Outcomes of Early Versus Delayed Anemia Treatment in Nondialysis-Dependent CKD

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Introduction: The association of hemoglobin level at treatment initiation with renal and cardiovascular outcomes in patients with anemia in nondialysis-dependent (NDD) chronic kidney disease (CKD) is unclear.

Methods: This retrospective cohort study utilized 2 Japanese databases (Medical Data Vision Co. Ltd., Tokyo, Japan [MDV]; and Real World Data Co. Ltd, Kyoto, Japan [RWD]). Patients initiated on long-acting erythropoiesis-stimulating agent (ESA) treatment were divided into early (hemoglobin levels $\geq$9.0 g/dl) and delayed (<9.0 g/dl) treatment groups. The primary outcome was a renal composite (renal replacement therapy, $\geq$50% estimated glomerular filtration rate [eGFR] reduction, eGFR <6.0 ml/min per 1.73 m^2, and all-cause mortality), and secondary outcomes were a cardiovascular composite (hospitalization by ischemic heart disease, including myocardial infarction, hospitalization by stroke and heart failure, and cardiovascular death) and components of the composite outcomes.

Results: After propensity score matching, 1472 (MDV) and 1264 (RWD) patients were evaluated. Delayed treatment was not associated with a risk of the renal composite outcome (MDV: hazard ratio [HR]: 1.15, 95% confidence interval [CI]: 0.99–1.33; RWD: HR: 1.08, 95% CI: 0.92–1.28). However, delayed treatment was associated with higher risks of the cardiovascular composite outcome (MDV: HR: 1.47, 95% CI: 1.16–1.84; RWD: HR: 1.34, 95% CI: 1.09–1.64), heart failure (MDV: HR: 1.50, 95% CI: 1.13–2.00; RWD: HR: 1.53, 95% CI: 1.20–1.96) and all-cause mortality (MDV: HR: 1.83, 95% CI: 1.32–2.54; RWD: HR: 1.64, 95% CI: 1.21–2.22).

Conclusion: Although the risk of renal events was not increased following delayed treatment of anemia in patients with NDD-CKD, the risks of cardiovascular events and all-cause mortality were increased, suggesting the importance of early intervention before hemoglobin falls below 9.0 g/dl.

CKD affects approximately 850 million people worldwide and 13.3 to 14.8 million people between 2005 and 2015 in Japan.[1,2] Anemia is common in patients with CKD, and its prevalence increases with CKD severity.[3-6] Patients with CKD and anemia have a reduced quality of life and are at higher risk of cardiovascular events.[7,8] The standard treatment for anemia in CKD is ESA therapy combined with iron supplementation. Recently, hypoxia-inducible factor prolyl hydroxylase inhibitors have been approved in several countries, including Japan.[9-11]

A previous Japanese clinical trial found that patients with anemia and NDD-CKD treated with ESAs to target hemoglobin levels of 11.0 to 13.0 g/dl had a 29% reduction in the risk of renal composite events compared with patients treated with lower target hemoglobin levels of 9.0 to 11.0 g/dl.[12] The "Guideline for Treatment of Anemia in CKD Patients" of the Japanese Society for Dialysis Therapy recommends anemia treatment to be started when hemoglobin decreases to <11.0 g/dl and to maintain the hemoglobin level at 11.0 to 13.0 g/dl.[13] However, there are limited reports comparing the prognosis of patients with different hemoglobin levels at the start of ESA treatment. The JET-STREAM study investigated the relationship between hemoglobin levels at the start of treatment for anemia and renal outcomes and found that patients with hemoglobin levels of 10.0 to 11.0 g/dl at the initiation of epoetin beta treatment had a lower risk of renal events than those with hemoglobin levels <9.0 g/dl.[14] Thus, earlier treatment of anemia in patients with short-acting ESAs may lead to improved renal

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outcomes. In recent years, long-acting ESAs (including darbepoetin alfa and epoetin beta pegol/continuous erythropoietin receptor activator) have been widely prescribed for Japanese patients with anemia in NDD-CKD.[15] To our knowledge, no previous study has investigated the relationship between hemoglobin levels at treatment initiation and renal outcomes of patients treated with long-acting ESAs in Japanese clinical practice.

Data from real-world clinical databases derived from Diagnosis Procedure Combination codes, electronic medical records, and health insurance claims are now widely available for epidemiologic and outcome studies of various medical conditions in Japan. This study utilized 2 Japanese databases to clarify the renal and cardiovascular outcomes of early versus delayed treatment with long-acting ESAs in patients with NDD-CKD, and explore the consistency of the results between the 2 databases.

METHODS

Study Design
This retrospective cohort study evaluated Japanese patients with anemia and NDD-CKD. Anonymized patient data were obtained from 2 databases: MDV, which includes inpatient and outpatient data, such as Diagnosis Procedure Combination data, from Japanese acute care hospitals; and RWD, which is maintained by the Health, Clinic, and Education Information Evaluation Institute (Kyoto, Japan) and integrates medical records, Diagnosis Procedure Combination data, and receipts. The data extraction period was between April 2008 and November 2021 (MDV database) and January 1985 and January 2022 (RWD database), and the index date was defined as the date of the first prescription of a long-acting ESA (either darbepoetin alfa or continuous erythropoietin receptor activator). The study period comprised a 180-day look-back period and an observation period of up to 720 days from the index date. Because this study utilized anonymized data from existing databases, informed consent was not required. The study was approved by the Ethics Review Committee of Mitsubishi Tanabe Pharma Corporation (approval number: H-22-013).

Study Population
The study adopted a new user design, and outpatients with anemia in NDD-CKD who were newly started on a long-acting ESA were eligible. The key inclusion criteria were patients aged ≥18 years with a first prescription of darbepoetin alfa or continuous erythropoietin receptor activator between January 2011 and December 2018; diagnosis of renal anemia in the same month as the index date; hemoglobin measurements

less than 11.0 g/dl in the 30 days before the index date (day −29 to day 0); and eGFR of 6 to 60 ml/min per 1.73 m² in the 90 days before the index date. Renal anemia was identified using the Japanese standardized disease code "renal anemia" (2858001). Patients who had received a dialysis procedure on or before the index date or were hospitalized on the index date were excluded. Further details of the inclusion and exclusion criteria are provided in Supplementary Table S1.

