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Original Article

ORIGINAL ARTICLE

Efficacy and safety of roxadustat for treating anaemia in patients with chronic kidney disease and heart failure: a retrospective cohort study

Jiang Liu[1,2,*], Zhen Meng[1,*], Lina Feng[1,2,*], Li Zhuo[3], Yan Liang[4], Mengxi Yang[1], Lina Su[1], Zhaoqi Zheng[1,2], Bowei Liu[1,2] and Jingyi Ren[1,2]

[1]Heart Failure Center of Department of Cardiology, China–Japan Friendship Hospital, Beijing, China, [2]Peking University China–Japan Friendship School of Clinical Medicine, Beijing, China, [3]Department of Nephrology, China–Japan Friendship Hospital, Beijing, China and [4]Department of Intensive Care, People's Liberation Army General Hospital, Beijing, China

*These authors contributed equally to this work.
Correspondence to: Jingyi Ren; E-mail: renjingyi1213@hotmail.com

ABSTRACT

Background. Anaemia is a common comorbidity in patients with chronic kidney disease (CKD) and heart failure (HF). Roxadustat has been approved for the treatment of anaemia in patients with CKD. However, its efficacy and safety in treating anaemia in patients with both CKD and HF remain unclear. We conducted a retrospective study with propensity score matching (PSM) to evaluate the efficacy and safety of roxadustat in this population.

Methods. This retrospective study enrolled patients diagnosed with HF comorbid with CKD and anaemia. The patients were divided into two groups: a roxadustat group and a control group. One-to-one PSM was used to balance baseline characteristics between the groups. The primary endpoint was the change in haemoglobin (Hb) at week 8. Secondary endpoints included Hb response, changes in haematocrit, iron parameters, echocardiographic parameters, B-type natriuretic peptides and lipid levels. Exploratory endpoints were mortality and rehospitalization rates over 30 days–2 years. Safety endpoints included the incidence of hyperkalaemia, liver damage and thrombotic events.

Results. A total of 1055 patients were screened. After PSM, 206 patients were included. Baseline characteristics were comparable between the matched cohorts. At week 8, the roxadustat group experienced a greater increase in Hb than the control group, with a difference of 0.8 g/dl (95% confidence interval 0.3–1.3; $P = .003$). The roxadustat group also demonstrated a higher Hb response (60.2% versus 28.2%; $P < .001$) and a greater increase in haematocrit ($4.7 \pm 0.9\%$ versus $2.8 \pm 0.6\%$; $P = .008$) than the control group. No significant differences were observed for other secondary endpoints. Thrombotic events were similar between the two groups and there were no differences in the risks of mortality or rehospitalization.

Conclusions. Roxadustat was effective in correcting and maintaining Hb levels in patients with anaemia, HF and CKD. It did not increase thrombotic and other adverse events, mortality or rehospitalization risks, making it a promising treatment option for anaemia in this population.

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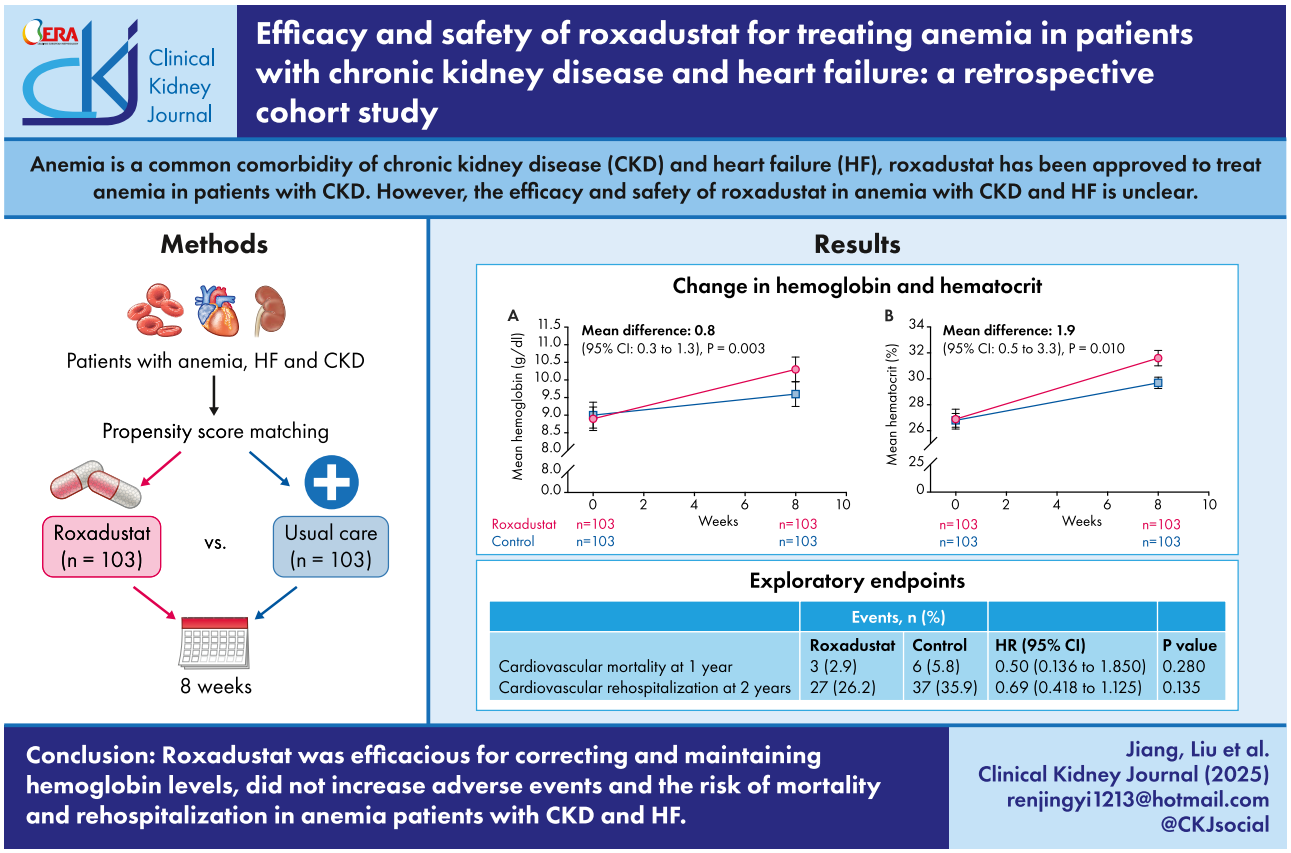
GRAPHICAL ABSTRACT



