

Red Cell Indices	Laboratory Investigations	Findings	Differential Diagnosis
MCV <80 fL Microcytic anemia	Serum ferritin preferred, Serum iron, TIBC, RDW (Ferritin: is an acute phase reactant that may be ↑ if concurrent liver congestion/dx, collagen dx, malignancy, infection or inflammation)	Ferritin <20mcg/L ⇒ Ferritin >20mcg/L ⇒	Iron deficiency anemia (IDA) high RDW, low-normal reticulocyte, low serum iron with high TIBC, ↑ transferrin, ↓ transferrin saturation & ferritin. Anemia chronic dx normal-↑ RDW, low serum iron, low-normal TIBC & transferrin saturation, only ~25% microcytic, Hemoglobinopathy, Lead Overload, Thalassemia normal TIBC, normal to ↑ serum iron & transferrin saturation major high RDW & minor normal RDW; Sideroblastic anemia ↑ RDW
MCV 80-100 fL Normocytic anemia	Consider loss of blood, Reticulocyte count	Blood loss, Hemolysis⇒ No blood loss ⇒	Treat cause GI or menstrual bleed (Use of ASA/NSAIDs, warfarin etc.), high reticulocyte Anemia of chronic dx normal-↑ RDW, low serum iron, low-normal TIBC, ↓ or normal transferrin, normal-↑ ferritin; Tx disease, ?transfusion, ?Epo & <u>not</u> iron if ↑ or normal ferritin. Aplastic anemia, Mixed deficiency anemia, Endocrine hypothyroidism, Hemoglobinopathy
MCV >100 fL Macrocytic anemia	Consider loss of blood, Reticulocyte count, Vitamin B ₁₂ & folate level, Blood film, TSH, LFTs	Blood loss ⇒ No Blood loss ⇒	Treat cause GI or menstrual bleed (Use of ASA/NSAIDs, warfarin etc.), high reticulocyte Liver dx normal RDW, Myelodysplasia high RDW, Folate or Vit B ₁₂ deficiency high RDW, low-normal reticulocyte, Hemolytic anemia

Drug induced **Aplastic anemia**: allopurinol, antithyroid meds, chemo, chloramphenicol, chlorpromazine, clopidogrel, corticosteroids, furosemide, gold, indomethacin, interferon^{α2a/2b}, isoniazid, methyldopa, NSAIDs, penicillamine, phenothiazines, procainamide, sulfonamides & ticlopidine.

Drug induced **Hemolysis in G6PD Deficiency**: ascorbic acid, benzocaine, chloroquine, dapsone, hydroxychloroquine, nitrofurantoin, phenazopyridine, primaquine, sulfacetamide, sulfamethoxazole, sulfanilamide & sulfapyridine.

Drug induced **Hemolytic anemia**: ACEI, acetaminophen, ASA/NSAIDs, cephalosporins, chlorpromazine, chlorpropamide, diclofenac, hydrochlorothiazide, interferon^{α2a/2b}, isoniazid, levodopa, levofloxacin, mefenamic acid, methadone, methyldopa, penicillins, probenecid, procainamide, quinine, quinidine, ribavirin, rifampin, sulfonamides, & tetracycline. (Direct antiglobulin test-DAT or Coomb's test is used to detect cause of hemolytic anemia)

Drug induced **Megaloblastic anemia**: Direct inhibitors of DNA synthesis- azathioprine, chemo meds, hydroxyurea & zidovudine. Folate antagonists- carbamazepine, methotrexate, pentamidine, phenobarbital, phenytoin fosphenytoin, primidone, trimethoprim & valproic acid.

Reduced Folate or Vitamin B₁₂ absorption- alcohol, aminosalicilyc acid, colchicine, cotrimoxazole, H₂ blockers, metformin, neomycin, nitrofurantoin, oral contraceptives, proton pump inhibitors, sulfasalazine & triamterene.