Patients were divided into 2 groups for each database according to their hemoglobin levels in the 30 days before the index date: the early treatment group (hemoglobin levels of ≥9.0 g/dl) and the delayed treatment group (hemoglobin levels of <9.0 g/dl). The cut-off value was decided based on the results of the JET-STREAM study, which indicated that patients with hemoglobin levels < 9.0 g/dl when initiating short-acting ESA treatment had a higher risk of renal events.[14] In addition, a previous Japanese retrospective database study revealed that the mean hemoglobin level of patients at the start of ESA (mostly long-acting) treatment was 9.1 g/dl.[15] The disease codes used in this study and the patient background characteristics collected are listed in Supplementary Table S2. The presence of comorbid hypertension, diabetes mellitus, and dyslipidemia were determined from the prescribing information. The presence or history of cardiovascular disease and connective tissue disease were determined from the diagnostic and procedural codes.

Study Outcomes
The primary outcome was a renal composite outcome composed of renal replacement therapy (dialysis and renal transplantation), a reduction of ≥50% in eGFR from baseline and an eGFR of <6.0 ml/min per 1.73 m² at 2 consecutive measurements, and all-cause mortality. The secondary outcomes were a cardiovascular composite outcome composed of hospitalization for ischemic heart disease, including myocardial infarction, stroke, and heart failure, and cardiovascular death, as well as individual components of the renal and cardiovascular composite outcomes. Regarding renal events during the 2-year observation period, the date closest to the index date was defined as the date of the event. For cardiovascular events during the 2-year observation period, the date of hospitalization (for myocardial ischemia, myocardial infarction, stroke, or heart failure) closest to the index date, or the date of death from cardiovascular causes, was defined as the date of the event. Additional exploratory outcomes included hemoglobin levels over time, mean monthly ESA dose, and frequency of ESA administration.

Sample Size and Statistical Analyses

This study did not have a predefined sample size because this was a real-world database study and data from all cases meeting the criteria were included in the analysis.

The covariate background was adjusted using a propensity score matching method with a 1:1 ratio of patients in the early treatment group and the delayed treatment group, and a caliper of 0.20. The covariates included age, sex (biological sex as described in the database records), baseline eGFR, baseline serum albumin, hypertension (with renin-angiotensin system inhibitor prescription), hypertension (with other antihypertensive drug prescription), diabetes mellitus, dyslipidemia, history of cardiovascular disease, history of rheumatic disease, and year of ESA treatment initiation.

Continuous data were summarized using mean and SD, and categorical data were summarized by number and percentage. Standardized differences were calculated between the early and delayed treatment groups. Patients with complete data sets, including baseline hemoglobin, serum creatinine, and albumin measurements, were included in the analysis, and data imputation was not applied.

The nonincidence of first renal composite outcome and all-cause mortality was calculated using the Kaplan-Meier method. A log–rank test was used to compare the early and delayed treatment groups. Kaplan-Meier cumulative incidence curves were generated as 1 minus the Kaplan-Meier estimate. HRs and 95% CIs were calculated using the Cox proportional hazards model. For the other outcomes, the incidences were analyzed using cumulative incidence curves treating all-cause mortality as a competing risk, and the intergroup difference was tested using Gray's test. HRs and 95% CIs for the delayed treatment group versus the early treatment group were calculated using the Fine–Gray subdistribution hazard model. Cardiovascular outcomes were analyzed in the same manner as the renal outcomes, taking the competing risk into account. The competing risk for the cardiovascular composite outcome and cardiovascular death was death due to causes other than cardiovascular death, and the competing risk for the other components of the cardiovascular composite outcome was all-cause mortality. Sensitivity analyses were performed with hemoglobin cut-off values of 8.5 g/dl and 9.5 g/dl. For the exploratory outcomes, hemoglobin measurements at the index date were used as the baseline values, and mean values were calculated each month for the first 2 months and every 2 months thereafter regardless of the presence or absence of an event. For patients who received blood transfusions, the last measurement day was set as the day before the blood transfusion. Hemoglobin values were not imputed for patients with missing hemoglobin measurements, and the hemoglobin data for these patients were not used in group calculations for the respective time point. The mean monthly ESA dose (μg/mo) and frequency of ESA dose (number of prescriptions/mo) were calculated from the total dose and total number of prescriptions of long-acting ESAs during the observation period, respectively. For patients who switched to another ESA after the index date, the analysis was performed using data up to the day before the switch. A subgroup analysis was performed on patient data stratified by background characteristics, and HRs and 95% CIs for the delayed treatment group versus the early treatment group were calculated.

All statistical analyses had a 2-sided significance level of 5% and were conducted using R version 4.2.2 and RStudio 2022.07.2+576 (R Foundation for Statistical Computing, Vienna, Austria).[16]

RESULTS

Patients

After propensity score matching, 1472 patients in the MDV database and 1264 patients in the RWD database were evaluated (Figure 1a and b). The reasons for exclusion are listed in Figure 1 and Supplementary Table S3. The baseline characteristics of patients in the early treatment and delayed treatment groups are shown in Table 1. The standardized difference for all covariates used for propensity matching was <0.1, indicating a good balance between the groups. The patient backgrounds of the eligible population before propensity score matching are presented in Supplementary Table S4, and density plots of the propensity score distribution before and after matching are shown in Supplementary Figure S1.

Renal Outcomes

The renal composite outcomes are shown in Figure 2. The Kaplan-Meier cumulative incidence curves of the renal composite outcomes had no notable differences between the early and delayed treatment groups for both the MDV ($P = 0.070$) and RWD ($P = 0.337$) data sets (Figure 2a and b). The HRs were 1.15 (95% CI: 0.99–1.33) and 1.08 (95% CI: 0.92–1.28) in the MDV and RWD data sets (Figure 2c and d), respectively.