Keywords: anaemia, chronic kidney disease, heart failure, roxadustat

KEY LEARNING POINTS

What was known:

- Anaemia is a common comorbidity in patients with chronic kidney disease (CKD) and heart failure (HF).
- Roxadustat has been approved for anaemia in patients with CKD. However, its efficacy and safety for anaemia with both CKD and HF remain unclear.

This study adds:

- Roxadustat was effective in correcting and maintaining haemoglobin levels in patients with anaemia, HF and CKD.
- Roxadustat did not increase thrombotic and other adverse events, mortality or rehospitalization risks in patients with anaemia, HF and CKD.

Potential impact:

- Roxadustat is a promising treatment option for anaemia in patients with both HF and CKD.

INTRODUCTION

The incidence of heart failure (HF) has increased rapidly in recent decades, presenting a complex clinical syndrome characterized by a high comorbidity burden and multi-organ systemic pathophysiology. Chronic kidney disease (CKD) is one of the most prevalent comorbidities, affecting up to 50% of patients with HF. CKD is often considered an adverse factor, contributing to the challenges in effective drug implementation, despite numerous treatment attempts for HF. These two conditions—HF and CKD—exert synergistic effects, with the presence of one accelerating the progression of the other. Consequently, there is a pressing need for novel therapeutic approaches that can mitigate both cardiovascular and renal risks in this population.

Anaemia frequently complicates the clinical course of both HF and CKD. Together, these three conditions—HF, CKD and anaemia—exacerbate one another, forming what has been termed a 'vicious cycle of deterioration'. This cycle leads to poor outcomes, including rapid progression to end-stage renal

disease and worsening chronic HF [1–4]. Accordingly, correcting anaemia may improve outcomes in patients with both HF and CKD. Previous studies have demonstrated that erythropoiesis-stimulating agents (ESAs) are effective in treating anaemia in patients with CKD. However, ESAs have not been shown to improve HF outcomes and are associated with an increased risk of stroke [5, 6].

Roxadustat, a hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor, has recently been shown to effectively treat anaemia in patients with CKD [7, 8]. The drug works by reversibly binding to and inhibiting HIF prolyl hydroxylase, an enzyme responsible for the degradation of HIF transcription factors under normal oxygen conditions. By inhibiting these enzymes, roxadustat reduces HIF breakdown and promotes HIF activity, leading to increased endogenous erythropoietin production and enhanced erythropoiesis. In addition, it also reduces the expression of the peptide hormone hepcidin, promoting iron absorption, transport and mobilization, which improves iron availability and increases haemoglobin (Hb) levels [9–11].

Given these mechanisms, we hypothesized that roxadustat may improve anaemia in patients with both HF and CKD, potentially benefiting HF outcomes. However, limited research has been conducted in this specific area. Therefore, this retrospective study aimed to evaluate the effects of roxadustat on Hb levels and adverse events to assess its efficacy and safety for treating anaemia in patients with HF and CKD.

MATERIALS AND METHODS

Study design

This retrospective cohort study enrolled patients admitted to the China–Japan Friendship Hospital between 1 June 2019 and 27 February 2022, who were diagnosed with HF comorbid with CKD and anaemia. HF was diagnosed according to clinical practice guidelines [6, 12], while CKD was identified based on the Kidney Disease: Improving Global Outcomes guidelines [13]. Anaemia was defined according to the World Health Organization standards. Based on the post-enrolment treatment, patients were divided into two groups, a roxadustat group and a control group. The patient selection process is illustrated in Fig. 1. The study protocol was approved by the Ethics Committee of the China–Japan Friendship Hospital and adhered to the principles outlined in the Declaration of Helsinki.

