SYSTEMATIC REVIEW AND META-ANALYSIS

Hypophosphataemia after treatment of iron deficiency with intravenous ferric carboxymaltose or iron isomaltoside—a systematic review and meta-analysis

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Aims: Hypophosphataemia is an increasingly recognized side-effect of ferric carboxymaltose (FCM) and possibly iron isomaltoside/ferric derisomaltose (IIM), which are used to treat iron deficiency. The aim of this study was to determine frequency, severity, duration and risk factors of incident hypophosphataemia after treatment with FCM and IIM.

Methods: A systematic literature search for articles indexed in EMBASE, PubMed and Web of Science in years 2005–2020 was carried out using the search terms 'ferric carboxymaltose' OR 'iron isomaltoside'. Prospective clinical trials reporting outcomes on hypophosphataemia rate, mean nadir serum phosphate and/or change in mean serum phosphate from baseline were selected. Hypophosphataemia rate and severity were compared for studies on IIM vs. FCM after stratification for chronic kidney disease. Meta-regression analysis was used to investigate risk factors for hypophosphataemia.

Results: Across the 42 clinical trials included in the meta-analysis, FCM induced a significantly higher incidence of hypophosphataemia than IIM (47%, 95% CI 36–58% vs. 4%, 95% CI 2–5%), and significantly greater mean decreases in serum phosphate (0.40 vs. 0.06 mmol/L). Hypophosphataemia persisted at the end of the study periods (maximum 3 months) in up to 45% of patients treated with FCM. Meta-regression analysis identified low baseline serum ferritin and transferrin saturation, and normal kidney function as significant predictors of hypophosphataemia.

Conclusion: FCM is associated with a high risk of hypophosphataemia, which does not resolve for at least 3 months in a large proportion of affected patients. More severe iron deficiency and normal kidney function are risk factors for hypophosphataemia.

KEYWORDS

anaemia, ferric derisomaltose, FGF23, phosphate

1 | INTRODUCTION

Introduction of the intravenous (i.v.) iron preparations ferric carboxymaltose (FCM) and iron derisomaltose/iron isomaltoside 1000 (IIM) represented major advances in intravenous iron therapy because both preparations allow rapid correction of total iron deficit in one or two infusions, while exhibiting low rates of hypersensitivity reactions.[1,2] Both drugs are frequently used to treat iron deficiency of various causes. The commonest indications include iron deficiency due to gastrointestinal blood loss, inflammatory bowel disease (IBD), heavy uterine bleeding and post-partum hemorrhage.[3,4] Iron infusions are also frequently given to correct pre- or postoperative iron deficiency anaemia. In patients with chronic kidney disease (CKD), i.v. iron increases response to erythropoiesis stimulating agents, while in patients with chronic heart failure, FCM improves exercise performance.[5-7]

Despite their overall favourable safety profile and simple administration schedule, hypophosphataemia appears to be a relevant side-effect of both iron preparations.[8,9] Reporting of this side effect in clinical trials is inconsistent, leading to a remarkable variability in the documentation of hypophosphataemia rates. The severity of hypophosphataemia in affected patients is also underestimated when only mean phosphate concentrations across all patients are reported, including those who remain free from hypophosphataemia. The finding that hypophosphataemia persists in a subgroup of patients through the end of study follow-up illustrates that the true duration of hypophosphataemia is unknown and can only be estimated from uncontrolled, retrospective studies.[10]

An increasing number of case reports suggests that hypophosphataemia after i.v. iron can cause acute, severe and/or chronic and potentially irreversible complications, especially after repeated administration. Reported clinical manifestations include asthaenia, fatigue, myopathy, respiratory failure, osteomalacia, bone pain and fractures, which are all recognized symptoms and signs of prolonged or severe hypophosphataemia.[11]

The mechanism of hypophosphataemia after i.v. iron is renal phosphate wasting where impaired kidney function partially protects against hypophosphataemia. Urinary phosphate excretion is regulated by the phosphaturic hormone, **fibroblast-growth factor-23** (FGF23).[12-14] Certain intravenous iron formulations cause a sharp increase in the full-length, intact plasma FGF23 (iFGF23) concentration and the severity and risk of hypophosphatemia correlates with the magnitude of increased iFGF23 and with higher glomerular filtration rate.[11] Besides its effects as phosphaturic hormone, FGF23 also inhibits activation of **25(OH)vitamin** D to **1,25(OH)$_2$vitamin D** (calcitriol), which could explain the mild hypocalcaemia and subsequent increase in circulating **parathyroid hormone** (PTH) concentration following i.v. iron treatment. Due to the phosphaturic effects of PTH, this mechanism may further prolong hypophosphataemia long after the increase in FGF23 returns towards normal.[15] This cascade of effects has been described as the 6H-syndrome.[16]

Differences in incidence, severity and possibly duration of hypophosphataemia, suggest that the specific pharmacological properties of the iron-carbohydrate complex may influence risk of hypophosphataemia.[11] Among i.v. iron preparations, saccharated iron oxide, iron sucrose and iron polymaltose have been reported to induce hypophosphataemia.[17-20]

The diversity in the underlying aetiology and variation in the severity of iron deficiency in patients included in different clinical trials limits direct comparison of safety data from prospective studies. To define the frequency and severity of hypophosphataemia after treatment with the internationally available high-dose i.v. iron preparations FCM and IIM, a systematic literature review and meta-analysis was carried out.[21]

2 | METHODS

The rationale for this systematic review was to determine the incidence of hypophosphataemia after administration of FCM or IIM. To assess the incidence, we included prospective studies reporting on phosphate as a safety outcome. The search strategy is described in Figure 1 and the Supporting Information. For the meta-analysis, data were extracted from each study by two authors independently. In case of inconsistent data entry, agreement was reached by discussion among authors. For each study included, we recorded study drug and dose, the threshold for the definition of hypophosphataemia, the number of patients developing hypophosphataemia and the absolute number in whom phosphate was measured (safety analysis set) or, if available, hypophosphataemia rate and mean or median nadir phosphate. In addition, the following trial data were collected: the time point after administration of the study drug at which phosphate was measured, hypophosphataemia rate at the end of the study period and study duration. The following pre-treatment parameters were assessed in the FCM or IIM treatment arms: median or mean concentration of ferritin, haemoglobin, transferrin saturation and phosphate concentration. A single study reported on relevant outcomes from a direct head to head comparison of IIM and FCM. For this meta-analysis of safety outcomes data on hypophosphataemia for the FCM or IIM treatment arm were assessed for each study individually. Due to the wide range of treatments in the comparator arms (placebo, standard medical care, various oral iron preparations, ferrumoxytol, iron dextran, iron sucrose, saccharated iron oxide), odds ratios are not comparable between studies. Criteria for risk bias assessment were predefined to consider potential limitations in study design and reporting that could potentially affect observed hypophosphataemia rate or severity. Each of the included studies was assessed according to the criteria listed in Figure S1 in the Supporting Information. According to these criteria, each study was graded and the overall score correlated with outcomes reported by Spearman rank correlation analysis. Risk of publication bias was assessed by funnel plot analysis.

