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Original Article

Safety Profile of Roxadustat in Anemic Patients: A Meta-Analysis of 21 RCTs

Anemili Hastalarda Roksadustat'ın Güvenlilik Profili: 21 RCT'nin Meta-Analizi

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ABSTRACT

Objective: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor used to treat anemia in patients with chronic kidney disease. We aimed to assess its safety and tolerability profile through a meta-analysis of randomized controlled trials (RCTs).

Methods: A systematic search of the Cochrane CENTRAL, Ovid Medline R, PubMed, and Web of Science databases was conducted up to January 1, 2025 was conducted. RCTs comparing roxadustat with control groups were included. Inverse-variance-weighted random-effects models were used. The primary outcome was the risk of any serious treatment-emergent adverse event (TEAE). Subgroup analyses were based on etiology, comparator, and prior erythropoiesis-stimulating agent (ESA) use.

Results: Twenty-one RCTs involving 11.686 patients were included. Roxadustat was not associated with a higher risk of any serious TEAE compared with placebo [risk ratio (RR) =1.37, 95% confidence interval (CI): 0.79-2.37] or with ESA (RR=1.05, 95% CI: 0.99-1.10). Similarly, cardiac serious adverse events (SAEs) did not differ significantly when compared with ESA (RR=1.11, 95% CI: 0.75-1.12) or placebo (RR=1.11, 95% CI: 0.92-1.35). Hyperkalemia incidence was significantly higher compared with placebo (RR=1.25, 95% CI: 1.02-1.53) but not compared with ESA (RR=1.03, 95% CI: 0.77-1.36). There were also no significant differences in the incidence of serious infections (RR=0.74, 95% CI: 0.21-2.59), azotemia (RR=0.96, 95% CI: 0.46-2.00), hypertension (RR=1.06, 95% CI: 0.93-1.21), or pneumonia (RR=0.96, 95% CI: 0.81-1.14) compared with ESA. Notably, withdrawal due to adverse events (RR=2.11, 95% CI: 1.59-2.79) was significantly higher compared with ESA. TEAEs leading to death were similar compared with ESA (RR=0.98, 95% CI: 0.85-1.13) but were increased compared with placebo (RR=1.21, 95% CI: 1.04-1.42). All-cause mortality was significantly lower than with placebo (RR=0.40, 95% CI: 0.28-0.57) but was similar to ESA (RR=0.89, 95% CI: 0.57-1.37). Subgroup analyses for the primary outcome by etiology and prior ESA use were not consistent with the main findings.

Conclusions: Roxadustat demonstrated a SAE profile generally comparable to that of ESA, with no significant differences in cardiac SAEs, serious infections, azotemia, hypertension, or pneumonia. Hyperkalemia was more frequent compared with placebo, and withdrawals due to adverse events were more frequent compared with ESA. TEAEs leading

ÖZ

Amaç: Roxadustat, kronik böbrek hastalığına bağlı aneminin tedavisinde kullanılan oral bir hipoksi ile indüklenebilir faktör prolil hidroksilaz inhibitörüdür. Bu çalışmada, randomize kontrollü çalışmaların (RKÇ) meta-analizi ile roksadustatın güvenlilik ve tolere edilebilirlik profilini değerlendirmeyi amaçladık.

Yöntemler: Cochrane CENTRAL, Ovid Medline R, PubMed ve Web of Science veri tabanlarında 1 Ocak 2025 tarihine kadar sistematik literatür taraması yapıldı. Roksadustat ile kontrol gruplarını karşılaştıran RKÇ'ler dahil edildi. Ters varyans ağırlıklı rastgele etki modeli kullanıldı. Birincil sonlanım noktası, herhangi bir ciddi tedaviyle ilişkili advers olay (TEAE) riskiydi. Alt grup analizleri etiyoloji, kontrol grubu ve geçmişte eritropoez uyarıcı ajan (ESA) kullanımı temelli yapıldı.

Bulgular: Toplam 11,686 hastayı içeren 21 RKÇ dahil edildi. Roksadustat, plasebo [risk oranı (RR)=1,37, %95 güven aralığı (GA): 0,79-2,37] veya ESA (RR=1,05, %95 GA: 0,99-1,10) ile karşılaştırıldığında herhangi bir ciddi TEAE riskinde artış göstermedi. Benzer şekilde, kardiyak ciddi advers olaylar ESA (RR=1,11, %95 GA: 0,75-1,12) veya plasebo (RR=1,11, %95 GA: 0,92-1,35) ile karşılaştırıldığında anlamlı farklılık göstermedi. Hiperkalemi plaseboya kıyasla anlamlı olarak daha yüksekti (RR=1,25, %95 GA: 1,02-1,53), ancak ESA ile karşılaştırıldığında farklı değildi (RR=1,03, %95 GA: 0,77-1,36). ESA'ya kıyasla ciddi enfeksiyonlar (RR=0,74, %95 GA: 0,21-2,59), azotemi (RR=0,96, %95 GA: 0,46-2,00), hipertansiyon (RR=1,06, %95 GA: 0,93-1,21) veya pnömoni (RR=0,96, %95 GA: 0,81-1,14) açısından anlamlı fark gözlenmedi. Advers olaylara bağlı tedavi kesilmesi ESA'ya göre anlamlı olarak yüksekti (RR=2,11, %95 GA: 1,59-2,79). Ölüme yol açan TEAE'ler ESA ile benzerdi (RR=0,98, %95 GA: 0,85-1,13), ancak plaseboya göre yüksekti (RR=1,21, %95 GA: 1,04-1,42). Tüm nedenlere bağlı mortalite plaseboya (RR=0,40, %95 GA: 0,28-0,57) kıyasla daha düşüktü, ancak ESA (RR=0,89, %95 GA: 0,57-1,37) ile karşılaştırıldığında farklı değildi. Birincil sonlanım noktası, etiyoloji ve geçmişte ESA kullanımına göre alt grup analizleri ile değerlendirildiğinde esas analizden farklılıklar tespit edildi.

