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Variability, Severity, Preventability, and Outcomes of Adverse Drug Reactions to HIF-PHIs in CKD Case Reports: A Systematic Review

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ABSTRACT

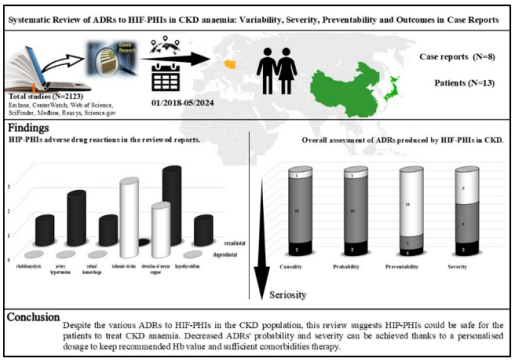
Background: Underdiagnosed and undertreated renal anaemia remains an issue among individuals with chronic kidney disease (CKD). Hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs) offer significant options. However, there are unmapped areas regarding adverse drug reactions (ADRs) to HIF-PHIs. Thus, this systematic review aims to find ADRs to HIF-PHIs and analyse their variability, severity, preventability, and outcomes in individual CKD patients reported as case reports.

Methods: A literature search of published case reports was conducted between 2018 and 2024 across various electronic sources. Of the total identified studies (N=2123), only 8 case reports (13 patients) were included after applying inclusion and exclusion criteria.

Results: ADRs to roxadustat (8/13;61.5%) and daprodustat (5/13;38.5%) included retinal haemorrhage (7.7%), hypertension (15.4%), stroke (23.1%), hypothyroidism (7.7%), rhabdomyolysis (7.7%), and elevation of serum copper (38.4%). The mean ADRs time-to-onset was 6.5 months. Specific causality and non-preventability of ADRs to HIF-PHIs were confirmed in one report (1/8;12.5%), and definite probability and severity in two reports (2/8;25%) due to HIF-PHIs ADRs.

Conclusion: This review suggests HIF-PHIs could be safe for patients to treat CKD anaemia. Thanks to personalised dosages that maintain the recommended Hb value and sufficient management of comorbidities, the probability and severity of ADRs could be decreased.

Graphical Abstract



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Keywords: Adverse Drug Reaction, Case Reports, CKD Anaemia, HIF-PHI, Systematic Review

Introduction

Chronic kidney disease (CKD) is a significant global health issue and one of the leading non-communicable deaths, affecting up to 15% of the world's population, with prevalence rates expected to increase [1-3]. CKD often leads to anaemia due to reduced erythropoietin (EPO) production in the kidneys, affecting up to 90% of end-stage kidney disease (ESKD) patient [4-7]. Over the past three decades, therapies for renal anaemia have improved, leading to decreased morbidity and hospitalisation risks. While erythropoiesis-stimulating agents (ESAs) and iron supplements have traditionally managed CKD anaemia, long-term ESA use carries increased cardiovascular risks and can be ineffective due to chronic inflammation [8].

In 2019, Kaelin, Ratcliffe, and Semenza were awarded the Nobel Prize for discovering hypoxia-inducible factor (HIF) proteins, which body's response to hypoxia by promoting gene expression in erythropoiesis and iron metabolism [9-11]. Under normal conditions, HIF proteins are inactivated by prolyl hydroxylase domain (PHD) enzymes, targeting HIF proteins for degradation [8]. However, in hypoxic conditions, PHD activity is downregulated, leading to stabilised high levels of HIF proteins [8]. HIF proteins stimulate producing EPO and other genes, including iron absorption, recycling, and transportation [8].

Hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs), like roxadustat, daprodustat, and vadadustat, mimic hypoxia, boosting EPO levels and iron metabolism [8]. Clinical trials (CTs) have shown HIF-PHIs are non-inferior to ESAs in maintaining CKD patients' haemoglobin (Hb) levels [8]. Because of HIF's pleiotropic functions, HIF pharmacologic activation in CKD anaemia is likely to have effects beyond erythropoiesis and iron metabolism, depending on drug's pharmacokinetics and pharmacodynamics, including administration, dosing and exposure [8-12].

Despite their efficacy and safety compared to ESAs, HIF-PHIs have been associated with adverse drug reactions (ADRs), including thromboembolic events, artery and pulmonary hypertension, pro-tumorigenic effects, worsening heart failure, and retinopathy [13-20]. Roxadustat, in particular, has been linked to increased risk of hypothyroidism, ADR not observed with daprodustat [21,22]. To what extent non-erythropoietic signalling pathways are activated in patients receiving HIF-PHIs is challenging to predict.

Thus, their safety profiles require careful ongoing research and post-marketing surveillance to ensure patient safety and long-term impact. Despite ADRs concerns, roxadustat was the first HIF-PHI approved in China (2018), followed by Japan (2019), the European Union (2021), and the USA (2022) [23-27]. This introduction has provided a novelty to manage CKD anaemia, particularly for patients not responding well to ESAs [28-32]. However, HIF-PHIs' benefits must be weighed against potential cardiovascular and thrombotic risks, with individual patient factors considered when selecting treatment regimens.

Surprisingly, no systematic reviews of case reports have identified ADRs for up to six years of HIF-PHI use. Thus, this systematic review aims to find ADRs on HIF-PHIs and analyse their variability, causality, preventability, probability, severity, and outcomes in individual CKD patients reported as case reports.

Methods

This systematic review was not pre-registered and was conducted following the guidelines laid out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33,34]. (The PRISMA Checklist 2020 for abstract and manuscript is provided in supplemental table ST1 at the end of this systematic review).

Study Selection and Database Search

We conducted a literature search for published case reports between January 2018 and May 2024 following the first 2018 approval in China [23-27]. The search included databases such as CenterWatch, Clarivate/Web of Science, Embase, PubMed/Medline, Reaxys, Science.gov, and SciFinder to identify ADR reports on HIF-PHIs. Additional searches were performed on Google Scholar, ResearchGate, and SpringerLink. Medical Subject Headings (MeSH) terms used included "adverse event," "Hypoxia-inducible factor prolyl hydroxylase inhibitor", "HIF-PHIs", "roxadustat", "molidustat", "vadadustat", "desidustat", "dialysis", "case study" ,"CKD" and "ADRs." The comprehensive search methodology is detailed in the supplementary ST2 table at the end of this review.

This review analysed ADRs documented in case reports and case series, which provide detailed clinical information about individual patients, aiding in understanding ADRs. Case reports include single patient cases with medical history, symptoms, diagnosis, treatment, and follow-up, highlighting new and unexpected ADRs and contributing to drug safety knowledge [35-39]. Case series include collections of similar individual case reports, documenting multiple patients treated under similar conditions [40]. Case series document multiple patients treated under similar conditions, but the term lacks a precise definition. According to Abu-Zidan et al (2012), case series should include at least four patients, while reports with four or fewer patients should be classified as case reports [40,41]. Thus, our final selected studies, with a maximum of four patients, were classified as case reports [42].

Eligibility Criteria

Studies were required to meet the following inclusion criteria: (a) published in English only; (b) must be only case reports on adults; (c) study population being only CKD patients with anaemia undergoing regular CKD treatment on HIF-PHIs medication and (d) case reports documenting ADRs linked explicitly to the HIF-PHIs in CKD.

Studies were excluded if they did not meet the inclusion criteria and/or met any of the following: (a) did not have an abstract and/or full text in English; (b) conference abstracts, thesis, comments, letters, abstracts, editorials, randomised controlled trials, experimental research, observational studies or grey literature; (c) narrative/systematic reviews and/or meta-analyses; (d) articles on any different pathology treatment and/or medications; (e) were carried out on not CKD patients and/or other consumers; (f) did not focus on the ADRs. Detailed information can be found in Figure 1. (Figure 1).

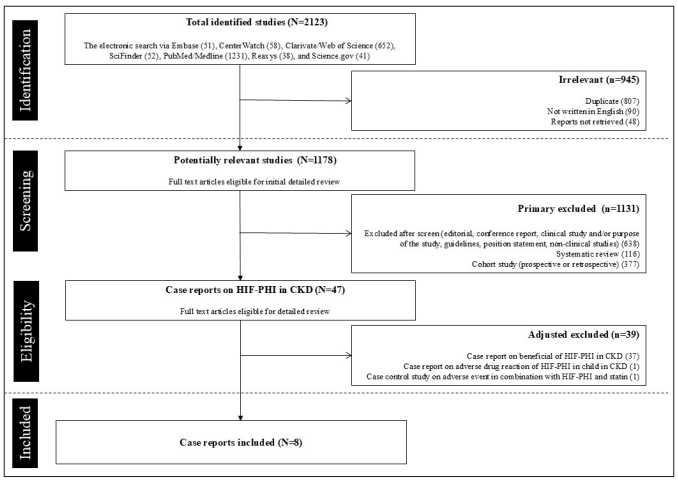

Figure 1

Study Selection

Selected papers were downloaded and stored in Rayyan. This platform offers marking papers for inclusion or exclusion, supplying reasons for these decisions and a 'maybe' option for further analysis and consideration. The initial screening examined the titles and abstracts of all case reports obtained after searching the selected databases. Each obtained article was screened

independently and then subjected to further full-text analysis to determine its appropriateness based on the study inclusion criteria. This analysis was also completed independently. The data extracted from selected studies were entered and screened using Microsoft Excel.

