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PHILOSOPHY DOCTORATE PROGRAM IN HEALTH SCIENCE RESEARCH

PHD THESIS:

THE EFFECTIVENESS OF IRON SUPPLEMENTATION FOR TREATING ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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For my loved ones

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Abstract

After relative erythropoietin deficiency, iron deficiency is the second most important contributing factor for anemia in chronic kidney disease (CKD) patients. Iron supplementation is a crucial part of the treatment of anemia in CKD patients, and intravenous (i.v.) iron supplementation is considered to be superior to per os (p.o.) iron supplementation. The differences between the available formulations are poorly characterized. This PhD manuscript presents results from pairwise and network meta-analyses carried out after a comprehensive search in sources of published and unpublished studies, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations (International prospective register of systematic reviews PROSPERO reference ID: CRD42020148155). Meta-analytic calculations were performed for the outcome of non-response to iron supplementation (*i.e.*, hemoglobin (Hgb) increase of <0.5–1.0 g/dL, or initiation/intensification of erythropoiesis-stimulating agent (ESA) therapy, or increase/change of iron supplement, or requirements of blood transfusión.). A total of 34 randomized controlled trials (RCT) were identified, providing numerical data for analyses and covering 93.7% (n = 10.097) of the total study population. At the network level, iron supplementation seems to have a more protective effect against the outcome of non-response before the start of dialysis than once dialysis is initiated, and some preparations seem to be more potent (*e.g.*, ferumoxytol, ferric carboxymaltose.), compared to the rest of iron supplements assessed (surface under the cumulative ranking area (SUCRA) >0.8). This PhD work provides parameters for adequately following-up patients requiring iron supplementation, by presenting the most performing preparations, and, indirectly, by making it possible to identify good responders among all patients treated with these medicines.

Chapter 1: Background

Anemia is a common complication of chronic kidney disease (CKD), and is associated with poor outcomes, due to cardiovascular complications (1). Erythropoietin (EPO) deficiency in CKD is mainly caused by two different mechanisms: first by damage of erythropoietin producing cells in the kidneys that may be treated by artificial supplementation of EPO (2). Second by absolute and functional iron deficiency. While absolute iron deficiency is defined as absence of iron stores due to blood loss occurs more often in chronic kidney disease, functional iron deficiency is due to diminished absorption and utilization of iron (3).

While iron plays a central role in cellular metabolism, its ability to receive and transfer electrons by changing from ferric to ferrous states, may lead to oxidative stress (3), which is naturally prevented via the hepcidin control on the iron kinetics within the body (4). Hepcidin binds to the iron transporter ferroportin which is located on the basal membrane of enterocytes, reticuloendothelial cells, and hepatocytes, and that binding causes internalization of ferroportin (4). As a result, iron is not absorbed or recycled from the reticuloendothelial cells and circulating iron are maintained into the desired levels.

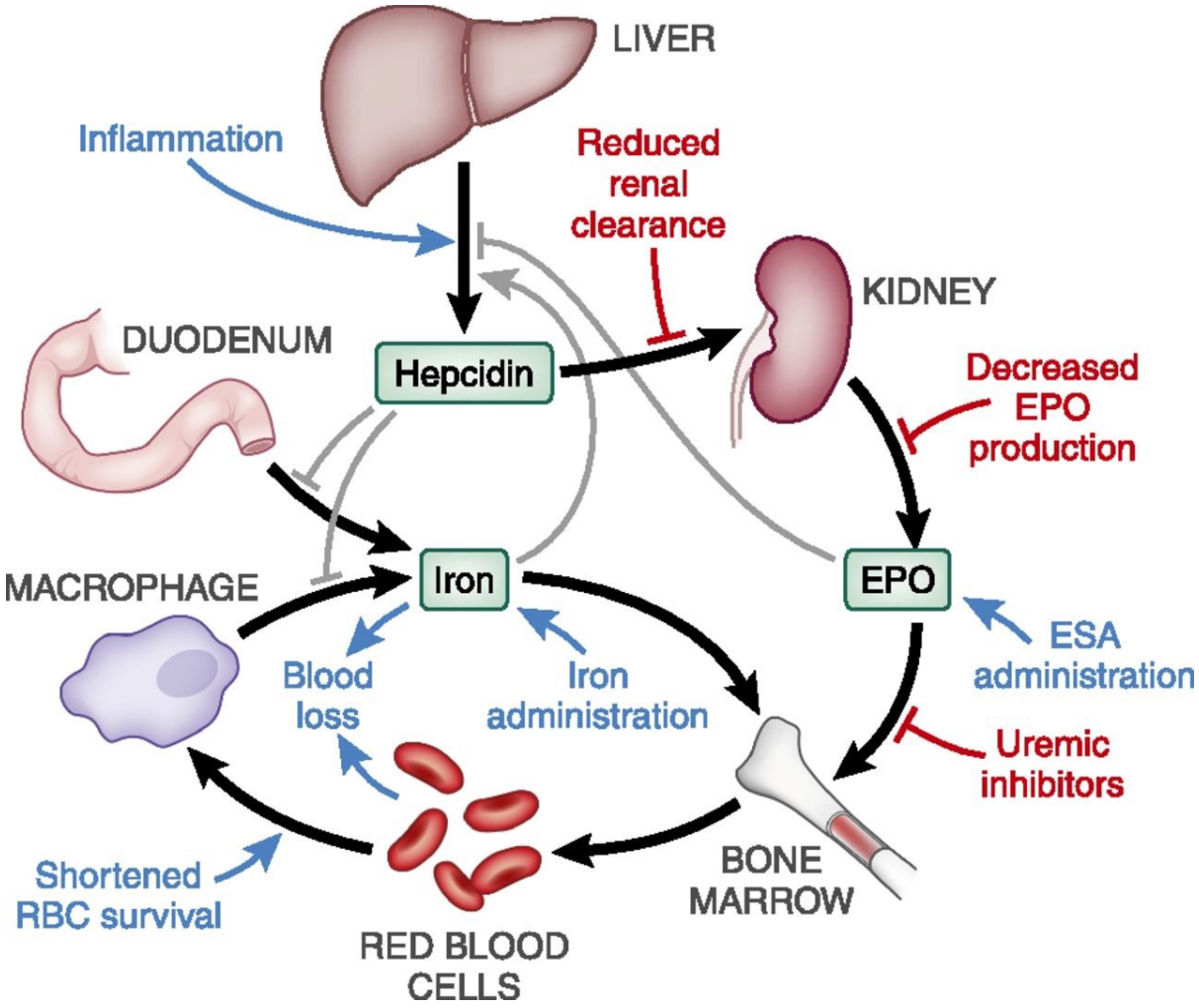

LIVER
Inflammation
Reduced renal clearance
KIDNEY
DUODENUM
Hepcidin
Decreased EPO production
MACROPHAGE
Iron
EPO
ESA administration
Blood loss
Iron administration
Uremic inhibitors
Shortened RBC survival
BONE MARROW
RED BLOOD CELLS

Figure 1

Schematic representation of the mechanisms and feedback loops centered on iron deficiency in the anemia of CKD.

In pathophysiological conditions of CKD characterized as a chronic inflammatory condition, increased hepatic hepcidin production and diminished renal clearance lead to an iron-restricted and thus inhibited erythropoiesis which together with especially EPO deficiency causes anemia.

Black and gray arrows represent normal physiology (black for iron and hormonal fluxes, gray for regulatory processes). Colored arrows represent the additional effects of CKD (blue for activation, red for inhibition).

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; EPO, erythropoietin; RBC, red blood cell.

From Babitt & Lin, 2012. (2)

Nevertheless, the equilibrium provided by hepcidin is disrupted in CKD (5). Renal hepcidin clearance is reduced as CKD progresses, and this situation is progressively aggravated by inflammation and reduction of erythropoietin levels, among other factors (**Figure 1**), leading to functional iron deficiency.

Finally, in end-stage kidney disease (ESKD) incorrect alimentation caused by poor apetite, increased rate of blood loss due to frequent phlebotomies during dialysis and laboratory tests as well as gastrointestinal bleeding, absolute iron deficiency develops (6).

As in other chronic disease states, inflammation plays an important role through several mechanisms in which hepcidin is once more a central protagonist, by perpetuating and aggravating iron deficiency, reaching its maximum in dialysis (7). In addition to all the above, with increasing erythropoiesis once treatment with erythropoiesis stimulating agents (ESA) is initiated, absolute iron deficiency appears more quickly, especially if higher doses of ESA are used. In this condition, iron release into the circulation from initially adequate total body iron stores is not fast enough replenished to provide sufficient iron to support the increased erythropoietic rate driven by ESA therapy (8). In summary, the role of iron deficiency in the pathophysiology of anemia of CKD underlines the need of investigations to improve this condition.

Iron supplementation for improving outcomes in CKD

The anemia of CKD is *per se* associated with poor outcomes, and particularly with a mortality excess, mostly in relation with cardiovascular complications, seen even long before the start of dialysis and soon across the natural history of CKD (1). As prevalence of anemia in patients with CKD is frequently higher than > 50% in patients with advanced disease (9), its treatment is of high clinical relevance. Observational data highlight that even moderate anemia with

hemoglobin (Hb) levels of 11–12 g/dL compared to Hb levels of 13 g/dL or more may have impact on survival (10–12) as well as on quality of life (13).

Both iron supplementation and ESA therapy play a critical role in this condition and guidance for prescribing these medicines will contibute to a better treatment of CKD patients (14,15).

Vigilance for the prescription of the medicines is required as in addition to the mortality and morbidity burden of CKD, there is an increased risk of death and cardiovascular events in relation to the administration of higher doses of ESAs (1). In this context, iron reprovision and, particularly, intravenous iron administration is central for preventing the need for more ESA doses, as well as for avoiding depletion of the existing iron pool when increasing erythropoiesis occurring under the effects of ESAs (8). Many studies evaluating the role of iron supplementation on either Hb increase and the achievement of Hb targets were focused on the use of less ESA doses or transfusions (16) as avoidance of these treatments helps to mitigate risks (such as cardiovascular events or transfusion reactions). Patient reported outcomes, that are much more difficult to assess, such as improve of symptoms related to anemia as well as quality of life (QoL) are getting in scientific focus in recent years.

As of the way of administration of iron supplements, since the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines the need of intravenous (i.v.) administration of iron for achieving a sustained Hb response and reducing the need for blood transfusions (17) has been validated in a series of clinical trials, notably the Ferinject Assessment in Patients with Iron Deficiency Anaemia (FIND-CKD) and the Proactive IV Iron Therapy in Dialysis Patients (PIVOTAL) trial (16). Despite concerns about adverse effects regarding oxidative stress and increased costs, i.v. galenic presentations are preferred over *per os* (p.o.) supplements as they provide a superior effectiveness and a suitable tolerance.

Another clinically relevant question is correct dosing of these medicaments, as due to hepcidin excess, large intravenous boluses of iron may have limited effectiveness because of increased

liver sequestration and further lead to perturbed recycling of cellular iron, and thus may treat anemia in this condition insufficiently (18).

At this point, it can be outlined that clear definitions of iron deficiency are essential when prescribing iron supplements, and that clear recommendations concering the galenic formulation and dosing as well as a better characterization of different medicines are urgently needed as the amount of administered elimentary iron not necessarily correlates with restitution of iron storages.

Definitions of iron deficiency in CKD patients

Anemia is defined as Hb <13 g/dL in men and Hb <12 g/dL in women, according to World Health Organization (WHO) criteria, and these thresholds established in 1968 are accepted by current guidelines and other recommendation documents influencing to date decision-making against the anemia of CKD (17,19). All CKD patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 (CKD stage 3a or more) should be screened for anemia on their initial evaluation. In patients with CKD stage 3a-3b, chronic kidney disease may contribute to anemia, but other causes of anemia should equally be excluded.

In patients with eGFR > 30 ml/min, anemia is commonly linked to CKD but other concomitant causes should be investigated (9).

In CKD patients with anemia different parameters are recommended to assess iron storages (Table 1), measurement of serum iron, total iron-binding capacity (TIBC), serum ferritin, and transferrin saturation (TSAT) are the recommended parameters to identify and follow up patients with iron deficiency. Absolute iron deficiency is suspected when TSAT is ≤20% and serum ferritin levels are ≤100 ng/mL in CKD stages 3 to 5 and among patients on peritoneal

dialysis (PD) or ≤200 ng/mL among patients receiving hemodialysis (HD). Functional iron deficiency is usually characterized by TSAT ≤20% and ferritin levels >800 ng/mL (20).

