Risk Factors for Thromboembolic Events in Patients With Dialysis-Dependent CKD: Pooled Analysis of Four Global Roxadustat Phase 3 Trials

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Supplementary Material

Methods: Component Studies

In this post hoc analysis, four phase 3, open-label, studies were pooled: PYRENEES (1517-CL-0613; NCT02278341), SIERRAS (FGCL-4592-064; NCT02273726), HIMALAYAS (FGCL-4592-063; NCT02052310), and ROCKIES (D574C00002; NCT02174731). These studies were conducted in Europe (PYRENEES), the United States (SIERRAS), and globally (HIMALAYAS, ROCKIES).

Patients were randomized 1:1 to roxadustat or an active comparator (epoetin alfa: PYRENEES, SIERRAS, HIMALAYAS, ROCKIES; or darbepoetin alfa: PYRENEES). There were 415 patients on stable dialysis randomly assigned to receive roxadustat in the PYRENEES study. There were 36 patients who were incident-dialysis dialysis-dependent (ie, initiated dialysis within the past 4 months; these patients were on ESA for ≥4 weeks prior to screening) and 334 patients on stable dialysis randomized to roxadustat in the SIERRAS study. There were 522 patients who were incident-dialysis dialysis-dependent and randomized to receive roxadustat in the HIMALAYAS study. There were 198 patients who were incident-dialysis dialysis-dependent and 852 patients on stable dialysis randomized to roxadustat in the ROCKIES study.

The baseline hemoglobin levels varied between studies; 9.5 to ≤12.0 g/dL for PYRENEES, 9.0 to ≤12.0 g/dL for SIERRAS, ≤10 g/dL for HIMALAYAS, and <10.0 g/dL (for incident-dialysis dialysis-dependent patients) and <12.0 g/dL (for stable dialysis patients) for ROCKIES.

Hemoglobin correction occurred for patients with low hemoglobin levels at baseline in the SIERRAS, HIMALAYAS, and ROCKIES studies; once target hemoglobin levels were reached, hemoglobin levels were maintained. ESA conversion occurred for patients who were previously treated with ESA and switched to roxadustat in the PYRENEES, SIERRAS, and ROCKIES studies.

The hemoglobin target was 10.0 to 12.0 g/dL for all four studies (10.0 to 12.0 g/dL applied to the stable dialysis subgroup in the SIERRAS, HIMALAYAS, and ROCKIES studies).

Methods: Nested Case-Control Analysis

A nested case-control analysis was conducted to investigate the potential causal role of potential risk factors for thromboembolic events. Relatively high statistical power was expected for the nested case-control analysis due to its flexibility to control for confounding effects via a matching technique, even when there are a small number of events and the naive model adjusted for multiple confounding factors may be challenging [1-4].

Case Definition

A case was a patient at the first recorded incidence of the event. Patients could only be included as a case once; if the same patient had subsequent events, they were not counted again.

Definition of Patients at Risk

Identifying appropriate potential controls (ie, appropriate patients at risk) from which controls were chosen allowed the nested case-control analysis to incorporate time-dependent data of the potential risk factors and to be adjusted for known confounders. Patients with events at given times were matched to patients with similar characteristics, accounting for important confounding variables, who had not experienced any events at the onset time of the case. Each time an event occurred (case), patients that were still at risk were eligible to be selected as a control. Controls with similar characteristics from these patients at risk were selected with a matching algorithm. Controls could go on to become

a case if they subsequently experienced the event of interest and could also be included in the patients at risk for other cases before they experienced the event.

Selection of Matching Variables

The appropriate selection of matching variables was an important consideration, as was identifying the optimum matching mechanism. Matching variables were selected based on the results from the Cox regression analysis. The matching variables used for the analysis of events with onset before Week 12 included:

- Type of dialysis: hemodialysis, peritoneal dialysis
- Previous treatment with epoetin, weekly dose category (IU/kg/wk): naive, <150, ≥150
- Baseline CRP category: ≤ upper limit of normal (ULN), >ULN
- Body weight
- Baseline ferritin
- Baseline transferrin saturation

The matching variable used for the analysis of events with onset after Week 12 included:

- Type of dialysis: hemodialysis, peritoneal dialysis
- History of thromboembolic disease: no, yes
- History of diabetes: no, yes
- Age
- Body weight

Selection of Controls

A combination of exact matching and nearest neighbor matching were used. Exact matching was used first; a case was matched to patients with the same levels of binary matching variables. Then, among such patients, nearest neighbor matching was used; the case was matched to patients with the smallest Mahalanobis distance of continuous matching variables. Patients could be selected more than once as a control. Future cases of developing thromboembolic events were also included as controls because their exclusion could lead to biased estimates of relative risk [5].