Patient population

Adults diagnosed with HF, CKD and anaemia were eligible. The inclusion criteria were as follows: patients ≥18 years of age, diagnosed with HF. For HF with preserved ejection fraction (HFpEF), patients were defined as having signs and symptoms of HF, a left ventricular ejection fraction (LVEF) ≥50% and objective evidence of cardiac structural and/or functional abnormalities consistent with left ventricular (LV) diastolic dysfunction or elevated LV filling pressures. These abnormalities include echocardiography at rest with an left atrial volume >34 ml/m^2 or >40 ml/m^2 in atrial fibrillation or early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler (E/e′) >9; or pulmonary artery systolic pressure >35 mmHg; or tricuspid regurgitation velocity >2.8 m/s; or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) >125 pg/ml in sinus rhythm; or >365 pg/ml in atrial fibrillation; or BNP >35 pg/ml in sinus rhythm; or >105 pg/ml in atrial fibrillation. For HF with reduced ejection fraction (HFrEF), the definition included an LVEF ≤40%, while HF with mildly reduced ejection fraction (HFmrEF) was defined as a LVEF of 41–49% with accompanying signs and symptoms of HF and NT-proBNP >125 pg/ml in sinus rhythm; or >365 pg/ml in atrial fibrillation; or BNP >35 pg/ml in sinus rhythm; or >105 pg/ml in atrial fibrillation [6, 12] and CKD stage 3–5 [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, with or without renal replacement therapy] and anaemia (defined as baseline Hb <13 g/dl for men and <12 g/dl for women and body weight of 45–160 kg. Exclusion criteria were as follows: any clinically significant infection or evidence of an active underlying infection; acute coronary syndrome, stroke, seizure or thromboembolic events (such as deep vein thrombosis or pulmonary embolism) within the past 52 weeks; acute or chronic active bleeding within 6 months prior to enrolment; other types of anaemia (e.g. thalassemia, sickle cell anaemia, pure red cell aplasia or haemolytic anaemia); chronic liver disease; blood transfusion within the past 12 weeks or anticipated need for transfusion; intravenous iron supplementation during the screening period and/or unwillingness to withhold intravenous iron; prior treatment with roxadustat or any HIF prolyl hydroxylase inhibitor; and lactation, breastfeeding or women preparing for pregnancy.

Treatment

Dialysis patients in the roxadustat group received a weight-based starting dose of 100 mg (for patients weighing 40–59 kg) or 120 mg (for patients weighing ≥60 kg) three times a week, while non-dialysis patients in the roxadustat group received a weight-based starting dose of 70 mg (for patients weighing 40–59 kg) or 100 mg (for patients weighing ≥60 kg) three times a week. The control group received standard care, including oral iron supplements, ESAs or dialysis.

Data collection and follow-up

This study collected clinical data from patients, including demographic and clinical measurements in the medical records at baseline and at 2, 4 and 8 weeks after treatment initiation. Adverse reactions were also recorded. Mortality and rehospitalization data were primarily obtained through telephone interviews.

Study outcomes

The primary endpoint was the mean change in Hb levels from baseline to week 8 among all the patients. The key secondary endpoint included the Hb response. Other secondary endpoints were the mean changes from baseline to week 8 in iron parameters, BNP levels, lipid profiles and echocardiographic parameters. The exploratory endpoint was the effect of roxadustat on mortality and rehospitalization over a follow-up period of 30 days–2 years. Safety endpoints included the incidence of hyperkalaemia, thrombotic events and liver damage. Detailed study outcomes are presented in Supplementary Table 1.

Statistical analyses

Given the non-randomized nature of the study, propensity score matching (PSM) was conducted to minimize selection bias. Using propensity scores, the greedy match macro was used to match the roxadustat group and control group patients in a 1:1 ratio. Confounding variables included in the model were age, sex, blood pressure, Hb concentration, eGFR, low-density lipoprotein

