Cardiovascular and renal safety outcomes of Hypoxia-inducible factor Prolyl-Hydroxylase Inhibitor Roxadustat for Anemia patients with chronic kidney disease: a systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis were conducted to evaluate the cardiac and kidney-related adverse effects of Roxadustat for the treatment of anemia in CKD patients. 17 trials with a total of 6673 participants were identified for analysis. Meta-analysis revealed no significant difference in the risk of occurrence of cardiac disorders when comparing CKD patients receiving Roxadustat with the placebo group (RR=1.049; CI [0.918 to 1.200]) or ESA (RR = 1.099; CI [0.907 to 1.331]) group, in both dialysis-dependent (DD) (RR = 1.181; CI [0.925 to 1.507]) or non-dialysis-dependent (NDD) (RR = 1.036; CI [0.916 to 1.171]) CKD patients. No significant difference was observed in the risk of kidney-related adverse events when comparing groups receiving Roxadustat with the placebo group (RR=1.088; CI [0.980 to 1.209]) or ESA group (RR = 0.968; CI [0.831 to 1.152]), in DD (RR = 2.649; CI [0.201 to 34.981]) or NDD (RR = 1.053; CI [0.965 to 1.149]) CKD patients. No significant risk of hyperkalemia was observed in the Roxadustat group whether in DD (RR = 1.145; CI [0.756 to 1.734]) or NDD (RR = 1.116; CI [0.930 to 1.339]) patients. Incidence of hypertension was higher in the Roxadustat group, compared to the placebo group (RR = 1.374; CI [1.153 to 1.638]). In summary, the risk of cardiac or kidney-related events observed in the Roxadustat was not significantly increase whether in DD or NDD patients. However, attention must be paid to the occurrence of hypertension in patients using Roxadustat.

Introduction

Chronic kidney disease (CKD) is an epidemic with global prevalence which can be attributed to the rising incidence of diabetes, hypertension, and obesity, as well as an aging population. Regardless of the underlying etiology, CKD poses a serious threat to human health because of its slow progress that leads to an irreversible loss of kidney units, and patients typically progress to end-stage kidney disease (ESKD) or death within 3-5 years of diagnosis. Globally, over 30,000 deaths annually are attributed to CKD[1]. Anemia, which is a major and clinically significant complication in patients with CKD is associated with a variety of adverse clinical outcomes such as increased risk of cardiovascular disease (CVD), hospitalization, and mortality [2, 3].

Currently, the main approach for correcting CKD associated anemia is the use of injectable erythropoiesis-stimulating agents (ESAs), administered either intravenously (IV) or subcutaneously (SC), as well as oral or IV supplemental iron therapy [4]. We have henceforth used the term ESA to encompass short-acting recombinant human erythropoietin (rhEPO; epoetin), intermediate-acting darbepoetin alfa, and long-acting epoetin beta pegol. ESA is effective for most patients, however, anemia continues to afflict CKD patients. This is partly attributed to limited response to ESA observed in some CKD patients. The most common causes

of ESA hyporesponsiveness include iron deficiency and inflammation, as well as secondary hyperparathyroidism, inadequate dialysis, and malnutrition [5]. ESA treatment does not enhance clinical outcomes in CKD patients with systolic heart failure or in patients with mild to moderate anemia. Moreover, a previously conducted study has reported that higher doses of ESA are associated with an enhanced risk of all-cause mortality and hypertension, independent of Hb levels [6]. In unadjusted analyses, failure to achieve target Hb and the use of high-dose darbepoetin were also observed to be significantly associated with increased risks of major endpoints, composite death, cardiovascular events (myocardial infarction, congestive heart failure), or stroke[7]. Recognizing this risk, the U.S. Food and Drug Administration updated ESA product labels in 2011, including a black box warning to flag the risk of death, serious adverse cardiovascular effects, and stroke when hemoglobin levels reached 11 g/dL added[8-12]. The high cost of recombinant ESA is also an issue in addition to its safety issues [13, 14], although concomitant iron supplementation may prove cost effective in reducing ESA dosage. However, excessive iron supplementation can cause an iron overload and can increase the risk of incidence of CVD and mortality in hemodialysis patients [15]. Hence, there is an urgent need to develop a safe and effective drug for correcting renal anemia, which can be used long-term without enhancing the risk of cardiovascular events in CKD patients.

Roxadustat is a novel orally administered, small molecule hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor that is used to treat anemia in patients with DD and NDD CKD. This drug works by reversibly binding and inhibiting HIF-prolyl hydroxylase, an enzyme responsible for degrading transcription factors in the HIF family under normal oxygen conditions. Inhibition of these enzymes may cause a reduction in HIF degradation, thereby promoting HIF activity and resulting in enhanced endogenous erythropoietin production and increased erythropoiesis. For NDD CKD anemia patients, Roxadustat dose-dependently elevates hemoglobin (Hb) levels, significantly decreases ferritin levels, and briefly increases endogenous EPO levels within or near the physiological range compared with placebo at high doses. Additionally, the orally administered Roxadustat reduces iron metabolism disorders in DD and NDD CKD-related anemia patients by elevating serum transferrin, enhancing intestinal iron absorption, as well as releasing stored iron [16, 17]. In a Phase three study, the efficacy and safety of Roxadustat was favorable when compared to that of the placebo and ESA, leading to its approval for the treatment of NDD and DD CKD in Chile, China, the European Union (EU), Japan and South Korea[18-21]. However, until now, no systematic review integrating and assessing the safety of Roxadustat on cardiovascular and renal events has been performed. Therefore, we conducted this systematic review and meta-analysis to summarize and assess the effects of oral Roxadustat on the incidence of cardiac and renal-related advance events (AEs) in anemia of CKD in patients for further evidence.

Results

Characteristics of included trials

The trial selection was done in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement flowchart demonstrated in Figure 1. To begin with, initial literature searches from PubMed, Embase and the Cochrane library helped us identify 991 articles, 294 of which were duplicates. Of the remaining 697 articles, 445 articles were excluded after reviewing their titles and/or abstract, leaving 252 articles to be further assessed via detailed full-article screening, following which, 17 trials were found to satisfy our inclusion criteria and were included in this systematic review and meta-analysis.

The characteristics of the included trials are depicted in Table1. A total of 6673 patients were enrolled in the 17 trials and thus were a part of our study. The included trials were published from 2015 to 2022, with the sample size in each trial ranging from 91 to 1043. All 17 trials were published in English. The patients' ages ranged from 18 to 80 years. The treatment durations also differed across trials, varying from 6 weeks to 52 weeks.

Risk of bias and quality evaluation of individual trials

Based on the Cochrane Collaboration tool for assessing different domains of study quality, the risk of bias was evaluated and the results are depicted in Figure 2. Among the 17 trials, 88.23% (15/17) of the trials

demonstrated adequate random sequence generation, while one study had unclear reporting. In addition, 82.35% (14/17) of the trials demonstrated allocation concealment, with two trial exhibiting unclear concealment status. 47.05% (8/17) of the trials were blinded trials. Appropriate methods were used to handle incomplete outcome data and the attrition and exclusion cases were also described in 88.23% (15/17) of the trials. However, in two trials, the handling of incomplete outcome data was not elaborately explained. In terms of selective outcome reporting, 88.23% (15/17) of the trials demonstrated a low risk of reporting bias (Figure 2A.B).

Effect of Roxadustat on cardiovascular-related events

Sixteen trials that reported cardiovascular-related events after the use of Roxadustat were eventually included in the study. Nine of these trials were conducted with NDD patients and six with DD patients. Meta-analysis indicated that oral Roxadustat did not cause serious adverse effects or cardiovascular-related events in anemic patients with CKD, irrespective of whether the patients received dialysis (RR = 1.181; CI [0.925 to 1.507]; P = 1.334, I^2 = 0.0%) or did not receive dialysis (RR = 1.036; CI [0.916 to 1.171]; P = 0.576, I^2 = 0.0%) (Figure 3A).Moreover, subgroup analysis also suggested that oral Roxadustat did not cause a significant difference in the risk of cardiovascular events in anemic patients with CKD when compared with placebo (RR = 1.049; CI [0.918 to 1.200]; P = 0.479, I^2 = 10.8%) or ESA (RR = 1.099; CI [0.907 to 1.331]; P = 0.336, I^2 = 0.0%) (Figure 3B). Additionally, there was a low degree of heterogeneity between the included trials on cardiovascular adverse events with Roxadustat compared to placebo. Removal of Besbrab's study from the sensitivity analysis reduced the heterogeneity to 0.0% (I^2 = 0.0%, P = 0.493).

Effect of Roxadustat on renal adverse events

Eleven trials reported the risk of renal adverse events associated with oral Roxadustat in the treatment of anemia in CKD. Nine of these trials included NDD patients and two included DD patients. The pooled results demonstrated no significant difference in the risk of renal adverse events observed in NDD (RR = 1.053; CI [0.965 to 1.149]; P = 0.244, I^2 = 0.0%) as well as DD (RR = 2.649; CI [0.201 to 34.981]; P = 0.459, I^2 = 41.8%) (Figure 4A) patients. However, moderate between-trial heterogeneity (I^2 = 41.8%, P = 0.190) was observed in the DD group. Furthermore, subgroup analysis also suggested that oral Roxadustat did not demonstrate a significant difference in the risk of renal adverse events in anemic patients with CKD when compared with placebo (RR=1.088; CI [0.980 to 1.209]; P = 0.115, I^2 = 0.0%) or ESA (RR = 0.968; CI [0.831 to 1.152]; P = 0.670, I^2 = 0.0%) (Figure 4B).

Nine trials evaluated the risk of progression to ESKD associated with treatment of anemia in CKD patients with oral Roxadustat, of which seven trials had recruited NDD patients and two trials had DD patients. The results of pooled analysis indicated that oral Roxadustat did not enhance the risk of progression to ESKD in patients with anemia in CKD, irrespective of DD (RR = 1.021; CI [0.917 to 1.136]; P = 0.154, I^2 = 0.0%) and NDD (RR = 1.033; CI [0.928 to 1.150]; P = 0.557, I^2 = 0.0%) (Figure 5A) patients. Moreover, subgroup analysis further illustrated that the risk of ESKD progression in patients with CKD anemia treated with oral Roxadustat did not significantly increase, when compared with placebo (RR = 1.062; CI [0.939 to 1.201]; P = 0.339, I^2 = 0.0%) or EAS (RR = 1.021; CI [0.917 to 1.136]; P = 0.283, I^2 = 0.0%) (Figure 5B).

Effect of Roxadustaton hyperkalemia

Fifteen trials reporting the risk of hyperkalemia associated with oral Roxadustat therapy for anemia in CKD patients were enrolled in this study, of which nine trials included NDD patients and six trials had included DD patients. The pooled analysis demonstrated no statistically significant difference in the risk of hyperkalemia in the oral Roxadustat therapy group irrespective of whether the patients were DD patients (RR = 1.145; CI [0.756 to 1.734]; P = 0.524, I^2 = 11.6%) or NDD (RR = 1.116; CI [0.930 to 1.339]; P = 0.236, I^2 = 0.0 %) patients (Figure 6A). Subgroup analysis based on the type of control intervention further demonstrated no significant difference in risk of hyperkalemia associated with the use of oral Roxadustat for treatment of anemia in CKD patients when compared to placebo group (RR = 1.205; CI [0.980 to 1.483]; P = 0.077, I^2 = 0.0%) or the ESA group (RR = 0.980; CI [0.740 to 1.324]; P = 0.888, I^2 = 0.4%) (Figure 6B).

