KDIGO 2025 Anemia in CKD Guideline
Public Review Draft
DATA SUPPLEMENT

Appendix A. Search strategies

Table S1. Search strategies for systematic review topics
See Appendix E for search dates for each question:

Database	Search strategy
Benefits and Harms of Iron Dosing Agents in People with CKD	
PubMed	"Iron dextran complex" [MeSH] "Ferric compounds"[mh] "Ferrous compounds"[mh] "iron sulfate"[tiab] "iron gluconate"[tiab] "iron fumarate"[tiab] "iron dextran"[tiab] "iron sucrose"[tiab] "iron saccharate"[tiab] "ferric gluconate"[tiab] "ferric compound"[tiab] "ferric compounds"[tiab] "ferric oxide"[tiab] "ferrous gluconate"[tiab] "ferrous bisglycinate"[tiab] "ferumoxytol"[tiab] "iron therapy"[tiab] "iron therapies"[tiab] "Iron supplement"[tiab] "iron supplements"[tiab] "iron supplementation"[tiab] "iron supplementations"[tiab] "IV iron"[tiab] "intravenous iron"[tiab] "iron infusion"[tiab] "iron infusions"[tiab] "Oral iron"[tiab] "iron treatment"[tiab] "iron treatments"[tiab] iron[tiab] AND Dialysate[tiab] #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[tiab]

	#31 AND #32 (animals[mh] NOT humans [mh]) #33 NOT #34
Embase	“Iron dextran”/exp OR “iron dextran”:ti,ab “Ferrous ion”/exp “ferric ion”/exp “ferrous sulfate”/exp OR “iron sulfate”:ti,ab “ferrous gluconate”/exp OR “iron gluconate”:ti,ab OR “ferrous gluconate”:ti,ab “ferrous fumarate”/exp OR “iron fumarate”:ti,ab “iron sucrose”:ti,ab “iron saccharate”/exp OR “iron saccharate”:ti,ab “ferric gluconate”/exp OR “ferric gluconate”:ti,ab “ferric compound”:ti,ab OR “ferric compounds”:ti,ab “ferric oxide”:ti,ab “ferrous bisglycinate”:ti,ab “ferumoxytol”:ti,ab “Iron therapy”/exp OR “iron therapy”:ti,ab OR “iron therapies”:ti,ab “Iron supplement”:ti,ab OR “iron supplements”:ti,ab OR “iron supplementation”:ti,ab OR “iron supplementations”:ti,ab “IV iron”:ti,ab OR “intravenous iron”:ti,ab “iron infusion”:ti,ab OR “iron infusions”:ti,ab “Oral iron”:ti,ab “iron treatment”:ti,ab OR “iron treatments”:ti,ab Iron:ti,ab AND Dialysate:ti,ab #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti #21 AND #22 (animals/exp NOT humans/exp) #23 NOT #24 “conference abstract”/it #25 NOT #26
CENTRAL	MeSH descriptor: [Iron-Dextran Complex] explode all trees MeSH descriptor: [Ferrous Compounds] explode all trees MeSH descriptor: [Ferric Compounds] explode all trees “iron sulfate”:ti,ab “ferrous sulfate”:ti,ab “iron gluconate”:ti,ab “ferrous gluconate”:ti,ab “iron fumarate”:ti,ab “ferrous fumarate”:ab,ti “iron dextran”:ti,ab “iron sucrose”:ti,ab “iron saccharate”:ti,ab “ferric gluconate”:ti,ab “ferric compounds”:ti,ab “ferric oxide”:ti,ab “ferrous gluconate”:ti,ab “ferrous bisglycinate”:ti,ab “ferumoxytol”:ti,ab

	“iron therapy”:ti,ab “iron therapies”:ti,ab “Iron supplement”:ti,ab “iron supplements”:ti,ab “iron supplementation”:ti,ab “iron supplementations”:ti,ab “IV iron”:ti,ab “intravenous iron”:ti,ab “iron infusion”:ti,ab “iron infusions”:ti,ab “Oral iron”:ti,ab “iron treatment”:ti,ab “iron treatments”:ti,ab Iron:ti,ab AND Dialysate:ti,ab #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 in trials
Benefits and Harms of HIF-PHIs in People with CKD	
PubMed	"Hypoxia-Inducible Factor-Proline Dioxygenases"[mh] "Hypoxia-Inducible Factor-Proline Dioxygenases"[tiab] "Prolyl-Hydroxylase Inhibitors"[mh] "Prolyl-Hydroxylase Inhibitors”[tiab] "Prolyl-Hydroxylase Inhibitor”[tiab] "HIF prolyl-hydroxylase inhibitor"[tiab] "HIF prolyl-hydroxylase inhibitors"[tiab] “hypoxia-inducible factor stabilizer”[tiab] “Hypoxia-inducible factor–prolyl hydroxylase inhibitors”[tiab] "HIF-PHI"[tiab] OR “HIF-PHIs”[tiab] “Hypoxia-inducible factors”[tiab] OR “Hypoxia-inducible factor”[tiab] Daprodustat[tiab] Desidustat[tiab] Enarodustat[tiab] Molidustat[tiab] Vadadustat[tiab] Roxadustat[tiab] "GSK1278863" [Supplementary Concept] "desidustat" [Supplementary Concept] "enarodustat" [Supplementary Concept] "molidustat" [Supplementary Concept] "vadadustat" [Supplementary Concept] “roxadustat” [Supplementary Concept] #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 “Renal Insufficiency, Chronic”[mh] “kidney glomerulus”[mh] “Kidney Diseases”[mh] “Chronic kidney disease”[tiab] CKD[tiab] “Chronic renal disease”[tiab]

	"end-stage kidney disease"[tiab] "end-stage renal disease"[tiab] ESRD[tiab] ESKD[tiab] ESKF[tiab] ESRF[tiab] "chronic renal failure"[tiab] "Renal replacement therapy"[Mesh] “Sorption Detoxification”[mh] “renal dialysis”[mh] “kidney transplantation”[mh] hemodialysis[tiab] "peritoneal dialysis"[tiab] ultrafiltration[mh] “ultrafiltration”[tiab] Hemofiltration[tiab] Haemofiltration[tiab] Hemodiafiltration[tiab] Haemodiafiltration[tiab] dialysis[tiab] haemodialysis[tiab] sorbtion[tiab] detoxification[tiab] (Transplant[tiab] OR transplants[tiab] OR graft[tiab] OR grafts[tiab] OR grafting[tiab]) AND (kidney[tiab] OR renal[tiab]) #25 OR #26 OR #27 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 #24 AND #55 randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] #56 AND #57 Animals[mh] NOT humans[mh] #58 NOT #60
Embase	"hypoxia inducible factor proline dioxygenase"/exp "Prolyl-Hydroxylase Inhibitor"/exp "Prolyl Hydroxylase Inhibitor":ti,ab "Prolyl Hydroxylase Inhibitors":ti,ab "HIF prolyl-hydroxylase inhibitor":ti,ab "HIF prolyl-hydroxylase inhibitors":ti,ab “hypoxia-inducible factor stabilizer”:ti,ab “hypoxia-inducible factor stabilizers”:ti,ab “Hypoxia-inducible factor–prolyl hydroxylase inhibitors”:ti,ab “Hypoxia-inducible factor–prolyl hydroxylase inhibitor”:ti,ab “Hypoxia inducible factor prolyl hydroxylase inhibitor”/exp "HIF-PHI":ti,ab OR “HIF-PHIs”:ti,ab “Hypoxia-inducible factors”:ti,ab OR “Hypoxia-inducible factor”:ti,ab Daprodustat:ti,ab Desidustat:ti,ab

	Enarodustat:ti,ab Molidustat:ti,ab Vadadustat:ti,ab Roxadustat:ti,ab "Daprodustat"/exp "desidustat"/exp "enarodustat"/exp "molidustat"/exp "vadadustat"/exp "roxadustat"/exp #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 "chronic kidney failure"/exp "glomerulus"/exp "Kidney Disease"/exp "Chronic kidney disease":ti,ab CKD:ti,ab "Chronic renal disease":ti,ab "end-stage kidney disease":ti,ab "end-stage renal disease":ti,ab ESRD:ti,ab ESKD:ti,ab ESKF:ti,ab ESRF:ti,ab "chronic renal failure":ti,ab "Renal replacement therapy"/exp "Sorption Detoxification"/exp "hemodialysis"/exp "kidney transplantation"/exp Hemodialysis:ti,ab "peritoneal dialysis":ti,ab Ultrafiltration/exp "ultrafiltration":ti,ab Hemofiltration:ti,ab Haemofiltration:ti,ab Hemodiafiltration:ti,ab Haemodiafiltration:ti,ab Dialysis:ti,ab Haemodialysis:ti,ab Sorbtion:ti,ab Detoxification:ti,ab (Transplant:ti,ab OR transplants:ti,ab OR graft:ti,ab OR grafts:ti,ab OR grafting:ti,ab) AND (kidney:ti,ab OR renal:ti,ab) #27 OR #28 OR #29 OR #30 OR #31 OR #32 Or #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 #26 AND #57 "Randomized controlled trial"/exp OR "controlled clinical trial"/exp OR randomized:ti,ab OR placebo:ti,ab "clinical trial"/exp OR randomly:ti,ab OR

	trial:ti,ab OR “random allocation”:ti,ab OR “double-blind method”:ti,ab OR “single-blind method”:ti,ab OR “clinical trial”:ti,ab #26 AND Animals/exp NOT humans/exp #73 NOT #74
CENTRAL	MeSH descriptor: [Hypoxia-Inducible Factor-Proline Dioxygenases] explode all trees MeSH descriptor: [Prolyl-Hydroxylase Inhibitors] explode all trees "Prolyl Hydroxylase Inhibitor":ti,ab "Prolyl Hydroxylase Inhibitors":ti,ab "HIF prolyl-hydroxylase inhibitor":ti,ab "HIF prolyl-hydroxylase inhibitors":ti,ab “hypoxia inducible factor stabilizers”:ti,ab "HIF-PHI":ti,ab OR “HIF-PHIs”:ti,ab "HIF PHI":ti,ab OR “HIF PHIs”:ti,ab “Hypoxia inducible factors”:ti,ab OR “Hypoxia inducible factor”:ti,ab Daprodustat:ti,ab Desidustat:ti,ab Enarodustat:ti,ab Molidustat:ti,ab Vadadustat:ti,ab Roxadustat:ti,ab (FG-4592):ti,ab ("BAY-85 3934"):ti,ab (GSK1278863):ti,ab (AKB-6548):ti,ab (JTZ-951):ti,ab #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees MeSH descriptor: [Kidney Glomerulus] explode all trees MeSH descriptor: [Kidney Diseases] explode all trees “Chronic kidney disease”:ti,ab CKD:ti,ab “Chronic renal disease”:ti,ab "end-stage kidney disease":ti,ab "end-stage renal disease":ti,ab ESRD:ti,ab ESKD:ti,ab ESKF:ti,ab ESRF:ti,ab "chronic renal failure":ti,ab MeSH descriptor: [Renal Replacement Therapy] explode all trees MeSH descriptor: [Sorption Detoxification] explode all trees MeSH descriptor: [Renal Dialysis] explode all trees MeSH descriptor: [Kidney Transplantation] explode all trees Hemodialysis:ti,ab "peritoneal dialysis":ti,ab MeSH descriptor: [Ultrafiltration] 1 tree(s) exploded “ultrafiltration”:ti,ab

	Hemofiltration:ti,ab Haemofiltration:ti,ab Hemodiafiltration:ti,ab Haemodiafiltration:ti,ab Dialysis:ti,ab Haemodialysis:ti,ab Sorbtion:ti,ab #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #25 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 #22 AND #51 #64 AND #22 in trials only
Benefits and Harms of ESAs in People with CKD	
PubMed	“Renal Insufficiency, Chronic”[mh] “kidney glomerulus”[mh] “Kidney Diseases”[mh] “Chronic kidney disease”[tiab] CKD[tiab] “Chronic renal disease”[tiab] "end-stage kidney disease"[tiab] "end-stage renal disease"[tiab] ESRD[tiab] ESKD[tiab] ESKF[tiab] ESRF[tiab] "chronic renal failure"[tiab] "Renal replacement therapy"[Mesh] “Sorption Detoxification”[mh] “renal dialysis”[mh] “kidney transplantation”[mh] hemodialysis[tiab] "peritoneal dialysis"[tiab] ultrafiltration[mh] “ultrafiltration”[tiab] Hemofiltration[tiab] Haemofiltration[tiab] Hemodiafiltration[tiab] Haemodiafiltration[tiab] dialysis[tiab] haemodialysis[tiab] sorbtion[tiab] detoxification[tiab] (Transplant[tiab] OR transplants[tiab] OR graft[tiab] OR grafts[tiab] OR grafting[tiab]) AND (kidney[tiab] OR renal[tiab]) #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 Erythropoietin[mh] “recombinant erythropoietin”[tiab]

	“Hematinics”[mh] "continuous erythropoietin receptor activator" [Supplementary Concept] “methoxy polyethylene glycol-epoetin beta”[tiab] CERA[tiab] “erythropoietin receptor activator”[tiab] Epoetin[tiab] epogen[tiab] Erythropoietin[tiab] “erythrocyte stimulat*”[tiab] darbepoetin[tiab] epokine[tiab] procrit[tiab] eprex[tiab] Dynepro[tiab] Epomax[tiab] Hemax[tiab] Silapo[tiab] Retacrit[tiab] Aranesp[tiab] Epo[tiab] Mircera[tiab] ESA[tiab] Erythropoiesis[tiab] #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 “Randomized controlled trial”[pt] OR “controlled clinical trial”[pt] OR randomized[tiab] OR placebo[tiab] “clinical trial”[pt] OR randomly[tiab] OR trial[tiab] OR “random allocation”[tiab] OR “double-blind method”[tiab] OR “single-blind method”[tiab] OR “clinical trial”[tiab] OR “clinical trial”[tiab] #31 AND #57 AND #58 Animals[mh] NOT humans[mh] #59 NOT #60 Date limited: October 2009 to present
Embase	“chronic kidney failure”/exp “glomerulus”/exp “Kidney Disease”/exp “Chronic kidney disease”:ti,ab CKD:ti,ab “Chronic renal disease”:ti,ab "end-stage kidney disease":ti,ab "end-stage renal disease":ti,ab ESRD:ti,ab ESKD:ti,ab ESKF:ti,ab ESRF:ti,ab "chronic renal failure":ti,ab "Renal replacement therapy”/exp “Sorption Detoxification”/exp “hemodialysis”/exp

	“kidney transplantation”/exp Hemodialysis:ti,ab "peritoneal dialysis":ti,ab Ultrafiltration/exp “ultrafiltration”:ti,ab Hemofiltration:ti,ab Haemofiltration:ti,ab Hemodiafiltration:ti,ab Haemodiafiltration:ti,ab Dialysis:ti,ab Haemodialysis:ti,ab Sorbtion:ti,ab Detoxification:ti,ab (Transplant:ti,ab OR transplants:ti,ab OR graft:ti,ab OR grafts:ti,ab OR grafting:ti,ab) AND (kidney:ti,ab OR renal:ti,ab) #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 Erythropoietin/exp “recombinant erythropoietin”:ti,ab “antianemic agent”/exp "continuous erythropoietin receptor activator"/exp “methoxy polyethylene glycol-epoetin beta”:ti,ab CERA:ti,ab “erythropoietin receptor activator”:ti,ab Epoetin:ti,ab Epogen:ti,ab Erythropoietin:ti,ab “erythrocyte stimulat*”:ti,ab Darbepoetin:ti,ab Epokine:ti,ab Procrit:ti,ab Eprex:ti,ab Dynepro:ti,ab Epomax:ti,ab Hemax:ti,ab Silapo:ti,ab Retacrit:ti,ab Aranesp:ti,ab Epo:ti,ab Mircera:ti,ab ESA:ti,ab Erythropoiesis:ti,ab #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti #31 AND #57 AND #58 Animals/exp NOT humans/exp #59 NOT #60

	Date limited: 2009 to present
CENTRAL	MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees MeSH descriptor: [Kidney Glomerulus] explode all trees MeSH descriptor: [Kidney Diseases] explode all trees “Chronic kidney disease”:ti,ab CKD:ti,ab “Chronic renal disease”:ti,ab "end-stage kidney disease":ti,ab "end-stage renal disease":ti,ab ESRD:ti,ab ESKD:ti,ab ESKF:ti,ab ESRF:ti,ab "chronic renal failure":ti,ab MeSH descriptor: [Renal Replacement Therapy] explode all trees MeSH descriptor: [Sorption Detoxification] explode all trees MeSH descriptor: [Renal Dialysis] explode all trees MeSH descriptor: [Kidney Transplantation] explode all trees Hemodialysis:ti,ab "peritoneal dialysis":ti,ab MeSH descriptor: [Ultrafiltration] 1 tree(s) exploded “ultrafiltration”:ti,ab Hemofiltration:ti,ab Haemofiltration:ti,ab Hemodiafiltration:ti,ab Haemodiafiltration:ti,ab Dialysis:ti,ab Haemodialysis:ti,ab Sorbtion:ti,ab Detoxification:ti,ab (Transplant:ti,ab OR transplants:ti,ab OR graft:ti,ab OR grafts:ti,ab OR grafting:ti,ab) AND (kidney:ti,ab OR renal:ti,ab) #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 MeSH descriptor: [Erythropoietin] explode all trees “recombinant erythropoietin”:ti,ab MeSH descriptor: [Hematinics] explode all trees “methoxy polyethylene glycol-epoetin beta”:ti,ab CERA:ti,ab “erythropoietin receptor activator”:ti,ab Epoetin:ti,ab Epogen:ti,ab Erythropoietin:ti,ab “erythrocyte stimulation”:ti,ab, word variations have been searced Darbepoetin:ti,ab Epokine:ti,ab Procrit:ti,ab Eprex:ti,ab Dynepro:ti,ab

	Epomax:ti,ab Hemax:ti,ab Silapo:ti,ab Retacrit:ti,ab Aranesp:ti,ab Epo:ti,ab Mircera:ti,ab ESA:ti,ab Erythropoiesis:ti,ab #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 #31 AND #57 Date limited: Oct 2009 to present
Benefits and Harms of ESAs versus HIF-PHIs in People with CKD	
PubMed	Erythropoietin[mh] “recombinant erythropoietin”[tiab] “Hematinics”[mh] "continuous erythropoietin receptor activator" [Supplementary Concept] “methoxy polyethylene glycol-epoetin beta”[tiab] CERA[tiab] “erythropoietin receptor activator”[tiab] Epoetin[tiab] epogen[tiab] Erythropoietin[tiab] “erythrocyte stimulat*”[tiab] darbepoetin[tiab] epokine[tiab] procrit[tiab] eprex[tiab] Dynepro[tiab] Epomax[tiab] Hemax[tiab] Silapo[tiab] Retacrit[tiab] Aranesp[tiab] Epo[tiab] Mircera[tiab] ESA[tiab] Erythropoiesis[tiab] #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #12 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 "Hypoxia-Inducible Factor-Proline Dioxygenases"[mh] "Hypoxia-Inducible Factor-Proline Dioxygenases"[tiab] "Prolyl-Hydroxylase Inhibitors"[mh] "Prolyl-Hydroxylase Inhibitors”[tiab] "Prolyl-Hydroxylase Inhibitor”[tiab] "HIF prolyl-hydroxylase inhibitor"[tiab] "HIF prolyl-hydroxylase inhibitors"[tiab] “hypoxia-inducible factor stabilizer”[tiab]

	“Hypoxia-inducible factor–prolyl hydroxylase inhibitors”[tiab] "HIF-PHI"[tiab] OR “HIF-PHIs”[tiab] “Hypoxia-inducible factors”[tiab] OR “Hypoxia-inducible factor”[tiab] Daprodustat[tiab] Desidustat[tiab] Enarodustat[tiab] Molidustat[tiab] Vadadustat[tiab] Roxadustat[tiab] "GSK1278863" [Supplementary Concept] "desidustat" [Supplementary Concept] "enarodustat" [Supplementary Concept] "molidustat" [Supplementary Concept] "vadadustat" [Supplementary Concept] “roxadustat” [Supplementary Concept] #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 “Renal Insufficiency, Chronic”[mh] “kidney glomerulus”[mh] “Kidney Diseases”[mh] “Chronic kidney disease”[tiab] CKD[tiab] “Chronic renal disease”[tiab] "end-stage kidney disease"[tiab] "end-stage renal disease"[tiab] ESRD[tiab] ESKD[tiab] ESKF[tiab] ESRF[tiab] "chronic renal failure"[tiab] "Renal replacement therapy"[Mesh] “Sorption Detoxification”[mh] “renal dialysis”[mh] “kidney transplantation”[mh] hemodialysis[tiab] "peritoneal dialysis"[tiab] ultrafiltration[mh] “ultrafiltration”[tiab] Hemofiltration[tiab] Haemofiltration[tiab] Hemodiafiltration[tiab] Haemodiafiltration[tiab] dialysis[tiab] haemodialysis[tiab] sorbtion[tiab] detoxification[tiab] (Transplant[tiab] OR transplants[tiab] OR graft[tiab] OR grafts[tiab] OR grafting[tiab]) AND (kidney[tiab] OR renal[tiab]) #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR

	#69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] #26 AND #50 AND #81 AND #82 Animals[mh] NOT humans[mh] #83 NOT #84
Embase	"hypoxia inducible factor proline dioxygenase"/exp "Prolyl-Hydroxylase Inhibitor"/exp "Prolyl Hydroxylase Inhibitor":ti,ab "Prolyl Hydroxylase Inhibitors":ti,ab "HIF prolyl-hydroxylase inhibitor":ti,ab "HIF prolyl-hydroxylase inhibitors":ti,ab “hypoxia-inducible factor stabilizer”:ti,ab “hypoxia-inducible factor stabilizers”:ti,ab “Hypoxia-inducible factor–prolyl hydroxylase inhibitors”:ti,ab “Hypoxia-inducible factor–prolyl hydroxylase inhibitor”:ti,ab “Hypoxia inducible factor prolyl hydroxylase inhibitor”/exp "HIF-PHI":ti,ab OR “HIF-PHIs”:ti,ab “Hypoxia-inducible factors”:ti,ab OR “Hypoxia-inducible factor”:ti,ab Daprodustat:ti,ab Desidustat:ti,ab Enarodustat:ti,ab Molidustat:ti,ab Vadadustat:ti,ab Roxadustat:ti,ab "Daprodustat”/exp "desidustat"/exp "enarodustat”/exp "molidustat"/exp "vadadustat"/exp “roxadustat”/exp #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 Erythropoietin/exp “recombinant erythropoietin”:ti,ab “antianemic agent”/exp "continuous erythropoietin receptor activator"/exp “methoxy polyethylene glycol-epoetin beta”:ti,ab CERA:ti,ab “erythropoietin receptor activator”:ti,ab Epoetin:ti,ab Epogen:ti,ab Erythropoietin:ti,ab “erythrocyte stimulat*”:ti,ab Darbepoetin:ti,ab Epokine:ti,ab Procrit:ti,ab Eprex:ti,ab

	Dynepro:ti,ab Epomax:ti,ab Hemax:ti,ab Silapo:ti,ab Retacrit:ti,ab Aranesp:ti,ab Epo:ti,ab Mircera:ti,ab ESA:ti,ab Erythropoiesis:ti,ab #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 “chronic kidney failure”/exp “glomerulus”/exp “Kidney Disease”/exp “Chronic kidney disease”:ti,ab CKD:ti,ab “Chronic renal disease”:ti,ab "end-stage kidney disease":ti,ab "end-stage renal disease":ti,ab ESRD:ti,ab ESKD:ti,ab ESKF:ti,ab ESRF:ti,ab "chronic renal failure":ti,ab "Renal replacement therapy”/exp “Sorption Detoxification”/exp “hemodialysis”/exp “kidney transplantation”/exp Hemodialysis:ti,ab "peritoneal dialysis":ti,ab Ultrafiltration/exp “ultrafiltration”:ti,ab Hemofiltration:ti,ab Haemofiltration:ti,ab Hemodiafiltration:ti,ab Haemodiafiltration:ti,ab Dialysis:ti,ab Haemodialysis:ti,ab Sorbtion:ti,ab Detoxification:ti,ab (Transplant:ti,ab OR transplants:ti,ab OR graft:ti,ab OR grafts:ti,ab OR grafting:ti,ab) AND (kidney:ti,ab OR renal:ti,ab) #53 OR #54 OR #55 OR #56 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 Randomized controlled trial”/exp OR “controlled clinical trial”/exp OR randomized:ti,ab OR placebo:ti,ab “clinical trial”/exp OR randomly:ti,ab OR

	trial:ti,ab OR “random allocation”:ti,ab OR “double-blind method”:ti,ab OR “single-blind method”:ti,ab OR “clinical trial”:ti,ab #26 AND #52 AND #70 AND #71 Animals/exp NOT humans/exp #72 NOT #73
CENTRAL	MeSH descriptor: [Hypoxia-Inducible Factor-Proline Dioxygenases] explode all trees MeSH descriptor: [Prolyl-Hydroxylase Inhibitors] explode all trees "Prolyl Hydroxylase Inhibitor":ti,ab "Prolyl Hydroxylase Inhibitors":ti,ab "HIF prolyl-hydroxylase inhibitor":ti,ab "HIF prolyl-hydroxylase inhibitors":ti,ab “hypoxia inducible factor stabilizers”:ti,ab "HIF-PHI":ti,ab OR “HIF-PHIs”:ti,ab "HIF PHI":ti,ab OR “HIF PHIs”:ti,ab “Hypoxia inducible factors”:ti,ab OR “Hypoxia inducible factor”:ti,ab Daprodustat:ti,ab Desidustat:ti,ab Enarodustat:ti,ab Molidustat:ti,ab Vadadustat:ti,ab Roxadustat:ti,ab (FG-4592):ti,ab ("BAY-85 3934"):ti,ab (GSK1278863):ti,ab (AKB-6548):ti,ab (JTZ-951):ti,ab #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 MeSH descriptor: [Erythropoietin] explode all trees “recombinant erythropoietin”:ti,ab MeSH descriptor: [Hematinics] explode all trees “methoxy polyethylene glycol-epoetin beta”:ti,ab CERA:ti,ab “erythropoietin receptor activator”:ti,ab Epoetin:ti,ab Epogen:ti,ab Erythropoietin:ti,ab “erythrocyte stimulation”:ti,ab, word variations have been searced Darbepoetin:ti,ab Epokine:ti,ab Procrit:ti,ab Eprex:ti,ab Dynepro:ti,ab Epomax:ti,ab Hemax:ti,ab Silapo:ti,ab Retacrit:ti,ab Aranesp:ti,ab Epo:ti,ab

	Mircera:ti,ab ESA:ti,ab Erythropoiesis:ti,ab #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees MeSH descriptor: [Kidney Glomerulus] explode all trees MeSH descriptor: [Kidney Diseases] explode all trees “Chronic kidney disease”:ti,ab CKD:ti,ab “Chronic renal disease”:ti,ab "end-stage kidney disease":ti,ab "end-stage renal disease":ti,ab ESRD:ti,ab ESKD:ti,ab ESKF:ti,ab ESRF:ti,ab "chronic renal failure":ti,ab MeSH descriptor: [Renal Replacement Therapy] explode all trees MeSH descriptor: [Sorption Detoxification] explode all trees MeSH descriptor: [Renal Dialysis] explode all trees MeSH descriptor: [Kidney Transplantation] explode all trees Hemodialysis:ti,ab "peritoneal dialysis":ti,ab MeSH descriptor: [Ultrafiltration] 1 tree(s) exploded “ultrafiltration”:ti,ab Hemofiltration:ti,ab Haemofiltration:ti,ab Hemodiafiltration:ti,ab Haemodiafiltration:ti,ab Dialysis:ti,ab Haemodialysis:ti,ab Sorbtion:ti,ab #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 #22 AND #48 AND #77trials only

Appendix B. Concurrence with Institute of Medicine (IOM) standards for guideline development

Table S2. Guideline development checklist - IOM standards for development of trustworthy clinical practice guidelines[1]

IOM Standard	Description	Addressed in 2024 KDIGO Anemia guideline
Establishing transparency	Clear description on the process of guideline development.	See *Methods for Guideline Development*
Management of conflicts of interests	Disclosure of a comprehensive conflict of interests of the Work Group against a set-criteria and a clear strategy to manage conflicts of interests	See *Work Group Financial Disclosures*
Guideline group composition and guideline development	Appropriate clinical and methodological expertise in the Work Group The processes of guideline development are transparent and allow for involvement of all Work Group Members	For guideline group composition – see *Work Group Membership* For guideline development process see *Methods for Guideline Development*
Establishing evidence foundations for rating strength of recommendations	Rationale is provided for the rating the strength of the recommendation and the transparency for the rating the quality of the evidence.	See *Methods for Guideline Development*
Articulation of recommendations	Clear and standardized wording of recommendations	All recommendations were written to standards of GRADE and were actionable statements. Please see *Methods for Guideline Development*
External review	An external review of relevant experts and stakeholders was conducted. All comments received from external review are considered for finalization of the guideline.	An external public review was undertaken in April 2024.
Updating	An update for the guidelines is planned, with a provisional timeframe provided.	The KDIGO clinical practice guideline will be updated. However, no set timeframe has been provided.

