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ORIGINAL RESEARCH

Erythropoietin Use and the Risk of Stroke in Patients on Hemodialysis: A Retrospective Cohort Study in Taiwan

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BACKGROUND: Targeting higher hemoglobin levels with erythropoietin to treat anemia in patients with chronic kidney disease is associated with increased cardiovascular risk, including that of stroke. The risks of the subtypes of stroke, ischemic, hemorrhagic, and unspecified, following the administration of erythropoietin in patients with end-stage renal disease receiving hemodialysis remain unclear.

METHODS AND RESULTS: Overall, 12 948 adult patients with end-stage renal disease treated during 1999 to 2010 who had undergone hemodialysis were included. The study end points were the incidences of stroke and its subtypes. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) of stroke and its subtypes in erythropoietin recipients compared with nonrecipients. Patients in the erythropoietin cohort did not have an increased risk of stroke compared with those in the nonerythropoietin cohort (adjusted HR, 1.03; 95% CI, 0.92–1.15). Compared with patients in the nonerythropoietin cohort, the risks of ischemic, hemorrhagic, or unspecified stroke were not higher in patients in the erythropoietin cohort (adjusted HRs, 1.08 [95% CI, 0.93–1.26], 0.96 [95% CI, 0.78–1.18], and 1.03 [95% CI, 0.80–1.32], respectively). Increased risks of stroke and its subtypes were not observed with even large annual defined daily doses of erythropoietin (>201).

CONCLUSIONS: Erythropoietin in patients receiving hemodialysis is not associated with increased risk of stroke or any of its subtypes.

Key Words: end-stage renal disease ■ erythropoietin ■ hemodialysis ■ ischemic stroke

Erythropoietin treatment increases blood hemoglobin levels in almost all patients with anemia of end-stage renal disease (ESRD) and has been the mainstay of management in these patients for decades.[1,2] Erythropoietin therapy renders many of these patients free of transfusions, and a plethora of studies (most uncontrolled) have documented the dramatic benefits on quality of life (particularly physical capacity), general well-being, and other physiological effects of increasing hemoglobin levels from 6 g/dL to approximately 11 to 12 g/dL.[3–5] Particularly, erythropoietin has been demonstrated to have a positive effect on the lesion size and outcomes in various experimental stroke models.[6–8] Independent of its hematopoietic effects, erythropoietin has been demonstrated to have neuroprotective effects in animal models of ischemia or hypoxia.[9,10] Despite a molecular weight of >30 000 Da, erythropoietin at high doses crosses the bloodbrain barrier in an amount sufficient to exert neuroprotection.[6,11]

Before 2009, there was no clear evidence of the risk of stroke with erythropoietin in patients with chronic kidney disease (CKD). Since 2009, however, several large randomized trials that have evaluated

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CLINICAL PERSPECTIVE

What Is New?

- Clinical outcomes of erythropoietin in relation to the risk of stroke and its subtypes in patients with end-stage renal disease on hemodialysis were evaluated.
- A well-characterized national database with adjustments for differences in baseline demographic characteristics was used, and defined daily dose of erythropoietin was included.

What Are the Clinical Implications?

- Erythropoietin in patients on hemodialysis is not associated with increased risk of stroke or its subtypes (ischemic, hemorrhagic, and unspecified stroke).
- A target hemoglobin concentration of 10 to 11 g/dL is recommended to provide the benefits of erythopoietin therapy while diminishing its potential risks.

Nonstandard Abbreviations and Acronyms

ATC	Anatomical Therapeutic Chemical
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database

erythropoietin treatment regimens in nondialysis-dependent CKD found that the risks of cardiovascular complications, including stroke, and early death were significantly increased when high doses of erythropoietin were used to maximize hemoglobin response.[12] These findings have raised concerns regarding the relative benefits and risks of erythropoietin treatment in correcting anemia in patients with ESRD on hemodialysis. Additionally, these findings suggest that in some patients with ESRD on hemodialysis, the potential risks associated with erythropoietin may outweigh the benefits, especially regarding the risk of stroke. However, the factors that may account for the excess risk of stroke are unclear.