Table 1 (adopted from 9,17,19,21)

International guidelines on iron assessment in chronic kidney disease (CKD)

Guideline	Recommended iron measures
KDOQI anemia guideline 2006, and 2007 amendment with revised hemoglobin target	Serum ferritin and TSAT in adults with non-dialysis CKD and on peritoneal dialysis; for adults on hemodialysis, either CHr or TSAT in combination with serum ferritin
KDIGO guideline, 2012	Ferritin and TSAT
Revised European for the management of anemia in patients with chronic renal failure, 2004	%HRC, TSAT, or CHr
NICE anemia guideline 2015 update	%HRC if processing of the blood sample is available within 6 h, or CHr or Ret-He if %HRC is not available
The British Committee for Standards in Haematology guideline for the laboratory diagnosis of functional iron deficiency, 2013	%HRC is considered to be the best established variable for identification of functional iron deficiency; CHr and Ret-He have predictive value for the likelihood of response to intravenous iron therapy in patients on hemodialysis; low serum ferritin has a role in the diagnosis of functional iron deficiency; TSAT alone is not recommended as a predictor of responsiveness to intravenous iron therapy
UK kidney association clinical practice guideline: update of anaemia of chronic kidney disease, 2025	ercentage of hypochromic red blood cells (% HRC), but only if processing of blood sample is possible within 6 h or • Reticulocyte Hb count (CHr) or equivalent tests e.g., reticulocyte Hb equivalent (RET-He) or • Combination of transferrin saturation (TSAT) and serum ferritin if the above tests are not available or the person has thalassemia or thalassemia trait • Serum ferritin to assess iron stores • Plasma/serum C-reactive protein (CRP) to assess possible inflammation

KDOQI The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, TSAT transferrin saturation, CHr reticulocyte hemoglobin content, Ret-He reticulocyte hemoglobin equivalent, KDIGO Kidney Disease: Improving Global Outcomes, %HRC proportion of hypochromic red cells

The percentage of hypochromic red blood cells (%HRC) and the reticulocyte Hb content (CHr) with cut-offs (CHr <29 pg and %HRC >6%) are porposed as markers of the red blood cells' Hb content, although in patients under iron supplementation these parameters provide only approximate values of recent iron availability for Hb synthesis rather than indicating replenishment of total iron stores (21). It is of note, that interpretation of these tests are difficult in patients with hemoglobinopathies such as thalassemia or sickle cell disease.

Treatment of iron deficiency across the spectrum of CKD

While cut-offs for serum ferritin levels and TSAT indicating initiation of iron reposition may vary among recommendations, as previously mentioned, there is a general agreement on a *quasi* exclusive intravenous iron supplementation in dialysis and preferably an intravenous iron reposition in CKD stages 3 to 5, not excluding p.o. supplements in those CKD stages (17,19,21). Uncertainty of p.o. supplementation n patients with CKD different increases when alternate-day dosing, once and bidaily dosing were used

According to the 2025 KDIGO guidelines (9), for adults with CKD and anemia not receiving dialysis or treatment with peritoneal dialysis, iron supplementation should be initiated if ferritin <100 ug/l and transferrin saturation < 40% or ferritin ≥ 100 and < 300 ug/l and TSAT < 25% with the aim to increase the Hb without starting ESA thus avoiding transfusion and improvement of anemia-related symptoms and QoL. Iron substitution may be a front line p.o. substituation and the choice between different formulations and dosing schedules is guided by

cost, individual patient preference, tolerability, and efficacy. When patients are on ESA treathment, i.v. iron, preferentially at a high dose low frequency administration sheme.

For adults with end-stage chronic kidney disease treated witih hemodialysis, i.v. iron substitution should be initiated if ferritin ≤ 500 ug/l and TSAT ≤ 30%.

The limit of TSAT of 30% and that of serum ferritin levels of 500 ng/mL should not be intentionally exceeded (9,17). On these limits, the ERBP position statement agrees with the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) commentary on the 2012 KDIGO recommendations, suggesting proceeding cautiously for avoinding undesired adverse effects (19).

The unanimous recommendation of intravenous iron supplementation in dialysis issued by the 2012 KDIGO guidelines (17), in the NKF-KDOQI commentary on the 2012 KDIGO recommendations (19), the NICE recommendations (21), and the ERBP position statement (16), was based on findings from systematic reviews and meta-analyses using HD patients' data assessed in several randomized controlled trials (RCT), which thereafter have been updated in other evidence summaries (23–26). Two Cochrane reviews (23,24) and two independent systematic reviews and meta-analyses (25,26) are consistent in efficacy analysis when i.v. iron compared to p.o. iron was used (23,24,25). Nevertheless, more pronounced increases in Hb levels may be observed in patients undergoing dialysis than patients before initiation of dialysis (23–26), which are associated to the dose iron dosages (26). In a similar way, TSAT and serum ferritin levels increased both in CKD stages 3 to 5 and in dialysis, but without apparent differences between these two groups in contrast to those observed for Hb levels (23–26). i.v. iron supplementation is a ssociated with a decreased need of ESA (23,24,26), but data are inconsistent (24,25). Efficacy on the need of blood transfusion could under i.v. supplements could not be shown (23,25,26).

Table 2

Available i.v. iron preparations (adapted from 27)

Product/ Manufacturer	**Scientific name**	**Availability (may differ according to country)**	**Elemental iron/recommended dose**
Ferrosig (Sigma Pharmaceuticals)	Iron polymaltose 100 mg; i.v.	Since 2007 in Great Britain, later in Spain, Germany and other European countries	No max. dose at a single administration
Venofer (Aspen Pharmacare)	Iron sucrose/iron saccharose	Since early 2000 in Europe	max. single dose 300 mg
Ferinject (Vifor)	Ferric carboxymaltose	Since 2007 in Europe	max. single dose 1000 mg
Monofer (Pharmacosmos A/S)	Iron isomaltoside or Ferric derisomaltose	Sine 2010 in Europe	No max. single dose at a rate of 20 mg/kg
Feraheme (AMAG Pharmaceuticals)	Ferumoxytol	Since 2012 in some European countries.	Max. single dose of 510 mg

Infed/Cosmofer (Pharmacosmos A/S)	Iron dextran	Since 2001	No max. single dose at a rate of 20 mg/kg

The recommendations generally promote to ideally reach the target Hb of 10-12 g/dl or an increase in Hb concentration of >1 g/dL before and once dialysis is initiated (17,19,21), although solely the increase in Hb levels may be sufficient (17,19). Importantly, it seems that there are no differences between iron sucrose and other classic iron formulations and the newer preparations ferric carboxymaltose and ferrumoxytol on the increase in Hb concentration, even if the newer ones allow infusion of higher doses than the older ones (25), which contradicts the positive association between increases in Hb levels and greater iron doses that could only be administred intravenously (26).

Safety concerns should also be addressed, especially with the administration of greater doses of iron, particularly regarding oxidative stress-related adverse effects. In any case, intuitively, cardiovascular events that may be feared due to oxidative stress did not increase among patients on i.v. supplements compared to those on p.o. supplements, as data are too scarse to allow conclusions (23–26).

There were no differences in the rates of all-cause death, serious and any adverse effects, and infections between patients on i.v. supplements compared to patients on p.o. supplements (23–26). However, hypotensive even ts including allergic reactions were higher patients treated with i.v. iron supplementation while gastrointestinal events were especially noted in patients with p.o. iron supplementation (23,25). In any case, findings on the safety profile of i.v. iron from available meta-analyses in CKD are consistent with those obtained by a

comprehensive meta-analysis which included 103 trials and performed with data from 14,434 patients with different pathologies including CKD patients (28).

Research gaps pending to be solved

At this point, the reader can appreciate that the benefit of i.v. iron supplementation outweighs its risks in patients with CKD. Nevertheless, considering the more acceptable safety profile and higher potency (in terms of total iron dosage) of the newer avalaible formulations ferric carboxymaltose and ferric isomaltose, these have until only now only shown similar efficacy in terms of increase of Hb levels as compared to older iron formulations such as iron sucrose and iron gluconate in published more than 15 years-old meta-analyses (25). To update knowledge and to improve decision-making in the treatment of anemia of CKD, an accurate description of the individual impact of the different available i.v. preparations is needed.

Chapter 2: Best treatment choice

Systematic review and meta-analysis of RCTs provide crucial information on the effects of treatments (interventions) concerning a given health problem, which findings will finally support decision-making to address the problem (29). However, the comparison of a single intervention with a single alternative (*e.g.*, placebo, standard of care.), that is, a head-to-head (direct) comparison, is not sufficient in real-life, as usually more than two treatment options exist and the effects from all available treatments should be considered. In this context of a comparative effectiveness research, network meta-analysis (NMA) or multiple-treatment comparison meta-analysis allows simultaneously comparison of three or more treatments by synthesizing evidence on direct comparisons provided by studies, and evidence on comparisons of treatments that have never been directly compared.

Treatments' ranking proceeding

Clinicians wish to offer to patients a choice among the most favorable treatments that are available for a given disease. A ranking of multiple competing treatments can be provided by NMA, which h constitutes an advantage over traditional pairwise meta-analysis by allowing to identify the most favorable treatment options between all assessed treatments (29). In the context of calculations, NMA presents the best, the second best, the third best (*etc.*) treatments in terms of their effect sizes on a given outcome, by using different metrics (quantities that compare the estimated treatment-specific effects) over those the surface under the cumulative ranking area (SUCRA) is the most popular. SUCRA presents a Bayesian treatments' rank distribution where each value provided for a given treament (ranging from 0 to 1) shows its position into the builded hierarchy with presenting the treatments that are inferior or superior than the evaluated treatments.

Nevertheless, the criteria according to which a treatment will be preferred over another include not only the obtained treatments' rank distribution values. The chosen health problem

(*e.g.*, cardiovascular disease in CKD.), depends on the definition of the outcome (*e.g.*, incident major adverse cardiovascular events.), and determination of the effect measure to compare each pair of competing interventions (*e.g.*, odds ratio.), are also crucial.

For binary outcomes, the hierarchy can be built on the basis of a model fitted by denoting as p_{ij} the probability of an event in arm $j = 1, \dots, a_i$ reported in trial i with a_i being the total number of treatment arms reported in the trial, and p_{ij} can be estimated as a binomial likelihood $r_{ij} \sim B(p_{ij}, n_{ij})$ with r_{ij} and n_{ij} being the numbers of events and total sample size, respectively (30). Under random effects model assumptions, parameters are linked to the study-specific log-odds ratios of treatment k (the reference treatment in trial) *versus* a specific treatment j —$\text{logit}\ (p_{ik}) = u_i$ and $\text{logit}\ (u_i) = u_i + \delta_{ikj}$— where u_i is a random parameter for the baseline. Then, the random effects have a normal distribution $\delta_{ikj} \sim N(\mu_{kj}, \tau_{kj}^2)$, where τ_{kj}^2 is the heterogeneity variance and $\exp\ (\mu_{kj})$ the odds ratio of treatment k compared with treatment j . The model fitted claims consistency in the effect sizes, that is, $\mu_{kj} = \mu_{kl} + \mu_{lj}$ for all treatments in the treatment comparisons' network, with assuming that the heterogeneity is independent of the comparison being made, that is, $\tau_{jk}^2 = \tau^2$ (31).

Random effects' rank distribution of the studied treatments are then performed after obtention of treatment-specific ranking probabilities *via* the Marcov chain Monte Carlo simulation, according to which a treatment j is ranked depending on the proportion of the cycles in which such treatment ranks first $P(j = 1)$, that is, "is the best" among the a available treatment options, and depending on the estimated effect size corresponding to the comparison of such treatment with its corresponding comparator (30). The treatments' rank distribution depends on the obtained ranking probabilities for each assessed treatment showing the second best one, the third best, and so —$P(j = b), b = 1, \dots, a$— and with considering that these probabilities sum to one for each treatment and each rank.

Facing continuous or dichotomous outcomes, more and more concerns arise and these concerns raise awareness of what ranking can and cannot do, with criticisms attributing the problem to the ranking metrics *per se* (32). Indeed, ranking metrics encompass the uncertainty in the estimation of the treatment effects in different ways, which results in different treatment hierarchies. For instance, treatments that have large uncertainty around their estimated effects are more likely to have higher probabilities of ranking best (33). Importantly, there is no universally accepted "gold standard" treatment hierarchy against which the hierarchy obtained by the existing ranking metrics is to be evaluated (32).

First of all, the ranking metric used to obtain the treatment hierarchy should be chosen depending on the systematic review question, with interpreting the produced treatments' rank distribution beyond inspection of the values from ranking measures and draw on the totality of the evidence synthesis results. In this sense, as in pairwise meta-analysis, assessment of the quality of the evidence should be made before scrutinizing the confidence in the NMA results (effect sizes and rankings), and for the moment while findings from ongoing research to assess specifically ranking confidence are not still available (34).

Secondly, but just as important, findings on treatments' ranking need plotting in order to present efficaciously the ranking of the assessed interventions (35). Once more, findings of the assessment of the quality of the evidence —high risk of bias (*e.g.,* no or unconcealed randomization, lack of blinding, large loss to follow-up, *etc.*), indirectness (*e.g.*, differences in the target population, differences in measuring outcomes.), and reporting bias including publication bias— regain importance as it should be considered to avoid misleading inferences.

Table 3

Illustrative example of a SUCRA-based ranking of complement C5 inhibitors as shown in the study by C. Bernuy-Guevara (36).

