogenesis of ESA-induced hypertension. These include an increase in RBC mass and viscosity associated with an improvement of renal anemia. Additionally, the vascular endothelium can be stimulated, resulting in increased circulating endothelin levels [8].

Rigorous BP control has an important role in managing and treating non-dialysis CKD to slow the progression of CKD and lower the risk of CVD [9, 10]. Therefore, investigating the effects of ESA treatment on BP is important. Because of the differences in pharmacologic mechanisms of action between CERA and DA, they have different half-lives. CERA has a longer half-life of approximately 130 h than the half-life of DA, which is only 24–

48 h [11, 12]. Therefore, several studies have compared CERA with DA [6, 7, 13]. However, little is known about the differences in BP control between CERA and DA.

With regard to BP management, accumulating evidence supports that “out-of-office” BP, particularly the ambulatory BP profile, is important for appropriate diagnosis of hypertension and estimation of BP control. Ambulatory BP monitoring (ABPM) is a better tool for predicting the risk of CVD, progression of CKD, ESRD, and death than office-based pressure in patients with CKD [14, 15].

In the present study, we investigated the effects of treatment with two long-acting ESAs on office and ambulatory BP profiles of patients with non-dialysis CKD.

Materials and Methods

Study Design

This was a randomized, open-label, parallel-group, controlled study and was conducted at the outpatient clinic of the Department of Internal Medicine, Yokohama City University Hospital (Yokohama, Japan). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committees of Yokohama City University Hospital (institutional review board approval number B120510011).

Study Participants

Patients with stage G3–G5 CKD who were not on dialysis with renal anemia and were not receiving treatment with ESAs were eligible for the study if they were aged ≥ 20 years, they had hemoglobin (Hb) levels < 11 g/dL, and their transferrin saturation was $\geq 20\%$. Because adults are defined as those aged 20 years or older in Japan, we adopted this definition as an inclusion criterion. Hb levels for recruitment were also determined from previous reports [3, 16]. The exclusion criteria included the following: previous treatment with any ESAs within 12 weeks before the screening period; overt gastrointestinal bleeding or RBC transfusions within 16 weeks before screening; a nonrenal cause of anemia that was evaluated by stool occult blood, saturation of transferrin, folic acid level, vitamin B12 level, and the presence of drugs that could interfere with erythropoiesis; severe hypertension (office diastolic BP ≥ 100 mm Hg); congestive heart failure (New York Heart Association functional class III or IV); women who were nursing or pregnant; and a history of myocardial infarction or stroke and malignancy.

Study Treatment

The eligible patients were randomized to receive subcutaneous CERA or DA injection therapy (Fig. 1a). The doses of ESAs were adjusted to maintain Hb levels within the target range of 10–12 g/dL during the 24 weeks of active treatment. Monitoring of Hb levels was performed roughly every 4 weeks. In both groups, antihypertensive therapy was aimed at achieving the office BP goal (BP $< 130/80$ mm Hg). These treatments were based on approved treatment recommendations from the Clinical Practice Guidebook for Diagnosis and Treatment of CKD 2012 [17].