The risks observed with erythropoietin treatment in a carefully selected patient population in a randomized clinical trial may not be generalizable to a "real-world" ambulatory clinical care setting. Additionally, data on erythropoietin treatment in stroke and stroke subtypes in patients on hemodialysis are lacking. Therefore, we conducted a population-based retrospective cohort study to investigate the clinical outcomes of erythropoietin in terms of the risk of stroke and its subtypes in patients with ESRD on hemodialysis. We used a well-characterized national database with adjustments for differences in the baseline demographic characteristics and evaluated the defined daily dose (DDD) of erythropoietin, as well as important clinical outcomes following the policy of Taiwan's universal National Health Insurance (NHI).

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Collection

A universal NHI program was implemented in Taiwan in March 1995. By the end of 2010, the Bureau of NHI had contracts with 97% of the hospitals and 90% of the clinics to join the NHI system.[13] As of 2013, over 99.9% of Taiwan's 23.4 million residents were enrolled in this program.[14] The National Health Research Institutes safeguards the privacy and confidentiality of all beneficiaries and provides health insurance data for research purposes only after ethical approval has been obtained. In this study, access to the NHI Research Database (NHIRD) was approved by the local institutional review board of the Chia-Yi Christian Hospital (approval number CYCH-IRB-2021033). This retrospective observational study was using deidentified and routine diagnosis/treatment data, thus CYCH-IRB-2021033 approved the waiver of informed consent from all patients for being included in the study.

Study Population

In this retrospective observational study, adult patients (aged >18 years) with newly diagnosed ESRD on maintenance hemodialysis between January 1, 1999, and December 31, 2010 (n=39 923), were included from the NHIRD. Patients with ESRD were defined as those with catastrophic illness registration codes for ESRD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 585) who were on maintenance hemodialysis.[15] We defined the index date as the first day of erythropoietin use in our analysis. Patients with ESRD who received a combination of hemodialysis and peritoneal dialysis, had undergone kidney transplantation, or were diagnosed with stroke before the index date were excluded. There were 6477 patients

without erythropoietin treatment and 33 446 patients with erythropoietin treatment. Table S1 compares the selected patients with erythropoietin treatment in this study (n=6474) and all patients with erythropoietin treatment (N=33 446). It was found that age and some comorbidities were significantly different, but there was no difference in the annual DDDs. After frequency matching by age, sex, and year of index date at a 1:1 ratio, 6474 patients without erythropoietin treatment were included in the nonerythropoietin cohort and 6474 patients with erythropoietin treatment were included in the erythropoietin cohort. Because not matching by suitable counterparts, 3 patients without erythropoietin treatment were excluded from this study.

For all individuals in the cohort, potential risk factors of stroke in the NHIRD were obtained from the following diagnoses: hypertension (codes 401–405), diabetes mellitus (code 250), coronary heart disease (codes 410–414 or 429.2), heart failure (code 428), atrial fibrillation (code 427.31), hyperlipidemia (code 272), and anemia (code 280-285). Patients with ESRD who were diagnosed with cancer before their first dialysis were also excluded.

Annual Cumulative Exposure of Erythropoietin

According to total duration (in days) and dosage of erythropoietin, we calculated DDD of erythropoietin, which was prescribed as epoetin α or β (IU), darbepoetin alfa (μg), or methoxy polyethylene glycol-epoetin beta (μg). To compare the different types of erythropoietin, weekly prescribed dosages were converted to DDD using the conversion factors provided by the World Health Organization Drug Classification (http://www.whocc.no/atcddd). DDD represents the assumed average maintenance dose per day for a drug in adults.[16] Accordingly, DDD for epoetin α and β (Anatomical Therapeutic Chemical [ATC] code B03XA01) is 1000 IU, darbepoetin alfa (ATC code B03XA02) is 4.5 μg, and methoxy polyethylene glycol-epoetin beta (ATC code B03XA03) DDD is 4.0 μg. Additionally, 1000 IU of erythropoietin is equal to 8.4 μg. Therefore, to investigate the dose-related effects, the cumulative dosage of erythropoietins was calculated as the total prescribed annual DDDs (ie, the same as total dispensed DDD in this system). At the time of a stroke, the cumulative erythropoietin dosage was recorded as the total of annual DDDs since drug initiation until the day before the diagnosis.

The follow-up period extended from the date of initiation of hemodialysis until December 31, 2011, and the incidences of stroke and its subtypes were estimated in each cohort. The subtypes of stroke included ischemic stroke (codes 433–435), hemorrhagic stroke (codes 430–432), and unspecified stroke (codes 436–438).[17] To investigate the effects of the dosage, the cumulative erythropoietin dosage in the year of stroke was estimated. The annual cumulative erythropoietin dosage was divided into 3 groups: low (<71), median (71–200), and high (≥201).

