Renal Replacement Therapy

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Cardiovascular events by different target hemoglobin levels in ESA-hyporesponsive hemodialysis patients: a multicenter, open-label, randomized controlled study

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Abstract

Background: The incidence of cardiovascular (CV) events is high in hemodialysis (HD) patients and is associated with hyporesponsiveness to erythropoiesis-stimulating agents (ESAs). However, there are no recommended target hemoglobin ranges for ESA-hyporesponsive patients.

Methods: We randomly assigned 304 ESA-treated HD patients with ESA hyporesponsiveness to a proactive treatment group (target hemoglobin level 11 g/dL) or maintenance treatment group (target hemoglobin level 9–10 g/dL), both of which received epoetin beta pegol. The primary outcome was time to the first CV event. CV events included cardiac death, heart failure, and acute coronary syndrome requiring hospitalization. The patients were followed for 24 months.

Results: The proactive and maintenance treatment groups had mean baseline hemoglobin levels of 9.34 and 9.32 g/dL, respectively. Mean hemoglobin levels during the observation period were 10.58 and 10.26 g/dL ($P < 0.001$), and mean durations of hemoglobin level > 10.5 g/dL were 11.5 and 8.6 months ($P < 0.001$), respectively. Cox proportional hazards analysis demonstrated a significantly lower risk of CV events in the proactive group (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.19–0.96). This lower risk was driven by lower incidence of hospitalization-required congestive heart failure. A longer duration of hemoglobin level > 10.5 g/dL was associated with a lower risk of CV events (HR, 0.92/month; 95% CI, 0.87–0.98).

Conclusions: Targeting hemoglobin levels of 11 g/dL with epoetin beta pegol reduces CV risk in Japanese HD patients with ESA hyporesponsiveness.

Trial registration: University Hospital Medical Information Network (UMIN) database (UMIN000010138), registered on March 1, 2013.

Keywords: ESA hyporesponsiveness, Cardiovascular events, Hemodialysis, Target hemoglobin

Background

Renal anemia is prevalent in most hemodialysis (HD) patients and is associated with an increased risk of cardiovascular (CV) events. Therefore, the appropriate treatment of renal anemia in HD patients is expected to relieve the symptoms of anemia, reduce the risk of fatal

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diseases such as heart failure, and improve prognosis [1, 2].

Erythropoiesis-stimulating agents (ESAs) and iron preparations are used for the treatment of renal anemia; however, treatment strategies using these agents differ between Japan and other countries [3, 4]. The guidelines of the Japanese Society for Dialysis Therapy (JSDT) state that the criterion for starting treatment with ESAs in HD patients is "when multiple tests show a decrease in the hemoglobin level to < 10 g/dL," whereas the standardized guidelines in Europe and the United States state that "hemoglobin levels should be kept above 9 g/dL in patients with hemoglobin levels of 9–10 g/dL, and the decision should be made on a case-by-case basis as a common complication of chronic kidney disease (CKD)." However, the optimal target hemoglobin levels for patients with various stages of CKD are unclear.

Recently, there has been increasing attention on the relationship between ESA responsiveness and prognosis. A Japanese observational study analyzing the relationship between ESA responsiveness and mortality in HD patients reported a high risk of death in patients with low hemoglobin levels (< 10 g/dL) receiving high-dose ESA therapy (≥ 6000 IU/week epoetin) [5]. Additionally, another Japanese observational study reported a high risk of death in HD patients with low hemoglobin levels receiving high-dose ESA therapy [6]. Furthermore, a Korean observational study showed a high incidence of CV events in HD patients with a poor response to ESAs [7]. However, there are no current treatment strategies taking ESA responsiveness into account; therefore, this issue remains to be addressed. We initiated a large-scale clinical trial enrolling ESA-hyporesponsive patients with renal anemia on HD, with a focus on the influence of different hemoglobin target ranges by ESA on the incidence of CV events.

Methods

Study design and subjects

This was a multicenter, open-label, randomized parallel-group study. Patients were enrolled at 85 institutions in Japan. Subjects were Japanese HD patients with ESA-hyporesponsive renal anemia who met all the following five inclusion criteria, but did not meet any of the five exclusion criteria. A flowchart of patient enrollment and analysis is shown in Fig. 1.

Inclusion criteria: (1) aged between 20 and 85 years at the time of informed consent; (2) receiving treatment for renal anemia with any ESA; (3) has been on HD for at least one year; (4) poor ESA responder, defined as no improvement in anemia after 6-month treatment with ESAs (a detailed definition of poor ESA responders is provided in Fig. 2); and (5) written consent to participate in this study.