The meta-analysis was performed using the metafor package (version 2.1–0) in R (R ver. 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) and RStudio (ver. 1.2.5001, RStudio, Inc., Boston, MA, USA) as described by Viechtbauer.[22] Effect sizes of

1337 records identified through database searching
323 EMBASE
542 Pubmed
472 Web of Science

925 records after duplicates removed

Records screened

701 Excluded
(did not meet eligibility criteria)

224 Full-text articles of prospective trials assessed for eligibility

182 Excluded articles
120 No/insufficient data on phosphate
56 Not a trial on FCM/IIM
4 Only data on reported adverse events
2 Double reporting of data

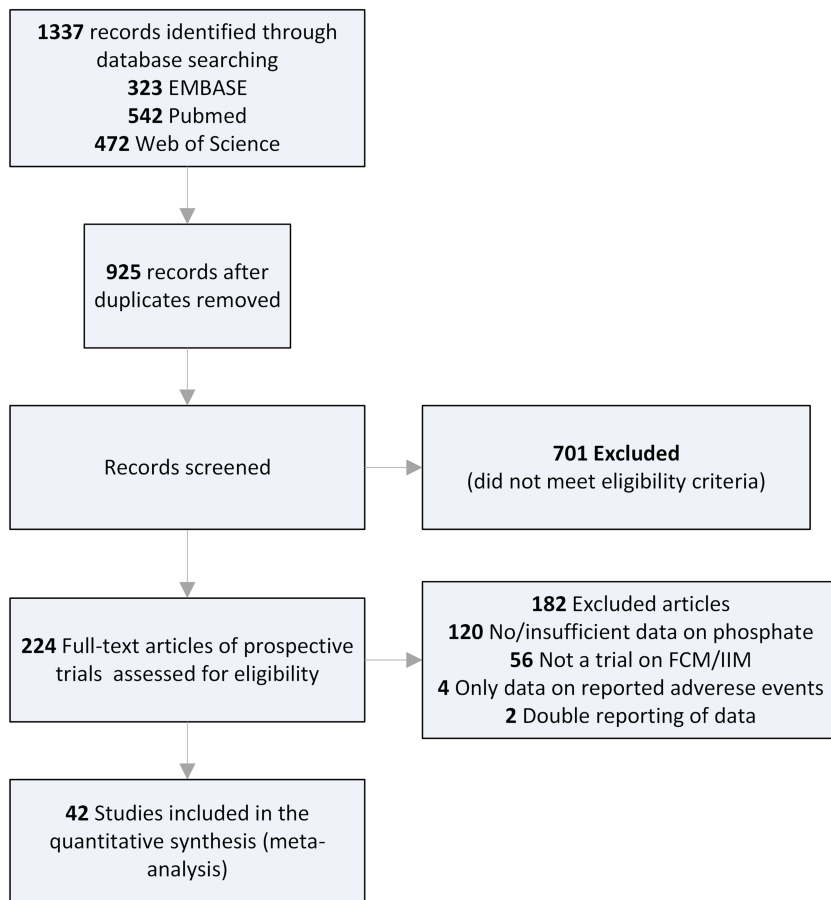**42** Studies included in the quantitative synthesis (meta-analysis)

FIGURE 1 PRISMA diagram. The search strategy and study selection for the meta-analysis of clinical trials

frequencies and counts were calculated as raw proportions. In case of zeroes, a value of 0.01 was added to the respective value to avoid division by zero; all other values remained unmodified. Effect sizes of mean phosphate levels and mean change of phosphate were calculated as mean differences of reported mean post-treatment phosphate minus mean pre-treatment phosphate concentration. For subgrouping, studies were stratified by iron preparation and the presence or absence of chronic kidney disease in the study population. Heterogeneity between studies was estimated by a restricted maximum-likelihood estimator and reported using the Cochrane Q and the I^2 statistic. Additional details of the statistical methods can be found in the Supporting Information.

For meta-regressions, mean serum ferritin, mean transferrin saturation and mean age were extracted from the studies' baseline characteristics. For ferritin, a log-linear weighted regression was performed, whereas transferrin saturation was treated as a potential linear modifier. The respective R syntax is given in the Supporting Information. Serum ferritin values were log10 transformed for further computations, as this parameter follows a log-normal distribution.

Frequencies were either calculated by dividing the number of patients developing hypophosphataemia by the number of patients in whom phosphate concentrations were available or the hypophosphataemia rate as reported in the study.

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[23]

3 | RESULTS

The systematic literature search identified 224 prospective studies. After manual selection, 42 clinical trials that used either FCM or IIM and reported relevant outcomes on phosphate were included in the meta-analysis (Figure 1). Outcomes were inconsistently reported (Table 1). Seventeen of 42 studies defined hypophosphataemia as a serum phosphate concentration <0.64 mmol/L or <2.0 mg/dL) and eight of 42 studies used serum phosphate up to 0.84 mmol/L (2.56 mg/dl) as cutoff. To assess if the frequency of hypophosphataemia depended on the threshold applied, this variable was included in the risk-bias assessment (Figure S1). Twenty-five of 42 studies included in the final analysis reported a threshold for the definition of hypophosphataemia. Other criteria that were included in the risk-bias assessment were the point in time when the phosphate was measured, mean nadir phosphate and hypophosphataemia rate at

TABLE 1 Characteristics of the 42 prospective clinical trials included in the meta-analysis

First author (year)	Study type	Therapeutic area	Threshold for hypophosphatemia	Study duration (days)	Time point lowest phosphate (days)	Iron preparation	Mean total dose (mg)	Single or multiple dosing
Allen et al. (2011)[24]	RCT	RLS	Na	168	Na	FCM	500	Multiple
Auerbach et al. (2019)[25]	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	105	Na	IIM	975	Single
Bailie et al. (2010)[26]	RCT	Mixed IDA	Na	14	Na	FCM	962	Single
Barish et al. (2012)[27] – multiple dose arm	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	42	Na	FCM	Na	Multiple
Barish et al. (2012)[27] – single dose arm	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	30	Na	FCM	Na	Single
Bhandari et al. (2015)[28]	RCT	HD-CKD	2 mg/dL (0.65 mmol/L)	42	Na	IIM	500	Multiple
Bhandari et al. (2020)[29]	RCT	NDD-CKD	2 mg/dL (0.65 mmol/L)	56	Na	IIM	933	Single
Biggar et al. (2016)[30]	SAT	HD-CKD	Na	274	Na	IIM	2574	Na
Birgegard et al. (2016)[31] – bolus arm	RCT	Malignancy	2 mg/dL (0.65 mmol/L)	168	Na	IIM	842	Multiple
Birgegard et al. (2016)[31] – infusion arm	RCT	Malignancy	2 mg/dL (0.65 mmol/L)	168	Na	IIM	857	Multiple
Breymann et al. (2017)[32]	RCT	GYN	0.6 mmol/L	84	21	FCM	1000	Multiple
Charytan et al. (2013)[33] – HD-arm	RCT	HD-CKD	Na	30	Na	FCM	200	Single
Charytan et al. (2013)[33] – NDD-HD arm	RCT	NDD-CKD	Na	30	Na	FCM	975.7	Single
Dahlerup et al. (2016)[34]	SAT	IDA digestive diseases	2 mg/dL (0.65 mmol/L)	112	Na	IIM	2023	Multiple

