### ANEMIA OF CKD: Control of Hemoglobin Level – Landmark Trials Summary

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<td><strong>Charytan et al.</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Oral vs IV iron for ND-CKD</td>
<td>FeSO4 325mg po TID x 29 days vs Iron sucrose 1g IV x2 doses over 14 days</td>
<td>ND-CKD: Age &lt;sup&gt;mean&lt;/sup&gt; = 61.9 yrs, mostly (71% oral, 60% LV); multi-racial (included: CrCl Gi&lt;40ml/min, Hgb&lt;105g/L; TSAT&lt;25%, ferritin&lt;300ug/L)</td>
<td>△Hgb (g/L): 97 oral vs 98 IV Ferritin (ng/ml): 103 oral vs 125 IV TSAT (%): 15.6 oral vs 16.6 IV</td>
<td>△Hgb (g/L): +7 oral vs +10 IV; NS △Ferritin (ng/ml): -5.1 oral vs 288 IV; p&lt;0.0001 △TSAT (%): day 36: 2% oral vs 1% LV; day 43: 0.5% oral vs 4.5% LV; <strong>NS</strong> for increase IV vs oral △% of pts achieved Hgb&lt;110g/L: 31.3% oral vs 54.2% IV (p=0.028) △OR: Ferritin &lt;100ug/L of effect from IV iron</td>
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<td><strong>Van Wyck et al.</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Oral vs IV iron for ND-CKD pts</td>
<td>FeSO4 325mg po TID x 56 days vs Iron sucrose 1g IV x2 doses over 14 days</td>
<td>Stage 3-5 ND-CKD; Age &lt;sup&gt;mean&lt;/sup&gt; = 63; mean EGF (mg/ml):172; 28.5 oral vs 30.4 LV; 98 pts/NT in Study included: Hgb&lt;110g/L; TSAT&lt;25%, ferritin&lt;300ug/L; if on Epo, no △ for 8 yrs prior or during study</td>
<td>Hgb (g/L): 101 oral vs 102 IV Ferritin (ug/l): 104 oral vs 93 IV TSAT (%): 17 oral vs 16 IV</td>
<td>△% of pts w/Hgb &lt;10g/L: 28% po vs 44.3% LV; p&lt;0.0004 △% of IV pts with outcome: 53.1 ESA-use oral vs 38.3 ESA NO △% of oral pts with outcome: 32.2 ESA-use oral vs 25.5 ESA NO; <strong>NS</strong> (Primary outcome or %&lt;14g/L) △EFG (mg/ml/L 1.73m2): -4.4 oral vs -4.5 IV; p&lt;0.01 △QOL: Not statistically significant differences</td>
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<td><strong>DeVita et al.</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>~5mos; n=36; RCT</td>
<td>Oral vs IV iron for ND-CKD on ESAs</td>
<td>Each subject before trial received an iron dextran load, Hgb was maintained between 12.5- 14.5% by adjusting Epo dose</td>
<td>Hct (%): 30.5 High vs 29.5 Low Ferritin (ug/L): 203 High vs 164 Low</td>
<td>△Hct (%): 3.0 High vs 3.6 Low (NS dif.) △Mean Ferritin (ug/L): 378 High ferritin vs 261 low ferritin</td>
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<td><strong>Besarab et al.</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>~6mos; n=42; RCT, OL, ITT, single-centre</td>
<td>Oral vs IV iron for ND-CKD pts on ESAs</td>
<td>Each subject before trial received an iron dextran load, Hgb was maintained between 12.5- 14.5% by adjusting Epo dose</td>
<td>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/3wk): 3782 control vs 3625 study</td>
<td>△Hgb (g/L): 103 control vs 104 study △Ferritin (ug/l): 288 control vs 273 study</td>
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<td><strong>Maccouglall et al.</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>~4mos; n=25; RCT</td>
<td>Oral or IV iron for HD-CKD pts on ESAs</td>
<td>Oral ferrum sulfamate 200mg 1xd iron to dextran sodium gluconate vial vs iron</td>
<td>Hgb (g/L): 47 oral, 47 IV vs 54 no iron</td>
<td>△Hgb (g/L): 7.2 oral vs 7.3 IV no iron △Ferritin (ug/l): 309 oral vs 345 IV vs 418 IV</td>
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<td><strong>Fishbane et al.</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td>~4mos; n=52</td>
<td>Oral or IV iron for HD-CKD pts on ESAs</td>
<td>Each subject before trial received an iron dextran load, Hgb was maintained between 12.5- 14.5% by adjusting Epo dose</td>
<td>Hgb (g/L): 106 oral vs 108 IV ESA dose (units/treatment): 6750 vs 7100</td>
<td>△Hgb (g/L): 106 oral vs 115 IV; p&lt;0.05 △Hct (%): 3.1% oral vs 3.4 IV; p&lt;0.05 △Ferritin (ug/l): 756 oral vs 4050 IV; p&lt;0.05 △Mean ferritin (ug/ml): 157 oral vs 735.9 IV; p&lt;0.05 △Hgb (g/L): 1.6 IV vs 1.1 oral; p&lt;0.028 △% of responders 220g/L: 49.6% oral vs 29.2% LV; p=0.041 △Hgb (g/L): 173 IV vs -174 no iron; p&lt;0.001 △% of responders ±100mg vs ±800 baseline ferritin (not powered to show safety) △TSAT (%): 7.5 IV vs 8.1 oral no iron</td>
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<td><strong>Drive 2</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
<td>~6wks; n=129 modified ITT; RCT, OL, multi-centre</td>
<td>Oral or IV iron in HD-CKD pts with high ferritin, low TSAT</td>
<td>Ferrous gluconate 125mg IV w/ 4 consecutive HD sessions daily in no iron pts, Epo doses △ ↑ in 25% of both groups at trial onset (no other △ permitted)</td>
<td>Epo dose in Drive (units/wk): 45,000 IV oral 43,700 no iron</td>
<td>△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</td>
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<td><strong>Revicki et al.</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
<td>~4wks; n=83; RCT, OL, ITT</td>
<td>Erthropoietin vs placebo in ND-CKD pts on health-related QOL trial</td>
<td>Initially 5050/45g/kg/3c low weekly or uncontrolled pts could have dosage max (450ug/kg) until Hct reached 36, then titrated to target 35</td>
<td>ND-CKD: Age &lt;sup&gt;mean&lt;/sup&gt; = 57, 67.5% female, mean GFR=10.1min/ml</td>
<td>△Hct (%): 26.8 ESA &amp; untreated pt Physical function score (1/100) 43.4 ESA vs 49.1 untreated</td>
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Used same pt population as Revicki.

