Pharmacist-driven interventions in patients with chronic kidney disease and end-stage renal failure

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CHAPTER 2

Algorithm-managed dosing and pharmacist-managed dosing of erythropoietin-stimulating agents in renal anaemia: a systematic review

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Abstract

Objectives

The goal of this systematic review was to identify and summarise algorithm- and pharmacist-managed dosing of erythropoietin-stimulating agents (ESA) in patients with renal anaemia and to determine the effects on available outcome parameters.

Methods

We followed the PRISMA guidelines for systematic reviews. Studies investigating algorithm-managed and pharmacist-managed dosing of ESA in adult patients with renal anaemia were evaluated for inclusion. No restrictions were set on outcome parameters. Observational and interventional studies available as full-text articles with a control group and follow-up ≥6 months were eligible for inclusion. Relevant databases were searched from their inception through August 2024. Two independent reviewers evaluated all studies. The risk of bias was assessed by the ROBINS-I and RoB1 tools. The protocol of this study was registered in PROSPERO (CRD42021243678). Franciscus Gasthuis and Vlietland Hospital funded this study.

Results

After screening 140 articles, 17 articles and 4313 patients could be included. Available evidence was of low to moderate quality with a high risk of bias. Data were summarised and tabulated. Meta-analysis was not possible due to the substantial heterogeneity in participants, study design, interventions, comparisons, and outcome parameters. However, standardised metrics could be identified and calculated for haemoglobin and ESA dose. The percentage in target range for haemoglobin varied between 3.5% lower (95%CI -18.67% to + 11.67%) to 32.0% higher (95%CI 14.07 to 49.93%) in the pharmacist-managed group versus the control group (n=1401). The range in reduction in ESA dose was 5.45% (95%CI -7.97% to + 18.87%) to 49.97% (95%CI 20.32% to 79.61%%) in the pharmacist-managed group versus the control group (n=2115).

Conclusion

Low-quality data with high risk of bias suggest that pharmacist-managed renal anaemia may improve the percentage of haemoglobin within target range and reduce the ESA dose. However, meta-analysis was impossible due to substantial heterogeneity. Therefore, no definite conclusions could be drawn on the effectiveness of pharmacist-managed dosing of ESA in renal anaemia.

Introduction

With the progression of chronic kidney disease (CKD), the prevalence of renal anaemia increases. Notwithstanding the emergence of new treatment strategies, erythropoietin-stimulating agents (ESA) still are the cornerstone of renal anaemia treatment. Up to 90 per cent of haemodialysis patients in Europe are on ESA [1]. For ESA to be optimally effective, iron status needs to be optimised. Therefore, iron supplementation is indicated when patients are on ESA unless otherwise contraindicated [2].

Haemoglobin target levels for the treatment of renal anaemia have changed over the years. Haemoglobin levels should not be fully corrected, as target levels towards the normal range are associated with increased mortality [3,4], whereas levels below 6.2 mmol/L are associated with a lower quality of life and a higher transfusion rate [5]. Therefore, current guidelines recommend target levels between 6.2 and 7.1 mmol/l for haemoglobin in haemodialysis patients [2,6].

In clinical practice, it is challenging to meet these target levels. Without the use of decision aids, only about 30% of the haemodialysis patients in Europe have within-target haemoglobin values [1]. Several factors impede the attainment of target levels, such as ESA hyporesponsiveness and infections, but also the suboptimal prescribing of ESA and iron plays a role [1,7]. Suboptimal prescribing may occur because of the clinician's focus on low haemoglobin levels and the prevention of transfusions, whereas high haemoglobin levels are frequently overlooked. This often leads to the erroneous continuation of a too-high dose of ESA, which occurs in more than a quarter of haemodialysis patients in Europe [1].

Various interventions to improve the treatment of renal anaemia have been investigated, such as the introduction of treatment algorithms [8,9], and pharmacist-managed anaemia programs [10–13]. However, the effectiveness of these interventions remains inconclusive, as outcomes are highly variable, and a structured, thorough analysis is lacking. To address this important knowledge gap, we systematically reviewed the available literature and summarised the evidence. We aimed to identify the various methods of algorithm-managed and pharmacist-managed dosing of erythropoietin-stimulating agents in adults with renal anaemia. In addition, we aimed to summarise the current literature

on the effectiveness of algorithm-managed and pharmacist-managed dosing of erythropoietin-stimulating agents in renal anaemia.

Methods

This systematic review on algorithm-managed and pharmacist-managed dosing of erythropoietin-stimulating agents (ESA) in adults with renal anaemia followed the PRISMA and PRISMA-P guidelines. The protocol of this study was registered in PROSPERO (International Prospective Register of Systematic Reviews, ID CRD42021243678).

Data sources and searches

The search strategy was designed and implemented in collaboration with a medical librarian. The following databases were searched from their inception through August 2024: PubMed, Embase, Web of Science, and the Cochrane Library. Search terms included a combination of keywords and the following MeSH terms: “chronic kidney disease”, ”renal failure”, “haemodialysis”, “peritoneal dialysis”, ”anaemia”, “renal anaemia”, “renal replacement therapy”, “ end-stage renal disease”, “pharmacist”, “erythropoietin stimulating agents”, “epoetin” and “algorithm”. The search strategy was tailored for each database. No language restrictions were placed on the search. Reference lists of relevant articles and previous systematic reviews [14–16] were manually searched for any additional relevant studies. The full search strategy is available as supplementary material.

Study selection and eligibility criteria

We included studies that explored the effect of algorithm-managed and pharmacist-managed dosing of ESA in adult patients with renal anaemia as compared to usual care. No restrictions were set on outcome parameters. All observational and interventional studies that included a control group without the use of algorithm-managed or pharmacist-managed dosing, and had a follow-up of at least six months, were eligible for inclusion.

Only full-length articles were considered for inclusion in this review. Titles and abstracts of the articles were screened to include relevant studies. When insufficient information was available from the title or abstract of a paper, a full

copy of the article was obtained and screened to determine eligibility. Each article was independently evaluated for inclusion by two reviewers (FJvdO and TvG) and disagreements between the reviewers were resolved by discussion with the third reviewer (PvdB).

Data extraction

Standardised data extraction forms were developed. Data extraction was carried out independently by two authors (FJvdO and MJED), and disagreements were resolved through discussion and consensus. Information extracted from the studies included: title, author, year of publication, country of origin, study design (retrospective, cross-sectional, etc.), setting, population details, number of patients, duration, comparison, and outcomes of interest. Furthermore, detailed information about the interventions and algorithms was extracted. This included an intervention description and determination of the type of intervention (algorithm-based or not, pharmacist-managed or not). Also, the quality of the intervention description was scored and reproducibility was assessed. Reproducibility was scored as yes or no, this score was assessed by determining if the intervention description was detailed enough to reproduce the intervention in clinical practice. Specific aspects of the used algorithms were determined, such as input and output parameters, whether it was computerized, and if its description was complete.

Quality assessment and risk of bias

Two reviewers (FJvdO and MJED) independently assessed the quality and risk of bias of the studies eligible for inclusion, except if one of them was involved as an author of an included study; in that case, a third reviewer (PvdB) assessed the quality and risk of bias instead of the author. For RCTs, the Risk of Bias (RoB2) tool for assessing the risk of bias in randomised trials was used [17]. For non-randomised interventional studies, The Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool was used [18]. To assess the quality of included studies, the Quality Assessment Tool for Quantitative Studies (Effective Public Health Practice Project 2007) was used (Ottawa Hospital Research Institute (ohri.ca), 2022-08-11). To reduce the risk of bias due to missing results, we checked the trial register clinicaltrial.gov.

