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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-managed 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 (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 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).

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.

PROSPERO registration number CRD42021243678.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The treatment of renal anaemia with erythropoietin-stimulating agents (ESA) is still suboptimal. Pharmacist interventions may improve ESA treatment in patients with renal anaemia; however, the available evidence is inconclusive. Earlier systematic reviews on this topic covered all sorts of clinical pharmacist activities in patients with chronic kidney disease, including those with renal anaemia. This systematic review focuses solely on algorithm-managed and pharmacist-managed renal anaemia in patients using ESA, describing these interventions and their effects.

WHAT THIS STUDY ADDS

⇒ Notwithstanding the inclusion of new evidence, no definite conclusions can be drawn on the effectiveness of algorithm-managed and pharmacist-managed renal anaemia on any outcome parameter. This is mainly due to a high risk of bias, high heterogeneity, and a limited intervention description. Evidence of low to moderate quality suggests that pharmacist-managed renal anaemia may improve haemoglobin outcomes and reduce ESA dose and expenditure, but this has yet to be confirmed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More high-quality research with a low risk of bias and adequate intervention descriptions is needed to support the possible future implementation of pharmacist-managed renal anaemia in clinical practice.

INTRODUCTION

With the progression of chronic kidney disease the prevalence of renal anaemia increases. Notwithstanding the emergence of new treatment strategies, erythropoietin-stimulating agents (ESA) are still the cornerstone of renal anaemia treatment. Up to 90% 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

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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 programmes.[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 ESA 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 ESA in renal anaemia.

METHODS

This systematic review on algorithm-managed and pharmacist-managed dosing of ESA in adults with renal anaemia followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) and PRISMA-P (for Protocols) guidelines. The protocol of this study was registered in PROSPERO (International Prospective Register of Systematic Reviews, crd.york.ac.uk/prospero/display_record.php?RecordID=243678) with 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 (medical subject headings) terms: 'chronic kidney disease', 'renal failure', 'hemodialysis', 'peritoneal dialysis', 'anemia', 'renal anemia', '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 online supplemental 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 compared with 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 6 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 whether 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 computerised, 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 randomised controlled trials (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), 11 August 2022). 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 to 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

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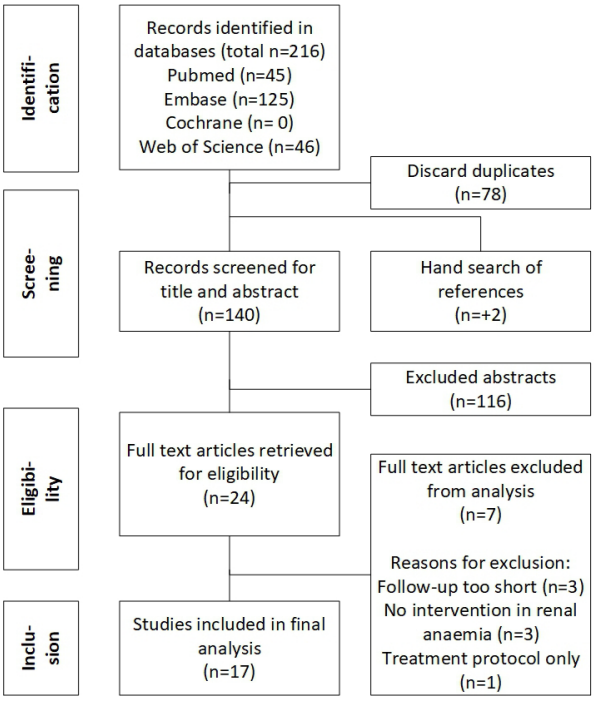

Figure 1 Flow chart of literature search and identification of relevant articles.

intention to summarise the effect estimates and provide GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) 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 17 studies. In one study, no patient numbers could be identified,[21] and in two articles the same patient population was studied.[11 12]

Study characteristics

Online supplemental 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 11 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 6 and 13 months.

Intervention characteristics

Online supplemental table 2 shows the intervention description, including the algorithm characteristics of the 17 included studies.

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 10 studies that used an algorithm. In six of these 10 studies, algorithms were also used for iron dosing.[10 22–26]

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; however,[21 23 25 27 28] some variation in the execution of the intervention might occur.

Risk of bias and study quality

Data regarding the risk of bias and study quality are depicted in online supplemental table 3.

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 RCTs differed: the study of Armstrong and Cherrick[22] was classified as having a high risk of bias; the study of Vanden-Oever *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 1).

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 standardized metrics as described below.

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 group 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 2.

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).

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 in the intervention group 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 3.

