The efficacy of Roxadustat for the treatment of anemia in dialysis dependent chronic kidney disease patients: an updated systematic review and meta-analysis of randomized clinical trials

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Background: Anemia is a common complication in chronic kidney disease (CKD) with increased morbidity and mortality. Recently published RCTs were conducted to compare the effect of the new medication roxadustat (ROX) with erythropoiesis-stimulating agent (ESA) in dialysis-dependent CKD (DD-CKD) patients. Our article aimed to meta-analyze published RCTs to investigate the efficacy and safety of ROX for anemia in DD-CKD patients and update the effect of the new studies on overall analysis with subsequent impact on management.

Methods: Electronic databases (PubMed, EMBASE, Scopus, Web of Science, Cochrane Central, and Google Scholar) were searched systematically from inception to July 2021 by using this search term (Roxadustat OR ASP1517 OR FG4592 OR "FG-4592") AND (kidney OR renal) AND (Anemia). We only included randomized control trials (RCTs) that reported the primary outcome of change in hemoglobin (Hb) level and iron utilization parameters, including ferritin, serum iron, TSAT, TIBC, transferrin, and hepcidin.

Results: Ten RCTs were finally included with 3031 patients in the ROX group and 2737 patients in the control group. ROX was associated with increase in Hb level (SMD: 0.2; 95% CI: 0.02, 0.39; P=0.03), TIBC (SMD: 0.79; 95% CI: 0.61, 0.98; P<0.00001), serum iron (SMD: 0.27; 95% CI: 0.18, 0.36; P<0.00001), transferrin (SMD: 0.98; 95% CI: 0.81, 1.15; P<0.00001) and decrease in hepcidin (SMD: −15.53; 95% CI: −28.07, −3.00; P<0.02) when compared with control group. There was no difference between ROX and the control group regarding ferritin level and TSAT. Sensitivity analysis by removing the most recent studies, Chen *et al*. or Hou *et al.* did not show significant difference in regard to change in Hb level. There was no difference between both groups regarding the serious side effects. However, ROX showed higher TEAEs when compared to the control group (RR: 1.03; 95% CI: 1.01, 1.05; P=0.002).

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Discussion: Our updated meta-analysis concluded that ROX increased Hb level and improved iron utilization parameters in DD-CKD patients, but ROX was associated with higher TEAEs. Our results support the use of ROX for DD-CKD patients with anemia. However, higher-quality RCTs are still needed to confirm the results of our review.

Keywords: Roxadustat; anemia; dialysis; chronic kidney disease; iron

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Introduction

Chronic kidney disease (CKD) is defined as kidney damage or diminished renal function for three months or more, regardless of cause (1). The worldwide prevalence of CKD is 13% (2), and over 2 million CKD people worldwide currently receive treatment with dialysis (3). However, CKD is associated with increased morbidity and mortality rate; the mortality risk among those requiring dialysis is the highest within the first year after starting dialysis (4). One of the most common complications of CKD is anemia, with 14.0% of CKD patients had anemia in the United States of America between 2007–2010 (5).

The pathogenesis of CKD-related anemia is multifactorial, including but not limited to erythropoietin (EPO) deficiency, EPO inhibition by the uremia, and disruption of the iron homeostasis (6). The standard of care of anemia in Dialysis dependent CKD (DD-CKD) patients is iron replacement, erythropoietin stimulating agents (ESA), and blood transfusion. Before starting the patients on ESA therapy, the adverse effects of ESA should be explained to the patients before starting the treatment. ESA's side effects include serious cardiovascular events, myocardial infarction (MI), stroke, and venous thromboembolism (7-9). In addition, ESA is given subcutaneously, and iron therapy requires a hospital or infusion center visit to deliver the intravenous (IV) iron. And both of those factors can affect patients' compliance.

Recently, a new medication called roxadustat (ROX) had been released to the market to treat anemia in patients with DD-CKD. ROX is an oral medication that inhibits the hypoxia-inducible factor prolyl hydroxylase (HIF-PH) enzyme. Hypoxia-inducible factor (HIF) is an important transcription factor that regulates the oxygen response at the tissue level and induces erythropoiesis. HIF-PH is an enzyme that inhibits the activity of HIF, and inhibiting HIF-PH will lead to an increase in the level of HIF, which in return will increase EPO production (10,11). ROX binds to plasma protein, mainly albumin, and the fraction unbound is about 1.2% in DD-CKD (12). ROX is mainly removed from the body by phase I oxidation (CYP2C8) and phase II conjugation (glucuronidation and glucosidation); thus, dialysis accounts for a small portion of the ROX elimination (12,13). Few RCTs studied the effect of ROX compared to ESA on DD-CKD patients, but there were conflicting results regarding the efficacy and safety of ROX on DD-CKP patients.

Our updated meta-analysis of randomized clinical trials (RCTs) will include the recently published RCTs by Provenzano *et al.* (14), Hou *et al.* (15), and Charytan *et al.* (16). We aim to investigate the safety and efficacy of ROX versus ESA on DD-CKD patients with anemia. In addition, our study will provide evidence to the internists and nephrologists on whether ROX should be considered in clinical practice. We present the following article in accordance with the PRIMSA reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4357).

Methods

This systematic review was registered with and was written and reported according to the guidelines of the Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) and Cochrane Handbook for Systematic Reviews of Interventions (17,18). We registered our review at OSF Registries with DOI: 10.17605/OSF.IO/MJRA2.

Data sources and search strategy

Systematic and comprehensive research was conducted on the online databases PubMed, EMBASE, Scopus, Web of Science, Cochrane Central, and Google Scholar. It was carried out from inception up to July 2021 to include

citations on HD CKD patients treated with ROX for anemia. A combination of the medical search terms and keywords were used to identify the potential articles of interest: (Roxadustat OR ASP1517 OR FG4592 OR "FG-4592") AND (kidney OR renal) AND (Anemia), and it varies depends on the database Table S1. We also used the related articles feature (19) to include any related articles and manually retrieved the bibliographies of relevant publications to avoid missing potential studies. Finally, we used EndNote (20) to save the search result. The search strategy was developed by (KSA and JS) and was peer-reviewed by BA.

Study selection and eligibility criteria

Studies included in this systematic review were RCTs that were in English and met the following criteria: (I) Types of participants: participant were patients diagnosed with CKD and on dialysis; (II) Types of interventions: interventions used ROX to treat anemia; (III) Types of comparators: comparators were ESA or placebo; (IV) Types of outcomes: primary outcomes: change in hemoglobin level and iron utilization parameters.

Studies were excluded if they were observational, non-randomized, or did not report a comparator group. Two independent reviewers (JS and KSA) used Covidence software (21) and screened the studies in three stages: title, abstract, and full text. BA resolved discrepancies between the reviewers.

Data extraction

Three reviewers (JS, KSA, and NA) independently extracted data from the included studies using Microsoft Excel. Any disagreements or discrepancies were resolved through discussion. Each included RCT was abstracted for the first author, published date, country, study design, phase, study period, study period, number of patients, age, gender, ROX dose.

Risk of bias assessment

The risk of bias was assessed independently by two Reviewers (KS and NA) using The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials (22). The following items were evaluated: (I) Random sequence generation; (II) Allocation concealment; (III) Blinding of participants and personnel; (IV) Blinding of outcome assessment; (V) Incomplete outcome data; (VI) and Selective reporting. The trial was judged to be a low, unclear, or high risk of bias.

Outcomes of interest

The primary outcomes are changes in hemoglobin (Hb) level and iron utilization parameters, including ferritin, serum iron, TSAT, TIBC, transferrin, hepcidin, and Hb in reticulocytes. Secondary outcomes are treatment-emergent adverse effects (TEAEs) and serious adverse events.

Statistical analysis

We reported the outcomes of interest in risk ratios (RRs) for dichotomous outcomes and the standardized mean difference (SMD) for the continuous outcomes using the Mantel-Haenszel method, and both presented it along with the corresponding 95% confidence interval (CI). Heterogeneity was estimated using the Cochran Q test and measured using I2 statistics. The fixed-effects model was used in case of low heterogeneity ($P<0.10$ and $I^2<50\%$), whereas the random-effects model in case of high heterogeneity ($P\geq0.10$ and $I^2\geq50\%$) (23). We conducted a sensitivity analysis in which one study was excluded at a time to assess the impact of each study on the overall pooled effects on the Hg level

Egger regression test was used to assess publication bias (24) using the Comprehensive Meta-analysis program (CMA) (25). Subgroup analyses were carried out using the trial phase to identify potential moderators and their effect on the Hb level. Two authors (KSA and NA) performed the meta-analysis using RevMan manager v5.3 (26), and the results were reviewed by (BA and JS).

