Not baseline but time-dependent erythropoiesis-stimulating agent responsiveness predicts cardiovascular disease in hemodialysis patients receiving epoetin beta pegol: A multicenter…

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(Citation)
International Journal of Cardiology,375:110-118

(Issue Date)
2023-03-15

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/0100481690

Highlights

Although erythropoietin resistance index (ERI) is variable and frequently fluctuates over time, ERI as a time-dependent variable has not been evaluated.

This study demonstrated that not baseline but time-dependent ERI was significantly associated with clinical outcomes, such as cardiac events, MACE, heart failure events, and all-cause death.

A mixed-effects model with time-dependent ERI as the dependent variable revealed that iron-containing medications and online HDF significantly improved ERI.

Not Baseline but time-dependent ERI was a predictor of cardiac events, all-cause mortality, MACE, and HF and the widespread use of iron-containing medications and HDF would ameliorate ESA hyporesponsiveness.

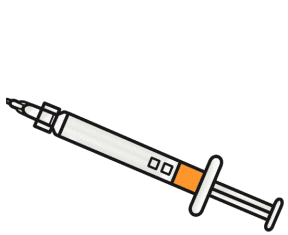
Graphical Abstract

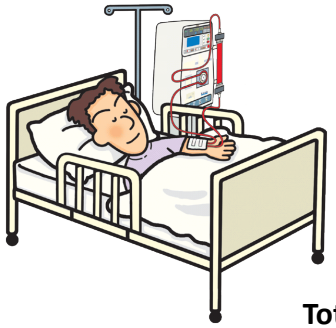
Not baseline but time-dependent erythropoiesis-stimulating agent responsiveness predicts cardiovascular disease in hemodialysis patients receiving epoetin beta pegol: A multicenter prospective PARAMOUNT-HD Study

Methods

Prospectively observational study in hemodialysis patients

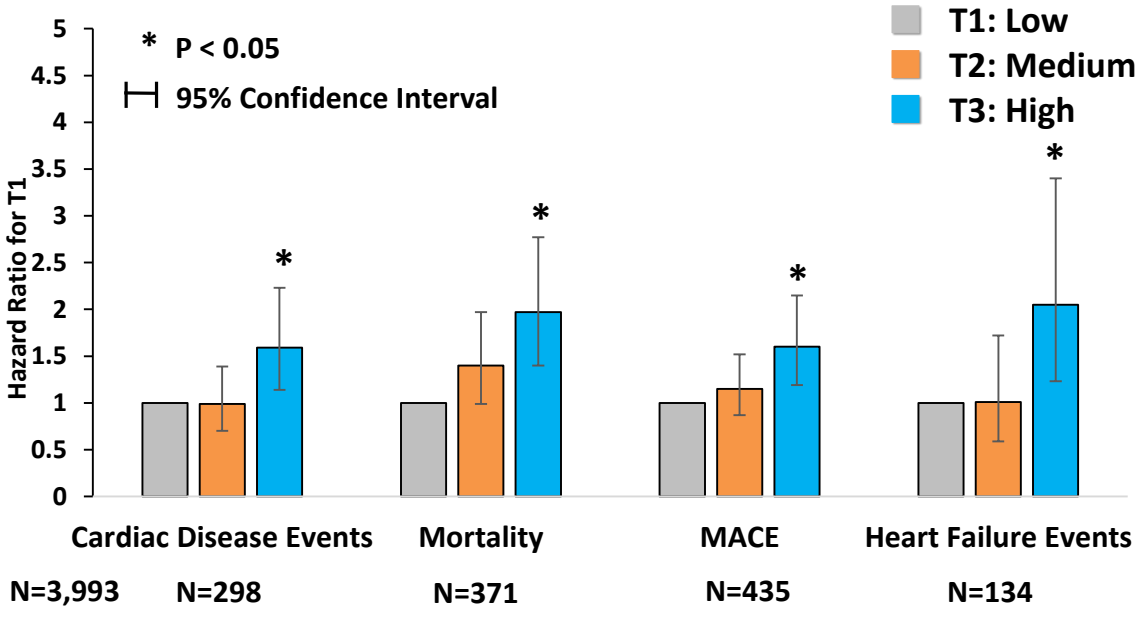
Eligible patients received hemodialysis at 297 different institutions between April 2013 and December 2015 were started on CERA treatment for renal anemia.





Full analysis set: n = 4,034
Landmark analysis set: n = 3,312
Marginal structural model analysis set: n = 3,993

Time-dependent ERI and clinical outcomes



Conclusion

Baseline ERI at six months predicted only all-cause mortality; however, time-dependent ERI was a predictor of cardiac events, all-cause mortality, MACE, and HF.

Not baseline but time-dependent erythropoiesis-stimulating agent responsiveness predicts cardiovascular disease in hemodialysis patients receiving epoetin beta pegol: A multicenter prospective PARAMOUNT-HD Study

Running title: ESA responsiveness and CVD in HD patients

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Word count: Abstract; 249, Text; 2,772

References; 30, Figures; 4, Tables; 3

Abstract

Background

Responsiveness to erythropoiesis-stimulating agents (ESAs) has been reported to be associated with increased cardiovascular disease (CVD) and mortality in patients undergoing hemodialysis (HD). However, the association between hyporesponsiveness to the long-acting ESA, epoetin beta pegol (CERA) and CVD remains unknown.

Methods

This multicenter prospective study included 4,034 patients undergoing maintenance HD. After shifting from prior ESA to CERA, we studied the association between erythropoietin resistance index (ERI), including cardiac events, major adverse cardiovascular events (MACE), and all-cause mortality, using Cox proportional hazards models (Landmark analyses) and marginal structural models to adjust for time-dependent confounding factors, including iron-containing medications and hemodiafiltration (HDF).

Results

The median dialysis vintage and the observational period were 5.0 years and 22.1 months, respectively. The landmark analyses revealed that the highest tertile of baseline ERI (T3) was associated with a significantly higher all-cause mortality than the lowest tertile (T1) (hazard ratio [HR]: 1.48, 95% CI: 1.03-2.13). Furthermore, marginal structural models revealed that time-dependent ERI T3 was significantly associated with increased cardiac events (HR: 1.59, 95% CI: 1.14-2.23), MACE (HR: 1.60, 95% CI: 1.19-2.15), all-cause mortality (HR: 1.97, 95% CI: 1.40-2.77), and heart failure (HF) (HR: 2.05, 95% CI: 1.23-3.40) compared to T1. A linear mixed effects model showed that iron-containing medications and HDF are negatively associated with time-dependent ERI.

Conclusions

Baseline ERI at six months predicted only all-cause mortality; however, time-dependent ERI was a predictor of cardiac events, all-cause mortality, MACE, and HF. The widespread use of iron-containing medications and HDF would ameliorate ESA hyporesponsiveness.

Keywords: cardiovascular disease, erythropoiesis-stimulating agent, epoetin beta pegol, erythropoietin resistance index, hemodialysis

1. **Introduction**

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD), including those on hemodialysis (HD) [1]. In these patients, CVD progression is not only related to traditional risk factors such as hypertension, smoking, diabetes mellitus, and hyperlipidemia, but also to CKD-specific non-traditional risk factors. These non-traditional risk factors involve activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, as well as oxidative stress, mineral bone disorder, uremic toxins, and volume overload, etc. Among them, anemia is a significant risk factor for CVD progression, and reduced hemoglobin (Hb) levels are closely related to the development of coronary artery disease and heart failure (HF) [2, 3]. However, previous randomized controlled trials (RCTs) aimed at normalizing serum Hb levels in patients with CKD failed to prevent CVD progression and mortality [4-7]. Intensive treatment of anemia did not result in reducing adverse outcomes; however, sub-analyses of these trials and another observational study revealed a reduction in CVD events in patients who could achieve the higher target Hb levels [4, 8, 9]. Based on these findings, higher target Hb levels may not always be harmful to patients with CKD. The major concern in treating anemia with erythropoiesis-stimulating agents (ESAs) is

hyporesponsiveness. In fact, many studies have been conducted to examine the correlation of ESA hyporesponsiveness with CVD and mortality [10, 11].