Anemia of CKD - Hemoglobin Control: Key Outcome Trials – Summary

Zack Dumont, Peter Ricci, Linda Gross, Bruce Lang

	Trials Mean follow-up, n	Intervention	Population CKD stage, age, etc.	Key Baseline Indices (e.g. Iron Studies)	Results	Comments
Iron Trials	Charytan et al. ³ 43 days; n=96; RCT, OL	Oral vs IV iron for ND-CKD FeSO ₄ 325mg po TID x 29 days vs Iron sucrose 200mg IV weekly x 5 doses; assessments made up to 14 days after last dose	ND-CKD; Age mean ~61; mostly ♀, (71% oral, 60% IV); multi-racial Included: CrCl(C-G)≤40ml/min, Hgb<105g/L, TSAT<25%, ferritin<300ug/L Excluded: iron tx or blood transfusion w/in last month, apparent GI bleed, alb<30g/L	Hgb (g/L): 97 oral vs 98 IV Ferritin (ng/mL): 103 oral vs 125 IV TSAT (%): 15.6 oral vs 16.6 IV	<ul style="list-style-type: none"> △ Hgb (g/L): +7 oral vs +10 IV; NS △ Ferritin (ng/mL): -5.1 oral vs 288 IV; p<0.0001 • Change in TSAT (%): day 36=2.1 oral vs 5.1 IV day 43=0.5 oral vs 4.5 IV; sig increase for IV, but not oral • # of pts achieved Hgb >110g/L: 31.3% vs 54.2% IV (p=0.028) • SE: similar btwn groups, most common is GI in oral group, & taste-disturbances more common in IV group 	<p>Iron therapy:</p> <ul style="list-style-type: none"> • Should be guided by iron status tests, Hgb levels, ESA dose, & pt status CSN 2008 Guidelines <p>Iron Therapy in Non-hemodialysis CKD pts (ND-CKD)</p> <ul style="list-style-type: none"> • Route of admin has been shown to have no difference in reaching Hgb targets Charytan, & IV is superior to oral Van Wyck; but in light of lack of conclusive superiority evidence & due to ↑ access risk problems & ↑ cost, recommend oral iron first CSN 2008 Guideline • QOL has not been shown to differ between pts treated with oral or IV iron Van Wyck • Studies show that ↑ Hgb may occur following iron tx with ferritin ~100ug/L Charytan & Van Wyck • IV iron produces greater results regardless of ESA use Van Wyck
	Van Wyck et al. ⁴ ~56 days; n=161; RCT, OL, ITT	Oral vs IV iron for ND-CKD pts FeSO ₄ 325mg po TID for 56 days vs Iron sucrose 1g IV x2 doses over 14 days	Stage 3-5 ND-CKD; Age mean ~63; mean eGFR ml/min/1.73m ² : 28.5 oral vs 30.4 IV; 98 pts NOT on ESAs Included: Hgb≤110g/L, TSAT≤25%, ferritin≤300ug/L; if on Epo, no △ for 8wks prior or during study	Hgb (g/L): 101 oral vs 102 IV Ferritin (ug/L): 104 oral vs 93 IV TSAT (%): 17 oral vs 16 IV	<ul style="list-style-type: none"> • % of pts w/Hgb ↑ of ≥10g/L: 28% oral vs 44.3% IV; p=0.0344 • % of IV pts with outcome: 53.1 ESA-use oral vs 38.3 no ESA; NS • % of oral pts with outcome: 32.2 ESA-use oral vs 25.5 no ESA; NS {Primary outcome was a Hgb increase > or =1 g/dL} • ΔeGFR (ml/min/1.73m²): -4.4 oral vs -1.45 IV; p=0.01 • ΔQOL: no statistically significant differences 	
	DeVita et al. ⁵ ~5mos; n=36; RCT	IV iron to high<400 vs low>200 ferritin for HD-CKD pts on ESAs Each subject below target received an IV iron dextran load, HCT was maintained between 32.5-36% by adjusting Epo dose	HD-CKD; Age mean ~66.5; Included: HCT≤33, Ferritin 70-400	HCT (%): 30.5 High vs 29.5 Low Ferritin (ug/L): 203.7 High vs 166.4 Low	<ul style="list-style-type: none"> • HCT (%): 34.0 High vs 36.1 Low {no sig. dif.} • Mean Ferritin (ug/L): 387 high-ferritin vs 261 low-ferritin • End Ferritin (ug/L): 298.6 high-ferritin vs 469.4 low-ferritin • ΔEpo dose (u/kg/wk): -154 high-ferritin vs -31 low-ferritin; p<0.001 	
	Besarab et al. ⁶ ~6mos; n=42; RCT, OL, ITT, single-centre	IV iron to high ₃₀₋₅₀ vs low ₂₀₋₃₀ TSAT for HD-CKD pts on ESAs {16-20wk run-in period with IV iron dextran & erythropoietin to get to study levels of TSAT=20- 30% & Hgb=95-120} 25-150mg IV iron dextran control VS load of 100mg x6 doses for 2wk then 25-150mg/lwk study	HD-CKD; Age mean ~60.8; 25 males, 17 females	Hgb (g/L): 105 control vs 106 study Ferritin (ug/L): 287 control vs 285 study TSAT (%): 23.9 control vs 24.6 study Epo dose (units 3X/wk): 3782 control vs 3625 study	<ul style="list-style-type: none"> • Hgb (g/L): 103 control vs 104 study • Ferritin (ug/L): 298 control vs 731 study • TSAT (%): 