Drug Design, Development and Therapy

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ORIGINAL RESEARCH

The role of hypoxia-inducible factor stabilizers in the treatment of anemia in patients with chronic kidney disease

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Introduction: The purpose of this study was to analyze the effects of hypoxia-inducible factor (HIF) stabilizers on anemia in non-dialysis-dependent (NDD) and dialysis-dependent (DD) chronic kidney disease (CKD) patients.

Methods: Published studies were extracted from PubMed, China Biological Medicine Database (CBM), Wanfang database, and Cochrane Library on March 10, 2018, and relevant studies were pooled and included in a meta-analysis. Data on hemoglobin (Hb), ferritin, and hepcidin levels, total iron-binding capacity (TIBC), and incidence of adverse events (AEs) were extracted and pooled using Review Manager Version 5.3.

Results: Data from nine selected studies were extracted. Meta-analysis of the included studies showed that HIF stabilizers reduced ferritin and hepcidin levels and increased Hb level and TIBC in NDD-CKD patients. However, HIF stabilizers only increased TIBC, and did not affect ferritin, hepcidin, and Hb levels in DD-CKD patients. Furthermore, no notable differences in AEs and severe AEs between NDD-CKD and DD-CKD patients were detected.

Conclusion: HIF stabilizers are effective for the treatment of anemia in NDD-CKD patients and safe for short-term use.

Keywords: hypoxia-inducible factor stabilizer, anemia, chronic kidney disease, meta-analysis

Introduction

Chronic kidney disease (CKD) has become a global public health problem and results in significant morbidity and mortality.[1,2] Anemia is one of the hallmarks of advanced CKD and is correlated with a lower quality of life and increased mortality.[3–5] Renal anemia develops secondary to CKD, and its incidence increases with CKD progression. With the development of disease, patients inevitably develop end-stage renal disease, which often requires dialysis or kidney transplantation.[6] Anemia is a common complication of CKD.[7] Currently, recombinant human erythropoietin (rhEPO) is a cornerstone in the treatment of anemia associated with CKD. In the past, super-physiological doses of erythropoiesis-stimulating agents were employed to treat anemia; however, this has been associated with risk of cardiovascular events, as well as induces endothelial dysfunction.[8]

Hypoxia-inducible factor (HIF) is a heterodimer composed of HIF-α and HIF-β subunits.[9] HIF-β is constitutively expressed, whereas HIF-α is modulated by oxygen tension via a family of HIF-prolyl hydroxylases (PHDs) regulating its degradation by the proteasome.[10] During hypoxia, HIF plays an important role in survival by regulating the levels of erythropoietin (EPO), glucose transporter-1, vascular endothelial

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growth factor, and pyruvate dehydrogenase kinases 1 and 4.[11] HIF-prolyl hydroxylase inhibitors (PHIs) are small-molecule oral agents that stabilize HIF, resulting in the activation of HIF-mediated gene expression.[12] With increased HIF levels, concomitant expression of downstream molecules, such as EPO, occurs. HIF-1α induces the production of inflammatory cytokines and autoantibodies by promoting the persistence of interactions between synovial fibroblasts, T cells, and B cells. Therefore, targeting HIF-1α may be a potential therapeutic strategy for persistent disease.[13] Anemia secondary to CKD is a type of chronic inflammatory anemia,[14,15] and HIF stabilizers may improve the inflammatory status of CKD patients.[16] Despite this theory, the therapeutic use of HIF stabilizers in the clinic has not been thoroughly analyzed. This meta-analysis was performed to assess the effects of HIF stabilizers on anemia resulting from CKD.

Materials and methods

Search strategy

The website www.ClinicalTrials.gov was queried to determine the HIF stabilizers that have been investigated in clinical trials up to March 10, 2018. The keywords roxadustat, vadadustat, daprodustat, and molidustat were entered into PubMed, China Biological Medicine Database (CBM), Wanfang database, and Cochrane Library, and relevant studies were identified without any language limitation. The references cited in the recruited articles were also checked to identify additional reports.

Inclusion and exclusion criteria

Inclusion criteria

The inclusion criteria for the studies were as follows: 1) study type: randomized controlled trials, randomized crossover studies, and prospective studies; 2) study subjects: patients who met the diagnostic criteria only for anemia of CKD, regardless of race; 3) interventions: HIF stabilizer (roxadustat, vadadustat, daprodustat, molidustat) for treatment; and 4) outcome: different HIF stabilizers were compared with placebo or traditional drugs.

Exclusion criteria

Exclusion criteria for the studies were as follows: 1) the study focused on primary anemia or anemia secondary to other causes, such as blood loss, blood diseases, and infectious diseases; 2) the clinical trial involved healthy individuals; 3) the study only described individuals treated with HIF stabilizers and did not include a reference group; and 4) the diagnostic criteria were not clear.