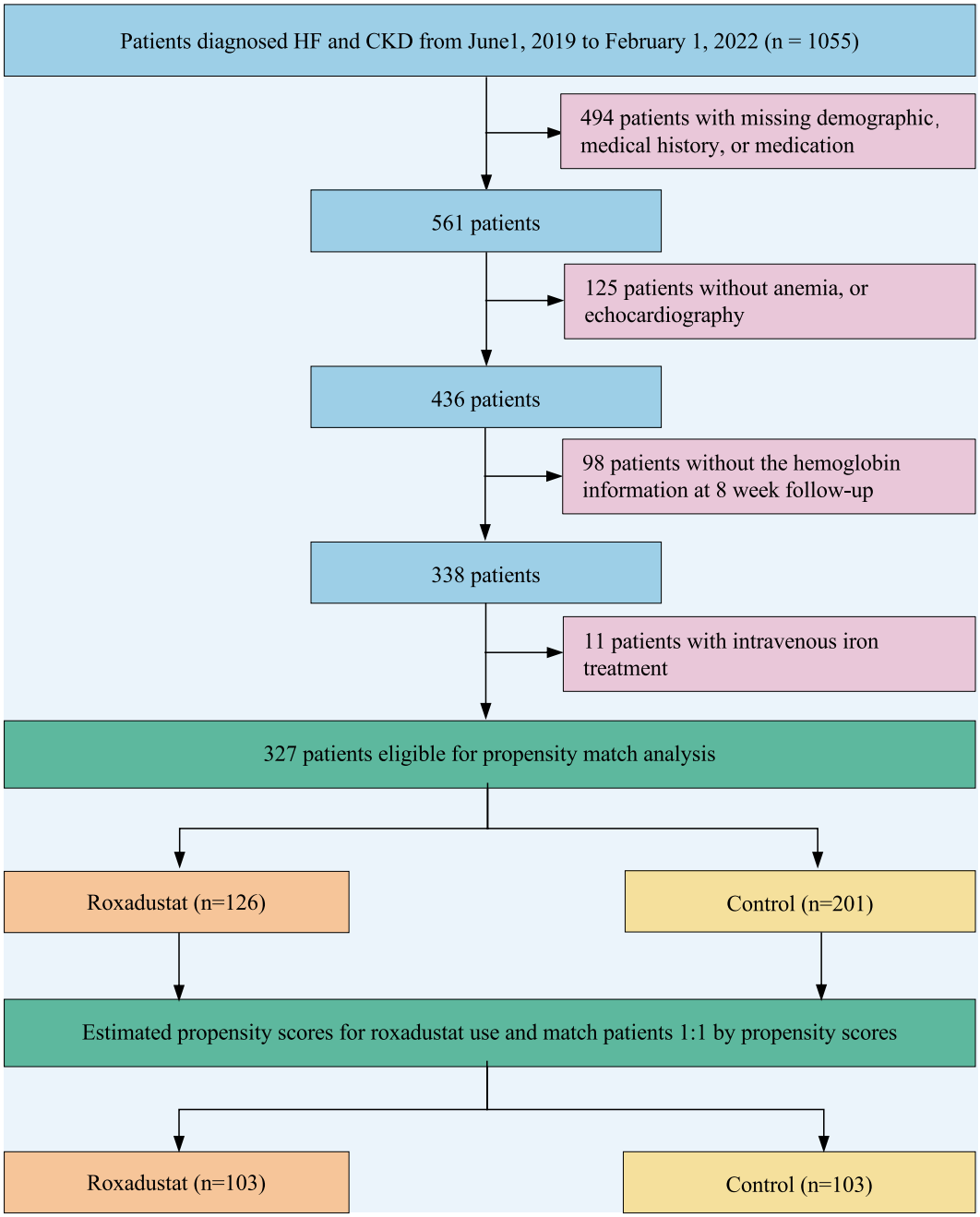


Figure 1: Flow chart of a matched cohort of patients with HF comorbid with CKD and anaemia. The flow chart illustrates the patient screening process. Following 1:1 PSM, there were 103 patients in each group.

(LDL) levels, LVEF and dialysis status. Detailed statistical methods are presented in Table 1.

Continuous data were presented as mean ± standard deviation (SD) or median [interquartile range (IQR)] and were compared using a two-sided Student's *t*-test or Wilcoxon test as appropriate. Categorical data were described as frequencies (%) and compared using the chi-squared test. All outcome analyses were performed using matched data. For the primary endpoint, analysis of covariance (ANCOVA) was used (adjusted for baseline Hb) to calculate the mean change in Hb levels from baseline to week 8. For secondary endpoints, the proportion of patients achieving an Hb response and the use of ESAs were calculated. Additionally, the mean changes from baseline to week 8 in haematocrit, iron parameters, BNP and lipid levels, as well as the mean changes in echocardiographic parameters during follow-up, were assessed. ANCOVA was used for continuous variables and the chi-squared test for categorical variables. For mortality and rehospitalization outcomes, patients were censored at the first event. Kaplan–Meier analysis was used to calculate survival and event rates, with hazard ratios (HRs) and 95% confidence intervals (CIs) used to assess the risk of events in the roxadustat group compared with the control group. A two-sided *P*-value $<.05$ was considered statistically significant. Statistical analyses were performed using SPSS for Mac version 25.0 (IBM,

Table 1: Baseline characteristics before and after propensity matching.