Exclusion criteria: (1) anemia of non-renal origin: patients were excluded if they had obvious hemorrhagic lesions or hematologic disease (e.g., leukemia, malignant lymphoma, myelodysplastic syndrome, aplastic anemia) or if they had obvious chronic inflammation (e.g., rheumatoid arthritis, inflammatory bowel disease); (2) hypersensitive to any portion of the epoetin beta pegol molecule or any ingredients in erythropoietin formulations or darbepoetin alfa; (3) malignancy: patients were eligible if 5 years had elapsed since the last surgery and it was deemed that the malignancy was cured; (4) pregnant or may be pregnant, breastfeeding, or wished to become pregnant while participating in the study (women only); and (5) judged by the investigator or sub-investigator to be unsuitable as a subject for this randomized study for other reasons.

A data center (EP-CRSU Co., Ltd, Tokyo, Japan) was responsible for patient enrollment and randomization, data monitoring, data collection, and checking the quality of the data. The members of the Executive Committee had access to all the study data. CV events (including hospitalization-required CV events), cerebrovascular events, and death for other reasons were adjudicated by the Event Evaluation Committee.

This study was conducted in compliance with the Declaration of Helsinki and "Ethical Guidelines for Clinical Studies" by the Ministry of Health, Labour and Welfare and in accordance with the International Council for Harmonization Good Clinical Practice guidelines. The study was approved by an independent central ethics committee and is registered in the University Hospital Medical Information Network (UMIN) database (UMIN000010138). Study treatments were covered by ordinary health insurance. This report was prepared according to Consolidated Standards of Reporting Trials.

Random assignment

The subjects were randomized after a centralized enrollment at the data center. They were dynamically assigned to the proactive treatment group or the maintenance treatment group at a ratio of 1:1 using a minimization method with randomization factors (Fig. 2). The details of the assignment procedures were determined by the person responsible for statistical analyses and were not communicated to the investigator or sub-investigator.

Treatment methods

In the proactive treatment group, epoetin beta pegol was administered with a target hemoglobin level of 11 g/dL. In the maintenance treatment group, epoetin beta pegol was administered to maintain the hemoglobin level in