Outcome measures

Hemoglobin (Hb; g/L or g/dL), ferritin (ng/mL or μg/L), and hepcidin (ng/mL or μg/L) levels, total iron-binding capacity (TIBC; μg/dL or μmol/L), and adverse events (AEs) were used as outcome measures.

Data collection

According to the predetermined inclusion criteria, two observers scanned the titles and abstracts, or read the full text to screen out possible relevant literature. Discordant opinions were resolved by the other reviewers. Only randomized controlled trials, randomized crossover studies, and prospective studies that were related to HIF stabilizer treatment were included in the analysis.

Statistical analysis

Using Review Manager Version 5.3 software, data were extracted from the included literature. On the basis of the heterogeneity test results, a fixed-effects model was used when the *P*-value was ≥0.1; otherwise, a random-effects model was used. The results were expressed as weighted mean differences for continuous data, and additionally, 95% CIs were calculated. Heterogeneity between included studies was assessed using chi-squared test with an alpha of 0.05 indicating statistical significance. Subgroup analysis was conducted to explore the underlying causes of heterogeneity in treatment outcomes. The following factors were identified for analysis in the experimental (HIF stabilizers) and control groups: 1) a change in mean Hb levels from baseline (ΔHb), 2) a change in mean ferritin levels from baseline (Δferritin), 3) a change in mean hepcidin levels from baseline (Δhepcidin), and 4) AEs between the experimental group and control group. For all analyses, a two-tailed *P*-value <0.05 indicated statistical significance.

Results

Search results

In this meta-analysis, nine articles,[17–25] describing 12 clinical trials, related to use of HIF stabilizers in anemia due to CKD (Table 1) were included. There were five multicenter, randomized, blinded, placebo-controlled studies[17–19,21,22] and three randomized, double-blinded, placebo-controlled studies.[20,23,25] Moreover, the meta-analysis included two open-label studies.[20,24] These nine studies comprised 353 cases and 234 controls (Table 1).

ΔHb values between the HIF stabilizer and placebo groups

All the nine reports[17–25] involved comparison of ΔHb levels between the case and placebo groups. ΔHb was statistically

Table 1 Characteristics of the studies included in this meta-analysis

Author (year)	Drug	Duration	Clinical trial	Study type	Laboratory measures	Patients type
Brigandi et al (2016)[19]	GSK1278863	4 weeks	Phase IIa	Multicenter, randomized, single-blind, placebo-controlled, parallel-group study	EPO, Ret, Hb, hepcidin	NDD-CKD, DD-CKD
Martin et al (2017)[22]	Vadadustat (AKBA6548)	6 weeks	Phase IIa	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial	Hb, TIBC, ferritin, hepcidin	NDD-CKD
Akizawa et al (2017)[17]	Daprodustat (GSK1278863)	4 weeks	Phase II	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study	Hb, EPO, VEGF, ferritin, transferrin, TIBC, serum iron, hepcidin, TSAT	DD-CKD
Holdstock et al (2016)[21]	GSK1278863	4 weeks	Phase IIa	Multicenter, randomized, blinded, controlled, parallel-group studies	Hb, EPO, hepcidin, ferritin, TSAT, transferrin, TIBC, serum iron, VEGF	NDD-CKD, DD-CKD
Chen et al (2017)[20]	FG-4592	12 weeks/ 7 weeks	Phase II	NDD study: randomized, double-blinded, placebo-controlled DD study: open-label, epoetin alfa-controlled	Hb, RBC, Ret, hematocrit, MCV, PLT, CHr, leukocytes, serum iron, TSAT, ferritin, sTfR, hepcidin, total cholesterol, HDL, LDL, VLDL, triglycerides	NDD-CKD, DD-CKD
Besarab et al (2015)[18]	FG-4592	18 weeks	Phase IIa	Multicenter, randomized, single-blind (subjects), placebo-controlled study	Hb, EPO, TSAT, serum iron, TIBC, ferritin, hepcidin	NDD-CKD
Provenzano et al (2016)[24]	FG-4592	6–19 weeks	Phase II	Multicenter, randomized, open-label, consecutive cohort, multidose study	Hb, EPO, ferritin, TSAT, serum iron, TIBC, sTfR, hepcidin, CHr, total cholesterol	DD-CKD
Pergola et al (2016)[23]	Vadadustat (AKB6548)	20 weeks	Phase IIb	Randomized, double-blind, placebo-controlled study	Urinary protein excretion rate, Hb, reticulocyte count, TIBC, TSAT, ferritin, hepcidin, VEGF	NDD-CKD
Ren (2013)[25]	FG-4592	8 weeks	Undefined	Randomized, double-blind, placebo-controlled clinical trial	Hb, Hct, Ret, % Rtc, cholesterol, LDL-C, TSAT, serum iron, TIBC, transferrin, ferritin, sTfR	NDD-CKD