Table S3. Adapted systematic review reporting standards checklist[2]

IOM Standard	Addressed in 2024 KDIGO Anemia guideline
Methods	
Include a research protocol with appropriate eligibility criteria (PICO format)	See *Table 44 clinical question and systematic review topics in PICO format*
Include a search strategy	See Appendix A
Include a study selection and data extraction process	See guideline development process see *Methods for Guideline Development – Literature searching and article selection, data extraction*
Methods on critical appraisal	See *Methods for Guideline Development – Critical appraisal of studies*
Methods of synthesize of the evidence	See *Methods for Guideline Development – Evidence synthesis and meta-analysis*
Results	
Study selection processes	See *Methods for Guideline Development – Figure 53 – Search yield and study flow diagram*
Appraisal of individual studies quality	The summary of findings tables in Appendix C provide an assessment of risk of bias for all studies in a comparison between intervention and comparator.
Meta-analysis results	See *Appendix C* for summary of findings tables for meta-analysis results for all critical and important outcomes
Table and figures	See *Appendix C* for summary of findings tables

References
1. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. Graham R, Mancher M, editors: National Academies Press Washington, DC; 2011.
2. Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness R. In: Eden J, Levit L, Berg A, Morton S, editors. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): National Academies Press (US) Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.

Appendix C. Data supplement - Summary of findings (SoF) tables cited in the guideline text

Chapter 2. Use of iron to treat iron deficiency and anemia in CKD

Table S4.
Population: Adults with anemia and CKD receiving hemodialysis and treated with ESAs/HIF-PHIs
Intervention: Iron dosing agents
Comparator: Placebo
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
Mortality											
10[3-11]	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	16/1059 (1.5%)	13/651 (2.0%)	**RR 1.10** (0.52 to 2.32)	**2 more per 1,000** (from 10 fewer to 26 more)	⊕◯◯◯ Very low
Total cardiovascular events*											
4[3, 5, 7, 8]	randomized trials	serious[c]	not serious	not serious	very serious[b]	none	23/180 (12.8%)	21/151 (13.9%)	**RR 0.93** (0.54 to 1.62)	**10 fewer per 1,000** (from 64 fewer to 86 more)	⊕◯◯◯ Very low
Stroke[†]											
2[7, 12]	randomized trials	serious[a]	not serious	not serious	extremely serious[d]	none	2/91 (2.2%)	2/67 (3.0%)	**RR 0.66** (0.10 to 4.35)	**10 fewer per 1,000** (from 27 fewer to 100 more)	⊕◯◯◯ Very low
Heart failure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Myocardial infarction											
2[3, 12]	randomized trials	serious[c]	not serious	not serious	extremely serious[d]	none	0/79 (0.0%)	2/79 (2.5%)	**RR 0.33** (0.04 to 3.13)	**17 fewer per 1,000** (from 24 fewer to 54 more)	⊕◯◯◯ Very low
Quality of life (Scale from: 0 to 40)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
1[13]	randomized trials	serious[e]	not serious	serious[f]	serious[g]	none	16	16	-	MD **6.57 lower** (8.19 lower to 4.95 lower)	⊕◯◯◯ Very low
Functional status - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
All-cause hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Total serious adverse events											
10[3-6, 8, 10, 11, 14-16]	randomized trials	serious[a]	not serious	not serious	serious[h]	none	126/970 (13.0%)	121/634 (19.1%)	**RR 0.94** (0.76 to 1.17)	**11 fewer per 1,000** (from 46 fewer to 32 more)	⊕⊕◯◯ Low
Serious gastrointestinal adverse events‡											
2[3, 12]	randomized trials	serious[c]	not serious	not serious	extremely serious[d]	none	3/79 (3.8%)	3/79 (3.8%)	**RR 1.05** (0.23 to 4.86)	**2 more per 1,000** (from 29 fewer to 147 more)	⊕◯◯◯ Very low
Serious hypersensitivity reactions											
1[8]	randomized trials	serious[i]	not serious	not serious	extremely serious[j]	none	0/54 (0.0%)	0/49 (0.0%)	not estimable		⊕◯◯◯ Very low
Infections§											
5[3, 5, 9, 12, 15]	randomized trials	serious[k]	not serious	not serious	very serious[b]	none	31/391 (7.9%)	18/218 (8.3%)	**RR 0.92** (0.51 to 1.68)	**7 fewer per 1,000** (from 40 fewer to 56 more)	⊕◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

* Studies had varying definitions for total cardiovascular disease events. The DRIVE trial and Besarab 2016 reported on cardiac disorders as adverse events.[3, 5] Gupta 2015 reported on cardiac disorders as treatment-emergent adverse events.[8] Fudin 1998 reported on cardiovascular mortality and cerebrovascular accidents.[7]

† Studies had varying definitions of stroke. Fudin 1998 reported on cerebrovascular accidents.[7] Kuo 2008 reported on cerebral infarcts.[12]

‡ Studies had varying definitions for the specific serious adverse events. Kuo 2008 reported on gastrointestinal bleeding that resulted in withdrawal from the study.[12] Besarab 2016 reported on gastrointestinal hemorrhage.[3]

§ Studies had varying definitions for infections. The DRIVE trial reported on infections, including bronchitis, cellulitis, conjunctivitis, fungal infections, furuncles, C. *difficile*, line infections, pneumonia, nasopharyngitis, sepsis, skin infections, upper respiratory infections, and urinary tract infections.[5] Besarab 2016 reported on infections and infestations that were considered to be treatment-emergent adverse events.[3] Sampson 2021 and Koiwa 2017 reported results by type of infections.[9, 15] For each study, we included the most frequent type of infection. The most frequent type of infection was upper respiratory tract infections for Sampson 2021 and nasopharyngitis for Koiwa 2017. Kuo 2008 reported on episodes of pneumonia that resulted in withdrawal from the study.[12]

Explanations

a. Studies were considered to have an unclear or a high risk of bias because there were concerns with selection bias, lack of blinding, and/or attrition bias.
b. Confidence interval was very wide, suggesting the possibility of a benefit and of a harm.
c. Studies were considered to have a high risk of bias because there were concerns with lack of blinding and/or attrition bias.
d. There were few than 10 events among all the participants in the included trials. The total number of events is much lower than the number needed to reach the optimal information size (i.e., 300). The confidence intervals were extremely wide.
e. Study was considered to have a high risk of bias because of concerns with allocation concealment.
f. The International Restless Leg Syndrome Study Group rating scale was the only quality of life measure assessed. Some aspects of quality of life may not have been captured.
g. Small sample size
h. There were fewer than 300 events among all the participants in the included trials. The total number of events is much lower than the number needed to reach the optimal information size (i.e., 300).
i. Study was considered to have a high risk of bias because of concerns with attrition bias.
j. There were no reported events.
k. Studies were considered to have an unclear or high risk of bias because of concerns with blinding and attrition bias.

Table S5.

Population: Adults with anemia and CKD receiving hemodialysis and treated with ESAs/HIF-PHIs

Intervention: Iron dosing agents

Comparator: Placebo

Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
Pediatric outcomes (growth, height, weight, and cognitive development) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Blood transfusions*											
3[6, 8, 17]	randomized trials	serious[b]	not serious	serious[f]	serious[c]	none	11/366 (3.0%)	26/264 (9.8%)	**RR 0.42** (0.21 to 0.84)	**57 fewer per 1,000** (from 78 fewer to 16 fewer)	⨁◯◯◯ Very low
Cancer[†]											
1[7]	randomized trials	serious[g]	not serious	not serious	extremely serious[d]	none	0/36 (0.0%)	1/12 (8.3%)	**RR 0.12** (0.01 to 2.70)	**73 fewer per 1,000** (from 82 fewer to 142 more)	⨁◯◯◯ Very low
ESA use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
ESA dose											
6[5, 6, 8, 17-19]	randomized trials	serious[b]	not serious	not serious	serious[h]	none	Multiple measures suggesting either a reduction or maintenance of ESA doses.				⨁⨁◯◯ Low
Reaching hemoglobin target[‡]											
3[3-5]	randomized trials	serious[i]	not serious	not serious	serious[c]	publication bias strongly suspected[j]	**Pooled RR ranged** from 0.92 to 1.60.				⨁◯◯◯ Very low
Hemoglobin (follow-up: range 1 weeks to 12 weeks)											
12[3, 5, 8, 9, 11, 13, 15-17, 20, 21]	randomized trials	serious[a]	not serious	not serious	not serious	none	754	358	**Pooled MD ranged** from 0.40 to 0.51 g/dL.		⨁⨁⨁◯ Moderate
Hemoglobin (follow-up: range 13 weeks to 24 weeks)											
1[8]	randomized trials	serious[e]	not serious	serious[k]	serious[h]	none	54	49	-	MD **0.53 g/dL higher** (0.05 higher to 1.01 higher)	⨁◯◯◯ Very low
Hemoglobin (follow-up: range 25 weeks to 52 weeks)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
3[6-8]	randomized trials	serious[b]	serious[l]	not serious	serious[h]	none	368	368	**Pooled MD ranged** from 0.40 to 4.00 g/dL.		⨁◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

* Studies did not report their indications for a blood transfusion.

† Fudin 1998 reported on withdrawals from study because of a malignancy.[7]

‡ Studies had varying hemoglobin targets. Besarab 2016 and Charytan 2013 targeted an increase in hemoglobin levels of at least 1 g/dL.[3, 4] The DRIVE trial targeted an increase in hemoglobin levels of at least 2 g/dL.[5]

Explanations

a. Studies were considered to have an unclear or a high risk of bias because there were concerns with selection bias, lack of blinding, and/or attrition bias.

b. Studies were considered to have a high risk of bias because there were concerns with lack of blinding and/or attrition bias.

c. There were fewer than 300 events among all the participants in the included trials. The total number of events is much lower than the number needed to reach the optimal information size (i.e., 300).

d. There were fewer than 5 events among all the participants in the included trials. The total number of events is much lower than the number needed to reach the optimal information size (i.e., 300).

e. Study was considered to have a high risk of bias because of concerns with attrition bias

f. We did not identify any studies that compared an oral iron dosing agent with placebo and reported on this outcome.

g. Study was considered to have an unclear risk of bias.

h. Confidence intervals were wide.

i. Studies were considered to have an unclear or high risk of bias due to concerns with allocation concealment and/or blinding.

j. Several studies that reported on hemoglobin values did not report on whether or not participants reached a hemoglobin target.

k. We did not identify any studies that compared an oral or intravenous iron dosing agent with placebo and reported on this outcome.

l. Overall I-squared was very high. Study population (iron deficient vs. iron replete) could be a potential effect modifier.

Table S6.
Population: Adults with anemia and CKD receiving hemodialysis
Intervention: I.v. iron dosing agents
Comparator: Oral iron dosing agents
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
Mortality											
6[3, 7, 22-25]	randomized trials	serious[a]	not serious	not serious	extremely serious[b]	none	3/271 (1.1%)	7/223 (3.1%)	**RR 0.49** (0.12 to 2.00)	**16 fewer per 1,000** (from 28 fewer to 31 more)	⊕◯◯◯ Very low
Total cardiovascular events*											
2[3, 7]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	3/36 (8.3%)	2/24 (8.3%)	**RR 0.92** (0.16 to 5.41)	**7 fewer per 1,000** (from 70 fewer to 368 more)	⊕◯◯◯ Very low
Stroke†											
1[7]	randomized trials	serious[d]	not serious	not serious	extremely serious[b]	none	1/24 (4.2%)	0/12 (0.0%)	**RR 1.56** (0.07 to 35.67)	not estimable	⊕◯◯◯ Very low
Heart failure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Myocardial infarction											
1[3]	randomized trials	serious[e]	not serious	not serious	extremely serious[f]	none	0/12 (0.0%)	0/12 (0.0%)	not estimable		⊕◯◯◯ Very low
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Functional status - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
All-cause hospitalizations											
1[23]	randomized trials	serious[g]	not serious	not serious	extremely serious[f]	none	0/88 (0.0%)	0/25 (0.0%)	not estimable		⊕◯◯◯ Very low
Total serious adverse events											
4[3, 24-26]	randomized trials	serious[h]	not serious	not serious	extremely serious[b]	none	14/151 (9.3%)	15/154 (9.7%)	**RR 0.97** (0.50 to 1.92)	**3 fewer per 1,000** (from 49 fewer to 90 more)	⊕◯◯◯ Very low
Serious gastrointestinal adverse events‡											
1[3]	randomized trials	serious[e]	not serious	not serious	extremely serious[f]	none	0/12 (0.0%)	0/12 (0.0%)	not estimable		⊕◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
Serious hypersensitivity adverse events[§]											
1[23]	randomized trials	serious[g]	not serious	not serious	extremely serious[f]	none	0/88 (0.0%)	0/25 (0.0%)	not estimable		⨁◯◯◯ Very low
Infections[‖]											
2[3, 24]	randomized trials	serious[i]	not serious	not serious	extremely serious[b]	none	0/122 (0.0%)	3/125 (2.4%)	**RR 0.26** (0.03 to 2.27)	**18 fewer per 1,000** (from 23 fewer to 30 more)	⨁◯◯◯ Very low

CKD = chronic kidney disease; CI = confidence interval; IV = intravenous; RR = risk ratio

* Studies had varying definitions for total cardiovascular disease events. Besarab 2016 reported on cardiac disorders as adverse events.[3] Fudin 1998 reported on cardiovascular mortality and cerebrovascular accidents.[7]

† Fudin 1998 reported on cerebrovascular accidents.[7]

‡ Besarab 2016 reported on gastrointestinal hemorrhage.[3]

§ Nissenson 1999 reported on type 1 immediate hypersensitivity reactions.[23]

‖ Studies had varying definitions for infections. Besarab 2016 reported on infections and infestations that were considered to be treatment-emergent adverse events.[3] Provenzano 2009 reported on cellulitis.[24]

Explanations

a. Studies were considered to have an unclear or high risk of bias because there were concerns with selection bias, lack of blinding, and/or attrition bias.

b. The confidence interval is extremely wide, suggesting the possibility of a significant benefit or a significant harm.

c. Studies were considered to have an unclear or high risk of bias because there were concerns with selection bias and lack of blinding.

d. Study was considered to have an unclear risk of bias because it was unclear how allocation concealment and blinding was addressed.

e. Study was considered to have a high risk of bias because there were concerns with the lack of blinding.

f. There were no events reported.

g. Study was considered to have an unclear risk of bias because it was unclear how participants were randomized and how allocation concealment was addressed.

h. Studies were considered to have a high risk of bias because there were concerns with selection bias and/or blinding.

i. Studies were considered to have a high risk of bias because there were concerns with the lack of blinding.

Table S7.
Population: Adults with anemia and CKD receiving hemodialysis
Intervention: I.v. iron dosing agents
Comparator: Oral iron dosing agents
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
Pediatric outcomes (growth, height, weight, and cognitive development) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Blood transfusions*											
2[22, 26]	randomized trials	serious[h]	not serious	not serious	extremely serious[b]	none	2/42 (4.8%)	3/68 (4.4%)	**RR 1.33** (0.24 to 7.47)	**15 more per 1,000** (from 34 fewer to 285 more)	⊕◯◯◯ Very low
Cancer†											
1[7]	randomized trials	serious[c]	not serious	not serious	extremely serious[e]	none	0/24 (0.0%)	0/12 (0.0%)	not estimable		⊕◯◯◯ Very low
ESA use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
ESA dose											
6[22, 25-29]	randomized trials	serious[a]	not serious	not serious	very serious[i]	none	Multiple measures suggesting no significant differences in ESA dose. See Table 1-5.				⊕◯◯◯ Very low
Reaching hemoglobin target‡											
2[3, 24]	randomized trials	serious[d]	serious[j]	not serious	very serious[k]	publication bias strongly suspected[l]	66/124 (53.2%)	40/128 (31.3%)	**RR 1.43** (0.80 to 2.57)	**134 more per 1,000** (from 62 fewer to 491 more)	⊕◯◯◯ Very low
Hemoglobin levels (follow-up: range 1 weeks to 12 weeks)											
3[3, 24, 29]	randomized trials	serious[g]	serious[j]	not serious	very serious[k]	none	196	194	-	MD **0.97 g/dL higher** (0.09 lower to 2.03 higher)	⊕◯◯◯ Very low
Hemoglobin levels (follow-up: range 13 weeks to 24 weeks)											
2[25, 26]	randomized trials	serious[f]	not serious	not serious	very serious[m]	none	29	29	-	MD **0.29 g/dL lower** (0.93 lower to 0.35 higher)	⊕◯◯◯ Very low
Hemoglobin levels (follow-up: range 25 weeks to 52 weeks)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
1[7]	randomized trials	serious[c]	not serious	not serious	very serious[n]	none	24	12	-	MD **3.4 g/dL higher** (2.97 higher to 3.83 higher)	⊕◯◯◯ Very low
Hemoglobin levels (follow-up: > 52 weeks)											
1[7]	randomized trials	serious[c]	not serious	not serious	very serious[n]	none	24	12	-	MD **4.9 g/dL higher** (4.5 higher to 5.3 higher)	⊕◯◯◯ Very low

CKD = chronic kidney disease; CI = confidence interval; IV = intravenous; MD = mean difference; RR = risk ratio

* Fishbane 1995 reported on patients who had significant bleeding episodes requiring transfusions.[22] In Warady 2004, children were eligible for a blood transfusion if their hematocrit was below 20% and not rising and/or the degree of anemia was considered clinically significant by their personal physician.[26]

† Fudin 1998 reported on withdrawals from study because of a malignancy.[7]

‡ Studies targeted an increase in hemoglobin of at least 1 g/dL from baseline.[3, 24]

Explanations

a. Studies were considered to have an unclear or high risk of bias because there were concerns with selection bias, lack of blinding, and/or attrition bias.

b. The confidence interval is extremely wide, suggesting the possibility of a significant benefit or a significant harm.

c. Study was considered to have an unclear risk of bias because it was unclear how allocation concealment and blinding was addressed.

d. Study was considered to have a high risk of bias because there were concerns with the lack of blinding.

e. There were no events reported.

f. Studies were considered to have a high risk of bias because there were concerns with selection bias and/or blinding.

g. Studies were considered to have a high risk of bias because there were concerns with the lack of blinding.

h. Studies were considered to have a high risk of bias because there were concerns with the lack of blinding and attrition bias.

i. Confidence intervals were very wide, suggesting the possibility of higher ESA doses and lower ESA doses with intravenous iron.

j. I-squared > 75%.

k. Confidence intervals were very wide, suggesting the possibility of significant benefit and some harm.

l. Only 2 of the 6 studies reporting on hemoglobin reported on reaching a hemoglobin target.

m. Confidence intervals were very wide, suggesting the possibility of some benefit and significant harm.

n. Confidence intervals were very wide but showed benefit.

Table S8.
Population: Adults with anemia and CKD not receiving dialysis or ESAs/HIF-PHIs
Intervention: Iron dosing agents
Comparator: Placebo
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
Mortality											
8[30-37]	randomized trials	not serious	not serious	not serious	extremely serious[a]	none	13/573 (2.3%)	17/400 (4.3%)	**RR 0.56** (0.28 to 1.13)	**19 fewer per 1,000** (from 31 fewer to 6 more)	⊕◯◯◯ Very low
Total cardiovascular events*											
6[30, 33, 34, 37, 38]	randomized trials	not serious	not serious	serious[b]	serious[c]	none	438/1475 (29.7%)	440/1332 (33.0%)	**RR 0.90** (0.77 to 1.06)	**33 fewer per 1,000** (from 76 fewer to 20 more)	⊕⊕◯◯ Low
Stroke											
1[32]	randomized trials	serious[d]	not serious	serious[e]	extremely serious[f]	none	0/28 (0.0%)	0/26 (0.0%)	not estimable		⊕◯◯◯ Very low
Heart failure†											
3[36-38]	randomized trials	not serious	not serious	not serious	extremely serious[g]	none	89/372 (23.9%)	105/338 (31.1%)	**RR 0.71** (0.26 to 1.96)	**90 fewer per 1,000** (from 230 fewer to 298 more)	⊕◯◯◯ Very low
Myocardial infarction											
1[34]	randomized trials	serious[h]	not serious	serious[i]	extremely serious[g]	none	0/117 (0.0%)	1/116 (0.9%)	**RR 0.33** (0.01 to 8.03)	**6 fewer per 1,000** (from 9 fewer to 61 more)	⊕◯◯◯ Very low
Quality of life											
4[30, 32, 38, 39]	randomized trials	not serious	serious[j]	serious[e]	serious[k]	none	Multiple measures showing either statistically significant benefit or no difference of effect.				⊕◯◯◯ Very low
Functional status											
5[30, 32, 36, 39, 40]	randomized trials	not serious	serious[j]	serious[e]	serious[k]	none	Multiple measures showing either statistically significant benefit or no difference of effect.				⊕◯◯◯ Very low
All-cause hospitalization											
3[30, 32, 36]	randomized trials	not serious	not serious	serious[e]	extremely serious[g]	none	15/176 (8.5%)	18/121 (14.9%)	**RR 0.40** (0.08 to 2.10)	**89 fewer per 1,000** (from 137 fewer to 164 more)	⊕◯◯◯ Very low
Total serious adverse events											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
8[33-38, 41, 42]	randomized trials	not serious	not serious	not serious	serious[c]	none	200/763 (26.2%)	199/642 (31.0%)	**RR 0.90** (0.77 to 1.04)	**31 fewer per 1,000** (from 71 fewer to 12 more)	⊕⊕⊕◯ Moderate
Serious gastrointestinal events											
3[33, 34, 42]	randomized trials	serious[l]	not serious	not serious	extremely serious[g]	none	4/267 (1.5%)	3/235 (1.3%)	**RR 0.97** (0.22 to 4.36)	**0 fewer per 1,000** (from 10 fewer to 43 more)	⊕◯◯◯ Very low
Serious hypersensitivity reactions											
1[32]	randomized trials	serious[d]	not serious	serious[e]	extremely serious[f]	none	0/26 (0.0%)	0/28 (0.0%)	not estimable		⊕◯◯◯ Very low
Infections‡											
9[30, 33-35, 37-39, 42, 43]	randomized trials	not serious	not serious	not serious	extremely serious[g]	none	83/790 (10.5%)	67/609 (11.0%)	**RR 0.89** (0.66 to 1.21)	**12 fewer per 1,000** (from 37 fewer to 23 more)	⊕◯◯◯ Very low

CI = confidence interval; RR = risk ratio

* Studies had varying definitions for total cardiovascular disease events. Block 2015 reported on treatment-emergent adverse cardiovascular events.[33] In Yokoyama 2014, congestive cardiac failure was listed as the only cardiac serious adverse event.[37] Fishbane 2017 reported on cardiac disorders as serious adverse events.[34] The FAIR-HF trial reported on cardiac disorders as adverse events.[30] The AFFIRM AHF trial reported on a composite of cardiovascular hospitalizations and cardiovascular death.[38]

† Studies had varying definitions for heart failure. Yokoyama 2014 reported on congestive heart failure as a serious adverse event.[37] The AFFIRM-AHF trial reported on heart failure hospitalizations.[38] Toblli 2007 reported on hospitalizations due to chronic heart failure.[36]

‡ Studies had varying definitions for infections. Yokoyama 2014 and Fishbane 2017 reported on infections that were coded as serious adverse events.[34, 37] Block 2015 and Pergola 2021 reported on treatment-emergent adverse infectious events.[33, 35] Mudge 2004 reported on infections (not further specified).[43] Singh 2006 reported on the number of infectious episodes by type of infection (peritonitis and catheter exit-site infections).[42] Greenwood 2023 reported on infectious adverse events, including pneumonia, urinary tract infections, septic shock, cellulitis, and genito-urinary infections.[39] The FAIR-HF trial reported on infections and infestations as adverse events.[30] The AFFIRM-AHF trial reported on serious infectious treatment-emergent adverse events.[38]

Explanations

a. The confidence interval is extremely wide, suggesting the possibility of a significant benefit or harm.

b. Outcome may not have been adequately captured and/or reported by the trials.

c. Confidence intervals are wide, precluding a conclusion.

d. Study was considered to have an unclear risk of bias because it was unclear if outcome assessors were blinded.

e. We did not identify any studies that compared oral iron with placebo and reported on this outcome.

f. There were no events reported.

g. The confidence interval is extremely wide, suggesting the possibility of a significant benefit or a significant harm.

h. Study was considered to have a high risk of bias because of concerns with attrition bias.

i. We did not identify any studies that compared intravenous iron with placebo and reported on this outcome.

j. Several measures of quality of life/functional status suggested a statistically significant positive effect of intravenous iron compared with placebo, but other measures did not.

k. Confidence intervals are wide.

l. Studies were considered to have an unclear to high risk of bias because there were concerns with randomization, blinding, and/or attrition bias.