Treatment (intervention)	**SUCRA**‡ for outcomes A/B/C§
Eculizumab	0.637/0.642/0.797
Ravulizumab	0.860/0.850/0.700
SOC (pre-/off-treatment state and/or placebo)	0.002/0.007/0.003

Following Marcov chain Monte Carlo simulation assumptions, a treatment j is ranked according to the proportion of the cycles in which such treatment ranks first out of the total studied treatments, and according to the estimated effect size for the comparison of such treatment with its corresponding comparator. In this way, the probability that treatment j "is the best" $P(j = 1)$ among the a available treatment options is calculated, as well as probabilities for the rest of treatments to known the second best one, the third best, and so on $P(j = b)$, $b = 1, \dots, a$.

‡If a treatment ranks first, then SUCRA = 1, and if it ranks last, it will have SUCRA = 0.

§Hemolysis (A) in PNH, and TMA (B) and AKI (C) in aHUS, were the outcomes assessed at the network level.

Abbreviations: aHUS, atypical hemolytic uremic syndrome; AKI, acute kidney injury; PNH, paroxysmal nocturnal hemoglobinuria; SOC, standard of care; SUCRA, surface under the cumulative ranking area; TMA, thrombotic microangiopathy.

From Bernuy-Guevara *et al.*, 2020. (36)

Finally, from a clinical perspective, the qualitative identification of a common comparator, for instance, the worst treatment choice, may help to choose the preferable treatment options (35). At this point, calculation of SUCRA for each treatment appears as a supplementary help in this qualitative selection by simplifying plotting, as well sa to allow to express the effect of each treatment into a single number (from 0 to 1).

In its simplest terms, for each treatment j out of the a competing treatments, to calculate SUCRA, it should be known the a vector of cumulative probabilities $cum_{j,b}$ corresponding to treatment j to be among the b best treatments, $= 1, \dots, a$. Then, SUCRA for treatment j is obtained according to the following formula:

$$SUCRA_j = \frac{\sum_{b=1}^{a-1} cum_{j,b}}{a-1}$$

Table 3 presents a real-life SUCRA-based treatments' ranking taken as example for developing skills on the basis of the above-mentioned explanations to interpret a treatments' ranking. In NMA calculations performed in a meta-analysis conducted by our group comparing the two available complement component 5 (C5) inhibitors eculizumab and ravulizumab with the standard of care (pre-/off-treatment state and/or placebo) on outcomes of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), on the basis of their SUCRA values, we may observe that both C5 inhibitors were similar and that there is an enormous difference between to treat with using these orphan medicines and to treat with the standard of care (36).

In fact, comparing these values, an intuitive estimation of the rating and the gradient in treatment effects across all the assessed treatments may be made. However, this SUCRA ranking was based on very low quality evidence. Thirteen non-randomized single-arm trials and only one randomized two-arms trial provided numerical data for this analysis (36). In addition, the amount of heterogeneity, even if the plausibility of the consistency assumption in the treatment network was reasonable, and the threat of publication bias, all limit as a whole the credibility of this treatment hierarchy.

Importantly, SUCRA cannot consider the magnitude of differences in treatment effects (*i.e.*, the first ranked treatment may be only slightly, or a great deal better than the second ranked treatment.), and chance may explain any apparent difference between the evaluated treatments (35). Therefore, facing treatments' ranking from the meta-analysis of Bernuy-Guevara *et al.* (36), clinicians cannot be at all certain that the differences between eculizumab and ravulizumab are real, but, qualitatively, at least one inference is very secure, that the standard of care is a poor choice for PNH and aHUS.

AKI

in green

0.02 (0.00–0.34)	0.01 (0.00–0.07)	**Pre-treatment/off-treatment state**
0.71 (0.02–19.43)	**Eculizumab** 2-week dosing intervals	0.13 (0.04–0.44)
Ravulizumab 8-week dosing intervals	0.59 (0.05–6.60)	0.08 (0.01–0.61)
0.68 (0.12–4.30)	**Eculizumab** 2-week dosing intervals	
0.02 (0.00–0.29)	0.03 (0.00–0.21)	**Pre-treatment/off-treatment state & placebo**
0.01 (0.00–0.06)	0.01 (0.00–0.04)	**Pre-treatment/off-treatment state**

aHUS

TMA

in blue

PNH

Hemolysis

in red

Figure 2

League table showing effects of the assessed complement C5 inhibitors eculizumab and ravulizumab.

Treatment's effect sizes are presented in OR and 95% CrI for the following outcomes: hemolysis (red) in PNH, and AKI (green) and TMA (blue) in aHUS.

Results from separate analyses considering pre-/off-treatment state and placebo and only pre-/off-treatment state for hemolysis (red) in PNH are provided.

95% CrI, 95% credible interval; aHUS, atypical hemolytic uremic syndrome; AKI, acute kidney injury; OR, odds ratio, PNH, paroxysmal nocturnal hemoglobinuria; TMA, thrombotic microangiopathy.

From Bernuy-Guevara *et al.*, 2020. (36)

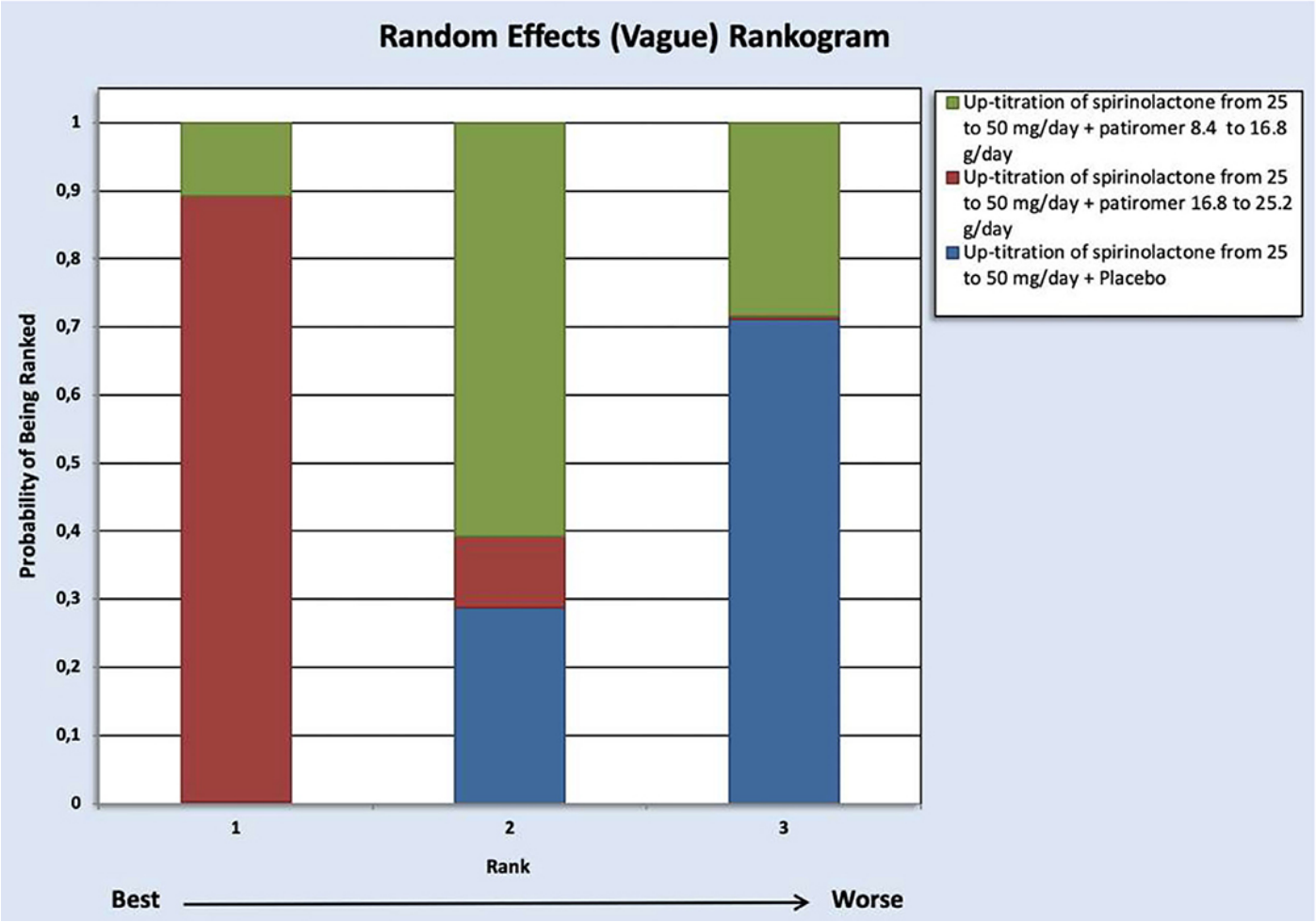

Random Effects (Vague) Rankogram
Probability of Being Ranked
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
1
2
3
Rank
Best
Worse
Up-titration of spirinolactone from 25 to 50 mg/day + patiromer 8.4 to 16.8 g/day
Up-titration of spirinolactone from 25 to 50 mg/day + patiromer 16.8 to 25.2 g/day
Up-titration of spirinolactone from 25 to 50 mg/day + Placebo

Figure 3

Barplots for the ranking probabilities "rankogram" of competing patiromer doses allowing spironolactone up-titration up to 50 mg/day.

On the horizontal axis is the possible rank of each treatment (from best to worse according to the outcome).

The size of each bar corresponds to the probability of each treatment to be at a specific rank.

Studied subjects were individuals with HF or resistant hypertension who may have or not CKD into KDIGO GFR categories G3a to G5 and were also receiving other RAASi.

CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitors.

From Lizaraso-Soto *et al.*, 2021. (37)

With the objective to point out the results from this meta-analysis, we decided then to present pairwise comparisons' effect sizes into a "league table", as the obtained treatments' ranking is based in such effect sizes (**Figure 2**). Indeed, this practice is recommended to be made routinely, as it is useful above all for clinical purposes, and particularly essential in decision-making processes.

Moreover, in order to more intuitively show the full information from a NMA, it is very recommendable that league tables are accompanying "rankograms" into the obtained rank probabilities $P(j = b)$ are plotted against the possible ranks $b = 1, \dots, a$ for all competing treatments. In this sense, "rankograms" may be presented as a bar chart where ranks are placed in the horizontal axis, and each treatment takes a portion of each bar proportional to the probability of having that specific rank, as presented by other meta-analysis conducted by our group (**Figure 3**, 36). This meta-analysis evaluating the effectiveness of binding potassium shows that only the new potassium-binding polymer patiromer (and not the other assessed polymers) can allow to most performing doses of spironolactone (up to 50 mg/day) in subjects affected by heart failure (HF) or with resistant hypertension needing treatment with other renin-angiotensin-aldosterone system inhibitors (RAASi).

Sensitivity issues concerning treatments' ranking

To our knowledge, robustness of SUCRA-based treatments' ranking has not been formally assessed in the literatura, which applies also for other types of ranking obtained by using other metrics. Indeed, a single study can change the pooled evidence enough to influence treatments' ranking, and this may be particularly observed into the cases of sparse networks due to limited direct evidence. When this occurs, this should serve as a flag for further investigation as to whether the change is important enough to impact confidence in the obtained hierarchy of treatments' effectiveness.

With respect to SUCRA-based treatments' ranking, differences between treatments in close proximity by their SUCRA values are reflected by changes in the obtained hierarchy. Importantly, similar SUCRA values might truly reflect treatments that work equally, and the small differences might be because of random error. However, similar SUCRA values might also reflect true but small (and sometimes clinically important) differences in treatments' effectiveness.

Aiming to take a step forward to a more pragmatical interpretation of SUCRA-based treatments' ranking, using Cohen's kappa, by weighting, this agreement measure can highlight which studies have a meaningful impact on changing the obtained treatments' ranking, with highlighting also differences in effects within and between treatments (38). However, while the motivation to assess robustness of ranking metrics is patent, examination of credible intervals of the estimated treatment effects should be made before. As mentioned above, any uncertainty in the obtained treatment effects will be reflected across all possible builded hierarchies, and SUCRA as a metric to construct treatment hierarchies drags this.

Interestingly, once more, plotting that are firstly wieved by readers should be included into the full assessment of treatments' ranking findings. Indeed, plots have a high impact, especially for clinicians, and more than other ways of presentations of findings from NMAs. To illustrate this, in another real-life example, the rankogram presented by Lizaraso-Soto *et al.* (**Figure 3**, 37) shows an overlap between patiromer doses ranging from 8.4 to 16.8 g/day and doses more than 16.8 g/day. Uncertainty in the treatment effects may be related to scarce direct evidence on comparisons of such patiromer doses providing only 5 RTCs (n = 1044), in addition to indirectness related to differences in the target population (*i.e.*, not all resistant hypertension cases are associated to HF and *vice versa* not all HF have occured as a consequence of resistant hypertension). Facing these findings, another narrative (qualitative) inference is in any case

true, that patiromer have an impact on improving spirinolactone treatment from the first doses.

Finally, the important takeaway message is that, into their most pragmatical terms, regardless of theroterical and methodological limits, the interpretation of treatments's ranking findings is mostly a qualitative proceeding. In this way, the expertise of clinicians treating the addressed conditions is of crucial importance, as statements to be issued should be referred to the actual context of such conditions for which treatments are assessed.