Statistical Analysis

Unadjusted hazard ratios (HRs) along with 95% CIs were estimated using Cox proportional hazard regression. Adjusted HRs were computed after adjusting for age, sex, and significant demographic characteristics and comorbidities. We further analyzed the incidence rates of stroke and its subtypes between the cohorts. All data analyses were performed using SAS (version 9.3) Statistical Package for Windows (SAS Institute Inc), and the significance level was set at 0.05 in 2-sided tests.

RESULTS

The demographic characteristics and comorbidities of patients are summarized in Table 1. We identified 6474 patients with hemodialysis who received erythropoietin and 6474 patients on hemodialysis who did not receive erythropoietin during the study period. There were no significant differences in the age, sex, and comorbidities (coronary heart disease, hypertension, diabetes mellitus, atrial fibrillation, heart failure, and anemia) between the cohorts. Patients in the nonerythropoietin cohort were more likely to live in urban areas than those in the erythropoietin cohort. The commonest comorbidities were hypertension (91.8%), anemia (67.6%), diabetes mellitus (56.8%), and hyperlipidemia (46.6%). Less than 5% of the patients had a history of atrial fibrillation, and nearly 31% were aged ≥60 years.

Factors Associated With Stroke Incidence

The results of our analysis examining the association between the use of erythropoietin and the risk of stroke are summarized in Table 2. Stratified Cox proportional hazard regressions demonstrated that the HR for stroke in the erythropoietin cohort was 1.04 (95% CI, 0.93–1.16; *P*=0.50) in comparison with the nonerythropoietin cohort. After adjusting the data for demographic characteristics, such as age, sex, and urbanization, HR in the erythropoietin cohort was 1.03 (95% CI, 0.92–1.15; *P*=0.55) compared with the nonerythropoietin cohort.

Risk of Stroke Between Different Dosages of Erythropoietin

Table 2 also summarizes the association between annual DDDs and the risk of stroke. Analyzing the annual DDDs of erythropoietin indicated that the low-, medium-, and high-dose groups did not demonstrate

Table 1. Demographic Characteristics and Comorbidities of the Hemodialysis Cohort in Taiwan

Variable	Total n=12 948		Nonerythropoietin Cohort n=6474		Erythropoietin Cohort n=6474		*P* Value
	No.	%	No.	%	No.	%	
Age, y							
Median (IQR)	62.8	(20.0)	62.8	(20.0)	62.8	(20.0)	0.82
18–40	2570	19.9	1285	19.9	1285	19.9	1.00
41–50	2990	23.1	1495	23.1	1495	23.1	
51–60	3348	25.9	1674	25.9	1674	25.9	
61–70	3032	23.4	1516	23.4	1516	23.4	
≥71	1008	7.8	504	7.8	504	7.78	
Sex							
Men	6332	48.9	3166	48.9	3166	48.9	1.00
Women	6616	51.1	3308	51.1	3308	51.1	
Urbanization							
Urban	7150	53.8	3665	56.6	3485	53.8	0.0007
Suburban	4265	33.4	2101	32.5	2164	33.4	
Rural	1533	12.7	708	10.9	825	12.7	
Comorbidity							
Coronary heart disease	6249	48.3	3117	48.2	3132	48.4	0.79
Hypertension	11 892	91.8	5920	91.4	5972	92.3	0.10
Diabetes mellitus	7350	56.8	3727	57.6	3623	56.0	0.07
Atrial fibrillation	530	4.09	275	4.25	255	3.94	0.38
Heart failure	4276	33.0	2110	32.6	2166	33.5	0.30
Hyperlipidemia	6033	46.6	3028	46.8	3005	46.4	0.69
Anemia	8749	67.6	4334	66.9	4415	68.2	0.13
Annual DDDs, median (IQR)					22.7	(15.1)	
Days between index date and drug use, median (IQR)					12	(21)	
Follow-up mean (SD), y	3.07	(2.77)	2.83	(2.64)	3.31	(2.88)	<0.0001
Follow-up, median (IQR), y	2.20	(3.73)	1.98	(3.40)	2.46	(4.01)	<0.0001
Quartile 1	0.85		0.77		0.96		
Quartile 2	2.20		1.98		2.46		
Quartile 3	4.58		4.17		4.97		

DDDs indicates defined daily doses; and IQR, interquartile range.

a significantly increased incidence of stroke compared with the nonerythropoietin cohort.