27.6 control vs 32.6 study • Epo dose @6mos: 40% lower dose for study group vs control group (significant) 	<p>Iron Therapy in Hemodialysis CKD pts (HD-CKD)</p> <ul style="list-style-type: none"> • Pts with higher ferritin (~400 vs 200 ug/L) require lower doses of ESAs DeVita, thus it is recommended to target ferritin >200 ug/L with iron therapy CSN 2008 Guidelines • Weigh benefits vs risks of initiating iron tx in pts with ferritin >800ug/L & TSAT <25% DRIVE • Pts with higher TSAT% (30-50 vs 20-30) maintain Hgb with lower doses of ESAs Besarab, therefore recommend to target TSAT >20% with iron therapy CSN 2008 Guidelines • Studies looking at oral iron vs placebo have shown that oral iron is no better than placebo (in Hgb improvements Mcdougall or ESA dose minimization) • IV iron has been shown to be superior to oral iron with respect to ↑Hgb Fishbane & Besarab & ↓ESA dose Fishbane
	Maddougall et al. ⁷ ~4mos; n=25; RCT	Oral vs IV iron vs No iron for HD-CKD pts on ESAs Oral ferrous sulfate 200mg TID vs iron dextran 250mg q2wks vs no iron	HD-CKD; Age mean ~58 oral, 47 IV, & 54 no iron	Hgb (g/L): 72 oral vs 73 IV vs 73 no iron Ferritin (ug/L): 309 oral vs 345 IV vs 458 no iron	<ul style="list-style-type: none"> • Hgb (g/L): 102 oral vs 119 IV vs 99 no iron; p<0.05 • ESA dose (unit/dose): 1294 oral vs 1202 IV vs 1475 no iron; NS 	
	Fishbane et al. ⁸ ~4mos; n=52	Oral vs IV iron for HD-CKD pts on ESAs Oral iron vs Iron dextran 100mg IV x2 weekly	HD-CKD; Age mean ~49.5 Included: TSAT>15%, ferritin<100ng/ml	Hgb (g/L): 106 oral vs 108 IV ESA dose (units/treatment): 6750 oral vs 7100 IV	<ul style="list-style-type: none"> • Hgb (g/L): 106 oral vs 115 IV; p<0.05 • HCT (%): 31.8 oral vs 34.4 IV; p<0.05 • ESA dose (units/treatment): 7563 oral vs 4050 IV; p<0.05 • Serum ferritin (ng/mL): 157.3 oral vs 753.9 IV; p<0.05 	
	DRIVE I ⁹ ~6wks; n=129 modified ITT; RCT, OL, multi-centre	IV iron vs No iron in HD-CKD pts with high ferritin, low TSAT Ferrous gluconate 125mg IV with 8 consecutive HD sessions vs no iron; epo doses ↑ 25% in both groups at trial onset (no other △ permitted)	HD-CKD; Age mean ~59-60; ~1:1 male:female; multi-racial Included: Hgb≤110g/L, TSAT≤25%, ferritin=500-1200ug/L (stratified before rand'n to < or > 800ug/L)	Hgb (g/L): 104 IV vs 102 no iron Ferritin (ug/L): 759 IV vs 765 no iron TSAT (%): 18 IV vs 19 no iron	<ul style="list-style-type: none"> • △ Hgb (g/dL): 1.6 IV vs 1.1 no iron; p=0.028 • % of responders ≥20g/L ↑ (%): 49.6 IV vs 29.2 no iron; p=0.041 • △ ferritin (ug/L): 173 IV vs -174 no iron; p<0.001 • baseline ferritin was not predictive of iron response • safety was no different if < or > 800 baseline ferritin (not powered to show safety) • △ TSAT (%): 7.5 IV vs 1.8 no iron; p<0.001 	
	DRIVE II ¹⁰ ~6wks; n=129	Observational study of duration of effect from IV iron under usual clinical mgt	Extension (i.e. used same DRIVE pts)	Epo dose in DRIVE (units/wk): 45,000 IV vs 43,700 no iron	<ul style="list-style-type: none"> • △ Epo dose (units/wk) from dose given in DRIVE: -7527 IV (p=0.003) vs 649 no iron (p=0.809) • % of pts with Hgb>110(g/L): 83.9 IV vs 67.9 no iron; p<0.05 	
ESA	Revicki et al. ¹¹ ~48wks; n=83; RCT, OL, ITT	Erythropoietin vs placebo in ND-CKD pts on health-related QOL ^{HRQL} Initially erythropoietin 50u/kg/dose SubQ 3xweekly or untreated; all treated pts could have dosage ↑ (max 450u/kg/wk) until HCT reached 36, then titrated to target 35	ND-CKD; Age mean ~57, ~67.5% female, mean GFR~10.1ml/min	HCT (%): 26.8 ESA & untreated gp Physical function score (I/100): 44.3 ESA vs 49.1 untreated	<ul style="list-style-type: none"> • HRQL Physical function: +7.8 ESA vs -4.8 untreated; p=0.006 / all other tests NS • △ HCT (%): +4.7 ESA vs -1 untreated (P < 0.0001) • Withdrawals: 53.5 % (23/43) ESA vs 62.5% (25/40) untreated 	<p>ESA Therapy:</p> <ul style="list-style-type: none"> • Goal of treating iron-replete pts with ESAs is to improve QOL, while minimizing any SE of the drug & decreasing the need for transfusions • ESAs: ↑ blood pressure; caution