Sonuçlar: Roksadustat, ESA ile karşılaştırıldığında genel olarak benzer ciddi advers olay profili göstermiş olup, kardiyak SAEs, ciddi enfeksiyonlar, azotemi, hipertansiyon veya pnömoni açısından anlamlı fark saptanmamıştır. Hiperkalemi plaseboya kıyasla daha yüksek

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to death were similar to ESA but higher than with placebo, whereas all-cause mortality was lower than with placebo and comparable to ESA. Taken together, current evidence supports the overall non-inferiority of roxadustat to ESA in terms of safety.

Keywords: Roxadustat, iron deficiency anemia, chronic kidney disease, hiperkalemi, meta-analysis

bulunmuş ve advers olaylara bağlı tedavi kesilmesi ESA'ya kıyasla artmıştır. Ölüme yol açan TEAE'ler ESA ile benzer, plaseboya göre ise daha yüksektir. Tüm nedenlere bağlı mortalite plaseboya göre daha düşük olup ESA'ya benzemektedir. Genel olarak mevcut kanıtlar, güvenlilik açısından roksadustatın ESA'ya karşı non-inferior olduğunu desteklemektedir.

Anahtar kelimeler: Roksadustat, demir eksikliği anemisi, kronik böbrek hastalığı, hiperkalemi, meta-analiz

INTRODUCTION

The World Health Organization defines anemia as a hemoglobin (Hb) level of <13.0 g/dL for adult males and postmenopausal women, and <12.0 g/dL for premenopausal women[1]. Patients with chronic kidney disease (CKD), as a distinct group, will still have anemia even when appropriately treated.

Anemia is a common complication in patients with CKD, with erythropoietin deficiency recognized as one of its principal underlying causes[2]. Iron deficiency constitutes the second most significant contributor to anemia in this population[3]. Current treatment strategies recommend oral iron supplementation as the first-line therapy for iron-deficiency anemia; however, in patients requiring a more rapid and effective correction, intravenous iron formulations are generally preferred[4].

Another therapeutic option for the treatment of anemia is hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). HIF-PHIs stimulate erythropoietin release from the kidneys and liver, thereby increasing endogenous erythropoietin levels[5-7]. Among the HIF-PHIs, vadadustat is approved by the US Food and Drug Administration (FDA) for the treatment of anemia due to CKD in adults receiving hemodialysis for at least 3 months, whereas daprodustat is approved for adults receiving hemodialysis for at least 4 months[8]. It is well established that anemia is associated with increased mortality and reduced quality of life in patients with CKD. The benefit of correcting anemia in this patient group is clear. It is anticipated that HIF-PH inhibitors will improve compliance in clinical practice because of their oral administration[7,9].

Roxadustat is the first orally administered HIF-PHI available for adult patients with anemia associated with CKD in Europe[10]. Beyond the class effects of HIF-PHIs, results on the safety of roxadustat are conflicting. Findings for hyperkalemia, all-cause mortality, and cardiovascular (CV) outcomes were inconsistent across published randomized controlled trials (RCTs).

This study aims to assess the safety and tolerability of roxadustat in anemic patients through a meta-analysis of RCTs, with particular attention to identifying patients at increased risk of adverse outcomes.

MATERIALS and METHODS

Study Design

A systematic review and meta-analysis were conducted to evaluate the safety of roxadustat for the treatment of iron-deficiency anemia in the CKD population, in patients with myelodysplastic syndrome (MDS), and in post-transplantation patients. Approval to conduct the study was obtained from the Malatya Non-Interventional Clinical Research Ethics Committee (approval number: 2025/7455, date: 25.03.2025). As this meta-analysis used only aggregated data from published RCTs, informed consent was not required.

Data Sources and Search Strategy

A comprehensive search of four electronic databases — Cochrane CENTRAL, PubMed, Ovid Medline R, and Web of Science — was performed from inception to January 1, 2025. The search was designed to identify RCTs evaluating the safety profile of roxadustat in anemic patients. Search terms included combinations of "Roxadustat" OR "FG-4592" OR "ASP1517" OR "AZD9941" (Supplementary File 1).

Eligibility Criteria

We included only RCTs that:

- Enrolled adult patients with anemia of any etiology,
- Compared roxadustat with a placebo, standard of care, or erythropoiesis-stimulating agents (ESAs),
- Reported safety outcomes included serious treatment-emergent adverse events (TEAEs), specific adverse events (AEs) (e.g., cardiac events, hypertension), and mortality.

Studies were excluded if they were:

- Non-randomized designs (e.g., observational, experimental studies),
- Focused on pharmacokinetics/pharmacodynamics without clinical endpoints,

- Not reporting original patient-level or aggregate data.

The search was limited to English-language, full-text publications.

Study Selection

Two independent reviewers screened the identified records for inclusion. Disagreements were resolved through discussion. Records that met the eligibility criteria were included.

Data Extraction and Synthesis

Data extraction was independently performed by two reviewers using a standardized form. Extracted data included study design, population characteristics, interventions, comparators, follow-up duration, and safety outcomes. Discrepancies were resolved through discussion or consultation with a third reviewer.

Assessment of Risk of Bias

Risk of bias (RoB) was assessed using the Cochrane Risk of Bias 2.0 tool for RCTs[11]. Domains evaluated included randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results.

Statistical Analysis

This meta-analysis was performed using an inverse variance–weighted random-effects approach. The between-study variance (τ^2) was estimated using the Paule-Mandel method. Summary effect estimates were expressed as pooled risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Statistical heterogeneity was evaluated using the I^2 statistic[12] and further examined using Cochran's Q test and I^2 values. I^2 values ranging from 30% to 60% were interpreted as indicating moderate heterogeneity, values exceeding 60% as indicating high heterogeneity, and values above 75% as indicating substantial heterogeneity. All statistical analyses and data synthesis were conducted using R for macOS (www.r-project.org, version 4.4.3; R Foundation for Statistical Computing, Vienna, Austria). Sensitivity analyses were undertaken by removing studies judged to be at high RoB. In addition, subgroup analyses were performed according to anemia etiology (e.g., CKD, MDS), comparator type, and prior use of ESAs. For subgroup comparisons, p for interaction 0.1 was considered statistically significant[13].

RESULTS

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[14].