Data synthesis and analysis

We planned to analyse data using a systematic quantitative synthesis of included studies, according to the Cochrane Handbook on Systematic Reviews [19]. Quantitative

synthesis was to be performed for data regarding the most frequently investigated haemoglobin outcomes and ESA dose or cost parameters. For quantitative synthesis, for each outcome of interest, at least three studies needed to be available. We planned to transform the intervention effects into the standardised metric by calculation. The predefined standardised metrics were the mean differences in the haemoglobin outcome and erythropoietin dose or expenditure. The standard metric would be selected based on the most frequently reported outcome parameter in included studies. In case a formal meta-analysis would not be possible, we would perform a SWiM (Synthesis Without Meta-analysis)[20], with the intention to summarise the effect estimates and provide GRADE recommendations. Study data were summarised and tabulated. Studies were prioritised based on study design, risk of bias assessment, and quality assessment. We planned to create forest plots to display the effects of the interventions on the predefined standardised metrics. Heterogeneity was informally explored: studies were grouped according to population (haemodialysis, peritoneal dialysis, and chronic kidney disease) and risk of bias.

Results

Search results and study selection

A flow chart of the literature search and identification of relevant articles for review is depicted in Figure 1. Overall, 140 eligible articles were identified. Seventeen articles complied with the inclusion criteria and are summarised and evaluated in this systematic review, with a total of 4313 patients in 16 studies. In one study, no patient numbers could be identified [21], in two articles, the same patient population was studied [11,12].

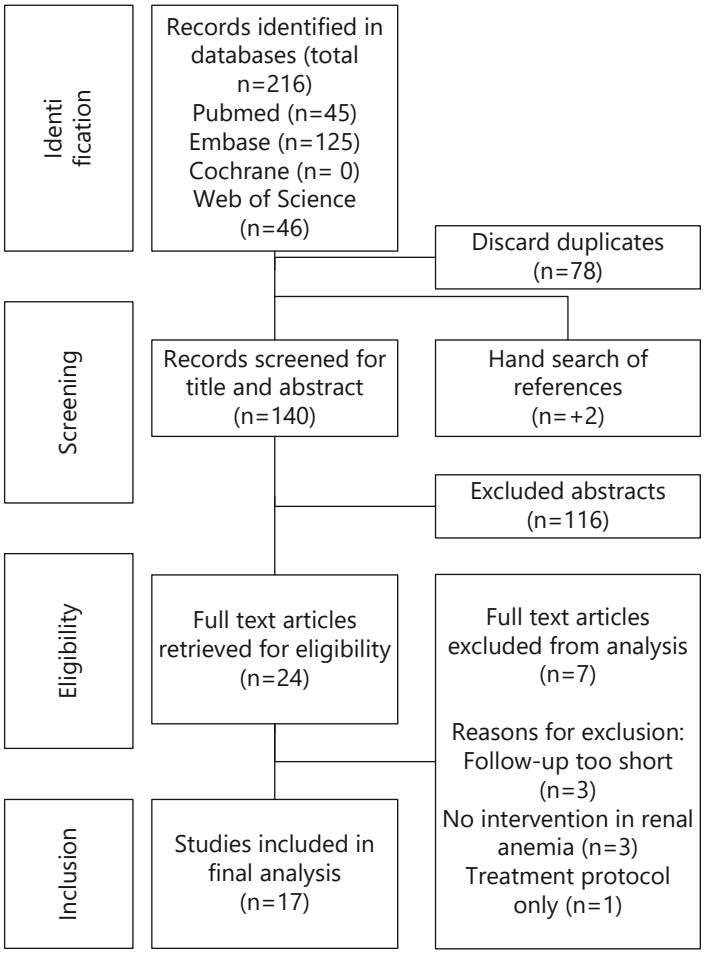

Figure 1. Flow chart of literature search and identification of relevant articles

Study characteristics

Table 1 shows the characteristics of included studies (n=17). Six studies were performed in patients with non-dialysis-dependent chronic kidney disease (NDD-CKD), and eleven studies were performed in patients on haemodialysis. In one of these studies, patients on peritoneal dialysis were also included. Study follow-up was relatively short, varying between six and thirteen months.

Table 1. Study characteristics and outcome data

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Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Armstrong 2000	I-RCT	HD Intervention n= 219 Control n=212 12 m FU	P&A	Anaemia management by the nephrologist	* Ht 33 ±3% current week 2 of last 4 Ht readings in last month within 33±3% 80% of Ht obtained over the last 6 months >30% and < 36%		Ht 33 ±3% current week I: 51.6% C:50.9% 2 of last 4 Ht readings in last month within 33±3% I:79.0% C:81.3% 80% of Ht obtained over the last 6 months >30% and < 36% I: 21.0% C: 15.4% No P-values or CIs reported

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Van den Oever 2020	I-RCT	HD Intervention n= 100 Control n= 100 13 m FU	P&A	Anaemia management by the nephrologist	Median percentage of monthly Hb values in the follow-up period that were in the target range (PTR, Hb target 11-12 g/dL)	Percentage of Hb levels in supratherapeutic range (PSTR, Hb >13 g/dL) PTR for iron (TSAT ≥ 20% and ferritin 200-500 mg/L) Percentage of Hb levels below target range (PBTR, Hb <6.8 mmol/L) Post-hoc analyses: Darbepoetin alfa (DA) dose (weekly) Iron sucrose dose (weekly) All-cause mortality Number of patients with at least one transfusion during follow-up Robustness	PTR for Hb I:38.5% C:23.1% p=0.001 PSTR for Hb I: 0.0% C: 7.7% p=0.034 PTR for iron I: 21.1% C: 8.3% p=0.003 PBTR for Hb I: 30.8% C: 30.8% p=0.864 DA dose (mcg) I: 34.0 C: 46.9 p=0.020 Iron sucrose dose (mg): I: 75.0 C: 0.0 p<0.001 All-cause mortality (n) I: 16 C: 26 p=0.096 Patients with at least 1 transfusion (n,%): I: 19 (20.2%) C: 31 (34.1%) p=0.046 Robustness (range PTR for Hb between different healthcare givers) I: 30.3% to 42.9% C: 15.4% to 43.0%

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Dashti-Kavidaki 2012	I-PP	HD n=86 6 m FU	P	Patients were their own controls Anaemia management by the nephrologist	# Aim of the study: effect of clinical pharmacy services on management of secondary complications such as anaemia Anaemia parameters; Hb, ferritin and TSAT		Hb in optimal range (11-12 g/dL): I: 15.1% C: 18.6% p=0.664 Ferritin in optimal range (100-800 ng/mL) I: 76.2% C: 48.8% p not reported TSAT in optimal range (20-50%) I: 34.7% C: 45.3% p not reported
Aspinall 2012	O-RC	CKD-NDD I: n= 314 UCE: n= 91 UC: n=167 6 m FU	P	Usual care site (UC) and usual care at ESA clinic (UCE) Anaemia management by the nephrologist	Proportion of Hb values in target range (Hb 10-12 g/dL) ESA dose Intra-and interpatient variance in haemoglobin values	Average number of Hb and iron tests per patient during the 6-month study period	Proportion of Hb values in target range I: 71.1% UC: 56.9% p <0.001 UCE: 51.7% ESA dose monthly (geometric means) Darbepoetin alfa: I: 115mcg UC: 156mcg p=0.049 UCE: 181 mcg

