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Original Paper

Possible Inhibitory Effect of Erythropoiesis-Stimulating Agents at the Predialysis Stage on Early-Phase Coronary Events after Hemodialysis Initiation

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Key Words

Anemia · Chronic kidney disease · Coronary plaque · Erythropoiesis-stimulating agent · Hemodialysis

Abstract

Background: We examined whether the use of erythropoiesis-stimulating agents (ESAs) to correct anemia at the predialysis stage could inhibit early-phase coronary events after hemodialysis initiation. *Methods:* We enrolled 242 patients with chronic kidney disease who had received continued medical treatments and initiated maintenance hemodialysis from 1 September 2000 to 31 December 2014 at Toujinkai Hospital. Patients with a previous history of blood transfusion or any cardiovascular events or interventions were excluded. The coronary events were followed for 1 year after initiation of hemodialysis. *Results:* Coronary events occurred in 51 of 242 patients: 10 patients had acute coronary syndrome [9 with percutaneous coronary intervention (PCI), 1 without intervention], and 41 had elective coronary revascularization (38 PCI and 3 coronary artery bypass graft). ESA was administered in 118 of 242 patients (48.8%). In stepwise logistic analysis, coronary events were positively associated with nonuse of ESA at the predialysis stage (odds ratio 2.66, p = 0.005) and diabetes mellitus (odds ratio 5.33, p < 0.001). When dividing the patients into 4 subgroups by blood hemoglobin (Hb) level (8.5 g/dl) and the use/nonuse of ESA, coronary event-free survival rates were higher (p = 0.005) in those with Hb ≥8.5 g/dl, ESA+ (86.6%, n = 82) and tended to be higher (p = 0.055) in those with Hb <8.5 g/dl, ESA+ (86.1%, n = 36) than in patients with Hb <8.5 g/dl, ESA– (68.6%, n = 86) in a Kaplan-Meier analysis. *Conclusions:* The use of ESA to correct anemia at the predialysis stage may inhibit early-phase coronary events after hemodialysis initiation.

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Introduction

Patients with end-stage renal disease undergoing maintenance dialysis have a 10- to 20-fold greater incidence of cardiovascular death compared with the general population [1], which is mainly due to a high prevalence of coronary artery disease (CAD). Several studies noted that significant coronary stenosis was found in 50% or more of asymptomatic dialysis patients who underwent coronary angiography at early stages after the initiation of hemodialysis [2–4]. These findings indicate the progression of coronary atherosclerosis in the predialysis stages of chronic kidney disease (CKD) [5, 6]. In previous studies, almost one quarter of acute myocardial infarctions (MI) occurred within 1 year after hemodialysis initiation [7, 8]. In this study, we examined whether the use of erythropoiesis-stimulating agent (ESA) to correct renal anemia at the predialysis stage could affect early-phase coronary events after hemodialysis initiation.

Subjects and Methods

Patients

The flow diagram for the recruitment of subjects is shown in figure 1. Eligibility criteria included CKD patients who have had continued medical treatment through stages 4–5 for at least 6 months at Toujinkai Hospital and initiated hemodialysis at Toujinkai Hospital from 1 September 2000 to 31 December 2014. Exclusion criteria were as follows: (1) hemorrhagic lesions; (2) blood disorders; (3) malignancy; (4) history of red blood cell transfusion; (5) congestive heart failure of New York Heart Association grades III–IV; (6) moderate or worse valvular heart disease, and (7) any history of coronary revascularization such as coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), or apparent CAD such as a history of acute MI. Of 265 patients who met the eligibility criteria, 23 patients were excluded based on the above criteria. Consequently, 242 patients (65.4 ± 13.1 years old, 155 men and 87 women) were enrolled in the study and followed for 1 year after starting dialysis.

