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

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CHAPTER 3

A pharmacist-managed dosing algorithm for darbepoetin alfa and iron sucrose in haemodialysis patients: a randomised, controlled trial

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Published in Pharmacology Research and Perspectives 2020: e00628. doi: 10.1002/prp2.628.

Abstract

The attainment of target haemoglobin levels in haemodialysis patients is low. Several factors play a role, such as hyporesponsiveness to erythropoiesis-stimulating agents (ESA), but also suboptimal prescribing of ESA and iron. The goal of this study is to investigate if a pharmacist-managed dosing algorithm for darbepoetin alfa (DA) and iron sucrose improves the attainment of target haemoglobin levels. In this randomised controlled trial, 200 haemodialysis patients from a Dutch teaching hospital were included. In the intervention group (n=100), a pharmacist monthly provided dose recommendations for DA and iron sucrose based on dosing algorithms. The control group (n=100) received usual care. In the intervention group, the percentage per patient within the target range (PTR) for haemoglobin (target range 6.8-7.4 mmol/l) and iron status was higher than in the control group (for haemoglobin median 38.5% versus 23.1%, p=0.001 and for iron status median 21.1% versus 8.3%, p=0.003). The percentage of high haemoglobin levels (>8.1 mmol/l) was lower in the intervention group (median 0.0% versus 7.7%, p=0.034). The weekly dose of DA was lower in the intervention group (median 34.0 vs 46.9 mcg, p=0.020), whereas iron dose was higher (median 75 versus 0 mg). No difference was found for the percentage of haemoglobin levels below the target range. In conclusion, a pharmacist-managed dosing algorithm for DA and iron sucrose increased the attainment of target levels for haemoglobin and iron status, reduced the percentage of high haemoglobin levels, and was associated with a lower DA and a higher iron sucrose dose.

Introduction

Up to 90 per cent of haemodialysis patients in Europe are on erythropoietin-stimulating agents (ESA) to treat renal anaemia[1]. A disadvantage of long-term use of ESA is the risk of thrombotic complications, particularly major adverse cardiovascular events (MACE). MACE comprise myocardial infarction, non-haemorrhagic stroke, and cardiovascular death, the latter being the leading cause of death in patients on haemodialysis.

Four major risk factors for MACE during ESA treatment have been established. First of all, this is a target haemoglobin value above 8.1 mmol/l [2 3]. Secondly, haemoglobin levels below 5.6-6.2 mmol/l not only raise the frequency of transfusions but are also known to increase the risk of MACE [4,5]. The third risk factor is a high ESA dose [2,6-9]. ESA hyporesponsiveness, the fourth risk factor, occurs in approximately one out of eight haemodialysis patients treated with ESA and is defined as the failure to achieve haemoglobin target levels with higher than usual ESA doses [1,10,11].

In 2010, the European Renal Best Practice Work Group recommended that haemoglobin levels of 6.8-7.4 mmol/l should generally be pursued, without intentionally exceeding the level of 8.1 mmol/l [12]. In clinical practice, it is challenging to meet this target range. 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 the aforementioned ESA hyporesponsiveness, infections, but also suboptimal prescribing of ESA and iron [1,13]. As clinicians focus mainly on avoiding low haemoglobin levels and transfusions, high haemoglobin levels are frequently overlooked. This 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].

Iron status needs to be sufficient for ESA to be optimally effective. Haemodialysis patients frequently have both an absolute and a functional iron deficiency, requiring iron supplementation. Targets for iron therapy in haemodialysis patients are a transferrin saturation (TSAT) of 30-50% and serum ferritin levels of 200-500 ng/ml [14]. Data on suboptimal prescribing of iron are scarce. Only one retrospective trial reported PTR per patient for ferritin (target range 300-800 mcg/L) and TSAT

(target range 20-50%) in dialysis units in Australia and New Zealand. These percentages ranged from 26 to 68% for ferritin and 65 to 73% for TSAT [15].