(Continues)

TABLE 1 (Continued)

First author (year)	Study type	Therapeutic area	Threshold for hypophosphatemia	Study duration (days)	Time point lowest phosphate (days)	Iron preparation	Mean total dose (mg)	Single or multiple dosing
Detlie et al. (2019)[35] – FCM arm	RCT	IDA digestive diseases	0.8 mmol/L	49	14	FCM	1000	Single
Detlie et al. (2019)[35] – IIM arm	RCT	IDA digestive diseases	0.8 mmol/L	42	14	IIM	1000	Single
Ding et al. (2020)[36] – 1000 mg cohort	RCT	Mixed IDA	0.8 mmol/L	6	Na	FCM	1000	Single
Ding et al. (2020)[36] – 500 mg cohort	RCT	Mixed IDA	0.8 mmol/L	6	Na	FCM	500	Single
Drexler et al. (2019)[37]	RCT	IDA/blood donation	0.84 mmol/L	84	Na	FCM	1000	Single
Evstatiev et al. (2011)[38]	RCT	IDA digestive diseases	Na	84	14	FCM	1377	Multiple
Favrat et al. (2014)[39]	RCT	Mixed IDA	0.8 mmol/L	56	7	FCM	1000	Single
Gybel-Brask et al. (2018)[40]	RCT	IDA/blood donation	2 mg/dL (0.65 mmol/L)	168	Na	IIM	Na	Single
Holm et al. (2017)[41]	RCT	GYN	2 mg/dL (0.65 mmol/L)	84	Na	IIM	1200	Single
Huang et al. (2018)[42] – CKD arm	SAT	NDD-CKD	Na	42	7	FCM	1000	Single
Huang et al. (2018)[42] – control arm	SAT	Mixed IDA	Na	42	7	FCM	1000	Single
Huang et al. (2018)[42] – pregnant arm	SAT	GYN	Na	42	7	FCM	1000	Single
Hussain et al. (2013)[43]	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	42	14	FCM	1450.9	Multiple
Ikuta et al. (2018)[44]	SAT	Mixed IDA	2.5 mg/dL (0.81 mmol/L)	8	Na	FCM	Na	Single
Ikuta et al. (2019)[45]	RCT	GYN	0.81 mmol/L	84	28	FCM	Na	Multiple

(Continues)

TABLE 1 (Continued)

First author (year)	Study type	Therapeutic area	Threshold for hypophosphatemia	Study duration (days)	Time point lowest phosphate (days)	Iron preparation	Mean total dose (mg)	Single or multiple dosing
Ikuta et al. (2019)[46]	SAT	IDA digestive diseases	2.5 mg/dL (0.81 mmol/L)	84	Na	FCM	1183.6	Multiple
Johansson et al. (2015)[47]	RCT	PBM	2 mg/dL (0.65 mmol/L)	28	Na	IIM	1000	Single
Kalra et al. (2016)[48] – bolus arm	RCT	NDD-CKD	2 mg/dL (0.65 mmol/L)	56	Na	IIM	Na	Multiple
Kalra et al. (2016)[48] – infusion arm	RCT	NDD-CKD	2 mg/dL (0.65 mmol/L)	56	Na	IIM	Na	Multiple
Macdougall et al. (2014)[49] – high ferritin arm	RCT	NDD-CKD	Na	392	Na	FCM	2685	Na
Macdougall et al. (2014)[49] – low ferritin arm	RCT	NDD-CKD	Na	392	Na	FCM	1040	Na
Mahey et al. (2016)[50]	RCT	GYN	Na	84	Na	FCM	1524.2	Multiple
Onken et al. (2014)[1] – cohort 1	RCT	Mixed IDA	Na	35	Na	FCM	1437.9	Multiple
Onken et al. (2014)[1] – cohort 2	RCT	Mixed IDA	Na	35	Na	FCM	1432.3	Multiple
Onken et al. (2014)[51]	RCT	NDD-CKD	Na	56	Na	FCM	1464	Multiple
Prats et al. (2013)[13]	RCT	NDD-CKD	Na	84	Na	FCM	971.7	Single
Qunibi et al. (2011)[52]	RCT	NDD-CKD	Na	56	Na	FCM	1218	Multiple
Reinisch et al. (2013)[9]	RCT	IDA digestive diseases	2 mg/dL (0.65 mmol/L)	56	Na	IIM	Na	Na
Roberts et al. (2016)[14]	RCT	HD-CKD	Na	42	2	FCM	200	Single
Seid et al. (2008)[53]	RCT	GYN	Na	42	7	FCM	1503.5	Multiple

(Continues)

TABLE 1 (Continued)

First author (year)	Study type	Therapeutic area	Threshold for hypophosphatemia	Study duration (days)	Time point lowest phosphate (days)	Iron preparation	Mean total dose (mg)	Single or multiple dosing
Seid et al. (2017)[54] – heavy menstrual bleeding arm	RCT	GYN	Na	30	Na	FCM	926	Single
Seid et al. (2017)[54] – post-partum anemia arm	RCT	GYN	Na	30	Na	FCM	970	Single
Stohr et al. (2019)[55] – CKD arm	SAT	NDD-CKD	0.8 mmol/L	28	7	FCM	1000	Single
Stohr et al. (2019)[55] – heart failure arm	SAT	Heart failure	0.8 mmol/L	28	14	FCM	1000	Single
Toledano et al. (2016)[56]	SAT	Malignancy	Na	90	30	FCM	1000	Mostly single
Van Wyck et al. (2007)[8]	RCT	GYN	Na	42	14	FCM	1403.1	Multiple
VanWyck et al. (2009)[57]	RCT	GYN	2 mg/dL (0.65 mmol/L)	6	15	FCM	1568	Multiple
Wolf et al. (2013)[15]	RCT	GYN	2 mg/dL (0.65 mmol/L)	5	14	FCM	918	Single
Wolf et al. (2018)[58]	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	35	14	FCM	1458	Multiple
Wolf et al. (2020)[59] – trial A FCM	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	35	14	FCM	1500	Multiple
Wolf et al. (2020)[59] – trial A IIM	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	35	14	IIM	1000	Single
Wolf et al. (2020)[59] – trial B FCM	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	35	14	FCM	1500	Multiple
Wolf et al. (2020)[59] – trial B IIM	RCT	Mixed IDA	2 mg/dL (0.65 mmol/L)	35	14	IIM	1000	Single