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Aspinall 2012 (continued)							Epoetin alfa: I: 29,677 IU UC: 32,856 IU p=0.6 UCE:39,258 IU Intrapatient variance Hb: I:0.66 UC:0.71 UCE:1.03 (no p-values) Interpatient variance Hb: I:0.51 UC: 1.89 UCE: 14.6 (no p-values) Number of Hb tests I: 5.8 ±2.6 UC: 3.6±3.0 UCE: 3.8 ±2.8 p=0.007 Number of iron tests I: 2.2±1.6 UC: 1.0±1.1 UCE:1.1±1.2 p=0.001 ≥ 1 TSAT measurement: I: 64.7% UC: 32.3% p=0.08 UCE:37.4%

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Aspinall 2013	O-RC	CKD-NDD I: n=314 C: n=167 Same population as in Aspinall 2012 6 m FU	P	Anaemia management by the nephrologist	# Objective: To compare the cost-effectiveness of pharmacist-managed erythropoiesis-stimulating agent (ESA) clinics with that of usual care in patients with non-dialysis-dependent (NDD) CKD.		PM: Cost per patient was $2,761 less, and ESA clinic strategy was more effective (+0.003 QALYs) Sensitivity analyses: Results were robust to variation
Bucaloiu 2007	O-RC	CKD-NDD I: n=62 C:n=74 6-12 m FU	P	Anaemia management by primary care physician	* Percentage of time at target Hb Percentage of time at target TSAT Time to target Hb Weekly ESA dose		Percentage of time at target Hb I: 69.8% C: 43.9% p<0.001 Percentage of time at target TSAT I: 64.8% C: 40.4% p=0.043 Time to target Hb I: 47.5 days C: 62.5 days p=0.11 Weekly ESA dose I: 6698 IU C: 12000 IU p<0.0001

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Debenito 2014	O-RC	CKD-NDD I: n=31 C: n=70 6 m FU	P	Anaemia management by the nephrologist	Rates of adherence to 6 monitoring recommendations for Hb and iron status (a) baseline Hb (b) first follow-up Hb < 4 weeks after start ESA (c) further follow-up Hb ≤ 4 weeks apart; (d) baseline ferritin and TSAT; (e) follow-up ferritin and TSAT levels measured at least once (f) iron therapy initiated within 14 days of lab test if ferritin < 100 ng/mL or TSAT <20%	Proportions of: -patients achieving target Hb levels -number of days required to achieve target -patients experiencing at least 1 Hb higher than 12 g/dL or below 10 g/dL -patients receiving at least 1 red blood cell transfusion -patients with at least 1 hospital visit defined as an anaemia- or ESA-related hospitalisation or emergency department visit Average weekly dose of ESA therapy and associated cost	Composite Hb monitoring endpoint (a-c, all three items) I: 32.3% C: 14.3% p=0.049 Composite iron monitoring endpoint (d and e) I: 62.3% C: 30.0% p=0.005 Patients achieving target Hb (Hb 10-12 g/dL) I: 96.8% C: 95.7% p=0.654 Mean days to achieve Hb target: I:28 C:41 p=0.135 Any follow-up Hb > 12 g/dL: I: 48.4% C: 54.3% p=0.715 Any follow-up Hb < 10 g/dL: I: 64.5% C: 60.0% p=0.673 Patients with at least one transfusion I: 9.7% C: 15.7% p=0.439

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Debenito 2014 (continued)					Composite outcomes consisting of Hb monitoring (items a-c), and iron monitoring (items d-e)		Patients with at least 1 hospital visit I: 3.2% C:20.0% p=0.067 Iron therapy started within 14 days if necessary; I: 75.0% C: 46.0% p=0.016 Weekly ESA dose I: 5509IE C: 6877 IE p<0.001 Annual ESA cost I: 5109$ C: 6397$ p<0.001

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Dubovetsky 2022	O-RC	HD I: n=61 C: n=68 6 m FU	P&A	Anaemia management by the nephrologist, historical controls	Percentage of time in therapeutic range (TTR) for Hb 9.5-10.9 g/dL	Differences in mean weekly ESA dose Number of red blood cell transfusions Percentage of Hb values in categories ≤8.5 g/dL, 8.6-9.4 g/dL, 9.5-10.9 g/dL, 11-11.9 g/dL, and≥12 g/d at end of study; Median ferritin values Median TSAT Total iron doses per patient ESA-associated costs	TTR for Hb: I: 30.7% C: 29.3% p=0.177 Weekly ESA dose: I: 10064 U C: 15227 U p=0.035 Red blood cell transfusions (n) : I: 0.3 C: 0.6 p=0.255 Percentage in different Hb categories: no differences Ferritin: I: 629 ng/mL C: 386 ng/mL p=0.016 TSAT: I: 24.5% C: 22% p=0.055 Total iron doses per patient: I: 1200 mg C: 900 mg p=0.060 ESA-associated costs: I: 154$ C: 233$ p=0.035

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
El Nekidy 2020	O-RC	HD N= 163 12 m FU before (C) and 12 months after intervention (I)	P&A	Anaemia management by the nephrologist, historical controls	# Aim of the study was to assess the impact of the nephrology pharmacist on the proportion of patients who achieve Hb goals with optimised ESA and iron consumption, iron indices (TSAT and ferritin), blood transfusions, and iron dosing strategy		Mean Hb: I:108.3±9.4 g/L C:109.5±9.5 g/L p=0.1586 Transfusion rate: I:1.8% C:1.3% p=0.196 Weekly ESA dose: I: 11364.1 ±52 U C:12315.6±8 U p=0.0556 Monthly iron dose (iv): I: 215.4 ±90 C: 215.4±100 p=0.9968 TSAT: I:0.307±0.05 C: 0.305±0.11 p=0.8386 Ferritin (ng/mL) I:317.1 ±12 C:273.5±22 p=0.0019

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Joy 2007	O-RC	CKD-NDD I:n=99 C:n=29 Total study period =28 months (follow-up per patient not mentioned)	P&A	Anaemia management by the nephrologist, historical controls	Proportion of patients with ≥ 30 days of ESA treatment who achieved target Hb level ≥ 11.0 g/dl	Hb level, darbepoetin alfa dose, and darbepoetin alfa administration frequency Secondary Hb outcomes: length of time to attain target Hb for naïve patients (Hb ≥ 11.0 g/dl) Hb at target attainment Last available Hb level	Attainment of Hb target level I: 78% (mean Hb ± SD 11.7 ± 7 g/dl) C: 41% Length of time to attain target Hb: I: 7.9±7.5 weeks C: 6.1 ± 2.7 weeks Mean Hb level at target achievement I: 11.7±0.7 g/dL C: 11.4 ±0.3 g/dL Last available Hb level for all patients (n=134): 10.9 ±1.5 g/dL Weekly dose DA: 10-100 mcg per week (no further data reported) Dosing interval DA: Every 2 weeks: 82% Every 3 weeks: 14% Every 4 weeks: 4% No P-values reported

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Kimura 2004	O-RC	HD N=41 FU=9 months	P&A	Anaemia management by the nephrologist, historical controls	# Therapeutic and pharmaco-economic outcomes were evaluated.		Haematocrit >30% (therapeutic target) I: 78.0% C: 17.1% Average Ht I: >30% C: 28.5% Monthly consumption of epoetin beta I: 624000 IU C: 915000 IU Change in monthly cost of epoetin beta I: 1.37 mln yen C: 1.86 mln yen No P-values reported