Chapter 3: Study aims

Anemia, a common complication of CKD, is pathophysiologically centered on an iron-restricted erythropoiesis phenomenon, that, regardless of other contributing factors (*e.g.*, inflammation, kidney function deterioration, gastrointestinal absorption, blood losses, *etc.*), worsing dramatically with artificial supplementation of EPO (8). Importantly, both the anemia itself and the use of higher doses of ESAs are associated with poor outcomes, particularly a more cardiovascular disease burden, seen even soon across the natural history of CKD (1), which justifying iron supplementation. Nevertheless, research highlights that both iron supplementation and ESA therapy play a critical role with the objective of avoinding the negative impact of the anemia of CKD, thus, right prescription of these medicines will contibute to a better performing treatment of CKD patients (13,14).

Study hypothesis

Current recommendations underline the importance of an intravenous iron supplementation in patients undergoing dialysis and also show preference for an i.v. iron reposition in patients with CKD stages 3 to 5 (17,19,21). Research supporting these recommendations highlights the benefit of i.v. supplements which apparently outweighs their risks, and such findings are summarized and presented by the available meta-analyses assessing dialysis and non-dialysis patients' data from RCTs (23–26). However, research gaps on the individual impact of the different i.v. preparations are pending to be solved. Similar increases in Hb levels are observed when different formulations were used (25), even if the amount of elementary iron to be infused differs among all avalaible preparations. Importantly, higher amounts of elementary iron showed to have limited effectiveness as they could aggravate iron deficiency *via* the increase in hepcidin levels (18), which may partially explain the apparent similar effects between newer and older iron formulations. In this context, ESA therapy furthermore may

contribute to an even more profound iron deficiency by aggravating the vicious circle of iron-restricted erythropoiesis in CKD (8). Other confounding factors such as age of the study patients but also inconsistent use of markers of iron storages may further contribute to bias in this setting (26).

The recommendations aim to achieve a sustained Hb response, defined as ideally reaching the target Hb or an increase in Hb concentration of >1 g/dL (17,19,21). This aim not be obtained in all patients. Thus, lesser increases in Hb levels that are also accepted (17,19), could extend our observations on the effectiveness of intravenous iron supplementation in CKD. For this purpose, new systematic review searches and new meta-analytic calculations with including the new RCTs with those already included in the available evidence summaries are needed. How the outcome will be defined —to bring reality closer to the use of iron supplements— and how the defined outcome can the most performantly be measured (*i.e.*, determination of the most appropriate effect measure), will aid to an efficient modelling following adequate assumptions. NMA calculations designing with attempting an i.v. supplements' ranking can then delimitate the effects of the available preparations.

Importantly, the assessement of the effects of different i.v. iron supplements neccessitates to retrieve the trials with higher level of pragmatism, as traditionally clinical trials aim to assess the efficacy of medicines (39). This will be crucial to update our knowledge on the effectiveness of i.v. iron supplementation in CKD.

Seemingly similar in meaning, "efficacy" and "effectiveness" express distinctly different concepts (40). In a simplified concept, "efficacy" describes how a drug works under conditions of clinical trials, whereas "effectiveness" describes how it works under conditions of everyday clinical practice, also referred to as "real world evidence". Differences between these two settings are known as the 'efficacy-effectiveness gap' (41). For instance, an anti-hypertensive

medicine that works well in a clinical trial —for a given and very narrowly definded population— could have in 'real life' a smaller or inexistent effect. Regardless of the adverse effects' profile of medicines, the proportion of non-responders to a previously studied medicine among patients in "real world" may be significant, even if clinicians adhere well to the prescription label constraints of the used medicine.

Not surprisingly, sources of variability in drug response are multiple and they include different genetic and non-genetic factors (*e.g.*, demographics, comorbities, *etc.*), the environment including co-medications and diet.

The named 'explanatory' trials do not consider the contributors for variability of drug response to guarantee their internal validity, that is, to present a confident cause-and-effect relationship to the evaluated medicine, which cannot be explained by other factors. Therefore, to assess the potential of a medicine in real life, the external validity of a trial (*i.e.*, generalizability or applicability of study findings) is essential, even though covering patients in a particular clinical setting, that is, that their results are relevant only to a defined group of patients (42). Indeed, to date, enrichement measures (*e.g.*, run-in phase, stratification, *etc.*), broad selection criteria, less control over patient management, *etc.* are still not sufficient to conclude on the effectiveness of a given medicine to less selectioned populations. Furthermore, extrapolation is commonly used in this context which may further widens the efficacy-effectiveness gap (41).

Study objectives

This PhD thesis study intends to evaluate the impact of different i.v. iron supplements for treating the anemia of CKD. Commonly encountered in the clinic, our assessments consider, and the presented findings differentiate the use of the evaluated iron supplements in both key moments of the disease, that is, before and once dialysis is initiated.

A systematic review and a meta-analysis were designed following current recommandations (43,44), with the aim to conform or confront findings from the previous systematic reviews and meta-analyses on intravenous iron supplementation in CKD (23–26). We are confident that the findings from the presented study will help to better identify the indications of i.v. supplementation for treating anemia of CKD and allow to better discriminate between different treatment options.

Chapter 4: Experimental section

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, published in 2009 and updated thereafter, were developed to transparently report systematic review findings, with especially harmonize methods of study searching details and data assessement thus helping to improve the reporting of systematic reviews (43,44). Taken into account the necessity to compare multiple treatments and facing the inherent challenges to perform that, PRISMA emits in 2015 the recommendations to report findings of systematic reviews incorporating network meta-analyses, with highlighting the key points of this type of synthesis which is crucial in effectiveness research (45).

We have designed and then updated a systematic review protocol presenting the methods leading to the inclusion of the studies and the assessement of the information to answer the defined review question aiming to present the individual impact of different i.v. preparations for treating the anemia of CKD. Both the final version and the first version of the protocol submitted to the International prospective register of systematic reviews PROSPERO, all of which are freely available online (https://www.crd.york.ac.uk/prospero/), conform to the recommendations of the 2015 PRISMA-P statement (46,47). The systematic review protocol was registered in PROSPERO on January 20, 2020, and it was published at this same day under the reference CRD42020148155. The update supplied by the systematic review authors were reflected by PROSPERO in the second and final version of the protocol, which was published on October 27, 2020. Changes performed in the update contained completing information as well as grammatical corrections.

This systematic review started on September 18, 2019. As scheduled, all the planned assessments were achieved on April 11, 2020.

Study searching

Published articles' databases, study registries, academic repositories, and meeting abstracts archives were searched. Briefly, MEDLINE *via* PubMed, Ovid, and Web of Science, EMBASE *via* Elsevier's Scopus, and the Cochrane Controlled Register of Trials CENTRAL were accessed, and the records were confronted and complemented with those identified through ClinicalTrials.gov, the European Union (EU) Clinical Trials Register, and the United Kingdom's International Standard Randomised Controlled Trial Number (ISRCTN) registry. The other accessed information sources were the research theses' repositories Digital Access to Research Theses (DART) – Europe and Open Access Theses and Dissertations (OATD), and several meeting abstracts archives *via* journals and websites of the physician societies organizing the meetings (see Chapter 8 – Supplementary material). Overall, our searches performed into published research sources and sources designated to as 'grey' literature because containing unpublished research, guarantee completeness and comprehensiveness of our systematic review searching process.

The guidance for literature search reporting provided by the 16-item PRISMA-S checklist allows to verify adequacy of our searching process of each of its component and guarantees the reproducibility of our study searching (48), which is reported below.

Table 4

Systematic review eligibility criteria.

Items	Criteria
Population	Adults with NKF or patients with CKD and eGFR >60 ml/min/1.73 m^2 (KDIGO GFR categories G1 to G2), or patients with CKD and eGFR ≤60 ml/min/1.73 m^2 (KDIGO GFR categories G3A to G5), or patients treated with chronic dialysis or kidney transplantation.
Interventions	Intravenous iron supplementation with using newer formulations.
Co-interventions	ESA therapy, blood transfusions.
Exposures	Hemoglobin, serum iron and ferritin levels, TSAT, TIBC, CHr, and HRC.
Comparators	Intravenous iron supplementation with using older formulations, oral iron supplementation.
Outcomes	Drug reponse.
Study type	RCTs, their follow-up extension studies and interim and post-hoc analyses.

Abbreviations: CHr, reticulocyte Hb content; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis stimulating agent; HRC, percentage of hypochromic red blood cells; KDIGO, Kidney Disease: Improving Global Outcomes; NKF, normal kidney function; RCT, randomized controlled trial; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

Table 4 presents study eligibility guiding searching in the accessed information sources. Search terms related to the study population, interventions, exposures, and study type, were used to build search strategy formulae, which were adapted to the characteristics and requirements of each of the accessed information sources. The produced search formulae are available to the reader at the end of this PhD manuscript (see Chapter 8 – Supplementary material).

To be eligible, the studies should evaluate drug response of the available i.v. supplements to conclude on the individual impact of these medicines for treating the anemia of CKD. As drug response, increases in Hb levels of 0.5–1 g/dL or more, or the achievement of a target Hb according to recommendations (17,19,21), without need for further increase of ESA doses or initiation of ESA therapy, and without requirements for blood transfusions, were defined.

This systematic review was intended to retrieve the known 'pragmatic' clinical trials (39) with external validation (42), which studied CKD patients with anemia. The included effectiveness trials studied the post-marketing use of both the newer and older iron formulations already assessed in previous meta-analyses. Importantly, these studies differentiated the use of the evaluated iron supplements in both key moments of CKD, that is, before and once dialysis is initiated.

Following the systematic review eligibility criteria, the review team consisting of two reviewers and one conciliator, were charged firstly to the screening of the titles/abstracts of records, and then, the examination of full-text reports of the potentially eligible studies. Decisions to the inclusion of a given study were found through an independent and parallel reviewing procedure that was carried out by both reviewers, and disagreements that arose were solved by discussion with/without the intervention of the conciliator. In all cases, the corresponding authors of the included studies were contacted whenever possible to retrieve missing information and to confirm study details. Finally, to ensure search saturation, a references'

search of all eligible studies as described above was carried out using Web of Science to identify all studies citing the included studies.

Synthesis assessments

Following a structurated synthesis approach, coding of the considered characteristics of the population, interventions (including co-interventions), comparators and outcomes were performed (49), and before tabulating with the purpose to compare findings from the included studies across the caracteristics of such components of the PICO (*i.e.*, population/participants, interventions/investigated condition, comparison, outcome.) acronym (50).

Table 5

Coding elements considered for the systematic review synthesis.

PICO component	**Elements**
Population/participants	Mean and SD for patient age (in yrs) Males (in %) DM patients (in %) Patients with CKD into KDIGO GFR categories G1 to G2 (including NKF), KDIGO GFR categories G3A to G5, KTR&, and KTX (in %) The following causes of CKD (in %): ADPKD, DM, GN/AID, TIN/HTN, unknown/other.

Interventions	Intravenous iron supplementation schemes with newer formulations.
Co-interventions	ESA therapy schemes. Blood transfusions.
Comparators	Intravenous iron supplementation schemes with older formulations, oral iron supplementation schemes.
Outcomes	Increases in Hb levels of 0.5–1 g/dL or more, or achievement of target Hb§. No increases in ESA doses or need for ESA therapy initiation. No need for blood transfusion. Any changes in either Hb, serum iron, serum ferritin levels, TSAT, TIBC, CHr, and HRC.

&Participants were ESKD patients on treated with chronic dialysis (HD and PD).

§The target Hb was established according to WHO thresholds of Hb <13 g/dL in men and Hb <12 g/dL in women, which define anemia and as they are considered by current recommendations (16,17,19,21).

Abbreviations: ADPKD, autosomal-dominant polycystic kidney disease; AID, autoimmune disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; GN, glomerulonephritis; GFR, glomerular filtration rate; Hb, hemoglobin; HD, hemodialysis; HTN, hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; KRT, kidney replacement therapy; KTX, kidney transplantation; NKF, normal kidney function; PD, peritoneal dialysis; PICO, population/participants, interventions/investigated condition, comparison, outcome; SD, standard deviation; TIN, tubulo-interstitial nephritis; WHO, World Health Organization.

Table 5 presents the coding elements considered to produce the synthesis table that was elaborated with extracting the information from the obtained datasets. All the studies eligible are presented in this synthesis table regardless of whether they provided, or not, pertinent data for meta-analytic calculations. The produced synthesis table is available to the reader at the end of this PhD manuscript (see Chapter 8 – Supplementary material).

Two separated syntheses were planned by comparing the main intervention, that is, intravenous iron supplementation with using newer formulations *versus* the use of older formulations or oral iron supplementation, against the groups of patients before and those having already started dialysis. These groups of patients were considered as subgroups for the purposes of mathematical assessments corresponding to each synthesis.

