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Research article

Effects of hypoxia-inducible factor prolyl hydroxylase inhibitors versus erythropoiesis-stimulating agents on iron metabolism and inflammation in patients undergoing dialysis: A systematic review and meta-analysis

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ABSTRACT

Aims: This study aimed to evaluate the effects of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) on iron metabolism and inflammation in dialysis-dependent chronic kidney disease (DD-CKD) patients.

Methods: PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov websites were searched for randomized controlled trials (RCTs) investigating HIF-PHIs versus ESAs for DD-CKD patients.

Key findings: Twenty studies with 14,737 participants were included in the meta-analysis, which demonstrated no significant difference in the effect of transferrin saturation and ferritin between HIF-PHIs and the ESAs group (MD, 0.65; 95%CI, −0.45 to 1.75; very low certainty; SMD, −0.03; 95% CI, −0.13 to 0.07; low certainty). However, HIF-PHIs significantly increased the iron (MD, 2.30; 95% CI, 1.40 to 3.20; low certainty), total iron-binding capacity (SMD, 0.82; 95% CI, 0.66 to 0.98; low certainty), and transferrin (SMD, 0.90; 95%CI, 0.74 to 1.05; moderate certainty) levels when compared with the ESAs group. In contrast, the hepcidin level and dosage of intravenous iron were significantly decreased in the HIF-PHIs group compared with the ESAs group (MD, −15.06, 95%CI, −21.96 to −8.16; low certainty; MD, −18.07; 95% CI, −30.05 to −6.09; low certainty). The maintenance dose requirements of roxadustat were independent of baseline CRP or hsCRP levels with respect to the effect on inflammation.

Abbreviations: HIF-PHIs:, hypoxia-inducible factor prolyl hydroxylase inhibitors; DD-CKD:, dialysis-dependent chronic kidney disease; RCTs:, randomized controlled trials; ESAs:, erythropoiesis-stimulating agents; rhEPO:, recombinant human erythropoietin; Hb:, hemoglobin; EPO:, erythropoietin; TSAT:, transferrin saturation; TIBC:, total iron-binding capacity; CRP:, C-reactive protein; hsCRP:, high-sensitivity C-reactive protein; PHD:, prolyl-hydroxyl domain.

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Significance: HIF-PHIs promote iron utilization and reduce the use of intravenous iron therapy. Furthermore, HIF-PHIs, such as roxadustat, maintain the erythropoietic response independent of the inflammatory state. Thus, HIF-PHIs may be an alternative treatment strategy for anemia in DD-CKD patients, where ESA is hyporesponsive due to iron deficiency and inflammation.

1. Introduction

Anemia is a common complication of chronic kidney disease and presents more than 90% prevalence in patients on dialysis, contributing to significant morbidity and mortality [1]. The clinical practice guidelines-approved treatment of anemia in dialysis-dependent chronic kidney disease (DD-CKD) patients includes the use of erythropoiesis-stimulating agents (ESAs) and iron supplementation [2,3]. Although therapy with recombinant human erythropoietin (rhEPO) alleviates renal erythropoietin deficiency [4], approximately 12% of DD-CKD patients with anemia do not respond adequately to ESAs [5,6], which creates higher dose requirements to achieve the recommended hemoglobin (Hb) target levels [7,8]. Moreover, numerous studies have proved that high ESA doses are associated with increased cardiovascular disease risks [6,9,10]. Iron deficiency and systemic inflammation are two crucial causes of ESA hypo-responsiveness in patients undergoing dialysis [11]. Therefore, safer and more effective interventions are worth investigating to improve iron utilization and overcome the inflammatory state in patients with anemia and DD-CKD.

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) represent a new class of therapeutic molecules for the treatment of anemia in CKD. Their action leads to the mimicking of a transient "pseudohypoxic" condition that increases HIF accumulation and activates several target genes for adaptive reactions, including the expression of erythropoietin (EPO) and, EPO receptors, and iron absorption, recycling, and transport promoting genes [12–14]. HIF not only regulates transferrin, transferrin receptor, and ferroportin to rapidly mobilize iron from macrophages and intestines [15] but also indirectly inhibits the expression of hepcidin [16], which critically regulates iron metabolism and promotes robust erythropoiesis. Currently, several randomized controlled trials (RCTs) have demonstrated obvious advantages of HIF-PHIs in dialysis patients, such as stimulating the Hb response without being influenced by apparent inflammation and improving iron utilization [17–19]. However, some results have been inconsistent due to the internal complexities of dialysis patients and the wide range of HIF targets [20,21]. Thus, we conducted a systematic review and meta-analysis to evaluate the actions of all kinds of HIF-PHIs on iron metabolism and inflammation in dialysis-dependent patients. Additionally, the interaction and mechanism of action of HIF, iron metabolism, and inflammation were analyzed for better use in clinical settings and to facilitate more in-depth research on these HIF-PHIs.

2. Method

The current research used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline statement [22]. The protocol of this systematic review and meta-analysis was registered at PROSPERO (CRD 42021271888).

2.1. Search strategy

We comprehensively searched PubMed, Embase, Web of Science, Cochrane Library database for clinical trials investigating HIF-PHIs for DD-CKD patients, and the ClinicalTrials.gov website for randomized trials that were completed but not yet published. Moreover, the bibliography of related studies, including prior meta-analysis work, were scrutinized to find potential missing studies. All searches were undertaken from inception of the databases through July 2022, and no language restrictions were applied. The details of our search strategy are provided in Table S1.

2.2. Study selection

We incorporated studies that satisfied the following criteria:*1*) RCTs, *2*) for anemia in CKD patients undergoing dialysis, *3*) used oral intake of HIF-PHIs (Roxadustat, Daprodustat, Vadadustat, Molidustat, Enarodustat or Desidustat), *4*) compared with ESAs (epoetin or darbepoetin), *5*) examined the effects of iron biomarkers: transferrin saturation (TSAT), ferritin, iron, transferrin, total iron-binding capacity (TIBC), hepcidin, mean monthly dose of intravenous iron; inflammatory biomarkers: *C*-reactive protein (CRP) or high-sensitivity *C*-reactive protein (hsCRP), and *5*) were performed in adults ($\geq$18 y old). The searches were limited to human studies with no language restrictions. Two authors (QY Z and PN Z) independently screened the titles and abstracts of all publications. Any disputes were settled with discussion. Exclusion criteria included the studies only compared one HIF–PHI agent with another HIF–PHI agent; or those from which we were unable to get the full text or the data of outcome indicators.

2.3. Data extraction

The following information of all eligible RCTs were extracted by 2 independent investigators (YL G and JY T) using a standardized predefined data extraction form. The first author's name, publication year, country, clinical registration number, participant characteristics (mean age, sex, weight), sample size, intervention and control (including drug, dose and administration method), period of treatment, duration of follow-up, reported outcomes, and information on methodology (randomization, blinding and other bias). If the

data of outcomes were present on figure, origin 2019 software was used to identify and extract the mean and standard deviation of outcomes from line graph.

2.4. Quality assessment

The Cochrane Collaboration tool was used to assess the quality of the studies [23]. All studies were judged for any source of bias, which included randomized sequence generation, allocation concealment, participant and staff blinding, outcome assessor blinding, inadequate outcome data, selective reporting, and other biases. Two reviewers (QY Z and Y K) separately assessed the quality of the work, and any discrepancies were discussed with a third party and resolved by consensus. Additionally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to assess the quality of evidence contributing to each estimate [24].

