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Original Article

ORIGINAL ARTICLE

Efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in patients with chronic kidney disease: meta-analysis of phase 3 randomized controlled trials

Roberto Minutolo [1], Maria Elena Liberti[1], Vittorio Simeon[2], Ferdinando C. Sasso[3], Silvio Borrelli[1], Luca De Nicola [1] and Carlo Garofalo[1]

[1]Nephrology Unit, University of Campania "Luigi Vanvitelli", Naples, Italy, [2]Medical Statistic Unit, University of Campania "Luigi Vanvitelli", Naples, Italy and [3]Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

Correspondence to: Roberto Minutolo; E-mail: roberto.minutolo@unicampania.it

ABSTRACT

Background. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are new therapeutic agents for anaemia in chronic kidney disease (CKD). We evaluated by meta-analysis and meta-regression the efficacy and safety of HIF-PHIs in patients with CKD-related anaemia.

Methods. We selected phase 3 randomized clinical trials (RCTs) comparing HIF-PHIs and erythropoiesis-stimulating agents (ESAs) in dialysis and non-dialysis patients. Efficacy outcomes were the changes from baseline of haemoglobin, iron parameters (hepcidin, serum iron, TIBC, TSAT, ferritin) and intravenous iron dose; as safety outcomes we considered cancer, adjudicated major adverse cardiovascular events (MACE), MACE+ (MACE plus hospitalization for hearth failure or unstable angina or thromboembolic event), thrombotic events (deep vein thrombosis, pulmonary embolism), arterovenous fistula (AVF) thrombosis and death.

Results. We included 26 RCTs with 24 387 patients. Random effect meta-analysis of the unstandardized mean difference between HIF-PHIs and ESAs showed a significant change in haemoglobin levels from baseline of 0.10 g/dL (95% CI 0.02 to 0.17). Meta-regression analysis showed a significantly higher haemoglobin change for HIF-PHIs in younger patients and versus short-acting ESA (0.21 g/dL, 95% CI 0.12 to 0.29 versus –0.01, 95% CI –0.09 to 0.07 in studies using long-acting ESA, $P < .001$). No significant effect on heterogeneity was found for type of HIF-PHIs. In comparison with ESAs, HIF-PHIs induced a significant decline in hepcidin and ferritin and a significant increase in serum iron and TIBC, while TSAT did not change; intravenous iron dose was lower with HIF-PHI (–3.1 mg/week, 95% CI –5.6 to –0.6, $P = .020$). Rate ratio of cancer (0.93, 95% CI 0.76 to 1.13), MACE (1.00, 95% CI 0.94 to 1.07), MACE+ (1.01, 95% CI 0.95 to 1.06), thrombotic events (1.08, 95% CI 0.84 to 1.38), AVF thrombosis (1.02, 95% CI 0.93 to 1.13) and death (1.02, 95% CI 0.95 to 1.13) did not differ between HIF-PHIs and ESAs.

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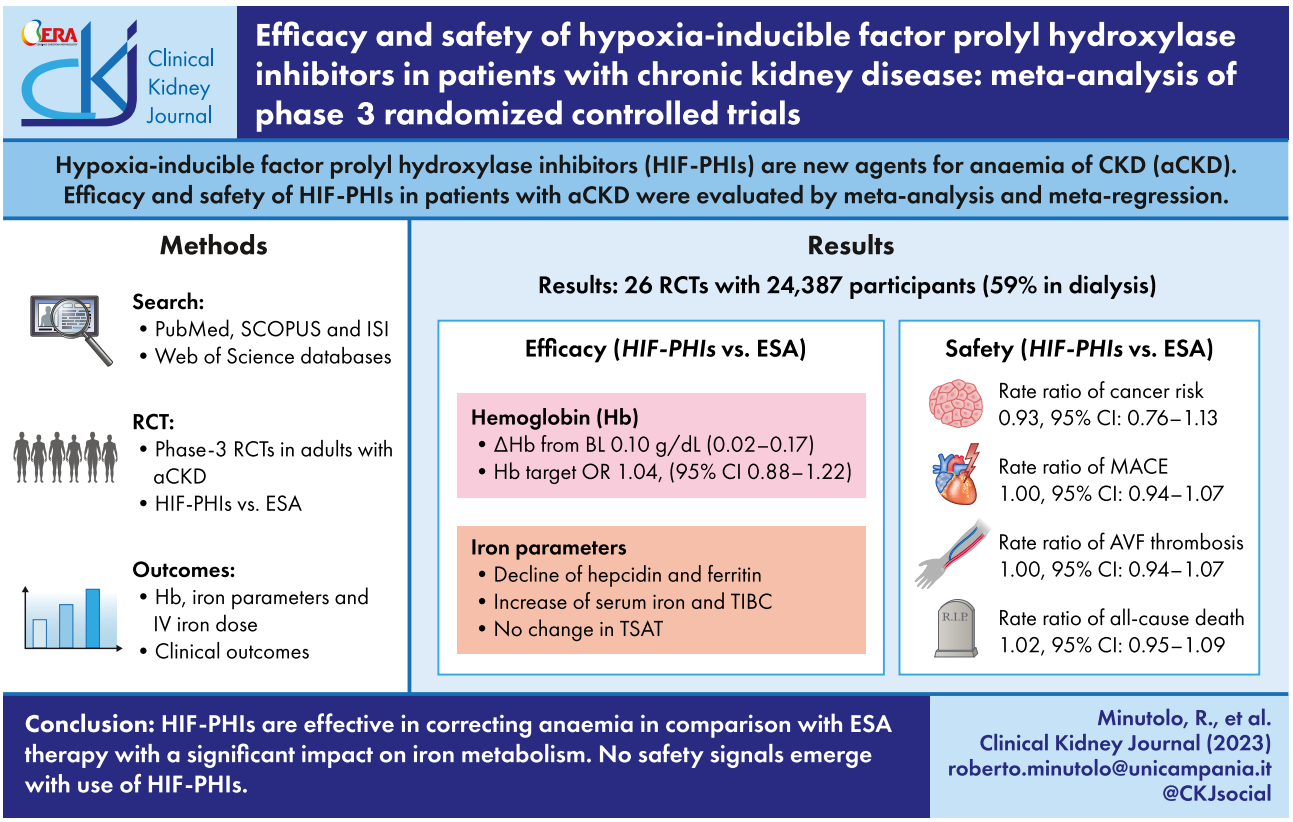
Conclusions. HIF-PHIs at the doses selected for the comparisons are effective in correcting anaemia in comparison with ESA therapy with a significant impact on iron metabolism without notable difference among various agents. No safety signals emerge with use of HIF-PHIs.

LAY SUMMARY

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are new drugs developed for the treatment of anaemia associated with chronic kidney disease (CKD). These drugs stimulate endogenous erythropoietin production and at the same time improve iron absorption and mobilization of iron stores. However, long-term studies (relevant for reassurance on safety) are limited. We designed the present meta-analysis and meta-regression to evaluate the efficacy of HIF-PHIs in comparison with standard therapy [erythropoiesis-stimulating agents (ESAs)] on haemoglobin levels and main clinical parameters of iron metabolism. Furthermore, we evaluated the safety profile of HIF-PHIs on main adverse outcomes (including cancer, cardiovascular events, thrombosis and death). We found a slightly greater effect of HIF-PHIs on haemoglobin and a significant improvement of iron parameters associated with lower need for intravenous iron. No difference between HIF-PHIs and ESAs was found for safety measures. These results suggest that HIF-PHIs are efficacious and safe in correcting CKD-related anaemia.