Recently, it has been reported that erythropoietin resistance index (ERI) is variable and frequently fluctuates over time in patients undergoing HD [12]. The importance of ERI as a time-dependent variable has been discussed; however, its related factors and outcomes remain unclear. In addition, although epoetin beta pegol, a continuous erythropoietin receptor activator (CERA), is a long-acting ESA frequently used in clinical settings, clinical evidence supporting its use in treating anemia is limited. Therefore, in this prospective cohort study, we investigated the association between baseline and time-dependent ESA hyporesponsiveness and CVD progression and other related-factors in patients on HD who received CERA.

2. **Methods**

2.1. Study design and population

This prospective observational study was conducted at multiple centers in Japan. Participation in the study was limited to 24 months based on the follow-up duration in previous studies of patients on HD [13, 14]. Eligible patients received hemodialysis at 297 different institutions between April 2013 and December 2015 were started on CERA

treatment for renal anemia. The original study consisted of two parts, a randomized part and an observational part, of which the present study was the latter. Patients scheduled to shift from any ESA to CERA in the randomized study were enrolled in this observational study (Figure 1). Among these patients, 4,034 were included in the present study because they met the following inclusion criteria: (1) age 20-85 years at the time of informed consent, (2) being treated for renal anemia with any ESA rather than CERA and being scheduled to be shifted to CERA, (3) receiving HD for at least one year, and (4) provided informed consent to participate in this study. The exclusion criteria were as follows: (1) anemia of non-renal origin: patients were excluded if they had apparent hemorrhagic lesions or hematological disease (e.g., leukemia, malignant lymphoma, myelodysplastic syndrome, aplastic anemia) or if there was evident chronic inflammation (e.g., rheumatoid arthritis, inflammatory bowel disease), (2) hypersensitivity to any component of the epoetin beta pegol molecule, as well as any constituent in erythropoietin formulations or darbepoetin alfa, (3) malignancy: patients were eligible if it had been five postoperative years and their malignancy had been cured, (4) pregnancy or suspected pregnancy, breastfeeding, or desire to become pregnant during the study, and (5) judged unsuitable for this study by the investigator or sub-investigator for other reasons. Thereafter, 723 patients were excluded due to CVD

events, death, or missing data, and the remaining 3,311 patients' data were used as baseline data six months after participation in this study. At six months, the study participants were divided into three groups based on their ERI. This prospective study was conducted prospectively in compliance with the Declaration of Helsinki Principles; the "Ethical Guidelines for Clinical Studies" of the Ministry of Health, Labor, and Welfare; and the International Council for Harmonization Good Clinical Practice guidelines. The study protocols were approved by an independent central ethics committee (approval no: 230019) and registered with the University Hospital Medical Information Network (ID: UMIN000010138). All participants provided informed consent. Treatments provided as a part of the study were covered by ordinary health insurance. This report adheres to Strengthening the Reporting of Observational Studies in Epidemiology.

2.2. Treatment methods

Medical care was provided routinely. CERA was administered in accordance with the manufacturer's instructions on the Mircera® insert package. The initial dose was determined using the CERA method of administration (setting the initial dose). During treatment, care was taken to ensure that Hb levels did not exceed 12 g/dL and that the maximum dose administered at one time does not exceed 250 μg.

2.3. Study outcomes

The primary outcome was the time to the first cardiac event, including cardiac death (due to HF, fatal myocardial infarction, or sudden cardiac death), HF requiring hospitalization, or acute coronary syndrome (non-fatal myocardial infarction or unstable angina) requiring hospitalization. The secondary outcomes were all-cause mortality, the incidence of major adverse cardiovascular events (MACE) (cardiac events, stroke, or death from stroke), and HF events. All events were adjudicated by an independent event evaluation committee composed of members who were not the investigators and sub-investigators. In the randomized part of the study, patient assessments were conducted while blinded to the study treatment group.

2.4. Statistical Analysis

The survival probability of the three ERI-based groups at six months for each outcome, including cardiac events, MACE, and all-cause mortality, was estimated using the Kaplan-Meier method. The association between ERI at six months and outcomes was assessed using Cox proportional hazards models and the landmark analyses method. Participants

who had an event before six months and those who discontinued the study were excluded from the landmark analysis. Age, sex, diabetes mellitus, CVD, calcium, phosphorus, Hb, albumin, intact parathyroid hormone, Kt/V, dialysis vintage, body mass index, systolic blood pressure, and pulse pressure measured at baseline, and ferritin, transferrin saturation (TSAT), iron, C-reactive protein (CRP), and online hemodiafiltration (HDF) measured at six months, and renin-angiotensin system inhibitors, β -blockers, antiplatelet, statin, and iron-containing medications, were included in the model to adjust for confounders. In addition, to adjust for time-dependent confounders, we also assessed ERI and the outcomes using marginal structural models, including ferritin, TSAT, iron, CRP, frequency of CERA administration (once every 2 weeks, once every 4 weeks, or others) and online HDF as time-dependent confounders. Continuous variables are expressed as mean ± standard deviation. A two-tailed *p*-value < 0.05 was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Chicago, IL, USA).

3. **Results**

3.1. Patients' characteristics

The clinical characteristics and laboratory data of the study participants at enrollment are presented in Table S1 and at baseline (six months after participation in this study) in Table 1. At baseline, the mean age was 65.5 ± 11.9 years, with 2,110 male patients (63.7%). There were 2,645 patients with hypertension (79.9%) and 1,364 with diabetes mellitus (41.2%). The median dialysis vintage was 7.9 years, and the observational time was 22.1 months. Although the high ERI group had a shorter HD time than the other groups, all three groups had similar Kt/V values. Furthermore, the high ERI group had lower Hb levels, slightly lower serum albumin, total cholesterol, iron, and TSAT levels, and higher serum CRP levels than the other two ERI groups. The percentage of patients who received iron supplements was comparable among the three groups.

3.2. ESA responsiveness and cardiovascular events and death

Figure 2. presented the Kaplan-Meier curves for each event. In crude analyses, ERI was a predictor of secondary outcomes such as all-cause mortality and MACE but not of the primary outcome, cardiac event. Among the cardiac events, HF events, including death from HF and HF requiring hospitalization, were the most frequently observed. However, the occurrence of HF events among the three ERI groups did not significantly

differ. Cox regression analysis revealed that the highest tertile of baseline ERI (T3) was associated with a significant increase in all-cause mortality (hazard ratio [HR]: 1.48; 95% confidence interval [CI]: 1.03-2.13, p = 0.033) compared to the lowest tertile (T1) (Table 2). A mixed-effects model with time-dependent ERI as the dependent variable revealed that iron-containing medications and online HDF significantly improved ERI (Table 3). Therefore, we used marginal structural models for additional analyses. The results revealed that time-dependent ERI T3 was significantly associated with increased cardiac events (HR: 1.59, 95% CI: 1.14-2.23, p = 0.007), all-cause mortality (HR: 1.97, 95% CI: 1.40-2.77, p < 0.001), MACE (HR: 1.60, 95% CI: 1.19-2.15, p = 0.002), and HF events (HR: 2.05, 95% CI: 1.23-3.40, p = 0.006) compared to time-dependent ERI T1 (Figure 3).