(Continues)

TABLE 1 Continued

First author (year)	Number of patients in analysis set	Number of patients with post-treatment hypophosphataemia	Hypophosphataemia rate (%)	Hypophosphataemia rate at end of study (%)	Mean/median change (mmol/L)	Mean nadir phosphate (mmol/L)
Allen et al. (2011)[24]	24	3	12.5	Na	Na	Na
Auerbach et al. (2019)[25]	989	39	3.9	Na	Na	Na
Bailie et al. (2010)[26]	559	90	16.1	Na	Na	Na
Barish et al. (2012)[27] – multiple dose arm	343	164	47.8	Na	Na	Na
Barish et al. (2012)[27] – single dose arm	366	66	18	Na	Na	Na
Bhandari et al. (2015)[28]	230	3	1.3	Na	Na	Na
Bhandari et al. (2020)[29]	1011	32	3.2	Na	Na	Na
Biggar et al. (2016)[30]	698	Na	Na	Na	0.02	1.57
Birgegard et al. (2016)[31] – bolus arm	117	10	8.5	Na	Na	Na
Birgegard et al. (2016)[31] – infusion arm	112	8	7.1	Na	Na	Na
Breymann et al. (2017)[32]	123	10	8.1	0	Na	Na
Charytan et al. (2013)[33] – HD-arm	50	Na	Na	Na	Na	Na
Charytan et al. (2013)[33] – NDD-HD arm	186	8	4.3	Na	−0.49	Na

(Continues)

TABLE 1 (Continued)

First author (year)	Number of patients in analysis set	Number of patients with post-treatment hypophosphataemia	Hypophosphataemia rate (%)	Hypophosphataemia rate at end of study (%)	Mean/median change (mmol/L)	Mean nadir phosphate (mmol/L)
Dahlerup et al. (2016)[34]	21	2	9.5	Na	Na	Na
Detlie et al. (2019)[35] – FCM arm	51	37	72.5	21.6	−0.42	0.65
Detlie et al. (2019)[35] – IIM arm	54	2	11.3	3.7	−0.08	1.07
Ding et al. (2020)[36] – 1000 mg cohort	12	11	91.7	Na	Na	Na
Ding et al. (2020)[36] – 500 mg cohort	12	7	58.3	Na	Na	Na
Drexler et al. (2019)[37]	86	15	17.4	Na	−0.03	0.96
Evstatiev et al. (2011)[38]	240	Na	Na	Na	−0.43	0.69
Favrat et al. (2014)[39]	145	125	86.2	8.1	Na	0.62
Gybel-Brask et al. (2018)[40]	41	1	2.4	Na	Na	Na
Holm et al. (2017)[41]	97	5	5	0	Na	Na
Huang et al. (2018)[42] – CKD arm	25	Na	Na	Na	−0.99	0.99
Huang et al. (2018)[42] – control arm	20	Na	Na	Na	−0.67	0.65
Huang et al. (2018)[42] – pregnant arm	20	Na	Na	Na	−0.80	0.79

(Continues)

TABLE 1 (Continued)

First author (year)	Number of patients in analysis set	Number of patients with post-treatment hypophosphataemia	Hypophosphataemia rate (%)	Hypophosphataemia rate at end of study (%)	Mean/median change (mmol/L)	Mean nadir phosphate (mmol/L)
Hussain et al. (2013)[43]	82	Na	Na	Na	−0.25	0.66
Ikuta et al. (2018)[44]	18	14	77.8	Na	Na	Na
Ikuta et al. (2019)[45]	119	77	64.7	31.1	Na	0.47
Ikuta et al. (2019)[46]	38	35	92.1	Na	Na	0.51
Johansson et al. (2015)[47]	30	0	0	0	Na	Na
Kalra et al. (2016)[48] – bolus arm	112	1	0.9	Na	Na	Na
Kalra et al. (2016)[48] – infusion arm	116	3	2.6	Na	Na	Na
Macdougall et al. (2014)[49] – high ferritin arm	153	Na	Na	Na	−0.18	Na
Macdougall et al. (2014)[49] – low ferritin arm	154	Na	Na	Na	Na	Na
Mahey et al. (2016)[50]	30	15	50	0	Na	Na
Onken et al. (2014)[1] – cohort 1	250	133	53.1	Na	Na	Na
Onken et al. (2014)[1] – cohort 2	253	103	40.7	Na	Na	Na
Onken et al. (2014)[51]	1154	213	18.5	Na	−0.41	Na

TABLE 1 (Continued)

First author (year)	Number of patients in analysis set	Number of patients with post-treatment hypophosphataemia	Hypophosphataemia rate (%)	Hypophosphataemia rate at end of study (%)	Mean/median change (mmol/L)	Mean nadir phosphate (mmol/L)
Prats et al. (2013)[13]	47	35	74.5	Na	−0.2	1.16
Qunibi et al. (2011)[52]	147	4	2.7	Na	Na	Na
Reinisch et al. (2013)[9]	162	11	7	1	Na	Na
Roberts et al. (2016)[14]	22	Na	Na	Na	−0.16	1.37
Seid et al. (2008)[53]	138	Na	Na	Na	−0.42	Na
Seid et al. (2017)[54] – heavy menstrual bleeding arm	606	129	21.3	Na	Na	Na
Seid et al. (2017)[54] – post-partum anemia arm	390	3	0.7	Na	Na	Na
Stohr et al. (2019)[55] – CKD arm	12	5	41.7	Na	−0.25	0.97
Stohr et al. (2019)[55] – heart failure arm	11	9	81.8	Na	−0.33	0.69
Toledano et al. (2016)[56]	367	Na	Na	Na	Na	0.9
Van Wyck et al. (2007)[8]	174	Na	Na	Na	−0.36	Na
VanWyck et al. (2009)[57]	224	157	70.1	Na	−0.61	0.58
Wolf et al. (2013)[15]	17	10	58.8	35.3	−0.23	Na

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TABLE 1 (Continued)

First author (year)	Number of patients in analysis set	Number of patients with post-treatment hypophosphataemia	Hypophosphataemia rate (%)	Hypophosphataemia rate at end of study (%)	Mean/median change (mmol/L)	Mean nadir phosphate (mmol/L)
Wolf et al. (2018)[58]	1000	508	50.8	29.1	Na	Na
Wolf et al. (2020)[59] – trial A FCM	60	45	75	41.4	−0.46	0.61
Wolf et al. (2020)[59] – trial A IIM	63	5	7.9	1.7	−0.03	1.03
Wolf et al. (2020)[59] – trial B FCM	57	42	73.7	44.6	−0.48	0.58
Wolf et al. (2020)[59] – trial B IIM	62	5	8.1	0	−0.13	0.97

the end of follow-up. Only four studies reported all relevant definitions and outcomes on hypophosphataemia (Figure S1). Risk-bias assessment showed that studies with higher risk score reported significantly lower hypophosphatemia rates (r = 0.348, P = 0.021). No significant correlation between overall risk score, mean change in phosphate or mean nadir phosphate was found. Independent analysis of studies on FCM and IIM by funnel blot analysis showed no evidence of publication bias (Figure S2).

