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Efficacy and safety of molidustat for the anemia of chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Aim: Anemia is a prevalent complication in chronic kidney disease (CKD) patients, necessitating effective management for improved clinical outcomes. This systematic review and meta-analysis aim to evaluate the efficacy and safety of molidustat for iron-deficient anemia in CKD patients.

Materials and Methods: A comprehensive search of Ovid MEDLINE, Web of Science, PubMed, and Cochrane CENTRAL was conducted. The primary efficacy outcomes included changes in hemoglobin (Hb) levels during follow-up and at week 16. Inverse variance random effects models were used for main analysis. The overall risk of bias (RoB) was assessed using the Cochrane RoB 2 tool.

Results: Six randomized controlled trials (RCTs) involving 999 patients were included. The meta-analysis for Hb change during follow-up revealed a mean difference (MD) of 0.09 (95% CI, -0.49 to 0.67), p=0.071, with an I^2 of 81% whereas Hb change at week 16 showed an MD of 0.12 (95% CI, -0.40 to 0.64), p=0.65 with an I^2 of 85%. Notably, changes in hepcidin levels during follow-up (MD -16.55, 95% CI -29.54 to -3.56) favored molidustat but not changes in total iron binding capacity at week 16 (MD 2.89, 95% CI 1.74 to 4.04). However, the impact of molidustat on transferrin saturation, iron levels, and ferritin levels showed comparable results. Regarding safety outcomes, no significant differences were observed in treatment emergent adverse events (TEAE) leading to death, patients with ≥1 major adverse cardiovascular event (MACE), hyperkalemia, any TEAE, and any serious TEAE. The risk of CKD worsening was increased with molidustat (MD 1.79, 95% CI 1.03 to 3.10). Subgroup analyses for primary outcomes were consistent with main analyses. RoB for Hb change was found as high/some concerns in 5/1 RCTs, respectively.

Conclusion: Molidustat exhibited noninferiority to ESAs in managing anemia in CKD patients. However, a concerning finding was the increased risk of CKD worsening associated with molidustat use. Well-designed RCTs are essential to enhance our understanding of molidustat's in CKD-related anemia.

Introduction

Chronic kidney disease (CKD) is a global health challenge that affects approximately 0.84 billion people Put reference numbering in square brackets like this [1]. with an additional 20 million new cases each year [2]. CKD is characterized by persistent kidney dysfunction or structural changes in kidney tissue lasting more than three months. It not only results in reduced kidney function but also leads to elevated levels of albumin in the urine, which significantly increase the risk of cardiovascular (CV) disease.

Anemia, marked by a decrease in circulating red blood cells (RBC), is a prevalent consequence of CKD progression. Several factors contribute to anemia in CKD, including impaired kidney erythropoietin production, reduced iron absorption, macrophage sequestration of iron due to uremic inflammation, and a shortened lifespan of RBCs [3]. Anemia is a crucial concern for individuals with CKD and can further compromise their health-related quality of life, leading to decreased work productivity [4]. Anemia

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in CKD is associated with increased mortality, including mortality related to CV disease and infections [5]. In the realm of treatment for anemia caused by CKD, therapeutic options include erythropoiesis-stimulating agents (ESAs), iron supplementation, and blood transfusions. Clinical practice guidelines recommend the correction of iron deficiency prior to initiating ESA therapy, emphasizing the minimization of RBC transfusions, especially to avoid allosensitization, except when a rapid correction of anemia is deemed necessary [6]. ESAs, when used to target higher hemoglobin (Hb) levels ($>$ 13 g/dL) in individuals with CKD, carry an increased risk of mortality and adverse CV events [7]. This has led to clinical practice recommendations that advocate the use of ESA therapy to avoid Hb concentrations below 9 g/dL [6].