To consider drug response into calculations, the increase in Hb concentration less than 0.5–1 g/dL, with increases in ESA doses or initiation of ESA therapy, with/without requirements for blood transfusions, was the combined 'bad' outcome. NMA calculations were made on random effects model and effect sizes obtained for the comparisons of i.v. and p.o. supplements are presented in odds ratios (OR) with their corresponding 95% credible intervals (95% CrI). The random effects' rank distribution of the studied treatments for each subgroup (patients before and those having already started dialysis) was then performed according to treatment-specific ranking probabilities obtained *via* the Marcov chain Monte Carlo simulation, depending on the proportion of cycles in which a given iron formulation scheme ranks first, second, third, and son on, out of the total schemes assessed, and depending on the estimated effect size for the comparison of such scheme with its corresponding comparator (see Chapter 2 – Best treatment choosing). Calculation of SUCRA for each iron formulation

scheme including oral iron supplementation, with plotting of values aiming a friendly assessment of findings were made.

NetMetaXL, a Microsoft-Excel-based tool that allow to run NMA using WinBUGS was used. This Excel-based tool is available from the Canada's Drug and Health Technology Agency (CADTH) online repository, and it is part of the Microsoft-based tools for Health Technology Assessment (HTA) interventions (http://www.cadth.ca/en/resources/hta-excel-tools). The WinBUGS 1.4.3 package was installed and the patch for WinBUGS 1.4.3 was downloaded and installed, as well as the key for unrestricted use following the instructions of the Medical Research Council (MRC) Biostatistics Unit of the University of Cambridge. WinBUGS is a stand-alone program for conducting Bayesian analysis using the Markov chain Monte Carlo simulation (51) and NetMetaXL was designed to allow users to run NMA *via* a more user-friendly Microsoft Excel interface (52).

The analysis using WinBUGS required to choose prior probability distributions for the unknown parameters and a likelihood function derived from a model that specifies the relation between the unknown parameters and the observed data (53,54).

The choice of prior distribution is crucial, because the precision with which effect sizes are estimated are affected when small amounts of data are entered in analysis (55). The inclusion of a prior distribution reduces the analysis complexity, that is, the 'difficulty in estimation', but depending on the data that are available (56). As there was no prior information and justified by the principle of indifference, wanting 'the data to dominate', 'vague' prior distributions were used to obtain the log odds ratios for all comparisons of i.v. and p.o. supplements being made.

NetMetaXL adjusts all zero values using an adjusted continuity correction factor accounting for potential differences in sample size and centered around 0.5 (57). The zero values correction within NetMetaXL keeps all studies for analysis, even those with multiple zero values, although

these do not contribute to the estimation of treatment effects and with the risk that the results may remain unstablewhich was not the case in the present study (58).

As indicated for hierarchical models, the Brooks-Gelman-Rubin method was applied to verify if the Markov chain Monte Carlo simulation converges, and comparisons between and within variances of $m \geq 1$ sequences of simulations, with different starting points which are overdispersed with respect to a multivariate target distribution $p(\theta)$, each of length n, $(\theta_{j1}, \theta_{j2}, \ldots, \theta_{jn})$, for a given treatment $j = 1, \ldots, a$ —in this notation, each θ_{jt} is a vector— were performed to verify whether or not stationarity has been reached across these m sequences (58). Nevertheless, under the assumptions of random effects model, a smaller Monte Carlo error when comparing treatment *j* with treatment *k* (the reference treatment in trial) indicates a higher accuracy, which means a good convergence, and NetMetaXL firstly checks whether the Monte Carlo error is less than 5% of the standard deviation (SD) of the estimated treatment effects and between-study variance τ^2 which corresponds to within-study variance $\tau_{jk}^2 = \tau^2$ (31).

NMA calculations were preceded by classical pairwise meta-analysis according to current recommendations (46). Random effects sizes obtained for the comparisons of i.v. and p.o. supplements are presented in odds ratios (OR) with their corresponding 95% confidence intervals (95% CI) under the assumptions of the Mantel–Haenszel method (60). Review Manager software (RevMan) version 5.3 (Cochrane Collaboration) was used to perform this analysis.

Treatment of limitations

The steps that have to be taken to minimize the risk of drawing incorrect conclusions from the comparisons when performing the NMA calculations assessing i.v. and p.o. supplements, and

the steps to minimize heterogeneity in pairwise meta-analysis preceding the NMA calculations, are explained below.

Given a connected network of comparisons, NMA produces an internally coherent set of estimates of the effects of any treatment in the network relative to any other under the key assumption of evidence consistency (61). Ideally, for given treatments A, B and C, consistency is assumed when there is no conflict between 'direct' evidence when comparing treatments B and C and 'indirect' evidence gained from comparisons between treatments A and C and between A and B under the assumptions of transitivity laws. Note that consistency concerns the relation between the treatment contrasts (the term contrast refers to a pairwise comparison between 2 treatments), and consistency equations offer a prediction about these relationships in the data that can be statistically tested.

In complex networks, a standard consistency model (57) is compared with a model not assuming consistency. In the consistency model, for an illustrative network with $nt = 4$ treatments, w , x , y , and z , the basic parameters $nt - 1 = 3$ are: μ_{wx} , μ_{wy} , and μ_{wz} . These basic parameters estimate all treatment effects relative to treatment w —chosen as the reference treatment— which are obtained from the corresponding treatment contrasts. Formally, for a set of m trials comparing these treatments, the study-specific treatment effects for a study i comparing treatment w to treatment x on random effects model, δ_{iwx} , are assumed to follow a normal distribution $\delta_{iwx} \sim N(\mu_{wx}, \tau^2_{wx})$ for $i = 1, \ldots, m$ (30). Thus, for this network, in the consistency model, the consistency equations defining all other possible contrasts are: $\mu_{xy} = \mu_{wy} - \mu_{wx}$, $\mu_{xz} = \mu_{wz} - \mu_{wx}$, $\mu_{yz} = \mu_{wz} - \mu_{wy}$. Note that the number of the other possible contrasts is iqual to the inconsistency degrees of freedom (ICDF) that are calculated from the number of treatments nt and the number of treatment contrasts $c = 6$ on which there is evidence as $c - (nt - 1)$. Importantly, for this network, in the inconsistency model, each comparison is treated independently, but with assuming as in the consistency

model that between-study variance τ^2 corresponds to within-study variance $\tau_{jk}^2 = \tau^2$ (31). Finally, based on the work of Spiegelhalter and others (54), Bayesian measures of 'adequacy' or fit of model, named as posterior mean deviance $\overline{D}$, and the complexity for the effective number of model parameters p_D were added to form the deviance information criterion (DIC) which were used for comparing the consistency and incosistency models being performed (60), given 'vague' prior distributions $\sim N(0, 100^2)$ in obtaining treatment effects in order to asign equal probabilities to all possibilities (principle of indifference).

Meta-analyses should include the quantity I^2 to help readers for assessing the consistency in treatment effect estimates providing pairwise comparisons (62). In order to determine the null hypothesis that all studies are evaluating the same effect, that is, whether there are true differences underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity), I^2 presents the percentage of total variation across studies that is due to heterogeneity rather than chance, as $I^2 = 100\% \times (Q - df/Q)$, were Q is Cochran's heterogeneity statistic and df the degrees of freedom. Note that Q is obtained by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting each study's contribution in the same manner as in the meta-analysis. P-values that are also obtained by comparing the statistic with a $\chi 2$ distribution with $k - 1$ degrees of freedom (where k is the number of studies), are presented with I^2 values. I^2 values are between 0% and 100%, with indicating a value of 0% no heterogeneity, the values near of 0% lowest heterogeneity, and larger values higher heterogeneity. A standard categorization of I^2 values, which consider as low, moderate, and high, respectively, the cut-off points of 25%, 50%, and 75%, was used to an intuitive interpretation of our meta-analytic findings.

τ^2, the among-study variance (an alternative test for quantification of heterogeneity in a meta-analysis), was also calculated and are presented in the comparisons of heterogeneity among the subgroups of patients before and those having already started dialysis, as a random effects model was assumed (62). Importantly, τ^2 values depend on the chosen treatment effect measure, and its use is highly recommended when the obtained effect sizes are presented in odds ratios (62).

Publication bias risks

We systematically explored potential publication bias with its impact on the presented synthesis. Of not4e, this systematic review and meta-analysis included not only significant or positive results of intravenous iron supplementation in CKD. In this context, the Egger test was used with the intention to avoid subjectivity of visual inspection of funnel plot asymmetry. A modified regression analysis of Galbraith's radial plot (63) necessitating calculation of the named standard normal deviate (SND), defined as the odds ratio divided by its standard error (SE), was performed with using the estimate's precision, defined as the inverse of the SE (64). In order to evaluate distance from the origin on the logarithmic scale, under ideal conditions, calculated regression for smaller studies will be close to zero on both Galbraith's plot axes, as precision depends largely on sample size. Therefore, in the cases of smaller studies showing big protective effects, deviation from the origin was searched and its pronounciation to know if those smaller studies presented effects that differed systematically from larger studies.

Chapter 5: Results and Discussion

According to PRISMA recommendations (43–45) and following the methods declared in our published protocol in PROSPERO that adheres to the 2015 PRISMA-P statement (46,47), the findings provided by our study searching and the assessements with the included studies for answering to our review question, are presented below.

Following the current PRISMA recommendations (43–45), the findings from our searching process are presented according the new PRISMA flow diagram (**Figure 4**). The flow diagram according to previous recommendations is also available to the reader (see Chapter 8 – Supplementary material).

The searching process led to the inclusion of 34 RCTs and were presented by a total of 42 reports. **Table 6** presents all the included studies in our systematic review. All these moderate to high quality studies corresponded to pharmaceutical industry sponsored and non-sponsored clinical trials investigating intravenous iron supplementation with using newer and older formulations in CKD patients, with assessing separately those patients before and those having already started dialysis. Characteristics of the participants, interventions, comparators and description of all outcomes evaluated in the included studies are available to the reader at the end of this PhD manuscript (see Chapter 8 – Supplementary material).

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

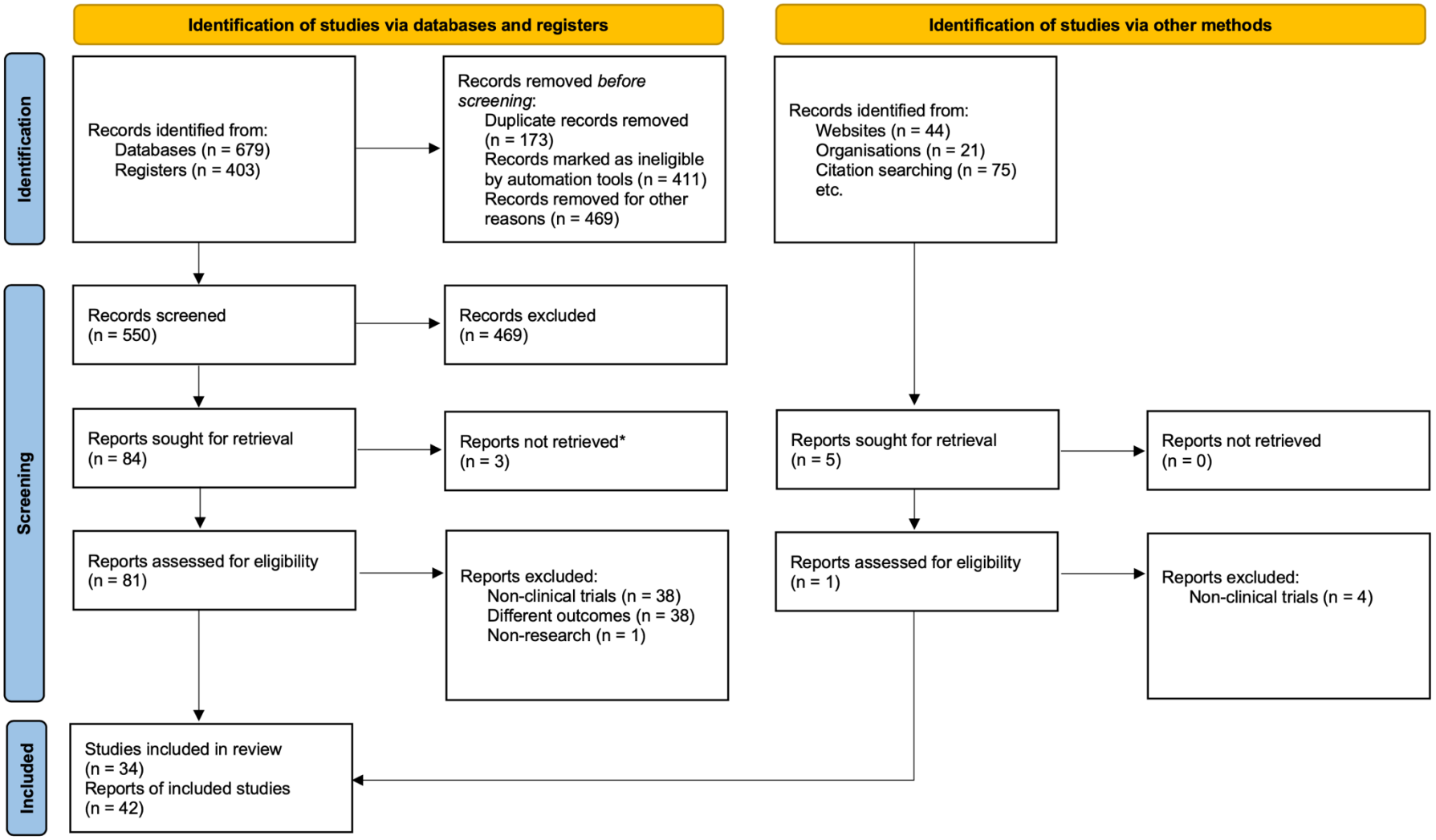


Figure 4

Presentation of our searching process into the current PRISMA flow diagram.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

From Page et al., 2021 (43)

Table 6

The included studies in the systematic review.