Abbreviations: EPO, erythropoietin; Ret, reticulocyte; Hb, hemoglobin; TIBC, total iron-binding capacity; VEGF, vascular endothelial growth factor; TSAT, transferrin saturation; RBC, red blood cell; MCV, erythrocyte mean corpuscular volume; PLT, platelets; CHr, reticulocyte hemoglobin content; sTfR, serum soluble transferrin receptor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; Hct, hematocrit; LDL-C, low-density lipoprotein cholesterol; NDD-CKD, non-dialysis-dependent chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease.

significant between the experimental and control groups ($P<0.00001$; Table 2). The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was 2.70 (95% CI: 1.79–3.61). A subgroup analysis was also conducted between NDD-CKD patients and DD-CKD patients to analyze the causes of heterogeneity. For the NDD-CKD patients, seven reports[18–23,25] that compared the ΔHb levels between the HIF stabilizer and placebo groups were included. The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was 3.51 (95% CI: 2.20–4.82). The difference in the ΔHb levels was statistically significant between the HIF stabilizer and placebo groups among the NDD-CKD patients ($P<0.00001$; Table 2 and Figure 1A).

For the DD-CKD patients, five reports[17,19–21,24] that compared the ΔHb levels between the HIF stabilizer and control groups were included. The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was 1.20 (95% CI: −0.12 to 2.51). The difference in the ΔHb levels between the HIF stabilizer and control groups among the DD-CKD patients was not statistically significant ($P=0.07$; Table 2 and Figure 1B).

ΔFerritin values between the HIF stabilizer and placebo groups

Nine reports[17–25] including data from 11 trials were included in this meta-analysis for the assessment of Δferritin levels. The pooled mean difference between the case and placebo groups was −0.65 (95% CI: −1.12 to −0.18). The difference in the Δferritin levels between the experimental and control groups was statistically significant ($P=0.006$; Table 2). The *P*-value of the heterogeneity test was <0.00001, prompting

Table 2 Meta-analysis of the association of HIF stabilizers with anemia due to chronic kidney disease

Indicators	Group and subgroups	Number of studies	Q test	Model selected	OR (95% CI)	*P*-value
			P-value			
Hb	Overall	12	<0.00001	Random	2.70 (1.79–3.61)	<0.00001
	NDD-CKD	7	<0.00001	Random	3.51 (2.20–4.82)	<0.00001
	DD-CKD	5	<0.00001	Random	1.20 (−0.12 to 2.51)	0.07
Ferritin	Overall	11	<0.00001	Random	−0.65 (−1.12 to −0.18)	0.006
	NDD-CKD	6	<0.00001	Random	−1.12 (−1.92 to −0.32)	0.006
	DD-CKD	5	0.05	Random	−0.22 (−0.65 to 0.21)	0.32
Hepcidin	Overall	8	<0.00001	Random	−1.65 (−2.86 to −0.44)	0.007
	NDD-CKD	5	<0.00001	Random	−2.55 (−4.60 to −0.49)	0.02
	DD-CKD	3	0.07	Random	−14.39 (−50.70 to 21.91)	0.44
TIBC	Overall	11	<0.00001	Random	1.64 (0.98–2.31)	<0.00001
	NDD-CKD	6	<0.00001	Random	2.05 (1.00–3.10)	0.0001
	DD-CKD	5	<0.00001	Random	1.30 (0.35–2.24)	0.007
Reverse effect	Overall	5	0.71	Fixed	1.16 (0.81–1.67)	0.42
SAE	Overall	4	0.72	Fixed	1.56 (0.91–2.66)	0.11

Abbreviations: HIF, hypoxia-inducible factor; Hb, hemoglobin; TIBC, total iron-binding capacity; SAE, severe adverse event; NDD-CKD, non-dialysis-dependent chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease.

us to utilize a random-effects model, and an additional subgroup analysis was conducted.

For the NDD-CKD patients, six reports[18,20–23,25] were included in the meta-analysis for comparing the Δferritin levels between the HIF stabilizer and placebo groups. The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was −1.12 (95% CI: −1.92 to −0.32). The difference in Δferritin levels between the HIF stabilizer and placebo groups among the NDD-CKD patients was statistically significant (*P*=0.006; Table 2 and Figure 2A). This indicates that Δferritin levels in the HIF stabilizer group