Number of Controls

It has been shown in standard case-control studies that there is little statistical efficiency from using more than four matched controls relative to each case [6,7]. Additionally, increasing the number of controls sampled per case could lead to an increase in repeated sampling, which would result in a larger number of duplicates in the overall matched control population. In the present study, there were limited numbers of patients who experienced thromboembolic events. Therefore, in order to preserve statistical accuracy, we limited the number of matched controls to three per case (ie, cases were matched to three controls with the smallest Mahalanobis distance of continuous matching variables and with the same level of binary matching variables). If more than three patients per

case had the smallest Mahalanobis distance, resulting from tied distance, all those patients were selected as controls.

Statistical Analysis

We compared the potential risk factors of patients who experienced thromboembolic events with the matched controls. The numbers and percentages of patients by case and matched control group were calculated for binary and categorical factors. Odds ratios were calculated with a conditional logistic regression model to compare cases with matched controls with 95% confidence intervals and *P* values. The conditional logistic regression model incorporated matching by using different contrast terms for each paired case-control, which was given by:

$$Y_{ij} \sim Bernoulli(p_{ij})$$

$$p_{ij} = \frac{\exp(\alpha_i + \beta X_{ij})}{1 + \exp(\alpha_i + \beta X_{ij})}$$

where Y_{ij} is a binary outcome ($Y_{ij} = 1$ for event and $Y_{ij} = 0$ for no event) for i-th case ($j = 0$) or his j-th control, and X_{ij} is a factor for i-th case ($j = 0$) or his j-th control.

References

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Figure S1. Medians ± Interquartile Ranges Plot of (a) MCV and (b) Platelet Counts in Patient Subgroups With and Without Thromboembolic Events
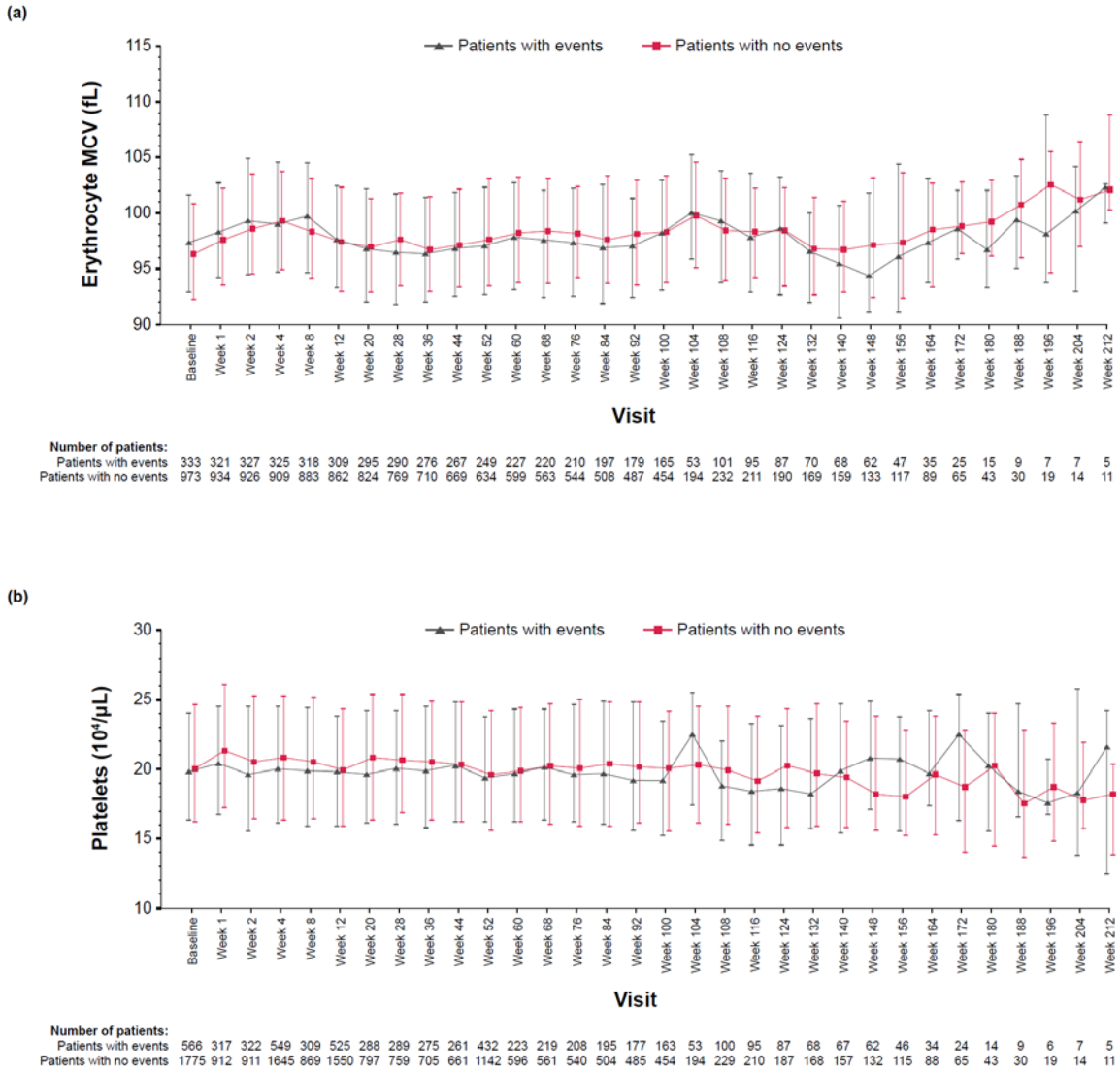