Regarding the components of the renal composite outcome (Figure 2c and d and Supplementary Figure S2A–D), the risk for all-cause mortality was significantly increased in the delayed treatment group compared with the early treatment group for both the MDV (HR: 1.83 [95% CI: 1.32–2.54]) and RWD data sets (HR: 1.64 [95% CI: 1.21–2.22]). The risks for the other renal components were not significantly different.
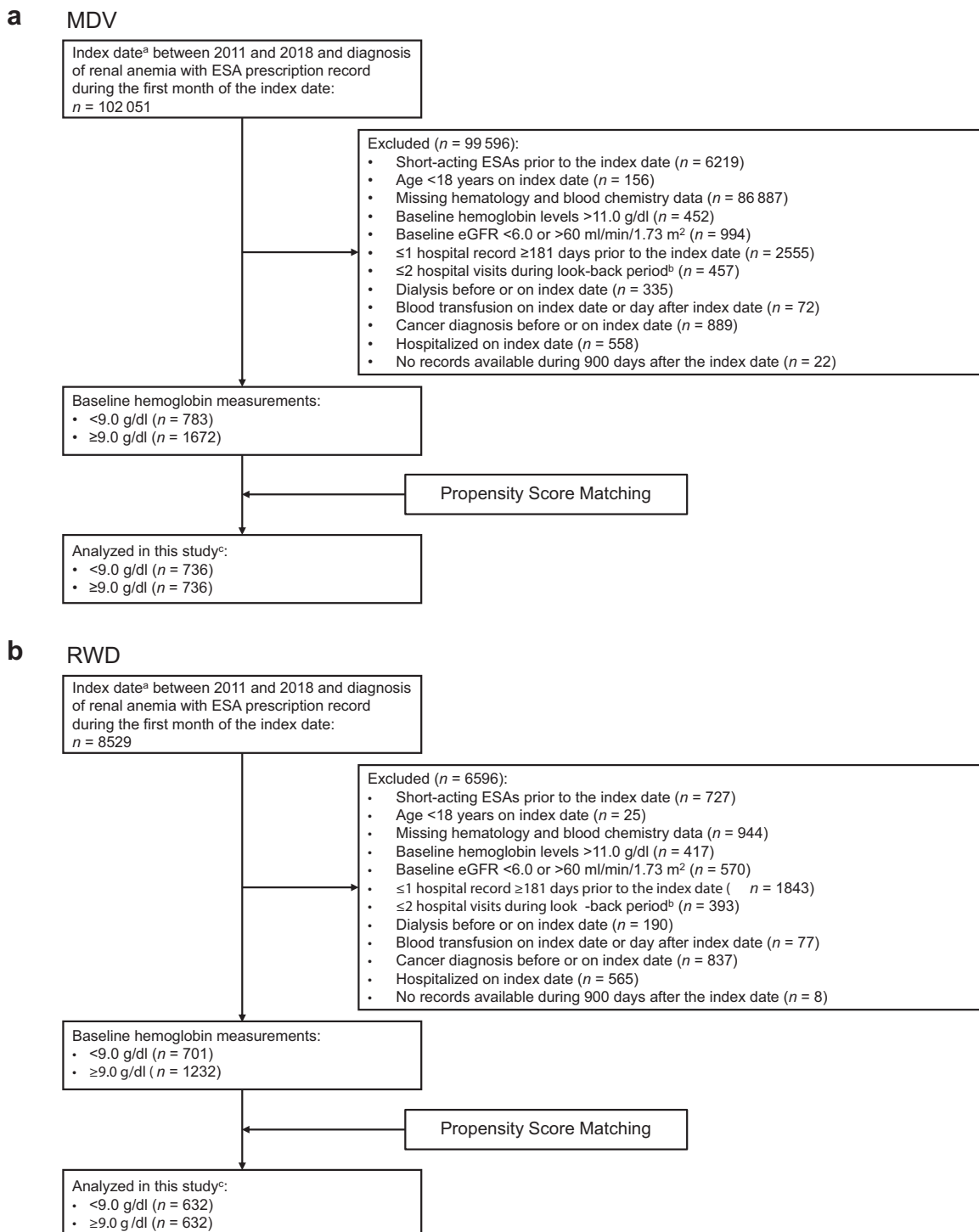
a MDV

Index date[a] between 2011 and 2018 and diagnosis of renal anemia with ESA prescription record during the first month of the index date:
n = 102 051

Excluded (*n* = 99 596):
- Short-acting ESAs prior to the index date (*n* = 6219)
- Age <18 years on index date (*n* = 156)
- Missing hematology and blood chemistry data (*n* = 86 887)
- Baseline hemoglobin levels >11.0 g/dl (*n* = 452)
- Baseline eGFR <6.0 or >60 ml/min/1.73 m^2 (*n* = 994)
- ≤1 hospital record ≥181 days prior to the index date (*n* = 2555)
- ≤2 hospital visits during look-back period[b] (*n* = 457)
- Dialysis before or on index date (*n* = 335)
- Blood transfusion on index date or day after index date (*n* = 72)
- Cancer diagnosis before or on index date (*n* = 889)
- Hospitalized on index date (*n* = 558)
- No records available during 900 days after the index date (*n* = 22)

Baseline hemoglobin measurements:
- <9.0 g/dl (*n* = 783)
- ≥9.0 g/dl (*n* = 1672)

Propensity Score Matching

Analyzed in this study[c]:
- <9.0 g/dl (*n* = 736)
- ≥9.0 g/dl (*n* = 736)

b RWD

Index date[a] between 2011 and 2018 and diagnosis of renal anemia with ESA prescription record during the first month of the index date:
n = 8529

Excluded (*n* = 6596):
- Short-acting ESAs prior to the index date (*n* = 727)
- Age <18 years on index date (*n* = 25)
- Missing hematology and blood chemistry data (*n* = 944)
- Baseline hemoglobin levels >11.0 g/dl (*n* = 417)
- Baseline eGFR <6.0 or >60 ml/min/1.73 m^2 (*n* = 570)
- ≤1 hospital record ≥181 days prior to the index date (*n* = 1843)
- ≤2 hospital visits during look-back period[b] (*n* = 393)
- Dialysis before or on index date (*n* = 190)
- Blood transfusion on index date or day after index date (*n* = 77)
- Cancer diagnosis before or on index date (*n* = 837)
- Hospitalized on index date (*n* = 565)
- No records available during 900 days after the index date (*n* = 8)

Baseline hemoglobin measurements:
- <9.0 g/dl (*n* = 701)
- ≥9.0 g/dl (*n* = 1232)

Propensity Score Matching

Analyzed in this study[c]:
- <9.0 g/dl (*n* = 632)
- ≥9.0 g/dl (*n* = 632)

Figure 1. Patient disposition. (a) MDV database and (b) RWD database.
[a]Defined as the first date of darbepoetin alfa or CERA prescription.
[b]180 days before the index date.
[c]After 1:1 propensity score matching.
CERA, continuous erythropoietin receptor activator; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; MDV, Medical Data Vision Co. Ltd. database; RWD, Real World Data Co. Ltd. database.