Hypoxia-inducible factors (HIFs) present a promising class of orally administered drugs for the treatment of anemia in individuals with CKD [8]. HIFs are cellular transcription factors formed by binding HIF-α andβ subunits. While HIF-β subunits are constantly expressed, HIF-α subunits are regulated through proline residue hydroxylation by HIF-prolyl-hydroxylases (HIF-PH). In times of tissue hypoxia, inhibiting HIF-PH stabilizes HIF-1 and HIF-2, which activate genes supporting erythropoiesis, angiogenesis, and metabolic processes [9]. HIF-PH inhibitors suppress HIF-PH activity, promoting erythropoiesis in CKD patients. Moreover, they reduce hepcidin production, the key regulator of systemic iron balance, aiding in intestinal iron absorption and mobilization from the reticuloendothelial system [10]. HIF-PH inhibitors offer a promising oral therapy for sustained anemia correction in CKD with reduced reliance on iron, particularly intravenous (IV) supplementation. Their potential to improve patient adherence and avoid known adverse effects associated with ESAs and blood transfusions makes them a compelling avenue of exploration. The oral HIF-PH inhibitor named molidustat has been researched as a potential therapy for renal anemia, primarily stimulates renal erythropoietin (EPO) production [11]. A normal hematocrit and Hb level are the results of an increase in endogenous renal EPO synthesis and, to a lesser extent, hepatic EPO production that occurs close to the normal physiological range [12,13].

Given the emerging evidence on the use of HIF-PH inhibitors for managing anemia in individuals with CKD, particularly from randomized controlled trials (RCTs), the need to evaluate the efficacy and safety of molidustat compared to other treatment strategies, including ESAs therapy, becomes evident.

Materials and Methods

Study design

A systematic review and meta-analysis were conducted to evaluate the efficacy and safety of molidustat in the treatment of anemia associated with CKD. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [14].

Data sources and search strategy

A comprehensive search of the following electronic databases was performed from inception to June 17, 2023: Ovid MEDLINE, Web of Science, PubMed, and The Cochrane Central Register of Controlled Trials. The search strategy employed a combination of medical subject headings, keywords related to the intervention (molidustat, BAY 85-3934), and randomized controlled trials. The search was not limited by language or publication status.

Study selection

Two independent reviewers screened the identified records for inclusion. In cases of disagreement, a third reviewer was consulted to reach a consensus. Records that met the following criteria were included: RCTs that compared the efficacy and/or safety of molidustat to any treatment in patients with CKD who were iron deficient.

Data extraction and synthesis

Data extraction was performed independently by two reviewers, and a third reviewer verified the extracted data. The primary efficacy outcomes assessed included changes in Hb levels during follow-up and at week 16. Secondary outcomes included changes in total iron binding capacity (TIBC), transferrin saturation (TSAT), iron levels, ferritin levels, hepcidin levels, and various clinical events, including treatment emergent adverse events (TEAE) leading to death, patients with $\geq$1 major adverse cardiovascular event (MACE), CKD worsening, hyperkalemia, any TEAE, and any serious TEAE.

Assessment of risk of bias

The Cochrane Risk of Bias (RoB) 2 tool was used to assess the overall risk of bias in the included RCTs. The tool evaluates bias across several domains, including randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Judgements of bias per domain can be "low" or "high", or can express "some concerns" [15].

Assessment of publication bias

Because the number of included studies was not more than 10 for a certain outcome, we could not evaluate the existence of publication bias by the inspection of funnel plots [16].

Data analysis

We primarily used inverse variance random effects models for all meta-analyses. Between-study variance τ^2 was calculated with the Paule-Mandel method [17], and adjustment of confidence intervals with the Hartung-Knapp method [18,19]. Effects on dichotomous outcomes was described with relative risks (RR) and their 95% confidence intervals (CI); effects on continuous outcomes with mean differences (MD) and their 95% CI. We explored the heterogeneity among study effects with the Cochran's Q test and I^2 statistics. An I^2 between 30 and 60% indicates moderate heterogeneity, above 60% high heterogeneity and above 75% substantial heterogeneity [20]. All statistical analysis and pooling were carried out with R software 4.1.2 (www.r-project.org) and Comprehensive Meta-Analysis v4. Subgroup analyses were performed based on

the comparison group, dialysis status, and prior use of ESAs. Relevant study-level covariates, defined as those able to decrease inconsistencies measured as I^2 statistics, were investigated to identify relevant subgroups. A P for interaction $< .1$ was considered statistically significant for a given subgroup [21].