Roth et al. ¹² (as with Revicki et al.)	Erythropoietin vs placebo in ND-CKD pts, effect on rate of CKD decline	Used same pt population as Revicki	GFR (ml/min): 10.2 ESA vs 10 untreated	• ΔGFR (ml/min): -2.1 ESA vs -2.8 untreated; NS $p=0.376$	• ESAs: ↓ need for blood transfusions, which come with their own set of complications • No clinical benefit has been shown with tx with ESAs early Levin & CREATE, therefore Tx should be withheld until Hgb is sustained below 100g/L & iron stores are repleted & other causes of anemia considered CSN 2008 Guidelines
Levin et al. ¹³ ~24mos; n=152; RCT, OL, ITT	Early ^{High} vs Delayed ^{Low} ESA in ND-CKD pts Erythropoietin 2000IU/wk initial dose given to: 1) study group to maintain Hgb 120-140g/L, 2) control group with a Hgb of 90g/L or less before treatment with a target of 90-105g/L	ND-CKD ; Age mean ~57, ~30% female, 38% DM, GFR _{mean} ~29ml/min; all pts "iron replete" (TSAT>20%, ferritin>60 _{ug/L})	Hgb (g/L): 117.3 delayed vs 117.6 early LVMI (g/m ²): 98.3 delayed vs 100.6 early	• ΔHgb (g/L): -3 delayed vs 9.8 early • ΔLVMI@24mos(g/m ²):+5.2 delayed vs +0.4 early;NS $p=0.28$	
CREATE ¹⁴ ~3yrs; n=603; RCT, OL	Early/High-Hgb vs Late/Low-Hgb Erythropoietin in CKD pts Erythropoietin beta given to target: 1) start when Hgb 110-125g/L, target 130-150g/L 2) start when Hgb 100g/L, target 105-115g/L	Stage 3-4 ND-CKD ; Age mean ~59, ~46% female, 26% DM Included: CrCl=15-35 _{ml/min} , Hgb<110 _{g/L} Excluded: uncontrolled HTN Of Note: Wt (kg): 74.7 early/high-hgb vs 71.8 late/low-hgb; $p=0.05$	Hgb (g/L): 116 early/high vs 116 late/low Ferritin (ug/L): 174 early/high vs 189 late/low TSAT (%): 25.6 early/high vs 38.1 late/low LVMI (g/m ²): 120 early/high vs 118 late/low GFR (ml/min): 24.9 early/high vs 24.2 late/low	• CV Composite (sudden death, MI, acute HF, stroke, TIA, hosp'n for angina, complication of PVD, or hosp'n for arrhythmia); 18% 58 events early/high vs 14% 47 events late/low; HR=0.78, NS $p=0.20$ • ΔLVMI @2yrs(g/m ²): -4.6 early/high vs -3.3 late/low; NS • ΔQOL@2yrs(SF-36): better general health with early/high $p=0.008$ & vitality $p=0.01$ • ΔeGFR (ml/min/yr): -3.6 early/high vs -3.1 late/low; NS • Dialysis: 127 early/high vs 111 late/low; $p=0.03$ • HTN (sys>160): 89 early/high vs 59 late/low; $p=0.005$	• LV mass: Pts treated to low or high Hgb targets do not show difference in progression of LV mass in HD-CKD Parfrey & Foley or ND-CKD Levin & CREATE • QOL in HD-CKD: high Hgb showed improvement in quality of life, but the effect waned over time Parfrey & Foley • QOL in ND-CKD: Varying results show few areas are improved by treating with ESAs early & to higher targets CREATE, CHOIR, & TREAT, & what effects are seen do diminish over time CREATE • Worsening kidney function in ND-CKD: No studies have shown significant difference in tx to high vs low Hgb targets & the contribution to worsening eGFR Roth & TREAT (may ↑ dialysis if tx to higher targets CREATE, or may have no association TREAT)