**NS-CKD pts**
- Effects rate of CKD decline

**Early/High-β-Gluc + Delayed Low ESA in NS-CKD pts**
- Expt: 2 groups (Glu + ESA vs Glu + placebo)
- Abs elt Glu in 4 groups: low-β-Gluc, high-β-Gluc, low-ESA, high-ESA
- α=0.015

**Stage 3-4 ND-CKD**
- Age range: ~57, ~30% female, 38% DM, GFR~<15 mL/min
- Expt: 2 groups (Glu + ESA vs placebo)
- Outcome: β-Gluc improved for both groups vs placebo

**CREATE 14**
- 3yr: n=603, RCT, OL, EARLY TERMINATION

**Choi et al. 15**
- Median 16 mos; n=14352; RCT, OL, EARLY TERMINATION

**Canadian EPO Study group et al. 16**
- 6mos; n=116, RCT, DB

**Parfrey et al. 17**
- ≥6Wks; n=596; RCT, DB

**Foley et al. 18**
- ≥4Wks; n=146; RCT

**Besarab 19**
- Median 16 mos; n=12,153; EARLY TERMINATION

**Tonelli 20**
- 20mos; n=3529, RCT, DB, ITT, multi-centred

**TREAT 21**
- Median 29mos; n=4038; RCT, DB, ITT, multi-centred

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**LVMI** = left ventricular mass index
**TSAT** = transferrin saturation
**Hb** = haemoglobin
**EMD** = epoetin delta
**ADH** = alendronate
**HCC** = hepatocellular carcinoma
**MCC** = multiple myeloma
**CADTH** = Canadian Agency for Drugs & Technologies in Health

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**LV mass**
- Pts treated to low or high Hgb targets do not show difference in progression of LV mass in HD-Parfrey & Foley or ND-CKD

**QOL in HD-Parfrey & Foley:**
- high Hgb showed improvement in quality of life, but the effect waned over time

**QOL in ND-CKD:**
- Varying results show few areas are improved by treating with ESA during early & to higher targets; **CREATE, CHOR & TREAT,** & what effects are seen do not last over time

**Cardiovascular events**
- Worse renal kidney function in ND-CKD.
- No studies have shown significant difference in tx to high vs low Hgb targets & the contribution to worsening eGFR in *both* Tx may be due to higher targets **CREATE** or may have no association **TREAT**

**Hard endpoints in HD-Parfrey:**
- Studies showing hard endpoints, such as time to death or 1st MI, show no difference in Hgb targets, but may produce more harm than good

**Harder endpoints in ND-CKD:**
- Studies comparing composite CV endpoints show tx to high Hgb targets ≥120 may lead to **CV events CREATE & CHOR & stroke TREAT,** though there are some limitations to studies (CREATE: underpowered, CHOR: “see no effects”; no protocol usage) & the phrase “placebo group” received study drug for rescue

**Meta-analysis of 9 RCTs**
- (all n=100, follow-up ≥12wks) with CKD patients who were primarily assigned to receive ESAs showed that targeting higher Hgb levels led 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 high Hgb levels in all types of patients 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**
- If Hgb >110, then assoc. ↑ Ml/stroke
References: Anemia - Hemoglobin Control: Outcome Management Trials – Summary (www.RxFiles.ca)


Kucirka LM, Grams ME, Lessler J, et al. Association of restrictive transfusion thresholds above 7 g/dL to 8 g/dL. Transfusing at a restrictive haemoglobin concentration of between 7 g/dL to 8 g/dL decreased the proportion of participants experiencing delayed in the onset of dialysis or adverse events. Based on the current evidence, decisions on the putative benefits in terms of quality of life are worth the extra costs of predialysis. preHuoEPO need careful evaluation.


150. Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. Cochrane Database Syst Rev. 2019 Jan 16;1(CD011204). It is likely that low dialysate [Na+] reduces intradialytic weight gain and BP, which are effects directionally associated with improved outcomes. However, the intervention probably also increases intradialytic hypotension and reduces serum [Na+], effects that are associated with increased mortality risk. The effect of the intervention on overall patient health and well-being is unknown.