2.5. Statistical analyses

Statistical analysis was conducted using Review Manager (version 5.3.3, Cochrane Collaboration). Mean difference (MD) or standard mean difference (SMD), with 95% confidence interval (95% CI) of the outcomes, was calculated as the effect measure. The $I2$-statistic was calculated for heterogeneity as a measure of the proportion of overall variation attributable to between-study heterogeneity. A fixed-effect (FE) model was used if $I^2 < 50\%$; otherwise, a random-effect (RE) model was used.

For studies that did not directly report changes in iron biomarkers, the mean difference was calculated by subtracting the mean value at baseline from that at the end of the study. The standard deviation (SD) of the mean difference was calculated using the following formula: SD = square root [(SD at baseline)^2 + (SD at the end of study)^2 – (2 r × SD at baseline × SD at the end of study)] [25]. For the study that only reported SE without SD, we used the Hozo et al. [26] approach to transform standard error (SE), 95% CI, and inter-quartile range (IQR) into SD. According to the Cochrane Collaboration, the correlation coefficient r is set at 0.8 for calculation [27].

Subgroup analysis was conducted to explore the influence of different HIF-PHIs and different trial intervention times (short-term, <52 weeks or long-term, ≥52 weeks) on treatment outcomes. The leave-one-out method (i.e., removing one trial at a time and recalculating the impact size) was used for the sensitivity analysis to determine the effect of each study on the pooled effect size. Publication bias was tested by visual inspection of funnel plots when more than 10 study comparisons were analyzed [28].

3. Results

3.1. Study characteristics

A total of 1467 studies were initially identified from a literature search of various electronic databases. Then, the NoteExpress software was used to exclude duplicates (n = 700) and irrelevant studies based on titles and abstracts (n = 709), which left 58 potentially relevant articles to be considered for full-text review. Finally, 20 eligible manuscripts [5,17–21,29–42] were included in the meta-analysis (Fig. 1). Two articles each described two different RCTs. Eckardt [39] described two RCTs that compared vadadustat and darbepoetin alfa. One RCT involved incident DD-CKD patients; while the other involved prevalent DD-CKD patients. Provenzano [18]

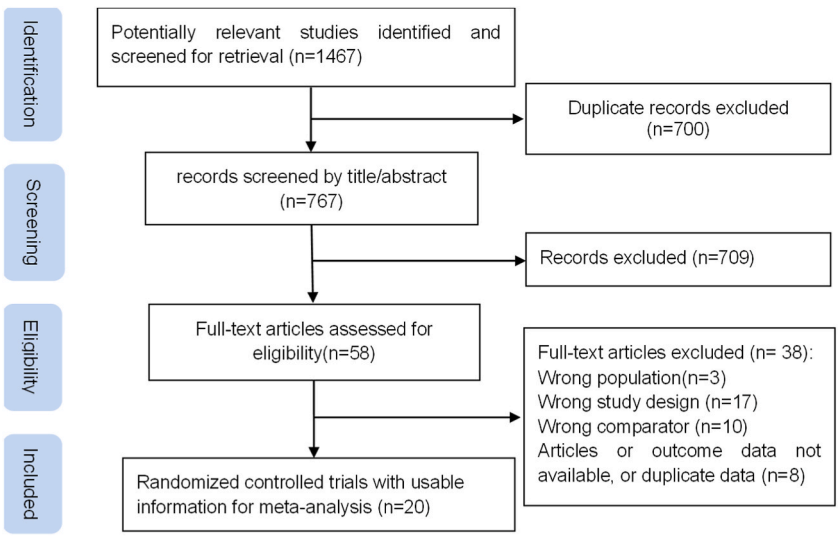

Fig. 1. Flow chart of literature search and selection.

included trials Part 1 and Part 2. Part 1 is a 6-week dose-ranging study for oral Roxadustat vs. intravenous epoetin alfa; Part 2 is a 19-week treatment study with various starting doses and adjustment rules (1.0–2.0 mg/kg or tiered weight based) in individuals with a range of epoetin alfa responsiveness. Details of screening process and its characteristics are listed in Table S1 and Table S2 respectively.

3.2. Qualitative data assessment

None of the RCTs had an overall low risk of bias. Most RCTs had low risk of bias for sequence generation, incomplete outcome data, selective reporting, and other bias. All RCTs had unclear risk of bias for blinding of the outcome, considering that detailed information was not provided. Most studies had high risk of bias for blinding of participants and personnel, because these could not be done. The risk of bias assessment of included trials is shown in Fig. 2.

3.3. Meta analysis

3.3.1. The change of transferrin saturation (TSAT) levels from baseline (△TSAT)

Twenty studies (n = 12,773) [5,17–21,29–42] provided data on the effect of HIF-PHIs therapy on △TSAT outcomes among DD-CKD patients. The pooled results (Fig. 3) revealed no significant difference in change of TSAT between HIF-PHIs and ESAs in DD patients (MD, 0.65; 95%CI, −0.45 to 1.75). Subgroup analysis results indicated that HIF-PHIs had a significantly higher TSAT level compared with ESAs in the short term (MD, 1.75; 95%CI, 0.72 to 2.78), but no significant difference was observed in changes of TSAT in the long term (Figure S1).

3.3.2. The change of ferritin levels from baseline (△Ferritin)

Nineteen studies (n = 3573) [5,17–21,29–37,39–42] provided data on the effect of HIF-PHIs therapy on Δferritin outcomes among DD-CKD patients. The pooled results indicated no significant difference in the changes of ferritin in the HIF-PHIs group compared to the ESAs group (SMD, −0.03; 95% CI, −0.13 to 0.07) (Fig. 4). For different HIF-PHIs, roxadustat showed a significant decrease in the ferritin level compared with the ESAs (SMD, −0.15; 95% CI, −0.27 to −0.03), while no difference was observed in other HIF-PHIs. Subgroup analyses of different intervention times were conducted, with no significant difference in △ferritin between the HIF-PHIs and ESAs groups, both in the short- and long-term (Figure S2).

3.3.3. The change of iron levels from baseline (△Iron)

Sixteen studies (n = 5551) [17–21,29–35,37,40–42] reported data on the effect of HIF-PHIs therapy on △iron outcomes among DD-CKD patients. Pooled results (Fig. 5) showed a significant increase in the iron level in the HIF-PHIs compared with that in the ESAs group (MD, 2.30; 95% CI, 1.40 to 3.20). Results of subgroup analysis for different HIF-PHIs showed that only roxadustat of HIF-PHIs had a significant increase in the iron level compared with the ESAs (MD, 3.25; 95% CI, 2.11 to 4.38), while no difference was observed in daprodustat, molidustat and enarodustat (Fig. 5). In addition, the subgroup analysis based on intervention time revealed that the effects of HIF-PHIs on iron in the short- or long-term were in the same direction as the whole analysis. (Figure S3).

3.3.4. The change of TIBC levels from baseline (△TIBC)

Seventeen studies (n = 7401) [17–21,29–38,40,42] reported data on the effect of HIF-PHIs therapy on △TIBC outcomes among DD-CKD patients. The meta-analysis (Fig. 6) showed that there was a significant increase in the TIBC level in all HIF-PHIs compared with the ESAs (SMD, 0.82; 95% CI, 0.66 to 0.98). Moreover, the subgroup analysis based on intervention time revealed that the effects of HIF-PHIs on iron in the short- or long-term were in the same direction as the whole analysis. (Figure S4).