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Linn 2023	O-RC	HD (hospitalised) N=264 (pre) N=272 (post) FU=6 months	P	Not described	Average acquisition cost of epoetin alfa-epbx (epoetin zeta) per patient	Average monthly purchasing cost during the study period Overall purchasing cost of epoetin alfa-epbx Average dose of epoetin alfa-epbx Average number of administered doses per patient Percentage of patients experiencing stroke or thrombosis Percentage of patients receiving blood transfusion(s) during admission	Average acquisition cost per patient: I: $1,041.35 C: $1,681.77 p<0.0001 Average monthly purchasing cost I: $21,312.21 C: $24,828.48 p=0.5594 Overall purchasing cost I: $127,873.25 C: $148,970.89 vs no p-value Average dose I: 10,112 units C: 13,694 p=0.0004 Average number of administered doses per patient I:1.79 C: 2.09 doses p = 0.0668 No differences between the incidence of stroke, thrombosis, and RBC transfusion

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Ohnishi 2011	O-RC	HD N=84 FU=12 months	P&A	Anaemia management by the nephrologist, historical controls	# Examination of the influence of having pharmacists actively manage Hb levels on therapeutic outcome		Number of patients with optimal levels of Hb at start of follow-up: I: 45 C: 40 p=0.07 Number of patients with optimal levels of Hb at end point: I: 61 C:46 p=0.03
Quercia 2001	O-RC	HD N=? 1994: historical control 1995 and 1998 after the intervention Cross-sectional	P	Anaemia management by the nephrologist, historical controls	# Goals were to initiate a continuing pharmacy service that results in safe and effective management of anaemia in haemodialysis patients and to determine if a pharmacist-managed anaemia program leads to cost avoidance with regard to epoetin alpha		Ht <31%: 1994: 32% 1995: 21% 1998: 14% Cost avoidance by pharmacy management: 1994: n=109 ESA dose per patient: 5.636 U total costs: $856.197 1995: n=114 patients ESA dose per patient: 4.425 U, total costs: $704.313 Cost avoidance: $191.159 1998: n=119 ESA dose per patient: 5764 U total cost $ 1.161.660 Cost avoidance: 203.985 No P-values reported

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Rogers 2011	O-RC	CKD-NDD C: n=390 I: n=494 FU= 6 months before and 6 months after intervention Non-inferiority design	A	Anaemia management by the nephrologist, historical controls	Percentage of measured Hb and transferrin saturation levels within target range (11-12 g/dL and 22%–50%, respectively)	Weekly dose and number of dose changes for epoetin alfa, darbepoetin, and iron	Percentage in target range Hb: I: 34.2% C: 33.3% CI for the difference: -2.5 to 4.4 Percentage in target range TSAT: I: 56.9% C: 58.8% CI for the difference: -3.4 to 7.7 Mean doses: epoetin alpha I: 3529 U C: 3270 U p= 0.85 Darbepoetin alfa I: 20.4 µg C: 18.8 µg p= 0.59 Iron I: 1042 mg C: 1044 mg p= 0.98

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Gonzalez Fernandez 2013	O-RCS	CKD-NDD HD PD I:n= 215 C:n=329 Cross-sectional	P&A	Anaemia management by the nephrologist, historical controls	# Aim of the study was to describe and evaluate the effectiveness of a program to adjust the prescription and dispensing of ESA		Hb in target range PD: I:73% C: 64% p=0.2 CKD-NDD: I: 75% C: 60% p=0.2 HD: I: 89% C: 57% p<0.001 Darbepoetin alfa dose (mcg) PD: I: 147.4±167.47 C:155.9±136.5 p=0.434 CKD-NDD: I: 73.105±69.64 C: 146.1 ±137.1 p=0.001 HD: I: 115.23±83.02 C: 162.3±127 p=0.012 Monthly ESA cost: PD: I: €121 C: €177 p not reported CKD-NDD: I: €84 C: €110 p not reported HD: I: €110 C: €209 p not reported
Walton 2005	&	HD N=278	P&A	Anaemia management by the nephrologist Comparison with USA averages	#		Hb: I: 11.8g/dL C: 9.5g/dL US average: 11.9g/dL Hb >11g/dL: I: 80% C: 25% US average: increase from 26.1 to 75%

Table 1. Study characteristics and outcome data (continued)

Study	Design	Population (including number of patients and duration of follow-up)	Inter-vention	Control group or comparison	Primary outcome	Secondary outcomes	Results
Walton 2005 (continued)					The primary objective of this study was to describe the pharmacist-managed anaemia program in an outpatient haemodialysis clinic and evaluate the program by comparing the results to the US averages		Ferritin: I: 431 ± 232.1 ng/ml C: 280.9 ± 326.4 ng/ml TSAT: I: 33±8% C: 21±7.9% Weekly ESA dose: I:121.6 U/kg/week US average: 229 U/kg/week Annual cost avoidance: $3000 per patient P-values not reported

Abbreviations: A: algorithm-based; C: control; CI: confidence interval; CKD-NDD: chronic kidney disease, non-dialysis dependent; DA: darbepoetin alfa; ESA: erythropoiesis stimulating agent, e.g. darbepoetin alfa, epoetin alfa, etc; FU: follow-up; Hb: haemoglobin; HD: hemodialysis; Ht: haematocrit I: intervention; I-PP: Interventional, pre post design, patient is own control; I-RCT: Interventional, RCT; O-RC: observational, retrospective cohort; O-RCS: observational, retrospective cross-sectional; N=number; P: pharmacist-based; PD : peritoneal dialysis; P&A: pharmacist-based and algorithm-based; QALY: quality adjusted life year; RCT: Randomized, controlled trial; TSAT: transferrin saturation; TTR: time in therapeutic range

* Outcome parameters not defined as primary or secondary

Outcome parameters not defined

& Study design could not be determined

Intervention characteristics

Table 2 shows the intervention description, including the algorithm characteristics of the sixteen included studies.

Table 2. Intervention description and algorithm characteristics

Study	Intervention description	Algorithm-based? If yes, manual algorithm or computer-based?	Algorithm description including input
I-RCTs			
Armstrong 2000	At least 1 pharmacist at each study site completed an intensive 4-day training session on the management of patients undergoing long-term haemodialysis, use of the software system and review of the specific DUE criteria. Education about the DUE (drug use evaluation) process and each criterion was also provided during each training session. In addition, a site validation visit was conducted to explain the data collection and processing of the DUE. Working in collaboration with the nephrologist responsible for each study patient, the trained pharmacist was responsible for monitoring, evaluating and recommending initial and subsequent epoetin alfa dosage regimens for patients in the treatment group. The pharmacist recommended dosages for epoetin alfa and iron based on a computer software program (EPO-CALC®). This program was based on computer-modelled algorithms for epoetin alfa and iron dose optimisation	Yes, computer-based	The software used its internal haematocrit and iron databases, along with blood pressure and laboratory data from databases manually entered by the pharmacist to calculate the DUE results. The software automatically determined whether 6- and 12-month criteria were met by examining process indicators (e.g. monitoring of iron stores) and clinical outcome measures (e.g. haematocrit values within the desired range).

