

GOPEN ACCESS

Citation: Abdelazeem B, Shehata J, Abbas KS, El-Shahat NA, Malik B, Savarapu P, et al. (2022) The efficacy and safety of roxadustat for the treatment of anemia in non-dialysis dependent chronic kidney disease patients: An updated systematic review and meta-analysis of randomized clinical trials. PLoS ONE 17(4): e0266243. https://doi.org/ 10.1371/journal.pone.0266243

Editor: Gianpaolo Reboldi, Universita degli Studi di Perugia, ITALY

Received: November 8, 2021

Accepted: March 16, 2022

Published: April 1, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0266243

Copyright: © 2022 Abdelazeem et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

RESEARCH ARTICLE

The efficacy and safety of roxadustat for the treatment of anemia in non-dialysis dependent chronic kidney disease patients: An updated systematic review and metaanalysis of randomized clinical trials

Basel Abdelazeem^{1,2}, Joseph Shehata³, Kirellos Said Abbas⁴, Nahla Ahmed El-Shahat⁵, Bilal Malik^{1,2}, Pramod Savarapu⁶, Mostafa Eltobgy^{7*}, Arvind Kunadi¹

 McLaren Health Care, Flint, Michigan, United States of America, 2 Michigan State University, East Lansing, Michigan, United States of America, 3 Faculty of Medicine, Cairo University, Cairo, Egypt, 4 Faculty of Medicine, Alexandria University, Alexandria, Egypt, 5 Faculty of Medicine for Girls, Al-Azher University, Cairo, Egypt, 6 Louisiana State University Health Sciences Center, Monroe, Louisiana, United States of America, 7 The Ohio State University, Columbus, Ohio, United States of America

* eltobgy.2@osu.edu

Abstract

Background

Roxadustat (ROX) is a new medication for anemia as a complication of chronic kidney disease (CKD). Our meta-analysis aims to evaluate the efficacy and safety of ROX, especially on the cardiovascular risks, for anemia in NDD-CKD patients.

Methods

Electronic databases were searched systematically from inception to July 2021 to look for randomized control trials (RCTs) that evaluated ROX NDD-CKD patients. Hemoglobin level and iron utilization parameters, including ferritin, serum iron, transferrin saturation (TSAT), total iron-binding capacity (TIBC), transferrin, and hepcidin were analyzed for efficacy. Pooled risk ratios (RRs) and standardized mean differences (SMDs) were calculated and presented with their 95% confidential intervals (CIs).

Results

Nine RCTs included a total of 3,175 patients in the ROX group and 2,446 patients in the control group. When compared the control group, ROX increased Hb level significantly (SMD: 1.65; 95% CI: 1.08, 2.22; P< 0.00001) and improved iron utilization parameters by decreasing ferritin (SMD: -0.32; 95% CI: -0.51, -0.14; P = 0.0006), TSAT (SMD: -0.19; 95% CI: -0.32, -0.07; P = 0.003), and hepcidin (SMD: -0.74; 95% CI: -1.09, -0.39; P< 0.0001) and increasing TIBC (SMD: 0.99; 95% CI: 0.76, 1.22; P< 0.00001) and transferrin (SMD: 1.20; 95% CI: 0.70, 1.71; P< 0.00001). As for safety, ROX was associated with higher serious adverse effects (RR: 1.07; 95% CI: 1.01, 1.13; P = 0.01), deep venous thrombosis (DVT)

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

(RR: 3.80; 95% CI: 1.5, 9.64; P = 0.08), and hypertension (HTN) (RR: 1.37; 95% CI: 1.13, 1.65; P = 0.001).

Conclusion

We concluded that ROX increased Hb level and improved iron utilization parameters in NDD-CKD patients, but ROX was associated with higher serious adverse effects, especially DVT and HTN. Our results support the use of ROX for NDD-CKD patients with anemia. However, higher-quality RCTs are still needed to ensure its safety and risk of thrombosis.

Introduction

Anemia is common in non-dialysis chronic kidney disease (ND-CKD) patients and, as the glomerular filtration rate (GFR) decreases, the prevalence increases [1, 2]. The prevalence of anemia in patients with stage 1 CKD is 8.4% compared to 53.4% at stage 5 CKD [3], and it is associated with increased hospitalization, mortality, and a decrease in the quality of life [4, 5]. Therefore, all patients require anemia screening when assessing CKD for the first time and before administering any therapy, and the patient should be monitored frequently for the therapy response [6]. The anemia in CKD patients is multifactorial [7]. Erythropoietin (EPO) is a hormone that stimulates red blood cell synthesis, and it is produced by renal EPO-producing cells located in the interstitium of the outer medulla and cortex [8]. CKD is characterized by interstitial fibrosis leading to EPO insufficiency [9]. Other factors include iron deficiency, decreased oxygen sensing, and accumulation of uremic toxins [10].

The treatment of anemia in ND-CKD patients depends on the anemia severity, and the main treatment options include iron and erythropoiesis-stimulating agents (ESAs) [5], but it is associated with increased risk of serious cardiovascular events, myocardial infarction (MI), stroke, and venous thromboembolism that limit its usage [10-12].

Roxadustat (ROX) is a new medication that reversibly inhibits hypoxia-inducible factor prolyl hydroxylase (HIF-PH) enzymes, leading to improved oxygen sensing and increasing hemoglobin levels. ROX showed efficacy and safety in NDD-CKD patients and had the first global approval in China to treat anemia in NDD-CKD patients [13].

Our study aims to conduct an updated meta-analysis of randomized clinical trials (RCTs) by analyzing previously published RCTs besides the most recent RCTs Akizawa et al. [14], Barratt et al. [15], and Shutov et al. [16]. We will investigate the efficacy and safety of ROX to placebo of ESAs in the treatment of anemia in NDD-CKD patients. Our study will help internists and nephrologists decide whether ROX should be considered in managing anemia in NDD-CKD patients.

Methods

Data sources and search strategy

We followed Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) to conduct this systematic review and meta-analysis [17, 18]. We registered our meta-analysis at OSF Registries with DOI 10.17605/OSF.IO/WGZ6C. Systematic research of PubMed, EMBASE, Scopus, Web of Science, Cochrane Central, and Google Scholar was searched systematically from inception through July 2021 to include citations on non-HD CKD patients treated with ROX for anemia.

The following search terms were used (Roxadustat OR ASP1517 OR FG4592 OR "FG-4592") AND (kidney OR renal) AND (Anemia), and it varies depending on the database (S1 Table). The related articles' feature [19] was used to include any related articles, and the references of the included studies were manually reviewed to include any relevant citation. EndNote [20] was used to save the search result, and the result was transferred to Covidence for screening [21]. A further manual search was done on November 1, 2021, to look for recently published articles.

Study selection and eligibility criteria

We included studies that met the following criteria: study design was RCTs; written English text; the target population was patients CKD and not on HD; the intervention was ROX and compared placebo or any other medications; primary outcomes changed in hemoglobin level and iron parameters and studies reported the outcomes of interest were included. We excluded the observational studies, studies that did not report a comparator group, and non-random-ized studies. Two independent reviewers (JS and KSA) completed the title, abstract, and full-text screening. Any conflict between the authors was resolved by a third author (BA).

Data extraction

The data from the included studies were extracted independently by three reviewers (JS, KSA, and NAE). The consensus was reached in case of any inconsistency by the fourth author (BA). Each included RCT was abstracted for the first author, published date, country, study design, phase, study period, number, age, gender of patients, and ROX dose.

Risk of bias assessment

Two Reviewer (KSA and NAE) performed the risk of bias assessment independently using the revised Cochrane risk of bias 2 tool (Rob 2) [22] to evaluate the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. The overall grade of each aspect was measured as low risk, high risk, or some concerns.

Outcomes of interest

The primary outcomes are changes in hemoglobin (Hb) level and iron utilization parameters, including ferritin, serum iron, transferrin saturation (TSAT), Total iron-binding capacity (TIBC), transferrin, and hepcidin. Secondary outcomes are serious adverse events, treatmentemergent adverse effects (TEAEs), and cardiovascular-related adverse effects; hypertension (HTN), hypertensive crisis, pulmonary edema, heart failure, coronary artery diseases, Myocardial infarction (MI), and deep venous thrombosis (DV).

Statistical analysis

Meta-analyses of all outcomes were performed using RevMan manager v5.3 [23] by Two authors (KSA and NAE) and reviewed by BA. Risk ratios (RRs) were used for the dichotomous outcomes and the standardized mean difference (SMD) for the continuous outcome, and both presented it along with the corresponding 95% confidence interval (CI). Data were analyzed using the Mantel–Haenszel method. A P-value less than 0.05 is considered significant. All outcomes were calculated according to the fixed-effects model (in the absence of significant heterogeneity) and the random-effects model (in the presence of significant heterogeneity). Statistical heterogeneity between trials was evaluated using the Cochran Q test and measured

using I² statistics. I²> 50% indicates significant heterogeneity across included RCTs [24]. The risk of publication bias was not performed because we included less than ten RCTs [25]. We excluded one study at a time and repeated the analysis to perform the sensitivity analysis by removing one study at a time to assess the impact of each study on the overall study effect on the Hb level. Subgroup analysis was carried out to investigate the impact of the trial phase and the different control groups (ROX Vs. ESA and ROX Vs. placebo) on the Hb level.

We used Comprehensive Meta-Analysis (CMA) [26] software to perform meta-regression to study the effect of rescue therapy or iron supplementation on the mean change of hemoglobin level. Standardized differences in means and the total of ROX versus control were tabulated with the status of rescue therapy and iron supplement; allowed or prohibited. A scatter plot was created for two models: rescue therapy and iron supplement.

Results

Search results and study selection

From a pool of 908 potentially relevant articles, we chose 62 for full full-text review according to our inclusion and exclusion criteria. Thus, a total of nine RCTs were included in our systematic review and meta-analysis [14–16, 27–32]. The process of inclusion and exclusion with the reasons for exclusion was shown in the PRISMA flow diagram Fig 1.

Characteristics of included studies

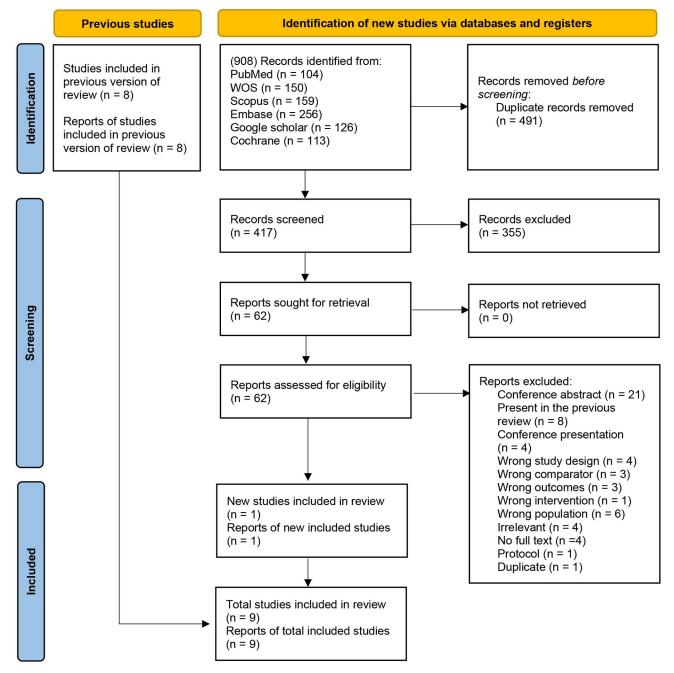
The main characteristics of the studies included are presented in Table 1. Six RCTs were double-blinded [16, 27–30, 32], one was single-blinded [31], and two were open-label [14, 15]. A total of six RCTs were phase 3 [14–16, 27, 28, 30], and three were phase 2 [29, 31, 32]. Two RCTs compared ROX to darbepoetin alfa [14, 15], and the rest of the RCTs compared ROX to placebo. The ROX dose ranged from 50 mg to 100 mg three times a week, and two studies used the dose according to the weight ranging from 0.7 to 2.25 mg/kg [29, 31]. The study duration ranged from 8 weeks to 104 weeks. The mean age of the included patient was 62 ± 14.8 years, and 43.5% were male. The primary causes of the CKD and the rest of the patients' demographics and baseline characteristics were summarized in Table 2.

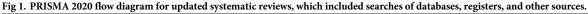
Risk of bias assessment

The overall risk of bias was judged as some concerns for three studies [27–29] and as high risk in six studies [14–16, 30–32]. All studies were judged with some concerns on the randomization process, except two had a low risk of bias [14, 32], and one was a high risk of bias [15]. All studies were judged with a low risk of bias for deviations from intended interventions and measurement of the outcome, except three studies have some concerns [14, 15, 31]. Six studies were judged low risk for the missing outcome data [14, 15, 27–29, 32] and three with some concerns [16, 30, 31]. Finally, all studies were judged with a low risk of bias for selective reporting, except two studies were judged as high risk of bias [31, 32]. Fig 2 demonstrated the risk of bias summary and graph, and the detailed assessment of the risk bias will be found in S1 File.

Primary endpoints

Hemoglobin level. ROX showed an increase in Hb level when compared to control (SMD: 1.65; 95% CI: 1.08, 2.22; P< 0.00001) (Fig 3, Forest plot A). Sensitivity analysis by omitting one study at a time showed a consistent result of ROX on Hb (S2 Table). Subgroup analysis to investigate the effect of the trial phase on the Hb level showed a similar result. Three RCTs were in Phase 2 (SMD: 3.01; 95% CI: 0.91, 5.11; P< 0.005) [29, 31, 32] and six RCTs





https://doi.org/10.1371/journal.pone.0266243.g001

were in phase three (SMD: 1.12; 95% CI: 0.49, 1.75; P< 0.0005) [14–16, 27, 28, 30] (S1 Fig). However, when we compared ROX to placebo, there was an increase in Hb level (SMD: 2.11; 95% CI: 1.58, 2.63; P< 0.00001), but when we compared ROX to darbepoetin alfa (DA), there was no difference between the two groups (SMD: -0.00; 95% CI: -0.14, 0.14; P< 1.00) (S2 Fig). There were only two RCTs that compared the effect of ROX to DA [14, 15], so more RCTs are needed to confirm the result.

Author, year	Location (sites number)	Study design	Study period	Groups	Number of patients	Age in years, Mean ± SD	Male ratio, %	Roxadustat dose	Study duration	Phase
Akizawa	izawa Japan (32)	Double-	2013-	Roxadustat	80	64.4 ± 8.7	48.80%	(50 mg,70 mg, and	24 weeks	2
et al. 2019 [<u>32]</u>		blinded RCT	2015	Placebo	27	61.9 ± 10.6	40.70%	100 mg) TIW		
Akizawa	Japan (71)	Open-label	2017-	Roxadustat	131	68.9 ± 11.6	63.40%	(70mg or 100mg) TIW	52 weeks	3
et al. 2021 [<u>14]</u>		RCT	2020	DA	131	70.9 ± 10.2	57.30%			
Barratt et al.	Europe (200)	Open-label	2014-	Roxadustat	323	66.8 ± 13.6	44.90%	(Weight 45 to 70 kg, 70	104 weeks	3
2021 [15]		RCT	2018	DA	293	65.7 ± 14.4	44%	mg; weight >70 to 160 kg, 100 mg) TIW		
Besarab	Besarab United States (29)	Single-	2008– 2010	Roxadustat	88	64	37.50%	(0.7, 1, 1.5 or 2 mg/kg)	4 weeks	2a
et al. 2015 [<u>33]</u>		blind RCT		Placebo	28	68.6	57.10%	BIW or TIW		
Chen et al.	Chen et al. China (11) 2017 [29]	Double-	2011– 2012	Roxadustat	61	48.9 ± 13.8	29.50%	low (1.1–1.75 mg/kg) or high (1.50–2.25 mg/kg) TIW	8 weeks	2
2017 [29]		blinded RCT		Placebo	30	51.4 ± 11.9	26.70%			
Chen et al.	China (29)	Double-	2015-	Roxadustat	101	54.7 ± 13.3	36%	(Weight 40 to <60 kg,	8 weeks	3
2019 [30]		blinded RCT	2016	Placebo	51	53.2 ± 13.1	39%	70mg; weight ≥60 kg, 100mg) TIW		
Coyne et al.	United States, South	Double-	2012-	Roxadustat	616	64.9 ± 12.6	39.10%	(Weight 45 to <70 kg,	28-52	3
2021 [28] America, Australia, New Zealand, and Asia (163)	blinded RCT	2018	Placebo	306	64.8 ± 13.2	43.50%	70mg; weight ≥70 kg, 100mg) TIW	weeks		
Fishbane	25 Countries (385)	Double-	2014-	Roxadustat	1384	60.9 ± 14.7	40.80%	70mg TIW	28-52	3
et al. 2021 [<u>34]</u>		blinded RCT	2018	Placebo	1377	62.4 ± 14.1	43.80%		weeks	
Shutov et al.	Different countries,	Double-	2013-	Roxadustat	391	58.25 ± 19.91	43.20%	(Weight 45 to \leq 70 kg,	52-104	3
2021 [16] mainly from Europe (138)	blinded RCT	2017	Placebo	203	60.5 ± 18.46	48.80%	70mg; weight >70 to ≤ 160 kg, 100mg) TIW	weeks		

Table 1. Characteristics of the included studies.

Continuous variables are expressed in mean \pm standard deviation.

RCT = randomized control trial; DA = darbepoetin alfa; TIW = three times a week; DIW = two times a week; SD: standard deviation.

https://doi.org/10.1371/journal.pone.0266243.t001

Iron parameters. When compared to the control group, ROX showed decrease in ferritin level (SMD: -0.32; 95% CI: -0.51, -0.14; P = 0.0006) (Fig 3, Forest plot B), TSAT (SMD: -0.19; 95% CI: -0.32, -0.07; P = 0.003) (Fig 3, Forest plot C), hepcidin (SMD: -0.74; 95% CI: -1.09, -0.39; P< 0.0001) (Fig 3, Forest plot D). And ROX showed increase in TIBC (SMD: 0.99; 95% CI: 0.76, 1.22; P< 0.00001) (Fig 3, Forest plot E), transferrin (SMD: 1.20; 95% CI: 0.70, 1.71; P< 0.00001) (Fig 3, Forest plot F). There was no difference between ROX and the control group regarding serum iron level (SMD: 0.53; 95% CI: -0.36, 1.42; P = 0.25) (Fig 3, Forest plot G).