3.3.5. The change of transferrin levels from baseline (△Transferrin)

Five studies (n = 908) [17,20,29,32,33] reported data on the effect of HIF-PHIs therapy on △transferrin outcome among DD-CKD patients. Pooled results (Fig. 7) indicated that there was a significant increase in the transferrin level in the HIF-PHIs group compared

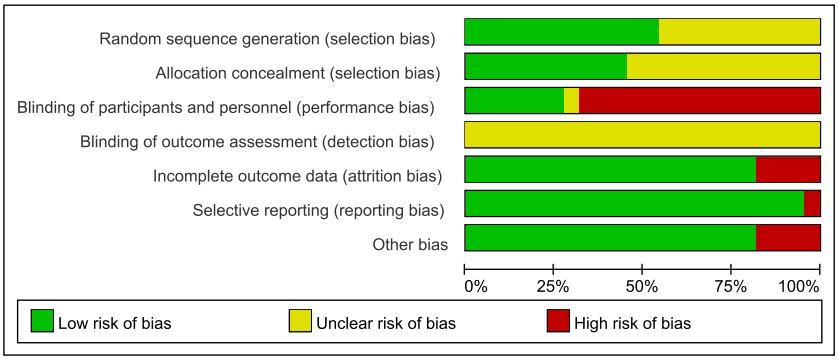

Fig. 2. Risk-of-bias summary of included RCTs using the cochrane risk-of-bias tool.

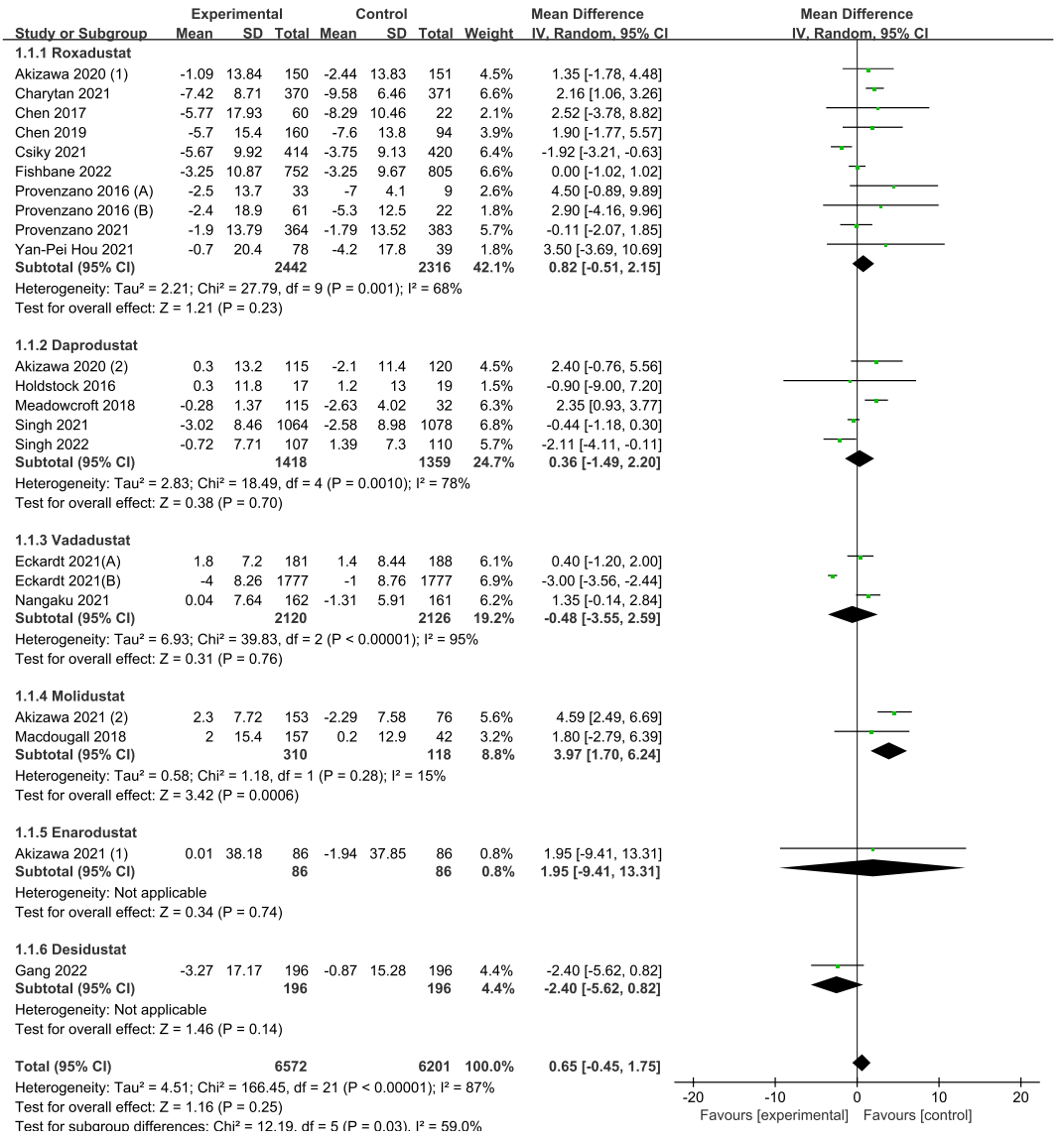

Fig. 3. Forest plots of changes from baseline in TSAT between different HIF-PHIs and ESAs.

with that in the ESAs (SMD, 0.90; 95% CI, 0.74 to 1.05). Subgroup analysis based on intervention time showed that the effects of HIF-PHIs on iron in the short- or long-term were in the same direction as the whole analysis. (Fig. S5).

3.3.6. The change of hepcidin levels from baseline (△Hepcidin)

Eighteen studies (n = 10,234) [5,17–19,21,29–37,39–42] reported data on the effect of HIF-PHIs therapy on △hepcidin outcomes among DD-CKD patients. Pooled results (Fig. 8) revealed that there was a significant reduction of hepcidin in the HIF-PHIs group when compared with that in the ESAs (MD, −15.06, 95%CI, −21.96 to −8.16). However, subgroup analysis for different HIF-PHIs showed that only roxadustat and vadadustat of HIF-PHIs had a significantly lower hepcidin level than ESAs (MD, −17.95, 95%CI, −28.96 to −6.94; MD, −13.60, 95%CI, −25.68 to −1.52; respectively), with no difference in daprodustat, molidustat, and enarodustat when compared with ESAs. In addition, the subgroup analysis indicated that HIF-PHIs could significantly lower the hepcidin level when compared with ESAs, both in the long- and short-term (Fig. S6).

3.3.7. Mean monthly dose of intravenous iron

Nine RCTs [5,19,21,31,33,35,37,38,42] compared the effect of dosage of intravenous iron in DD-CKD patients. Only 6 RCTs [5,19,21,35,37,38] were pooled for meta-analysis, and the results indicated a significant decrease in intravenous iron level use in the HIF-PHIs compared with that in the ESAs group (MD, −18.07; 95% CI, −30.05 to −6.09; Fig. 9). Results of subgroup analysis for different HIF-PHIs showed that only roxadustat of HIF-PHIs could significantly reduce the mean monthly dose of intravenous iron