Results

Study Selection The systematic review and meta-analysis followed the PRISMA guidelines and initially identified 236 records from four prominent electronic databases: Ovid MEDLINE, Web of Science, PubMed, and The Cochrane Central Register of Controlled Trials. Subsequently, after screening for eligibility, 109 unique records were selected for comprehensive analysis (Figure 1). Within this pool, six RCTs met the inclusion criteria, collectively encompassing a sample of 999 patients with CKD [22-25].

Characteristics of included randomized controlled trials

Table 1 displays features of the 6 trials in CKD patients. The selected RCTs were thoughtfully categorized into distinct groups based on patient profiles: two trials [22, 23] comprised hemodialysis patients with a history of prior exposure to ESAs (n=428), two trials [22, 25] involved nondialysis-dependent CKD patients with a prior ESA history (n=288), and two trials [22, 24] enrolled nondialysis-dependent CKD patients who had never received ESAs (n=283). One, four, and one of the studies had molidustat compared with placebo, darbepoetin, and epoetin, respectively. The follow-up period was 16 weeks for 3 studies [22] and 52 weeks for the other 3 studies [23-25].

All trials assessed change in Hb, total iron binding capacity, TSAT, hepcidin, serum iron, serum ferritin levels. There were only 3 trials assessing the any TEAE, TEAE leading to death, any serious TEAE in accordance with MedDRA, and MACE including undetermined death.

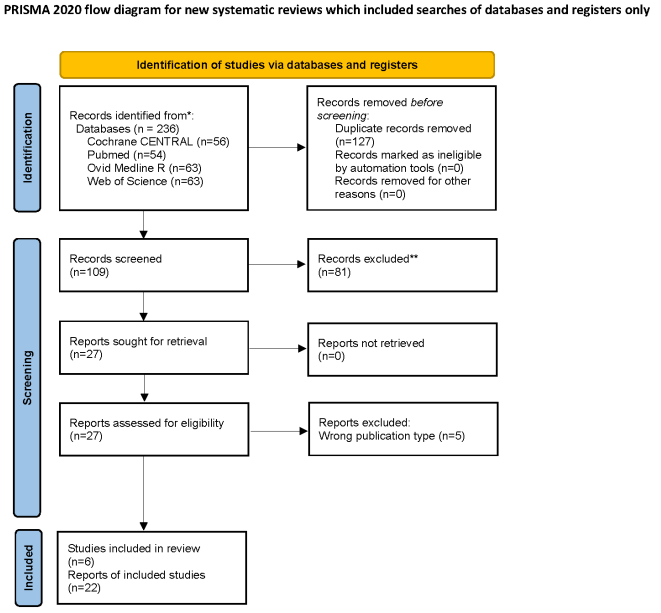

Figure 1. PRISMA flow diagram of eligible studies.

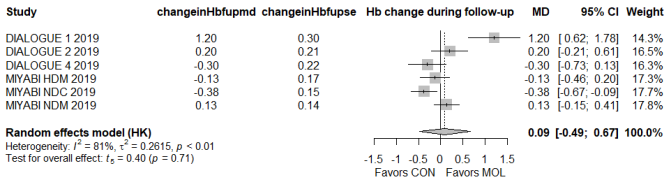

Figure 2. Effect of molidustat compared with ESA or placebo on Hb change in CKD patients during follow-up.

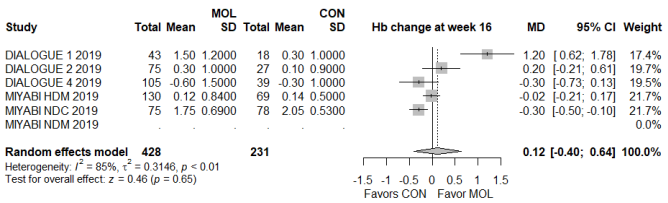

Figure 3. Effect of molidustat compared with ESA or placebo on Hb change in CKD patients at week 16.

Figure 4. Risk of bias assessment of included trials.