Secondary endpoints

The ROX group showed higher serious adverse effects when compared to the control group (RR: 1.07; 95% CI: 1.01, 1.13; P = 0.01) (Fig 4, Forest plot A). Subgroup analysis comparing ROX to placebo showed a similar result (RR: 1.07; 95% CI: 1.01, 1.13; P = 0.03), However, subgroup analysis comparing ROX to DA showed no difference between the two groups (RR: 1.07; 95% CI: 0.95, 1.21; P = 0.26) (S3 Fig). There was no difference between both groups regarding the TEAEs (RR: 1.02; 95% CI: -1.00, 1.04; P = 0.08) (Fig 4, Forest plot B).

Cardiovascular-related adverse effect; Our results did not show a significant difference in the risk ratio of hypertensive crisis, pulmonary edema, heart failure, coronary artery diseases,

Author, Year	Groups	Race, n (%)	Bodyweight (kg)	eGFRc (mL/min/1.73 m2)	CKD stage	
Akizawa et al. 2019	Roxadustat	Japanese 80 (100%)	59.07 ± 9.83	16.3 ± 7.8	2 to 5	
[32]	Placebo	Japanese 27 (100%)	60.17 ± 8.72	16.3 ± 8.5]	
Akizawa et al. 2021	Roxadustat	Japanese 131 (100%)	N/A	17.9 ± 8.2		
[14]	DA	Japanese 131 (100%)	N/A	18.2 ± 8.8		
Barratt et al. 2021	Roxadustat	White 306 (94.7%), Black 8 (2.5%), Asian 9 (2.8%)	76.90 ± 16.33	20.31 ± 11.49	3 to 5	
[15]	DA	White 281 (95.9%), Black 2 (0.7%), Asian 10 (3.4%)	78.39 ± 17.68	20.34 ± 10.73		
Besarab et al. 2015	Roxadustat	White 49 (55.7%), Black 34 (38.6%), Asian 2 (2.3%)	N/A	34.3 ± 12.7	3 to 4	
[33]	Placebo	White 15 (53.6%), black 11 (39.3%), Asian 2 (7.1%)	N/A	31.4 ± 12.4		
Chen et al. 2017	Roxadustat	Chinese 61 (100%)	57.4 ± 11	19.4 ± 9.5	1 to 4	
[29]	Placebo	Chinese 30 (100%)	56.9 ±10.3	23.0 ±13.4		
Chen et al. 2019	Roxadustat	N/A	N/A	16.5 ± 8	3 to 5	
[30]	Placebo	N/A	N/A	14.5 ± 7.6		
Coyne et al. 2021	Roxadustat	N/A	N/A	21.9 ± 11.5	3 to 5	
[28]	Placebo	N/A	N/A	22.4 ± 11.4]	
Fishbane et al. 2021 [<u>34]</u>	Roxadustat	White 623 (45%), Black 112 (8.1%), Asian 544 (39.3%), American Indian 24 (1.7%)	69.9 ± 18.5	19.7 ± 11.7	3 to 5	
	Placebo	White 611 (44.4%), Black 115(8.4%), Asian 538 (39.1%), American Indian 29 (2.1%), Native Hawaiian 2 (0.1%)	70.6 ± 18.8	20 ± 11.7		
Shutov et al. 2021	Roxadustat	White 335 (85.7%), Black 10 (2.6%), Asian 9 (2.3%)	73.86 ± 16.49	16.5 ± 10.2	3 to 5	
[16]	Placebo	White 182 (89.7%), Black 3 (1.5%)	76.50 ± 16.51	17.2 ± 11.7		

Table 2. The patient demographics and baseline characteristics.

Continuous variables are expressed in mean \pm standard deviation.

DA = darbepoetin alfa; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; CPN = chronic pyelonephritis; PKD = Polycystic kidney disease; N/ A = not applicable.

https://doi.org/10.1371/journal.pone.0266243.t002

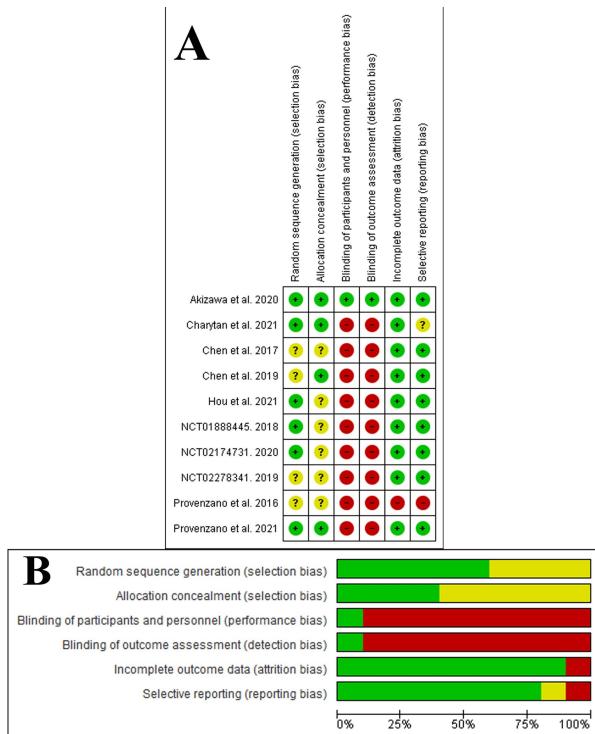
and MI (S4–S8 Figs). Meanwhile, significant risk was associated with ROX for HTN and (RR: 1.37; 95% CI: 1.13, 1.65; P = 0.001) (Fig 4, Forest plot C) and DVT (RR: 3.80; 95% CI: 1.5, 9.64; P = 0.08) (Fig 4, Forest plot D) respectively.

Meta-regression

Meta-regression on eight studies showed that resume therapy and iron supplementation led to decrease in the mean difference between the ROX and control group; (SMD: 1.65; 95% CI: 1.08, 2.22; P< 0.00001) before meta-regression versus (SMD: 2.78; 95% CI: .89,4.669; P = 0.009) after regression. A Scatter plot was created for better visualization (S9 and S10 Figs).

Discussion

In our updated meta-analysis of RCTs, we included 5359 NDD-CKD patients to evaluate the safety and efficacy of ROX compared to placebo or ESA. We concluded that ROX increased Hb level and improved iron utilization parameters by decreasing ferritin, TSAT, hepcidin, and increasing TIBC and transferrin. Those results can be contributed by the effect of ROX on HIF. Hypoxia-inducible factor (HIF) is a transcription factor protein that participates in iron homeostasis and regulates the expression of genes that stimulate erythropoiesis. It consists of an alpha-subunit (HIF- α) and a beta-subunit (HIF- β). HIF- α is oxygen-sensitive and induced by hypoxia, while HIF- β is a constitutive component [7]. Therefore, when the body's oxygen content is normal, the Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) will increase the breakdown of HIF [35]. Conversely, reduced oxygen transport in anemia induces



Low risk of bias 🗾 Unclear risk of bias 📕 High risk of bias

Fig 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; (?) some concerns. B Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