Improvement of guideline adherence for ESA prescribing may reduce the risk of complications. Various interventions to improve ESA prescribing have shown promising results in patients with CKD, e.g. the introduction of treatment algorithms [16,17], and pharmacist-managed anaemia programs [18–21]. However, all published trials have low patient numbers, a relatively short follow-up and often an observational design. Therefore, based on the available literature, no definite conclusions on the effectiveness of interventions to improve ESA prescribing can be drawn, and high-quality evidence is needed to confirm the promising results of earlier studies.

To fill this knowledge gap, we performed a randomised controlled trial investigating whether a pharmacist-managed dosing algorithm for darbepoetin alfa and iron sucrose could improve the PTR per patient for haemoglobin and iron.

Methods

Study design

We performed a single-centre randomised controlled study, comparing DA and iron sucrose dosing through a pharmacist-managed dosing algorithm with conventional dosing by the nephrologist alone (usual care).

The follow-up period was 13 months per patient. The study was conducted at the Franciscus Gasthuis, Rotterdam, the Netherlands. The Franciscus Gasthuis is a general teaching hospital with a haemodialysis facility for 180 patients.

Participants

Patients were eligible if they were undergoing intermittent, maintenance haemodialysis, and were treated with DA. Written informed consent was required before inclusion. The inclusion was open to both incident and prevalent haemodialysis patients. Exclusion criteria were allergic reactions to DA or iron preparations, and failure to comprehend the inclusion procedure due to intellectual disabilities or poor Dutch language proficiency. Blood transfusions

were permitted in both treatment arms and did not influence dose advice in the intervention group, as this parameter was not incorporated in the algorithms.

Recruitment

The start of recruitment was in April 2010, the first dose advice for the intervention group was generated in May 2010. The last patient was included in March 2013. The total study period ranged from April 2010 to March 2014. Follow-up ended prematurely in case of kidney transplantation, change to another dialysis modality, relocation, mortality, or on the patient's request.

Intervention

Before the start of the study, the pharmacist investigators (FJvdO and CFMHM) developed treatment algorithms for the dosing of DA and iron sucrose in the intervention group (see figures 1 and 2). The algorithms were based on the summary of product characteristics of DA and iron sucrose, and the prevailing anaemia treatment guideline [12]. Principles incorporated in the treatment algorithms were discussed among pharmacist investigators and nephrologists and agreed upon in a consensus meeting:

- The maximum dose of DA in the intervention group is 150 mcg per week.
- If raising the DA dose to 150 mcg per week does not increase haemoglobin, DA dose will be reduced to the previous dose.
- A period of at least three weeks is required between two dose adjustments for DA.
- DA is always combined with iron sucrose unless ferritin is >800 mcg/L.
- The standard dose of iron sucrose is 100 mg, administered during haemodialysis.
- The dosing frequency of iron sucrose varies between once every two weeks, once every week, and thrice weekly.
- In case of a decrease in haemoglobin of 1.0 to 2.0 mmol/L, the nephrologist will be contacted to inform if there has been a bleeding or infection. If this is the case, the DA dose will not be increased. If there hasn't been any bleeding or infection, the DA dose will be increased using the algorithm.
- In case of bleeding, operation, or infection leading to a decrease of more than 2 mmol/L in haemoglobin, the DA dose will not be adjusted; in other cases DA dose will be increased in accordance with the algorithm.

- Blood transfusions are not incorporated in the algorithm and do not influence dose advice.
- Trends in haemoglobin are used to generate dose advice.
- Cut-off values for dose adjustments are slightly higher and lower than the target range for haemoglobin to prevent cycling.
- The dose of DA and iron sucrose will not be changed during hospitalisation, unless on the nephrologist's explicit request.
- Only the pre-planned, monthly laboratory measurements are used to generate dose advice; for example, haemoglobin levels during hospitalisations are excluded.

After the consensus meeting, the treatment algorithms were developed. Subsequently, the two participating pharmacists were instructed by the pharmacist investigators (FJvdO and CFMHM) to use the algorithms for both DA and iron sucrose. These four pharmacists provided dose advice in the intervention group.