Sponsor study name / full official study title	Registration IDs	Reference
FACT / Ferumoxytol for Anemia of CKD Trial: A Phase IV, Open-Label, Multicenter Trial, With MRI Substudy, Of Repeated Doses Of Ferumoxytol Compared With Iron Sucrose For Treatment Of IDA In CKD Patients On Hemodialysis.	NCT01227616	65
King's College Hospital NHS Foundation Trust PIVOTAL / UK Multicentre Open-Label Randomised Controlled Trial Of IV Iron Therapy In Incident Haemodialysis Patients.	EudraCT-2013-002267-25	66
NA / A Phase III, Randomized, Comparative, Open-Label Study of Intravenous Iron Isomaltoside 1000 (Monofer®) Administered As Maintenance Therapy By Single Or Repeated Bolus Injections In Comparison With Intravenous Iron Sucrose In Subjects With Stage 5 Chronic Kidney Disease on Dialysis Therapy (CKD-5D).	NCT01222884 / EudraCT-2010-023471-26	67
NA / Intravenous Versus Oral Iron Supplementation For Correction Of Post-Transplant Anaemia In Renal Transplant Patients.	ACTRN12608000186358	68
Ferumoxytol Authorization Study 1. / A Phase III Study Of The Safety And Efficacy of Ferumoxytol (Compared	NCT00233597	69,70

With Oral Iron) As An Iron Replacement Therapy In Hemodialysis Patients Who Are Receiving Supplemental EPO Therapy.		
DRIVE / Dialysis Patients' Response to IV Iron With Elevated Ferritin. DRIVE-II / 6-Week Observational Extension Study	NCT00224081	71,72
NA / Intravenous Iron Sucrose in Chinese Hemodialysis and Peritoneal Dialysis Patients with Renal Anemia.	NA	73–75
NA / Effect of Intravenous Iron Sucrose in Peritoneal Dialysis Patients Who Receive Erythropoiesis-Stimulating Agents For Anemia: A Randomized, Controlled Trial.	NA	76
NA / A Randomized, Controlled Parallel-Group Trial on Efficacy And Safety of Iron Sucrose (Venofer®) Vs Iron Gluconate (Ferrlecit®) In Haemodialysis Patients Treated With rHuEpo.	NA	77
NA / A Randomized Controlled Study Of Iron Supplementation In Patients Treated With Erythropoietin.	NA	78
NA / Reduction In Recombinant Human Erythropoietin Doses By The Use Of Chronic Intravenous Iron Supplementation.	NA	79
CKD-201 (FIRST) / A Trial Comparing Ferumoxytol To Iron Sucrose For The Treatment Of Iron Deficiency Anemia In Adult Subjects With Chronic Kidney Disease.	NCT01052779, NCT01114204	80–82

IDA-302 / A Phase III, Randomized, Open-Label, Active-Controlled, Trial Comparing Ferumoxytol With Iron Sucrose For The Treatment Of Iron Deficiency Anemia.		
NA / A Multi-center, Randomized Controlled Study To Investigate The Safety And Tolerability of IV Ferric Carboxymaltose (FCM) Vs Standard Medical Care In Treating Iron Deficiency Anemia In Chronic Kidney Disease Patients.	NCT00548691	83
NA / Iron Isomaltoside 1000 (Monofer®) In Non-Dialysis Dependent Chronic Kidney Disease And With Renal-Related Anaemia.	NCT01102413	84
REVOKE / A Randomized Trial Of Intravenous And Oral Iron In Chronic Kidney Disease.	NA	85
NA / Effect of Oral Liposomal Iron Versus Intravenous Iron For Treatment Of Iron Deficiency Anaemia In CKD Patients: A Randomized Trial.	NA	86
FIND-CKD / An Open-label, Multicentre, Randomised, 3-Arm Study To Investigate The Comparative Efficacy And Safety Of Intravenous Ferric Carboxymaltose (Ferinject High and Low Dosage Regimens) Versus Oral Iron For The Treatment Of Iron Deficiency Anaemia in Subjects With Non-Dialysis-Dependent Chronic Kidney Disease.	NCT00994318	87
REPAIR-IDA / Randomized Evaluation Of Efficacy And Safety Of Ferric Carboxymaltose In Patients With Iron Deficiency Anemia and Impaired Renal Function.	NCT00981045	88

Ferumoxytol authorization study 2. / A Phase III Study Of The Safety And Efficacy Of Ferumoxytol (Compared With Oral Iron) As An Iron Replacement Therapy in Chronic Kidney Disease Patients Not On Dialysis	NCT00255424	69,89–91
NA / A Randomized Controlled Trial Comparing Intravenous Ferric Carboxymaltose With Oral Iron For Treatment Of Iron Deficiency Anaemia Of Non-Dialysis-Dependent Chronic Kidney Disease Patients.	NA	92
NA / Maintenance Of Elevated Versus Physiological Iron Indices In Non-Anaemic Patients With Chronic Kidney Disease: A Randomized Controlled Trial.	NA	93
NA / A Randomized, Controlled Trial Comparing IV Iron Sucrose To Oral Iron In Anemic Patients With Nondialysis-Dependent CKD.	NA	94
NA / Comparison Of Intravenous Iron Sucrose To Oral Iron In The Treatment Of Anemic Patients With Chronic Kidney Disease Not On Dialysis.	NA	95
NA / A Randomized Study Of Oral Vs Intravenous Iron Supplementation In Patients With Progressive Renal Insufficiency Treated With Erythropoietin.	NA	96
NA / Multi-frequency Low-Dose Intravenous Iron On Oxidative Stress In Maintenance Hemodialysis Patients	NA	97
NA / Comparison Of Parenteral Iron Sucrose And Ferric Chloride During Erythropoietin Therapy Of Haemodialysis Patients.	NA	98

NA / Parenteral Iron Therapy In Treatment Of Anemia In End-Stage Renal Disease Patients: A Comparative Study Between Iron Saccharate And Gluconate.	NA	99
NA / Comparison Of Oral Versus Intravenous Iron Therapy In Predialysis Patients Of Chronic Renal Failure Receiving Recombinant Human Erythropoietin.	NA	100
NA / Sodium Ferric Gluconate Complex In Sucrose Is Safe And Effective In Hemodialysis Patients: North American Clinical Trial.	NA	101
NA / Maintenance Therapy With Intravenous Iron In Hemodialysis Patients Receiving Erythropoietin.	NA	102
NA / Iron Supplementation During Erythropoietin Therapy In Patients On Hemodialysis.	NA	103
NA / The Therapeutic Equivalence Of Oral And Intravenous Iron In Renal Dialysis Patients.	NA	104
NA / Heme Iron Polypeptide For The Treatment Of Iron Deficiency Anemia In Non-Dialysis Chronic Kidney Disease Patients: A Randomized Controlled Trial.	NA	105
NA / A Randomized Controlled Trial Of Oral Versus Intravenous Iron In Chronic Kidney Disease.	NA	106

Abbreviations: DRIVE, Dialysis patients' Response to IV iron with Elevated Ferritin; FACT, Ferumoxytol for Anemia of Ckd Trial: a phase IV, open-label, multicenter trial, with MRI substudy, of repeated doses of ferumoxytol compared with iron sucrose for treatment of IDA in CKD patients on hemodialysis; FIND-CKD, an open-label, multicentre, randomised, 3-arm study to investigate the comparative efficacy and safety of intravenous Ferric carboxymaltose

(Ferinject high and low dosage regimens) versus oral Iron for the treatment of iron Deficiency anaemia in subjects with non-dialysis-dependent Chronic Kidney Disease; NA, non-available; PIVOTAL, UK multicentre oPen-label randomised controlled trial of IV irOn Therapy In Incident hAemodiaLysis patients; REPAIR-IDA, Randomized Evaluation of efficacy and safety of ferric carboxymaltose in PAtIents with Iron Deficiency Anemia and impaired renal function; REVOKE, a RandomizEd trial of intraVenous and Oral iron in chronic Kidney disEase.

Non-research studies, observational studies, as well as studies assessing different outcomes, were excluded (**Figure 4**). Interestingly, meeting abstracts, PhD and Master theses, and industry reports did not provide other studies different than those published. However, more than one report presented the results from one study, and in all cases these reports contained the results of extension follow-up studies/post-hoc analyses corresponding to the following trials: ferumoxytol authorization studies (69,89–91), DRIVE and DRIVE II studies (71,72), and the studies CKD-201 and IDA-302 (80–82).

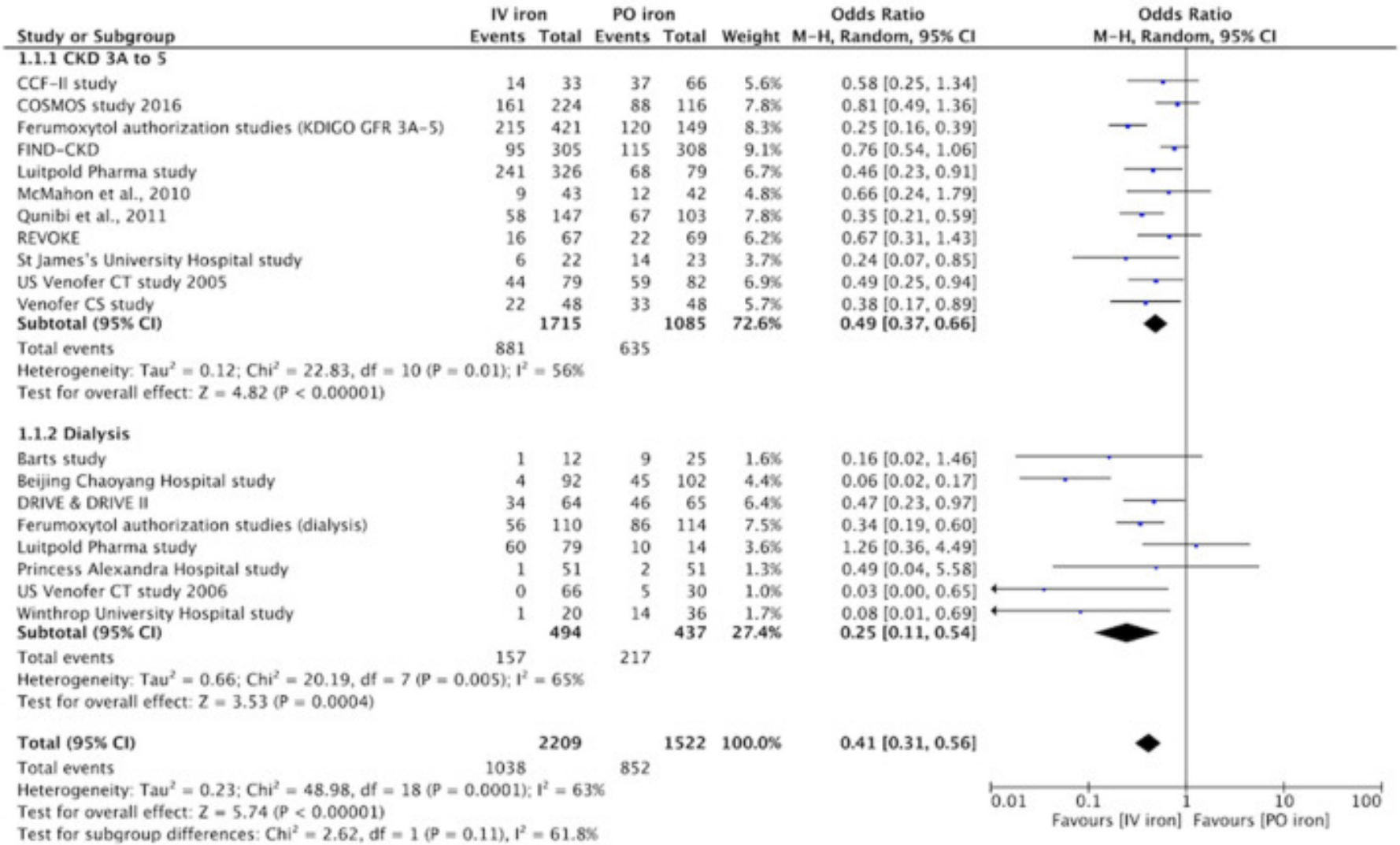
Meta-analytic findings

Ten out of the finally included 34 trials did not provide numerical data for the presented meta-analysis (97–106), and the mathematical findings covered 93.7% (n = 10.097) of the total study population. Importantly, calculation of pooled effect estimates for common efficacy parameters (*e.g.*, Hgb and serum transferrin and ferritin levels.) was not possible, even if six out of the analyzable 24 trials (66,67,71,72,76,78,88,94) performed a stratified randomization of study participants on these parameters and other efficacy and non-efficacy variables (e.g.,

ESA therapy and transfusion requirements, study participants characteristics). The heterogenous definition of such variables was the main impeding cause to avoid this analysis.