Association Between Erythropoietin and Risk of Stroke Subtypes

The Figure illustrates HR analysis of stroke between the cohorts according to the stroke subtypes. In comparison with patients in the nonerythropoietin cohort, those in the erythropoietin cohort were not more likely to experience some type of stroke during the follow-up period. It is noteworthy that the adjusted HRs for ischemic, hemorrhagic, and unspecified stroke in patients with hemodialysis were 1.08 (95% CI, 0.93–1.26; *P*=0.32), 0.96 (95% CI, 0.78–1.18; *P*=0.68), and 1.03 (95% CI, 0.80–1.32; *P*=0.83), respectively.

Risk of Stroke Subtypes Between Different Dosages of Erythropoietin

When estimating reduced risk of stroke subtypes based on the tertiles of annual DDDs, low erythropoietin dosage was associated with a significantly elevated risk of ischemic stroke (HR, 1.29; 95% CI, 1.06–1.57 [*P*=0.01]) (Figure). However, the relationship between erythropoietin and the risk of ischemic stroke was clearly not dose-dependent (Figure).

DISCUSSION

The findings of this population-based retrospective cohort study revealed that long-term administration of erythropoietin was not associated with increased risk of stroke or any of its subtypes in patients with

Table 2. Incidence and HRs for Stroke Among the Hemodialysis Cohort Treated With Erythropoietin

Treatment	No.	Event	PY	Rate*	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)†	*P* Value
Erythropoietin (annual DDDs)								
No	6474	584	18 303	31.91	Reference		Reference	
Yes	6474	703	21 443	32.78	1.04 (0.93–1.16)	0.50	1.03 (0.92–1.15)	0.55
Low (<71)	2208	251	6964	36.04	1.15 (0.99–1.32)	0.07	1.16 (1.00–1.35)	0.05
Median (71–200)	2115	193	6776	28.48	0.90 (0.76–1.06)	0.19	0.88 (0.75–1.03)	0.11
High (≥201)	2151	259	7703	33.62	1.07 (0.92–1.24)	0.37	1.07 (0.92–1.23)	0.40

DDDs indicates defined daily doses; and HR, hazard ratio.
*Incidence rate, per 1000 patient-years (PYs).
†Adjusted for age, sex, and urbanization level.

ESRD on hemodialysis. Additionally, although low-dose erythropoietin was associated with a significantly elevated risk of ischemic stroke, the relationship was clearly not dose-dependent.

CKD anemia is a complex process that involves relative erythropoietin deficiency, erythropoietin resistance, and disorders of iron homeostasis. Optimal management of CKD anemia remains a challenge to clinicians. Several previous large randomized controlled trials have demonstrated that higher target hemoglobin levels with erythropoietin therapy are associated with increased vascular access thrombosis in patients on hemodialysis, increased major cardiovascular events including nonfatal or fatal stroke, and increased mortality.[12,18,19] The increased risk of ischemic stroke at higher target hemoglobin levels is more problematic and could be caused by increased blood viscosity, larger erythropoietin doses required to achieve the levels, or a combination of the two. This, in turn, predisposes patients to increased vascular resistance and hypertension.[20] In contrast, our results demonstrated that long-term administration of erythropoietin in patients on hemodialysis was not associated with increased risk of stroke or any of its subtypes. Szczech et al[21] demonstrated that patients who achieved higher target hemoglobin levels with low doses of erythropoietin had better major cardiovascular event outcomes than those randomized to lower target hemoglobin levels