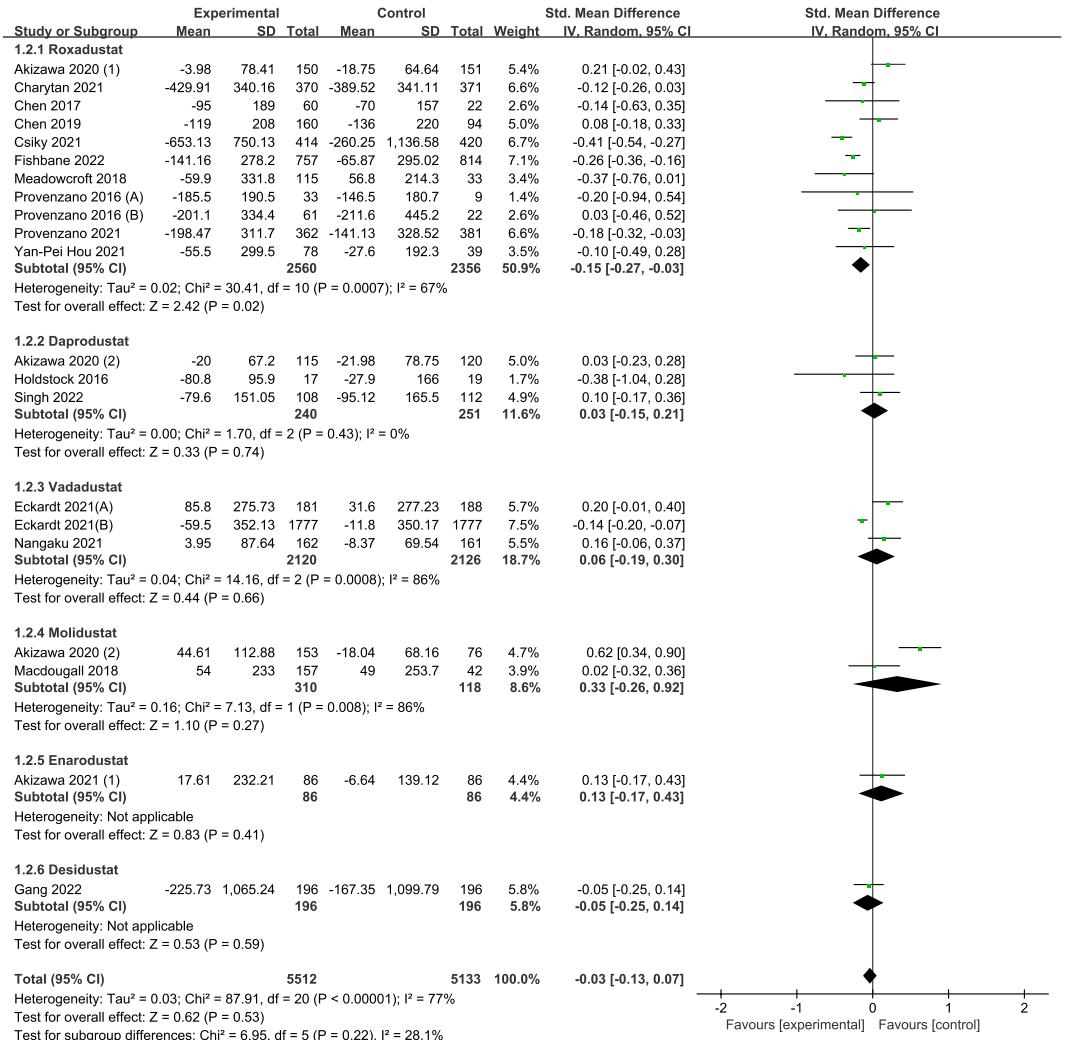

Fig. 4. Forest plots of changes from baseline in ferritin between different HIF-PHIs and ESAs.

when compared with ESA (MD=-28.15,[95%CI, −36.14 to −20.17], P < 0.00001), while daprodustat and enarodustat did not show any significant increase in intravenous iron use when compared with ESA. In addition, a study [42] that was not included in the pooled analysis, indicated that the mean monthly dose of IV iron was significantly lower with roxadustat versus epoetin alfa from week 36 until EOS (58.71 mg versus 91.37 mg, respectively; P < 0.001 for superiority). Besides, a study on daprodustat [33] showed that fewer participants used IV iron in the daprodustat than that in the darbepoetin alfa group during weeks 40–52 (18% daprodustat, 27% darbepoetin alfa), and the mean monthly dose of IV iron was 14 mg (daprodustat) versus 25 mg (darbepoetin alfa). Another study of daprodustat [31] stated that the median IV iron dose was similar for the daprodustat and control groups (44.1 versus 42.7 mg/week) during treatment phase.

3.3.8. Effect on inflammation

Inflammation is considered a factor in ESA hypo-responsiveness, which is reflected by baseline serum *C*-reactive protein (CRP) or high-sensitivity *C*-reactive protein (hsCRP). Ten studies [17–21,32,34,35,37,42] compared the Hb response and maintenance dose requirements of HIF-PHIs versus ESAs at different baseline levels of inflammation. Among them, 7 studies [17–19,32,34,37,42] focused on roxadustat, indicating that patients with higher CRP levels in the ESAs group had a lower Hb response than those with normal CRP levels, and inflammation increased the dose requirements for ESAs in the DD-CKD patients. In contrast, the maintenance dose requirements for roxadustat were independent of baseline CRP or hsCRP levels. These results suggest that roxadustat more efficiently maintains Hb levels in DD-CKD patients under inflammatory conditions than ESA. However, one study [35] on enarodustat showed that the Hb level and dose of enarodustat or DA stratified by CRP (high group: CRP ≥0.3 mg/dL; low group: CRP <0.3 mg/dL) in each arm were comparable. And one study [21] on daprodustat reported that the Hb response both to daprodustat and darbepoetin alfa was maintained regardless of the baseline hsCRP level. Another study [20] compared the effect of daprodustat treatment on hsCRP

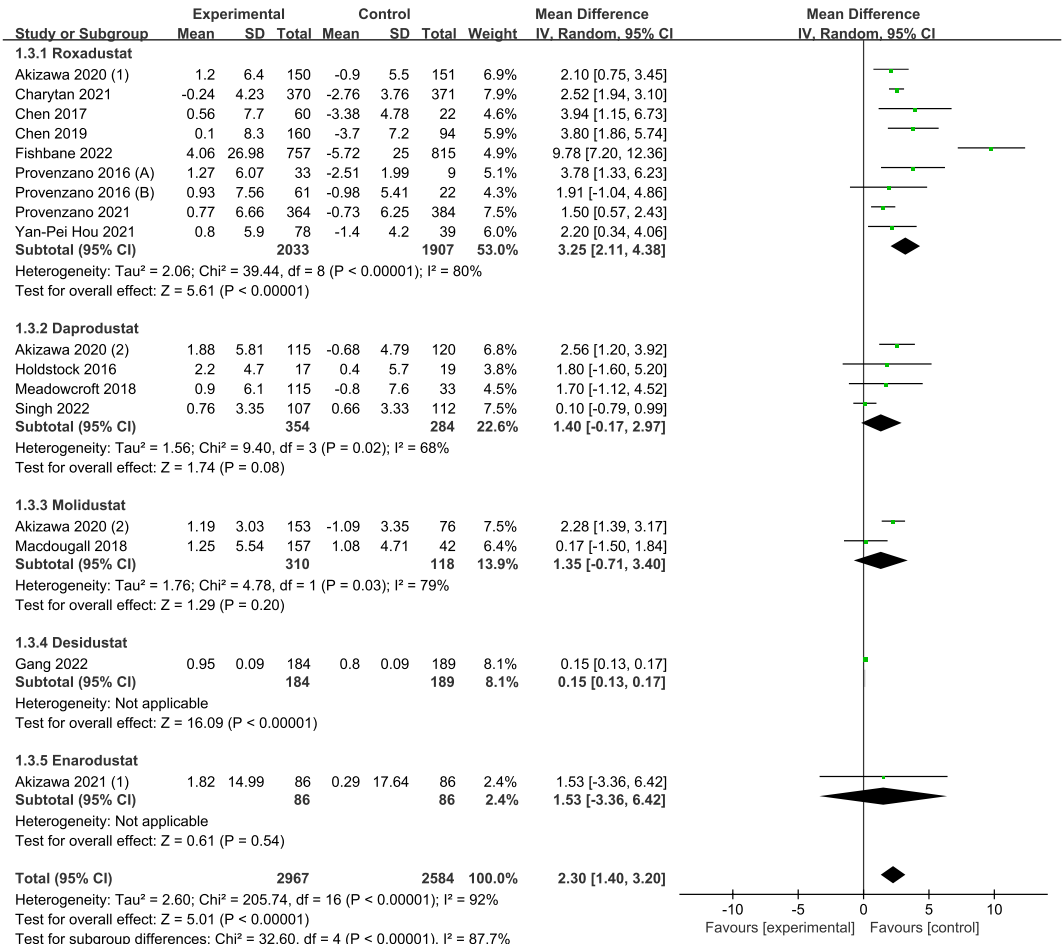

Fig. 5. Forest plots of changes from baseline in iron between different HIF-PHIs and ESAs.

level, showing no effect of daprodustat on hsCRP level. More details can be seen in Table 1.