In the control group, patients received usual care. This comprised dosing of DA and iron sucrose by the nephrologist alone. Dosing occurred according to prevailing guidelines, the clinical situation of the patient, and the clinician's experience, without proactive pharmacist involvement or the use of an algorithm. None of the nephrologists had access to the developed treatment algorithms.

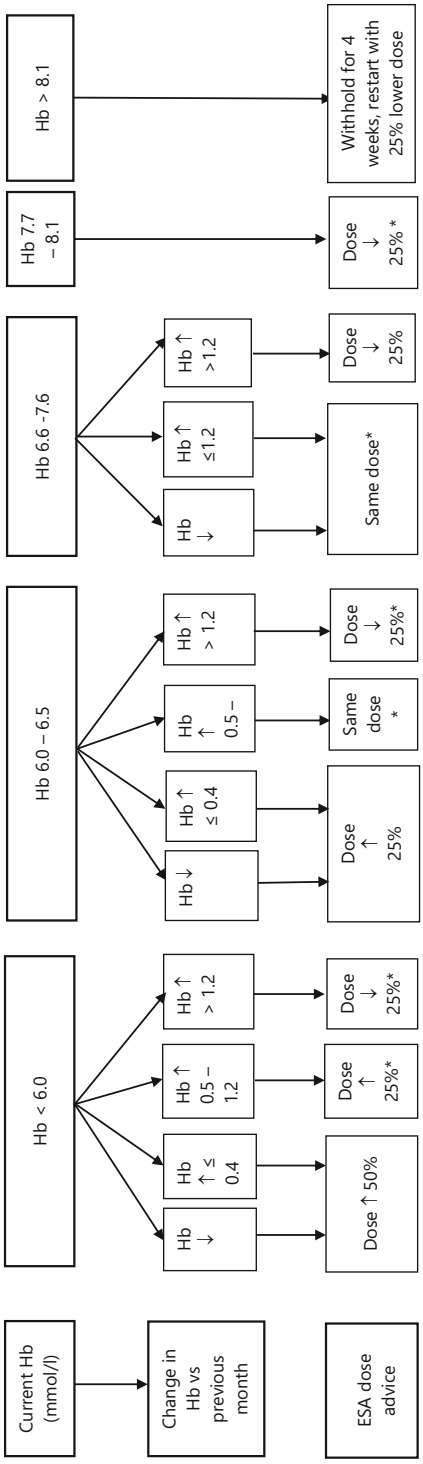

Figure 1. Treatment algorithm for darbepoetin alfa dosage

Hb ↑ = haemoglobin increase (as compared with the previous month); Hb ↓ = haemoglobin decrease (as compared with the previous month).