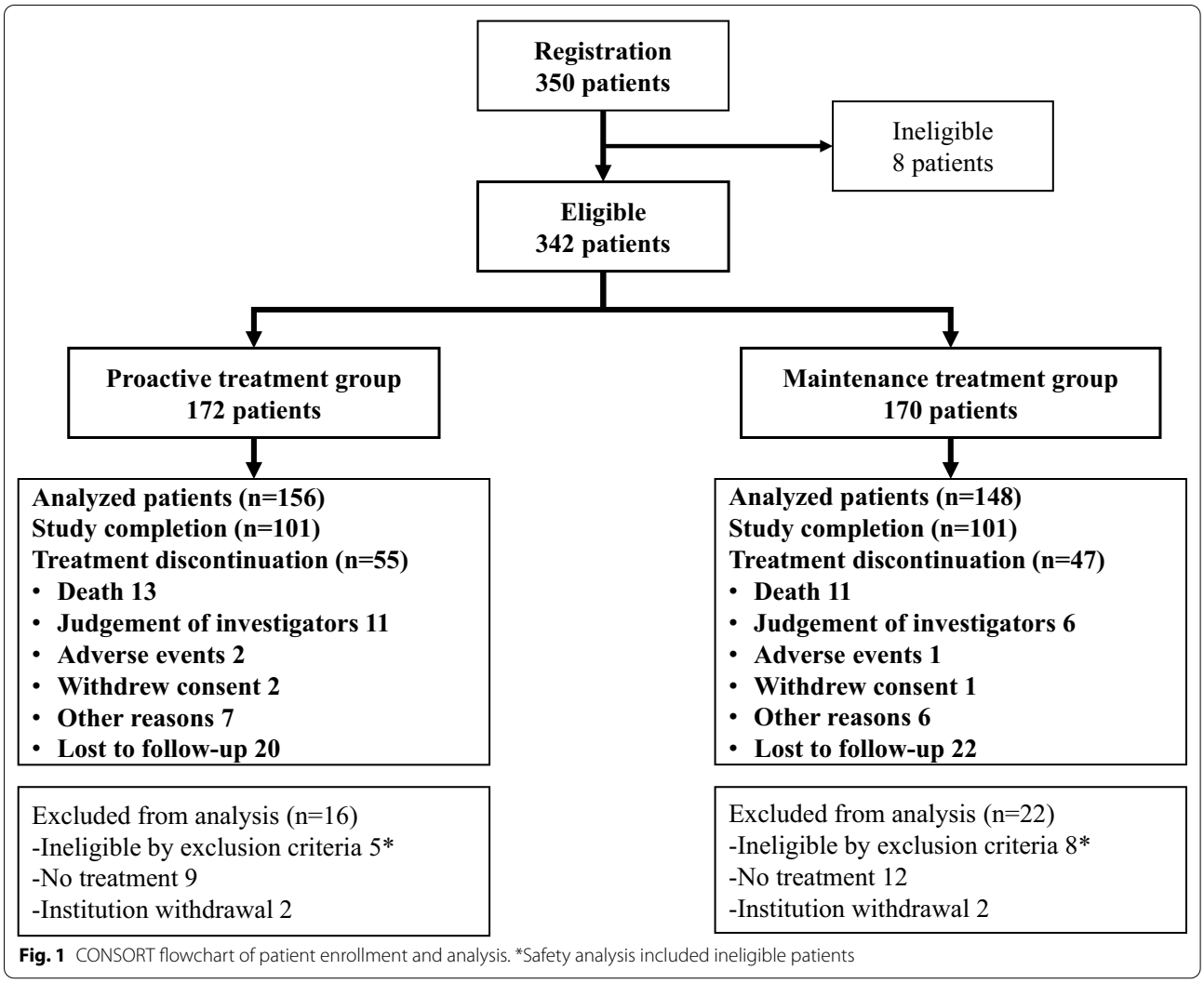

Fig. 1 CONSORT flowchart of patient enrollment and analysis. *Safety analysis included ineligible patients

the range of 9–10 g/dL. Study treatments were continued for 24 months. Dose of epoetin beta pegol was titrated as follows: In the proactive treatment group, if a subject's hemoglobin level did not exceed 10 g/dL and did not increase by at least 0.5 g/dL/4 weeks, epoetin beta pegol was increased by 1 step (25 μg). Also, if the epoetin beta pegol dose was increased by 1 step, an interval of at least 4 weeks from previous administration was kept. If the hemoglobin level increased to 10 g/dL or higher in a subject who received epoetin beta pegol every 2 weeks, the dose of epoetin beta pegol was doubled and the interval was changed to 4 weeks, and then, the dose was adjusted to maintain the hemoglobin level of 10 g/dL or higher. If the administration of once every 4 weeks could not maintain the hemoglobin level of 10 g/dL or higher, the dose was halved and the frequency of administration was changed to once every 2 weeks, and then, the dose was adjusted to maintain the hemoglobin level of 10 g/dL or higher.

In the maintenance treatment group, if the enrollment hemoglobin level was maintained in the range of 9 to10 g/dL in a subject who received epoetin beta pegol every 2 weeks, the dose of epoetin beta pegol was doubled and the interval was changed to 4 weeks, and then, the dose was adjusted to maintain the hemoglobin level in the range of 9 to 10 g/dL. If the hemoglobin level fell below 9 g/dL, the dose was adjusted to maintain a level of at least 9 g/dL.

Endpoints

The primary endpoint was CV event consisting of cardiac death (death due to heart failure, fatal myocardial infarction, or sudden cardiac death), heart failure requiring hospitalization, or acute coronary syndrome (non-fatal