Table S9.
Population: Adults with anemia and CKD not receiving dialysis or ESAs/HIF-PHIs
Intervention: Iron dosing agents
Comparator: Placebo
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
Pediatric outcomes (growth, height, weight, and cognitive development) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Blood transfusions - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Cancer											
1[32]	randomized trials	serious[a]	not serious	not serious	extremely serious[b]	none	0/26 (0.0%)	1/28 (3.6%)	**RR 0.36** (0.02 to 8.42)	**23 fewer per 1,000** (from 35 fewer to 265 more)	⊕◯◯◯ Very low
ESA use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
ESA dose											
1[44]	randomized trials	serious[d]	not serious	not serious	very serious[e]	none	Multiple measures suggesting either a reduction in or maintenance of ESA doses.				⊕◯◯◯ Very low
Reaching hemoglobin target*											
3[31, 34, 42]	randomized trials	serious[f]	serious[g]	not serious	serious[c]	publication bias strongly suspected[h]	115/217 (53.0%)	43/177 (24.3%)	**RR 1.90** (1.20 to 3.02)	**219 more per 1,000** (from 49 more to 491 more)	⊕◯◯◯ Very low
Hemoglobin values (follow-up: range 1 weeks to 12 weeks)											
11[32, 33, 35-39, 42, 44-46]	randomized trials	not serious	serious[g]	not serious	not serious	none	761	569	-	Range in pooled MD, 0.47 to 0.87 g/dL	⊕⊕⊕◯ Moderate
Hemoglobin values (follow-up: range 13 weeks to 24 weeks)											
5[34-36, 38, 44]	randomized trials	not serious	serious[g]	not serious	not serious	none	575	502	-	Range in pooled MD, 0.70 to 1.46	⊕⊕⊕◯ Moderate
Hemoglobin values (follow-up: range 25 weeks to 52 weeks)											
2[36, 38]	randomized trials	not serious	not serious	not serious	not serious	none	312	308	-	MD **0.7 g/dL higher** (0.42 higher to 0.98 higher)	⊕⊕⊕⊕ High

CI = confidence interval; MD = mean difference; RR = risk ratio

* All three studies reported on the same hemoglobin target: an increase in hemoglobin of at least 1 g/dL from baseline.[31, 34, 42]

Explanations

a. Study was considered to have an unclear risk of bias because it was unclear if outcome assessors were blinded.

b. The confidence interval is extremely wide, suggesting the possibility of a significant benefit or a significant harm.

c. Confidence intervals are wide.

d. Study was considered to have an unclear risk of bias because it was unclear if there was potential for selection bias and unclear if there was blinding.

e. There were multiple measures for ESA dose. Some of the confidence intervals were very wide, precluding a conclusion.

f. Studies were considered to have a high risk of bias because there were concerns with the lack of blinding and the potential for attrition bias.

g. I-squared was greater than 50%.

h. Among the 13 studies that reported on hemoglobin values, only three reported on reaching a hemoglobin target.

Table S10.
Population: Adults with anemia and CKD receiving peritoneal dialysis
Intervention: Iron dosing agents
Comparator: Placebo
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
Mortality - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Total cardiovascular events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Stroke - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Heart failure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Myocardial infarction - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Functional status - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
All-cause hospitalization – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Total serious adverse events*											
1[42]	randomized trials	serious[a]	not serious	serious[b]	extremely serious[c]	none	2/75 (2.7%)	2/46 (4.3%)	**RR 0.61** (0.09 to 4.21)	**17 fewer per 1,000** (from 40 fewer to 140 more)	⨁◯◯◯ Very low
Serious gastrointestinal adverse events*											
1[42]	randomized trials	serious[a]	not serious	serious[b]	extremely serious[c]	none	2/75 (2.7%)	2/46 (4.3%)	**RR 0.61** (0.09 to 4.21)	**17 fewer per 1,000** (from 40 fewer to 140 more)	⨁◯◯◯ Very low
Serious hypersensitivity reactions - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Infections[†]											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
1[42]	randomized trials	serious[a]	not serious	serious[b]	extremely serious[c]	none	6/75 (8.0%)	5/46 (10.9%)	**RR 0.74** (0.24 to 2.28)	**28 fewer per 1,000** (from 83 fewer to 139 more)	⨁◯◯◯ Very low

CI: confidence interval; **RR:** risk ratio

* Singh 2006 described episodes of peritonitis as serious adverse events.[42]

† Singh 2006 reported on different types of infections separately. In this table, we are reporting the results for episodes of peritonitis. Results for catheter exit-site infections yield similar conclusions.

Explanations

a. Study was considered to have a high risk of bias because there were concerns with randomization, attrition bias, and reporting bias.

b. We did not identify any studies that compared oral iron with placebo and reported on this outcome.

c. Confidence intervals are extremely wide, suggesting the possibility of a benefit and a harm.

Table S11.
Population: Adults with anemia and CKD receiving peritoneal dialysis
Intervention: Iron dosing agents
Comparator: Placebo
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron dosing agents	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)	
Pediatric outcomes (growth, height, weight, and cognitive development - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Blood transfusions - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
ESA use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
ESA dose											
1[44]	randomized trials	serious[d]	not serious	not serious	very serious[e]	none	Multiple measures suggesting either a reduction in or maintenance of ESA doses.				⨁◯◯◯ Very low
Reaching hemoglobin target*											
1[42]	randomized trials	serious[a]	not serious	serious[b]	serious[e]	none	39/66 (59.1%)	10/30 (33.3%)	**RR 1.77** (1.03 to 3.06)	**257 more per 1,000** (from 10 more to 687 more)	⨁◯◯◯ Very low
Hemoglobin values (follow-up: range 1 weeks to 12 weeks)											
2[42, 44]	randomized trials	serious[f]	not serious	not serious	very serious[e]	none	91	42	-	Range in MD, 0.60 to 1.09 g/dL[†]	⨁◯◯◯ Very low
Hemoglobin values (follow-up: range 13 weeks to 24 weeks)											
1[44]	randomized trials	serious[d]	not serious	not serious	very serious[e]	none	25	12	-	Range in MD, 0.30 to 2.00 g/dL[†]	⨁◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
* Singh 2006 reported on the percent of patients who experienced an increase in hemoglobin of at least 1 g/dL from baseline.[42]
† Because one of the studies is a multi-arm study, we are unable to provide an overall summary estimate of the effects on any modality of iron dosing agent compared with placebo. The mean difference in hemoglobin values at 12 weeks was 0.60 g/dL (95% CI, -0.70 to 1.90) comparing oral iron with placebo and was 1.09 g/dL (95% CI, -0.36 to 2.54) comparing intravenous iron with placebo. The mean difference in hemoglobin values at 16 weeks was 0.30 g/dL (95% CI, -0.84 to 1.44) comparing oral iron with placebo and was 2.00 g/dL (95% CI, 0.91 to 3.09) comparing intravenous iron with placebo.
Explanations
a. Study was considered to have a high risk of bias because there were concerns with randomization and attrition bias.

b. We did not identify any studies that compared oral iron with placebo and reported on this outcome.
c. There were fewer than 5 events among all the participants in the included trial. The total number of events is much lower than the number needed to reach the optimal information size (i.e., 300).
d. Study was considered to have an unclear risk of bias because it was unclear if there was potential for selection bias and unclear if there was blinding.
e. Confidence intervals were wide.
f. Studies were considered to have an unclear to high risk of bias. There were concerns with the potential for selection bias, attrition bias, detection bias, and reporting bias.

Table S12.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: I.v. iron dosing agents
Comparator: Oral iron dosing agents
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
Mortality											
8[47-54]	randomized trials	serious[a]	not serious	not serious	extremely serious[b]	none	27/964 (2.8%)	20/816 (2.5%)	**RR 1.17** (0.64 to 2.15)	**4 more per 1,000** (from 9 fewer to 28 more)	⊕◯◯◯ Very low
Total cardiovascular events*											
3[47, 50, 52]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	26/518 (5.0%)	22/484 (4.5%)	**RR 1.13** (0.65 to 1.99)	**6 more per 1,000** (from 16 fewer to 45 more)	⊕◯◯◯ Very low
Stroke†											
3[47, 50, 52]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	2/518 (0.4%)	1/484 (0.2%)	**RR 1.15** (0.16 to 23.70)	**0 fewer per 1,000** (from 2 fewer to 47 more)	⊕◯◯◯ Very low
Heart failure‡											
3[47, 50, 52]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	6/523 (1.1%)	5/484 (1.0%)	**RR 1.13** (0.30 to 4.25)	**1 more per 1,000** (from 7 fewer to 34 more)	⊕◯◯◯ Very low
Myocardial infarction§											
3[47, 50, 52]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	11/523 (2.1%)	13/489 (2.7%)	**RR 0.86** (0.40 to 1.87)	**4 fewer per 1,000** (from 16 fewer to 23 more)	⊕◯◯◯ Very low
Quality of life											
5[47, 49, 50, 54, 55]	randomized trials	serious[d]	not serious	not serious	extremely serious[b]	none	Multiple measures suggesting no statistically significant difference. See Figure 8 and Table 5.				⊕◯◯◯ Very low
Functional status - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
All-cause hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Total serious adverse events											
9[47-50, 52, 54, 56-58]	randomized trials	serious[e]	not serious	not serious	extremely serious[b]	none	148/1155 (12.8%)	126/901 (14.0%)	**RR 0.97** (0.74 to 1.28)	**4 fewer per 1,000** (from 36 fewer to 39 more)	⊕◯◯◯ Very low
Serious gastrointestinal events‖											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
5[47, 49, 50, 52, 53]	randomized trials	serious[c]	serious[f]	not serious	extremely serious[b]	none	9/768 (1.2%)	12/624 (1.9%)	**RR 0.39** (0.06 to 2.59)	**12 fewer per 1,000** (from 18 fewer to 31 more)	⊕◯◯◯ Very low
Serious hypersensitivity reactions¶											
6[48-50, 53, 58, 59]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	5/831 (0.6%)	2/586 (0.3%)	**RR 1.62** (0.20 to 12.93)	**2 more per 1,000** (from 3 fewer to 41 more)	⊕◯◯◯ Very low
Infections**											
4[47, 50, 52, 60]	randomized trials	serious[c]	not serious	not serious	very serious[g]	none	153/574 (26.7%)	134/540 (24.8%)	**RR 1.12** (0.92 to 1.36)	**30 more per 1,000** (from 20 fewer to 89 more)	⊕◯◯◯ Very low

CKD = chronic kidney disease; CI = confidence interval; IV = intravenous; RR = risk ratio

* Studies had varying definitions for total cardiovascular disease events. Qunibi 2011 reported on total severe cardiovascular adverse events.[52] Agarwal 2015 reported on cardiovascular adverse events.[47] The FIND-CKD trial reported on cardiac disorders as serious adverse events.[50]

† Studies had varying definitions for stroke. Agarwal 2015 and the FIND-CKD trial reported on stroke.[47, 50] Qunibi 2011 reported on cerebrovascular accident.[52]

‡ Studies had varying definitions for heart failure. Agarwal 2015 reported on congestive heart failure as a serious adverse event.[47] The FIND-CKD trial reported on cardiac failure.[50] Qunibi 2011 reported on congestive cardiac failure.[52]

§ Studies had varying definitions for myocardial infarction. Agarwal 2015 reported on myocardial infarction as serious adverse event.[47] The FIND-CKD trial reported on acute myocardial infarction.[50] Qunibi 2011 reported on myocardial infarction or myocardial ischemia.[52]

‖ Studies had varying definitions for serious gastrointestinal adverse events. Stoves 2001 reported on withdrawals from trial due to severe constipation.[53] Kalra 2016 reported an episode of serious esophagitis.[49] Qunibi 2011 reported on participants who experienced serious adverse event of a gastrointestinal outcome, such as gastrointestinal hemorrhage or intestinal hemorrhage.[52] The FIND-CKD trial reported on gastrointestinal disorders as serious adverse events.[50] Agarwal 2015 reported on transfusions due to a gastrointestinal bleed.[47]

¶ Studies had varying definitions of serious hypersensitivity reactions. Stoves 2001 reported on withdrawals from trial due to allergic reactions.[53] Kalra 2016 did not define hypersensitivity reactions.[49] The FIND-CKD trial reported on rash that was considered to be a serious adverse event.[50] Arogundade 2013 reported on severe anaphylaxis.[59] Charytan 2005 reported on hypersensitivity reactions, including anaphylaxis, rash, urticaria, asthma, bronchospasm, hypotension, pruritus, or shortness of breath, that was related to the study drugs.[48] Spinowitz 2008 treatment-related serious injection-site swelling.[58]

** Studies had varying definitions for infections. Mudge 2012 reported on infectious episodes and results of subsequent microbiological investigations.[60] Qunibi 2011 reported on infections and infestations as adverse events, including bronchitis, upper respiratory tract infection, and urinary tract infection.[52] The FIND-CKD trial and Agarwal 2015 reported on infectious adverse events.[47, 50]

Explanations

a. Studies were considered to have a high risk of bias because of concerns with attrition bias.

b. The confidence interval is extremely wide, suggesting the possibility of a significant benefit or a significant harm.

c. Studies were considered to have a high risk of bias because of concerns with lack of blinding and/or attrition bias.

d. Studies were considered to have an unclear or high risk of bias because of concerns with lack of blinding, attrition bias, and/or selective outcome reporting.

e. Studies were considered to have an unclear or high risk of bias because of concerns with randomization, allocation concealment, lack of blinding, and/or attrition bias.

f. I-squared > 50%.

g. The confidence interval was very wide, precluding a conclusion.

Table S13.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: I.v. iron dosing agents
Comparator: Oral iron dosing agents
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
Pediatric outcomes (growth, height, weight, and cognitive development) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Blood transfusions*											
4[47, 50, 60, 61]	randomized trials	serious[d]	not serious	not serious	extremely serious[a]	none	40/445 (9.0%)	47/446 (10.5%)	**RR 0.86** (0.58 to 1.28)	**15 fewer per 1,000** (from 44 fewer to 30 more)	⊕◯◯◯ Very low
Cancer[†]											
3[47, 50, 52]	randomized trials	serious[b]	not serious	not serious	extremely serious[a]	none	14/518 (2.7%)	4/484 (0.8%)	**RR 2.59** (0.59 to 11.39)	**13 more per 1,000** (from 3 fewer to 86 more)	⊕◯◯◯ Very low
ESA use[‡]											
5[47, 51, 57, 60, 61]	randomized trials	serious[d]	not serious	not serious	extremely serious[a]	none	28/225 (12.4%)	33/252 (13.1%)	**RR 0.78** (0.50 to 1.22)	**29 fewer per 1,000** (from 65 fewer to 29 more)	⊕◯◯◯ Very low
ESA dose											
6[47, 50, 53, 58, 61, 62]	randomized trials	serious[c]	not serious	not serious	extremely serious[e]	none	Multiple measures suggesting no statistically significant difference in ESA dose.				⊕◯◯◯ Very low
Reaching hemoglobin target[§]											
7[48, 50, 52-54, 57, 58]	randomized trials	serious[b]	not serious	not serious	not serious	publication bias strongly suspected[f]	408/859 (47.5%)	231/704 (32.8%)	**RR 1.48** (1.23 to 1.77)	**158 more per 1,000** (from 75 more to 253 more)	⊕⊕◯◯ Low
Hemoglobin values (follow-up: range 1 weeks to 12 weeks)											
10[44, 47, 49, 52, 54-58, 62]	randomized trials	serious[c]	not serious	not serious	not serious	none	869	602	-	MD **0.45 g/dL higher** (0.29 higher to 0.62 higher)	⊕⊕⊕◯ Moderate
Hemoglobin values (follow-up: range 13 weeks to 24 weeks)											
2 [44, 47]	randomized trials	serious[c]	very serious[g]	not serious	extremely serious[a]	none	79	82	-	MD **0.91 g/dL higher** (0.45 lower to 2.27 higher)	⊕◯◯◯ Very low
Hemoglobin values (follow-up: range 25 weeks to 52 weeks)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute (95% CI)	
3[44, 47, 51]	randomized trials	serious[b]	not serious	not serious	serious[h]	none	263	419	-	MD **0.27 g/dL higher** (0.05 higher to 0.48 higher)	⊕⊕◯◯ Low
Hemoglobin values (follow-up: > 52 weeks)											
1[47]	randomized trials	serious[b]	not serious	not serious	serious[h]	none	67	69	-	MD **0.3 g/dL higher** (0.07 higher to 0.53 higher)	⊕⊕◯◯ Low

CKD = chronic kidney disease; CI = confidence interval; IV = intravenous; MD = mean difference; RR = risk ratio

* Studies had varying indications for a blood transfusion. In Mudge 2012, blood transfusions were indicated for hemoglobin concentrations ≤ 6.5 g/dL, intra- or postoperative hemorrhage resulting in hemodynamic instability, a decrease in hemoglobin concentration ≥ 3 g/dL, or at the treating clinician's discretion if symptomatic for anemia.[60] Blood transfusions were not allowed during the first 8 weeks after randomization in the FIND-CKD trial.[50] Additional anemia management, including blood transfusions, were allowed after the first 8 weeks of treatment if the hemoglobin concentration decreased to < 10 g/dL. Nagaraju 2013 and Agarwal 2015 did not specify the criteria for blood transfusion.[47, 61]

† Studies had varying definitions of cancer. Qunibi 2011 reported on ovarian cancer and colon cancer.[52] The FIND-CKD trial reported on benign and malignant neoplasms.[50] Agarwal 2015 reported on new cancer diagnoses.[47]

‡ Studies had different indications for adding ESA therapy. In Mudge 2012, ESA was indicated if hemoglobin concentrations was ≤ 9 g/dL.[60] A weekly dose of 0.5 µg/kg subcutaneous darbepoetin alfa was administered. In Pisani 2015, 4% of the participants randomized to ferric gluconate and 5% of the participants randomized to liposomal iron were taking an ESA at baseline.[57] The ESA dose was increased if hemoglobin values were < 10 g/dL. In Nagaraju 2013, 27% of the participants randomized to iron sucrose and 39% of the participants randomized to heme iron polypeptide were on an ESA at baseline.[61] ESA administration was started if hemoglobin was < 10 g/dL and the participant was iron replete (transferrin saturation 20-50% and ferritin 100-500 ng/dL). In Agarwal 2015, ESA were administered to maintain a target hemoglobin between 10 and 12 g/dL.[47] McMahon 2010 did not report the criteria for when an ESA would be administered.[51]

§ Studies used different hemoglobin targets. Charytan 2005 targeted a hemoglobin concentration over 11.0 g/dL.[48] The mean baseline hemoglobin value was 9.8 g/dL among those randomized to intravenous iron and was 9.7 g/dL among those randomized to oral iron. Stoves 2011 reported on the number of people who reached a hemoglobin level > 12 g/dL during the first 3 months of treatment.[53] The median baseline hemoglobin value was 9.9 g/dL among those randomized to intravenous iron and was 9.7 g/dL among those randomized to oral iron. Qunibi 2011, the FIND-CKD trial, and Spinowitz 2008 targeted an increase in hemoglobin of at least 1 g/dL from baseline.[50, 52, 58] In Quinibi 2011, the mean baseline hemoglobin value was 10.1 g/dL among those randomized to intravenous iron and was 10.0 g/dL among those randomized to oral iron.[52] In the FIND-CKD trial, the mean baseline hemoglobin value was 10.3 to 10.5 g/dL among those randomized to the intravenous iron arms and was 10.4 g/dL among those randomized to placebo.[50] In Spinowitz 2008, the mean baseline hemoglobin value was 9.96 g/dL among those randomized to intravenous iron and was 9.96 g/dL among those randomized to oral iron.[58] Pisani 2015 targeted an increase in hemoglobin of at least 0.6 g/dL from baseline.[57] The mean baseline hemoglobin value was 10.7 g/dL among those randomized to intravenous iron and was 10.8 g/dL among those randomized to placebo. Van Wyck 2005 reported on two different criteria for hemoglobin targets: (1) an increase of hemoglobin ≥ 1 g/dL and (2) a hemoglobin level ≥ 11 g/dL.[54] The data in this figure uses the first criterion for the hemoglobin target for Van Wyck 2005.

Table S14.
Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: Placebo
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality*, all-cause (follow-up: range 6 weeks to 52 weeks)											
10[63-72]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	38/1348 (2.8%)	47/577 (8.1%)	**RR 0.37** (0.24 to 0.56)	**51 fewer per 1,000** (from 62 fewer to 36 fewer)	⊕⊕◯◯ Low
Cardiovascular disease, heart failure (follow-up: range 6 weeks to 52 weeks)											
2[63, 67]	randomized trials	serious[a,c]	not serious	not serious	very serious[d]	none	10/691 (1.4%)	6/332 (1.8%)	**RR 0.79** (0.29 to 2.16)	**4 fewer per 1,000** (from 13 fewer to 21 more)	⊕◯◯◯ Very low
Cardiovascular disease, acute coronary syndrome (follow-up: range 6 weeks to 52 weeks)											
4[63, 64, 67, 68]	randomized trials	very serious[e]	not serious	not serious	very serious[d]	none	6/839 (0.7%)	3/361 (0.8%)	**RR 0.87** (0.22 to 3.50)	**1 fewer per 1,000** (from 6 fewer to 21 more)	⊕◯◯◯ Very low
Cardiovascular disease, stroke - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thromboembolism (other timepoints)											
4[68, 73-75]	randomized trials	serious[f]	serious[g]	not serious	serious[h]	none	20/1604 (1.2%)	32/1623 (2.0%)	**RR ranged from** 0.47 to 4.68	see comment 1	⊕◯◯◯ Very low
Vascular access thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hospitalization, all-cause - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events, total (follow-up: range 6 weeks to 52 weeks)											
10[63-72]	randomized trials	serious[a]	serious[i]	not serious	serious[b]	none	7/1310 (0.5%)	121/577 (21.0%)	**RR 1.17** (0.91 to 1.51)	**36 more per 1,000** (from 19 fewer to 107 more)	⊕◯◯◯ Very low
Quality of life											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	placebo	Relative (95% CI)	Absolute (95% CI)	
2[67, 74]	randomized trials	serious[k]	not serious	serious[l]	not serious	none	1890	1540	-	**Range in mean differences** across selected subdomains of SF-36, 0.44 to 0.88; see comment 2	⨁⨁◯◯ Low
Functional assessment - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; HIF-PHI: hypoxia-inducible factor–prolyl hydroxylase domain inhibitors; RR: risk ratio; SF-36: Short Form-36

Explanations

a. Five of the 10 studies had a high risk of bias in at least one domain; eight of the 10 studies did not provide sufficient detail to assess at least one domain.
b. Less than 300 participants experienced this event.
c. Both studies had a high risk of bias in one domain; one study did not provide sufficient detail to assess two domains.
d. Less than 30 participants experienced this event
e. Three of the four studies had a high risk of bias in at least one domain; one study did not provide sufficient detail to assess half of the domains.
f. Sufficient detail was not provided to assess three domains.
g. Outcome reported at end of followup; followup surpassed end of treatment.
h. Small single study with less than 300 participants in the active arm, and less than 30 participants in the placebo arm.
i. Outcome assessors were not blinded.
j. While all confidence intervals crossed 1, the studies reported a wide range of total serious adverse events across the studies.
k. In one study, blinding of participants and outcome assessors was not reported; all other domains had a low risk of bias. Low risk of bias in the second study.
l. Studies only reported on selected domains of quality of life; not all aspects of quality of life may have been captured.
* Note on mortality: There are few events, but the results show a clear benefit

Comments

1. Thromboembolism was reported at end of followup in two studies and at 16 weeks in one study. End of followup surpassed the treatment period; these data was not pooled.
2. Quality of life, SF-36 physical function was reported in one study, and SF-36 vitality in two studies: data were not amenable to pooling.