3.3. Changes in the percentage of patients receiving oral iron-containing medications and those on online HDF and ERI

During the study period, the percentage of patients receiving oral iron-containing medications increased from 11.1% at baseline to 25.0% at 24 months (Figure S1). In contrast, the mean TSAT level increased from 24.5% to 27.4% at 24 months (Figure S2). In addition, the percentage of patients using online HDF increased from 13.5% to 22.6%

(Figure S3). Furthermore, the ERI gradually decreased over time, with a significant improvement in the highest ERI group (Figure 4).

4. **Discussion**

The present prospective observational study indicated that in HD patients treated with a long-acting ESA, CERA, baseline ERI at six months might predict eventual all-cause mortality but not cardiac events. Additionally, a high time-dependent ERI was a significant predictor of cardiac events, all-cause mortality, MACE, and HF in these patients. Furthermore, ERI decreased and the number of patients treated with iron-containing medications and online HDF increased during the study period.

Several studies have assessed the relationship between ESA hyporesponsiveness and clinical events such as CVD and mortality [10, 11]. A retrospective study including 95,460 Japanese patients on HD observed that ESA responsiveness, as defined by the combination of the ESA dose and Hb level, was significantly associated with CVD progression and 1-year all-cause mortality [11]. In the present study, survival analysis using the Kaplan-Meier method revealed that MACE and all-cause mortality were significantly higher in the highest ERI group than in the lowest ERI group, while cardiac

events were not. Additionally, Cox regression analysis revealed that ERI at the landmark was only associated with mortality but not significantly associated with cardiac events or MACE. This finding differed slightly from those of previous studies. The most important and unique aspect of this study was the detailed patient data collection and prospective design. In addition, we considered time-dependent ERI variations and conducted additional analyses using a marginal structural model. Surprisingly, time-dependent ERI was significantly associated with all outcomes.

Various clinical factors, including iron deficiency, persistent hemorrhage, chronic inflammation, malnutrition, secondary hyperparathyroidism, and renin-angiotensin system inhibitor use, contribute to ESA hyporesponsiveness in patients on HD [15, 16]. Among them, iron deficiency and chronic inflammation were the most significant, as they are most frequently detected in these patients. The present study focused mainly on these factors and conducted a detailed analysis. During the study period, iron-containing phosphate binders were used in clinical settings, and the number of patients receiving this type of medication had increased. Since a significant negative correlation between the use of iron-containing phosphate binders and ERI was detected, patients with ESA hyporesponsiveness appeared to have an iron deficiency. In addition, during this period, Japan revised its remuneration for medical care. consequently, the number

of patients receiving online HDF increased. Previous studies have indicated that HDF can decrease ERI by reducing chronic inflammation and hepcidin [17, 18], which is consistent with our findings. In this study, the ERI was significantly correlated with all outcomes after adjusting for important ESA hyporesponsiveness-related clinical factors. We believe that these findings are highly informative and crucial. Thus, narrowly defined ESA hyporesponsiveness that is not improved by appropriate treatment, including iron status correction and HDF, is considered important in clinical settings. However, the exact mechanism by which ESA hyporesponsiveness contributes to CVD progression and death remains unclear.

The association between anemia and CVD has been well established in patients with CKD, and several clinical studies have been conducted to elucidate the underlying mechanisms so far. As mentioned above, no RCT could confirm that the higher target Hb level with ESA therapy is beneficial for patients with CKD [4-7]. As a result, several guidelines recommend that the target Hb level in ESA treatment should not exceed 13 g/Dl [19, 20]. One of the important studies in this field, the TREAT study, revealed that patients with a poor initial response to ESA had a higher rate of CVD events than those with a better response, despite the fact that using ESA to achieve a Hb level of approximately 13 g/dL did not reduce CVD events in patients with CKD [10]. Several sub-

analyses of previous RCTs indicated that the clinical issue might not be the high target Hb level, but rather patient characteristics associated with ESA hyporesponsiveness. Thus, the present study used ERI to prospectively determine, in more detail, the association of ESA hyporesponsiveness with cardiac events, CVD, and death. Consistent with previous studies, our findings also indicated that a lower Hb level was associated with higher ERI and ESA dosage. Furthermore, we studied the correlation between the ERI and each type of cardiac disease, including coronary artery disease, HF, and cardiac death. As the term “cardio-renal-anemia syndrome” implies, HF is closely related to anemia and crucial for ESA hyporesponsiveness [21, 22]. The results of the landmark analysis revealed no significant association between ERI and HF events. However, analysis using the marginal structural model revealed that high ERI was significantly associated with HF events. Even with stroke, similar results were observed. In contrast, no significant association was detected between ERI and cardiac death or acute coronary syndrome. A possible explanation for the significant association of ERI with HF and stroke but not with coronary artery disease is the improvement in iron metabolism during the course of the study. It has been reported that most patients with HF have absolute and functional iron deficiencies [23, 24]. Iron deficiency impairs cardiac function by reducing intracellular oxygen supply, increasing oxidative stress, and

impairing mitochondrial function [25]. Transferrin levels were found to be elevated in patients with ischemic stroke, and iron deficiency was found to increase transferrin levels, resulting in hypercoagulability [26]. Thus, improving ERI via iron deficiency correction would contribute to reducing HF and stroke events. In the present study, we speculated that the number of iron-deficient patients would reduce by the emergence of iron-containing phosphate binders and the shift from HD to online HDF. Thus, time-dependent ERI rather than baseline ERI may be associated with HF and stroke events.

Several studies have been conducted using CERA to determine the occurrence of clinical events [27, 28]. A retrospective observational nationwide study of Japanese patients on HD revealed that long-acting ESAs, such as CERA and darbepoetin, may be associated with a higher risk of death than short-acting ESAs [29]. Although all study participants received a long-acting ESA, CERA, in our prospective observational study, their mortality rate (7.0%) was lower than that of long- and short-acting ESAs users in the study (17.2% for Darbepoetin/CERA and 14.6% for Epoetin). Furthermore, a meta-analysis of CERA has reported low certainty evidence that CERA had no or minimal effect on clinical outcomes such as CVD events and all-cause mortality compared to placebo and short-acting ESAs [30]. Although multiple serious adverse events were detected in this study, and the most prevalent being pneumonia (3.1%), the reported rates may be

low compared to previous studies.

This study has several limitations. First, since this was an observational study, unlike RCT, Hb levels were not precisely controlled. However, the average Hb level at the end of the present study was 10.9 ± 1.1 g/dL, and most patients were well-controlled according to the anemia treatment guideline. Second, this study included only patients treated using CERA; therefore, the effect of CERA on clinical events and ERI cannot be compared to that of other ESAs. Third, the observation period may have been insufficient to assess clinical events, as CVD events and deaths were less frequent in Japanese HD patients than in patients from other countries.

5. **Conclusions**

Baseline ERI at six months did not predict subsequent cardiac events; however, a high time-dependent ERI was a predictor of cardiac events, all-cause mortality, and MACE in patients on HD treated with CERA. We speculate that the widespread use of iron-containing medications and online HDF would ameliorate ESA hyporesponsiveness.