Study Selection

The initial database search yielded a total of 2.044 records, including 230 from Cochrane CENTRAL, 504 from PubMed, 497 from Ovid MEDLINE, and 812 from Web of Science. After removing 1.056 duplicate records, 980 unique records remained for title and abstract screening. Of these, 916 records were excluded based on irrelevance to the study objective.

The full texts of 64 reports were sought. However, eleven reports were not included: two were post-hoc analyses and nine were secondary data analyses. Thus, 53 reports were assessed for full eligibility. Following full-text review, 15 reports were excluded: 4 due to inappropriate comparator groups and 11 due to ineligible study designs.

A total of 38 reports, representing 21 RCTs, met all inclusion criteria and were included in the qualitative and quantitative synthesis. The complete study selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

Study Characteristics

This systematic review and meta-analysis included 21 RCTs[15-34] comprising a total of 11.686 adult patients with anemia regardless of etiology. Studies published between 2015 and 2024 were conducted in diverse international settings, including Asia[15-17,21-23,28,32,34], North America[19,20,29], and Europe[18,25,31]. The study populations included dialysis-dependent (DD-CKD) patients[17,20,21,23,25,26,29,30,32,34], non-dialysis-dependent (NDD-CKD) patients[15,16,18,19,22-24,31,33], patients with MDS[27], and patients with posttransplant anemia[28].

The sample sizes across trials ranged from 91 to 2.761 participants. Follow-up durations ranged from 4 to 208 weeks. All included trials investigated roxadustat, an oral HIF-PHI, administered either at fixed doses or at doses titrated based on Hb response. The Comparator was ESAs[16-18,20,21,23,25,26,29,30,32,34] or placebo[15,19,22-24,27,31,33] in the vast majority of the included trials, whereas oral iron[28] was used in post-transplant anemia.

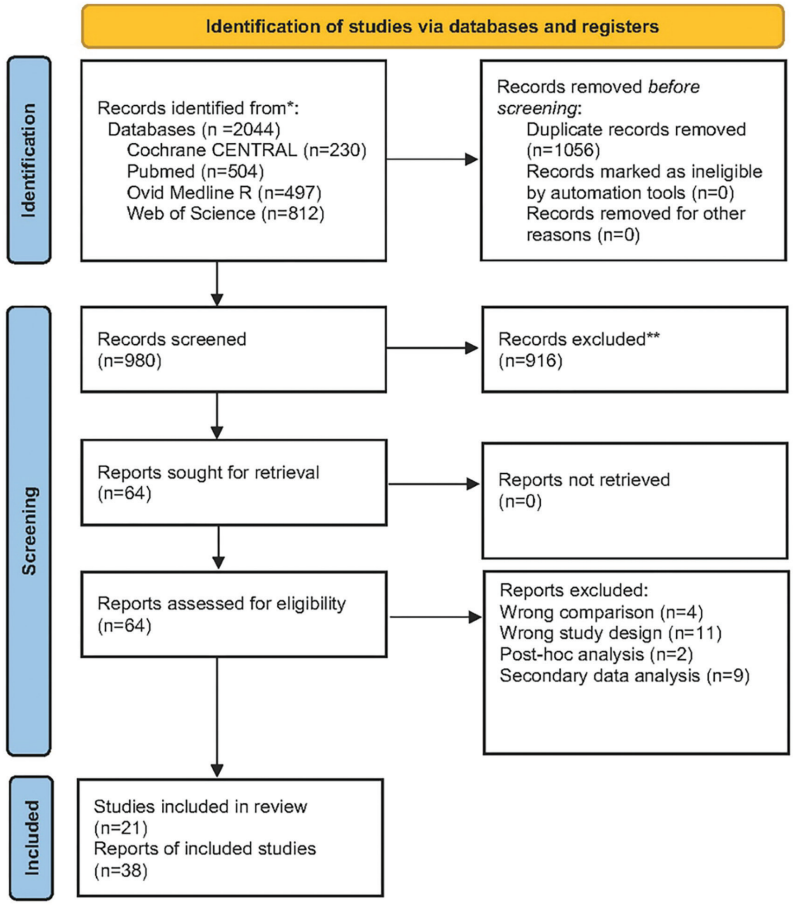

Figure 1. PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Primary safety outcomes reported included TEAEs, serious adverse events (SAEs), and AEs leading to withdrawal or death. Many studies reported specific AEs of interest, including hypertension, hyperkalemia, infections, and CV events. A minority of studies[18,25,31] also reported quality of life and functional status, although these were not the focus of this study.

A detailed summary of each study's design, population characteristics, and follow-up duration is provided in Table 1.

Risk of Bias Assessment

The Cochrane Collaboration's RoB 2 tool was used to evaluate the RoB in the included RCTs, focusing on the primary safety outcome. Overall, the quality of most studies was acceptable, with the vast majority of the trials judged to be at low RoB for the randomization process, missing outcome data, and selective reporting (Figure 2). However, the majority of trials were rated as having "some concerns" in at least one domain, most often due to the use of "as-treated" or "safety analysis set" population analyses instead of strict intention-to-treat (ITT), and to the prevalence of open-label designs. Open-label designs, used in most trials, introduce concerns regarding deviations from intended interventions and potential measurement bias in subjective safety outcomes. Two studies, including three trials[23,30], were judged to be at high RoB overall, primarily because of open-label designs, non-ITT safety analyses and potential co-intervention differences (i.e., oral iron), which increased the RoB.

Primary Outcome and Subgroup Analysis

A total of 13 RCTs involving 9.386 patients contributed data on the primary outcome of any serious TEAE[15-18,21,25-27,29-31,33,34]. In the pooled analysis, roxadustat was not associated with a significant increase in the risk of any serious TEAE compared with the ESA (RR=1.05, 95% CI: 0.99 to 1.10; I^2=59%) or with placebo (RR=1.37, 95% CI: 0.79 to 2.37; I^2=51%) (Figure 3). The absolute risk difference was 2.9 percentage points (95% CI: 0.5 to 5.2), corresponding to more events in the roxadustat group (absolute risks: 50.5% vs. 47.6% in the control group).

Table 1. Study characteristics of included trials.