	Algorithm output	Algorithm available?	Level of detail of intervention description? Description complete?	Quality of the intervention description	Is intervention reproducible?
	Process indicators Adverse effects	No	Reasonably detailed intervention description Description not complete	Moderate	No

Table 2. Intervention description and algorithm characteristics (continued)

Study	Intervention description	Algorithm-based? If yes, manual algorithm or computer-based?	Algorithm description including input
Van den Oever 2020	Two pharmacist investigators developed treatment algorithms for darbepoetin alfa (DA) and iron sucrose, based on SPC and the renal anaemia guideline. Principles of the treatment algorithms were discussed with the nephrologists and agreed upon. Four pharmacists provided dose advice, two of them being the investigators and two additional pharmacists, after instruction. Monthly laboratory analyses were performed (Hb, TSAT, ferritin). Pharmacists monthly recommended dosages for epoetin alfa and iron based on treatment algorithms, depending on laboratory analyses. Dose recommendations were communicated by email and when agreement was reached, the nephrologist prescribed the agreed doses.	Yes, manual	Algorithm for DA based on actual Hb and change in Hb Algorithm for iron sucrose based on TSAT and ferritin
Intervention pre-post study			
Dashti-Kavidaki 2012	Patients on maintenance HD were managed by clinical pharmacists participating in medical team rounds; all patients were evaluated for anaemia parameters (serum Hb, ferritin concentrations and TSAT). Ferritin concentrations and TSAT were evaluated every three months in stable subjects, and monthly in patients whose drugs were dose-adjusted. Parenteral erythropoietin and intravenous iron sucrose were used to manage anaemia.	Unknown	NA
Observational, retrospective cohort study			
Aspinall 2012	Pharmacist-managed ESA clinics: Pharmacists' scope of practice allowed them to dose and monitor ESA therapy. Patients at most sites were referred to the pharmacist-managed ESA clinic by a medical provider. Study clinics had been operational since at least August 1, 2008, and evidence-based protocols were in place for the management of patients receiving ESAs. Pharmacists were responsible for dosing and management of ESA therapy. Iron testing (ferritin, serum iron or TSAT) was performed. It is unclear whether pharmacists also prescribed iron therapy. No further description was available.	Unknown	NA

	Algorithm output	Algorithm available?	Level of detail of intervention description? Description complete?	Quality of the intervention description	Is intervention reproducible?
	Dose advice DA: withhold DA for 4 weeks, after that, restart with 25% lower dose; dose decrease with 25%; same dose; dose increase with 25%; and dose increase with 50% Dose advice iron sucrose: no iron sucrose, iron sucrose 100 mg every two weeks, iron sucrose 100 mg once a week, and iron sucrose 100 mg thrice a week	Yes	Quite detailed intervention description Intervention description complete	Moderate to high	Yes
	NA	NA	Intervention minimally described Description not complete	Low	No
	NA	NA	Intervention minimally described Description not complete	Low	No

Table 2. Intervention description and algorithm characteristics (continued)

Study	Intervention description	Algorithm-based? If yes, manual algorithm or computer-based?	Algorithm description including input
Aspinall 2013	Pharmacist-managed ESA clinics: Pharmacists' scope of practice allowed them to dose and monitor ESA therapy. Patients at most sites were referred to the pharmacist-managed ESA clinic by a medical provider. Study clinics had been operational since at least August 1, 2008, and evidence-based protocols were in place for the management of patients receiving ESAs. Pharmacists were responsible for dosing and management of ESA therapy. Iron testing (ferritin, serum iron or TSAT) was performed. No further description was available.	Unknown	NA
Bucaloiu 2007	A protocol-driven, pharmacist-managed program with monthly measurements of Hb and TSAT. Iron was given intravenously in the pharmacist group, not mentioned how this was in the physician-managed group.	Unknown	NA
Debenito 2014	A protocol-driven, pharmacist-managed program. ESA service operated under a Collaborative Drug Therapy Management agreement, whereby a clinical pharmacist and physician established written protocols authorising the pharmacist to manage drug therapy for a given indication, including initiation or discontinuation of specified medications, dose adjustment, and ordering appropriate laboratory tests. Patients were monitored using a population management database.	Unknown	NA

	Algorithm output	Algorithm available?	Level of detail of intervention description? Description complete?	Quality of the intervention description	Is intervention reproducible?
	NA	NA	Intervention minimally described Description not complete	Low	No
	NA	NA	Intervention minimally described Description not complete	Low	No
	NA	NA	Intervention minimally described Description not complete	Low to moderate	No

Table 2. Intervention description and algorithm characteristics (continued)

Study	Intervention description	Algorithm-based? If yes, manual algorithm or computer-based?	Algorithm description including input
Dubovetsky 2022	Epoetin protocolized dosing was based on patient weight, Hb concentration, and subsequent Hb changes defined as percentage over a period of time. Patient's Hb values were measured every 2 to 4 weeks. Iron stores were assessed on a monthly basis by measuring ferritin and transferrin saturation (TSAT), according to preexisting practice standards. Epoetin alfa doses were administered via the IV route with each scheduled haemodialysis three times a week in accordance with preexisting practice by nephrologists on the unit. Epoetin adjustments varied based on the patient's Hb change over a 14-day period and current Hb concentration. Patients were screened by pharmacists for eligibility to receive parenteral iron sucrose; this was recommended for eligible patients if ferritin <1000 ng/mL and TSAT <25%.	Yes, manual	Algorithm for epoetin alfa based on actual Hb and change in Hb
El Nekidy 2020	Dedicated, nephrology-trained pharmacists clinically dose and monitor ESA and iron therapies within a multidisciplinary team. Hb levels, iron indices, and ESA consumption were collected; Hb levels were measured monthly, and iron indices were measured quarterly according to guidelines. The nephrology-trained pharmacists monthly reviewed patient labs and devised the anaemia management plan. These plans were discussed during weekly rounds with the nephrologists.	Yes, manual	Algorithm for epoetin alfa based on actual Hb, change in Hb and symptoms. Differentiation between start or change of epoetin alfa. Algorithm for iron based on Hb, TSAT, and ferritin
Joy 2007	Development of a multidisciplinary nephrology outpatient clinic for the management of renal anaemia. The clinical pharmacist co-ordered anaemia therapies and other drugs and conducted basic clinical assessments during patient visits. The patients were evaluated for response to therapies and assessed for complications of CKD. The clinical pharmacist also ordered laboratory tests pertinent to patient care; reviewed the test results; provided patient education concerning CKD, drugs, and diet; and coordinated indigent drug program entry for patients receiving erythropoietic agents.	Yes, manual (ESA)	Algorithm based on Hb values and changes in Hb

	Algorithm output	Algorithm available?	Level of detail of intervention description? Description complete?	Quality of the intervention description	Is intervention reproducible?
	Dose advice epoetin alfa: Hold dose, -25%, no change, +25%	Yes	Quite detailed intervention description Intervention description complete	Moderate to high	Yes
	Dose change: withhold epoetin alfa, decrease dose by 25 or 50% or increase dose up to 100%. Start epoetin: 50-100 IU epoetin per kg/week Iron: weekly, every two weeks, monthly, no iron (hold iron)	Yes	Intervention minimally described Description not complete	Low	No
	Dose advice for ESA including dose and dosing interval	Yes	Intervention reasonably described Description not complete	Moderate	No

Table 2. Intervention description and algorithm characteristics (continued)