GRAPHICAL ABSTRACT



Keywords: anemia, CKD, haemoglobin, HIF-PHI, meta-analysis

INTRODUCTION

Anaemia is a common complication of chronic kidney disease (CKD); the prevalence and incidence of anaemia progressively increase as glomerular filtration rate (GFR) declines, with nearly 80% of dialysis patients affected [1–5]. Pathogenesis is multifactorial, with relative deficiency of erythropoietin production playing a major role [6]. Traditional key anaemia treatment is the combination of erythropoiesis-stimulating agents (ESAs) and iron supplementation [7]; however, in large randomized controlled trials (RCTs), ESA therapy has been associated with a risk of cardiovascular events [8–10], particularly when high doses were administered to reach near-normal haemoglobin (Hb) levels [11, 12].

In the last few years, a new class of drugs [hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs)] has been

developed based on seminal molecular biology studies describing the mechanisms underlying HIF oxygen sensing [13]. These drugs, by inhibiting the enzyme prolyl hydroxylase, prevent the degradation of the HIF-α subunit thus allowing its dimerization with subunit HIF-β; this heterodimer acts as transcription factor for the erythropoietin gene [14–16]. Furthermore, activation of the HIF pathway inhibits hepcidin production and it also induces transcription of genes coding for carriers of iron (ferroportin, duodenal cytochrome B, transferrin and transferrin receptor), thus coordinating erythropoietin synthesis with iron need [14–16]. Phase 2 studies have proven the ability of these drugs to increase Hb at the doses selected for the comparisons and to reduce hepcidin in patients with CKD not on dialysis and in dialysis, thus paving the way for several large phase 3 RCTs.

These trials have uniformly testified that new agents are not inferior to standard therapy in anaemia correction, suggesting that the class of HIF-PHIs is effective; however, a formal assessment of differences between this new class and traditional ESAs, as well as among individual HIF-PHIs, has never been evaluated. This holds true also for safety issues because the activation of the HIF pathway is involved in the control of multiple biologic processes, including cell proliferation, angiogenesis and tumour growth [16, 17]; therefore, the risk of adverse effects induced by systemic HIF-PHIs administration remains poorly defined mainly because of the short duration of trials. Previous meta-analyses have shown that HIF-PHIs are effective and safe for treatment of CKD-related anaemia [18–24]. However, these previous studies were limited by the heterogeneity of studies selected (inclusion of trials with placebo as comparator and phase 2 trials with short duration), by evaluation of a single HIF-PHI (roxadustat), by estimating effects in only dialysis or non-dialysis CKD, or focusing exclusively on cardiovascular safety or mortality risk.

To fill this important gap in knowledge, we performed a meta-analysis of phase 3 RCTs testing the effects of HIF-PHIs versus ESAs in non-dialysis and dialysis CKD. The aim was to evaluate formally the efficacy and safety of HIF-PHIs as class and as single agents in comparison with ESA.

MATERIALS AND METHODS

The present review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [25]. We searched relevant articles published from inception until 31 December 2022 by using PubMed, SCOPUS and ISI Web of Science databases. The search strategy is reported in Supplementary data, Table S1. References of articles and reviews found in research were further screened to identify additional studies. The present systematic review and meta-analysis was registered in Prospero CRD42023397997.

Study selection

Criteria for inclusion were: (i) phase 3 RCTs evaluating the efficacy and safety of HIF-PHIs in comparison with ESA; (ii) adult patients ($\geq$18 years) with anaemia secondary to CKD (at dialytic or non-dialytic stages); (iii) duration of at least 24 weeks. In the case of overlapping studies or *post hoc* analysis of the same cohort, we examined those with the most complete information (considering the year of first publication). Abstracts, letters to editors, commentaries, reviews and publications not in English were excluded.

The titles and abstracts, found with search strategy, were screened independently by three investigators (C.G., M.E.L. and S.B.). The full reports of potentially relevant studies were obtained, and each paper was reviewed using predefined eligibility criteria. Any discrepancy between the two authors on study eligibility was resolved through discussion. Data extraction was performed independently by three authors using standard data extraction forms. Risk of bias in included studies was assessed according to Sterne *et al*. [26] (Supplementary data Table S2).

Statistical analysis

We quantified the inter-rater agreement for study selection and quality assessment. To evaluate the efficacy of HIF-PHIs, we performed a random-effect meta-analysis of the unstandardized mean difference between HIF-PHIs and ESA-comparator arms on the changes from baseline of Hb, hepcidin, transferrin saturation (TSAT), total iron-binding capacity (TIBC), ferritin, serum iron, iron dose and low-density lipoprotein (LDL). Since Hb change from baseline could be potentially affected by the difference of dose of either HIF-PHIs or ESA across studies, we also performed meta-analysis for studies reporting odds ratio (OR) and 95% confidence intervals (CI) for achievement of Hb target according to the definition in each study. Calculations performed are described in the Supplementary Appendix [27, 28].

For safety evaluation we performed a random-effect meta-analysis by expressing results as rate ratio with 95% CI on the following outcomes: (i) cancer, (ii) major adverse cardiovascular events (MACE), (iii) MACE+, including MACE plus hospitalization for heart failure or unstable angina or thromboembolic event (excluding vascular access failure), (iv) deep vein thrombosis, pulmonary embolism, (v) arterovenous fistula (AVF) thrombosis and (vi) all-cause death. Analyses of MACE and MACE+ outcomes were performed using data from studies in which these were adjudicated endpoints. Two sensitivity analyses were performed for MACE and MACE+ outcomes: first, we repeated analyses by including also studies in which these events were not adjudicated; second, we repeated the meta-analyses by using studies reporting hazard ratio (HR) and 95% CI; this latter sensitivity analysis was also carried out for mortality risk.

We assumed a conservative approach in pooling results by using a random-effects model, which allows for variation of true effects across studies. We analysed heterogeneity with the I^2 statistic with 95% CI [29]. I^2 values of 25%, 50% and 75% correspond to cut-off points for low, moderate and high degrees of heterogeneity. For all efficacy and safety outcomes, sensitivity analyses were conducted to exclude the possibility that a study was exerting excessive influence on the heterogeneity [30]; sources of heterogeneity were explored by univariate random-effects meta-regression and moderator analyses. Meta-regression was used to test difference between moderators. Restricted maximum likelihood estimators were used to estimate model parameters [31]. We evaluated as continuous variable publication year, baseline GFR, baseline age, and the proportion of patients who were female, diabetic and iron replete. As categorical moderator we evaluated: number of participants ($<$100 or $\geq$100), CKD stage (dialysis versus non-dialysis), previous ESA treatment (yes versus no), HIF-PHIs drug, type of ESA comparator [short-acting ESA (epoietin-α or -β), versus long-acting ESA (darbepoetin or methoxy polyethylene glycol-epoetin beta, continuous erythropoietin receptor activator)] and study duration ($\leq$52 versus $>$52 weeks). Publication bias was assessed by Begg's rank correlation test and Egger's linear regression