First author, year	Country (ies)	Blinding status	Population	Sample size	Intervention	Control	Male (%)	Follow-up (weeks)
Besarab 2015	United States	Blinded	NDD-CKD	116	Roxadustat	Placebo	49	4
Provenzano 2016	United States	Open-label	DD-CKD	144	Roxadustat	Epoetin-alfa	66	19
Chen 2017[c]	China	Blinded	NDD-CKD	91	Roxadustat	Placebo	28.6	8
Chen 2017[d]	China	Open-label	DD-CKD	96	Roxadustat	Epoetin-alfa	60.4	6
Akizawa 2019	Japan	Blinded	NDD-CKD	107	Roxadustat	Placebo	46.7	24
Chen 2019[a]	China	Blinded	NDD-CKD	152	Roxadustat	Placebo	54.9	8
Chen 2019[b]	China	Open-label	DD-CKD	304	Roxadustat	Epoetin-alfa	60.5	26
Akizawa 2020	Japan	Blinded	DD-CKD	302	Roxadustat	Darbepoetin-alfa	69.1	24
Akizawa 2021	Japan	Open-label	NDD-CKD	262	Roxadustat	Darbepoetin-alfa	58.1	52
Barratt 2021	International (primarily European)	Open-label	NDD-CKD	616	Roxadustat	Darbepoetin-alfa	44.5	104
Charytan 2021	United States	Open-label	DD-CKD	740	Roxadustat	Epoetin-alfa	54.2	52
Coyne 2021	United States, South America, Australia, New Zealand, and Asia.	Blinded	NDD-CKD	916	Roxadustat	Placebo	39.6	52
Csiky 2021	International (primarily European)	Open-label	DD-CKD	834	Roxadustat	Epoetin-alfa, darbepoetin-alfa	57.6	52
Fishbane 2021	Multinational (Americas, Europe, and Asia)	Blinded	NDD-CKD	2761	Roxadustat	Placebo	42.3	164
Henry 2021	Multinational (North America, Europe, Asia, and Australia)	Open-label	MDS	140	Roxadustat	Placebo	50	52
Hou 2021	China	Open-label	DD-CKD	129	Roxadustat	ESAs	55.8	24
Provenzano 2021	Multinational (North America, South America, Europe, and Asia)	Open-label	DD-CKD	1039	Roxadustat	Epoetin-alfa	59	52
Shutov 2021	Multinational (Europe, South America, Central America, and Africa)	Blinded	NDD-CKD	594	Roxadustat	Placebo	45.1	104
Fishbane 2022	Multinational (North America, Europe, Asia, South America, and Australia)	Open-label	DD-CKD	2101	Roxadustat	Epoetin-alfa	59.4	208
Kong 2024	China	Open-label	PTA	128	Roxadustat	Oral iron	21	12
Tan 2024	China	Open-label	DD-CKD	114	Roxadustat	Epoetin-alfa	53.5	52

CKD: Chronic kidney disease, DD-CKD: Dialysis dependent CKD, NDD-CKD: Non-dialysis dependent CKD, MDS: Myelodysplastic syndrome, PTA: Posttransplant anemia, ESAs: Erythropoiesis-stimulating agents, [a, b]: Distinct study populations (NDD-CKD and DD-CKD, respectively) derived from the same trial. [c, d]: correspond to different independent studies.

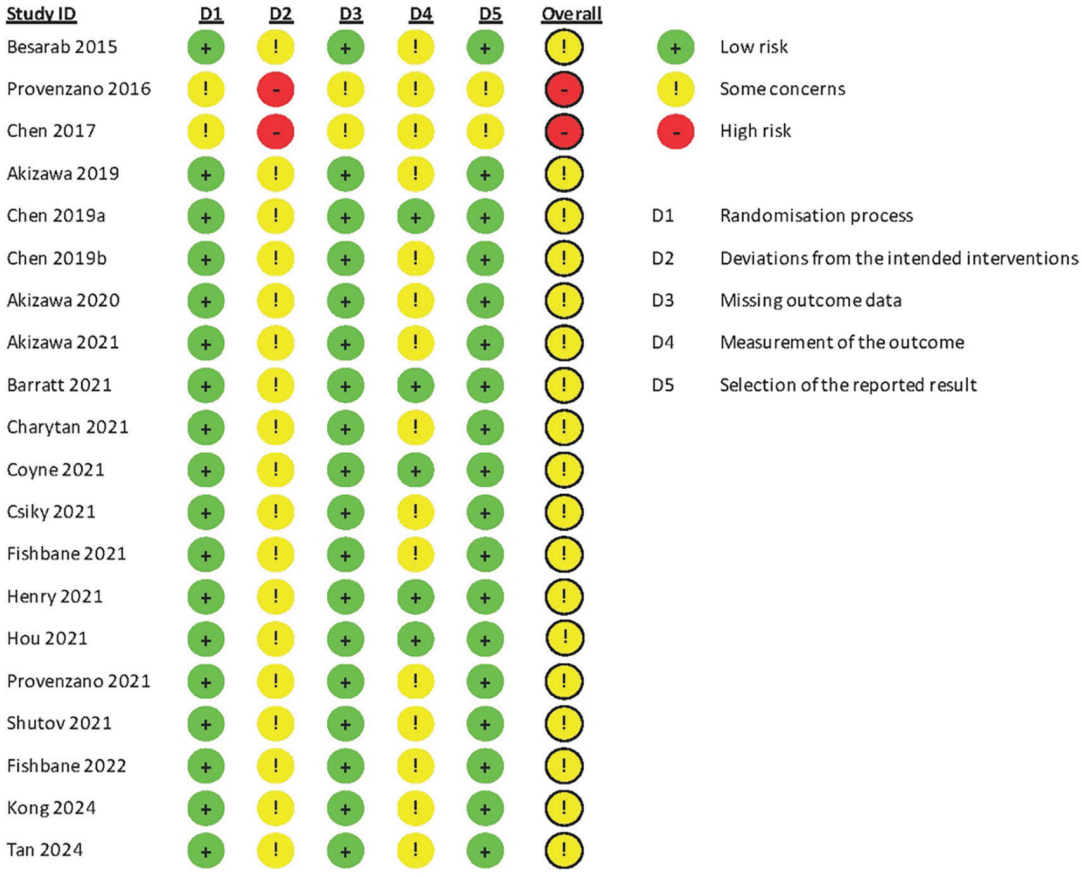

Figure 2. Risk of bias assessments of the included studies.