CHOIR ¹⁵ Median 16mos; n=1432; RCT, OL EARLY TERMINATION	Erythropoietin to High- ¹³⁰ (130-135) vs Low-Hgb ¹¹³ (105-110) in CKD pts	Stage 3-4 ND-CKD ; Age mean ~66, ~55% female, GFR~27 _{ml/min} Included: CrCl=15-50 _{ml/min} , Hgb<110 _{g/L} Excluded: uncontrolled HTN Of Note: HTN (%): 95.8 high-hgb vs 93.2 low-hgb; $p=0.03$ CABG (%): 17.4 vs 13.5; $p=0.05$	Hgb (g/L): 101 high vs 101 low Ferritin(ug/L): 168 high vs 179 low TSAT (%): 25.2 high vs 24.6 low	• Composite (death, MI, hosp'n for CHF, stroke): 125 events (18%) high vs 97 events (14%) low; HR=1.34, $p=0.03$, NNH=25 • Death: 52 high vs 36 low; NS, HR=1.48, $p=0.07$ • ΔQOL: significant differences in only 1 of 12 categories (emotional role) • Any serious AE: 376 (54.8%) high vs 334 (48.5%) low; $p=0.02$ • Any serious AE assoc'd w/ESA: 10 (1.5%) high vs 3 (0.4%) low; $p=0.05$ • CHF: 77 (11.2%) high vs 51 (7.4%) low; $p=0.02$	• Hard endpoints in HD-CKD: Studies showing hard endpoints, such as time to death or 1 st MI Besarab, show treating to high Hgb targets >130 may produce more harm than good FDA warnings • Hard(er) endpoints in ND-CKD: Studies comparing composite CV endpoints show tx to high Hgb targets >130 may lead to ↑ CV events CREATE & CHOIR and stroke TREAT, though there are some limitations to studies {CREATE: ?under-powered, CHOIR: see "Of note"; no iron protocol used, TREAT: 46% of "placebo" group received study drug for rescue}
Canadian EPO Study group ¹⁶ ~6mos; n=118; RCT, DB	Erythropoietin to high-Hgb ¹¹⁵⁻¹³⁰ vs Erythropoietin to low-Hgb ⁹⁵⁻¹¹⁰ vs Placebo in HD-CKD pts Initially erythropoietin 100u/kg/dose 3xweekly; all pts with ferritin<250ug/L received oral or IV iron 1 month prior, & prn during the study	HD-CKD ; Age mean ~43-44 epo vs 48 placebo; Hgb<90g/L	Hgb (g/L): 71 high vs 69 low vs 71 placebo	• ΔSickness impact profile: 7.8 high vs 5.3 low vs 2.9 placebo • ΔStress test m walked: 51 high vs 33 low vs 19 placebo • Mean dose (units/kg/wk): 248 high vs 204 low • Hgb (g/L): 117 high vs 102 low vs 74 placebo • Dialysis access site clots: 7/38 high vs 4/40 low vs 1/40 placebo • ΔBP (sys/dia): 0/+7 high vs 0/+2 low vs -4/-1 placebo	
Parfrey et al. ¹⁷ ~96wks; n=596; RCT, DB	Erythropoietin to High ¹³⁵⁻¹⁴⁵ vs Low ⁹⁵⁻¹¹⁵ Hgb in dialysis pts without symptomatic heart dx or LV dilation Arms divided into "concentric LVH" & "LV dilation"	HD-CKD ; Age mean ~50.8, ~60% male Of Note: Age: 52.2 high-hgb vs 49.4 low-hgb; $p=0.02$ SBP _{mmHg} : 144 high-hgb vs 140 low-hgb; $p=0.02$	LVMI (ml/m ²) gp: 296 high vs 300 low LVMI (g/m ²) gp: 122 high vs 123 low Hgb (g/L): 110 high vs 110 low TSAT (%): 35.7 high vs 36.8 low	• %ΔLVMI (%): 7.6 high-hgb vs 8.3 low-hgb; NS • %ΔLVMI (%): 16.8 high vs 14.2 low; NS • Mean Hgb (g/L) @24wks: 133 high vs 109 low • ΔQOL @ (SF-36): 1.21 high vs -2.31 low; $p=0.036$ • TSAT (%): 34.6 high vs 34.2 low	
Foley et al. ¹⁸ ~48wks; n=146; RCT	Erythropoietin to High ¹³⁵ (130-140) vs Low ¹⁰⁰ (95-105) Hgb effect on cardiomyopathy in dialysis pts	HD-CKD ; Age mean ~62, ~45% male in LVH group, ~78% male in dilation group	LVMI (g/m ²): 147 high vs 139 low LVCVI (g/m ²): 122 high vs 123 low	• ΔLVMI @48wks (g/m ²): NS; $p=0.35$ Mann-Whitney U-test • ΔLVCVI @48wks (g/m ²): NS; $p=0.13$ Mann-Whitney U-test • ΔHgb (g/L): 122.5 high vs 104 low • Improvement in high group: fatigue $p=0.008$, depression $p=0.02$, & relationship $p=0.004$	