https://doi.org/10.1371/journal.pone.0266243.g002

Study or Subgroup	Rox Mean	adustat SD T	otal I	Co Mean	ntrol SD T	otal V		I. Mean Difference IV, Random, 95% CI		IV, Random	ifference	
kizawa et al. 2021	0.15		131				11.6%	-0.10 [-0.34, 0.14]		+	,	
Akizwa et al. 2019	1.32	0.8	80		0.61		0.8%	1.95 [1.44, 2.46]			-	
Barratt et al. 2021	1.71		287				11.7%	0.04 [-0.12, 0.21]		+		
Besarab et al. 2015	1.75	0.34			0.11	23	8.8%	5.97 [4.99, 6.95]				-
Chen et al. 2017 Chen et al. 2019	1.97 1.9	1.4 1.2	61 93	0.37	0.87		10.9%	1.27 [0.79, 1.74] 2.11 [1.67, 2.54]			T_	
Coyne et al. 2013	2		608	0.16			1.7%	1.97 [1.80, 2.13]				
Fishbane et al. 2021	1.75		334		1.24 1		1.8%	1.10 [1.02, 1.18]				
Shutov et al. 2021	1.98		321				11.6%	1.65 [1.43, 1.87]				
Tetel (DEV CI)		2	988		2	204 4	00.0%	4 65 14 00 2 221				
Total (95% CI)	0.721.014			0 (0 -		304 1		1.65 [1.08, 2.22]			•	
Heterogeneity: Tau² = Test for overall effect:				8 (P <	0.0000	1), 1-= :	18 %		-4	-2 0	2 4	
				rimo		toom		amai 1 2 Earriti		Control F	Roxadustat	
B-Forest plot c			1:1 P			tcom	es, outo	come: 1.2 Ferriti Std. Mean Difference	n.			
Study or Subgroup	Mean	cadustat	Total	Mean	Control	D Tota	Weight			Std. Mean I IV, Randor		
Akizawa et al. 2021	-23.37	47.42	131	-33.16				0.25 [0.01, 0.50]		IV, Kalluo	1, 35% CI	
Akizwa et al. 2019	-32.7	53.9	80	-16.5				-0.33 [-0.76, 0.11]			-	
Barratt et al. 2021	-89.28	476.17	323	26.45				-0.19 [-0.35, -0.03]				
Besarab et al. 2015	-68.8	70.1	66	-37.8				-0.47 [-1.00, 0.05]			-	
Chen et al. 2017 Chen et al. 2019	-110 -93.3	131 146.3	61 85	-28				-0.72 [-1.17, -0.27] -0.52 [-0.89, -0.15]	_			
Covne et al. 2021	-48.43	252.39	478	6.53				-0.24 [-0.41, -0.07]				
ishbane et al. 2021			1200		241.2			-0.22 [-0.31, -0.14]		-		
Shutov et al. 2021	-76.92	121.64	391	31.67			3 13.5%	-0.73 [-0.90, -0.55]		-		
Fotal (95% CP			2815			100	2 100.0%	0321054 044				
Fotal (95% CI) Heterogeneity: Tau² = (106:06#	= 57 62 -		0 < 0.00	0011-12		2 100.0%	-0.32 [-0.51, -0.14]		-		
Heterogeneity: Tau= = 1 Fest for overall effect: 2	= 3,45 (P	= 02.03, 0 = 0,0009	л = 8 (ł j)	~ 0.00	1001); I*	- 00%			-1	-0.5 0		1
					~		2			Roxadustat	Control	
C-Forest plot o			1: 1 P			tcom		come: 1.3 TSAT	(%).	C44 11		
Study or Subgroup	Rox Mean	adustat SD 1	Total I	Co Mean	ontrol SD	Total	S1 Weight	d. Mean Difference IV, Random, 95% CI		Std. Mean D IV, Randon		
Akizawa et al. 2021		13.33	131		13.05	131	11.7%	-0.15 [-0.40, 0.09]				
Akizwa et al. 2019	-1.2	12.2	80	0.2	10.2	27	6.0%	-0.12 [-0.55, 0.32]				
Barratt et al. 2021	0.5	11.9	323	5	13.3	293	15.5%	-0.36 [-0.52, -0.20]		-		
Besarab et al. 2015	-8.1	9.3	67	-3.1	7.8	18	4.5%	-0.55 [-1.08, -0.02]		-		
Chen et al. 2017 Chen et al. 2019	-6.35	9.78	61	0.24	7.92	30 43	5.7%	-0.71 [-1.16, -0.26]				
Chen et al. 2019 Covne et al. 2021	-5.2 1.13	10.4 13.41	85 476	-1.7	9.2 10.71	43	7.5% 15.0%	-0.35 [-0.72, 0.02] 0.00 [-0.17, 0.17]		1		
Fishbane et al. 2021						1047	18.9%	-0.05 [-0.14, 0.03]		-		
Shutov et al. 2021	-0.81		391		19.91		15.0%	-0.07 [-0.24, 0.10]				
										•		
Total (95% CI)			2813			1977	100.0%	-0.19 [-0.32, -0.07]		•		1
Heterogeneity: Tau ² = Test for overall effect:				(P = 0.1	002); 1*:	= 67%			-1	-0.5 0 Roxadustat	0.5	1
Study or Subgroup		xadustat			Control			std. Mean Difference		Std. Mean D	lifference	
Akizawa et al. 2021	Mean -14.22	SD 34.22	201	Mean -9.953	s 35.4	D Tota 6 131	Weight	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10]	H		hifference n, 95% Cl	
Akizawa et al. 2021 Akizwa et al. 2019	Mean -14.22 -9.7	SD 34.22 26.7	201 80	Mean -9.953 2.4	35.4 39.	D Tota 6 131 6 21	I Weight 13.8% 7 11.9%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04]	H	Std. Mean D	Vifference n, 95% Cl	
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2015	Mean -14.22	SD 34.22 26.7	201	Mean -9.953	s 35.4 39. 39. 14	D Tota 6 131 6 21 4 18	Veight 13.8% 11.9% 10.9%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10]		Std. Mean D	Vifference n, 95% Cl	
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2019	Mean -14.22 -9.7 -144.58 -37.5 -56.14	SD 34.22 26.7 165.36 6.73 63.4	201 80 67 61 86	Mean -9.953 2.4 -17.8 -4.8 -15.1	s 35.4 39. 39. 39. 39. 39. 39. 39. 39. 39. 39.	D Tota 6 131 6 27 4 18 7 30 6 44	Weight 13.8% 11.9% 10.9% 10.9% 10.9% 12.5%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04] -0.78 [-1.31, -0.26] -4.48 [-5.28, -3.69] -0.70 [-1.07, -0.32]		Std. Mean D	vifference n, 95% CI	
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2019 Coyne et al. 2021	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11	SD 34.22 26.7 165.36 6.73 63.4 80.9	201 80 67 61 86 396	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88	s 35.4 39. 39. 30. 30. 30. 30. 30. 30. 30. 30. 30. 30	D Tota 6 131 6 23 4 18 7 30 6 44 3 153	Weight 13.8% 11.9% 10.9% 8.3% 12.5% 14.0%	Std. Mean Difference IV, Random, 95% Cl -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04] -0.78 [-1.31, -0.26] -4.48 [-5.28, -3.69] -0.70 [-1.07, -0.32] -0.32 [-0.51, -0.13]		Std. Mean D	Nifference n, 95% Cl	
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2019	Mean -14.22 -9.7 -144.58 -37.5 -56.14	SD 34.22 26.7 165.36 6.73 63.4	201 80 67 61 86	Mean -9.953 2.4 -17.8 -4.8 -15.1	S 35.4 39.35.4 39. 14 8.1 48.0 80.9 2115.8 115.8	D Tota 6 131 6 23 4 18 7 30 6 44 3 152 6 604	Weight 13.8% 11.9% 10.9% 8.3% 12.5% 14.0% 14.4%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04] -0.78 [-1.31, -0.26] -4.48 [-5.28, -3.69] -0.70 [-1.07, -0.32] -0.32 [-0.51, -0.13] -0.39 [-0.50, -0.28]		Std. Mean D	vifference n, 95% Cl	
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2019 Chen et al. 2017 Chen et al. 2019 Coyne et al. 2021 Fishbane et al. 2021 Shutov et al. 2021	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8	201 80 67 86 396 658 391	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42	S 35.4 39.35.4 39. 14 8.1 48.0 80.9 2115.8 115.8	D Tota 6 131 6 21 4 18 7 30 6 44 3 152 6 604 9 203	Weight 13.8% 11.9% 10.9% 8.3% 12.5% 14.0% 14.2%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04] -0.78 [-1.31, -0.25] -4.48 [-5.28, -3.69] -0.70 [-1.07, -0.32] -0.32 [-0.51, -0.13] -0.39 [-0.50, -0.28] -0.23 [-0.40, -0.06]		Std. Mean D	hifference n, 95% CI	
Akizawa et al. 2021 Akizawa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Coyne et al. 2021 Coyne et al. 2021 Shutov et al. 2021 Total (95% CI)	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46	201 80 67 61 86 396 658 391 1940	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715	S 35.4 39.35.4 39.3 14 39.3 8 14 8 8.1 48.0 80.9 2 115.8 5 53.0	D Tota 6 131 6 23 4 18 7 30 6 44 3 152 6 604 9 203 1209	Weight 13.8% 11.9% 10.9% 10.9% 11.25% 14.0% 14.0% 14.2% 10.0%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04] -0.78 [-1.31, -0.26] -4.48 [-5.28, -3.69] -0.70 [-1.07, -0.32] -0.32 [-0.51, -0.13] -0.39 [-0.50, -0.28]		Std. Mean D	hifference n, 95% CI	1
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Coyne et al. 2021 Shutov et al. 2021 Total (95% CI) Heterogeneity: Tau ² =	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi [≥]	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37	201 80 67 61 86 396 658 391 1940 , df = 7	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715	S 35.4 39.35.4 39.3 14 39.3 8 14 8 8.1 48.0 80.9 2 115.8 5 53.0	D Tota 6 131 6 23 4 18 7 30 6 44 3 152 6 604 9 203 1209	Weight 13.8% 11.9% 10.9% 10.9% 11.25% 14.0% 14.0% 14.2% 10.0%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04] -0.78 [-1.31, -0.25] -4.48 [-5.28, -3.69] -0.70 [-1.07, -0.32] -0.32 [-0.51, -0.13] -0.39 [-0.50, -0.28] -0.23 [-0.40, -0.06]		Std. Mean D IV, Randon	n, 95% CI	4
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2019 Chen et al. 2017 Chen et al. 2019 Coyne et al. 2021 Fishbane et al. 2021 Shutov et al. 2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect. 2	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi ² ; Z= 4.18 (P	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001	201 80 67 61 86 396 658 391 1940 df = 7	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715 (P < 0.0	S 35.4 39.35.4 39.3 14 39.3 14 8.1 48.0 80.9 115.8 53.0 500001);1 100001);1	D Tota 6 133 6 23 4 18 7 36 6 44 3 152 6 604 9 203 1209 *= 94%	I Weight 13.8% 11.9% 7 11.9% 3 10.9% 0 8.3% 4 12.5% 2 14.0% 4 14.4% 3 14.2% 9 100.0%	Std. Mean Difference IV, Random, 95% Cl -0.12 (-0.34, 0.10) -0.40 (-0.83, 0.04) -0.78 (-1.31, -0.25) -4.48 (-5.28, -3.69) -0.70 (-1.07, -0.32) -0.32 (-0.51, -0.13) -0.39 (-0.50, -0.28) -0.23 (-0.40, -0.06) -0.74 [-1.09, -0.39]	-4	Std. Mean D	n, 95% CI	4
Akizawa et al. 2021 Akizwa et al. 2019 Besarab et al. 2019 Chen et al. 2017 Chen et al. 2019 Coyne et al. 2021 Fishbane et al. 2021 Shutov et al. 2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect. 2	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi ² , Z = 4.18 (P	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001	201 80 67 61 86 396 658 391 1940 df = 7	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima	S 35.4 39.35.4 39.3 14 39.3 8 14 8 8.1 48.0 38.9 2 115.8 5 53.0 000001); I Image: State of the	D Tota 6 131 6 21 4 18 7 30 6 44 3 152 6 604 9 203 ² =94%	I Weight 1 13.8% 1 13.8% 1 10.9% 3 10.9% 4 12.5% 2 14.0% 3 14.2% 9 100.0%	Std. Mean Difference IV, Random, 95% CI -0.12 [-0.34, 0.10] -0.40 [-0.83, 0.04] -0.78 [-1.31, -0.25] -4.48 [-5.28, -3.69] -0.70 [-1.07, -0.32] -0.32 [-0.51, -0.13] -0.39 [-0.50, -0.28] -0.23 [-0.40, -0.06]	-4	Std. Mean D IV, Randon	n, 95% CI	4
Akizawa et al. 2021 Akizawa et al. 2019 Besarab et al. 2016 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Fishbane et al. 2021 Shutov et al. 2021 Total (95% CI) Heterogeneity: Tau ^a = Test for overall effect. 2 E.Forest plot of Study or Subgroup	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi ² , Z = 4.18 (P pof comj Rox Mean	SD 34.22 26.7 165.36 6.73 6.34 80.9 116.8 47.46 = 115.37 < 0.0001 pariso xadustat SD	201 80 67 61 396 658 391 1940 df = 7)) n: 1 I	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima Mean	s 35.4 39. 14 8.1 48.0 80.9 115.8 53.0 00001); 1 00001); 1 00001]; 1 000001]; 1 0000001]; 1 0000001]; 1 0000001]; 1 0000001]; 1 0000000]; 1 0000000]; 1 0000000]; 1 0000000]; 1 000000]; 1 0000000]; 1 0000000]; 1 0000000]; 1 0000000]; 1 000000]; 1 00000]; 1 0000]; 1 00000]; 1 000000]; 1 00000]; 1 00000]; 1 00000]; 1 00000]; 1 00000];	D Tota 6 131 6 21 4 18 7 30 6 44 3 152 6 60 9 203 1209 2 94% 1209 2 94%	Weight 13.8% 7 11.9% 10.9% 10.9% 11.5% 2 14.0% 14.4% 14.4% 14.0% 10.0% 100.0%	Std. Mean Difference W. Random, 95% CI 0.12 (0.34, 0.10) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.478 (1.31, -0.25) -4.46 (5.28, -369) -0.32 (1.63, -0.28) -0.32 (1.63, -0.28) -0.32 (1.64, -0.08) -0.74 (-1.09, -0.39) CCOME: 1.5 TIBC Std. Mean Difference V, Random, 95% C	 (µg/dL).	Std. Mean D IV, Randon	n, 95% CI	4
Akizawa et al. 2021 Akizawa et al. 2021 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2019 Come et al. 2021 Soutov et al. 2021 Shutov et al. 2021 Total (95% CI) Heterogeneity: Tau* = Test for overail effect : E.Forest plot et Study or Subgroup Witzawa et al. 2021	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi ² , Z = 4.18 (P of comp Rox Mean 5.5	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001 pariso cadustat SD 7.49	201 80 67 61 86 396 658 391 1940 , df = 7)) n: 1 I Total 131	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima Mean 0.6	S 35.4 39.35.4 39.3 14 39.3 14 8.0 8 80.9 115.8 53.0 00001); I 1 00001); I 1 Control SI 4.1: 5.1	D Tota 6 13' 6 23 4 18 7 30 6 44 3 152 6 604 9 203 1209 ² = 94% 1209 ² = 100 ² = 1000 ² =	Weight 13.8% 7 11.9% 10.9% 8.3% 12.5% 2 2 4 14.0% 3 14.2% 100.0%	Std. Mean Difference //, Random, 95% cf -0.12 (0.34, 0.01) -0.40 (0.63, 0.04) -0.78 (1.31, 0.22) -0.74 (1.32, 0.22) -0.21 (0.1, 0.13) -0.23 (0.40, 0.06) -0.23 (0.40, 0.03) -0.23 (0.40, 0.03) -0.74 (-1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference (V, Random, 95% C 0.81 (0.56, 1.06)		Std. Mean D IV, Randon	n, 95% CI	4
Akizawa et al. 2021 Akizawa et al. 2021 Besarab et al. 2015 Chenn et al. 2017 Chen et al. 2017 Chen et al. 2017 Fishbane et al. 2021 Shutor et al. 2021 Total (95% CI) Heterogeneity: Tau" = Test for overall effect : E.Forest plote et Study or Subgroup Micrawa et al. 2021	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi² Z = 4.18 (P of comp Mean 6.5 37.42	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001 pariso cadustat SD 7.49 45.23	201 80 67 61 86 396 658 391 1940 df = 7) n: 1 I Total 131 80	Mean -9.953 2.4 -17.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima Mean 0.6 5.03	S 35.4 39.35.4 39.3 143 8.1 8 8.1 8 8.1 8 8.1 9 115.8 5 53.0 000001); I 1	D Tota 6 13 6 23 4 18 7 30 6 44 3 15 6 60 9 20 1209 ² = 94% 1209 ² = 94% ² = 94% ² = 94% ² = 94% ² = 94% ² = 94% ² = 94% ² = 94% ² = 94% ² = 94% ² =	Weight 13.8% 7 11.9% 3 10.9% 3 10.9% 3 11.9% 2 10.9% 11.1% 11.2% 11.1% 11.1% 11.1% 11.1% 11.6%	Std. Mean Difference W. Random, 95% CI 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.433, 0.04) 0.41 (0.17, 0.23) 0.32 (0.50, 0.28) 0.32 (0.50, 0.28) 0.32 (0.40, 0.06) 0.74 (1.09, 0.39) CCOME: 1.5 TIBC Std. Mean Difference W. Random, 95% C 0.81 (0.56, 1.06) 0.79 (0.34, 1.24)		Std. Mean D IV, Randon	n, 95% CI	4
Akizawa et al. 2021 Akizawa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Fishbane et al. 2021 Total (95% CI) Heterogeneity, Tau ² = Test for overall effect: E.F.Orest plot (Study of Subgroup Widzawa et al. 2021 Widzwa et al. 2021	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi ² , Z = 4.18 (P of comp Rox Mean 5.5	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001 pariso cadustat SD 7.49	201 80 67 61 86 396 658 391 1940 , df = 7)) n: 1 I Total 131	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima Mean 0.6	S 35.4 39.3 14 39.3 14 81.1 48.0 82.115.8 53.0 000001);1 115.8 000001);1 53.0 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 000001);1 115.8 011 115.8 02 115.8 03 115.8 04.11 115.8 05.8 115.8 05.8	D Tota 6 131 6 23 4 18 7 30 6 44 3 152 6 604 9 203 1209 ≈ = 94% 1209 ≈ = 94% 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 1209 12	Weight 13.8% 11.9% 10.9% 10.9% 10.9% 10.9% 10.9% 11.9% 10.9% 11.9% 11.1% 11.1% 11.1% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0%	Std. Mean Difference //, Random, 95% cf -0.12 (0.34, 0.01) -0.40 (0.63, 0.04) -0.78 (1.31, 0.22) -0.74 (1.32, 0.22) -0.21 (0.1, 0.13) -0.23 (0.40, 0.06) -0.23 (0.40, 0.03) -0.23 (0.40, 0.03) -0.74 (-1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference (V, Random, 95% C 0.81 (0.56, 1.06)		Std. Mean D IV, Randon	n, 95% CI	4
Akizawa et al. 2021 Akizawa et al. 2021 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Fichbane et al. 2021 Total (95% C) Heterogeneity. Tau* = Test for overal effect: E.F.Orest plot (Study of Subgroup Ukdzawa et al. 2021 Ukdzwa et al. 2021 Ukdzwa et al. 2021 Chen et al. 2019	Mean -14.22 -9.7 -144.58 -37.5 -566.14 -22.11 -35.94 -13.22 0.21; Chi ²¹ ; 0.21; Chi ²¹ ; 60 f comj Rox Mean 537.42 41.8 84.3 101.64	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001 pariso cadustat SD 7.49 45.23 45.4 55.1 66.79	201 80 67 61 996 658 391 1940 , df=7)) n: 1 I 131 80 67 61 85	<u>Mean</u> -9.953 2.4 -17.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima 0.6 5.03 -7.6 1.2 -1.84	S 35.4 39.35.4 39.3 143 8.14 8.14 88.1 48.09 80.9 2.115.8 53.0 000001);1 1 000001);1 1 000001);1 1 000001);1 2 000001);1 2 000001);1 2 000001);1 2 000001);1 2 000001);1 2 000001);1 2 000001);1 2 000001);1 2 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1 3 000001);1	D Tota 6 133 6 27 7 3(6 4/ 13 155 7 3(6 4/ 9 203 1209 9 203 1209 1209 1209 1209 1209 1209 1209 1209	Weight 13.8% 11.9% 10.9% 11.9% 10.9% 10.9% 12.5% 14.12% 14.2% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 10.3% 10.3%	Std. Mean Difference //, Random, 95% cf -0.12 { 0.34, 0.10, 95% cf -0.12 { 0.34, 0.10, 95% cf -0.40 { 0.63, 0.04, -0.78 { 0.34, 0.10, 95% cf -0.40 { 0.63, 0.04, -0.78 { 0.34, 0.10, -0.34 { 0.34, 0.10, 0.34} 0, -0.74 { 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.35, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34, 0.34 { 0.	 (µg/dL).	Std. Mean D IV, Randon	n, 95% CI	4
Akizawa et al. 2021 Akizawa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Shutov et al. 2021 Shutov et al. 2021 Test for overall effect 2 E.Forest plot et Study or Subgroup Maxwa et al. 2021 Skizawa et al. 2019 Besarab et al. 2019 Besarab et al. 2017 Chen et al. 2017 Chen et al. 2017	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi² 2 0.21; Chi² 6.61 Rox Mean 5.5 37.42 41.8 84.3 101.64 35.07	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001 pariso cadustat SD 7.49 45.23 45.4 55.1 66.79 62.14	201 80 67 61 89 658 396 658 391 1940 df=7) Total 131 80 67 61 85 608	<u>Mean</u> -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima 0.6 5.03 -7.6 1.2 -1.84 -3.58	S 35.4 39.35.4 39.3 144 8.1 48.0 80.9 2115.85 53.0 00001); I 1 Intry Ou 0 Control 51 26.1 22. 54.1 26.1 26.1 22. 54.1 26.1	D Tota 6 131 7 3(6 44) 7 3(6 44) 6 649 9 203 1209 1209 1209 1209 1209 1209 1209 1209	Weight 13.8% 11.9% 10.9% 11.9% 10.9% 11.9% 10.9% 12.5% 14.4% 14.4% 14.4% 14.2% 100.0% ess, out Weight 16.7% 116.8% 9.5% 10.3% 12.3%	Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.41 (0.15, 0.23) 0.42 (0.15, 0.13) 0.32 (0.50, 0.28) 0.32 (0.40, 0.05) 0.74 (1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% C 0.81 (0.56, 1.06) 0.79 (0.34, 1.24) 1.75 (1.25, 2.26) 1.64 (1.22, 2.06) 0.83 (0.49, 0.77) 0.84 (1.22, 2.06) 0.83 (0.49, 0.77)	 (µg/dL).	Std. Mean D IV, Randon	n, 95% CI	