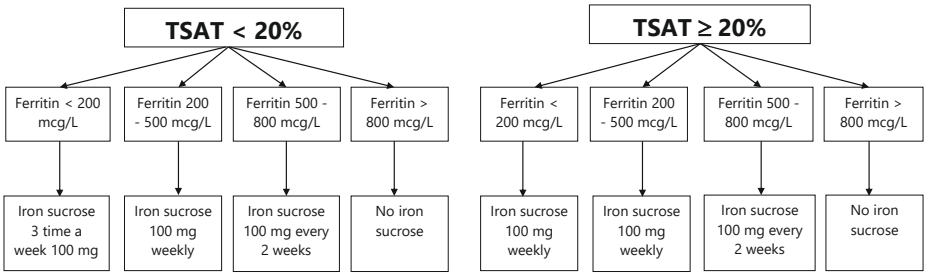

Figure 2. Treatment algorithm for intravenous iron sucrose

Procedures

Monthly laboratory analyses were performed for haemoglobin levels and iron status (transferrin saturation and serum ferritin) in both treatment groups. In the intervention group, after obtaining lab results for haemoglobin, ferritin, and transferrin saturation, each pharmacist provided DA and iron sucrose dose recommendations to the treating nephrologist for one of the four dialysis groups. Transfusion strategy was restrictive; transfusions were considered in the presence of stringent indications, for example, in case of 1) very low haemoglobin levels (below 4.3 mmol/L), 2) haemoglobin levels below 5.0 mmol/L and symptoms, 3) pre-existing cardiovascular disease, 4) previous surgery or ESA hyporesponsiveness. Dose recommendations were communicated by email. If the nephrologist did not agree with the recommendations, a discussion followed. Cases in which the suggested dose was not accepted were registered, including the reason for the deviation. After consensus regarding the doses was reached, the nephrologist prescribed the agreed doses of DA and iron sucrose. Both drugs were administered at the end of the dialysis sessions. Dose changes were carried out within one week after approval of the dose advice by the nephrologist.

Outcomes

The primary outcome measure was the median percentage of monthly haemoglobin values in the follow-up period that were in the target range (PTR, haemoglobin 6.8-7.4 mmol/l). Secondary outcome measures were: 1) the percentage of haemoglobin levels in supratherapeutic range (PSTR, haemoglobin >8.1 mmol/l) as a surrogate marker for suboptimal prescribing; 2) the PTR for iron (defined as a transferrin saturation of at least 20% and ferritin 200-500 mg/l), and 3) percentage of haemoglobin levels below target range (PBTR, haemoglobin <6.8 mmol/l).

Post-hoc data were analysed for additional outcome measures, including DA dose, all-cause mortality (according to Kaplan-Meier, log-rank to test differences and incidence density ratio (IDR) for the intervention vs the control group), the number of patients with at least one transfusion during follow-up, and the robustness of the PBD method. Robustness was defined as the interindividual variation of the primary outcome measure amongst pharmacists and nephrologists. The algorithm was considered robust if the inter-pharmacist variation was less than the inter-nephrologist variation.

Sample size calculation

The sample size calculation was based on the assumption that PTR per patient for haemoglobin would be 23% in the control group, based on historical data from our hospital (data not shown). We estimated that the intervention could approximately double this percentage to 45%. We calculated that at least 150 patients needed to be randomised (α of 0.05 (two-sided), β of 0.20, randomisation ratio 1:1) to be able to reject the null hypothesis that the intervention and usual care result in the same PTR per patient. To adjust for 25% loss to follow-up (due to missing laboratory values and loss to follow-up due to high mortality in patients on haemodialysis), at least 200 patients were needed.

Randomisation

Participating patients were randomised to the intervention or the control group, irrespective of dialysis group or treating nephrologist. Randomisation was performed by computer-generated sequencing (computer-generated 1:1 variable block randomisation). The random allocation sequence was provided by an independent party not involved in the conduct of the study or patient care. Three pharmacists enrolled participants. One pharmacist was responsible for treatment assignment by opaque sealed envelopes.

Statistical methods

Data from all patients with at least three months of follow-up were included for assessment of all endpoints. This period was chosen because it takes approximately four weeks for ESA to increase haemoglobin values. This means that the effect of the intervention could not be properly assessed if follow-up was shorter than three months.

The non-parametric Mann-Whitney U test was used to test for differences in continuous variables with skewed distributions, which was the case for all primary and predefined secondary outcome measures. Differences in proportions between the treatment groups were tested with a chi-square test. Survival analysis was carried out according to Kaplan-Meier, and the incidence density ratio (IDR) was tested with the Mid-P exact test. Analyses were performed with SPSS 22.0.0 (IBM Corp, SPSS Statistics, Armonk, USA) and OpenEpi (Open Source Epidemiologic Statistics for Public Health, Version 3.01. www.OpenEpi.com) for the IDR for mortality. A p-level < 0.05 (two-sided) was considered to indicate a statistically significant difference.

Ethical considerations

The procedures followed were in accordance with the Declaration of Helsinki. The Medical Research Ethics Review Board TWOR, Rotterdam, approved the study (number NL 27341.101.09; 2009-33).

Results

We included 100 patients per treatment arm, of whom data from 94 patients in the intervention group were available for the primary analysis and from 91 patients in the control group (Figure 3). The mean follow-up time in the intervention group did not differ from the control group (10.6 versus 10.2 months) (p=0.470).