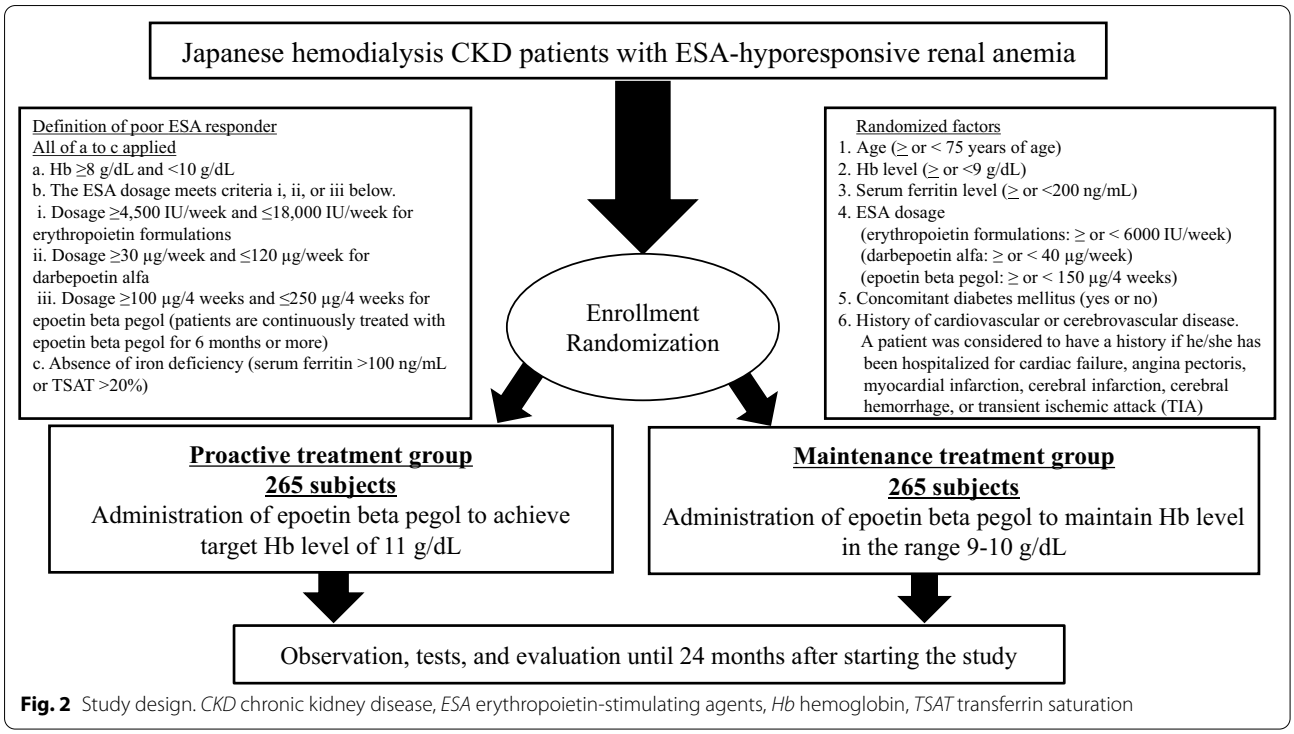

Fig. 2 Study design. *CKD* chronic kidney disease, *ESA* erythropoietin-stimulating agents, *Hb* hemoglobin, *TSAT* transferrin saturation

myocardial infarction or unstable angina) requiring hospitalization. The time from the date of study treatment initiation to the first CV event was evaluated. Secondary endpoints included (a-i) incidence of cerebrovascular events, (a-ii) incidence of composite events, (b) total deaths, and (c) safety.

Statistical analyses

Based on previous Japanese nationwide clinical studies [5, 6], we assumed the incidence of CV events would be 30% lower in the group with a target hemoglobin of 11 g/dL (proactive treatment group) than that in the group in which hemoglobin was maintained at 9–10 g/dL (maintenance treatment group).

We calculated the required number of randomized subjects at 508 for the two groups combined when the statistical power was set to be 80%, with a one-sided level of significance of 5% and a follow-up period of 24 months. Assuming a dropout rate of 5%, the number of subjects to be recruited was 530.

All analyses followed the intention-to-treat principle. The efficacy analysis set was the full analysis set, which included all assigned subjects excluding subjects who (1) were judged to be ineligible after enrollment, (2) did not receive the study drug at all after randomization, and (3) had no efficacy data after starting treatment. The primary outcome (time from the date of study treatment initiation to the first CV event) was compared using the log-rank test with Kaplan–Meier curves. The Cox proportional hazards model was used to calculate the hazard ratio (HR) of the proactive group as compared with the maintenance treatment group with its corresponding 95% confidence interval (CI). A similar method was used for secondary endpoints (incidence of cerebrovascular events, composite events, and all-cause deaths). In addition, time-dependent hemoglobin levels were analyzed using the mixed model repeated measures with post-treatment hemoglobin levels assessed at each visit point (at least once every 4 weeks) as response values; treatment group, visit (time), baseline hemoglobin levels, and interaction term of treatment group and visit as fixed effects; and each patient as a random effect. Ferritin and transferrin saturation (TSAT) values were similarly assessed. Safety was analyzed using the safety analysis set, which comprised all randomized subjects who received the study treatment at least once. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Between April 2013 and December 2015, 350 patients were registered, and 342 patients who met the eligibility criteria were enrolled as subjects and randomly assigned. After excluding assigned subjects who withdrew consent or received no treatment, the full analysis set comprised 304 subjects: 156 in the proactive

treatment group and 148 in the maintenance treatment group. Details of the enrolled subjects are shown in Fig. 1 and their background characteristics are shown in Table 1.

Changes in hemoglobin level, dose of epoetin beta pegol, and iron status

At 6 months, the mean hemoglobin levels in the proactive and maintenance treatment groups increased from