ESAs and Medications

ESAs used at the predialysis stage were recombinant human erythropoietin (rHuEPO; epoetin beta) or long-acting ESAs (darbepoetin alpha or epoetin beta pegol). ESAs were administered in 118 of 242 patients (48.8%) from at least 6 months before hemodialysis initiation. Epoetin beta was used in 74 patients (3,000–36,000 units/month), epoetin beta pegol in 34 (25–100 µg/month), and darbepoetin alpha in 10 (30–120 µg/month). Oral iron preparation was administered before dialysis in 148 patients (61.3%). Cardiovascular medications, including statins, were continued during the study period.
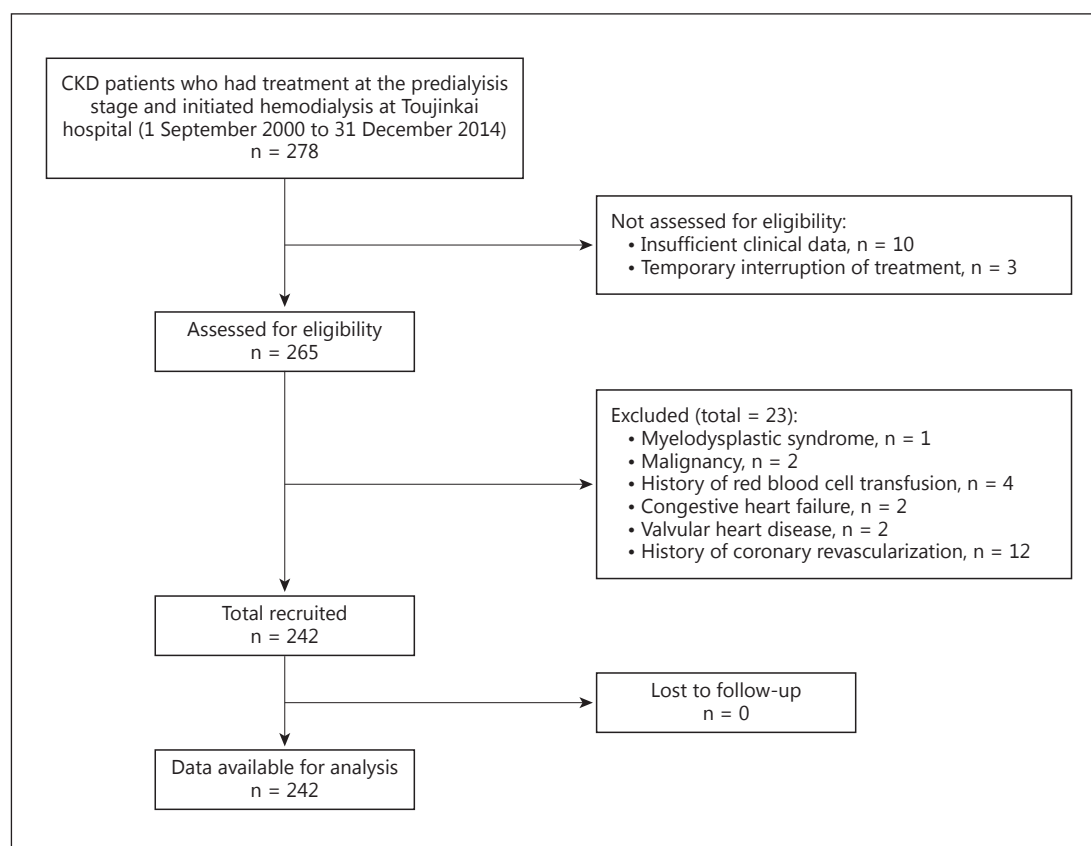
Radionuclide Imaging

Single-photon emission computed tomography (SPECT) using an iodinated fatty acid analogue, iodine-123-β-methyl iodophenyl-pentadecanoic acid (^{123}I-BMIPP), was performed on a midweek, non-dialysis day. The sensitivity, specificity, and accuracy of detecting CAD by BMIPP SPECT in hemodialysis patients was 96.1, 70.3, and 90.8%, respectively [9]. The methods are described in detail elsewhere [9–11].

Echocardiography

The participants underwent echocardiography on a midweek non-dialysis day within 1 month after hemodialysis initiation, when the patients were in a state without apparent overfluid. Left ventricular ejection fraction was quantified using the biplanar Simpson's rule, and left ventricular mass was normalized to body surface area and is described herein as left ventricular mass index.

Determination of Clinical Factors

Values of blood pressure, cardiothoracic ratio, blood hemoglobin (Hb) concentration, and serum concentrations of creatinine, albumin, C-reactive protein, or ferritin were determined at 6 and 3 months (ferritin was determined at 3 months) before the initiation of hemodialysis. These values after the initiation of hemodialysis were measured before the dialysis session and determined at the point of hemodialysis initiation,

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Fig. 1. Flow diagram for the recruitment of subjects.

and the mean values of the month were determined at 3, 6, 9, and 12 months after dialysis initiation. Blood samples (5 ml) were collected every 2 weeks before the first hemodialysis session of the week.

End Point

The end point was atherosclerotic coronary events, acute coronary syndrome such as unstable angina pectoris or acute MI, and obstructive CAD needing coronary revascularization.