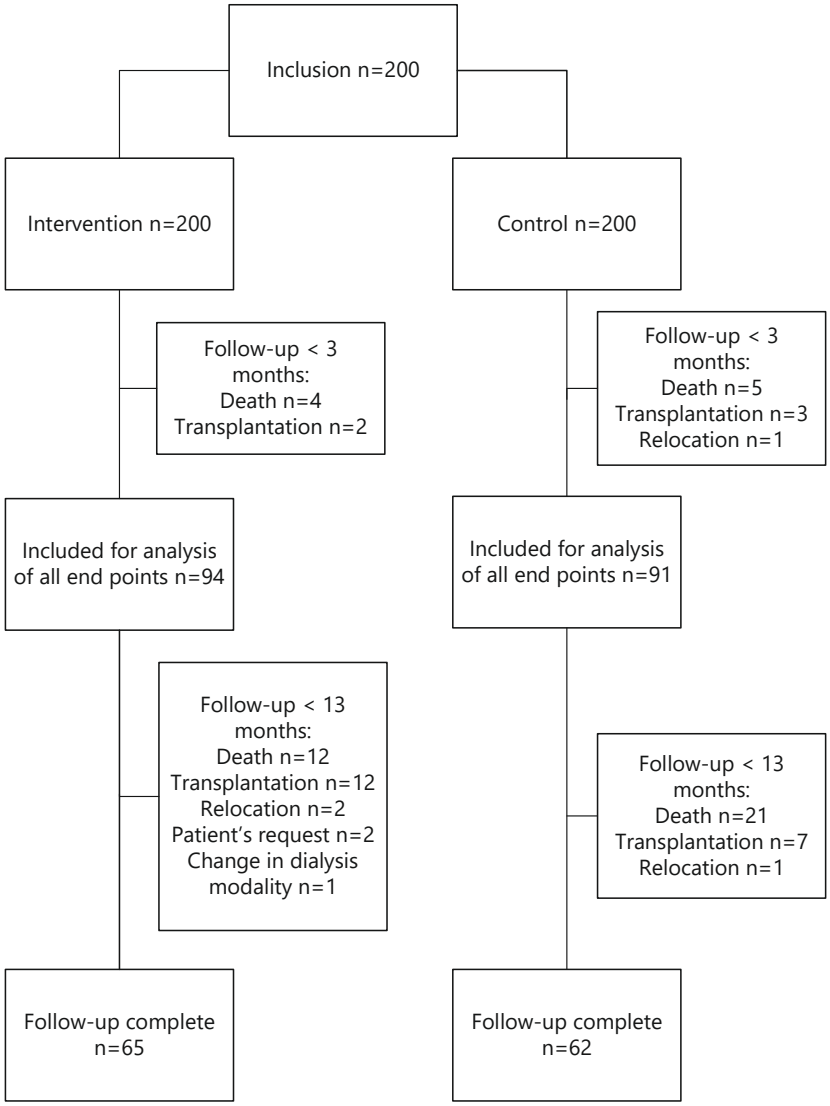

Figure 3. Patient flow chart

Table 1 shows the baseline characteristics of the study population.

Table 1. Baseline characteristics

	Intervention group (n=94)	Control group (n=91)
Male sex	61 (65)	66 (73)
Age (years) (median, range)	66.6 (27-91)	71.2 (21-88)
DA dose (mcg per week) (median, IQR)	40 (20-60)	40 (30-80)
Iron sucrose (mg per week) (median, IQR)	100 (50-100)	100 (0-100)
DA dose ≥ 100 mcg per week	14 (15)	12 (13)
Ferritin (mcg/L) (median, IQR)	379 (177-558)	334 (153-707)
Transferrin saturation (%) (median, IQR)	21 (17-29)	21 (15-29)
Country of origin		
Netherlands – including Netherlands Antilles	69	61
Europe – other	1	1
Asia – including Turkey	5	8
Africa	7	4
Other	12	17
Diabetes mellitus	37 (39.4)	42 (46.1)
Heart failure	18 (19.1)	17 (18.7)
Ischaemic heart disease	26 (27.7)	35 (38.5)
Peripheral vascular disease	14 (14.9)	27 (29.7)
Stroke/TIA	22 (23.4)	15 (16.5)
Atrial fibrillation	24 (25.5)	13 (14.3)
Active malignancy	6 (6.4)	6 (6.6)
Time since start haemodialysis (months, median and IQR)	8.7 (3.7-30.6)	9.6 (4.3-30.9)