Primary efficacy outcomes

The primary efficacy outcomes in this meta-analysis revolved around the pivotal parameter of Hb levels during two distinct time points, namely follow-up and week 16. Notably, the meta-analysis for Hb change during follow-up yielded a mean difference (MD) of 0.09 (95% CI, -0.49 to 0.67) (Figure 2). Notwithstanding the potential clinical implications, the statistical evaluation introduced a nuanced perspective, as indicated by the substantial heterogeneity (I^2 = 81%) and a non-significant p-value for the pooled effect size at 0.71. Similarly, the corresponding meta-analysis for Hb change at week 16 demonstrated an MD of 0.12 (95% CI, -0.40 to 0.64). Nevertheless, consistent with the follow-up analysis, a notable level of heterogeneity persisted (I^2 = 85%), and the p-value for the pooled effect size was non-significant at 0.65 (Figure 3).

Secondary outcomes

Beyond the primary endpoints, the secondary outcomes extended the scope of this investigation to encompass a comprehensive examination of biochemical markers and clinical events. The array of parameters explored included changes in TIBC, TSAT, iron levels, ferritin levels, hepcidin levels, and the incidence of various clinical events. Of particular note were the significant findings of an increase in TIBC at week 16 (MD 2.89, 95% CI 1.74 to 4.04) and

Table 1. Characteristics of the included trials.

First Author, Year	Country (ies)	Population		Sample size	Intervention, mean dose (SD)	Control, mean dose (SD)	Mean age (SD), years	Male (%)	Reported Outcomes	Time of follow up (weeks)
DIALOGUE 1, 2019	Australia, Bulgaria, France, Germany, Hungary, Israel, Italy, Japan, Korea, Poland, Romania, Spain, Türkiye, United Kingdom	Non-dialysis-depended CKD iron deficiency anemia ESA-naïve patients	Induction and Maintenance	121	Molidustat, 25, 50, or 75 mg once daily, or 25 or 50 mg twice daily	Placebo	68.4 (12.6)	53.7	Change in Hb concentration between baseline and the evaluation phase (defined as the average of all measurements taken during the last 4 weeks of the treatment phase), Variables of iron metabolism parameters (hepcidin, serum ferritin, iron concentrations, serum TSAT, and TIBC) at baseline, week 5, 9, 13, and 17	16
DIALOGUE 2, 2019	Australia, Bulgaria, France, Germany, Hungary, Israel, Italy, Japan, Korea, Poland, Romania, Spain, Türkiye, United Kingdom	Non-dialysis-depended CKD and iron deficiency anemia priori ESA-treated patients	Induction and Maintenance	124	Molidustat, once daily (25, 50, or 75 mg)	Darbepoetin, according to prescribing information and the site's standard practice	67.9 (10.0)	50.8	Change in Hb concentration between baseline and the evaluation phase (defined as the average of all measurements taken during the last 4 weeks of the treatment phase), Variables of iron metabolism parameters (hepcidin, serum ferritin, iron concentrations, serum TSAT, and TIBC) at baseline, week 5, 9, 13, and 17	16
DIALOGUE 4, 2019	Japan, United States	Dialysis-dependent CKD and iron deficiency anemia priori ESA-treated patients	Induction and Maintenance	199	Molidustat, once daily (25, 50, 75, or 150 mg)	Epoetin, according to prescribing information and the site's standard practice	59.3 (11.8)	60.3	Change in Hb concentration between baseline and the evaluation phase (defined as the average of all measurements taken during the last 4 weeks of the treatment phase), Variables of iron metabolism parameters (hepcidin, serum ferritin, iron concentrations, serum TSAT, and TIBC) at baseline, week 5, 9, 13, and 17	16
MIYABI HD-M 2019	Japan	Dialysis-dependent CKD and iron deficiency anemia priori ESA-treated patients	Maintenance	229	Molidustat, 75 mg/day	Darbepoetin, Weekly or once every two weeks	65.7 (NA)	61.1	Mean Hb level during the evaluation period (weeks 33–36) and its change from baseline, Included Hb level and change from baseline in Hb level at each visit, TEAE, Incidence of MACEs	52
MIYABI ND-C 2019	Japan	Non-dialysis-dependent CKD and iron deficiency anemia ESA- naïve patients	Induction and Maintenance	162	Molidustat, 46.30 (30.64) mg/day	Darbepoetin, 60.09 (52.72) mg/day	71.7 (9.6)	61.7	Mean Hb level and its change from baseline during the evaluation period (weeks 30–36) , Included evaluation of all adverse events, Included all TEAEs, Incidence of MACEs, eGFR, Mean serum cholesterol, iron, TIBC, UIBC, hepcidin , ferritin and TSAT	52
MIYABI ND-M 2019	Japan	Non-dialysis-dependent CKD and iron deficiency anemia priori ESA-treated patients	Maintenance	164	Molidustat, 51.21 (32.35) mg/day	Darbepoetin, 22.01 (13.13) µg/week	70.7 (10.4)	60.4	Mean Hb level during the evaluation period, with a target Hb range of ≥11.0 g/dL–<13.0 g/dL, and its change from baseline, Hb levels at each visit, TEAE, Incidence of MACEs, eGFR	52

