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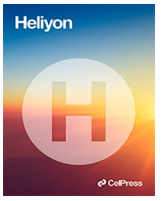

Research article

The efficacy and safety of molidustat for anemia in dialysis-dependent and non-dialysis-dependent chronic kidney disease patients: A systematic review and meta-analysis

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ABSTRACT

Objective: Molidustat is a novel agent investigated for the treatment of anemia in both dialysisdependent (DD) and non-dialysis-dependent (NDD) patients. Its efficacy and safety are still unclear.

Methods: We searched five databases to identify randomized controlled trials comparing molidustat to erythropoiesis-stimulating agents (ESAs) or placebo in patients with anemia.

Results: Six studies containing 2025 eligible participants were identified. For NDD patients, the change in Hb levels from baseline (ΔHb) was significantly higher for molidustat than for placebo [mean difference (MD) = 1.47 (95 % CI: 1.18 to 1.75), P < 0.00001] and ΔHb was also significantly higher for molidustat than for ESAs [MD = 0.25 (95 % CI 0.09 to 0.40), P = 0.002]. For NDD patients, Δhepcidin was significantly lower for molidustat than for placebo [MD = −20.66 (95 % CI: −31.67 to −9.66), P = 0.0002] and Δhepcidin was also significantly lower for molidustat than for ESAs [MD = −24.51 (95 % CI: −29.12 to −19.90), P < 0.00001]. For NDD patients, Δiron was significantly lower for molidustat than for ESAs [MD = −11.85 (95 % CI: −15.52 to −8.18), P < 0.00001], and ΔTSAT was also significantly lower for molidustat than for ESAs [MD = −5.29 (95 % CI: −6.81 to −3.78), P < 0.00001]. For NDD patients, Δferritin was significantly lower for molidustat than for placebo [MD = −90.01 (95 % CI: −134.77 to −45.25), P < 0.00001]. However, for DD-CKD patients, molidustat showed an effect similar to that of ESAs on increasing the Hb level [MD = −0.18 (95 % CI: −0.47 to 0.11), P = 0.23], Δiron level [MD = 3.78 (95 % CI: −7.21 to 14.76), P = 0.5], Δferritin level [MD = 25.03 (95 % CI: −34.69 to 84.75), P = 0.41], and Δhepcidin level [MD = 1.20 (95 % CI: −4.36 to 6.76), P = 0.67]. For DD-CKD patients, compared with the placebo or ESA group, molidustat showed a significantly higher level on ΔTSAT[MD = 3.88 (95 % CI: 2.10 to 5.65), P < 0.0001] and a slightly increased level on ΔTIBC level [MD = 1.08 (95 % CI: −0.07 to 2.23), P = 0.07]. There was no significant difference

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in the incidence of severe adverse events (SAEs), death, and cardio-related adverse events between molidustat and the ESAs groups.
Conclusions: Moricizine can effectively improves Hb levels in NDD patients and corrects anemia in DD patients without increasing adverse event incidence.

1. Introduction

Anemia, a prevalent complication of chronic kidney disease (CKD), increases with CKD severity and is accompanied by poor quality of life, significant hospitalizations, and mortality [1,2]. The pathogenesis of anemia is multifactorial, involving insufficient production of erythropoietin (EPO) and impaired iron availability. Currently, the recommendations for renal anemia management consist of erythropoiesis-stimulating agents (ESAs) and iron supplementation [3,4]. Although ESA is effective in increasing hemoglobin (Hb) levels to improve both dialysis and non-dialysis CKD anemia with the decreased need for blood transfusions [5], the increased risk of cardiovascular events, elevated blood pressure, and death raise safety concerns [6–8]. In addition, ESA is ineffective in raising the levels of Hb in 10%–20 % of patients with CKD, associated with chronic inflammation and inadequate iron utilization [9]. Given the limitations of ESAs and its analogs, alternative therapeutic approaches are being investigated.

Molidustat (BAY 85–3934) represents a novel HIF–PHI being investigated as an oral agent for treating anemia in both dialysis-dependent (DD) and nondialysis-dependent (NDD) patients [10]. HIF, an oxygen-sensitive transcription factor, regulates multiple genes involved in the transcription of EPO and the maturation of red blood cells in the bone marrow associated with iron sensing [11]. Under normal oxygen conditions, HIF-α subunits can be tagged by HIF-PH enzymes to degrade. However, in hypoxic conditions, the activity of HIF-PH enzymes is reduced, resulting in dimerization of HIF-α subunits with HIF-β and followed by their translocation into the nucleus [12]. In addition, several target genes of HIFs that promote iron absorption and recycling with a decrease in hepcidin are involved in iron homeostasis [13,14]. Molidustat stabilizes HIF-α subunits that stimulate erythropoiesis production through the HIF pathway in adaptation to hypoxia. HIF-α indirectly inhibits hepcidin expression through erythropoietic activity, resulting in enhanced iron absorption and export. Based on its action mechanism, molidustat is postulated to improve hemoglobin levels and enhance the body's ability to utilize iron for erythropoiesis [15]. Currently, the efficacy of molidustat in increased Hb levels with improving iron utilization has been demonstrated in several Phase 2 and 3 clinical studies [16,17]. Therefore, our systematic review and meta-analysis evaluated the efficacy and safety of molidustat on anemia and iron metabolism among both DD and NDD patients.

2. Methods

We structured this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [18]. The protocol of this review was prospectively registered on PROSPERO database (Registration number: CRD42022333168).

2.1. Data sources and search strategy

We conducted a comprehensive search of the PubMed, Embase, Cochrane Library, Web of Science, and Controlled Trials (CENTRAL) databases from inception until January 2024 for clinical trials investigating molidustat for anemia in adults with CKD. Our search strategy included both free-text and medical subject headings for "chronic kidney disease," "anemia," "molidustat," and "BAY85-3934," and selected publications without restrictions on origin, country, or language. Additionally, we reviewed references cited in relevant reviews and original studies to identify any additional relevant publications.

2.2. Eligibility criteria

Only randomized controlled trials (RCTs) assessing the efficacy and safety in patients with renal anemia were included. The inclusion criteria were as follows: 1) adult CKD patients diagnosed with renal anemia with or without dialysis; 2) molidustat used as treatment without dose or frequency restrictions and compared with placebo or ESAs; 3) at least one of the outcomes was available: for efficacy indicators, we focused on hematological parameters including Hb, iron, ferritin, transferrin saturation (TSAT), total iron-binding capacity (TIBC) (changes of five outcomes levels from baseline) and hepcidin; for safety indicators, we encompased severe adverse events (SAEs), mortality, cardiac-related adverse events, and renal-related adverse events; and 4) limited to RCTs. In cases where one cohort was reported in multiple publications, only the article with the largest sample size and longest duration was included. Studies were excluded if participants had primary anemia or anemia secondary to other causes, or if both the intervention and comparator arms received molidustat.

2.3. Data extraction and quality assessment

Using a standardized form, two reviewers (Yi Kang and Mengqi Zhou) independently extracted data from original trial reports. The extracted data included study characteristics (such as first author, publication year, single or multicenter, sample size, intervention and control, and treatment period), patient characteristics (mean age, proportion of men, baseline estimated glomerular filtration rate

[eGFR], and baseline Hb levels), reported outcomes (Hb, iron, transferrin, ferritin, TSAT, TIBC, hepcidin, SAEs, mortality, cardiac-related adverse events, and renal-related adverse events), and methodological information. In addition, the risk of bias of RCTs was evaluated utilizing the Cochrane Collaboration's tool [19]. Any disagreements were resolved by a third reviewer.

2.4. Data analysis

We used the mean difference (MD) analysis to compare continuous outcomes between the intervention and control groups from baseline to the end of the trial. For binary variables such as SAEs, mortality, cardiac-related adverse events and renal-related adverse events, we conducted analyses using odds ratios (OR). We calculated the 95 % confidence interval (CI) for each effect size estimate. Heterogeneity between studies was estimated by the I^2 statistic and considered low if $I^2 < 50$ %, then a fixed-effect model was used; otherwise, the random-effect model was used. To identify potential sources of heterogeneity in the meta-analysis, subgroup analyses were conducted based on population characteristics (NDD-CKD versus DD-CKD), control group (ESA versus placebo), and the use of molibresib, aiming to explore the origins of heterogeneity. $P < 0.05$ was indicative of statistical significance. Publication bias was assessed via visual inspection of the funnel plots. However, given the limited number of studies included in the analysis, the power of the tests was deemed too low. Therefore, examination for publication bias was only conducted if > 10 study comparisons were included in the analysis [20]. Finally, sensitivity analysis was performed on the meta-analysis results of I^2>40 %, and all analyses were conducted using the meta-package in R studio (4.3.1).