Results

Search results and study selection

As shown in the PRISMA flow diagram *Figure 1*, a total of 908 articles were identified from our literature search, with one more identified through other sources. Once we applied the inclusion and exclusion criteria, a total of 64 studies were chosen for full full-text review. Finally, we included ten RCTs in our systematic review and meta-analysis (14-16,27-33).

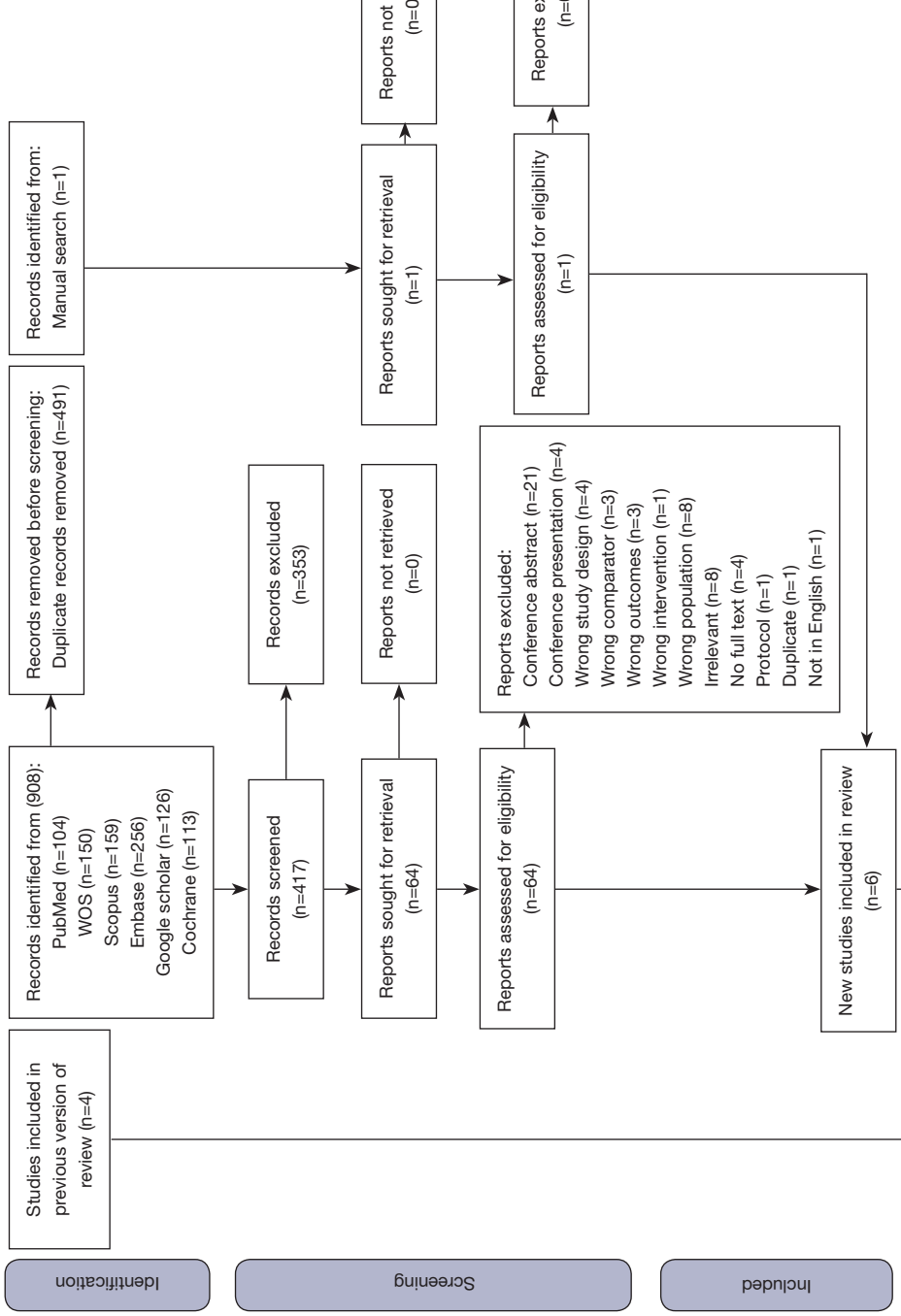


Figure 1 PRISMA 2020 flow diagram for updated systematic reviews, which included searches of databases, registers, and other sources.

Characteristics of included studies

Detailed characteristics of the individual studies and the patients' demographics are summarized in *Table 1*. Three studies in China (15,32,33), three studies in the United States of America (14,16,30), two studies in Japan (27,31), and two studies were global (28,29). One RCTs were double-blinded (31), and the rest were open-label. A total of six RCTs were phase 3 (14,16,28,29,31,32), three were phase 2 (27,30,33), and one was phase 4 (15). A total of 5768 patients were included, with 3031 patients in the ROX group compared to 2737 patients in the control group. All studies compared ROX to ESA. ROX doses range from 50 mg to 200 mg three times a week, and two studies use doses ranging from 1.0 to 2.3 mg/kg depending on body weight (30,33). The duration of the included studies ranged from 6 weeks up to 4 years. The average age of the included patients was 55 years, and 62% were male. In the ROX group, the Hg ranged from 8.4 to 11 g/dL, TSAT% ranged from 27% to 43%, ferritin ranged from 190.2 to 1,002.02 ng/mL, and finally, hepcidin ranged from 142.8 to 327.1 ng/mL. The baseline laboratory values of the included patients are summarized in Table S2. Five RCTs reported the role of ROX in the inflammatory process, and they assessed the C-reactive protein (CRP) as a factor (14-16,31,32). The patients were divided into two groups according to the upper limit of normal (ULN) for CRP. The ULN was 3 in (15,31) and 4.9 in (32). The CRP for most of the included patients was less than the ULN, and CRP was less in the ROX than the control group (Table S3).

Risk of bias of the included studies and publication bias

Figure 2 displayed a summary of the risk of bias assessment. Only Randomized control trials were included in this review. The risk of performance bias and detection bias was low in one RCTs (31), and the rest of the included RCTs were at a high risk of bias. Random sequence generation was low risk in seven RCTs (14-16,27,28,31) and unclear risk of bias in four RCTs (29,30,32,33). Allocation concealment was a low risk of bias in four RCTs (14,16,31,32), and six RCTs were unclear risk of bias (15,27-30,33). Attrition bias was low risk for all included RCTs, except one was high risk (14). Finally, the reporting bias was low risk for most of the included RCTs, except one had a high risk of bias, and one had an unclear risk of bias (16). Using Egg's test, no evidence of publication bias was found in any of the outcomes (Table S4).

Primary endpoints

Hemoglobin level

There was an increase in the Hb level in the ROX group when compared to the control group (SMD: 0.21; 95% CI: 0.02, 0.39; P=0.03) (*Figure 3*, Forest plot A). We performed sensitivity analysis by omitting one study at time. We found that were no difference between the ROX and control groups when we excluded Chen *et al.* (33) or Hou *et al.* (15), (SMD: 0.18; 95% CI: −0.01, 0.37; P=0.06), (SMD: 0.10; 95% CI: −0.04, 0.24; P=0.16), respectively (Table S5). This outcome was further subgrouped based on the RCTs trial phase 2 or 3, and no significant difference was found between the ROX and control group. Three RCTs were in phase two (SMD: 0.19; 95% CI: −0.18, 0.57; P=0.31) (27,30,33) and six RCTs were in phase three (SMD: 0.08; 95% CI: −0.07, 0.24; P=0.31) (14,28,29,31,32) (Figure S1).