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate Hb, hemoglobin; IDA, iron deficiency anemia; MACE, major adverse cardiovascular events; TSAT, transferrin saturation; TIBC, total iron binding capacity; TEAE, treatment emergent adverse event; UIBC, unsaturated iron binding capacity.

a decrease in hepcidin levels during the follow-up period (MD -16.55, 95% CI -29.54 to -3.56), of which favored the use of molidustat. In contrast, the impact of molidustat on other biochemical markers yielded results comparable to the comparison treatments (Table 2).

Safety outcomes

Turning the spotlight towards the critical aspect of safety, the outcomes analysis revealed a lack of statistically significant differences. Specifically, there were no significant disparities in TEAE leading to death, the incidence of patients with ≥1 MACE, hyperkalemia, any TEAE, and any serious TEAE. Nevertheless, a distinct and concerning ob-

Table 2. Effect of molidustat compared with ESA or placebo on iron parameters in CKD patients.

Outcomes	Number of studies	Number of participants	Pooled Effect Size MD (95% CI)	P value	I-square (%)
Change in hepcidin levels during follow-up	6	768	-16.55 (-29.54; -3.56)	0.02	82
Change in ferritin levels at week 16	5	703	-17.44 (-40.96; 6.08)	0.15	22
Change in ferritin levels during follow-up	6	768	-10.97 (-59.09; 37.15)	0.58	81
Change in iron levels at week 16	5	703	-2.42 (-10.37; 5.52)	0.55	79
Change in iron levels during follow-up	6	772	-3.24 (-14.92; 8.44)	0.51	87
TSAT change at week 16	5	702	-2.04 (-4.13; 0.05)	0.06	54
TSAT change during follow-up	6	767	-2.04 (-6.77; 2.69)	0.32	88
TIBC change at week 16	5	703	2.89 (1.74; 4.04)	<0.01	21
TIBC change during follow-up	6	768	1.19 (0.14; 2.25)	0.03	0

Abbreviations: TSAT, transferrin saturation; TIBC, total iron binding capacity.

Table 3. Safety of molidustat compared with ESA or placebo in CKD patients.

Outcomes	Number of studies	Number of participants	Pooled Effect Size RR (95% CI)	P value	I-square (%)
Any serious TEAEs	3	554	1.16 (0.88; 1.53)	0.28	0
Any TEAEs	3	554	0.99 (0.95; 1.03)	0.69	0
Hyperkalemia	3	554	0.61 (0.27; 1.39)	0.24	33
CKD worsening	2	325	1.79 (1.03; 3.10)	0.04	0
Patients with ≥1 MACE	3	554	2.38 (0.72; 7.84)	0.16	0
TEAEs leading to death	3	555	1.53 (0.31; 7.54)	0.60	18

Abbreviations: TEAE, treatment emergent adverse event; CKD, chronic kidney disease; MACE, major adverse cardiovascular events.

servation emerged concerning the risk of CKD worsening. In this context, molidustat use was associated with an elevated risk, as evidenced by a RR of 1.79 (95% CI, 1.03 to 3.10) (Table 3).