3. Results

3.1. Literature search

A total of 201 records were obtained by the initial search strategy. After removing 47 duplicate records, remaining 154 records were evaluated, leaving 6 articles (1350 participants) that evaluated the efficacy and safety of molidustat for anemia in patients with

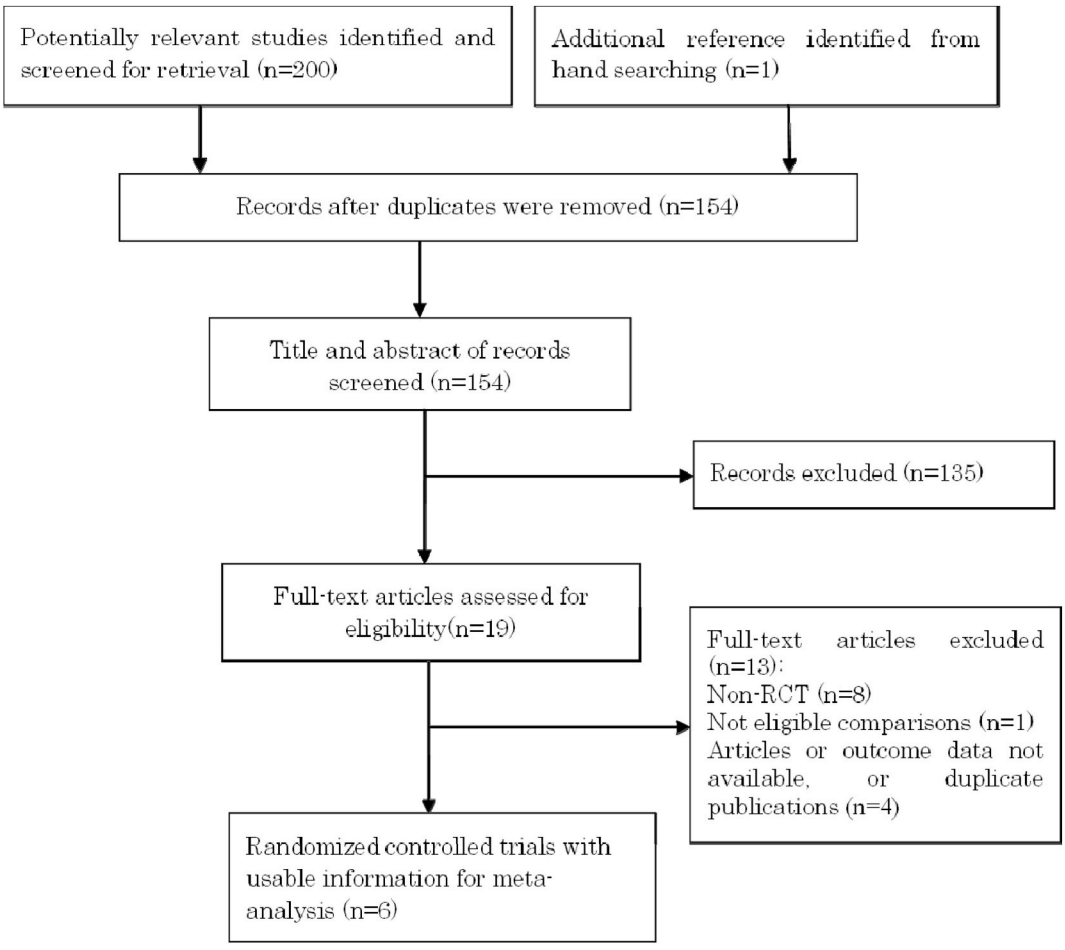

Fig. 1. Flow chart of literature search and selection.

Table 1
Characteristics of the included studies.

StudyID	Single-/ multi center	Dialysis method	Group	Sample size (n)	Sex (male/ female)	Ethnicity	eGFR	Baseline Hemoglobin (Hb)(g/dL)	CRP (mg/dL)	CKD duration (y)	Treatment	Dosage of medication	Period of treatment	follow up
Macdougall 2018 (Macdougall et al., 2019)	multicenter	DIALOGUE 1	Molidustat 25 mg once daily	19	14/5	White/Asian/ Black/other:14/ 5/0/0	25 (14)	9.4 (0.7)	8.8 (12.6) mg/L	3.8 (4.1)	Molidustat 25 mg once daily	Fixed doses of 25 mg once daily	16 w	8 w
		NDD-CKD	Molidustat 50 mg once daily	21	9/12	White/Asian/ Black/other:11/ 10/0/0	23 (11)	9.5 (0.7)	4.9 (10.1) mg/L	6.6 (6.2)	Molidustat 50 mg once daily	Fixed doses of 50 mg once daily	16 w	
			Molidustat 75 mg once daily	22	13/9	White/Asian/ Black/other:13/ 9/0/0	24 (10)	9.6 (0.6)	6.0 (9.8) mg/L	4.2 (3.5)	Molidustat 75 mg once daily	Fixed doses of 75 mg once daily	16 w	
			Molidustat 25 mg twice daily	19	10/9	White/Asian/ Black/other:15/ 4/0/0	25 (12)	9.3 (0.5)	13.3 (31.8) mg/L	2.2 (2.9)	Molidustat 25 mg twice daily	Fixed doses of 25 mg twice daily	16 w	
			Molidustat 50 mg twice daily	20	10/10	White/Asian/ Black/other:10/ 10/0/0	21 (14)	9.5 (1.1)	3.5 (6.0) mg/L	5.1 (4.3)	Molidustat 50 mg twice daily	Fixed doses of 50 mg twice daily	16 w	
			Molidustat combined	101	56/45	White/Asian/ Black/other:63/ 38/0/0	23 (12)	9.5 (0.7)	7.2 (16.4) mg/L	4.5 (4.5)	Molidustat combined		16 w	
			Placebo	20	9/11	White/Asian/ Black/other:15/ 5/0/0	23 (12)	9.5 (0.6)	4.3 (5.1) mg/L	3.5 (2.7)	Placebo	not mentioned daily	16 w	
		DIALOGUE 2	Molidustat 25 mg once daily	30	12/18	White/Asian/ Black/other:21/ 9/0/0	20 (10)	10.9 (0.7)	5.9 (7.6) mg/L	6.6 (7)	Molidustat 25 mg once daily	starting doses of 25 mg + 15, 100, and 150 mg; M (SD)[min, median, max] 26.3 (12.4) [10,23.8,58]	16 w	8 w
		NDD-CKD	Molidustat 50 mg once daily	30	17/13	White/Asian/ Black/other:23/ 7/0/7	18 (9)	10.7 (0.7)	7.7 (15.4) mg/L	8.2 (8)	Molidustat 50 mg once daily	starting doses of 50 mg + optional 15, 100, and 150 mg M (SD) [min, median, max] 45.6 (17.1) [22,46,93]	16 w	
			Molidustat 75 mg once daily	32	16/16	White/Asian/ Black/other:25/ 6/1/1	23 (14)	10.7 (0.7)	8.7 (19.2) mg/L	5.5 (3)	Molidustat 75 mg once daily	starting doses of 75 mg + optional 15, 100, and 150 mg M (SD) [min, median, max] 63.1 (26.2) [20,61,119]	16 w	
			Molidustat combined	92	45/47	White/Asian/ Black/other:69/ 22/1/1	20 (11)	10.8 (0.7)	6.5 (11.2) mg/L	6.7 (6)	Molidustat combined	M (SD) [min,median, max] 45.4 (24.6) [10,43.2119]	16 w	
			Darbepoetin	32	18/14	White/Asian/ Black/other:25/ 6/1/0	22 (12)	10.9 (0.7)	7.4 (14.10) mg/L	5.8 (5)	Darbepoetin	darbepoetin treatment	16 w	
		DIALOGUE 4	Molidustat 25 mg once daily	44	26/18	White/Asian/ Black/other:20/ 10/13/1	–	10.4 (0.6)	0.9 (1.7) mg/L	8 (6.8)	Molidustat 25 mg once daily	starting doses of 25 mg + optional 15, 100, 200 mg once daily M (SD) [min, median, max] 36.6 (16.2) [10,31.7,72]	16 w	8 w

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Table 1 (*continued*)

StudyID	Single-/ multi center	Dialysis method	Group	Sample size (n)	Sex (male/ female)	Ethnicity	eGFR	Baseline Hemoglobin (Hb)(g/dL)	CRP (mg/dL)	CKD duration (y)	Treatment	Dosage of medication	Period of treatment	follow up
		DD-CKD	Molidustat 50 mg once daily	40	23/17	White/Asian/ Black/other:19/ 8/13/0	–	10.4 (0.6)	0.6 (0.8) mg/L	6 (6.0)	Molidustat 50 mg once daily	starting doses of 50 mg + optional 15, 100, 200 mg once daily M (SD) [min, median, max] 57.5 (23.6) [13,58.5,94]	16 w	
			Molidustat 75 mg once daily	44	24/20	White/Asian/ Black/other:28/ 6/8/2	–	10.4 (0.7)	0.8 (1.2) mg/L	6 (6.0)	Molidustat 75 mg once daily	starting doses of 75 mg + optional 15, 100, 200 mg once daily M (SD) [min, median, max] 71.7 (27) [17,72.2120]	16 w	
			Molidustat 150 mg once daily	29	18/11	White/Asian/ Black/other:17/ 5/6/1	–	10.7 (0.6)	0.8 (1.7) mg/L	5 (5.5)	Molidustat 150 mg once daily	starting doses of 150 mg + optional 15, 100, 200 mg once daily M (SD) [min,median, max] 114.5 (40.5) [25,112.2188]	16 w	
			Molidustat combined	157	91/66	White/Asian/ Black/other:18/ 7/17/0	–	10.5 (0.6)	0.7 (1.1) mg/L	6 (6.2)	Molidustat combined	M (SD) [min,median, max] 66.2 (37.6) [10,61.1188]	16 w	
			Epoetin	42	29/13	White/Asian/ Black/other:84/ 29/40/5	–	10.6 (0.5)	0.8 (1.5) mg/L	6 (4.3)	Epoetin	epoetin treatment	16 w	
Akizawa 2019 (1) (Akizawa, Macdougall, Berns, Bernhardt et al., 2019)	multicenter	DIALOGUE 3	molidustat	118	57/61	White/Black/ Asian:73/0/45		11.28 ± 0.55	5.1 (10.2) mg/L		molidustat	40.2 ± 30.3 mg per day	36 months	
		NDD-CKD	darbepoetin	42	22/20	White/Black/ Asian:32/1/9		11.08 ± 0.51	10.8 (21.6) mg/L		darbepoetin	2.4 ± 2.0 μg per day	36 months	
			Total	160	79/81	White/Black/ Asian:105/1/54	23 (15) n = 153		6.7 (14.4) mg/L					
	multicenter	DIALOGUE 5	molidustat	57	33/24	White/Black/ Asian/others/ Not reported:28/16/ 10/2/1		10.40 ± 0.70	0.7 (1.2) mg/L		molidustat	69.7 ± 47.8 mg per day	36 months	
		DD-CKD	epoetin	30	23/7	White/Black/ Asian/others/ Not reported:14/10/ 6/0/0		10.52 ± 0.53	0.6 (0.8) mg/L		epoetin	1087.4 ± 764.3 IU per day	36 months	
			Total	87	56/31	White/Black/ Asian/others/ Not reported:42/26/ 16/2/1			0.7 (1.1) mg/L					

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Table 1 (*continued*)