Table 1. Patient baseline characteristics

Characteristics	MDV			RWD		
	Early treatment (n = 736)	Delayed treatment (n = 736)	Standardized difference	Early treatment (n = 632)	Delayed treatment (n = 632)	Standardized difference
Age, yr	73.8 ± 12.8	74.1 ± 13.2	0.023	74.7 ± 10.2	74.8 ± 10.8	0.008
Sex, female	337 (45.8)	326 (44.3)	0.030	298 (47.2)	296 (46.8)	0.006
Baseline hemoglobin, g/dl	9.7 ± 0.5	8.3 ± 0.6	NA	9.8 ± 0.5	8.1 ± 0.8	NA
Baseline eGFR, ml/min per 1.73 m^2	18.9 ± 9.6	18.9 ± 10.1	< 0.001	21.0 ± 10.4	20.9 ± 11.3	0.008
<15	300 (40.8)	329 (44.7)	0.080	212 (33.5)	241 (38.1)	0.096
15 to <30	331 (45.0)	294 (39.9)	0.102	302 (47.8)	268 (42.4)	0.108
30 to <45	93 (12.6)	102 (13.9)	0.036	99 (15.7)	97 (15.3)	0.009
45 to <60	12 (1.6)	11 (1.5)	0.011	19 (3.0)	26 (4.1)	0.060
Baseline albumin, g/dl	3.5 ± 0.6	3.5 ± 0.5	0.005	3.4 ± 0.6	3.4 ± 0.5	0.011
Comorbidities[a]						
Hypertension (with RASi)	436 (59.2)	447 (60.7)	0.031	320 (50.6)	327 (51.7)	0.022
Hypertension (without RASi)	598 (81.3)	596 (81.0)	0.007	495 (78.3)	489 (77.4)	0.023
Diabetes mellitus	268 (36.4)	273 (37.1)	0.014	209 (33.1)	210 (33.2)	0.003
Dyslipidemia	305 (41.4)	302 (41.0)	0.008	221 (35.0)	225 (35.6)	0.013
Medical history[b]						
Cardiovascular disease	477 (64.8)	485 (65.9)	0.023	471 (74.5)	466 (73.7)	0.018
Connective tissue disease	64 (8.7)	66 (9.0)	0.010	46 (7.3)	50 (7.9)	0.024
Year of long-acting ESA initiation						
2011	28 (3.8)	31 (4.2)	0.021	16 (2.5)	20 (3.2)	0.038
2012	51 (6.9)	64 (8.7)	0.066	30 (4.7)	43 (6.8)	0.088
2013	59 (8.0)	56 (7.6)	0.015	53 (8.4)	44 (7.0)	0.054
2014	98 (13.3)	85 (11.5)	0.054	62 (9.8)	63 (10.0)	0.005
2015	120 (16.3)	111 (15.1)	0.034	92 (14.6)	83 (13.1)	0.041
2016	115 (15.6)	122 (16.6)	0.026	98 (15.5)	106 (16.8)	0.034
2017	133 (18.1)	128 (17.4)	0.018	126 (19.9)	125 (19.8)	0.004
2018	132 (17.9)	139 (18.9)	0.025	155 (24.5)	148 (23.4)	0.026
Darbepoetin alfa	342 (46.5)	428 (58.2)	0.236	335 (53.0)	344 (54.4)	0.029
CERA	394 (53.5)	308 (41.8)	0.236	297 (47.0)	288 (45.6)	0.029

CERA, continuous erythropoietin receptor activator; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; MDV, Medical Data Vision Co. Ltd. database; NA, not applicable; RASi, renin-angiotensin system inhibitor; RWD, Real World Data Co. Ltd. database.
[a]Presence of comorbid hypertension, diabetes mellitus and dyslipidemia was determined from prescribing information.
[b]Past medical history of cardiovascular disease and connective tissue disease was determined from disease codes.
Data are shown as n (%) or mean ± SD.
The early treatment group had hemoglobin levels of ≥9.0 to 11.0 g/dl, and the delayed treatment group had hemoglobin levels of <9.0 g/dl.

Cardiovascular Outcomes

The cardiovascular composite outcomes are shown by cumulative incidence curves in Figure 3. There were significant differences between the early and delayed treatment group curves for the cardiovascular composite outcomes in both the MDV ($P = 0.001$) and RWD data sets ($P = 0.006$) (Figure 3a and b). The risk for the cardiovascular composite outcome was significantly increased in the delayed treatment group compared with the early treatment group in both the MDV (HR: 1.47 [95% CI: 1.16–1.84]) and RWD data sets (HR: 1.34 [95% CI: 1.09–1.64]) (Figure 3c and d).

Regarding the components of the cardiovascular composite outcome (Figure 3c and d, and Supplementary Figure S3A–D), the risks for heart failure were significantly higher in the delayed treatment group in both the MDV data set (HR: 1.50 [95% CI: 1.13–2.00]) and the RWD data set (HR: 1.53 [95% CI: 1.20–1.96]). The history of heart failure and hospitalization due to heart failure within 3 months before the index date were not included in the covariates for

propensity score matching; however, the standardized difference was below the criterion value of 0.1 in both cases, indicating no significant bias between the groups (Supplementary Table S5). The risk for cardiovascular death was significantly increased in the delayed treatment group (HR: 2.00 [95% CI: 1.25–3.18]) only in the MDV data set. The risks for the other cardiovascular components were not significantly different.