Statements and Declarations

Competing Interests

H. F. received speaker fees as honoraria from Chugai and Kyowa Kirin, advisory board fees as honoraria from Chugai, and scholarship grants from Chugai and Kyowa Kirin. T. H. received speaker fees as honoraria from Chugai, Kyowa Kirin, Kissei, Ono, Torii, Otsuka, Bayer, Asahi Kasei and Astellas; grants from Chugai, Kyowa Kirin, Kissei, Ono, Torii, Otsuka, Terumo, Fuso, Bayer, Asahi Kasei, Eisai, and Takeda; advisory board fees as honoraria from Kyowa Kirin, Ono, Glaxo SmithKline and Astellas. K. T. received speaker fees as honoraria from Chugai, Kyowa Kirin, Otsuka, Ono and Bayer; grants from Chugai, Kyowa Kirin, Otsuka, Ono, Kissei, Baxter and Tanabe Mitsubishi; and advisory board fees as honoraria from Chugai, Kissei, and Sanwa. T. K. received speaker fees as honoraria from Chugai and Kyowa Kirin. N. J. received speaker fees as honoraria from Chugai, Kyowa Kirin and Torii, and grants from Chugai, Kyowa Kirin and Torii. K. T. received speaker fees as honoraria from Chugai and Kyowa Kirin and grants from Chugai and Kyowa Kirin. H. H. received speaker fees as honoraria from Chugai, Kissei, Torii, Tanabe Mitsubishi and Astellas. Y. U. received speaker fees as honoraria from Chugai. K. N. received speaker fees as honoraria from Chugai and Kyowa Kirin and grants from Chugai and Kyowa Kirin.

Funding

Funding for this study was provided by Chugai Pharmaceutical Co., Ltd., based on a commissioning contract. The funding company, Chugai Pharmaceutical Co., Ltd., was involved in the conception of the study and provision of information but not with planning or conducting the study or analyzing or interpreting the results.

Author contributions

H.F. wrote the text. T.H. and K.T. revised it critically for important intellectual content. Y.U. analyzed the data. T.K., N.J., and H.H. interpreted the data. K.T. and K.N drafted this study. All co-authors reviewed and approved this paper.

Acknowledgments

The authors would like to thank the staffs at the 297 dialysis clinics for their great effort to ensure the accurate charting of clinical data in the EDC system and for their contributions to data collection. We also thank the staffs of EP-CRSU Co., Tokyo, Japan, for managing the data; Drs. Hiroshi Ito, Takanari Kitazono, and Satoshi Iimuro for evaluating cardiovascular and cerebrovascular events; Drs. Masashi Suzuki, Yoshiharu

Tsubakihara and Satoshi Morita for independent data monitoring; and other investigators, nurses and clinical research coordinators who contributed to this study.

Finally, we thank Yasuo Ohashi, the Department of Integrated Science and Engineering for Sustainable Society, Chuo University, for assisting with the study design, statistical analysis, and interpretation of the results.

This work was presented in part at the 2020 Annual Meeting of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA).

Ethical disclosures

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data availability statement

The protocol of this study was registered in the University hospital Medical Information Network (UMIN). The registration number was UMIN000047684. Data underlying this study can be accessed through the UMIN repository system at: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000011871.

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Figure Legends

Figure 1. Enrollment flow of study patients

*Ineligible due to exclusion criteria, such as non-adherence to treatment or withdrawal of consent.

#excluded due to CVD events, death, or missing data.

Figure 2. Rates of each outcome among study patients according to their baseline ER

A. Cardiac events.

B. All-cause mortality.

C. MACE.

D. HF events.

ERI, erythropoietin resistance index; MACE, major adverse cardiovascular events; HF, heart failure.

Figure 3. Relationship between time-dependent ERI and each outcome

ERI, erythropoietin resistance index; MACE, major adverse cardiovascular events

The colors of the bars represent the same ERI group for each outcome (low ERI group, gray bar; middle ERI group, orange bar; and high ERI group, light blue bar).

Figure 4. ERI changes during the study period

ERI, erythropoietin resistance index.

Supplemental figures

Supplemental Figure 1 (Figure S1). Changes in the prescription of iron-containing medications during the study period

Supplemental Figure 2 (Figure S2). Changes in TSAT during the study period

TSAT, transferrin saturation.

Supplemental Figure 3 (Figure S3). Changes in the percentage of patients on on-line HDF during the study period

HD, hemodialysis; HF, hemofiltration; HDF, hemodiafiltration.

Figure 1

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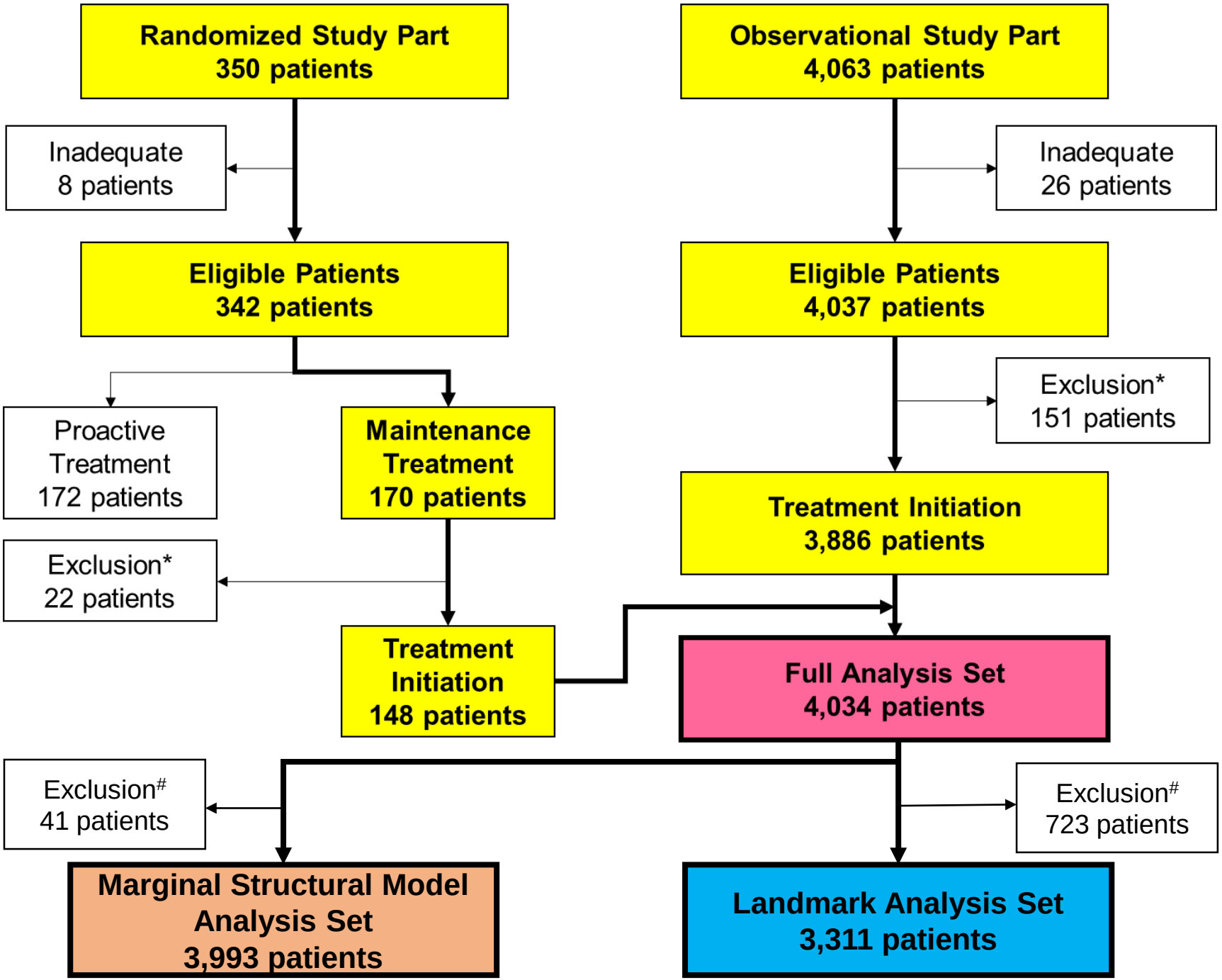