	Before propensity matching ($n = 327$)			After propensity-matching ($n = 206$)		
Characteristics	Control ($n = 201$)	Roxadustat ($n = 126$)	*P*-value	Control ($n = 103$)	Roxadustat ($n = 103$)	*P*-value
Demographics						
Age (years), mean ± SD	71.9 ± 14.6	64.4 ± 16.2	.000	69.4 ± 15.6	67.4 ± 14.8	.332
Female, *n* (%)	89 (44.3)	53 (42.1)	.694	43 (41.7)	46 (44.7)	.673
Clinical measurements						
Systolic BP (mmHg), mean ± SD	141.3 ± 25.4	150.2 ± 22.7	.002	144.6 ± 22.3	146.8 ± 19.7	.483
Diastolic BP (mmHg), mean ± SD	76.5 ± 14.6	81.9 ± 13.1	.002	78.3 ± 14.9	80.9 ± 12.5	.166
Heart rate (bpm), mean ± SD	79.9 ± 16.3	80.3 ± 12.2	.791	78.4 ± 14.3	79.5 ± 10.8	.550
Body mass index (kg/m^2), mean ± SD	25.4 ± 5.7	26.8 ± 16.3	.385	25.2 ± 5.6	25.7 ± 4.9	.480
HF phenotype, *n* (%)						
HFpEF	182 (90.5)	113 (89.7)	.849	93 (90.3)	92 (89.3)	>.999
HFrEF or HFmrEF	19 (9.5)	13 (10.3)	.849	10 (9.7)	11 (10.7)	>.999
Comorbidities, *n* (%)						
Coronary artery disease	68 (33.8)	32 (25.4)	.107	29 (28.2)	26 (25.2)	.637
Hypertension	177 (88.1)	116 (92.1)	.426	95 (92.2)	99 (96.1)	.234
Diabetes mellitus	113 (56.2)	70 (57.4)	.734	63 (61.2)	56 (54.4)	.340
Cerebral infarction	53 (26.4)	25 (20.8)	.352	31 (30.1)	22 (21.4)	.151
Thyroid dysfunction	27 (13.4)	13 (11.8)	.568	12 (11.1)	11 (10.7)	.825
Dialysis	75 (37.3)	62 (49.2)	.034	36 (35.0)	46 (44.7)	.155
Haemodialysis	66 (32.8)	55 (43.7)	.049	34 (33.0)	43 (41.7)	.179
Smoking history	25 (12.4)	14 (11.8)	.783	17 (16.5)	12 (11.7)	.565
Admission laboratory values						
Hb (g/dl), mean ± SD	9.5 ± 2.0	8.8 ± 1.7	.001	9.0 ± 1.9	8.9 ± 1.7	.612
HCT (%), mean ± SD	27.9 ± 5.8	26.8 ± 7.4	.147	26.8 ± 5.4	26.9 ± 7.8	.969
eGFR (ml/min/1.73 m^2), mean ± SD	23.5 ± 20.6	11.7 ± 9.8	.000	15.4 ± 13.5	13.2 ± 9.3	.180
<15, *n* (%)	83 (41.3)	89 (70.6)	.000	63 (61.2)	74 (71.8)	.104
≥15, *n* (%)	118 (58.7)	37 (29.4)		40 (38.8)	29 (28.2)	
Glucose (mmol/l), mean ± SD	7.1 ± 3.1	6.8 ± 3.0	.411	7.1 ± 3.1	6.7 ± 3.2	.299
HbA1c (%),mean ± SD	6.3 ± 1.5	6.1 ± 1.5	.939	6.0 ± 1.2	6.2 ± 1.4	.509
Triglyceride (mmol/l), mean ± SD	1.3 ± 0.8	1.5 ± 2.0	.113	1.4 ± 0.7	1.5 ± 0.9	.266
Total cholesterol (mmol/l), mean ± SD	3.8 ± 1.1	4.1 ± 1.8	.117	3.9 ± 1.2	4.1 ± 1.6	.339
LDL-C (mmol/l), mean ± SD	2.3 ± 0.6	2.5 ± 1.1	.026	2.4 ± 0.7	2.5 ± 1.1	.114
HDL-C (mmol/l), mean ± SD	1.0 ± 0.3	1.1 ± 0.4	.524	1.0 ± 0.3	1.1 ± 0.3	.241
Potassium (mmol/l), mean ± SD	4.2 ± 0.5	4.3 ± 0.7	.067	4.4 ± 0.6	4.3 ± 0.6	.509
Serum ferritin (μg/l), median (IQR)	133.1 (56.0–260.9)	124.5 (56.1–290.6)	.839	150.1 (70.5–250.2)	128.1 (63.4–282.9)	.957
≥300, *n* (%)	23 (11.4)	23 (18.2)	.914	14 (13.6)	17 (16.5)	.873
100–<300, *n* (%)	137 (68.2)	68 (54.0)		63 (61.2)	59 (57.3)	
<100, *n* (%)	41 (20.4)	35 (27.8)		26 (25.2)	27 (26.2)	
Ferritin >100 and TAST >20%, *n* (%)	25 (21.2)	27 (21.4)	.963	20 (19.4)	24 (23.3)	.497
TAST (%), mean ± SD	23.8 ± 15.6	21.5 ± 12.4	.308	22.2 ± 13.5	21.8 ± 12.5	.841
>20%, *n* (%)	153 (76.1)	86 (68.2)	.119	69 (67.0)	69 (67.0)	>.999
≤20%, *n* (%)	48 (23.9)	40 (31.8)		34 (33.0)	34 (33.0)	
Medications at admission, *n* (%)						
ACEI/ARB/ARNI	85 (42.3)	46 (36.5)	.299	33 (32.0)	35 (34.0)	.767
Beta-blocker	138 (68.7)	89 (71.8)	.847	71 (68.9)	69 (67.0)	.765
MRA	28 (13.9)	14 (11.8)	.437	6 (5.8)	9 (8.7)	.421
Loop diuretic agent	116 (57.7)	83 (66.9)	.181	62 (60.2)	71 (68.9)	.190
Nitrate	35 (17.4)	41 (32.5)	.674	30 (29.1)	30 (29.1)	>.999
Statin	143 (71.1)	83 (65.9)	.315	77 (74.8)	70 (68.0)	.281
ESA	55 (27.4)	41 (32.5)	.317	26 (25.2)	35 (34.0)	.170
Oral iron	160 (79.6)	108 (85.7)	220	83 (80.6)	86 (83.3)	.586

BP: blood pressure; HCT: haematocrit; HbA1c: glycosylated haemoglobin; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TSAT: transferrin saturation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist.

Armonk, NY, USA) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

A total of 1055 patients were admitted to the China–Japan Friendship Hospital with a diagnosis of HF and CKD from 1 June 2019 to 1 February 2022. Of these, 494 patients were excluded due to missing values in demographic characteristics, medical history or medication information. Another 125 patients without anaemia or echocardiography data, 98 patients lacking Hb information at the 8-week follow-up and 11 patients with a history of intravenous iron treatment were also excluded. Thus 327 patients were included in our cohort, of which 126 were in the roxadustat group and 201 in the control