Iron parameters

When compared to the control group, ROX showed decrease in hepcidin (SMD: −15.53; 95% CI: −28.07, −3.00; P<0.02) (*Figure 3*, Forest plot B). And ROX showed increase in TIBC (SMD: 0.79; 95% CI: 0.61, 0.98; P<0.00001) (*Figure 3*, Forest plot C), serum iron (SMD: 0.27; 95% CI: 0.18, 0.36; P<0.00001) (*Figure 3*, Forest plot D), transferrin (SMD: 0.98; 95% CI: 0.81, 1.15; P<0.00001) (*Figure 3*, Forest plot E). There was no difference between ROX and control group regarding ferritin level (SMD: −0.08; 95% CI: −0.21, 0.05; P=0.20) (*Figure 3*, Forest plot F), TSAT (SMD: 0.04; 95% CI: −0.04, 0.11; P=0. 33) (*Figure 3*, Forest plot G).

Secondary endpoints

Neither group showed any difference regarding the serious side effects (RR: 1.04; 95% CI: 0.99, 1.10; P=0.11) (*Figure 4*, Forest plot A). However, the ROX group showed higher TEAEs when compared to the control group (RR: 1.03; 95% CI: 1.01, 1.05; P=0.002) (*Figure 4*, Forest plot B).

The ROX group showed more gastrointestinal adverse effects compared to the control group (RR: 1.40; 95% CI: 1.04, 1.88; P=0.03) (*Figure 4*, Forest plot C). However, there was no difference between both groups regarding cardiovascular adverse effects; injury, poisoning, and procedural complications; muscle spasm; infection or infestation; upper respiratory tract infections; hypertension; and hyperkalemia (Figures S2-S8).

Table 1 Baseline characteristics and summary of the included studies

Study name	Country [n of sites]	Study design	Study period	Groups	Patients number	Age (years)	Male, n (%)	Body weight (kg)	Roxadustat dose	Study duration (weeks)	Trial phase	Duration of dialysis
Akizawa *et al.* 2020 (31)	Japan [58]	Double-blinded RCT	2016–2018	Roxadustat	150	64.6±11.7	101 (67.3)	57.82±11.97	(70 or 100 mg) TIW	24	3	>12 weeks
				DA	151	64.9±10.1	107 (70.9)	58.78±12.90				
Charytan *et al.* 2021 (16)	USA [76]	Open-label RCT	2015–2018	Roxadustat	370	57.6±13.6	187 (50.5)	84.3±22.3	(70–200) mg TIW	52	3	>3 months (dialysis for >2 weeks to >4 months at randomization)
				Epoetin alfa	371	58.4±13.3	215 (58.0)	86.6±23.0				
Chen *et al.* 2017 (33)	China [8]	Open-label RCT	2011–2012	Roxadustat	74	49.96±11.9	45 (60.8)	61.69±10.9	low weight:1.1; 1.8 mg/kg TIW medium weight: 1.5–2.3 mg/kg TIW; high weight: 1.7 –2.3 mg/kg TIW	6	2	≥4 months
				rhEPO	22	53.8±610.0	13 (95.1)	60.9±69.5				
Chen *et al.* 2019 (32)	China	Open-label RCT	2015–2016	Roxadustat	204	47.6±11.7	126 (61.8)	62.8±11.8	100 mg (45 to <60 kg) or 120 mg (≥60 kg)	26	3	≥16 weeks
				Epoetin alfa	100	51.0±11.8	58 (58.0)	61.5±9.9				
Provenzano *et al.* 2016 (30)	USA	Open-label, RCT	2010–2012	Roxadustat	67	56.9±12.1	45 (67.0)	86.6±22.5	1.0, 1.5, 1.8, or 2.0 mg/kg TIW	19	2	4 or more months
				Epoetin alfa	23	57.0±11.6	14 (61.0)	84.3±23.4				
Provenzano *et al.* 2021 (14)	USA	Open-label, RCT	2014–2018	Roxadustat	522	53.8±14.7	309 (59.2)	76.0±18.5	70, 100 mg	52	3	≥2 weeks and ≤4 months
				Epoetin alfa	521	54.3 ±14.6	307 (58.9)	76.7±19.1				
NCT02278341 (29)	Worldwide [150]	Open-label, RCT	2014–2018	Roxadustat	415	61±13.8	246 (59.3)	NR	100, 150, 200 mg	104	3	≥4 months
				ESA	421	61.8±13.4	236 (56.1)	NR				
Hou *et al.* 2021 (15)	China	Open-label, RCT	2019–2020	Roxadustat	86	48±12	47 (54.65)	NR	100 mg (45 to <60 kg) 120 mg (≥60 kg)	24	4	≥12 months
				ESA	43	48.3±13	25 (58.1)	NR				
NCT01888445 (27)	Japan [28]	Open-label, RCT	2013–2014	Roxadustat	95	62.1± 9.3	71 (74.7)	60.52±8.89	50, 70, 100 mg TIW	24	2	2–5weeks
				DA	32	60±7.9	22 (68.8)	61.29±10.8				
NCT02174731 (28)	18 countries [197]	Open-label, RCT	2014–2018	Roxadustat	1,048	53.5 ±15.30	625 (59.5)	NR	NR	4 years	3	2 weeks to 4 months
				Epoetin alfa	1,053	54.5±14.97	626 (59.3)	NR	NR			

Continuous variables are expressed in mean ± standard deviation. RCT, randomised control trial; DA, Darbepoetin Alfa; rhEPO, recombinant human erythropoietin; ESA, erythropoiesis-stimulating agent; TIW, three times a week; NR, not reported; N/A, not applicable.

Discussion

Ten RCTs were included in our updated meta-analysis to evaluate the safety and efficacy of ROX compared to ESA in DD-CKD patients with anemia. We concluded that ROX increases Hb level, but when we excluded Chen *et al.* (33) or Hou *et al.* (15), no difference between both groups was noted. DD-CKD patients will need higher doses of ESA to treat anemia, likely secondary to the effect of inflammation on ESA (34). Inflammation can increase hepcidin and impair erythropoiesis (35,36). So higher doses of ESA were used in the included RCTs, which can contribute to comparable effects in both groups. Another factor to be considered is the time of initiating dialysis and the ROX. Provenzano *et al.* and Charytan *et al.* conducted their study on patients on DD-CKS who started dialysis for more than two weeks and less than four months. They concluded that ROX increased Hb level by (mean ± SD) 2.57±1.27 and 0.39±0.93 compared to 2.36±1.21 and –0.09±0.84 in the epoetin alfa (EA) group (14,16), respectively. In addition, Chen *et al.* include patients who started dialysis for at least 16 weeks, and they found that ROX increased hemoglobin level by 0.7±1.1 compared to 0.5±1 in the EA group (32).

We also observed that ROX improved iron parameters by decreasing hepcidin and increasing TIBC, serum iron, and transferrin. There was no difference noted between the two groups regarding ferritin and TSAT. This effect contributed to the mobilization of iron stores by ROX. ROX acts as an iron sensor and regulator by stimulating the genes involved in iron metabolism, leading to a decrease in hepcidin and an increase in cellular transferrin uptake and transferrin receptor, which increase iron absorption from the intestine. Also, ROX will promote heme-oxygenase-1 and ferroportin, which will help in iron oxidation and recycling of iron, respectively (10). Hepcidin is described by Ruchala *et al.* to be "iron gatekeeper or ferrostat" due to its regulatory action on iron reflux (37). Hepcidin works on iron sequestration in macrophage and hepatocytes, limiting its absorption in the intestine.

Moreover, hepcidin downregulates ferroportin preventing iron reflux (38). Erythropoietic stimulators negatively regulate hepcidin (39). Newly discovered drugs like ROX bind to HIF-prolyl hydroxylase enzymes, inhibiting their action with subsequent increase in HIF concentration. HIF increases expression of erythropoietin, works on a 3' enhancer of the erythropoietin gene, reduces hepcidin, and regulates genes responsible for iron metabolism (40,41).

Our results also showed that ROX had higher TEAEs when compared to the ESA. Still, there was no difference between both groups regarding the serious side effects indicating similar safety concerns between both groups. Hyperkalemia is one of the TEAEs, and studies showed different incidences. Charytan *et al.* reported an almost similar percentage of hyperkalemia between the ROX group, 16.2%, compared with 15.1% in the EA group (16). Some studies showed a low incidence of hyperkalemia in the ROX group compared with EA (5% *vs.* 7%) (14). However, other studies showed higher incidence in the ROX group, such as Hou *et al.*, who reported 9% in the ROX group and 5% in the ESA group suffered from hyperkalemia (15). In our meta-analysis, there was no difference between ROX and the control group regarding hyperkalemia.