Figure 2A

A Cardiac events

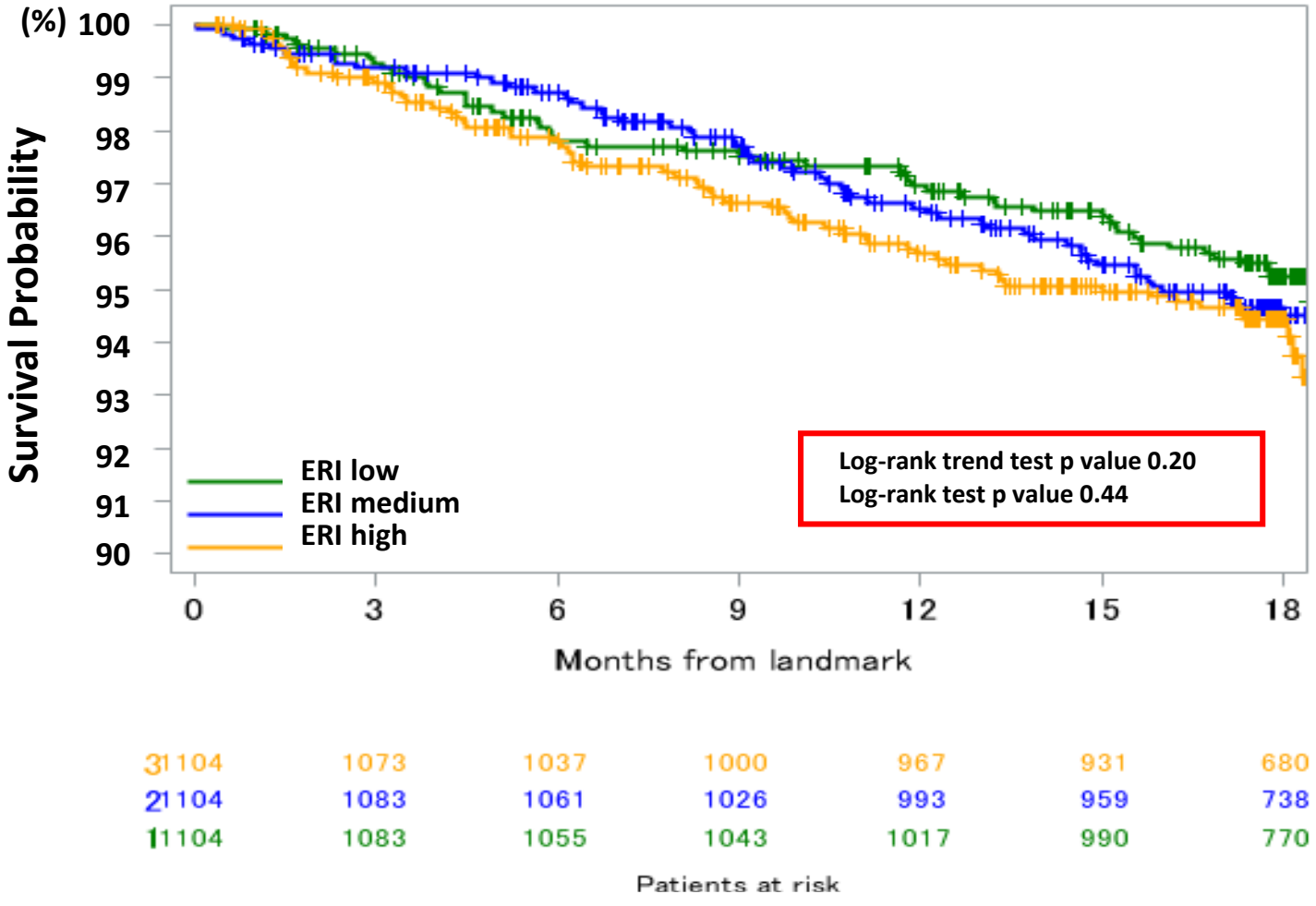

Figure 2B

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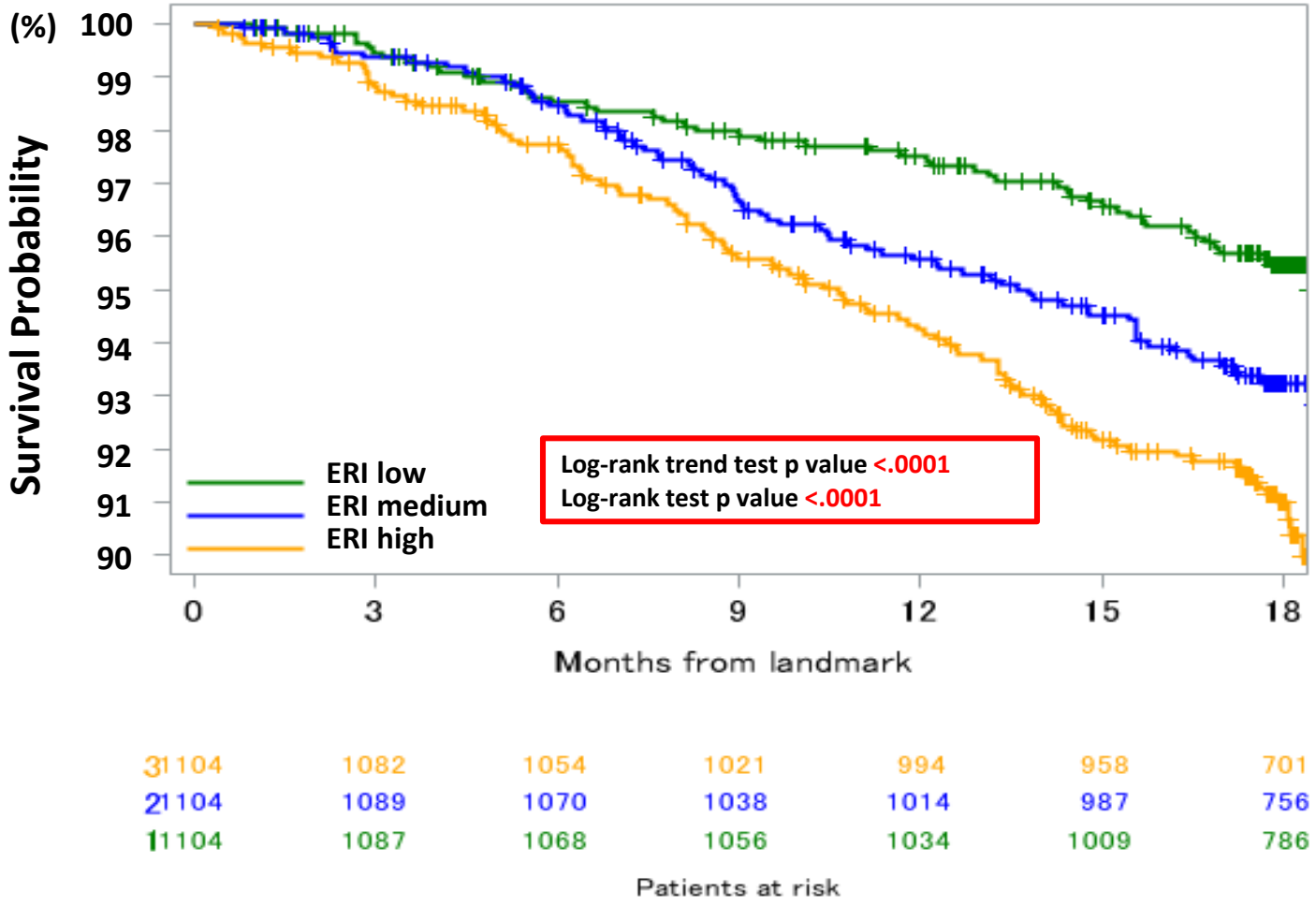
B All-cause mortality