StudyID	Single-/ multi center	Dialysis method	Group	Sample size (n)	Sex (male/ female)	Ethnicity	eGFR	Baseline Hemoglobin (Hb)(g/dL)	CRP (mg/dL)	CKD duration (y)	Treatment	Dosage of medication	Period of treatment	follow up
Akizawa 2019 (2) (Akizawa, Macdougall, Berns, Yamamoto et al., 2019)		NDD-CKD	D1										16w	
			FAS											
			molidustat	101	56/45	White/Asian/ black/other:63/ 38/0/0	23.4 (12.3)	9.5 (0.7)	7.2 (16.4) mg/L	4.5 (4.5)		25, 50, or 75 mg once daily, or 25 or 50 mg twice daily		
			placebo	20	9/11	White/Asian/ black/other:15/ 5/0/0	23.0 (11.6)	9.5 (0.6)	4.3 (5.1)	3.5 (2.7)				
			Non-iron users											
			molidustat	53	28/25	White/Asian/ black/other:34/ 19/0/0	25.2 (12.5)	9.4 (0.8)	7.4 (20.7)	4.5 (5.0)				
			placebo	8	4/4	White/Asian/ black/other:6/ 2/0/0	28.8 (13.0)	9.4 (0.7)	3.3 (4.0)	2.7 (2.3)				
		NDD-CKD	D2									25, 50, or 75 mg	16w	
			FAS											
			molidustat	92	45/47	White/Asian/ Black/other:69/ 22/1/0	20.4 (11.4)	10.8 (0.7)	7.4 (14.9)	6.7 (6.4)				
			darbepoetin alfa	32	18/14	White/Asian/ Black/other:25/ 6/1/0	21.9 (12.1)	10.9 (0.7)	6.5 (11.2)	5.8 (5.0)				
			Non-iron users											
			molidustat	42	23/19	White/Asian/ Black/other:33/ 9/0/0	19.0 (9.6)	10.8 (0.7)	6.3 (12.8)	7.2 (6.7)				
			darbepoetin alfa	16	10/6	White/Asian/ Black/other:12/ 3/1/0	20.6 (12.3)	10.8 (0.9)	8.8 (15.2)	6.3 (5.8)				
		DD-CKD	D4									25, 50, 75, or 150 mg	16w	
			FAS											
			molidustat	157	91/66	White/Asian/ Black/Other:84/ 29/40/4		10.5 (0.6)	7.9 (13.5)	6.4 (6.2)				
			epoetin alfa or beta	42	29/13	White/Asian/ Black/Other:18/ 7/17/0		10.6 (0.5)	7.1 (11.1)	5.5 (4.3)				
			Non-iron users											

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Table 1 (*continued*)

StudyID	Single-/ multi center	Dialysis method	Group	Sample size (n)	Sex (male/ female)	Ethnicity	eGFR	Baseline Hemoglobin (Hb)(g/dL)	CRP (mg/dL)	CKD duration (y)	Treatment	Dosage of medication	Period of treatment	follow up
			molidustat	59	32/27	White/Asian/ Black/Other:29/ 18/12/0		10.5 (0.6)	5.4 (10.4)	7.6 (6.8)				
			epoetin alfa or beta	15	10/5	White/Asian/ Black/Other:5/ 3/7/0		10.6 (0.6)	7.8 (10.8)	5.6 (4.6)				
Yamamoto 2021 (1) (Yamamoto et al., 2021a)	multicenter	NDD-CKD	molidustat	82	50/32	Japanese	19.0 (8.5)	9.84 (0.64)	0.317 (0.630)	7.369 (7.823)	molidustat	orally once daily after breakfast at a starting dose of 25 mg	52 w	4 w
			darbepoetin	80	50/30	Japanese	22.1 (12.0)	10.00 (0.61)	0.148 (0.241)	8.564 (10.604)	darbepoetin	injected subcutaneously every 2 weeks at a starting dose of 30 μg.	52 w	4 w
Yamamoto 2021 (2) (Yamamoto et al., 2021b)	multicenter	NDD-CKD	molidustat	82	45/37	Japanese	18.7 (10.7)	11.31 (0.68)	0.211 (0.441)	7.3 (7.2)	molidustat	the starting dose of 25 mg or 50 mg in accordance with the previous ESA dose	52 w	4 w
			darbepoetin	82	54/28	Japanese	17.5 (9.0)	11.27 (0.64)	0.194 (0.479)	7.8 (8.5)	darbepoetin	the starting dose as the previous ESA dose	52 w	4 w
Akizawa 2021 (Akizawa et al., 2021)	multicenter	DD-CKD	Molidustat	153	91/62	Japanese		10.77 (0.64)	0.256 (0.623)	12.067 (9.390)	molidustat + placebo	the starting dose of 75 mg/day; the mean (SD) dosage was 79.02 (42.65) mg/day	52 w	4 w
			darbepoetin	76	49/27	Japanese		10.84 (0.65)	0.217 (0.629)	10.842 (8.841)	darbepoetin + placebo	administrated weekly or once every 2 weeks; the mean (SD) dosage was 20.16 (14.70) mg/week	52 w	4 w

CKD [16,17,21–24]. Fig. 1 illustrates the screening process. Table 1 presents the main characteristics of the included trials.

3.2. Characteristics of included studies

The systematic review encompassed eleven RCTs derived from six studie, with 2025 participants from the European Union, the United States, Japan and other places. The characteristics of included studies were summarized in Table 1. Of the eleven trials, 6 trials evaluated the efficacy and safety of molidustat versus placebo or ESA in NDD-CKD patients [16,17,21–24]. Another 4 trials evaluated the efficacy and safety of molidustat versus ESA in DD-CKD patients [16,21–23]. The follow-up duration ranged from 4 to 8 weeks. The demographic characteristics of the molidustat and control groups were similar at baseline in all trials.

3.3. Risk-of-bias assessment

None of the RCTs were deemed to have an overall low risk of bias. The majority of trials had an unclear risk of bias regarding sequence generation and allocation concealment, as detailed information was not provided. However, 8 trails of 5 studies had a high risk of bias related to participant, personnel, and outcome assessment blinding because an open-label design carries an inherent bias that might affect the safety reporting [16,17,21,23,24]. In terms of incomplete outcome data, 4 trails of 2 studies had a high risk of bias because the dropout rate of participants exceeded 20 % of the total number [16,23]. (Fig. 2).

3.4. Efficacy

3.4.1. Change in Hb level from baseline (ΔHb)

For NDD-CKD patients, two trials compared the ΔHb levels for molidustat (n = 93) versus placebo (n = 37) [16,23], and five trials compared the ΔHb levels for molidustat (n = 389) versus ESAs (n = 246) [16,17,21,23,24]. For DD-CKD patients, four trials compared the ΔHb levels for molidustat (n = 401) versus ESAs (n = 175) [16,21–23]. The results of meta-analysis indicated that in NDD-CKD patients, the ΔHb level was significantly higher for the molidustat group than for the placebo group [MD = 1.47 (95 % CI: 1.18 to 1.75), P < 0.00001]. The ΔHb level in the molidustat group was significantly higher than in the ESA group [MD = 0.25 (95 % CI 0.09 to 0.40), P = 0.002]. For DD-CKD patients, molidustat showed an effect similar to that of ESAs on increasing the Hb level [MD = −0.18 (95 % CI: −0.47 to 0.11), P = 0.23] (Fig. 3).

For NDD-CKD patients, based on subgroup analysis of short-term treatment (16 weeks) trials, the ΔHb level was significantly higher for the molidustat group than for the control group [MD = 0.93 (95 % CI: 0.54 to 1.32), P < 0.00001]. And in subgroup analysis of long-term treatment (52 weeks-36mouths) trials, there was increasing trend of ΔHb level in the molidustat group than in the control group [MD = 0.20 (95 % CI: 0.01 to 0.40), P = 0.06]. For DD-CKD patients, in subgroup analysis of short-term treatment (16 weeks) or long-term treatment (52 weeks-36mouths) trials, no significant difference in the ΔHb level between molidustat and control was detected [MD = −0.21 (95 % CI: −0.55 to 0.13), P = 0.22; MD = −0.12 (95 % CI: −0.78 to 0.55), P = 0.73] (Supplementary Fig. S1). Furthermore, for NDD-CKD patients, molidustat showed a dose–response effect on Hb levels, that is, the effect of Molidustat on Hb is enhanced with the increase of dosage. For DD-CKD patients, it also showed that the effect of molidustat on Hb levels is not good enough at low dose (≤50 mg/d), while the effect of molidustat on maintaining Hb levels is better at medium and high dose (>50 mg/d) (Supplementary Fig. S2).

3.4.2. Change in iron level from baseline (ΔIron)

For NDD-CKD patients, two trials compared the Δiron levels for molidustat (n = 141) versus placebo (n = 38) [21,23], and four

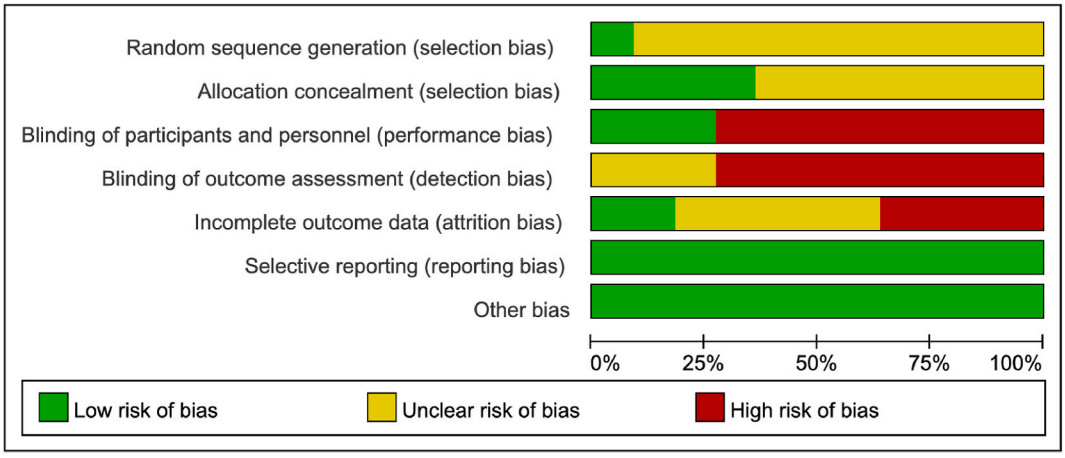

Fig. 2. Risk-of-bias summary of included randomized trials using the Cochrane Risk-of-Bias tool.