Measurements of Office BP, Brachial-Ankle Pulse Wave Velocity, and ABPM

Office BP was measured in a sitting position using a calibrated standard mercury sphygmomanometer and the recommended cuff size immediately before ESA administration. Two measurements were taken at 1- to 2-min intervals, and their average value was regarded as office BP. Ambulatory BP and heart rate (HR) were monitored every 30 min with a fully automated device (TM-2425; A&D, Tokyo, Japan), as described previously [18]. ABPM was performed before and 24 weeks after the initial ESA administration. Brachial-ankle pulse wave velocity (baPWV) values were determined by a PP analyzer (model: BP-203-RPE2; Omron Healthcare, Kyoto, Japan), as described previously [18, 19]. Pulse volume waveforms were recorded with sensors placed over the right brachial artery and both tibial arteries. The baPWV values obtained by this method are correlated with aortic PWV as determined by the catheter method [20]. ABPM was repeated in patients who had $> 20\%$ of missing values, a $> 30\%$ error rate for the total readings, or values missing for more than 2 consecutive hours. The following readings were omitted because of technical artifacts: systolic BP > 250 mm Hg or < 70 mm Hg, diastolic BP > 130 mm Hg or < 30 mm Hg, pulse pressure > 160 mm Hg or < 20 mm Hg, and systolic differences > 60 mm Hg or diastolic differences > 30 mm Hg compared with the immediately preceding or subsequent values. The patients were instructed to fill out a diary to record the times of sleeping, rising, and other daytime activities. Therefore, the terms “daytime” and “nighttime” in the present study reflect the average period during which the subjects were awake/upright and asleep/supine, respectively. Short-term BP

variability was based on the coefficients of variation of the BP values obtained from ABPM. This variability was defined as the within-subject standard deviation of all of the systolic and diastolic readings at 30-min intervals divided by the mean BP during the course of the measurement periods [18, 19].

Laboratory Measurements and Erythropoietin Resistance Index

Blood and urine sampling was performed in the fasted state at baseline and after 24 weeks of treatment. The parameters were determined by routine methods in the Department of Clinical Chemistry, Yokohama City University School Hospital.

Outcomes

The primary end points were comparison of office BP and ambulatory BP profiles, including short-term BP variability after 24 weeks of ESA treatment, between the CERA group and the DA group. Comparison of renal function, effect of ESAs on maintenance of Hb levels, the number of patients who required dialysis, and the number of CVD events and other adverse events during the treatment period between the CERA and DA groups were assessed as secondary endpoints.

Statistical Analysis

The data are shown as mean $\pm$ standard deviation, as percentage, or in milligrams. Differences between the CERA and DA groups were assessed by the unpaired *t* test for continuous variables and the χ^2 test for qualitative variables. Differences between baseline and 24 weeks of ESA treatment were assessed by the paired *t* test. SPSS software (version 22.0, Chicago, IL, USA) was used for statistical analysis. A *p* value < 0.05 was considered statistically significant.

Results

Study Population

Thirty-six eligible patients with renal anemia were enrolled and were randomly assigned to the CERA group ($n = 18$) or the DA group ($n = 18$) (Fig. 1b). Of these, 33 patients received at least one dose of ESAs, while 1 patient who was assigned to the CERA group did not receive treatment because of elevated Hb levels without drug therapy. One patient who was assigned to the DA group initiated hemodialysis because of hyperkalemia before ESA treatment. Another patient who was assigned to the DA group withdrew consent before ESA treatment. Six patients withdrew from the study during the treatment period, with three in the CERA group and three in the DA group. One patient in each group initiated dialysis. Two patients in the CERA group withdrew consent. In the DA group, 1 patient was diagnosed with gastrointestinal malignancy and 1 patient had a stroke event. The baseline characteristics of the patients are shown in Table 1. The mean age of participants was 74.0