Study	Intervention description	Algorithm-based? If yes, manual algorithm or computer-based?	Algorithm description including input
Kimura 2004	Pharmacists performed clinical activities , including four main activities as follows: 1) compiling guidelines for proper use of recombinant human erythropoietin in collaboration with physicians; 2) providing drug information on renal anaemia to physicians; 3) MUE (medication-use evaluation) based on laboratory test data; 4) Proposing plans to change prescriptions based on MUE	Yes, manual	Algorithm based on ferritin, Ht values, and changes in Ht;
Linn 2023	Pharmacist-led epoetin alfa-epbx (epoetin-zeta) initial dose consultation for hospitalised patients. Nephrologists consulted pharmacists through a haemodialysis order set or order browse. The consultation was an opt-out feature and was the default on the order set. The starting dose for epoetin-epbx was 50 units/kg iv 3 times a week. If a patient was already on ESA, the dose was converted (using the conversion table given).	No	NA
Ohnishi 2011	Pharmacists performed clinical management including five main activities 1) providing drug information on renal anaemia to physicians; 2) compiling guidelines for proper use of recombinant human erythropoietin and iron in collaboration with physicians; 3) medication use evaluation (MUE) based on laboratory data; 4) proposing plans to change prescriptions based on medication use evaluations and 5) providing drug information and lifestyle care point to patients.	Yes, manual	Algorithm based on ferritin, TSAT, Hb values, and changes in Hb
Quercia 2001	A drug use evaluation (DUE) protocol was set up, in which a pharmacist evaluated epoetin alpha doses. Monthly, the pharmacist provided dose recommendations for epoetin alpha and iron (full protocol available)	No	NA
Rogers 2011	A nurse-driven anaemia management protocol was implemented, based on a regional anaemia management protocol. Nurses were trained to use this protocol and to dose ESA and iron using this protocol.	Yes, manual	Algorithms for ESA and iron based on Hb, change in Hb, and TSAT

	Algorithm output	Algorithm available?	Level of detail of intervention description? Description complete?	Quality of the intervention description	Is intervention reproducible?
	ESA dose (start) plus change in ESA dose; iv iron (40 mg/week) cease or continue	Yes	Intervention minimally described Description not complete	Low	No
	NA	NA	Intervention minimally described Description not complete	Low	No
	ESA dose (maintain, increase or decrease one dose level) Standard iv iron (ferric oxide) 40 mg when iron parameters low (ferritin ≤60 ng/ml and TSAT ≤ 20%)	Yes (for ESA)	Intervention minimally described Description not complete	Low	No
	NA	NA	Intervention reasonably described Description not complete	Moderate	No
	ESA and iron dose; notification of the physician in specific situations (e.g. very low Hb, great Hb increases etcetera)	Yes	Intervention minimally described Description not complete	Low	No

Table 2. Intervention description and algorithm characteristics (continued)

Study	Intervention description	Algorithm-based? If yes, manual algorithm or computer-based?	Algorithm description including input
Observational, retrospective, cross-sectional study			
Gonzalez Fernandez 2013	When ESA is prescribed, the pharmacist analyses the patient's pharmacotherapeutic profile (ESA dose and frequency) and evolution in time of Hb. In case of Hb>12.5 g/dL and no change in dosage, the pharmacist sends an email to the treating nephrologist to inform him of the patient's risk. In case of Hb >12.5 g/dL and dosage change, no action is taken. In case of Hb >13.5 g/dL or <8.5 g/dL and no dosage change, the pharmacist contacts the nephrologist by telephone to discuss how to proceed.	Yes (partially described)	Algorithm based on Hb values. Action described for Hb >12.5 g/dL and Hb <8.5 g/dL. No description for Hb >8.5 g/dL and 12.5 g/dL
Study with an unknown design			
Walton 2005	A clinical pharmacist monitored laboratory, medication, and other patient information to initiate and adjust erythropoietin and iron therapy on a monthly basis in the outpatient haemodialysis unit. The pharmacist wrote orders for each of the chronic haemodialysis patients, which were reviewed by the unit's medical director. Protocols for erythropoietin and iron therapy were developed by a multidisciplinary group of physicians, pharmacists, and nurses using the K-DOQI guidelines as a reference	Yes, manual	Algorithms for ESA and iron based on Ht or Hb (ESA) and ferritin and TSAT (iron)

Abbreviations: DA: darbepoetin alfa; DUE: drug use evaluation; ESA: erythropoietin stimulating agents; Hb: haemoglobin; HD: haemodialysis; Ht: haematocrit; MUE: medication use evaluation; TSAT: transferrin saturation

In seven studies, ESA dosing was pharmacist-managed, and in one study, ESA dosing was algorithm-managed. In nine studies, pharmacist-managed and algorithm-managed dosing of ESA were combined. In six of the seven pharmacist-managed studies, it was unknown if an algorithm was used. In one study, no algorithms were used: dosing was protocol-based and pharmacist-managed.

The description of the algorithms was complete in all ten studies that used an algorithm. In six of these ten studies, algorithms were also used for iron dosing [10,22–26].

	Algorithm output	Algorithm available?	Level of detail of intervention description? Description complete?	Quality of the intervention description	Is intervention reproducible?
	Pharmacist action for Hb >12.5 g/dL; Hb >13.5 g/dL and Hb <8.5 g/dL	No	Intervention minimally described Description not complete	Low	No
	Change in ESA dose in %: increase by 10, 15, or 25% and decrease with 20%; hold ESA or no change in dose	Yes	Intervention reasonably described Description not complete	Moderate	No

In general, the quality of the intervention description was low to moderate and interventions were not reproducible. Five studies might be reproducible to some extent [21,23,25,27,28], some variation in the execution of the intervention might, however, occur.

Risk of bias and study quality

Data regarding the risk of bias and study quality are depicted in Table 3.

Table 3. Risk of bias, quality assessment, and design of included studies.

Study	Risk of bias	Quality assessment	Design
Van den Oever 2020	Some concerns	Weak	RCT
Rogers 2011	Serious	Moderate	Observational, retrospective cohort
Aspinall 2012	Serious	Weak	Observational, retrospective cohort
Aspinall 2013	Serious	Weak	Observational, retrospective cohort
Debenito 2014	Serious	Weak	Observational, retrospective cohort
El Nekidy 2020	Serious	Weak	Observational, retrospective cohort
Dubovetsky 2022	Serious	Weak	Observational, retrospective cohort
Linn 2023	Serious	Weak	Observational, retrospective cohort
Gonzalez Fernandez 2013	Serious	Weak	Observational, retrospective cross-sectional
Kimura 2004	Serious	Weak	Observational, retrospective cohort
Ohnishi 2011	Serious	Weak	Observational, retrospective cohort
Armstrong 2000	Critical	Weak	RCT
Dashti-Kavidaki 2012	Critical	Weak	Interventional, pre-post
Bucaloiu 2007	Critical	Weak	Observational, retrospective cohort
Joy 2007	Critical	Weak	Observational, retrospective cohort
Quercia 2001	Critical	Weak	Observational, retrospective cohort
Walton 2005	Critical	Weak	Design could not be determined

All but three included studies [22,23,29] were retrospective analyses. The risk of bias in observational studies was serious to critical as assessed with the ROBIN-S assessment tool. The risk of bias in the randomised controlled trials (RCTs) differed: the study of Armstrong & Cherrick [22] was classified as having a high risk of bias; the study of VandenOever et al [23] as having some concerns. Overall study quality was weak to moderate. The clinical trial register clinicaltrial.gov did not

provide any evidence for bias due to missing results, as no trials without reported results were found.

Data synthesis

Clinical and methodological heterogeneity was high between studies, due to differences in participants, study design, interventions, comparisons, and outcome parameters (Table 4).

Overall, we concluded that the clinical and methodological heterogeneity was too high to perform a meaningful meta-analysis, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions [30]. However, data could be synthesised for pharmacist-managed renal anaemia for the haemoglobin outcome and ESA dose using standardised metrics as described below.

Table 4. Description of clinical and methodological heterogeneity.