3.3.9. Sensitivity analysis

Leave-one-out method was used for sensitivity analysis and no study was found to affect the overall results for all outcomes. Details are presented in Table S3-S8.

3.3.10. Publication bias

Publication bias was tested for the above outcomes for more than 10 studies. Visual inspection of the funnel plots showed evidence of publication bias in relation to all outcomes (Figure S7-S11).

3.3.11. GRADE for the outcomes

We evaluated all outcome indicators using GRADEprofiler 3.6 from the following aspects: downgrade quality of evidence, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Following comprehensive analysis, the evidentiary body was formed, and we determined that the majority of outcome indicators were of low quality (Table 2). The details can be seen in Table S9.

4. Discussion

This study aimed to investigate the effects of HIF-PHIs on iron regulation and inflammation in DD-CKD patients. Results showed that HIF-PHIs were superior to ESAs in increasing serum iron, transferrin, and TIBC, and reducing hepcidin level significantly, although notable differences in TSAT and ferritin levels were not detected. Moreover, HIF-PHIs could significantly reduce the mean monthly dose of intravenous iron compared to ESAs. It should be noted that, based on the subgroup analysis, the above results were more applicable to roxadustat, daprodustat, and vadadustat, because of the small number of included studies related to other HIF-PHIs (such as molidustat and enarodustat). For evaluating the impact of the inflammatory state on different agents, a comprehensive analysis of the literature suggested that apparent inflammation, assessed on the basis of CRP level, did not affect the hemoglobin

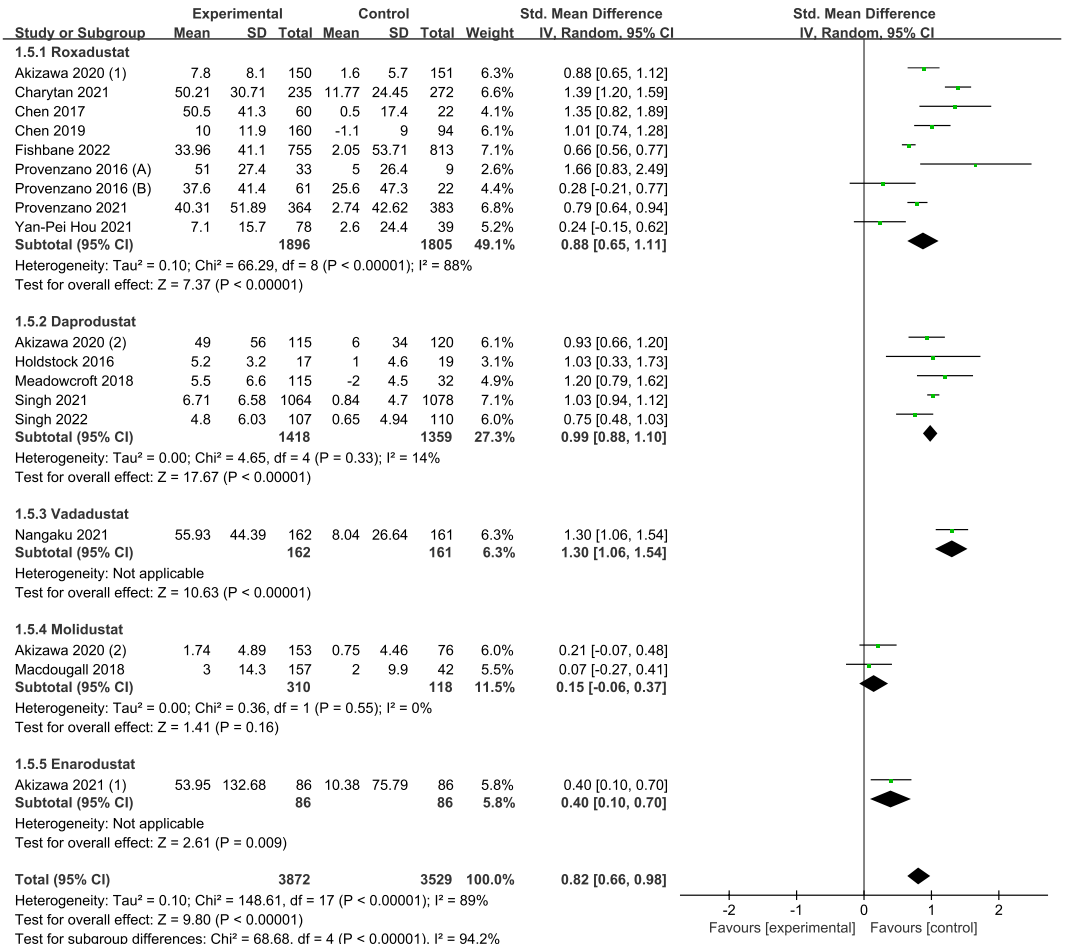

Fig. 6. Forest plots of changes from baseline in TIBC between different HIF-PHIs and ESAs.

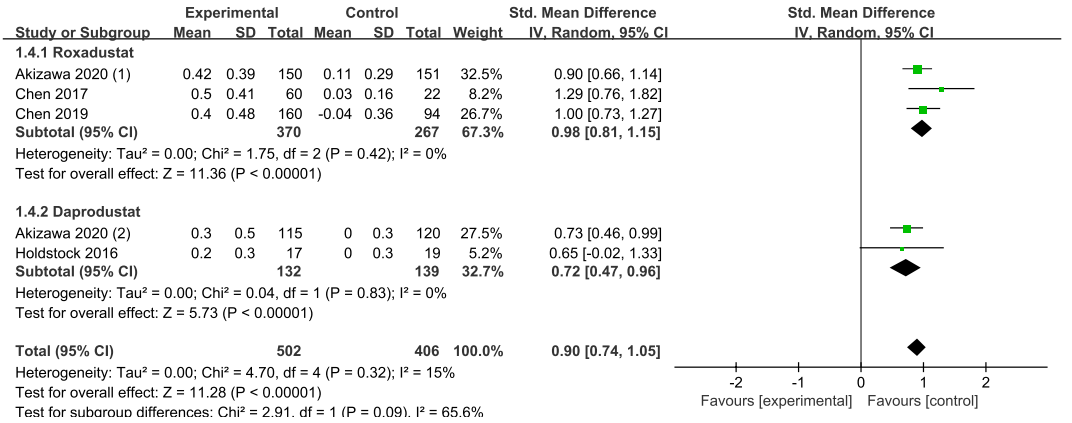

Fig. 7. Forest plots of changes from baseline in transferrin between different HIF-PHIs and ESAs.

response with HIF-PHIs, such as roxadustat. However, other HIF-PHIs lack sufficient data for clinical research to support them. For the quality of evidence, except for TSAT (*very low* quality) and transferrin (*moderate* quality), the other provided low-quality evidence.