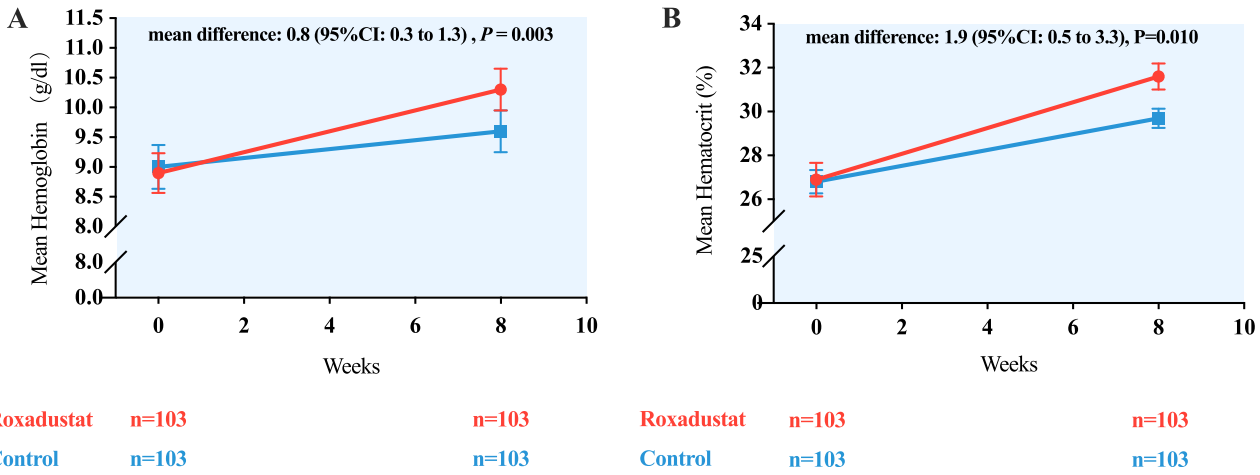


Figure 2: The primary and secondary endpoints. **(A)** The mean (SD) of Hb from baseline to week 8, with an increase of 1.4 ± 0.2 g/dl in the roxadustat group versus 0.7 ± 0.2 g/dl in the control group. **(B)** The mean (SD) of HCT from baseline to week 8. The HCT in the roxadustat group was significantly higher than in the control group at week 8 (31.6 ± 6.0% versus 29.7 ± 4.5%). HCT: haematocrit.

group. Following 1:1 PSM, there were 103 patients in each group (Fig. 1).

Before matching, patients in the roxadustat group were younger (64.4 ± 16.2 versus 71.9 ± 14.6 years; $P < .001$) and had higher systolic blood pressure (150.2 ± 22.7 versus 141.3 ± 25.4 mmHg; $P = .002$), a higher proportion undergoing dialysis (49.2% versus 37.3%; $P = .034$), lower Hb levels (8.8 ± 1.7 versus 9.5 ± 2.0 g/dl; $P = .001$), lower eGFR (11.7 ± 9.8 versus 23.5 ± 20.6 ml/min/1.73 m^2; $P < .001$) and higher LDL cholesterol (2.5 ± 1.1 versus 2.3 ± 0.6 mmol/l; $P = .026$) than the control group. After PSM, the baseline characteristics between the two groups were well balanced. The mean age was 68.4 years, with 117 (56.8%) male patients. In the roxadustat and control groups, 46 (44.7%) versus 36 (35.0%) patients were on dialysis, 92 (89.3%) versus 93 (90.3%) had HFpEF, 86 (83.3%) versus 83 (80.6%) received oral iron and 35 (34.0%) versus 26 (25.2%) were treated with ESAs, respectively. Further details are provided in Table 1.

Efficacy outcomes

Primary endpoint

During the primary analysis period, the mean change in Hb levels from baseline to week 8 was significantly greater in the roxadustat group, with an increase of 1.4 ± 0.2 g/dl in the roxadustat group versus 0.7 ± 0.2 g/dl in the control group, resulting in a between-group difference of 0.8 g/dl (95% CI 0.3–1.3; $P = .003$) (Fig. 2A).

Secondary endpoints

Hb response and haematocrit. A significantly higher percentage of patients receiving roxadustat (60.2%) achieved an Hb response (defined as Hb ≥10.0 g/dl) than the control group (28.2%) during the first 8 weeks of treatment ($P < .001$). Additionally, 50.5% of the patients in the roxadustat group and 38.8% in the control group experienced an Hb increase ≥1.0 g/dl from baseline ($P = .093$). Similarly, the percentage of patients with an Hb increase ≥1.0 g/dl (if baseline Hb was >8.0 g/dl) or ≥2.0 g/dl (if baseline Hb was ≤8.0 g/dl) was 46.6% in the roxadustat group versus 35.0% in the control group ($P = .089$) (Table 2).

Table 2: Hb response.

Definition	Controls ($n = 103$)	Roxadustat ($n = 103$)	P-value
Definition[a], *n* (%)	29 (28.2)	62 (60.2)	< 0.001
Definition[b], *n* (%)	40 (38.8)	52 (50.5)	0.093
Definition[c], *n* (%)	36 (35.0)	48 (46.6)	0.089

[a]The percentage of patients with a mean Hb level of at least 10.0 g/dl at week 8.
[b]The percentage of patients with a Hb increase from baseline ≥1.0 g/dl in the Hb level at week 8.
[c]The percentage of patients with a Hb increase from baseline ≥1.0 g/dl (if >8.0 g/dl at baseline) or ≥2.0 g/dl (if ≤8.0 g/dl at baseline).

The haematocrit was significantly higher in the roxadustat group than in the control group at week 8 (31.6 ± 6.0% versus 29.7 ± 4.5%; $P = .008$), with a mean increase of 4.7 ± 0.9% versus 2.8 ± 0.6%, respectively ($P = .008$) (Fig. 2B).