Table 1 Patients' baseline characteristics

Baseline characteristics	Proactive treatment group ($n=156$)		Maintenance treatment group ($n=148$)		*P* value
	Number	Mean ± SD or median (IQR)	Number	Mean ± SD or median (IQR)	
Age, years	156	68 ± 10	148	68 ± 12	0.73
Dry weight, kg	154	55.6 ± 11.1	147	55.2 ± 13.2	0.77
Dialysis vintage, years	156	8.9 ± 7.2	148	8.2 ± 7.7	0.41
Hb level, g/dL	156	9.3 ± 0.5	148	9.3 ± 0.5	0.82
Ferritin, ng/mL	156	123.5 (59.5, 194.7)	148	100.7 (57.0, 160.7)	0.035[a]
TSAT%	134	28.4 ± 10.6	133	29.2 ± 10.6	0.54
Iron, μg/dL	143	53.4 ± 23.3	128	58.5 ± 25.5	0.09
UIBC, μg/dL	33	184.1 ± 47.8	33	184.2 ± 44.2	0.99
TIBC, μg/dL	103	227.2 ± 46.5	84	237.3 ± 49.0	0.15
Systolic blood pressure, mmHg	154	151.7 ± 24.0	148	152.5 ± 22.9	0.78
Diastolic blood pressure, mmHg	154	77.5 ± 13.8	148	77.3 ± 13.5	0.91
Serum albumin, g/dL	155	3.5 ± 0.4	148	3.5 ± 0.4	0.15
CRP	156	0.22 (0.06, 0.60)	148	0.18 (0.06, 0.60)	0.86
Prior ESA therapy	**Number**	**Median (IQR)**	**Number**	**Median (IQR)**	***P*-value[a]**
Epoetin beta pegol, μg/4Ws	29	150 (100, 150)	24	100 (100, 200)	0.69
Darbepoetin, μg/W	74	60 (40, 60)	74	40 (40, 60)	0.50
Erythropoietin, IU/W	53	9,000 (6,000, 9,000)	50	9,000 (6,000, 9,000)	0.80
Primary disease[b]	**Number**	**Ratio (%)**	**Number**	**Ratio (%)**	***P*-value**
Chronic glomerulonephritis	30	19	35	24	0.35
Diabetic nephropathy	65	42	53	36	0.30
Nephrosclerosis	17	11	16	11	0.98
Other disease	45	29	45	30	0.77
Complicating disease[b]	**Number**	**Ratio (%)**	**Number**	**Ratio (%)**	***P*-value**
Cardiac disease	76	49	81	55	0.30
Cardiac failure	27	17	29	20	0.66
Angina pectoris	48	31	39	26	0.45
Myocardial infarction	8	5	5	3	0.57
Arrhythmia	4	3	10	7	0.10
Others	40	26	38	26	1.00
Cerebrovascular disease	36	23	32	22	0.78
Arteriosclerosis obliterans	43	28	40	27	1.00
Diabetes mellitus	69	44	61	41	0.64
Hyperlipidemia	26	17	23	16	0.88
Concomitant medication	**Number**	**Ratio (%)**	**Number**	**Ratio (%)**	***P* value**
RAS-I	70	45	75	51	0.31
β-blocker	18	12	15	10	0.69
Antiplatelet	75	48	77	52	0.49

P values were determined by *t*-test except for [a]Wilcoxon rank-sum test. [b]Multiple answers allowed

ESA erythropoiesis-stimulating agent, *Hb* hemoglobin, *IQR* interquartile range, *SD* standard deviation, *TIBC* total iron binding capacity, *TSAT* transferrin saturation, *UIBC* unsaturated iron binding capacity, *CRP* C-reactive protein, *W* week, *RAS-I* renin–angiotensin–aldosterone inhibitor

treatment initiation (9.88 g/dL and 9.84 g/dL) to 10.77 g/dL and 10.20 g/dL, respectively, and the mean hemoglobin levels during the intervention period were 10.58 g/dL and 10.26 g/dL, respectively (mixed model repeated measures: $P<0.001$) (Additional file 1: Fig. S1).

The median monthly dose of epoetin beta pegol for 6 months after treatment initiation was not significantly different between the groups (Wilcoxon test: $P=0.30$). However, the frequency of epoetin beta pegol administration during 6 months after treatment initiation was significantly different between the groups. Epoetin beta pegol was administered once every 2 weeks in 86.5% of patients in the proactive treatment group and in 72.3% of patients in the maintenance treatment group (Fisher's exact test: $P<0.001$; Additional file 1: Table S1). There was no significant difference in changes of ferric status such as serum ferritin levels, but TSAT showed a significant difference ($P<0.05$) (Additional file 1: Fig. S2).

Primary endpoint

CV events occurred in 27 patients in the two groups (9 patients in the proactive treatment group and 18 patients in the maintenance treatment group). Cumulative incidence of primary CV events was significantly different between the two groups (Kaplan–Meier analysis, log-rank test: $P=0.03$). In HD patients with ESA-hyporesponsive renal anemia, the proactive treatment group (target hemoglobin level of 11 g/dL) had significantly lower CV events compared with the maintenance treatment group (maintained hemoglobin level in the range 9–10 g/dL; Fig. 3).

The incidence of CV events was 5.8% in the proactive treatment group and 12.2% in the maintenance treatment group. Cox proportional hazards analysis showed a significantly lower risk of CV events in the proactive group (HR, 0.43; 95% CI, 0.19–0.96) compared with the maintenance treatment group (Table 2). In terms of type of CV event, the frequencies of cardiac death, acute coronary syndrome requiring hospitalization, and heart failure requiring hospitalization in the proactive and maintenance treatment groups were 3.2% and 4.7%, 1.3% and 2.0%, and 1.9% and 6.1%, respectively.