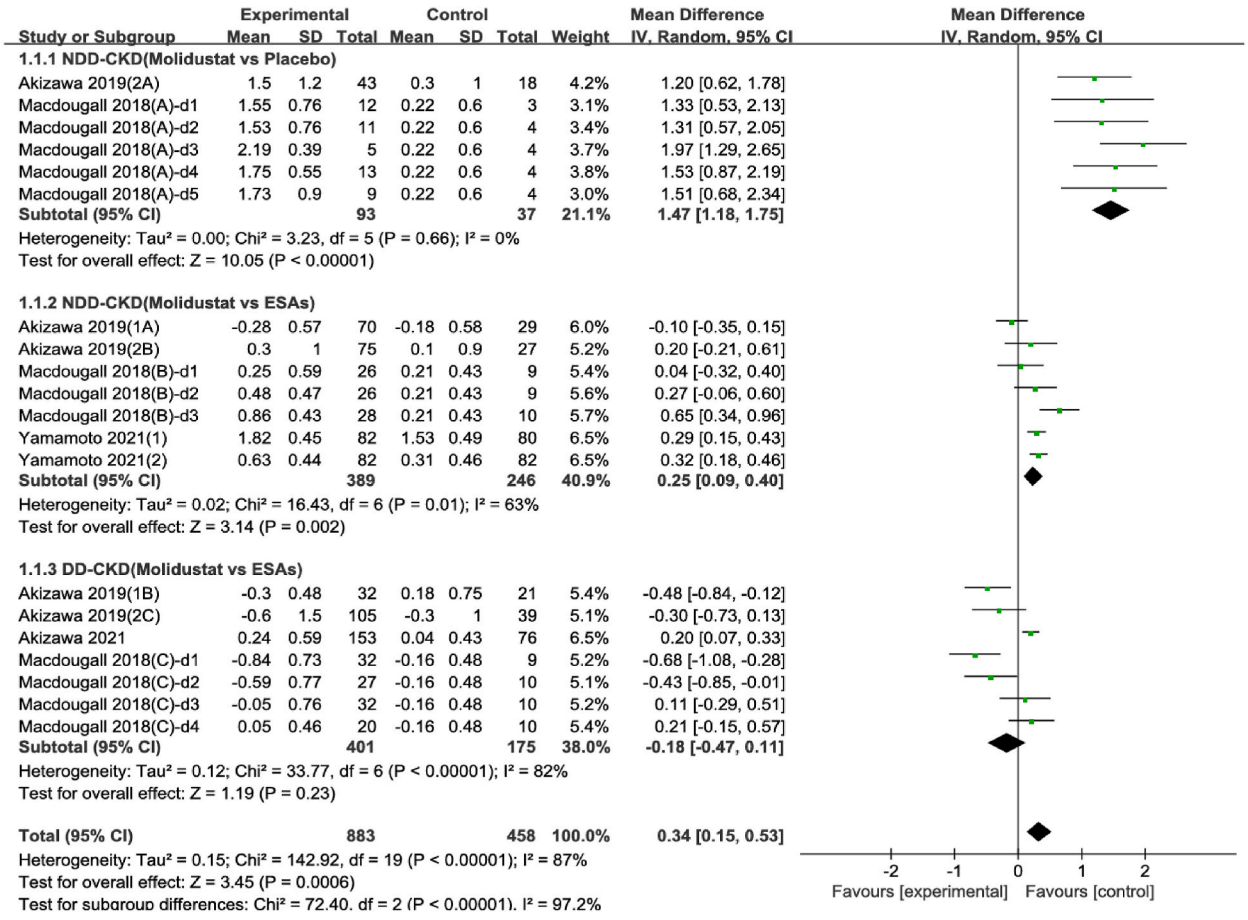

Fig. 3. Meta-analysis results of molidustat for ΔHb.

trials compared the Δiron levels for molidustat (n = 326) versus ESAs (n = 221) [17,21,23,24]. For DD-CKD patients, three trials compared the Δiron levels for molidustat (n = 467) versus ESAs (n = 157) [21–23]. The results of meta-analysis indicated that in NDD-CKD patients, the Δiron level was significantly lower for the molidustat group than for the ESA group [MD = −11.85 (95 % CI: −15.52 to −8.18), P < 0.00001], but the Δiron level in the molidustat group was similar to that in the placebo [MD = 2.97 (95 % CI: −10.25 to 16.20), P = 0.66]. And for DD-CKD patients, molidustat showed an effect similar to that of ESAs on Δiron level [MD = 3.78 (95 % CI: −7.21 to 14.76), P = 0.50] (Fig. 4).

3.4.3. Change in ferritin level from baseline (ΔFerritin)

For NDD-CKD patients, two trial compared the Δferritin level for molidustat (n = 141) versus placebo (n = 38)[21.23], and four trials compared the Δferritin levels for molidustat (n = 326) versus ESAs (n = 221) [17,21,23,24]. For DD-CKD patients, three trials compared the Δferritin level for molidustat (n = 471) versus ESAs (n = 157) [21–23]. The results of the meta-analysis indicated that for NDD-CKD patients, the Δferritin level was significantly lower for the molidustat group than for the placebo group [MD = −90.01 (95 % CI: −134.77 to −45.25), P < 0.00001]. And there was decreasing trend of Δferritin level in the molidustat group than in the ESA group [MD = −15.0 (95 % CI:-31.37 to 1.71), P = 0.08]. But for DD-CKD patients, molidustat showed an effect similar to that of ESAs on the Δferritin level [MD = 25.03 (95 % CI: −34.69 to 84.75), P = 0.41] (Fig. 5).

3.4.4. Change in TSAT level from baseline (ΔTSAT)

For NDD-CKD patients, two trials compared the ΔTSAT level for molidustat (n = 141) versus placebo (n = 38)[21.23], and four trials compared the ΔTSAT levels for molidustat (n = 326) versus ESAs (n = 221) [17,21,23,24]. For DD-CKD patients, three trials compared the ΔTSAT level for molidustat (n = 467) versus ESAs (n = 156) [21–23]. The results of the meta-analysis indicated that for NDD-CKD patients, the ΔTSAT level was significantly lower for the molidustat group than for the ESA group [MD = −5.29 (95 % CI: −6.81 to −3.78), P < 0.00001], but the ΔTSAT level in the molidustat group was similar to that in the placebo [MD = −1.24 (95 % CI: -6.11 to 3.62), P = 0.62]. For DD-CKD patients, the ΔTSAT level was significantly higher for the molidustat group than for the placebo or ESA group [MD = 3.88 (95 % CI: 2.10 to 5.65), P < 0.0001] (Fig. 6).

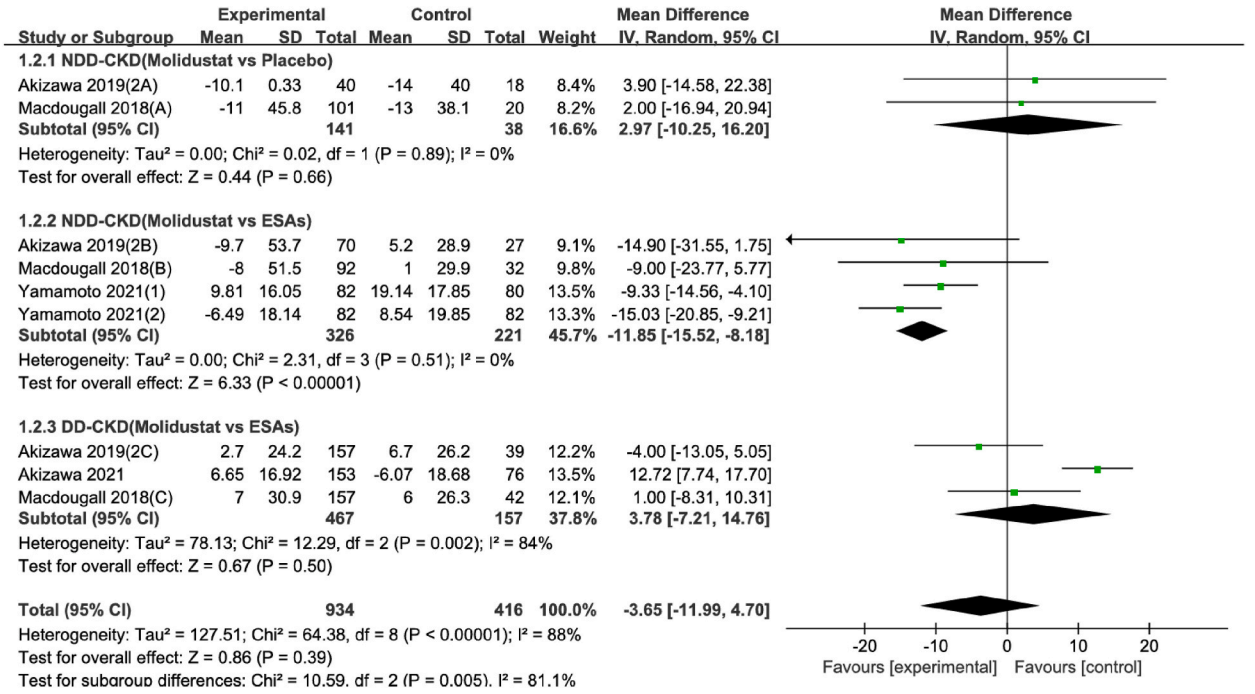

Fig. 4. Meta-analysis results of molidustat for Δiron.