There was no significant difference in ESA usage at baseline between the roxadustat and the control groups (34.0% versus 25.2%; $P = .170$). However, during the follow-up, the use of ESAs decreased significantly in the roxadustat group compared with the control group (8.7% versus 26.1%; $P = .001$) (Supplementary Table 2).

Iron parameters. At baseline, the median ferritin levels were 128.1 µg/l (IQR 65.4–282.9) in the roxadustat group and 150.1 µg/l (IQR 70.5–250.2) in the control group ($P = .957$). At week 8, the median ferritin levels in the roxadustat and control groups were 83.1 µg/l (IQR 39.8–197.7) and 145.0 µg/l (IQR 69.3–198.3), respectively ($P = .184$). Transferrin saturation levels remained stable during the treatment and did not differ significantly between the two groups (Supplementary Table 3).

Cardiac biomarkers, structure and function. No significant differences were found in the mean change in natriuretic peptide levels, a biomarker for HF, from baseline to week 8 between the groups ($P = .118$). Moreover, an evaluation of cardiac structure and function at follow-up (mean follow-up duration

6.3 ± 4.7 months) revealed no adverse effects of roxadustat on cardiac structure or function (Supplementary Table 4).

Lipid parameters. Although there was a trend toward reductions in total cholesterol, LDL cholesterol and triglyceride levels in the roxadustat group compared with the control group, these differences were not statistically significant (Supplementary Table 5).

Exploratory endpoints

Mortality and rehospitalization. A 2-year follow-up of all patients revealed no increased risk of mortality or rehospitalization in the roxadustat group compared with the control group. Nominal reductions in cardiovascular rehospitalizations at 30 days [HR 0.51 (95% CI 0.165–1.592), $P = .248$], cardiovascular mortality at 1 year [HR 0.50 (95% CI 0.136–1.850), $P = .280$] and cardiovascular rehospitalizations at 2 years [HR 0.69 (95% CI 0.418–1.125), $P = .135$] were observed (Supplementary Table 6).

Adverse events. The incidence of hyperkalaemia at week 8 was 10.7% in the roxadustat group and 11.7% in the control group. Liver damage was reported in 4 (3.9%) patients in the roxadustat group versus 3 (2.9%) patients in the control group with respect to aspartate aminotransferase levels and in 6 patients in the roxadustat group (5.8%) versus 6 patients in the control group (5.8%) regarding alanine aminotransferase levels. Deep vein thrombosis occurred in 3 (2.9%) patients in each group. Overall, the incidence of adverse events was similar between the two groups (Supplemental Table 7).

Subgroup analyses

Subgroup analyses for the primary endpoint, including sex, age, LVEF, eGFR, ischaemic aetiology, diabetes, dialysis, ESA use and oral iron administration, showed that Hb changes were consistent across all subgroups (Supplementary Fig. 1).

DISCUSSION

The findings of this retrospective PSM cohort of 206 patients with HF, CKD and anaemia provided insights into the efficacy and safety of roxadustat as a treatment option. After 8 weeks of follow-up, the roxadustat group experienced a significant increase in Hb levels compared with the control group, with a between-group difference of 0.8 g/dl (95% CI 0.3–1.3; $P = .003$), consistent with previous research [7, 8]. However, there were no observed differences between the two groups regarding mortality or HF-related rehospitalizations. These findings offer real-world evidence supporting roxadustat as a potential therapeutic option for anaemia in patients with HF and CKD, affirming its efficacy and safety.

Cardiorenal anaemia syndrome affects ≈20% of patients hospitalized for HF [1]. Current treatments for anaemia, including the correction of haematinic deficiencies (iron, B12 and folate), ESAs and blood transfusion, have limitations. The Reduction of Events with Darbepoetin alfa in Heart Failure trial (NCT00358215) demonstrated that ESAs do not significantly affect clinical outcomes, including death or rehospitalization due to worsening HF, and may increase the risk of stroke [5]. Blood transfusions, while effective as short-term therapies in cases of severe anaemia, are associated with many risks, including disease transmission. This highlights the need for novel, efficient and convenient treatments that can address anaemia and improve outcomes in patients with HF and CKD.

Recent studies have highlighted the benefits of HIF prolyl hydroxylase inhibitors, including roxadustat, which enhance iron bioavailability and increase Hb levels without the side effects associated with ESAs in patients with CKD [7, 8]. Our data further supported roxadustat's role in alleviating anaemia in patients with HF and CKD. Although our study found a smaller Hb increase than previous studies, where the between-group difference was 2.2 g/dl (95% CI 1.9–2.6; $P < .001$), the comorbidities and diverse anaemia treatments in our population likely contributed to these variations in response.

It is worth noting that oral iron supplements and erythropoiesis were not restricted in our study, and there were no differences between the groups at baseline. In our study, the addition of roxadustat reduced the need for ESAs, likely because roxadustat administered three times per week induced intermittent activation of hypoxia-inducible target genes. These genes include erythropoietin, erythropoietin receptors, enzymes involved in haem biosynthesis and proteins that facilitate iron absorption and transport, all of which contribute to coordinated erythropoiesis. Roxadustat also increases endogenous erythropoietin production while suppressing inflammatory cytokines, further enhancing erythropoiesis.