Effect of Roxadustaton hypertension

Fifteen trials reporting the risk of hypertension related to oral Roxadustat therapy for anemia in CKD patients were enrolled in our study. Eight of these trials had recruited NDD patients and seven had recruited DD patients. The pooled results indicated that a higher risk of hypertension was observed in NDD (RR = 1.198; CI [1.042 to 1.377]; P = 0.011, I^2 = 36.0%) patients, but no significant statistical difference was observed in the risk of hypertension in the oral Roxadustat therapy group for DD patients (RR = 1.125; CI [1.014 to 1.249]; P = 0.650, I^2 = 10.1%) (Figure 7A). Moreover, subgroup analysis based on the type of control intervention further demonstrated a higher risk of hypertension associated with the use of oral Roxadustat for the treatment of anemia in CKD patients, when compared to the placebo (RR=1.374; CI [1.153 to 1.638]; P = 0.000, I^2 = 0%), but there was no statistically significant difference in the risk of hypertension in the oral Roxadustat therapy group when compared with ESA group (RR = 1.125; CI [1.014 to 1.249]; P = 0.877, I^2 = 0.4%)(Figure 7B).

Methods

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The review protocol has been registered on the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO; registration no. CRD42023387347).

Data sources and search strategies

Two independent investigators conducted a comprehensive assessment followed by literature selection of relevant studies on Roxadustat for cardiovascular and renal outcome events in patients with CKD published before October 11, 2022 using the search engines PubMed, Embase database and Cochrane Central Register of Controlled Trials, with the search limited to English-language trials. Moreover, references of selected trials as well as relevant previous meta-analyses were screened to identify eligible trials that had not been identified by the database searches. All articles identified by electronic and manual selects were entered into EndNote X9. Duplicates were extracted and a database was eventually prepared for further screening.

Inclusion criteria and data extraction

The trials which met the following criteria were included in this systematic review and meta-analysis:1) the trial population comprised of CKD patients either receiving dialysis or not receiving dialysis, and who had anemia (age>18 years);2) oral Roxadustat was used as intervention 3) comprised of a control group which received either placebo or ESA 4) included assessment of cardiac disorders and kidney-related AEs as primary outcomes. Cardiac disorders mainly consisted of cardiovascular death, myocardial infarction, ischemic stroke as well as other cardiac diseases and major adverse cardiovascular events. Renal-related AEs included worsening of CKD or reduced estimated glomerular filtration rate (eGFR), ESKD or renal failure or dialysis, acute kidney injury, or "renal disease" "renal-related adverse event" which were reported in the trials. Secondary outcomes comprised of the incidence of hypertension and hyperkalemia. Finally, 17 trials met the inclusion criteria though full-text screening, and were included in our systematic review and meta-analysis.

Quality Assessment

The Cochrane Collaboration's risk of bias tool was utilized to assess the methodological quality of the included trials. Two investigators separately conducted the quality assessment. In the event of disagreements during the screening and evaluation process, the issue was discussed, mediated upon and resolved with the help of a third party. The risk of bias for every item was classified as low, high, and unclear in accordance with the Cochrane Handbook for systematic Reviews.

Statistical analysis

We pooled risk ratios (RRs) with 95% confidence interval (CI) to determine the treatment effect of Roxadustat on cardiac and renal disorders. All statistical analyses were performed using the Stata MP Software

(version 14). In the statistical analysis of the effect of Roxadustat on cardiac and renal disorders, $P < 0.05$ was deemed as a significant statistical difference. Heterogeneity between trials was evaluated by employing Cochrane's Q test and reported as I-squared (I^2). Heterogeneity was categorized as low (I^2 [?] 40%), moderate (I^2 [?] 70%) or high ($I^2 > 70\%$). I^2 [?] 40% and $p < 0.1$ indicated that there was a lack of homogeneity among the trials, and the fixed-effects model was employed in the result analysis; otherwise, a random-effects model was used. The source of heterogeneity was explored by the following methods: (A) through sensitivity analysis, each trial was eliminated one by one to identify the trial that caused the heterogeneity. (B) subgroup analysis was conducted based on gender, age, country, and follow-up duration

Discussion

This study conducted a systematic review and meta-analysis of previous clinical studies on Roxadustat to evaluate its impact on cardiovascular and renal adverse events in CKD anemic patients either requiring or not requiring dialysis. The meta-analysis of the 17 trials included in this study revealed that there were no significant differences in terms of cardiovascular events, renal-related adverse events, the risk of progression to ESKD, or hyperkalemia between the Roxadustat group and the placebo group or ESA group, regardless of whether dialysis was received or not. However, a higher risk of hypertension was identified in NDD patients who received oral Roxadustat, whereas no significant risk of hypertension risk was detected in DD patients treated with oral Roxadustat. A higher risk of hypertension in CKD patients with anemia treated with oral Roxadustat compared to those receiving placebo, but no significant hypertension risk was observed in the Roxadustat treatment group compared to the ESA group. The results obtained in the aforementioned study indicate that although treatment with oral Roxadustat is associated with an increased risk of hypertension in dialysis patients when compared to placebo, these risks do not seem to translate into clinical outcomes related to cardiovascular or renal risk events.

CVD is the primary cause of death in CKD patients [22], and anemia is an independent risk factor for developing CVD in CKD patients [23]. Although the management of anemia is crucial for CKD patients, the current treatment regime comprising of the use of ESA and iron supplements is far from satisfactory [24]. Hence, we evaluated a novel drug called Roxadustat for the correction of renal anemia. As a hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI), Roxadustat promotes the production of endogenous EPO (erythropoietin), increases sensitivity to EPO receptors, and improves iron homeostasis in CKD patients [25]. In terms of cardiovascular outcomes, our analysis suggests that there is no correlation between intake of oral Roxadustat and adverse reactions related to cardiovascular events in CKD anemia patients, regardless of whether the patients are undergoing dialysis treatment or not. Previous studies have also demonstrated Roxadustat to be relatively safe [26, 27]. Furthermore, compared to participants receiving ESA treatment, patients treated with Roxadustat exhibit a lower incidence of composite cardiovascular safety endpoints. First, this may be attributed to the fact that Roxadustat, as described above, can generate endogenous EPO levels close to the physiological range, fully stimulating red blood cell production without exposing the patients to excessively concentrated EPO levels that could potentially exert a negative impact on vascular biology [28]. Second, the potential improvement brought about by Roxadustat or its neutral effect on certain traditional cardiovascular risk factors may be attributed to its ability to lower serum cholesterol. Studies have confirmed the total cholesterol and LDL cholesterol reducing effect exerted by Roxadustat [29-31]. Its mechanism of action involves inhibition of cholesterol synthesis and promoting its intestinal excretion [32]. Roxadustat is not only involved in regulating lipid metabolism, but may plays a part in adapting to acute and chronic ischemia, atherosclerosis, and vascular calcification [33, 34]. However, the current results have not been proven to be conclusive or consistent. Third, the protective myocardial cell effect exerted by Roxadustat against ischemic injury to cardiac cells can be attributed to its ability to enhance anaerobic respiration and promote the production of oxygen-independent ATP, thereby maintaining energy supply to the myocardial cells [35]. Finally, previous studies have indicated that Roxadustat stabilizes the expression of HIF-1α and enhances GLUT1 and GLUT4, thereby promoting glycolysis in cardiac myocytes and partially improving myocardial cell death caused by elevated β-oHb levels[36]. However, current summary data from three Phase 3 studies indicate that in NDD CKD patients with concomitant anemia, Roxadustat's cardiovascular safety is similar to that of placebo, and there is no evidence suggesting that HIF-PHIs confer significant cardiovascular

protective advantages[37]. This is consistent with our conclusion. While HIF-1α promotes glycolysis during hypoxia, it also affects metabolism under normoxic conditions. Deletion of HIF-1α in cardiac myocytes leads to reduced levels of ATP, as well as impaired myocardial contractility [38]. Paradoxically, overexpression of cardiac HIF-1α has also been observed to cause contractile dysfunction [39]. In summary, HIF-PHIs may exert cardioprotective effects under low-level inhibition/stabilization, and further research is needed to investigate the dose and duration of HIF-PHI use.

In terms of renal endpoints, our analysis indicates that oral Roxadustat does not elevate the risk of progression to ESKD in patients with chronic kidney disease-associated anemia, regardless of whether they are on dialysis or not. Currently, some studies have partially supported this conclusion by conducting in-depth investigations into the mechanisms of Roxadustat. One study has demonstrated that Roxadustat can protect against renal ischemia/reperfusion injury by regulating inflammatory responses[40]. Additionally, the non-inferior efficacy of Roxadustat in ESKD might be because of its ability to regulate oxidative stress [41].

According to reports, activation of HIF can prevent the enhanced occurrence of kidney oxidative stress induced by diabetes mellitus and also prevent and ameliorate the progression of DN[42]. Roxadustat does not increase the risk of hyperkalemia in patients with CKD in DD as well as NDD patients. Currently, there is a lack of in-depth research on the effects of Roxadustat on blood potassium levels. The impact of Roxadustat on blood potassium levels may vary among individuals. Roxadustat is primarily metabolized in the liver and is mainly excreted through the bile, with a small portion being eliminated by the kidneys[43]. In certain cases, Roxadustat may interfere with the renal excretion of potassium, which could result in elevated potassium levels in the blood. However, there is currently no reliable evidence available.

Regarding the effect of Roxadustat on hypertension, our results indicated that a higher risk of hypertension was observed in NDD patients. Additionally, subgroup analysis based on the type of control intervention further revealed a higher risk of hypertension associated with oral Roxadustat treatment of anemia in CKD patients when compared to the placebo group, but no statistically significant difference was observed when compared with ESA group. However, considering the relatively limited overall effect size and the instability of sensitivity analysis results, further research is needed. Previous animal studies have indicated that Roxadustat, in Angiotensin II (Ang II)-induced hypertension models, prevented vascular thickening and myocardial hypertrophy by downregulating AGTR1 expression. It also enhanced AGTR2 and endothelial nitric oxide synthase (eNOS) protein levels in the mouse aorta, thereby mitigating the hypertensive response [41]. Current research on Roxadustat's effects on blood pressure and its potential mechanisms has not yet yielded consistent results. Further studies with larger sample sizes are needed to conduct in-depth and systematic research in the future.

Limitations and Strengths

Our meta-analysis has several limitations. First, this study did not evaluate specific laboratory indicators related to cardiac and renal function outcomes in the included trials. Second, since the evaluation of Roxadustat is currently ongoing in Phase II or III clinical trials, there were inconsistencies in the dosages and observation periods of Roxadustat among the included studies. Different doses and durations of Roxadustat may affect the regulation of HIF-α on multiple target genes to varying degrees, potentially impacting the results of the analysis. Additionally, our meta-analysis included 16 studies that met the inclusion criteria, and every included trial being industry-sponsored, could influence the results of the analysis. Meta-analysis cannot substitute for adequately powered randomized controlled trials. In spite of these limitations, this is the first systematic review and meta-analysis of clinical studies on cardiovascular and renal adverse events of roxadustat in anemic DD and NDD CKD patients. The meta-analysis of the 17 trials included in this study revealed that there were no significant differences in terms of cardiovascular events, renal-related adverse events, or the risk of progression to ESKD between the Roxadustat group and the placebo group or ESA group, regardless of whether dialysis was received or not. However, a higher risk of hypertension was identified in NDD patients who received oral Roxadustat, whereas no significant risk of hypertension risk was detected in DD patients treated with oral Roxadustat.

Conclusion

To conclude, Roxadustat as a novel orally administered for the treatment of anemia for CKD. This meta-analysis of the 17 trials with a total of 6673 patients revealed that there were no significant differences in terms of cardiovascular events, renal-related adverse events, the risk of progression to ESKD, or hyperkalemia using Roxadustat for treating anemia in CKD, regardless of whether dialysis was received or not. However, attention must be paid to the occurrence of hypertension in patients with CKD anemia treated with Roxadustat.