Hypophosphataemia rates ranged from 0% to 92%. To assess to what extend heterogeneity could be explained by use of IIM or FCM, studies were grouped by study population (CKD vs. non-CKD). The pooled hypophosphataemia rate after FCM was significantly higher than after IIM (47% vs. 4%; P < 0.001). Since reduced glomerular filtration rate impairs urinary phosphate excretion, we next assessed kidney function as a cause of heterogeneity, which was reduced by analysing CKD patients independently. In CKD patients, hypophosphataemia rates were 27% after FCM vs. 2% after IIM (Figure 2). Despite significant heterogeneity among studies in non-CKD patients, pooled hypophosphataemia rates were significantly higher after FCM than after IIM treatment (51 vs. 5%; P < 0.001).

Studies reporting mean nadir plasma phosphate concentrations in the treatment arms after administration of FCM or IIM are shown in Figure 3A. Pooled analysis shows that in few studies mean nadir phosphate reaches a concentration <0.6 mmol/L. The overall pooled mean nadir phosphate concentration after FCM was 0.69 mmol/L (95% CI 0.60–0.78) in patients without CKD vs. 1.11 mmol/L (95% CI 0.96–1.27) in the subgroup of patients with CKD.

Figure 3B shows analysis of mean change in phosphate from baseline. The pooled analysis of reported results across aetiologies shows that the mean decrease in phosphate after FCM is −0.40 (95% CI −0.50−−0.31) mmol/L vs. 0.06 (95% CI −0.14−0.02) mmol/L after IIM.

The duration of hypophosphataemia was not reported in any of the studies, but hypophosphataemia rate at the end of the study period ranged from 0 to 45% after a follow-up of up to 3 months (Table 1).

Meta-regression analysis was carried out to test if serum iron parameters are predictors of hypophosphataemia. As shown in Figure 4, serum ferritin and transferrin saturation at baseline showed a significant association with a hypophosphataemia rate after stratification of trials by study drug. In trials on both study drugs, more severe iron deficiency was associated with a greater risk of post-treatment hypophosphataemia, but the overall risk for hypophosphataemia was lower for IIM. A stronger negative association between hypophosphataemia rate and log (ferritin) was noted for FCM than for IIM. The same was observed for the association between transferrin saturation and hypophosphataemia rate (Figure 4, Table S1). No association between mean total iron dose and hypophosphataemia rate was found when studies using FCM or IIM were analysed independently. When mean total iron dose was correlated with nadir phosphate concentration, a significant association was found on meta-regression analysis (Figure S3).
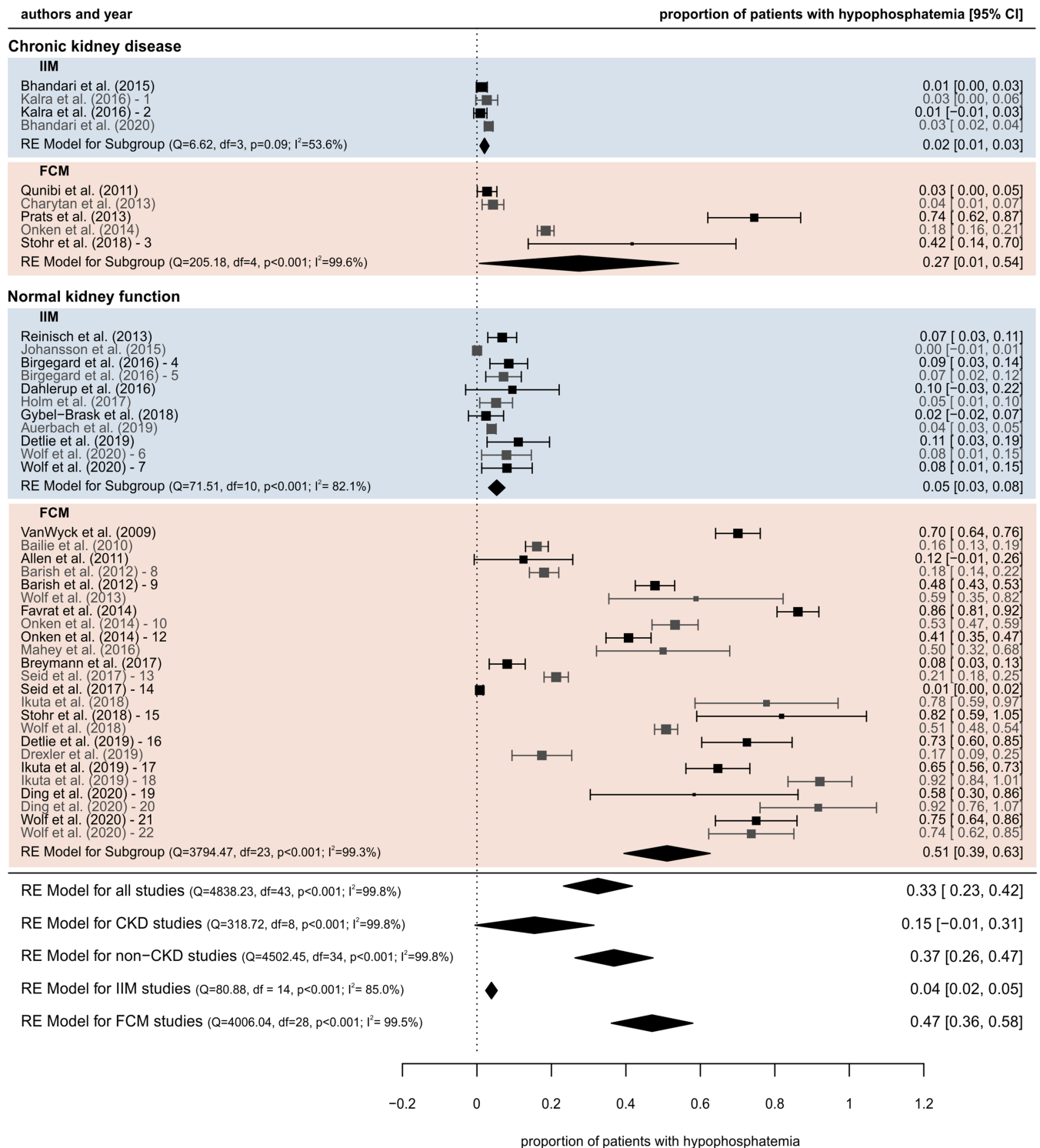
FIGURE 2   Forest plot on hypophosphataemia rate according to iron preparation and presence of chronic kidney disease