Disturbed iron homeostasis and inflammation are major contributors to the etiology of anemia in CKD patients and may be largely responsible for the ESA hyporesponse [43]. However, unlike HIF-PHIs, the mechanism of action of ESAs are limited to stimulation of the erythropoietin receptor, while HIF-PHIs not only increase endogenous erythropoietin production but also directly regulate many

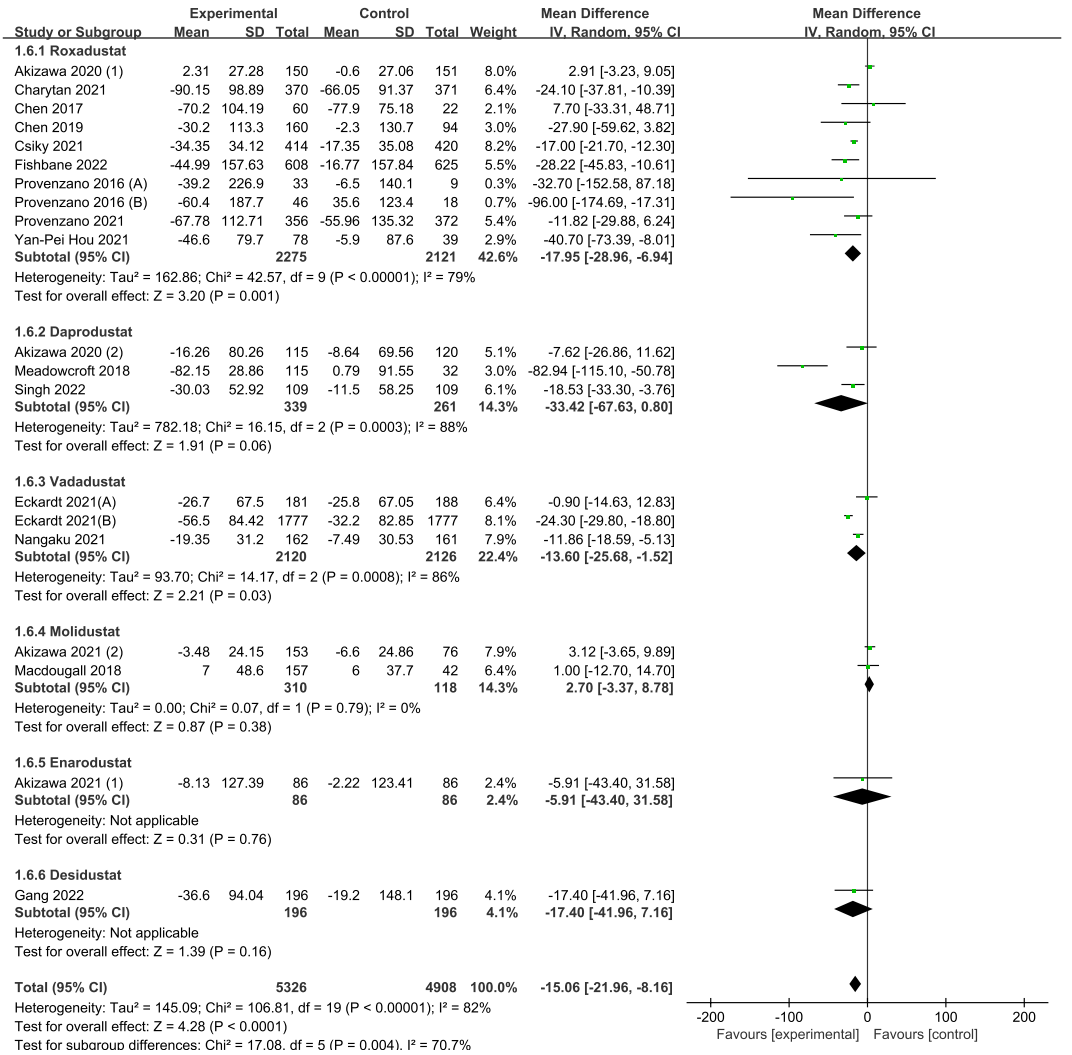

Fig. 8. Forest plots of changes from baseline in hepcidin between different HIF-PHIs and ESAs.

genes related to iron uptake, mobilization, and transport. As shown in the current study, the key mechanism of HIF-PHIs involved inhibiting the prolyl-hydroxyl domain (PHD) to stabilize HIF-α subunits (containing HIF-1α, HIF-2α, and HIF-3α) and increase HIF transcriptional activity [44]. Indeed, HIF regulates several critical proteins in iron mobilization and utilization, including transferrin and transferrin receptors that transport iron in its ferric form (Fe^{3+}), ceruloplasmin that oxidizes Fe^{2+} to Fe^{3+}, and haeme-oxygenase-1, which contributes to the recycling of iron from phagocytosed erythrocytes [45–49]. In addition, HIF-2α has the role to increase transcription of the genes that encode divalent metal transporter 1 (DMT1) and duodenal cytochrome *b* reductase 1 to promote intestinal iron absorption [14,16,50,51]. Additionally, HIF-2α could directly upregulates ferroportin expression, the only known iron exporter to increase iron availability from stores in macrophages [52,53]. Besides, HIF-2α could indirectly suppress hepcidin expression via erythropoietic activity leading to an increase in iron absorption and export [54,55]. The relationship between the HIF oxygen-sensing pathway and hepcidin regulation provides an additional way to coordinate the upregulation of erythropoietin and ferroportin, which further promotes erythropoiesis by activating HIF to optimize iron metabolism.

In summary, pharmacological mechanism of HIF-PHIs that activates the HIF axis also regulates iron metabolism. Consistent with the above mechanism, our meta-analysis indicated that the decrease in TSAT and ferritin levels, the proteins that reflect the intracellular storage of iron, were comparable between the treatment groups, which is likely related to the frequent intravenous iron administration in dialysis patients. A more significant increase in serum iron, transferrin, and TIBC levels occurred in the HIF-PHIs treatment group compared to that in the ESA-treated group. Simultaneously, hepcidin, which impairs iron absorption, transport, and iron release, was significantly inhibited by HIF-PHIs. More importantly, the HIF-PHIs group achieved more significant serum iron increases with a lower mean monthly dose of intravenous iron. These data were consistent with the expected positive impact of HIF-PHIs on iron availability. Our meta-analysis thus highlights how for anemia treatment in dialysis patients, HIF-PHIs are superior to ESAs for their ability to enhance iron absorption, mobilization, and transport, which could result in a reduced use of intravenous iron

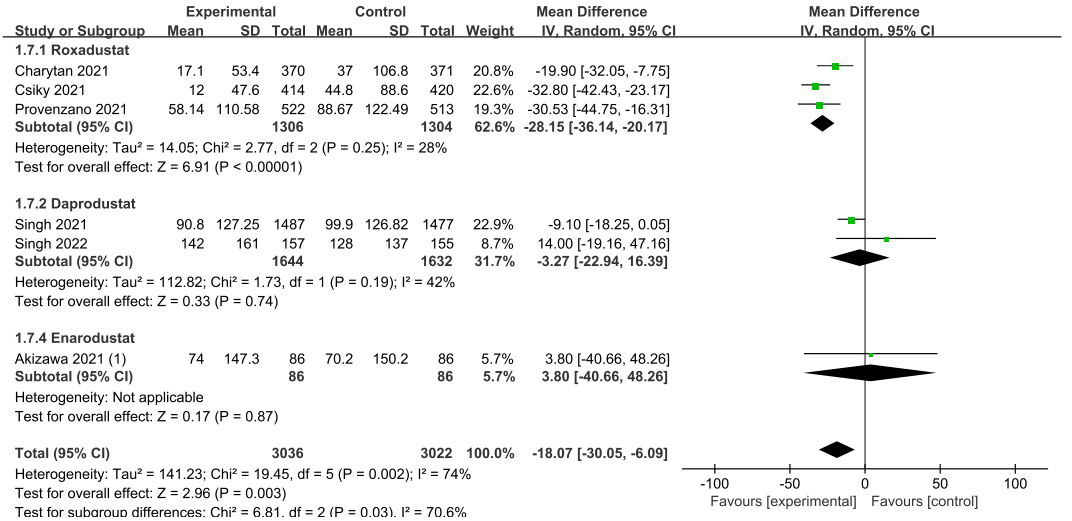

Fig. 9. Forest plots of mean monthly dose of intravenous iron between different HIF-PHIs and ESAs.

supplementation.