Sensitivity Analyses

In the sensitivity analysis, when a hemoglobin cut-off of 8.5 g/dl was applied, the HRs for the renal composite outcome were 1.33 (95% CI: 1.09–1.62) and 1.28 (95% CI: 1.04–1.58) for the MDV and RWD data sets, respectively (Supplementary Figure S4A). The HRs for all-cause mortality were 2.55 (1.69–3.85) and 2.87 (1.94–4.24) for the MDV and RWD data sets, respectively. However, the HRs for the other renal outcome components (renal replacement therapy, eGFR ≥50% reduction, and eGFR <6.0 ml/min per 1.73 m^2) were not statistically significant except for the eGFR ≥50%
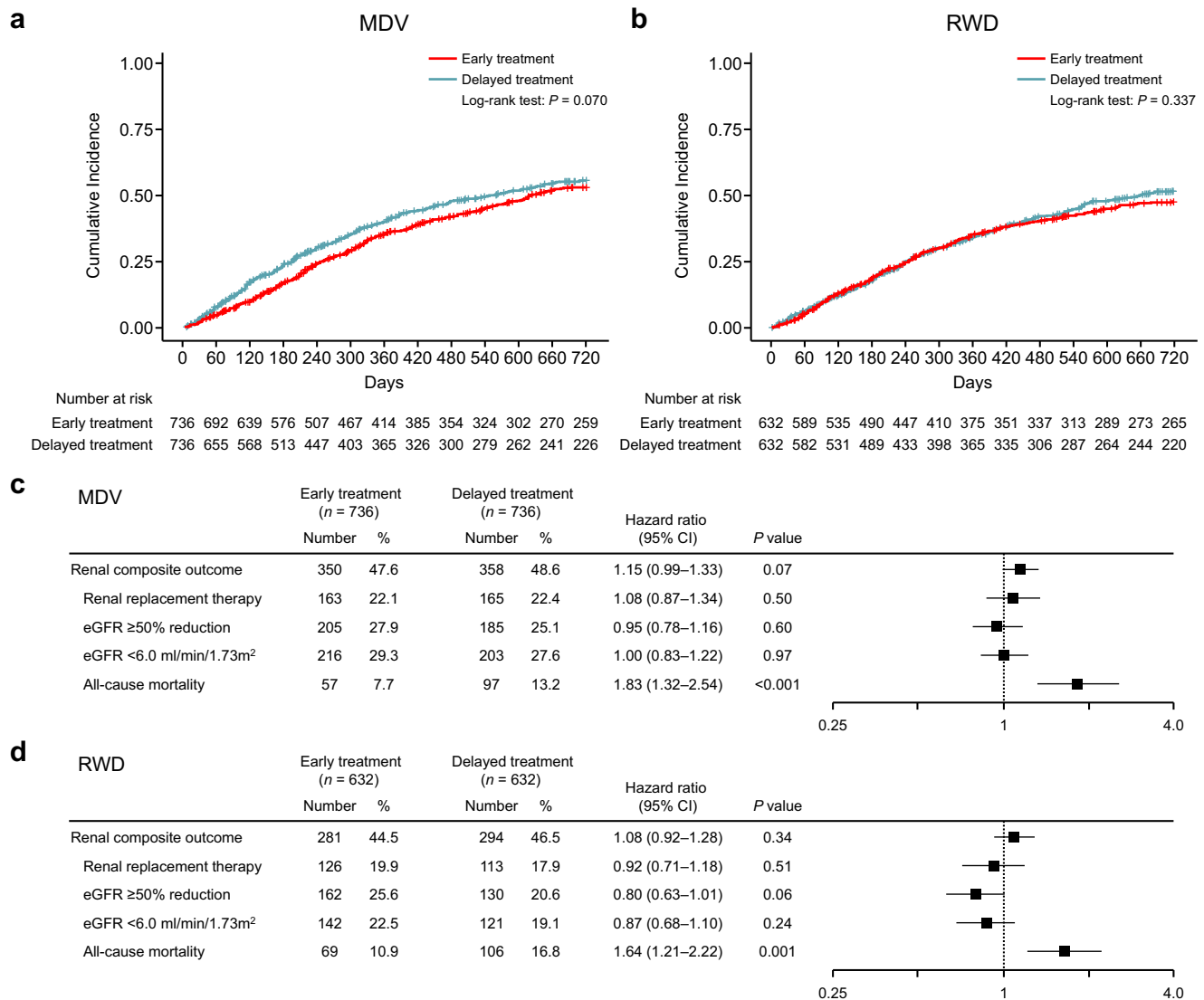
a MDV

b RWD

Number at risk (MDV)

Early treatment	736	692	639	576	507	467	414	385	354	324	302	270	259
Delayed treatment	736	655	568	513	447	403	365	326	300	279	262	241	226

Number at risk (RWD)

Early treatment	632	589	535	490	447	410	375	351	337	313	289	273	265
Delayed treatment	632	582	531	489	433	398	365	335	306	287	264	244	220

c MDV

	Early treatment (n = 736)		Delayed treatment (n = 736)		Hazard ratio (95% CI)	P value
	Number	%	Number	%		
Renal composite outcome	350	47.6	358	48.6	1.15 (0.99–1.33)	0.07
Renal replacement therapy	163	22.1	165	22.4	1.08 (0.87–1.34)	0.50
eGFR ≥50% reduction	205	27.9	185	25.1	0.95 (0.78–1.16)	0.60
eGFR <6.0 ml/min/1.73m²	216	29.3	203	27.6	1.00 (0.83–1.22)	0.97
All-cause mortality	57	7.7	97	13.2	1.83 (1.32–2.54)	<0.001

d RWD

	Early treatment (n = 632)		Delayed treatment (n = 632)		Hazard ratio (95% CI)	P value
	Number	%	Number	%		
Renal composite outcome	281	44.5	294	46.5	1.08 (0.92–1.28)	0.34
Renal replacement therapy	126	19.9	113	17.9	0.92 (0.71–1.18)	0.51
eGFR ≥50% reduction	162	25.6	130	20.6	0.80 (0.63–1.01)	0.06
eGFR <6.0 ml/min/1.73m²	142	22.5	121	19.1	0.87 (0.68–1.10)	0.24
All-cause mortality	69	10.9	106	16.8	1.64 (1.21–2.22)	0.001

Figure 2. Renal outcomes and all-cause mortality in patients treated with ESAs. (a) Kaplan-Meier cumulative incidence curves of the renal composite outcome from the MDV database; (b) Kaplan-Meier cumulative incidence curves of the renal composite outcome from the RWD database; (c) incidence of renal events from the MDV database; and (d) incidence of renal events from the RWD database in propensity score-matched patients. The early treatment group had baseline hemoglobin levels of ≥9.0 to 11.0 g/dl and the delayed treatment group had baseline hemoglobin levels of <9.0 g/dl. CI, confidence interval; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; MDV, Medical Data Vision Co. Ltd. database; RWD, Real World Data Co. Ltd. database.

reduction in the RWD data set. At cut-off values of 8.5 and 9.5 g/dl, the delayed treatment group had a significantly higher HR for the cardiovascular composite outcome compared with the early treatment group for both data sets (Supplementary Figure S4B).