Secondary endpoints

The incidence of cerebrovascular events, composite events, and all-cause deaths were not significantly different between the two groups (Table 2). Serious adverse events (SAEs) that occurred in the safety analysis set ($n=317$) were comparable between the two groups (Additional file 1: Table S2). Major SAEs were as follows in the two groups (proactive treatment group and maintenance group): pneumonia, 18 patients (10 and 8);

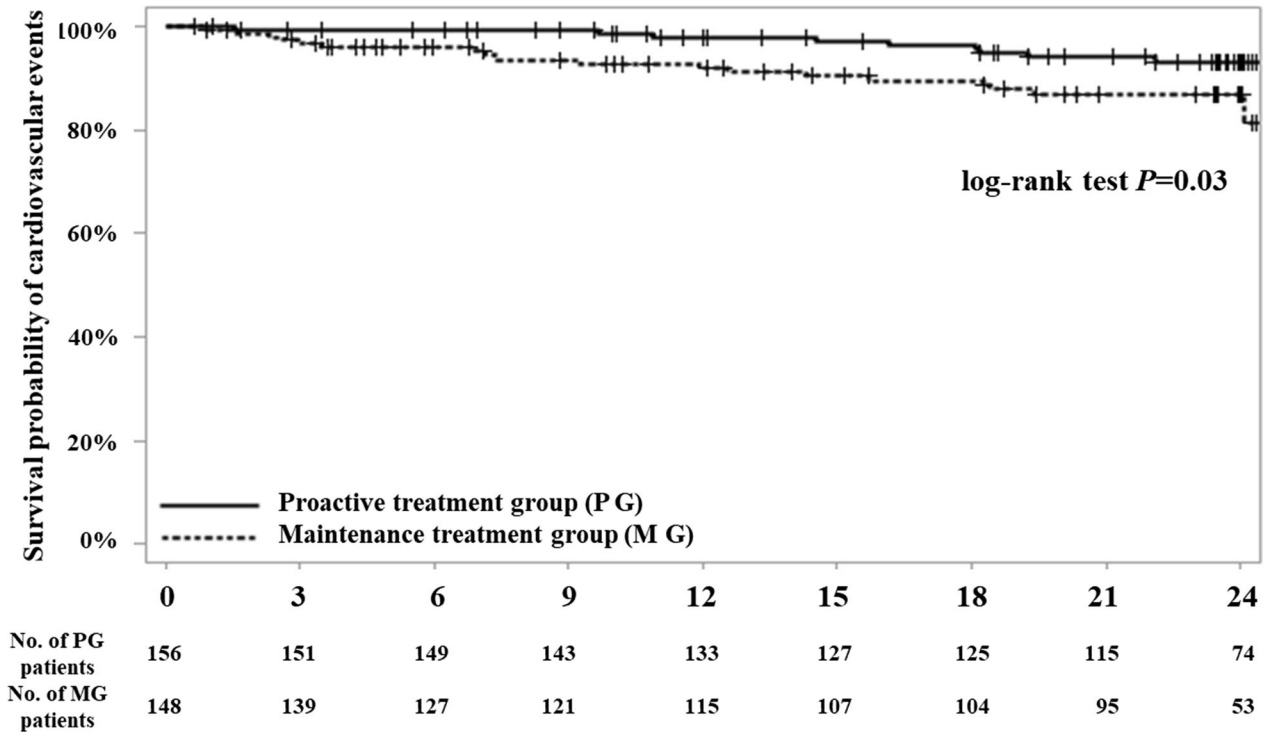

Fig. 3 Cardiovascular events by treatment group

Table 2 Incidence of events

Cardiovascular events	**Number of patients**	**Number of events**	**Ratio (%)**	**HR**	**95% CI**			***P* value**
Proactive treatment group	156	9	5.8	0.43	0.19	–	0.96	0.04
Maintenance treatment group	148	18	12.2					
Detail of cardiovascular events		**Proactive treatment group (*n* = 156)**			**Maintenance treatment group**			
		Number	**Ratio (%)**		**Number**		**Ratio (%)**	
Total cardiovascular events		9	5.8		18		12.2	
Cardiac death		5	3.2		7		4.7	
Fatal myocardial infarction		1	0.6		1		0.7	
Death due to heart failure		1	0.6		1		0.7	
Sudden cardiac death		3	1.9		5		3.4	
Acute coronary syndrome requiring hospitalization		2	1.3		3		2.0	
Non-fatal myocardial infarction		1	0.6		0		0.0	
Unstable angina		2	1.3		3		2.0	
Heart failure requiring hospitalization		3	1.9		9		6.1	
Cerebrovascular events	**Number of patients**	**Number of events**	**Ratio (%)**	**HR**	**95% CI**			***P* value**
Proactive treatment group	156	8	5.1	0.87	0.33	–	2.32	0.78
Maintenance treatment group	148	8	5.4					
Composite events	**Number**	**Number of events**	**Ratio (%)**	**HR**	**95% CI**			***P* value**
Proactive treatment group	156	17	10.9	0.59	0.32	–	1.09	0.09
Maintenance treatment group	148	25	16.9					
All-cause deaths	**Number**	**Number of events**	**Ratio (%)**	**HR**	**95% CI**			***P* value**
Proactive treatment group	156	18	11.5	0.97	0.50	–	1.88	0.93
Maintenance treatment group	148	17	11.5					

HR and its 95%CI, *P* values were obtained by Cox proportional hazards model. Multiple answers allowed

HR hazard ratio, *CI* confidence interval

angina pectoris, 13 patients (7 and 6); peripheral arterial occlusive disease, 11 patients (7 and 4); large intestine polyp, 10 patients (7 and 3); cerebral infarction, 9 patients (4 and 5); and fever, 8 patients (3 and 5). However, the proportion of patients with shunt occlusion and any cancer (Additional file 1: Table S3) was higher in the proactive group than in the maintenance group.