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C MACE

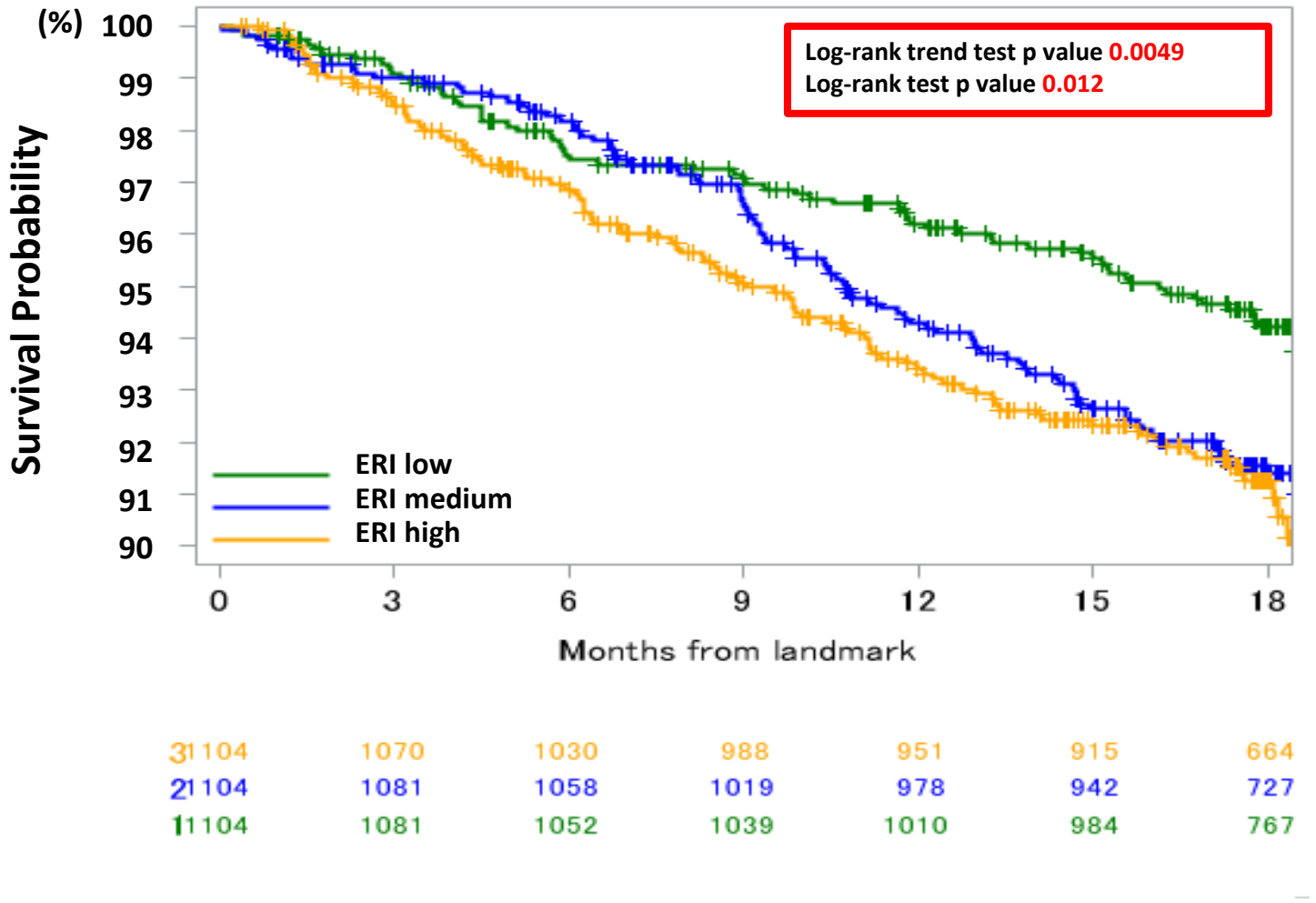

Figure 2D

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D Heart failure