Abbreviations

CKD: Chronic kidney disease; **ESRD:** End-stage renal disease; **CVD:** cardiovascular disease; **ESA** : erythropoiesis-stimulating agent; **IV:** intravenously**SC:** subcutaneously; **PRISMA:** Preferred reporting items for systematic reviews and meta-analyses; **FDA:** Food and Drug Administration; **rhEPO:** recombinant human erythropoietin;**HIF:** hypoxia-inducible factor; **HIF-PHI:**hypoxia-inducible factor-prolyl hydroxylase inhibitor **Hb:**hemoglobin non- **NDD:** dialysis dependence; **DD** : dialysis dependence; **AE:** advance events; **MACE:** Major adverse cardiovascular events; **RR:** risk ration; **CI:** Confidence interval; **eGFR:** Estimated glomerular filtration rate;**DN:** Diabetic Nephropathy; **BP:** Blood pressure;**HIΦ-1α:**hypoxia-inducible factor 1α· **DM:** diabetes mellitus;**eNOS:** endothelial nitric oxide synthase

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Authors' contributions

L.T: Conceptualization, Methodology and Writing. **M.W:**Software and Original draft preparation. **M.L and Y.P** : Data curation, **J.Z** : Assessed the risk of bias. **B.Z** : Supervision. **Y.W** : Validation. **W.Z:** Conceived and designed the experiments. All authors reviewed the manuscript.

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Declarations

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Consent for publication

Manuscript is approved by all authors for publication.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable

Reference

1. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020; 16:269-288.

2. Amaral S, Hwang W, Fivush B, et al. Association of mortality and hospitalization with achievement of adult hemoglobin targets in adolescents maintained on hemodialysis. J Am Soc Nephrol. 2006; 17:2878-2885.

3. Matteucci MC, Wühl E, Picca S, et al. Left ventricular geometry in children with mild to moderate chronic renal insufficiency. J Am Soc Nephrol. 2006; 17:218-226.

4. Kular D, Macdougall IC. HIF stabilizers in the management of renal anemia: from bench to bedside to pediatrics. Pediatr Nephrol. 2019; 34:365-378.

5. Kalantar-Zadeh K, Lee GH, Miller JE, et al. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. Am J Kidney Dis. 2009; 53:823-834.

6. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. Am J Kidney Dis. 2013; 61:44-56.

7. Szczech LA, Barnhart HX, Inrig JK, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008; 74:791-798.

8. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998; 339:584-590.

9. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009; 361:2019-2032.

10. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355:2085-2098.

11. Fishbane S, Schiller B, Locatelli F, et al. Peginesatide in patients with anemia undergoing hemodialysis. N Engl J Med. 2013; 368:307-319.

12. Manns BJ, Tonelli M. The new FDA labeling for ESA–implications for patients and providers. Clin J Am Soc Nephrol. 2012; 7:348-353.

13. Crathorne L, Huxley N, Haasova M, et al. The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer treatment-induced anaemia (including review of technology appraisal no. 142): a systematic review and economic model. Health Technol Assess. 2016; 20:1-588, v-vi.

14. Schmid H. Cost-effectiveness of continuous erythropoietin receptor activator in anemia. Clinicoecon Outcomes Res. 2014; 6:319-330.

15. Rostoker G. When should iron supplementation in dialysis patients be avoided, minimized or withdrawn? Semin Dial. 2019; 32:22-29.

16. Besarab A, Provenzano R, Hertel J, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. Nephrol Dial Transplant. 2015; 30:1665-1673.

17. Chen N, Qian J, Chen J, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. Nephrol Dial Transplant. 2017; 32:1373-1386.

18. Chen N, Hao C, Liu BC, et al. Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. N Engl J Med. 2019; 381:1011-1022.

19. Chen N, Hao C, Peng X, et al. Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis. N Engl J Med. 2019; 381:1001-1010.

20. Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. J Am Soc Nephrol. 2020; 31:1628-1639.

21. Akizawa T, Yamaguchi Y, Otsuka T, Reusch M. A Phase 3, Multicenter, Randomized, Two-Arm, Open-Label Study of Intermittent Oral Dosing of Roxadustat for the Treatment of Anemia in Japanese

Erythropoiesis-Stimulating Agent-Naïve Chronic Kidney Disease Patients Not on Dialysis. Nephron. 2020; 144:372-382.

22. Thompson S, James M, Wiebe N, et al. Cause of Death in Patients with Reduced Kidney Function. J Am Soc Nephrol. 2015; 26:2504-2511.

23. Wen Y, Xu Y, Tian H, et al. Cardiovascular Protective Effects of Oral Hypoxia Inducible Factor Prolyl Hydroxylase Inhibitor Roxadustat in the Treatment of Type 4 Cardiorenal-Anemia Syndrome: Protocol of a Randomized Controlled Trial. Front Med (Lausanne). 2022; 9:783387.

24. Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med. 2013; 368:1210-1219.

25. Chang WT, Lo YC, Gao ZH, Wu SN. Evidence for the Capability of Roxadustat (FG-4592), an Oral HIF Prolyl-Hydroxylase Inhibitor, to Perturb Membrane Ionic Currents: An Unidentified yet Important Action. Int J Mol Sci. 2019; 20.

26. Tang M, Zhu C, Yan T, et al. Safe and Effective Treatment for Anemic Patients With Chronic Kidney Disease: An Updated Systematic Review and Meta-Analysis on Roxadustat. Front Pharmacol. 2021; 12:658079.

27. Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. Am J Kidney Dis. 2016; 67:912-924.

28. Gupta N, Wish JB. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: A Potential New Treatment for Anemia in Patients With CKD. Am J Kidney Dis. 2017; 69:815-826.

29. Shutov E, Sułowicz W, Esposito C, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, double-blind, placebo-controlled study (ALPS). Nephrol Dial Transplant. 2021; 36:1629-1639.

30. Miki K, Nakamura Y, Yokoyama T, Kamiyama M, Ishii Y. Therapeutic Effect of Roxadustat on Patients With Posttransplant Anemia. Transplant Proc. 2022; 54:671-677.

31. Hirai K, Kaneko S, Minato S, et al. Effects of roxadustat on anemia, iron metabolism, and lipid metabolism in patients with non-dialysis chronic kidney disease. Front Med (Lausanne). 2023; 10:1071342.

32. Nguyen AD, McDonald JG, Bruick RK, DeBose-Boyd RA. Hypoxia stimulates degradation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase through accumulation of lanosterol and hypoxia-inducible factor-mediated induction of insigs. J Biol Chem. 2007; 282:27436-27446.

33. Fang T, Ma C, Zhang Z, Sun L, Zheng N. Roxadustat, a HIF-PHD inhibitor with exploitable potential on diabetes-related complications. Front Pharmacol. 2023; 14:1088288.

34. Zhang X, Zhang Y, Wang P, et al. Adipocyte Hypoxia-Inducible Factor 2α Suppresses Atherosclerosis by Promoting Adipose Ceramide Catabolism. Cell Metab. 2019; 30:937-951.e935.

35. Deguchi H, Ikeda M, Ide T, et al. Roxadustat Markedly Reduces Myocardial Ischemia Reperfusion Injury in Mice. Circ J. 2020; 84:1028-1033.

36. Ma X, Dong Z, Liu J, et al. β-Hydroxybutyrate Exacerbates Hypoxic Injury by Inhibiting HIF-1α-Dependent Glycolysis in Cardiomyocytes-Adding Fuel to the Fire? Cardiovasc Drugs Ther. 2022; 36:383-397.

37. Provenzano R, Szczech L, Leong R, et al. Efficacy and Cardiovascular Safety of Roxadustat for Treatment of Anemia in Patients with Non-Dialysis-Dependent CKD: Pooled Results of Three Randomized Clinical Trials. Clin J Am Soc Nephrol. 2021; 16:1190-1200.

38. Hölscher M, Schäfer K, Krull S, et al. Unfavourable consequences of chronic cardiac HIF-1α stabilization. Cardiovasc Res. 2012; 94:77-86.

39. Janbandhu V, Tallapragada V, Patrick R, et al. Hif-1a suppresses ROS-induced proliferation of cardiac fibroblasts following myocardial infarction. Cell Stem Cell. 2022; 29:281-297.e212.

40. Miao AF, Liang JX, Yao L, Han JL, Zhou LJ. Hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) protects against renal ischemia/reperfusion injury by inhibiting inflammation. Ren Fail. 2021; 43:803-810.

41. Yu J, Wang S, Shi W, et al. Roxadustat prevents Ang II hypertension by targeting angiotensin receptors and eNOS. JCI Insight. 2021; 6.

42. Feng X, Wang S, Sun Z, et al. Ferroptosis Enhanced Diabetic Renal Tubular Injury via HIF-1α/HO-1 Pathway in db/db Mice. Front Endocrinol (Lausanne). 2021; 12:626390.

43. Czock D, Keller F. Clinical Pharmacokinetics and Pharmacodynamics of Roxadustat. Clin Pharmacokinet. 2022; 61:347-362.

Figure Legends

Figure 1. A) PRISMA flow diagram of study selection process

Figure 2. Risk of bias graph. A) Risk of bias summary B) Risk for each included study.

Figure 3. Forest Plots of the effect of Roxadustat on cardiovascular-related events. A) Forest Plots of the effect of Roxadustat on cardiovascular-related events based on NDD or DD patients. B) Forest Plots of the effect of Roxadustat on cardiovascular-related events compared with placebo or ESA. All outcomes are reported in risk ratios (RRs) for treatment vs the comparator and 95% credible intervals (95%-CI).

Figure 4. Forest Plots of the effect of Roxadustat on renal adverse events A) Forest Plots of the effect of Roxadustat on renal adverse events based on NDD or DD patients. B) Forest Plots of the effect of Roxadustat on renal adverse events compared with placebo or ESA. All outcomes are reported in risk ratios (RRs) for treatment vs the comparator and 95% credible intervals (95%-CI).

Figure 5. Forest Plots of the effect of Roxadustat on ESKD A) Forest Plots of the effect of Roxadustat on ESKD based on NDD or DD patients. B) Forest Plots of the effect of Roxadustat on ESKD compared with placebo or ESA. All outcomes are reported in risk ratios (RRs) for treatment vs the comparator and 95% credible intervals (95%-CI).

Figure 6. Forest Plots of the effect of Roxadustat on hyperkalemia A) Forest Plots of the effect of Roxadustat on hyperkalemia based on NDD or DD patients. B) Forest Plots of the effect of Roxadustat on hyperkalemia compared with placebo or ESA. All outcomes are reported in risk ratios (RRs) for treatment vs the comparator and 95% credible intervals (95%-CI).

Figure 7. Forest Plots of the effect of Roxadustat on hypertension A) Forest Plots of the effect of Roxadustat on hypertension based on NDD or DD patients. B) Forest Plots of the effect of Roxadustat on hypertension compared with placebo or ESA. All outcomes are reported in risk ratios (RRs) for treatment vs the comparator and 95% credible intervals (95%-CI).

Table1. Study Participant Characteristics

The Table represents data from studies stratified by the intervention and comparator.