Inflammation is the common denominator of anemia, frequently observed in CKD patients, and increases the dose requirements of rhEPO in end-stage renal disease patients [7,56]. Accordingly, our descriptive analysis also showed that patients with elevated CRP levels in the ESAs group had lower hemoglobin responses than those with normal CRP levels, despite receiving higher doses of epoetin or darbepoetin, thereby corroborating findings of other studies showing the suppressive effect of inflammation on response to ESAs [57,58]. In contrast, the dose requirements of HIF-PHIs to maintain erythropoietic response were independent of baseline CRP levels [17–19,32,34,37]. These results suggest the potential of HIF-PHIs, such as roxadustat, to overcome the therapeutic barrier to erythropoiesis from the inflammatory component present in DD-CKD patients, providing clear differentiation from ESAs.

Notably, inflammation-induced elevated hepcidin levels may increase ESAs doses or resistance to ESAs in DD-CKD patients [18,59,60]. Elevated hepcidin levels limiting iron availability, promote internalization of ferroportin into the cell for degradation and prevent the release of stored iron from enterocytes, macrophages, or hepatocytes, resulting in the sequestration of iron into storage organs [61,62]. Hepcidin also impairs iron absorption in the duodenum by downregulating the expression of apical DMT1 in enterocytes [63]. Sasu et al. [64] showed that suppression of hepcidin mRNA improves anemia in a murine inflammation model. Thus, hepcidin's impairment in iron absorption and export, which produces functional iron deficiency, is an important mechanism leading to the increase in ESAs requirements during inflammation and accounting for the linear correlation of ESAs doses with baseline serum CRP levels in the ESAs group. Pharmacological mechanism of HIF-PHIs effectively inhibiting the expression of hepcidin also further explains the rationality that HIF-PHIs could overcome iron deficiency in the inflammatory state to maintain erythropoiesis. Finally, Figure A and B summarize the disturbances of iron metabolism in the inflammatory state and the specific mechanism by which HIF-PHIs regulate iron metabolism and inflammation, respectively (Fig. 10).

It should be noted that this study included five types of HIF-PHIs for advanced clinical development. Although all compounds are potent inhibitors of PHD1, PHD2, and PHD3 and stabilize both HIF-1α and HIF-2α [65], they may display differences in their pharmacokinetic and pharmacodynamic profiles owing to their different molecular structures. Therefore, different HIF-PHIs are likely to exert different effects on iron metabolism and inflammation. Results of the subgroup analysis in our meta-analysis show that only roxadustat, daprodustat, and vadadustat sub-combinations of iron metabolism indicators were consistent with the overall results. Simultaneously, other HIF-PHIs such as molidustat and enarodustat were insufficient to draw reliable conclusions due to the small number of relevant studies. For the mean monthly dose of intravenous iron, only roxadustat showed significant superiority over ESAs based on the present studies. In terms of the impact of inflammation on interventions, only roxadustat has sufficient evidence to demonstrate its therapeutic advantage in addressing multiple etiologic contributors to anemia in dialysis patients with central common initiators such as inflammation. Thus, more large-scale clinical studies are needed to confirm the effects of other HIF-PHIs on iron metabolism and inflammation in anemia treatment for dialysis patients.

This study was strengthened by incorporating observations from recently published studies and by analyzing the influence of HIF-PHIs on iron metabolism in dialysis patients and drug response in the inflammatory state. However, this study has several limitations. First, the standards and methods of iron supplementation in the included studies were not completely consistent, resulting in limited stability of the evaluation results of iron metabolism. Second, the potential for meta-analyses was further hampered by poor data reporting in many instances, especially the lack of direct reporting of SD. Third, although all HIF-PHIs are potent inhibitors of PHD1, PHD2, and PHD3 and stabilize HIF-α [66], they display differences in their pharmacokinetic and pharmacodynamic profiles. Therefore, the differences in the effects of different HIF-PHIs on iron metabolism and inflammation require further exploration.

Table 1
Effect of HIF-PHIs versus ESAs on inflammation.

Study ID	Interventions	CRP/ hsCRP	Baseline CRP/ hsCRP		No.	Effect on inflammation	Conclusion
Holdstock 2016	rhEPO	hsCRP (mg/dl)	7.8 (16.5)		20	There was no effect of daprodustat on levels of hsCRP, but there was considerable variability and insufficient sample size in this measurement.	Daprodustat comparable to rh EPO
	Daprodustat		7.5 (8.5)		19		
Singh 2022	Daprodustat	hsCRP (mg/dl)	0.3 (0.1–0.7) median (IQR)		157	The Hb response to daprodustat and darbepoetin alfa from baseline to the evaluation period was maintained regardless of the baseline hsCRP level.	Daprodustat comparable to Darbepoetin
	Darbepoetin		0.4 (0.1–0.9)		155		
Fishbane 2022	Roxadustat	hsCRP (mg/dl)	0.4 (0.2–1.1) median (IQR)		1051	Roxadustat resulted in statistically significant greater increases in Hb from baseline averaged over weeks 28–52 in patients with hsCRP >0.5 mg/dL compared with epoetin alfa	Roxadustat superior to epoetin alfa
	epoetin alfa		0.4 (0.2–1.0)		1055		
Provenzano2016	Roxadustat	CRP	–	–	67	The baseline CRP levels was associated with increased epoetin alfa maintenance dose requirements. While roxadustat maintenance dose requirements were independent of baseline CRP levels.	Roxadustat superior to epoetin alfa
	epoetin alfa		–	–	23		
Akizawa2021	Enarodustat	CRP (mg/dL)	–	–	86	The Hb level and dose of enarodustat or DA stratified by CRP (high group: CRP ≥0.3 mg/dL; low group: CRP <0.3 mg/dL) in each arm were comparable.	Enarodustat comparable to DA
	DA		–	–	86		
Akizawa2020		hs-CRP (mg/l)	<3.0	≥3.0		In patients with hsCRP ≥3.000 mg/L, a higher median doses of DA was needed to maintain target Hb levels compared with patients with hsCRP <3.000 mg/L; in the roxadustat group, this trend was not visible.	Roxadustat superior to DA
	Roxadustat		136 (90.7)	14 (9.3)	150		
	DA		129 (85.4)	22 (14.6)	151		
Chen 2019		CRP (no, %)	≤ULN *	> ULN		The epoetin alfa group (despite receiving higher doses) who had elevated CRP levels still had lower Hb responses than those with normal CRP levels. With elevated CRP levels, patients in the roxadustat group had a greater increase in the Hb level than those in the epoetin alfa group.	Roxadustat superior to epoetin
	Roxadustat		158 (77.5)	46 (22.5)	204		
	Epoetin		80 (80.0)	20 (20.0)	100		
Provenzano2021		CRP (no, %)	≤ULN	> ULN		Roxadustat dose requirements were similar in patients with hsCRP > ULN and those with hsCRP ≤ ULN. In contrast, mean epoetin alfa doses were higher in patients with baseline hsCRP > ULN vs. those with hsCRP ≤ ULN to maintain similar Hb levels.	Roxadustat superior to epoetin alfa
	Roxadustat		289 (55.4)	289 (55.5)	522		
	epoetin alfa		228 (43.7)	226 (43.4)	521		
Hou 2021		CRP (no, %)	≤ULN#	> ULN		The average Hb levels in Roxadustat group were similar between the patients with an elevated CRP level and those with a normal CRP level. Patients with elevated CRP level had a lower Hb level than those with normal CRP level in the ESAs group. And the CFB in the Hb level of roxadustat was higher than that of ESAs when with elevated CRP level.	Roxadustat superior to ESAs
	Roxadustat		48 (56)	38 (44)	86		
	ESAs		25 (58)	18 (42)	43		
Charytan2021		CRP (no, %)	≤ULN	> ULN		For roxadustat treatment, mean increases in Hb levels were comparable between patients with baseline hsCRP greater than > ULN and hsCRP ≤ ULN with stable mean weekly dosing. Patients with baseline hsCRP > ULN required larger increases in mean weekly epoetin alfa doses versus those with baseline hsCRP ≤ ULN.	Roxadustat superior to epoetin alfa
	Roxadustat		178 (48.1)	189 (51.1)	370		
	Epoetin alfa		192 (51.8)	177 (47.7)	371		

