Erythropoiesis Stimulating Agents Cannot Improves Circulating Endothelial Progenitor Cell Counts in Patients with End-Stage Renal Disease on Maintenance Hemodialysis Because of Erythropoietin Resistance

Hong Joo Lee[1], Ju Young Moon[2], Sang Ho Lee[2], Chun Gyoo Ihm[2], Tae Won Lee[2], and Kyung Hwan Jeong[2]

Department of Nephrology, Seoul Red Cross Hospital[1] and Kyung Hee University Medical Center[2], Seoul, Korea

BACKGROUND

- Decreased circulating endothelial progenitor cells (EPCs) associate with occurrence of cardiovascular disease and all cause mortality in end stage renal disease(ESRD) patients on hemodialysis.

- It is known that erythropoiesis stimulating agents(ESA) connect to vasculoprotective effects such as enhanced nitric oxide production in endothelial cells and mobilization of EPCs.

- Patients with ESRD on hemodialysis have markedly decreased EPC counts although they are often treated with ESA.

- We investigated that ESA can improve EPC levels in hamodialysis patients. Or not, we hypothesized that erythropoietin resistance index(ERI) may associate with decreased effect of ESA on EPC.

METHODS

- We quantified ESA dose and EPCs in blood samples from 86 patients with ESRD on hemodialysis.

- The ERI was calculated by dividing the weekly erythropoietin dose per kilogram of weight (μg/wk.kg) by the Hb level (g/dL).

- Participants were divided into 4 groups based on the
  - ✓ lowest ERI, Median ERI, highest ERI and no use of ESA group

- Circulating EPCs were counted by flow cytometry as the number of$CD45^{low}CD34^+VEGFR2^+$ cells.

- Cardiovascular events served as outcome variables over a median follow-up period of 20 months.
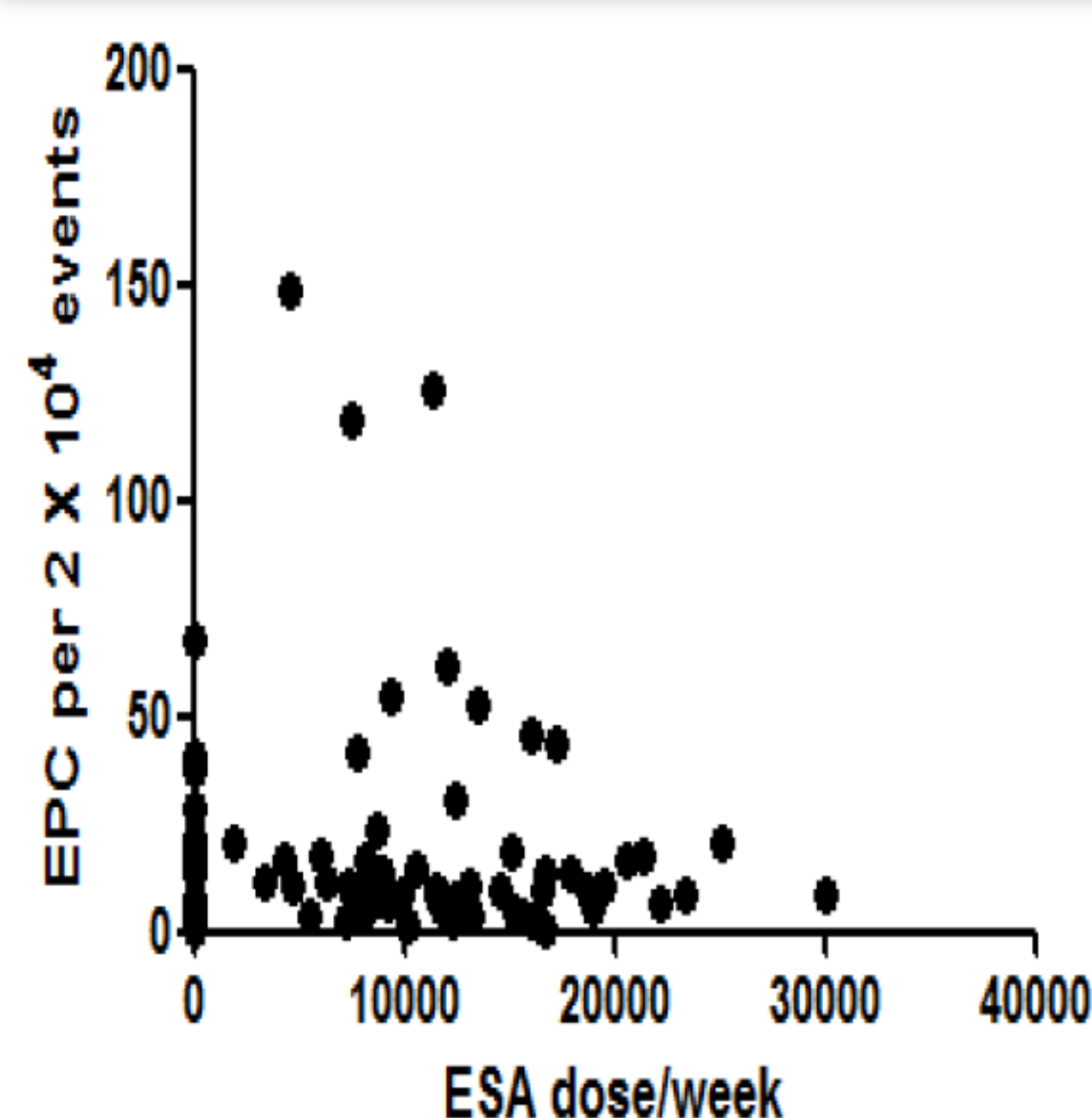
RESULTS

