NEPHROLOGY - ORIGINAL PAPER



Hypoxia inducible factor-prolyl hydroxylase inhibitors in anemic patients with non-dialysis dependent chronic kidney disease: a meta-analysis of randomized clinical trials

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Abstract

Purpose Anemia persists as a challenge in chronic kidney disease (CKD) patients. Current therapies are the injectable erythropoietin stimulating agents (ESA). Concerns have been raised regarding ESA cardiovascular safety, therefore search for an alternative, convenient and safe therapy is underway. Hypoxia inducible factors-prolyl hydroxylase inhibitors (HIF-PHI) are oral agents with promising results. Numerous small studies reported favorable effects with lack of large, powered studies.

Methods We conducted a meta-analysis of randomized clinical trials to assess the efficacy and safety of HIF-PHI in nondialysis-dependent CKD patients. Primary outcome was hemoglobin (Hb) concentration post intervention. Secondary outcomes were all-cause mortality, MACE, and changes in iron metabolism (ferritin, hepcidin). We reported total and serious adverse effects. Data were pooled using a random effect model via RevMan 5.4 software.

Results We identified 7 trials comprising of 8228 patients (mean age 66.5 ± 13.2 years, 42% were females, 53% used iron replacement) with a mean follow-up of 52 weeks. Compared with the standard of care (ESA), HIF-PHI were non-inferior for treatment of anemia, with comparable effect on mortality and major adverse cardiovascular events. HIF-PHI showed no major safety concerns. Main side effect of HIF-PHI was diarrhea.

Conclusion HIF-PHI might represent a safe, and convenient alternative to ESA in non-dialysis dependent CKD patients with anemia.

Keywords Anemia · Chronic kidney disease · Erythropoietin · Transfusion

Introduction

Anemia remains a challenge in patients with chronic kidney disease (CKD) as it is associated with disease progression, decreased quality of life, and increase in all-cause mortality

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[1]. Proper management of anemia in these patients is important for overall survival. Currently, erythropoietin stimulating agents (ESAs) such as epoetin and darbepoetin alfa are among the only Food and Drug Administration (FDA) approved drugs for improving hemoglobin in anemic patients with CKD. Due to their increased adverse effects profile and associated high cardiovascular events, especially in patients with hemoglobin > 11 g/dl, the lowest dose sufficient to reduce the need for transfusion of packed red cells is recommended [2]. As a result, search for an alternative to ESA is underway. Oral hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) are promising therapies for the treatment of anemia in non-dialysis dependent chronic kidney disease (NDD CKD) patients. HIF-PHIs stimulate the production of endogenous erythropoietin through inhibition of the prolyl hydrolase enzymes and increase iron levels in these patients [3, 4]. Randomized controlled trials (RCTs) have evaluated the efficacy and safety

of several HIF-PHIs as an oral alternative to parenterally administered epoetin and its derivatives. More recent evidence accumulated suggesting promising results, with lack of large, powered studies. Hence, we conducted a systematic review and meta-analysis of RCTs to compare the efficacy and safety of HIF-PHIs versus ESAs regarding hemoglobin concentration, iron metabolism and adverse effects in anemic patients with NDD CKD.

Methods

Search strategy and eligibility criteria

We performed a comprehensive search of multiple electronic databases (PubMed/Medline, Embase, Cochrane, Google scholar), from inception till December/20/2021. We used the following pre-specified search terms (hypoxia-inducible factor-prolyl hydroxylase inhibitors) OR (HIF-PHI) AND (epoetin) OR (erythropoietin) OR (erythropoietin stimulating agent) AND (anemia) OR (low hemoglobin) AND (nondialysis renal disease) OR (non-dialysis kidney disease) OR (non-dialysis chronic kidney disease). Search was restricted to English language.

We included only RCTs with active comparator reported (ESA). Placebo-controlled trials and observational studies/ registries were excluded. CKD was defined as an estimated glomerular filtration rate (GFR) < 60 ml/min/1.73 m² or CKD stage \geq 3 per CKD Epidemiology Collaboration (CKD-EPI) formula.

Data extraction/quality assurance

Two investigators (MO, SS) screened the trials abstracts, and if suitable the full manuscript including supplement/ appendix and extracted pre-defined variables independently in a pre-designed excel sheet. Data included baseline demographics, intervention, duration of follow-up, clinical outcomes, among others. Quality of studies regarding methods of randomization, concealment of allocation, blinding, and incomplete data were assessed on categorical scale. Disagreement, if any, was resolved by consensus. Units for different variables were standardized using respective calculators and rounded to one decimal.

