Classification of Anemias [1,2] {Normal hemoglobin (Hgb) Male: **130-180g**/L; Female:**120-160** g/L; ↑ Hgb if live at high altitude, ↓ Hgb if live near the coast}.

 Apr 2020

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 & not 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, hydroxychloroqine, 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 DNA inhibitors– allopurinol, azathioprine, **chemo meds**, hydroxyurea, leflunomide, mycophenolate & zidovudine. Folate antagonists- carbamazepine, methotrexate, pentamidine, phenobarbital, phenytoin fosphenytoin, primidone, trimethoprim & valproic. Reduced Folate or Vitamin B_{12} absorption- alcohol, aminosalicylic acid, colchicine, cotrimoxazole, H_2 blockers, isoniazid, metformin, neomycin, nitrofurantoin, oral contraceptives, proton pump inhibitors, sulfasalazine, tetracyclines & triamterene.

ANEMIA OF CKD: Hemoglobin Control – Landmark Trials Summary

Z Dumont BSP, P Ricci, L Gross, B 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 FeSO4 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	• △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) • AE: similar between groups, most common is GI in oral group, & taste-disturbances more common in IV group	**Iron therapy:** • Should be guided by iron status tests, Hgb levels, ESA dose, & pt status CSN 2008 Guidelines **Iron Therapy in *Non*-hemodialysis CKD pts (ND-CKD)** • 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 patients 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 **Iron Therapy in Hemodialysis CKD pts (HD-CKD)** • Patients with higher ferritin (~400 vs 200 mcg/L) require lower doses of ESAs DeVita, thus it is recommended to treat when **ferritin ≤500 mcg/L** with iron therapy KDIGO 2012 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 treat when **TSAT ≤30%** with iron therapy KDIGO 2012Guidelines • 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
	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**	• Hct (%): 34.0 High vs 36.1 Low {NS diff.} • **Mean Ferritin (ug/L): 387 high-ferritin vs 261 low-ferritin** • **End Ferritin (ug/L): 298.6 high-ferritin vs 469.4 low-ferritin** • △Epo 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/wk 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	• 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)	
	Macdougall *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	• 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 wkly	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	• 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	• △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	• △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 SC 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 (/100): 44.3 ESA vs 49.1 untreated	• **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	**ESA Therapy:** • Goal of treating iron-replete pts with ESAs is to improve QOL, while minimizing any AE 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	• △GFR (ml/min): -2.1 ESA vs -2.8 untreated; NS $_{p=0.376}$
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}~29$_{ml/min}$; all pts "iron replete" (TSAT>20%, ferritin>60$_{ug/L}$)	Hgb (g/L): 117.3 delayed vs 117.6 early **LVMI (g/m²): 98.3 delayed vs 100.6 early**	• △Hgb (g/L): -3 delayed vs 9.8 early • **△LVMI@24mos(g/m²):+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/m²): 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 $_{p=0.20}$ • △LVMI @2yrs(g/m2): -4.6 early/high vs -3.3 late/low; NS • △QOL@2yr(SF-36): better general health with early/high $_{p=0.008}$ & **vitality** $_{p=0.01}$ • △eGFR (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**
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 HF, stroke): 125 events (18%) high vs 97 events (14%) low; HR=1.34, **p=0.03**, **NNH=25** over 16months (driven by death & hosp'ns) • Death: 52 high vs 36 low; NS, HR=1.48, **p=0.07** • △QOL: 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 • HF: 77 (11.2%) high vs 51 (7.4%) low; p=0.02; [? ↑CKD $^{Inrig'12}$]
ND-CKD PEARL $^{n=983,\ ≥52wks}$ peginesatide ^{monthly} vs darbepoetin ^{q2wk}: Hgb target 110-120g/L, peg ↑CV mortality HR=1.32				
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	• △Sickness $^{impact\ profile}$: 7.8 high vs 5.3 low vs 2.9 placebo • △ Stress 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 • △BP (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	LVVI (ml/m²) gp: 296 high vs 300 ^{low} LVMI (g/m²) gp: 122 high vs 123 low Hgb (g/L): 110 high vs 110 low TSAT (%): 35.7 high vs 36.8 low	• %△LVVI (%): 7.6 high-Hgb vs 8.3 low-Hgb; NS • %△LVMI (%): 16.8 high vs 14.2 low; NS • Mean Hgb (g/L) @24wks: 133 high vs 109 low • **△QOL @ (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/m²): 147 high vs 139 low LVCVI (g/m²): 122 high vs 123 low	• △LVMI @48wks (g/m²): NS; p=0.35 $_{Mann\text{-}Whitney\ U\text{-}test}$ • △LVCVI @48wks (g/m²): NS; p=0.13 $_{Mann\text{-}Whitney\ U\text{-}test}$ • △Hgb (g/L): 122.5 high vs 104 low • Improvement in high group: fatigue $_{p=0.009}$, depression $_{p=0.02}$, & relationship $_{p=0.004}$
Besarab [19] 1998 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 1st non-fatal MI: didn't reach SS, term'd early • Death/1st non-fatal MI: 202 high vs 164 ^{low}; RR=1.3 $_{95\%\ CI\ 0.9\text{-}1.9}$; Deaths: 183 high vs 150 low; Non-fatal MI: 19 high vs 14 low • reportedly improved physical functioning originally, but not confirmed in reanalysis • reanalysis: ↑Death/MI 1.28 $_{95\%\ CI\ 1.06\text{-}1.56}$; ↑Death 1.27 $_{95\%\ CI\ 1.04\text{-}1.54}$ $^{Coyne\ '12}$
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
HD-CKD EMERALD $^{n=1608,\ ≥52wks}$ peginesatide $^{\sim 5mg/monthly}$ vs epoetin $^{4600\text{-}9900\ IU/1\text{-}3x/week}$: Hgb target 100-120g/L, peginesatide as effective as epoetin.				
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 $_{mean}$ ~68, ~56% female, eGFR ~33ml/min, BMI=30, CV hx ~65%, DM: 15yr history, A1C ~7%, on iron tx ~44% Included: $eGFR_{MDRD}$ 20-60$_{ml/min/1.73m^2}$, 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.	• 1° outcome (death or CV event nonfatal MI, HF, stroke, hosp'n for angina): 632 $^{31.4\%}$ High $_{130\ Target}$ vs 302 $^{29.7\%}$Low $_{90\ Target}$; NS • 1° 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** • **Transfusions: 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 ↓QOL**