Table S15.
Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: Placebo
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	Placebo	Relative (95% CI)	Absolute (95% CI)	
Receiving blood transfusion (follow-up: mean 6 weeks)											
5[66, 68, 70, 72, 74]	randomized trials	serious[a]	not serious	not serious	not serious	none	180/1726 (10.4%)	322/1512 (21.3%)	**RR 0.55** (0.46 to 0.65)	**96 fewer per 1,000** (from 115 fewer to 75 fewer)	⊕⊕⊕◯ Moderate
Hypertension (follow-up: range 4 weeks to 8 weeks)											
7[64-68, 70, 72]	randomized trials	serious[b]	not serious	not serious	serious[c]	none	133/1110 (12.0%)	36/501 (7.2%)	**RR 1.37** (0.65 to 2.86)	**27 more per 1,000** (from 25 fewer to 134 more)	⊕⊕◯◯ Low
Change in blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mean change in hemoglobin (up to 12 weeks)											
7[63, 65, 69, 71, 74-76]	randomized trials	not serious	very serious[d]	not serious	serious[c]	none	1833	1478	-	**MD ranged from** 0.74 g/dL to 2.30 g/dL	⊕◯◯◯ Very low
Mean change in hemoglobin (12 to 28 weeks)											
3[63, 74, 75]	randomized trials	serious[e]	not serious	not serious	not serious	none	1515	1267	-	MD **1.36 g/dL higher** (1.25 higher to 1.46 higher)	⊕⊕⊕◯ Moderate
Mean change in hemoglobin (52 weeks to end of treatment)											
2[74, 75]	randomized trials	serious[e]	not serious	not serious	serious[c]	none	1393	1123	-	MD **1.31 g/dL higher** (0.96 higher to 1.65 higher)	⊕⊕◯◯ Low
Participants reaching hemoglobin target											
9[65-67, 69, 70, 72-75]	randomized trials	serious[f]	very serious[d]	not serious	not serious	none	1236/2947 (41.9%)	200/903 (22.1%)	**RR ranged from** 1.07 to 30.78	-	⊕◯◯◯ Very low
Cancer – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
CKD-related measures, progression of CKD											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	Placebo	Relative (95% CI)	Absolute (95% CI)	
1[67]	randomized trials	serious[g]	not serious	not serious	very serious[h]	none	11/611 (1.8%)	5/305 (1.6%)	**RR 1.01** (2.49 to 10.19)	**0 fewer per 1,000** (from 24 more to 151 more)	⨁◯◯◯ Very low
CKD-related measures, progression to ESKD											
2[65, 67]	randomized trials	serious[i]	not serious	not serious	serious[j]	none	48/712 (6.7%)	15/356 (4.2%)	**RR 1.21** (0.68 to 2.18)	**9 more per 1,000** (from 13 fewer to 50 more)	⨁⨁◯◯ Low
IV iron use											
3[66, 67, 72, 74]	randomized trials	serious[k]	not serious	not serious	very serious[h]	none	20/813 (2.5%)	15/407 (3.7%)	**RR 0.54** (0.27 to 1.07)	**17 fewer per 1,000** (from 27 fewer to 3 more)	⨁◯◯◯ Very low
Oral iron use											
2[72, 74]	randomized trials	serious[l]	serious[m]	not serious	not serious	none	821/1520 (54.0%)	769/1449 (53.1%)	**RR ranged from** 1.01 to 1.13	not estimable	⨁⨁◯◯ Low
IV or oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; CKD: chronic kidney disease; ESKD: end-stage kidney disease; HIF-PHI: hypoxia-inducible factor–prolyl hydroxylase domain inhibitors; IV: intravenous; RR: risk ratio

Explanations

a. At least one study had high risk of bias in one of the following domains: blinding of outcome assessors, intention to treat analysis. More than one study did not describe at least one of the following domains: allocation concealment, blinding of participants, blinding of the outcome assessor.

b. At least one study had high risk of bias in one of the following domains: allocation concealment, blinding of participants, blinding of outcome assessors, intention to treat analysis. More than one study did not describe at least one of the following domains: allocation concealment, blinding of participants, blinding of the outcome assessor.

c. Wide confidence intervals across studies and the pooled analysis

d. Unable to pool results due to considerable statistical heterogeneity (I-squared > 75%).

e. One study did not blind the outcome assessor, and there was unequal withdrawal from the study across arms.

f. At least three studies had high risk of bias in the following domains: incomplete outcome reporting, intention to treat analysis. One study in each of the following domains had a high risk of bias: blinding of the participants, blinding of the outcome assessor. At least two studies each did not describe the following domains: randomizations, allocation concealment blinding of the participants.

g. Study had a high risk of bias in the incomplete outcome reporting domain.

h. Sum of participants with event less than 50

i. One study had high risk of bias in incomplete outcome reporting. One study did not describe randomization, allocation concealment, or blinding of outcome assessors.

j. Less than 300 participants experienced this event.

k. One study each had a high risk of bias in the following domains: blinding of the participants, blinding of the outcome assessor, and intention to treat analysis. Randomization, allocation concealment, and blinding of participants was not described in at least one study each.

l. One study each had a high risk of bias in the blinding of outcome assessors, and intention to treat domains. One study did not describe randomization, allocation concealment, or blinding of participants.

m. Iron use is recorded as widely different in the placebo arms.

Table S16.
Population: People with anemia and CKD receiving dialysis
Intervention: HIF-PHI
Comparator: Placebo
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality, all cause (follow-up: range 4 weeks to 8.1 weeks)											
4[64, 70, 77, 78]	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	0/238 (0.0%)	0/58 (0.0%)	not estimable		⨁◯◯◯ Very low
Cardiovascular events, heart failure (follow-up: mean 4.1 weeks)											
1[78]	randomized trials	very serious[c]	not serious	not serious	extremely serious[b]	none	2/84 (2.4%)	0/19 (0.0%)	**RR 1.18** (0.06 to 23.56)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low
Thromboembolism - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis (follow-up: mean 4.1 weeks)											
1[78]	randomized trials	very serious[c]	not serious	not serious	extremely serious[b]	none	0/84 (0.0%)	1/19 (5.3%)	**RR 0.08** (0.00 to 1.89)	**48 fewer per 1,000** (from -- to 47 more)	⨁◯◯◯ Very low
Hospitalization, all-cause - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events, total (follow-up: range 4 weeks to 8 weeks)											
5[64, 70, 77-79]	randomized trials	very serious[d]	not serious	not serious	very serious[e]	none	13/205 (6.3%)	4/63 (6.3%)	**RR 0.85** (0.29 to 2.47)	**10 fewer per 1,000** (from 45 fewer to 93 more)	⨁◯◯◯ Very low
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Functional assessment - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase domain inhibitors RR: risk ratio
Explanations:
a. All studies had at least one domain with a high risk of bias and at least one domain that was insufficiently described.
b. Less than 5 participants experienced this event.
c. Blinding of participants and assessors was not described.
d. Four studies had at least one domain with a high risk of bias; four studies had at least two domains that were insufficiently described.

e. Less than 30 participants experienced this event.

Table S17.
Population: People with anemia and CKD receiving dialysis
Intervention: HIF-PHI
Comparator: Placebo
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	Placebo	Relative (95% CI)	Absolute (95% CI)	
Receiving blood transfusion (follow-up: mean 6 weeks)											
1[70]	randomized trials	serious[a]	not serious	not serious	extremely serious[b]	none	1/84 (1.2%)	3/14 (21.4%)	**RR 0.06** (0.01 to 0.50)	**201 fewer per 1,000** (from 212 fewer to 107 fewer)	⊕◯◯◯ Very low
Hypertension (follow-up: range 4 weeks to 8 weeks)											
2[64, 77]	randomized trials	very serious[c]	not serious	not serious	extremely serious[b]	none	2/109 (1.8%)	0/24 (0.0%)	**RR 4.87** (0.01 to 2712.50)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low
Change in blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mean change in hemoglobin (up to 6 weeks)											
2[77, 80]	randomized trials	not serious	not serious	not serious	serious[d]	none	38	37	-	MD **1.86 mg/dL higher** (1.45 higher to 2.27 higher)	⊕⊕⊕◯ Moderate
Participants reaching hemoglobin target											
4[64, 70, 77, 78]	randomized trials	very serious[e]	not serious	not serious	extremely serious[b]	none	0/238 (0.0%)	0/58 (0.0%)	not pooled	see comment	⊕◯◯◯ Very low
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
CKD-related measures - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV or oral iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV or oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; HIF-PHI = Hypoxia-inducible factor–prolyl hydroxylase domain inhibitors; MD: mean difference; RR: risk ratio
Explanations:
a. Study is limited overall by small sample size and short followup period of 6 weeks.
b. Less than 5 participants experienced this event.

c. Both studies either did not, or poorly described blinding of outcome assessors; one study did not blind participants; one study each included concerns about allocation concealment, and selective outcome reporting.
d. Wide confidence intervals.
e. Information regarding allocation concealment was not provided in three studies; two studies had high or unclear risk of bias in regards to blinding of participants, risk of bias about blinding of outcome assessors was either unclear or high; one study had selective reporting bias.
Comment:
Four studies reported zero events in both study arms.

Table S18.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	ESAs	Relative (95% CI)	Absolute (95% CI)	
Mortality											
21[66, 68, 76, 81-97]	randomized trials	serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	1018/7748 (13.1%)	994/7125 (14.0%)	**RR 1.01** (0.94 to 1.10)	**1 more per 1,000** (from 8 fewer to 14 more)	⨁◯◯◯ Very low
Cardiovascular events, heart failure											
6[81, 82, 85, 92, 94]	randomized trials	serious[d]	not serious	not serious	very serious[e]	publication bias strongly suspected[f]	40/1457 (2.7%)	44/1374 (3.2%)	**RR 0.84** (0.55 to 1.29)	**5 fewer per 1,000** (from 14 fewer to 9 more)	⨁◯◯◯ Very low
Cardiovascular events, acute coronary syndrome											
13[68, 81, 83-85, 87, 92, 93, 95, 96, 98]	randomized trials	serious[g]	not serious	not serious	very serious[e]	publication bias strongly suspected[h]	168/3848 (4.4%)	173/3283 (5.3%)	**RR 0.91** (0.74 to 1.12)	**5 fewer per 1,000** (from 14 fewer to 6 more)	⨁◯◯◯ Very low
Cardiovascular events, MACE											
6[83, 86, 87, 95, 96, 98]	randomized trials	serious[i]	not serious	not serious	serious[b]	publication bias strongly suspected[j]	438/2234 (19.6%)	425/1906 (22.3%)	**RR 0.96** (0.86 to 1.08)	**9 fewer per 1,000** (from 31 fewer to 18 more)	⨁◯◯◯ Very low
									HR 0.94 (0.85 to 1.04)		
Cardiovascular events, stroke											
11[68, 81-83, 85, 87, 92, 94-96, 98]	randomized trials	serious[k]	not serious	not serious	very serious[e]	publication bias strongly suspected[l]	67/4329 (1.5%)	72/3904 (1.8%)	**RR 0.90** (0.63 to 1.27)	**2 fewer per 1,000** (from 7 fewer to 5 more)	⨁◯◯◯ Very low
Thromboembolism, pulmonary embolism											
3[84, 87, 95]	randomized trials	not serious	serious[m]	not serious	very serious[n]	publication bias strongly suspected[o]	7/1844 (0.4%)	8/1710 (0.5%)	**RR 0.95** (0.32 to 2.85)	**0 fewer per 1,000** (from 3 fewer to 9 more)	⨁◯◯◯ Very low
Thromboembolism, DVT											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	ESAs	Relative (95% CI)	Absolute (95% CI)	
3[81, 87, 95]	randomized trials	serious[p]	not serious	not serious	very serious[e]	publication bias strongly suspected[q]	28/2007 (1.4%)	19/1999 (1.0%)	**RR 1.39** (0.77 to 2.50)	**4 more per 1,000** (from 2 fewer to 14 more)	⊕◯◯◯ Very low
Vascular access thrombosis (follow-up: range 52 weeks to 156 weeks)											
5[85, 87, 88, 94, 95]	randomized trials	serious[r]	very serious[s]	not serious	serious[t]	publication bias strongly suspected[u]	279/3063 (9.1%)	268/2920 (9.2%)	**RR range**, 0.83 to 1.84		⊕◯◯◯ Very low
Hospitalization, all-cause (follow-up: mean 104 weeks)											
1[88]	randomized trials	very serious[v]	not serious	not serious	serious[w]	none	195/414 (47.1%)	190/420 (45.2%)	**RR 1.04** (0.90 to 1.21)	**18 more per 1,000** (from 45 fewer to 95 more)	⊕◯◯◯ Very low
Serious adverse events, total (follow-up: range 6 weeks to 130 weeks)											
15[66, 68, 81-85, 87, 88, 91-93, 95, 96, 97]	randomized trials	serious[x]	not serious	not serious	serious[b]	publication bias strongly suspected[y]	1603/4120 (38.9%)	1455/3561 (40.9%)	**RR 1.02** (0.95 to 1.09)	**8 more per 1,000** (from 20 fewer to 37 more)	⊕◯◯◯ Very low
Quality of life											
1[88]	randomized trials	very serious[z]	not serious	not serious	not serious	none	386	397	see comment		⊕⊕◯◯ Low

CI = confidence interval; DVT = deep vein thrombosis; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MACE = major adverse cardiovascular events; RR = risk ratio

* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.

Explanations

a. Eight studies did not blind outcome assessors; eight experienced attrition bias, Seventeen of the 21 studies did not blind participants to the intervention, this is common across studies as the mode of administration for the two interventions is different, ESAs (injected), HIF-PHI (oral).

b. The confidence interval indicates that there may be a clinically important increase or decrease in this outcome.

c. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES study but not reported in the published literature.

d. One third of the studies did not blind outcome assessors; two had attrition bias.

e. Number of events less than 300; with a wide confidence interval.

f. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES, PYRENESE, and ASCEND-D studies but not reported in the published literature.

g. Nine studies did not blind outcome assessors. Two studies each had high risk of bias for attrition bias, not conducting intention to treat analyses. Nine studies did not blind participants to the intervention, this is common across studies as the mode of administration for the two interventions is different, ESAs (injected), HIF-PHI (oral).

h. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES, and PYRENESE studies but not reported in the published literature.

i. Three studies did not blind outcome assessors. Two studies each had high risk of bias for attrition bias, not conducting intention to treat analyses. Three studies did not blind participants to the intervention, this is common across studies as the mode of administration for the two interventions is different, ESAs (injected), HIF-PHI (oral).

j. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES, PYRENESE, SIERRAS, and HYMALAYAS studies but not reported in the published literature

k. Six studies did not blind outcome assessors. Three studies had high risk of bias for attrition bias. Six studies did not blind participants to the intervention, this is common across studies as the mode of administration for the two interventions is different, ESAs (injected), HIF-PHI (oral).
l. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES and PYRENESE studies but not reported in the published literature
m. Studies exhibit effects both in favor of HIF-PHIs and ESAs.
n. Number of events <30 with a wide confidence interval.
o. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES, PYRENESE, SIERRAS, and HYMALAYAS studies but not reported in the published literature.
p. Two studies did not blind participants or outcome assessors. One study exhibited incomplete outcome reporting.
q. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES, PYRENESE, and HYMALAYAS studies but not reported in the published literature.
r. Four studies did not blind outcome assessors. Three studies had high risk of bias for attrition bias. Four studies did not blind participants to the intervention, this is common across studies as the mode of administration for the two interventions is different, ESAs (injected), HIF-PHI (oral).
s. Unable to pool results, I-squared > 75%.
t. Range in risk ratio is large.
u. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES, study but not reported in the published literature.
v. This study only described randomization procedures, and had a low risk of selection bias. All other domains were high risk of bias.
w. The confidence interval indicates that there may be a clinically important increase or decrease in this outcome in a single study.
x. Nine studies did not blind outcome assessors. Four studies each had attrition bias. Two studies each selectively reported outcomes, or did not conduct an intention to treat analysis, Nine studies did not blind participants to the intervention, this is common across studies as the mode of administration for the two interventions is different, ESAs (injected), HIF-PHI (oral).
y. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES study but not reported in the published literature
z. Single study that did not blind participants or outcome assessors, exhibited both incomplete outcome reporting and selective outcome reporting, and did not conduct an intention-to-treat analysis.

Comment

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.
1. A single study reported that HIF-PHIs may positively affect or maintain certain aspects of quality of life.

Table S19.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion											
13[66, 68, 83, 85, 87-91, 94-96]	randomized trials	very serious[a]	not serious	not serious	serious[b]	none	589/8403 (7.0%)	649/6428 (10.1%)	**RR 0.80** (0.71 to 0.89)	**20 fewer per 1,000** (from 29 fewer to 11 fewer)	⊕◯◯◯ Very low
Hypertension											
11[66, 68, 81, 84-88, 94-96]	randomized trials	very serious[c]	not serious	not serious	serious[b]	none	238/3873 (6.1%)	530/3458 (15.3%)	**RR 1.02** (0.92 to 1.14)	**3 more per 1,000** (from 12 fewer to 21 more)	⊕◯◯◯ Very low
Reaching pre-defined Hb target											
13[68, 81-87, 89, 91, 93, 94]	randomized trials	serious[d]	very serious[e]	not serious	serious[f]	none	2530/4188 (60.4%)	2319/3779 (61.4%)	**RR range**: 0.77 to 1.6		⊕◯◯◯ Very low
Cancer (malignant tumor)											
2[83, 84]	randomized trials	not serious	not serious	not serious	extremely serious[g]	none	8/240 (3.3%)	2/162 (1.2%)	**RR 2.49** (0.52 to 12.03)	**18 more per 1,000** (from 6 fewer to 136 more)	⊕◯◯◯ Very low
Cancer (Gastric cancer)											
2[81, 92]	randomized trials	not serious	not serious	not serious	extremely serious[h]	none	2/312 (0.6%)	1/313 (0.3%)	**RR 1.44** (0.11 to 18.32)	**1 more per 1,000** (from 3 fewer to 55 more)	⊕◯◯◯ Very low
Chronic kidney disease: Progression of CKD											
1[86, 92, 96]	randomized trials	not serious	not serious	not serious	extremely serious[i]	none	3/204 (1.5%)	0/100 (0.0%)	**RR 3.44** (0.18 to 65.96)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low
Chronic kidney disease: Progression to ESKD											
1[86, 92, 96]	randomized trials	serious[j]	not serious	not serious	extremely serious[i]	none	6/149 (4.0%)	0/150 (0.0%)	**RR 13.09** (0.74 to 230.26)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low
IV iron use											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
7[66, 82, 87, 88, 92, 93]	randomized trials	serious[k]	very serious[e]	not serious	serious[b]	none	344/1171 (29.4%)	421/911 (46.2%)	**RR range** 0.23 to 1.02		⨁◯◯◯ Very low
Oral iron use											
5[81, 82, 86, 92, 94]	randomized trials	serious[l]	not serious	not serious	serious[b]	none	594/1110 (53.5%)	571/1003 (56.9%)	**RR 0.97** (0.88 to 1.07)	**17 fewer per 1,000** (from 68 fewer to 40 more)	⨁⨁◯◯ Low
IV iron dose											
11[82-85, 87, 88, 90, 92, 94-96]	randomized trials	very serious[m]	serious[n]	not serious	not serious	none	3961	3336	see comment 2		⨁◯◯◯ Very low
Oral iron dose											
2[83, 94]	randomized trials	serious[o]	serious[n]	not serious	not serious	none	617	561	see comment 2		⨁⨁◯◯ Low

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoietin stimulating agents; Hb = hemoglobin; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; IV = intravenous; RR = risk ratio

* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.

Explanations

a. All but two studies didn't blind participants or outcome assessors. Most studies exhibited incomplete outcome reporting. Two studies each exhibited selective outcome reporting or did not conduct an intention-to-treat analysis.

b. Confidence interval indicates that there may be a clinically important increase or decrease in this outcome.

c. Randomization and allocation concealment was not described in all studies. Eight studies did not blind participants or outcome assessors. Incomplete outcome assessing was detected in 4 studies and one study exhibited selective outcome reporting.

d. Seven studies did not blind participants or outcome assessors. Incomplete outcome assessing was detected in six studies and two studies exhibited selective outcome reporting.

e. Unable to pool results, I-squared > 75%.

f. A wide range in risk ratios indicates that there may be a clinically important increase or decrease in this outcome.

g. Less than 30 events reported with an extremely wide confidence interval

h. Less than 5 events reported.

i. Less than 5 events with an extremely wide confidence interval.

j. Single study that did not describe randomization or allocation concealment.

k. Four studies did not blind participants or outcome assessors. One study each exhibited incomplete outcome reporting, or selective outcome reporting. Two studies did not conduct intention-to-treat analyses.

l. Two studies did not blind participants or outcome assessors. One study each exhibited incomplete outcome reporting.

m. Over half of the studies did not blind participants or outcome assessors, and exhibited incomplete outcome reporting. One study exhibited selective outcome reporting, and one did not conduct an intention-to-treat analysis.

n. Studies report different averages (monthly, weekly, daily) with inconsistent values across studies.

o. One study did not blind participants or outcome assessors. Both exhibited incomplete outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

1. Individual studies reported on different CKD-related outcomes including progression of CKD, and progression to ESKD.
2. IV and oral iron dose was not pooled; studies reported over varying timepoints that did not lend themselves to standardization.

Table S20.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Blood pressure outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Change in diastolic BP (up to 12 weeks)											
2[89†]	randomized trials	very serious[a]	not serious	not serious	not serious	none	1693	1756	**MD 0.64 mmHg lower** (1.58 lower to 0.31 higher)		⊕⊕◯◯ Low
Change in diastolic BP (12 up to 26 weeks)											
3[89, 91†]	randomized trials	very serious[b]	not serious	not serious	not serious	none	1841	1901	**MD 0.35 mmHg lower** (1.23 lower to 0.52 higher)		⊕⊕◯◯ Low
Change in diastolic BP (26 to 52 weeks)											
6[82, 85, 89, 95-97†]	randomized trials	very serious[c]	not serious	not serious	not serious	none	1893	1929	**MD 0.24 mmHg lower** (1.12 lower to 0.65 higher)		⊕⊕◯◯ Low
Change in diastolic BP (52 to 104 weeks)											
2[89†]	randomized trials	serious[a]	very serious[d]	not serious	serious[e]	none	486	553	**MD range**, 0.13 lower to 7.60 mmHg higher		⊕◯◯◯ Very low
Change in diastolic BP (104 weeks to end of treatment)											
3[89, 95†]	randomized trials	very serious[b]	not serious	not serious	serious[e]	none	338	387	**MD 0.65 mmHg higher** (0.23 lower to 1.53 higher)		⊕⊕◯◯ Low
Change in systolic BP (up to 12 weeks)											
2[89†]	randomized trials	very serious[a]	not serious	not serious	not serious	none	1693	1756	**MD 0.67 mmHg higher** (0.92 lower to 2.27 higher)		⊕⊕◯◯ Low
Change in systolic BP (12 to 26 weeks)											
3[89, 91†]	randomized trials	very serious[b]	not serious	not serious	not serious	none	1841	1901	**MD 0.14 mmHg lower** (1.64 lower to 1.36 higher)		⊕⊕◯◯ Low
Change in systolic BP (26 to 52 weeks)											
5[82, 85, 89, 95-97†]	randomized trials	very serious[c]	not serious	not serious	not serious	none	1893	1929	**MD 0.42 mmHg lower** (1.57 lower to 0.73 higher)		⊕⊕◯◯ Low
Change in systolic BP (52 to 104 weeks)											
2[89†]	randomized trials	serious[a]	very serious[d]	not serious	serious[e]	none	486	553	**MD 3.89 mmHg higher** (4.07 lower to 11.86 higher)		⊕⊕◯◯ Low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Change in systolic BP (104 weeks up to end of treatment)											
2[89†]	randomized trials	very serious[a]	not serious	not serious	not serious	none	1693	1756	**MD 2.31 mmHg higher** (6.66 lower to 11.28 higher)		⨁◯◯◯ Very low

BP = blood pressure; CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference
* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.
†Two studies were reported in one reference.

Explanations

a. Neither study blinded participants or outcome assessors, and exhibited incomplete outcome reporting. Due to the nature of the interventions, not blinding participants was not a factor used to downgrade overall RoB.
b. All studies did not blind participants or outcome assessors. Two studies each exhibited incomplete outcome reporting and one exhibited selective outcome reporting. Due to the nature of the interventions, not blinding participants was not a factor used to downgrade overall RoB.
c. Four studies did not blind participants or outcome assessors. Three studies exhibited incomplete outcome reporting and two exhibited selective outcome reporting. Due to the nature of the interventions, not blinding participants was not a factor used to downgrade overall RoB.
d. Unable to pool results, I-squared > 75%.
e. Large 95% confidence interval around the mean difference.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S21.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Hemoglobin outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Change in hemoglobin (up to 12 weeks)											
13[66, 76, 81-85, 89, 91, 92, 94, 96]	randomized trials	Serious[a]	very serious[b]	not serious	not serious	none	3664	3634	**MD range**, 0.78 lower to 0.93 g/dL higher		⊕◯◯◯ Very low
Change in hemoglobin (12 to 28 weeks)											
13[81-86, 89, 91, 92, 94-97]	randomized trials	very serious[a]	very serious[b]	not serious	not serious	none	5060	4937	**MD range**, 0.35 lower to 0.57 g/dL higher		⊕◯◯◯ Very low
Change in hemoglobin (28 to 52 weeks)											
11[82, 83, 85, 88-90, 92, 94-97]	randomized trials	very serious[c]	very serious[b]	not serious	not serious	none	5068	5149	**MD range**, 0.39 lower to 0.48 g/dL higher		⊕◯◯◯ Very low
Change in hemoglobin (52 weeks to end of treatment)											
5[81, 84, 89, 90, 95, 97]	randomized trials	very serious[d]	not serious	not serious	not serious	none	894	949	**MD 0.03 g/dL lower** (0.14 lower to 0.07 higher)		⊕⊕◯◯ Low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference
* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.