Statistical Analysis

Values are expressed as the means ± SD. The means of continuous variables were compared using nonpaired t tests. Categorical data were analyzed using the χ^2 test. The means of variables among the 4 subgroups were compared using one-way analysis of variance. The associations of clinical factors with coronary lesions were analyzed using logistic analysis. Stepwise logistic analysis was performed among significant ($p < 0.05$) factors in univariate analysis. Coronary event-free survival rates were assessed using the Kaplan-Meier method and the log-rank test. p values <0.05 were considered significant. All statistical analyses were performed using IBM SPSS Statistics software, version 23.

Results

Of the 242 patients, 5 changed to other dialysis centers within 1 year after hemodialysis initiation; however, these 5 patients were included in the analysis, because we could confirm their coronary events and rate of survival. The other 237 patients were followed at Toujinkai Hospital to the end of this study.

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Table 1. Differences in clinical data at the point of hemodialysis initiation between patients with or without coronary events

	Event+ (n = 51)	Event– (n = 191)	p value
Males, n (%)	38 (74.5)	117 (61.3)	0.080
Age, years	67.2±11.0	65.0±13.5	0.292
Body mass index	18.4±3.8	19.3±4.1	0.125
Diabetes mellitus, n (%)	42 (82.4)	91 (47.6)	<0.001
Systolic blood pressure, mm Hg	154.7±23.2	154.9±26.2	0.941
Diastolic blood pressure, mm Hg	78.8±14.8	79.8±14.6	0.666
Cardiothoracic ratio, %	53.2±6.7	52.1±5.7	0.261
Left ventricular ejection fraction, %	61.4±11.4	61.9±12.8	0.796
Left ventricular mass index	155.1±103.3	145.6±51.4	0.359
Blood Hb, g/dl	8.1±1.3	8.6±1.4	0.015
Serum creatinine, mg/dl	8.0±2.8	8.9±3.3	0.086
Serum albumin, g/dl	3.3±0.5	3.4±0.5	0.061
Serum ferritin, ng/ml	194.0±167.0	182.6±260.6	0.767
Serum C-reactive protein, mg/dl	0.250±0.148	0.249±0.169	0.987
Use of ESAs, n (%)	16 (31.4)	102 (53.4)	0.005
Medications, n (%)			
Oral iron	85 (61.2)	157 (61.8)	0.927
Calcium channel blockers	39 (76.5)	139 (72.8)	0.597
RAS inhibitors	22 (43.1)	115 (60.2)	0.169
Alpha-1 blockers	9 (17.7)	37 (19.4)	0.781
Beta blockers	13 (25.5)	37 (19.4)	0.340
Antiplatelet drugs	10 (19.6)	43 (22.5)	0.657
Statins	8 (15.7)	40 (20.9)	0.405

Coronary Events

Coronary events were recognized in 51 of 242 patients (21%) within 1 year after hemodialysis initiation. Acute coronary syndrome was observed in 10 patients: 7 acute MI and 3 unstable angina pectoris; 9 needed emergent PCI, and 1 patient was treated with tissue plasminogen activator. Elective coronary revascularization was performed in 41 patients (38 PCI and 3 CABG). Of these 41 patients, 16 had symptoms of effort angina; the other 25 patients were asymptomatic, but had significant changes in routine electrocardiography and abnormal findings in echocardiography and/or BMIPP SPECT. The coronary event group showed a higher rate of diabetes mellitus, a lower mean blood Hb concentration at hemodialysis initiation, and a lower use of ESAs at the predialysis stage than the non-event group (table 1).

Factors Relevant to Coronary Events

In univariate logistic analysis, coronary events were associated with diabetes mellitus, mean blood Hb concentration at hemodialysis initiation, and nonuse of ESAs (table 2). In stepwise logistic analysis of these factors, coronary events were associated with nonuse of ESA (odds ratio 2.66, 95% CI 1.34–5.27; p = 0.005), independently of diabetes mellitus (odds ratio 5.33, 95% CI 2.43–11.69; p < 0.001). The positive association of nonuse of ESAs with coronary events was consistently recognized in adjustment with mean blood Hb concentrations at hemodialysis initiation (odds ratio 2.04; p = 0.048), 3 months (odds ratio 2.40; p = 0.013) and 6 months before dialysis (odds ratio 2.52; p = 0.009). When coronary events were limited to obstructive CAD needing coronary revascularization, coronary events were similarly associated with diabetes mellitus (odds ratio 5.00; p < 0.001), mean blood Hb concen-