Exploratory analyses

The mean duration of hemoglobin level > 10.5 g/dL was significantly longer in the proactive treatment group (11.5 months) than in the maintenance treatment group (8.6 months), and the proportion of subjects with a hemoglobin level > 10.5 g/dL throughout the study period, except for the first month, was more than 50% in the proactive treatment group (mixed model repeated measure: $P < 0.001$; Additional file 1: Fig. S3A). Furthermore, the risk of CV events decreased by approximately 8% as mean length of hemoglobin level of > 10.5 g/dL increased by 1 month (Additional file 1: Fig. S3B).

Discussion

In this study, HD patients with ESA hyporesponsiveness were randomized into two epoetin beta pegol groups that differed in target hemoglobin level (i.e., a proactive treatment group and a maintenance treatment group) to compare the time from study treatment initiation to the first CV event, and we found that it was significantly prolonged in the proactive treatment group.

Recent studies have reported that ESA hyporesponsiveness is associated with a poor prognosis, including heart disease-related and other deaths [5–7]. The 2015 Guidelines for Renal Anemia in Chronic Kidney Disease issued

by the JSDT [3] recommended that a target hemoglobin range of 10 g/dL to < 12 g/dL at first blood sampling every week should be maintained in adult HD patients, but the guidelines did not advocate an optimal target hemoglobin level, especially for ESA-hyporesponsive patients, or recommend therapeutic strategies in view of responses to ESA, which leaves these clinical issues unresolved. Studies of long-acting recombinant erythropoietin preparations such as epoetin beta pegol in HD patients should focus on the influence of different ESA treatment strategies on the prognosis of poor responders to ESA, or the detailed influence of different ESA responsiveness levels during ESA therapy on prognosis.

This is the first prospective two-group comparative study to evaluate CV events of dialysis patients with ESA hyporesponsiveness treated with epoetin beta pegol for different target hemoglobin levels. In this study, the time from treatment initiation to the first CV event was significantly different between the proactive and maintenance treatment groups, which might be related to two factors. First is the between-group difference in mean hemoglobin change throughout the study period. The significantly higher mean hemoglobin level in the proactive treatment group (10.58 g/dL) compared with the maintenance treatment group (10.26 g/dL) might be partly responsible for the significant difference in time to the first CV event. However, the between-group difference of approximately 0.3 g/dL might be too small clinically to have a significant role in preventing CV events. Therefore, an exploratory post hoc analysis was also performed to compare the duration of hemoglobin level > 10.5 g/dL between the two groups. We confirmed a longer duration of hemoglobin level > 10.5 g/dL in the proactive treatment group and believe that this sustained higher hemoglobin level may have contributed to the prevention of CV events in this group (Additional file 1: Fig. S3B). It should be noted that proactive treatment reduced mainly hospitalization due to heart failure in our study. In fact, the RED-HF trial failed to show the decreased incidence of CV events in patients with congestive heart failure and mild to moderate renal anemia [8], but a systematic review of randomized trials of ESA showed improved exercise tolerance and quality-of-life indicators along with improvement of New York Heart Association class and ejection fraction [9]. Moreover, that meta-analysis showed reduced heart failure-related hospitalizations with ESA therapy. Therefore, the results of our study are consistent with those of the meta-analysis.

Second, the dose of epoetin beta pegol (per 4 weeks) did not differ significantly between the proactive and maintenance treatment groups, but the proportion of subjects who received epoetin beta pegol every 2 weeks was significantly higher in the proactive treatment group than in the maintenance treatment group. Additionally, the proportion of subjects who received epoetin beta pegol every 2 weeks was more than 80% in the proactive treatment group for 17 months after treatment initiation (mixed model repeated measures: $P < 0.05$ Additional file 1: Fig. S4). Therefore, a relatively high hemoglobin level was maintained in the proactive treatment group without a significant increase in epoetin beta pegol dose by the use of biweekly administration of epoetin beta pegol. This observation is compatible with a previous trial in HD patients with crossover design showing that twice-monthly administration of epoetin beta pegol can maintain hemoglobin levels comparable to those of once-monthly administration but at a lower total monthly dose [10].

Because the additional exploratory analysis showed no significant difference in time from the date of study treatment initiation to the first CV event between regimens of epoetin beta pegol every 2 weeks and every 4 weeks (data not shown), it is unclear whether the biweekly administration of epoetin beta pegol had a direct role in preventing CV events. However, considering reports that rapid changes in hemoglobin level may be associated with increased mortality [11] and that the biweekly administration of epoetin beta pegol might be more useful for iron utilization compared with administrations every 4 weeks [12], a biweekly administration of epoetin beta pegol might contribute to the prevention of CV events.