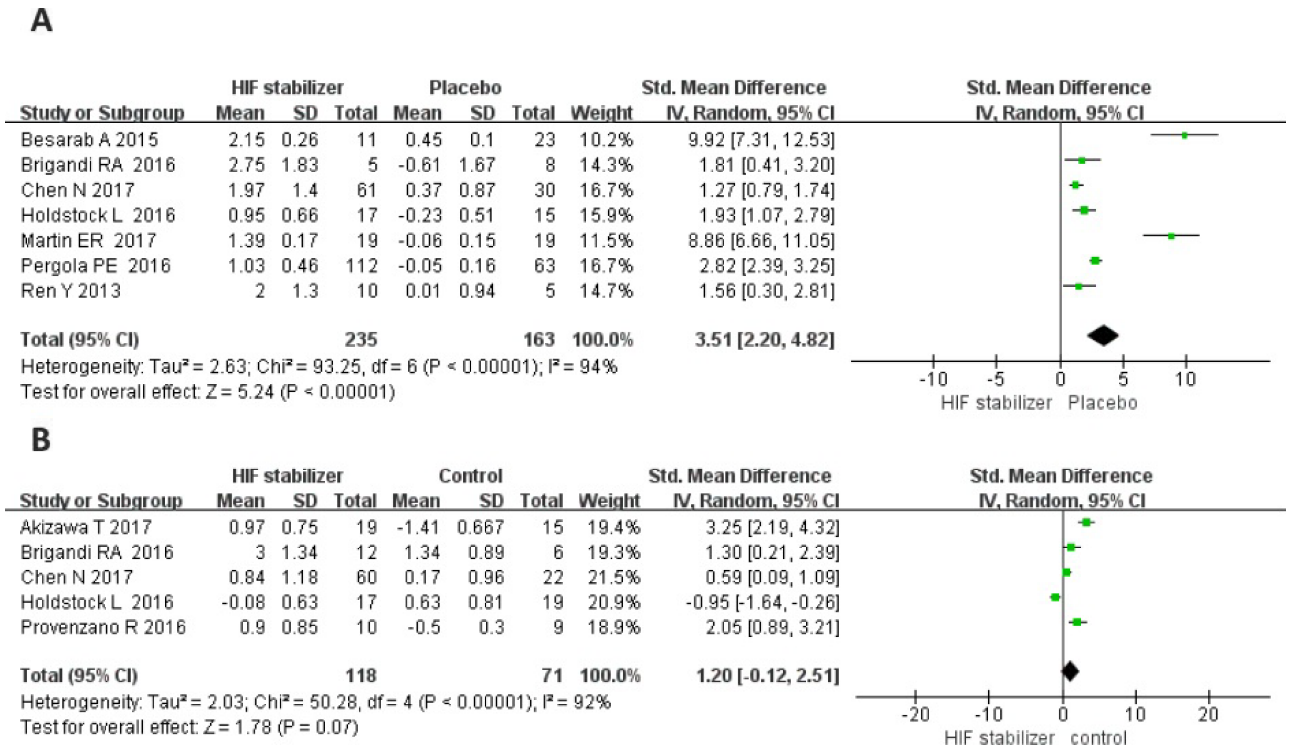

Figure 1 Association between HIF stabilizers and Hb in patients with CKD.
Notes: (**A**) NDD-CKD subgroup. (**B**) DD-CKD subgroup.
Abbreviations: HIF, hypoxia-inducible factor; Hb, hemoglobin; CKD, chronic kidney disease; NDD-CKD, non-dialysis-dependent chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease.