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Table 2. Univariate logistic analysis for coronary events

	Odds ratio	95% CI	p value
Male gender	1.85	0.92–3.70	0.083
Age (years)	1.01	0.99–1.04	0.291
Body mass index	0.94	0.87–1.02	0.126
Diabetes mellitus	5.13	2.37–11.12	<0.001
Systolic blood pressure (mm Hg)	1.00	0.99–1.01	0.941
Diastolic blood pressure (mm Hg)	0.99	0.97–1.02	0.665
Cardiothoracic ratio (%)	1.03	0.98–1.09	0.260
Left ventricular ejection fraction (%)	1.00	0.97–1.02	0.795
Left ventricular mass index	1.00	1.00–1.01	0.368
Blood Hb (g/dl)	0.75	0.59–0.95	0.017
Serum creatinine (mg/dl)	0.91	0.82–1.01	0.087
Serum albumin (g/dl)	0.56	0.30–1.03	0.063
Serum ferritin (ng/ml)	1.00	0.99–1.00	0.766
Serum C-reactive protein (mg/dl)	1.02	0.16–6.67	0.987
Nonuse of ESA	2.51	1.30–4.83	0.006
Medications			
Oral iron	0.98	0.57–1.68	0.926
Calcium channel blockers	1.22	0.59–2.50	0.595
RAS inhibitors	0.61	0.33–1.14	0.119
Alpha-1 blockers	0.89	0.40–1.99	0.780
Beta blockers	1.42	0.69–2.94	0.339
Antiplatelet drugs	0.84	0.39–1.81	0.656
Statins	0.70	0.31–1.61	0.405

tration at hemodialysis initiation (odds ratio 0.75; p = 0.031), and nonuse of ESAs (odds ratio 3.60; p = 0.001). Further, we analyzed the data by dividing the entrée periods into 2000–2008 and 2009–2014, because Japanese guidelines for treating renal anemia in the predialysis stage had been released in June 2008 [12]. In patients within the entrée period of 2000–2008, coronary events were associated with nonuse of ESAs (odds ratio 3.75; p = 0.047) and diabetes mellitus (odds ratio 7.21; p < 0.001), but not with blood Hb concentration at hemodialysis initiation (odds ratio 0.84; p = 0.382). The ratio of nonuse of ESAs was 0.68, and the mean blood Hb concentration at hemodialysis initiation was 7.9 ± 1.2 g/dl. In patients within the entrée period of 2009–2014, coronary events were associated with nonuse of ESAs (odds ratio 2.59; p = 0.026), blood Hb concentration at hemodialysis initiation (odds ratio 0.67; p = 0.017), and diabetes mellitus (odds ratio 4.451; p = 0.009). The ratio of nonuse of ESAs was 0.39, and the mean blood Hb concentration at hemodialysis initiation was 8.8 ± 1.4 g/dl. The use of renin-angiotensin system (RAS) inhibitors tended to be inversely associated with coronary events in patients within the entrée period of 2000–2008 (odds ratio 0.38; p = 0.083), but not in those of within the period of 2009–2014 (odds ratio 0.78; p = 0.497).
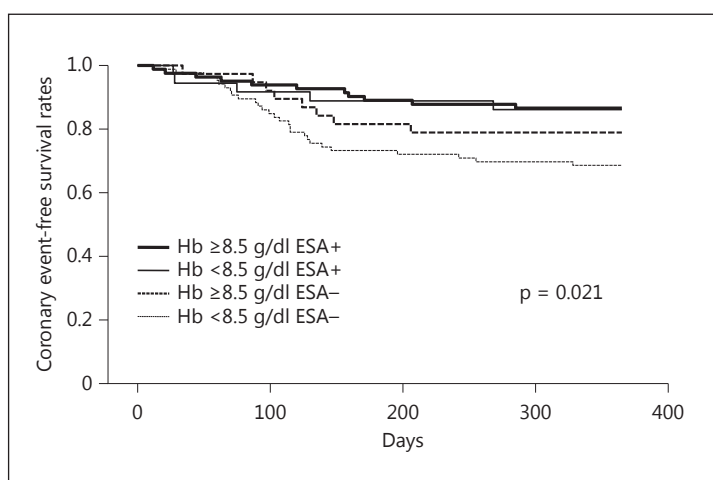
Blood Hb and ESA Use/Nonuse