SAEs reported in the present study had already been observed in ESA users, with no significant difference between the groups. However, thromboembolism-related SAEs were observed in 16 subjects in the proactive treatment group, which was slightly higher than the maintenance treatment group (10 subjects); these SAEs included shunt occlusion (5 in the proactive group and 1 in the maintenance group), cerebral infarction (4 and 5), and peripheral arterial occlusive disease (7 and 4). We cannot rule out that increased blood viscosity due to increased hemoglobin levels might have resulted in the somewhat increased risk of thromboembolism. Furthermore, a slightly increased incidence of cancer was observed in the proactive treatment group (Additional file 1: Table S3). While it was difficult to draw conclusions from the results of this study due to the small number of subjects enrolled, we should be cautious of the risk of thromboembolism and cancer especially when prescribing high-dose ESA to ESA-hyporesponsive patients.

This study had several limitations. First, a target hemoglobin level of 11 g/dL was defined in the proactive treatment group, but this target was not achieved: Many subjects failed to achieve the target hemoglobin level

despite a mean epoetin beta pegol dose of 180 μg/4 weeks for 6 months after treatment initiation, which was much higher than its common clinical dose in Japan. The JSDT reported that the average dose of epoetin beta pegol in Japan was 110.1 μg/4 weeks in clinical practice [13]. This indicates that ESA-hyporesponsive patients, as defined by the guidelines of the JSDT, were enrolled in the study. This might explain the lower increase in hemoglobin level than that predicted by the investigators based on the ESA dose. Second, different dialysis methods such as online hemodiafiltration (online HDF) were used in the study. However, because the proportion of subjects on online HDF was lower than 20% in this study and comparable between the groups (16% vs. 18.9%), the impact of online HDF on the study results might be limited. Third, there were fewer CV events than had been predicted. CV events occurred in only 27 subjects in both groups combined, which is less than half the number predicted, leading to lower statistical power than we had planned. However, we succeeded in finding the significant signal. This clearly indicates the effect size (HR 0.43) of proactive treatment was much greater than we had expected and, hence, clinically relevant. In fact, we had hypothesized that the risk would be decreased by 30% in the proactive treatment group. Fourth, the use of ESA hyporesponsiveness as a criterion for subject selection was based on the description of ESA hyporesponsiveness as stated in the 2015 Guidelines for Renal Anemia in Chronic Kidney Disease issued by the JSDT, namely failure to increase hemoglobin levels or maintain target hemoglobin levels at approved doses under health insurance coverage in Japan. However, hemoglobin levels were adequately controlled by low doses of epoetin beta pegol in some enrolled subjects, which indicates that some enrolled patients were not ESA-hyporesponsive in this study. Finally, a considerable number of patients were lost to follow-up. Because dialysis clinics in Japan commonly do not provide medical care for other diseases, patients with any complications are often referred from a clinic to hospital to receive treatment. Therefore, this is unavoidable when conducting clinical trials with dialysis patients in Japan.

Conclusions

Proactive epoetin beta pegol treatment of renal anemia with a target hemoglobin level of 11 g/dL reduced CV risk in Japanese HD patients with ESA hyporesponsiveness.

Abbreviations

CI: Confidence interval; CKD: Chronic kidney disease; CV: Cardiovascular; ESA: Erythropoiesis-stimulating agent; HD: Hemodialysis; HR: Hazard ratio; JSDT: Japanese Society for Dialysis Therapy; SAE: Serious adverse event; TSAT: Transferrin saturation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-022-00450-3.

Additional file 1. **Fig. S1**. Hemoglobin levels during the treatment period by treatment group. **Fig. S2**. Ferritin and TSAT levels during the treatment period by treatment group. **Fig. S3**. (A) Proportion of patients with hemoglobin level > 10.5 g/dL during the treatment period by treatment group. (B) Relationship between hemoglobin level and cardiovascular events. **Fig. S4**. Proportion of patients with epoetin beta pegol administered every 2 weeks during the treatment period by treatment group. **Table S1**. Epoetin beta pegol dose and administration schedule during 6 months after treatment initiation. **Table S2**. Number of serious adverse events by treatment group. **Table S3**. Malignant tumor cases.

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Author contributions

KN led this study as a principal investigator. KN, KTsuchiya, TK, NJ, KTsuruya, HH, TH, HF, YU, and YO participated in the interpretation of study results, and were involved in study design and approval of the manuscript. HH was an investigator of this study. YU conducted statistical analyses. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data that support the findings of this study are available from EPS Corporation, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of EPS Corporation.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Non-Profit Organization MINS Institutional Review Board (approval no. 130201). Written informed consent to participate in this study was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

KN has received speakers fee as honoraria from Chugai and Kyowa Kirin, and grants from Chugai and Kyowa Kirin. KTsuchiya has received speakers fee as honoraria from Chugai, Kyowa Kirin, Otsuka, Ono, and Bayer, grants from Chugai, Kyowa Kirin, Otsuka, Ono, Kissei, Baxter, and Tanabe Mitsubishi,

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