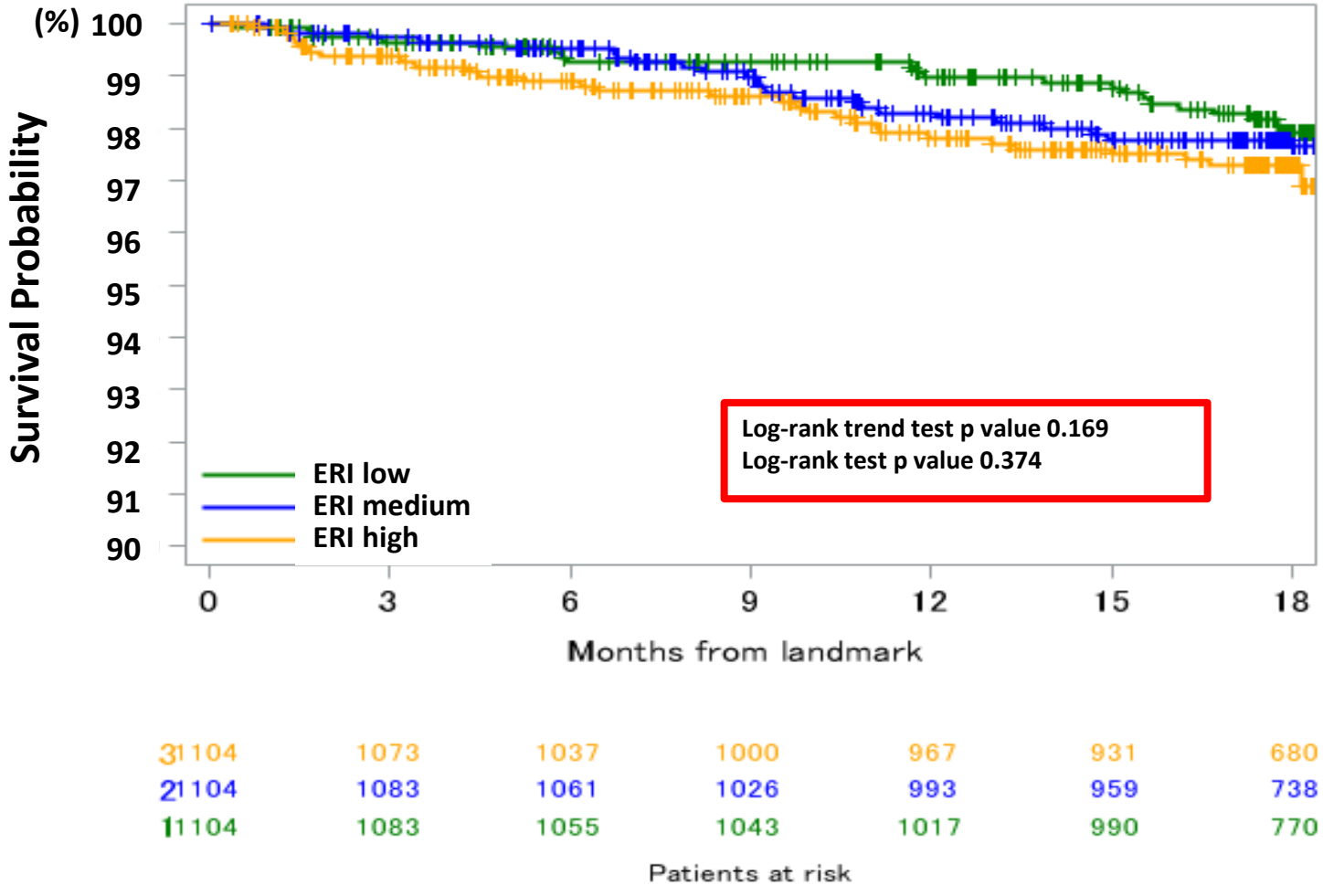

Figure 3

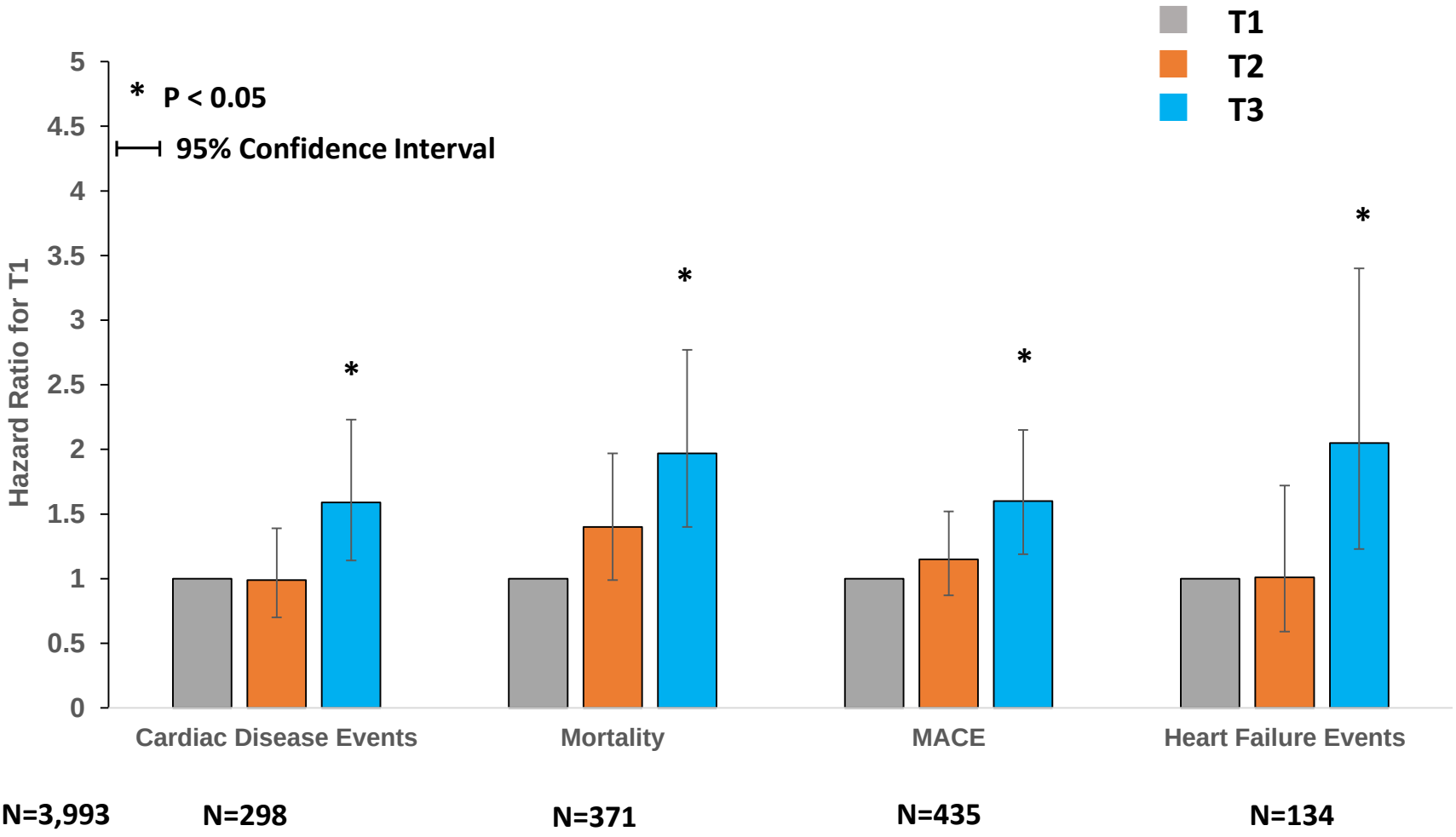

Figure 4

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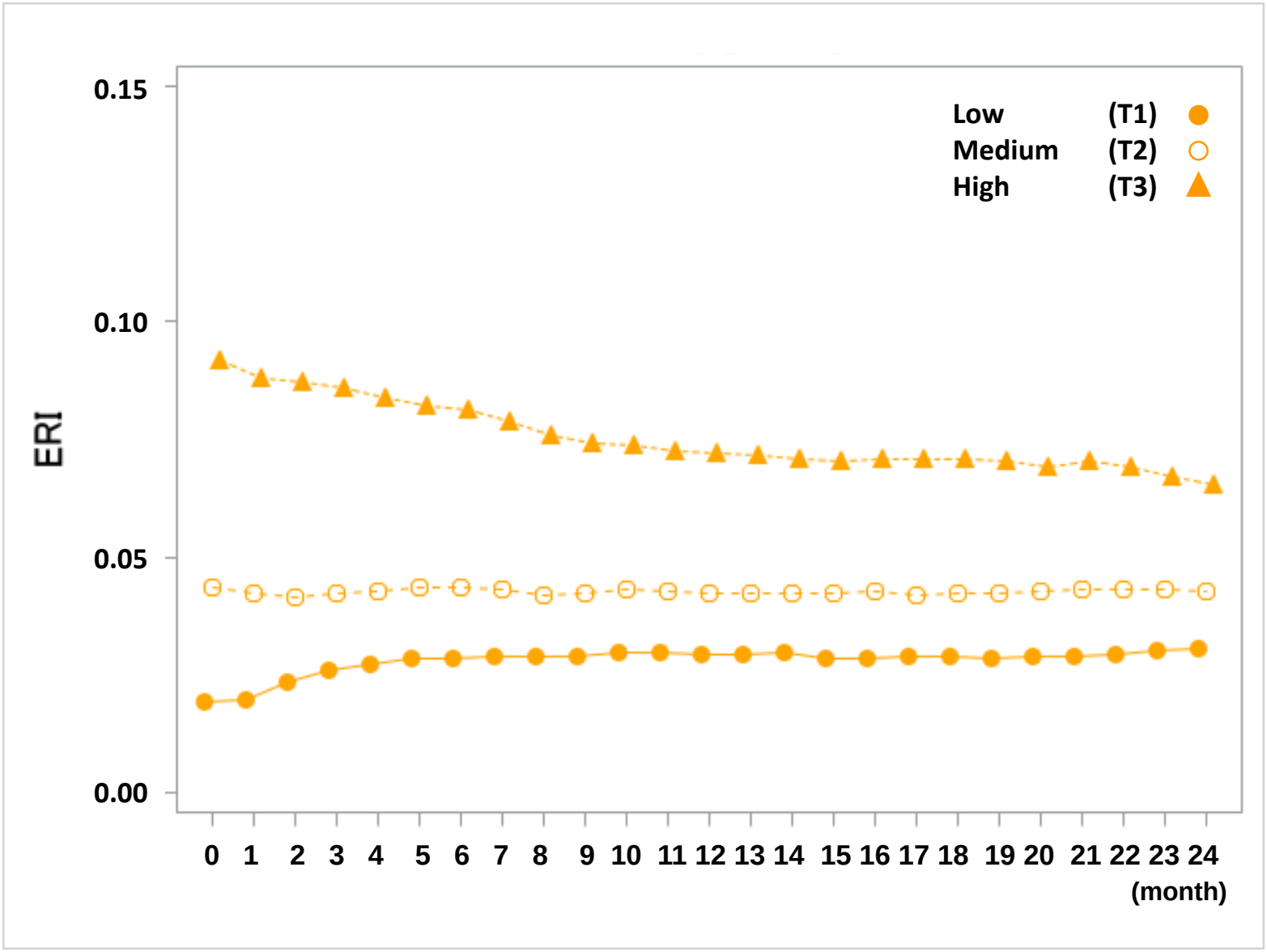