Pairwise meta-analysis of 19 trials, comparing exclusively i.v. and p.o. supplements for the combined 'bad' outcome of non-response (*i.e.*, Hgb increase of <0.5–1.0 g/dL, or initiation/intensification of ESA therapy, or increase/change of iron supplement, or requirements of blood transfusion.) are presented bellow (**Figure 5**). The two Bayesian network diagrams built with all 24 trials presenting all possible comparisons between different i.v. to p.o. supplements, respectively, into the subgroups of patients before and those having already started dialysis, are then presented (**Figure 6**).

Our meta-analysis presents the effect sizes corresponding to the comparisons of intravenous iron supplementation with using newer and older formulations and shows that more iron supplements appear to have an impacting effect against the combined outcome of non-response before the start of dialysis than once dialysis is initiated (**Figure 7**). Indeed, 400 mg or more of iron sucrose *per* month (OR, 95% CrI; 0.46, 0.30 to 0.68), 100 to 300 mg of iron sucrose *per* month (0.48, 0.31 to 0.77), 1020 mg of ferumoxytol *per* month (0.28, 0.16 to 0.47), and 750 to 1500 mg of ferric carboxymaltose *per* month (0.36, 0.24 to 0.53) were the most performing formulations among patients with an eGFR <60 mL/min/1.73 m^2 (CKD stage 3 or more), compared to p.o. iron (and no iron administration). In dialysis, only 400 mg or more of iron sucrose *per* month (0.13, 0.02 to 0.50) and 400 mg or more of iron dextran *per* month (0.08, 0.01 to 0.64) were the most performing supplements.


Study or Subgroup
IV iron Events Total
PO iron Events Total
Weight
Odds Ratio M-H, Random, 95% CI
Odds Ratio M-H, Random, 95% CI
1.1.1 CKD 3A to 5
CCF-II study 14 33 37 66 5.6% 0.58 [0.25, 1.34]
COSMOS study 2016 161 224 88 116 7.8% 0.81 [0.49, 1.36]
Ferumoxytol authorization studies (KDIGO GFR 3A-5) 215 421 120 149 8.3% 0.25 [0.16, 0.39]
FIND-CKD 95 305 115 308 9.1% 0.76 [0.54, 1.06]
Luitpold Pharma study 241 326 68 79 6.7% 0.46 [0.23, 0.91]
McMahon et al., 2010 9 43 12 42 4.8% 0.66 [0.24, 1.79]
Qunibi et al., 2011 58 147 67 103 7.8% 0.35 [0.21, 0.59]
REVOKE 16 67 22 69 6.2% 0.67 [0.31, 1.43]
St James's University Hospital study 6 22 14 23 3.7% 0.24 [0.07, 0.85]
US Venofer CT study 2005 44 79 59 82 6.9% 0.49 [0.25, 0.94]
Venofer CS study 22 48 33 48 5.7% 0.38 [0.17, 0.89]
Subtotal (95% CI) 1715 1085 72.6% 0.49 [0.37, 0.66]
Total events 881 635
Heterogeneity: Tau² = 0.12; Chi² = 22.83, df = 10 (P = 0.01); I² = 56%
Test for overall effect: Z = 4.82 (P < 0.00001)
1.1.2 Dialysis
Barts study 1 12 9 25 1.6% 0.16 [0.02, 1.46]
Beijing Chaoyang Hospital study 4 92 45 102 4.4% 0.06 [0.02, 0.17]
DRIVE & DRIVE II 34 64 46 65 6.4% 0.47 [0.23, 0.97]
Ferumoxytol authorization studies (dialysis) 56 110 86 114 7.5% 0.34 [0.19, 0.60]
Luitpold Pharma study 60 79 10 14 3.6% 1.26 [0.36, 4.49]
Princess Alexandra Hospital study 1 51 2 51 1.3% 0.49 [0.04, 5.58]
US Venofer CT study 2006 0 66 5 30 1.0% 0.03 [0.00, 0.65]
Winthrop University Hospital study 1 20 14 36 1.7% 0.08 [0.01, 0.69]
Subtotal (95% CI) 494 437 27.4% 0.25 [0.11, 0.54]
Total events 157 217
Heterogeneity: Tau² = 0.66; Chi² = 20.19, df = 7 (P = 0.005); I² = 65%
Test for overall effect: Z = 3.53 (P = 0.0004)
Total (95% CI) 2209 1522 100.0% 0.41 [0.31, 0.56]
Total events 1038 852
Heterogeneity: Tau² = 0.23; Chi² = 48.98, df = 18 (P = 0.0001); I² = 63%
Test for overall effect: Z = 5.74 (P < 0.00001)
Test for subgroup differences: Chi² = 2.62, df = 1 (P = 0.11), I² = 61.8%
0.01 0.1 1 10 100
Favours [IV iron] Favours [PO iron]

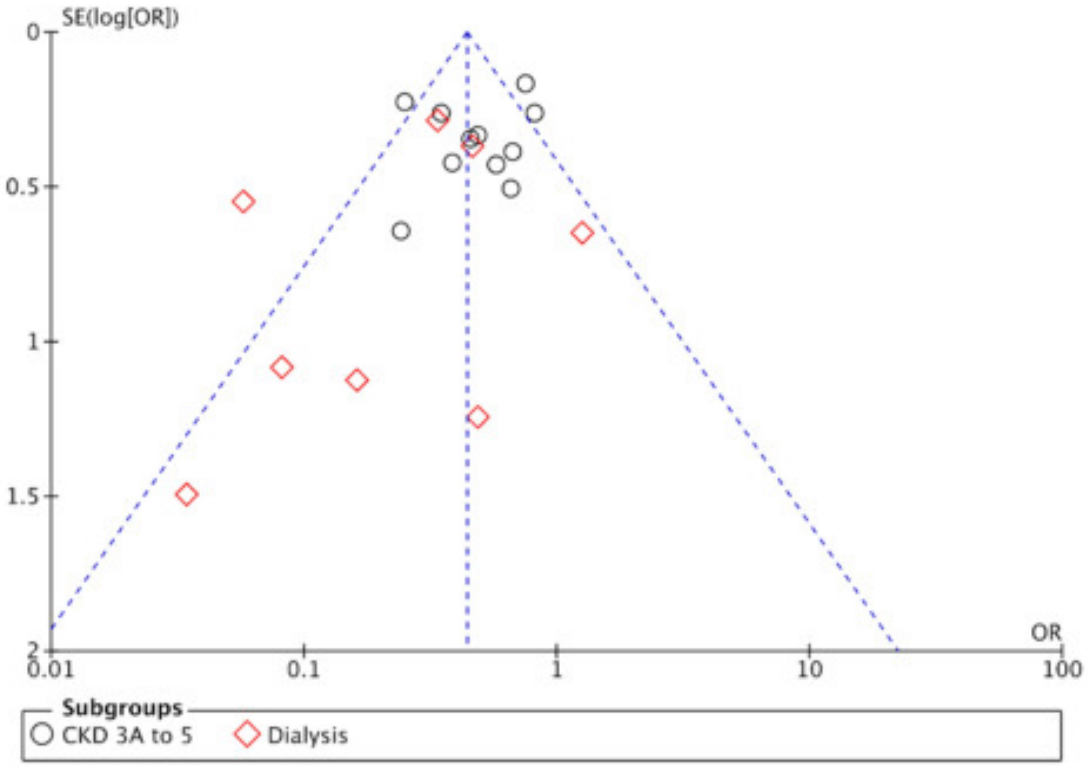

SE(log[OR])
0
0.5
1
1.5
2
0.01
0.1
1
10
100
OR
Subgroups
CKD 3A to 5
Dialysis

Figure 5

Forest and funnel plots presenting comparisons' effect sizes for i.v. versus p.o. iron.

The two subgroups of patients before and those having already started dialysis are presented.

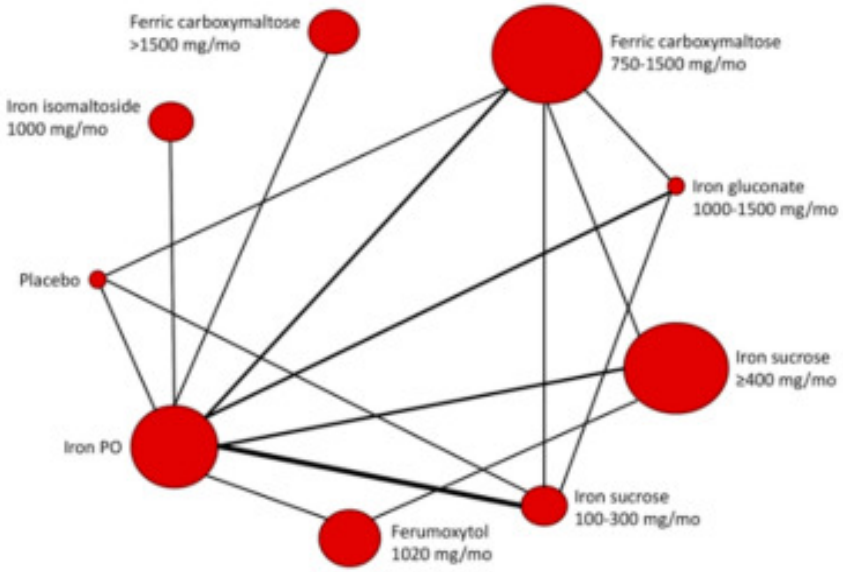
CCF-II study, COSMOS study 2016, Luitpold Pharma study, McMahon et al. 2010, Qunibi et al. 2011, St James´s University Hospital study, US Venofer CT study 2005, Venofer CS study, Barts study, Beijing Chaoyang Hospital study, Princess Alexandra Hospital study, US Venofer CT study 2006, and Winthrop University Hospital study, are referred differently in the capture than in this PhD manuscript, and they correspond, respectively, to studies with the references 86, 84, 83, 93, 921, 96, 94, 95, 78, 73–75, 68, 76, and 79.

IV and PO in the capture refer to abbreviations i.v. and p.o..

CI, confidence interval; i.v., intravenous; M-H, Mantel–Haenszel test; PBO, placebo; p.o., *per os*; SE, standard error.

From Adler *et al.*, 2020 (107)

(a)


Ferric carboxymaltose
>1500 mg/mo
Ferric carboxymaltose
750-1500 mg/mo
Iron isomaltoside
1000 mg/mo
Iron gluconate
1000-1500 mg/mo
Placebo
Iron sucrose
≥400 mg/mo
Iron PO
Iron sucrose
100-300 mg/mo
Ferumoxytol
1020 mg/mo

(b)

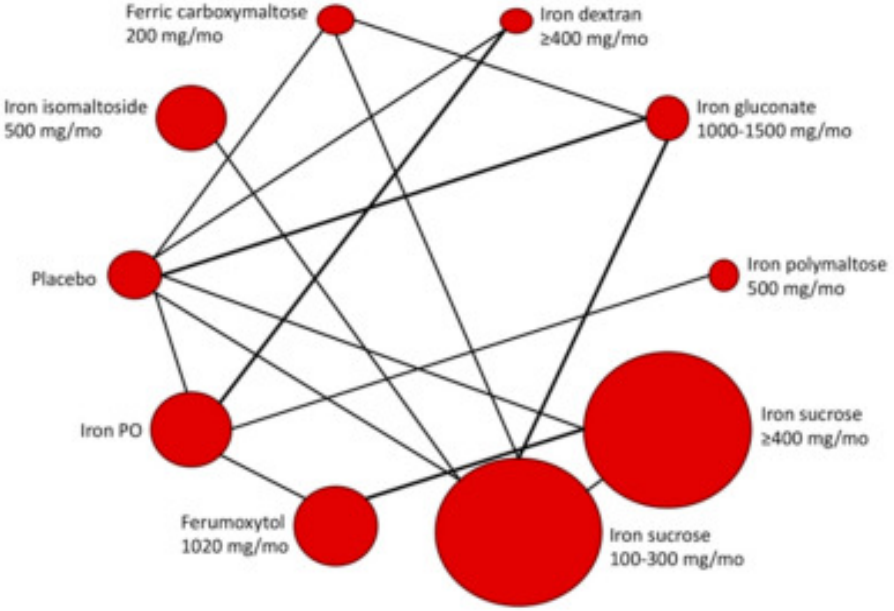

Ferric carboxymaltose
200 mg/mo
Iron dextran
≥400 mg/mo
Iron isomaltoside
500 mg/mo
Iron gluconate
1000-1500 mg/mo
Placebo
Iron polymaltose
500 mg/mo
Iron PO
Iron sucrose
≥400 mg/mo
Ferumoxytol
1020 mg/mo
Iron sucrose
100-300 mg/mo

Figure 6

Bayesian network diagrams presenting comparisons of different i.v. and p.o. supplements.