Hosted file

`0718table.docx` available at https://authorea.com/users/646548/articles/658411-cardiovascular-and-renal-safety-outcomes-of-hypoxia-inducible-factor-prolyl-hydroxylase-inhibitor-

roxadustat-for-anemia-patients-with-chronic-kidney-disease-a-systematic-review-and-meta-analysis

Figure 1

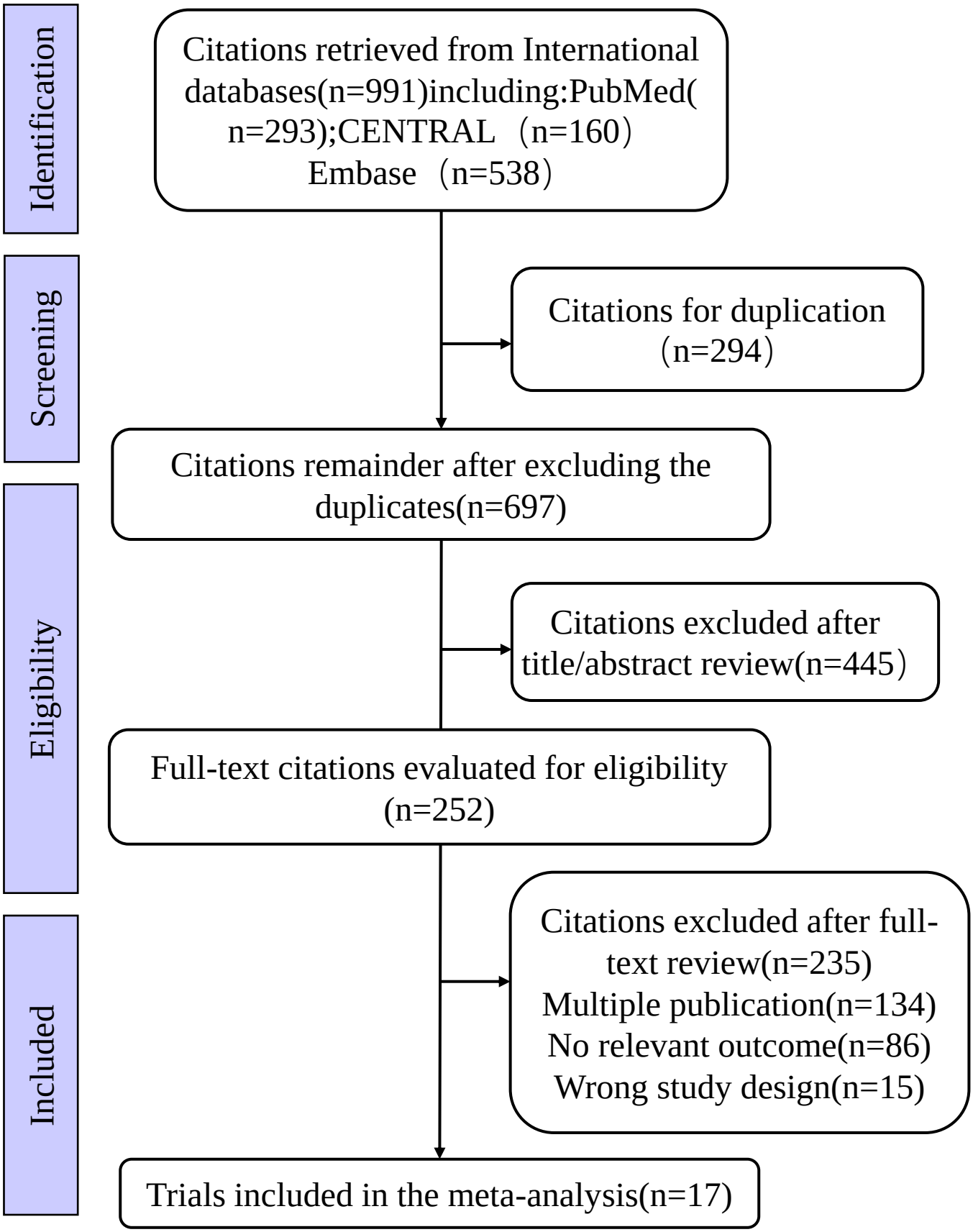
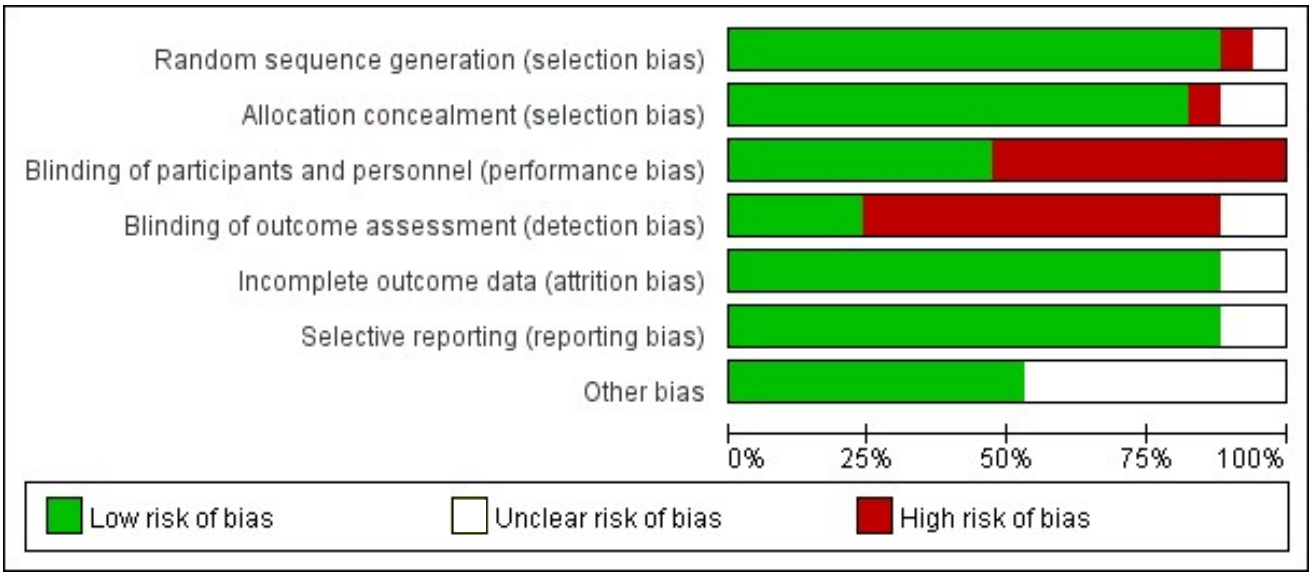

Identification
Screening
Eligibility
Included
Citations retrieved from International databases(n=991)including:PubMed(n=293);CENTRAL（n=160）Embase（n=538）
Citations for duplication（n=294）
Citations remainder after excluding the duplicates(n=697)
Citations excluded after title/abstract review(n=445）
Full-text citations evaluated for eligibility (n=252)
Citations excluded after full-text review(n=235)
Multiple publication(n=134)
No relevant outcome(n=86)
Wrong study design(n=15)
Trials included in the meta-analysis(n=17)

Figure 2

A.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

B.

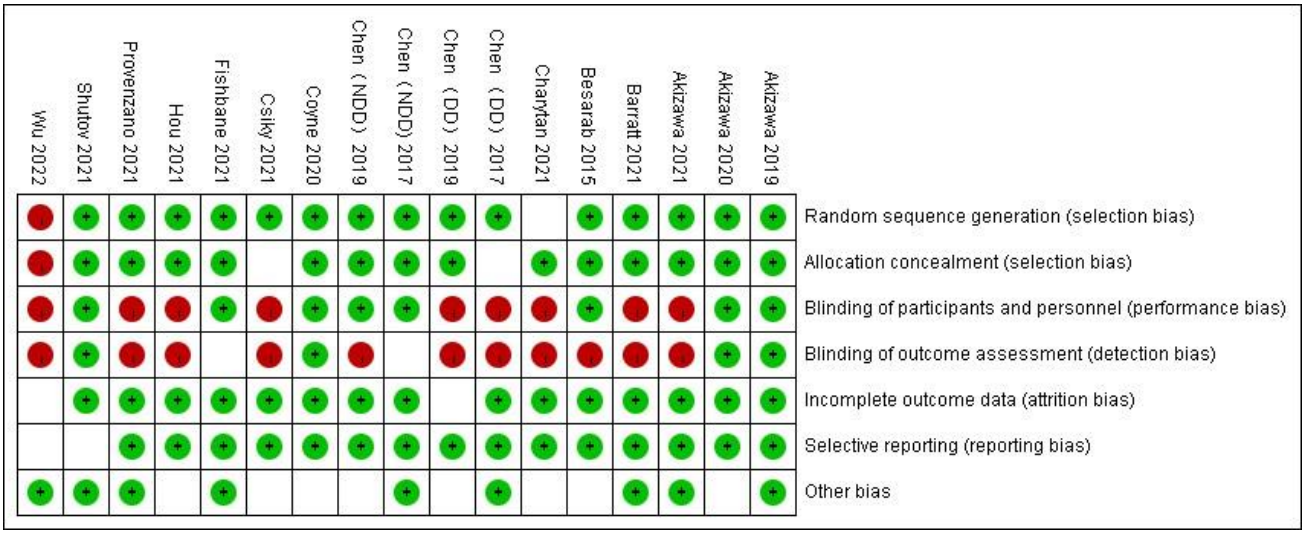
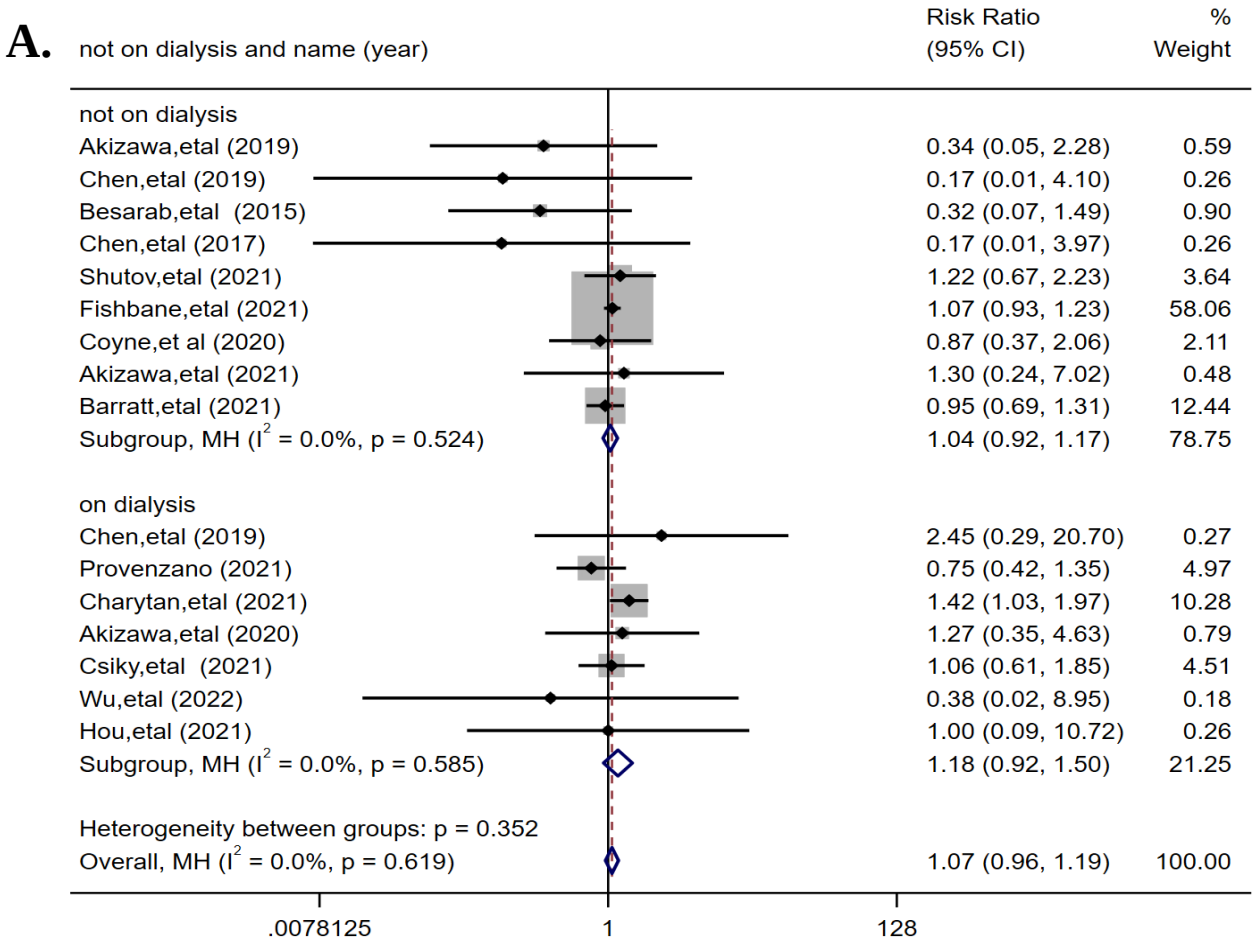

Wu 2022
Shutov 2021
Provenzano 2021
Hou 2021
Fishbane 2021
Csiky 2021
Coyne 2020
Chen (NDD) 2019
Chen (NDD) 2017
Chen (DD) 2019
Chen (DD) 2017
Charytan 2021
Besarab 2015
Barratt 2021
Akizawa 2021
Akizawa 2020
Akizawa 2019
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