Data Extraction and Quality Assessment

We evaluated the selected studies and extracted key information: author name, country, publication year, age, gender, CKD details, haemoglobin level at the start, type of HIF-PHI, ADR, predisposing diagnoses, severity (hospitalisation needed or not), and outcome (recovered, not yet recovered, recovered with sequelae, fatal, unknown). We also noted the number of patients, all reported ADRs, dechallenge, and rechallenge. "Challenge" refers to drug administration during an adverse event (AE) or treatment [43,44]. "Dechallenge" involves stopping the drug to see if the AE diminishes or disappears, while "rechallenge" means restarting the therapy to confirm ADR causality. We used these terms to evaluate ADR causality: a positive dechallenge if the ADR disappeared, a positive rechallenge if the ADR reappeared [45,46].

We used World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale, Naranjo's ADR questionnaires, Schumock and Thornton Assessment, and Hartwig and Siegel's scale to assess ADR causality, probability, preventability, and severity [47-51]. The Newcastle-Ottawa Scale (NOS) and the Methodological Index for Non-Randomised Studies (MINORS) were employed to address biases in case studies [52,53]. MINORS includes twelve items, with eight for non-comparative studies and all twelve for comparative studies, scoring each item from 0-2, and a total score out of 16 was used for quality evaluation. Scores of 14-16 indicated high quality, 10-13 modest quality, and less than 9 low quality [52]. NOS assessed selection, comparability, and outcome/exposure, with a maximum score of nine stars, categorising studies as high quality (7-9 stars), moderate quality (4-6 stars), and low quality (less than 3 stars) [54].

We also used the Murad tool and Oxford criteria to enhance quality assessment rigour [55,56]. The Murad tool evaluated case reports using four domains: selection, ascertainment, causality, and reporting, scoring each from 0-1, with a total score of 8. Scores of 6-8 indicated high quality, 4-5 moderate quality, and less than 3 low quality. The Oxford criteria graded case series as level 4 and case reports as level 5 evidence [55,56].

This review did not use the Cochrane Collaboration tool, as it is specific to randomised controlled trials. We also did not use funnel plots or tests for funnel plot asymmetry due to the small number of studies (eight), as these methods are unreliable with fewer than ten studies and complicated by heterogeneity and variability in case study methodologies [18,57-59].

Involvement of Patients

Patients were not involved in the formulation of the review question or results evaluation. No patients were contacted for input on the interpretation or writing up of the data. The outcomes will not be shared with research participants or the relevant patient group. All studies included into analyses were in accordance with the inclusion criteria and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards in the informed consents for clinical trials included into this review. In line with that, ethics approval was not required. Therefore, Human Ethics and Consent to Participate declarations, and the name of the Approval Committee are not applicable.

Statistical and Quantitative Analysis

Descriptive statistical analysis was performed using GraphPad Prism version 10. Mean was used to express continuous values, whereas frequency and percentage were used to express categorical variables. Our study's inclusion criteria focused exclusively on case reports. As a result, we did not conduct a meta-analysis because of insufficient available data.

Results

Level of Evidence and Methodological Quality Assessment

The high quality of the reviewed and selected case reports is evidenced by the MINORS and NOS assessments, with detailed information provided in Tables 1 and 2 (Table 1, Table 2). The level of evidence was evaluated according to the Oxford Criteria 2011, offering a comprehensive framework for assessing evidence levels [55,56]. The Murad tool was also used to synthesise the reviewed cases [55,56]. Both assessments are shown in Table 3, which details the methodological quality assessment scale (Table 3).

Table 1: Minors Quality Assessment

Author name (Year)	Aims clearly stated	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate	Unbiased assessment of study endpoint	Follow-up period appropriate	Loss to follow-up<5%	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence	Adequate statistical analyses	Total score	Quality of the study
Ariyoshi et al. (2024)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High
Cygulska et al. (2019)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High
Nakamura et al. (2022)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High
Nakamura et al. (2023)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High
Uchio et al. (2024)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High
Yamashita et al. (2024)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High
Yang & Wang (2020)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High
Yu et al. (2020)	2	2	1	2	1	2	2	0	N/A	N/A	N/A	2	14	High

Table 2: NOS Quality Assessment

Author name (Year)	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome absent at start	Comparability of cohorts	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	Total score	Quality of the study
Ariyoshi et al. (2024)	★	★	★	★	★★	★	★	★	9	High
Cygulska et al. (2019)	★	★	★	★	★★	★	★	★	9	High
Nakamura et al. (2022)	★	★	★	★	★★	★	★	★	9	High
Nakamura et al. (2023)	★	★	★	★	★★	★	★	★	9	High
Uchio et al. (2024)	★	★	★	★	★★	★	★	★	9	High
Yamashita et al. (2024)	★	★	★	★	★★	★	★	★	9	High
Yang & Wang (2020)	★	★	★	★	★★	★	★	★	9	High
Yu et al. (2020)	★	★	★	★	★★	★	★	★	9	High

Table 3: Methodological Quality Assessment Scale

Author name (Year)	Level of evidence	Methodological quality assessment scale								Total score	Quality of the study
		Selection	Ascertainment		Causality			Reporting			
	Case reports (5)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8		
Ariyoshi et al. (2024)	5	1	1	1	0	1	0	1	1	6	High
Cygulska et al. (2019)	5	1	1	1	0	1	0	1	1	6	High
Nakamura et al. (2022)	5	1	1	1	1	1	0	1	1	7	High
Nakamura et al. (2023)	5	1	1	1	1	1	0	1	1	7	High
Uchio et al. (2024)	5	1	1	1	1	1	0	1	1	7	High
Yamashita et al. (2024)	5	1	1	1	1	1	0	1	1	7	High
Yang & Wang (2020)	5	1	1	1	1	0	1	1	1	7	High
Yu et al. (2020)	5	1	1	1	1	1	1	1	1	8	High

Abbreviations: A – anaemia in CKD, CKD – chronic kidney disease, D – dialysis, DD – dialysis dependent, G – grade, HD – haemodialysis, KTx – kidney transplantation, NA – not applicable, NDD – non-dialysis dependent, No – number, PD – peritoneal dialysis, RRT – renal replacement therapy

Characteristics of Study Reports and Patients

A total of eight case reports involving thirteen patients who experienced ADRs induced by HIF-PHIs were identified [42-67]. Among these patients, 10 (76.9%) were males, with a mean age of 67.8 years (ranging 32-85 years). ADRs were reported in Japan (5 reports, 10 patients, 62.5% of reports, 76.9% of patients), China (2 reports, 2 patients, 25% of reports, 15.4% of patients), and Poland (1 report, 1 patient, 12.5% of reports, 7.7% of patients; ADR during CT phase III: ID NCT02174627). Figure 2 shows CKD anaemia prevalence according to the literature sources linked to the CKD stages in the reviewed case reports [56-73]. Among these patients, 8 (61.6%) were undergoing dialysis, and 4 (30.8%) were in CKD advanced stages (Figure 2).

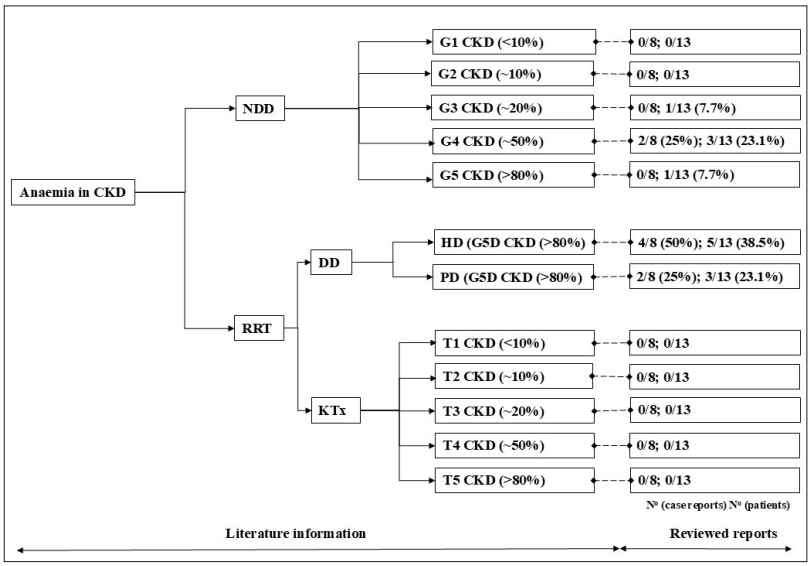

Figure 2

Table 4 provides detailed characteristics of the included case reports, organised based on the drug. It includes information about the study author, year of publication, country, age, gender, CKD grade, HIF-PHI used, ADR and its onset, Hb values during the transition to HIF-PHI, discontinuation and resumption of HIF-PHI, predisposing diagnoses, dechallenge, rechallenge, severity, and outcomes. Notably, 5 out of 13 patients (38.5%) had missing Hb values during the transition to HIF-PHI. The minimum Hb value at transition was 6g/dL, and the maximum was 11.3g/dL, with a mean of 8.9g/dL (Table 4).