Akizawa et al. 2021 Akizawa et al. 2021 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Shutov et al. 2021 Shutov et al. 2021 Total (95% C) Heterogeneity: Tau" = E.Forest plote Study or Subgroup Mazawa et al. 2021 Mazawa et al. 2019 Besarab et al. 2019 Shen et al. 2017 Chen et al. 2017 Chen et al. 2017	Mean -14.22 -9.7 -144.58 -37.5 -566.14 -22.11 -35.94 -13.22 0.21; Chi ²¹ ; 0.21; Chi ²¹ ; 60 f comj Rox Mean 537.42 41.8 84.3 101.64	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001 pariso cadustat SD 7.49 45.23 45.4 55.1 66.79 62.14	201 80 67 61 89 658 396 658 391 1940 df=7) Total 131 80 67 61 85 608	<u>Mean</u> -9.953 2.4 -17.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima 0.6 5.03 -7.6 1.2 -1.84	S 35.4 39.35.4 39.3 144 8.1 48.0 80.9 2115.85 53.0 00001); I 1 Intry Ou 0 Control 51 26.1 22. 54.1 26.1 26.1 22. 54.1 26.1	D Tota 6 131 7 3(6 44) 7 3(6 44) 6 649 9 203 1209 1209 1209 1209 1209 1209 1209 1209	Weight 13.8% 11.9% 10.9% 11.9% 10.9% 11.9% 10.9% 12.5% 14.4% 14.4% 14.4% 14.2% 100.0% ess, out Weight 16.7% 116.8% 9.5% 10.3% 12.3%	Std. Mean Difference //, Random, 95% cf -0.12 { 0.34, 0.10, 95% cf -0.12 { 0.34, 0.10, 95% cf -0.40 { 0.63, 0.04, -0.78 { 0.34, 0.10, 95% cf -0.40 { 0.63, 0.04, -0.78 { 0.34, 0.10, -0.34 { 0.34, 0.10, 0.34} 0, -0.74 { 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34} 0, -0.34 { 0.34, 0.10, 0.34 { 0.34, 0.10, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34} 0, -0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.34, 0.35, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34} 0, -0.34 { 0.35, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34, 0.34 { 0.34, 0.34, 0.34, 0.34, 0.34 { 0.	 (µg/dL).	Std. Mean D IV, Randon	n, 95% CI	<u>+</u> -
Akizawa et al. 2021 Akizawa et al. 2021 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Fishbane et al. 2021 Bishutor et al. 2021 Total (95% CI) Total (95% CI) Total (95% CI) E.F.Grees theorem Bishorem et al. 2021 Kizawa et al. 2018 Bisearab et al. 2019 Bisearab et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi² 2 0.21; Chi² 6.61 Rox Mean 5.5 37.42 41.8 84.3 101.64 35.07	SD 34.22 26.7 165.36 6.73 63.4 80.9 116.8 47.46 = 115.37 < 0.0001 pariso cadustat SD 7.49 45.23 45.4 55.1 66.79 62.14	201 80 67 61 89 658 396 658 391 1940 df=7) Total 131 80 67 61 85 608	<u>Mean</u> -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.715 (P < 0.0 Prima 0.6 5.03 -7.6 1.2 -1.84 -3.58	S 35.4 39.35.4 39.3 144 8.1 48.0 80.9 2115.85 53.0 00001); I 1 Intry Ou 0 Control 51 26.1 22. 54.1 26.1 26.1 22. 54.1 26.1	D Tota 6 131 7 3(6 44) 7 3(6 44) 6 649 9 203 1209 1209 1209 1209 1209 1209 1209 1209	I Weight 1 13.8% 7 11.9% 8 3% 9 8.3% 4 12.5% 2 14.0% 4 14.2% 9 100.0% ees, out 1 Meight 16.7% 9.5% 10.3% 9.5% 10.3% 12.3% 20.2% 20.2%	Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.41 (0.15, 0.23) 0.42 (0.15, 0.13) 0.32 (0.50, 0.28) 0.32 (0.40, 0.05) 0.74 (1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% C 0.81 (0.56, 1.06) 0.79 (0.34, 1.24) 1.75 (1.25, 2.26) 1.64 (1.22, 2.06) 0.83 (0.49, 0.77) 0.84 (1.22, 2.06) 0.83 (0.49, 0.77)	 (µg/dL).	Std. Mean D IV, Randon	n, 95% CI	
Akizawa et al. 2021 Akizawa et al. 2021 Akizawa et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Shutov et al. 2021 Shutov et al. 2021 E.Forest plot et al. 2021 E.Forest plot et al. 2021 E.Forest plot et al. 2021 B.Forest plot et al. 2021 Diseasa et al. 2021 Diseasa et al. 2017 Chen et al. 2021 Total (95% C) eterscoperior Laver	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.211 -35.94 -13.22 0.21; Chi ^p 2= 4.18 (P pof comp Rox Mean 5.5 37.42 41.8 84.3 101.64 35.07 177.95 0.07; Chi ^p	SD 34.22 34.22 26.7 185.36 6.73 6.73 80.9 116.8 80.9 116.8 47.46 = 115.37 26.7 pariso 26.7 7.49 45.23 45.4 55.1 66.79 45.24 267.48 267.48 = 37.43, ' 27.43, '	201 80 67 18 86 396 658 391 1940 df = 7) Total 131 80 67 131 80 67 608 1200 2232 2df = 6 (0	<u>Mean</u> -9.953 2.44 -17.8 -17.8 -4.8 -17.1 9.42 -1.715 (P < 0.0 Prima (P < 0.0 Prima 0.6 5.03 -7.6 5.03 -7.1.84 -3.58 -21.33	I S 3 35.4 3 36.4 8 3.1 4 8.1 48.0 80.9 2 115.8 5 53.0 000001); 1 1 rry Ou SI 4.1:: 21.7: 26:: 22: 5 60.1 26:1.2: 26:1.2:	D Tota 6 13:1 6 2: 4 11 7 3: 1209 1209 1209 1209 1209 1209 1209 1209	Weight 13.8% 11.9% 11.9% 11.9% 11.9% 211.0% 214.0% 412.5% 14.4% 14.4% 14.2% 100.0% ess, out 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% </td <td>Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.41 (0.15, 0.23) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.34 (1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% C 0.81 (0.51, 106) 0.79 (0.34, 1.24) 1.75 (1.25, 2.26) 1.64 (1.22, 2.06) 0.83 (0.49, 0.77) 0.73 (0.64, 0.82)</td> <td></td> <td>Std. Mean L V, Randou + + + + + + + + + + + + +</td> <td>1 2 Control Difference m, 95% Cl</td> <td>+ + + + -</td>	Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.41 (0.15, 0.23) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.34 (1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% C 0.81 (0.51, 106) 0.79 (0.34, 1.24) 1.75 (1.25, 2.26) 1.64 (1.22, 2.06) 0.83 (0.49, 0.77) 0.73 (0.64, 0.82)		Std. Mean L V, Randou + + + + + + + + + + + + +	1 2 Control Difference m, 95% Cl	+ + + + -
Akizawa et al. 2021 Akizawa et al. 2021 Akizawa et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Shutov et al. 2021 Shutov et al. 2021 E.Forest plot et al. 2021 E.Forest plot et al. 2021 E.Forest plot et al. 2021 B.Forest plot et al. 2021 Diseasa et al. 2021 Diseasa et al. 2017 Chen et al. 2021 Total (95% C) eterscoperior Laver	Mean -14.22 -9.7 -144.58 -37.5 -56.14 -22.211 -35.94 -13.22 0.21; Chi ^p 2= 4.18 (P pof comp Rox Mean 5.5 37.42 41.8 84.3 101.64 35.07 177.95 0.07; Chi ^p	SD 34.22 34.22 26.7 185.36 6.73 6.73 80.9 116.8 80.9 116.8 47.46 = 115.37 26.7 pariso 26.7 7.49 45.23 45.4 55.1 66.79 45.24 267.48 267.48 = 37.43, ' 27.43, '	201 80 67 18 86 396 658 391 1940 df = 7) Total 131 80 67 131 80 67 608 1200 2232 2df = 6 (0	<u>Mean</u> -9.953 2.44 -17.8 -17.8 -4.8 -17.1 9.42 -1.715 (P < 0.0 Prima (P < 0.0 Prima 0.6 5.03 -7.6 5.03 -7.1.84 -3.58 -21.33	I S 3 35.4 3 36.4 8 3.1 4 8.1 48.0 80.9 2 115.8 5 53.0 000001); 1 1 rry Ou SI 4.1:: 21.7: 26:: 22: 5 60.1 26:1.2: 26:1.2:	D Tota 6 13:1 6 2: 4 11 7 3: 1209 1209 1209 1209 1209 1209 1209 1209	Weight 13.8% 11.9% 11.9% 11.9% 11.9% 211.0% 214.0% 412.5% 14.4% 14.4% 14.2% 100.0% ess, out 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% </td <td>Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.41 (0.15, 0.23) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.34 (1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% C 0.81 (0.51, 106) 0.79 (0.34, 1.24) 1.75 (1.25, 2.26) 1.64 (1.22, 2.06) 0.83 (0.49, 0.77) 0.73 (0.64, 0.82)</td> <td></td> <td>Std. Mean L V, Randoo Roxadustat Std. Mean IV, Randoo</td> <td>1 2 Control Difference m, 95% Cl</td> <td>- - -</td>	Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.41 (0.15, 0.23) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.34 (1.09, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% C 0.81 (0.51, 106) 0.79 (0.34, 1.24) 1.75 (1.25, 2.26) 1.64 (1.22, 2.06) 0.83 (0.49, 0.77) 0.73 (0.64, 0.82)		Std. Mean L V, Randoo Roxadustat Std. Mean IV, Randoo	1 2 Control Difference m, 95% Cl	- - -
Akizawa et al. 2021 Akizawa et al. 2021 Akizawa et al. 2018 Chen et al. 2016 Chen et al. 2017 Chen et al. 2021 Fishbane et al. 2021 Total (95% C) Heterogenetiy. Tau ² =: E.F.Orest plot et Study or Subproup Mitsawa et al. 2021 Mitsawa et al. 2021 Bearanb et al. 2019 Dearanb et al. 2019 Dearanb et al. 2019 Dearanb et al. 2019 Dearanb et al. 2021 Shenn e	Mean -14.22 -9.7 -14.458 -56.14 -22.11 -35.94 -13.22 -56.14 -13.22 -56.14 -13.22 -56.14 -13.22 -35.94 -13.22 -35.94 -13.22 -35.94 -13.22 -35.94 -13.22 -35.94 -13.22 -35.94 -13.22 -35.94 -13.22 -35.94 -13.22 -35.94 -13.22 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.12 -14.14 -14.14 -14.14 -14.14 -14.14 -14.14 -14.14 -14.14 -14.14 -14.	SD 34.22 26.7 265.36 6.73 63.4 80.9 1165.36 63.4 80.9 116.8 47.46 90.0001 pariso cadustat SD 45.1 66.79 62.14 267.48 93.74.3, < 0.0000	201 80 67 61 86 658 391 1940 , df = 7) Total 131 80 67 61 85 608 1200 2232 df = 6 (0 11)	<u>Meam</u> -9.953 2.4 -17.8 -4.8 9.942 9.942 9.42 9.42 9.42 9.42 9.42 9.	I S 3 35.4 3 35.4 3 31.4 3 31.4 3 31.4 3 31.4 48.0 39.9 11.1 48.0 3 80.9 2 115.8 8 80.9 00001); I 115.8 00001); I 115.8 00001); I 22: 261.2 20001); I 00001); I 77	D Tota 6 13: 6 13: 6 13: 6 13: 6 14: 13 15: 9 20: 120: 9 20: 13: 13: 13: 13: 13: 120: 14: 13: 13: 13: 13: 13: 13: 13: 13: 14: 14: 14: 14: 14: 14: 14: 14: 14: 14	I Weight 1 13.8% 7 11.9% 10.9% 10.8% 1 12.5% 1 21.6% 1 21.6% 1 21.6% 1 12.5% 1 14.4% 3 14.2% 9 100.0% EES, out 11.3% 1.23% 9.5% 1.23% 12.3% 1.23% 12.3% 1.23% 10.0%	Std. Mean Difference /V. Random, 95% cf -0.12 [0.34, 0.10] -0.40 [0.38, 0.04] -0.40 [0.38, 0.04] -0.40 [0.38, 0.04] -0.40 [0.38, 0.04] -0.41 [0.38, 0.04] -0.41 [0.41, 0.38, 0.04] -0.21 [0.40, -0.06] -0.21 [0.40, -0.06] -0.21 [0.40, -0.08] -0.21 [0.4	 (µg/dL).	Std. Mean L V, Randon Roxadustat Std. Mean N, Rando	1 Control Difference m, 95% Cl	- - 2
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2019 Chen et al. 2017 Chen et al. 2021 Fichban et al. 2021 Shudov et al. 2021 Total (95% C) Heterogeneity: Tau" = Test for overall effect: Study or Subgroup. Kutyawa et al. 2019 Chen et al. 2021 Fishbane et al. 2021	Mean -14.22 -9.7 -7.44.58 -37.5 -56.14 -22.11 -35.94 -13.22 -35.94 -13.22 -21.1 -35.94 -13.22 -21.1 -35.94 -13.22 -21.1 -35.94 -13.22 -21.1 -35.94 -13.22 -21.1 -13.22 -21.1 -13.22 -21.1 -13.22 -21.1 -13.22 -21.1 -13.22 -21.1 -13.22 -21.1 -21.21 -21.1 -21.21 -21.1 -21.21 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1 -21.1	SD 34.22 26.7 186.36 6.73 63.4 83.4 83.4 93.4 83.4 83.4 80.9 116.8 81.4 93.4 83.4 93.4 83.4 93.4 83.4 93.4 93.4 94.5 93.4 94.5 94.5 94.5 94.5 94.5 94.5 94.5 94.5 96.7 7.49 45.4 56.7 96.21.4 267.48 93.7.43, 0.0000 94.5 94.5 94.5 94.5 94.5 95.7 94.4 96.7 94.4 96.7 94.4 97.43 94.4 97.43 94.4 96.7 94.4 97.43 94.4 97.43 94.4 97.43 94.4 97.43 94.4	201 80 67 61 86 396 658 391 1940 , df=7) n: 1 I 80 67 61 85 608 1200 2232 2df=6 (11) n: 1 F	<u>Meam</u> -9.953 2.4 -17.8 -4.8 9.42 9.42 9.42 9.42 9.42 9.42 9.42 9.42	I S 3 35.4.4 3 35.4.4 3 8.1.4 3 8.1.4 3 8.1.4 3 8.1.4 3 8.1.9.8 2 115.8.0 00001); I 1 rry Ou S 00001); I 21.7.7 26.1.2 20.1.2 00001); I 7 00001); I 7 00001); I 7	D Tota 6 13' 6 2' 7 3' 6 4' 3 15' 1209 9 20' 1209 9 20' 130 8 20' 100 100 100 100 100 100 100 100 100 1	I Weight 13.8% 11.3.8% 11.9% 11.1% 11.25% 11.1% 12.5% 2 14.0% 2 14.0% 2 14.0% 3 100.0% • • • 14.4% • 11.6% • 11.2% • 10.0% • 10.0% • 10.2 • 10.0% • 10.0% • 10.0% • 10.0% • 10.0%	Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	- - 2
Akizawa et al. 2021 Akizawa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Fichbane et al. 2021 Total (95% CI) Heterogeneity. Tau ^e et Test for overal et al. 2021 Mizwa et al. 2021 Chen et al. 2021 Chen et al. 2021 Chen et al. 2021 For et al. 2021 For et al. 2021 Chen et al. 2021 Mizwa et al. 2021 Mizwa et al. 2021 Mizwa et al. 2021 Mizwa et al. 2021 Chen et al. 20	Mean -14.22 -9.7 -37.5 -56.14 -35.94 -13.22 0.21; Chi ^p = 4.18 (P dean -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.24 -13.22 -13.24 -13.22 -13.24 -13.22 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24 -13.24	SD 34.22 26.7 34.22 26.7 34.22 26.7 36.34 47.46 6.73 63.4 80.9 26.7 116.8 64.73 63.4 47.46 64.74 47.46 47.46 45.23 45.24 45.23 45.24 45.23 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 45.24 44.26 44.26 44.26 44.26 44.26 44.26 44.26 44.26 44.26 44.26 44.26 44.26 44.26 44.26	201 80 67 80 87 61 86 83 91 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 391 1940 658 839 1940 67 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 67 80 80 80 67 80 80 80 80 80 80 80 80 80 80	<u>Mean</u> -9.953 2.4 -17.8 -15.1 3.88 9.42 -1.716 (P < 0.0 Prima Cco Mean Cco Mean	I S 3 35.4 3 35.4 4 39.4 3 35.4 43.9 31.1 48.0 38.1 3 81.4 3 81.4 3 81.4 3 81.4 3 81.1 41.1 53.0 00001);1 1 21.7 261.2 60.1 261.2 00001);1 2 00001);1 2 00001);1 7 00001);1 7 00001);1 7 00001);1 7	D Tota 6 13' 6 2' 7 3' 6 4' 1200 9 20' 1200 9 20' 1200 9 20' 1200 9 20' 1200 9 20' 1200 9 20' 1200 9 20' 1200 9 20' 1200 9 20' 1200 9 20' 1200 1200 1200 1200 1200 1200 1200 1	I Weight 13.8% 11.9% 11.13.8% 10.9% 11.13.8% 10.9% 11.13.8% 10.9% 11.13.8% 11.25% 11.14.2% 11.0% 11.14.2% 11.0% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 9.5% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15% 11.15%	Std. Mean Difference W. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.038, 0.04) -0.40 (0.038, 0.04) -0.78 (1.31, 0.25) -0.32 (0.51, 0.13) -0.32 (0.51, 0.13) -0.32 (0.51, 0.13) -0.32 (0.51, 0.13) -0.32 (0.40, 0.06) -0.74 (-1.09, -0.39) Come: 1.5 TIBC Std. Mean Difference W. Random, 95% cf -0.81 (0.56, 1.06) -0.79 (0.34, 1.24) -1.61 (0.56, 1.06) -0.79 (0.34, 1.24) -0.79 (0.34, 0.25) -0.71 (0.46, 0.82) -0.71 (0.56, 1.06) -0.71 (0.56, 1.06) -0.7	 (µg/dL).	Std. Mean L V, Randon Roxadustat Std. Mean N, Rando	Control Difference m, 95% CI	- - 2
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Finbane et al. 2021 Shutov et al. 2021 Total (95% C) E.Forest plot et Study or Subgroup E.Forest plot et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2019 Chen et al. 2021 Chen et al. 202	Mean -14.22 -9.7 -14.45 -37.5 -37.5 -22.11 -35.94 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -14.18 (P -14.18 (P -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -14.18 (P -14.18 (P -10.10 (P) -11.20 (P)<	SD 34.22 26.7 186.36 6.73 63.4 80.9 116.8 47.46 63.4 47.46 0.0001 pariso cadustat 5D 7.49 45.23 45.4 56.14 267.48 = 37.43, 39.6 50.11	201 80 67 61 86 396 658 391 1940 , df= 7) n: 1 I 80 67 61 85 608 1200 2232 2df= 6 (0 11) n: 1 F	<u>Mean</u> -9.953 2.4 -17.8 -4.8 9.422 -1.715 (P < 0.0 Prima Co Co Co Mean -6.7 :	I S 3 35.4.4 3 35.4.4 3 8.1.4 3 8.1.4 3 8.1.4 3 8.1.4 3 8.1.9.8 2 115.8.0 00001); I 1 rry Ou S 00001); I 21.7.7 26.1.2 20.1.2 00001); I 7 00001); I 7 00001); I 7	D Tota 6 13' 6 21' 7 3' 6 4' 120' 7 3' 120' 7 3' 7 3' 6 6' 7 3' 7 3' 7 3' 7 3' 7 3' 7 3' 7 3' 7 3	I Weight 13.8% 11.3.8% 11.9% 11.1% 11.25% 11.1% 12.5% 2 14.0% 2 14.0% 2 14.0% 3 100.0% • • • 14.4% • 11.6% • 11.2% • 10.0% • 10.0% • 10.2 • 10.0% • 10.0% • 10.0% • 10.0% • 10.0%	Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134, 0.134	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	1 4 -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Finbane et al. 2021 Shutov et al. 2021 Test for overall effect : E.Forest plot et Study or Subgroup E.Forest plot et al. 2021 Chen et al. 2021 Chen et al. 2021 Chen et al. 2019 Chen et al. 2021 Test for overall effect. 2 F.Forest plot et al. 2021 Mizzawa et al. 2021 Barrat et al. 2021 Barrat et al. 2021 Barrat et al. 2021 Barrat et al. 2021	Mean -14.22 -9.7 -14.58 -37.5 -35.94 -13.25 -22.11 -35.94 -13.25 -13.25 -14.18 (P Mean -56.14 -37.5 -35.94 -35.94 -13.25 -37.4 -35.94 -13.25 -37.4 -35.94 -13.25 -37.4 -35.94 -13.25 -11.25 -37.4 -11.25 -37.4 -37.4 -37.4 -37.4 -37.4 -37.4 -37.4 -36.07 -41.11 -51.12	SD 34 22 26.7 34 22 26.7 185.36 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 7.49 9 116.8 47.46 7.49 9 7.49 45.4 55.1 66.79 66.79 62.14 267.48 9 7.43 45.4 55.1 7.49 9.27.43 9.36 34.57 39.6 34.57 39.6 34.57 23.3 34.57 33.6 34.57 33.6 34.57 33.6 34.57 33.6 34.57 33.6 34.57 33.6 34.57 33.6 34.57 33.6 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57 34.57	201 800 67 61 86 658 391 1940 , df=7)) n: 1 I 80 67 77 608 1200 2232 df=6 () 11) n: 1 I 131 85 608 1200 2232 df=6 () 11) 131 85 67	Mean -9.953 2.4 -17.8 2.4 -17.8 2.4 -17.8 -4.8 9.42 -15.1 3.88 9.42 -1.715 - Prima 0.6 5.03 -7.6 1.2 -1.84 -21.33 -21.33 P < 0.000	Image: system Image: system 1 35.4 39.4 39.4 3 34.4 39.9 31.4 80.9 1 480.9 2 115.8 80.9 2 115.8 5 53.0 100011;1 Image: system 115.8 5 53.0 1000011;1 117.7 26.6 1.1 21.7 2 2.4 2.6 5.1 2.2 2.4 2.2 60.1 2.6 3.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3 31.94 19.3	D Tota 6 13: 6 2: 7 3: 6 44 11 7 3: 6 64. 9 20: 1209 = 94% tcom 0 Tota 8 2: 6 18: 8 4: 8 4: 8 105 1600 = 84% tcom Tota 1600 1311 131 131 18 16 16 16 16 16 16 16 16 16 16	I Weight 138% 119% 119% 119% 3 109% 3 119% 1125% 119% 2 140% 4 125% 9 100.0% ees, out 117% 1125% 123% 123% 123% 100.0% 123% 100.0% 123% 100.0% 123% 1123% 144%	Std. Mean Difference W. Random, 95% cf 0.12 (0.34, 0.14) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.40 (0.083, 0.04) 0.47 (0.14, 0.01) 0.47 (0	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	- - 2