Figure 1. Correlation between circulating level of endothelial progenitor cells (EPCs) and erythropoiesis stimulating agents(ESA) dose.
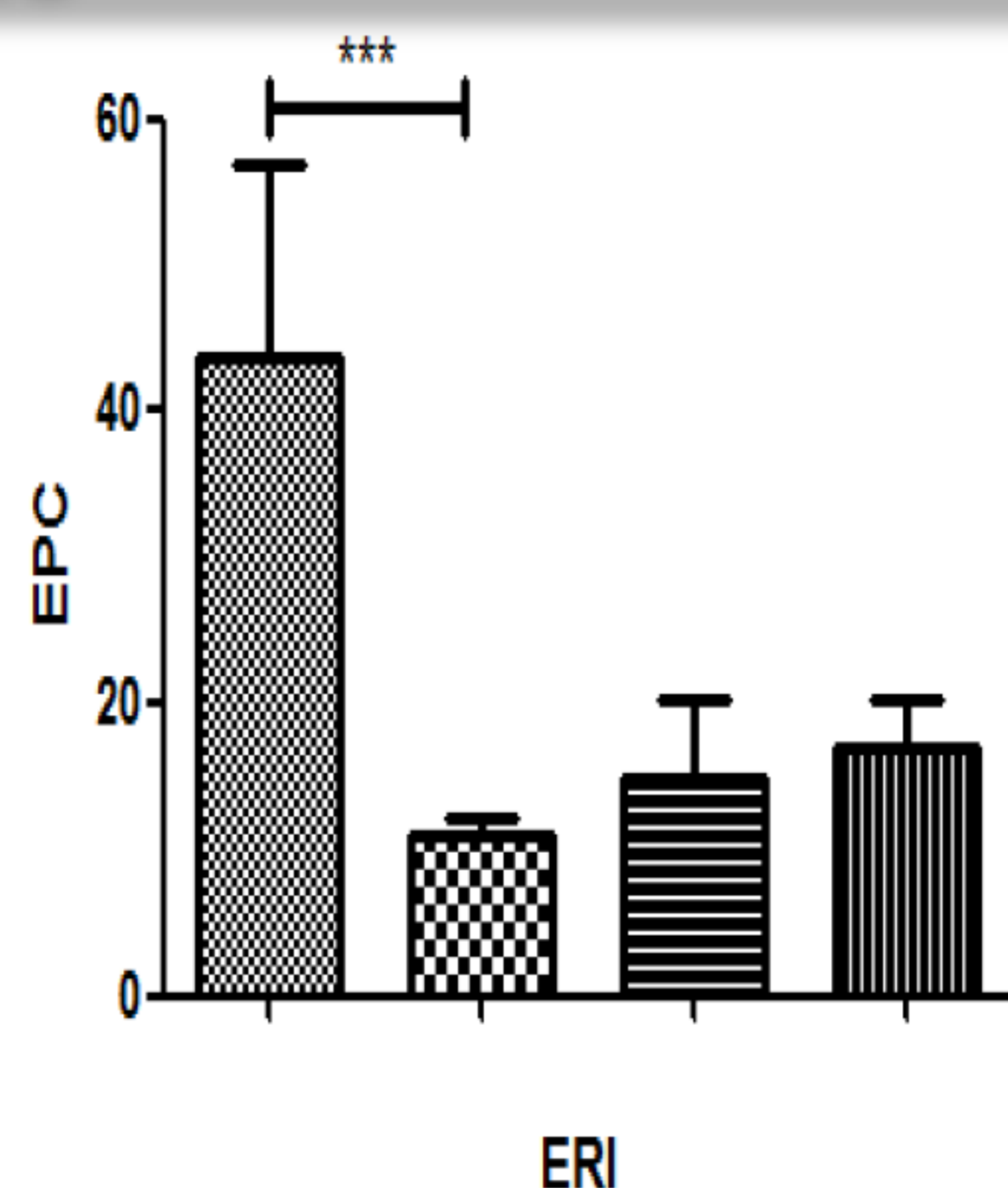