Prespecified subgroup analyses were conducted based on the dialysis status (DD-CKD vs. NDD-CKD), prior use of ESAs (ESA-naive vs. ESA-used), and comparators (placebo, ESA, or oral iron).

By Dialysis Status: In patients with DD-CKD, roxadustat did not significantly increase the risk of any serious TEAEs compared to control (RR=1.04, 95% CI: 0.98 to 1.10; I^2=0%). In contrast, among patients with NDD-CKD, a higher but not statistically significant risk was observed (RR=1.18, 95% CI: 0.85 to 1.63; I^2=29.1%). The test for subgroup interaction was not statistically significant (p=0.3884) (Figure S1).

Subgroup analysis by ESA status revealed an inconsistency. The RR for serious TEAEs in ESA-mixed patients was 1.04 (95% CI: 1.00 to 1.09); in ESA-experienced patients it was 1.10 (95% CI: 1.01 to 1.21); and in ESA-naive patients it was 5.50 (95% CI: 1.26 to 24.03, 1 RCT), with overlapping 95% CIs. The interaction test did not show significant subgroup differences (p=0.42; Figure S2).

According to the RoB assessment, only one study[29] that reported any serious TEAE; it had a high RoB (Figure S3). The RoB study assessed as "some concerns" reported an RR of 1.06 (95% CI: 1.01 to 1.11), whereas the high-RoB study showed an RR of 1.41 (95% CI: 0.65 to 3.23). Studies with some concerns about RoB remained consistent with the main analysis. Therefore, no definitive conclusion can be drawn regarding the influence of RoB on the treatment effect.

Secondary Outcomes

Cardiac Safety Outcomes: Six outcomes were analyzed to evaluate the cardiac safety of roxadustat: any cardiac AEs, any serious cardiac AEs, any TEAEs, hyperkalemia, hypertension, and peripheral edema (Table 2). The pooled analysis revealed comparable risks between roxadustat and control groups for any cardiac AEs (RR=0.93, 95% CI: 0.76 to 1.13; I^2=39.3%), any serious cardiac AEs (RR=1.01, 95% CI: 0.88 to 1.16; I^2=0%), any TEAE (RR=1.03, 95% CI: 0.97 to 1.09; I^2=21% vs. ESA, RR=0.79, 95% CI: 0.37 to 1.71; I^2=0% vs. oral iron and RR=1.02, 95% CI: 0.97 to 1.06; I^2=2%

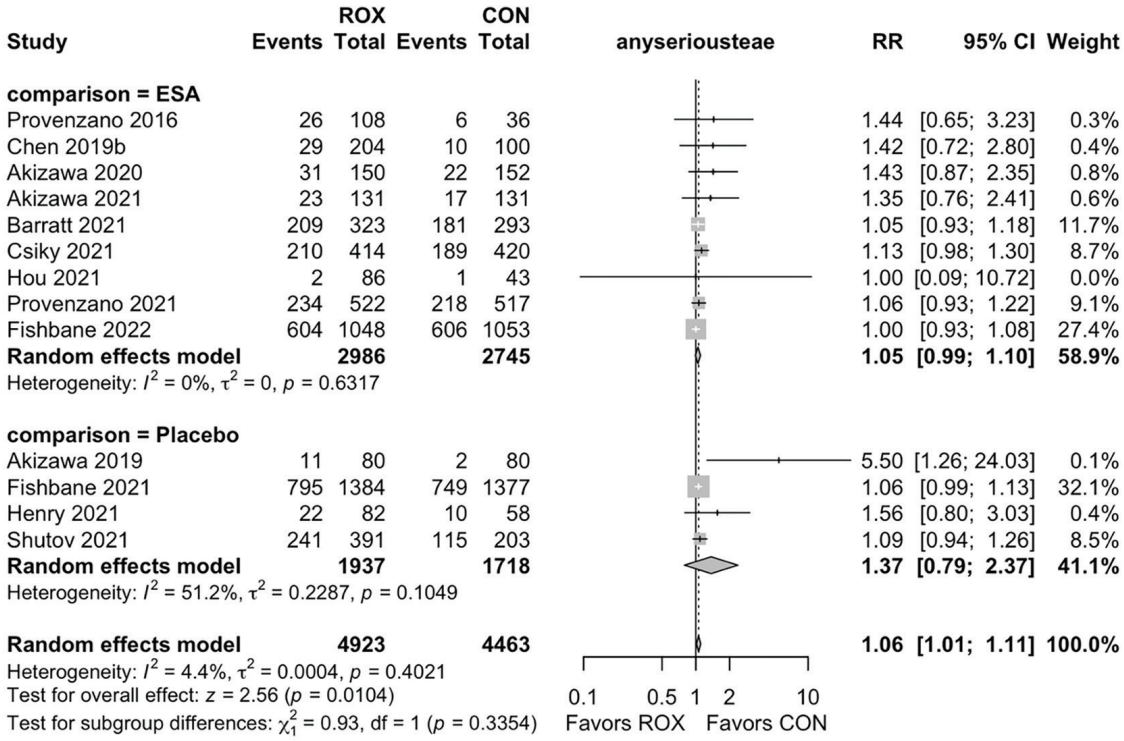

Figure 3. Effect of roxadustat on any serious TEAE by comparator ROX: Roxadustat, CON: Control, RR: Risk ratio, CI: Confidence interval, ESA: Erythropoiesis-stimulating agent, TEAE: Treatment-emergent adverse event

Table 2. Effects of roxadustat on cardiac safety outcomes.