Numbers indicate specific treatment arms: 1 – infusion arm; 2 – bolus arm; 3 – NDD-CKD arm; 4 – bolus arm; 5 – infusion arm; 6 – IIM arm; 7 – trial A; 8 – trial B; 9 – single dose arm; 10 – multiple dose arm; 11 – cohort 1; 12 – cohort 2; 13 – heavy menstrual bleeding arm; 14 – post-partum anemia arm; 15 – non-CKD/heart-failure arm; 16 – FCM arm; 17 – Ref. 45:; 18 – Ref. 46; 19–500 mg dose; 20–1000 mg dose; 21 – trial A; 22 – trial B

(A)

authors and year	serum phosphate nadir in mmol/L [95% CI]

Chronic Kidney Disease

FCM

Stohr et al. (2019) - 1	0.97 [0.65, 1.29]
Huang et al. (2018) - 2	0.99 [0.85, 1.13]
Roberts et al. (2016)	1.37 [1.10, 1.64]
Prats et al. (2013)	1.16 [1.01, 1.31]
RE Model for subgroup (Q=7.43, df=3, p=0.06; I²=60.7%)	1.11 [0.96, 1.27]

IIM

Biggar et al. (2016)	1.57 [1.54, 1.60]

Normal kidney function

FCM

Wolf et al. (2019) - 3	0.58 [0.49, 0.67]
Wolf et al. (2019) - 4	0.61 [0.51, 0.71]
Stohr et al. (2019)	0.69 [0.51, 0.87]
Ikuta et al. (2019) - 5	0.51 [0.44, 0.58]
Ikuta et al. (2019) - 6	0.47 [0.43, 0.51]
Drexler et al. (2019)	0.96 [0.91, 1.01]
Detlie et al. (2019)	0.65 [0.55, 0.75]
Huang et al. (2018) - 7	0.65 [0.49, 0.81]
Huang et al. (2018) - 8	0.79 [0.63, 0.95]
Toledano et al. (2016)	0.90 [0.86, 0.94]
Favrat et al. (2014)	0.62 [0.53, 0.71]
Hussain et al. (2013)	0.97 [0.89, 1.05]
Evstatiev et al. (2011)	0.69 [0.65, 0.73]
VanWyck et al. (2009)	0.58 [0.54, 0.62]
RE Model for subgroup (Q=429.13, df=13, p<0.001; I²=96.1%)	0.69 [0.60, 0.78]

IIM

Wolf et al. (2019) - 9	0.97 [0.90, 1.04]
Wolf et al. (2019) - 10	1.03 [0.96, 1.10]
Detlie et al. (2019)	1.07 [0.98, 1.16]
RE Model for subgroup (Q=3.22, df=2, p=0.20; I²=37.4%)	1.02 [0.96, 1.07]

RE Model for all Studies (Q=3582.97, df=21, p<0.001; I²=98.6%)	0.85 [0.73, 0.97]
RE Model for FCM Studies (Q=514.41, df=17, p<0.001; I²=97.4%)	0.77 [0.67, 0.88]
RE Model for IIM Studies (Q=464.02, df=3, p<0.001; I²=98.9%)	1.16 [0.89, 1.43]
RE Model for CKD Studies (Q=103.10, df=4, p<0.001; I²=93.2%)	1.22 [0.99, 1.46]

Mean lowest serum phosphate [mmol/L]
(0, 0.5, 1, 1.5, 2)

(B)

authors and year	mean change in serum phosphate in mmol/L [95% CI]

Chronic kidney disease

IIM

Biggar et al. (2016)	0.02 [0.00, 0.04]

FCM

Stohr et al. (2019) - 1	−0.25 [−0.44, −0.06]
Huang et al. (2018) - 2	−0.99 [−1.12, −0.86]
Roberts et al. (2016)	−0.16 [−0.30, −0.02]
Onken et al. (2014)	−0.41 [−0.43, −0.39]
Macdougall et al. (2014)	−0.18 [−0.23, −0.13]
Prats et al. (2013)	−0.20 [−0.32, −0.08]
Charytan et al. (2013)	−0.49 [−0.54, −0.44]
RE Model for subgroup (Q=181.13, df=6, p<0.001; I²=98.8%)	−0.38 [−0.60, −0.17]

Normal kidney function

IIM

Wolf et al. (2020) - 3	−0.13 [−0.20, −0.06]
Wolf et al. (2020) - 4	−0.03 [−0.10, 0.04]
Detlie et al. (2019)	−0.15 [−0.26, −0.04]
RE Model for subgroup (Q=5.43, df=2, p=0.07; I²=62.3%)	−0.10 [−0.17, −0.02]

FCM

Van Wyck et al. (2007)	−0.36 [−0.41, −0.31]
Seid et al. (2008)	−0.42 [−0.48, −0.36]
VanWyck et al. (2009)	−0.61 [−0.65, −0.57]
Evstatiev et al. (2011)	−0.43 [−0.47, −0.39]
Hussain et al. (2013)	−0.25 [−0.33, −0.17]
Wolf et al. (2013)	−0.23 [−0.39, −0.07]
Huang et al. (2018) - 5	−0.80 [−0.95, −0.66]
Huang et al. (2018) - 6	−0.67 [−0.82, −0.53]
Detlie et al. (2019)	−0.42 [−0.52, −0.32]
Drexler et al. (2019)	−0.03 [−0.10, 0.04]
Stohr et al. (2019) - 7	−0.33 [−0.53, −0.13]
Wolf et al. (2020) - 8	−0.42 [−0.52, −0.32]
Wolf et al. (2020) - 9	−0.45 [−0.55, −0.35]
RE Model for subgroup (Q=292.81, df=12, p<0.001; I²=96.6%)	−0.42 [−0.52, −0.31]

