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<th>Trials</th>
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| Charytan et al. | 43 days; n=96; RCT, OL | Oral vs IV iron for ND-CKD | Ferrugine 325mg po TID ± 29 days vs iron sucrose 200mg IV weekly ± 5 doses; assessments made up to 14 days after last dose | Hgb (g/L); 97 oral vs 98 IV Ferritin (ng/ml); 103 oral vs 125 IV TSAT (%) 15.6 oral vs 16.1 IV | • ΔHgb (g/L): +7 oral vs +10 IV; NS | • Should be guided by iron status tests, Hgb levels, ESA dose, & pt status |\n
| Van Wyck et al. | ~56 days; n=161; RCT, OL, ITT | Oral vs IV iron for ND-CKD pts | Ferrugine 325mg po TID ± 56 days vs iron sucrose 1g IV x 2 doses over 14 days | Hgb (g/L): 101 oral vs 102 IV Ferritin (ug/L): 104 oral vs 93 IV TSAT (%): 17 oral vs 16 IV | • % of pts w/Hgb >10g/L: 28% po vs 44.3% IV; p=0.0344 | • Route of admin has been shown to have no difference in reaching Hgb targets |\n
| Macdougall et al. | ~4mos; n=25; RCT | Oral vs IV iron for ND-CKD pts on ESAs | Ferrugine 200mg IV x2 daily vs no iron | Hgb (g/L): 102 oral vs 101 IV Ferritin (ug/L): 309 oral vs 345 IV vs 458 no iron | • ΔHgb (g/L): +7 oral vs +10 IV; NS | • QOL has not been shown to differ between patients treated with oral or IV iron |\n
| Fishbane et al. | ~4mos; n=52 | Oral vs IV iron for HD-CKD pts on ESAs | Ferrugine 100mg IV x2 weekly & ↓ESA dose | 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 use (units/treatment): 3782 control vs 3625 study | • IV iron produces greater results regardless of ESA use |\n
| DRIVE 1 | ~6wks; n=129 modified ITT; RCT, OL, multi-centre | IV iron vs No iron in HD-CKD patients with high ferritin, low TSAT | Ferrugine 125mg IV x2 wks vs no iron | Hgb (g/L): 104 oral vs 102 IV Ferritin (ug/L): 759 IV vs 765 no iron TSAT (%): 18 IV vs 19 no iron | • ΔHgb (g/L): 1.6 IV vs 1.1 no iron; p=0.028 | • Iron Therapy in Hemodialysis |\n
| DRIVE II | ~6wks; n=129 | Observational study of duration of effect from IV iron under usual clinical mg | Extension (i.e. used same DRIVE pts) | Epo dose in DRIVE (units/wk): 45,000 IV vs 43,700 no iron | • ΔEpo dose (units/wk) from dose given in DRIVE: -7527 IV (p=0.003) vs 649 no iron (p=0.809) | • IV iron has been shown to be superior to oral iron with respect to ↑Hgb |\n
| PIVOTAL | 2.1 years; n=2141; ITT, RCT, OL, multi-centre (UK) | IV iron sucroh monthly: High-dose (400ug unless ferritin >700ug/L or TSAT >40%) vs low-dose (0-400ug when ferritin <200ug/L or TSAT <20%). Median HD 264mg vs LD 145mg qmo | Hgb (g/L);106 high vs 105 low Ferritin (ug/L); 214 high vs 217 low ESA dose (IU/wk): 8000 high vs 8000 low | • Hard, patient-meaningful 1’ end-point: composite (nonfatal MI/stroke, hospitalization for HF, or death) | • PIVOTAL | • Proactive IV iron sucrose doses (400mg) given monthly when ferritin ≤700 & TSAT ≤40% shown to decrease CV events & ESA doses |
Erythropoietin vs placebo in ND-CKD pts on health-related QOL (HRQoL) study:
- Initial erythropoietin 50kU/dose SC 3weekly or untreateed; all treated pts could have dosage ↑ (max 450kU/dose) until Hct reached 36%, then titrated to 35%

**Early/High-Hgb vs Low-Hgb**

- Erythropoietin 2000U/wk initial dose given to:
  - 1study group to maintain Hgb >120-130g/L
  - 2control group with a Hgb of 90g/L or less before treatment with a target of 105-115g/L.

**Create**
- Sys; n=603; RCT, RO
- Early/High-Hgb vs Late/Low-Hgb in Epoetin in ND-CKD patients
  - Stage 3-4 ND-CKD: Age mean =59, 46% female, 26% DM, included: CtrCl=15-35, Hgb>110g/L. Excluded: uncontrolled HTN
  - Of Note: Wt (Kg): 74.7 early/high-Hgb vs 71.8 late/low-Hgb; p=0.005

**Choir**
- Medium 16mos; n=1432; RCT, RO
- Early termination
- Termination: ~78% male in dilation group
- Termination: ~46% female, 26% DM
- Of Note: CtrCl=15-35, Hgb>110g/L. Excluded: uncontrolled HTN
- Of Note: TSAT (%): 34.6 high vs 34.2 low

**PD**
- n=1120; 120wks; 140-95105
- Darbeepoetin vs peginesatide vs placebo in ND-CKD pts with type 2 diabetes
- Treat
- Median 29mos; n=4038; RCT, RO, ITT, multi-centred
- Darbeepoetin to High- vs Low-Hgb in CKD pts with type 2 diabetes
- Target Hgb ≥ 100-120g/L, peg ↑ CV mortality HR=1.32
- Peg vs placebo: Hgb>90g/L
- Study drug for rescue}

**ESAs**
- ESA Therapy:
  - Goal of treating iron-replete pts with ESAs to improve QOL, while minimizing any AE of the drug & decreasing the need for transfusions
  - ESA: ↑ blood pressure; caution

**Tx should be withheld until Hgb is sustained below 100g/L & iron stores are replenited & other causes of anemia considered

**LV mass:** Pts treated to low or high Hgb targets do not show difference in progression of LV mass in HD-CKD
- Parfrey & Foley
- ND-CKD
- QOL in HD-CKD: high Hgb showed improvement in quality of life, but the effect waned over time
- Parfrey & Foley
- ND-CKD: Varying results show few areas are improved by treating with ESAs early & to higher targets CREATE, CHORE & 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 in both groups (may) ↑ dialysis if tx to higher targets CREATE, or may have no effect

**Hard endpoints in HD-CKD:** Studies showing hard endpoints, such as time to death or 1st MI event, should show treating to high Hgb targets ≥120 may produce more harm than good ⊕ warnings

**Harder endpoints in ND-CKD:** Studies comparing composite CV endpoints show tx to high Hgb targets ≥120 may lead to ↑ CV events & stroke, though there are some limitations & studies (CREATE) powered, CHORE: see “Of note”; no iron protocol used, treatments of composite “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=0.001)

**Results of TREAT** reinstate that treating to higher Hgb levels in ND-CKD: Target 100g/L, achieved 125 may come with significant risks & only modest improvements in quality of life. Those with a poor initial hematopoietic response to darbeepoetin had worse CV outcomes & death.
References: Anemia - Hemoglobin Control: Landmark Outcome Trials – Summary (www.RxFiles.ca)