Note: inflammation as reflected by baseline serum CRP or hsCRP; CRP = *C*-reactive protein levels; hsCRP = high-sensitivity *C*-reactive protein; Hb = hemoglobin; No. = number of participants; DA = darbepoetin alfa; ULN = The upper limit of the normal range; CFB = change from baseline; * ULN for the CRP level was 4.9 mg per liter; # ULN for the CRP level was 3.0 mg per liter.

5. Conclusions

Overall, changes in iron biomarker levels, such as transferrin, TIBC, and hepcidin, significantly improved with HIF-PHIs compared to ESAs. HIF-PHIs treatment increased the serum iron level and decreased the mean monthly dose of intravenous iron. These results indicate that HIF-PHIs could promote iron utilization and resulted in a reduced use of intravenous iron therapy. Furthermore, HIF-PHIs, such as roxadustat, maintain the erythropoietic response independent of the inflammatory state. Thus, we propose that HIF-PHIs may be a considerable choice for anemia in dialysis-dependent patients when ESAs are hyporesponsive because of iron deficiency and inflammation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be

Table 2
Summary of findings of GRADE for the outcomes.

Outcomes	N° of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Anticipated absolute effects	
			Risk with ESAs	Risk difference with HIF-PHIs
TSAT	12,773 (22 RCTs)	⨁◯◯◯ Very low[a,b]	The mean TSAT was 0	MD **0.65 higher** (0.45 lower to 1.75 higher)
Ferritin	10,645 (20 RCTs)	⨁⨁◯◯ Low[c,d]	–	SMD **0.03 lower** (0.13 lower to 0.07 higher)
Iron	5551 (16 RCTs)	⨁⨁◯◯ Low[e,f]	The mean iron was **0**	MD **2.30 higher** (1.40 higher to 3.20 higher)
Transferrin	908 (5 RCTs)	⨁⨁⨁◯ Moderate[g]	–	SMD **0.9 higher** (0.74 higher to 1.05 higher)
TIBC	7401 (18 RCTs)	⨁⨁◯◯ Low[h,i]	–	SMD **0.82 higher** (0.66 higher to 0.98 higher)
Hepcidin	10,234 (20 RCTs)	⨁⨁◯◯ Low[j,k]	The mean hepcidin was **0**	MD **15.06 lower** (21.96 lower to 8.16 lower)
Mean monthly dose of IV iron	6058 (6 RCTs)	⨁⨁◯◯ Low[l,m]	The mean monthly dose of IV iron was **0**	MD **18.07 lower** (30.05 lower to 6.09 lower)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MD: mean difference; SMD: standardized mean difference. a: Risk of bias, b: Inconsistency, c: Indirectness, d: Imprecision, e: Other considerations, IV: intravenous.

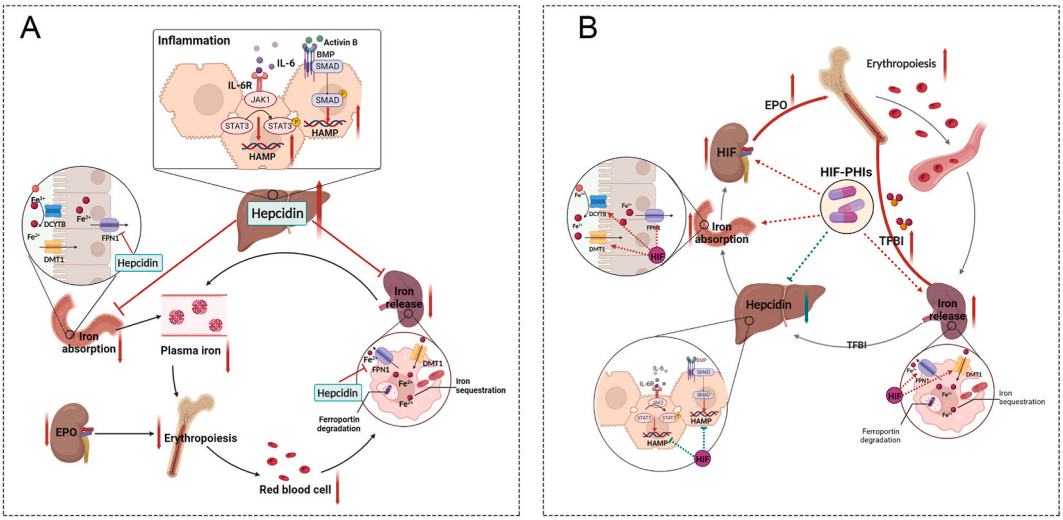

Fig. 10. Relationship between HIF-PHIs, inflammation and iron metabolism.

directed to the corresponding author.

Author contribution statement

Conceived and designed the experiments: Qiyan Zheng, Shunmin Li, Airong Qi. Performed the experiments: Qiyan Zheng, Pingna Zhang, Yunling Geng, Jingyi Tang, Yi Kang. Analyzed and interpreted the data: Qiyan Zheng, Huisheng Yang, Shunmin Li, Airong Qi. Contributed reagents, materials, analysis tools or data: Qiyan Zheng, Pingna Zhang, Huisheng Yang, Shunmin Li, Airong Qi. Wrote the paper: Qiyan Zheng, Pingna Zhang.

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CRediT author statement

Zheng Qiyan: Conceptualization, Protocol design, Search strategy, Studies selection, Software, Writing- Reviewing and Editing, Validation; ***Zhang Pingna:*** Studies selection, Data extraction, Manuscript writing, Validation; ***Yang Huisheng:*** Search strategy,

Software, Data interpretation, Validation, Review and editing; ***Geng Yunling:*** Data extraction, Validation; ***Tang Jingyi:*** Data extraction, Validation; ***Kang Yi:*** Data extraction, Validation; ***Li Shunmin:*** Protocol design, Supervision, Review and editing, Validation; ***Qi Airong:*** Protocol design, Supervision, Review and editing, Validation.

Declaration of competing interest

The authors declare that they have no conflicts of interest related to the content of this article (Validation: QZ, PZ, HY, YG, JT, YK, AQ and SL).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15310.

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