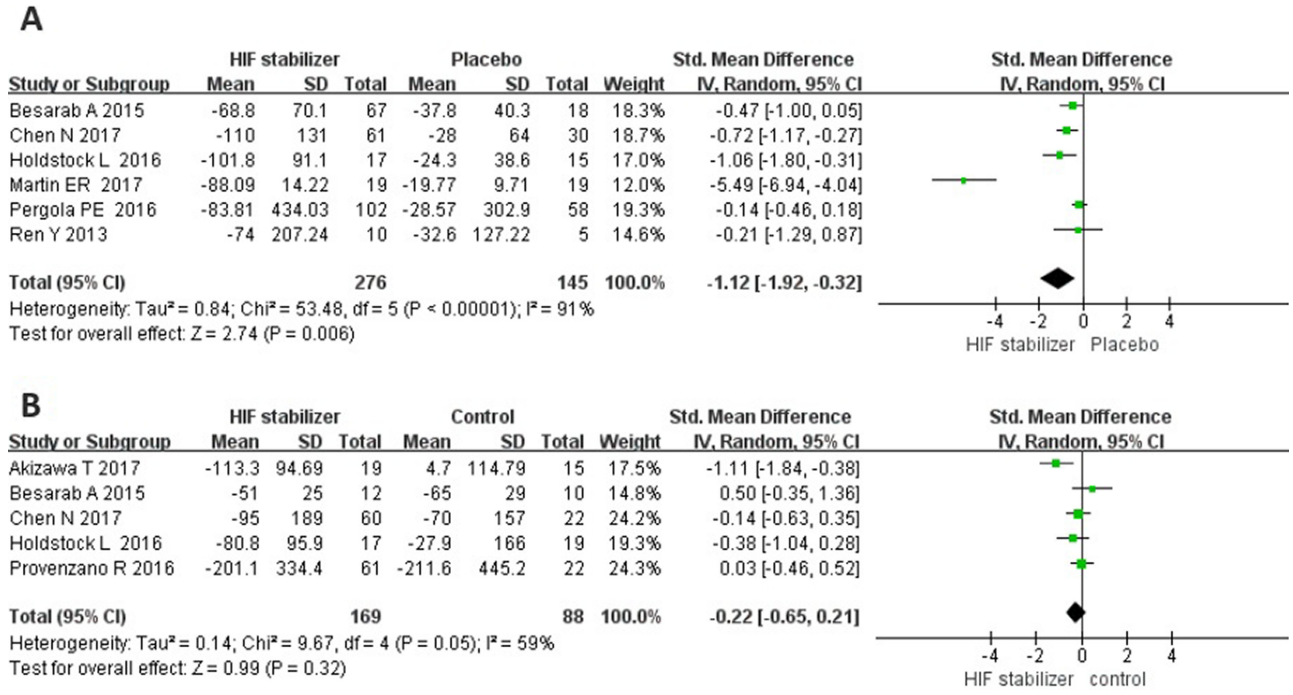

Figure 2 Association between HIF stabilizers and ferritin in patients with CKD.
Notes: (**A**) NDD-CKD subgroup. (**B**) DD-CKD subgroup.
Abbreviations: HIF, hypoxia-inducible factor; CKD, chronic kidney disease; NDD-CKD, non-dialysis-dependent chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease.

were lower than the placebo group among the NDD-CKD patients.

For the DD-CKD patients, five reports[17,18,20,21,24] were included in the meta-analysis for assessing the Δferritin levels. The *P*-value of the heterogeneity test was 0.05, so a random-effects model was chosen. The pooled mean difference was −0.22 (95% CI: −0.65 to 0.21). The difference in Δferritin levels between the HIF stabilizer and the control group among the DD-CKD patients was not statistically significant (*P*=0.32; Figure 2B and Table 2).

ΔHepcidin values between the HIF stabilizer and placebo groups

Six reports[18–20,22–24] including eight clinical trials were included in this meta-analysis for assessing the Δhepcidin levels between the case and placebo groups. The difference in Δhepcidin between the experimental and the control group was statistically significant (*P*=0.007; Table 2). The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was −1.65 (95% CI: −2.86 to −0.44). A subgroup analysis was conducted as well.

For the NDD-CKD patients, five reports[18–20,22,23] were included in the meta-analysis for assessing the Δhepcidin levels. The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was −2.55 (95% CI: −4.60 to −0.49). The difference in Δhepcidin levels between the HIF stabilizer and the placebo group among the NDD-CKD patients was statistically significant (*P*=0.02; Figure 3A and Table 2). This indicates that the Δhepcidin levels in the HIF stabilizer group were lower than the placebo group among the NDD-CKD patients.

For the DD-CKD patients, three reports[19,20,24] were included in the meta-analysis for assessing the Δhepcidin levels. The *P*-value of the heterogeneity test was <0.1, so a random-effects model was chosen. The pooled mean difference was −0.19 (95% CI: −0.64 to 0.26). The difference in Δhepcidin levels was not statistically significant between the two groups among the DD-CKD patients (*P*=0.41; Figure 3B and Table 2).

ΔTIBC between the HIF stabilizer and the placebo group

Nine reports[17–25] including 11 trials were included in this meta-analysis for assessing the ΔTIBC between the case and placebo groups. The difference in ΔTIBC between the experimental and the control group was statistically significant (*P*<0.00001; Table 2). The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was 1.64 (95% CI: 0.98–2.31).