Table 4: Characteristics of the Reviewed Study Reports

Author (Country, Year)	Age Gender	CKD	T0 Hb-value (g/dL)	HIF-PHI	HIF-PHI dose and its change over time (mg)	T1 Hb-value (g/dL)	ADR onset (months)	ADR	Diagnosis predisposition	Severity	Dechallenge	Switched drug	Rechallenge	T2 Hb-value (g/dL)	Outcome
Ariyoshi et al. (Japan, 2024)	32M	HD	-	roxadustat	120 TIW	-	1.9	retinal haemorrhage	diabetes-related retinopathy artery hypertension	yes	partial positive	ESA	NA	-	recovered with sequelae
Cygulska et al. (Poland, 2019)*	74F	G4	-	roxadustat	-	10.6	24.0	pulmonary hypertension	artery hypertension heart failure	yes	complete positive	ESA	NA	-	recovered with sequelae
Nakamura et al. (Japan, 2022)	79M	HD	8.5	roxadustat	100 TIW	9.0	2.2	elevation of serum copper	none	no	complete positive	ESA	NA	-	recovered
	67M	PD	10.7	roxadustat	70 TIW	12.1	6.0	elevation of serum copper	none	no	complete positive	daprodustat ESA	NA	-	recovered
	80M	G5	8.8	daprodustat	4 QD	12.6	12.0	elevation of serum copper	None	no	complete positive	ESA	NA	-	recovered
	66M	HD	9.2	daprodustat	2 QD	10.9	1.2	elevation of serum copper	none	no	complete positiv	ESA	NA	-	recovered
Nakamura et al. (Japan, 2023)	80F	PD	9.1	roxadustat	100 TIW	10.0	0.25	elevation of serum copper	none	yes	complete positive	mis	NA	-	recovered
Uchio et al. (Japan, 2024)	79M	G3b	-	daprodustat	4 QD	14.2	1.0	ischemic stroke	CVD	yes	complete positive	mis	NA	-	recovered

	85M	G4	-	daprodustat	2 QD	13.4	5.0	ischemic stroke	CVD	yes	complete positive	mis	NA	-	recovered
	74M	G4	-	daprodustat	2 QD	11.4	2.0	ischemic stroke	CRM	yes	complete positive	mis	NA	-	recovered
Yamashita et al. (Japan, 2024)	53M	HD	6.0	roxadustat	150 TIW	6.1	24.0	hypothyroidism	lymphocytic leukemia (BTs) hemochromatosis	yes	complete positive	vadadustat	NA	-	recovered
Yang & Wang (China, 2021)	54M	PD	11.3	roxadustat	120→150 TIW	11.3	4.0	rhabdomyolysis	none	yes	complete positive#	ESA	partial positive	6.2	recovered
Yu et al. (China, 2020)	59F	HD	7.2	roxadustat	100 TIW	7.2	1.0	artery hypertension	artery hypertension	no	partial positive	NA	partial negative	6.2	recovered

Abbreviation: ADR – adverse drug reaction, BTs – blood transfusions, CRM – cardio renal metabolic syndrome, CVD – cardiovascular disease, dL – decilitre, F – female, G – grade, g – gram, Hb – haemoglobin, HD – haemodialysis, M – male, NA – not applicable, PD – peritoneal dialysis, QD – one a day, T0 – starting in HIF-PHI, T1 – time of ADR, T2 – time of returning of HIF-PHI, TIW – three times per week, * – ADR during the RCT phase III (NCT02174627), # – 2-times/repetitive.

Reported ADRs

A total of thirteen patients with ADRs from eight case reports were identified following the use of HIF-PHIs: roxadustat (8 patients,61.5%) and daprodustat (5 patients,38.5%). The mean Hb value at the time of transition to HIF-PHI was 8.9g/dL and 10.7g/dL when HIF-PHI was discontinued. The mean onset time for ADRs was 6.5 months (ranging from 1 week to 2 years). Of these ADRs, 12 (92.3%) were classified as drug-induced, while one was due to a drug interaction that worsened an existing comorbidity.

HIF-PHIs were withdrawn in 12 cases (92.3%), with one case being interrupted due to arterial hypertension. 2 patients (15.4%) were switched to another HIF-PHI; however, 1 was later switched to ESA during the follow-up. 6 patients (46.2%) were directly switched to ESA, and information on the continuation or discontinuation of HIF-PHIs was missing for 4 patients (30.8%). 5 patients (38.5%) did not require hospitalisation due to ADRs, and 11 (84.6%) recovered. Cardiovascular ADRs, like arterial or pulmonary hypertension and stroke, appeared at a mean Hb value of 11.4g/dL, while ischemic stroke was associated with a mean Hb value of 13g/dL. The dose of HIF-PHI varied according to drug dosing recommendations, and no interruptions were confirmed when the Hb value was ≥ 12g/dL. More detailed ADR characteristics are shown in Table 4 (Table 4). A Venn diagram in Figure 3 compares ADRs and HIF-PHIs according to CKD stratification, and Figure 4 links HIF-PHIs to the type and number of ADRs (Figure 3, Figure 4).

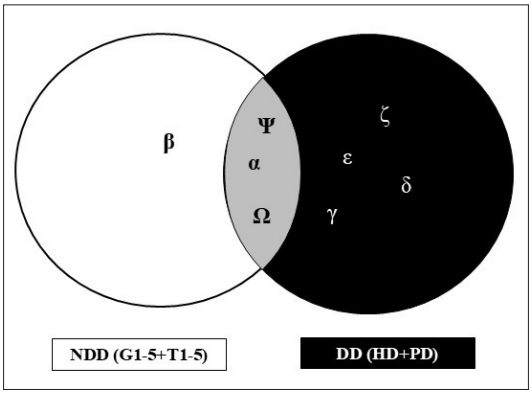

Figure 3

α – hypertension (artery or pulmonary), β – ischemic stroke, γ – hemorrhage, δ – rhabdomyolysis, ε – hypothyroidism, ζ – elevation of serum copper; Ψ – daprodustat, Ω – roxadustat.

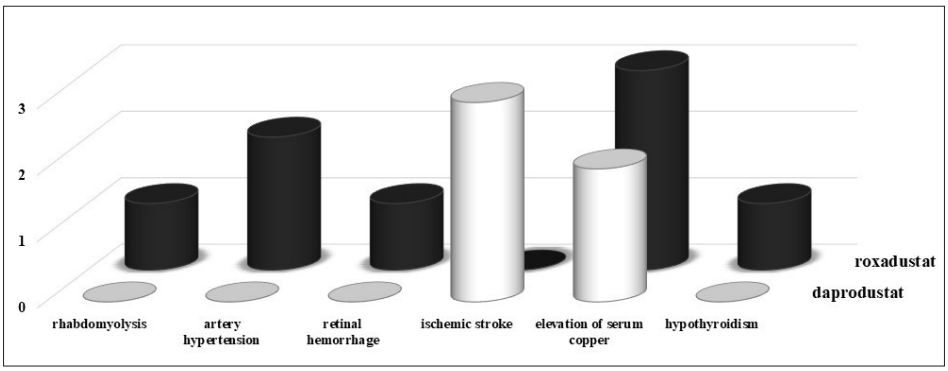

Figure 4

ADRs reported in these descriptive case reports were analysed using several assessment scales: causality (WHO-UMC scale), probability (Naranjo's adverse drug reaction probability scale), preventability (The Schumock and Thornton Preventability Assessment Scale), and severity (Hartwig and Siegel's severity assessment scale). Table 5 provides the results of these assessments (Table 5).