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Table 1 Description of clinical and methodological heterogeneity

	Description in studies (n)
Participants	A description of patient characteristics was missing in 4 studies, and limited (eg, 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 years (1) to 75 years (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)
Outcomes	In 8 studies, the outcome parameters were not clearly defined. In 2 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 online supplemental 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 one study, no control group was mentioned

ESA, erythropoietin stimulating agents; Hb, haemoglobin; Ht, haematocrit; RCT, randomised controlled trials.

The forest plot of the reduction in ESA dose in the intervention group 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 (n=2115).

Qualitative description of iron outcomes

Iron status

Seven studies reported iron status (transferrin saturation or ferritin levels or both) as an outcome.[23–26 28 29 32] In five of the 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 outcomes.[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 ESA in renal anaemia is scarce and generally of low to moderate quality with a substantial risk of bias. Only two RCTs could be identified; all other studies were observational in nature and the follow-up was relatively short with a range of 6–13 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 about the internal and external validity regarding the

Table 2 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 *et al*, 2020[23] HD	Pharmacist and algorithm	RCT	Some concerns	200	0.001	15.4	6.26	24.54
Dubovetsky *et al*, 2022[28] HD	Pharmacist and algorithm	Observational, retrospective	Serious	129	0.177	1.4	−0.63	3.43
Gonzalez-Fernandez *et al*, 2013[31] HD	Pharmacist and algorithm	Observational, retrospective	Serious	146	<0.001	32	14.07	49.93
Gonzalez-Fernandez *et al*, 2013[31] CKD-NDD	Pharmacist and algorithm	Observational, retrospective	Serious	135	0.2	15	−7.87	37.87
Gonzalez-Fernandez *et al*, 2013[31] PD	Pharmacist and algorithm	Observational, retrospective	Serious	90	0.2	9	−4.72	22.72
Aspinall *et al*, 2012[11] CKD-NDD	Pharmacist	Observational, retrospective	Serious	481	<0.001	14.2	6.25	22.15
Bucaloiu *et al*, 2007[32] CKD	Pharmacist	Observational, retrospective	Critical	134	<0.001	25.9	11.39	40.41
Dashti-Kavidaki *et al*, 2012[29] HD	Pharmacist	Observational, retrospective	Critical	86	0.664	−3.5	−18.67	11.67

CKD, chronic kidney disease; CKD-NDD, chronic kidney disease, non-dialysis dependent; HD, haemodialysis; PD, peritoneal dialysis; RCT, randomised controlled trial.

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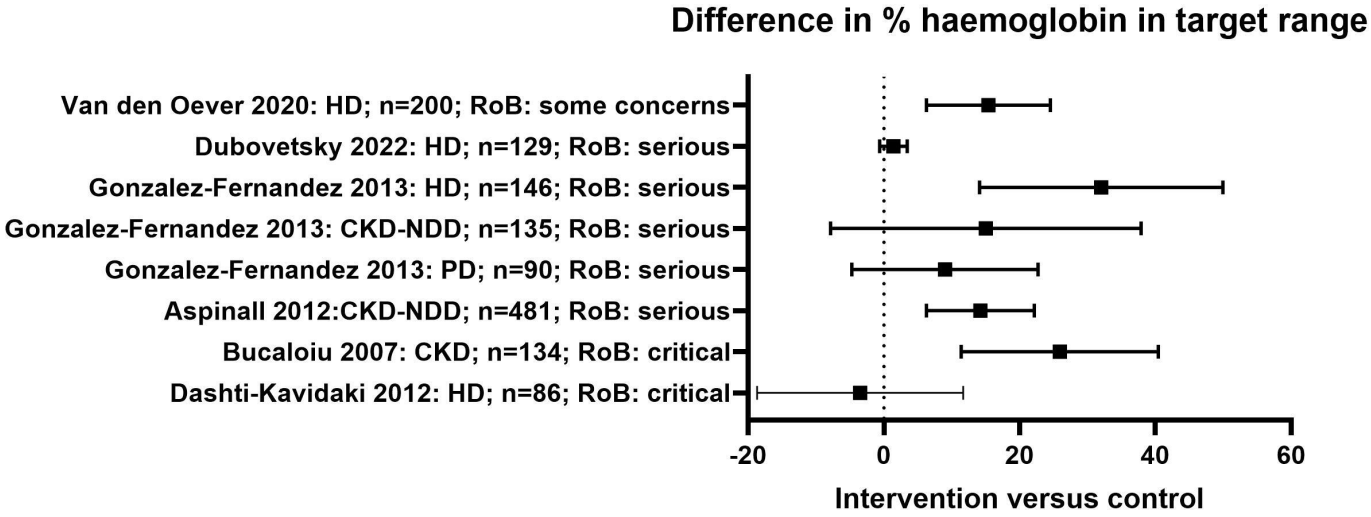

Figure 2 Forest plot regarding the percentage of haemoglobin (Hb) within target range in the intervention versus the control group. CKD, chronic kidney disease; CKD-NDD, chronic kidney disease, non-dialysis dependent; HD, haemodialysis; PD, peritoneal dialysis; RoB, risk of bias.