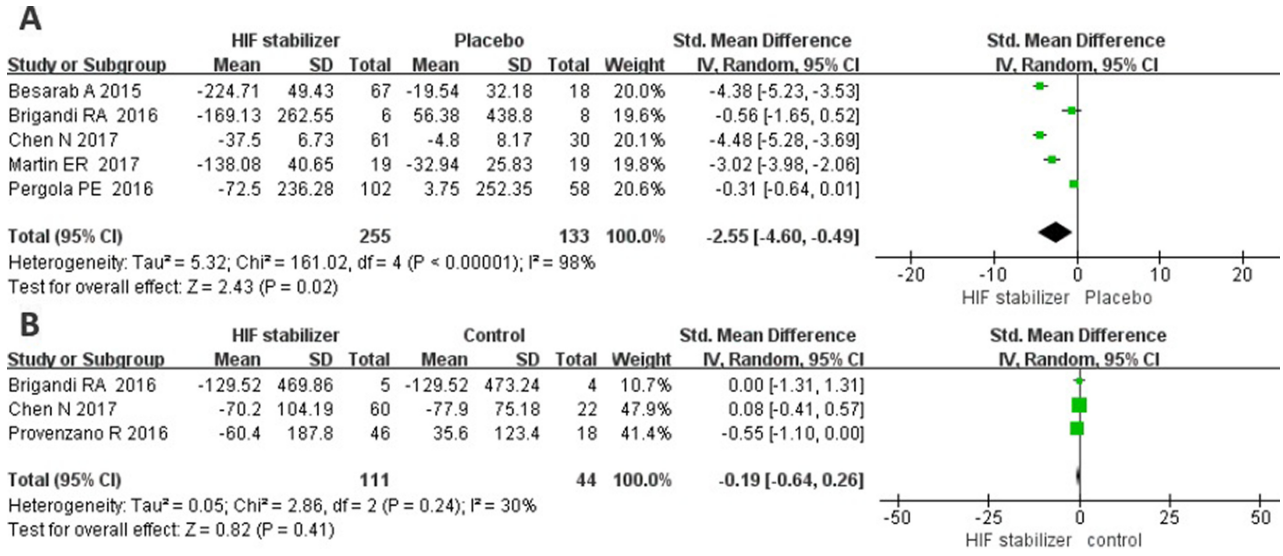

Figure 3 Association between HIF stabilizers and hepcidin in patients with CKD.
Notes: (**A**) NDD-CKD subgroup. (**B**) DD-CKD subgroup.
Abbreviations: HIF, hypoxia-inducible factor; CKD, chronic kidney disease; NDD-CKD, non-dialysis-dependent chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease.

In addition, a subgroup analysis comparing the NDD-CKD and DD-CKD patients was performed. For the NDD-CKD patients, six reports[18,20–23,25] describing the ΔTIBC levels between the HIF stabilizer and placebo groups were included. The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was 2.05 (95% CI: 1.00–3.10). The difference in ΔTIBC levels between the HIF stabilizer and placebo groups among the NDD-CKD patients was statistically significant (*P*=0.0001; Figure 4A and Table 2). This indicates that ΔTIBC levels in the HIF stabilizer group were higher than the placebo group among the NDD-CKD patients.

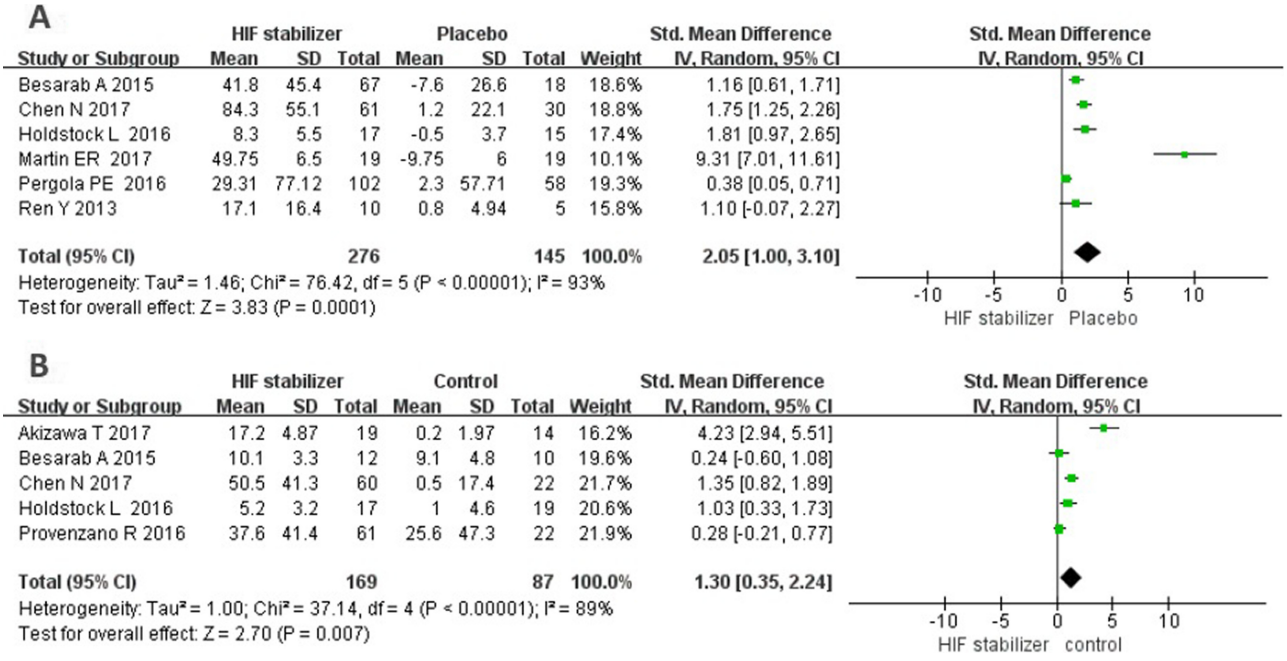

Figure 4 Association between HIF stabilizers and TIBC in patients with CKD.
Notes: (**A**) NDD-CKD subgroup. (**B**) DD-CKD subgroup.
Abbreviations: HIF, hypoxia-inducible factor; TIBC, total iron-binding capacity; CKD, chronic kidney disease; NDD-CKD, non-dialysis-dependent chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease.