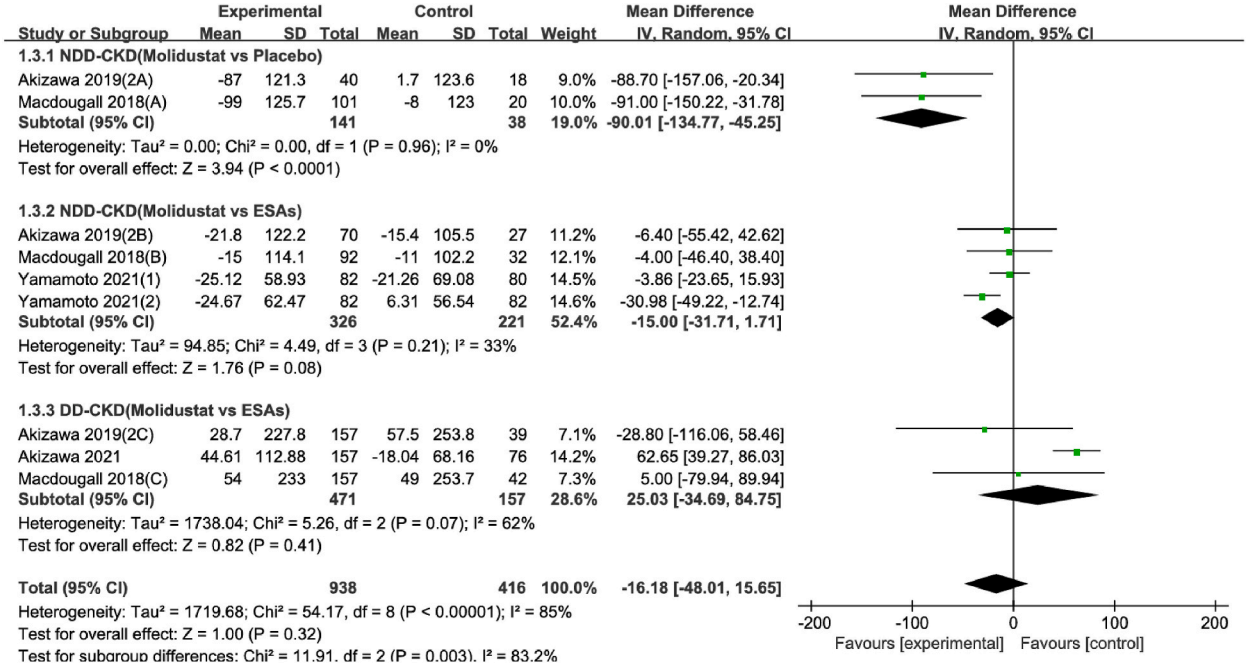

Fig. 5. Meta-analysis results of molidustat for Δferritin.

3.4.5. Change in TIBC level from baseline (ΔTIBC)

For NDD-CKD patients, two trials compared the ΔTIBC level for molidustat (n = 141) versus placebo (n = 38) [21,23], and four trials compared the ΔTIBC levels for molidustat (n = 326) versus ESAs (n = 221) [17,21,23,24]. For DD-CKD patients, three trials compared the ΔTIBC level for molidustat (n = 467) versus ESAs (n = 157) [21–23]. The results of the meta-analysis indicated that for NDD-CKD patients, the ΔTIBC level was significantly higher for the molidustat group than for the placebo or ESA group [MD = 3.85 (95 % CI: 1.86 to 5.85), P = 0.0002; MD = 0.96 (95 % CI: 0.07 to 1.85), P = 0.03, respectively]. And for DD-CKD patients, the ΔTIBC

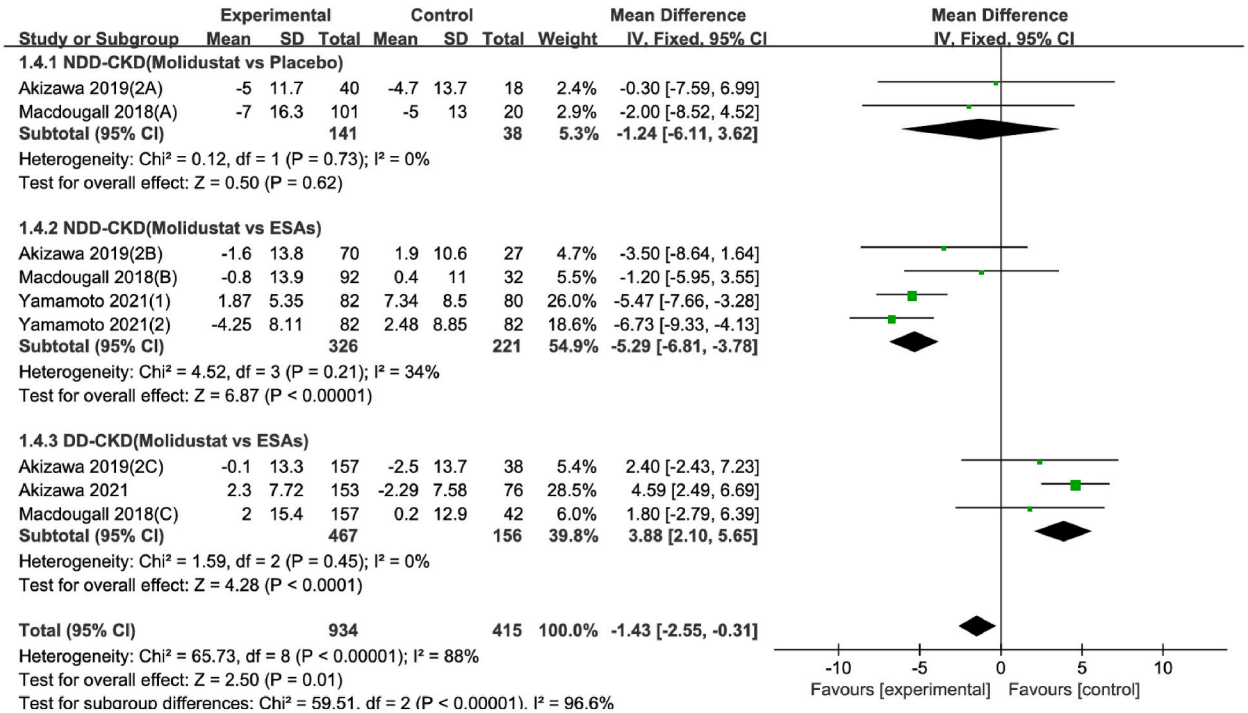

Fig. 6. Meta-analysis results of molidustat for ΔTSAT.

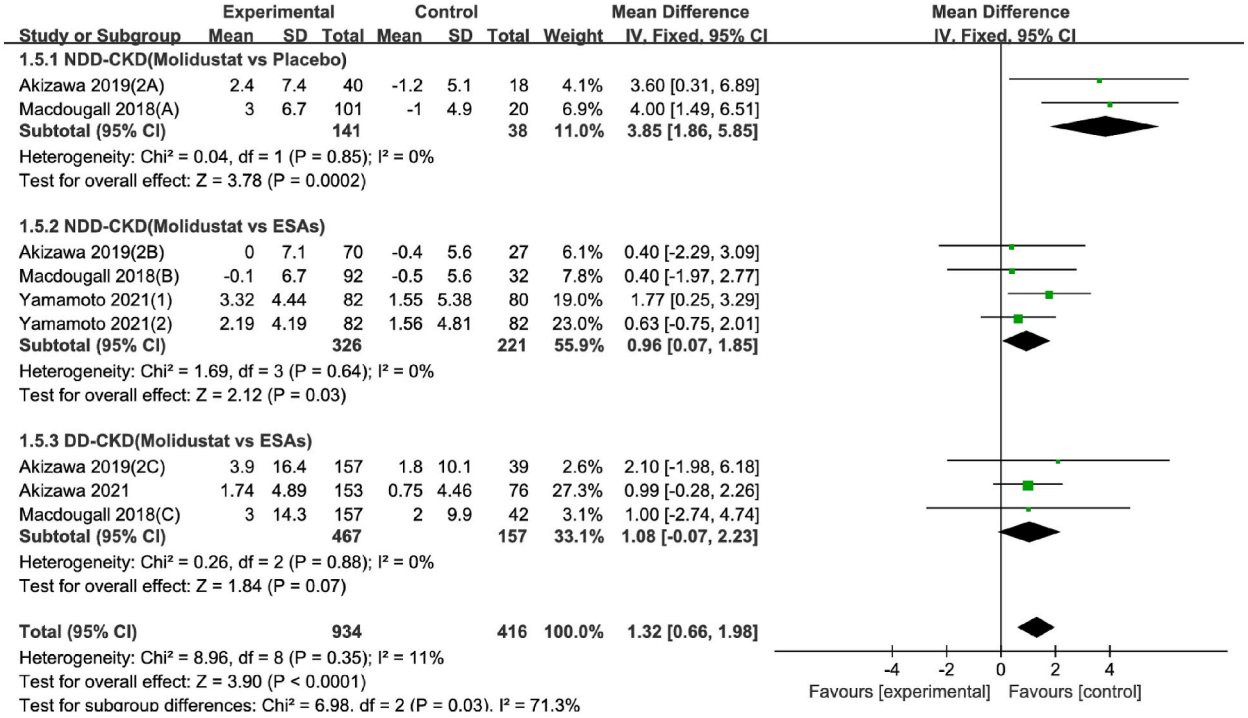

Fig. 7. Meta-analysis results of molidustat for ΔTIBC.

level was significantly higher for the molidustat group than for the placebo or ESA group [MD = 1.08 (95 % CI: −0.07 to 2.23), P = 0.07] (Fig. 7).

3.4.6. Change in hepcidin level from baseline (ΔHepcidin)

For NDD-CKD patients, two trials compared the Δhepcidin level for molidustat (n = 141) versus placebo (n = 38) [21,23], and four trials compared the Δhepcidin levels for molidustat (n = 328) versus ESAs (n = 221) [17,21,23,24]. For DD-CKD patients, three trials compared the Δhepcidin level for molidustat (n = 466) versus ESAs (n = 156) [21–23]. The results of the meta-analysis indicated that for NDD-CKD patients, the Δhepcidin level was significantly lower for the molidustat group than for the placebo or ESA group [MD = −20.66 (95 % CI: −31.67 to −9.66), P = 0.0002; MD = −24.51 (95 % CI: −29.12 to −19.90), P < 0.00001, respectively]. But for DD-CKD patients, molidustat showed an effect similar to that of ESAs on the Δhepcidin level [MD = 1.20 (95 % CI: −4.36 to 6.76), P = 0.67] (Fig. 8).