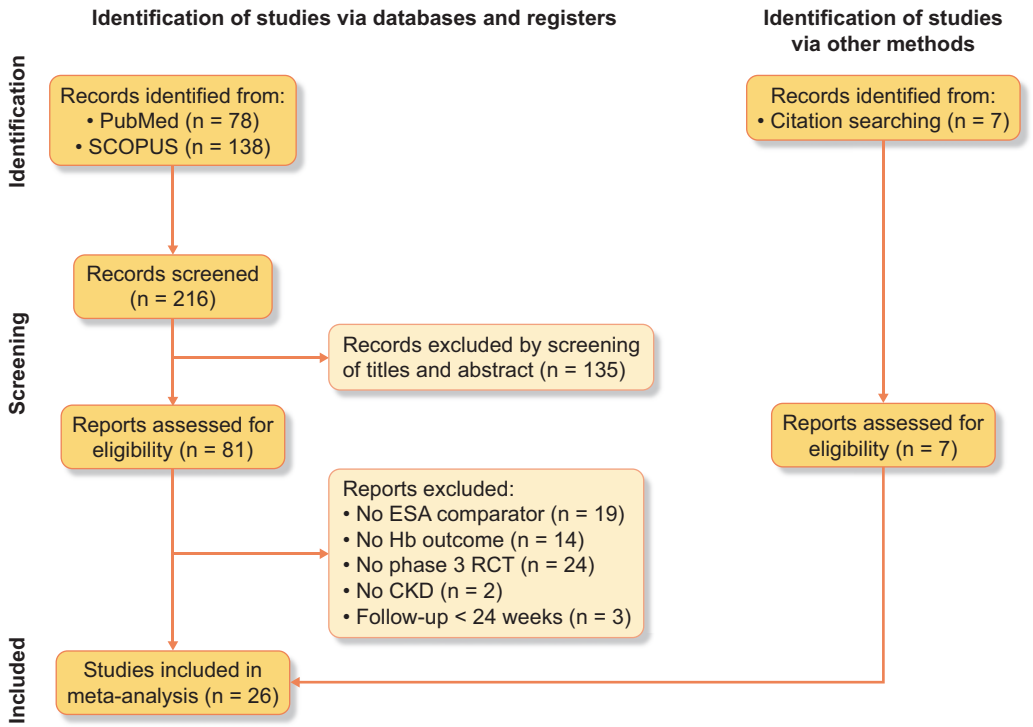


Figure 1: Flow chart of selected studies.

[32]. Analyses were performed using PROMETA 2 (INTERNOVI, Cesena, Italy), and STATA 16.0 (StataCorp LLC College Station, TX, USA).

RESULTS

Following the screening of titles and abstracts, we considered 88 studies out of 223 references and after article review 26 trials were identified (Fig. 1) [33–58]. Two studies reported data separately for ESA-naïve and ESA-treated patients [42] and for patients prevalent and incident to dialysis [57]; these were considered as different cohorts in the comparisons for efficacy outcomes but not for safety because events were reported as cumulative numbers. Agreement of three reviewers was very good for study selection (Kappa = 0.825).

Overall, the selected studies included information on 24 387 participants (range 129–3923) (Table 1). Length of follow-up averaged 16.5 months (range 6–42). Mean baseline estimated GFR ranged from 15.9 to 22.1 mL/min/1.73 m^2. Mean age at baseline was 67.1 years (range 48–72). Prevalence of prior cardiovascular disease was available in eight studies, ranging from 29.5% to 49.5%. Mean systolic blood pressure (SBP) was available in 10 studies (range 133–150 mmHg). All included studies had low risk of bias (Table 1). The primary efficacy endpoint in the 26 RCTs that were the object of this meta-analysis was the change from baseline in Hb values (19 RCTs), the difference of Hb between arms during the evaluation period (6 RCTs) and the achievement of Hb target (1 RCT). Sensitivity analyses for each efficacy and safety endpoint did not evidence that a single study had a significant effect on heterogeneity. Publication bias was not detected for any efficacy and safety outcome considered (Supplementary data, Table S2).

Efficacy

Change in Hb levels from baseline

Eighteen studies reported change from baseline in Hb values (20 comparisons). We found a significantly higher change in Hb levels from baseline between HIF-PHIs at the doses selected for the comparisons and ESA of 0.10 g/dL (95% CI 0.02 to 0.17) in favour of HIF-PHIs, with high heterogeneity (Fig. 2A). Meta-regression analysis showed a significant role for baseline age on heterogeneity ($P = .040$) with higher Hb change in younger patients (Fig. 3), while the proportion of females, diabetics and iron replete patients, and prior cardiovascular disease baseline GFR and SBP had no role on heterogeneity. Conversely, moderator analysis found a significant influence on heterogeneity of type of ESA comparator; indeed, HIF-PHIs induced a greater change in Hb levels in studies using short-acting ESA as comparator (0.21 g/dL; 95% CI 0.12 to 0.29) versus those using long-acting ESA (–0.01 g/dL; 95% CI –0.09 to 0.07) ($P < .001$). Other factors did not have a significant effect on heterogeneity (Table 2).

Hb target achievement

Random effect meta-analysis of OR did not show a significant difference in Hb target achievement between HIF-PHIs at the doses selected for the comparisons and ESA comparator (OR 1.04, 95% CI 0.88–1.22) (Fig. 2B). Moderator analysis disclosed a significant influence on heterogeneity of type of ESA comparator (higher probability of achieving target in comparison with short-acting) and HIF-PHIs (higher probability of achieving target with desidustat) (Table 2). Only four studies reported the prevalence of Hb below and above the target; no difference was found between HIF-PHIs at the doses selected for the comparisons and ESA comparator for Hb below the target (OR 1.25, 95%

Table 1: Characteristics of selected trials.