Gastrointestinal disorder is a common adverse event, and it occurs at a higher rate in the ROX group (14,15,31,32). And our results confirmed that the ROX group had higher gastrointestinal adverse effects compared to the control group. In Charytan *et al.*, a higher rate of diarrhea and constipation in the EA group were observed (16), and in NCT01888445 higher incidence in gastrointestinal disorders were reported in the darbepoetin alfa group (27). Upper respiratory tract infection and nasopharyngitis are common TEAEs and usually occurred in the ROX group more frequently than in the control group (14-16). In addition, hypertension occurred more frequently in the ROX group than in the EA group (14,16); while, it was also reported to occur in a lower incidence in the ROX group (15,32,33).

ESA therapy is associated with an increased risk of cardiovascular adverse events (9,42). Our results showed no significant difference between ROX and the control group regarding cardiovascular adverse events. However, few of the included studies were not powered to detect the cardiovascular adverse effects like Akizawa *et al.* In other RCTs, the included patients with any cardiovascular events in the past were excluded (33). However, Provenzano *et al.* 2016, reported three deaths for patients who had significant cardiovascular risks, but none of the deaths was attributed to ROX. Clearly, further research will be needed to validate the cardiovascular effects of ROX.

However, ROX was well tolerated, and the patients were more compliant with it due to the oral route of the medication compared to the subcutaneous route in the ESA. In addition, iron supplementation is associated with iron overload and hypersensitivity reaction, which ROX can avoid (35).

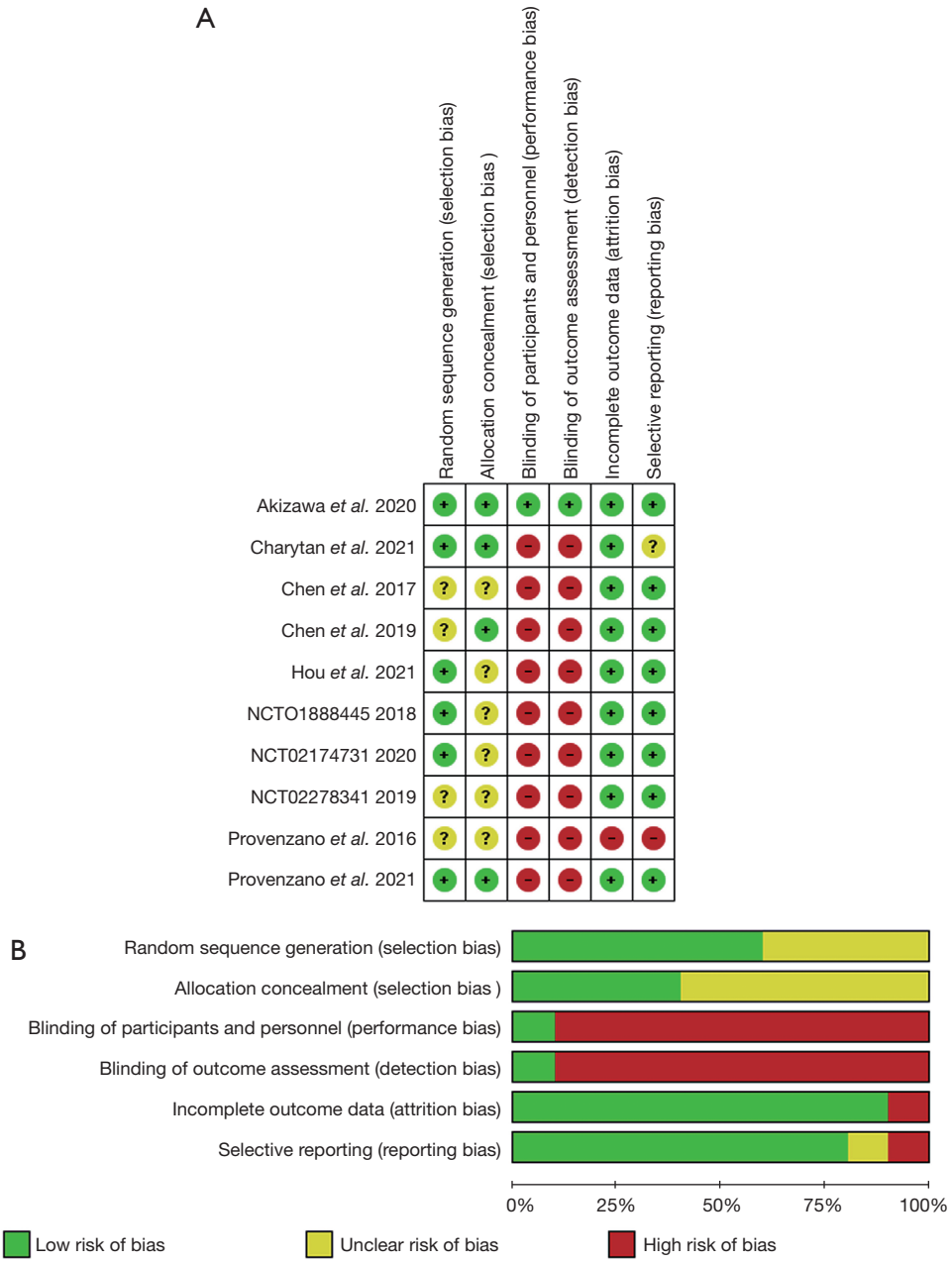
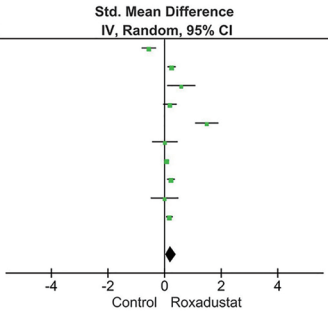


Figure 2 Risk of bias assessment. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. The items are scored (+) low risk; (-) high risk; (?) unclear risk of bias. (B) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

A **Forest plot of comparison: 1 Primary Outcomes, outcome: 1.1 Hemoglobin.**

Study or Subgroup	Roxadustat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Akizawa et al. 2020	-0.4	0.654	114	-0.03	0.672	131	10.5%	-0.56 [-0.81, -0.30]
Charytan et al. 2021	0.39	0.93	370	0.17	0.84	371	12.2%	0.25 [0.10, 0.39]
Chen et al. 2017	0.84	1.18	60	0.17	0.96	22	6.7%	0.59 [0.09, 1.09]
Chen et al. 2019	0.7	1.1	204	0.5	1	100	10.8%	0.19 [-0.05, 0.43]
Hou et al. 2021	2.5	0.2	86	2.2	0.2	43	8.0%	1.49 [1.08, 1.90]
NCT01888445. 2018	1.43	0.91	63	1.42	1.02	27	7.4%	0.01 [-0.44, 0.46]
NCT02174731. 2020	0.77	1.298	1003	0.68	1.275	1016	12.8%	0.07 [-0.02, 0.16]
NCT02278341. 2019	0.363	0.778	413	0.192	0.737	420	12.3%	0.23 [0.09, 0.36]
Provenzano et al. 2016	-0.5	1.562	61	-0.5	1.407	22	6.9%	0.00 [-0.49, 0.49]
Provenzano et al. 2021	2.57	1.27	522	2.36	1.21	521	12.5%	0.17 [0.05, 0.29]
Total (95% CI)			**2896**			**2673**	**100.0%**	**0.21 [0.02, 0.39]**

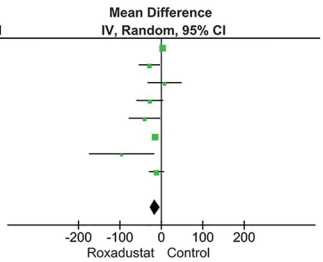
Heterogeneity: Tau² = 0.07; Chi² = 80.35, df = 9 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.22 (P = 0.03)