Outcomes

The primary outcome of interest was hemoglobin concentration (Hb) g/dl post intervention at the longest follow-up duration. Secondary outcomes included all-cause mortality, major adverse cardiovascular events (MACE) (defined as all-cause mortality, non-fatal myocardial infarctions (MI), and non-fatal stroke), and change in iron metabolism in the form change of ferritin and hepcidin. We also reported all, serious, and specific adverse effects (AE).

Statistical analysis

Effect estimates were extracted from each study in the form of events or means depending on variable type, directly from the article or calculated indirectly based on the available data from the text. Correspondent authors of respective studies were contacted via email if there was a missing data. We calculated risks ratios (RRs) and weighted mean differences (MDs) with their corresponding 95% confidence intervals (CIs) for dichotomous and continuous data, respectively. Heterogeneity between studies was explored by Cochran Q statistic (P < 0.05) and *I*-squared (I^2) statistic. All statistical tests were two-sided, and *P* values ≤ 0.05 were considered significant. All analyses were conducted via RevMan 5.4 software using a random-effects model.

Results

We identified 7 RCTs reported in 6 articles [5-10] with a total of 8228 patients (HIF-PHI=4185, ESA=4043), with a mean age of 66.5 ± 13.2 years, 42% were females and a median follow-up of 52 weeks. Patients with diabetes and hypertension represented 41% and 59%, respectively. The mean Hb and estimated GFR for both groups (HIF-PHI) and (ESA) were 9.8 \pm 1.0 g/dl and 20.3 \pm 11.5 ml/min/1.73 m², respectively.

Patients receiving iron replacement represented 53%.

Regarding Hb concentration post intervention, our analysis showed that HIF-PHI and ESA were not statistically different [MD - 0.03, 95% CI (- 0.18, 0.11); P = 0.66] (Fig. 1).

Our analysis also showed no statistical difference between groups regarding all-cause mortality [RR 1.02, 95% CI (0.92, 1.13); P = 0.71] and MACE [RR 1.08; 95% CI (0.99, 1.18); P = 0.08] (Fig. 2).

Regarding iron metabolism, HIF-PHIs showed a significant reduction of ferritin (μ g/L) and hepcidin (ng/ml) compared to the ESA group [MD – 18.89, 95% CI (– 29.08, – 8.69); *P* < 0.001] and [MD – 28.21, 95% CI (– 40.73, – 15.68); *P* < 0.001], respectively (Fig. 3).

In term of adverse effects (AE) (total AE, serious AE, hypertension, hyperkalemia), we found no statistical difference between HIF-PHI and ESA groups [RR 1.01, 95% CI (0.99, 1.04); P = 0.28], [RR 1.04, 95% CI (0.94, 1.15); P = 0.41], [RR 0.88, 95% CI (0.75, 1.04); P = 0.13], [RR 0.88, 95% CI (0.68, 1.15); P = 0.35], respectively, except diarrhea, which was reported more in the HIF-PHI group compared to ESA, [RR 1.45, 95% CI (1.21, 1.73); P < 0.01], (Fig. 4).