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, 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 for 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 standards. Last, this systematic review was conducted and reported following PRISMA 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

Table 3 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 *et al*, 2020[23] HD; P&A	RCT	Some concerns	DA	200	0.02	27.51%	4.30%	50.71%
Linn *et al*, 2023[33] HD; P	Observational, retrospective	Serious	EPO	536	<0.001	26.16%	11.50%	40.81%
El Nekidy *et al*, 2020[26] HD; P&A	Observational, retrospective	Serious	EPO	163	0.0556	7.73%	−0.20%	15.65%
Gonzalez-Fernandez *et al*, 2013[31] HD; P&A	Observational, retrospective	Serious	DA	146	0.012	29.02%	6.37%	51.67%
Dubovetsky *et al*, 2022[28] HD; P&A	Observational, retrospective	Serious	EPO	129	0.177	33.91%	−15.22%	83.03%
Aspinall *et al*, 2012[11] CKD-NDD; P	Observational, retrospective	Serious	DA	481	0.049	26.28%	0.07%	52.49%
Gonzalez-Fernandez *et al*, 2013[31] CKD-NDD; P&A	Observational, retrospective	Serious	DA	135	0.001	49.97%	20.32%	79.61%
Debenito *et al*, 2014[13] CKD-NDD; P	Observational, retrospective	Serious	EPO	101	<0.001	19.89%	8.75%	25.58%
Gonzalez-Fernandez *et al*, 2013[31] PD; P&A	Observational, retrospective	Serious	DA	90	0.434	5.45%	−7.97%	18.87%
Bucaloiu *et al*, 2007[32] CKD; P	Observational, retrospective	Critical	EPO	134	<0.001	44.18%	19.43%	68.94%

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.

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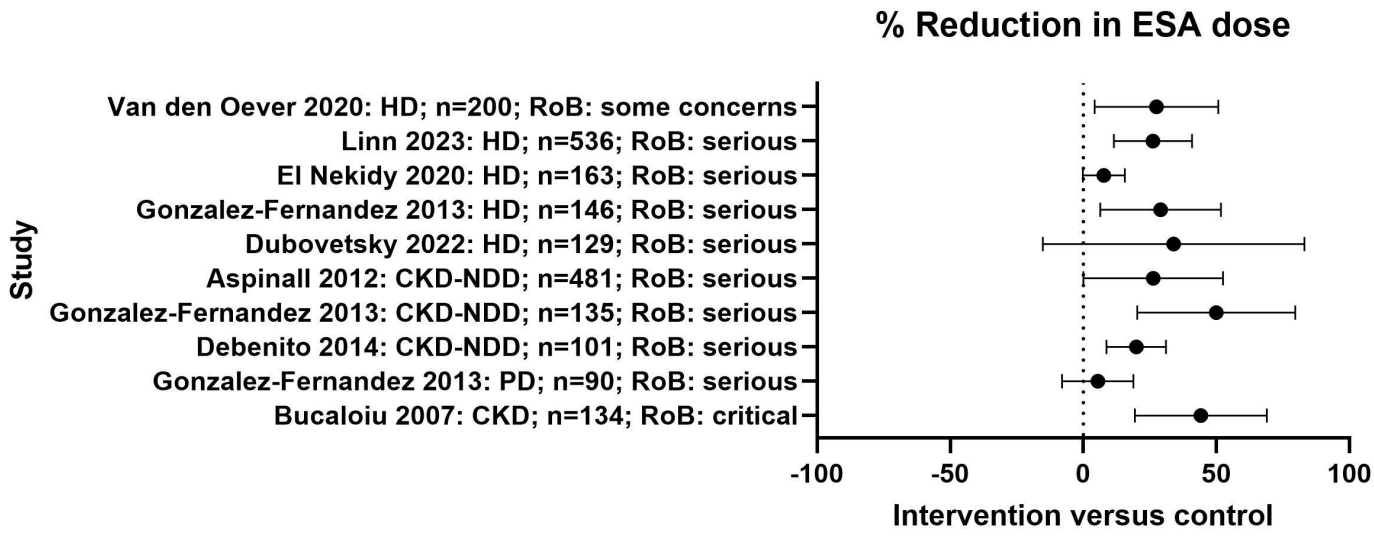

Figure 3 Forest plot regarding the relative dose of erythropoietin stimulating agents (ESA) in the intervention versus the control group. CKD, chronic kidney disease; CKD-NDD, chronic kidney disease, non-dialysis dependent; HD, haemodialysis; PD, peritoneal dialysis; RoB, risk of bias.

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 to 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 ESA 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.

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