Exploratory Outcomes: Hemoglobin Measurements, ESA Dose, and Frequency of ESA Administration

Hemoglobin measurements over time are shown in Figure 4. The mean differences between the groups at the start of ESA treatment were 1.49 g/dl and 1.62 g/dl for the MDV and RWD data sets, respectively; these differences gradually decreased to 0.30 g/dl (MDV)

and 0.31 g/dl (RWD) at the end of the observation period. ESA dose and frequency are tabulated in Table 2. There was a trend toward higher doses of ESA administration in the delayed treatment group in both data sets.

Subgroup Analyses

When patients were stratified by background characteristics such as age, sex, baseline eGFR, and baseline albumin, no significant interaction in common with the databases was identified between the subgroups in renal (Supplementary Figure S5A and B) or cardiovascular (Supplementary Figure S5C and D) composite outcomes.
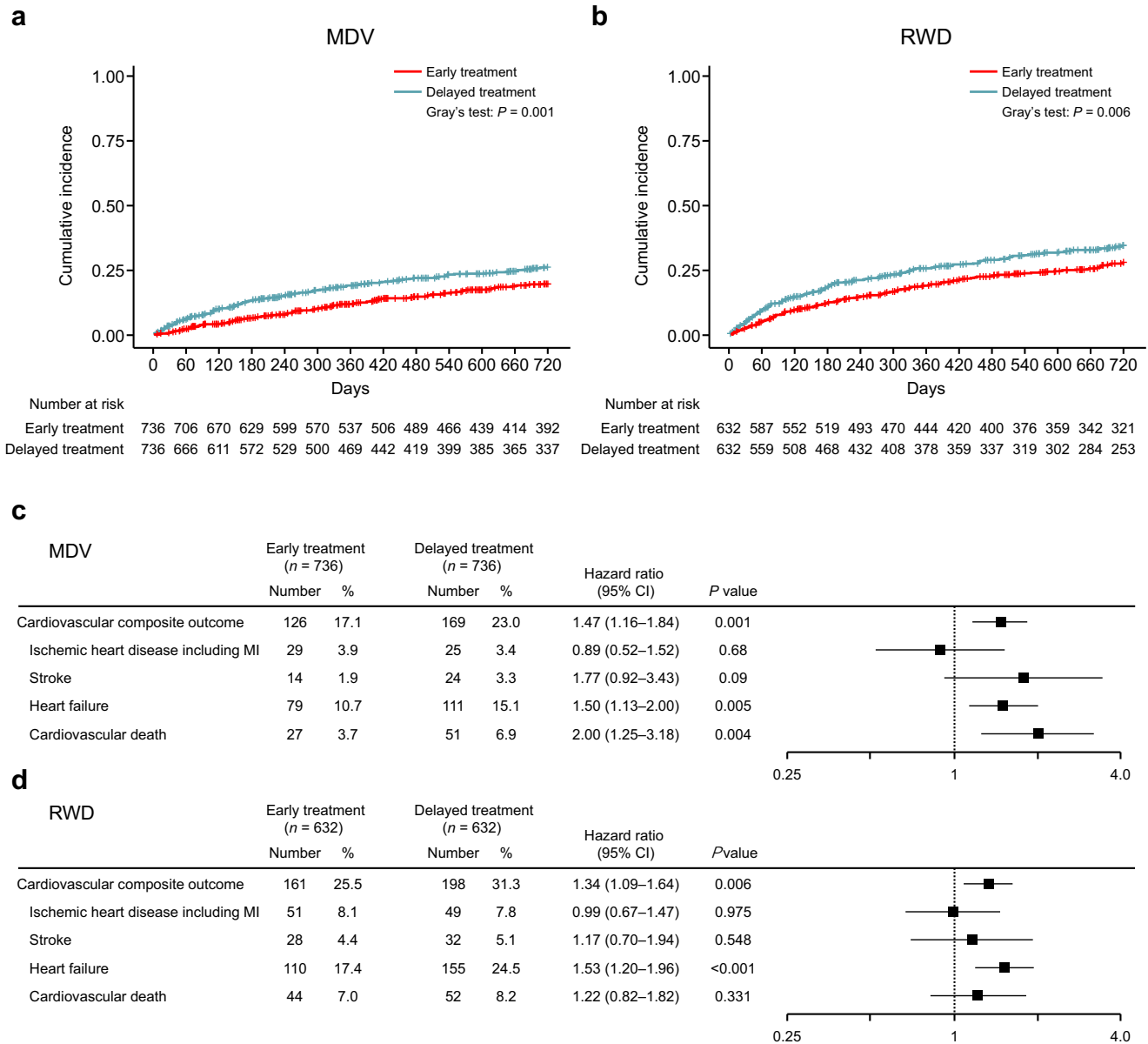
a

b

c

MDV	Early treatment (n = 736)		Delayed treatment (n = 736)		Hazard ratio (95% CI)	P value
	Number	%	Number	%		
Cardiovascular composite outcome	126	17.1	169	23.0	1.47 (1.16–1.84)	0.001
Ischemic heart disease including MI	29	3.9	25	3.4	0.89 (0.52–1.52)	0.68
Stroke	14	1.9	24	3.3	1.77 (0.92–3.43)	0.09
Heart failure	79	10.7	111	15.1	1.50 (1.13–2.00)	0.005
Cardiovascular death	27	3.7	51	6.9	2.00 (1.25–3.18)	0.004

d

RWD	Early treatment (n = 632)		Delayed treatment (n = 632)		Hazard ratio (95% CI)	P value
	Number	%	Number	%		
Cardiovascular composite outcome	161	25.5	198	31.3	1.34 (1.09–1.64)	0.006
Ischemic heart disease including MI	51	8.1	49	7.8	0.99 (0.67–1.47)	0.975
Stroke	28	4.4	32	5.1	1.17 (0.70–1.94)	0.548
Heart failure	110	17.4	155	24.5	1.53 (1.20–1.96)	<0.001
Cardiovascular death	44	7.0	52	8.2	1.22 (0.82–1.82)	0.331

Figure 3. Cardiovascular outcomes in patients treated with ESAs. (a) Two-year cumulative incidence curves of the cardiovascular composite outcome from the MDV database; (b) 2-year cumulative incidence curves of the cardiovascular composite outcome from the RWD database; (c) incidence of cardiovascular events from the MDV database; and (d) incidence of cardiovascular events from the RWD database in propensity score-matched patients. The early treatment group had baseline hemoglobin levels of ≥9.0 to 11.0 g/dl and the delayed treatment group had baseline hemoglobin levels of <9.0 g/dl. CI, confidence interval; ESA, erythropoiesis-stimulating agent; MDV, Medical Data Vision Co. Ltd. database; MI, myocardial infarction; RWD, Real World Data Co. Ltd. database.