									LON			mean birer enee	moun pinor circo
me; Hemoglobin (Hb) con-	Study or Subgroup			Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
intration g/ut post intervention	ASCE	ND-ND 2	021		10.64	0.9	1937	10.46	0.9	1935	17.8%	0.18 [0.12, 0.24]	+
	Cher	tow et al (E	SA treated) 2	021	10.83	0.9	862	10.84	0.9	863	17.2%	-0.01 [-0.09, 0.07]	+
	Cher	tow et al (E	SA untreated	0 2021	10.62	0.8	879	10.58	0.8	872	17.4%	0.04 (-0.03, 0.11)	+-
	Hold	stock et al	2019	,	10.2	0.77	156	10.7	0.67	70	13.8%	-0.50 (-0.69 -0.31)	
	Mach	ounall /DL		010	11.2	0.11	02	11.1	0.01	22	10.0%	0.20 [0.00, 0.01]	
	Matu	ouyan (Di	NEUUUUE 2) 2	015	11.0	1.0405	400	44.0	1.0504	400	40.00	0.20 [-0.00, 0.40]	
	Nang	ivarigaku et al (Dap) 2021					108	11.9	1.0534	109	10.8%	0.10 [-0.18, 0.38]	
	Nang	Nangaku et al (Vad) 2021					151	11.93	1.0643	153	12.2%	-0.27 [-0.51, -0.03]	
	Total	(95% CI)				4185			4043	100.0%	-0.03 [-0.18, 0.11]	•	
	Hotor	$U_{2} = 0.00 + 0.00 + 0.00 + 0.00 + 0.0000 + 0.0000 + 0.000 + 0.000 + 0.000 + 0.000 + 0.000 $											
	Telei	ogeneny.	rau = 0.03, 0	/III = 01.4	10, u1 = 0 (F < 0.00001), 1 = 30%								-1 -0.5 0 0.5 1
	lest	rest for overall effect. Z = 0.44 (P = 0.86)											HIF-PHI effect ESA effect
	HIF-P	HI	ES/	1				Risk	Ratio				Risk Ratio
Study or Subgroup	Events	Total	Events	Total	We	ight	M-H,	Ran	dom, 9	95%	CI	M-F	I, Random, 95% Cl
1.2.1 All cause mortality													
ASCEND-ND 2021	301	1937	298	1935	47	.8%		1.01	[0.87	, 1.1	7]		- + -
Chertow et al (PRO2TECT) 2021	319	1739	307	1732	51	.5%		1.03	3 [0.90	, 1.1	9]		
Holdstock et al 2019	4	170	1	80	0	.2%		1.88	[0.21,	16.5	7] —		
Macdougall (DIALOGUE 2) 2019	1	92	1	32	0	.1%		0.35	5 [0.02	, 5.4	o] ←	•	
Nangaku et al (Dap) 2021	1	149	2	150	0	.2%		0.50	0 [0.05	, 5.4	9] 🕂		
Nangaku et al (Vad) 2021 Subtotal (95% CI)	0	151 4238	1	153 4082	0 100	.1% . 0 %		0.34 1.02	[0.01 [0.92	, 8.2	3] ← 3]		•
Total events	626		610										
Heterogeneity: Tau ² = 0.00; Chi ² =	1.75, df=	5 (P = (0.88); I² =	0%									
Test for overall effect: Z = 0.38 (P =	0.71)												
1.2.2 MACE													
ASCEND-ND 2021	464	1937	441	1935	55	.9%		1.05	5 [0.94	, 1.1	8]		+

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ECA

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Discussion

Chertow et al (PRO2TECT) 2021

Test for overall effect: Z = 1.76 (P = 0.08)

Holdstock et al 2019

Subtotal (95% CI)

Total events

Nangaku et al (Dap) 2021

Our meta-analysis showed that HIF-PHIs are non-inferior compared to ESA, the current standard of care for treatment of anemia in non-dialysis dependent CKD patients. There were no significant differences between groups in terms of Hb concentration post intervention, all-cause mortality, or MACE. However, HIF-PHIs were associated significant iron metabolism changes in term of lower ferritin, hepcidin. HIF-PHI were also significantly associated with more diarrhea compared with ESAs.

382 1739

860

Heterogeneity: Tau² = 0.00; Chi² = 1.78, df = 3 (P = 0.62); I² = 0%

5 170

9 151

3997

Fig. 2 Safety outcomes; all-cause mortality and major adverse cardiovascular events (MACE)

344 1732

791

1

5 153

80

3900

43.3%

0.2%

0.6%

100.0%

1.11 [0.97, 1.26]

1.82 [0.63, 5.32]

1.08 [0.99, 1.18]

0.2

2.35 [0.28, 19.81]

HIF-PHIs as an oral agent are a more attractive and appealing option. This favorable pharmacokinetic property might reduce the need for further outpatient visits required with epoetin/darbepoetin which are given subcutaneously

or intravenously. We believe that convenience of administration is vital for patients' satisfaction and compliance.

0.5

HIF-PHI ESA effect

Our findings of reduction in ferritin and hepcidin emphasize the role of HIF-PHIs in iron metabolism. HIF-PHI might lead to excessive iron consumption, as reduced levels of hepcidin, might indicate increase in iron absorption and/ or utilization, which in turn might necessitate increase in iron supplementation in NDD CKD patients. [11, 12] As the long-term effect of this change in iron metabolism is not yet clear, more studies are needed and awaited.