B **Forest plot of comparison: 1 Primary Outcomes, outcome: 1.2 Hepcidin.**

Study or Subgroup	Roxadustat Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akizawa et al. 2020	2.308	27.279	150	-0.6	27.061	151	23.1%	2.91 [-3.23, 9.05]
Charytan et al. 2021	-95.53	148.27	230	-66.66	141.61	265	12.1%	-28.87 [-54.52, -3.22]
Chen et al. 2017	-70.2	104.19	60	-77.9	75.18	22	6.8%	7.70 [-33.31, 48.71]
Chen et al. 2019	-30.2	113.3	155	-2.3	130.7	90	9.3%	-27.90 [-60.26, 4.46]
Hou et al. 2021	-46.6	79.7	57	-5.9	87.6	29	7.5%	-40.70 [-78.71, -2.69]
NCT02278341. 2019	-32.709	42.342	310	-17.522	47.307	357	22.8%	-15.19 [-21.99, -8.38]
Provenzano et al. 2016	-60.4	187.8	46	35.6	123.4	18	2.3%	-96.00 [-174.71, -17.29]
Provenzano et al. 2021	-67.78	112.71	356	-55.96	135.32	372	16.2%	-11.82 [-29.88, 6.24]
Total (95% CI)			**1364**			**1304**	**100.0%**	**-15.53 [-28.07, -3.00]**

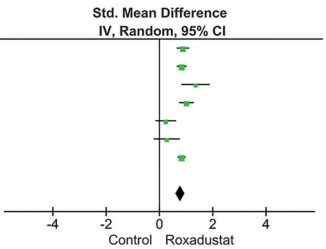
Heterogeneity: Tau² = 167.55; Chi² = 28.65, df = 7 (P = 0.0002); I² = 76%
Test for overall effect: Z = 2.43 (P = 0.02)



C **Forest plot of comparison: 1 Primary Outcomes, outcome: 1.3 TIBC.**

Study or Subgroup	Roxadustat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Akizawa et al. 2020	7.8	8.1	150	1.6	5.7	151	16.8%	0.88 [0.65, 1.12]
Charytan et al. 2021	252.09	50.04	235	214.66	39.94	272	19.0%	0.83 [0.65, 1.01]
Chen et al. 2017	50.5	41.3	60	0.5	17.4	22	8.0%	1.35 [0.82, 1.89]
Chen et al. 2019	10	11.9	159	-1.1	9	93	15.5%	1.01 [0.74, 1.28]
Hou et al. 2021	7.1	15.7	78	2.6	24.4	39	11.6%	0.24 [-0.15, 0.62]
Provenzano et al. 2016	37.6	41.4	61	25.6	47.3	22	8.9%	0.28 [-0.21, 0.77]
Provenzano et al. 2021	37.7	43.1	364	1.65	43.641	383	20.2%	0.83 [0.68, 0.98]
Total (95% CI)			**1107**			**982**	**100.0%**	**0.79 [0.61, 0.98]**

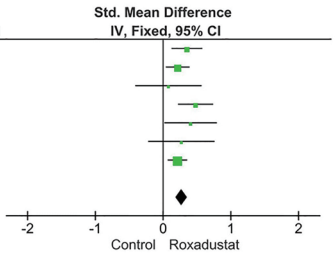
Heterogeneity: Tau² = 0.04; Chi² = 19.71, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 8.34 (P < 0.00001)



D **Forest plot of comparison: 1 Primary Outcomes, outcome: 1.4 Serum Iron.**

Study or Subgroup	Roxadustat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Akizawa et al. 2020	1.2	6.4	150	-0.9	5.5	151	14.8%	0.35 [0.12, 0.58]
Charytan et al. 2021	6.95	32.47	238	0.35	28.81	273	25.2%	0.22 [0.04, 0.39]
Chen et al. 2017	3.1	43	60	0	26.7	22	3.2%	0.08 [-0.41, 0.57]
Chen et al. 2019	0.1	8.3	160	-3.7	7.2	94	11.5%	0.48 [0.22, 0.74]
Hou et al. 2021	0.8	5.9	78	-1.4	4.2	39	5.1%	0.40 [0.02, 0.79]
Provenzano et al. 2016	5.2	42.2	61	-5.5	30.2	22	3.2%	0.27 [-0.22, 0.76]
Provenzano et al. 2021	2.14	32.24	364	-4.72	32.53	384	37.0%	0.21 [0.07, 0.36]
Total (95% CI)			**1111**			**985**	**100.0%**	**0.27 [0.18, 0.36]**

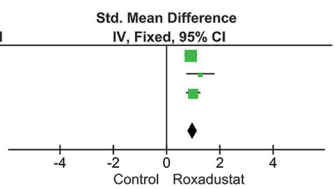
Heterogeneity: Chi² = 5.07, df = 6 (P = 0.54); I² = 0%
Test for overall effect: Z = 6.08 (P < 0.00001)



E **Forest plot of comparison: 1 Primary Outcomes, outcome: 1.5 Transferrin.**

Study or Subgroup	Roxadustat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Akizawa et al. 2020	0.418	0.393	150	0.105	0.288	151	50.5%	0.91 [0.67, 1.14]
Chen et al. 2017	0.495	0.409	60	0.033	0.161	22	10.2%	1.27 [0.74, 1.80]
Chen et al. 2019	0.4	0.48	160	-0.04	0.36	94	39.3%	1.00 [0.73, 1.27]
Total (95% CI)			**370**			**267**	**100.0%**	**0.98 [0.81, 1.15]**

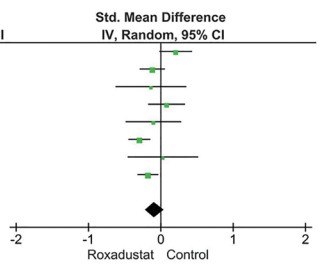
Heterogeneity: Chi² = 1.53, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 11.38 (P < 0.00001)



F **Forest plot of comparison: 1 Primary Outcomes, outcome: 1.6 Ferritin.**

Study or Subgroup	Roxadustat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Akizawa et al. 2020	-3.98	78.41	150	-18.75	64.64	151	14.1%	0.21 [-0.02, 0.43]
Charytan et al. 2021	-429.91	340.16	238	-389.52	341.11	273	17.1%	-0.12 [-0.29, 0.06]
Chen et al. 2017	-95	189	60	-70	157	22	5.5%	-0.14 [-0.63, 0.35]
Chen et al. 2019	-119	208	160	-136	220	94	12.6%	0.08 [-0.18, 0.33]
Hou et al. 2021	-55.5	299.5	78	-27.6	192.3	39	7.8%	-0.10 [-0.49, 0.28]
NCT02278341. 2019	-615.19	677.97	318	-347.58	1,058.87	365	18.5%	-0.30 [-0.45, -0.15]
Provenzano et al. 2016	-201.1	334.4	61	-211.6	445.2	22	5.5%	0.03 [-0.46, 0.52]
Provenzano et al. 2021	-198.47	311.7	362	-141.13	328.52	381	18.9%	-0.18 [-0.32, -0.03]
Total (95% CI)			**1427**			**1347**	**100.0%**	**-0.08 [-0.21, 0.05]**

Heterogeneity: Tau² = 0.02; Chi² = 16.51, df = 7 (P = 0.02); I² = 58%
Test for overall effect: Z = 1.27 (P = 0.20)



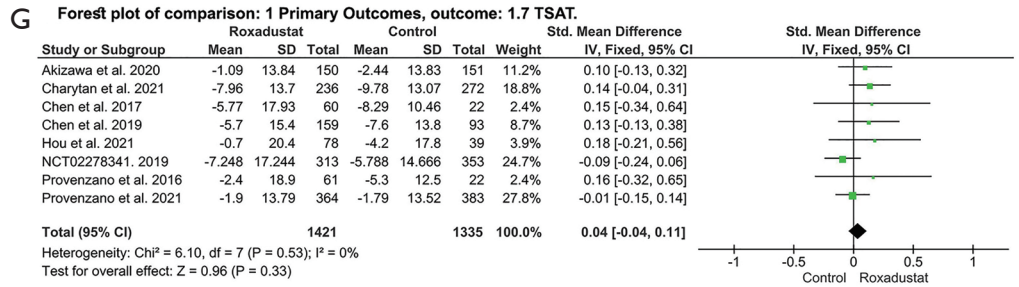


Figure 3 Forest plots of the primary outcomes. Hemoglobin (g/dL); hepcidin (ng/mL); TIBC (μmol/L); serum iron (μmol/L); transferrin (g/L); ferritin (ng/mL); TSAT (%). df, degrees of freedom; IV, inverse variance; CI, confidence interval.