Study year [ref]	ESA treated	Active drug	Control	Duration (months)	Active arm (*N*)	Control arm (*N*)	Mean age (years)	Females (%)	DM (%)	Iron replete (%)	Risk of bias
Non-dialysis patients											
DOLOMITES 2021 [33]	Treated	Roxadustat	Darbepoetin	104	323	293	66.3	55.6	33.6	54.2	Low
Akizawa 2021 [34]	Treated	Roxadustat	Darbepoetin	24	131	131	69.9	39.7	51.9	51.5	Low
MIYABI-NDM 2021 [35]	Treated	Molidustat	Darbepoetin	52	82	82	70.7	39.6	31.1		Low
MIYABI-NDC 2021 [36]	Naïve	Molidustat	Darbepoetin	52	82	80	71.7	38.3	34.6		Low
ASCEND-ND 2021 [37]	Mixed	Daprodustat	Darbepoetin	148	1937	1935	67.0	56.1	56.7	100	Low
Nangaku 2021 [38]	Mixed	Daprodustat	CERA	52	149	150	70.0	37.7	45	100	Low
DREAM-ND 2022 [39]	Naïve	Desidustat	Darbepoetin	24	294	294	52.8	49.7	48.5	100	Low
SYMPHONY ND 2021 [40]	Mixed	Enarodustat	Darbepoetin	24	97	96	69.7	44	32.1		Low
Nangaku 2021 [41]	Mixed	Vadadustat	Darbepoetin	52	151	153	72.0	51.3	39.1	100	Low
PROT2TECT 2021 [42]	Mixed	Vadadustat	Darbepoetin	168	1741	1735	66.5	55.7	63.7	100	Low
Dialysis patients											
HIMALAYAS 2021 [43]	Naïve	Roxadustat	Epoetin	52	522	521	54.1	40.9	39.2	77.9	Low
SIERRAS, 2021 [44]	Treated	Roxadustat	Epoetin	52	370	371	58.0	45.7	68	97.6	Low
PYRENEES 2021 [45]	Treated	Roxadustat	Epoetin	104	414	420	61.4	42.4	28.4	86.6	Low
ROCKIES 2022 [46]	Treated	Roxadustat	Epoetin	164	1051	1055	54.0	40.6	40.1	100	Low
Akizawa 2020 [47]	Treated	Roxadustat	Darbepoetin	24	151	150	64.8	30.9	35.9	30.6	Low
Chen 2019 [48]	Treated	Roxadustat	Epoetin	27	204	100	48.7	39.5	15.5		Low
Hou 2022 [49]	Mixed	Roxadustat	Epoetin	24	86	43	48.1	44.2	16	76.7	Low
MIYABI-HDM 2021 [50]	Treated	Molidustat	Darbepoetin	52	153	76	65.7	38.9	31.4	100	Low
ASCEND-D 2021 [51]	Treated	Daprodustat	Epoetin	148	1487	1477	58.0	42.7	41.6	100	Low
ASCEND-ID 2022 [52]	Treated	Daprodustat	Darbepoetin	52	157	155	54.0	37.8	44.9	100	Low
NCT02969655 2020 [53]	Treated	Daprodustat	Darbepoetin	52	136	135	64.0	33.6	39.9		Low
ASCEND-TD 2022 [54]	Treated	Daprodustat	Epoetin	52	270	137	59.0	43	39	100	Low
DREAM-D 2022 [55]	Treated	Desidustat	Epoetin	24	196	196	51.0	31.4	35.96	100	Low
SYMPHONY HD 2021 [56]	Treated	Enarodustat	Darbepoetin	24	86	86	64.0	29.1	39	50.0	Low
INNO2VATE 2021 [57]	Treated	Vadadustat	Darbepoetin	116	1958	1965	58.0	43.6	55.3	100	Low
Nangaku 2021 [58]	Treated	Vadadustat	Darbepoetin	52	162	161	65.5	34.1	26		Low

DM: diabetes mellitus; CERA: continuous erythropoietin receptor activator.

CI 0.64–2.45, $P = .515$) as well as for Hb above the target (OR 0.72, 95% CI 0.28–1.82, $P = .488$).

Change in iron parameters and intravenous iron dose from baseline

We found a significant reduction of hepcidin levels from baseline in the HIF-PHIs arm versus ESA (14 studies, –19.2 ng/mL, 95% CI –28.4 to –10.0), with high heterogeneity (Fig. 4A). Meta-regression analysis showed a marginally significant trend in greater decline of hepcidin levels in RCTs with more females enrolled ($P = .047$). Previous ESA treatment was found to significantly influence heterogeneity (higher decline in mixed population) (Table 3). To explore whether hepcidin decline was dependent on Hb changes, we performed two meta-regression analyses showing that hepcidin decline was not associated with Hb increase either when HIF-PHIs were compared with ESA ($P = .639$) or when considering only HIF-PHIs arms ($P = .510$) (Supplementary data, Fig. S2).

HIF-PHIs as compared with ESA showed a significant change from baseline in serum iron (12 studies, +9.7 µg/dL, 95% CI 5.7 to 13.8) with high heterogeneity (Fig. 4B). Moderator analysis found a significant influence on heterogeneity of CKD stage (larger increase in dialysis patients) (Table 3).

A larger increase from baseline in TIBC levels was detected for HIF-PHIs (11 studies, +36.3 µmol/L, 95% CI 31.9 to 40.8) (Fig. 4C). A high degree of heterogeneity was found with CKD stage, type of HIF-PHI used and study duration acting as significant moderators (Table 3).

No significant difference was found for change from baseline in TSAT between HIF-PHIs and ESA (14 studies, –0.3%, 95% CI –1.7 to 1.0) (Fig. 4D). High heterogeneity was mainly explained by the significantly greater decline of TSAT in RCTs with long-acting ESA as comparator, in non-dialysis CKD and in studies using vadadustat (Table 3).

Serum ferritin levels (available in 13 studies) significantly declined in HIF-PHIs as compared with ESA (–16.8 ng/mL, 95% CI –32.4 to –1.3) (Fig. 4E). Heterogeneity was significantly influenced by the type of ESA comparator (greater decline with short-acting ESA) (Table 3).

Weekly intravenous iron dose (10 studies) was reduced in HIF-PHIs arms versus ESA comparator (–3.1 mg/week, 95% CI –5.6 to –0.6) with high heterogeneity (Fig. 4F), dependent on type of HIF-PHIs (lower iron need with roxadustat) and previous ESA treatment (lower need in ESA-naïve patients) (Table 3).

Change in LDL values from baseline

Change from baseline in the LDL levels (eight studies) is reported in Supplementary data, Fig. S1A. Overall, we found a greater decline in LDL from baseline with HIF-PHIs (–10.5 mg/dL, 95% CI –14.6 to –6.4). Heterogeneity was high and mainly dependent on the type of HIF-PHI, with greater difference ($P < .001$) in LDL reduction with roxadustat (–15.7 mg/dL, 95% CI –18.5 to –13.0) than with desidustat (–7.5 mg/dL, 95% CI –11.1 to –3.9) and daprodustat (–5.7 mg/dL, 95% CI –8.5 to –3.0). Furthermore, we found a greater decline in high-density lipoprotein (HDL) from