Our analysis is consistent with current literature. Chen and his colleagues conducted a similar meta-analysis of > 13,000 patients ^[12]. They studied effect of HIF-PHI in comparison to both active intervention (ESA) and placebo, and they included both dialysis dependent and non-dialysis dependent CKD patients. They reported increase Hb level

Moon Difference

5

		HIF-PHI			ESA			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.4.1 change in Ferritin									
ASCEND-ND 2021	-27	216	1937	-13	206.2	1933	58.7%	-14.00 [-27.31, -0.69]	
Holdstock et al 2019	-37.9	118	138	-10.6	71.2	66	15.2%	-27.30 [-53.43, -1.17]	
Macdougall (DIALOGUE 2) 2019	-15	114	92	-11	102	32	5.8%	-4.00 [-46.33, 38.33]	
Nangaku et al (Dap) 2021	-53	89	108	-22	81	109	20.3%	-31.00 [-53.65, -8.35]	
Subtotal (95% CI)			2275			2140	100.0%	-18.89 [-29.08, -8.69]	-
Heterogeneity: Tau ² = 0.00; Chi ² =	2.49, df	= 3 (P = 0.	48); l² =	:0%					
Test for overall effect: Z = 3.63 (P =	0.0003)	E.							
1.4.2 change in Hepcidin ASCEND-ND 2021 Holdstock et al 2019 Macdougall (DIALOGUE 2) 2019 Nangaku et al (Dap) 2021 Subtotal (95% CI)	-22.9 -17.3 -8 -28	77.3 47.7635 27.8 75	1937 136 92 108 2273	14.8 -4.9 15 11	80.6 53.2442 28.5 83	1933 64 32 109 2138	32.8% 22.8% 26.9% 17.5% 100.0 %	-37.70 [-42.68, -32.72] -12.40 [-27.72, 2.92] -23.00 [-34.39, -11.61] -39.00 [-60.04, -17.96] - 28.21 [-40.73, -15.68]	
Heterogeneity: Tau ² = 118.14; Chi ² Test for overall effect: Z = 4.41 (P <	= 13.54 0.0001)	, df = 3 (P	= 0.004	l); ² = 70	8%				
									-50 -25 0 25 50 HIF-PHI effect ESA effect

Fig. 3 Iron metabolism, change between baseline and end of treatment **a** Ferritin (µg/L), **b** Hepcidin (ng/ml)

