

A Table of Contents

Supplementary Table 1. Statistical models used in this study

Supplementary Table 2. Comparison of baseline characteristics between patients with and without missing data on the types of ESA

Supplementary Table 3. Comparison of baseline characteristics after propensity score-matching

Supplementary Table 4. The average dose of ESA in each ESA dose tertile

Supplementary Table 5. Baseline characteristics according to 4 types of ESA

Supplementary Table 6. Hazard ratios for deaths across the 4 types of ESA

Supplementary Table 1. Statistical models used in this study

Models	Covariates
Cox proportional hazards model	
<i>Unadjusted</i>	-
<i>Model 1</i>	age, sex, body mass index, pre-dialysis systolic blood pressure, dialysis duration, dialysis vintage, single-pool Kt/V, diabetes mellitus, a past history of cardiovascular diseases, laboratory data [albumin, urea nitrogen, C-reactive protein, hemoglobin, ferritin, albumin-adjusted calcium, phosphate, and intact parathyroid hormone], standardized erythropoietin resistance index
<i>Model 1'</i>	Multiple imputation for all covariates in Model 1
<i>Model 2</i>	Covariates in Model 1 + facility indicators
<i>Model 2'</i>	Model 2 + facility size and region
<i>Model 3</i>	PS created from covariates in Model 1 + facility indicators
<i>IPTW</i>	Covariates in Model 2
<i>PS-matched</i>	Covariates in Model 2
<i>Subgroup analyses</i>	Covariates in Model 2
Instrumental variable analysis	Covariates in Model 2
Facility-level analysis	Covariates in Model 2

Abbreviations: IPTW, inverse probability of treatment weighting; PS, propensity score

Supplement Table 2. Comparison of baseline characteristics between patients with and without missing data on the types of ESA

	Study participants	Patients with missing data	Standardized difference
	n = 194,698	n = 75,695	
age, yr	67.5 (12.4)	67.5 (12.5)	<0.001
male, %	61.6	63.6	0.04
body mass index, kg/m ²	22.2 (3.9)	22.3 (3.9)	0.02
HD vintage, yr	6 [3, 11]	6 [3, 11]	0.01
HD duration, hours/week	11.7 (1.8)	11.7 (1.8)	<0.001
single-pool Kt/V	1.43 (0.32)	1.41 (0.33)	0.08
pre-dialysis sBP, mmHg	152.1 (24.0)	150.2 (25.3)	0.08
pre-dialysis dBp, mmHg	77.6 (14.4)	78.1 (15.2)	0.04
urea nitrogen, mg/dL	61.9 (16.1)	62.6 (16.6)	0.04
albumin, g/dL	3.63 (0.44)	3.65 (0.45)	0.05
C-reactive protein, mg/dL	0.1 [0.1, 0.4]	0.1 [0.1, 0.5]	<0.001
albumin-adjusted Ca, mg/dL	9.22 (0.75)	9.21 (0.81)	0.02
phosphate, mg/dL	5.17 (1.44)	5.20 (1.51)	0.02
intact PTH, pg/mL	125 [66, 205]	130 [67, 216]	0.06
hemoglobin, g/dL	10.5 (1.2)	10.6 (1.5)	0.06
ferritin, ng/mL	80 [34, 169]	82 [32, 189]	0.04
TSAT, %	25.9 (13.3)	25.8 (13.3)	0.01
diabetes mellitus, %	37.9	38.1	0.003

Past history of MI, %	9.2	11.5	0.08
Past history of CH, %	5.7	7.2	0.06
Past history of CI, %	17.9	21.6	0.095
Past history of amputation, %	3.3	4.8	0.08

Abbreviations: ESA, erythropoietin stimulating agents; HD, hemodialysis; sBP, systolic blood pressure; dBP, diastolic blood pressure; Ca, calcium; PTH, parathyroid hormone; TSAT, transferrin saturation; MI, myocardial infarction; CH, cerebral hemorrhage; CI, cerebral infarction.

Data presented as mean (standard deviation) or median [interquartile range]

Standardized difference of <0.1 denotes a negligible difference between groups.