Table 1. Baseline characteristics

	CERA <i>n</i> = 18	DA <i>n</i> = 18	<i>p</i> value
Gender (male/female)	12/6	7/11	0.095
Age, years	72.1±9.4	75.9±8.0	0.197
BMI, kg/m ²	24.1±4.3	22.3±4.0	0.218
Office BP			
Systolic BP, mm Hg	134.4±18.2	140.1±14.4	0.313
Diastolic BP, mm Hg	76.4±10.8	65.7±12.3	0.009
HR, beats/min	71.4±9.5	73.7±12.3	0.527
Cause of CKD, <i>n</i> (%)			0.691
Diabetic nephropathy	6 (33.3)	5 (27.8)	
Nephrosclerosis	4 (22.2)	7 (38.9)	
Chronic glomerulonephritis	2 (11.1)	1 (5.6)	
Polycystic kidney disease	1 (5.6)	0 (0)	
Others	5 (27.8)	5 (27.8)	
Risk factors for cardiovascular events, <i>n</i> (%)			
Hypertension	17 (94.4)	18 (100.0)	0.500
Dyslipidemia	11 (61.1)	12 (66.7)	0.729
Diabetes mellitus	7 (38.9)	7 (38.9)	1.000
CVD	4 (22.2)	4 (22.2)	0.655
Current smoking	2 (11.1)	2 (11.1)	0.699
Antihypertensive agents, <i>n</i> (%)			
Direct renin inhibitor	0 (0)	2 (11.1)	0.243
ARB	12 (66.7)	13 (72.2)	0.717
ACE inhibitor	3 (16.7)	1 (5.6)	0.301
CCB	13 (72.2)	17 (94.4)	0.089
Loop diuretics	4 (22.2)	8 (44.4)	0.157
Thiazide diuretics	0 (0)	2 (11.1)	0.243
Thiazide-like diuretics	0 (0)	1 (5.6)	0.500
Potassium-sparing diuretics	0 (0)	1 (5.6)	0.500
β-Blocker	7 (38.9)	8 (44.4)	0.735
α-Blocker	5 (27.8)	2 (11.1)	0.201
Iron supplementation, <i>n</i> (%)	7 (38.9)	7 (38.9)	1.000
Serum Cr, mg/dL	2.6±1.0	2.9±1.4	0.469
eGFR, mL/min/1.73 m ²	20.3±6.3	20.7±14.0	0.930
Urinary protein/Cr ratio, g/g Cr	2.7±3.5	1.8±2.5	0.368
Hb, g/dL	10.0±0.6	9.4±0.7	0.009
Hb ≥10 g/dL, <i>n</i> (%)	7 (38.9)	7 (38.9)	1.000
Hematocrit, %	29.6±1.9	28.0±1.9	0.017
Ferritin, ng/mL	141.5±128.2	265.4±202.8	0.035
Transferrin saturation, %	28.0±7.7	32.9±14.7	0.237

Values are means ± SD or number (percentage). BP, blood pressure; HR, heart rate; CVD, cardiovascular disease; Hb, hemoglobin; ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; CERA, continuous erythropoietin receptor activator; DA, darbepoetin alfa.

± 8.8 years. In total, 27 participants were at least 70 years old. The mean BMI and estimated glomerular filtration rate were 23.2 ± 4.5 kg/m² and 20.5 ± 10.7 mL/min/1.73 m², respectively. Most participants had hypertension (97.2%). There were several significant differences in the baseline characteristics between the CERA and DA

groups. First, the mean Hb level was higher in the CERA group than in the DA group (10.0 ± 0.6 vs. 9.4 ± 0.7 g/dL, $p = 0.009$; Table 1). Second, the mean office diastolic BP was higher in the CERA group than in the DA group (76.4 ± 10.8 vs. 65.7 ± 12.3 mm Hg, $p = 0.009$; Table 1). Third, the mean ferritin level was lower in the CERA

Table 2. Comparison of ESA doses and frequencies of ESA administration in the CERA and DA groups

	CERA <i>n</i> = 14	DA <i>n</i> = 13	<i>p</i> value
ESA administrations/24 weeks, <i>n</i>	5.1±1.5	5.2±0.9	0.750
Total dose/24 weeks, µg	316.1±157.4	459.2±256.4	0.090

Values are means ± SD. ESA, erythropoiesis-stimulating agent; CERA, continuous erythropoietin receptor activator; DA, darbepoetin alfa.