Risk of bias assessment and subgroup analysis

Moreover, the systematic assessment of RoB was undertaken employing the Cochrane RoB2 tool. In this context, the examination of RoB for the primary outcome of Hb change revealed an uneven distribution of high and some concerns, with five out of the six RCTs falling into the high RoB category, and the remaining RCT showing some concerns. Deviations from the intended interventions were the item most likely to receive a high risk of bias in this literature set (Figure 4). This nuanced assessment underlines the importance of critical appraisal of study quality in the interpretation of the results. Subgroup analyses were conducted to explore the impact of various factors on the efficacy of molidustat in managing anemia in CKD. These factors included the type of comparator used, dialysis status, prior ESA use, and combinations of these variables. Notably, when comparing the effect of molidustat on Hb levels at week 16, there was a small but significant reduction in Hb levels in studies with a higher RoB (p=0.06), as well as when molidustat was compared to ESAs (p=0.06). Subgroup analyses also indicated a consistent effect of molidustat on Hb levels, irrespective of dialysis status, prior ESA use, or a combination of these factors (Table 4).

Discussion

This meta-analysis presents a comprehensive exploration of molidustat's efficacy in addressing anemia associated with CKD, offering an in-depth examination not found in previous studies [1]. Notably, our findings highlight the noninferiority of molidustat when compared to ESAs in managing CKD-related anemia. The analysis goes beyond the typical focus on hemoglobin (Hb) levels, shedding light on specific biochemical markers, particularly hepcidin, which plays a pivotal role in iron-deficient anemia in this population. While molidustat exhibits positive effects on Hb parameters, our study reveals a notable concern-the elevated risk of CKD worsening associated with its use. This underscores the imperative need for vigilant monitoring when considering molidustat as a therapeutic option for CKD patients, emphasizing the delicate balance between efficacy and potential adverse consequences.

Hemoglobin serves as a crucial diagnostic marker for renal anemia in CKD, reflecting oxygen-carrying capacity and anemia severity. Our meta-analysis delves into the impact of molidustat on Hb parameters, showcasing its consistent efficacy in improving Hb levels in both dialysis and non-dialysis-dependent CKD patients [26]. Importantly, our analysis extends beyond Hb to encompass iron metabolism parameters, demonstrating comparable effects on hepcidin, ferritin, and TSAT compared to ESAs.

Aligning with broader evidence, our study supports the class effect of HIF-PH inhibitors, including molidustat, known for its selective modulation of Hb through EPO mechanisms, has consistently shown significant efficacy in improving Hb levels in dialysis and non-dialysis-dependent CKD patients and in enhancing hemoglobin-related parameters in CKD patients [27]. Notably, decreases in hepcidin levels following molidustat treatment may enhance iron utilization, addressing iron-deficient anemia such as ESAs. In the broader context, the Cochrane review (27) provided a comprehensive analysis of HIF-PH inhibitors, including multiple studies involving 30,994 adults. The

Table 4. Subgroup analysis for the primary efficacy outcomes in the study.