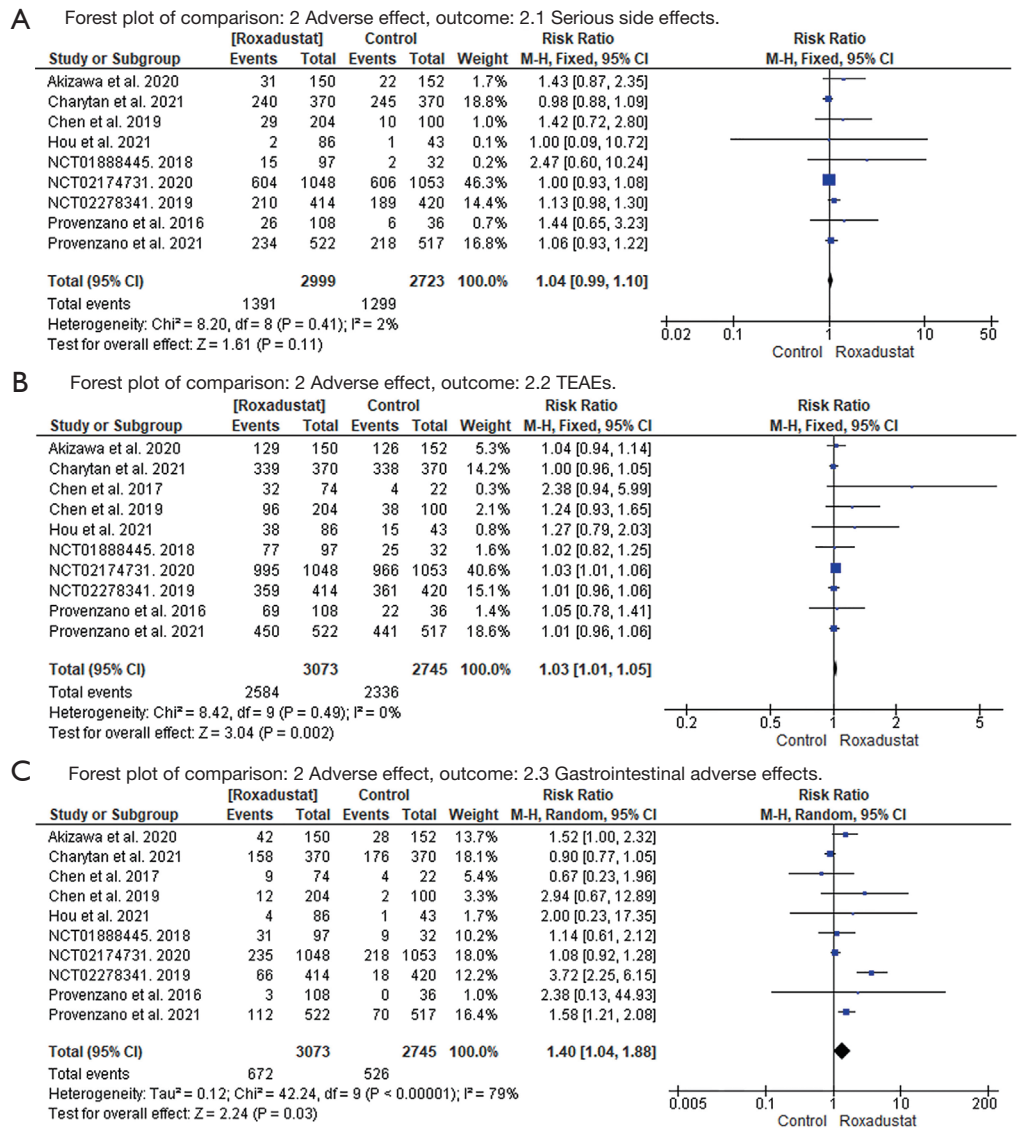


Figure 4 Forest plots of the secondary outcomes. TEAEs, treatment-emergent adverse effects; df, degrees of freedom; M-H, Mantel-Haenszel; CI, confidence interval.

The previous meta-analysis of RCTs by Tang *et al.* (43) included seven RCTs with a total of 4,810 DD-CKD patients. They concluded that ROX was associated with increased hemoglobin level [weighted mean difference (WMD): 0.14; 95% CI:0.05–0.23; P<0.001], transferrin level (WMD: 0.40; 95% CI: 0.30–0.50; P<0.00001), and TIBC level (WMD: 43.65; 95% CI:33.78–53.53; P<0.00001) and lowered the hepcidin level (WMD: −11.49 ng/mL; 95% CI: −14.58, −8.41; P<0.00001) and lowered the ferritin and TAST levels in DD-CKD patients. Also, they reported that there is no difference between the treatment-emergent adverse events (TEAEs) of ROX and ESAs or placebo except for serious TEAEs, which was higher in the ROX group (OR: 1.12; 95% CI: 0.99–1.26; P<0.07). Tang *et al.* published their article before the release of Hou *et al.* (15), which limits their ability to assess and evaluate the article. They also used weighted mean difference during their meta-analysis; although different RCTs reported different measurement units and reference ranges, meanwhile we used standardized mean difference. We only did our meta-analysis on DD-CKD to focus on this patient's group, and we were able to do a detailed meta-analysis with all possible shared outcomes between the included RCTs and detailed sensitivity and subgroup analyses. We are currently conducting another updated systematic review and meta-analysis to assess the efficacy of ROX in treating anemia in non-dialysis-dependent CKD and was registered at OSF Registries with DOI 10.17605/OSF.IO/WGZ6C.

Strength and limitations

To reduce the possibility of heterogeneity, we conducted our meta-analysis on DD-CKD patients. We comprehensively searched the literature and included 10 RCTs, one of which is a recent phase 4 trial (15) that had not previously been included in any systematic review and meta-analysis. As a result, we were able to assess publication bias using Egger's test, which many previous systematic reviews on the same topic could not do. The included RCTs spanned various ethnicities and geographical locations, allowing us to generalize the meta-analysis findings. However, our study has significant limitations. First, all of the trials included -except one (31) are open-label, which may increase performance bias. Second, different ROX dosages were used in the included RCTs, which may have resulted in some heterogeneity. Third, the majority of the included studies were financed by pharmaceutical manufacturers, which may have resulted in some bias. Finally, although the included studies reflect short-term findings, a long-term evaluation of the medication and its effect is also required. As a result, more high-quality, multinational, phase 3 and phase 4 studies with long-term evaluation and a large population are still required.

Conclusions

Our review included ten RCTs to assess the effect of ROX on DD-CKD patients with anemia. We conclude that ROX was associated with increased Hb level and improved iron utilization parameters by increasing TIBC, serum iron, transferrin, and decreasing hepcidin. In addition, ROX was associated with higher TEAEs and no difference between both groups regarding the serious side effects. However, higher-quality RCTs are still needed to confirm the results of our review.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting Checklist. Available at https://dx.doi.org/10.21037/atm-21-4357

Peer Review File: Available at https://dx.doi.org/10.21037/atm-21-4357

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-4357). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The informed consent was waived because this study was a meta-analysis of previously published RCTs and did not involve any processing of individual patient data.

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Supplementary

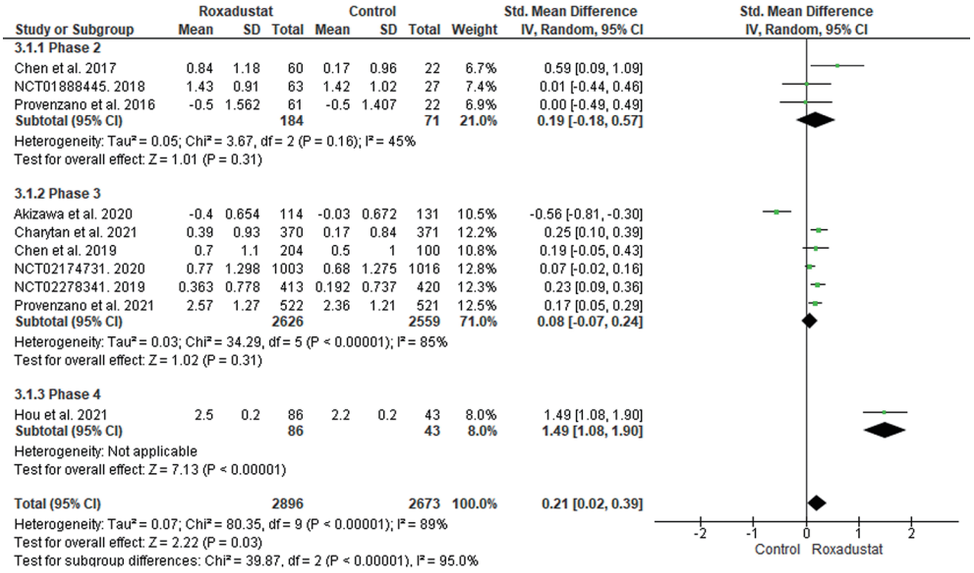

Figure S1 Forest plot of the Subgroup analysis.