Besarab ¹⁹ Median 14mos; n=1233; EARLY TERMINATION	Erythropoietin to "Normal"- ^{42%} vs Low-HCT ^{30%} in CKD pts w/ clinical evidence of HF or ischemic heart dx "Normal Hematocrit Study"	HD-CKD ; Age mean ~65, ~50% female, Dialysis duration ~3.2yrs, ~44% DM, ~51% Class II NYHA _{HF} (no class IV)	HCT (%): 30.5 high vs 30.5 low	• Time to death or 1 st non-fatal MI: did not reach SS _{term'd} early • Death/1 st non-fatal MI: 202 high vs 164 low; RR=1.3 95% CI 0.9-1.9; Deaths: 183 high vs 150 low; Non-fatal MI: 19 high vs 14 low • improved physical functioning	
Tonelli et al. ²⁰	Erythropoietin to High- vs Low-Hgb in CKD pts: Cost-effectiveness Target Hgb _{g/L} : 110-120, 120-125, 140 vs 95-105	HD-CKD ; "typical US dialysis centre" population	IV Dose (units 3x/wk) to achieve Hgb targets: 95-105=3523, 110-120=5078, 120-125=6097, 140=9341	• Cost/QALY: 110-120 vs 95-105 = \$ 55,295; 120-125 vs 110-120 = \$ 613,015; 140 vs 120-125 = \$ 828,215	
TREAT ²¹ Median 29mos; n=4038; RCT, DB, ITT, multi-centred	Darbepoetin to High- vs Low-Hgb in CKD pts with type 2 diabetes Target Hgb _{g/L} : 130 in study group vs "placebo" control (≥90 placebo or if <90, then darbepoetin to >90)	ND-CKD & diabetes Age mean ~68yrs, ~56% female, eGFR ~33ml/min, BMI=30, CV hx ~65%, DM: 15yr history, A1C ~7%, on iron tx ~44% Included: eGFR _{MDRD} 20-60 _{ml/min/1.73m²} , Hgb<110 _{g/L} , TSAT>15% Excluded: uncontrolled HTN, kidney transplant, CA, HIV, bleeding, preg	Hgb (g/L): 105 High vs 104 Low Ferritin (ug/L): 131 darbe vs 137 Low TSAT (%): 23 High vs 23 Low Heart Failure (%): 31.5 High vs 35.2 low; $p=0.01$ FACT-Fatigue score (0 _{least tired} -52 _{most tired}): 30.2 High vs 30.4 Low;	• 1st outcome (death or CV event nonfatal MI, CHF, stroke, hosp'n for angina): 632 31.4% High 130 Target vs 302 29.7% Low 90 Target; NS • 1st outcome (death or ESRD): 652 32.4% High vs 618 30.5% Low; NS • ↑stroke 101 5% High vs 53 2.6% Low, HR=1.92 95%CI 1.38-2.68; $p<0.001$, NNH=42 / 2.4yr • Hgb (g/L) achieved: 125 High vs 106 Low • Venous Thromboembolisms: 41 2.0% High vs 23 1.1% Low; $p=0.02$ • Arterial Thromboembolisms: 178 8.9% High vs 144 7.1% Low; $p=0.04$ • ESRD: 338 16.8% High vs 330 16.3% Low; NS • Fatalities: 15% High vs 25% Low; $p<0.001$ • Fatigue: +4.2 High vs. +2.8 Low; $p<0.001$ Note: 46% "placebo" had darbepoetin rescue, but ↓QALY	• Meta-analysis of 9 RCTs (all n>100, follow-up >12wks) with CKD pts who were randomly assigned to receive ESAs showed that targeting higher Hgb levels lead to ↑ all-cause mortality (RR=1.17, $p=0.031$) & AV access thrombosis (RR=1.34, $p=0.0001$) • Results of TREAT reinforce that treating to higher i.e. physiologic Hgb levels Target: 130 g/L, achieved 125 may come with significant risks & only modest improvements in quality of life. Those with a poor initial hematopoietic response to darbepoetin had worse CV outcomes & death. • ESA: FDA June/11 if Hg >110, then assoc. ↑MI/stroke.