3.5. Safety

3.5.1. SAEs

For NDD-CKD patients, one trial compared the incidence of SAEs for molidustat (n = 101) versus placebo (n = 20) [23], and four trials compared the incidence of SAEs for molidustat (n = 374) versus ESAs (n = 236) [16,17,23,24]. For DD-CKD patients, three trials compared the incidence of SAEs for molidustat (n = 374) versus ESAs (n = 236) [16,22,23]. The results of the meta-analysis indicated that for NDD patients, whether compared with placebo (n = 20) or ESAs (n = 236), molidustat (n = 101; n = 374, respectively) did not show significantly increase the risk of SAEs [OR = 0.48 (95 % CI: 0.15 to 1.54), P = 0.22; OR = 1.24 (95 % CI: 0.82 to 1.88), P = 0.31, respectively]. And for DD, molidustat (n = 360) did not obviously increase the risk of SAEs compared with that of the ESAs group (n = 114) [OR = 1.49; (95 % CI: 0.93 to 2.38), P = 0.10] (Fig. 9).

3.5.2. Death

For NDD-CKD patients, one trial compared the incidence of death for molidustat (n = 101) versus placebo (n = 20) [23], and four trials compared the incidence of death for molidustat (n = 374) versus ESAs (n = 236) [16,17,23,24]. For DD-CKD patients, two trials compared the incidence of death for molidustat (n = 214) versus ESAs (n = 72) [16,22,23]. The results of the meta-analysis indicated that for NDD patients, there were no deaths in the molidustat group (n = 101) versus placebo (n = 20), while compared with ESAs (n = 236), molidustat (n = 374) did not show significantly increase the risk of death [OR = 1.95 (95 % CI: 0.59 to 6.46), P = 0.27]. And for DD, molidustat (n = 214) did not obviously increase the risk of death compared with that of the ESAs group (n = 72) [OR = 0.81; (95 % CI: 0.03 to 20.36), P = 0.90] (Fig. 10).

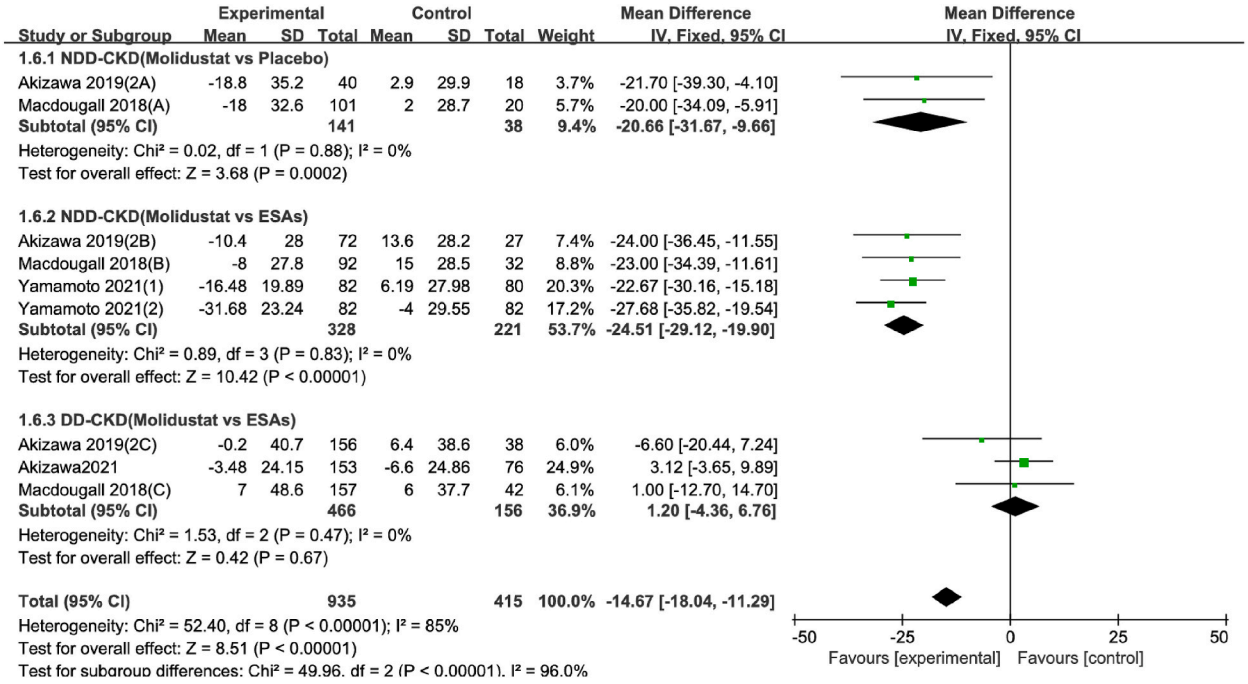

Fig. 8. Meta-analysis results of molidustat for Δhepcidin.

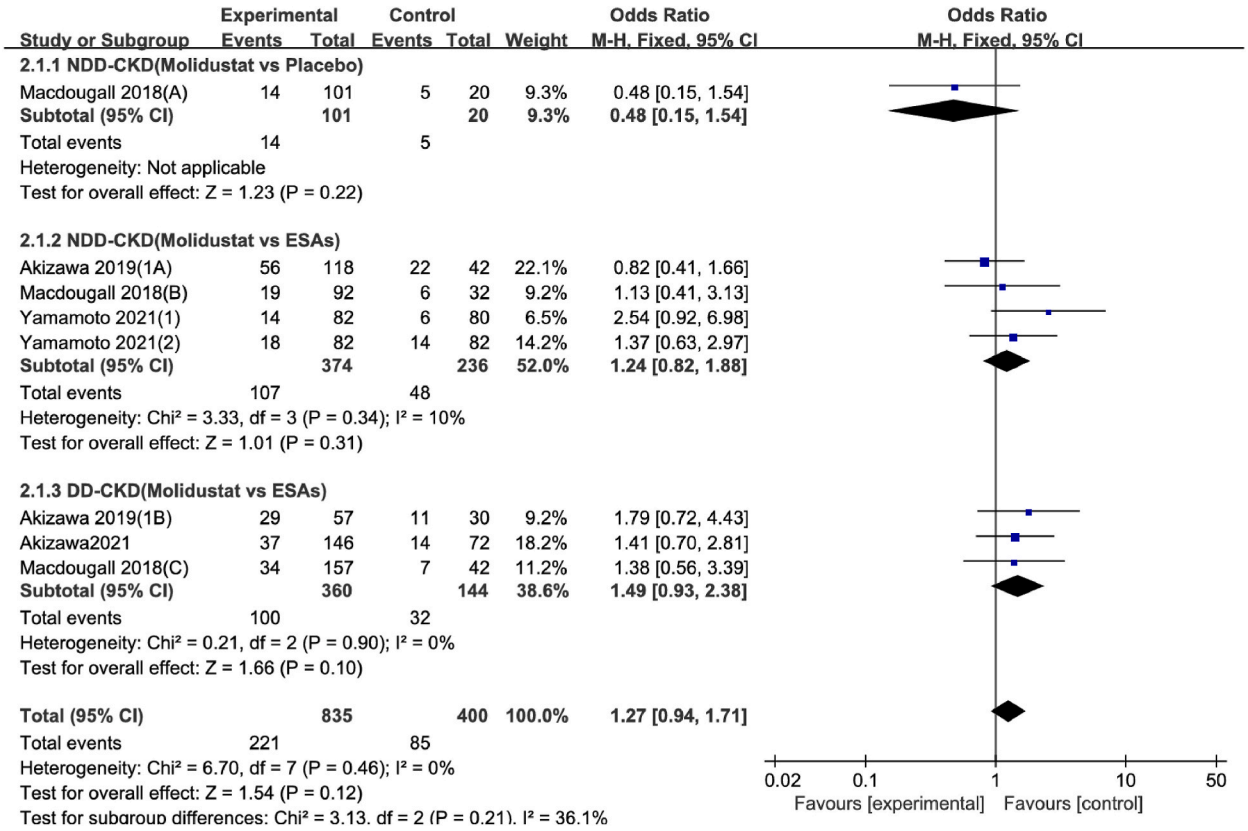

Fig. 9. Meta-analysis results of molidustat for SAEs.

3.5.3. Cardio-related adverse events

For NDD-CKD patients, one trial compared the incidence of cardio-related adverse events for molidustat (n = 157) versus placebo (n = 42) [23], and four trials compared the incidence of cardio-related adverse events for molidustat (n = 383) versus ESAs (n = 224) [16,17,23,24]. For DD-CKD patients, two trials compared the incidence of cardio-related adverse events for molidustat (n = 149) versus ESAs (n = 62) [16,22,23]. The results of the meta-analysis indicated that for NDD patients, whether compared with placebo (n = 42) or ESAs (n = 224), molidustat (n = 157; n = 383, respectively) did not show significantly increase the risk of cardio-related adverse events [OR = 1.37 (95 % CI: 0.06 to 29.01), P = 0.84; OR = 1.51 (95 % CI: 0.78 to 2.90), P = 0.22, respectively]. And for DD, molidustat (n = 149) did not obviously increase the risk of cardio-related adverse events compared with that of the ESAs group (n = 62) [OR = 0.73; (95 % CI: 0.26 to 2.05), P = 0.55] (Fig. 11).

3.5.4. Kidney-related adverse events

Three studies compared the incidence of kidney-related adverse events for molidustat (n = 256) versus ESAs (n = 194) [17,23,24]. Kidney-related adverse events refer to CKD worsening including deterioration of CKD and exacerbation of CKD. The meta-analysis, comprising a total of 450 participants, indicated that molidustat (n = 41) could elevate the risk of kidney-related adverse events compared to the ESAs group (n = 17) [OR = 2.27; (95 % CI: 1.23 to 4.19); P = 0.009] (Fig. 12).

3.6. Publication bias and sensitivity analysis

Publication bias was not assessed as all outcome indicators were observed in <10 studies. Sensitivity analysis was conducted on the results with I^2>40 % in the meta-analysis. The items 1.1.2 and 1.1.3 in Fig. 3 were subjected to sensitivity analysis using the literature exclusion method, and the results were robust. And the sensitivity analysis of items 1.2.3 in Fig. 4 and 1.3.3 in Fig. 5 was compared using a random effects model and a fixed effects model, but the results lacked robustness (Supplementary Fig. 1, Fig. 2). This indicates that for DD patients, there is greater heterogeneity in the regulation of iron and ferritin levels by molidustst compared to ESAs.