Table 5: Overall assessment of ADRs produced by HIF-PHIs in CKD

ADRs	Assessment scale	Case reports (N;%)	Patients (N;%)
Causality	WHO-UMC scale		
	Certain	1/8; 12.5%	2/13; 15.4%
	Probable	6/8; 75%	10/13; 76.9%
	Possible	1/8; 12.5%	1/13; 7.7%
Probability	Naranjo's adverse drug reaction probability scale questionnaires		
	Definite	2/8; 25%	2/13; 15.4%
	Probable	5/8; 62.5%	10/13; 76.9%
	Possible	1/8; 12.5%	1/13; 7.7%
Preventability	The Schumock and Thornton Scale		
	Definitely preventable	5/8; 62.5%	10/13; 76.9%
	Probably preventable	2/8; 25%	2/13; 15.4%
	Non-preventable	1/8; 12.5%	1/13; 7.7%
Severity	Hartwig and Siegel's severity assessment scale		
	Severe	2/8; 25%	2/13; 15.4%
	Moderate	4/8; 50%	6/13; 46.1%
	Mild	2/8; 25%	5/13; 38.5%

Discussion

Despite the various ADRs to HIF-PHIs in the CKD population and the limited number of reviewed case reports, this systematic review suggests that HIF-PHIs could be safe for treating CKD anaemia. Only about 15% of the reviewed cases showed a specific causality and definite probability with severe severity, and less than 10% were classified as non-preventable. These findings indicate that adequate management of comorbidities is crucial, as multiple disease conditions can increase susceptibility to ADRs. Furthermore, the probability and severity of ADRs can be reduced through personalised and recommended HIF-PHI dosages, aiming to maintain Hb values within the target range. Reviewed reports on stroke, with a mean Hb value of 13 g/dL, support this approach [74]. These outcomes align with the guidelines for diagnosing and managing CKD anaemia, which state that the Hb response to HIF-PHIs is dose-dependent and varies by agent, as some agents increase Hb more rapidly than others [74].

When comparing CKD anaemia prevalence across different stages, the ADR distribution to HIF-PHIs in the reviewed reports was similar to the standard prevalence, except in NDD patients [75]. The prevalence in DD patients matched the literature [75,76]. These findings align with the percentage of renal anaemia prevalence among CKD stages and the recent approval of HIF-PHIs for marketing one to four years ago[75-79]. Consequently, publication of these case reports or non-trial studies has been limited, mostly focusing on dialysed populations and/or advanced CKD stages, including those reporting ADRs to HIF-PHIs. About 90% of the reviewed reports originated from Asia, with only 10% from Europe. The European case report was part of CT. No reports were found from the Americas, other Asian regions, Africa, Australia, or Oceania [61]. Our reviewed case reports align with the drug approval timeline across continents. Roxadustat was first approved in China (2018), followed by daprodustat in Japan (2020) [80,81]. The FDA initially rejected roxadustat in 2021 and vadadustat in 2022 due to major adverse cardiovascular events. After revaluation, the FDA's final decision on roxadustat came in 2022, and for vadadustat and daprodustat in 2023, but only for adults on dialysis [31-83]. The EMA's approval was more straightforward, with roxadustat approved in 2021, and daprodustat and vadadustat in 2023 [32-85]. Our reviewed reports on daprodustat were solely from Japan, while roxadustat reports came from Japan, China, and Poland. The average time to onset for ADRs was 6.5 months, consistent with evidence showing the median time for HIF-PHI-associated ADRs is over three months [86]. This timing may also contribute to the lower number of reported ADR cases in the CKD population according to the drug approval process across different regions and continents.

Roxadustat and daprodustat, both HIF-PHIs, exhibit similar treatment effects, including improving renal anaemia and regulating iron metabolism, along with comparable ADRs, including thromboembolism, hypertension, stroke, and retinal haemorrhage [32-82]. Both case reports on arterial and pulmonary hypertension related to roxadustat indicated possible causality and probability with definitive preventability. The authors noted that they cannot conclusively prove a causal relationship between roxadustat and the development of hypertension. However, it is plausible that the mode of action of roxadustat is linked to the pathophysiology of hypertension [67-87]. Hypertension is a known adverse effect associated with ESAs, and HIF transcription factors play a role in regulating vascular tone and blood pressure. However, pooled results indicated that the risk of hypertension is lower with HIF-PHIs compared to ESAs. This supports research evidence suggesting that HIF-PHIs have a minor blood pressure lowering effect [13].

HIF-PHIs did not significantly increase the risk of cardiac ADRs, such as ischemic stroke. However, one reviewed case report documented a stroke as an ADR to daprodustat [63]. Upon thorough examination, it was found that only one patient had a Hb value below 12 g/dL. This suggests that ischemic stroke may occur when Hb levels rise above 13 g/dL or within the first two

months after daprodustat administration, likely due to excessive stimulation of erythropoiesis [63]. Therefore, it could be argued that daprodustat did not play a significant role in the development of the stroke. Indeed, ischemic stroke is rare in patients receiving HIF-PHIs, as confirmed by phase III trials in Japan, Europe, and the USA [63-88]. However, if an ischemic stroke does occur, HIF-PHI treatment should be paused or discontinued, depending on the current Hb value, to prevent recurrence and ensure patient safety.

The final identified ADR associated with the vascular component was retinal haemorrhage [60]. The case report documented the patient's comorbidities, specifically diabetes-related retinopathy and high blood pressure. These conditions can independently lead to retinal haemorrhage, regardless of renal anaemia treatment [60]. Additionally, HIF-PHIs increase vascular endothelial growth factor, which plays a crucial role in the progression of such complications. Thus, given the known comorbidities and the use of roxadustat, this complication was anticipated. The retinal haemorrhage resolved after switching to ESA and stabilising the patient's relative blood pressure.

Diverse outcomes have been confirmed regarding the impact of different types of HIF-PHIs on endocrine gland function, particularly on pituitary stimulation. Roxadustat-associated hypothyroidism is more frequently reported in males, with similar trends observed for daprodustat [86-88]. One reviewed case report noted the effect of iron overload and its accumulation in the pituitary and thyroid glands, leading to pan-hypopituitarism in the patient [65]. To examine the effect of roxadustat on hypothyroidism, the medication was switched to another HIF-PHI, vadadustat. One month after the switch, a normal TSH response was observed, indicating that central hypothyroidism was induced by roxadustat treatment. Although the mechanism of roxadustat-induced hypothyroidism remains unknown, it is suggested that the molecular structure of roxadustat, which is similar to that of T3, may allow it to bind to the thyroid hormone receptor. This binding may suppress TSH release through a thyroid hormone feedback mechanism, causing hypothyroidism [21]. Additionally, case report has shown that the decrease in TSH levels following the administration of roxadustat was reversed after discontinuation of the drug, implying that roxadustat-induced hypothyroidism is a reversible ADR. In contrast, the structures of vadadustat and daprodustat are not similar to T3, and therefore, these drugs cannot bind to the thyroid hormone receptor, which could explain why hypothyroidism has not been observed with vadadustat [21]. These results suggest that monitoring thyroid function may be necessary during roxadustat administration.

The following positive, yet questionable, impact of HIF-PHI treatment relates to iron metabolism and its direct connection to copper regulation. This pathway was highlighted in two reports involving five patients treated with either roxadustat or daprodustat [42-62]. These findings suggest that HIF-PHI administration can influence serum values of ferritin, transferrin saturation (TSAT), iron, copper, and ceruloplasmin. The reviewed case reports showed that HIF-PHIs induce an imbalance between iron absorption and utilisation, resulting in increased levels of these iron-related parameters. Therefore, iron supplementation should be stopped or withdrawn if there is a tendency towards iron overload in the serum. Additionally, there is a direct connection between iron metabolism and serum copper levels due to ceruloplasmin, which is the leading copper transport protein in the plasma and a known HIF-1 target [62]. Consequently, careful initiation of HIF-PHI treatment is needed, considering the presence of iron supplementation and/or normal serum levels to prevent accumulation and corresponding gastrointestinal symptoms. Conversely, excess serum copper may occur during HIF-PHI treatment regardless of the agent type, dose, or treatment duration, but it is fully reversible with a favourable recovery outcome for patients.

The last identified ADR was rhabdomyolysis, based on clinical manifestations and laboratory tests [66]. This was the only ADR confirmed as non-preventable with severe severity, according to the Schumock and Thornton Preventability and Hartwig and Siegel's severity assessments. After the authors had excluded all non-confirmed potential causes, roxadustat remained the sole possible trigger [66]. Before using roxadustat, the patient had been continuously treated with statins without experiencing any clinical symptoms or serum changes associated with rhabdomyolysis. However, after the first use of roxadustat in combination with atorvastatin, the patient experienced clinical symptoms and serum changes indicative of rhabdomyolysis. These symptoms were improved when roxadustat was discontinued while the patient continued the same dose of atorvastatin. This led to the consideration of roxadustat as the cause of rhabdomyolysis. The specific cause and mechanism behind this ADR remain to be studied. Possible secondary impacts of this mechanism could include known AEs of HIF-PHIs, such as tissue hypoxia, the release of potassium and phosphorus from damaged muscle cells, and cumulative effects with statins. Surprisingly, the authors did not report the serum values of potassium and phosphorus. Therefore, it is recommended for clinicians to be cautious about rhabdomyolysis when using roxadustat, especially in the presence of risk factors like hyperkalaemia, hyperphosphatemia, or potential pseudo-crush syndrome due to statin use. The authors of the reviewed case report, however, only advised monitoring creatine kinase (CK) and myoglobin levels [66].