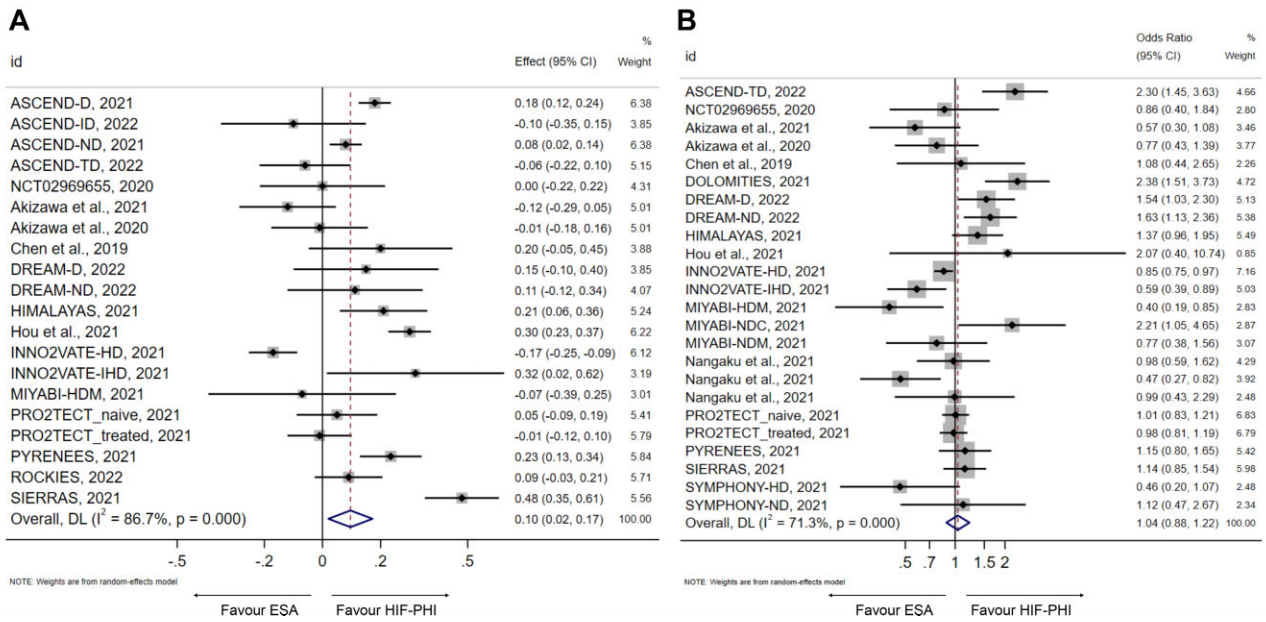


Figure 2: Random effect meta-analysis of unstandardized mean difference in change of Hb levels from baseline (**A**) and Hb target achievement (**B**) between HIF-PHI and ESA comparator.

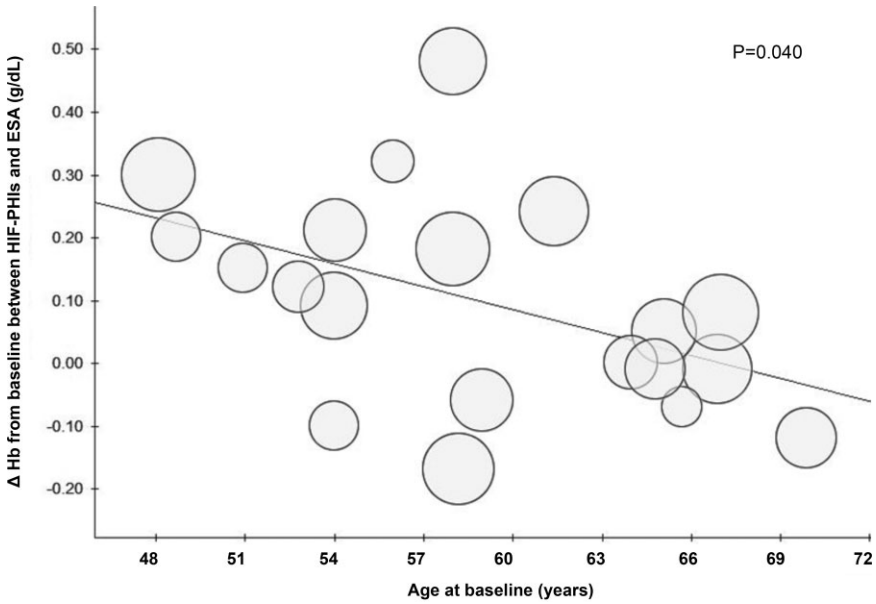


Figure 3: Meta-regression of effects of baseline age on change in Hb levels from baseline between HIF-PHI and ESA comparator.

baseline with HIF-PHIs (six studies, –2.9 mg/dL, 95% CI –3.9 to –2.0) (Supplementary data, Fig. S1B). Heterogeneity was moderate and mainly dependent on the type of HIF-PHI, with greater difference in HDL reduction with roxadustat (–4.5 mg/dL, 95% CI –5.5 to –3.5) than with desidustat (–1.2 mg/dL, 95% CI –1.7 to 0.3) and daprodustat (–2.7 mg/dL, 95% CI –3.4 to –2.1).

Safety

Cancer risk

Eighteen trials reported data of patients developing cancer (Fig. 5A). Rate ratio of cancer risk was similar between HIF-PHIs and ESA (0.93, 95% CI 0.76–1.13). Despite the lack of heterogeneity, we performed a moderator analysis considering study duration (≤52 or >52 weeks) but we did not find any significant difference ($P = .392$).

Cardiovascular risk

Random effect meta-analysis of rate ratio did not show a significant difference in adjudicated MACE events (10 trials) between HIF-PHIs and ESA comparator (1.00, 95% CI 0.94–1.07) (Fig. 5B). No heterogeneity was found. Similar results were detected in the random effect meta-analysis of six studies reporting HR (Supplementary data, Fig. S3A).

Table 2: Moderator analyses of change in Hb levels from baseline and Hb target achievement between HIF-PHI and ESA comparator.

	Hb change, g/dL [OR (95% CI)]	P	Target achievement [OR (95% CI)]	P
ESA comparator		**<.001**		**.003**
Long-acting ESA	–0.01 (–0.09 to 0.07)		0.91 (0.76 to 1.10)	
Short-acting ESA	0.21 (0.12 to 0.29)		1.38 (1.13 to 1.68)	
CKD stage		.144		.634
Non-dialysis	0.03 (–0.04 to 0.10)		1.08 (0.83 to 1.42)	
Dialysis	0.12 (0.02 to 0.22)		1.00 (0.80 to 1.24)	
HIF-PHI		.290		**.005**
Roxadustat	0.18 (0.06 to 0.30)		1.17 (0.88 to 1.55)	
Molidustat	–0.07 (–0.39 to 0.25)		0.88 (0.34 to 2.29)	
Daprodustat	0.06 (–0.04 to 0.15)		1.30 (0.63 to 2.67)	
Desidustat	0.13 (–0.04 to 0.30)		1.59 (1.21 to 2.08)	
Enarodustat	NA		0.71 (0.30 to 1.69)	
Vadadustat	0.00 (–0.15 to 0.16)		0.85 (0.72 to 1.00)	
Previous ESA therapy		.594		.154
Naïve	0.12 (0.02 to 0.23)		1.36 (1.00 to 1.86)	
ESA	0.07 (–0.03 to 0.18)		0.98 (0.80 to 1.19)	
Mixed	0.19 (–0.03 to 0.40)		0.83 (0.46 to 1.49)	
Study duration		.795		.691
≤52 weeks	0.10 (–0.02 to 0.22)		1.08 (0.87 to 1.35)	
>52 weeks	0.08 (–0.02 to 0.18)		1.02 (0.81 to 1.27)	
No. of patient/arm		.742		.540
<100	0.15 (–0.21 to 0.51)		0.88 (0.49 to 1.58)	
≥100	0.09 (0.01 to 0.17)		1.07 (0.90 to 1.26)	

Long-acting ESA: darbepoetin or continuous erythropoietin receptor activator; short-acting ESA: epoetin-α or epoetin-β; NA: not available.
In bold are indicated significant *P* values.