Akizawa et al. 2021 Akizawa et al. 2021 Besarab et al. 2015 Chen et al. 2016 Chen et al. 2017 Chen et al. 2021 Fichbane et al. 2021 Total (95% CI) Heterogeneity. Tau ^e et Test for overal et al. 2021 Mizwa et al. 2021 Mizwa et al. 2021 Mizwa et al. 2021 Mizwa et al. 2021 Den et al. 2019 Chen et al. 2021 For et al. 2021 For et al. 2021 For et al. 2021 Besarab et al. 2021	Mean -14.22 -74.25 -75.56.144.58 -75.56.144.58 -75.56.144.58 -75.56.144.58 -75.57.57 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.57.42 -75.5	SDD 34.22 34.22 26.7 36.3 46.73 6.73 63.4 80.9 166.8 80.9 116.8 80.9 116.8 80.9 116.8 80.9 116.8 80.9 116.8 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.7 149.5 80.7 149.5 80.7 149.5 80.7 149.5 80.7 149.5 80.8 14.5 80.9 14.5 97.43 199.6 34.57 23.3 28.6 14.5	201 800 67 61 866 658 391 1940 df = 7)) Total 131 80 67 618 1200 2232 2df = 6 () 11) n: 1 F 608 1200 2232 2df = 6 () 131 80 67 608 1200 233 608 1200 233 608 1200 233 608 1200 131 131 808 608 1200 233 608 1200 131 131 808 608 1200 131 131 808 608 1200 131 131 808 608 1200 131 131 808 608 1200 131 131 808 608 1200 131 131 808 608 807 131 131 808 608 1200 2322 247 131 131 807 608 1200 233 247 608 131 131 807 608 1200 233 608 131 131 807 608 131 131 807 608 131 131 807 608 131 131 131 131 131 131 131 13	Mean -9.953 2.4 -17.8 2.4 -17.8 9.42 -17.15 9.42 -1.715 9.42 -1.716 9.42 -1.715 9.42 -1.716 9.42 -1.715 9.42 -1.715 9.42 -1.716 9.42 -1.716 9.42 -1.716 9.42 -1.84 -3.58 -21.33 9.4 -21.33 -21.33 P < 0.00	Image Image 3 35.4 3 35.4 3 35.4 3 35.4 3 35.4 48.0 8.1.1 48.0 8.1.1 48.0 8.1.1 48.0 8.1.1 41.1 215.8 5 53.0 100011);1 1 control SI 41.1 21.7: 261.2 60.1 261.2 60.1 20001); P Fry Outontrol SD 50 SD 50 226.53 31.94 19.3 23.7	D Tota 6 13' 6 2' 7 3' 6 4 17 3' 6 6 9 20' 120' 3' 2 13' 2 13' 2 13' 2 13' 3 2' 6 1' 1 3' 160' 8 4 30' 160' 8 4 30' tcom 1' 131' 2'	I Weight 1 13.8% 1 13.8% 1 13.8% 3 10.9% 3 10.9% 4 12.2% 4 14.4% 1 14.4% 1 14.4% 1 14.4% 1 14.4% 1 10.0% 1 10.0% 1 10.0% 1 10.0% 1 10.0% 1 10.0% 1 10.0% 1 10.3% 2 12.3% 1 10.3% 2 10.0% 1 10.3% 1 10.3% 1 10.0% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3%	Std. Mean Difference W. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.038, 0.04) -0.40 (0.038, 0.04) -0.78 (1.31, 0.25) -0.32 (0.51, 0.13) -0.32 (0.51, 0.15) -0.31 (0.55, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.15) -0.31 (0.45, 0.22) 0.64 (0.82) 0.99 (0.76, 1.22) -0.07 (0.16, 0.82) -0.71 (0.15, 0.002) -0.71 (0.53, 0.02) -0.71 (0.53, 0.02) -0.71 (0.53, 0.02) -0.71 (0.53, 0.02) -0.71 (0.53, 0.02) -0.71 (0.53, 0.02) -0.71 (0.53, 0.02) -0.72 (0.53, 0.15) -0.72 (0.53, 0.45) -0.72 (0.73, 0.15) -0.72 (0.7	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	1 4 -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Shutov et al. 2021 Shutov et al. 2021 E.Forest plot E.Forest plot Study or Subgroup E.Forest plot Study or Subgroup Chen et al. 2017 Chen et al. 2017 Chen et al. 2019 Chen et al. 2019 Chen et al. 2019 Chen et al. 2021 Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2021 Akizawa et al. 2021 Aki	Mean -14.22 -7-14.58 -37.5 -37.5 -56.14 -35.94 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -13.22 -11.32 -11.32 -11.32 -11.32 -1.34 -1.34	SD 34.22 26.7 185.36 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 7.49 7.49 45.23 7.49 45.4 56.71 56.74 56.74 56.73 66.79 62.14 267.48 50.71 39.6 34.57 23.3 26.6 35.24	201 800 67 61 866 658 391 1940 df = 7)) Total 131 80 67 61 85 608 1200 2232 df = 6 (01) n: 1 I 131 85 67 85	Mean -9.953 2.4 -17.8 2.4 -17.8 9.42 -17.13 9.42 -1.715 9.42 -1.716 9.42 -1.716 9.42 -1.716 9.42 -1.716 9.42 -1.716 -1.84 -1.2 -1.368 -21.33 -21.33 P < 0.00	1 5 3 3 3 3 3 3 4 3 4 8 1 48 48 8 48 8 48 8 48 8 48 8 48 8 48 8 48 8 48 8 48 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 19 9 10	D Tota 6 133 6 23 7 3(6 6 44 11 7 3(6 6 60) 9 203 1209 1209 1209 1209 1209 1209 1209 1209	I Weight 138% 119% 138% 119% 3 109% 3.3% 4 125% 125% 9 100.0% 3.42% 9 100.0% 3.42% 1 14.4% 11.7% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 1.13.3% 1 10.3% 1.13.3% 1 10.3% 1.13.3%	Std. Mean Difference W. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.83, 0.04) -0.74 (1.03, 0.04) -0.74 (1.13, 0.21) -0.74 (1.13, 0.21) -0.74 (1.03, 0.02) -0.74 (1.04, 0.03) -0.74 (1.04, 0.03) come: 1,5 TIBC Std. Mean Difference W. Random, 95% cf 0.81 (0.56, 1.06 0.79 (0.34, 1.23) -0.71 (1.04, 0.03) -0.74 (1.09, 0.39) come: 1,5 TIBC Std. Mean Difference W. Random, 95% cf 0.81 (0.56, 1.06 0.79 (0.34, 1.23) -0.31 (0.64, 0.82) 0.99 (0.76, 1.22) come: 1,6 Serund d. Mean Difference W. Random, 95% cf 0.77 (0.50, 0.43) -0.74 (1.03, 0.01) -0.74 (1.03, 0.04)	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	- - -
Akizawa et al. 2021 Akizawa et al. 2021 Akizawa et al. 2018 Chen et al. 2016 Chen et al. 2017 Chen et al. 2021 Fishbane et al. 2021 Total (95% CI) Heterogeneity. Tau [#] et Test for overal et al. 2021 Akizawa et al. 2021 Chen et al. 2021 Total (95% CI) Heterogeneity. Tau [#] et Sel for overal effect 2 F-Forest plot et Akizawa et al. 2021 Akizawa et al. 2021 Besarab et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017	Mean -14.22 -14.75 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; ChiP B -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -101 -101 -10.34 -10.34 -10.34 -11.34 -11.34 -11.34 -11.34 -11.34	SDD 34.22 26.7 185.36 6.73 6.73 6.73 6.73 6.74 80.9 116.8 47.46 900 cadustat 500 7.49 62.14 45.23 45.4 45.4 45.4 45.23 45.4 45.23 45.4 55.1 66.79 62.14 267.48 93.6 34.57 23.3 35.24 1.91	201 800 67 61 396 658 391 1940 , df = 7) n: 11 131 800 67 61 1200 2222 df = 6 () 11) n: 1F i 131 800 67 67 61 1200 2232 df = 6 () 1323 67 64 85 85 85 85 85 85 85 85 85 85	Mean -9.953 2.4 -17.8 2.4 -17.8 4.8 -15.1 3.86 9.42 -1.715 (P < 0.0	1 5 1 35.4 35.4 39.4 3 34.4 8.1 8.1 48.0 8.1 48.0 8.1 48.0 8.1 48.0 8.1 48.0 8.1 48.1 48.0 90001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 0001);1 115.8 0001);1 115.8 0001);1 115.8 0001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 115.8 00001);1 119.3	D Tota 6 13: 6 2: 7 33 15: 6 60 44 3 15: 6 60 44 3 15: 7 33 15: 7 30 15: 7	I Weight 1 13.8% 1 13.8% 1 13.8% 3 10.9% 3 10.9% 4 12.5% 4 14.4% 1 14.4% 1 14.4% 1 14.4% 1 10.7% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3% 1 10.3%	Std. Mean Difference /V. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.038, 0.04) -0.40 (0.038, 0.04) -0.78 (1.31, 0.25) -0.72 (1.07, 0.32) -0.32 (0.51, 0.13) -0.32 (0.51, 0.13) -0.74 (1.10, 0.13) -0.71 (1.55, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.36, 0.32) -0.71 (0.13, 0.02) -0.71 (0.50, 0.04) -0.74 (0.10, 0.02) -0.74 (0.10, 0.02) -0	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	1 4 -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Fishbane et al. 2021 Total (95% CI) Heterogeneity. Tau [*] et Test for overall et al. 2021 Maximum et al. 2021 Schen et al. 2019 Come et al. 2021 For et al. 2021 For et al. 2021 Start et al. 2021 Besarab et al. 2021	Mean -14.22 -14.75 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; ChiP B -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -101 -101 -10.34 -10.34 -10.34 -11.34 -11.34 -11.34 -11.34 -11.34	SD 34.22 26.7 185.36 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 6.73 7.49 7.49 45.23 7.49 45.4 56.71 56.74 56.74 56.73 66.79 62.14 267.48 50.71 39.6 34.57 23.3 26.6 35.24	201 800 67 61 396 658 391 1940 , df = 7) n: 11 131 800 67 61 1200 2222 df = 6 () 11) n: 1F i 131 800 67 67 61 1200 2232 df = 6 () 1323 67 64 85 85 85 85 85 85 85 85 85 85	Mean -9.953 2.4 -17.8 2.4 -17.8 4.8 -15.1 3.86 9.42 -1.715 (P < 0.0	1 5 3 3 3 3 3 3 4 3 4 8 1 48 48 8 48 8 48 8 48 8 48 8 48 8 48 8 48 8 48 8 48 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 19 3 10	D Tota 6 13: 6 2: 7 33 15: 6 60 44 3 15: 6 60 44 3 15: 7 33 15: 7 30 15: 7	I Weight 138% 119% 138% 119% 3 109% 3.3% 4 125% 125% 9 100.0% 3.42% 9 100.0% 3.42% 1 14.4% 11.7% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 9.100.0% 1 10.3% 1.13.3% 1 10.3% 1.13.3% 1 10.3% 1.13.3%	Std. Mean Difference W. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.83, 0.04) -0.74 (1.03, 0.04) -0.74 (1.13, 0.21) -0.74 (1.13, 0.21) -0.74 (1.03, 0.02) -0.74 (1.04, 0.03) -0.74 (1.04, 0.03) come: 1,5 TIBC Std. Mean Difference W. Random, 95% cf 0.81 (0.56, 1.06 0.79 (0.34, 1.23) -0.71 (1.04, 0.03) -0.74 (1.09, 0.39) come: 1,5 TIBC Std. Mean Difference W. Random, 95% cf 0.81 (0.56, 1.06 0.79 (0.34, 1.23) -0.31 (0.64, 0.82) 0.99 (0.76, 1.22) come: 1,6 Serund d. Mean Difference W. Random, 95% cf 0.77 (0.50, 0.43) -0.74 (1.03, 0.01) -0.74 (1.03, 0.04)	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	- -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2019 Chen et al. 2017 Chen et al. 2021 Fichban et al. 2021 Shudov et al. 2021 Total (95% C) Heterogeneity: Tau" = Test for overall effect: Study or Subgroup. Kutyawa et al. 2019 Chen et al. 2021 Fishbane et al. 2021	Mean -14.22 -14.75 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; ChiP B -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -101 -101 -10.34 -10.34 -10.34 -11.34 -11.34 -11.34 -11.34 -11.34	SD O 34.22 26.7 34.22 26.7 165.36 6.73 63.4 80.9 116.8 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 116.3 80.9 207.48 207.48 207.43 1.91 213.3 26.6 35.24 1.91 1.91 27.23	201 800 67 61 396 658 391 1940 , df = 7) n: 11 131 800 67 61 1200 2222 df = 6 () 11) n: 1F i 131 800 67 67 61 1200 2232 df = 6 () 1323 67 64 85 85 85 85 85 85 85 85 85 85	Mean -9.953 2.4 -17.8 2.4 -17.8 4.8 -15.1 3.86 9.42 -1.715 (P < 0.0	Image: Second	D Tota 6 13: 6 2: 7 33 15: 6 60 44 3 15: 6 60 44 3 15: 7 33 15: 7 30 15: 7	I Weight 1 13.8% 1 13.9% 1 13.9% 3 10.9% 3 10.9% 3 10.9% 4 12.5% 1 14.2% 9 100.0% 9 100.0% 1 14.2% 1 14.2% 1 14.2% 1 14.2% 1 14.2% 1 14.2% 1 14.2% 1 10.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 14.4% 1 14.5%	Std. Mean Difference /V. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.038, 0.04) -0.40 (0.038, 0.04) -0.78 (1.31, 0.25) -0.72 (1.07, 0.32) -0.32 (0.51, 0.13) -0.32 (0.51, 0.13) -0.74 (1.10, 0.13) -0.71 (1.55, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.34, 1.24) -1.61 (0.51, 0.16) -0.79 (0.36, 0.32) -0.71 (0.13, 0.02) -0.71 (0.50, 0.04) -0.74 (0.10, 0.02) -0.74 (0.10, 0.02) -0	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	- -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Total (95% CI) Heterogeneity. Tau* et al. 2017 Total (95% CI) Heterogeneity. Tau* et al. 2017 Chen et al. 2021 Maxwa et al. 2021 Maxwa et al. 2021 Maxwa et al. 2021 Chen et al. 2019 Come et al. 2021 For et al. 2019 Come et al. 2021 For et al. 2021 For et al. 2021 Besarab et	Mean -14.22 -9.7 -14.58 -37.5 -56.14 -22.11 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.95 -35.94 -35.94 -35.97 -35.94 -35.97 -35.94 -35.94 -35.97 -35.94 -35.97 -35.97 -35.94 -35.97 -35.94 -35.97 -37.19 -36.11 -36.41 -36.41 -171.95 -36.63 -341 -11.34 -11.34 -11.34 -11.34 -11.34 -11.34 -11.34 -11.34 </td <td>SD O 34.22 26.7 34.22 26.7 165.36 80.9 91.65.36 80.9 91.65.36 80.9 91.65.36 80.9 91.7 81.6 91.7 83.4 91.7 80.9 91.7 80.9 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7</td> <td>201 800 67 61 86 396 658 391 1940 4f=7 1) n: 1 I 80 67 61 85 608 1200 2232 4f=6 (1) 11) n: 1 I 131 323 67 61 85 67 61 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 85 85 85 85 85 85 85 85 85</td> <td>Mean -9.953 2.4 -17.6 4.8 -15.1 3.86 9.42 -1.716 (P < 0.0</td> Prima Mean 0.6 5.03 -7.8 -8.04 -9.5 2.7 -3.57 2.107	SD O 34.22 26.7 34.22 26.7 165.36 80.9 91.65.36 80.9 91.65.36 80.9 91.65.36 80.9 91.7 81.6 91.7 83.4 91.7 80.9 91.7 80.9 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.6 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7 91.7	201 800 67 61 86 396 658 391 1940 4f=7 1) n: 1 I 80 67 61 85 608 1200 2232 4f=6 (1) 11) n: 1 I 131 323 67 61 85 67 61 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 60 85 85 85 85 85 85 85 85 85 85	Mean -9.953 2.4 -17.6 4.8 -15.1 3.86 9.42 -1.716 (P < 0.0	a s a 35.4 a 36.4 a 36.4 a 8.1 48.0 80.9 215.8 80.9 215.8 53.0 00001); 1 1 Control SI 44.10 26.1 226.5 54.2 00001); 1 FY Ou ontrol SD starts 2.3.7 24.35 2.86 33.15 -	D Total 6 13: 6 2: 7 3: 1209 7 200 1209 7 200 1209 7 200 1209 7 200 1209 7 200 1209 7 200 1209 7 200 1209 8 22 6 16 8 22 6 16 8 22 6 16 8 43 8 43 6 16 8 105 1 13 1 1 203 1 16 1 203 1 203	I Weight 1 13.8% 1 13.8% 1 19.8% 3 10.9% 3 10.9% 4 14.4% 4 14.4% 9 100.0% ees, out 1 1 10.3% 5 19.3% 5 19.3% 1 12.9% 1 10.0% ees, out 14.4% 1 13.9% 1.2.3% 12.3% 1.3.9% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4% 14.4%	Std. Mean Difference /V. Random, 95% cf -0.12 {0.34, 0.10 -0.40 {0.38, 0.04 -0.78 {1.31, -0.25 -0.32 {0.41, 0.13 -0.32 {0.41, 0.13 -0.32 {0.41, 0.13 -0.32 {0.41, 0.13 -0.32 {0.41, 0.13 -0.32 {0.40, -0.06} -0.74 {1.40, -0.39} Come: 1.5 TIBC Std. Mean Difference /V. Random, 95% cf -0.81 {0.41, 0.24 -0.81 {0.41, 0.24 -0.85 {0.41, 0.24 -0.71 {0.43, 0.44 -0.74 {0.43, 0.02 -0.71 {0.43, 0.44 -0.74 {0.43, 0.02 -0.74 {0.43, 0.24 -0.74 {0.44, 0.44, 0.44 -0.74 {0.44, 0.44, 0.44 -0.74 {0.4	 (µg/dL).	Std. Mean D	Control Difference m, 95% CI	
Akizawa et al. 2021 Akizawa et al. 2021 Akizawa et al. 2018 Chen et al. 2016 Chen et al. 2017 Chen et al. 2017 Total (95% CI) Heterogeneity. Tau [*] et E. Forest poveral at 2021 Total (95% CI) Heterogeneity. Tau [*] et al. 2017 Akizawa et al. 2021 Akizawa et al. 2021	Mean 14.22 9.7 14.4.28 -37.5 -56.14 -22.11 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.95 -35.94 -35.94 -35.97 -35.94 -35.97 -35.94 -35.94 -35.97 -35.94 -35.97 -35.94 -35.97 -35.94 -35.97 -37.19 -36.11 -36.11 -36.11 -36.11 -36.11 -37.12 -37.12 -37.12 -37.12 -37.11 -37.12 -37.12 -37.12 -37.12 -37.12 </td <td></td> <td>201 800 67 61 86 396 658 391 1940 6ff 7)) Total 131 80 67 61 82 608 1200 2232 (ff 6 () 131 323 67 61 85 63 86 63 86 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 67 78 10 10 10 10 10 10 10 10 10 10</td> <td>Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.716 (P < 0.0</td> Prima 0.6 5.03 -7.6 -1.84 -3.58 -21.33 P < 0.00		201 800 67 61 86 396 658 391 1940 6ff 7)) Total 131 80 67 61 82 608 1200 2232 (ff 6 () 131 323 67 61 85 63 86 63 86 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 67 78 10 10 10 10 10 10 10 10 10 10	Mean -9.953 2.4 -17.8 -4.8 -15.1 3.88 9.42 -1.716 (P < 0.0	s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s s	D Tota 6 13: 6 2: 7 34 14 7 34 14 7 34 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1311 1311 1313 130 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000	I Weight 1 13.8% 1 13.8% 1 13.9% 1 19.9% 3 10.9% 3 10.9% 4 12.5% 9 100.0% 9 100.0% 9 100.0% 1 1.2% 9 100.0% 9 100.0% 1 1.2% 9 100.0% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.2% 1 1.4.5% 100.0%	Std. Mean Difference W. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.41 (0.38, 0.04) -0.41 (0.40, 0.06) -0.74 (1.09, -0.39) come: 1.5 TIBC Std. Mean Difference V. Random, 95% C 0.81 (0.56, 1.06) 0.79 (0.34, 1.24) 1.16 (0.61, 0.22) 0.64, 0.82 0.99 (0.76, 1.22) come: 1.6 Serund d. Mean Difference 0.47 (0.40, 0.02) -0.76 (1.22) come: 1.6 Serund d. Mean Difference 0.47 (0.40, 0.02) -0.76 (0.30, 0.44) -0.76 (0.30, 0.02) -0.76 (0.30, 0.44) -0.76 (0.30, 0.02) -0.76 (0.30, 0.44) -0.76 (0.70, 0.18) -0.76 (0.70,	(µg/dL).	Std. Mean Di V, Random Roxadustat Std. Mean Di V, Rando	2 Control Difference m, 95% CI	