Explanations

a. Over half of the studies did not blind participants or outcome assessors. Five studies exhibited incomplete outcome reporting, and one selective outcome reporting.
b. Unable to pool results, I-squared > 75%.
c. Over half of the studies did not blind participants or outcome assessors, and exhibited incomplete outcome reporting.
d. Four of the studies did not blind participants or outcome assessors. Three studies exhibited incomplete outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S22.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Transferrin saturation

Certainty assessment							№ of patients		Effect		Certainty Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
TSAT (up to 12 weeks)											
6[76, 83, 88, 91-93]	6	randomized trials	serious[a]	not serious	not serious	serious[b]	none	961	**MD 1.33% higher** (1.04 higher to 1.62% higher)		⨁⨁◯◯ Low
TSAT (12 to 28 weeks)											
9[68, 82, 83, 86-88, 92, 93, 95, 97]	9	randomized trials	very serious[c]	serious[d]	not serious	serious[b]	none	2628	**MD range**, 1.9 lower to 2.9% higher		⨁◯◯◯ Very low
TSAT (28 to 52 weeks)											
12[81-83, 85, 87-90, 92, 95-97]	12	randomized trials	very serious[e]	very serious[f]	not serious	serious[b]	none	4909	**MD range**, 2.5 lower to 3.8% higher		⨁◯◯◯ Very low
TSAT (52 weeks to end of treatment)											
3[81, 88, 95, 97]	3	randomized trials	serious[g]	not serious	not serious	serious[b]	none	584	**MD 0.89% lower** (2.4 lower to 0.64 higher)		⨁⨁◯◯ Low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference; RR = risk ratio; TSAT = transferrin saturation.
* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.

Explanations

a. Over half of the studies did not blind the participants or outcome assessors, one exhibited incomplete outcome reporting.
b. Range in mean differences indicates that there may be a clinically important increase or decrease in this outcome.
c. Over half of the studies did not blind the participants or outcome assessors, four exhibited incomplete outcome reporting, two exhibited selective outcome reporting.
d. I-squared between 50 and 75%
e. Over half of the studies did not blind participants or outcome assessors, and exhibited incomplete outcome reporting. One study exhibited selective outcome reporting.
f. Unable to pool results, I-squared > 75%.
g. Two studies did not blind participants or outcome assessors. One study each exhibited incomplete outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S23.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Total iron binding capacity (TIBC)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
TIBC (up to 12 weeks)											
4[66, 76, 83, 93]	randomized trials	serious[a]	very serious[b]	not serious	serious[c]	none	228	126	**MD range,** 16.2 to 50.1 ug/dL higher		⨁◯◯◯ Very low
TIBC (12 to 28 weeks)											
7[68, 82, 83, 87, 93-95, 97]	randomized trials	serious[d]	very serious[b]	not serious	serious[c]	none	2253	1944	**MD range,** 5.59 to 37.57 ug/dL higher		⨁◯◯◯ Very low
TIBC (28 to 52 weeks)											
8[82, 83, 85, 87, 88, 90, 92, 95, 97]	randomized trials		very serious[b]	not serious	serious[c]	none	3032	3009	**MD range,** 7.26 to 43 ug/dL higher		⨁◯◯◯ Very low
TIBC (52 weeks to end of treatment)											
3[81, 87, 95, 97]	randomized trials	serious[f]	not serious	not serious	serious[g]	none	584	463	**MD 31.49 ug/dL higher** (25.73 to 37.25 higher)		⨁⨁◯◯ Low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference; RR = risk ratio; TIBC = total iron binding capacity
* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.
Explanations
a. Three of the studies did not blind the participants or outcome assessors, one study each exhibited incomplete outcome reporting or did not conduct an intention-to-treat analysis.
b. Unable to pool results, I-squared > 75%.
c. Range in mean differences indicates that there may be a clinically important increase or decrease in this outcome.
d. Over half of the studies did not blind the participants or outcome assessors, one exhibited incomplete outcome reporting.
e. Over half of the studies did not blind participants or outcome assessors, and exhibited incomplete outcome reporting.
f. Participants or outcome assessors were not blinded in one study, and one study exhibited selective outcome reporting
g. Range in mean differences indicates that the increase may not be clinically important.
Comments
Due to the nature of the interventions, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S24.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Serum ferritin

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Serum ferritin (up to 12 weeks)											
8[66, 76, 83, 85, 88, 91-93]	randomized trials	very serious[a]	very serious[b]	not serious	serious[c]	none	1383	1269	**MD range**, 121.61 lower to 24.53 ng/mL higher		⊕◯◯◯ Very low
Serum ferritin (12 to 28 weeks)											
9[68, 83, 85-88, 91-93]	randomized trials	very serious[d]	not serious	not serious	serious[c]	none	1856	1476	**MD 1.42 ng/mL higher** (24.88 lower to 27.72 higher)		⊕◯◯◯ Very low
Serum ferritin (28 to 52 weeks)											
9[83, 85, 87-90, 92, 96]	randomized trials	very serious[e]	very serious[b]	not serious	serious[c]	none	4324	3878	**MD range** 44.21 lower to 76.93 ng/mL higher		⊕◯◯◯ Very low
Serum ferritin (52 weeks to end of treatment)											
3[81, 87, 88]	randomized trials	serious[f]	very serious[b]	not serious	serious[c]	none	668	415	**MD range** 272.02 lower to 14.77 ng/mL higher		⊕◯◯◯ Very low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference
* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.

Explanations

a. Over half of the studies did not blind participants or outcome assessors. Four studies exhibited incomplete outcome reporting, and two selective outcome reporting.
b. Unable to pool results, I-squared > 75%.
c. Range in mean differences indicates that there may be a clinically important increase or decrease in this outcome.
d. Over half of the studies did not blind participants or outcome assessors. Five studies exhibited incomplete outcome reporting, and two selective outcome reporting.
e. Over half of the studies did not blind participants or outcome assessors and exhibited incomplete outcome reporting. One study exhibited selective outcome reporting.
f. One study each did not blind participants or outcome assessors and exhibited selective outcome reporting. Two studies exhibited incomplete outcome reporting. reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S25.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Serum hepcidin

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Serum hepcidin (up to 12 weeks)											
5[66, 81, 88, 92, 93]	randomized trials	very serious[a]	not serious	not serious	serious[b]	none	614	471	**MD 1.86 ng/mL lower** (9.02 lower to 5.3 higher)		⨁◯◯◯ Very low
Serum hepcidin (12 to 28 weeks)											
6[68, 81, 86, 87, 92, 93]	randomized trials	Serious[c]	Serious[d]	not serious	serious[b]	none	856	556	**MD range** 96 lower to 4.43 ng/mL higher		⨁◯◯◯ Very low
Serum hepcidin (28 to 52 weeks)											
9[83, 85, 87-89, 92, 94, 96]	randomized trials	very serious[e]	Serious[d]	not serious	serious[b]	none	3328	3138	**MD range** 21.59 lower to 2.14 ng/mL higher		⨁◯◯◯ Very low
Serum hepcidin (52 weeks to end of treatment)											
2[81, 88]	randomized trials	Serious[f]	very serious[g]	not serious	serious[b]	none	409	283	**MD range**, 24.39 lower to 2.91 ng/mL higher		⨁◯◯◯ Very low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference
* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.

Explanations

a. Three studies did not blind the participants, or outcome assessors. Two studies exhibited incomplete outcome reporting, and one selective outcome reporting.
b. Range in mean differences indicates that there may be a clinically important increase or decrease in this outcome.
c. Two studies did not blind participants or outcome assessors, and one exhibited selective outcome reporting.
d. I-squared between 50 and 75%
e. Over half of the studies did not blind participants or outcome assessors, and exhibited incomplete outcome reporting. One study exhibited selective outcome reporting.
f. One study did not blind the participants, or outcome assessors, exhibited selective outcome reporting, and did not conduct an intention-to-treat analysis.
g. Unable to pool results, I-squared > 75%.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S26.
Population: People with anemia and CKD receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Serum iron

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Serum iron (up to 12 weeks)											
5[66, 76, 83, 93, 94]	randomized trials	very serious[a]	not serious	not serious	not serious	none	750	639	-	**MD 6.22 ug/dL higher** (3.16 higher to 9.28 higher)	⊕⊕◯◯ Low
Serum iron (12 to 28 weeks)											
7[68, 82, 83, 86, 87, 93, 94]	randomized trials	very serious[b]	very serious[c]	not serious	not serious	none	1397	986	-	**MD range** 1 to 15 ug/dL higher	⊕◯◯◯ Very low
Serum iron (28 to 52 weeks)											
8[82, 83, 85, 87, 88, 90, 94, 96]	randomized trials	very serious[d]	very serious[c]	not serious	not serious	none	2487	2427	-	**MD range** 0.3 to 15 ug/dL higher	⊕◯◯◯ Very low
Serum iron (52 weeks to end of treatment)											
2[81, 87]	randomized trials	very serious[e]	not serious	not serious	not serious	none	409	283	-	**MD 2.22 ug/dL higher** (0.91 higher to 3.54 higher)	⊕⊕◯◯ Low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference
* Includes studies of patients treated with hemodialysis or peritoneal dialysis, not stratified.

Explanations

a. Most studies did not blind participants or outcome assessors, and two exhibited incomplete outcome reporting. One study did not conduct an intention-to treat analysis.
b. Over half of the studies did not blind participants or outcome assessors, and three exhibited incomplete outcome reporting. One study exhibited selective outcome reporting.
c. Unable to pool results, I-squared > 75%.
d. Over half of the studies did not blind participants or outcome assessors, and exhibited incomplete outcome reporting. One study exhibited selective outcome reporting.
e. It is unclear if the outcome assessors were blinded in either study. One study exhibited selective outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S27.
Population: People with anemia and CKD receiving peritoneal dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	ESAs	Relative (95% CI)	Absolute (95% CI)	
Mortality (followup 26 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	1/86 (1.2%)	1/43 (2.3%)	**RR 0.50** (0.03 to 7.80)	**12 fewer per 1,000** (from 23 fewer to 158 more)	⊕◯◯◯ Very low
Cardiovascular disease, acute coronary syndrome (followup 26 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	1/86 (1.2%)	0/43 (0.0%)	**RR 1.51** (0.06 to 36.27)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low
Thromboembolism - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hospitalization, all-cause - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events, total (follow-up: range 6 weeks to 130 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	2/86 (2.3%)	1/43 (2.3%)	**RR 1.00** (0.09 to 10.72)	**0 fewer per 1,000** (from 21 fewer to 226 more)	⊕◯◯◯ Very low
Quality of life and functional status - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; RR = risk ratio
Explanations
a. Single study: randomization not described, and the study exhibited selective outcome reporting. Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.
b. Less than 5 events reported.

Table S28.
Population: People with anemia and CKD receiving peritoneal dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hypertension											
1[99]	randomized trials	very serious[a]	not serious	not serious	very serious[b]	none	5/89 (5.6%)	3/43 (7.0%)	**RR 0.81** (0.20 to 3.21)	**13 fewer per 1,000** (from 56 fewer to 154 more)	⊕◯◯◯ Very low
Change in diastolic BP - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in systolic BP - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in hemoglobin (up to 12 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	serious[c]	none	86	43	see comment 1		⊕◯◯◯ Very low
Change in hemoglobin (24 to 52 weeks)											
2[95, 97, 99]	randomized trials	very serious[d]	not serious	not serious	serious[c]	none	178	202	see comment 2		⊕◯◯◯ Very low
Reaching pre-defined Hb target											
1[99]	randomized trials	very serious[a]	not serious	not serious	serious[e]	none	72/86 (83.7%)	35/43 (81.4%)	**RR 1.03** (0.87 to 1.22)	**24 more per 1,000** (from 106 fewer to 179 more)	⊕◯◯◯ Very low
TSAT (up to 12 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	serious[c]	none	78	39	-	see comment 1	⊕◯◯◯ Very low
TIBC (up to 12 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	serious[c]	none	78	39	-	see comment 1	⊕◯◯◯ Very low
Serum ferritin (up to 12 weeks)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
1[99]	randomized trials	very serious[a]	not serious	not serious	serious[c]	none	86	43	-	see comment 1	⊕◯◯◯ Very low
Serum hepcidin (up to 12 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	serious[c]	none	86	43	see comment 1		⊕◯◯◯ Very low
Serum iron (up to 12 weeks)											
1[99]	randomized trials	very serious[a]	not serious	not serious	serious[c]	none	86	43	see comment 1		⊕◯◯◯ Very low
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Chronic kidney disease related - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Iron use (IV or oral) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Iron dose (IV or oral) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

BP = blood pressure; CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; IV = intravenous; RR = risk ratio; TIBC = total iron binding capacity; TSAT = transferrin saturation

Explanations

a. Single study: randomization not described, there was no blinding of participants or outcome assessors, and the study exhibited selective outcome reporting.
b. Less than 30 events reported.
c. Study does not provide sufficient data to assess precision.
d. In both studies there was no blinding of participants or outcome assessors. one study did not describe randomization. and the study exhibited selective outcome reporting.
e. Less than 300 events reported.

Comment

1. Insufficient data available to calculate the effect in the single study.
2. Insufficient data available to pool the data.

Table S29.
Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	ESAs	Relative (95% CI)	Absolute (95% CI)	
Mortality (follow-up: range 6 weeks to 250 weeks)											
12[68, 100-110]	randomized trials	very serious[a]	not serious	serious[b]	serious[c]	none	503/4305 (11.7%)	484/4208 (11.5%)	**RR 1.03** (0.92 to 1.16)	**3 more per 1,000** (from 9 fewer to 18 more)	⊕◯◯◯ Very low
Cardiovascular events, heart failure											
5[101, 103, 104, 106, 107]	randomized trials	very serious[d]	not serious	not serious	very serious[e]	none	36/1483 (2.4%)	36/1597 (2.3%)	**RR 0.96** (0.57 to 1.60)	**1 fewer per 1,000** (from 10 fewer to 14 more)	⊕◯◯◯ Very low
Cardiovascular events, acute coronary syndrome (follow-up: range 26 weeks to 250 weeks)											
8[68, 100, 103, 104, 107-110]	randomized trials	very serious[f]	not serious	not serious	very serious[e]	none	117/3839 (3.0%)	117/3739 (3.1%)	**RR 1.01** (0.78 to 1.30)	**0 fewer per 1,000** (from 7 fewer to 9 more)	⊕◯◯◯ Very low
Cardiovascular events, MACE (follow-up: mean 52 weeks)											
6[103-105, 108-110]	randomized trials	very serious[g]	not serious	not serious	serious[h]	none	837/4333 (19.3%)	765/4201 (18.2%)	**RR 1.07** (0.98 to 1.17)	**13 more per 1,000** (from 4 fewer to 31 more)	⊕◯◯◯ Very low
									HR 1.08 (0.96 to 1.21)		
Cardiovascular disease, stroke (follow-up: range 16 weeks to 250 weeks)											
8[68, 100, 103, 104, 107-110]	randomized trials	very serious[f]	not serious	not serious	very serious[e]	none	57/3839 (1.5%)	54/3739 (1.4%)	**RR 1.11** (0.75 to 1.66)	**2 more per 1,000** (from 4 fewer to 10 more)	⊕◯◯◯ Very low
Thromboembolism, DVT (follow-up: range 26 weeks to 52 weeks)											
5[101, 103, 104, 106, 108]	randomized trials	very serious[i]	not serious	not serious	very serious[e]	none	28/3287 (0.9%)	29/3379 (0.9%)	**RR 0.89** (0.52 to 1.52)	**1 fewer per 1,000** (from 4 fewer to 4 more)	⊕◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHIs	ESAs	Relative (95% CI)	Absolute (95% CI)	
Thromboembolism, PE (follow-up: range 52 weeks to 99 weeks)											
2[107, 108]	randomized trials	very serious[j]	Serious[k]	not serious	extremely serious[l]	none	6/2088 (0.3%)	2/2088 (0.1%)	**RR 2.38** (0.08 to 71.06)	**1 more per 1,000** (from 1 fewer to 67 more)	⊕◯◯◯ Very low
Vascular access thrombosis (follow-up: range 99 weeks to 250 weeks)											
2[104, 108]	randomized trials	very serious[m]	Serious[n]	not serious	very serious[e]	publication bias strongly suspected[o]	52/2815 (1.8%)	40/2805 (1.4%)	**RR 1.30** (0.86 to 1.95)	**4 more per 1,000** (from 2 fewer to 14 more)	⊕◯◯◯ Very low
Hospitalization, all-cause - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events											
11[68, 100-104, 106-110]	randomized trials	very serious[p]	very serious[q]	not serious	Serious[r]	publication bias strongly suspected[s]	2347/4996 (47.0%)	2127/4988 (42.6%)	**RR range** 0.78 to 1.46		⊕◯◯◯ Very low
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Functional status - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; RR = risk ratio

Explanations

a. Four studies exhibited incomplete outcome reporting; six exhibited selective outcome reporting.
b. The confidence interval indicates that there may be a clinically important increase or decrease in this outcome
c. The confidence interval indicates that there may be a clinically important increase or decrease in this outcome.
d. No study blinded participants or study personnel; all but one did not blind outcome assessors. One study exhibited incomplete outcome reporting; one exhibited selective outcome reporting.
e. Less than 300 participants experienced this event; the confidence interval indicates that there may be a clinically important increase or decrease in this outcome
f. No study blinded participants or study personnel or outcome assessors. Three studies exhibited incomplete outcome reporting; four exhibited selective outcome reporting.
g. None of the studies sufficiently described blinding of outcome assessors, study personnel, or study participants. Three studies exhibited incomplete outcome reporting, and four exhibited selective outcome reporting.
h. The confidence interval indicates that there may be a clinically important increase in this outcome.
i. All studies did not blind the participants or outcome assessors. All studies included an intention to treat analysis.
j. Neither study blinded the outcome assessor, both had other biases around how outcome data were reported.
k. Two studies reporting opposite estimate of effect.
l. Less than 30 participants experienced this event with an extremely large confidence interval.

m. No study blinded participants or study personnel or outcome assessors. Both studies exhibited incomplete outcome reporting; one exhibited selective outcome reporting.
n. One study favored HIF-PHI over the others which were neutral or favored ESAs (see note on Chertow studies).
o. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES, study but not reported in the published literature.
p. No study blinded participants or study personnel; all but one did not blind outcome assessors. Four studies exhibited incomplete outcome reporting; five exhibited selective outcome reporting.
q. Unable to pool data, I-squared >75%
r. A wide range in confidence intervals indicates that there may be an important increase or decrease in this outcome.
s. Data are available in the unpublished literature (FDA/EMA data) for the ROCKIES study but not reported in the published literature

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall RoB.

Table S30.
Population: People with anemia and CKD not receiving dialysis*
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion											
7[68, 100, 104, 105, 108-110]	randomized trials	very serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	272/3535 (7.7%)	281/3373 (8.3%)	**RR 0.95** (0.81 to 1.12)	**4 fewer per 1,000** (from 16 fewer to 10 more)	⊕◯◯◯ Very low
Hypertension											
10[68, 100-104, 106-109]	randomized trials	very serious[d]	not serious	not serious	serious[e]	none	451/4144 (10.9%)	522/4047 (12.9%)	**RR 0.77** (0.61 to 0.99)	**30 fewer per 1,000** (from 50 fewer to 1 fewer)	⊕◯◯◯ Very low
Reaching pre-defined Hb target											
11[68, 100-106, 109, 110]	randomized trials	serious[f]	serious[g]	not serious	serious[b]	none	1400/2138 (65.5%)	1266/1997 (63.4%)	**RR 1.04** (0.98 to 1.11)	**25 more per 1,000** (from 13 fewer to 70 more)	⊕◯◯◯ Very low
Cancer (total)											
2[106, 107]	randomized trials	serious[h]	not serious	not serious	very serious[i]	none	5/300 (1.7%)	9/303 (3.0%)	**RR 0.58** (0.19 to 1.79)	**12 fewer per 1,000** (from 24 fewer to 23 more)	⊕◯◯◯ Very low
Cancer (renal)											
2[106, 107]	randomized trials	serious[h]	not serious	not serious	extremely serious[i]	none	0/300 (0.0%)	3/303 (1.0%)	**RR 0.09** (0.00 to 8.91)	**9 fewer per 1,000** (from -- to 78 more)	⊕◯◯◯ Very low
Cancer (basal cell carcinoma)											
3[103, 104, 107]	randomized trials	serious[k]	not serious	not serious	very serious[i]	none	10/1352 (0.7%)	9/1316 (0.7%)	**RR 0.78** (0.28 to 2.19)	**2 fewer per 1,000** (from 5 fewer to 8 more)	⊕◯◯◯ Very low
Chronic kidney disease related (progression of CKD)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
3[101, 105, 108]	randomized trials	serious[l]	not serious	not serious	serious[b]	none	353/1512 (23.3%)	366/1476 (24.8%)	**RR 0.99** (0.88 to 1.12)	**2 fewer per 1,000** (from 30 fewer to 30 more)	⊕⊕◯◯ Low
Chronic kidney disease relates (progression to ESKD)											
3[103, 104, 108]	randomized trials	serious[m]	not serious	not serious	serious[b]	none	468/3138 (14.9%)	464/3098 (15.0%)	**RR 0.98** (0.88 to 1.09)	**3 fewer per 1,000** (from 18 fewer to 13 more)	⊕⊕◯◯ Low
IV iron use											
4[102, 103, 109, 110]	randomized trials	very serious[n]	not serious	not serious	very serious[o]	none	27/591 (4.6%)	43/560 (7.7%)	**RR 0.56** (0.35 to 0.90)	**34 fewer per 1,000** (from 50 fewer to 8 fewer)	⊕◯◯◯ Very low
Oral iron use											
4[102, 103, 109, 110]	randomized trials	very serious[n]	serious[p]	not serious	serious[q]	none	270/591 (45.7%)	253/560 (45.2%)	**RR range** 0.88 to 1.44		⊕◯◯◯ Very low
IV iron dose											
3[103, 109, 110]	randomized trials	very serious[r]	serious[s]	not serious	not serious	none	182	199	- see comment 1		⊕⊕◯◯ Low
Oral iron dose											
5[105-107, 109, 110]	randomized trials	very serious[t]	serious[s]	not serious	not serious	none	485	504	- see comment 1		⊕◯◯◯ Very low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; RR = risk ratio

Explanations

a. No study blinded participants or outcome assessors. Six studies exhibited incomplete outcome reporting. Two studies exhibited selective outcome reporting. One study reported outcomes as "values" undefined.

b. The confidence interval indicates that there may be a clinically important increase or decrease in this outcome

c. Data is available in the unpublished literature (FDA/EMA data) for the DOLOMITES, study but is not reported in the published literature; published literature on the ASCEND-ND study includes outcomes not reported in the unpublished literature (FDA/EMA).

d. No study blinded participants and one did not blind outcome assessors. Five studies exhibited incomplete outcome reporting. Three studies had exhibited selective outcome reporting. One study reported outcomes as "values" undefined.

e. The confidence interval points to a potentially non-clinically significant difference.

f. No study blinded participants or outcome assessors. Four studies exhibited incomplete outcome reporting. One study exhibited incomplete outcome reporting. Six studies exhibited selective outcome reporting. One study reported outcomes as "values" undefined.

g. I-squared between 50 to 75%

h. Neither study blinded participants nor outcome assessors.

i. Less than 30 events with a wide confidence interval.
j. Less than 5 events with an extremely wide confidence interval.
k. No study blinded participants or outcome assessors. One study exhibited incomplete outcome reporting
l. No study blinded participants or outcome assessors. One study exhibited selective outcome reporting.
m. No study blinded participants or outcome assessors. One study exhibited incomplete and selective outcome reporting.
n. No study blinded participants or outcome assessors. All studies exhibited incomplete outcome reporting; three exhibited selective outcome reporting.
o. Less than 300 events with a confidence interval pointing to a non-clinically meaningful difference.
p. Unable to pool data, I-squared >75%
q. Confidence interval in a single study indicates a potentially important decrease or increase in this outcome.
r. None of the studies blinded participants, two did not blind outcome assessors, and one exhibited selective outcome reporting.
s. Studies report different averages (monthly, weekly, daily) with inconsistent values across studies.
t. All studies did not blind participants, all but one did not blind outcome assessors. Two studies exhibited incomplete outcome reporting and three exhibited selective outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

1. IV and oral iron dose was not pooled; studies reported over varying timepoints that did not lend themselves to standardization.