Figure 3


A.
not on dialysis and name (year)
Risk Ratio (95% CI)
% Weight
not on dialysis
Akizawa,etal (2019) 0.34 (0.05, 2.28) 0.59
Chen,etal (2019) 0.17 (0.01, 4.10) 0.26
Besarab,etal (2015) 0.32 (0.07, 1.49) 0.90
Chen,etal (2017) 0.17 (0.01, 3.97) 0.26
Shutov,etal (2021) 1.22 (0.67, 2.23) 3.64
Fishbane,etal (2021) 1.07 (0.93, 1.23) 58.06
Coyne,et al (2020) 0.87 (0.37, 2.06) 2.11
Akizawa,etal (2021) 1.30 (0.24, 7.02) 0.48
Barratt,etal (2021) 0.95 (0.69, 1.31) 12.44
Subgroup, MH (I² = 0.0%, p = 0.524) 1.04 (0.92, 1.17) 78.75
on dialysis
Chen,etal (2019) 2.45 (0.29, 20.70) 0.27
Provenzano (2021) 0.75 (0.42, 1.35) 4.97
Charytan,etal (2021) 1.42 (1.03, 1.97) 10.28
Akizawa,etal (2020) 1.27 (0.35, 4.63) 0.79
Csiky,etal (2021) 1.06 (0.61, 1.85) 4.51
Wu,etal (2022) 0.38 (0.02, 8.95) 0.18
Hou,etal (2021) 1.00 (0.09, 10.72) 0.26
Subgroup, MH (I² = 0.0%, p = 0.585) 1.18 (0.92, 1.50) 21.25
Heterogeneity between groups: p = 0.352
Overall, MH (I² = 0.0%, p = 0.619) 1.07 (0.96, 1.19) 100.00
.0078125
1
128

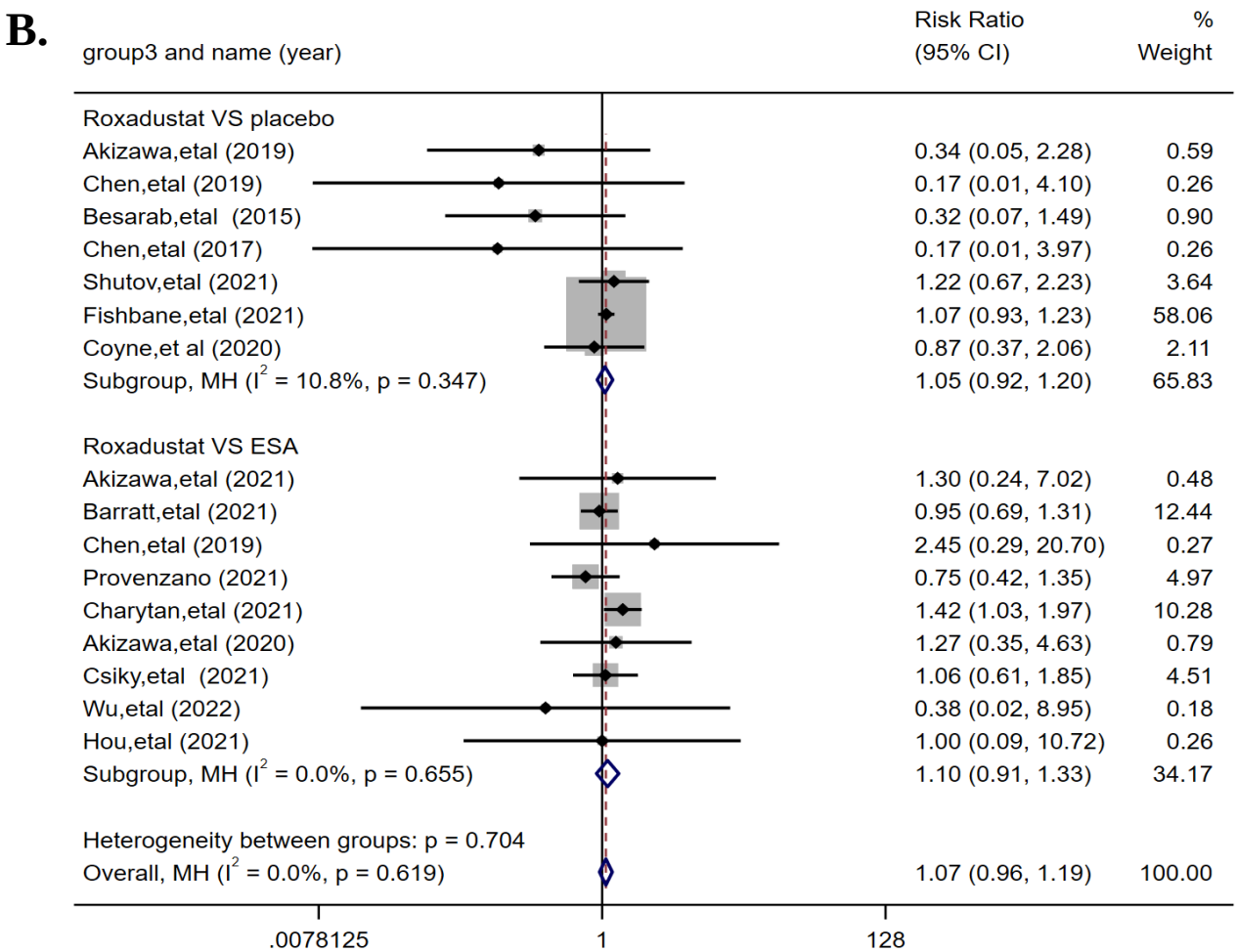
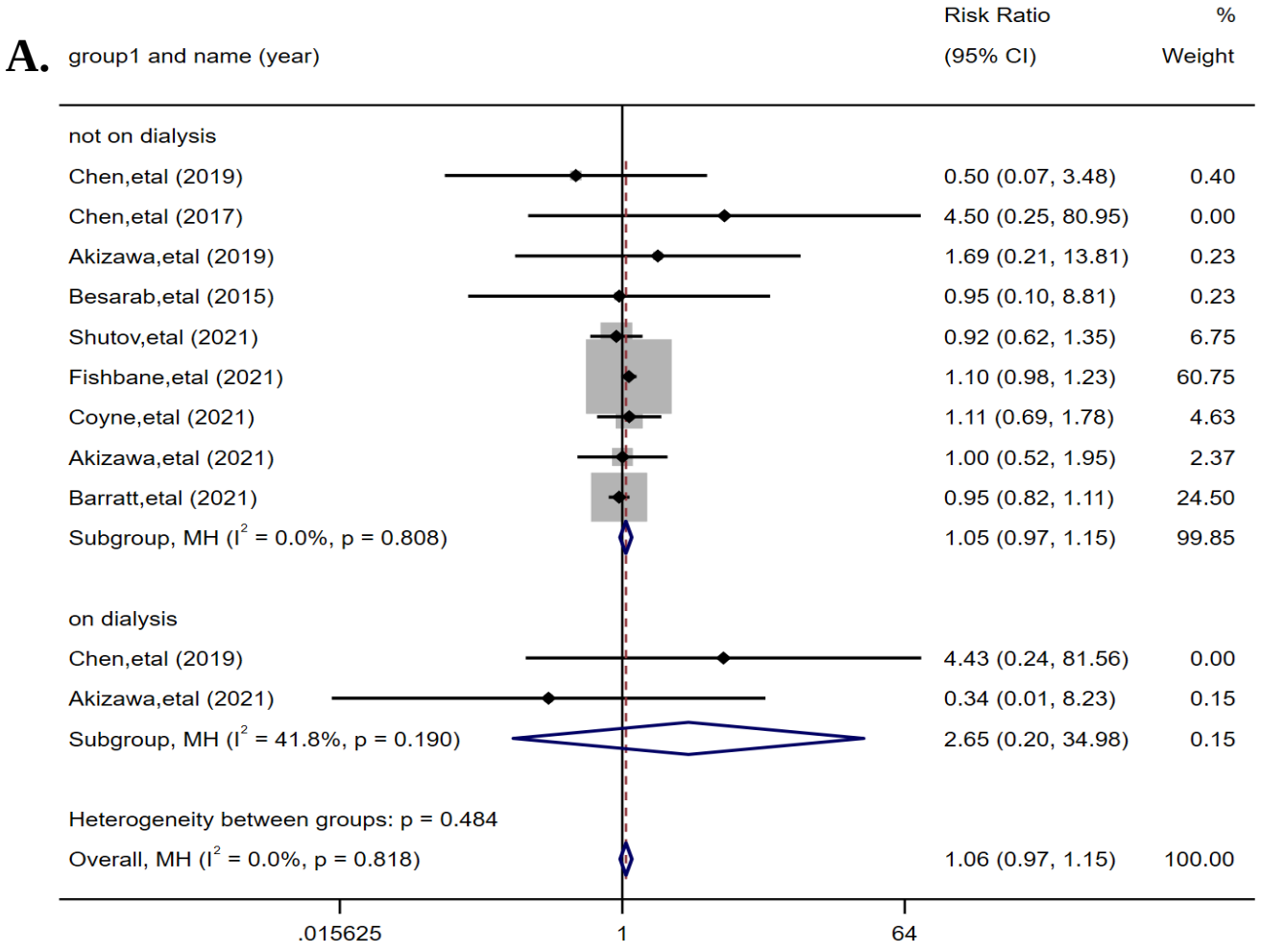

B.
group3 and name (year)
Risk Ratio (95% CI)
% Weight
Roxadustat VS placebo
Akizawa,etal (2019) 0.34 (0.05, 2.28) 0.59
Chen,etal (2019) 0.17 (0.01, 4.10) 0.26
Besarab,etal (2015) 0.32 (0.07, 1.49) 0.90
Chen,etal (2017) 0.17 (0.01, 3.97) 0.26
Shutov,etal (2021) 1.22 (0.67, 2.23) 3.64
Fishbane,etal (2021) 1.07 (0.93, 1.23) 58.06
Coyne,et al (2020) 0.87 (0.37, 2.06) 2.11
Subgroup, MH (I² = 10.8%, p = 0.347) 1.05 (0.92, 1.20) 65.83
Roxadustat VS ESA
Akizawa,etal (2021) 1.30 (0.24, 7.02) 0.48
Barratt,etal (2021) 0.95 (0.69, 1.31) 12.44
Chen,etal (2019) 2.45 (0.29, 20.70) 0.27
Provenzano (2021) 0.75 (0.42, 1.35) 4.97
Charytan,etal (2021) 1.42 (1.03, 1.97) 10.28
Akizawa,etal (2020) 1.27 (0.35, 4.63) 0.79
Csiky,etal (2021) 1.06 (0.61, 1.85) 4.51
Wu,etal (2022) 0.38 (0.02, 8.95) 0.18
Hou,etal (2021) 1.00 (0.09, 10.72) 0.26
Subgroup, MH (I² = 0.0%, p = 0.655) 1.10 (0.91, 1.33) 34.17
Heterogeneity between groups: p = 0.704
Overall, MH (I² = 0.0%, p = 0.619) 1.07 (0.96, 1.19) 100.00
.0078125
1
128

Figure 4


A.
group1 and name (year)
Risk Ratio (95% CI)
% Weight
not on dialysis
Chen,etal (2019) 0.50 (0.07, 3.48) 0.40
Chen,etal (2017) 4.50 (0.25, 80.95) 0.00
Akizawa,etal (2019) 1.69 (0.21, 13.81) 0.23
Besarab,etal (2015) 0.95 (0.10, 8.81) 0.23
Shutov,etal (2021) 0.92 (0.62, 1.35) 6.75
Fishbane,etal (2021) 1.10 (0.98, 1.23) 60.75
Coyne,etal (2021) 1.11 (0.69, 1.78) 4.63
Akizawa,etal (2021) 1.00 (0.52, 1.95) 2.37
Barratt,etal (2021) 0.95 (0.82, 1.11) 24.50
Subgroup, MH (I^2 = 0.0%, p = 0.808) 1.05 (0.97, 1.15) 99.85
on dialysis
Chen,etal (2019) 4.43 (0.24, 81.56) 0.00
Akizawa,etal (2021) 0.34 (0.01, 8.23) 0.15
Subgroup, MH (I^2 = 41.8%, p = 0.190) 2.65 (0.20, 34.98) 0.15
Heterogeneity between groups: p = 0.484
Overall, MH (I^2 = 0.0%, p = 0.818) 1.06 (0.97, 1.15) 100.00
.015625
1
64