	Description in studies (n)
Participants	A description of patient characteristics was missing in 4 studies, and limited (e.g. age, gender, ethnic background) in another 4 studies. In 9 studies, a more elaborate description of patient characteristics was provided. Mean patient age varied from 46 (1) to 75 (1, Veteran Affairs Medical Centres). In 3 studies, the mean patient age was around 55 years; in 6 studies, the mean age was around 65. The percentage of male participants varied between 45 and 68%, except for 1 study with 97% male participants (in Veteran Affairs Medical Centres). When described, the participants differed substantially in ethnic background, varying from 7% to 86% of patients of colour. Studies were conducted in patients with chronic kidney disease (7), haemodialysis (11), and peritoneal dialysis (1).
Interventions	ESA dosing: pharmacist-managed (7), algorithm-managed (1), combined pharmacist-managed and algorithm-managed (9). In 6 out of 7 pharmacist-managed studies, it was unknown if an algorithm was used. The intervention descriptions were generally of low to moderate quality and insufficient to comprehend and reproduce the intervention. Only two studies (VandenOever and Dubovetsky) provided an intervention description of moderate to high quality.
Comparisons	Usual care by the nephrologist (15), primary care physician (1), no comparison (1) Usual care was not further described in all but one study (VandenOever).

Table 4. Description of clinical and methodological heterogeneity. (continued)

	Description in studies (n)
Outcomes	In eight studies, the outcome parameters were not clearly defined. In two studies, outcome parameters were not defined as primary or secondary. When the outcome parameters were described, they varied substantially: Hb in target range (6), Ht (3), monitoring laboratory parameters (2), time to achieve target Hb/Ht (3), iron status (7), iron dose (4), ESA dose (8), transfusions (4), and more (see also Supplementary Table 1)
Design	RCT (2), pre-post (1), observational with a control group (13): historical controls (8), other sites or primary care physician (3), USA average (1), other (1). In 1 study, no control group was mentioned.

Study outcomes

Outcomes varied substantially between studies. Outcome categories most frequently reported were haemoglobin or haematocrit levels, ESA dose, ESA expenditure, iron status, and iron dose.

Standardised metrics regarding haemoglobin and ESA for pharmacist-managed renal anaemia

The selected standardised metric regarding the haemoglobin outcome was the percentage of haemoglobin within target range in the intervention versus the control group. This metric was reported in six studies [11,23,28,29,31,32]. The characteristics of these studies are displayed in Table 5.

Table 5. Summary table: difference in percentage in target range for haemoglobin in pharmacist-managed renal anaemia versus the control group

Study and population	Type of intervention	Study design	Risk of bias	n	p-value	difference in % haemoglobin in target range	95% CI lowest value	95% CI highest value
Van den Oever 2020 HD	Pharmacist and algorithm	RCT	Some concerns	200	0.001	15.4	6.26	24.54
Dubovetsky 2022 HD	Pharmacist and algorithm	observational, retrospective	Serious	129	0.177	1.4	-0.63	3.43
Gonzalez-Fernandez 2013 HD	Pharmacist and algorithm	observational, retrospective	Serious	146	<0.001	32	14.07	49.93
Dashti-Kavidaki 2012 HD	Pharmacist	observational, retrospective	Critical	86	0.664	-3.5	-18.67	11.67
Gonzalez-Fernandez 2013 CKD-NDD	Pharmacist and algorithm	observational, retrospective	Serious	135	0.2	15	-7.87	37.87
Aspinall 2012 CKD-NDD	Pharmacist	observational, retrospective	Serious	481	<0.001	14.2	6.25	22.15
Bucaloiu 2007 CKD	Pharmacist	observational, retrospective	Critical	134	<0.001	25.9	11.39	40.41
Gonzalez-Fernandez 2013 PD	Pharmacist and algorithm	observational, retrospective	Serious	90	0.2	9	-4.72	22.72

CI: confidence interval; CKD: chronic kidney disease; CKD-NDD: chronic kidney disease, non-dialysis dependent; HD: haemodialysis; PD: peritoneal dialysis; RCT: randomised controlled trial

A forest plot of the results of these studies regarding the haemoglobin outcome is displayed in Figure 2. The percentage in target range for haemoglobin in the intervention group varied between 3.5% lower (95%CI -18.67% to + 11.67%) [29] to 32.0% higher [31] (95%CI 14.07 to 49.93%) in the pharmacist-managed group versus the control group (n=1401).

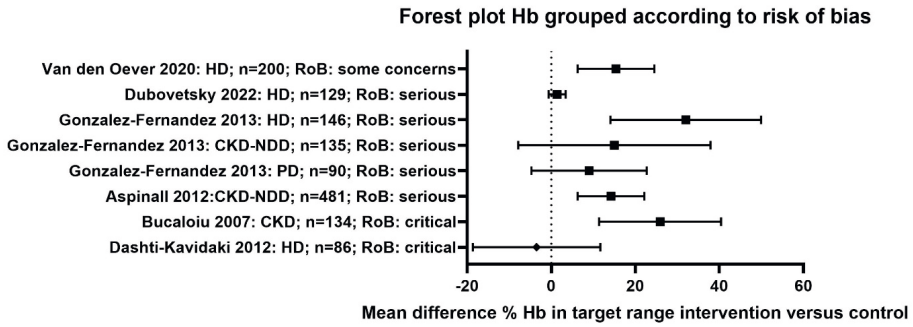

Figure 2. Forest plot regarding the percentage of haemoglobin within target range in the intervention versus the control group.

The standardised metric regarding ESA dose was the relative ESA dose in the intervention versus the control group, as a percentage. This metric was calculated based on the actual dose of epoetin (alfa, beta or zeta) and darbepoetin alfa (DA) in the intervention versus the control group. ESA dose was reported in eight studies [11,13,23,26,28,31–33]. The characteristics of these studies are displayed in Table 6.

Table 6. Summary table: percentage reduction in ESA dose in pharmacist-managed renal anaemia versus the control group

Study and population; pharmacist- and algorithm-managed or only pharmacist-managed renal anaemia	Study design	Risk of bias	Type of ESA	n	p-value	% reduction in ESA dose	95% CI lowest value	95% CI highest value
Van den Oever 2020 HD; P&A	RCT	Some concerns	DA	200	0.02	27.51%	4.30%	50.71%
Linn 2023 HD; P	observational, retrospective	Serious	epo	536	<0.001	26.16%	11.50%	40.81%
El Nekidy 2020 HD; P&A	observational, retrospective	Serious	epo	163	0.0556	7.73%	-0.20%	15.65%
Gonzalez-Fernandez 2013 HD; P&A	observational, retrospective	Serious	DA	146	0.012	29.02%	6.37%	51.67%
Dubovetsky 2022 HD; P&A	observational, retrospective	Serious	epo	129	0.177	33.91%	-15.22%	83.03%
Aspinall 2012 CKD-NDD; P	observational, retrospective	Serious	DA	481	0.049	26.28%	0.07%	52.49%
Gonzalez-Fernandez 2013 CKD-NDD; P&A	observational, retrospective	Serious	DA	135	0.001	49.97%	20.32%	79.61%
Debenito 2014 CKD-NDD; P	observational, retrospective	Serious	epo	101	<0.001	19.89%	8.75%	25.58%
Bucaloiu 2007 CKD; P	observational, retrospective	Critical	epo	134	<0.001	44.18%	19.43%	68.94%
Gonzalez-Fernandez 2013 PD; P&A	observational, retrospective	Serious	DA	90	0.434	5.45%	-7.97%	18.87%

CI: confidence interval; CKD: chronic kidney disease; CKD-NDD: chronic kidney disease, non-dialysis dependent; DA: darbepoetin alfa; epo: epoetin alfa, beta or zeta; ESA: erythropoietin stimulating agent; HD: haemodialysis; P: pharmacist-managed renal anaemia; P&A: pharmacist- and algorithm-managed renal anaemia; PD: peritoneal dialysis; RCT: randomised controlled trial

The forest plot of the reduction in ESA dose in the intervention versus the control group is displayed in Figure 3. The range in reduction in ESA dose was 5.45% (95%CI -7.97% to + 18.87%) [31] to 49.97% (95%CI 20.32% to 79.61%%) [31] in the pharmacist-managed group versus the control group.