Table 3. Comparison of BMI, office BP, vascular function, increase in antihypertensive agents, and laboratory measurements in the CERA and DA groups after ESA treatment for 24 weeks

	CERA <i>n</i> = 14	DA <i>n</i> = 13	<i>p</i> value
Office BP			
Systolic BP, mm Hg	131.6±16.4	145.7±22.0	0.069
Diastolic BP, mm Hg	76.3±8.6	67.8±13.9	0.072
HR, beats/min	75.0±10.0	73.7±9.8	0.734
ABI	1.19±0.04	1.13±0.10	0.111
BaPWV	1,879±345	1,911±498	0.846
Increase in antihypertensive agents, <i>n</i> (%)	6 (42.9)	9 (69.2)	0.252
Serum Cr, mg/dL	3.0±1.2	3.0±1.7	0.916
eGFR, mL/min/1.73 m ²	17.9±6.3	20.1±14.7	0.614
Urinary protein/Cr ratio, g/g Cr	3.0±3.5	1.8±1.9	0.300
Hb, g/dL	10.7±0.6	10.5±0.7	0.420
Hematocrit, %	32.0±1.9	31.5±2.2	0.499
Ferritin, ng/mL	142.4±114.0	202.1±151.3	0.255
Transferrin saturation, %	30.9±8.3	33.4±14.0	0.589

Values are means ± SD or number (percentage). BP, blood pressure; HR, heart rate; ABI, ankle-brachial pressure index; BaPWV, brachial-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; CERA, continuous erythropoietin receptor activator; DA, darbepoetin alfa; ESA, erythropoietin-stimulating agent.

group than in the DA group (141.5 ± 128.2 vs. 265.4 ± 202.8 ng/mL, $p = 0.035$; Table 1). With regard to causes of CKD and risk factors for cardiovascular events, the characteristics were comparable between the CERA and DA groups.

Doses and Frequencies of ESAs over 24 Weeks of ESA Treatment and Efficacy for Maintaining Hb Levels

The doses and frequencies of ESA administration over 24 weeks of ESA treatment are shown in Table 2. They were comparable in the CERA and DA groups. One patient in the CERA group received ESA treatment only twice within the initial 8 weeks. Other patients received the treatment more than three times. In most patients, ESAs were administered every 4–5 weeks. Hb levels after 24 weeks of ESA treatment were comparable between the

CERA and DA groups (10.7 ± 0.6 vs. 10.5 ± 0.7 g/dL, $p = 0.420$; Table 3), and Hb levels in both groups were within the target range. Additionally, the iron status (ferritin and transferrin saturation levels) was comparable between the two groups (Table 3).

Comparison of Office BP, Vascular Function, and Increase in Antihypertensive Agents and Renal Function in the CERA and DA Groups after 24 Weeks of ESA Treatment

Office BP, HR, and vascular function parameters, such as the ankle-brachial pressure index and baPWV, after 24 weeks of ESA treatment are shown in Table 3. There were no significant differences in these parameters between the CERA and DA groups. Additionally, renal function, including serum Cr levels, the estimated glomerular filtra-

Table 4. Comparison of ambulatory BP profile in the CERA group and the DA group after the 24 weeks of ESA treatment

	CERA <i>n</i> = 14	DA <i>n</i> = 13	<i>p</i> value
<i>Ambulatory BP and HR</i>			
Daytime			
Systolic BP, mm Hg			
Baseline	144.3±19.1	141.2±16.4	0.653
After treatment	134.9±14.9	141.0±15.2	0.305
Diastolic BP, mm Hg			
Baseline	83.1±12.0	75.9±9.1	0.088
After treatment	79.0±9.0	73.5±8.3	0.114
HR, beats/min			
Baseline	75.2±8.2	73.9±10.9	0.713
After treatment	77.7±12.3	72.9±10.0	0.271
Nighttime			
Systolic BP, mm Hg			
Baseline	132.6±20.0	129.9±14.0	0.688
After treatment	125.6±20.6	128.5±14.3	0.677
Diastolic BP, mm Hg			
Baseline	75.1±12.7	69.5±9.7	0.211
After treatment	71.9±10.7	67.5±8.2	0.245
HR, beats/min			
Baseline	62.6±7.5	65.6±10.8	0.420
After treatment	67.6±11.4	63.5±8.3	0.298
<i>Ambulatory BP and HR variability</i>			
Daytime			
Systolic BP variability, %			
Baseline	12.1±3.7	11.7±3.1	0.757
After treatment	12.5±5.0	13.1±3.7	0.714
Diastolic BP variability, %			
Baseline	15.3±6.7	14.6±5.3	0.751
After treatment	18.2±8.4	16.0±5.6	0.437
HR variability, %			
Baseline	14.8±4.6	12.7±4.0	0.220
After treatment	13.0±4.3	13.1±5.5	0.940
Nighttime			
Systolic BP variability, %			
Baseline	10.8±4.9	11.9±3.9	0.549
After treatment	8.4±2.9	10.7±2.9	0.058
Diastolic BP variability, %			
Baseline	12.9±5.6	13.7±5.0	0.693
After treatment	12.4±6.6	11.6±3.4	0.689
HR variability, %			
Baseline	8.3±4.8	6.5±3.2	0.241
After treatment	6.7±2.3	6.3±2.8	0.691