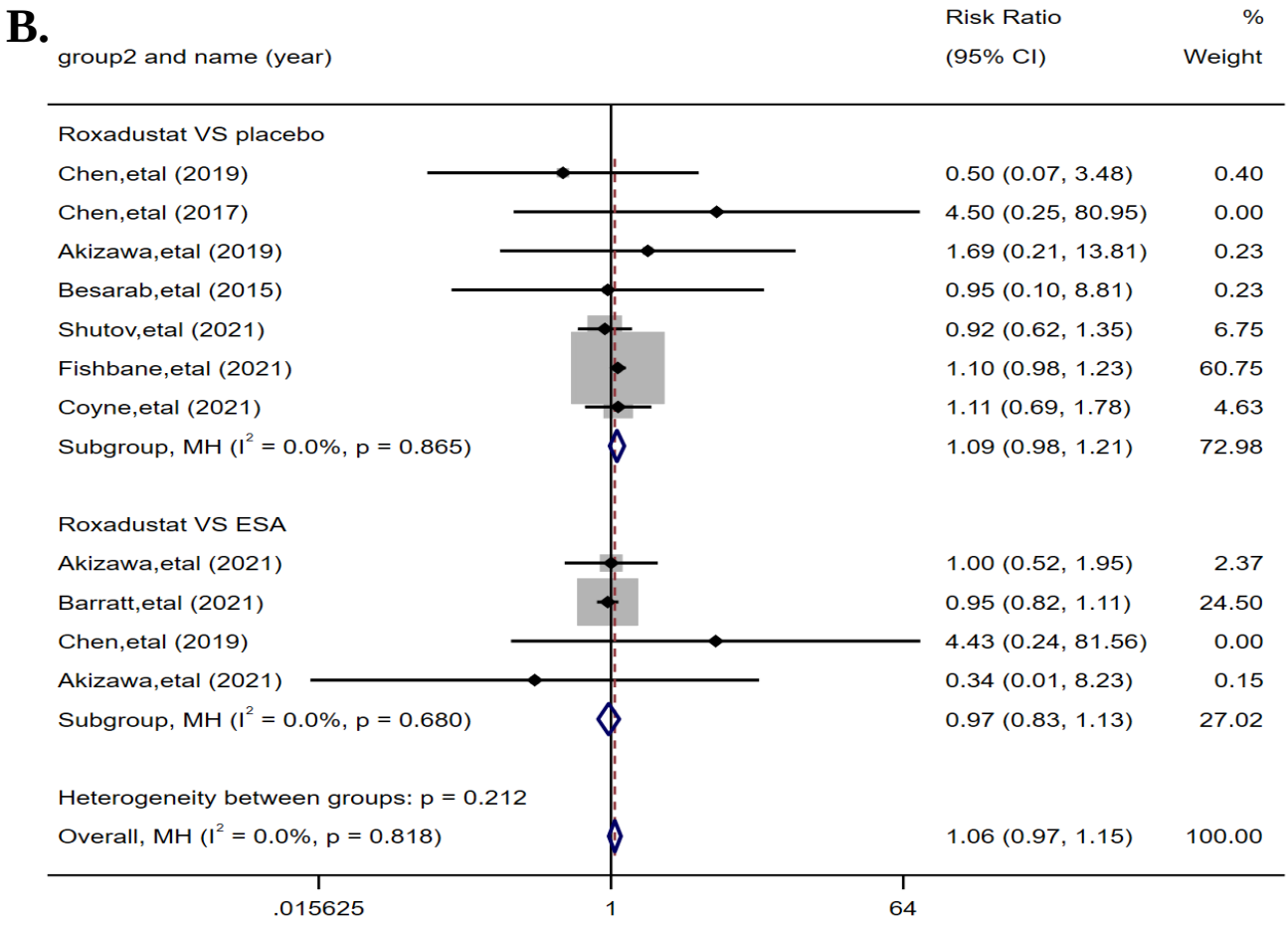
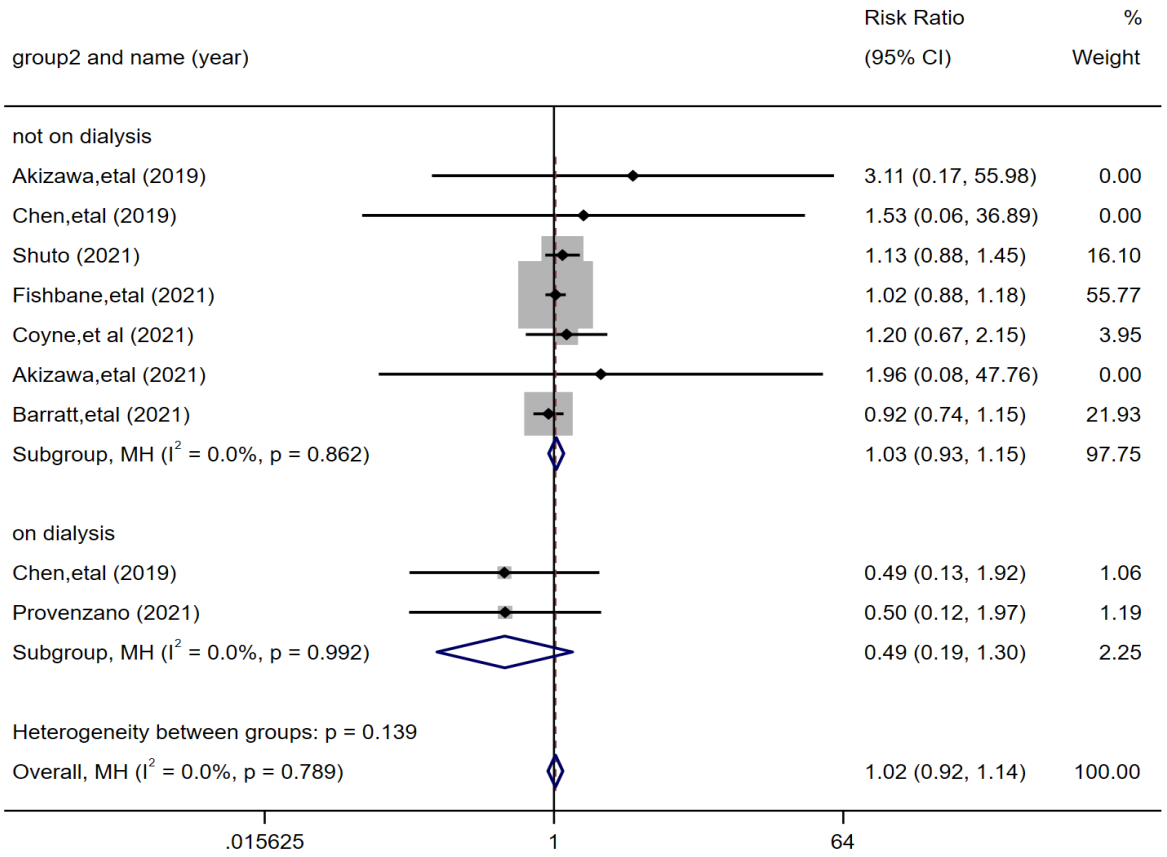

B.
group2 and name (year)
Risk Ratio (95% CI)
% Weight
Roxadustat VS placebo
Chen,etal (2019) 0.50 (0.07, 3.48) 0.40
Chen,etal (2017) 4.50 (0.25, 80.95) 0.00
Akizawa,etal (2019) 1.69 (0.21, 13.81) 0.23
Besarab,etal (2015) 0.95 (0.10, 8.81) 0.23
Shutov,etal (2021) 0.92 (0.62, 1.35) 6.75
Fishbane,etal (2021) 1.10 (0.98, 1.23) 60.75
Coyne,etal (2021) 1.11 (0.69, 1.78) 4.63
Subgroup, MH (I^2 = 0.0%, p = 0.865) 1.09 (0.98, 1.21) 72.98
Roxadustat VS ESA
Akizawa,etal (2021) 1.00 (0.52, 1.95) 2.37
Barratt,etal (2021) 0.95 (0.82, 1.11) 24.50
Chen,etal (2019) 4.43 (0.24, 81.56) 0.00
Akizawa,etal (2021) 0.34 (0.01, 8.23) 0.15
Subgroup, MH (I^2 = 0.0%, p = 0.680) 0.97 (0.83, 1.13) 27.02
Heterogeneity between groups: p = 0.212
Overall, MH (I^2 = 0.0%, p = 0.818) 1.06 (0.97, 1.15) 100.00
.015625
1
64

Figure 5

A.


group2 and name (year)
Risk Ratio (95% CI)
% Weight
not on dialysis
Akizawa,etal (2019) 3.11 (0.17, 55.98) 0.00
Chen,etal (2019) 1.53 (0.06, 36.89) 0.00
Shuto (2021) 1.13 (0.88, 1.45) 16.10
Fishbane,etal (2021) 1.02 (0.88, 1.18) 55.77
Coyne,et al (2021) 1.20 (0.67, 2.15) 3.95
Akizawa,etal (2021) 1.96 (0.08, 47.76) 0.00
Barratt,etal (2021) 0.92 (0.74, 1.15) 21.93
Subgroup, MH (I² = 0.0%, p = 0.862) 1.03 (0.93, 1.15) 97.75
on dialysis
Chen,etal (2019) 0.49 (0.13, 1.92) 1.06
Provenzano (2021) 0.50 (0.12, 1.97) 1.19
Subgroup, MH (I² = 0.0%, p = 0.992) 0.49 (0.19, 1.30) 2.25
Heterogeneity between groups: p = 0.139
Overall, MH (I² = 0.0%, p = 0.789) 1.02 (0.92, 1.14) 100.00
.015625
1
64

B.