Outcomes	Number of RCTs	Number of patients	Overall efect estimate RR (95% CI)	p-value	I-square (%)
Any cardiac AEs	7	5990	0.93 (0.76-1.13)	0.44	39
Any serious cardiac AEs	5	6020	1.01 (0.88-1.16)	0.8	0
Hyperkalemia	17	10315	1.12 (0.97-1.30)	0.10	0
Hypertension	16	10865	1.13 (1.01-1.26)	0.03	0
Pulmonary edema	8	5703	1.25 (0.98-1.60)	0.07	19

AEs: Adverse events, RCT: Randomized controlled trials, RR: Risk ratio, CI: Confidence interval

vs. placebo; Figure S4) and hyperkalemia (RR=1.03, 95% CI: 0.77 to 1.36; I^2=15% vs. ESA). Furthermore, roxadustat was associated with a 25% increased risk of hyperkalemia compared with placebo (RR=1.25, 95% CI: 1.02 to 1.53; I^2=0%) (Figure 4). Similarly, hypertension was significantly more frequent in patients treated with roxadustat compared with placebo (RR=1.31, 95% CI: 1.08 to 1.60; I^2=0%), but not when compared with ESA (RR=1.06, 95% CI: 0.93 to 1.21; I^2=0%) (Figure S5). Roxadustat was associated with a non-significant increase in the risk of peripheral edema (RR=1.25, 95% CI: 0.98 to 1.60; I^2=19.1%).

Mortality and Tolerability Outcomes: We examined how well patients tolerated roxadustat (Table 3). Patients receiving roxadustat were more likely to discontinue treatment because of AEs, with the risk of withdrawal nearly doubling compared with ESA (RR=2.11, 95% CI: 1.59 to 2.79; I^2=0%), but not compared with placebo (RR=1.57, 95% CI: 0.79 to 3.13; I^2=0%) (Figure S6). Importantly, roxadustat did not increase the risk of TEAEs leading to death (RR=1.07, 95% CI: 0.95-1.21; I^2=29.5%). Accordingly, we observed a notable reduction in all-cause mortality among those receiving roxadustat compared to placebo (RR=0.40, 95% CI: 0.28 to 0.57; I^2=13%), but not compared

to ESA (RR=0.89, 95% CI: 0.57 to 1.37; I²=0%) or to oral iron (RR=1.00, 95% CI: 0.01 to 71.75) (Figure S7). A sensitivity analysis excluding two trials that assessed posttransplant anemia or MDS did not change the direction of the effect estimate (Figure S8).

Infection-related Outcomes: We also examined whether roxadustat influenced the risk of infection (Table 4). The risk of experiencing any infection was similar between the roxadustat and control groups (RR=1.01, 95% CI: 0.68 to 1.49; I²=26.9%). When we focused on more severe events, such as infections (e.g., pneumonia), the results remained consistent. Serious infections occurred at similar rates (RR=1.05, 95% CI: 0.69 to 1.60; I²=0%) (Figure S9), and the risk of pneumonia showed no significant increase (RR=1.04, 95% CI: 0.91 to 1.19; I²=10.3%) (Figure S10). Again, when examining specific types of infections, such as urinary tract infections (UTIs) and upper respiratory tract infections, no notable differences were observed. Overall, these results suggest that roxadustat does not increase the likelihood of infectious complications.

Kidney-related Outcomes: We assessed several kidney-specific outcomes to explore whether roxadustat might adversely affect renal function (Table 5). The risk of any kidney-related AEs was similar among groups (RR=1.09, 95% CI: 0.88 to 1.36; I²=0%) (Figure S11). Similarly, the risks of azotemia (RR=1.00, 95% CI: 0.77 to 1.30; I²=0%), worsening CKD, and progression to end-stage kidney disease (ESKD) were comparable (Figures S12-S14).

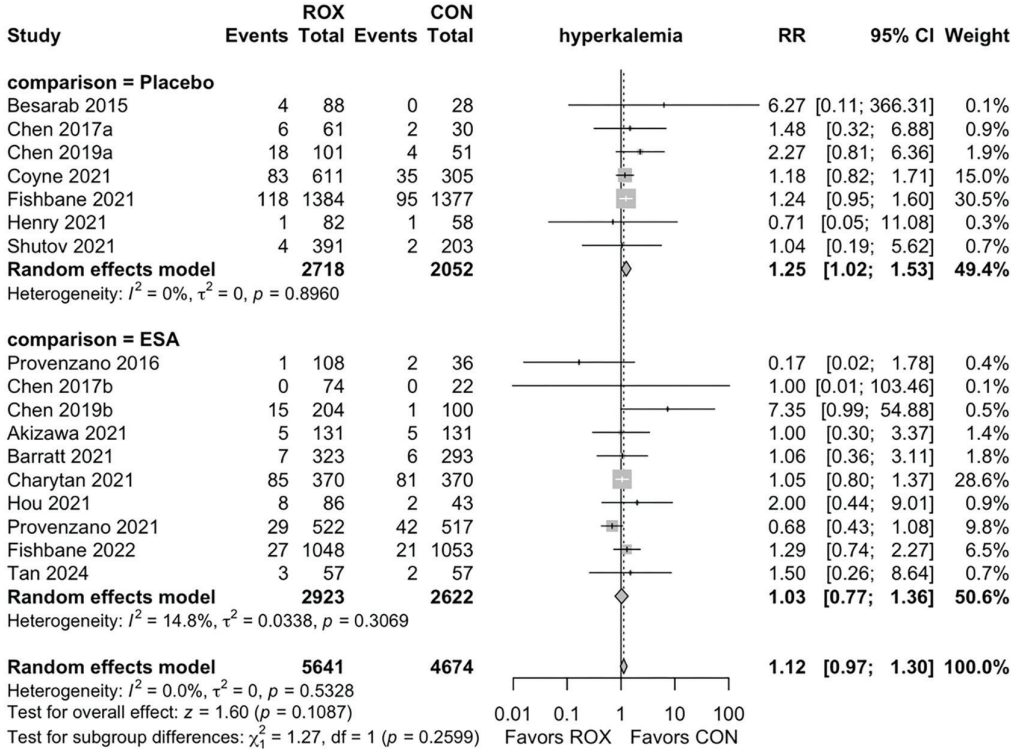

Figure 4. Effect of roxadustat on hyperkalemia by comparator ROX: Roxadustat, CON: Control, RR: Risk ratio, CI: Confidence interval, ESA: Erythropoiesis-stimulating agent

Table 3. Effects of roxadustat on mortality and tolerability outcomes.