Figure 2. Comparison of circulating level of EPCs among no use of ESA, lowest ERI, median ERI and highest ERI groups
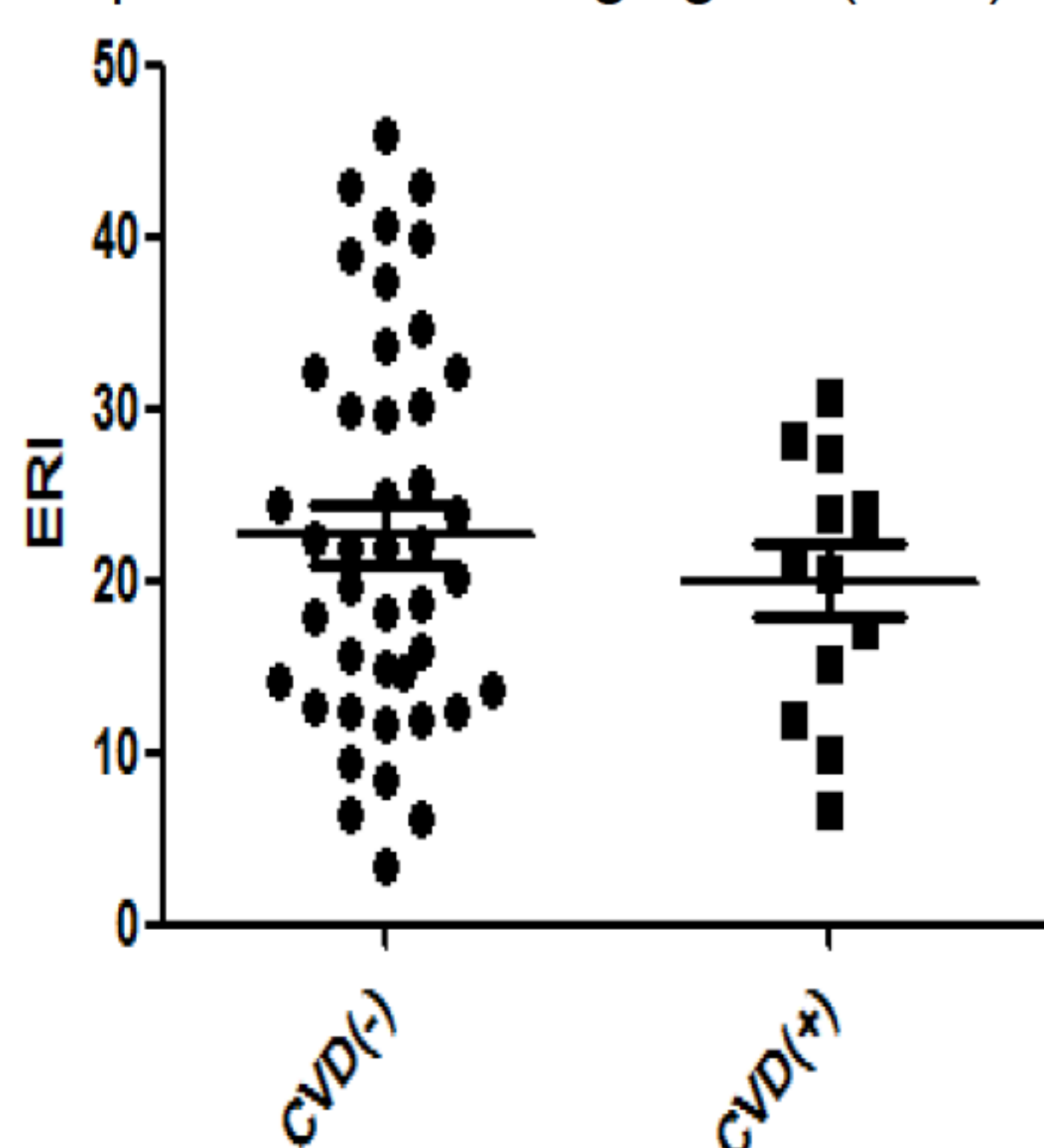