RE Model for all studies (Q=1539.37, df=23, p<0.001; I²=98.6%)	−0.35 [−0.45, −0.25]
RE Model for FCM studies (Q=484.26, df=19, p<0.001; I²=98.1%)	−0.40 [−0.50, −0.31]
RE Model for IIM studies (Q=23.63, df=3, p<0.001; I²=85.6%)	−0.06 [−0.14, 0.02]
RE Model for CKD studies (Q=932.26, df=7, p<0.001; I²=99.4%)	−0.33 [−0.54, −0.12]
RE Model for non−CKD studies (Q=496.49, df=15, p<0.001; I²=97.2%)	−0.36 [−0.46, −0.25]

mean change in serum phosphate [mmol/L]
(−1.5, −1, −0.5, 0, 0.5)

FIGURE 3 Forest plot on severity of hypophosphataemia rate according to iron preparation and presence of chronic kidney disease. (A) Mean lowest serum phosphate concentration. Numbers indicate specific treatment arms: 1 – NDD-CKD arm; 2 – NDD-CKD arm; 3 – trial B; 4 – trial A; 5 – Ref. 46; 6 – Ref. 45; 7 – control arm; 8 – pregnant arm; 9 – trial A; 10 – trial B. (B) Mean changes in serum phosphate from baseline. 1 – NDD-CKD arm; 2 – NDD-CKD arm; 3 – trial B; 4 – trial A; 5 – pregnant arm; 6 – control arm; 7 – non-CKD/heart-failure arm; 8 – trial A; 9 – trial B
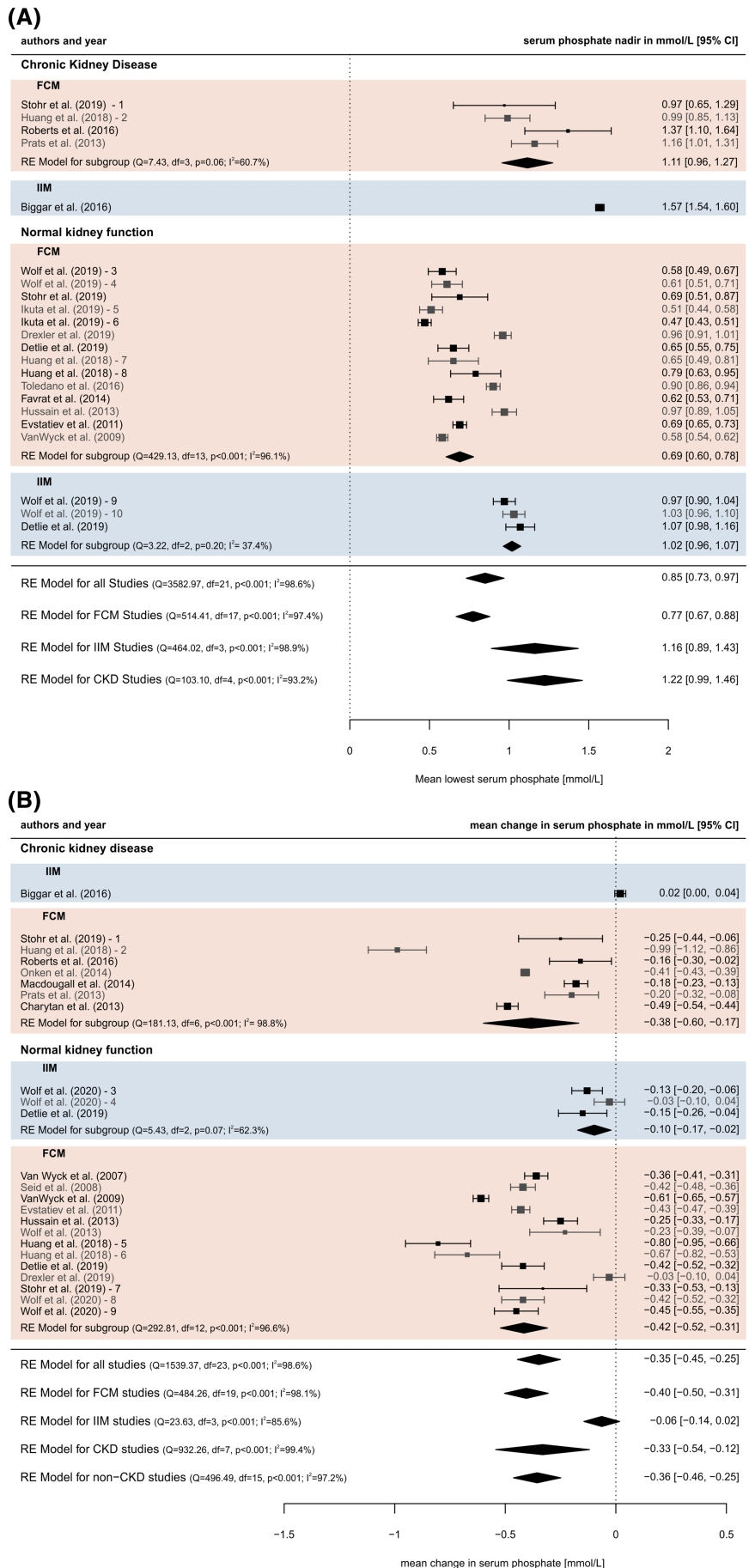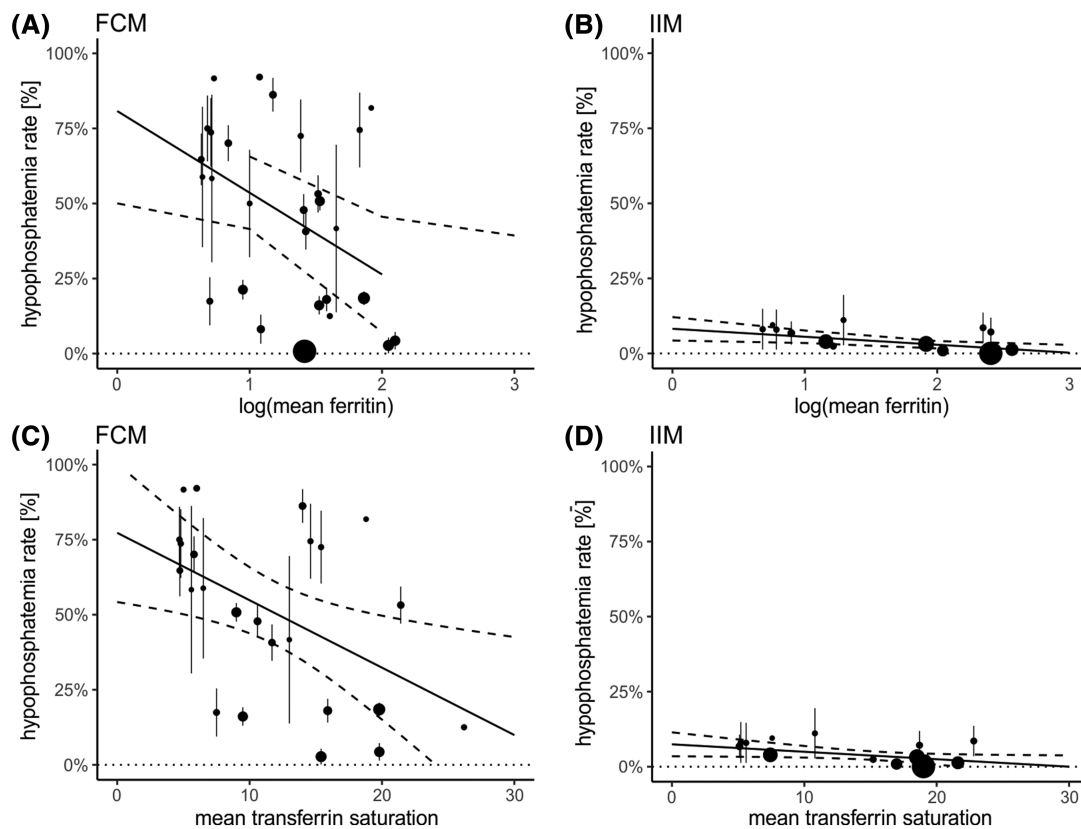
FIGURE 4 Meta regression of hypophosphataemia rate in relation to either log (mean ferritin) (A,B) or mean transferrin saturation (C,D) in studies on FCM (A,C) or IIM (B,D). Numerical outputs are reported in Table S1