Outcomes	Number of RCTs	Number of patients	Overall effect estimate RR (95% CI)	p-value	I-square (%)
All cause mortality	18	10510	0.56 (0.41-0.75)	0.0001	32
Withdrawal due to AE	7	4816	2.02 (1.56-2.62)	<0.0001	0
TEAE leading to death	6	7945	1.07 (0.95-1.21)	0.26	29
Any TEAE	15	8664	1.01 (0.99-1.04)	0.25	5

AE: Adverse event, RCT: Randomized controlled trials, TEAE: Treatment emergent adverse events, RR: Risk ratio, CI: Confidence interval

Table 4. Effects of roxadustat on infection-related outcomes.					
Outcomes	**Number of RCTs**	**Number of patients**	**Overall effect estimate RR (95% CI)**	**p-value**	**I-square (%)**
Any infections	4	669	1.01 (0.68-1.49)	0.97	27
Any serious infections	3	1027	1.05 (0.69-1.60)	0.81	0
Pneumonia	12	10299	1.04 (0.91-1.19)	0.58	10
Upper respiratory tract infection	15	8425	1.02 (0.85- 1.23)	0.79	29
Urinary tract infection	10	8993	1.03 (0.72-1.47)	0.88	58
RCT: Randomized controlled trials, RR: Risk ratio, CI: Confidence interval					

Table 5. Effects of roxadustat on kidney-related outcomes.					
Outcomes	**Number of RCTs**	**Number of patients**	**Overall Effect Estimate RR (95% CI)**	**p-value**	**I-square (%)**
Any kidney-related AEs	5	1383	1.09 (0.88-1.36)	0.41	0
Azotemia	7	7402	1.00 (0.77-1.30)	0.99	0
CKD worsening	5	1585	0.97 (0.64-1.46)	0.88	0
End-stage kidney disease	4	4423	1.06 (0.94-1.19)	0.37	0
AEs: Adverse events, CKD: Chronic kidney disease, RCT: Randomized controlled trials, RR: Risk ratio, CI: Confidence interval					

Stratified Analysis by Blinding Status: We stratified the included trials by blinding status to evaluate the potential influence of study design on key safety outcomes. For several outcomes—including pneumonia, hypertension, TEAEs leading to death, and all-cause mortality—the pooled effect estimates were consistent between blinded and open-label trials, with no statistically significant interaction observed (p for interaction >0.1 for all outcomes). Detailed results of these stratified analyses have been presented in Supplementary Figures S15-S[22].

DISCUSSION

We included nine trials on NDD-CKD, ten on DD-CKD, one on MDS, and one on post-transplant anemia. Data on kidney transplant recipients and children were scarce. In sum, our analysis revealed that roxadustat has uncertain effects on any TEAE, TEAEs leading to death, and CV AEs (e.g., hyperkalemia and pulmonary edema), but is associated with a mild increase in hypertension risk and a significant decrease in all-cause mortality. Comparable risks were also observed for infection-related parameters (any serious infections, pneumonia, UTIs etc.) and for kidney-related outcomes (azotemia, progression of CKD, ESKD, etc.) compared with placebo or ESA. However, we found that withdrawals due to AEs were 102% higher with roxadustat than with placebo or ESA.

The FDA did not approve the use of roxadustat for the treatment of anaemia in people with CKD, including those requiring dialysis, because HIF stabilisers were associated with a higher risk of thrombosis than placebo or ESA[35]. However, Roxadustat is currently approved for both indications in the European Union, China, Japan, Chile, South Korea, and Türkiye[36].

There were inconsistencies in adverse effects reported among published clinical trials, particularly regarding SAEs such as hyperkalemia, all-cause mortality, and serious infections. Several meta-analyses that assess the safety of roxadustat in specific populations or physiological systems, such as CV and renal systems employing different inclusion criteria and methodologies.

The Cochrane systematic review by Natale et al.[6] comprehensively evaluated the safety and efficacy of HIF-PHIs as a class effect in CKD. Across the class, HIF-PHIs were generally comparable to ESAs in achieving target Hb levels, with little or no difference in all-cause mortality (RR=0.98, 95% CI: 0.91 to 1.06; I^2=0%), myocardial infarction (RR=0.91, 95% CI: 0.76 to 1.10; I^2=0%), and hyperkalemia (RR=0.92, 95% CI: 0.82 to 1.04; I^2=10%) when compared with ESAs; however, roxadustat may be associated with an increased risk compared with placebo (RR= 1.29, 95% CI: 1.01 to 1.64; I^2=18%). However, subgroup analysis based on specific agents was not applied in the study.

In a meta-analysis conducted by Zhou et al.[37] to assess the safety of roxadustat in patients with DD-CKD — which included 10 RCTs (published in 9 studies) and 5698 patients —the risk of any TEAE (RR=1.02, 95%CI: 1.00-1.05, p=0.11), any serious TEAE (RR=1.05, 95%CI: 0.99-1.12, p=0.11), and major CV events (RR=1.04, 95% CI: 0.85-1.28, p=0.70) was found to be comparable to ESAs. The main difference between our study and others is that ours included studies regardless of etiology or comparator (21 RCTs involving 11,546 patients). Furthermore, we found a mild but statistically significant increase in the risk of any serious TEAE with roxadustat (RR=1.06, 95% CI: 1.01-1.11, p=0.0104). In addition, Zhou et al.[37] used the Mantel-Haenszel (M-H) fixed-effect weighting model for any serious TEAE. This is problematic because, when data are sparse—either due to low event risks or small study sizes— the estimates of the standard errors of the effect estimates used in inverse-variance methods may be poor[38]. M-H has been recommended by the Cochrane Collaboration as having better statistical properties when there are few events[39]. Also, the authors[37] used Cochrane RoB v1 for assessing RoB, which was updated to the Cochrane RoB2 tool that we used. These methodological differences were the main causes of our results.