Table 1. Baseline characteristics of patients

	All (n = 3,312)	Low ERI (n = 1,104)	Medium ERI (n = 1,104)	High ERI (n = 1,104)	p-value
Age (year)	65.5 ± 11.9	63.3 ± 12.1	65.7 ± 11.8	67.6 ± 11.5	<.0001
Sex (male) (%)	2,110 (63.7)	763 (69.1)	700 (63.4)	647 (58.6)	<.0001
BMI (kg/m^2)	22.0 ± 3.7	22.8 ± 3.8	22.0 ± 3.7	21.2 ± 3.4	<.0001
Systolic BP (mmHg)	150.3 ± 21.7	150.2 ± 22.2	150.5 ± 21.5	150.2 ± 21.4	0.943
Diastolic BP (mmHg)	78.1 ± 13.6	79.7 ± 13.5	77.6 ± 13.5	77.1 ± 13.6	<.0001
Pulse pressure (mmHg)	72.2 ± 17.0	70.5 ± 17.1	72.9 ± 16.9	73.1 ± 16.8	<.001
HT (%)	2,656 (80.2)	871 (78.9)	886 (80.3)	889 (81.4)	0.592
DM (%)	1,373 (41.5)	466 (42.2)	465 (42.1)	442 (40.0)	0.503
CVD (%)	1,725 (52.1)	543 (49.2)	572 (51.8)	610 (55.3)	0.017
RAS-I (%)	1,716 (51.8)	512 (46.4)	597 (54.1)	607 (55.0)	<.0001
β-blocker (%)	287 (8.7)	105 (9.5)	89 (8.1)	93 (8.4)	0.452
Statin (%)	654 (19.7)	245 (22.2)	225 (20.4)	184 (16.7)	0.004
Antiplatelet (%)	1,440 (43.5)	484 (43.8)	448 (40.6)	508 (46.0)	0.035
Vitamin D (%)	1,591 (48.0)	550 (49.8)	519 (47.0)	522 (47.3)	0.350
Phosphate binder (%)	2735 (82.6)	950 (86.1)	896 (81.2)	889 (80.5)	<.001

Calcium containing (%)	1,972 (59.5)	672 (60.9)	658 (59.6)	642 (58.2)	0.429
Iron containing (%)	167 (5.0)	74 (6.7)	60 (5.4)	33 (3.0)	<.001
Others (%)	1,789 (54.0)	639 (57.9)	579 (52.4)	571 (51.7)	0.006
Iron agents (%)	816 (24.6)	283 (25.6)	268 (24.3)	265 (24.0)	0.640
HD vintage (years)	7.9 ± 7.4	7.7 ± 7.3	7.7 ± 7.1	8.4 ± 7.7	0.037
HD time (hours)	11.5 ± 2.5	11.7 ± 2.4	11.6 ± 2.4	11.2 ± 2.7	<.0001
Online HDF (%)	450 (13.6)	170 (15.4)	143 (13.0)	137 (12.4)	0.215
Type of blood access					
A-V fistula (%)	3,041 (91.8)	1,022 (92.6)	1,030 (93.3)	989 (89.6)	0.032
Graft (%)	215 (6.5)	64 (5.8)	62 (5.6)	89 (8.1)	
Catheter (%)	12 (0.4)	5 (0.5)	1 (0.1)	6 (0.5)	
Others (%)	44 (1.3)	13 (1.2)	11 (1.0)	20 (1.8)	
Kt/V	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.4	0.168
Hemoglobin (g/dL)	10.7 ± 1.0	10.9 ± 0.9	10.7 ± 1.0	10.4 ± 1.0	<.0001
Alb (g/dL)	3.7 ± 0.4	3.7 ± 0.4	3.7 ± 0.4	3.6 ± 0.4	<.0001
CRP (mg/dL)	0.4 ± 1.0	0.3 ± 0.9	0.3 ± 0.8	0.5 ± 1.1	<.0001
T-Chol (mg/dL)	154.2 ± 34.1	157.4 ± 32.9	153.9 ± 33.9	151.4 ± 35.1	<.001
cCa (mg/dL)	9.1 ± 0.8	9.1 ± 0.7	9.1 ± 0.7	9.1 ± 0.9	0.649

P (mg/dL)	5.3 ± 1.3	5.4 ± 1.3	5.3 ± 1.4	5.2 ± 1.3	0.010
iPTH (pg/mL)	167.3 ± 146.1	170.0 ± 129.0	165.6 ± 146.8	166.3 ± 161.1	0.794
Fe (μg/dL)	60.6 ± 26.6	62.0 ± 25.2	63.0 ± 27.2	57.2 ± 27.0	<.0001
Ferritin (ng/mL)	111.1 ± 228.5	103.3 ± 130.2	121.8 ± 325.7	108.0 ± 181.2	0.149
TSAT (%)	24.9 ± 11.6	24.8 ± 10.9	25.5 ± 11.9	24.2 ± 12.1	0.046

BMI, body mass index; BP, blood pressure; HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease; RAS-I, renin-angiotensin-aldosterone inhibitor; HD, hemodialysis; HDF, hemodialysis filtration; A-V fistula, arteriovenous fistula; Alb, albumin; CRP, C-reactive protein; T-Chol, total cholesterol; cCa, corrected calcium; P, phosphate; iPTH, intact parathyroid hormone; Fe, iron; TSAT, transferrin saturation.

Values are presented as mean ± standard deviation.

Table 2. Cox regression analysis

	Reference	Tertile of ERI	HR	95% CI	p-value
Cardiac events	Low	Medium	1.04	0.71-1.53	0.82
		High	1.06	0.72-1.58	0.76
All-cause mortality	Low	Medium	1.36	0.94-1.97	0.10
		High	1.48	1.03-2.13	0.03
MACE	Low	Medium	1.37	0.99-1.90	0.05
		High	1.31	0.94-1.84	0.11
Heart failure	Low	Medium	1.02	0.56-1.86	0.94
		High	1.12	0.62-2.04	0.71

MACE, major adverse cardiovascular events; ERI, erythropoietin resistance index; HR, hazard ratio; CI, confidence interval.

Table 3. The positive effect of iron containing medications and online HDF on ESA sensitivity

	Estimate value	Standard error	p
Iron containing medications	-0.00198	0.000537	0.0002
Online HDF	-0.00188	0.000738	0.0158

HDF, hemodiafiltration.