Strengths and limitations

The strengths of this systematic review stem from its comprehensive search across multiple electronic sources between January 2018 and May 2024, and the application of very specific inclusion and exclusion criteria. These criteria were carefully chosen to minimise bias, reflecting the recent improvements in CKD anaemia guidelines, consistent with our findings. Additionally, this review synthesised effects from case reports, providing a clearer picture of ADRs, including their causality, preventability, probability, and severity, compared to individual case report results. We employed assessments tailored to address biases specific to case reports, enhancing the quality of non-randomised studies and the rigour of our quality assessment.

However, there are several limitations. Our study is constrained by the information available in the original case reports concerning HIF-PHIs in adult patients with CKD anaemia and their associated ADRs. We excluded a single child's case report to prevent selection bias [89]. The study was excluded due to potential bias in drawing conclusions or generalising findings based on a single case report because the available data on one infant was deemed insufficient for reliable analysis [89]. Furthermore, no reports conducted head-to-head comparisons of different HIF-PHIs in CKD patients, whether on dialysis or not. Significant differences in potency, dose requirements, and potential drug interactions were not accounted for, which could affect the interpretation of ADR differences.

Future Implications

Importantly, prevention should be the primary focus for future implications. Following early diagnosis, it is crucial to develop a comprehensive therapy plan that includes not only ESAs or HIF-PHIs but also all necessary agents to prevent underdiagnosis and undertreatment of renal anaemia in the CKD population.

Our findings can give insights into the ADRs associated with HIF-PHIs and might help clinicians treat and manage ADRs. Regular monitoring of Hb value, hypertension, hypothyroidism, and other ADRs should be practised. HIF-PHIs' safety profiles are as important as their efficiency; thus, ongoing research and post-marketing surveillance are critical in optimising their dosage and ensuring safety and long-term impact. Additionally, it is recommended that clinicians adhere to the HIF-PHIs guidelines for discontinuation and re-initiation of roxadustat when Hb levels fall below 12 g/dL in DD patients [74-92]. Therefore, future research and follow-up analyses should aim to determine best practices and areas of uncertainty in preventing HIF-PHIs.

Conclusion

Our findings provide insights into the ADRs associated with HIF-PHIs and might help clinicians treat and manage ADRs. To prevent ADRs and reduce their severity and likelihood, regular monitoring of Hb, potassium, phosphorus, iron metabolism, T3, and TSH levels, along with adequate hypertension management, should be practiced when using HIF-PHIs. These measures also enhance the preventability of ADRs. HIF-PHIs have the potential to be powerful new agents for treating renal anaemia, thereby reducing morbidity and improving the quality of life for individuals with CKD.

Declarations

Ethics approval and consent to participate

No patients were contacted for input on the interpretation or writing up of the data. All studies included into analyses were in accordance with the inclusion criteria and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards in the informed consents for clinical trials included into this review. No clinical trials were analysed In line with that, ethics approval was not required. Therefore, Human Ethics and Consent to Participate declarations, and the name of the Approval Committee are not applicable.

The review was not pre-registered in PROSPERO due to the completion of data extraction prior to registration.

Consent for Publication

"Not Applicable": No images or other personal or clinical details of participants from reviewed cases are presented in the manuscript.

Availability of Data and Materials

"Not Applicable": This manuscript does not report data generation or analysis. All analysed data are available from the supplement files and/or from the corresponding author on reasonable request from Rayyan.

For additional information please see supplemental material: Table 1: PRISMA Checklist 2020 for abstract and manuscript.

Disclosure Statement/Competing Interest

No potential conflict of interest was reported by the author(s) and/or her relatives. The author declares that she has no competing interests that might be perceived to influence the results and/or discussion reported in this paper.

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Authors' Contributions

Sara Maria Majernikova wrote the main manuscript text, did the analyses and created all Figures and Tables.

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91. Charytan C, Manllo-Karim R, Martin ER, Steer D, Bernardo M, Dua SL, et al. (2021) A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study. Kidney Int Rep 6: 1829-1839.
92. (2021) ANNEX Guidelines.

Supplementary Material

Table ST1:  PRISMA Checklist 2020 for abstract and manuscript (From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71).

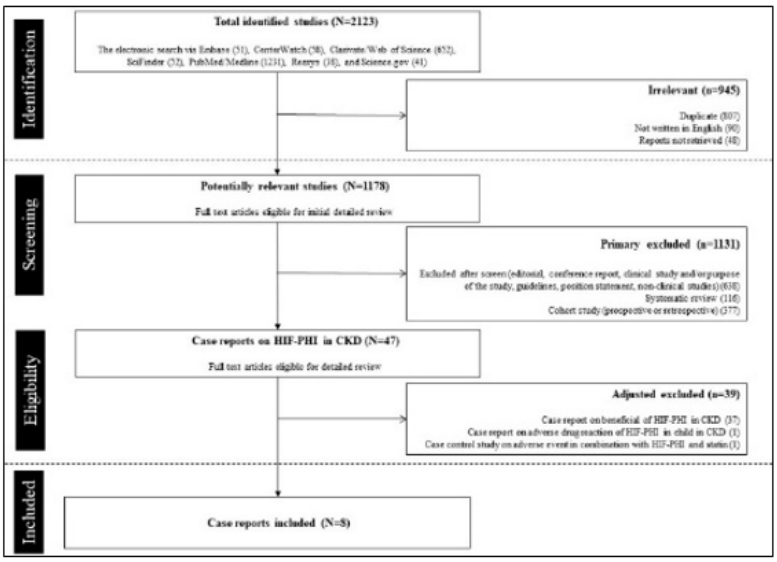
Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic article. Variability, Severity, Preventability, and Outcomes of Adverse Drug Reactions to HIF-PHIs in CKD Case Reports: A systematic review	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist. Standard abstract: Background Underdiagnosed and undertreated renal anaemia remains an issue among individuals with chronic kidney disease (CKD). Hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs) offer significant options. However, there are unmapped areas regarding adverse drug reactions (ADRs) to HIF-PHIs. Thus, this systematic review aims to find ADRs to HIF-PHIs and analyse their variability, severity, preventability, and outcomes in individual CKD patients reported as case reports. Methods A literature search of published case reports was conducted between 2018 and 2024 across various electronic sources. Of the total identified studies (N=2123), only 8 case reports (13 patients) were included after collecting inclusion/exclusion criteria. Results ADRs to roxadustat (8/13;61.5%) and daprodustat (5/13;38.5%) were presented: the retinal haemorrhage (7.7%), hypertension (15.4%), stroke (23.1%), hypothyroidism (7.7%), rhabdomyolysis (7.7%), and elevation of serum copper (38.4%). The mean time-to-onset of ADRs was 6.5 months. Specific causality and non-preventability of ADRs to HIF-PHIs were confirmed in one report (1/8;12.5%), and definite probability and severity in two reports (2/8;25%) due to ADRs to HIF-PHIs. Conclusion This review suggests HIP-PHIs could be safe for patients to treat CKD anaemia. Thanks to personalised dosages that maintain the recommended Hb value and sufficient comorbidities, therapy decreased ADRs' probability and severity can be achieved. Graphical abstract separately attaches	page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge. Chronic kidney disease (CKD) is a significant global health issue and one of the leading non-communicable deaths worldwide, affecting approximately up to 15% of the world's population, with prevalence rates expected to increase. CKD is associated with numerous complications, including anaemia, which significantly impacts patient morbidity and mortality. Higher CKD stages are associated with a higher prevalence of CKD anaemia, leading to its incidence in approximately 50% of patients with grade 4 CKD and up to 90% of end-stage kidney disease. Hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs), have emerged as promising treatments for CKD anaemia. Despite their efficacy and safety compared to ESAs, using HIF-PHIs comes with risks. CTs and real-world studies have identified several potential adverse drug reactions (ADR), including thromboembolic events, artery and pulmonary hypertension, pro-tumorigenic effects, worsening heart failure and retinopathy.	pages 5-6

Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses. Surprisingly, no systematic reviews of case reports have identified the ADR for up to six years of HIF-PHI use. Thus, this systematic review aims to find ADRs on HIF-PHIs and analyse their variability, causality, preventability, probability, severity, and outcomes in individual CKD patients reported as case reports.	page 6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. Studies were required to meet the following inclusion criteria: (a) published in English only; (b) must be only case reports on adults; (c) study population being only CKD patients with anaemia undergoing regular CKD treatment on HIF-PHIs medication and (d) case reports documenting ADRs linked explicitly to the HIF-PHIs in CKD. Studies were excluded if they did not meet the inclusion criteria and/or met any of the following: (a) did not have an abstract and/or full text in English; (b) conference abstracts, thesis, comments, letters, abstracts, editorials, randomised controlled trials, experimental research, observational studies or grey literature; (c) narrative/systematic reviews and/or meta-analyses; (d) articles on any different pathology treatment and/or medications; (e) were carried out on not CKD patients and/or other consumers; (f) did not focus on the ADRs. Detailed information is shown in Figure 1: Flowchart of design and study selection procedure.	page 7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. We conducted a literature search of published case reports and case studies between January 2018 and May 2024 due to the first 2018 approval in China. This search was conducted in the CenterWatch, Clarivate/Web of Science, Embase, PubMed/Medline, Reaxys, Science.gov and SciFinder databases to identify case reports on the ADR when on HIF-PHIs. Furthermore, additional searches were undertaken on Google Scholar, ResearchGate and SpringerLink to detect case reports from alternative sources.	page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used. Search terms used Medical Subject Headings (MeSH) terms, like “adverse event”, “Hypoxia-inducible factor prolyl hydroxylase inhibitor”, “HIF-PHIs”, “roxadustat”, “molidustat”, “vadadustat”, “desidustat”, “dialysis”, “case study”, “CKD” and “ADRs”. (The supplementary ST2 table contains a comprehensive search methodology executed in all search databases at the end of this systematic review). The combinations between the terms were made by AND/OR.	page 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. Studies were included into the analyses when a study met the inclusion criteria and did not meet the exclusion criteria as it is mentioned in points 5, 6 and 7. There was no more independent reviewer.	pages 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process: Selected papers were downloaded and stored in Rayyan. This platform offers marking papers for inclusion or exclusion, supplying reasons for these decisions and a ‘maybe’ option for further analysis and consideration. The initial screening examined the titles and abstracts of all case studies obtained after searching the selected databases. Each obtained article was screened independently and then subjected to further full-text analysis to determine its appropriateness based on the study inclusion criteria. This analysis was also completed independently. The data extracted from selected studies were entered and screened using Microsoft Excel. A data extraction sheet was developed. After finalizing the data extraction sheet, the author performed the initial data extraction for all included articles and checked all proceedings. No more independent reviewer screened or correct data from each record.	pages 6-8

Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. Search terms used Medical Subject Headings (MeSH) terms, like "adverse event", "Hypoxia-inducible factor prolyl hydroxylase inhibitor", "HIF-PHIs", "roxadustat", "molidustat", "vadadustat", "desidustat", "dialysis", "case study", "CKD" and "ADRs". (The supplementary ST2 table contains a comprehensive search methodology executed in all search databases at the end of this systematic review). This systematic review analysed ADRs documented in case reports and case series. The selected studies were evaluated, and the following essential information was extracted: author name, country of origin, the year of publishing, age, gender, CKD information, haemoglobin value at the beginning, discontinued and returning to HIF-PHI therapy, type of HIF-PHI, ADR, predisposing diagnoses, severity (divided into yes/no dependent on hospitalisation needed), and the outcome (stratified by recovering: recovered, not yet recovered, recovered with sequelae, fatal, and unknown). We also noted the number of patients, all ADRs reported, dechallenge, and rechallenge. We used World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale, Naranjo's adverse drug reaction questionnaires, The Schumock and Thornton Assessment, and Hartwig and Siegel's scale to asses causality, probability, preventability and severity of ADRs based on HIF-PHIs.	pages 6-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. Regarding to use descriptive statistics and no quantitative analysis, we did not analyse missing data from reviewed reports on ADRs. Only known information was included into statistics and quality/sensitive assessments. We analysed type of ADR to HIF-PHIs, its causality, preventability, probability and severity; so far, our interest based on ADRs outcomes, predisposing diagnoses or factors.	pages 7-10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. All reports on the ADRs to HIF-PHIs in CKD population were included into our review to prevent selection bias. Newcastle-Ottawa Scale (NOS) and the Methodological Index for Non-Randomised Studies (MINORS) were employed, as they cater to the specific biases relevant to case studies. MINORS assesses the quality of non-randomised studies. It includes 12 items, with the first eight applicable to non-comparative studies and all twelve applicable to comparative studies. We scored each case report from 0-2, where 0 was not reported, 1 was reported but inadequate, and two were reported and adequate. We also used NA, which indicates items that do not apply to our case report, such as comparative elements in non-comparative studies. Then, the total score out of 16 was considered for the methodological quality evaluation. We considered a score of 14-16 high quality, 10-13 modest quality and less than nine a low-quality study. NOS assessed the quality of non-randomised case reports as it evaluates selection (4 stars), comparability (2 stars), and outcome/ exposure (3 stars), with a maximum score of nine stars. Each of our selected case report studies was rated based on the representativeness of cohorts, comparability, and adequacy of outcome assessment. We considered a score of 7-9 stars as a high-quality study, 4-6 stars as a moderate quality and less than three as low-quality evidence.	pages 7-9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. Mean was used to express continuous values, whereas frequency and percentage were used to express categorical variables. Our study's inclusion criteria focused exclusively on case reports and case studies. As a result, we did not conduct a meta-analysis because of insufficient data.	pages 8-10

Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). We conducted a literature search of published case reports and case studies. Search terms used Medical Subject Headings (MeSH) terms, like "adverse event", "Hypoxia-inducible factor prolyl hydroxylase inhibitor", "HIF-PHIs", "roxadustat", "molidustat", "vadadustat", "desidustat", "dialysis", "case study", "CKD" and "ADRs". (The supplementary ST2 table contains a comprehensive search methodology executed in all search databases at the end of this systematic review). This systematic review analysed ADRs documented in case reports and case series. Studies were required to meet the following inclusion criteria: (a) published in English only; (b) must be only case reports on adults; (c) study population being only CKD patients with anaemia undergoing regular CKD treatment on HIF-PHIs medication and (d) case reports documenting ADRs linked explicitly to the HIF-PHIs in CKD. Studies were excluded if they did not meet the inclusion criteria and/or met any of the following: (a) did not have an abstract and/or full text in English; (b) conference abstracts, thesis, comments, letters, abstracts, editorials, randomised controlled trials, experimental research, observational studies or grey literature; (c) narrative/systematic reviews and/or meta-analyses; (d) articles on any different pathology treatment and/or medications; (e) were carried out on not CKD patients and/or other consumers; (f) did not focus on the ADRs. Detailed information can be found in Figure 1. Selected papers were downloaded and stored in Rayyan. This platform offers marking papers for inclusion or exclusion, supplying reasons for these decisions and a 'maybe' option for further analysis and consideration. The initial screening examined the titles and abstracts of all case studies obtained after searching the selected databases. Each obtained article was screened independently and then subjected to further full-text analysis to determine its appropriateness based on the study inclusion criteria. This analysis was also completed independently. The data extracted from selected studies were entered and screened using Microsoft Excel.	pages 7-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. The selected studies were evaluated, and the following essential information was extracted: author name, country of origin, the year of publishing, age, gender, CKD information, haemoglobin value at the beginning, discontinued and returning to HIF-PHI therapy, type of HIF-PHI, ADR, predisposing diagnoses, severity (divided into yes/no dependent on hospitalisation needed), and the outcome (stratified by recovering: recovered, not yet recovered, recovered with sequelae, fatal, and unknown). We also noted the number of patients, all ADRs reported, dechallenge, and rechallenge. Pharmacovigilance defines "challenge" as administering a drug to a patient during an adverse event (AE) or treatment. "Dechallenge" refers to the cessation of the suspected treatment, aiming to see if the AE diminishes or disappears upon withdrawal of the drug. "Rechallenge" involves restarting the same therapy after stopping it, typically to confirm the causality of an ADR. In our systematic review, we used these terms to evaluate ADR causality. A positive reaction was noted during dechallenge if the ADR disappeared, while an adverse reaction indicated the ADR persisted. Similarly, a positive reaction was recorded if the ADR reappeared during the rechallenge, whereas an adverse reaction meant the ADR did not reoccur. Partial and complete reactions were noted based on the extent of ADR resolution or reappearance. We used WHO-UMC scale, Naranjo's adverse drug reaction questionnaires, The Schumock and Thornton Assessment, and Hartwig and Siegel's scale to asses causality, probability, preventability and severity of ADRs based on HIF-PHIs.	page 8
Synthesis methods	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses. MINORS, NOS assessments, the level of evidence (the Murad tool + the Oxford criteria), WHO-UMC, Naranjo's, the Schumock and Thornton, Hartwig and Siegel's assessments scales, which are displayed in Tables 1-5. Figure 2 shows the reviewed case reports on anaemia prevalence in the CKD population. Venn diagram (Figure 3) displayed HIP-PHIs adverse drug reactions in the reviewed reports, which are compared by the CKD. Figure 4 visualizes HIP-PHIs adverse drug reactions in the reviewed reports, which are compared by the ADRs' number.	pages 11-16
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. We did not conduct a meta-analysis because of insufficient data. Descriptive statistical analysis was performed using GraphPad Prism version 10 and Microsoft Excel version 11. Mean was used to express continuous values, whereas frequency and percentage were used to express categorical variables. Our study's inclusion criteria focused exclusively on case reports and case studies. Both case reports and case series were screened due to their detailed clinical information about individual patients and methodological similarities, which enhance understanding of ADRs. Case reports include detailed presentations of single patient cases documenting medical history, symptoms, diagnosis, treatment, and follow-up, helping to identify potential risks associated with drug use. They can highlight new and unexpected ADRs, contributing to a more comprehensive understanding of drug safety. Case series include collections of similar individual case reports, documenting multiple patients treated under similar conditions.	pages 5, 9-10