Table displays n (percentage) unless stated otherwise. DA: darbepoetin alfa, IQR: inter quartile range, TIA: transient ischemic attack

In the control group, a higher prevalence was found of previous ischemic cardiac disease (38.5% versus 27.7%) and peripheral vascular disease (29.7% versus 14.9%). The prevalence of previous stroke or transient ischemic attack and atrial fibrillation was higher in the intervention than in the control group (23.4% versus 16.5%, and 25.5% versus 14.3%).

In the intervention group, dose advice was generated 916 times during follow-up, of which 894 recommendations were directly accepted by the treating

nephrologist. A total of 22 recommendations were subject to discussion between pharmacists and nephrologists, of which 13 were finally rejected. Protocol adherence was therefore 98.6 per cent. The primary reason for rejection was the patient's clinical situation: the nephrologist sometimes chose a higher dose of DA than advised. The main discussion point for iron supplementation was the dosing frequency: the pharmacist recommended thrice a week 100 mg in some cases, whereas the nephrologist preferred dosing twice a week. Analysis was performed according to the intention-to-treat principle.

Outcomes

As shown in Table 2, the PTR per patient for haemoglobin was 38.5% in the intervention group versus 23.1% in the control group.

Table 2. Primary and secondary outcomes

Outcome (definition)	Intervention	Control	P
PTR per patient for haemoglobin (6.8-7.4 mmol/L) (%, mean, sd)	38.5 (16.7-53.9)	23.1 (9.1-46.2)	0.001
PTR per patient for haemoglobin, broad range (6.8-8.1 mmol/L)	61.5 (50.0-76.9)	46.2 (36.4-69.2)	0.003
PSTR per patient for haemoglobin)	0.0 (0.0-12.9)	7.7 (0.0-27.3)	0.034
PBTR per patient for haemoglobin	30.8 (15.4-40.0)	30.8 (9.1-50.0)	0.864
PTR per patient for iron	21.1 (7.7-38.9)	8.3 (0.0-30.8)	0.003

Table displays median (interquartile range). PTR: percentage in target range, PSTR: percentage in supratherapeutic range, PBTR: percentage below target range

The percentage in the supratherapeutic range (PSTR) per patient was lower in the intervention than in the control group (0.0 vs 7.7%). The only parameter that did not differ between the two groups was the percentage of haemoglobin levels below the target range (in both groups 30.8%, p=0.864).

Post-hoc analyses

The DA dose in the intervention group was lower than in the control group, and the variability in dose was high in both groups, as shown by the large interquartile range (see Table 3).

Table 3. DA dose, patients with DA dose ≥90 mcg per week, iron sucrose dose, mortality, and patients with at least 1 transfusion

Outcome	Intervention	Control	P
DA dose (mcg/week) median and IQR	34.0 (20.0-60.5)	46.9 (25.8-77.7)	0.020
Patients with mean dose of ≥ 90 mcg DA per week (number and percentage)	12 (12.8)	16 (17.6)	0.415
Iron sucrose dose (mg/week) median and IQR	75 (50-100)	0 (0-100)	<0.001
Mortality (percentage during follow-up)	16	26	0.096
Patients with at least 1 transfusion during follow-up (number and percentage)	19 (20.2)	31 (34.1)	0.046

DA: darbepoetin alfa, IQR: inter quartile range

The iron sucrose dose was higher in the intervention than in the control group, with a median of 75 mg (IQR 50-100 mg) in the intervention group versus 0 mg (IQR 0-100 mg) in the control group. The Incidence Density Ratio (IDR) for mortality was 0.59 for the intervention versus the control group (95% CI 0.31-1.10).