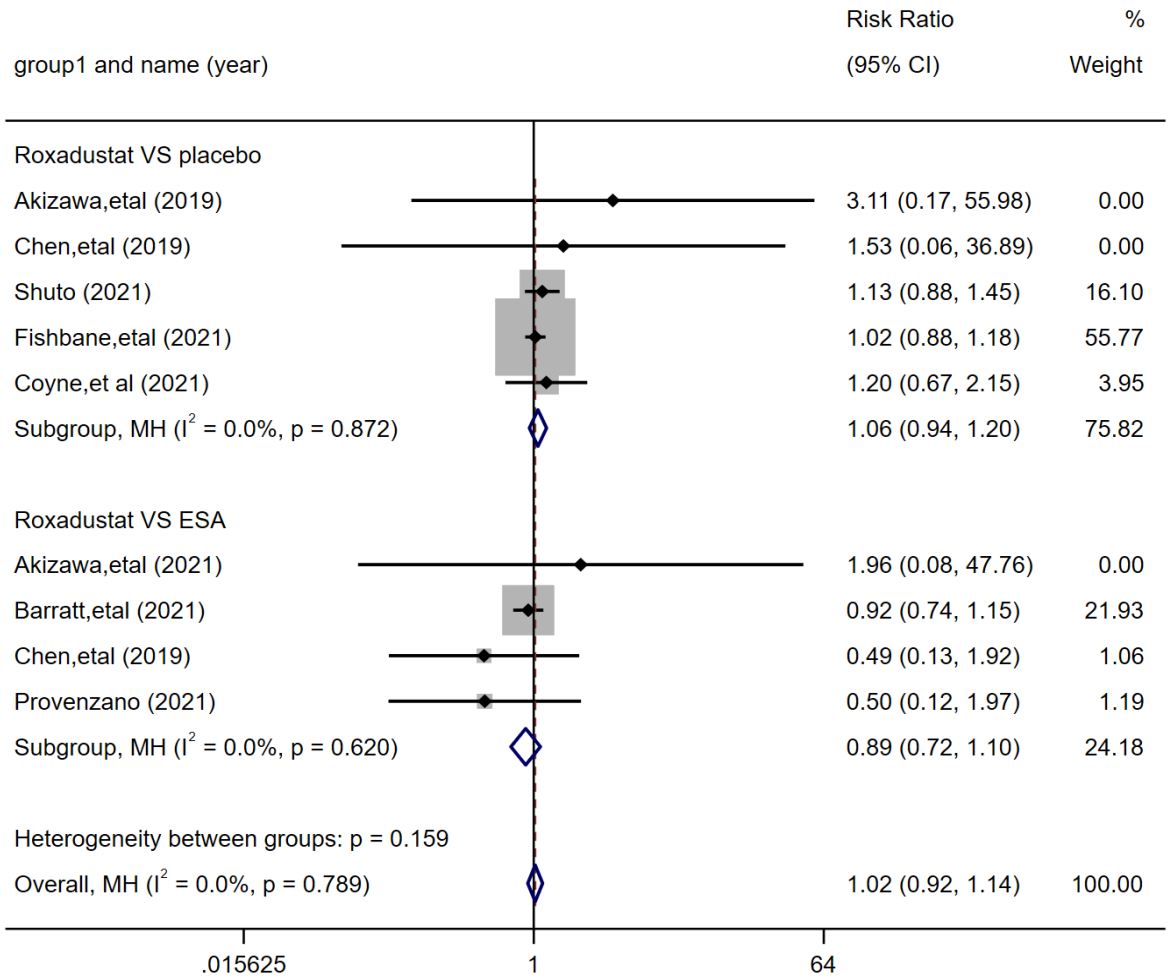
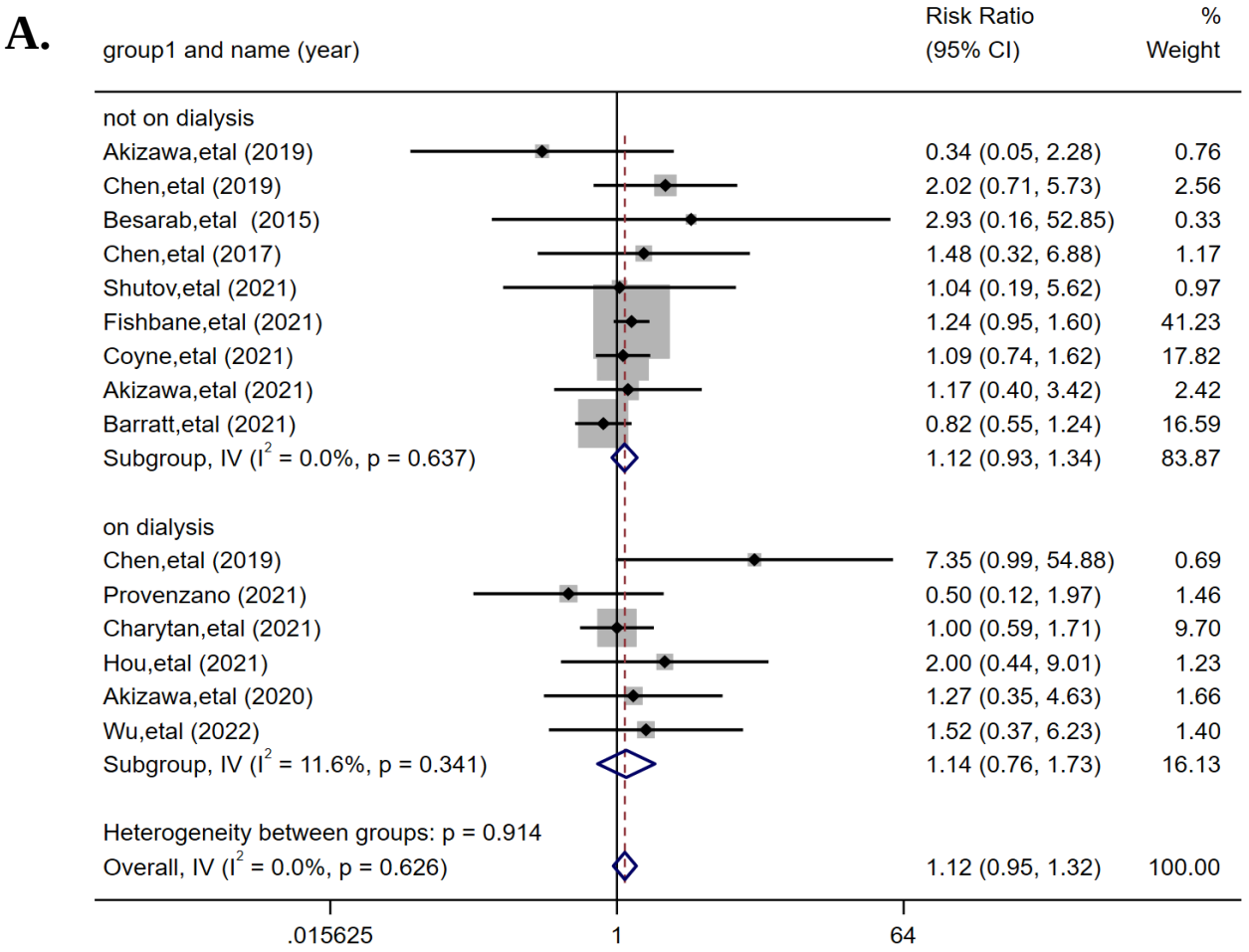

group1 and name (year)
Risk Ratio (95% CI)
% Weight
Roxadustat VS placebo
Akizawa,etal (2019) 3.11 (0.17, 55.98) 0.00
Chen,etal (2019) 1.53 (0.06, 36.89) 0.00
Shuto (2021) 1.13 (0.88, 1.45) 16.10
Fishbane,etal (2021) 1.02 (0.88, 1.18) 55.77
Coyne,et al (2021) 1.20 (0.67, 2.15) 3.95
Subgroup, MH (I² = 0.0%, p = 0.872) 1.06 (0.94, 1.20) 75.82
Roxadustat VS ESA
Akizawa,etal (2021) 1.96 (0.08, 47.76) 0.00
Barratt,etal (2021) 0.92 (0.74, 1.15) 21.93
Chen,etal (2019) 0.49 (0.13, 1.92) 1.06
Provenzano (2021) 0.50 (0.12, 1.97) 1.19
Subgroup, MH (I² = 0.0%, p = 0.620) 0.89 (0.72, 1.10) 24.18
Heterogeneity between groups: p = 0.159
Overall, MH (I² = 0.0%, p = 0.789) 1.02 (0.92, 1.14) 100.00
.015625
1
64

Figure 6


A.
group1 and name (year)
Risk Ratio (95% CI)
% Weight
not on dialysis
Akizawa,etal (2019) 0.34 (0.05, 2.28) 0.76
Chen,etal (2019) 2.02 (0.71, 5.73) 2.56
Besarab,etal (2015) 2.93 (0.16, 52.85) 0.33
Chen,etal (2017) 1.48 (0.32, 6.88) 1.17
Shutov,etal (2021) 1.04 (0.19, 5.62) 0.97
Fishbane,etal (2021) 1.24 (0.95, 1.60) 41.23
Coyne,etal (2021) 1.09 (0.74, 1.62) 17.82
Akizawa,etal (2021) 1.17 (0.40, 3.42) 2.42
Barratt,etal (2021) 0.82 (0.55, 1.24) 16.59
Subgroup, IV (I² = 0.0%, p = 0.637) 1.12 (0.93, 1.34) 83.87
on dialysis
Chen,etal (2019) 7.35 (0.99, 54.88) 0.69
Provenzano (2021) 0.50 (0.12, 1.97) 1.46
Charytan,etal (2021) 1.00 (0.59, 1.71) 9.70
Hou,etal (2021) 2.00 (0.44, 9.01) 1.23
Akizawa,etal (2020) 1.27 (0.35, 4.63) 1.66
Wu,etal (2022) 1.52 (0.37, 6.23) 1.40
Subgroup, IV (I² = 11.6%, p = 0.341) 1.14 (0.76, 1.73) 16.13
Heterogeneity between groups: p = 0.914
Overall, IV (I² = 0.0%, p = 0.626) 1.12 (0.95, 1.32) 100.00
.015625
1
64