Supplement Table 3. Comparison of baseline characteristics after propensity score-matching

	Long-acting ESA users	Short-acting ESA users	Standardized
	n = 42,473	n = 42,473	difference
age, yr	67.0 (12.3)	67.1 (12.3)	0.009
male, %	61.9	62.0	0.001
body mass index, kg/m ²	22.3 (3.6)	22.3 (3.6)	0.008
HD vintage, yr	6 [3, 11]	6 [3, 11]	0.006
HD duration, hours/week	11.8 (1.7)	11.8 (1.6)	0.006
single-pool Kt/V	1.45 (0.31)	1.45 (0.31)	<0.001
pre-dialysis sBP, mmHg	152.3 (23.9)	152.2 (23.7)	0.002
pre-dialysis dBP, mmHg	77.9 (14.4)	77.8 (14.3)	0.007
urea nitrogen, mg/dL	62.1 (15.6)	61.9 (15.4)	0.007
albumin, g/dL	3.67 (0.40)	3.67 (0.40)	0.02
C-reactive protein, mg/dL	0.1 [0.1, 0.4]	0.1 [0.1, 0.4]	0.003
albumin-adjusted Ca, mg/dL	9.24 (0.73)	9.23 (0.73)	0.005
phosphate, mg/dL	5.17 (1.40)	5.16 (1.39)	0.006
intact PTH, pg/mL	125 [67, 202]	125 [67, 203]	0.005
hemoglobin, g/dL	10.5 (1.2)	10.5 (1.1)	<0.001
ferritin, ng/mL	77 [33, 164]	87 [37, 178]	0.04
TSAT, %	26.1 (13.5)	25.6 (12.1)	0.03
diabetes mellitus, %	38.1	38.1	<0.001
Past history of MI, %	9.6	9.2	0.01

Past history of CH, %	5.8	5.5	0.01
Past history of CI, %	17.6	18.1	0.01
Past history of amputation, %	3.2	2.9	0.02

Abbreviations: ESA, erythropoietin stimulating agents; HD, hemodialysis; sBP, systolic blood pressure; dBP, diastolic blood pressure; Ca, calcium; PTH, parathyroid hormone; TSAT, transferrin saturation; MI, myocardial infarction; CH, cerebral hemorrhage; CI, cerebral infarction.

Data presented as mean (standard deviation) or median [interquartile range].

Standardized difference of <0.1 denotes a negligible difference between groups.

Supplement Table 4. The average dose of ESA in each ESA dose tertile

	ESA dose tertile			Total
	1st	2nd	3rd	
Epoetin alfa/beta (U/week)	1,960 (854)	4,169 (1,041)	7,618 (2,071)	4,546 (2,786)
Darbepoetin alfa (µg/week)	12.0 (4.0)	24.9 (7.6)	56.1 (26.3)	30.4 (23.8)
Epoetin beta pegol (µg/month)	48.0 (18.9)	98.1 (24.2)	181.6 (65.4)	110.6 (69.5)
Epoetin kappa (U/week)	1,965 (862)	4,214 (1,042)	7,841 (2,144)	4,991 (2,963)

Abbreviations: ESAs, erythropoietin stimulating agents

Data presented as mean (standard deviation).