4 | DISCUSSION

Despite the advantages of latest generation intravenous preparations FCM and IIM, which allow safe correction of total iron deficit in 1–2 infusions in the majority of patients, hypophosphataemia is increasingly recognized as a delayed adverse drug reaction. Although listed in the drug label as a potential side effect, the overall incidence and the clinical relevance of this adverse event are largely unknown.[11,60,61]

This systematic review and meta-analysis show that the reported incidence of hypophosphataemia after infusion of FCM or IIM ranges from 0% to 92% of in prospective clinical trials. Our systematic review and meta-analysis show that this wide range is in part attributable to inconsistent assessment and reporting of hypophosphataemia in clinical studies. As determinants and predictors of hypophosphataemia we have identified preserved renal function, the severity of iron deficiency and possibly dose.

The present analysis highlights inconsistencies in reporting of relevant endpoints. Some studies only report on mean phosphate concentrations before and after treatment or relative changes. Incidence of hypophosphataemia and the proportion of patients developing severe hypophosphataemia (<0.3 mmol/L) are much more relevant for the care of individual patients. Study protocols of ongoing clinical trials, which include assessment of the prevalence of the different degrees of hypophosphataemia (<0.3 mmol/L,

0.3–0.6 mmol/L, 0.6–0.8 mmol/L) during follow-up visits are preferable and should become standard in reporting this side effect, because the risk for complications of hypophosphataemia increases with its severity.[62]

Further, the duration of hypophosphataemia should be prospectively assessed by following up on patients who develop hypophosphataemia during the study. Accordingly, the description of 'i.v. iron-induced hypophosphataemia' as 'transient decrease of phosphate levels' may be applicable to a study population but inappropriate in describing the side-effect in individual patients, because recovery is unpredictable for individual patients. Retrospective studies have suggested that the median time to recovery is 40–80 days, but this is insufficient to assess the true duration of hypophosphataemia in individual patients who developed this side-effect.[10] None of the prospective studies reported on the actual duration of hypophosphataemia. Hence, the risk of long-term complications is also unknown.

Among patients with impaired renal function, the pooled risk of hypophosphataemia was significantly lower when compared with studies in other patient populations. The result supports previous findings that FCM and to a lesser degree IIM cause hypophosphataemia by renal wasting. Urinary phosphate excretion is controlled by iFGF23, which is induced by FCM through incompletely defined mechanisms.[63]

The difference in incidence between FCM and IIM across aetiologies supports the notion that hypophosphataemia is not a class effect of all i.v. irons, but rather a specific effect of FCM. This conclusion is supported by clinical trials confirming that, despite comparable dosing of FCM and the comparator (iron dextran or ferumoxytol), hypophosphataemia was far more common after FCM.[15,58] Pharmacologically, i.v. iron preparations are 'non-biological complex drugs (NBCD)', where the active drug is not a homo-molecular structure but consists of different closely related structures. The composition, characteristics and in-vivo effects of NBCD are highly dependent on manufacturing processes, which limits the possibilities to study the carbohydrate moiety independently of iron.[64]

The clinical manifestations of inappropriately high FGF23 with consequent hypophosphataemia are diverse and best known from patients with defects in genes regulating phosphate homeostasis and patients with tumour-induced osteomalacia. Weakness of proximal muscles, dental problems, bone pain and osteomalacia are typical manifestations of these diseases. As treatment with certain i.v. iron preparations is a novel cause of inappropriate FGF23 elevation, it can be expected that severely and chronically affected patients could also develop symptoms mimicking TIO or genetic hypophosphataemia.[65] Accordingly, a number of cases with clinical complications of hypophosphataemia have been reported.[11] How to best prevent such complications is unclear but monitoring of phosphate has recently been recommended by the Pharmacovigilance Risk Assessment Committee (PRAC). Patients treated with ferric carboxymaltose should be informed to seek medical advice if they experience worsening fatigue with myalgias or bone pain as clinical signs of hypophosphataemia. It is also recommended that serum phosphate should be monitored in patients who receive multiple administrations at higher doses, or long-term treatment, and in those with existing risk factors for hypophosphataemia.[66]

Treatment should be guided by the severity and clinical presentation of hypophosphataemia. It is not possible to predict the risk for severe and prolonged hypophosphataemia. Considering the association between low ferritin and high hypophosphataemia risk shown in this study, underlying conditions causing iron deficiency should be identified and treated. Oral or intravenous phosphate supplements are recommended for the treatment of hypophosphataemia, but do not sustainably correct low plasma phosphate in patients with high iFGF23. Calcitriol could correct secondary hyperparathyroidism but its efficacy and safety in the context of 6H syndrome remain uncertain.[11] One case report described the successful use of burosumab, a monoclonal antibody against FGF23 in a patient with severe iron-induced osteomalacia.[67] The uncertainties about diagnosis and management of iron-included hypophosphataemia, should be considered when selecting a specific iron formulation for the treatment of iron deficiency.

5 | CONCLUSION

In conclusion, this systematic review and meta-analysis shows that hypophosphataemia is a common medical problem after administration of FCM, especially in patients with preserved kidney function and more severe iron deficiency. The incidence is higher and the severity and duration are more severe after FCM infusion as compared to IIM.

DATA AVAILABILITY STATEMENT

For original data, please contact the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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