Table S31
Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Blood pressure outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Change in diastolic BP (up to 12 weeks)											
1[104]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	796	811	MD **0.94 mmHg lower** (1.94 lower to 0.12 higher)		⊕⊕◯◯ Low
Change in diastolic BP (12 to 24 weeks)											
2[104, 105]	randomized trials	serious[c]	not serious	not serious	serious[b]	none	895	845	MD **0.69 mmHg lower** (1.72 lower to 0.34 higher)		⊕⊕◯◯ Low
Change in diastolic BP (24 to 52 weeks)											
2[104, 106]	randomized trials	serious[d]	not serious	not serious	serious[b]	none	701	728	MD **0.02 mmHg lower** (1.13 lower to 1.09 higher)		⊕⊕◯◯ Low
Change in diastolic BP (52 to 104 weeks)											
1[104]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	313	340	MD **0.25 mmHg higher** (1.07 lower to 1.57 higher)		⊕⊕◯◯ Low
Change in diastolic BP (104 weeks to end of treatment)											
2[104, 108]	randomized trials	serious[d]	very serious[e]	not serious	serious[f]	none	1286	1289	Range in MD -12.24 to 0.10		⊕◯◯◯ Very low
Change in systolic BP (up to 12 weeks)											
1[104]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	796	811	MD **1.26 mmHg lower** (3.09 lower to 0.87 higher)		⊕⊕◯◯ Low
Change in systolic BP (12 to 24 weeks)											
2[104, 105]	randomized trials	serious[c]	not serious	not serious	serious[b]	none	895	845	MD **0.93 mmHg lower** (2.72 lower to 0.87 higher)		⊕⊕◯◯ Low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Change in systolic BP (24 to 52 weeks)											
2[104, 106]	randomized trials	serious[d]	not serious	not serious	serious[b]	none	895	845	MD **0.41 mm Hg lower** (1.71 lower to 2.53 higher)		⊕⊕◯◯ Low
Change in systolic BP (52 to 104 weeks)											
1[104]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	313	340	MD **0.23 mm Hg lower** (3.34 lower to 2.88 higher)		⊕⊕◯◯ Low
Change in systolic BP (104 weeks to end of treatment)											
2[104, 108]	randomized trials	serious[d]	very serious[e]	not serious	serious[b]	none	1286	1289	MD **1.67 mm Hg lower** (9.19 lower to 5.84 higher)		⊕◯◯◯ Very low

CI: confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = Hypoxia-inducible factor–prolyl hydroxylase inhibitors; RR: risk ratio

Explanations

a. Neither study blinded participants or outcome assessors. Both studies exhibited selective outcome reporting. Two studies had selective outcome reporting.
b. Changes in mean difference indicate that there may be an important increase or a decrease in this outcome.
c. No study blinded participants or outcome assessors. All studies exhibited selective outcome reporting.
d. No study blinded participants or outcome assessors. Two studies exhibited selective outcome reporting.
e. Unable to pool data, I-squared >75%
f. Point estimates and confidence intervals vary considerably.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall RoB.

Table S32
Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Hemoglobin outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Change in hemoglobin (up to 12 weeks)											
8[101-104, 106, 107, 109, 110]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	1724	1701	Range in MD **-0.6to 0.5g/dL**		⊕◯◯◯ Very low
Change in hemoglobin (12 to 28 weeks)											
10[100-104, 106-110]	randomized trials	serious[c]	serious[d]	not serious	not serious	none	3410	3415	Range in MD **-0.27 to 0.3 g/dL**		⊕⊕◯◯ Low
Change in hemoglobin (28 to 52 weeks)											
6[103, 104, 106-110]	randomized trials	serious[e]	serious[f]	not serious	not serious	none	1937	1901	MD **0.02 mg/dl higher** (0.01 lower to 0.04 higher)		⊕⊕◯◯ Low
Change in hemoglobin (52 weeks to end of treatment)											
3[103, 104, 108]	randomized trials	serious[g]	not serious	not serious	not serious	none	614	627	**0.07 g/dl lower** (0.23 lower to 0.09 higher)		⊕⊕⊕◯ Moderate

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; RR = risk ratio

Explanations

a. No study blinded participants, and only one blinded outcome assessors. Five studies exhibited selective outcome reporting, and four exhibited incomplete outcome reporting.
b. Unable to pool data, I-squared >75%
c. No study blinded participants and one did not blind outcome assessors. Four studies exhibited incomplete outcome reporting. Six studies had exhibited selective outcome reporting.
d. Unable to pool data, I-squared >50%
e. No study blinded participants and one did not blind outcome assessors. Five studies exhibited incomplete outcome reporting. Three studies exhibited incomplete outcome reporting. Three studies exhibited selective outcome reporting. One study reported outcomes as "values" undefined.
f. Effect is inconsistent across included studies
g. No study blinded participants or outcome assessors. Five studies exhibited incomplete outcome reporting. One study exhibited incomplete outcome reporting. two studies exhibited selective outcome reporting. One study reported outcomes as "values" undefined.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S33

Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Transferrin saturation

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
TSAT (up to 12 weeks)											
5[101, 103, 107, 109, 110]	randomized trials	very serious[a]	not serious	not serious	serious[b]	none	757	734	MD **1.02 % lower** (2.56 lower to 0.51 higher)		⊕◯◯◯ Very low
TSAT (12 to 28 weeks)											
7[68, 101, 106-110]	randomized trials	very serious[c]	serious[d]	not serious	very serious[e]	none	1892	2008	MD **4.18 % lower** (6.29 to 2.08 lower)		⊕◯◯◯ Very low
TSAT (28 to 52 weeks)											
6[103, 106-110]	randomized trials	very serious[c]	Serious[d]	not serious	very serious[e]	none	1880	1872	MD **4.78 % lower** (6.33 to 3.22 lower)		⊕◯◯◯ Very low
TSAT (52 weeks to end of treatment)											
2[103, 108]	randomized trials	serious[f]	not serious	not serious	not serious	none	531	530	MD **4.13 % lower** (5.61 lower to 2.65 lower)		⊕⊕⊕◯ Moderate

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; RR = risk ratio; TSAT = transferrin saturation

Explanations

a. One study blinded the outcome assessor, none blinded participants, three exhibited incomplete outcome reporting, two exhibited selective outcome reporting.
b. Changes in mean difference indicate that there may be an important increase or a decrease in this outcome.
c. None of the studies blinded the participants, four did not blind outcome assessors, three exhibited incomplete outcome reporting, two exhibited selective outcome reporting.
d. I-squared between 50 and 75%
e. Changes in mean difference indicate that there may be an important decrease in this outcome.
f. Both studies did not blind the participants, or outcome assessors. One study exhibited incomplete outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S34

Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Total iron binding capacity (TIBC)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
TIBC (Up to 12 weeks)											
2[101, 107]	randomized trials	serious[a]	not serious	not serious	not serious	none	270	279	MD **45.41 ug/dL higher** (43.65 higher to 47.16 higher)		⊕⊕⊕◯ Moderate
TIBC (12 to 28 weeks)											
5[68, 101, 106-108]	randomized trials	serious[b]	very serious[c]	not serious	serious[d]	none	1864	1628	Range in MD 2.23 to 49 ug/dl higher		⊕◯◯◯ Very low
TIBC (28 to 52 weeks)											
3[106-108]	randomized trials	serious[e]	very serious[c]	not serious	serious[d]	none	1393	1420	Range in MD 30.39 to 52.98 ug/dl higher		⊕◯◯◯ Very low
TIBC (52 weeks to end of treatment)											
1[108]	randomized trials	serious[f]	not serious	not serious	serious[g]	none	208	237	MD **34.3 ug/dL higher** (25.99 higher to 42.61 higher)		⊕⊕◯◯ Low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference; TIBC = total iron binding capacity

Explanations

a. Both studies did not the participants, or outcome assessors, three exhibited incomplete outcome reporting, two exhibited selective outcome reporting.
b. No study blinded participants or outcome assessors. Two studies exhibited selective outcome reporting and incomplete outcome reporting.
c. Unable to pool data, I-squared >75%
d. Wide range in mean differences across studies
e. One study blinded the outcome assessor, none blinded participants, three exhibited incomplete outcome reporting, two exhibited selective outcome reporting.
f. This study did not blind participants or outcome assessors.
g. Single study with a wide range of values.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S35

Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Serum ferritin

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Serum ferritin (up to 12 weeks)											
5[101, 103, 107, 109, 110]	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	751	729	MD **13.52 ng/ml lower** (43.56 lower to 16.51 higher)		⊕◯◯◯ Very low
Serum ferritin (12 to 28 weeks)											
5[68, 101, 107, 109, 110]	randomized trials	serious[d]	not serious	not serious	serious[e]	none	474	423	MD **25.38 ng/ml lower** (43.24 lower to 11.6 lower)		⊕⊕◯◯ Low
Serum ferritin (28 to 52 weeks)											
4[106, 107, 109, 110]	randomized trials	serious[f]	not serious	not serious	serious[e]	none	423	424	MD **19.62 ng/ml lower** (39.17 lower to 0.08 lower)		⊕⊕◯◯ Low
Serum ferritin (52 weeks to end of treatment)											
1[103]	randomized trials	serious[g]	not serious	not serious	serious[h]	none	323	293	MD **115.74 ng/ml lower** (212.24 lower to 19.4 lower)		⊕⊕◯◯ Low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference

Explanations

a. None of the studies blinded the participants, four did not blind outcome assessors, two exhibited incomplete outcome reporting.
b. I-squared between 50 and 75%
c. None of the studies blinded the participants, four did not blind outcome assessors, three exhibited incomplete outcome reporting, two exhibited selective outcome reporting.
d. This study did not blind participants or outcome assessors, and exhibited incomplete outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S36

Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Serum hepcidin

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Serum hepcidin (up to 12 weeks)											
2[101, 107]	randomized trials	serious[a]	very serious[b]	not serious	serious[c]	none	270	279	Range in MD 20.33 to 0.64 ng/ml lower		⨁◯◯◯ Very low
Serum hepcidin (12 to 28 weeks)											
6[68, 101, 106, 107, 109, 110]	randomized trials	very serious[d]	very serious[b]	not serious	serious[e]	none	652	578	Range in MD 32.46 to 5.92 ng/ml lower		⨁◯◯◯ Very low
Serum hepcidin (28 to 52 weeks)											
4[106, 107, 109, 110]	randomized trials	very serious[f]	not serious	not serious	serious[e]	none	423	424	MD **30.39 ng/ml lower** (37.41 lower to 23.36 lower)		⨁◯◯◯ Very low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference

Explanations

a. Both studies did not blind the participants, or outcome assessors.
b. Unable to pool data, I-squared >75%
c. Effect is inconsistent across included studies
d. None of the studies blinded the participants, four did not blind outcome assessors, two exhibited incomplete outcome reporting and selective outcome reporting.
e. Wide range in mean differences across studies
f. None of the studies blinded the participants, three did not blind outcome assessors, two exhibited incomplete outcome reporting and selective outcome reporting.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S37
Population: People with anemia and CKD not receiving dialysis
Intervention: HIF-PHI
Comparator: ESA
Outcomes: Serum iron

b) Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI	ESA	Relative (95% CI)	Absolute (95% CI)	
Serum iron (Up to 12 weeks)											
4[101, 103, 109]	randomized trials	very serious[a]	very serious[b]	not serious	serious[c]	none	606	581	Range in MD 18 ug/ml lower to 1.58 ug/ml higher		⊕◯◯◯ Very low
Serum iron (12 to 28 weeks)											
5[68, 101, 106, 109, 110]	randomized trials	very serious[d]	very serious[b]	not serious	serious[e]	none	474	423	Range in MD 9 ug/ml lower to 1.59 ug/ml higher		⊕◯◯◯ Very low
Serum iron (28 to 52 weeks)											
4[103, 106, 109, 110]	randomized trials	very serious[f]	very serious[b]	not serious	serious[e]	none	595	564	Range in MD 15.4 to 1.06 ug/ml lower		⊕◯◯◯ Very low
Serum iron (52 weeks to end of treatment)											
1[103]	randomized trials	serious[g]	not serious	not serious	serious[h]	none	323	293	MD **0.83 ug/ml lower** (1.77 lower to 0.11 higher)		⊕⊕◯◯ Low

CI = confidence interval; ESA = erythropoietin stimulating agents; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase inhibitors; MD = mean difference

Explanations

a. None of the studies blinded the participants, or outcome assessors, three exhibited incomplete outcome reporting and 2 exhibited selective outcome reporting.
b. Unable to pool data, I-squared >75%
c. Changes in mean difference indicate that there may be an important increase or a decrease in this outcome.
d. None of the studies blinded the participants, three did not outcome assessors, two studies exhibited incomplete outcome and selective outcome reporting
e. Wide range in mean differences across studies
f. None of the studies blinded the participants, three did not blind outcome assessors, and exhibited incomplete outcome reporting, two exhibited selective outcome reporting.
g. Both studies did not blind the participants, or outcome assessors. One study exhibited incomplete outcome reporting.
h. Single study with a wide range of values.

Comments

Due to the nature of the intervention, not blinding participants was not a factor used to downgrade overall risk of bias.

Table S38.
Population: Adults with anemia and CKD receiving dialysis
Intervention: ESA
Comparator: Placebo or standard of care
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality - not reported											
4† [111-114]	randomized trials	serious[a]	serious[b]	not serious	extremely serious[c]	none	11/211 (5.2%)	5/214 (2.3%)	**RR 2.82** (0.83 to 9.55)	**43 more per 1,000** (from 4 fewer to 200 more)	⊕◯◯◯ Very low
Cardiovascular events not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis - not reported											
3†[111-113]	randomized trials	serious[d]	not serious	not serious	extremely serious[c]	none	20/142 (14.1%)	8/147 (5.4%)	**RR 2.35** (1.00 to 5.52)	**73 more per 1,000** (from 0 fewer to 246 more)	⊕◯◯◯ Very low
All-cause hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Quality of life											
1[111, 113, 115]	randomized trials	not serious	not serious	not serious	serious[a]	none	78	40	Results favored ESA over placebo See comment		⊕⊕⊕◯ Moderate
Functional assessment											
1[111, 113, 115]	randomized trials	not serious	not serious	not serious	serious[e]	none	78	40	Results favored neither ESA or placebo, p = NS		⊕⊕⊕◯ Moderate

* The KDIGO 2012 guideline[116] classified study quality in the following manner: Good: Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT); Fair: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If

study of intervention, must be prospective; Poor: High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

† There are two comparisons in the CanEPO, 1990[111, 113] study.

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; No = number; RR = risk ratio

Explanations

a. All included studies are from the 2012 KDIGO guideline[116]. Two of these were rated as low risk of bias and two were rated as moderate

b. The direction of effect was different across studies with the smaller studies favoring ESA and the larger studies favoring ESAs

c. Less than 30 events reported with an extremely wide confidence interval around the pooled estimate.

d. All included studies are from the 2012 KDIGO guideline[116]. Two of these were rated as low risk of bias and one was rated as moderate

e. Less than 300 events reported.

Comment

One study assessed quality of life with the KDQ, SIP and TTO. Results favored ESA over placebo in 4 domains in the KDQ (fatigue, physical symptoms, relationships, and depression), and favored neither in the fifth domain (frustration); results favored two domains in the SIP (global QoL and physical), and favored neither in one (psychosocial); neither group was favored when assessed by the TTO.

Table S39.
Population: Adults with anemia and CKD receiving dialysis
Intervention: ESA
Comparator: Placebo or standard of care
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion											
3[111-113, 115]	randomized trials	not serious	not serious	not serious	serious[a]	none	11/142 (7.7%)	83/147 (56.5%)	**RR 0.10** (0.40 to 0.25)	**508 fewer per 1,000** (from 423 fewer to 339 fewer)	⊕◯◯◯ Very low
Hypertension - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in diastolic blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in systolic blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in mean hemoglobin											
1[117]	randomized trials	not serious	not serious	not serious	Very serious[b]	none	23	22	Small effect See comment 1		⊕⊕◯◯ Low
Reaching a predefined hemoglobin target - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

IV iron dose - not reported

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; ESA = erythropoiesis stimulating agent; No = number; RR = risk ratio

Explanations

a. Less than 300 events reported.

b. Single study with varying change in outcome over time.

Comments

1) A single study comparing ESA to placebo demonstrated a small difference favoring ESA, however, at 26 weeks there was an increase in hemoglobin in both arms.

Table S40

Population: Adults with anemia and CKD receiving dialysis
Intervention: ESA administered to reach a higher hemoglobin target
Comparator: ESA administered to reach a lower hemoglobin target
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high Hb target	ESA low Hb target	Relative (95% CI)	Absolute (95% CI)	
Mortality											
5[113, 115, 118-122]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	241/1243 (19.4%)	211/1226 (17.2%)	**RR 1.15** (0.98 to 1.35)	**26 more per 1,000** (from 3 fewer to 60 more)	⊕⊕◯◯ Low
Cardiovascular events--total											
1 [119]	randomized trials	not serious	not serious	not serious	extremely serious[c]	none	10/73 (13.7%)	10/73 (13.7%)	**RR 1.00** (0.44 to 2.26)	**0 fewer per 1,000** (from 77 fewer to 173 more)	⊕◯◯◯ Very low
Cardiovascular events--stroke											
1 [121, 122]	randomized trials	not serious	not serious	not serious	extremely serious[c]	none	12/296 (4.1%)	4/300 (1.3%)	**RR 3.04** (0.99 to 9.32)	**27 more per 1,000** (from 0 fewer to 111 more)	⊕◯◯◯ Very low
Cardiovascular events--heart failure											
2 [118, 121, 122]	randomized trials	not serious	not serious	not serious	very serious[d]	none	91/914 (10.0%)	102/915 (11.1%)	**RR 0.89** (0.68 to 1.16)	**12 fewer per 1,000** (from 36 fewer to 18 more)	⊕⊕◯◯ Low
Cardiovascular events—acute coronary syndrome											
2 [118, 121, 122]	randomized trials	not serious	not serious	not serious	extremely serious[e]	none	26/557 (4.7%)	18/907 (2.0%)	**RR 2.76** (1.53 to 4.97)	**35 more per 1,000** (from 11 more to 79 more)	⊕◯◯◯ Very low
Thromboembolism											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high Hb target	ESA low Hb target	Relative (95% CI)	Absolute (95% CI)	
1†[118, 123]	randomized trials	not serious	not serious	not serious	extremely serious[e]	none	138/618 (22.3%)	108/615 (17.6%)	**RR 1.27** (1.04 to 1.54)	**47 more per 1,000** (from 7 more to 95 more)	⊕◯◯◯ Very low
Vascular access thrombosis											
5[113, 115, 118-122]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	241/1392 (17.3%)	210/1328 (15.8%)	**RR 1.04** (0.77 to 1.38)	**6 more per 1,000** (from 36 fewer to 60 more)	⊕⊕◯◯ Low
All-cause hospitalization											
1‡	randomized trials	not serious	serious[f]	not serious	very serious[f]	publication bias strongly suspected[g]	445/618 (72.0%)	425/618 (68.8%)	**RR** 1.04 (0.97 to 1.12) ‡ **RR** 1.14 (0.99 to 1.30)‖		⊕◯◯◯ Very low
Serious adverse events--total - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Quality of life											
4[111, 113, 115, 119-122]	randomized trials	serious[a]	not serious	not serious	not serious	none	925		Generally similar results See comment 1		⊕⊕⊕◯ Moderate
Functional status											
2[113, 115, 121, 122]	randomized trials	not serious	not serious	not serious	not serious	none	596		Generally similar results See comment 2		⊕⊕⊕⊕ High

* The KDIGO 2012 guideline[116] classified study quality in the following manner: Good: Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT); Fair: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If study of intervention, must be prospective; Poor: High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

† Data extracted from Coyne, 2012[123], a commentary and update on data reported citing differences between the Besarab, 1998[118] paper and the Amgen Clinical Trial Report.

‡ Data extracted from Besarab, 1998[118]

‖ Data Extracted from Coyne, 2012[123]

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; No = number; RR = risk ratio

Explanations:

a. All of the included studies are from the 2012 KDIGO Guideline [116]; of these one was rated as high risk of bias, and four rated as low.

b. The confidence interval indicates that there may be a clinically important increase or decrease in this outcome

c. Less than 30 events with a very wide confidence interval in a single study.

d. Less than 300 events reported with a confidence interval that indicates that there may be a clinically important increase or decrease in this outcome

e. Less than 300 events with an extremely wide confidence interval.

f. Minor differences in the data reported in Besarab, 1998[118] and Coyne, 2012 [123]
g. Data reported in Besarab, 1998[118] are not consistent with data reported in Coyne, 2012 [123] which reports on the data provided by Amgen to the FDA.

Comments

1. One study assessed 20 subscales of the KDQOL, 11 subscales favored neither high or low hemoglobin targets, and nine favored higher targets. Three studies assessed 6 subscales of the KDQ, at six months followup on study showed that neither high nor low target was favored; two studies with 12 months followup showed mixed outcomes of ESAs being favored across all subscales to not being favored by either across all subscales. One study each assessed the TTO and HUI, neither scale showed a difference between high and low hemoglobin targets.
2. The FACIT fatigue scale was used to assess functional status in one study and demonstrated no difference between high and low hemoglobin targets. The six-minute walk test was used to assess functional status in one study and favored neither high or low hemoglobin targets.

Table S41.
Population: Adults with anemia and CKD receiving dialysis
Intervention: ESA administered to reach a higher hemoglobin target
Comparator: ESA administered to reach a lower hemoglobin target
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high Hb target	ESA low Hb target	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion											
2*[113, 115, 118]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	130/658 (19.8%)	193/653 (29.6%)	**RR 0.67** (0.55 to 0.81)	**98 fewer per 1,000** (from 133 fewer to 56 fewer)	⊕⊕◯◯ Low
Hypertension - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in diastolic blood pressure- not reported											
1*[113, 115]	randomized trials	not serious	serious[c]	not serious	serious[d]	none	33 (high target 11.5 to 13.5 g/dL) 31 (low target 9.5 to 11 g/dL)	31 (Hb target 9g/dL)	See comment 1		⊕⊕◯◯ Low
Change in systolic blood pressure- not reported											
1*[113, 115]	randomized trials	not serious	serious[e]	not serious	serious[d]	none	33 (high target 11.5 to 13.5 g/dL) 31 (low target 9.5 to 11 g/dL)	31 (Hb targe 9g/dL)	See comment 2		⊕⊕◯◯ Low
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in mean hemoglobin- not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Reaching a predefined hemoglobin target - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high Hb target	ESA low Hb target	Relative (95% CI)	Absolute (95% CI)	
IV iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

* The KDIGO 2012 guideline[116] classified study quality in the following manner: Good: Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT); Fair: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If study of intervention, must be prospective; Poor: High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; IV = intravenous; No = number; RR = risk ratio

Explanations

a. Both included studies are from the 2012 KDIGO Guideline[116] ; one was rated as low risk of bias, and the other was rated as unclear.

b. Less than 300 events reported; one study has a large confidence interval indicating that there may not be a clinically important effect in this study.

c. Comparisons were inconsistent Hb target of <9/dl compared to a target of >9.5 g/dL; and Hb target of 9.5 to 11 g/dL compared to a target of 11.5 to 13 g/dL.

d. Less than 300 events reported.

e. Results were inconsistent across comparisons: when a Hb target of <9/dl was compared to a target of >9.5 g/dL the results are reported as significant (p<0.001); when a target of 9.5 to 11 g/dL was compared to a target of 11.5 to 13 g/dL, the difference was not significant.

Comments

1. When high and low Hb targets were compared to the placebo (Hb target 9g/dl) p<0.001; when high Hb target was compared to low Hb target, p = 0.063.
2. Differences between groups were not significant.
3. Reports on the average monthly dose of IV iron in participants who survived to the end of study; high Hb average monthly dose = 119mg IV iron, low Hb average monthly dose = 152mg IV iron.