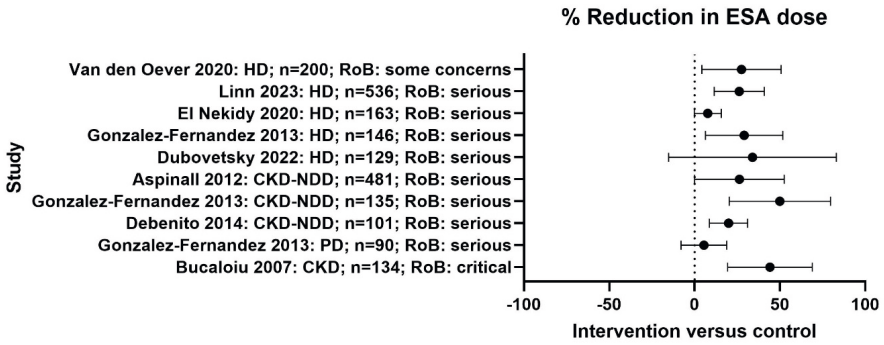

Figure 3. Forest plot regarding the relative dose of ESA in the intervention versus the control group.

Qualitative description of iron outcomes

Iron status

Seven studies reported iron status (transferrin saturation or ferritin levels or both) as outcome [23–26,28,29,32]. In five of seven studies, iron status was significantly higher in the intervention group [23,26,28,29,32]. No significant difference in iron status was found in one study, which was a non-inferiority study [24]. One study did not report statistical significance [25].

Iron dose

Four studies reported on iron doses as outcome [23,24,26,28]. One of these studies reported a significantly higher iron dose in the intervention group [23], whereas the other three studies reported no significant difference[24,26,28]. The iron dose in the study from Dubovetsky and colleagues showed a trend towards a higher total iron dose in the intervention group (1200 mg vs 900 mg, p=0.060) [28].

Discussion

In this systematic review, we show that evidence regarding algorithm-managed and pharmacist-managed dosing of erythropoietin-stimulating agents in renal anaemia is scarce and generally of low to moderate quality with a substantial risk of bias. Only two randomised, controlled trials could be identified; all other studies were observational in nature and follow-up was relatively short with a range of 6 to 13 months.

Meta-analysis was not possible due to heterogeneity and high risk of bias. However, standardised metrics regarding haemoglobin outcome and ESA dose in this study suggest that pharmacist-managed dosing of ESA may improve the percentage in target range for haemoglobin and may reduce ESA dose. As meta-analysis was not possible, no definite conclusion could be drawn on the effectiveness of these strategies. Therefore, no GRADE recommendations could be provided.

Three previous systematic reviews reported on the effectiveness of pharmacist-managed renal anaemia as part of a review of all sorts of pharmacist interventions in patients with chronic kidney disease [14,15]. Salgado and colleagues concluded in 2012 that controlled and uncontrolled studies (n=8) on pharmacist-managed renal anaemia failed to demonstrate a significant impact on anaemia parameters and the high heterogeneity between studies precluded a quantitative synthesis of the results. On the other hand, Al Raiisi and colleagues [14] concluded in 2019, based on four studies published after the review of Salgado, that pharmacist-managed anaemia did improve haemoglobin outcomes [10,11,13,34]. Recently, Ardavani et al also concluded in their systematic review that pharmacist-managed renal anaemia improved haemoglobin outcomes [16]. However, we have serious concerns regarding the internal and external validity of the haemoglobin outcome in this last systematic review. Our three concerns regarding the internal validity relate to the choice of haemoglobin outcome parameter, the methodology, and the risk of bias of included studies. First, regarding the haemoglobin outcome, Ardavani et al reported an increase in haemoglobin of 0.76 g/dL (0.47 mmol/L) in the intervention versus the control group. However, they did not take into account the differences in baseline haemoglobin levels between the intervention and the control groups. Second, the risk of bias was not reported per study, but only as part of a general

quality assessment. Third, in the three RCTs included in the meta-analysis regarding the haemoglobin outcome, haemoglobin was one of several primary or secondary outcome parameters; none of these RCTs were specifically designed to determine the effect of pharmacist-managed renal anaemia on haemoglobin. Regarding the external validity of the haemoglobin outcome in the systematic review of Ardavani et al, we have concerns about the origin of the three included RCTs, as they all were performed in non-Western countries (India, Iraq, and Jordan). We therefore doubt that these results are representative of clinical practice in Europe and other Western countries. To underscore this concern, the included RCT from Mateti et al from India reported very low haemoglobin levels, especially in the governmental hospital setting. All in all, we think that the conclusions of the previous three systematic reviews may not represent the true effects of pharmacist-managed renal anaemia, due to the high risk of bias and heterogeneity of available literature and limited internal and external validity of the three systematic reviews.

This systematic review has several strengths. First of all, the included studies were performed in different countries, which suggests that the interventions can be performed in multiple health system models. Second, the absence of restrictions regarding study outcomes helped us to cover all possible outcomes to provide a wide overview of all possible benefits of algorithm-managed and pharmacist-managed dosing of ESA in patients with chronic kidney disease. Third, we followed all recommendations regarding registering and performing systematic reviews: the protocol was registered with PROSPERO, the international prospective register of systematic reviews. Furthermore, the protocol was drafted following PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) standards. Last, this systematic review was conducted and reported following PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines.

Of course, this systematic review also has limitations. First, the quality of the included studies was generally low to moderate. Only two randomised controlled trials and one interventional prospective study could be included. All other studies had an observational design, were often uncontrolled, generally had a poor description of the studied intervention, and provided limited information about the included population. In several studies, P-values or other measures of statistical significance were not mentioned, which made it impossible to determine the precision of the effect estimate. All these limitations preclude a

definite conclusion on the effectiveness of algorithm-managed and pharmacist-managed dosing of ESA in patients with renal anaemia.

Second, the high risk of bias and the large degree of heterogeneity between studies did not permit combining the study results into a formal meta-analysis. However, standardised metrics for haemoglobin and ESA dose suggest that pharmacist-managed dosing of ESA may improve the percentage in target range for haemoglobin and reduce ESA dose.

Third, we did not contact the authors for further details on the interventions if the intervention description was unclear. This was a deliberate choice as we aimed to determine the reproducibility of the method as described in the original publication.

Finally, an inherent limitation of all reviews is the inclusion of published literature only. Although our search was performed in several databases, we consulted clinicaltrials.gov, and included some studies with negative results, we cannot exclude publication bias towards studies with positive findings.

Conclusions

Available evidence on the effectiveness of algorithm-managed and pharmacist-managed dosing of ESA in renal anaemia was scarce and showed heterogeneous results, with a high risk of bias. Therefore, no definite conclusions could be drawn on the effectiveness of both strategies. Consequently, recommendations on the implementation of either of the two strategies could not be made. However, there is some evidence of low to moderate quality that pharmacist-managed dosing of erythropoietin-stimulating agents in renal anaemia may improve the percentage in target range for haemoglobin and reduce ESA dose. This effect may be explained by better guideline adherence and improved prescribing of ESA and iron. Prospective and randomised studies of better quality are needed to provide evidence that can lead to broad implementation in clinical practice.

Acknowledgments

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