Akizawa et al. 2021 Akizawa et al. 2021 Akizawa et al. 2018 Chen et al. 2016 Chen et al. 2017 Chen et al. 2017 Total (95% CI) Heterogeneity. Tau [*] et E. Forest poveral at 2021 Total (95% CI) Heterogeneity. Tau [*] et al. 2017 Akizawa et al. 2021 Akizawa et al. 2021	Mean 14.22 -14.23 -14.23 -14.25 -35.94 -35.94 -35.94 -35.94 -13.22 -13.22 -13.22 -13.22 -13.24 -13.24 -13.25 -13.27 -10.67 -11 -11 -11 -11 -11 -11 -13.44 -1.34 -1.34 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14	SD SD 34.22 26.7. 34.22 26.7. 36.34 80.9 36.34 80.9 36.34 80.9 36.34 80.9 36.34 80.9 36.34 80.9 37.43 80.9 37.43 85.1 36.67.9 62.14 45.23 367.48 39.6 207.48 23.3 26.6 35.24 .9.1.91 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.24 20.25 27.25	201 800 67 61 86 396 658 391 1940 6ff 7)) Total 131 80 67 61 82 608 1200 2232 (ff 6 () 131 323 67 61 85 63 86 63 86 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 65 65 88 67 78 10 10 10 10 10 10 10 10 10 10	Mean -9.953 2.4 -17.8 -4.8 -17.13 9.943 -1.715 (P < 0.0	Image: style	D Tota 6 13: 6 2: 7 34 14 7 34 14 7 34 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1311 1311 1313 1310 1300 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 100	I Weight 1 13.8% 1 13.8% 1 13.8% 1 19.8% 3 10.9% 4 14.4% 4 14.4% 9 100.0% • 11.8% • 11.8% • 11.1% • 11.3% • 10.0% • 10.0% • 12.3% • 10.0% • 10.0% • 11.4% • 11.4% • 10.0% • 10.0% • 10.0% • 10.0% • 10.0%	Std. Mean Difference 1, Random, 95% CI 0, 21 (0.34, 0.14) -0.40 (0.83, 0.04) -0.40 (0.83, 0.04) -0.40 (0.83, 0.04) -0.40 (0.83, 0.04) -0.41 (0.33, 0.04) -0.41 (0.33, 0.04) -0.41 (0.41, 0.34) -0.21 (0.40, -0.08) -0.21 (0.30, 0.44) -0.21 (0.30, 0.44) -0.21 (0.30, 0.44) -0.21 (0.30, 0.44) -0.21 (0.30, 0.44) -0.21 (0.30, 0.44) -0.25 (0.30, 1.42] -0.53 (0.36, 1.42] -0.53 (0.36, 1.42)	(µg/dL).	Std. Mean D V, Randon Roxadustat Std. Mean Di V, Rando	A 95% CI	- - -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Total (95% CI) Heterogeneity. Tau ² =: Test for overall et al. 2017 Waizawa et al. 2021 Waizawa et al. 2021 Shen et al. 2021 Total (95% CI) Heterogeneity. Tau ² =: Test for overall effect 2 Total (95% CI) Chen et al. 2021 Waizawa et al. 2021 Waizawa et al. 2021 Fer for os Ubigroup Waizawa et al. 2021 Waizawa et al. 2021 Total (95% CI) Heterogeneity. Tau ² =: Test for overall effect 2 Total (95% CI) Heterogeneity. Tau ² =: Test for overall effect 2 CF-Greeft plot (05% CI) Heterogeneity. Tau ² =: Test for overall effect 2 CF-Greeft plot (05% CI)	Mean 14.22 -14.23 -14.23 -14.25 -35.94 -35.94 -35.94 -35.94 -13.22 -13.22 -13.22 -13.22 -13.24 -13.24 -13.25 -13.27 -10.67 -11 -11 -11 -11 -11 -11 -13.44 -1.34 -1.34 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14 -1.14		2011 800 67 61 86 396 658 391 1940 df = 7 7) 131 80 67 61 85 608 1200 2232 24f = 6 (0) 131 323 67 61 348 8, df = 6 131 348 8, df = 6 131 131 131 131 131 131 131 13	Mean -9.953 2.4 -17.8 -17.13 9.42 -1.715 (P < 0.0	s 36.4 39.4 39.4 30.4 39.4 30.4 8.1.1 48.0 80.9 2115.8 80.9 00001); I 1 rry Ou Control SD 20.5 26.53 23.7 24.35 2.86 33.15	D Tota 6 13: 6 2: 7 34 14 7 34 14 7 34 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1200 1311 1311 1313 1310 1300 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 100	I Weight I 13.8% I 13.8% I 13.9% I 19.9% I 10.0% I 10.0% I 10.7% I 10.0% I 10.0% I 10.0% I 10.0%	Std. Mean Difference W. Random, 95% cf -0.12 (0.34, 0.14) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.40 (0.38, 0.04) -0.41 (0.38, 0.04) -0.41 (0.40, 0.06) -0.74 (1.09, -0.39) come: 1.5 TIBC Std. Mean Difference V. Random, 95% C 0.81 (0.56, 1.06) 0.79 (0.34, 1.24) 1.16 (0.61, 0.22) 0.64, 0.82 0.99 (0.76, 1.22) come: 1.6 Serund d. Mean Difference 0.47 (0.40, 0.02) -0.76 (1.22) come: 1.6 Serund d. Mean Difference 0.47 (0.40, 0.02) -0.76 (0.30, 0.44) -0.76 (0.30, 0.02) -0.76 (0.30, 0.44) -0.76 (0.30, 0.02) -0.76 (0.30, 0.44) -0.76 (0.70, 0.18) -0.76 (0.70,	(µg/dL).	Std. Mean Di V, Random Roxadustat Std. Mean Di V, Rando	Control Difference m, 95% CI	- - - -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Total (95% CI) Heterogeneity. Tau" = Test for overall effect: Test for overall effect: Heterogeneity. Tau" = Test for overall effect: Study of Subgroup Mitzawa et al. 2017 Mitzawa et al. 2017 Mitzawa et al. 2017 Chen et al. 2021 Desarab et al. 2021 Desarab et al. 2021 Desarab et al. 2021 Desarat	Mean 14.22 9.7 14.4.28 9.7 14.58 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 <	SD O 34.22 26.7 34.22 26.7 165.36 36.3 65.36 36.3 80.9 116.8 47.46 80.9 9116.8 47.46 927.749 116.8 927.749 52.14 45.23 45.4 45.24 45.1 96.7.48 55.1 927.43 12 23.3 26.6 35.24 1.91 27.23 1 2 26.6 35.24 1.91 27.23 1 2 26.6 35.24 5.0 92 0.25) 92 9.20 93.54 5.0 92 1.91 2 2.33 2 2.35.24 9.75.25 2.35.24	2011 80 67 61 86 396 658 391 1940 67 7 131 85 608 608 67 85 608 608 67 7 131 85 608 608 7 131 85 608 7 131 85 608 7 131 85 608 83 67 85 80 85 80 85 80 85 80 85 80 85 80 85 80 80 80 80 80 80 80 80 80 80 80 80 80	Mean -9.953 2.4 -77.8 2.4 -77.6 -4.8 -17.15 0.6 5.03 -7.65 -1.716 0.6 5.03 -7.6 0.6 5.03 -7.75 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 0.710 <td>Image Image 1 36.4 3 36.4 3 36.4 3 8.4 3 1.4 8 1.4 8 1.4 8 1.4 9 1.15.8 9 1.15.8 9 1.15.8 100001);1 1 1170 Control S0 1.1 261.2 22.2 60.1 26.53 31.94 2.66 32.19 2.266 32.19 .00001) 19.3 2.2.66 0.00001) 1.9 19.3 2.66 0.00001) 1.9 19.00001) 1.9 19.3 2.66 0.00001) 1.9 19.00001) 1.9 19.3 3.10 19.3 3.10 19.3 3.10 19.3 3.10</td> <td>D Tota 6 13:3 6 13:4 7 33 12:0 ==94% 12:0 9 20: 12:0 ==94% 12:0 12:0 12:0 ==94% 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 1</td> <td>I Weight I 13.8% I 13.8% I 13.9% I 19.9% I 10.0% I 10.0% I 10.7% I 10.0% I 10.0% I 10.0% I 10.0%</td> <td>Std. Mean Difference W. Random, 955 cl 0.74 [-0.36, 0.42] 0.74 [-0.36, 0.42] 0.74 [-0.36, 0.42] 0.74 [-0.36, 0.42] 0.74 [-1.09, -0.39] come: 1.5 TIBC Std. Mean Difference W. Random, 955 cl 0.74 [-0.16, 0.32] 0.79 [0.34, 1.22] 0.79 [0.34, 1.22] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.71 [0.36, 0.26] 0.73 [-0.36, 0.42] 0.75 [0.36, 0.42] 0.53 [-0.36, 1.42] come: 1.7 Trans Mean Difference</td> <td>(µg/dL).</td> <td>Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did</td> <td>Control Difference m, 95% CI</td> <td>1 4 - - - -</td>	Image Image 1 36.4 3 36.4 3 36.4 3 8.4 3 1.4 8 1.4 8 1.4 8 1.4 9 1.15.8 9 1.15.8 9 1.15.8 100001);1 1 1170 Control S0 1.1 261.2 22.2 60.1 26.53 31.94 2.66 32.19 2.266 32.19 .00001) 19.3 2.2.66 0.00001) 1.9 19.3 2.66 0.00001) 1.9 19.00001) 1.9 19.3 2.66 0.00001) 1.9 19.00001) 1.9 19.3 3.10 19.3 3.10 19.3 3.10 19.3 3.10	D Tota 6 13:3 6 13:4 7 33 12:0 ==94% 12:0 9 20: 12:0 ==94% 12:0 12:0 12:0 ==94% 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 10:0 1	I Weight I 13.8% I 13.8% I 13.9% I 19.9% I 10.0% I 10.0% I 10.7% I 10.0% I 10.0% I 10.0% I 10.0%	Std. Mean Difference W. Random, 955 cl 0.74 [-0.36, 0.42] 0.74 [-0.36, 0.42] 0.74 [-0.36, 0.42] 0.74 [-0.36, 0.42] 0.74 [-1.09, -0.39] come: 1.5 TIBC Std. Mean Difference W. Random, 955 cl 0.74 [-0.16, 0.32] 0.79 [0.34, 1.22] 0.79 [0.34, 1.22] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.34, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.79 [0.36, 1.24] 0.71 [0.36, 0.26] 0.73 [-0.36, 0.42] 0.75 [0.36, 0.42] 0.53 [-0.36, 1.42] come: 1.7 Trans Mean Difference	(µg/dL).	Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did	Control Difference m, 95% CI	1 4 - - - -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2016 Chen et al. 2017 Chen et al. 2017 Total (95% CI) Heterogeneity. Tau" = Test for overall effect: 3 E.F.Orest plot of Study of Subgroup Mitzawa et al. 2021 Mitzawa et al. 2021 Mitzawa et al. 2019 Chen et al. 2021 Total (95% CI) Heterogeneity. Tau" = Est for overall effect: 3 Chen et al. 2021 Start et	Mean 14.22 9.7 14.4.28 -37.5 -36.14 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi ² -11 -13.4 -17.195 -0.07; Chi ² -17.195 -0.07; Chi ² -11.10, 38 -6.63 14.42; Chi ² -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.14 -1.13.4 -1.13.4 -1.14 -1.13.4 -1.14 -1.13.4 -1.13.4 -1.13.4 -1.13.4	SD SD 34.22 26.7 36.23 36.24 26.7 36.34 80.9 116.8 47.46 80.9 9116.8 47.46 47.47 50.7 7.49 52.14 45.23 45.4 45.23 45.4 55.1 56.79 52.14 56.1 267.48 55.1 56.79 26.6 35.24 54.1 27.23 1 27.23 1 27.23 1 27.23 1 27.23 1 27.33 1 27.33 1 27.33 1 27.33 1 27.33 1 27.33 1 28 730.96 0.25 20.25 0.32 20.4	2011 80 67 61 86 396 658 391 1940 , df = 7) n: 1 I 80 67 61 85 608 1200 22322 2232 2201 348 85 480 348 85 480 131 85 67 85 480 131 85 67 85 85 85 85 85 85 85 85 85 85	Mean -9.953 -9.953 -17.8 -17.8 -18.9 -17.9 (P < 0.0	Image Image 1 36.4 3 36.4 3 8.4 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 1 8.09.9 115.8 60.0 5 5.3.0 io0001);1 1 rry Ou 1.1 261.2 2.66 331.94 2.4.35 2.666 33.15 .000001); P 19.3 2.666 33.15 .000001) 19.3 19.3 2.3.6 .000001) 19.3 19.3 2.3.1 .000001) 19.3 19.3 19.3 .0.00001) 19.3 19.3 10.2	D Total 6 13' 6 12' 6 14' 7 33' 7 34' 120' 120' *= 94% * 0 Total 2 13' 2 13' 2 13' 2 13' 2 13' 3 16' 113' 12' 293' 160' 1293' 18' 300 43' 131' 12' 17'5' 1' 17'-5' 1' 17'-5' 1' 17'-5' 1' 16' 1' 11' 1'' 11'' 1'' 12'' 2''' 12'' 2'''	I Weight 1 13.8% 1 13.8% 1 13.8% 3 10.9% 3 10.9% 4 12.5% 4 14.4% 9 100.0% ees, out 11.3% 1 12.3% 1 12.3% 1 12.3% 1 10.0% ees, out 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 14.4% 14.4% 5% 000.0% % Stdd. 31% 1.1% 12.3%	Std. Mean Difference IV. Random, 95% CI 0.47 (20.34, 0.14) 0.40 (0.83, 0.04) 0.40 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.47, 0.47) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.37 (0.14, 0.04) 0.47 (0.165, 0.16) 0.79 (0.34, 1.24) 1.16 (0.01, 0.55) 0.33 (0.46, 0.32) 0.37 (0.15, 0.16) 0.37 (0	(µg/dL).	Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did	Control Difference m, 95% CI	- - - -
Akizawa et al. 2021 Akizawa et al. 2019 Akizawa et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Fiehbane et al. 2021 Shutov et al. 2021 E.Forest plot E.Forest plot Study or Subgroup E.Forest plot Study or Subgroup Chen et al. 2021 Chen et al. 2021 Chen et al. 2017 Chen et al. 2017	Mean 14.22 -14.23 -14.25 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.95 -35.94 -35.94 -35.94 -35.95 -35.94 -35.94 -35.95 -35.94 -35.94 -35.94 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34		2011 80 67 61 86 396 658 391 1940 67 7 11 131 85 608 1200 2232 2232 df = 6 10 10 10 10 67 61 85 480 201 11 131 323 67 61 85 480 10 10 10 10 10 10 10 10 10 1	Mean -9.953 -2.4 -17.8 -1.715 (P < 0.0	Image Sec 1 35.4 3 35.4 3 36.4 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 4 8.0 100001);1 1 22;2 54.2 60.1;2 22;2 20001);1 26.53 93.19 19.3 93.19 2.66 93.19 2.37 24.35 2.86 93.15	D Tota 6 13:6 13:6 13:6 14:1 13:7 6 44:3 15:7 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 12:0 13:0 13:0 14:0 14:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0 15:0	I Weight 138% 10.9% 139% 10.9% 3 10.9% 3.3% 1 25% 3.14.2% 1 14.4% 3.14.2% 1 12.5% 9.5% 1 12.5% 9.5% 1 12.3% 12.2% 1 13.3% 12.2% 1 13.3% 12.3% 1 13.3% 12.3% 1 13.3% 12.3% 1 13.3% 12.3% 1 13.3% 12.3% 1 13.3% 12.3% 1 14.4% 14.4% 1 14.4% 14.1% 1 13.3% 12.3% 1 13.3% 12.3% 1 13.3% 12.3% 1 14.4% 14.1% 1 14.4% 14.1% 1 14.5% 100.0% 3 1% 12.3%	Std. Mean Difference W. Random, 95% CI 0.47 (E0.34, 0.14) 0.40 (E0.83, 0.04) 0.40 (E0.83, 0.04) 0.41 (E0.83, 0.04) 0.41 (E0.94, 0.04) 0.41	(µg/dL).	Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did	Control Difference m, 95% CI	
Akizawa et al. 2021 Akizawa et al. 2018 Beasarab et al. 2015 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Total (95% C) Heterogeneity. Tau" = Test for overall effect: Test for overall effect: Bearab et al. 2017 Mizzawa et al. 2021 Witzawa et al. 2017 Mizzawa et al. 2017 Mizzawa et al. 2017 Study or Subgroup Witzawa et al. 2019 Coment et al. 2017 Forenest plot of effection Total (95% C) Heterogeneity. Tau" = 1 Test for overall effect: Study or Subgroup Mizzawa et al. 2021 Startet el. 2021 Startet el. 2021 Startet el. 2021 Startet el al. 2021 Generest plot of elstarter elstartero Startet el al. 2021 Generest plot of elstartero Startero 2	Mean 14.22 9.7 14.4.28 -37.5 -36.14 -37.5 -56.14 -22.11 -35.94 -13.22 0.21; Chi ² -11 -13.4 -17.195 -0.07; Chi ² -17.195 -0.07; Chi ² -11.10, 38 -6.63 14.42; Chi ² -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.13.4 -1.14 -1.13.4 -1.13.4 -1.14 -1.13.4 -1.14 -1.13.4 -1.13.4 -1.13.4 -1.13.4		2011 80 67 61 86 396 658 391 1940 67 7 11 131 85 608 1200 2232 2232 df = 6 10 10 10 10 67 61 85 480 201 11 131 323 67 61 85 480 10 10 10 10 10 10 10 10 10 1	Mean -9.953 -2.4 -17.8 -1.715 (P < 0.0	Image Sec 1 35.4 3 35.4 3 36.4 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 4 8.1 4 8.0 100001);1 1 22;2 54.2 60.1;2 22;2 20001);1 26.53 93.19 19.3 93.19 2.66 93.19 2.37 24.35 2.86 93.15	D Tota 6 13: 6 13: 7 315: 7 4 11: 7 33 15: 7 4 13: 7 5 4 7 13: 0 Tota 2 13: 8 4: 7 13: 0 Tota 2 13: 8 4: 1 30: 8 4: 1 30: 8 4: 1 30: 8 4: 1 30: 8 4: 1 30: 8 4: 1 30: 8 4: 1 30: 1 30:	I Weight 1 13.8% 1 13.8% 1 13.8% 3 10.9% 3 10.9% 4 12.5% 4 14.4% 9 100.0% ees, out 11.3% 1 12.3% 1 12.3% 1 12.3% 1 10.0% ees, out 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 14.4% 14.4% 5% 000.0% % Stdd. 31% 1.1% 12.3%	Std. Mean Difference IV. Random, 95% CI 0.47 (20.34, 0.14) 0.40 (0.83, 0.04) 0.40 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.47, 0.47) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.32 (0.51, 0.13) 0.37 (0.14, 0.04) 0.47 (0.165, 0.16) 0.79 (0.34, 1.24) 1.16 (0.01, 0.55) 0.33 (0.46, 0.32) 0.37 (0.15, 0.16) 0.37 (0	(µg/dL).	Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did	Control Difference m, 95% CI	
Akizawa et al. 2021 Akizawa et al. 2021 Akizawa et al. 2019 Chen et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2021 Fishbane et al. 2021 Test for overall effect 2 E.Forest plot (Study or Subgroup Letter or overall effect 2 B.Forest plot (Study or Subgroup Letter or overall effect 2 Chen et al. 2021 Fishbane et al. 2021 Gerearb et al. 2021 Gerearb et al. 2021 Chen et al. 2019 Chen et al. 2019 Chen et al. 2021 Chen et al. 2019 Chen et al. 2021 Chen et al. 2019 Chen et al. 2021 Chen et al. 2019 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017 Chen et al. 2017	Mean 14.22 -14.23 -14.25 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.95 -35.94 -35.94 -35.94 -35.95 -35.94 -35.94 -35.95 -35.94 -35.94 -35.94 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34 -1.34		2011 80 87 81 86 396 858 391 1940 67 85 191 131 80 67 61 85 608 1200 2232 201 2232 201 2232 201 2348 85 480 201 348 85 480 201 85 480 85 67 61 85 85 85 85 80 85 80 85 80 85 80 85 80 85 80 85 80 80 80 80 80 80 80 80 80 80 80 80 80	Mean -9.953 -2.4 -17.8 -1.715 (P < 0.0	s s 3 35.4 3 35.4 3 35.4 3 35.4 3 8.0.9 14 8.0.9 8 0.00001); 1 217.7 26.1 20001); 121.7 26.1 20001); 121.7 26.1 20001); 121.7 26.5 331.94 22.65 331.94 24.35 2.060 53.15 .000001); 19 19.3 2.00001); 19 19.3 .000001); 10 19.3 .000001); 10 19.3 .000001); 10 19.3 .000001); 10 19.3 .000001); 10 19.3 .000001); 10 19.3 .000001); 10 19.3 .000001); 10 19.3 .000001); 10 19.3 .00001); 10 19.3 .00001); 10 19.3 .00001); 10 19.3 .00001); 10 19.3 <t< td=""><td>D Totato 6 137 7 33 6 42 4 11 7 33 6 49 1205 2 131 8 23 1205 7 Totato 8 43 8 43 1 6 1 6 1 1 3 165 1 6 1 1 1 3 1 6 1 6 1 205 1 205</td><td>I Weight 13.8% 13.8% 13.8% 10.9% 3 10.9% 3.10.9% 4 14.4% 3.10.0% 4 14.4% 14.2% 1 10.0% 10.0% 8 10.0% 10.0% 9 100.0% 10.0% 1 10.0% 10.0% 9 100.0% 10.0% 9 100.0% 10.0% 9 100.0% 10.0% 9 100.0% 10.3% 9 100.0% 10.3% 9 100.0% 10.3% 9 100.0% 11.14% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 12.3% 3.0% 8.8% 3.0%</td><td>Std. Mean Difference W. Random, 95% CI 0.47 (20.34, 0.14) 0.40 (0.83, 0.04) 0.40 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.47, 0.23) 0.23 (0.40, 0.08) 0.23 (0.40, 0.08) 0.74 (1.40, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% CI 0.79 (0.34, 1.22) 0.99 (0.76, 1.22) COME: 1.6 Serund 4. Mean Difference W. Random, 95% CI 0.07 (0.13, 0.34) 0.47 (0.30, 0.44) 3.44 (3.59, 4.11) 0.47 (0.30, 0.44) 3.44 (3.59, 4.14) 0.47 (0.30, 0.44) 3.44 (3.59, 4.11) 0.47 (0.13, 0.34) 0.47 (0.13, 0.34) 0.47 (0.13, 0.34) 0.47 (0.13, 0.34) 0.47 (0.13, 0.44) 3.44 (3.59, 4.11) 0.45 (0.22, 0.45) 0.53 (0.35, 1.42] COME: 1.7 Trans Mean Difference V. Random, 95% CI 0.40 (0.57, 1.02) 0.74 (0.29, 1.14) 1.74 (1.23, 2.24) 1.53 (1.21, 2.05)</td><td>(µg/dL).</td><td>Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did</td><td>Control Difference m, 95% CI</td><td></td></t<>	D Totato 6 137 7 33 6 42 4 11 7 33 6 49 1205 2 131 8 23 1205 7 Totato 8 43 8 43 1 6 1 6 1 1 3 165 1 6 1 1 1 3 1 6 1 6 1 205 1 205	I Weight 13.8% 13.8% 13.8% 10.9% 3 10.9% 3.10.9% 4 14.4% 3.10.0% 4 14.4% 14.2% 1 10.0% 10.0% 8 10.0% 10.0% 9 100.0% 10.0% 1 10.0% 10.0% 9 100.0% 10.0% 9 100.0% 10.0% 9 100.0% 10.0% 9 100.0% 10.3% 9 100.0% 10.3% 9 100.0% 10.3% 9 100.0% 11.14% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 14.1% 12.3% 3.0% 8.8% 3.0%	Std. Mean Difference W. Random, 95% CI 0.47 (20.34, 0.14) 0.40 (0.83, 0.04) 0.40 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.83, 0.04) 0.47 (0.47, 0.23) 0.23 (0.40, 0.08) 0.23 (0.40, 0.08) 0.74 (1.40, 0.39) COME: 1.5 TIBC Std. Mean Difference W. Random, 95% CI 0.79 (0.34, 1.22) 0.99 (0.76, 1.22) COME: 1.6 Serund 4. Mean Difference W. Random, 95% CI 0.07 (0.13, 0.34) 0.47 (0.30, 0.44) 3.44 (3.59, 4.11) 0.47 (0.30, 0.44) 3.44 (3.59, 4.14) 0.47 (0.30, 0.44) 3.44 (3.59, 4.11) 0.47 (0.13, 0.34) 0.47 (0.13, 0.34) 0.47 (0.13, 0.34) 0.47 (0.13, 0.34) 0.47 (0.13, 0.44) 3.44 (3.59, 4.11) 0.45 (0.22, 0.45) 0.53 (0.35, 1.42] COME: 1.7 Trans Mean Difference V. Random, 95% CI 0.40 (0.57, 1.02) 0.74 (0.29, 1.14) 1.74 (1.23, 2.24) 1.53 (1.21, 2.05)	(µg/dL).	Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did	Control Difference m, 95% CI	
Akazawa et al. 2021 Akazawa et al. 2019 Besarab et al. 2015 Chen et al. 2017 Shutov et al. 2021 Shutov et al. 2021 Shutov et al. 2021 Shutov et al. 2021 Katy or Subgroup Katwa et al. 2017 Katwa et al. 2018 Chen et al. 2011 Shohen et al. 2011 Shohen et al. 2019 Oyme et al. 2019 Oyme et al. 2021 Maxawa et al. 2019 Oyme et al. 2021 Shohan et al. 2017 Katawa et al. 2019 Oyme et al. 2021 Katawa et a	Mean -14.22 -9.7 -14.28 -37.5 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.94 -35.95 0.21; Chi ² -11 -12 -11.95 0.07; Chi ² -11.16 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18 -11.18		2011 80 87 87 87 86 83 96 658 39 1940 67 83 94 1940 67 81 131 85 1200 22232 47 61 80 67 61 85 480 711 1131 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 480 67 85 85 85 85 85 85 85 85 85 85 85 85 85	Mean -9.953 -9.953 -9.953 -17.8 -17.8 -17.8 -17.8 -17.8 9.42 -17.8 9.42 -17.8 9.42 -17.8 9.42 -17.8 9.42 -17.8 0.6 5.03 -7.6 -1.84 -2.133 P<0.00	Image: system is a set of the system is a set	D Totate 6 13:1 6 13:3 4 11:3 6 4:3 6 6:60:0 9 20:0 2 1216 1200 1218 2 1218 12 131 293 18 300 1131 293 1160 43 18 3050 1755 17 22 21 131 293 1600 43 16 43 1755 17 12 31050 1755 11 17 203 22 21 23 22 12 12 12 131 10	I Weight 1 13.8% 1 13.8% 1 13.8% 1 13.8% 1 13.8% 1 14.4% 1 14.2% 1 14.4% 1 14.2% 1 14.2% 1 14.4% 1 10.0% es, out 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 12.3% 1 14.4% 1 14.4% 14.4% 14.5% 000.0% % std. 13.9% 3.1% 12.2% 3.3% 12.3% 3.3% 14.2% 3.3% 14.3% 3.3% 14.3% 3.3% 14.3% 3.3% 12.3%	Std. Mean Difference W. Random, 95% CI 0.47 (E0.34, 0.14) 0.40 (E0.83, 0.04) 0.40 (E0.83, 0.04) 0.41 (E0.83, 0.04) 0.41 (E0.94, 0.04) 0.41	(µg/dL).	Std. Mean Did V, Random Roxadustat Std. Mean Did Std. Mean Did	Control Difference m, 95% CI	- - - 4