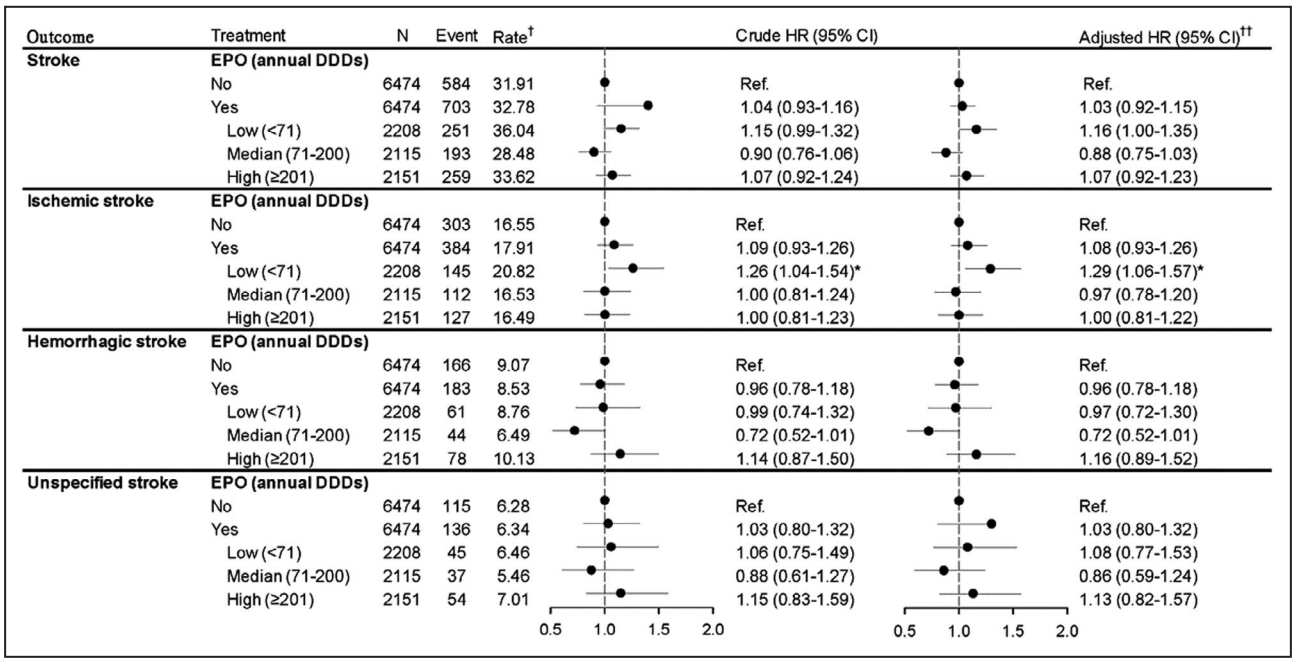

Figure 1. Incidence and hazard ratios (HRs) for stroke subtypes in patients on hemodialysis treated with erythropoietin. Ischemic stroke (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] 433-435), hemorrhagic stroke (*ICD-9-CM* 430-432), unspecified stroke (*ICD-9-CM* 436-438). *Incidence rate, per 1000 patient-years (PY). †Adjusted for age, sex, and urbanization level. DDDs indicates defined daily doses; and EPO erythropoietin.

who required high doses of erythropoietin; however, these analyses were highly confounded by comorbidities that may have led to both erythropoietin resistance and adverse outcomes. Their findings are similar to our observations. The CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) and CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta) trials, which randomized patients with nondialysis CKD and anemia to high and low hemoglobin targets, did not find increased risk of stroke with higher hemoglobin goals.[18,22] Similarly, in this population-based retrospective cohort study, we found that erythropoietin <71, 71 to 200, and >201 annual DDDs were not associated with increased risk of stroke compared after controlling for potential confounders.

We did find an increased risk of stroke in the low erythropoietin group, although this effect was not dose-dependent. The NHIRD of Taiwan applied more restrictive reimbursement criteria for erythropoietin in patients with CKD since 1996. Erythropoietin is to be initiated when patients with nondialysis CKD have serum creatinine >6 mg/dL and hematocrit <28% to maintain a hematocrit level not exceeding 30%.[23] The monthly maximal dose of epoetin α or β and darbepoetin alfa or methoxy polyethylene glycol-epoetin beta was 20 000 IU and 100 μg.[11] The target hemoglobin range and dose limitations of erythropoietin were the same for patients with CKD undergoing dialysis. According to the strategy of the NHI Bureau of Taiwan, the hemoglobin or hematocrit values in patients on dialysis who were prescribed low-dose erythropoietin were relatively high. When the values of hemoglobin or hematocrit were relatively low, these patients may be prescribed median- or high-dose erythropoietin. Therefore, in patients in whom low-dose erythropoietin was used, the hemoglobin values were more likely to exceed 12 g/dL, which could have resulted in higher risk of ischemic stroke in our study. The relationship between erythropoietin and the risk of ischemic stroke in patients on hemodialysis was clearly not dose-dependent (Figure). Therefore, our conclusions with regards to the relative effects of erythropoietin dose on the risk of stroke are limited. Because of limitations of the dose-response relationship (Figure), specific dosing strategies and treatment goals in these patients could not be ascertained. To the best of our knowledge, this is the first study to focus on the clinical outcomes in an investigation of the risk of stroke in relation to erythropoietin in "real-world" patients with hemodialysis. Further investigations are needed to elucidate the relationship between erythropoietin and risk of stroke in different independent cohorts of patients with hemodialysis.