Supplement Table 5. Baseline characteristics according to 4 types of ESA

Characteristics	Epoetin alfa/beta	Epoetin kappa	Darbepoetin alfa	Epoetin beta pegol	P-value*
	n = 50,809	n = 19,822	n = 97,391	n = 26,676	
age, yr	67.0 (12.4)	67.5 (12.5)	67.7 (12.3)	67.6 (12.4)	<0.001
male, %	61.5	61.6	61.6	61.7	0.97
body mass index, kg/m ²	22.3 (3.9)	22.3 (3.8)	22.2 (3.9)	22.3 (3.9)	<0.001
HD vintage, yr	6 [3, 11]	5 [3, 10]	6 [3, 11]	6 [3, 11]	<0.001
HD duration, hours/week	11.9 (1.9)	11.7 (1.7)	11.7 (1.7)	11.7 (1.8)	<0.001
single-pool Kt/V	1.44 (0.32)	1.42 (0.31)	1.42 (0.32)	1.44 (0.32)	<0.001
pre-dialysis sBP, mmHg	152.1 (23.8)	152.1 (23.8)	152.1 (24.1)	151.9 (24.2)	0.73
pre-dialysis dBp, mmHg	77.8 (14.5)	77.3 (14.0)	77.5 (14.4)	77.6 (14.5)	<0.001
urea nitrogen, mg/dL	62.1 (15.8)	62.0 (16.0)	61.7 (16.3)	62.2 (16.0)	<0.001
albumin, g/dL	3.65 (0.42)	3.67 (0.41)	3.60 (0.45)	3.63 (0.43)	<0.001
C-reactive protein, mg/dL	0.1 [0.1, 0.4]	0.1 [0.1, 0.4]	0.1 [0.1, 0.5]	0.1 [0.1, 0.4]	<0.001
albumin-adjusted Ca, mg/dL	9.24 (0.75)	9.18 (0.75)	9.22 (0.75)	9.21 (0.76)	<0.001
phosphate, mg/dL	5.16 (1.42)	5.12 (1.41)	5.17 (1.44)	5.21 (1.48)	<0.001
intact PTH, pg/mL	126 [67, 206]	124 [65, 204]	125 [66, 206]	125 [65, 204]	0.013
hemoglobin, g/dL	10.5 (1.1)	10.4 (1.1)	10.5 (1.2)	10.4 (1.2)	<0.001
ferritin, ng/mL	82 [35, 169]	98 [40, 212]	73 [31, 158]	89 [41, 177]	<0.001
TSAT, %	25.7 (12.4)	26.0 (12.8)	25.4 (13.3)	28.5 (15.1)	<0.001
diabetes mellitus, %	37.3	39.2	38.1	37.5	<0.001
Past history of MI, %	9.0	9.5	9.3	9.0	0.071

Past history of CH, %	5.6	5.8	5.8	5.7	0.73
Past history of CI, %	17.5	19.1	17.8	17.8	<0.001
Past history of amputation, %	3.1	3.3	3.5	3.2	<0.001

Abbreviations: ESA, erythropoietin stimulating agents; HD, hemodialysis; sBP, systolic blood pressure; dBP, diastolic blood pressure; Ca, calcium; PTH, parathyroid hormone, TSAT, transferrin saturation; MI, myocardial infarction; CH, cerebral hemorrhage; CI, cerebral infarction.

Data presented as mean (standard deviation) or median [interquartile range].

*Analysis of variance or Kruskal-Wallis Test

Supplement Table 6. Hazard ratios for deaths across the 4 types of ESA

<i>1) All-cause death</i>		n	HR	95% CI	P-value
Unadjusted	Epoetin alfa/beta	50,809	1.00	-	-
	Epoetin kappa	19,822	1.09	1.04 to 1.14	<0.001
	Epoetin beta pegol	26,676	1.15	1.11 to 1.19	<0.001
	Darbepoetin alfa	97,391	1.25	1.21 to 1.28	<0.001
Model 1	Epoetin alfa/beta	30,243	1.00	-	-
	Epoetin kappa	12,497	1.06	1.00 to 1.12	0.044
	Epoetin beta pegol	16,038	1.12	1.07 to 1.18	<0.001
	Darbepoetin alfa	59,420	1.16	1.12 to 1.21	<0.001
Model 2	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.07	1.01 to 1.13	0.014
	Epoetin beta pegol	16,013	1.11	1.06 to 1.17	<0.001
	Darbepoetin alfa	59,278	1.16	1.12 to 1.21	<0.001
IPTW	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.09	1.03 to 1.16	0.004
	Epoetin beta pegol	16,013	1.12	1.06 to 1.18	<0.001
	Darbepoetin alfa	59,278	1.17	1.13 to 1.22	<0.001
<i>2) Cardiovascular death</i>		n	HR	95% CI	P-value
Unadjusted	Epoetin alfa/beta	50,809	1.00	-	-
	Epoetin kappa	19,822	1.03	0.96 to 1.11	0.36
	Epoetin beta pegol	26,676	1.15	1.09 to 1.22	<0.001
	Darbepoetin alfa	97,391	1.20	1.15 to 1.26	<0.001
Model 1	Epoetin alfa/beta	30,243	1.00	-	-
	Epoetin kappa	12,497	0.97	0.89 to 1.07	0.56
	Epoetin beta pegol	16,038	1.10	1.02 to 1.19	0.017
	Darbepoetin alfa	59,420	1.12	1.05 to 1.18	<0.001
Model 2	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	0.99	0.91 to 1.09	0.87
	Epoetin beta pegol	16,013	1.09	1.01 to 1.18	0.028
	Darbepoetin alfa	59,278	1.12	1.06 to 1.19	<0.001
IPTW	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	0.99	0.90 to 1.09	0.90
	Epoetin beta pegol	16,013	1.10	1.01 to 1.19	0.027