The HIF oxygen-sensing pathway has been shown to be upregulated in isolated iron deficiency patients with HF, suggesting that iron deficiency in HF is associated with hypoxia-related pathways [14, 15]. In this study, changes in iron parameters showed improvement with roxadustat as compared with the control group. A reduction in ferritin was observed with roxadustat, consistent with previous studies, which may indicate that roxadustat improves anaemia by reducing inflammation, and promoting iron utilization for erythropoiesis. These findings suggest that roxadustat may attenuate the functional iron deficiency in patients with HF and CKD. Previous studies have attributed the improvement in iron metabolism to reductions in hepcidin levels and an increase in soluble transferrin receptors [8, 16].

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, a class of therapies proven to improve outcomes in patients with HF, have also been shown to reduce hepcidin and ferritin levels, thereby alleviating the inflammation-mediated functional iron deficiency observed in HF [17]. In our study, there was no significant difference between the groups regarding the use of oral iron at baseline (83.3% versus 80.6%; $P = .586$), and patients receiving intravenous iron were excluded. Furthermore, only a few patients were using SGLT2 inhibitors, as the majority had an eGFR <20 ml/min/1.73 m^2 and SGLT2 inhibitors were not yet included in HF treatment guidelines when the study began in China in 2019. Thus roxadustat may offer additional benefits beyond anaemia correction by improving iron metabolism, whereas ESAs did not significantly affect iron metabolism.

Studies have demonstrated that the HIF pathway plays a crucial role in myocardial ischaemia, where HIF-α promotes vasodilation, myocardial resilience, metabolic reprogramming and increases in capillary density. Roxadustat has been shown to reduce the myocardial infarct area and improve heart function in ischaemic HF [18]. In contrast, our study did not observe any significant effects of roxadustat on cardiac structure, function or biomarkers of HF. This discrepancy may be due to the diverse causes of HF in our study population, with coronary heart disease present in only one-quarter of the patients, while most had HF of other aetiologies. Additionally, severe anaemia can lead to high-output HF in patients with normal left ventricular function, as cardiac output and LVEF decrease proportionally with increased Hb levels in patients with CKD and anaemia [19].

Previous studies have also demonstrated that roxadustat can lower total cholesterol and LDL cholesterol levels in patients with CKD through HIF-dependent effects on cholesterol synthesis and the upregulation of adenosine triphosphate–binding cassette transporter A1, which reduces intracellular cholesterol [20, 21]. However, in our study, total cholesterol, triglycerides and LDL cholesterol showed no significant differences between the control and roxadustat groups over 8 weeks. The high prevalence of statin use in our study population likely contributed to a more intensive lipid-lowering effect, potentially masking the lipid-lowering effects of roxadustat [16].

Although previous studies in patients with CKD have reported a higher frequency of hyperkalaemia and thromboembolic events with roxadustat [7, 8, 16, 22], the overall frequency of liver damage, hyperkalaemia and thromboembolic events was balanced between groups in our study. The lower incidence of these adverse events in our population may be attributed to better renal function and a lower frequency of dialysis. Additionally, roxadustat may not increase the risk of thromboembolism due to its minimal effect on platelets [23]. Moreover, there were no differences between the treatment groups in the incidence of cardiovascular adverse events, including all-cause mortality, cardiovascular mortality and rehospitalization related to cardiovascular diseases over 2 years. Cardiovascular adverse events should be considered safety signals rather than primary markers of efficacy in studies addressing comorbidities in patients with HF. Our results suggest that roxadustat is a safe and effective treatment for anaemia in patients with HF without increasing cardiovascular risk.

Our study included a large number of HFpEF patients, suggesting that roxadustat may have a more pronounced effect in this population. However, the subgroup analysis did not reveal significant differences between those with LVEF $\geq$50% and those with LVEF <50%. Additionally, subgroup analysis indicated no significant interaction between dialysis and non-dialysis patients. Future research should include a larger cohort of patients with HFpEF or HFrEF and CKD with or without dialysis.

Limitations

Our study has several limitations. First, as a single-centre retrospective study with a small sample size, roxadustat therapy was not randomly assigned and baseline characteristics were not fully comparable between the two groups. However, to mitigate this limitation, a PSM was used, which resulted in comparable baseline characteristics between the groups. Additionally, we are currently conducting a prospective, randomized controlled trial to further evaluate the efficacy and safety of roxadustat in patients with HF, anaemia and CKD (NCT05691257). Second, the follow-up period for laboratory tests in our study was limited to 8 weeks. A longer follow-up period may provide further insights into the potential cardioprotective effects of roxadustat. Third, we did not measure the quality of life of the patients, which could potentially improve as iron deficiency is corrected. Additionally, repeated echocardiographic assessments were not available for many patients, preventing us from assessing improvements in cardiac structure or function during follow-up. Future research should address these areas to better understand the effects of roxadustat.

CONCLUSIONS

Roxadustat was effective in correcting and maintaining Hb levels in patients with anaemia, HF and CKD. It did not increase the incidence of cardiovascular or other adverse events compared with usual care. A key advantage of roxadustat was its oral mode of administration, which is particularly beneficial for outpatient management of HF. These findings suggest that roxadustat is a promising treatment option for anaemia in patients with both HF and CKD.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

J.L., Z.M., L.F. and J.R. were responsible for conceptualization, methodology and project administration. J.L., Z.M., L.F., Y.L., M.Y., L.S., Z.Z. and B.L. were responsible for data curation. J.L., Z.M. and J.R. were responsible for formal analysis. J.R. and L.Z. were responsible for the investigation. J.L. and Z.M. were responsible for validation and wrote the original draft. J.R. and L.Z. were responsible for review and editing of the manuscript.

DATA AVAILABILITY STATEMENT

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

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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