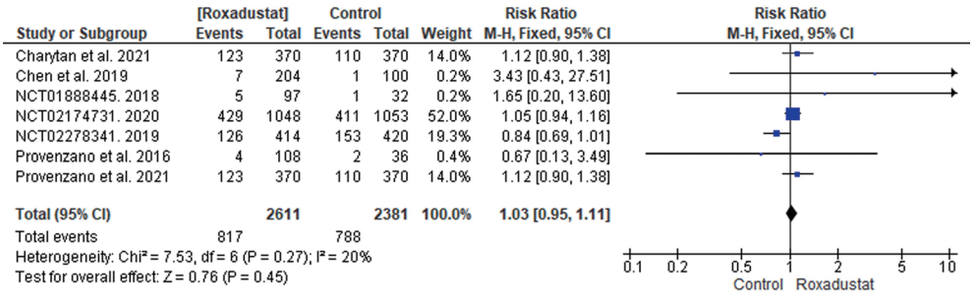

Figure S2 Forest plot of comparison: 2 Adverse effects, outcome: 2.4 Cardiovascular adverse effects.

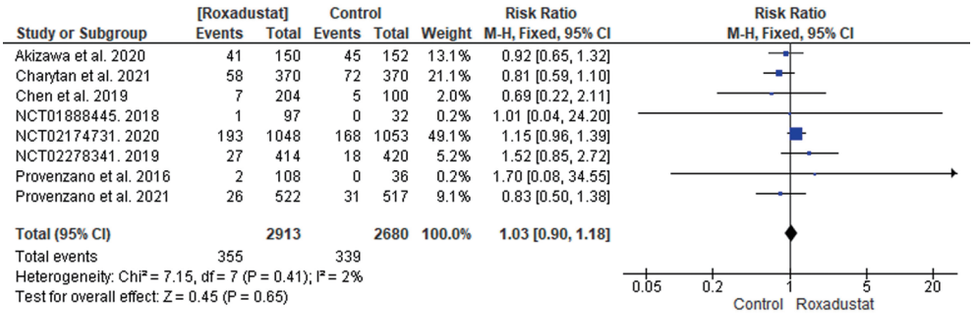

Figure S3 Forest plot of comparison: 2 Adverse effects, outcome: 2.5 Injury, poisoning, and procedural complications.

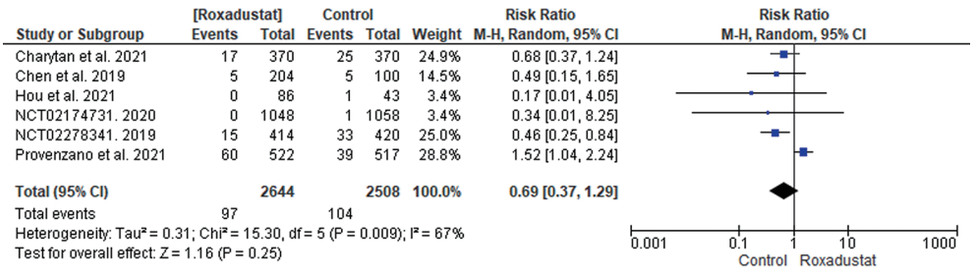

Figure S4 Forest plot of comparison: 2 Adverse effects, outcome: 2.6 Muscle spasm.

https://dx.doi.org/10.21037/atm-21-4357

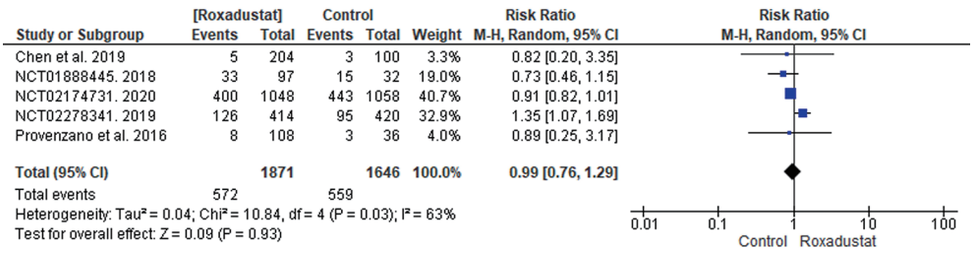

Figure S5 Forest plot of comparison: 2 Adverse effects, outcome: 2.7 Infection or infestation.

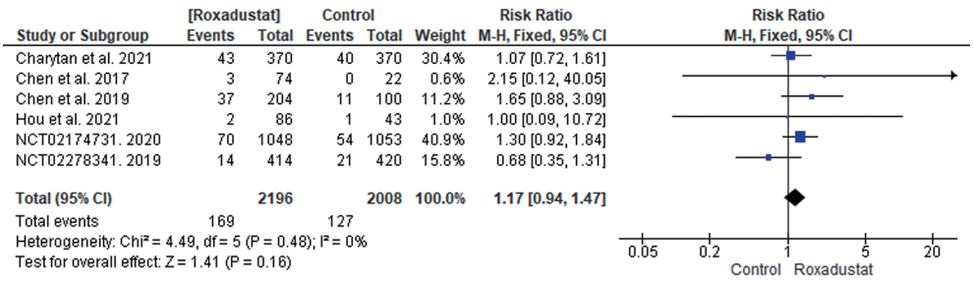

Figure S6 Forest plot of comparison: 2 Adverse effects, outcome: 2.8 Upper respiratory tract infections.

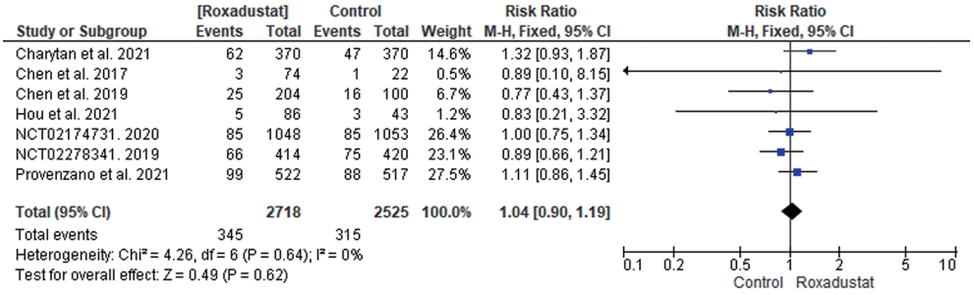

Figure S7 Forest plot of comparison: 2 Adverse effects, outcome: 2.9 Hypertension.

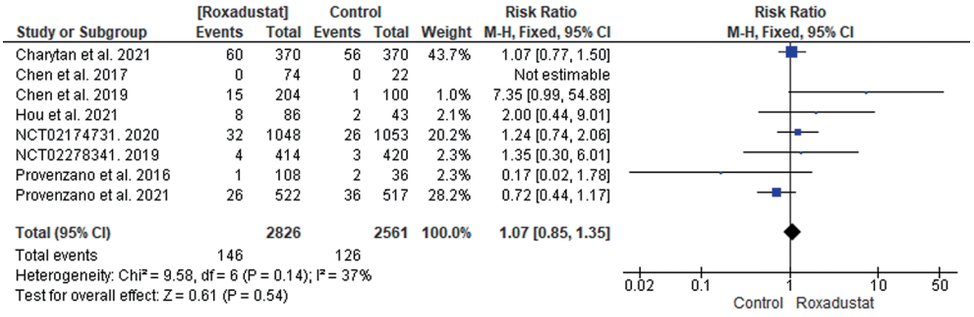

Figure 8 Forest plot of comparison: 2 Adverse effects, outcome: 2.10 Hyperkalemia.