This study had certain limitations. First, the NHIRD does not provide patient details that might have been risk factors for stroke, such as body mass index, lifestyle factors (eg, physical activity, smoking, and alcohol consumption), environmental exposure, and family history of stroke; therefore, these data were not available for analysis. Some observational and prospective studies of the general population,[24–26] and in patients undergoing hemodialysis,[27] have shown an association between low hemoglobin concentrations and a high incidence of composite stroke. However, there was no information on the hemoglobin or hematocrit values in the database. These values could potentially be confounding factors, and these were metrics used in the major randomized trials referenced. Second, the therapeutic effects of erythropoietin could not be directly evaluated. However, in clinical practice of erythropoietin prescription in patients on hemodialysis, physicians in Taiwan should follow the NHI reimbursement criteria to achieve a hemoglobin level of 10 to 11 g/dL during erythropoietin therapy.[23] The target hemoglobin range and dose limitation for erythropoietin are the same for patients undergoing hemodialysis. Third, we relied exclusively on claims data, which may have resulted in potential bias in terms of disease classification. Fourth, this study was restricted to a Taiwanese cohort and, therefore, the findings may not be generalizable to other populations. In terms of economic considerations, Taiwan is the first country in the world to use a bundled payment system for hemodialysis.[23] Thus, the management strategy for anemia in patients with CKD is different from that in many other parts of the world. Additionally, this study may be limited by 2 local factors: (1) the relatively low permitted erythropoietin dose, and (2) the tight hemoglobin targets with a maximum value of 11 g/dL. Therefore, based on previous studies and our results, erythropoietin treatment in patients with CKD provides clear benefits for patients with baseline hemoglobin concentrations <11 g/dL and moderate treatment goals. In contrast, there are risks associated with extended treatment with target hemoglobin values >13 g/dL. It is likely that as hemoglobin concentration exceeds 11 g/dL and approaches 13 g/dL, the potential benefits of the treatment diminish and the risks increase.

In Taiwan, long-term administration of erythropoietin in patients on hemodialysis was not associated with the risk of stroke or its subtypes. Our recommendation is to target hemoglobin concentration in accordance with the strategy of the NHI Bureau of Taiwan, which is different from the targets in other parts of the world, in order to provide the benefits of therapy while diminishing its potential risks.

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Disclosures

None.

Supplementary Material

Table S1

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Supplemental Material

Table S1. Demographic characteristics and comorbidities of the hemodialysis cohort treated with EPO

Variable	EPO patients selected in study N=6474		All EPO patients N=33446		p-value
	n	%	n	%	
Age (y)					<0.0001
Median (IQR)	62.8	(20.0)	59.9	(19.7)	
18–40	1285	19.9	8434	25.2	
41–50	1495	23.1	8365	25.0	
51–60	1674	25.9	8606	25.7	
61–70	1516	23.4	6258	18.7	
≥71	504	7.78	1783	5.33	
Sex					0.14
Male	3308	51.1	16756	50.1	
Female	3166	48.9	16690	49.9	
Urbanization					0.20
Urban	3485	53.8	18262	54.6	
Suburban	2164	33.4	11179	33.4	
Rural	825	12.7	4005	12.0	
Comorbidity					
Coronary heart disease	3132	48.4	15270	45.7	<0.0001
Hypertension	5972	92.3	30463	91.1	0.002
Diabetes	3623	56.0	17959	53.7	0.0008
Atrial fibrillation	255	3.94	1122	3.35	0.02
Heart failure	2166	33.5	10513	31.4	0.001
Hyperlipidemia	3005	46.4	15042	45.0	0.03
Anemia	4415	68.2	22993	68.8	0.38
Annual DDDs, median (IQR)	23.6	(15.8)	23.7	(16.0)	0.64

DDDs, defined daily doses; EPO, erythropoietin; IQR, interquartile range.