Fig 3. Forest plot of the primary outcomes. A: hemoglobin level; B: ferritin; C: TSAT; D: hepcidin; E: TIBS; F: serum iron; G: transferrin; CI: confidence interval; M-H: Mantel-Haenszel; df: degrees of freedom; I², I-squared.

https://doi.org/10.1371/journal.pone.0266243.g003

	Roxadustat		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Akizawa et al. 2021 23 131		17	131	1.4%	1.35 [0.76, 2.41]		
Akizwa et al. 2019	11	80	2	27	0.2%	1.86 [0.44, 7.85]	
Barratt et al. 2021	209	323	181	293	15.2%	1.05 [0.93, 1.18]	+
Besarab et al. 2015	4	88	1	28	0.1%	1.27 [0.15, 10.92]	
Chen et al. 2017	8	61	4	30	0.4%	0.98 [0.32, 3.01]	
Chen et al. 2019	9	101	6	51	0.6%	0.76 [0.29, 2.01]	
Coyne et al. 2021	203	611	91	305	9.7%	1.11 [0.91, 1.37]	
Fishbane et al. 2021	795	1384	749	1377	60.2%	1.06 [0.99, 1.13]	
Shutov et al. 2021	241	391	115	203	12.1%	1.09 [0.94, 1.26]	+
Total (95% CI)		3170		2445	100.0%	1.07 [1.01, 1.13]	•
Total events	1503		1166				
Heterogeneity: Chi ² = 2	.16, df = 8	8 (P = 0.	98); I ² = 0	1%			
Test for overall effect: Z = 2.45 (P = 0.01)							0.1 0.2 0.5 1 2 5 10 Control Roxadustat
B-Forest plot of co	omparis	on: 3	Secon	dary d	outcom	es, outcome: 3.	2 TEAEs.
•	Roxadus	stat	Risk Ratio				

A-Forest plot of comparison: 3 Secondary outcomes, outcome: 3.1 Serious adverse events.



	Roxadustat		Control		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl
Akizawa et al. 2021	103	131	92	131	4.0%	1.12 [0.97, 1.29]		
Akizwa et al. 2019	63	80	19	27	1.2%	1.12 [0.85, 1.47]		
Barratt et al. 2021	296	323	271	293	12.4%	0.99 [0.95, 1.04]		+
Besarab et al. 2015	52	88	13	28	0.9%	1.27 [0.82, 1.96]		
Chen et al. 2017	36	61	19	30	1.1%	0.93 [0.66, 1.31]		
Chen et al. 2019	37	101	25	51	1.4%	0.75 [0.51, 1.09]		
Coyne et al. 2021	564	611	273	305	15.8%	1.03 [0.99, 1.08]		-
Fishbane et al. 2021	1243	1384	1216	1377	53.0%	1.02 [0.99, 1.04]		•
Shutov et al. 2021	343	391	176	203	10.1%	1.01 [0.95, 1.08]		+
Total (95% CI)		3170		2445	100.0%	1.02 [1.00, 1.04]		•
Total events	2737		2104					
Heterogeneity: Chi ² = 7.67, df = 8 (P = 0.47			47); l² = ()%				
Test for overall effect: Z = 1.73 (P = 0.08)						0.5	0.7 1 1.5 2 Control Roxadustat	
								Control Rozadustat

C-Forest plot of comparison: 4 Cardiovascular side effects, outcome: 4.1 Hypertension.

	Roxadustat		Control			Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl				
Akizawa et al. 2021	7	201	5	131	2.7%	0.91 [0.30, 2.81]					
Barratt et al. 2021	8	323	5	293	2.8%	1.45 [0.48, 4.39]					
Chen et al. 2017	4	61	0	30	0.4%	4.50 [0.25, 80.95]					
Chen et al. 2019	6	101	2	51	1.4%	1.51 [0.32, 7.24]					
Coyne et al. 2021	95	611	27	305	21.3%	1.76 [1.17, 2.63]					
Fishbane et al. 2021	159	1384	125	1377	70.6%	1.27 [1.01, 1.58]					
Shutov et al. 2021	4	391	1	203	0.7%	2.08 [0.23, 18.46]					
Total (95% CI)		3072		2390	100.0%	1.37 [1.13, 1.65]	◆				
Total events	283		165								
Heterogeneity: Tau ² = 0	0.00; Chi²	= 3.27,	df = 6 (P	= 0.77)	; I² = 0%						
Test for overall effect: Z	= 3.27 (P	= 0.00	1)				Control Roxadustat				

D.Forest plot of comparison: 4 Cardiovascular side effects, outcome: 4.7 Deep vein thrombosis.

	Roxadustat					Risk Ratio	Risk Ratio				
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI			
Barratt et al. 2021	4	323	1	293	18.2%	3.63 [0.41, 32.28]				_	
Fishbane et al. 2021	15	1384	4	1377	71.6%	3.73 [1.24, 11.21]			—— — —		
Shutov et al. 2021	4	391	0	203	10.2%	4.68 [0.25, 86.57]			•		
Total (95% CI)		2098		1873	100.0%	3.80 [1.50, 9.64]			•		
Total events	23		5								
Heterogeneity: Tau ² = 0	1.00; Chi ²	= 0.02,	df = 2 (P	= 0.99)	; I² = 0%					100	
Test for overall effect: Z	= 2.81 (P	= 0.00	5)				0.01 0.1	Control	10 Roxadustat	100	

Fig 4. Forest plot of the secondary outcomes. A: serious adverse effect; B; treatment-emergent adverse effects (TEAE); C: hypertension; D: deep venous thrombosis; CI: confidence interval; M-H: Mantel-Haenszel; df: degrees of freedom; I², I-squared.

https://doi.org/10.1371/journal.pone.0266243.g004

tissue hypoxia, which stimulates erythropoietin (EPO) production through activation of the HIF system [36]. Erythropoietin induces erythropoiesis by stimulating the division and differentiation of erythroid progenitor cells by activating several signaling pathways, including Janus kinase /signal transducer and activator of transcription 5, phosphatidylinositol 3-kinase /protein kinase B, and Ras-Raf-MEK-ERK pathways [37].

Roxadustat, also known as FG-4592 or ASP1517, is a HIF- prolyl hydroxylase inhibitor and induces EPO production. ROX is an oral medication with peak concentration achieved in one to three hours, with a mean half-life of 12 to 14 hours [38]. ROX increases the hemoglobin level in a dose-dependent manner. RCTs studies the effect of different doses of ROX; Chen et al. reported that ROX showed a dose-response effect on Hb levels. Hg level increase ≥ 1 g/dl from baseline was seen in 80.0% of the patients on low dose regimen (1.1–1.75 mg/kg) compared to 87.1% of the patients with high dose regimen (1.50–2.25 mg/kg) [29]. Akizawa et al. used ROX 50 mg, 70 mg, and 100 mg TIW and reported mean (SD) rate of rise of + 0.200 (5), + 0.453 (5), and + 0.570 (5) for the Hb over the first 6 weeks [32]. Similar findings reported by Besarab et al., the Hb response ranged from 30% in the 0.7 mg/kg two times a week group to 100% in the 2.0 mg/kg two times a week and three times a week groups [31].