- 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
- 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)
- Hard endpoints in HD-CKD: Studies showing hard endpoints, such as time to death or 1st 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}
- Meta-analysis of 9 RCTs (all n>100, follow-up >12wks) with CKD patients 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 Hgb >110**, then assoc. ↑MI/stroke.

CKD=chronic kidney dx **C-G**=Cockcroft-Gault **dx**=disease **ESA**=Erythropoiesis stimulating agent **ESRD**=end-stage renal dx **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 **LVVI**=left ventricular volume 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 △=changes

Anemia Management Recommendations	CSN 2008 Guide [22] 2013 Commentary 90	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 2012 [28]
Hgb (g/L) target	100-110	110-120	>110	105-125	110-120 (120-140 if no CVD)	110	<115 (start when Hgb 90-100)
range	95-115	<130	<120 if severe CVD <140 pre-dialysis	Adjust dose when <110 or >120	<130g/L		{Range: 95-115, & target of 100-110} Canadian Society Nephrology 2013 90 (If malignancy, hx stroke/cancer, initiate <90 & target 90-105) (115-130 if patient accepts risk trade-off for possible ↑ QOL)
TSAT (%)	>20	>20			>20 consider 30-40 in HD		Treat when ≤ 30 {little evidence of benefit in treating beyond these TSAT & ferritin numbers}
Ferritin (ug/L) in ND-CKD	>100	>100			>100		Treat when ≤ 500; decision to continue past these parameters based on patient response, Hgb conc, ESA dose in ESA-treated, ongoing blood loss, trends in Hgb/TSAT/Ferritin, and clinical status
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.

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