When patients were divided into 4 subgroups by blood Hb level (8.5 g/dl, the mean value for the study patients) and use/nonuse of ESAs, the incidences of coronary events were as follows: Hb ≥8.5 g/dl, ESA+, 11/82 (13.4%); Hb <8.5 g/dl, ESA+, 5/36 (13.9%); Hb ≥8.5 g/dl, ESA–, 8/38 (21.1%), and Hb <8.5 g/dl, ESA–, 27/86 (31.4%). The incidence of coronary events was lower (p = 0.042) in patients with Hb ≥8.5 g/dl, ESA+ than in those with Hb <8.5 g/dl, ESA–. Coronary event-free survival rates at 1 year after starting hemodialysis were higher

Table 3. Differences in clinical data at hemodialysis initiation among the subgroups divided by blood Hb concentration and the use of ESAs

	Hb ≥8.5 g/dl, ESA+ (n = 82)	Hb <8.5 g/dl, ESA+ (n = 36)	Hb ≥8.5 g/dl, ESA– (n = 38)	Hb <8.5 g/dl, ESA– (n = 86)
Males, n (%)	52 (63.4)	23 (63.9)	28 (73.7)	52 (60.5)
Age, years	64.2±14.4	64.5±12.2	63.7±15.0	67.8±10.6
Body mass index	18.8±3.8	19.1±3.6	19.5±4.3	19.2±4.4
Diabetes mellitus, n (%)	47 (57.3)	17 (47.2)	21 (55.3)	48 (55.8)
Systolic blood pressure, mm Hg	155.6±26.2	149.4±23.4	158.7±26.8	154.9±25.2
Diastolic blood pressure, mm Hg	82.4±15.7[b]	76.9±12.9	83.7±12.8	76.2±14.1
Cardiothoracic ratio, %	52.4±6.4	50.9±4.7	51.3±6.2	53.4±5.7
Left ventricular ejection fraction, %	62.2±13.6	60.7±13.6	61.0±12.5	62.2±10.9
Left ventricular mass index	139.5±49.7	140.3±58.3	158.9±51.5	153.2±84.6
Blood Hb, g/dl	9.8±0.9[a,c,d]	7.5±0.7	9.2±0.7[a,c]	7.3±0.8
Serum creatinine, mg/dl	8.4±2.7	9.6±3.7	8.4±3.4	8.8±3.3
Serum albumin, g/dl	3.5±0.5[b]	3.4±0.5	3.4±0.5	3.3±0.5
Serum ferritin, ng/ml	52.3±6.4	50.9±4.7	51.3±6.2	53.4±5.7
Serum C-reactive protein, mg/dl	0.245±0.157	0.299±0.156	0.242±0.187	0.239±0.163
Medications, n (%)				
Oral iron	52 (63.4)	25 (69.4)	25 (65.8)	47 (54.7)
Calcium channel blockers	67 (81.7)	30 (83.3)	24 (63.2)	57 (66.3)
RAS inhibitors	65 (79.3)[b]	14 (38.9)	24 (63.2)	35 (40.7)
Alpha-1 blockers	18 (22.0)	6 (16.7)	7 (18.4)	15 (17.4)
Beta blockers	20 (24.4)	7 (19.4)	8 (21.1)	15 (17.4)
Antiplatelet drugs	20 (24.4)	7 (19.4)	10 (26.3)	16 (18.6)
Statins	19 (23.2)	6 (16.7)	11 (29.0)	12 (14.0)