Outcomes by subgroup	Number of studies	Number of participants	Pooled Effect Size MD (95% CI)	P value	I-square (%)
Change in Hb levels at week 16-subgroup by comparator					
Molidustat vs. Placebo	1	61	1.20 (0.62; 1.78)	NA	NA
Molidustat vs. Darbepoetin	3	454	-0.12 (-0.25; 0.01	0.03	70
Molidustat vs. Epoeitin	1	144	-0.30 (-0.73; 0.13)	NA	NA
Molidustat vs. ESA	5	598	-0.13 (-0.26; -0.01)	0.06	59
Change in Hb levels during follow-up-subgroup by comparator					
Molidustat vs. Placebo	1	61	1.20 (0.62; 1.78)	NA	NA
Molidustat vs. Darbepoetin	3	NA	-0.07 (-0.23; 0.09)	0.04	63
Molidustat vs. Epoeitin	1	144	-0.30 (-0.73; 0.13)	NA	NA56
Molidustat vs. ESA	5	NA	-0.10 (-0.25; 0.05)	0.06	
Change in Hb levels at week 16-subgroup by RoB					
Some concerns	1	61	1.20 (0.62; 1.78)	NA	NA
High	4	598	0.13 (-0.26; -0.01)	0.06	59
Change in Hb levels during follow-up-subgroup by RoB					
Some concerns	1	61	1.20 (0.62; 1.78)	NA	NA
High	5	NA	-0.10 (-0.25; 0.05)	0.06	56
Change in Hb levels at week 16-subgroup by dialysis-ESA status					
No/Naive	2	214	-0.15 (-0.33; 0.04)	<0.01	96
No/Used	1	132	0.20 (-0.21; 0.61)	NA	NA
Yes/Used	2	343	-0.07 (-0.24; 0.11)	0.24	28
Change in Hb levels during follow-up-subgroup by dialysis-ESA status					
No/Naive	2	NA	-0.07 (-0.33; 0.19)	<0.01	96
No/Used	2	NA	0.15 (-0.08; 0.38)	0.78	0
Yes/Used	2	NA	-0.19 (-0.45; 0.07)	0.54	0
Change in Hb levels at week 16-subgroup by ESA status					
Naive	2	214	-0.15 (-0.33; 0.04)	<0.01	96
Used	4	445	-0.03 (-0.18; 0.13)	0.25	28
Naive	2	NA	-0.07 (-0.33; 0.19)	<0.01	96
Used	4	NA	0.00 (-0.17; 0.17)	0.23	30
Change in Hb levels during follow-up-subgroup by ESA status					
No	4	316	-0.09 (-0.26; 0.08)	<0.01	92
Yes	2	343	-0.07 (-0.24; 0.11)	0.24	28
Change in Hb levels during follow-up-subgroup by dialysis status					
No	4	NA	0.06 (-0.12; 0.23)	<0.01	88
Yes	2	NA	-0.19 (-0.45; 0.07)	0.54	0

Abbreviations: MD, mean difference; CI, confidence interval; Hb, hemoglobin; ESA, erythropoiesis stimulating agents; RoB, risk of bias.

Cochrane review systematically evaluated the therapeutic effects of HIF-PH inhibitors, in addressing anemia associated with CKD. Their findings suggested that HIF-PH inhibitors, when compared to a placebo, likely elevated the proportion of patients achieving the target Hb levels. This observation aligns harmoniously with the outcomes of our meta-analysis, where molidustat demonstrated efficacy by significantly improving Hb levels in comparison to placebo and noninferiority to ESAs. Our meta-analysis, alongside the studies by Jia et al. [28] and the Cochrane review [27], collectively supports the class effect of HIF-PH inhibitors, including molidustat, in enhancing hemoglobin-related parameters in patients with CKD. Specifically, the observed increases in Hb levels and positive Hb response align with the evidence from these studies, reinforcing the efficacy of HIF-PH inhibitors in addressing anemia associated with CKD. While the Cochrane review focused on broader outcomes, our meta-analysis and Jia et al.'s study provide more granular insights into Hb-related parameters, contributing to a comprehensive understanding of the efficacy

of molidustat in managing anemia in CKD. These consistent findings across multiple studies strengthen the validity of the observed improvements in Hb levels associated with HIF-PH inhibitors.

In a meta-analysis evaluating the safety and effectiveness of HIF-PH inhibitors and ESAs in non-dialysis-dependent CKD patients, it was reported that Hb levels increased in both groups and there was no statistically significant difference between the two groups [29]. Our risk of bias assessment, using the Cochrane RoB 2 tool, revealed an uneven distribution in study quality, with deviations from intended interventions identified as a common source of bias. This echoes the findings of Zeng et al. [30] and underscores the importance of critically appraising study quality in interpreting results.