DISCUSSION

In this retrospective cohort study using 2 Japanese databases, we evaluated the renal and cardiovascular outcomes of early versus delayed treatment with long-acting ESAs in patients with anemia and NDD-CKD in Japan. Our analysis showed that delayed ESA treatment (initial hemoglobin levels <9.0 g/dl) was not associated with worse renal outcomes compared with early ESA treatment (initial hemoglobin levels ≥9.0 g/dl). However, there was a significantly increased risk of all-cause mortality and cardiovascular events in patients who received delayed ESA treatment.

In clinical practice, treatment for anemia in CKD can be delayed for a variety of reasons. However, assessing the outcomes of delaying renal anemia treatment through prospective trials is not practical because of ethical considerations. Therefore, we compared the renal and cardiovascular outcomes of early versus delayed treatment using real-world databases. The 2 databases revealed generally consistent results, suggesting that our findings are robust and widely applicable to clinical practice in Japan.
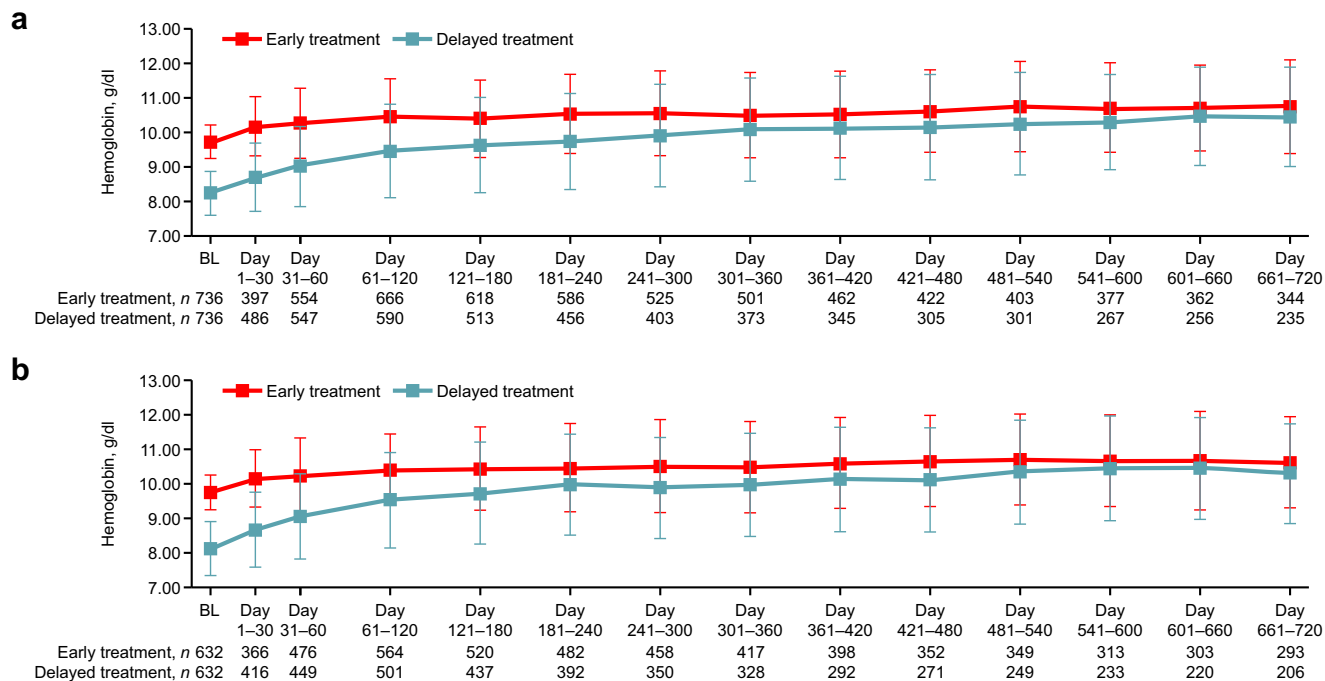
Figure 4. Hemoglobin measurements over time in patients treated with ESAs. (a) Data from the MDV database and (b) data from the RWD database. Symbols indicate the mean value; error bars show SD. BL, baseline; ESA, erythropoiesis-stimulating agent; MDV, Medical Data Vision Co. Ltd. database; RWD, Real World Data Co. Ltd. database.

Delayed ESA treatment was not associated with a risk in the renal composite outcome and component events, such as renal replacement therapy, reduction in eGFR $\geq$50%, or eGFR <6.0 ml/min per 1.73 m^2, unlike the previous JET-STREAM study.[14] A possible explanation may be that the differences in hemoglobin levels between groups at the start of treatment were relatively small ($\sim$1.5 g/dl), whereas the previous study reported a difference of 2.1 g/dl between the groups.[14] Furthermore, an increased risk of renal events was identified in the group with initial hemoglobin levels <9 g/dl versus the 10 to <11 g/dl group when the 9 to <10 g/dl group was excluded, which may be one of the reasons the increased risk was clearly identified.[14] Therefore, a larger mean

difference in hemoglobin levels may have been necessary to identify a difference in renal event risk. Other observational studies focusing on patients who achieved hemoglobin levels of 11 g/dl after 3 months of long-acting ESA treatment revealed a reduced risk of renal events.[17,18] Therefore, although the connection was not clearly identified in the current study, future investigations regarding the relationship between anemia treatment and renal outcomes are warranted. Consistent with previous reports[19-21] that severe anemia is a risk factor for mortality in CKD and end-stage renal disease, delayed treatment for anemia was associated with a significantly increased risk of all-cause mortality in this study. A previous observational cohort study revealed that higher hemoglobin