The developed algorithms proved to be robust for inter-pharmacist variation: the PTR for haemoglobin ranged from 30.3% to 42.9% (pharmacists, intervention group) versus 15.4% to 43.0% (nephrologists, control group).

The percentage of patients in the intervention group with at least one transfusion during follow-up was lower than in the control group (20.2 % vs 34.1 %, p=0.046). The number of transfused units of red blood cells per patient was comparable for both groups (range: 0-41 in the control group vs 0-36 in the intervention group).

Discussion

In this trial, we demonstrated that a pharmacist-managed dosing algorithm of DA and iron sucrose is effective in improving the percentage within the target range (PTR) per patient for haemoglobin, reducing ESA dose and reducing suboptimal prescribing. These results may be explained by restricting dose increases of DA during infections and bleeding, more focus on preventing supratherapeutic haemoglobin levels, and more proactive iron supplementation in the intervention group, which led to improved iron status. This last aspect is in accordance with

results from the PIVOTAL trial, in which proactive administration of iron sucrose was safe and effective in reducing ESA dose in haemodialysis patients [22].

The higher PTR per patient for haemoglobin in the intervention group is in line with the results from earlier studies regarding algorithm-based dosing and pharmacist-managed renal anaemia programs. In these studies in patients with different stages of CKD, pharmacist and algorithm-based interventions led to higher percentages of haemoglobin levels within the target range [16,17,18,19,23] However, a comparison with our results is difficult, as the applied target ranges for haemoglobin in earlier studies were broader than recommended in the prevailing guidelines, and patients in our study were older and had more comorbidities. Most of the previous studies included only a small percentage of all assessed patients. This raises questions about the external validity of these earlier data. The best comparison can probably be made with real-life data from the EURODOPPS database. In this database, which comprises registry data of haemodialysis patients from seven European countries, 31.2% of haemodialysis patients had haemoglobin levels within target range in the period of 2009 to 2011, with large variation between countries [1]. Target levels were the same as in our trial. So, in the EURODOPPS database, the PTR per patient was slightly lower than the PTR in the intervention group (38.5%), which implies that the use of a pharmacist-managed dosing algorithm exceeds the standard level of care in Europe.

Apart from increasing the percentage of within-target haemoglobin levels, our algorithm-based dosing regimen also led to a lower weekly dose of DA with a median of 34.0 mcg in the intervention versus 46.9 mcg in the control group. This reduction was comparable to the results of earlier studies of pharmacist-managed renal anaemia programs and algorithm-based dosing, with reported dose reductions of 10 to 62% [19,21,23–25]. The reduction in ESA dose in our study was not counterbalanced by an increase in transfusions, as transfusions were less frequent in the intervention group.

Due to proactive prescribing in the pharmacist-managed treatment group, the dose of intravenous iron sucrose and the percentage of iron status within the target range were higher in the intervention than in the control group (median 75 vs 0 mg, and 21.1 vs 8.3%, respectively). The median weekly iron sucrose dose of 0 mg in the control group indicates that for at least 50% of the time, patients in the control group have not received iron sucrose. This indicates a suboptimal

treatment of renal anaemia in the control group, since a sufficient iron status is necessary for ESA to be most effective [12].

The percentage in supratherapeutic range (PSTR) per patient for haemoglobin, another marker for suboptimal prescribing, was lower in the intervention group (median 0.0% versus 7.7%). In the EURODOPPS database,13% of haemodialysis patients had haemoglobin levels higher than 8.1 mmol/L. Of these patients, 8.9% still used ESA [1]. Although the outcome parameters vary, data from our study and EURODOPPS show that suboptimal prescribing is a common and relevant problem in haemodialysis patients.