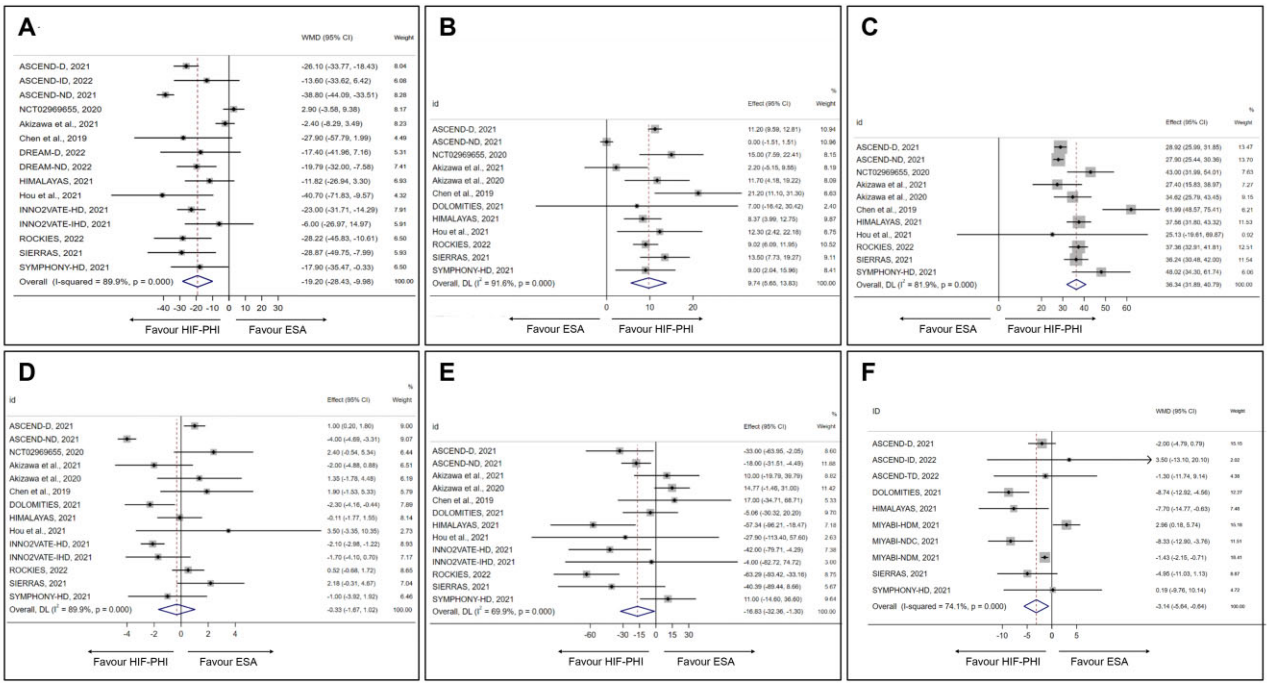


Figure 4: Random effect meta-analysis of unstandardized mean difference from baseline between HIF-PHI and ESA comparator in change of serum hepcidin (**A**), serum iron (**B**), TIBC (**C**), TSAT (**D**), serum ferritin (**E**) and intravenous iron dose (**F**).

The rate ratio of MACE+ risk did not differ between HIF-PHIs and ESA (1.01, 95% CI 0.95–1.06); no heterogeneity was found (Fig. 5C). Similar findings were obtained in the meta-analysis of seven studies reporting HR of MACE+ (Supplementary data, Fig. S3B).

Sensitivity analysis including also studies in which MACE and MACE+ were not adjudicated events provided similar results. Indeed, random effect meta-analysis of rate ratio did not show a significant difference between HIF-PHIs and ESA comparator in MACE risk (15 studies) (1.01, 95% CI

Table 3: Moderator analyses of change in iron parameters from baseline between HIF-PHI and ESA comparator.

	Hepcidin, ng/mL (95% CI)	*P*	Iron, µg/dL (95% CI)	*P*	TIBC, µmol/L (95% CI)	*P*	TSAT, % (95% CI)	*P*	Ferritin, ng/mL (95% CI)	*P*	IV iron, mg/week (95% CI)	*P*
ESA comparator		.208		.266		.562		**.002**		**.008**		.523
Long-acting ESA	−15.0 (−28.7; −1.3)		7.1 (0.9; 13.4)		35.0 (27.4; 42.6)		−1.5 (−2.9; −0.2)		−3.1 (−18.3; 12.1)		−2.8 (−6.6; 1.0)	
Short-acting ESA	−24.6 (−30.3; −18.8)		10.9 (8.8; 13.0)		37.9 (31.4; 44.5)		0.9 (0.3; 1.4)		−39.4 (−61.1; −17.6)		−4.5 (−8.0; −1.0)	
CKD stage		.892		**<.001**		**<.001**		**<.001**		.336		.226
Non-dialysis	−20.4 (−46.2; 5.5)		0.1 (−1.4; 1.6)		27.9 (25.5; 30.3)		−3.2 (−4.6; −1.8)		−8.7 (−24.3; 6.9)		−5.9 (−11.6; −0.1)	
Dialysis	−18.5 (−27.5; −9.4)		10.9 (9.3; 12.5)		38.8 (33.5; 44.2)		0.3 (−0.8; 1.4)		−22.4 (−45.5; 0.7)		−1.6 (−5.4; 2.3)	
HIF-PHIs		.522		.903		**.009**		**.027**		.114		**.045**
Roxadustat	−14.3 (−24.7; −3.9)		10.2 (7.2; 13.2)		37.8 (32.6; 43.1)		0.2 (−1.0; 1.4)		−17.3 (−42.2; 7.6)		−7.6 (−10.7; −4.5)	
Molidustat	NA		NA		NA		NA		NA		−1.8 (−6.2; 2.5)	
Daprodustat	−28.8 (−41.2; −16.4)		8.3 (−0.9; 17.5)		30.1 (25.9; 34.3)		−0.3 (−4.4; 3.7)		−20.4 (−3.3; −8.0)		−1.7 (−6.8; 3.5)	
Desidustat	−19.3 (−30.3; −8.4)		NA		NA		NA		NA		NA	
Enarodustat	−17.9 (−35.5; −0.33)		9.0 (2.0; 16.0)		48.0 (34.3; 61.7)		−1.0 (−3.9; 1.9)		11.0 (−14.6; 36.6)		−0.2 (−9.8; 10.1)	
Vadadustat	−17.3 (−33.0; −1.5)		NA		NA		−2.1 (−2.9; −1.2)		−34.9 (−69.0; −0.9)		NA	
Previous ESA		**<.001**		.439		**<.001**		.968		.126		**.013**
No	−16.6 (−26.1; −7.2)		8.4 (4.0; 12.8)		37.6 (31.8; 43.3)		−0.1 (−1.8; 1.6)		−57.3 (−96.2; −18.5)		−8.1 (−12.0; −4.3)	
Yes	−15.9 (−24.8; −7.1)		10.8 (8.5; 13.2)		38.2 (32.4; 44.1)		−0.1 (−1.3; 1.0)		−12.8 (−31.9; 6.2)		−2.1 (−5.0; 0.9)	
Mixed	−38.9 (−44.1; −33.6)		5.1 (−6.8; 17.0)		27.9 (25.4; 30.4)		−1.1 (−8.2; 6.1)		−18.2 (−31.60; −4.9)		NA	
Patient/arm (*N*)		.501		.936		.136		.770		.138		.074
<100	−25.5 (−46.6; −4.4)		10.1 (4.4; 15.8)		46.1 (32.9; 59.2)		0.1 (−3.7; 4.0)		7.8 (−16.7; 32.3)		−1.6 (−5.5; 2.4)	
≥100	−17.4 (−28.0; −6.9)		9.8 (4.5; 15.0)		35.4 (30.5; 40.3)		−0.5 (−2.0; 1.1)		−14.3 (−30.1; 1.5)		−6.0 (−8.7; −3.2)	
Study duration		.059		.305		**.026**		.075		.097		.357
≤52 weeks	−13.5 (−21.6; −5.5)		11.1 (7.7; 14.4)		39.8 (33.8; 45.8)		0.7 (−0.5; 1.8)		−4.9 (−26.1; 16.3)		−2.5 (−5.6; 0.6)	
>52 weeks	−26.6 (−36.1; −17.1)		6.7 (−0.8; 14.3)		31.1 (26.3; 35.9)		−1.4 (−3.4; −0.5)		−28.2 (−45.8; −10.6)		−5.8 (−12.1; 0.5)	

IV: intravenous; CERA, continuous erythropoietin receptor activator;.
In bold are indicated significant *P* values.