4. Discussion

This systematic review and meta-analysis was aimed to evaluate the effectiveness and safety of molidustat in treating anemia among patients with NDD and DD. Based on current guidelines for managing anemia in patients with CKD, there are existing concerns

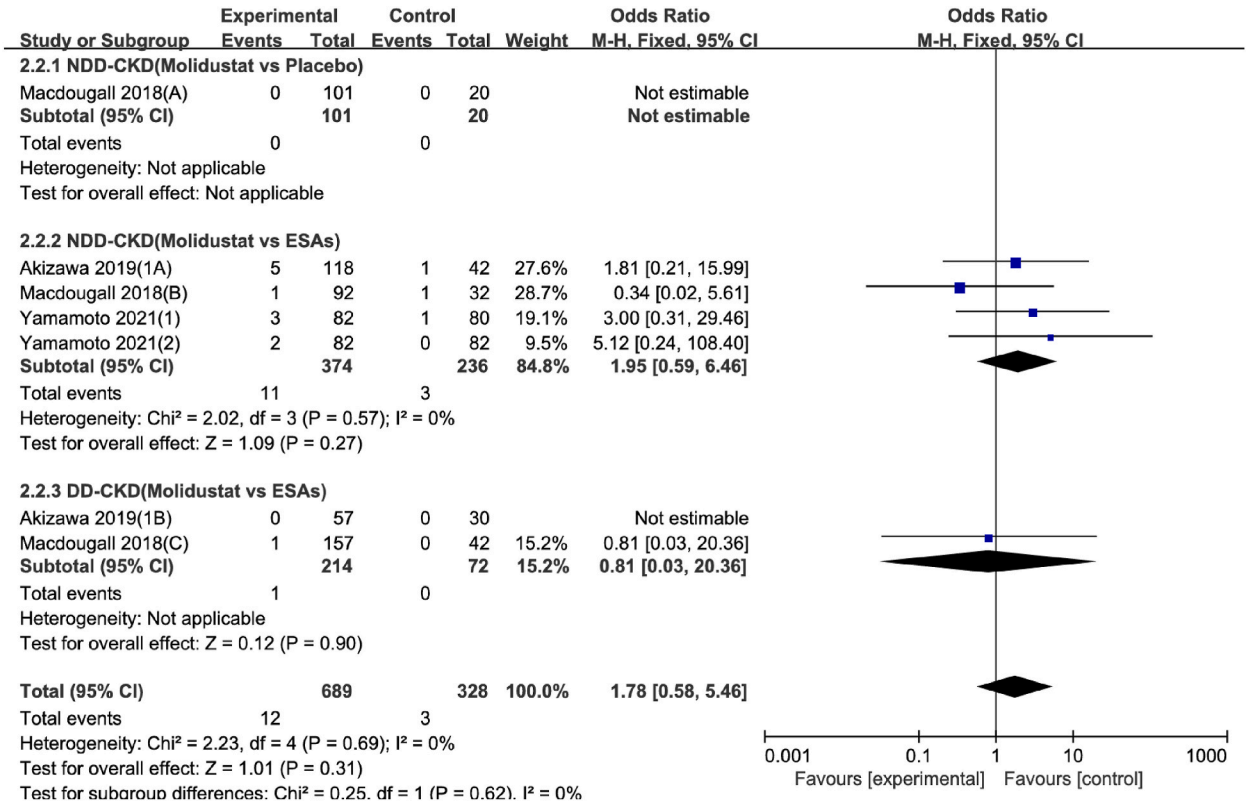

Fig. 10. Meta-analysis results of molidustat for death.

regarding adverse reactions, tolerability, and inadequate treatment efficacy. Molidustat may emerge as a promising new therapeutic choice for the management of anemia associated with CKD. The analysis indicated that molidustat has favorable effects in increasing Hb levels in NDD patients compared to placebo or ESAs. There was a dose-response relationship, where higher doses of molidustat were more effective in correcting anemia. For DD patients, the efficacy of molidustat in increasing Hb was comparable to that of ESAs. In addition, molidustat was more effective at maintaining Hb levels when administered at medium and high doses (>50 mg/d). Furthermore, the results of the iron metabolism parameters were particularly noteworthy. For NDD patients, the molidustat group exhibited significantly decreased levels of serum hepcidin and ferritin compared to those in the placebo group. Additionally, in the molidustat group, serum levels of hepcidin, iron, and TSAT exhibited significant decreases compared to those in the ESAs group. Compared to the ESAs group, patients with DD experienced a significant increase in serum TSAT levels following treatment with molidustat. The incidences of SAEs, death, and cardio-related adverse events were comparable in the molidustat and the placebo or ESAs groups. However, there was a rising trend in the occurrence of kidney-related adverse events in molidustat treated subjects.

Molidustat (BAY 85–3934) represents a novel class of agents developed by Bayer for patients with CKD suffering from anemia [25]. Through pharmacological inhibition of PHDs, molidustat reduces the hydroxylation of HIF-α and heterodimerizes with HIF-1β, forming the functional HIF heterodimers. After the recruitment of coactivators, the HIF complex stimulates the transcription of many genes via activating hypoxia response elements in the promoter. The ultimate hypoxic response is involved in EPO synthesis and directly enhances erythropoiesis in the bone marrow. Heightened EPO-driven erythropoiesis inducing relative iron deficiency could suppress hepcidin production and augment iron absorption [26]. Furthermore, HIF directly inhibits hepcidin induction in response to signals originating from both the bone marrow and liver [27]. The link between the HIF pathway and hepcidin regulation offers an additional mechanism to promote erythropoiesis by enabling the HIF pathway to optimize iron metabolism. Notably, molidustat transiently induces the HIF pathway and increases the physiological level of EPO, allowing for the maintenance of Hb in a physiological range without supraphysiologic increases in EPO levels induced by ESAs [28]. Thus, molidustat inhibiting HIF prolyl-hydroxylases can improve the level of plasma Hb. In addition, basic experimental studies have suggested that molidustat could elevate circulating EPO and bone marrow EpoR mRNAs to improve anemia in a CKD mice model [29]. In this study, two trials compared molidustat with the placebo and assessed the effectiveness of molidustat in correcting renal anemia in NDD patients who had the Hb level below the target range at baseline [21,23]. The results showed that molidustat provided increases in Hb levels and effectively corrected anemia in NDD patients. In the other trials, molidustat was compared with ESAs to evaluate its effectiveness in maintaining treatment efficacy for renal anemia among CKD patients who were previously treated with ESAs and had Hb levels within the target range (10.0–12.0 g/dL) at baseline [16,17,22,24]. Our results are consistent with studies reporting that molidustat effectively improved Hb levels in NDD patients and was non-inferior to ESAs in sustaining Hb levels within the target range of 10.0–12.0

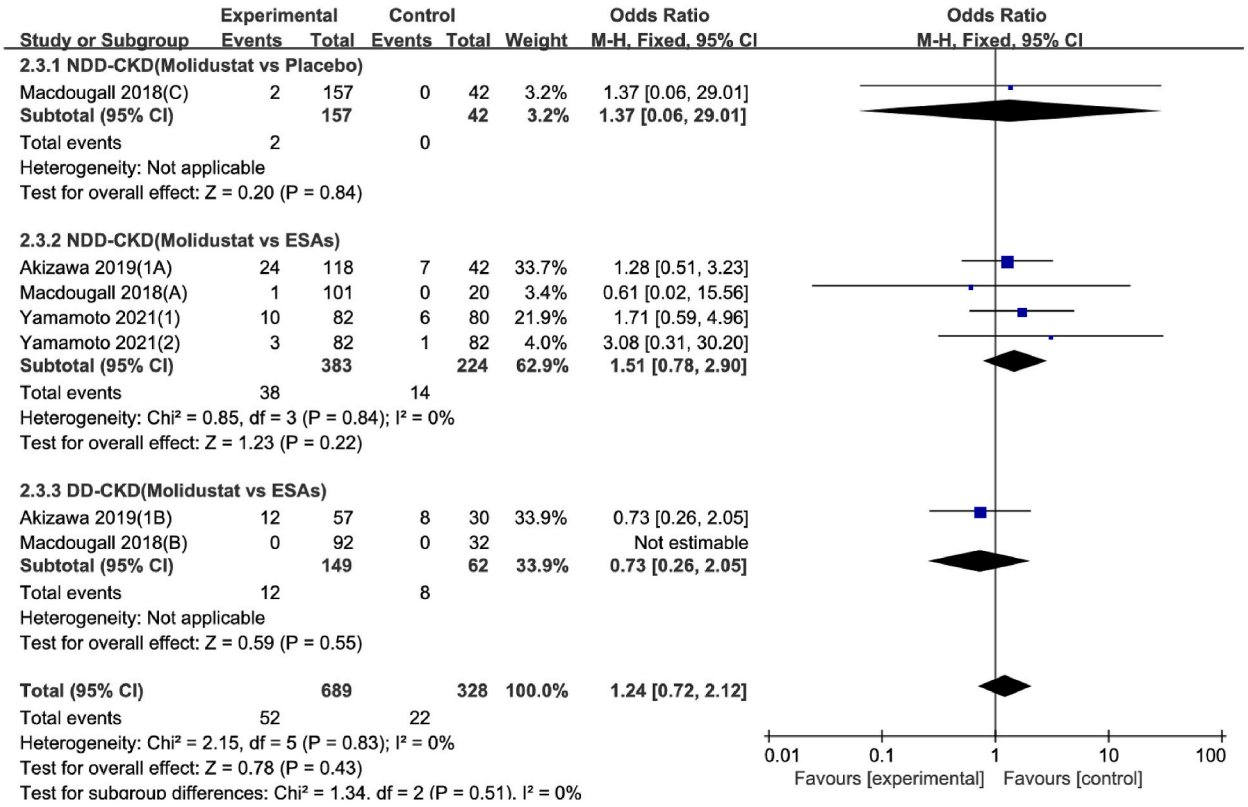

Fig. 11. Meta-analysis results of molidustat for cardio-related adverse events.

g/dl in DD patients.