CKD=chronic kidney dx ESRD=end-stage renal dx C-G=Cookcroft-Gault dx=disease ESA=Erythropoiesis stimulating agent FeSO4=ferrous sulfate Hct=hematocrit HD-CKD=dialysis-CKD HF=heart failure Hgb=hemoglobin HRQL=health-related QOL ITT=intention to treat LFT=liver function tests LVMI=left ventricular mass index LVCVI=left ventricular cavity volume index MCV=Mean corpuscular volume MI=myocardial infarction ND-CKD=non-dialysis CKD OL=open label pt=patient QALY=quality-adjusted life year QOL=quality of life RCT=randomized control trial RDW=Red cell distribution width TIBC=total iron binding capacity TSAT=transferrin saturation TSH=thyroid stimulating hormone ♀=female Δ=changes

Anemia Management Recommendations	CSN 2008 Guideline ²²	K/DOQI 2007 Guideline Update ²³	EBPG 2004 Guideline ²⁴	UK-RA 2006 Guideline ²⁵	CARI 2008 Hgb & 2006 Iron Guideline ²⁶	CADTH 2008 Systematic Review & Economic Evaluation ²⁷	K/DIGO Summary ²⁸
Hgb (g/L) target range	110 100-120	110-120 <130	>110 <120 if severe CV dx <140 pre-dialysis	105-125 Adjust dose when <110 or >120	110-120 (120-140 if no CV dx) <130g/L	110	• Hgb>130 can be associated with harm • Hgb=95-115g/L associated with better outcomes than >130 • For Hgb=115-130 there is no evidence to suggest harm or benefit compared with ↑ or ↓ levels • Recommended iron levels are directed at optimizing ESA use & target hgb levels • Lack of info comparing efficacy/safety of various iron preps, regimens & administration routes
TSAT (%)	>20	>20			>20 consider 30-40 in HD		
Ferritin (ug/L) in ND-CKD	>100	>100			>100		
Ferritin (ug/L) in HD-CKD	>200	>200			200-500		

CADTH=Canadian Agency for Drugs & Technologies in Health CARI=Caring for Australians with Renal Insufficiency CSN=Canadian Society of Nephrologists EBPG=European Best Practice guidelines K/DIGO=Kidney Disease Improving Global Outcomes K/DOQI=Kidney Disease Outcomes Quality Initiative UK-RA=United Kingdom Renal Assoc.

References: Anemia - Hemoglobin Control: Landmark Outcome Trials – Summary (www.RxFiles.ca)

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