Synthesis methods	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). Descriptive statistical analysis was only performed. We used additional assessments, such as MINORS, NOS, the MURAD, and the Oxford criteria. This systematic review did not use the Cochrane Collaboration tool for assessing the risk of bias due to its design specificity for randomised controlled trials. We were also unable to use funnel plots and tests for funnel plot asymmetry in this systematic review, with only eight case studies, because these methods are generally unreliable with fewer than ten studies, have low power to detect asymmetry, and the inherent heterogeneity and variable methodological rigour of case studies further complicate the interpretation, making it difficult to distinguish between actual bias and natural variability in results. The last, the scales to asses causality, probability, preventability and severity of ADRs based on HIF-PHIs were done by WHO-UMC, Naranjo's, the Schumock and Thornton, Hartwig and Siegel's assessments.	pages 8-10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results. The searching via more databases was done with all relevant search terms. We adjusted data with the respect to the HIF-PHIs' marketing approval timing. We compared ADRs in accordance to the different CKD stages (NDD versus DD) as well as the variety HIF-PHIs according to ADRs. The results obtained using the descriptive statistics were compared to the literature data. Pharmacovigilance defines "challenge" as administering a drug to a patient during an adverse event or treatment. "Dechallenge" refers to the cessation of the suspected treatment, aiming to see if the AE diminishes or disappears upon withdrawal of the drug. "Rechallenge" involves restarting the same therapy after stopping it, typically to confirm the causality of an ADR. In our systematic review, we used these terms to evaluate ADR causality. A positive reaction was noted during dechallenge if the ADR disappeared, while an adverse reaction indicated the ADR persisted. Similarly, a positive reaction was recorded if the ADR reappeared during the rechallenge, whereas an adverse reaction meant the ADR did not reoccur. Partial and complete reactions were noted based on the extent of ADR resolution or reappearance. We used World Health Organization-Uppsala Monitoring Centre scale, Naranjo's adverse drug reaction questionnaires, The Schumock and Thornton Assessment, and Hartwig and Siegel's scale to asses causality, probability, preventability and severity of ADRs based on HIF-PHIs.	page 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). This systematic review did not use the Cochrane Collaboration tool for assessing the risk of bias due to its design specificity for randomised controlled trials. We were also unable to use funnel plots and tests for funnel plot asymmetry in this systematic review, with only eight case studies, because these methods are generally unreliable with fewer than ten studies, have low power to detect asymmetry, and the inherent heterogeneity and variable methodological rigour of case studies further complicate the interpretation, making it difficult to distinguish between actual bias and natural variability in results.	page 10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. NOS and MINORS were employed, as they cater to the specific biases relevant to case studies. MINORS assesses the quality of non-randomised studies. It includes 12 items, with the first eight applicable to non-comparative studies and all twelve applicable to comparative studies. We scored each case report from 0-2, where 0 was not reported, 1 was reported but inadequate, and two were reported and adequate. We also used NA, which indicates items that do not apply to our case report, such as comparative elements in non-comparative studies. Then, the total score out of 16 was considered for the methodological quality evaluation. We considered a score of 14-16 high quality, 10-13 modest quality and less than nine a low-quality study. NOS assessed the quality of non-randomised case reports as it evaluates selection (4 stars), comparability (2 stars), and outcome/exposure (3 stars), with a maximum score of nine stars. Each of our selected case report studies was rated based on the representativeness of cohorts, comparability, and adequacy of outcome assessment. We considered a score of 7-9 stars as a high-quality study, 4-6 stars as a moderate quality and less than three as low-quality evidence. We also utilised the Murad tool and the Oxford criteria to enhance the rigour of our quality assessment. The Murad tool is particularly useful for synthesising case reports, while the Oxford criteria provide a comprehensive framework for evaluating evidence. The evidence level was considered as per the Oxford criteria, in which case series were graded as level 4 and case reports as level 5. Additionally, we used the four domains from the Murad tool to evaluate the methodological quality of case reports: selection (question 1), ascertainment (questions 2 and 3), causality (questions 4-7) and reporting (question 8). If the specific case reports fulfilled the criteria and the answer to the question was yes, a score of 1 was given in the column; otherwise, it was scored as 0. Then, a total score of 8 was considered for the methodological quality evaluation. We considered a score of 6-8 as high quality, 4-5 as moderate quality and less than three as low-quality evidence.	page 9
RESULTS			

Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. Figure 1: Flowchart of design and study selection procedure. 	page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. Selected papers were downloaded and stored in Rayyan. This platform offers marking papers for inclusion or exclusion, supplying reasons for these decisions and a 'maybe' option for further analysis and consideration. The initial screening examined the titles and abstracts of all case studies obtained after searching the selected databases. Each obtained article was screened independently and then subjected to further full-text analysis to determine its appropriateness based on the study inclusion criteria. This analysis was also completed independently. The data extracted from selected studies were entered and screened using Microsoft Excel. We excluded a single child's case report to prevent selection bias (Yang et al., 2024. Compassionate use of roxadustat for treatment of refractory renal anemia in an infant. Pediatric Nephrology 39:911–914, https://doi.org/10.1007/s00467-023-06240-1).	pages 6-8, 15
Study characteristics	17	Cite each included study and present its characteristics. Ariyoshi et al. (2024), Cygulska et al. (2019), Nakamura et al. (2022), Nakamura et al. (2023), Uchio et al. (2024), Yamashita et al. (2024), Yang & Wang (2020), Yu et al. (2020). Table 4 shows characteristics of these reviewed study reports. Their detailed citations are displayed in References.	page 11, 15-16
Risk of bias in studies	18	Present assessments of risk of bias for each included study. Methodological quality (risk of bias) of the reviewed and selected case reports is evidenced by the MINORS and NOS assessments, with detailed information provided in Tables 1 and 2. The level of evidence was evaluated according to the Oxford Criteria 2011, offering a comprehensive framework for assessing evidence levels. The Murad tool was also used to synthesise the reviewed cases. Both assessments are shown in Table 3, which details the methodological quality assessment scale.	pages 9

Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. All outcomes are show in Figures and Tables. Here is summarizing of the characteristics of the reviewed reports: A total of eight case reports involving thirteen patients who experienced ADRs induced by HIF-PHIs were identified. Among these patients, 10 (76.9%) were males, with a mean age of 67.8 years (ranging from 32 to 85 years). The ADRs were reported in Japan (5 reports involving 10 patients, accounting for 62.5% of reports and 76.9% of patients), China (2 reports involving 2 patients, accounting for 25% of reports and 15.4% of patients), and Poland (1 report involving 1 patient, accounting for 12.5% of reports and 7.7% of patients; ADR during CT phase III: ID NCT02174627). Among these patients, 8 (61.6%) were undergoing dialysis, and 4 (30.8%) were in advanced stages of CKD. Table 4 provides detailed characteristics of the included case reports, organised based on the drug. It includes information on the study author, year of publication, country, age, gender, CKD grade, HIF-PHI used, ADR and its onset, Hb values during the transition to HIF-PHI, discontinuation and resumption of HIF-PHI, predisposing diagnoses, dechallenge, rechallenge, severity, and outcomes. Notably, 5 out of 13 patients (38.5%) had missing Hb values during the transition to HIF-PHI. The minimum Hb value at transition was 6 g/dL, and the maximum was 11.3 g/dL, with a mean of 8.9 g/dL. Reported ADRs: A total of 13 patients with ADRs from 8 case reports were identified following the use of HIF-PHIs: roxadustat (8 patients, 61.5%) and daprodustat (5 patients, 38.5%). The mean Hb value at the time of transition to HIF-PHI was 8.9 g/dL and 10.7 g/dL when HIF-PHI was discontinued. The mean onset time for ADRs was 6.5 months (ranging from 1 week to 2 years). Of these ADRs, 12 (92.3%) were classified as drug-induced, while one was due to a drug interaction that worsened an existing comorbidity. HIF-PHIs were withdrawn in 12 cases (92.3%), with one case being interrupted due to arterial hypertension. Two patients (15.4%) were switched to another HIF-PHI; however, one was later switched to an ESA during the follow-up. Six patients (46.2%) were directly switched to an ESA, and information on the continuation or discontinuation of HIF-PHIs was missing for four patients (30.8%). Five patients (38.5%) did not require hospitalisation due to ADRs, and 11 (84.6%) recovered. Cardiovascular ADRs, such as arterial or pulmonary hypertension and stroke, appeared at a mean Hb value of 11.4 g/dL, while ischemic stroke was associated with a mean Hb value of 13 g/dL. The dose of HIF-PHI varied according to drug dosing recommendations, and no interruptions were confirmed when the Hb value was ≥12 g/dL. More detailed ADR characteristics are shown in Table 4. A Venn diagram in Figure 3 compares ADRs and HIF-PHIs according to CKD stratification, and Figure 4 links HIF-PHIs to the type and number of ADRs. ADRs reported in these descriptive case reports were analysed using several assessment scales: causality (WHO-UMC scale), probability (Naranjo's adverse drug reaction probability scale), preventability (The Schumock and Thornton Preventability asment Scale), and severity (Hartwig and Siegel's severity assessment scale). Table 5 provides the results of these assessments. HIF-PHIs according to CKD stratification, and Figure 4 links HIF-PHIs to the type and number of ADRs. ADRs reported in these descriptive case reports were analysed using several assessment scales: causality (WHO-UMC scale), probability (Naranjo's adverse drug reaction probability scale), preventability (The Schumock and Thornton Preventability Assessment Scale), and severity (Hartwig and Siegel's severity assessment scale). Table 5 provides the results of these assessments.	pages 10-16
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. We compared ADRs in accordance to the different CKD stages (NDD versus DD) as well as the variety HIF-PHIs according to ADRs. The results obtained using the descriptive statistics were compared to the literature data. The scales to asses causality, probability, preventability and severity of ADRs based on HIF-PHIs were done by WHO-UMC, Naranjo's, the Schumock and Thornton, Hartwig and Siegel's assessments. We compared ADRs in accordance to the different CKD stages (NDD versus DD) as well as the variety HIF-PHIs according to ADRs. The results obtained using the descriptive statistics were compared to the literature data. Partial and complete reactions were noted based on the extent of ADR resolution or reappearance. We used World Health Organization-Uppsala Monitoring Centre scale, Naranjo's adverse drug reaction questionnaires, The Schumock and Thornton Assessment, and Hartwig and Siegel's scale to asses causality, probability, preventability and severity of ADRs based on HIF-PHIs. All detailed information is showed in Tables and Figures.	pages 10-16
Results of syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. The prevalence of CKD anaemia according to the literature sources linked to the CKD stages in the reviewed case reports is showed in Figure 2. Among these patients, 8 (61.6%) were undergoing dialysis, and 4 (30.8%) were in advanced stages of CKD (Figure 2). ADRs reported in these descriptive case reports were analysed using several assessment scales: causality (WHO-UMC scale), probability (Naranjo's adverse drug reaction probability scale), preventability (The Schumock and Thornton Preventability Assessment Scale), and severity (Hartwig and Siegel's severity assessment scale). Table 5 provides the results of these assessments (Table 5).	pages 11, 11-16

	20c	Present results of all investigations of possible causes of heterogeneity among study results. A Venn diagram in Figure 3 compares ADRs and HIF-PHIs according to CKD stratification, and Figure 4 links HIF-PHIs to the type and number of ADRs. The second possible cause of heterogeneity among reviewed reports might be diversity between CKD stages which is showed in Figure 2.	pages 10-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. All sensitivity analyses were conducted by using several assessment scales: causality (WHO-UMC scale), probability (Naranjo's adverse drug reaction probability scale), preventability (The Schumock and Thornton Preventability Assessment Scale), and severity (Hartwig and Siegel's severity assessment scale). Table 5 provides the results of these assessments. The results are displayed in Table 5.	page 11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. We did not perform any specific assessments of risk of bias to missing results because we did not analyse an individual data separately. We just performed descriptive statistics with the comparing our results these data. The findings are showed in the tables and figures in the results part.	pages 10-16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. MINORS and NOS assessments presented certainty/confidence. and the level of evidence was evaluated according to the Oxford Criteria 2011 and the Murad tool was used to synthesise the reviewed cases. All these findings are showed in Tables 1, 2 and 3. Furthermore, ADRs reported in these descriptive case reports were analysed using several assessment scales: causality (WHO-UMC scale), probability (Naranjo's adverse drug reaction probability scale), preventability (The Schumock and Thornton Preventability Assessment Scale), and severity (Hartwig and Siegel's severity assessment scale). Table 5 provides the results of these assessments.	pages 13-22
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence. Despite the various ADRs to HIF-PHIs in the CKD population and the limited number of reviewed case reports, this systematic review suggests that HIF-PHIs could be safe for treating CKD anaemia. Only about 15% of the cases reviewed showed a specific causality and definite probability with severe severity, and less than 10% were classified as non-preventable. These findings indicate that adequate management of comorbidities is crucial, as multiple disease conditions can increase susceptibility to ADRs. To prevent ADRs and reduce their severity and likelihood, regular monitoring of potassium, phosphorus, iron metabolism, T3, and TSH levels, along with adequate hypertension management, should be practiced when using HIF-PHIs. These measures also enhance the preventability of ADRs. Moreover, reviewed reports on stroke, with a mean Hb value of 13 g/dL, support this approach. These outcomes align with the guidelines for diagnosing and managing CKD anaemia, which state that the Hb response to HIF-PHIs is dose-dependent and varies by agent, as some agents increase Hb more rapidly than others. HIF-PHIs have the potential to be powerful new agents for treating renal anaemia, thereby reducing morbidity and improving the quality of life for individuals with CKD.	page 11-16
	23b	Discuss any limitations of the evidence included in the review. Our study is constrained by the information available in the original case reports concerning HIF-PHIs in patients with CKD anaemia and their associated ADRs. Significant differences in potency, dose requirements, and potential drug interactions were not accounted for, which could affect the interpretation of ADR differences.	page 15
	23c	Discuss any limitations of the review processes used. However, there are several limitations. We excluded a single child's case report to prevent selection bias (Yang et al., 2024). Furthermore, no reports conducted head-to-head comparisons of different HIF-PHIs in CKD patients, whether on dialysis or not.	page 15
	23d	Discuss implications of the results for practice, policy, and future research. Importantly, prevention should be the primary focus for future implications. Following early diagnosis, it is crucial to develop a comprehensive therapy plan that includes not only ESAs or HIF-PHIs but also all necessary agents to prevent underdiagnosis and undertreatment of renal anaemia in the CKD population. Our findings can give insights into the ADRs associated with HIF-PHIs and might help clinicians treat and manage ADRs. Regular monitoring of Hb value, hypertension, hypothyroidism, and other ADRs should be practised. HIF-PHIs' safety profiles are as important as their efficiency; thus, ongoing research and post-marketing surveillance are critical in optimising their dosage and ensuring safety and long-term impact. Therefore, future research and their analyses should aim to determine best practices and areas of uncertainty in preventing HIF-PHIs.	page 16
OTHER INFORMATION			

Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered. There is neither registration information for the review, nor register name and registration number.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared. A protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol. Because there was neither registration information for the review, nor register name and registration number, any amendments to information provided at registration or in the protocol are not relevant.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. No sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors. The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author wrote the main manuscript text, did the analyses and created Graphical Abstract, Figures and Tables. No third party participated in this study. The datasets analysed during the current study available from the author on reasonable request. All data generated or analysed during this study are included in this published article.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. None of the following have been publicly available yet; thus, they can not be found. However, the authors proclaim that all template data collection forms (excel files, data extracted from included studies; data used for all analyses; any other materials used in the review) will be sent for request.	NA

Supplementary Material

Table ST2: A comprehensive search methodology executed in all search databases

MeSH search words
ADRs
adverse drug reactions
AKB-6548
anaemia
anemia
ASP1517
BAY 85-3934
case series
case study
chronic kidney disease
CKD
daprodustat
desidustat
dialysis
FG-4592
GSK-1278863
haemodialysis
hemodialysis
HIF prolyl-hydroxylase inhibitor
HIF-PHIs
hypoxia-inducible factor stabiliser
hypoxia-inducible factor stabilizer
kidney

kidney failure
molidustat
MT-6548
renal
renal anaemia
renal anemia
renal failure
renal insufficiency
roxadustat
vadadustat
transplant
kidney transplant
renal transplant