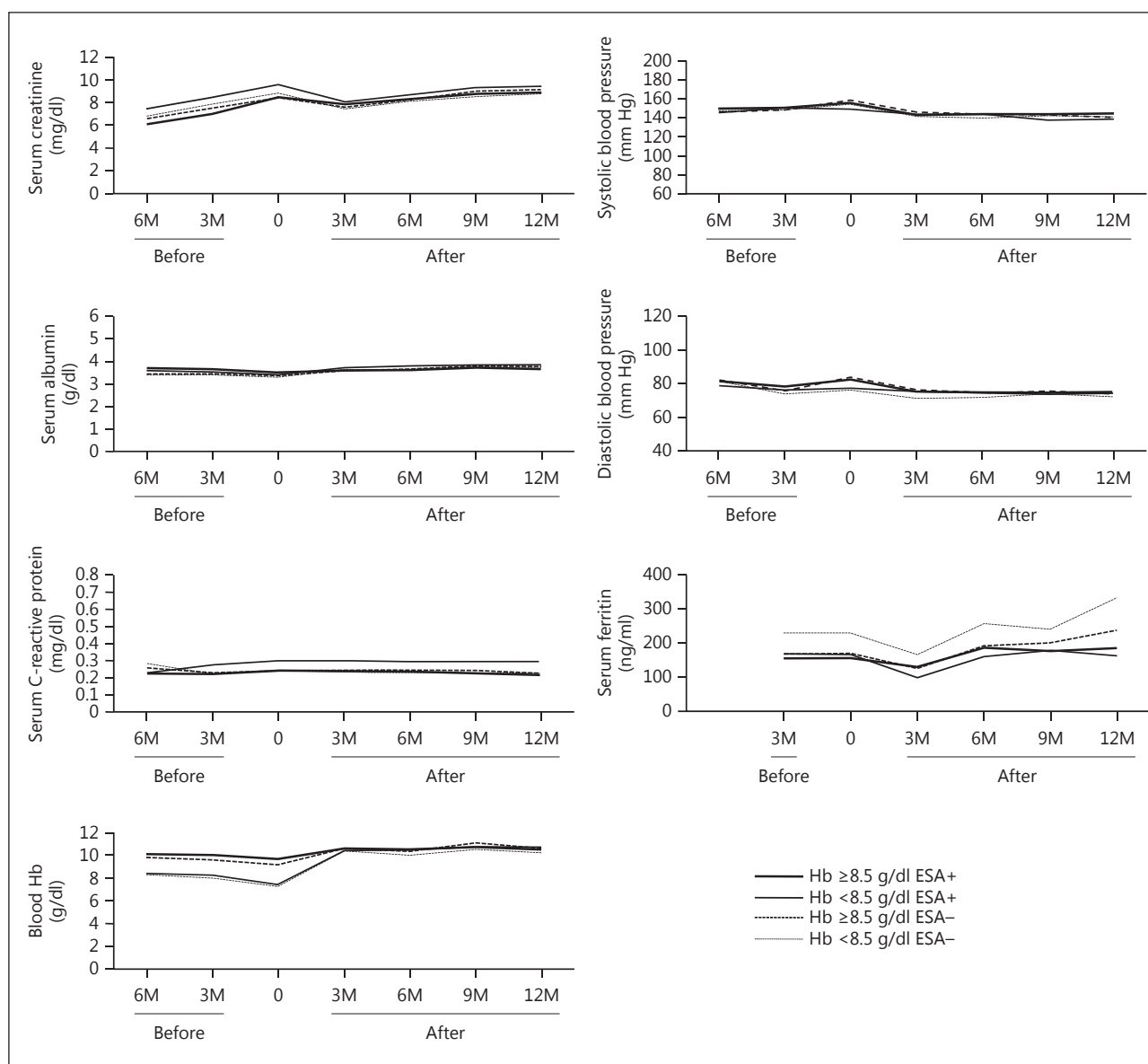[a] p < 0.001 versus Hb <8.5 g/dl, ESA–; [b] p < 0.05 versus Hb <8.5 g/dl, ESA–; [c] p < 0.001 versus Hb <8.5 g/dl, ESA+; [d] p < 0.05 versus Hb ≥8.5 g/dl, ESA–.

Fig. 2. Coronary event-free survival rates within 1 year after hemodialysis initiation among patients divided into 4 subgroups by blood Hb concentration at hemodialysis initiation (8.5 g/dl) and use/nonuse of ESA in Kaplan-Meier analysis.

(p = 0.005) in patients with Hb ≥8.5 g/dl, ESA+ and tended to be higher (p = 0.055) in those with Hb <8.5 g/dl, ESA+ than in patients with Hb <8.5 g/dl, ESA– in a Kaplan-Meier analysis (fig. 2). In patients with Hb ≥8.5 g/dl, ESA+, the mean blood Hb concentration at hemodialysis initiation was higher than in the other subgroups, and the mean serum albumin concentration and the administration rate of RAS inhibitors were higher than in patients with Hb <8.5 g/dl, ESA– (table 3).

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Fig. 3. Profiles of changes in blood pressure, blood Hb, and serum concentrations of creatinine, albumin, C-reactive protein, or ferritin during the study period among patients divided into 4 subgroups by blood Hb concentration at hemodialysis initiation (8.5 g/dl) and use/nonuse of ESA. M = Months; Before = before hemodialysis initiation; After = after hemodialysis initiation; 0 = hemodialysis initiation.