Values are means ± SD. BP, blood pressure; HR, heart rate; CERA, continuous erythropoietin receptor activator; DA, darbepoietin alfa; ESA, erythropoietin-stimulating agent.

tion rate, and the urinary protein/Cr ratio, was comparable in the two groups. Although some patients required an increase in antihypertensive agents in the CERA and DA groups, the rate of these patients was comparable between the two groups (*n* [%], 6 [42.9] vs. 9 [69.2], *p* = 0.252; Table 3).

Comparison of the Ambulatory BP Profile in the CERA and DA Groups after 24 Weeks of ESA Treatment

The ambulatory BP profile at baseline and after 24 weeks of ESA treatment in the CERA and DA groups is shown in Table 4. There were no significant differences in daytime and nighttime systolic/diastolic BP between the two groups. There were also no significant differences in daytime and nighttime systolic/diastolic BP variability between the two groups.

Comparison of the Office BP and Ambulatory BP Profiles at Baseline and after 24 Weeks of ESA Treatment

Because we found some differences in baseline characteristics (e.g., Hb levels and office diastolic BP) between the two groups, we performed a before-and-after comparative analysis of 24-week ESA treatment in each group. In the CERA group, the daytime ambulatory systolic BP was significantly decreased after 24 weeks of ESA treatment compared with the baseline value (144.3 ± 19.1 vs. 134.9 ± 14.9 mm Hg, *p* = 0.011; Table 5). The daytime ambulatory diastolic BP also tended to decrease in the CERA group after 24 weeks of ESA treatment versus baseline (83.1 ± 12.0 vs. 79.0 ± 9.0 mm Hg, *p* = 0.057; Table 5). In addition, the nighttime ambulatory HR in the CERA group was significantly increased after 24 weeks of ESA treatment compared with the baseline value (62.3 ± 7.5 vs. 67.6 ± 11.4 beats/min, *p* = 0.017; Table 5). On the other hand, there were no differences in the office and ambulatory BP profiles between baseline and after 24 weeks of ESA treatment in the DA group. In addition, we performed analysis of all of the data that were compiled from the groups of per-protocol population to examine the effects of ESA treatment on the office and ambulatory BP profiles. Comparison of the office and ambulatory BP profiles of 27 patients who received 24-week ESA treatment between baseline and after 24 weeks of treatment is shown in Table 5. There were no significant differences in the office BP profile between baseline and after 24 weeks of ESA treatment. However, the daytime ambulatory diastolic BP was significantly decreased after 24 weeks of ESA treatment compared with baseline (79.6 ±

Table 5. Comparison of office BP and ambulatory BP profiles in the baseline and after 24 weeks of ESA treatment