(a)

(b)

Table S1. Univariate Cox Regression Analysis for Thromboembolic Events With Onset Before/After Week 12

Category	Before Week 12 Hazard Ratio (95% CI)[a]	P Value[b]	After Week 12 Hazard Ratio (95% CI)[a]	P Value[b]
Age (years), vs <65				
≥65	1.03 (0.70–1.51)	0.894	**1.53 (1.28–1.84)**	**<0.001**
Sex, vs male				
Female	1.12 (0.79–1.60)	0.517	1.03 (0.86–1.23)	0.730
Race, vs White				
Asian	**0.51 (0.25–1.06)**		**0.72 (0.52–1.00)**	
Black	**1.21 (0.77–1.89)**	**0.011**	**1.84 (1.48–2.27)**	**<0.001**
Other	**0.12 (0.02–0.84)**		**0.61 (0.37–0.99)**	
BMI (kg/m², vs <25				
25 to <30	**1.34 (0.85–2.12)**		**1.02 (0.82–1.27)**	
30 to <35	**1.81 (1.09–3.01)**	**0.005**	**1.15 (0.89–1.49)**	**<0.001**
≥35	**2.35 (1.42–3.90)**		**1.64 (1.27–2.11)**	
Type of dialysis, vs peritoneal dialysis				
Hemodialysis	**3.04 (1.12–8.24)**	**0.021**	**1.93 (1.29–2.89)**	**0.001**
Dialysis vintage (months), vs >4				
≤4	1.23 (0.85–1.77)	0.271	**0.81 (0.66–0.99)**	**0.043**
History of diabetes, vs no				
Yes	**1.52 (1.06–2.16)**	**0.020**	**1.63 (1.37–1.95)**	**<0.001**
History of thromboembolism, vs no				
Yes	1.19 (0.52–2.70)	0.680	**2.02 (1.44–2.83)**	**<0.001**
History of CV disease, vs no				
Yes	**1.88 (1.32–2.69)**	**<0.001**	**1.64 (1.37–1.95)**	**<0.001**
Previous epoetin treatment weekly dose (IU/kg/wk), vs naive				
≤150	0.76 (0.50–1.14)	0.312	**1.29 (1.04–1.61)**	**0.021**
>150	1.02 (0.55–1.90)		**1.54 (1.10–2.16)**	
Previous ESA treatment, vs ESA-naive				
Conversion	0.80 (0.54–1.19)	0.270	**1.31 (1.05–1.62)**	**0.014**
Concomitant iron therapy (oral or IV) use, vs yes				
No	1.33 (0.93–1.89)	0.117	**1.64 (1.37–1.95)**	**<0.001**
Concomitant iron therapy (oral) use, vs yes				
No	1.21 (0.82–1.77)	0.330	**1.44 (1.20–1.73)**	**<0.001**
Concomitant iron therapy (IV) use, vs yes				
No	1.26 (0.81–1.95)	0.309	**1.47 (1.22–1.77)**	**<0.001**
Baseline Hb level (g/dL), vs <8.0				
≥8.0	0.86 (0.49–1.49)	0.582	1.23 (0.89–1.70)	0.206
Baseline ferritin level (ng/mL), vs ≥400				
<100	1.47 (0.68–3.19)	0.382	**1.34 (0.91–1.99)**	**0.021**
100 to <400	0.86 (0.58–1.26)		**0.82 (0.67–0.99)**	
Baseline TSAT (%), vs ≥30				
<30	**1.56 (1.09–2.23)**	**0.015**	**1.22 (1.02–1.45)**	**0.026**
Baseline hsCRP level (mg/dL), vs ≤0.5				
>0.5	**1.95 (1.35–2.84)**	**<0.001**	**1.35 (1.12–1.62)**	**0.002**