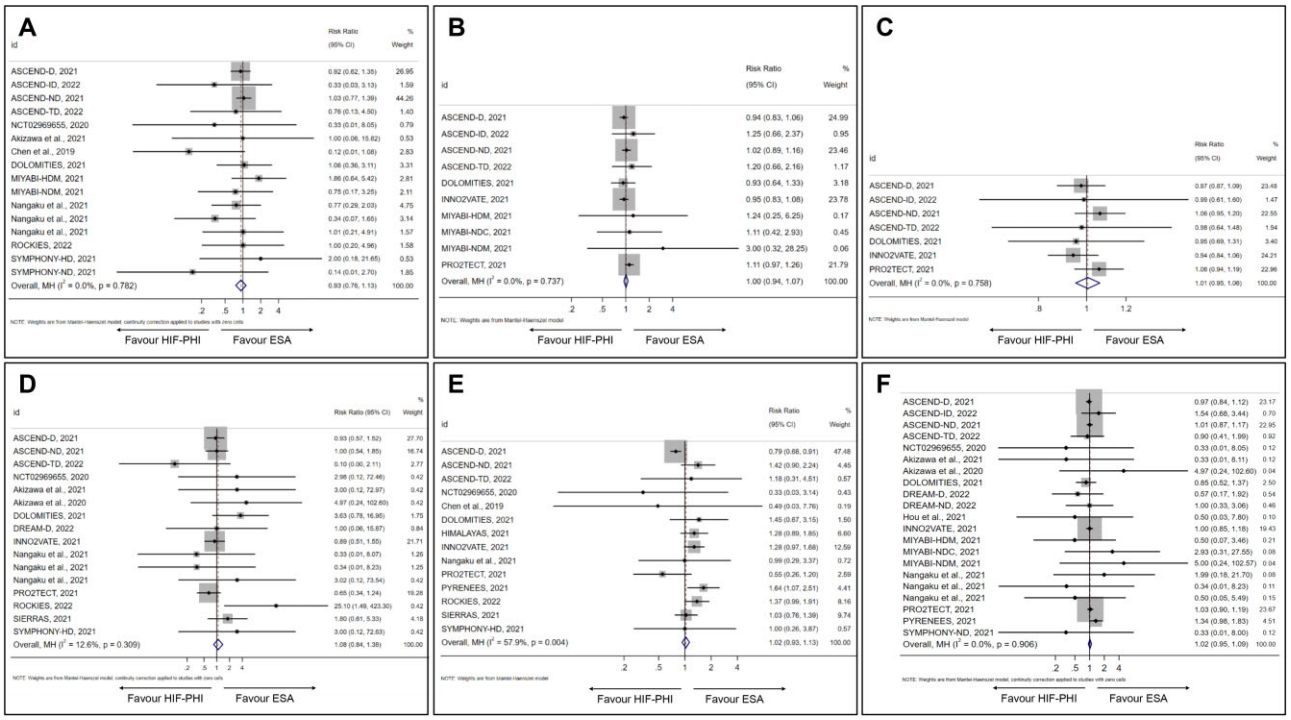


Figure 5: Random effect meta-analysis of rate ratio for cancer (**A**), MACE (**B**), MACE+ (**C**), deep venous thrombosis/pulmonary embolism (**D**), arteriovenous thrombosis (**E**) and all-cause death (**F**) between HIF stabilizers and ESA comparator.

0.94–1.08) as well as in MACE+ risk (10 studies) (1.00, 95% CI 0.94–1.07).

Thrombotic risk

Seventeen trials reported the number of deep vein thrombosis and pulmonary embolisms; we found no difference between the HIF-PHIs and ESA arms (Fig. 5D). Similarly, no significant difference in AVF thrombosis between HIF stabilizers and ESA comparator was disclosed in the 14 trials with available data (Fig. 5E). Moderate heterogeneity was found (I^2: 57.9; $P = .004$) but no significant moderators were disclosed.

Mortality risk

Twenty-two trials reported number of deaths in each arm (Fig. 5F). Random effect meta-analysis of rate ratio did not show a significant difference in death risk between HIF-PHIs and ESA comparator, and no heterogeneity was found. No difference in mortality risk was detected in the six studies reporting data as HR (Supplementary data, Fig. S3C).

DISCUSSION

In this meta-analysis, we provide evidence that HIF-PHIs are effective in correcting anaemia in comparison with ESA therapy with a significant impact on iron metabolism, and that no safety signals clearly emerge with new agents as compared with standard of care.

Change from baseline in Hb levels between HIF-PHIs and ESA is statistically significant ($P = .012$) though clinically not so pronounced (+0.10 g/dL) to substantiate a clear advantage of these drugs over ESA administration (Fig. 2A). Indeed, when considering achievement of Hb target in the two arms as an efficacy measure, no significant difference between HIF-PHIs and ESA became evident (Fig. 2B). The same held true when considering the probability of having Hb values either below or above the target range. It is interesting to note, however, that the efficacy of HIF-PHIs (in terms of Hb changes from baseline and Hb target achievement) at the doses selected for the comparisons is significant greater when compared with short-acting ESA, while no difference emerged when the comparator was a long-acting ESA (Table 2). The reason for this difference is not readily apparent. It cannot be explained by the predominant use of short-acting in dialysis population and long-acting in non-dialysis patients, as CKD stage (non-dialysis versus dialysis) did not play a significant role in explaining heterogeneity in Hb response ($P = .144$) or achieving Hb target ($P = .634$). We can hypothesize a lower efficacy of short-acting ESA when these drugs are used with a longer interval of administration; indeed, as previously reported, converting epoetin-β from thrice weekly to once a week induced a progressive decline in Hb, with Hb levels significantly lower in comparison with patients randomized to weekly darbepoetin [59]. However, we cannot formally test this hypothesis because such information was lacking in the majority of trials, in which epoetin dosing was left to the investigator's discretion [43–46, 49, 55]. In the two studies with available data on epoetin interval administration, the prescription of once a week epoetin was frequent and occurred in the majority of patients [51, 54]. The significant role of mean age on the change from baseline in Hb levels between HIF-PHIs and ESA comparator could be explained by a less effective erythropoietic response of bone marrow in older patients, as suggested by the higher rate of ESA resistance and the need for a higher ESA dose to reach the target as compared with younger patients [60–62]. Other factors, such as CKD setting, previous anaemia treatment and number of enrolled patients, did not affect the Hb difference between two strategies.