Figure 3. Comparison of circulating level of ERIs between the patients with cardiovascular disease(CVD) and no CVD patients

CONCLUSION

- Administration of ESA may not always increase the number of circulating EPCs in ESRD patients on HD.

- The resistance to erythropoietin may associate with decreased circulation EPC counts.

Table 1. Anthropometric and biochemical parameters for lowest, median, highest ERI and no use of ESA groups

Variable	Lowest (n=22)	Median (n=23)	Highest (n=23)	No use of ESA (n=18)	p *
Age (years)	58.8 ± 12.9	60.9 ± 12.8	51.3 ± 11.4	61.5± 12.2	0.062
Gender (male, %)	11 (50%)	13 (57%)	14 (61%)	11 (61%)	0.835
Body mass index (kg/m²)	23.9 ± 4.0	21.2 ± 2.9	23.0 ± 3.8	22.0 ± 3.1	0.114
Systolic blood pressure (mmHg)	158.4 ± 28.9	163.7 ± 28.8	173.3 ± 32.7	156.3 ± 37.3	0.489
Diastolic blood pressure (mmHg)	80.4 ± 13.2	78.4 ± 17.7	88.7 ± 20.4	75.7 ± 18.1	0.245
Co-morbidities					
Hypertension	21 (94%)	19 (84%)	21 (89%)	14 (77%)	0.422
Diabetes	5 (22%)	11 (47%)	12 (53%)	7 (38%)	0.635
Previous cardiovascular disease	2 (11%)	5 (21%)	4 (16%)	6 (31%)	0.215
Hemodialysis duration (Mo)	56.7 ± 46.4	54.7 ± 35.1	56.5 ± 37.6	54.5 ± 53.1	0.453
Weekly Kt/Vurea	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.3	1.5 ± 0.2	0.399
Laboratory findings					
Hemoglobin (g/dL)	10.4 ± 0.8ᵃ	9.8 ± 1.0ᵃ	9.4 ± 0.9ᵇ	11.3 ± 1.6	**0.000**
Blood urea nitrogen (mg/dL)	69.4 ± 12.0	63.2 ± 12.9	75.2 ± 14.7	74.8 ± 18.0	**0.052**
Creatinine (mg/dL)	11.0 ± 3.0	10.0 ± 3.2	12.8 ± 1.9	10.2 ± 3.6	**0.021**
Sodium (mg/dL)	136.5 ± 2.4	135.9 ± 3.0	137.0 ± 2.7	134.4 ± 2.8	0.082
Potassium (mg/dL)	5.0 ± 1.0	5.1 ± 0.8	5.4 ± 0.8	5.1 ± 0.9	0.556
Phosphorus (mg/dL)	5.3 ± 1.1	4.5 ± 2.0	5.5 ± 1.2	5.0± 1.7	0.266
Calcium (mg/dL)	8.8 ± 0.9	8.6 ± 0.6	8.4 ± 0.7	8.4 ± 0.6	0.264
Ca X Pi	47.1 ± 10.7	39.0 ± 17.6	45.8 ± 10.7	42.3 ± 15.4	0.291
Intact PTH (pg/mL)	109.5 ± 114.8	127.1 ± 95.2	110.9 ± 73.7	118.9 ± 303.0	0.511
Vitamin D	10.7 ± 3.8	11.1 ± 4.6	11.9 ± 3.3	8.8 ± 1.2	0.148
Total cholesterol (mg/dL)	137.3 ± 77.0	117.9 ± 49.2	103.3 ± 46.4	92.7 ± 33.4	0.152
Triglyceride (mg/dL)	151.2 ± 24.2	142.1 ± 28.3	132.7 ± 23.4	142.0 ± 40.1	0.289
LDL-cholesterol (mg/dL)	85.7 ± 29.9	82.4 ± 26.4	73.2 ± 19.4	85.1 ± 34.2	0.495
HbA1c (%)	7.2 ± 2.3	6.8 ±1.6	6.4 ± 1.4	6.8 ± 1.4	0.787
β2 microglobulin (mg/dL)	16.9 ± 5.7	18.5 ± 9.1	18.1 ± 6.9	19.1 ± 6.7	0.863
hsCRP (mg/dL)	1.9 ± 2.7	2.4 ± 1.9	1.3 ± 2.2	1.7 ± 2.6	0.517
ESA dose (X1,000IU/week)	7.3 ± 2.9	11.3 ± 2.7	19.1 ± 4.0	0.0 ± 0.0	**0.000**
ERI (IU/kg/week)	10.9 ± 3.4	20.7 ± 2.8	34.1 ± 6.3	0.0 ± 0.0	**0.000**
EPCs (cells/200μl)	35.7 ± 46.5	15.6 ± 15.8	14.3 ± 12.3	19.9 ± 18.8	**0.080**

SUMMARY

- Of the total of 86 patients enrolled for follow-up preiod of 20 months, 68 patients were treated with ESA.

- Mean ESA dose was 12669 ± 5853 units/week in patients treated withe ESA

- The number of circulating EPCs at baseline ranged from 1 to 350cells/200μl, with a mean ± SD of 26.0± 48.2 cells/200μL.

- There was no significant association with ESA dose and EPC counts in ESRD patients on hemodialysis.

- Baseline characteristics such as Age, sex, blood pressure and co-morbidities and laboratory findings is no different in each groups except hemoglobin, ESA dose and ERI

- Overall, ESA resistant patients had lower hemoglobin and higher ESA dose.

- The EPCs counts of lowest ERI group were significantly higher than the medium, highest EPI and no use of ESA group.

- However, There was no different ERI according to the occurrence of cardiovascular events.

Cell signalling. Cell biology. Hormones.

Hong joo

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