						Disk Datis	Diele Detie
Sturby or Subgroup	HIF-P	Total	Esp	Total	Moight	Risk Ratio	Risk Ratio
1.5.1 Total adverse effect	Events	Total	Lvents	Total	weight	M-H, Random, 55% Cr	M-H, Kandolli, 55% Cl
ASCEND-ND 2021	1545	1937	1487	1933	25 5%	1 04 (1 00 1 07)	
Chertow et al (ESA treated) 2021	767	861	756	862	24.8%	1.02 (0.98, 1.05)	↓
Chertow et al (ESA untreated) 2021	798	878	797	870	28.7%	0.99 (0.96, 1.02)	-
Holdstock et al 2019	119	170	54	80	1.8%	1.04 [0.87, 1.24]	
Macdougall (DIALOGUE 2) 2019	67	92	17	32	0.5%	1.37 [0.97, 1.94]	
Nangaku et al (Dap) 2021	137	149	134	150	9.1%	1.03 [0.96, 1.11]	+
Nangaku et al (Vad) 2021	136	151	141	153	9.7%	0.98 [0.91, 1.05]	
Subtotal (95% CI)		4238		4080	100.0%	1.01 [0.99, 1.04]	•
Total events	3569		3386				
Heterogeneity: Tau ² = 0.00; Chi ² = 9.0	7, $df = 6$ (P = 0.1	7); I ² = 34	\$			
Test for overall effect: $Z = 1.08$ (P = 0.3)	28)						
1 E 2 Sorious advorse offect							
1.5.2 Serious adverse effect	0.50	1007	700	1000	07.00	1 01 /1 10 1 00	
ASCEND-ND 2021	850	1937	703	1933	27.8%	1.21 [1.12, 1.30]	
Chertow et al (ESA treated) 2021	504	861	488	862	27.4%	1.03 [0.95, 1.12]	T
Chertow et al (ESA untreated) 2021	573	170	561	870	28.9%	1.01 [0.94, 1.08]	
Masdougall (DIALOGUE 2) 2019	10	02	6	32	1 4 %	1 10 [0 49 2 61]	
Nangaku et al (Dan) 2021	34	149	44	150	5 5 96	0.78 [0.53, 1.14]	
Nangaku et al (Jad) 2021	42	151	49	153	6.6%	0.87 [0.61 1 23]	
Subtotal (95% CI)	42	4238	45	4080	100.0%	1.04 [0.94, 1.15]	•
Total events	2048		1864				
Heterogeneity: Tau ² = 0.01; Chi ² = 16.	93, df = 6	(P = 0.	010); I ² =	65%			
Test for overall effect: Z = 0.82 (P = 0.4	41)						
1.5.3 Hypertension							
ASCEND-ND 2021	344	1937	363	1933	38.9%	0.95 [0.83, 1.08]	
Chertow et al (ESA treated) 2021	124	861	128	862	25.5%	0.97 [0.77, 1.22]	
Chertow et al (ESA untreated) 2021	155	878	192	870	30.4%	0.80 [0.66, 0.97]	
Macdougall (DIALOGUE 2) 2019	14	92	4	32	2.3%	1.22 [0.43, 3.43]	
Nangaku et al (Dap) 2021	4	149	8	150	1.8%	0.50 [0.15, 1.64]	
Nangaku et al (Vad) 2021 Subtotal (95% CI)	2	151	11	153	1.1%	0.18 [0.04, 0.82]	
Total events	643	4008	706	4000	100.0%	0.88 [0.75, 1.04]	
Heterogeneity: Tau ² = 0.01: Chi ² = 8.0	5 df = 5 (P = 0.1	5) I ² = 38	296			
Test for overall effect: $Z = 1.53$ (P = 0.1	13)	- 0.1	57.1 - 50				
	,						
1.5.4 Hyperkalemia							
Chertow et al (ESA treated) 2021	81	861	85	862	40.9%	0.95 [0.71, 1.27]	
Chertow et al (ESA untreated) 2021	108	878	136	870	49.3%	0.79 [0.62, 0.99]	
Nangaku et al (Dap) 2021	12	149	8	150	8.3%	1.51 [0.64, 3.59]	
Nangaku et al (Vad) 2021	1	151	5	153	1.5%	0.20 [0.02, 1.71]	•
Subtotal (95% CI)		2039		2035	100.0%	0.88 [0.68, 1.15]	
Total events	202		234				
Heterogeneity: Tau [*] = 0.02; Chi [*] = 4.4	3, df = 3 (P = 0.2	2); $I^{*} = 32$	2%			
rest for overall effect: $z = 0.94$ (P = 0.3	35)						
1.5.5 Diarrhea							
Chertow et al (ESA treated) 2021	119	861	76	862	42.1%	1.57 [1.19.2.06]	
Chertow et al (ESA untreated) 2021	122	878	87	870	46.6%	1.39 [1.07, 1.80]	
Holdstock et al 2019	10	170	6	80	3.3%	0.78 (0.30, 2.08)	• • • • • • • • • • • • • • • • • • • •
Macdougall (DIALOGUE 2) 2019	5	92	1	32	0.7%	1.74 [0.21, 14.33]	• • • • •
Nangaku et al (Dap) 2021	5	149	7	150	2.5%	0.72 [0.23, 2.21]	•
Nangaku et al (Vad) 2021	18	151	8	153	4.8%	2.28 [1.02, 5.08]	→
Subtotal (95% CI)		2301		2147	100.0%	1.45 [1.21, 1.73]	-
Total events	279		185				
Heterogeneity: Tau ² = 0.00; Chi ² = 4.6	9, df = 5 (P = 0.4	6); I ² = 09	X6			
Test for overall effect: $Z = 4.11$ (P < 0.0	0001)						
							0.5 0.7 1 1.5 2
							ESA effect HIF PHI effect

Fig. 4 Adverse effects, a Total AE, b Serious AE, c Hypertension, d Hyperkalemia and e Diarrhea

and iron utilization with good long-term tolerability. In contrast, we included only non-dialysis dependent CKD patients, and active comparison (ESA) arm to maintain homogeneity, but our findings are similar in terms of Hb level, iron utilization, and safety measured as MACE.

Adverse effects analysis was consistent with literature. Gastrointestinal upset is commonly reported in HIF-PHI due to altered epithelial cell metabolism but is usually mild to moderate. We did not find any major safety concerns, which should be reassuring for both potential patients and providers.

Our meta-analysis is the first to report head-to-head comparison with the current standard of care for anemia in NDD-CKD. The major limitations of our analysis are heterogeneity and relatively short follow-up duration. Further large RCTs with long-term follow-up are needed.

In conclusion, among patients with anemia and NDD CKD, HIF-PHIs are non-inferior to ESAs for treatment of anemia. MACEs were also similar between the two groups. HIF-PHIs are associated with reduced iron metabolism, and more diarrheal episodes.

Author contributions Research idea and study design: SS; MM: data acquisition; MO, MM, SS: data analysis/interpretation; MM, AO, MO: editing and review; AO, BK, CN: supervision or mentorship; BK, CN. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated, and resolved, including with documentation in the literature if appropriate.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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