Interestingly, we found no difference in Hb change from baseline among different types of HIF-PHIs even though the response to roxadustat seemed more pronounced (Table 2). In terms of target achievement, we found a difference among different types of HIF-PHI, with desidustat more frequently associated with target achievement as compared with other agents (Table 2). This could be due to the fact that target assessment was planned earlier (16–24 weeks) in studies with desidustat [39, 55] as compared with studies evaluating other drugs (24–36 weeks or 28–52 weeks) [33–36, 38, 40–47, 49, 50, 53–58] rather than to the potency of the drug.

The evaluation of changes in iron parameters confirms that the significant reduction of hepcidin is a distinctive signature of the new drugs in comparison with standard of care. Interestingly, meta-regression demonstrated that hepcidin decline was not associated with Hb increase, indicating a predominant direct effect of HIF-PHI on hepcidin. Hepcidin decline allows a better intestinal iron absorption and mobilization of iron stores by improving ferroportin expression [6, 14, 16]. HIF-PHIs also stimulate the transcription of transferrin in order to transport iron to the bone marrow [14, 16]. In line with these mechanisms, we found that HIF-PHIs induced a significant increase in serum iron and TIBC and a significant reduction of ferritin levels (as demonstration of iron store mobilization) [6]. According to the beneficial effects of HIF-PHIs on iron metabolism, we found a significantly lower need for intravenous iron dose in comparison with ESA therapy that was more evident with roxadustat.

Reduction of LDL cholesterol (greater with roxadustat) has been considered an ancillary effect of this class of drugs with potentially cardioprotective effects (Supplementary data, Fig. S1A). However, our analysis evidences that the entity of LDL decline, albeit statistically significant, is of limited clinical relevance. Overall, a decline of about 11 mg/dL seems not large enough to have an impact on outcome, as suggested by the meta-analysis by Koskinas *et al*. showing that each 39 mg/dL reduction in LDL was associated with 19% relative decrease in major vascular events [63]. It is important to note, however, that HDL cholesterol levels also slightly declined with HIF-PHIs thus further limiting the cardioprotective impact of new drugs.

Some concerns have been raised on the safety profile of HIF-PHIs. It has been postulated that these drugs could theoretically be involved in tumorigenesis based on some experimental data showing an increased expression of HIF-1α and HIF-2α in neoplastic cells and a stimulation of vascular endothelial growth factor (VEGF) which plays a role in the growth and metastasis of some neoplasms. However, serum VEGF levels did not differ between HIF-PHIs and ESA in CKD patients [14, 16, 64]. Similarly, reassuring findings were provided by our meta-analysis in more than 24 000 non-dialysis patients and dialysis patients; indeed, we did not disclose any imbalance in the incidence of neoplasms between HIF-PHIs and comparator arms (Fig. 5A). The risk estimate of cancer was 7% lower in HIF-PHIs compared with ESA, but not significant and without heterogeneity, a finding in agreement with results of recent Cochrane meta-analysis that assessed cancer risk in only seven studies [18]. However, these results must be interpreted with caution because of the relatively short follow-up of trials. Furthermore, our finding only deals with the risk on the incidence of new cases of cancer and not the worsening of neoplastic disease, because history of cancer was an exclusion criterion common to all studies evaluated.

A further concern of HIF-PHIs treatment relates to the cardiovascular safety. We provided evidence that cardiovascular risk was not different between HIF-PHIs and ESA; the lack of risk is consistent when considering as outcomes MACE and MACE+ and when each outcome was assessed by either rate ratio or HR. No significant cardiovascular risk has been reported by three other recent meta-analyses focusing on the safety of HIF-PHIs [18–20]. Natale *et al*. reported the results for the risk of single components of MACE and MACE+ and they did not found any significant adverse effect of HIF-PHIs as compared with ESA for any endpoint [18]. Similar findings were reported by Takkavatakarn *et al*., including unpublished data also [20]. In another meta-analysis limited to non-dialysis CKD patients, the risk of cardiac disorders was evaluated in 20 studies with 14 561 individuals, including 11 placebo-controlled trials [19]. When considering RCTs with ESA as comparator (nine studies with 9470 participants), as in the present meta-analysis, the authors found no difference in the cardiovascular risk between the HIF-PHIs and ESA arms [19]. Therefore, based on our and previous findings, it is possible to exclude an evident cardiovascular safety signal in patients using HIF-PHIs. Additional safety outcomes analysed included thrombotic events and all-cause death. As found for cancer and cardiovascular risk, these outcomes did not differ in patients receiving HIF-PHIs or ESA. Similar findings have been reported in other meta-analyses but this is not surprising when considering that in phase 2 trials (included by others) occurrence of death is an uncommon event due to short follow-up. It is important to note that study durations were not sufficiently long to exclude with certainty an impact of new drugs on those adverse events requiring a long follow-up to occur (cancer, death and possibly cardiovascular events).

Drug regulatory agencies across the world have provided conflicting conclusions on approval of these drugs for clinical use. In Japan, almost all HIF-PHIs have been approved, while in the USA only daprodustat for dialysis patients has been authorized. In Europe, roxadustat has been approved for all CKD patients and vadadustat only for dialysis patients (daprodustat is currently under revision). Conclusions of the Food and Drug Administration and the European Medicines Agency are focused on a single drug and mainly derived from on-treatment analyses that are susceptible to biased estimates of risk because an on-treatment comparison is not protected by randomization [65, 66]. The present study and other meta-analyses reporting no safety issues with HIF-PHIs [18–24] cannot affect decisions of regulatory agencies on each single drug, but they may add fuel to the discussion. A large post-marketing surveillance is advocated to help clinicians to detect potential harm and to implement mitigation strategies [67].

In conclusion, this meta-analysis provides evidence that Hb change obtained with HIF-PHIs at the doses selected for the comparisons is slightly but significantly higher in comparison with standard therapy with ESA. The difference becomes more evident in younger patients and when the new drugs are compared with short-acting ESA. Overall, an improvement of iron metabolism becomes evident with HIF-PHIs as compared with ESA even though no substantial differences in anaemia correction emerge among the various HIF-PHIs. Finally, the present meta-analysis also demonstrates that the risk of major adverse events with HIF-PHIs is similar to that estimated with ESA therapy. Long-term surveillance from post-marketing data are, however, of fundamental importance to definitely confirm the lack of safety signals.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Research idea and study design: R.M., L.D.N.
Data acquisition: S.B., C.G., M.E.L.
Data analysis/interpretation: R.M., S.B., V.S.
Drafting the article or revising it: R.M., L.D.N., F.C.S., G.C.
Each author contributed important intellectual content during manuscript drafting or revision and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

R.M. has been a member of Advisory Boards for Amgen, Astellas and GSK, consulted for Bayer and GSK, and has been an invited speaker at meetings supported by Amgen, Astellas, Vifor Pharma and AstraZeneca. M.E.L.: none. V.S.: none. F.C.S. has been a member of Advisory Boards for Boehringer and Ely-Lilly, and has received fees for scientific consultation and/or lectures by Jansen, Roche Diagnostics, Novo Nordisk, Sanofi, MSD and AstraZeneca. S.B.: none. L.D.N. has received fees for scientific consultation and/or lectures by Amgen, Astellas, AstraZeneca, GSK, Mundibiopharma and Vifor Pharma. C.G.: none.

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