		Darbepoetin alfa	59,278	1.12	1.06 to 1.19	<0.001
3) Death from cardiac diseases		n	HR	95% CI	P-value	
Unadjusted	Epoetin alfa/beta	50,809	1.00	-	-	
	Epoetin kappa	19,822	1.05	0.97 to 1.13	0.24	
	Epoetin beta pegol	26,676	1.13	1.06 to 1.21	<0.001	
	Darbepoetin alfa	97,391	1.21	1.15 to 1.27	<0.001	
Model 1	Epoetin alfa/beta	30,243	1.00	-	-	
	Epoetin kappa	12,497	1.00	0.90 to 1.10	0.95	
	Epoetin beta pegol	16,038	1.07	0.98 to 1.17	0.142	
	Darbepoetin alfa	59,420	1.12	1.05 to 1.20	0.001	
Model 2	Epoetin alfa/beta	30,135	1.00	-	-	
	Epoetin kappa	12,477	1.02	0.92 to 1.13	0.74	
	Epoetin beta pegol	16,013	1.06	0.97 to 1.16	0.201	
	Darbepoetin alfa	59,278	1.12	1.05 to 1.20	<0.001	
IPTW	Epoetin alfa/beta	30,135	1.00	-	-	
	Epoetin kappa	12,477	1.02	0.92 to 1.13	0.70	
	Epoetin beta pegol	16,013	1.06	0.97 to 1.17	0.190	
	Darbepoetin alfa	59,278	1.13	1.06 to 1.21	<0.001	
4) Death from strokes		n	HR	95% CI	P-value	
Unadjusted	Epoetin alfa/beta	50,809	1.00	-	-	
	Epoetin kappa	19,822	0.98	0.83 to 1.14	0.77	
	Epoetin beta pegol	26,676	1.24	1.08 to 1.41	0.002	
	Darbepoetin alfa	97,391	1.18	1.07 to 1.30	0.001	
Model 1	Epoetin alfa/beta	30,243	1.00	-	-	
	Epoetin kappa	12,497	0.89	0.72 to 1.08	0.24	
	Epoetin beta pegol	16,038	1.23	1.03 to 1.45	0.018	
	Darbepoetin alfa	59,420	1.10	0.96 to 1.25	0.160	
Model 2	Epoetin alfa/beta	30,135	1.00	-	-	
	Epoetin kappa	12,477	0.90	0.73 to 1.10	0.31	
	Epoetin beta pegol	16,013	1.22	1.03 to 1.44	0.021	
	Darbepoetin alfa	59,278	1.10	0.97 to 1.25	0.142	
IPTW	Epoetin alfa/beta	30,135	1.00	-	-	
	Epoetin kappa	12,477	0.89	0.72 to 1.09	0.26	
	Epoetin beta pegol	16,013	1.22	1.03 to 1.45	0.020	
	Darbepoetin alfa	59,278	1.10	0.97 to 1.25	0.135	