Changes in Blood Hb and Other Factors

The mean blood Hb concentrations of patients with Hb ≥8.5 g/dl, ESA+ were higher than those of patients with Hb <8.5 g/dl, ESA+ or Hb <8.5 g/dl, ESA– at 6 and 3 months before dialysis initiation (fig. 3, online suppl. data, www.karger.com/doi/10.1159/000448009) and higher than those of the other 3 subgroups at the initiation of hemodialysis (table 2). Mean serum albumin concentrations of patients with Hb ≥8.5 g/dl, ESA+ were higher than those of patients with Hb <8.5 g/dl, ESA– at 6 and 3 months before dialysis initiation (fig. 3, online suppl. data) and at the initiation of hemodialysis (table 2). Mean values of other factors did not differ among the 4 subgroups during the study (fig. 3, online suppl. data).

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Types of ESAs and Coronary Events

In the participants administered with ESAs at the predialysis stages (n = 118; 64.5 ± 13.7 years old; 75 men and 43 women), the rates of coronary events were lower (p = 0.027) in patients with long-acting ESAs (2/44, 4.6%) than in those with rHuEPO (14/74, 18.9%). In Kaplan-Meier analysis, coronary event-free survival rates at 1 year after starting hemodialysis were higher (p = 0.029) in patients with long-acting ESAs (95.5%) than in those with rHuEPO (81.1%).

Discussion

Coronary plaque is likely to progress with the stages of CKD. CKD patients of stage 3 had a higher percentage of lipid volume and a lower percentage of fibrous volume in coronary plaques compared with patients without CKD [5]. Recently, Kashiyama et al. [6] showed that coronary plaques progress with the CKD stages, and both lipid and fibrotic volumes of the plaques became greater as CKD advanced, particularly in stage 4 or 5. Coronary plaques are likely to progress as CKD worsens, and these morphological changes in coronary plaques are thought to lead to the occurrence of coronary events after hemodialysis initiation. To reduce early-phase coronary events after hemodialysis, it is important to inhibit the progression of coronary plaques at the predialysis CKD stages.

Iwasaki et al. [13] reported that the prevalence of CAD gradually declined from 69 to 25% over 18 years in hemodialysis patients, and the use of ESAs seemed to be associated with this decrease in CAD. Erythropoietin (Epo) and Epo receptor are expressed in a variety of tissues, including the vascular system [14]. Epo derivatives had antiapoptotic effects via inhibition of caspase 3 [15] and stabilization of the BAX/Bcl-2 ratio in apo E-deficient mice [16, 17]. Epo diminished the production of inflammatory cytokines [18] and oxidative stress [19] and had beneficial effects on the morphology of atherosclerotic lesions of apo E knockout mice via reduction of the lipid content of macrophages and the subsequent formation of foam cells [20]. Darbepoetin alpha, a long-acting ESA, suppressed oxidative stress, inflammation in the heart and aorta, plaque stage, and plaque cholesterol content in subtotally nephrectomized rats [21]. The positive association of nonuse of ESA from the predialysis stage with obstructive CAD needing coronary revascularization found in this study would indicate the inhibitory effect of ESA on the progression of coronary plaque. ESA might play a role in inhibiting the process of coronary atherosclerosis in CKD patients, although further investigation is needed to clarify this important point.

Among the participants administered ESAs from the predialysis stage, long-acting ESAs led to a better prognosis in the occurrence of coronary events than rHuEPO. However, we cannot insist that long-acting ESAs are superior to rHuEPO in the inhibition of coronary events, because the administration of ESAs was not randomized, and these types of ESAs had been used at different times; rHuEPO was mainly used before 2012, and long-acting ESAs were used after 2012.

This study has several limitations. It was a retrospective, observational cohort study performed in a single center. Use or nonuse of ESA and types of ESAs were not randomized among the participants. A multicenter, randomized, and prospective trial would be needed to confirm the effects of the use of ESAs at the predialysis stage on coronary events. Many differences among the background factors may have affected the findings of this study, since the study period was very long, and rHuEPO and long-acting ESAs had been used at different times. The clinical factors presented in this study may not have been sufficient for proper conduction of the analysis; other factors that were not examined might have affected the results of this study.

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The present study indicated the inhibitory effect of ESA at the predialysis stage on the early-phase coronary events after hemodialysis initiation, irrespective of the correction of anemia. Since the entrée duration was very long from 2000 to 2014, the clinical background including medication or medical care, such as the administration of ESAs or RAS inhibitors and target blood Hb levels for correction of renal anemia, has changed during this period. However, the positive association of nonuse of ESA with coronary events was similarly found in patients of the former (2000–2008) and latter (2009–2014) periods of this study. We have reported in previous studies the importance of detecting CAD in asymptomatic hemodialysis patients using myocardial scintigraphy such as fatty acid imaging [9, 10]. The use of ESAs from the predialysis stage may play an important role in improving the prognosis of hemodialysis patients by inhibiting early-phase coronary events after hemodialysis initiation as well as improving renal anemia.