Table S42.
Population: Adults with anemia, CKD, and heart failure
Intervention: ESA administered to reach a lower hemoglobin target
Comparator: ESA administered to reach a higher hemoglobin target
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low Hb target (10+/-1 g/dL)	High Hb target (14+/-1 g/dL)	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion (followup 61 weeks)											
1[118]	randomized trials	not serious*	not serious	not serious	not serious	none	192/625 (30.7%)	129/601 (21.5%)	**RR 1.43** (1.18 to 1.74)	**92 more per 1,000** (from 39 more to 159 more)	⊕⊕⊕⊕ High
Hypertension - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in diastolic blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in systolic blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in mean hemoglobin - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Reaching a predefined hemoglobin target - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV iron dose - not reported											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low Hb target (10+/-1 g/dL)	High Hb target (14+/-1 g/dL)	Relative (95% CI)	Absolute (95% CI)	
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

* This study was rated as having "good quality" in the KDIGO 2012 Guideline[116]. Good quality is defined as: Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT)
CI: confidence interval; Hb = hemoglobin; RR: risk ratio

Table S43.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: ESA administered to reach a higher hemoglobin target
Comparator: ESA administered to reach a lower hemoglobin target
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA: high Hb target	ESA: low Hb target	Relative (95% CI)	Absolute (95% CI)	
Mortality											
8[124-134]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	514/3732 (13.8%)	469/3741 (12.5%)	**RR 1.09** (0.97 to 1.22)	**11 more per 1,000** (from 4 fewer to 28 more)	⊕⊕◯◯ Low
									HR 1.17 (0.86 to 1.60)		
Cardiovascular events--total											
8[124, 126-129, 131-133, 135-137]	randomized trials	serious[c]	serious[d]	not serious	serious[e]	none	839/3621 (23.2%)	479/3618 (13.2%)	**RR range** 0.02 to 2.04		⊕◯◯◯ Very low
Cardiovascular events--stroke											
4[124, 127-129, 132, 133, 137]	randomized trials	serious[f]	serious[g]	not serious	serious[h]	none	125/3202 (3.9%)	72/3207 (2.2%)	**RR 1.74** (1.30 to 2.31)	**17 more per 1,000** (from 7 more to 29 more)	⊕◯◯◯ Very low
									HR 1.55 (0.86 to 2.81)		
Cardiovascular events--heart failure											
5[127-129, 132, 133, 135, 137, 138]	randomized trials	serious[i]	serious[j]	not serious	serious[b]	none	210/2368 (8.9%)	240/2348 (10.2%)	**RR 0.89** (0.74 to 1.06)	**11 fewer per 1,000** (from 27 fewer to 6 more)	⊕◯◯◯ Very low
									HR 1.08 (0.69 to 1.68)		
Cardiovascular events--acute coronary syndrome											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA: high Hb target	ESA: low Hb target	Relative (95% CI)	Absolute (95% CI)	
3[124, 127-129, 132, 133]	randomized trials	not serious	not serious	not serious	very serious[h]	none	132/2305 (5.7%)	136/2311 (5.9%)	**RR 0.97** (0.77 to 1.23)	**2 fewer per 1,000** (from 14 fewer to 14 more)	⊕⊕◯◯ Low
									HR 0.95 (0.76 to 1.20)		
Cardiovascular events--MACE											
4[124, 125, 127-129, 132, 133]	randomized trials	serious[k]	serious[l]	not serious	serious[m]	none	709/2544 (27.9%)	665/2551 (26.1%)	**RR 1.07** (0.98 to 1.17)	**18 more per 1,000** (from 5 fewer to 44 more)	⊕◯◯◯ Very low
									HR 1.15 (0.91 to 1.45)		
Thromboembolism (PE or DVT) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis											
2[125, 127-129, 133]	randomized trials	serious[n]	not serious	not serious	extremely serious[o]	none	4/243 (1.6%)	3/249 (1.2%)	**RR 1.34** (0.30 to 5.96)	**4 more per 1,000** (from 8 fewer to 60 more)	⊕◯◯◯ Very low
All-cause hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events--total											
2[127-129, 132, 133]	randomized trials	not serious	serious[l]	not serious	serious[b]	none	1611/2690 (59.9%)	1231/2343 (52.5%)	**RR 1.06** (0.96 to 1.17)	**32 more per 1,000** (from 21 fewer to 89 more)	⊕◯◯◯ Very low
Quality of life											
9[124, 127-133, 135, 136, 138, 139]	randomized trials	serious[p]	not serious	not serious	not serious	none	7295†		Generally similar results See comment 1		⊕⊕⊕◯ Moderate -
Functional status											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA: high Hb target	ESA: low Hb target	Relative (95% CI)	Absolute (95% CI)	
2[127-129, 133, 138]	randomized trials	serious[q]	not serious	not serious	not serious	none	4360†		Favors higher hemoglobin target See comment 2		⊕⊕⊕◯ Moderate -

* The KDIGO 2012 guideline[116] classified study quality in the following manner: Good: Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT); Fair: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If study of intervention, must be prospective; Poor: High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

† Total N for both groups reported

CI = confidence interval; CKD = chronic kidney disease; DVT = deep vein thrombosis; ESA = erythropoiesis stimulating agent; No = number; PE= pulmonary embolism; RR = risk ratio

Explanations

a. Six of the included studies are from the 2012 KDIGO Guideline [116]; of these, one was rated as high risk of bias, one was rated unclear, and four rated as low. Of the two studies assessed during the update, one study had low overall risk of bias, and the other did not provide information on randomization, and exhibited issues with allocation concealment, and did not blind participants, study personnel, or outcome assessors.

b. The confidence interval indicates that there may be a clinically important increase or decrease in this outcome.

c. Six of the included studies are from the 2012 KDIGO Guideline [116]; of these one was rated as high risk of bias, one was rated unclear, and four rated as low. Of the two studies assessed during the update, one study had low overall risk of bias; one study did not describe any elements except for randomization; one study did not provide information on randomization or allocation concealment, and did not blind participants, study personnel, or outcome assessors.

d. Unable to pool data, I-squared > 75%

e. The range in risk ratios indicates that there may be a clinically important increase or decrease in this outcome.

f. Three of the included studies is from the KDIGO 2012 Guideline,[116] and two were rated as having low risk of bias; one had moderate risk of bias. The one study assessed during the update did not describe randomization, and exhibited poor allocation concealment, and did not blind participants, study personnel, and outcome assessors.

g. The risk ratio indicates that there may be an effect in favor of a higher target while the hazard ratio indicates that the effect may either increase or decrease the probability of this outcome.

h. Less than 300 events reported with a confidence interval that indicates there may be an increase of decrease in this outcome.

i. One of the included studies is from the KDIGO 2012 Guideline,[116] and was rated as having low risk of bias. The three studies assessed during the update did not describe randomization, exhibited poor allocation concealment, and did not blind participants, study personnel, and outcome assessors.

j. The risk ratio and hazard ratios show effect in different directions.

k. Two of the included studies is from the KDIGO 2012 Guideline,[116] and were rated as having low risk of bias. The one study assessed during the update did not describe blinding of participants, study personnel.

l. The I-squared value for the hazard ratio was between 50 and 75%.

m. The confidence intervals around both the risk ration and the hazard ratio indicate that there may be a clinically important increase or decrease in this outcome.

n. One study is from the KDIGO 2012 Guideline,[116] and was rated as having low risk of bias. The one study assessed during the update did not describe blinding of participants, or study personnel.

o. Less than 30 events reported. The confidence interval is very wide and may indicate a clinically important increase or decrease.

p. Five of the included studies are from the 2012 KDIGO Guideline [116]; of these of these one was rated as high risk of bias, one was rated unclear, and three rated as low. Of the fours studies assessed during the update. Three either did not describe or rated as high risk of bias allocation concealment, and blinding of participants, study personnel, and outcome assessors; two studies did not describe randomization; one study exhibited selective outcome reporting.

q. One of the included studies is from the KDIGO 2012 Guideline,[116] and was rated as having low risk of bias. The one study assessed during the update did not describe randomization, and exhibited poor allocation concealment, and did not blind participants, study personnel, and outcome assessors.

Comments

1. Eight studies evaluated quality of life using the SF-36 tool. In general, across all timepoints, and domains, there was not a difference between high and low hemoglobin targets on the SF-36. There was no difference between high and low hemoglobin targets for the following scales: RQoLP, LASA, and KDQ. The Kidney Transplant Questionnaire favored higher hemoglobin target in the fatigue subscale.
2. One study assessed functional status using FACT, and EQ-5d, and the other used FACT. Overall functional status was higher in the high hemoglobin target group.

Table S44.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: ESA administered to reach a higher hemoglobin target
Comparator: ESA administered to reach a lower hemoglobin target
Outcomes: Important outcomes: categorical

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high Hb target	ESA low Hb target	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion											
2[124, 127-129, 133]	randomized trials	not serious	not serious	not serious	not serious	none	323/3528 (9.2%)	529/3604 (14.7%)	**RR 0.62** (0.52 to 0.74)	**56 fewer per 1,000** (from 70 fewer to 38 fewer)	⊕⊕⊕⊕ High
Hypertension											
6[124, 127-131, 133, 138, 140]	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	652/2771 (23.5%)	556/2831 (19.6%)	**RR 1.39** (1.08 to 1.79)	**77 more per 1,000** (from 16 more to 155 more)	⊕◯◯◯ Very low
Cancer											
2[125, 127-129, 133]	randomized trials	serious[d]	not serious	not serious	serious[e]	none	143/2251 (6.4%)	134/2266 (5.9%)	**RR range** 1.00 to 1.08 see comment 1		⊕⊕◯◯ Low
Reaching a predefined hemoglobin target - not reported											
-	-	-	-	-	-	-	-	-	-		-
IV iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

* The KDIGO 2012 guideline[116] classified study quality in the following manner: Good: Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT); Fair: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If

study of intervention, must be prospective; Poor: High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; IV = intravenous; NDD = non-dialysis dependent; No = number; RR = risk ratio

Explanations

a. Five of the included studies are from the 2012 KDIGO Guideline [116]; of these one was rated as high risk of bias, and three rated as low. The one study assessed during the update did not describe randomization, allocation concealment, and did not blind participants, study personnel, and outcome assessors.

b. The I-squared value for the hazard ratio was between 50 and 75%

c. The lower limit of the confidence interval is below 1.25 indicating that the results may not be clinically meaningful.

d. One included study is from the 2012 KDIGO Guideline [116]; it was rated as low risk of bias. The one study assessed during the update did not describe blind participants or study personnel.

e. Less than 300 events reported.

Comments

1. Two studies reported on cancer as cancer-related events or malignant neoplasms
2. Once study reported on the percentage of participants reaching pre-defined hemoglobin targets at two different timepoints across three separate targets.

Table S45.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: ESA administered to reach a higher hemoglobin target
Comparator: ESA administered to reach a lower hemoglobin target
Outcomes: Important outcomes: continuous

b) Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high Hb target	ESA low Hb target	Relative (95% CI)	Absolute (95% CI)	
Change in diastolic blood pressure											
1[139]	randomized trials	very serious[a]	not serious	not serious	not serious	none	743	744	No difference to small mean increase See comment 1		⊕⊕◯◯ Low
Change in systolic blood pressure											
2[132, 139]	randomized trials	very serious[b]	not serious	not serious	not serious	none	28	9	No difference to small mean increase See comment 2		⊕⊕◯◯ Low
Change in mean hemoglobin (followup up to 12 weeks)											
3[135, 137, 138]	randomized trials	very serious[c]	very serious[d]	not serious	not serious	none	407	238	**MD** range, 0.6 to 1.6 g/dL higher		⊕◯◯◯ Very low
Change in mean hemoglobin (followup 26 weeks)											
5[129, 135, 137-139]	randomized trials	very serious[e]	very serious[d]	not serious	not serious	none	2203	2157	**MD** range, 0.6 to 1.76 g/dL higher		⊕◯◯◯ Very low
Change in mean hemoglobin (followup 52 weeks to end of treatment)											
5[129, 135, 137, 139, 141]	randomized trials	very serious[f]	very serious[d]	not serious	not serious	none	427	384	**MD** range, 0.4 to 2.25 g/dL higher		⊕◯◯◯ Very low

* The KDIGO 2012 guideline[116] classified study quality in the following manner: Good: Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT); Fair: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If study of intervention, must be prospective; Poor: High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.
CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; MD = mean difference; NDD = non-dialysis dependent; No = number; RR = risk ratio

Explanations
a. Single study that did not describe allocation concealment, did not blind participant, study personnel, or outcome assessors, and exhibited selective reporting.
b. One of the studies is from the 2012 KDIGO Guideline [116] and was rated as fair (interpreted as high risk of bias), and the other study did not describe allocation concealment, and did not blind of participants, study personnel, and outcome assessors; this study also exhibited selective outcome reporting.
c. Two studies did not describe randomization, or allocation concealment, and did not blind participants, study personnel, and outcome assessors. One study described randomization, but did not describe blinding of the participants, study personnel, or outcome assessors, and exhibited both selective outcome reporting and attrition bias.

d. Unable to pool data, I-squared > 75%.
e. Two studies did not describe randomization; four studies did not describe allocation concealment, and did not blind participants, study personnel, and outcome assessors; a single study exhibited selective outcome reporting.
f. Two studies did not describe randomization, and four did not describe allocation concealment; four studies did not blind participants, study personnel, and outcome assessors; one study exhibited selective outcome reporting.
Comment
1) A single study reported on diastolic blood pressure at baseline, 12 and 24 weeks. Mean difference over time ranged from 0.1 to 5.3 g/dL
2) Two studies reported systolic blood pressure at 12, 24, and 52 weeks. Mean difference ranged from increases of 2.0 to 9.5 g/dL increase at 12 and 24 months, and a net decrease of 0.3 g/dL at 52 weeks.

Table S46.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: ESA
Comparator: Placebo or standard of care
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality											
3[142-144]	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	20/178 (11.2%)	8/99 (8.1%)	**RR 0.99** (0.45 to 2.20)	**1 fewer per 1,000** (from 44 fewer to 97 more)	⊕◯◯◯ Very low
Cardiovascular events – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thromboembolism											
1[142]	randomized trials	serious[c]	not serious	not serious	extremely serious[d]	none	2/44 (4.5%)	0/52 (0.0%)	**RR 5.90** (0.29 to 119.70)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low
Vascular access thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
All-cause hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events--total											
2[143, 144]	randomized trials	very serious[e]	not serious	not serious	very serious[f]	none	38/134 (28.4%)	14/59 (23.7%)	**RR 0.93** (0.57 to 1.52)	**17 fewer per 1,000** (from 102 fewer to 123 more)	⊕◯◯◯ Very low
Quality of life											
1[145]	randomized trials	serious[g]	not serious	not serious	serious[f]	none	51		Generally similar results See comment 1		⊕⊕◯◯ Low
Functional status											
2[143, 145]	randomized trials	serious[h]	not serious	not serious	serious[f]	none	208		Generally similar results See comment 2		⊕⊕◯◯ Low

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; NDD = non-dialysis dependent; No = number; RR = risk ratio

Explanations

a. None of the included studies described randomization or reasons for withdrawals form the study. Two studies did not describe allocation concealment, and did not blind participants, study personnel, or outcome assessors. All of the studies exhibited selective outcome reporting.

b. Less than 30 events reported. The confidence interval indicates a potential increase or decrease in this outcome.

c. The included study exhibited selective outcome reporting.

d. Less than 5 events reported.

e. Neither study described randomization or reasons for withdrawals form the study. Two studies did not describe allocation concealment, and did not blind participants, study personnel, or outcome assessors. All of the studies exhibited selective outcome reporting.

f. Less than 300 events reported with a very wide confidence interval indicating either an increase or decrease in this outcome.

g. Study did not describe allocation concealment, and it did not blind participants, study personnel, or outcome assessors.

h. Less than 300 events reported.

i. Neither study blinded participants, study personnel, or outcome assessors. One study did not describe randomization, or withdrawals.

Comments

1. Of the 10 SF-36 subscales assessed, ESA use was favored over placebo in the following: bodily pain, role-physical, physical component score.

2. The two studies used multiple functional status tools including assessments of falls, mobility, ADL; none of these assessments favored ESAs or placebo. There was no difference between the placebo and ESA groups using the EQ-5D scale; seven FACT-An subscales were included, function, anemia, and total score favored ESA at 24 weeks.

Table S47.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: ESA
Comparator: Placebo or standard of care
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion											
2[142, 143]	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	16/158 (10.1%)	15/91 (16.5%)	**RR 0.97** (0.51 to 1.85)	**5 fewer per 1,000** (from 81 fewer to 140 more)	⊕◯◯◯ Very low
Hypertension – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in diastolic blood pressure											
-	-	-	-	-	-	-	-	-	-	-	-
Change in systolic blood pressure											
0	-	-	-	-	-	-	-	-	-	-	-
Cancer – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in mean hemoglobin											
1[144]	randomized trials	serious[c]	not serious	not serious	not serious	none	20	20	Similar results across groups See comment 1		⊕⊕⊕◯ Moderate -
Reaching a predefined hemoglobin target											
2[145, 146]	randomized trials	serious[d]	serious[e]	not serious	serious[f]	none	26	99/23 (39.1%)	See comment 2		⊕◯◯◯ Very low
IV iron use											
1[127-129, 133]	randomized trials	not serious	not serious	not serious	not serious	none	298/2012 (14.8%)	413/2026 (20.4%)	**RR 0.73** (0.63 to 0.83)	**55 fewer per 1,000** (from 75 fewer to 35 fewer)	⊕⊕⊕⊕ High
Oral iron use											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
1[127-129, 133]	randomized trials	not serious	not serious	not serious	serious[g]	none	1344/2012 (66.8%)	1389/2026 (68.6%)	**RR 0.97** (0.93 to 1.02)	**21 fewer per 1,000** (from 48 fewer to 14 more)	⨁⨁⨁◯ Moderate
IV iron dose – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose – not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; NDD = non-dialysis dependent; No = number; RR = risk ratio

Explanations

a. One study did not describe randomization, allocation concealment, or withdrawals; also did not blind participants, study personnel, or outcome assessors. The other study exhibited selective outcome reporting.

b. Less than 300 events reported.

c. One study did not describe randomization and did not describe withdrawals from the study.

d. One study came from the 2012 guideline[116] and had low risk of bias,, a single study identified in the update allocation concealment and blinding of study personnel and participants were not described.

e. Across two studies there were inconsistent results.

Comment

1. A single study reported on change in mean hemoglobin at 26 weeks with both the ESA and placebo arms reporting an increase in both arms at 26 weeks.

2. Two studies reported percent of participants reaching the pre-defined hemoglobin target; targets vary, and results varied from favoring ESA, favoring placebo, and no difference between groups.

Table S48.
Population: Children with anemia and CKD
Intervention: ESA
Comparator: Placebo or standard of care
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality (followup 24 weeks)											
1[147] (DD)	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	0/6 (0.0%)	0/5 (0.0%)	not estimable		⨁◯◯◯ Very low
Cardiovascular events—total (followup 24 weeks)											
1[147] (DD)	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	0/6 (0.0%)	0/5 (0.0%)	not estimable		⨁◯◯◯ Very low
Thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
All-cause hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events--total - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-		-
Functional status - not reported											
-	-	-	-	-	-	-	-	-	-		-

CI: confidence interval; DD = dialysis dependent (either hemodialysis or peritoneal dialysis); ESA = erythropoiesis-stimulating agents; RR: risk ratio

Explanations

a. Study assessed as "poor" for this outcome in the KDIGO 2012 Guideline.[116] Poor quality is defined as: High risk of bias or cannot exclude possible significant biases, poor methods, incomplete data, reporting errors. Prospective or retrospective.

b. Less than 5 events reported.

c. Study assessed as "fair" for this outcome in the KDIGO 2012 Guideline.[116] Fair quality is defined as: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If a study of intervention, must be prospective.
d. Single small study.

Table S49.
Population: Children with anemia and CKD
Intervention: ESA
Comparator: Placebo or standard of care
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
Growth, height, weight, cognitive development - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Blood transfusion (followup 24 weeks)											
1[147] (DD)	randomized trials	serious[a]	not serious	not serious	extremely serious[b]	none	0/6 (0.0%)	0/5 (0.0%)	not estimable		⊕◯◯◯ Very low
Hypertension - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in diastolic blood pressure (followup 52 weeks)											
1[148] (ND)	randomized trials	very serious[c]	not serious	not serious	serious[d]	none	20	20	MD 4 mmHg higher		⊕◯◯◯ Very low
Change in systolic blood pressure (followup 52 weeks)											
1[148] (ND)	randomized trials	very serious[c]	not serious	not serious	serious[d]	none	20	20	MD 0.5 mmHg lower		⊕◯◯◯ Very low
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in mean hemoglobin (followup 52 weeks)											
1[148] (ND)	randomized trials	very serious[c]	not serious	not serious	serious[d]	none	20	20	MD 1.66 mmHg higher		⊕◯◯◯ Very low
Reaching a predefined hemoglobin target - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV iron use (followup 52 weeks)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA	placebo	Relative (95% CI)	Absolute (95% CI)	
1[148] (ND)	randomized trials	very serious[c]	not serious	not serious	very serious[e]	none	16/20 (80.0%)	12/20 (60.0%)	**RR 1.33** (0.88 to 2.03)	**198 more per 1,000** (from 72 fewer to 618 more)	⊕◯◯◯ Very low
Oral iron use (followup 52 weeks)											
1[148] (ND)	randomized trials	very serious[c]	not serious	not serious	very serious[e]	none	1/20 (5.0%)	8/20 (40.0%)	**RR 0.13** (0.02 to 0.91)	**348 fewer per 1,000** (from 392 fewer to 36 fewer)	⊕◯◯◯ Very low
IV iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; DD = dialysis dependent (either hemodialysis or peritoneal dialysis); ESA = erythropoiesis-stimulating agents; MD = mean difference; ND = non-dialysis dependent; RR: risk ratio.

Explanations

a. Study assessed as "poor" for this outcome in the KDIGO 2012 Guideline.[116] Poor quality is defined as: High risk of bias or cannot exclude possible significant biases, poor methods, incomplete data, reporting errors. Prospective or retrospective.

b. Less than 5 events reported.

c. Study did not describe randomization, blinding of participants or study personnel, or report on withdrawals. Study exhibited selective outcome reporting and did not describe analyses.

d. Small single study.

e. Less than 30 events reported.

Appendix D. Data supplement - Summary of findings (SoF) tables not cited in the guideline

Table S50.
Population: People with anemia and CKD not receiving dialysis
Intervention: Lower HIF-PHI dose
Comparator: Higher HIF-PHI dose
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI Roxa 50mg	HIF-PHI Roxa 70mg	Relative (95% CI)	Absolute (95% CI)	
Mortality											
1[149]	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	0/49 (0.0%)	0/50 (0.0%)	not estimable		⊕◯◯◯ Very low
Cardiovascular events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thromboembolism - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hospitalization, all-cause - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events, total											
1[149]	randomized trials	very serious[a]	not serious	not serious	very serious[c]	none	5/49 (10.2%)	6/50 (12.0%)	**RR 0.85** (0.28 to 2.61)	**18 fewer per 1,000** (from 86 fewer to 193 more)	⊕◯◯◯ Very low
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Functional status - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase domain inhibitors; Roxa = roxadustat

Explanations
a. Both participant blinding and outcome assessor blinding at high risk of bias.
b. Less than 5 participants experienced this event.
c. Less than 30 participants experienced this event.

Table S51.
Population: People with anemia and CKD not receiving dialysis
Intervention: Lower HIF-PHI dose
Comparator: Higher HIF-PHI dose
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI Roxa 50mg	HIF-PHI Roxa 70mg	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hypertension											
1[149]	randomized trials	very serious[a]	not serious	not serious	very serious[b]	none	1/49 (2.0%)	5/50 (10.0%)	**RR 0.20** (0.03 to 1.68)	**80 fewer per 1,000** (from 97 fewer to 68 more)	⨁◯◯◯ Very low
Change in blood pressure – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mean change in Hb											
1[149]	randomized trials	very serious[a]	not serious	not serious	very serious[c]	none	49	50	-	**Range in MD across timepoints**, -0.25 g/dL to 0.06 g/dL	⨁◯◯◯ Very low
Percentage patients reaching hemoglobin target (follow-up: range 18 weeks to 24 weeks)											
1[149]	randomized trials	very serious[a]	not serious	not serious	serious[d]	none	39/49 (79.6%)	40/50 (80.0%)	**RR 0.99** (0.82 to 1.21)	**8 fewer per 1,000** (from 144 fewer to 168 more)	⨁◯◯◯ Very low
Cancer – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
CKD-related outcomes – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Iron use (IV or oral) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Iron dose (IV or oral) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoietin stimulating agents; Hb = hemoglobin; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase domain inhibitors; Roxa = roxadustat

Explanations

a. Both descriptions of participant blinding and outcome assessor blinding had high risk of bias.

b. Less than 30 participants experienced this event.
c. Wide confidence intervals.
d. Less than 300 participants experienced this event.

Table S52.
Population: People with anemia and CKD receiving peritoneal or hemodialysis
Intervention: Lower HIF-PHI dose
Comparator: Higher HIF-PHI dose
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI Lower dose	HIF-PHI Higher dose	Relative (95% CI)	Absolute (95% CI)	
Mortality (hemodialysis*)											
1[82]	randomized trials	very serious[a]	not serious	not serious	extremely serious[b]	none	0/38 (0.0%)	0/37 (0.0%)	not estimable		⨁◯◯◯ Very low
Mortality (peritoneal dialysis†)											
1[150]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	0/50 (0.0%)	0/50 (0.0%)	not estimable		⨁◯◯◯ Very low
Cardiovascular events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thromboembolism - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hospitalization, all-cause - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events, total (hemodialysis*)											
1[82]	randomized trials	serious[d]	not serious	not serious	very serious[e]	none	9/37 (24.3%)	13/38 (34.2%)	**RR 0.71** (0.35 to 1.46)	**99 fewer per 1,000** (from 222 fewer to 157 more)	⨁◯◯◯ Very low
Serious adverse events, total (peritoneal dialysis*)											
1[150, 151]	randomized trials	serious[c]	not serious	not serious	extremely serious[b]	none	2/6 (33.3%)	1/7 (14.3%)	**RR 2.30** (0.28 to 19.80)	**186 more per 1,000** (from 103 fewer to 1,000 more)	⨁◯◯◯ Very low
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Functional status - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase domain inhibitors; MD = mean difference; Roxa = Roxadustat
* Comparison in studies on participants receiving hemodialysis or peritoneal dialysis: 50 mg roxadustat versus 70 mg roxadustat.

† Comparison in studies on participants receiving peritoneal dialysis: low dose roxadustat versus standard dose roxadustat (not defined).
Explanations
a. Both descriptions of participant blinding and outcome assessor blinding had high risk of bias.
b. Less than 5 participants experienced this event.
c. There was no blinding of participants and outcome assessors. One study did not conduct an ITT.
d. Blinding of participants and outcome assessors was high; open-label study.
e. Less than 30 participants experienced this event.

Table S53.
Population: People with anemia and CKD receiving peritoneal or hemodialysis
Intervention: Lower HIF-PHI dose
Comparator: Higher HIF-PHI dose
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI Lower dose	HIF-PHI Higher dose	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hypertension - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mean change in Hb (hemodialysis*) (follow-up: range 18 weeks to 24 weeks)											
1[82]	randomized trials	very serious[a]	not serious	not serious	serious[b]	none	33	32	-	**Range in MD across timepoints**, -0.16 g/dL to 0.14 g/dL	⨁◯◯◯ Very low
Mean change in Hb (peritoneal dialysis*) (follow-up: range 18 weeks to 24 weeks)											
1[151]	randomized trials	very serious[a]	not serious	not serious	very serious[c]	none	6	7	-	**Range in MD across timepoints**, -0.11 g/dL to 0.06 g/dL	⨁◯◯◯ Very low
Percentage of participants reaching hemoglobin target (hemodialysis*) (follow-up: range 18 weeks to 24 weeks)											
1[82]	randomized trials	very serious[a]	not serious	not serious	serious[d]	none	28/37 (75.7%)	32/37 (86.5%)	**RR 1.08** (0.82 to 1.42)	**69 more per 1,000** (from 156 fewer to 363 more)	⨁◯◯◯ Very low
Percentage of participants reaching hemoglobin target (peritoneal dialysis*†) (follow-up: range 12 weeks to 24 weeks)											
2[150, 151]	randomized trials	very serious[e]	not serious	not serious	serious[d]	none	38/57 (66.7%)	31/56 (55.4%)	**RR 1.19** (0.93 to 1.53)	**105 more per 1,000** (from 39 fewer to 293 more)	⨁◯◯◯ Very low
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
CKD-related events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Iron use (IV or oral) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIF-PHI Lower dose	HIF-PHI Higher dose	Relative (95% CI)	Absolute (95% CI)	
Iron dose (IV or oral) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; CKD = chronic kidney disease; Hb = hemoglobin; HIF-PHI = hypoxia-inducible factor–prolyl hydroxylase domain inhibitors; MD = mean difference; RR = risk ratio

* Comparison in studies on participants receiving hemodialysis or peritoneal dialysis: 50 mg roxadustat versus 70 mg roxadustat.