One of the strengths of our study is the small number of exclusion criteria. As a result, our study population is representative of patients in routine clinical practice, as is demonstrated by the advanced age, the high frequency of comorbidities, and diverse ethnic backgrounds. Another strength is its randomised design: this is the first RCT investigating a pharmacist-managed dosing algorithm in renal anaemia with sufficient follow-up time and sufficient power. Protocol adherence was high, and post hoc power for the primary outcome was calculated to be 99.3%. Also, the loss to follow-up during the trial was very limited (15 patients).

Notwithstanding these strengths, several limitations need to be mentioned. First, despite randomisation, differences in baseline characteristics were observed between the two groups. In the control group, patients were more often male, the mean age was almost five years higher, and diabetes, ischemic heart disease, and peripheral vascular disease were more prevalent. In the intervention group, more patients suffered from atrial fibrillation and stroke/TIA. The influence of these comorbidities on the percentage of haemoglobin within-target levels has not been described in the literature, but may explain why mortality in the study population, especially in the control group, was higher than reported elsewhere [26,27]. We could not determine a cause for the age difference between treatment groups, as the randomisation procedure was adequate and strictly followed. No differences in reasons for dropout were seen between patients excluded from analysis in the intervention and the control group.

The second limitation is the manual generation and e-mail communication of the dosing advice. This method was time-consuming and potentially susceptible to

typing errors, inadequate follow-up of emails, and delays in the implementation of dose changes. As delays of dose changes were very rare, we do not expect this to have influenced our results.

The third limitation is the open-label design of the study. Although patients were blinded to the intervention, nephrologists and pharmacists were not. In theory, this could have contaminated the treatment strategy in the control group. Post hoc, we conducted two exploratory analyses to examine possible contamination. First, a retrospective, exploratory analysis of data from twenty randomly selected patients in the control group was performed. In the six months before inclusion, the median percentage in target range (PTR) per patient for haemoglobin in this group was 31.5% versus 28.4% in the six months after inclusion (supplementary table 1). Secondly, we compared the results of the first group of participants (n=93) with the last group (n=92) (supplementary table 2). The differences in PTR per patient for haemoglobin between the intervention and the control group were comparable for the first and last group of patients, which argues against contamination. As both exploratory analyses did not show any sign of contamination, we do not consider it a relevant source of bias.

Although the good internal validity of this trial supports a firm conclusion in the study population, its external validity and applicability to other countries, such as the United States and Japan, need further investigation to verify the influence of health care structure and patient characteristics, such as ferritin levels, dialysis vintage, and intra-patient haemoglobin variability, which are known to be highly variable between regions worldwide [17,18,25,28]. Although recent changes in haemoglobin target range hamper direct extrapolation and use of existing algorithms in current practice, this trial shows that our intervention is effective in improving the percentage per patient in the target range for haemoglobin. As the algorithms can easily be adapted to comply with current guidelines, there is no major barrier to the implementation of our intervention. An individualised haemoglobin target range, based on guidelines, patient characteristics, and shared decision making, could readily be integrated into adapted algorithms for pharmacist-managed anaemia programs in the future.

In this article, we described algorithm-based dosing by a pharmacist. However, international data show that renal anaemia dosing by other healthcare

professionals, such as trained nurse practitioners, leads to comparable benefits. Therefore, we emphasise that our intervention may be equally effective when carried out by another independent, trained healthcare professional.

Future research should focus on the effectiveness of our intervention when using an individualised target range. Cardiovascular morbidity and mortality, and all-cause mortality, should be assessed as outcomes. To fully utilise the potential of our intervention, the procedure of implementing proposed dose changes should be as simple as possible, and the incorporation of the algorithms in a clinical decision support system or web-/digital application is recommended.

Our trial confirms the superiority of pharmacist-managed dosing algorithms on the attainment of target levels for haemoglobin in haemodialysis patients. This intervention also reduces the ESA dose and ESA expenditure. In our opinion, there is sufficient evidence to start the implementation of algorithm-based treatment of renal anaemia in clinical practice, as it increases the percentage of within-target haemoglobin levels and reduces ESA dose.

Acknowledgments

The authors would like to thank Prof. Dr. P.M.L.A. van den Bemt, and Prof. Dr. T van Gelder, for their valuable comments on this manuscript.

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