5) <i>Non-cardiovascular death</i>		n	HR	95% CI	P-value
Unadjusted	Epoetin alfa/beta	50,809	1.00	-	-
	Epoetin kappa	19,822	1.12	1.07 to 1.19	<0.001
	Epoetin beta pegol	26,676	1.15	1.09 to 1.21	<0.001
	Darbepoetin alfa	97,391	1.28	1.23 to 1.32	<0.001
Model 1	Epoetin alfa/beta	30,243	1.00	-	-
	Epoetin kappa	12,497	1.12	1.04 to 1.20	0.002
	Epoetin beta pegol	16,038	1.13	1.06 to 1.21	<0.001
	Darbepoetin alfa	59,420	1.20	1.14 to 1.25	<0.001
Model 2	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.13	1.05 to 1.21	0.001
	Epoetin beta pegol	16,013	1.13	1.06 to 1.20	<0.001
	Darbepoetin alfa	59,278	1.19	1.14 to 1.25	<0.001
IPTW	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.16	1.07 to 1.25	<0.001
	Epoetin beta pegol	16,013	1.13	1.06 to 1.21	<0.001
	Darbepoetin alfa	59,278	1.20	1.15 to 1.27	<0.001
6) <i>Death from infectious diseases</i>		n	HR	95% CI	P-value
Unadjusted	Epoetin alfa/beta	50,809	1.00	-	-
	Epoetin kappa	19,822	1.09	0.99 to 1.19	0.089
	Epoetin beta pegol	26,676	1.21	1.11 to 1.31	<0.001
	Darbepoetin alfa	97,391	1.30	1.22 to 1.38	<0.001
Model 1	Epoetin alfa/beta	30,243	1.00	-	-
	Epoetin kappa	12,497	1.09	0.96 to 1.23	0.165
	Epoetin beta pegol	16,038	1.17	1.05 to 1.31	0.004
	Darbepoetin alfa	59,420	1.18	1.09 to 1.28	<0.001
Model 2	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.11	0.98 to 1.25	0.098
	Epoetin beta pegol	16,013	1.17	1.05 to 1.30	0.005
	Darbepoetin alfa	59,278	1.18	1.09 to 1.27	<0.001
IPTW	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.15	1.01 to 1.30	0.040
	Epoetin beta pegol	16,013	1.19	1.06 to 1.33	0.002
	Darbepoetin alfa	59,278	1.19	1.10 to 1.30	<0.001
7) <i>Death from malignancy</i>		n	HR	95% CI	P-value

Unadjusted	Epoetin alfa/beta	50,809	1.00	-	-
	Epoetin kappa	19,822	1.07	0.93 to 1.23	0.36
	Epoetin beta pegol	26,676	1.11	0.97 to 1.26	0.115
	Darbepoetin alfa	97,391	1.33	1.22 to 1.46	<0.001
Model 1	Epoetin alfa/beta	30,243	1.00	-	-
	Epoetin kappa	12,497	1.06	0.88 to 1.27	0.54
	Epoetin beta pegol	16,038	1.08	0.92 to 1.28	0.35
	Darbepoetin alfa	59,420	1.19	1.05 to 1.34	0.005
Model 2	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.06	0.88 to 1.27	0.56
	Epoetin beta pegol	16,013	1.08	0.92 to 1.27	0.36
	Darbepoetin alfa	59,278	1.18	1.05 to 1.33	0.006
IPTW	Epoetin alfa/beta	30,135	1.00	-	-
	Epoetin kappa	12,477	1.08	0.89 to 1.30	0.45
	Epoetin beta pegol	16,013	1.07	0.91 to 1.27	0.40
	Darbepoetin alfa	59,278	1.18	1.05 to 1.34	0.007

Abbreviations: ESA, erythropoietin stimulating agents; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; -, not applicable.

Model 1 adjusted for age, sex, body mass index, pre-dialysis systolic blood pressure, dialysis duration, dialysis vintage, single-pool Kt/V, diabetes mellitus, a past history of cardiovascular diseases, laboratory data (albumin, urea nitrogen, C-reactive protein, hemoglobin, ferritin, albumin-adjusted calcium, phosphate, and parathyroid hormone), and standardized erythropoietin resistance index

Model 2 adjusted for covariates in Model 1 + facility indicators.

IPTW model was adjusted for covariates in Model 2