Hepcidin, a 25-amino-acid peptide synthesized by hepatocytes, plays a pivotal role in regulating iron dynamics within tissues, ensuring a constant iron supply to the erythron and other tissues while limiting systemic iron circulation. Anemia and inflammation, prevalent features in CKD, influence hepcidin levels. In individuals with renal anemia, hepcidin levels rise alongside functional iron deficiency. Notably, human studies have demonstrated a reduction in hepcidin following molidustat treatment in CKD patients [22, 24, 25]. Similar results in our analysis were observed in CKD patients using molidustat, where hepcidin levels significantly decreased during follow-up. Molidustat, by stimulating erythropoietin production and subsequent erythroferrone increase, may suppress hepcidin, potentially enhancing iron utilization and ameliorating renal anemia [10] such as other class agents [28].

Adding depth to our interpretation, we consider results from Zeng et al.'s class-effect meta-analysis of HIF-PH inhibitors, emphasizing the importance of nuanced safety considerations [30]. Their study, encompassing 23 studies and 15,144 participants, found no significant difference in cardiac and kidney-related adverse events between the HIF-PH inhibitors group and placebo or ESA. Conflicts arise regarding the safety profile of molidustat, with potential associations with adverse events such as hypertension and hyperkalemia. Our safety outcomes align with these observations, emphasizing the need for a nuanced understanding of molidustat's safety profile, especially concerning the risk of CKD worsening. On the other side, findings from Natalie et al. [27] indicated uncertain effects on cardiovascular outcomes, fatigue, and kidney-related events. In their meta-analysis comparing HIF-PH inhibitors, Chen et al. reported that molidustat may be preferable in patients at risk of hypertension and thrombosis [31]. While our safety outcomes did not reveal statistically significant differences in various parameters such as TEAE leading to death, MACE, hyperkalemia, any TEAE, and any serious TEAE, a distinct and concerning observation regarding the risk of CKD worsening was identified (RR 1.79, 95% CI, 1.03 to 3.10). This conflict, wherein molidustat use was associated with an elevated risk of CKD worsening, underscores the complexity of the drug's impact on renal outcomes. Molidustat has been reported to be associated with an increased risk of MACE in nondialysis-dependent CKD [32]. It introduces a potential risk-benefit consideration that needs careful evaluation in the clinical context. Notably, our safety outcomes aligned with these observations, emphasizing the importance of a nuanced understanding of molidustat's safety profile.

Limitations

Despite the comprehensive nature of our systematic review and meta-analysis, several limitations should be acknowledged. Heterogeneity in study design, patient populations, and exposure to ESAs introduces variability, and the overall risk of bias underscores the need for cautious interpretation. Longer trial durations and standardized outcome reporting would provide a more thorough understanding of molidustat's long-term effects. Readers and clinicians should exercise caution, acknowledging the inherent uncertainties associated with the included studies.

Conclusion

In conclusion, our systematic review and meta-analysis present a comprehensive evaluation of the efficacy and safety of molidustat in addressing iron-deficient anemia in patients with CKD. Our findings indicate that molidustat, when compared to ESAs, demonstrates noninferiority and positive impacts on relevant biomarkers. However, the heightened risk of CKD worsening, as highlighted in our analysis, underscores the importance of cautious clinical management.

The potential clinical implications of our results are twofold. First, the noninferiority of molidustat to ESAs suggests a viable alternative for managing anemia in CKD patients, offering clinicians an additional therapeutic option. Second, the observed association with an increased risk of CKD worsening emphasizes the critical need for vigilant monitoring and individualized treatment decisions when considering molidustat for CKD-related anemia.

Our findings emphasize the complexity of managing anemia in the context of CKD and underscore the importance of tailoring treatment decisions to individual patient profiles. While molidustat shows promise, clinicians should exercise caution and consider the potential risk of CKD progression in their treatment strategies. This necessitates ongoing monitoring and long-term studies to refine our understanding of molidustat's role in the broader landscape of CKD-related anemia management. The results of our meta-analysis thus contribute valuable insights to guide clinical practice, encouraging a nuanced and personalized approach to the treatment of anemia in CKD patients.

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Conflict of interest

None to declare.

Ethical approval

No human subject participants were involved. Therefore, ethical approval or informed content are not required because this study retrieved and synthesis data from already published studies.

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