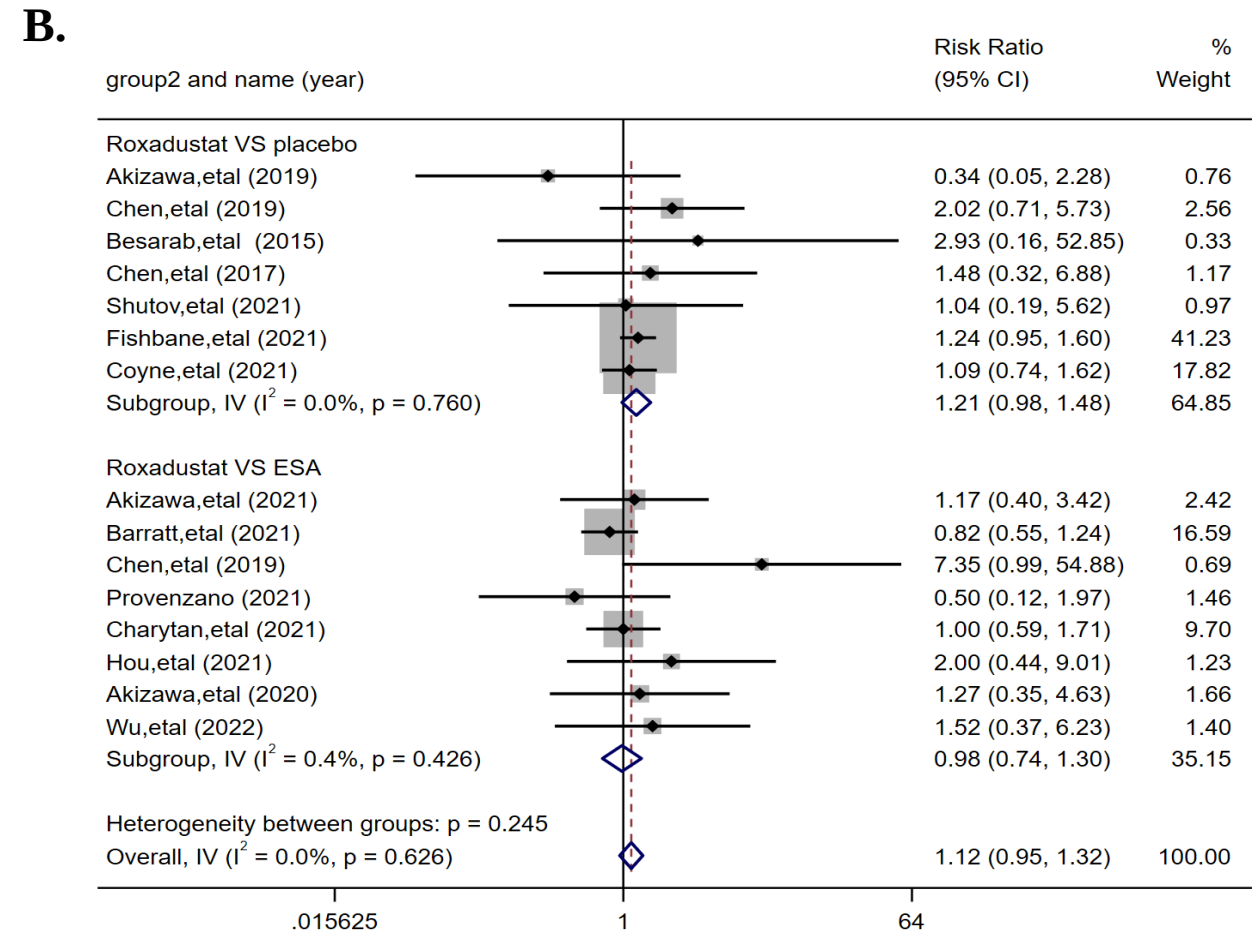
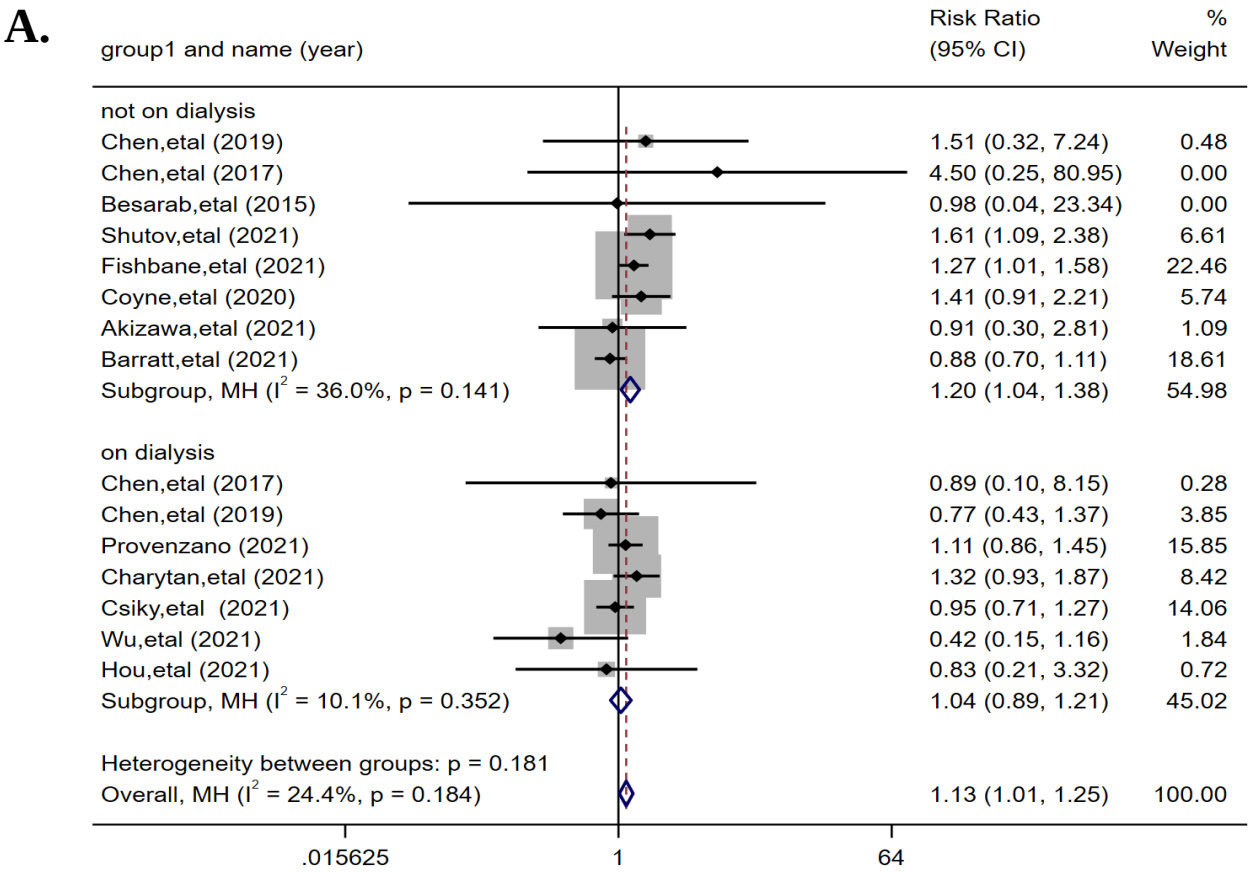
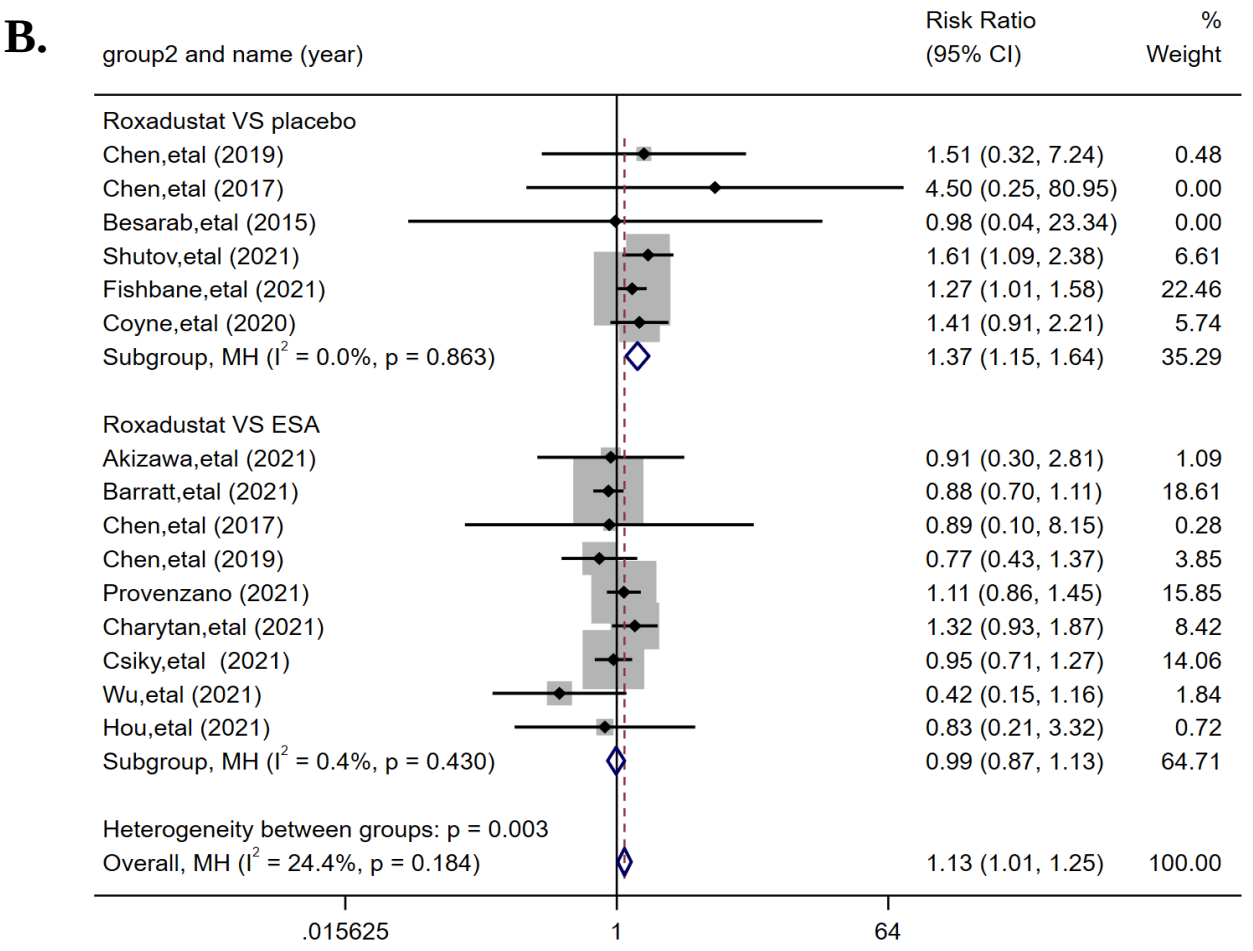

B.
group2 and name (year)
Risk Ratio (95% CI)
% Weight
Roxadustat VS placebo
Akizawa,etal (2019) 0.34 (0.05, 2.28) 0.76
Chen,etal (2019) 2.02 (0.71, 5.73) 2.56
Besarab,etal (2015) 2.93 (0.16, 52.85) 0.33
Chen,etal (2017) 1.48 (0.32, 6.88) 1.17
Shutov,etal (2021) 1.04 (0.19, 5.62) 0.97
Fishbane,etal (2021) 1.24 (0.95, 1.60) 41.23
Coyne,etal (2021) 1.09 (0.74, 1.62) 17.82
Subgroup, IV (I² = 0.0%, p = 0.760) 1.21 (0.98, 1.48) 64.85
Roxadustat VS ESA
Akizawa,etal (2021) 1.17 (0.40, 3.42) 2.42
Barratt,etal (2021) 0.82 (0.55, 1.24) 16.59
Chen,etal (2019) 7.35 (0.99, 54.88) 0.69
Provenzano (2021) 0.50 (0.12, 1.97) 1.46
Charytan,etal (2021) 1.00 (0.59, 1.71) 9.70
Hou,etal (2021) 2.00 (0.44, 9.01) 1.23
Akizawa,etal (2020) 1.27 (0.35, 4.63) 1.66
Wu,etal (2022) 1.52 (0.37, 6.23) 1.40
Subgroup, IV (I² = 0.4%, p = 0.426) 0.98 (0.74, 1.30) 35.15
Heterogeneity between groups: p = 0.245
Overall, IV (I² = 0.0%, p = 0.626) 1.12 (0.95, 1.32) 100.00
.015625
1
64

Figure 7


A.
group1 and name (year)
Risk Ratio (95% CI)
% Weight
not on dialysis
Chen,etal (2019) 1.51 (0.32, 7.24) 0.48
Chen,etal (2017) 4.50 (0.25, 80.95) 0.00
Besarab,etal (2015) 0.98 (0.04, 23.34) 0.00
Shutov,etal (2021) 1.61 (1.09, 2.38) 6.61
Fishbane,etal (2021) 1.27 (1.01, 1.58) 22.46
Coyne,etal (2020) 1.41 (0.91, 2.21) 5.74
Akizawa,etal (2021) 0.91 (0.30, 2.81) 1.09
Barratt,etal (2021) 0.88 (0.70, 1.11) 18.61
Subgroup, MH (I^2 = 36.0%, p = 0.141) 1.20 (1.04, 1.38) 54.98
on dialysis
Chen,etal (2017) 0.89 (0.10, 8.15) 0.28
Chen,etal (2019) 0.77 (0.43, 1.37) 3.85
Provenzano (2021) 1.11 (0.86, 1.45) 15.85
Charytan,etal (2021) 1.32 (0.93, 1.87) 8.42
Csiky,etal (2021) 0.95 (0.71, 1.27) 14.06
Wu,etal (2021) 0.42 (0.15, 1.16) 1.84
Hou,etal (2021) 0.83 (0.21, 3.32) 0.72
Subgroup, MH (I^2 = 10.1%, p = 0.352) 1.04 (0.89, 1.21) 45.02
Heterogeneity between groups: p = 0.181
Overall, MH (I^2 = 24.4%, p = 0.184) 1.13 (1.01, 1.25) 100.00
.015625
1
64


B.
group2 and name (year)
Risk Ratio (95% CI)
% Weight
Roxadustat VS placebo
Chen,etal (2019) 1.51 (0.32, 7.24) 0.48
Chen,etal (2017) 4.50 (0.25, 80.95) 0.00
Besarab,etal (2015) 0.98 (0.04, 23.34) 0.00
Shutov,etal (2021) 1.61 (1.09, 2.38) 6.61
Fishbane,etal (2021) 1.27 (1.01, 1.58) 22.46
Coyne,etal (2020) 1.41 (0.91, 2.21) 5.74
Subgroup, MH (I^2 = 0.0%, p = 0.863) 1.37 (1.15, 1.64) 35.29
Roxadustat VS ESA
Akizawa,etal (2021) 0.91 (0.30, 2.81) 1.09
Barratt,etal (2021) 0.88 (0.70, 1.11) 18.61
Chen,etal (2017) 0.89 (0.10, 8.15) 0.28
Chen,etal (2019) 0.77 (0.43, 1.37) 3.85
Provenzano (2021) 1.11 (0.86, 1.45) 15.85
Charytan,etal (2021) 1.32 (0.93, 1.87) 8.42
Csiky,etal (2021) 0.95 (0.71, 1.27) 14.06
Wu,etal (2021) 0.42 (0.15, 1.16) 1.84
Hou,etal (2021) 0.83 (0.21, 3.32) 0.72
Subgroup, MH (I^2 = 0.4%, p = 0.430) 0.99 (0.87, 1.13) 64.71
Heterogeneity between groups: p = 0.003
Overall, MH (I^2 = 24.4%, p = 0.184) 1.13 (1.01, 1.25) 100.00
.015625
1
64