The density in the comparisons (thickness of lines according to the number of RCTs in each comparison) across all the competing iron supplements (node size according to the number of participants undergoing interventions) may be perceived.

The diagrams correspond to the subgroups of (a) patients in the KDIGO GFR categories 3A to 5, and (b) dialysis patients.

PO in the capture refers to abbreviation p.o..

GFR, Glomerular filtration rate; i.v., intravenous; KDIGO, Kidney Disease—Improving Global Outcomes; p.o., *per os*; RCT, randomized controlled trial.

From Adler *et al.*, 2020 (107)

Ferumoxytol 1020 mg/mo								
0.77 (0.42 – 1.42)	**Ferric carboxymaltose 750-1500 mg/mo**							
0.60 (0.35 – 1.08)	0.77 (0.54 – 1.20)	**Iron sucrose ≥400 mg/mo**						
0.57 (0.29 – 1.12)	0.73 (0.43 – 1.22)	0.96 (0.53 – 1.61)	**Iron sucrose 100-300 mg/mo**					
0.51 (0.20 – 1.31)	0.65 (0.28 – 1.56)	0.85 (0.35 – 2.02)	0.88 (0.38 – 2.26)	**Iron gluconate 1000-1500 mg/mo**				
0.50 (0.01 – 3.27)	0.65 (0.01 – 4.01)	0.84 (0.02 – 5.43)	0.87 (0.02 – 5.25)	0.95 (0.02 – 7.11)	**No iron**			
0.36 (0.17 – 0.80)	**0.47 (0.24 – 0.94)**	0.61 (0.29 – 1.20)	0.65 (0.31 – 1.32)	0.73 (0.27 – 1.86)	0.74 (0.11 – 30.23)	**Ferric carboxymaltose >1500 mg/mo**		
0.34 (0.14 – 0.83)	**0.44 (0.20 – 0.99)**	0.57 (0.26 – 1.27)	0.60 (0.27 – 1.40)	0.68 (0.24 – 1.86)	0.69 (0.09 – 27.11)	0.94 (0.39 – 2.30)	**Iron isomaltoside 1000 mg/mo**	
0.28 (0.16 – 0.47)	**0.36 (0.24 – 0.53)**	**0.46 (0.30 – 0.68)**	**0.48 (0.31 – 0.77)**	0.55 (0.24 – 1.18)	0.56 (0.09 – 22.48)	0.75 (0.43 – 1.34)	0.81 (0.40 – 1.60)	**Iron PO**

(a)

Iron dextran ≥400 mg/mo									
0.60 (0.05 – 5.26)	Iron sucrose ≥400 mg/mo								
0.39 (0.03 – 3.80)	0.64 (0.19 – 2.32)	Ferumoxytol 1020 mg/mo							
0.32 (0.01 – 5.11)	0.56 (0.04 – 4.29)	0.88 (0.05 – 8.22)	Iron isomaltoside 500 mg/mo						
0.31 (0.02 – 2.81)	0.54 (0.10 – 1.67)	0.83 (0.10 – 3.74)	0.96 (0.15 – 6.03)	Iron sucrose 100-300 mg/mo					
0.19 (0.01 – 1.77)	0.31 (0.04 – 1.34)	0.49 (0.05 – 2.77)	0.57 (0.06 – 5.63)	0.60 (0.16 – 2.24)	Iron gluconate 1000-1500 mg/mo				
0.09 (0.00 – 2.34)	0.15 (0.01 – 3.12)	0.23 (0.01 – 4.92)	0.28 (0.01 – 14.04)	0.29 (0.01 – 8.90)	0.48 (0.02 – 15.91)	Iron polymaltose 500 mg/mo			
0.09 (0.00 – 1.29)	0.16 (0.01 – 1.10)	0.25 (0.02 – 2.12)	0.29 (0.02 – 4.07)	0.30 (0.05 – 2.00)	0.51 (0.08 – 3.17)	1.05 (0.02 – 33.39)	Ferric carboxymaltose 200 mg/mo		
0.09 (0.01 – 0.58)	**0.15 (0.04 – 0.55)**	**0.24 (0.06 – 0.88)**	0.27 (0.03 – 4.37)	0.29 (0.06 – 2.12)	0.48 (0.09 – 4.11)	1.01 (0.06 – 16.41)	0.96 (0.12 – 11.85)	Iron PO	
0.08 (0.01 – 0.64)	**0.13 (0.02 – 0.50)**	0.21 (0.03 – 1.05)	0.25 (0.02 – 2.68)	0.26 (0.06 – 1.11)	0.44 (0.12 – 1.66)	0.90 (0.03 – 19.36)	0.85 (0.13 – 5.72)	0.88 (0.15 – 3.90)	No iron

(b)

Figure 7

League tables showing pairwise comparisons' effect sizes for i.v. versus p.o. iron.

Effect sizes corresponding to the assessed i.v. iron supplements into the subgroups of (a) patients in the KDIGO GFR categories 3A to 5, and (b) dialysis patients, are expressed in ORs and 95% CrIs.

PO in the capture refers to abbreviation p.o..

CrI, credible intervals; i.v., intravenous; OR, odds ratio; p.o., *per os*.

From Adler *et al.*, 2020 (107)

Table 7

SUCRA-based ranking of iron supplements evaluated.

Treatment (intervention)	**SUCRA**‡ for CKD 3A-5/dialysis§
Ferumoxytol 1020 mg/mo	0.926/0.673
Ferric carboxymaltose 750–1500 mg/mo	0.808/NA
Iron sucrose ≥400 mg/mo	0.598/0.840
Iron sucrose 100–300 mg/mo	0.567/0.614
Iron isomaltoside 500 mg/mo	NA/0.615
Iron gluconate 1000–1500 mg/mo	0.502/0.439
Iron polymaltose 500 mg/mo	NA/0.293
Ferric carboxymaltose >1500 mg/mo	0.280/NA
Iron isomaltoside 1000 mg/mo	0.248/NA
p.o. iron	0.091/0.176

Iron supplements were ranked according to probabilities for being the best, the second best, the third best, and so on $(j = b)$, $b = 1, \ldots, a$, following Marcov chain Monte Carlo simulation assumptions.

‡If a treatment ranks first, then SUCRA = 1, and if it ranks last, it will have SUCRA = 0.

§SUCRA values are expressed for each of the two subgroups conformed.

Abbreviations: CKD, chronic kidney disease; NA, non-available; p.o., per os; SUCRA, surface under the cumulative ranking area.

From Adler *et al.*, 2020 (107)

Table 7 presenting SUCRA values for all preparations shows also that iron is more performing before the start of dialysis, especially ferumoxytol (>0.9) and ferric carboxymaltose (0.808), than once dialysis is initiated. Indeed, 1020 mg of ferumoxytol *per* month was differently effective before than once dialysis is initiated. In addition, ferumoxytol and ferric carboxymaltose showed different results than iron sucrose (<0.6) and the other i.v. supplements assessed before dialysis, and iron sucrose and the rest of preparations were similar among dialysis patients (0.4 to 0.6). It should be noted the difference of the SUCRA value for 500 mg of iron polymaltose *per* month and the SUCRA values for the other supplements assessed in dialysis, as well as the similar SUCRA values for 1500 mg or more of ferric carboxymaltose *per* month and 1000 mg of iron isomaltoside *per* month before dialysis. The model chosen for calculating SUCRA values shows convergence, but it is affected by inconsistency (see Chapter 8 – Supplementary material).

Heterogeneity was particularly evident (I^2 >50%). The asymmetry of funnel plots involving comparisons' effect sizes on both types of patients, into the KDIGO GFR categories G3A to G5 and dialysis patients was also important (Egger's test (t) / degrees of freedom (df) / p-value: −2.3591, 17, 0.0305).

Finally, effect sizes presented here should be considered as provided by a low-quality body of evidence according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. Following this standard, quality rating fell by two levels for heterogeneity and risk of reporting bias, even if there were not influence of indirectness in terms of participants/population, interventions, comparators and outcomes, nor of important imprecision in summary estimates (*i.e.*, no wide confidence or credible intervals.).

Key messages

A sufficient body of evidence supports the effectiveness of intravenous iron supplementation compared to oral iron in both situations, before and once dialysis is initiated. However, according to our meta-analytic findings, in terms of drug response, not all galenic iron preparations have an equal impacting effect. Indeed, ferumoxytol and ferric carboxymaltose are the most potent over the others, especially before dialysis, with sensible limits once dialysis is initiated. Importantly, the unanimous recommendation of intravenous iron supplementation in dialysis issued by the 2012 KDIGO guidelines (17), in the NKF-KDOQI commentary on the 2012 KDIGO recommendations (19), the NICE recommendations (21), and the ERBP position statement (16), was based on findings from systematic reviews and meta-analyses (23–26) preceding findings from our meta-analysis. In fact, previous meta-analyses found more pronounced increases in Hb levels in patients undergoing dialysis than before dialysis is initiated (23–26). In addition, previous summaries did not find differences between older formulations and the newer preparations ferrumoxytol and ferric carboxymaltose on the increase in Hb concentration, even if only newer formulations allow the infusion of greater amounts of elementary iron (25).

The recommendations aim achieving a sustained Hb response, and they consider ideally reaching the target Hb or an increase in Hb concentration of >1 g/dL (17,19,21), but that may not be observed in all patients. Thus, lesser increases in Hb levels (17,19), could extend our observations on the effectiveness of intravenous iron supplementation in CKD. In any case, our work attempted an adequate match between the medicine of interest and a given patient population to conclude on the medicine's effectiveness (41).

We are confident that the findings from this PhD thesis work will help to improve to define the indication of i.v. supplementation for treating the anemia of CKD and enhance current and future recommendations. Indeed, by contributing to better define the indication of a given medicine the efficacy-effectiveness gap narrows, allowing a more precise use of the investigated medicaments (40). Our findings suggest that less potent formulations may be useful in patients needing to achieve lower goals, in the investigated situation this may concern patients with early stage CKD. However, availability of the products, clinical practicability and cost-benefit analysis that have not been considered in this study should be imperatively integrated in the decision making of administrating potential less potent medicines.

Safety of iron supplementation was not evaluated by our study. However, safety concerns should also be addressed, especially with the administration of greather doses of iron, particularly regarding oxidative stress-related adverse effects. In any case, previous meta-analyses did not find an increase in cardiovascular events that may be feared due to oxidative stress among patients on i.v. supplements compared to those on p.o. supplements (23–26). There were no differences in the rates of all-cause death, serious and any adverse effects, and infections between patients on i.v. supplements compared to patients on p.o. supplements (23–26). However, hypotensive events including allergic reactions were more often

documented in association with i.v. iron infusions and all types of gastrointestinal events were noted more often when p.o. iron supplements were used (23,25).

This meta-analysis was performed according to a planned, registered, and prospectively updated systematic review protocol. Methods including data assessment and calculations were performed according to current recommendations (46,47). As a sign of maintaining our analysis provided transparency in the systematic review process (108), avoiding future changes, which may be associated with reporting biases (109), and showied the suitability and non-duplicity (110). However, various limitations should be mentioned. Publication bias is most likely the cause of the observed and corroborated mathematically funnel plot asymmetry (111). Publication and other reporting biases can lead to overly optimistic conclusions in a meta-analysis (112). Heterogeneity should also be taken into account, as conclusions from meta-analyses are less clear when the included studies have differing results (62). Furthermore, summary estimates presented here included data from extension follow-up studies/post-hoc analyses of some of the eligible RCTs (69,71,72,80–82,89–91), which invite cautious interpretation, as findings from unplanned analyses are of lesser value (113).

Finally, this meta-analysis includes trials of less than 1000 participants, so our findings contribute to clarify false substantial effects reported by such small trials (114). Probably more research is needed to exclude the absence of effects from 1500 mg or more of ferric carboxymaltose per month, which was observed in the 400 participants who underwent these doses, compared to the 3200 participants using lesser doses.

Chapter 6: Conclusions

According to our meta-analytic findings, in terms of drug response as defined for performing calculations, not all galenic iron preparations have an equal impacting effect, which contradicts results from previous systematic reviews and meta-analyses showing no differences between the classic iron sucrose and other older preparations and the newer preparations ferumoxytol and ferric carboxymaltose.

The newer i.v. iron supplements ferumoxytol and ferric carboxymaltose appear to be the best performing preparations in CKD patients before dialysis.

However, the results of our study show that other commercial iron supplements, such as the classic iron sucrose, have effectiveness in patients undergoing dialysis and also show that their earlier use in early CKD stages may be indicated to reduce the need for ESA doses or initiation of ESA therapy and the need for blood transfusions.

In sup attempted an adequate match between the medicine of interest and a given patient population to conclude on the medicine's effectiveness.

This PhD thesis work provides physicians with arguments for identifying good responders among all patients treated with these medicines, which may contribute to improve probably the indications of i.v. supplements for treating the anemia of CKD. Indeed, evidence-based treatment strategies can lead to individualized treatment strategies in CKD.

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