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Table S1 Search terms and results in different databases

Database name	Search terms	Search fields	Result
PubMed	(Roxadustat OR ASP1517 OR FG4592 OR "FG-4592") AND (kidney OR renal) AND (Anemia)	All Field	104
Web Of Science	(Roxadustat OR ASP1517 OR FG4592 OR "FG-4592") AND (kidney OR renal) AND (Anemia)	Topic	150
Scopus	(Roxadustat OR ASP1517 OR FG4592 OR "FG-4592") AND (kidney OR renal) AND (Anemia)	Title, Abstract, Keywords	159
Cochrane	((Roxadustat) OR (ASP1517) OR (FG4592) OR (FG-4592)) AND ((kidney) OR (renal)) AND ((Anemia))	Title, Abstract Keyword	113
Embase	(roxadustat OR asp1517 OR fg4592 OR 'fg 4592') AND (kidney OR renal) AND anemia	All Field	256
Google Scholar	with all of the words: Roxadustat OR FG4592 OR "FG-4592" with at least one of the words: kidney anemia In the title of the article		126

Table S2 The baseline laboratory values of the included patients

Study	Group	Hb level (g/dL), Mean ± SD	TSAT (%), Mean ± SD	Ferritin (ng/mL), Mean ± SD	Hepcidin (ng/mL), Mean ± SD	TIBC (μg/dL), Mean ± SD
Charytan *et al.* 2021	Roxadustat	10.30 ± 0.66	33.60 ± 10.10	1002.02 ± 459.68	272.85 ± 129.70	201.88 ± 33.56
	Epoetin alfa	10.31 ± 0.66	33.65 ± 9.86	959.24 ± 414.30	270.67 ± 134.52	202.89 ± 36.81
Chen *et al.* 2017	Roxadustat	10.8 ± 0.7	31.6 ± 16.7	450.5 ± 368.2	176.3 ± 120	217.3 ± 49.6
	rhEPO	10.6 ± 61.0	34.1 ± 14.6	458 ± 361	209.0 ± 127.1	214 ± 38
Chen *et al.* 2019	Roxadustat	10.4 ± 0.7	33.8 ± 16.6	498.5 ± 487.4	NR	264.7 ± 63.7
	Epoetin alfa	10.5 ± 0.7	30.0 ± 13.8	420.1 ± 406.8	NR	269.7 ± 50.3
Provenzano *et al.* 2016	Roxadustat	11.2 ± 0.7	29.2 ± 10.0	827.7 ± 474.3	327.1 ± 178.8	199.7 ± 34.0
	Epoetin alfa	11.2 ± 1.0	28.1 ± 14.4	1065.8 ± 657.2	298.7 ± 123.1	202.1 ± 26.7
Provenzano *et al.* 2021	Roxadustat	8.4 ± 1.0	27.02 ± 9.27	441.38 ± 337.02	173.21 ± 120.21	241.04 ± 43.00
	Epoetin alfa	8.5 ± 1.0	27.55 ± 8.90	436.65 ± 311.67	169.91 ± 127.98	238.06 ± 37.04
NCT02278341	Roxadustat	10.75 ± 0.62	NR	NR	NR	NR
	ESA	10.77 ± 0.62	NR	NR	NR	NR
Hou *et al.* 2021	Roxadustat	9.0 ± 1.4	31.3 ± 14.2	268.8 ± 297.2	142.8 ± 112.5	237.3 ± 65.3
	ESA	9.0 ± 1.2	29.6 ± 13.2	257.4 ± 190.8	122.0 ± 82.2	230.6 ± 83.2
Nct01888445	Roxadustat	8.84 ± 0.47	43.66 ± 16.01	190.20 ± 187.67	NR	226.2 ± 35.2
	DA	8.8 ± 0.51	37.26 ± 16.06	156.99 ± 102.49	NR	234.5 ± 32.9
Nct02174731	Roxadustat	NR	NR	NR	NR	NR
	Epoetin alfa	NR	NR	NR	NR	NR
Akizawa *et al.* 2020	Roxadustat	11.02 ± 0.56	28.28 ± 11.70	102.31 ± 83.45	26.44 ± 21.50	242.4 ± 39.1
	DA	11.01 ± 0.60	29.04 ± 10.18	96.28 ± 75.14	24.44 ± 20.99	242.9 ± 34.6

DA, Darbepoetin Alfa; rhEPO, recombinant human erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; SD, standard deviation; TIBC, total iron-binding capacity; TSAT, transferrin saturation; NR, not reported.

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Table S3 The studies assessed C-reactive protein

Study	Group	CRP, Number of patients (%)	
		≤ULN	>ULN
Charytan *et al.* 2021	Roxadustat	178 (48.1%)	189 (51.1%)
	Epoetin alfa	192 (51.8%)	177 (47.7%)
Chen *et al.* 2019	Roxadustat	158 (77.5%)	46 (22.5%)
	Epoetin alfa	80 (80.0%)	20 (20.0%)
Provenzano *et al.* 2021	Roxadustat	289 (55.4%)	228 (43.7%)
	Epoetin alfa	289 (55.5%)	226 (43.4%)
Hou *et al.* 2021	Roxadustat	48 (56%)	38 (44%)
	ESA	25 (58%)	18 (42%)
Akizawa *et al.* 2020	Roxadustat	<ULN, 136 (90.7%) ≥ULN, 14 (9.3%)	
	DA	<ULN, 129 (85.4%) ≥ULN, 22 (14.6%)	

DA, Darbepoetin Alfa; ESA, erythropoiesis-stimulating agent; CRP, C-reactive protein; ULN, upper limit of normal.

Table S4 Publication bias using Egger's regression

Outcome	Intercept	Standard error	Lower limit	Upper limit	t-value	P-value
Hemoglobin	1.26	1.89	-3.09	5.62	0.669	0.523
Ferritin	1.629	1.3211	-1.604	4.86	1.233	0.264
TSAT	1.382	0.7	-0.33	3.1	3.1	0.1
Hepcidin	-0.43	1.4	-3.84	2.99	0.306	0.77
TIBC	-0.95	1.82	-5.63	3.74	0.52	0.63
Serum Iron	0.63	0.9	-1.68	2.94	0.7	0.52
Transferrin	2.46	0.574	-4.833	9.76	4.29	0.146
TEAEs	0.6	0.87	-0.141	2.603	0.689	0.511
Serious TEAEs	0.985	0.421	-0.01	1.98	2.341	0.052

TSAT, transferrin saturation; TIBC, total iron-binding capacity; TEAEs, treatment-emergent adverse effects

Table S5 Meta-analysis of the primary outcomes and sensitivity analysis

Outcome	No. of participants Roxadustat/Control)	No. of trials	Quantitative data synthesis				Heterogeneity analysis		
			SMD	95% CI	Z value	P value	df	P value	I^2 (%)
Hemoglobin level									
All studies	2896/2673	10	0.21	[0.02, 0.39]	2.22	0.03	9	0.00001	89
Omitting Akizawa et al. 2020	2782/2542	9	0.29	[0.12, 0.45]	3.43	0.0006	8	0.00001	84
Omitting Charytan et al. 2021	2526/2302	9	0.21	[-0.00, 0.42]	1.92	0.05	8	0.00001	90
Omitting Chen et al. 2017	2836/2651	9	0.18	[-0.01, 0.37]	1.87	0.06	8	0.00001	90
Omitting Chen et al. 2019	2692/2573	9	0.21	[0.01, 0.42]	2.07	0.04	8	0.00001	90
Omitting Hou et al. 2021	2810/2630	9	0.10	[-0.04, 0.24]	1.40	0.16	8	0.00001	79
Omitting NCT01888445. 2018	2833/2646	9	0.23	[0.03, 0.42]	2.27	0.02	8	0.00001	90
Omitting NCT02174731. 2020	1893/1657	9	0.24	[0.00, 0.47]	2.00	0.05	8	0.00001	89
Omitting NCT02278341. 2019	2483/2253	9	0.21	[-0.00, 0.43]	1.93	0.05	8	0.00001	90
Omitting Provenzano et al. 2016	2835/2651	9	0.23	[0.03, 0.42]	2.28	0.02	8	0.00001	90
Omitting Provenzano et al. 2021	2374/2152	9	0.22	[-0.00, 0.45]	1.95	0.05	8	0.00001	90

CI, confidence interval; df, degrees of freedom; SMD, standardized mean difference.

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