ROX improves iron utilization parameters by decreasing ferritin, TSAT, and hepcidin and increasing TIBC and transferrin, thus enhancing the utilization of iron in the body; this may lead to iron deficiency. Therefore, it's advisable to receive proper iron supplementation during the treatment period to avoid any adverse event. ROX was associated with higher serious side effects when compared to placebo. Fishbone et al. reported the most common adverse effect of ROX was end-stage kidney disease, urinary tract infection, pneumonia, and HTN [27]. Our meta-analysis result showed no difference regarding the TEAEs between ROX and placebo or DA. The pooled analysis of global phase III study by FibroGen and AstraZeneca, including 4270 NDD-CKD patients showed comparable risks of a major adverse cardiovascular event (MACE) (HR = 1.08, 95%CI 0.94,1.24), MACE + unstable angina and heart failure requiring hospitalization (HR = 1.04, 95% CI 0.91,1.18) in patients received ROX to the patients received placebo [39]. Those results were consistent with Provenzano et al., who reported that there were no increased risks of MACE (HR, 1.10; 95% CI, 0.96 to 1.27), MACE+ (HR, 1.07; 95% CI, 0.94 to 1.21), and all-cause mortality (HR, 1.08; 95% CI, 0.93 to 1.26) between ROX and placebo groups [40]. Our results showed a significant risk of HTN and DVT in ROX groups which warrant close monitoring. When we compared ROX to DA, there was no difference between the two drugs regarding the serious adverse effect, but only two RCTs were compared ROX to DA in NDD-CKD patients [14, 15].

The previous meta-analysis of RCTs by Tang et al. [41] included eight RCTs with a total of 5,379 NDD-CKD patients. They concluded that ROX was associated with increased hemoglobin level weighted mean difference {WMD}: 1.36 g/dL; 95% CI: 0.90, 1.82; p < 0.00001, transferrin level (WMD: 0.6 g/L; 95% CI: 0.24, 0.95; p < 0.0009), and TIBC level (WMD: 59.90 μ g/dL; 95% CI: 38.85, 80.96; <0.00001). In addition, they reported that ROX lowered the hepcidin level (WMD: -51.31 ng/ml; 95% CI: -67.88, -28.12; p <0.00001) and the ferritin and TAST levels in NDD-CKD patients, and these results were almost similar to other previous systematic reviews [42–44]. Also, Tang et al. [41] 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: 1.15; 95% CI: 1.02–1.29; p < 0.02). Tang et al. published their article before the release of Barratt et al. [15], limiting their ability to assess and evaluate the article. We used standardized mean differences for outcomes with different units from the RCTs that used different scales to standardize the outcomes. Even though we added one more study [14] in our included studies, our analysis has a higher number of patients and studies in different outcomes showing our more detailed and focused analysis on

NDD-CKD only patients. Liu et al. reported similar results regarding TEAEs as they reported no significant difference among different study groups, but they found an increased risk of developing hyperkalemia in the ROX group [42]. We added an analysis for safety with focusing on cardiovascular adverse effects. We were able to do a detailed meta-analysis with all possible shared outcomes among the included RCTs, detailed sensitivity, subgroup analyses, and meta-regression for concomitant iron supplementations.

The limitation of this study is as follows. First, the overall risk of bias was high in six studies and with some concerns in the other three RCTs, and it is likely due to the lack of a clear randomization process in most of the studies. Therefore, high-quality RCTs are needed in the coming future. Currently, there is an ongoing phase 4 trial assessing the effect ROX versus recombinant human erythropoietin on patients with anemia and CKD (NCT04655027). Second, a high level of heterogeneity detected between the RCTs limits the generalization of our results. The high level of heterogeneity is likely due to different ROX doses and populations. Also, only included RCTs were few in some subgroup analyses, which considered a limitation to our analysis. Third, the included RCTs were sponsored by pharmaceutical companies, and data analysis might be subject to some bias. Fourth, the duration of the included RCTs was short, and they reported only short terms results and could not assess the long-term efficacy and adverse effects of ROX.

In contrast, our study has some strengths. Firstly, we included three RCTs that were recently published. Secondly, we did a detailed meta-analysis and focused on NDD-CKD patients to decrease the potential sources of heterogeneity and bias.

Conclusions

Our review included nine RCTs to assess the effect of ROX on NDD-CKD patients with anemia. We conclude that ROX was associated with increased Hb level and improved iron utilization parameters by decreasing ferritin, TSAT, and hepcidin and increasing TIBC and transferrin. In addition, ROX was associated with higher serious adverse effects, HTN, DVT when compared to placebo. However, higher-quality RCTs are still needed to confirm the results of our review.

Supporting information

S1 Checklist. PRISMA 2020 checklist. Preferred reporting items for systematic review and meta-analysis. (DOCX)

S1 Fig. Forest plot of the effect of trial phase on hemoglobin level. (DOCX)

S2 Fig. Forest plot of the effect of control arm type on hemoglobin level. (DOCX)

S3 Fig. Forest plot of the effect of control arm type on serious adverse effects. (DOCX)

S4 Fig. Forest plot of comparison: 4 Cardiovascular side effects, outcome: 4.2 Hypertensive crisis.

(DOCX)

S5 Fig. Forest plot of comparison: 4 Cardiovascular side effects, outcome: 4.3 Pulmonary edema. (DOCX)

S6 Fig. Forest plot of comparison: 4 Cardiovascular side effects, outcome: 4.4 Heart failure. (DOCX)

S7 Fig. Forest plot of comparison: 4 Cardiovascular side effects, outcome: 4.5 Coronary artery disease.

(DOCX)

S8 Fig. Forest plot of comparison: 4 Cardiovascular side effects, outcome: 4.6 Myocardial infarction.

(DOCX)

S9 Fig. Regression of standardized difference in means on rescue. (DOCX)

S10 Fig. Regression of standardized difference in means on iron. (DOCX)

S1 Table. Search terms and results in different databases. (DOCX)

S2 Table. Meta-analysis of the primary outcomes and sensitivity analysis. (DOCX)

S1 File. The detailed assessment of the risk bias. (XLSX)

Author Contributions

Conceptualization: Basel Abdelazeem, Kirellos Said Abbas, Arvind Kunadi.

- **Data curation:** Basel Abdelazeem, Joseph Shehata, Kirellos Said Abbas, Nahla Ahmed El-Shahat, Bilal Malik, Pramod Savarapu, Mostafa Eltobgy, Arvind Kunadi.
- Formal analysis: Basel Abdelazeem, Joseph Shehata, Nahla Ahmed El-Shahat.

Funding acquisition: Kirellos Said Abbas.

Investigation: Basel Abdelazeem, Joseph Shehata, Kirellos Said Abbas, Nahla Ahmed El-Shahat, Pramod Savarapu, Mostafa Eltobgy.

Methodology: Basel Abdelazeem, Joseph Shehata, Kirellos Said Abbas, Nahla Ahmed El-Shahat, Bilal Malik.

Project administration: Basel Abdelazeem, Kirellos Said Abbas, Bilal Malik, Pramod Savarapu, Mostafa Eltobgy, Arvind Kunadi.

Resources: Basel Abdelazeem, Kirellos Said Abbas, Nahla Ahmed El-Shahat.

Software: Basel Abdelazeem, Joseph Shehata, Kirellos Said Abbas.

Supervision: Basel Abdelazeem, Kirellos Said Abbas, Pramod Savarapu, Mostafa Eltobgy, Arvind Kunadi.

- Validation: Basel Abdelazeem, Joseph Shehata, Kirellos Said Abbas, Nahla Ahmed El-Shahat, Bilal Malik, Pramod Savarapu, Mostafa Eltobgy, Arvind Kunadi.
- Visualization: Basel Abdelazeem, Joseph Shehata, Kirellos Said Abbas, Bilal Malik, Mostafa Eltobgy, Arvind Kunadi.

Writing - original draft: Basel Abdelazeem.

Writing – review & editing: Basel Abdelazeem, Joseph Shehata, Kirellos Said Abbas, Nahla Ahmed El-Shahat, Bilal Malik, Pramod Savarapu, Mostafa Eltobgy, Arvind Kunadi.

References

- Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med. 2002; 162 (12):1401–8. Epub 2002/06/22. https://doi.org/10.1001/archinte.162.12.1401 PMID: 12076240.
- Hsu CY. Epidemiology of anemia associated with chronic renal insufficiency. Curr Opin Nephrol Hypertens. 2002; 11(3):337–41. Epub 2002/05/01. <u>https://doi.org/10.1097/00041552-200205000-00011</u> PMID: 11981265.
- Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One. 2014; 9(1):e84943. Epub 2014/01/07. https://doi.org/10.1371/journal.pone.0084943 PMID: 24392162; PubMed Central PMCID: PMC3879360.
- Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012; 23(10):1631–4. Epub 2012/ 09/01. https://doi.org/10.1681/ASN.2011111078 PMID: 22935483; PubMed Central PMCID: PMC3458456.
- Kdoqi, National Kidney F. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis. 2006; 47(5 Suppl 3):S11–145. Epub 2006/05/ 09. https://doi.org/10.1053/j.ajkd.2006.03.010 PMID: 16678659.
- 6. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease2012.
- Shih HM, Wu CJ, Lin SL. Physiology and pathophysiology of renal erythropoietin-producing cells. J Formos Med Assoc. 2018; 117(11):955–63. Epub 2018/04/16. https://doi.org/10.1016/j.jfma.2018.03.017 PMID: 29655605.
- Suzuki N, Matsuo-Tezuka Y, Sasaki Y, Sato K, Miyauchi K, Kato K, et al. Iron attenuates erythropoietin production by decreasing hypoxia-inducible transcription factor 2alpha concentrations in renal interstitial fibroblasts. Kidney Int. 2018; 94(5):900–11. Epub 2018/09/25. <u>https://doi.org/10.1016/j.kint.2018.06.</u> 028 PMID: 30245128.
- Frassetto LA, Hsu CY. Metabolic acidosis and progression of chronic kidney disease. J Am Soc Nephrol. 2009; 20(9):1869–70. Epub 2009/08/22. https://doi.org/10.1681/ASN.2009070710 PMID: 19696222.
- Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006; 355(20):2071–84. Epub 2006/11/17. https://doi.org/10.1056/NEJMoa062276 PMID: 17108342.
- Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009; 361(21):2019–32. Epub 2009/ 11/03. https://doi.org/10.1056/NEJMoa0907845 PMID: 19880844.
- Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355(20):2085–98. Epub 2006/11/17. https://doi.org/ 10.1056/NEJMoa065485 PMID: 17108343.
- Dhillon S. Roxadustat: First Global Approval. Drugs. 2019; 79(5):563–72. Epub 2019/02/26. https://doi. org/10.1007/s40265-019-01077-1 PMID: 30805897.
- Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. Phase 3 Study of Roxadustat to Treat Anemia in Non-Dialysis-Dependant CKD. Kidney Int Rep. 2021; 6(7):1810–28. Epub 2021/07/27. https://doi.org/10.1016/j.ekir.2021.04.003 PMID: 34307976; PubMed Central PMCID: PMC8258605.
- Barratt J, Andric B, Tataradze A, Schomig M, Reusch M, Valluri U, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a phase 3, randomised, open-label, activecontrolled study (DOLOMITES). Nephrol Dial Transplant. 2021. Epub 2021/06/03. <u>https://doi.org/10. 1093/ndt/gfab191</u> PMID: 34077510.
- Shutov E, Sulowicz W, Esposito C, Tataradze A, Andric B, Reusch M, 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. Epub 2021/02/26. https://doi.org/10.1093/ndt/gfab057 PMID: 33630072.
- Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021; 372: n160. Epub 2021/03/31. https://doi.org/10.1136/bmj.n160 PMID: 33781993; PubMed Central PMCID: PMC8005925.

- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021; 10(1):89. Epub 2021/03/31. https://doi.org/10.1186/s13643-021-01626-4 PMID: 33781348; PubMed Central PMCID: PMC8008539.
- Sampson M, Shojania KG, McGowan J, Daniel R, Rader T, Iansavichene AE, et al. Surveillance search techniques identified the need to update systematic reviews. J Clin Epidemiol. 2008; 61(8):755–62. Epub 2008/07/01. https://doi.org/10.1016/j.jclinepi.2007.10.003 PMID: 18586179.
- 20. The EndNote Team. EndNote. EndNote X9 ed. Philadelphia, PA: Clarivate; 2013.
- 21. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.
- Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366:I4898. Epub 2019/08/30. https://doi.org/10. 1136/bmj.I4898 PMID: 31462531.
- 23. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- 24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21 (11):1539–58. Epub 2002/07/12. https://doi.org/10.1002/sim.1186 PMID: 12111919.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629–34. Epub 1997/10/06. https://doi.org/10.1136/bmj.315.7109.629
 PMID: 9310563; PubMed Central PMCID: PMC2127453.
- 26. Borenstein M, Hedges L., Higgins J., & Rothstein H. Comprehensive Meta-Analysis Version 3. Biostat, Englewood, NJ 2013.
- Fishbane S, El-Shahawy MA, Pecoits-Filho R, Van BP, Houser MT, Frison L, et al. Roxadustat for Treating Anemia in Patients with CKD Not on Dialysis: Results from a Randomized Phase 3 Study. J Am Soc Nephrol. 2021; 32(3):737–55. Epub 2021/02/12. https://doi.org/10.1681/ASN.2020081150 PMID: 33568383; PubMed Central PMCID: PMC7920165.
- Coyne DW, Roger SD, Shin SK, Kim SG, Cadena AA, Moustafa MA, et al. Roxadustat for CKD-related Anemia in Non-dialysis Patients. Kidney Int Rep. 2021; 6(3):624–35. Epub 2021/03/19. https://doi.org/ 10.1016/j.ekir.2020.11.034 PMID: 33732977; PubMed Central PMCID: PMC7938196.
- Chen N, Qian J, Chen J, Yu X, Mei C, Hao C, 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 (8):1373–86. Epub 2017/04/04. <u>https://doi.org/10.1093/ndt/gfx011</u> PMID: <u>28371815</u>; PubMed Central PMCID: PMC5837707.
- Chen N, Hao C, Peng X, Lin H, Yin A, Hao L, et al. Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis. N Engl J Med. 2019; 381(11):1001–10. Epub 2019/07/25. <u>https://doi.org/10.1056/NEJMoa1813599 PMID: 31340089</u>.
- Besarab A, Provenzano R, Hertel J, Zabaneh R, Klaus SJ, Lee T, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysisdependent chronic kidney disease (NDD-CKD) patients. Nephrol Dial Transplant. 2015; 30(10):1665– 73. Epub 2015/08/05. https://doi.org/10.1093/ndt/gfv302 PMID: 26238121; PubMed Central PMCID: PMC4569392.
- 32. Akizawa T, Iwasaki M, Otsuka T, Reusch M, Misumi T. Roxadustat Treatment of Chronic Kidney Disease-Associated Anemia in Japanese Patients Not on Dialysis: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. Adv Ther. 2019; 36(6):1438–54. Epub 2019/04/07. https://doi.org/10.1007/s12325-019-00943-4 PMID: 30953333; PubMed Central PMCID: PMC6824366.
- NCT02174731. A Phase 3, Multicenter, Randomized, Open-Label, Active Controlled Study of theSafety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients. [Online]. Available at: https://clinicaltrials.gov/ct2/show/NCT02174731. 2020.
- NCT02278341. Roxadustat in the Treatment of Anemia in End Stage Renal Disease (ESRD) Patients on Stable Dialysis (Pyrenees) Available at: <u>https://clinicaltrials.gov/ct2/show/results/NCT02278341</u>. 2019.
- Becker K, Saad M. A New Approach to the Management of Anemia in CKD Patients: A Review on Roxadustat. Adv Ther. 2017; 34(4):848–53. Epub 2017/03/16. https://doi.org/10.1007/s12325-017-0508-9 PMID: 28290095.
- Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol. 2015; 11(7):394–410. Epub 2015/06/10. https://doi.org/10.1038/nrneph.2015.82 PMID: 26055355; PubMed Central PMCID: PMC4497972.

- Tothova Z, Tomc J, Debeljak N, Solar P. STAT5 as a Key Protein of Erythropoietin Signalization. Int J Mol Sci. 2021; 22(13). Epub 2021/07/21. https://doi.org/10.3390/ijms22137109 PMID: 34281163; PubMed Central PMCID: PMC8268974.
- Groenendaal-van de Meent D, Adel MD, Noukens J, Rijnders S, Krebs-Brown A, Mateva L, et al. Effect of Moderate Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Roxadustat, an Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor. Clin Drug Investig. 2016; 36(9):743–51. Epub 2016/06/29. https://doi.org/10.1007/s40261-016-0422-y PMID: 27352308; PubMed Central PMCID: PMC4987405.
- Provenzano R, Fishbane S, Wei L-J, Szczech L, Leong R, Saikali KG, et al. Pooled Efficacy and Cardiovascular (CV) Analyses of Roxadustat in the Treatment of Anemia in CKD Patients on and Not on Dialysis. Available at: https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx? controlld=3275139. 2019.
- 40. Provenzano R, Szczech L, Leong R, Saikali KG, Zhong M, Lee TT, 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(8):1190–200. Epub 2021/08/08. https://doi.org/10.2215/CJN.16191020 PMID: 34362786.
- Tang M, Zhu C, Yan T, Zhou Y, Lv Q, Chuan J. 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. Epub 2021/07/20. https://doi.org/10.3389/fphar.2021.658079 PMID: 34276361; PubMed Central PMCID: PMC8283176.
- 42. Liu C, Fu Z, Jiang J, Chi K, Geng X, Mao Z, et al. Safety and Efficacy of Roxadustat for Anemia in Patients With Chronic Kidney Disease: A Meta-Analysis and Trial Sequential Analysis. Front Med (Lausanne). 2021; 8:724456. Epub 2021/09/18. https://doi.org/10.3389/fmed.2021.724456 PMID: 34532333; PubMed Central PMCID: PMC8438137.
- 43. Zhang L, Hou J, Li J, Su SS, Xue S. Roxadustat for the treatment of anemia in patients with chronic kidney diseases: a meta-analysis. Aging (Albany NY). 2021; 13(13):17914–29. Epub 2021/06/12. https:// doi.org/10.18632/aging.203143 PMID: 34115611; PubMed Central PMCID: PMC8312415.
- 44. Qie S, Jiao N, Duan K, Li J, Liu Y, Liu G. The efficacy and safety of roxadustat treatment for anemia in patients with kidney disease: a meta-analysis and systematic review. Int Urol Nephrol. 2021; 53 (5):985–97. Epub 2021/01/04. https://doi.org/10.1007/s11255-020-02693-7 PMID: 33389461.