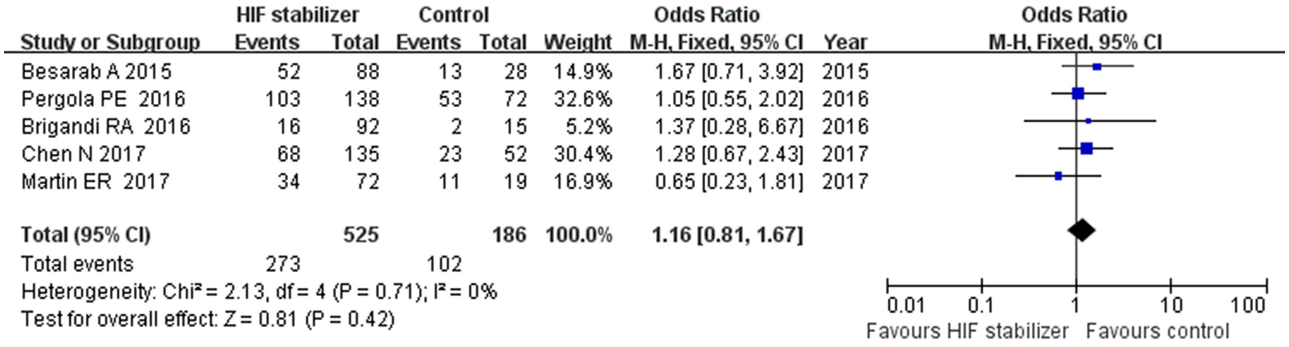

Figure 5 Association between HIF stabilizers and rate of AEs in patients with CKD.
Abbreviations: HIF, hypoxia-inducible factor; AEs, adverse events; CKD, chronic kidney disease.

For the DD-CKD patients, five reports[17,18,20,21,24] were included in this meta-analysis for assessing the ΔTIBC levels between the HIF stabilizer and control groups. The *P*-value of the heterogeneity test was <0.00001, so a random-effects model was chosen. The pooled mean difference was 1.30 (95% CI: 0.35–2.24). The difference in ΔTIBC levels between the two groups was not statistically significant (*P*=0.007; Table 2 and Figure 4B). This indicates that the differences in ΔTIBC levels between the HIF stabilizer and control groups among the DD-CKD patients were not statistically significant.

AEs between the experimental and the control groups

The most common AEs included gastrointestinal disorders, hyperkalemia, nausea, dizziness, headache, infections, and infestations. The proportion of patients with one or more AEs[18–20,22,23] was similar between the experimental and control groups. The *P*-value of the heterogeneity test was 0.71, so a fixed-effects model was chosen. The pooled mean difference was 1.16 (95% CI: 0.81–1.67). There was no difference in AEs between the two groups (*P*=0.42; Figure 5 and Table 2).

Severe AEs (SAEs) included vascular access complications, femoral neck fracture, noncardiac chest pain, and dyspnea. Four reports[21–24] were included in this meta-analysis for patients with SAEs. The *P*-value of the heterogeneity test was 0.72, so a fixed-effects model was chosen. The pooled mean difference was 1.56 (95% CI: 0.91–2.66). The SAEs between the experimental and control groups were not statistically different (*P*=0.11; Figure 6 and Table 2).

Discussion

HIF stabilizers promote erythropoiesis by stimulating endogenous EPO secretion via PHD inhibition.[19,21] This meta-analysis showed that treatment with HIF stabilizers resulted in higher ΔHb levels in CKD patients. HIF stabilizers have been shown to effectively ameliorate anemia resulting from CKD. Based on the results of heterogeneity test (*P*<0.00001, I^2=93%), we made a subanalysis of the NDD-CKD (HIF stabilizer group vs placebo group) and DD-CKD (HIF stabilizer group vs control group) subgroups. The pooled mean difference in the NDD-CKD subgroup was 3.51 (95% CI: 2.20–4.82, *P*<0.00001); however, the mean difference in the DD-CKD subgroup was 1.20 (95% CI: −0.12 to 2.51, *P*=0.07), although it was not statistically significant.