Table 2. Erythropoiesis-stimulating agent dose and frequency

Types of ESA	MDV		RWD	
	Early	Delayed	Early	Delayed
Darbepoetin alfa				
n	342	428	335	344
Dose, μg/mo	39.87 ± 32.21	53.90 ± 58.45	45.91 ± 42.67	58.55 ± 53.59
Dose frequency/mo	0.75 ± 0.51	0.88 ± 0.70	0.60 ± 0.39	0.66 ± 0.47
CERA				
n	394	308	297	288
Dose, μg/mo	49.89 ± 45.86	57.15 ± 43.05	60.24 ± 95.21	88.91 ± 169.47
Dose frequency/mo	0.72 ± 0.47	0.75 ± 0.51	0.75 ± 0.62	0.85 ± 0.84

CERA, continuous erythropoietin receptor activator; ESA, erythropoiesis-stimulating agent; MDV, Medical Data Vision Co. Ltd. database; RWD, Real World Data Co. Ltd. database.
Data are shown as n or mean ± SD.
The early treatment group had hemoglobin levels of ≥9.0–11.0 g/dl, and the delayed treatment group had hemoglobin levels of <9.0 g/dl. ESA dose and frequency were evaluated from the first administration on the index date over the follow-up window (180-day follow-up after the observation period) until last hospital visit, the day before blood transfusion (up to 720 days from the index date), or death. ESA administration data after switching ESA type (darbepoetin alfa to CERA or vice versa) were not included.

levels (10 or 11 g/dl) at ESA treatment initiation were associated with improved survival compared with the entire study cohort of patients with CKD and those who did not receive any treatment.[22] Moreover, the study showed that the 3-year survival rate decreased as hemoglobin levels at ESA initiation decreased from 11.0 to 9.0 g/dl, which also suggests the importance of early intervention for anemia. When analyzing the current data with a hemoglobin cut-off of 8.5 g/dl in the sensitivity analysis, the risk of all-cause mortality was numerically increased, indicating that the severity of anemia at the start of ESA treatment may be linked to an elevated risk of death from any cause.

We observed an increased risk of cardiovascular composite outcome and heart failure in the delayed treatment group across both databases. This is consistent with previous studies that have reported that anemia is a risk factor for heart failure.[23,24] The oxygen shortage caused by renal anemia exacerbates left ventricular hypertrophy and subsequent progression of heart failure, leading to a worse prognosis.[25,26] This mechanism may also have contributed to the increased risk of heart failure and cardiovascular death in the delayed treatment group in the present study. Conversely, the risks of stroke and ischemic heart disease, including myocardial infarction, were not increased in the delayed treatment group. Japanese patients with CKD have been reported to have a lower cardiovascular burden compared with Western patients with CKD.[27] Therefore, the changes in the risk of stroke and ischemic heart disease including myocardial infarction associated with hemoglobin levels at the start of ESA treatment may be difficult to evaluate because these events are less likely to occur in Japanese patients with CKD.

Our study provides new insights into clinical practice regarding hemoglobin levels at the start of long-acting ESA treatment and outcomes in patients with anemia in NDD-CKD, for which there has been little evidence to date. Furthermore, we have highlighted the potential risks associated with delayed ESA treatment of anemia. Previous Japanese and international observational studies have reported that the proportion of patients with anemia who receive ESA treatment is low, even among patients with hemoglobin levels below the guideline range.[3,28] We have previously reported that the mean hemoglobin level at ESA treatment initiation in patients with anemia and NDD-CKD was 9.1 g/dl,[15] which is below the Japanese guideline's recommendation, suggesting that an evidence–practice gap exists in anemia treatment. Combined with the findings of the present study, earlier intervention than current practice for anemia in NDD-CKD may be desirable to avoid cardiovascular events and mortality in these patients.

The results of this study should be interpreted in light of several limitations. The assignment of diagnoses based on health insurance claims data may have resulted in the inclusion of inaccurate data.[29] In this study, patients were classified into early and delayed groups based on hemoglobin levels just before the start of ESA treatment. Although serial hemoglobin measurements were not used to categorize patients, only a few patients in the delayed group had rapid anemia progression defined as a decrease in hemoglobin levels >2.0 g/dl over 30 days (data not shown). We were unable to adjust for some confounding factors, such as transferrin saturation[30] and C-reactive protein[31] levels, because of an insufficient number of cases with these data. Unmeasured confounding factors and the lack of information on the severity of comorbidities may also have resulted in a bias between the groups. Furthermore, patients who transferred to another facility could not be identified in these databases, and thus the number of events may be underestimated.

In conclusion, delayed treatment of anemia in Japanese patients with NDD-CKD was not associated with a risk of renal events; however, it was associated with risks of cardiovascular events and all-cause mortality, highlighting the importance of early intervention before hemoglobin values fall below 9.0 g/dl.

DISCLOSURE

ACKNOWLEDGMENTS

DATA AVAILABILITY STATEMENT

The data sets generated and/or analyzed during the current study are not publicly available because the data were obtained from Medical Data Vision Co. Ltd. and Real World Data Co. Ltd., but they are available from the corresponding author with the permission of Medical Data Vision Co. Ltd., and Real World Data Co. Ltd on reasonable request.

AUTHOR CONTRIBUTIONS

KK contributed to the conception or design of the work, interpretation of data for the work, and drafting the work or revising it critically for important intellectual content. MI contributed to the conception or design of the work, interpretation of data for the work, drafting the work or revising it critically for important intellectual content, and planning of the data analysis (but did not perform the data analysis). YK contributed to the conception or design of the work, interpretation of data for the work, and drafting the work or revising it critically for important intellectual content. TH contributed to the conception or design of the work, interpretation of data for the work, and drafting the work or revising it critically for important intellectual content. JH contributed to the conception or design of the work, interpretation of data for the work, and drafting the work or revising it critically for important intellectual content. All the authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work, including ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Propensity score distribution before and after propensity score matching.

Figure S2. Renal outcomes by early and delayed ESA treatment groups.

Figure S3. Cardiovascular outcomes by early and delayed ESA treatment groups.

Figure S4. Sensitivity analyses of renal and cardiovascular outcomes.

Figure S5. Subgroup analysis for renal and cardiovascular composite outcomes by patient characteristics.

Table S1. Detailed inclusion and exclusion criteria.

Table S2. Database codes used in this study.

Table S3. Detailed reasons for patient exclusion.

Table S4. Patient baseline characteristics before propensity score matching.

Table S5. Patient baseline characteristics for those with a medical history of heart failure.

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