† Comparison in studies on participants receiving peritoneal dialysis: low dose roxadustat versus standard dose roxadustat (not defined).

Explanations

a. Both descriptions of participant blinding and outcome assessor blinding had high risk of bias.

b. Wide confidence interval; less than 300 participants total across studies.

c. Very wide confidence interval; total study population is less than 20.

d. Less than 300 participants experienced this event.

e. In both studies neither participants nor outcome assessors were blinded; one study did not perform an intention-to-treat analysis.

Table S54.
Population: Adults with anemia and CKD not receiving dialysis
Intervention: Higher ESA dose
Comparator: Lower ESA dose
Outcomes: Blood pressure outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
Change in diastolic blood pressure, Peg 0.04 mg/kg Q4W versus ESA Peg 0.025 mg/kg Q4W (Followup 12 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 0.10 lower to 1.30 higher		⊕◯◯◯ Very low
Change in diastolic blood pressure, Peg 0.04 mg/kg Q4W versus ESA Peg 0.025 mg/kg Q4W (Followup 24 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 0.10 to 2.4 lower		⊕◯◯◯ Very low
Change in diastolic blood pressure, Peg 0.04 mg/kg Q4W versus ESA Peg 0.025 mg/kg Q4W (Followup 60 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 1.9 lower to 0.8 higher		⊕◯◯◯ Very low
Change in diastolic blood pressure, Peg 0.75 mg/kg Q2W versus Peg 0.025 mg/kg Q4W or 0.04 mg/kg Q4W (Followup 12 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	327	328	**RR** range mmHg, 0 to 1.7 higher		⊕◯◯◯ Very low
Change in diastolic blood pressure, Peg 0.75 mg/kg Q2W versus Peg 0.025 mg/kg Q4W or 0.04 mg/kg Q4W (Followup 24 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	327	328	**RR** range mmHg, 1.30 lower to 1.10 higher		⊕◯◯◯ Very low
Change in diastolic blood pressure, Peg 0.75 mg/kg Q2W versus Peg 0.025 mg/kg Q4W or 0.04 mg/kg Q4W (Followup 60 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	327	328	**RR** range mmHg, 1 lower to 0.9 higher		⊕◯◯◯ Very low
Change in systolic blood pressure, Peg 0.04 mg/kg Q4W versus ESA Peg 0.025 mg/kg Q4W (Followup 12 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 0 to 3.1 lower		⊕◯◯◯ Very low
Change in systolic blood pressure, Peg 0.04 mg/kg Q4W versus ESA Peg 0.025 mg/kg Q4W (Followup 26 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 0.8 to 4.5 lower		⊕◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
Change in systolic blood pressure, Peg 0.04 mg/kg Q4W versus ESA Peg 0.025 mg/kg Q4W (Followup 60 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 0.5 higher to 2.5 lower		⨁◯◯◯ Very low
Change in systolic blood pressure, Peg 0.75 mg/kg Q2W versus Peg 0.025 mg/kg Q4W or 0.04 mg/kg Q4W (Followup 12 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 0.2 to 3.3 lower		⨁◯◯◯ Very low
Change in systolic blood pressure, Peg 0.75 mg/kg Q2W versus Peg 0.025 mg/kg Q4W or 0.04 mg/kg Q4W (Followup 24 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 1.2 higher to 3.3 lower		⨁◯◯◯ Very low
Change in systolic blood pressure, Peg 0.75 mg/kg Q2W versus Peg 0.025 mg/kg Q4W or 0.04 mg/kg Q4W (Followup 60 weeks)											
2[152]	randomized trials	serious[a]	very serious[b]	not serious	not serious	none	328	328	**RR** range mmHg, 0.2 higher to 3.2 lower		⨁◯◯◯ Very low

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; No = number; Peg = peginesatide; RR = risk ratio; Q2W: every 2 weeks; Q4W = every 4 weeks

Explanations

a. A single publication reporting on two studies (different populations) did not describe allocation concealment, and did not blind participants, study personnel, or outcome assessors.

b. Unable to pool data, I-squared > 75%.

Table S55.
Population: Adults with anemia and CKD receiving dialysis
Intervention: Higher ESA dose
Comparator: Lower ESA dose
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
Mortality											
1[153]	randomized trials	not serious	not serious	not serious	very serious[a]	none	43/332 (13.0%)	40/324 (12.3%)	**RR 1.05** (0.70 to 1.57)	**6 more per 1,000** (from 37 fewer to 70 more)	⊕⊕◯◯ Low
Cardiovascular events--total - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis											
1[153]	randomized trials	serious[b]	not serious	not serious	very serious[a]	none	20/332 (6.0%)	16/324 (4.9%)	**RR 1.22** (0.64 to 2.31)	**11 more per 1,000** (from 18 fewer to 65 more)	⊕◯◯◯ Very low
All-cause hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events--total - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Quality of life											
1[153]	randomized trials	serious[b]	not serious	not serious	not serious	none	656		Generally similar results See Comment		⊕⊕⊕◯ Moderate
Functional assessment - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

* Low dose ESA = epoetin alfa or beta 4,000 IU or darbepoetin alfa 20 mcg weekly; high dose ESA = epoetin alfa or beta 18,000 IU or darbepoetin alfa 90 mcg weekly.
CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; No = number; RR = risk ratio
Explanations

a. Less than 300 events reported; the confidence interval indicates that there may be a clinically important increase or decrease in this outcome.
b. Study did not blind participants or study personnel.

Comment

Twenty-one subscales of the KDQOL SF-36 were assessed in one study at 12 months. The scores for physical function, role limitations (emotional), and physical composite favored low dose. The remainder of the subscales showed no difference between high and low dose.

Table S56.
Population: Adults with anemia and CKD receiving dialysis
Intervention: Higher ESA dose
Comparator: Lower ESA dose
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
Blood transfusion											
1[153]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	15/332 (4.5%)	30/324 (9.3%)	**RR 0.49** (0.27 to 0.89)	**47 fewer per 1,000** (from 68 fewer to 10 fewer)	⊕⊕◯◯ Low
Hypertension - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in diastolic blood pressure											
1[153]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	332	324	No difference to small mean increase See comment 1		⊕⊕◯◯ Low
Change in systolic blood pressure											
1[153]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	332	324	No difference to small mean increase See comment 2		⊕⊕◯◯ Low
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in mean hemoglobin											
1[153]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	332	324	No difference to small mean increase See comment 3		⊕⊕◯◯ Low
Reaching a predefined hemoglobin target - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
IV iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron use - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
IV iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI = confidence interval; ESA = erythropoiesis stimulating agent; No = number; RR = risk ratio

Explanations

a. Study did not blind participants or study personnel.

b. Less than 300 events reported.

c. Single study with varying change in outcome over time.

Comments

1) A single study reported on diastolic blood pressure at baseline, 12, 26, and 52 weeks. Mean difference over time between groups ranged from 1 mmHg lower to 2.1 mmHg higher.

2) A single study reported on systolic blood pressure at baseline, 12, 26, and 52 weeks. Mean difference between groups over time ranged from 2.7 mmHg lower to 3.3 mmHg higher.

3) A single study reported on hemoglobin values at baseline, 26, and 52 weeks. Mean difference between groups ranged from 0.04 g/dL lower to 0.32 g/dL higher.

Table S57.
Population: Children with anemia and CKD
Intervention: Higher ESA dose
Comparator: Lower ESA dose
Outcomes: Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
Mortality - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Vascular access thrombosis - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
All-cause hospitalization (followup 24 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	11/58 (19.0%)	10/56 (17.9%)	**RR 1.06** (0.49 to 2.30)	**11 more per 1,000** (from 91 fewer to 232 more)	⊕◯◯◯ Very low
Serious adverse events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Quality of life (PedsQL [Parent reported]) (followup 24 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	58	56	Total score favors higher dose ESA at 13 weeks (net difference3.92) and end of study (net difference, 1.25); p<0.05†		⊕⊕◯◯ Low
Quality of life (PedsQL [Patient reported]) (followup 24 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	58	56	Total score favors higher dose ESA at 13 weeks (net difference 4.17) and end of study (net difference, 2.42); p<0.05‡		⊕⊕◯◯ Low
Functional status - not reported											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
-	-	-	-	-	-	-	-	-	-	-	-

* Study includes a mixed population of children not treated with dialysis (57.9%) and children treated with hemodialysis (42.1%) or peritoneal dialysis (16.7%).
† Five subscales are reported for the PedsQL [Parent reported]: The following favored a higher ESA dose at both 13 weeks and end of study: emotional function, social function, school function, and psychosocial composite score; The following favored a higher ESA dose 13 weeks and a lower ESA dose at end of study: physical function
‡ Five subscales are reported for the PedsQL [Patient reported]: The following favored a higher ESA dose at both 13 weeks and end of study: physical function, emotional function, and social function. School function was not favored by either dosing regimen. The psychosocial composite score was favored at 13 weeks by higher dose, and neither dosing regimen at the end of the study.

CI: confidence interval; ESA = erythropoiesis-stimulating agents; RR: risk ratio
Explanations
a. Study does not report on blinding of the outcomes assessor, and it is unclear if there are other sources of reporting bias.
b. Less than 30 events reported.
c. Small single study.

Table S58.
Population: Children with anemia and CKD
Intervention: Higher ESA dose
Comparator: Lower ESA dose
Outcomes: Important outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
Growth, height, weight, cognitive development - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Blood transfusion (followup 24 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	9/58 (15.5%)	5/56 (8.9%)	**RR 1.74** (0.62 to 4.87)	**66 more per 1,000** (from 34 fewer to 346 more)	⊕◯◯◯ Very low
Hypertension - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in diastolic blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in systolic blood pressure - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Cancer - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Change in mean hemoglobin (followup 12 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	58	56	MD 1.06 g/dL higher		⊕⊕◯◯ Low
Change in mean hemoglobin (followup 24 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	58	56	MD 0.12 g/dL lower		⊕⊕◯◯ Low
Reaching a predefined hemoglobin target (followup 24 weeks)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESA high dose	ESA low dose	Relative (95% CI)	Absolute (95% CI)	
1*[154]	randomized trials	serious[a]	not serious	not serious	serious[d]	none	55/58 (94.8%)	44/56 (78.6%)	**RR 1.21** (1.04 to 1.40)	**165 more per 1,000** (from 31 more to 314 more)	⊕⊕◯◯ Low
IV iron use (followup 24 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	13/58 (22.4%)	29/56 (51.8%)	**RR 0.43** (0.25 to 0.74)	**295 fewer per 1,000** (from 388 fewer to 135 fewer)	⊕⊕◯◯ Low
Oral iron use (followup 24 weeks)											
1*[154]	randomized trials	serious[a]	not serious	not serious	serious[d]	none	45/58 (77.6%)	27/56 (48.2%)	**RR 1.61** (1.19 to 2.18)	**294 more per 1,000** (from 92 more to 569 more)	⊕⊕◯◯ Low
IV iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Oral iron dose - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

* Study includes a mixed population of children not treated with dialysis (57.9%) and children treated with hemodialysis (42.1%) or peritoneal dialysis (16.7%).
CI: confidence interval; ESA = erythropoiesis-stimulating agents; MD = mean difference; RR: risk ratio

Explanations

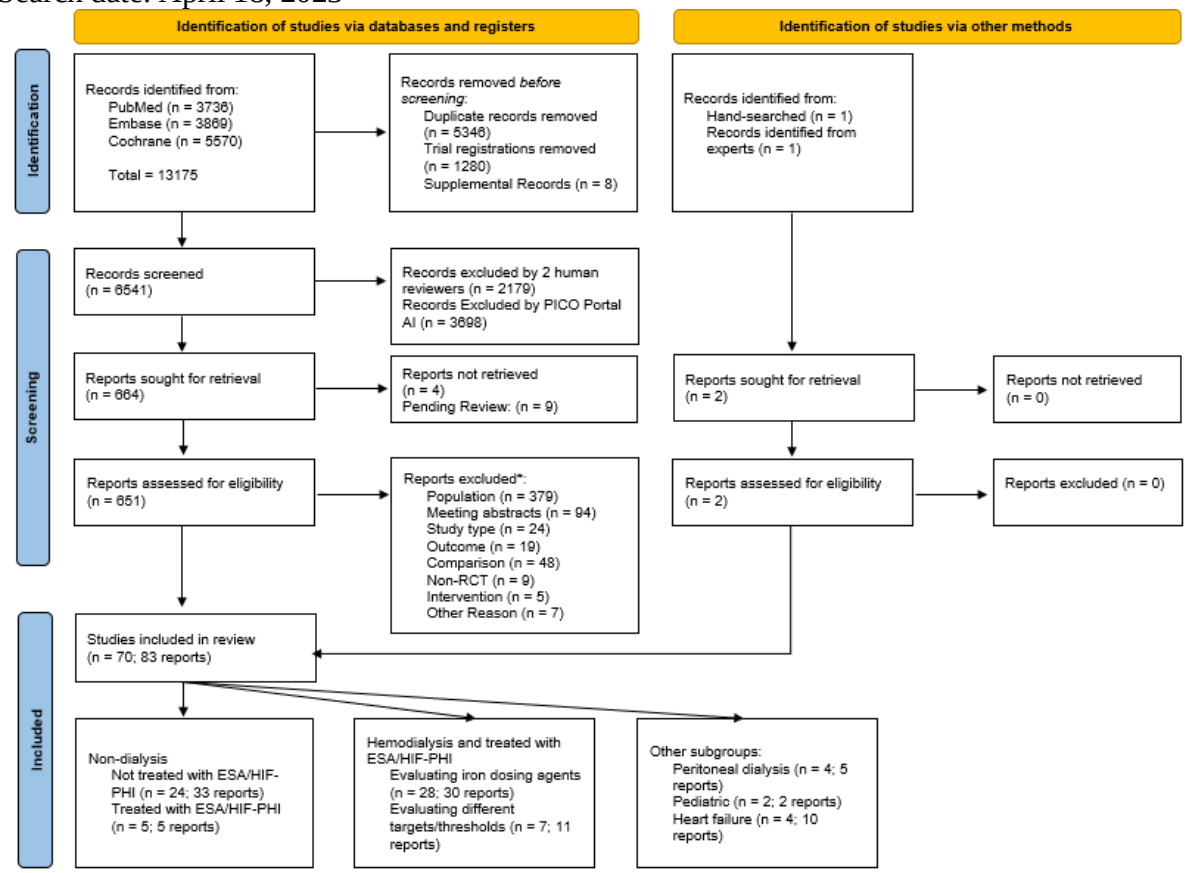
a. Study does not report on blinding of the outcomes assessor, and it is unclear if there are other sources of reporting bias.
b. Less than 30 events reported.
c. Small single study.
d. Less than 300 events reported.

Appendix E: PRISMA Diagrams

Chapter 2. Use of iron to treat iron deficiency and anemia in CKD

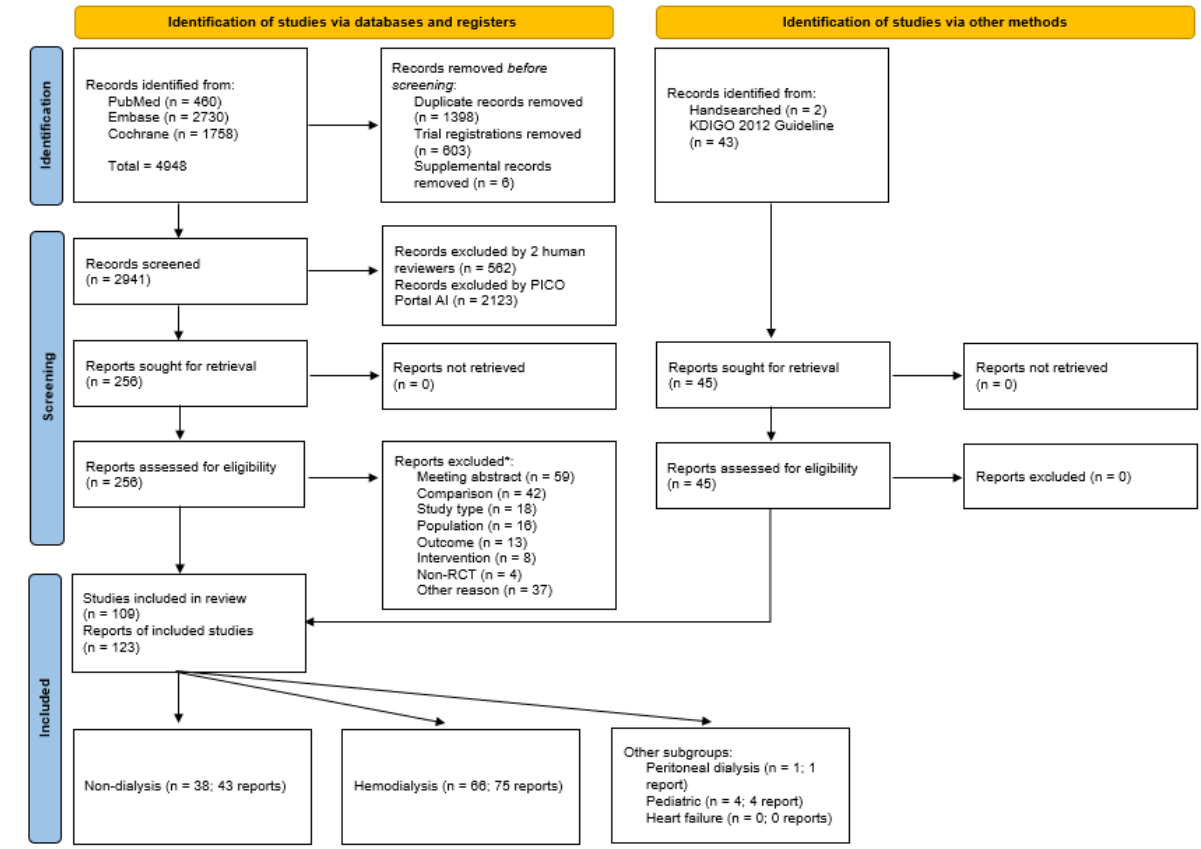
Figure S1. PRISMA diagram for the clinical question "What are the benefits and harms of iron dosing agents in people with anemia and CKD?"

Search date: April 18, 2023



*Number of reasons for exclusion exceeds 568 because articles could be excluded for more than one reason

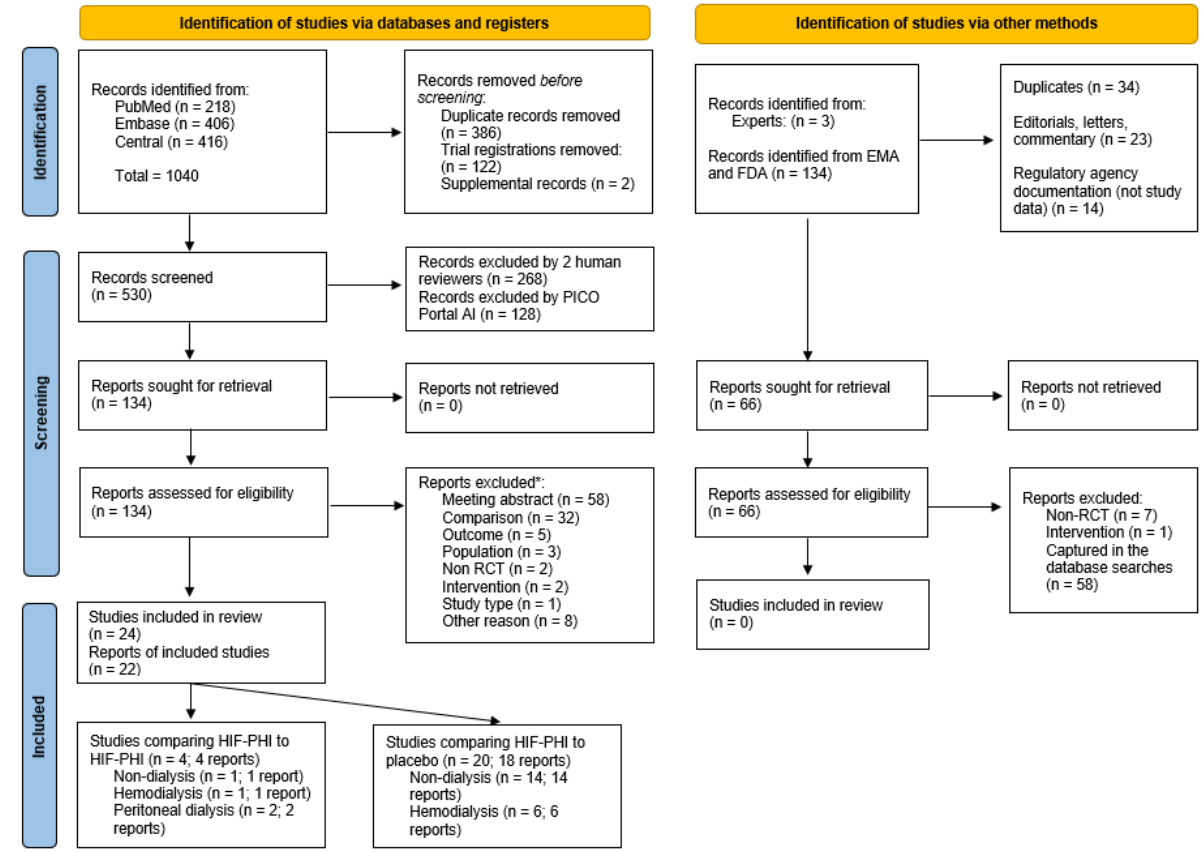
Figure S2. PRISMA diagram for the clinical question "What are the benefits and harms of ESAs in people with anemia and CKD?"
Search date: April 19, 2023



*Number of reasons for exclusion exceeds 133 because articles could be excluded for more than 1 reason

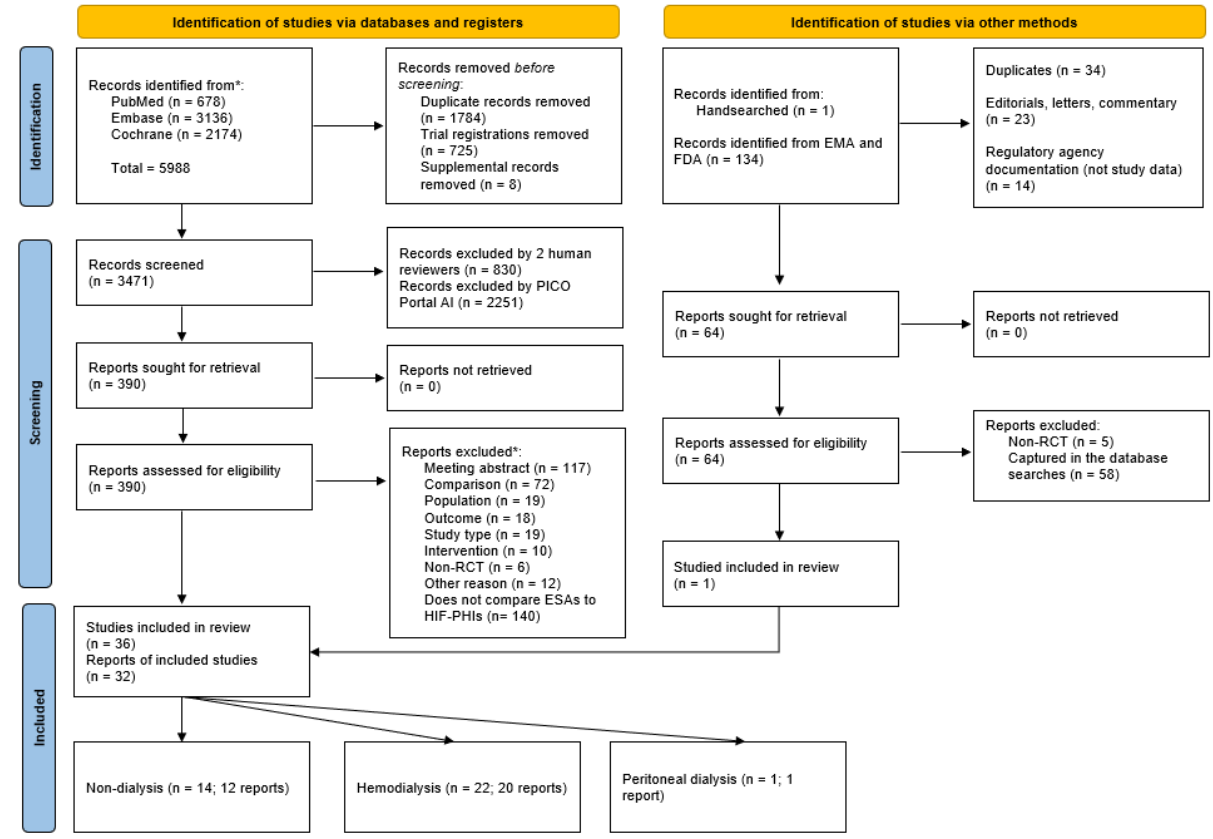
Figure S3. PRISMA diagram for the clinical question "What are the benefits and harms of HIF-PHIs in people with anemia and CKD"?

Search date: April 19, 2023



*Number of reasons for exclusions exceeds 120 because articles could be excluded for more than one reason.

Figure S4. PRISMA diagram for the clinical question "What are the benefits and harms of HIF-PHIs versus ESAs in people with anemia and CKD?"
Search date: April 19, 2023



*Number of reasons for exclusions exceeds 358 because articles could be excluded for more than one reason.

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