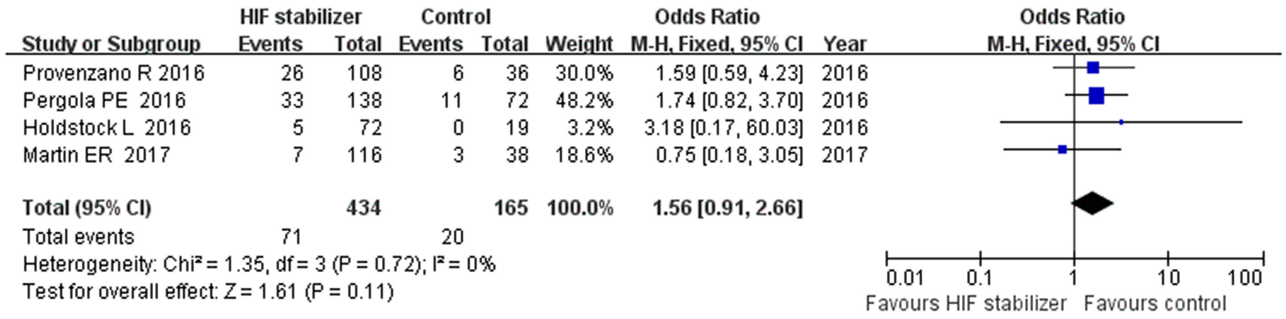

Figure 6 Association between HIF stabilizers and SAEs in patients with CKD.
Abbreviations: HIF, hypoxia-inducible factor; SAEs, severe adverse events; CKD, chronic kidney disease.

Iron metabolism indexes between the NDD-CKD and DD-CKD subgroups were found to be varied. The findings of the present study were discordant with those of earlier investigations,[9,17,21,24,26] showing that HIF stabilizers correct anemia in DD-CKD patients. This discrepancy in findings may be attributable to three reasons. First, due to a moderate sample size and a short treatment period, we were unable to generate a robust conclusion on the effect of HIF stabilizers in DD-CKD patients. Second, anemia secondary to CKD is generally due to endogenous EPO deficiency,[20] and desensitization of the oxygen-sensing mechanism may result in abnormally low EPO production under hypoxia. Third, HIF stabilizers are essentially less effective in DD-CKD than in NDD-CKD patients. Regardless of the mechanism of normal feedback control of erythropoiesis in CKD patients, stimulation of endogenous EPO production by HIF serves as a novel method for the treatment of anemia.[9]

CKD anemia is a type of chronic inflammatory anemia, and hepcidin is induced in large quantities in infected and inflammatory states, resulting in intracellular iron retention and decreased plasma iron levels, eventually leading to anemia. PHIs induce erythropoiesis by improving the bioavailability and utilization of iron.[27] Our meta-analysis indicated that in the NDD-CKD subgroup, the Δferritin and Δhepcidin levels in the HIF stabilizer group were lower than the placebo group. The HIF stabilizer group exhibited higher ΔTIBC compared to the placebo group. However, we did not find such changes in the DD-CKD subgroup. Our results on iron metabolism index in the DD-CKD subgroup were similar to those described by Holdstock et al.[21] In their hemodialysis-dependent study, the authors hypothesized that the mean levels of hepcidin in patients who needed to receive rhEPO were suppressed before detection. Solak et al suggested that hepcidin gene suppression is not due to a direct effect of HIFs, but rather is secondary to erythropoiesis induced by EPO.[28] Similarly, our analysis of the DD-CKD subgroup showed that there were no statistically significant differences in the ΔHb and Δhepcidin levels between the HIF stabilizer and control groups. However, it is also possible that we were unable to detect subtle differences due to our small sample size. Therefore, we plan to conduct further investigations to confirm the role of HIF stabilizers in hepcidin metabolism.

This study has some limitations, thereby requiring confirmation using additional studies. The chemical formulas of roxadustat, daprodustat, molidustat, and vadadustat are all different. However, no clinical trial to determine whether these have differential efficacies has been conducted to date. The sample size used in EPO measurements was relatively small, thereby preventing us from conducting meta-analysis for EPO levels. Furthermore, the present study was conducted for a short term, and thus, no long-term follow-up in terms of mortality, cardiovascular morbidity, and quality of life was performed.

Conclusion

In this meta-analysis, HIF stabilizers reduced ferritin and hepcidin levels, and increased Hb level and TIBC in NDD-CKD patients. However, HIF stabilizers only increased the TIBC, and did not affect the ferritin, hepcidin, and hemoglobin levels in DD-CKD patients. In summary, HIF stabilizers increase Hb levels and TIBC, and decrease the levels of ferritin and hepcidin in NDD-CKD patients, indicating that these are safe for short-term use in the treatment of anemia in NDD-CKD patients. However, the long-term safety and efficacy of HIF stabilizers in DD-CKD patients remain to be investigated.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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