	CERA			DA			Total		
	baseline <i>n</i> = 14	after treatment <i>n</i> = 14	<i>p</i> value	baseline <i>n</i> = 13	after treatment <i>n</i> = 13	<i>p</i> value	baseline <i>n</i> = 27	after treatment <i>n</i> = 27	<i>p</i> value
<i>Office BP</i>									
Systolic BP, mm Hg	132.7±17.9	131.6±16.4	0.711	140.9±14.8	145.7±22.0	0.528	136.7±16.7	138.4±20.2	0.660
Diastolic BP, mm Hg	76.1±8.7	76.3±8.6	0.937	69.1±11.2	67.8±13.9	0.740	72.7±10.4	72.2±12.0	0.786
HR, beats/min	73.9±8.9	75.0±10.0	0.541	75.4±11.4	73.7±9.8	0.370	74.6±10.0	74.4±9.7	0.837
<i>Ambulatory BP and HR</i>									
<i>Daytime</i>									
Systolic BP, mm Hg	144.3±19.1	134.9±14.9	0.011	141.2±16.4	141.0±15.2	0.973	142.8±17.6	137.9±15.1	0.092
Diastolic BP, mm Hg	83.1±12.0	79.0±9.0	0.057	75.9±9.1	73.5±8.3	0.262	79.6±11.1	76.4±8.9	0.026
HR, beats/min	75.2±8.2	77.7±12.3	0.249	73.9±10.9	72.9±10.0	0.504	74.6±9.4	75.4±11.3	0.537
<i>Nighttime</i>									
Systolic BP, mm Hg	132.6±20.0	125.6±20.6	0.214	129.9±14.0	128.5±14.3	0.689	131.3±17.1	127.0±17.5	0.193
Diastolic BP, mm Hg	75.1±12.7	71.9±10.7	0.321	69.5±9.7	67.5±8.2	0.403	72.4±11.5	69.7±9.7	0.184
HR, beats/min	62.6±7.5	67.6±11.4	0.017	65.6±10.8	63.5±8.3	0.150	64.1±9.2	65.7±10.1	0.239
<i>Ambulatory BP and HR variability</i>									
<i>Daytime</i>									
Systolic BP variability, %	12.1±3.7	12.5±5.0	0.607	11.7±3.1	13.1±3.7	0.145	11.9±3.4	12.8±4.4	0.139
Diastolic BP variability, %	15.3±6.7	18.2±8.4	0.126	14.6±5.3	16.0±5.6	0.477	15.0±5.9	17.1±7.1	0.102
HR variability, %	14.8±4.6	13.0±4.3	0.243	12.7±4.0	13.1±5.5	0.763	13.8±4.4	13.1±4.8	0.447
<i>Nighttime</i>									
Systolic BP variability, %	10.8±4.9	8.4±2.9	0.166	11.9±3.9	10.7±2.9	0.094	11.3±4.4	9.5±3.1	0.052
Diastolic BP variability, %	12.9±5.6	12.4±6.6	0.842	13.7±5.0	11.6±3.4	0.259	13.3±5.2	12.0±5.2	0.405
HR variability, %	8.3±4.8	6.7±2.3	0.193	6.5±3.2	6.3±2.8	0.914	7.4±4.1	6.5±2.5	0.282

Values are means ± SD. BP, blood pressure; HR, heart rate; CERA, continuous erythropoietin receptor activator; DA, darbepoetin alfa; ESA, erythropoietin-stimulating agent.

11.1 vs. 76.4 ± 8.9 mm Hg, $p = 0.026$; Table 5). There was also a trend toward a decrease in nighttime ambulatory systolic BP variability after 24 weeks of ESA treatment compared with baseline (11.3% ± 4.4 vs. 9.5% ± 3.1%, $p = 0.052$; Table 5), but this difference did not reach significance.

Discussion

This is the first study to evaluate BP using ABPM during ESA induction. The present study was designed as a randomized, controlled trial to compare the effects of initiating CERA and DA, two main long-acting ESAs, on the ambulatory BP profile of patients with non-dialysis CKD. The findings in this study suggested that CERA and DA had similar effects on office BP; vascular function parameters; anemia-related parameters, including iron status (ferritin and transferrin saturation); renal function; and

the ambulatory BP profile after 24 weeks of ESA treatment (Tables 3, 4). However, because of the limited number of patients in the per-protocol population and significant differences in Hb levels and office diastolic BP between the CERA and DA groups at baseline, we cannot unequivocally conclude that CERA and DA have identical effects on the BP profile of patients with non-dialysis CKD.