In the meta-analysis conducted by Tian et al.[40], data from 18 studies with a total of 8.806 CKD patients were included. Serious cardiac-related AEs were not significantly increased in the roxadustat group, regardless of dialysis status[40]. However, we found that roxadustat notably increased the incidence of hypertension (RR=1.13; 95% CI: 1.01-1.26; p=0.03). Our finding overlapped with that of this study, highlighting an increased incidence of hypertension, particularly in NDD-CKD populations, compared to placebo[40]. Also, both studies found that the risk of hypertension was comparable among DD-CKD patients. Furthermore, that study[40] evaluated the risk of hypertension using a meta-regression analysis by continent (US, Asia, and Europe), but no significant differences were found.

Hou et al.[41] also evaluated the safety profile of roxadustat in patients with CKD. They reported that the incidence of AEs and SAEs was significantly higher in the roxadustat group than in the control group[41]. In another study, Zhang et al.[42] reported no differences in any TEAEs and any serious AEs between roxadustat and placebo or ESA groups in the same population; however, hyperkalemia and withdrawal due to AEs were more common in the roxadustat group than in the control group[42]. Our findings align with the study by Zhang et al.[42] but not with Hou et al.[41], as roxadustat was associated with a significantly higher risk of any serious TEAE, and withdrawals due to AEs were significantly increased in the roxadustat group compared with the control group. As M-H methods are fixed-effect meta-analysis methods using different weighting schemes[39], Zhang et al.[42] used M-H random effects, which resulted in differences in pooled effect sizes. Also, one of the major strengths of our study is the inclusion of 21 RCTs (published in 20 studies) with detailed subgroup analyses based on comparator, ESA status, and etiology of the anemia.

Our findings for all-cause mortality (RR=0.56, 95% CI: 0.41-0.75; p=0.0001) and hyperkalemia (RR=1.12, 95% CI: 0.97-1.30; p=0.11) were notable. There was inconsistency between these two outcomes in the published literature. Several meta-analysis found an increase in risk of hyperkalemia[40,42,43] but some not[6,37,44]. Similarly, some meta-analyses showed a comparable risk of all-cause mortality associated with roxadustat. Lei et al.[43] (included 16 RCTs, 6518 patients) and Tian et al.[40] reported that roxadustat treatment increased the risk of hyperkalemia by 36% in NDD-CKD and by 41% regardless of dialysis status, respectively. However, Zhou et al.[37] (2023) (10 RCTs, 5698 DD-CKD) reported no increased risk of hyperkalemia (RR=1.07; 95% CI: 0.70-1.64; p=0.75).

The study by Li et al.[45] aimed to compare the CV safety of roxadustat and ESAs in patients with CKD-related anemia, using a combination of meta-analysis and bioinformatics approaches. While the authors reported that their pooled analysis included data on 143,065 patients from 15 articles, this study is poorly substantiated[45]. Only three of the included RCTs (20, 26, 30) in study[45] actually assessed the safety of roxadustat, whereas the remaining trials primarily evaluated the safety profiles of ESAs. The authors applied an indirect comparison between the two groups; however, no justification was provided for excluding other eligible roxadustat trials. This lack of transparency in trial selection raises concerns regarding selection bias. Given the small number of roxadustat-specific RCTs and the predominance of ESA studies, pooled estimates for roxadustat[45] may be disproportionately influenced by indirect evidence, thereby posing a high risk of selection bias[46] and reducing the reliability of the conclusions.

Study Limitations

This meta-analysis has several limitations. First, although we included 21 RCTs, heterogeneity in study design, patient populations, follow-up durations, and comparator arms may have influenced the pooled estimates. Second, most trials were open-label and assessed safety outcomes using "as-treated" or "safety analysis set" populations rather than strict ITT, which may introduce bias. Third, missing outcome data and selective reporting of AEs, combined with variability in outcome definitions across trials, may further bias results.

CONCLUSION

Roxadustat was associated with a mildly increased risk of hypertension and a markedly higher rate of withdrawal from treatment due to AEs, while risks of serious cardiac AEs, serious infections, and kidney-related outcomes remained comparable to controls. Notably, all-cause mortality was significantly lower in the roxadustat group. Across 21 trials involving NDD-CKD, DD-CKD, MDS, and posttransplant anemia, evidence for kidney transplant recipients and children was scarce. Overall, roxadustat showed uncertain effects on the occurrence of any TEAEs, any serious TEAEs, and CV events such as hyperkalemia and pulmonary edema, but demonstrated a consistent mortality benefit. Future studies should address the use of roxadustat in specific populations (e.g., children and patients with post-transplant anemia), switching from ESAs, cost-effectiveness, important outcomes such as health-related quality of life and patient-reported measures.

In this meta-analysis of 21 RCTs including 11.686 patients, roxadustat demonstrated an overall safety profile comparable to that of ESAs. Rates of SAEs, including cardiac events, serious infections, azotemia, hypertension, and pneumonia, did not differ significantly between roxadustat and ESA. Hyperkalemia occurred more frequently than with placebo, and treatment withdrawal due to AEs was more frequent than with ESA. While all-cause mortality was reduced compared with placebo and was similar to that with ESA, treatment-emergent events leading to death were increased compared with placebo but not with ESA. Notably, stratified analyses by blinding status did not materially alter the direction or significance of key outcomes, supporting the robustness of the primary findings. Overall, current evidence indicates that roxadustat is non-inferior to ESA with respect to safety.

Ethics

Ethics Committee Approval: Approval to conduct the study was obtained from the Malatya Non-Interventional Clinical Research Ethics Committee (approval number: 2025/7455, date: 25.03.2025).

Informed Consent: As this meta-analysis used only aggregated data from published RCTs, informed consent was not required.

Footnotes

Author Contributions

Concept: L.H.T., A.S., M.A.E., H.B.B., Design: L.H.T., M.A.E., H., Data Collection and/or Processing: L.H.T., A.S., H.B.B., Analysis or Interpretation: L.H.T., M.A.E., H.B.B., Literature Search: L.H.T., A.S., H.B.B., Writing: L.H.T., A.S., M.A.E., H.B.B.

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Supplementary Figures: https://d2v96fxpocvxx.cloudfront.net/07d42497-fb2b-47e0-be2f-8805fa940376/content-images/a2f75693-b42d-42a0-af5b-3e0c997cce26.pdf