BMI, body mass index; CV, cardiovascular; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; TSAT, transferrin saturation.

[a]Estimated using univariate Cox proportional hazards model.
[b]*P* values based on log-rank test to test the null hypothesis of no difference in incidence across subgroup categories.

Table S2. Matching Variables and Other Baseline Characteristics in Nested Case-Control Analysis for Thromboembolic Events With Onset Before Week 12

Variable	Statistics/Category	Case (n=111) n (%)	Control (n=330)[a] n (%)
Race	Asian	6 (5.4)	18 (5.5)
	Black	23 (20.7)	69 (20.9)
	White	81 (73.0)	240 (72.7)
	Other	1 (0.9)	3 (0.9)
Type of dialysis	Hemodialysis	108 (97.3)	324 (98.2)
	Peritoneal dialysis	3 (2.7)	6 (1.8)
History of diabetes	Yes	59 (53.2)	176 (53.3)
Previous epoetin treatment weekly dose category (IU/kg/wk)	Naive	34 (30.6)	101 (30.6)
	<150	64 (57.7)	192 (58.2)
	≥150	13 (11.7)	37 (11.2)
Baseline Hb level (g/dL)	Mean (SD)	9.80 (1.16)	9.79 (1.14)
	<10	63 (56.8)	175 (53.0)
Baseline ferritin level (ng/mL)	Median (Q1, Q3)	550.4 (269.9, 925.0)	544.5 (267.2, 897.9)
	<100	7 (6.3)	6 (1.8)
Baseline TSAT (%)	Mean (SD)	31.0 (12.5)	30.6 (11.3)
	<20	15 (13.5)	39 (11.8)
Baseline hsCRP level (mg/dL)	≤0.5	42 (37.8)	126 (38.2)

Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; SD, standard deviation; TSAT, transferrin saturation.
[a]Number of unique controls, n=293

Table S3. Matching Variables and Other Baseline Characteristics in Nested Case-Control Analysis for Thromboembolic Events With Onset After Week 12

Variable	Statistics/Category	Case (n=495) n (%)	Control (n=1473)[a] n (%)
Age (years)	Mean (SD)	58.9 (13.6)	58.8 (12.9)
	≥65	184 (37.2)	521 (35.4)
Race	Asian	39 (7.9)	117 (7.9)
	Black	112 (22.6)	324 (22.0)
	White	328 (66.3)	984 (66.8)
	Other	16 (3.2)	48 (3.3)
BMI (kg/m^2)	Mean (SD)	28.66 (7.38)	28.33 (6.65)
	≥30	168 (33.9)	477 (32.4)
Type of dialysis	Hemodialysis	471 (95.2)	1404 (95.3)
	Peritoneal dialysis	24 (4.8)	69 (4.7)
History of diabetes	Yes	252 (50.9)	749 (50.8)
History of thromboembolic disease	Yes	34 (6.9)	94 (6.4)

BMI, body mass index; SD, standard deviation.
[a]Number of unique controls, n=941.