Dialysis was initiated before the end of 24 weeks in 1 patient from each of the CERA and DA groups, both of whom were progressive cases classified as CKD stage 5 at baseline. CVD events occurred in 1 patient in the DA group (cerebral infarct). However, these events occurred after an initial dosage at the initial administration, and no notable changes in BP were confirmed before onset. A recent systematic review did not show any differences between CERA and DA regarding their effects on the overall death rate and incidence of CVD events [21]. Our results are not inconsistent with previous reports. However,

patient number was insufficient to compare the CVD event rates between the CERA and DA groups.

With regard to ESA dosage, the frequency of ESA administration up to 24 weeks in the CERA and DA groups was equal at approximately once a month. In addition, the total ESA dose was also comparable between the CERA and DA groups (Table 2). Similarly, a previous Japanese study, which compared administering CERA and DA to patients with non-dialysis CKD every 4 weeks, showed equivalent efficacy in maintaining Hb levels with a similar dose conversion ratio at these ESAs (CERA:DA = 1:1.05) [22]. Inhibition of the renin-angiotensin system is involved in anemia progression [23]. In this study, more than 80% of subjects in both groups were taking any renin-angiotensin system inhibitor (i.e., direct renin inhibitor, angiotensin II receptor blocker, and angiotensin-converting enzyme inhibitor). Therefore, these antihypertensive agents may have affected the achieved Hb level and ESA dose.

There were significant differences in Hb levels and office diastolic BP between the CERA and DA groups at baseline. Therefore, we performed a before-and-after comparative analysis of 24-week ESA treatment. In the CERA group, the daytime ambulatory systolic BP was decreased after 24 weeks of ESA treatment compared with the baseline value. Similarly, in a compiled analysis of all of the data from the two groups, the daytime ambulatory diastolic BP was decreased after 24 weeks of ESA treatment compared with the baseline value. These results suggest that BP could be lowered toward the target value. More importantly, the dose of antihypertensive agents was increased in more than half of the patients after 24 weeks of ESA treatment (Table 3). This finding suggests that ESA treatment increased BP or compromised BP control in the present study.

This study had several limitations. First, our study had a small sample size. Second, the Hb target range in this study was based on approved treatment recommendations from the 2012 CKD practice guide at the start of this study. In the latest CKD practice guideline in Japan, the Hb target range was increased from 10–12 g/dL to 11–13 g/dL based on the improvement in renal prognosis [24]. Thus, the achieved Hb values in this study were lower than this recommended range. Third, although the effect of the dose of ESAs on BP is extremely important, patients with poor responses to different types of ESAs were not included in the present study. Fourth, this is a single-center study. Fifth, many patients' residual renal function is maintained because of the initiation phase of ESA treatment. Therefore, BP may have increased if the sample had included a higher proportion of patients with progressive CKD requiring a high dose of ESA [25, 26].

Conclusion

In this pilot study investigating the effects of long-acting ESAs on office/ambulatory BP in patients with non-dialysis CKD, BP profiles, including short-term BP variability after 24 weeks of ESA treatment, were comparable between the CERA and DA groups. However, long-acting ESAs require increases in the doses of antihypertensive agents to ensure appropriate BP control in patients with non-dialysis CKD and renal anemia.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committees of Yokohama City University Hospital (institutional review board approval number B120510011).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.O., H.W., K.U., and K.T. designed and conducted the research. K.O., H.W., K.U., K.A., K.H., S.K., S.U., T.Y., T.Y., R.K., T.K., S.M., T.I., T.F., T.Y., and K.T. collected the data. K.O., H.W., and K.U. analyzed the data. O.K., H.W., K.U., and K.A. wrote the manuscript. All authors read and approved the final manuscript.

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