The effect of molidustat therapy on iron metabolism is noteworthy since iron shortage is another major driver that results in anemia in impaired kidney function. In the CKD state, a high concentration of hepcidin which functions as the main hormone of iron homeostasis limits intestinal iron uptake and inhibits iron release from macrophages, resulting in iron-restricted erythropoiesis [30]. The HIF system can simultaneously regulate iron metabolism factor genes, including hepcidin, transferrin, and ferroportin, to efficiently utilize iron [15]. Activating the HIF axis by molidustat could optimize iron utilization through the mobilization of iron from the intestine and macrophages to coordinate erythropoiesis without being influenced by inflammation [31]. Ferritin, a widely existing iron storage protein in the human body, reflects iron storage [32]. As TIBC represents the total iron-binding capacity of transferrin, its determination is influenced by the level of transferrin. TSAT that reflects the accessibility of iron for erythropoiesis is the ratio of serum iron to TIBC. Therefore, TSAT and TIBC act as iron deficiency biomarkers that reflect iron availability for erythropoiesis [33]. Consistent with the action mechanism, treatment of molidustat elevated the levels of erythroferrone and transferrin receptors, and downregulated the expression of liver Bmp-6 and hepcidin, supporting that it could improve iron utilization in CKD mice [29]. According to our meta-analysis, the molidustat group had greater Hb levels than the ESAs group in NDD patients, with more demand of iron for erythropoiesis. Furthermore, molidustat dramatically lowered serum iron, TSAT and hepcidin levels, demonstrating improved utilization of iron stores than ESAs. Moreover, despite iron was consumed for erythropoiesis, the molidustat group exhibited higher Hb levels compared to the placebo with the lower ferritin and hepcidin, which further supported that molidustat better promoted iron utilization in NDD patients. For DD patients, there was no significant difference in serum iron, hepcidin, and ferritin between molidustat and the ESAs groups. However, in comparison to the placebo or ESA group, molidustat showed a significantly higher level on ΔTSAT, and a slightly increased level on ΔTIBC level. These results may be associated with the higher dose of intravenous iron supplementation in hemodialysis, which has demonstrated a more pronounced effect on TSAT compared to oral iron supplementation [34]. Besides, hemodialysis is linked to elevated levels of inflammatory activity [35]. Therefore, intravenous iron supplementation combined with high levels of background inflammatory activity may have obscured the impact of molidustat on iron metabolism in DD patients. In addition, three studies provided dosage of intravenous and oral iron supplements between molidustat and ESAs (Table 2) [17,22,24]. However, due to the limited number of samples included, the data cannot be systematically analyzed. For NDD patients, the dosage of iron supplement in the molidustat group was less than that in the ESA group, either orally or intravenously. These data align with the beneficial effect of molidustat on iron availability. For DD patients, one study stated that the median IV iron dosage was slightly higher for the molidustat than control groups (18.16 versus 15.20 mg/week) throughout the treatment period. Due to the small number of publications on molidustat, further large-scale and longer-duration trials are needed to investigate the effect of molidustat on iron mobilization. Inflammation is the main reason for the undertreatment of ESAs in patients with CKD [36,37]. Accordingly, the

included study demonstrated that the baseline inflammatory state had no significant effect on the actual dosage of molidustat [17]. In addition, patients in the darbepoetin group who had the highest CRP levels required higher dosages of darbepoetin, this trend was not observed for molidustat. Meanwhile, this potential advantage of molidustat in the inflammatory state was worth investigating in clinical studies.

Apart from the therapeutic effect, the safety of molidustat in treating anemia is also crucial. Included studies demonstrated consistent overall incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs. The severity of most drug-related adverse events was mild to moderate. Meta-analysis showed no significant difference for NDD and DD patients in SAEs associated with molidustat compared with the placebo or ESAs. Moreover, there was no rise in the occurrence of death or cardiovascular-related adverse events among subjects treated with molidustat. Nevertheless, the upward trend in the incidence of kidney-related adverse events, indicative of CKD worsening, was more pronounced in the molidustat group compared to the ESAs group. Nonetheless, only 3 trials compared molidustat with ESAs, and sample sizes were relatively small. In addition, it should be noted that 3 included trials were open-label, which might have a risk of bias against AE reporting [23]. Likewise, the baseline characteristics including SBP, eGFR, and the main cause of CKD were imbalanced between molidustat and darbepoetin, which may partially explain those results [17,24]. Hence, the incidence of kidney-related adverse events in molidustat have yet to be determined, further trials are needed to monitor the relationship between molidustat and kidney-related adverse events. In addition, related indicators of renal function need to be closely observed during treatment. One should also pay attention to the cardiovascular safety. Currently, the Japanese Society of Nephrology and the Asian Pacific Society of Nephrology recommend a cautious use in patients with cardiovascular disease, considering that over-activation of HIF could induce defective energy utilization of the cardiac myocytes [37]. However, only four trials with short-term follow-up (ranged from 6 to 20 weeks) compared vadadustat with placebo, and the sample sizes were relatively small. Consequently, the long-term impact of vadadustat on the cardiovascular system in patients with CKD remains uncertain and warrants further investigation. HIF- PHIs could induce the VEGF gene to increase VEGF levels, which was essential for pathogenesis of tumor growth and metastasis. In this study, one trial reported that for DD patients there was an increasing trend of serum VEGF in the molidustat group when compared to ESA group, while the clinical impact remained unclear in this trial [22]. In addition, study of healthy Japanese showed that molidustat had no dose-dependent effect on serum VEGF concentration during the treatment[38]. Hence, the assessment of serum VEGF levels should be considered in the clinical application of molidustat.

This study represents the inaugural assessment of molidustat's efficacy and safety for addressing anemia in both NDD and DD patients. It is worth noting that publication bias is typically evaluated through funnel plots and the Egger test. There are less than 10 literatures in this paper, so publication bias was not assessed. However, it cannot be ruled out that potential publication bias, especially for unpublished or unreported studies, could have an impact on the overall effect, leading to increased uncertainty in the conclusions. In addition, publication bias may make the included studies not representative of the overall study population, thus limiting the generality and applicability of the findings.

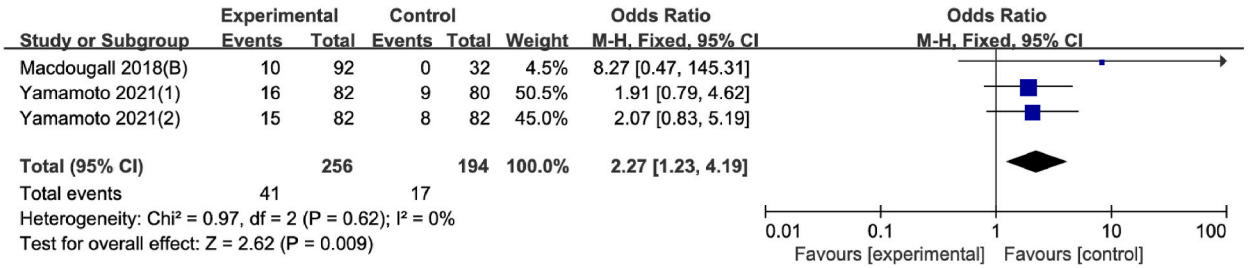

Fig. 12. Meta-analysis results of molidustat for kidney-related adverse events.

Table 2
Dosage of iron supplements.

Study ID	Dialysis method	Interventions	Treatment	No.	Dose of iron mean (SD)
Yamamoto 2021 (1)	NDD	molidustat	intravenous iron	4	2.89 (4.13) mg/week
		darbepoetin		4	11.22 (20.43) mg/week
		molidustat	oral iron	41	48.98 (41.81) mg/day
		darbepoetin		32	60.09 (52.72) mg/day
Yamamoto 2021 (2)	NDD	molidustat	intravenous iron	2	0.77 (1.09) mg/week
		darbepoetin		2	2.20 (3.12) mg/week
		molidustat	oral iron	46	44.54 (34.03) mg/day
		darbepoetin		32	50.58 (41.65) mg/day
Akizawa 2021	DD	molidustat	intravenous iron	95	18.16 (11.81) mg/week
		darbepoetin		48	15.20 (9.14) mg/week
		molidustat	oral iron	19	29.18 (29.64) mg/day
		darbepoetin		3	42.99 (49.38) mg/day

5. Limitation

Our meta-analysis has several limitations worth noting. Firstly, the number of studies included on molidustat is small–three Phase 2 and three Phase 3 studies,thus, the molidustat efficacy and safety could not be fully assessed. Secondly, the dosage of molidustat varied among the included studies; in several Phase 2 studies molidustat increased Hb levels in a dose-dependent manner. Thus, the most efficacious and safest dose could not be evaluated in NDD and DD patients. Thirdly, differences in the characteristics of the participants in each study, the therapeutic dose and course of molidustat, and the use of iron contributed to the heterogeneity of the results and may have an impact on iron-related indicators (iron, ferritin, TSAT, TIBC). Lastly, although the included trials are multicenter and global, most of the included RCTs focus on Asians and whites and performed in Japan. Therefore, we offer solely a preliminary overview of the immediate impact and short-term adverse effects of molidustat, and the efficacy of molidustat in the Occident remains uncertain. More large-scale RCTs involving in Occident and examining several doses over a long treatment time are necessary to thoroughly investigate the efficacy and safety of molidustat.

6. Conclusion

In conclusion, molidustat can effectively improves Hb levels in NDD patients and corrects anemia in DD patients without increasing the incidence of adverse events. Through a comprehensive evaluation of molidulistat, we have provided a new treatment option for patients with CKD that can improve their quality of life and prognosis. However, we should also note the limitations of our study and encourage future studies to further explore the efficacy and safety of molidulistat in different patient populations to more fully understand its potential for clinical use. In addition, further in-depth exploration of the mechanism of action of molidustat, as well as its effects on erythropoiesis and other biological processes, may help to understand its role in the treatment of anemia in patients with CKD.

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Data availability statement

All data utilized in this study are accessible upon request by contacting the corresponding author.

CRediT authorship contribution statement

Yi Kang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Mengqi Zhou:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Qian Jin:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation. **Yun Ling Geng:** Validation, Supervision, Methodology, Data curation. **Yaoxian Wang:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Formal analysis. **Jie Lv:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30621.

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