Acknowledgments

Statement of Ethics

The Ethics Committee for Human Research of Toujinkai Hospital approved this study. All patients provided informed consent to all procedures associated with the study prior to participation.

Disclosure Statement

The authors declare no conflicts of interest.

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Erratum

In the article by Nishimura M et al., entitled 'Possible inhibitory effect of erythropoiesis-stimulating agents at the predialysis stage on early-phase coronary events after hemodialysis initiation' [Cardiorenal Med 2017;7:21–30, DOI:10.1159/000448009], an error in the serum ferritin concentrations included in table 3 was identified after online publication of this paper in *CardioRenal Medicine*. This is a simple technical error and does not affect the point of any argument of this paper.

The corrected values of serum ferritin concentrations in table 3 are as follows: Hb ≥8.5 g/dl, ESA+: 155.1 ± 139.3 ng/ml; Hb <8.5 g/dl, ESA+: 165.5 ± 132.3 ng/ml; Hb ≥8.5 g/dl, ESA–: 168.2 ± 220.1 ng/ml; Hb <8.5 g/dl, ESA–: 229.1 ± 344.1 ng/ml.

Table 3. Differences in clinical data at hemodialysis initiation among the subgroups divided by blood Hb concentration and the use of ESAs

	Hb ≥8.5 g/dl, ESA+ (n = 82)	Hb <8.5 g/dl, ESA+ (n = 36)	Hb ≥8.5 g/dl, ESA– (n = 38)	Hb <8.5 g/dl, ESA– (n = 86)
Males, n (%)	52 (63.4)	23 (63.9)	28 (73.7)	52 (60.5)
Age, years	64.2±14.4	64.5±12.2	63.7±15.0	67.8±10.6
Body mass index	18.8±3.8	19.1±3.6	19.5±4.3	19.2±4.4
Diabetes mellitus, n (%)	47 (57.3)	17 (47.2)	21 (55.3)	48 (55.8)
Systolic blood pressure, mm Hg	155.6±26.2	149.4±23.4	158.7±26.8	154.9±25.2
Diastolic blood pressure, mm Hg	82.4±15.7[b]	76.9±12.9	83.7±12.8	76.2±14.1
Cardiothoracic ratio, %	52.4±6.4	50.9±4.7	51.3±6.2	53.4±5.7
Left ventricular ejection fraction, %	62.2±13.6	60.7±13.6	61.0±12.5	62.2±10.9
Left ventricular mass index	139.5±49.7	140.3±58.3	158.9±51.5	153.2±84.6
Blood Hb, g/dl	9.8±0.9[a,c,d]	7.5±0.7	9.2±0.7[a,c]	7.3±0.8
Serum creatinine, mg/dl	8.4±2.7	9.6±3.7	8.4±3.4	8.8±3.3
Serum albumin, g/dl	3.5±0.5[b]	3.4±0.5	3.4±0.5	3.3±0.5
Serum ferritin, ng/ml	**155.1±139.3**	**165.5±132.3**	**168.2±220.1**	**229.1±344.1**
Serum C-reactive protein, mg/dl	0.245±0.157	0.299±0.156	0.242±0.187	0.239±0.163
Medications, n (%)				
Oral iron	52 (63.4)	25 (69.4)	25 (65.8)	47 (54.7)
Calcium channel blockers	67 (81.7)	30 (83.3)	24 (63.2)	57 (66.3)
RAS inhibitors	65 (79.3)[b]	14 (38.9)	24 (63.2)	35 (40.7)
Alpha-1 blockers	18 (22.0)	6 (16.7)	7 (18.4)	15 (17.4)
Beta blockers	20 (24.4)	7 (19.4)	8 (21.1)	15 (17.4)
Antiplatelet drugs	20 (24.4)	7 (19.4)	10 (26.3)	16 (18.6)
Statins	19 (23.2)	6 (16.7)	11 (29.0)	12 (14.0)

[a] $p < 0.001$ versus Hb <8.5 g/dl, ESA–; [b] $p < 0.05$ versus Hb <8.5 g/dl, ESA–; [c] $p < 0.001$ versus Hb <8.5 g/dl, ESA+; [d] $p < 0.05$ versus Hb ≥8.5 g/dl, ESA–.