

Anemia and Iron Deficiency in CHF

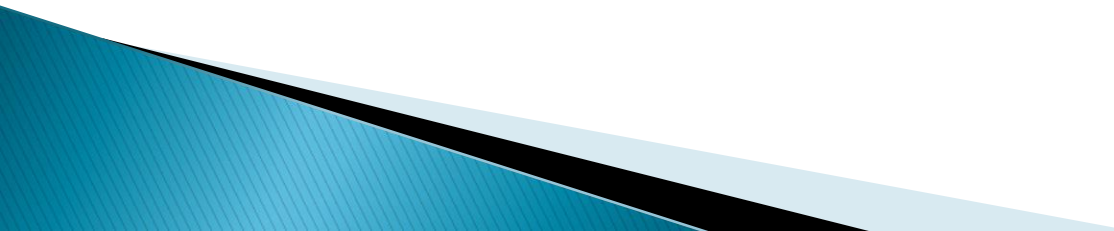
New Insights into an Old Problem

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OBJECTIVES

- ▶ Understand iron physiology in muscle mechanics
 - ▶ Identify the risks and adverse effects of iron deficiency
 - ▶ Define the difference between anemia and iron deficiency in CHF outcomes
 - ▶ Describe the evaluation and management of iron deficiency in CHF
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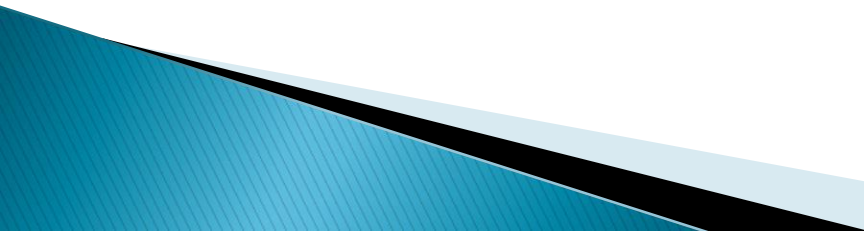
PREVELENC

- ▶ SOLVD Trial
 - 22% of patients enrolled had Hct <39%
 - 4% had Hct <35%
- ▶ Ezekotz et al, (Circ 2003)
 - 12,800 CHF pts
 - 19% with anemia

PREVELENCE

- ▶ Silverberg, et al, (JACC 2001)
 - Incidence of anemia increases with worsening function
 - 4% of pts with NYHA I had anemia
 - 79% of pts with NYHA IV had anemia

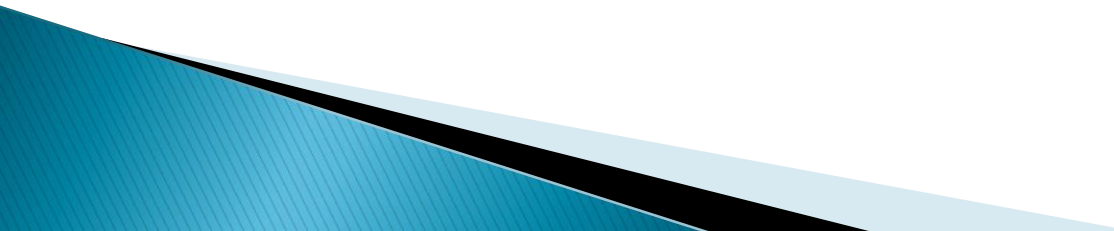
Consequences of Anemia

- ▶ Decrease tissue O₂ delivery
 - ▶ Increased reflex cardiac demand
 - ▶ Increased tissue O₂ extraction
 - ▶ With normal LV function, compensation adequate for Hb as low as 7, and as low as 5.5 in chronic anemias
 - ▶ With LV dysfunction, compensation inadequate at higher Hb levels
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Associations with Heart failure

- ▶ Increased circulating inflammatory cytokines
 - TNFalpha
 - IL-6
 - CRP
- ▶ Similar to chronic inflammatory disease

Associations

- ▶ Hemodilution as determined by I131 albumen
 - ▶ Hyponatremia
 - ▶ Hct as marker of true anemia not consistent
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Iron Deficiency

- ▶ Ferritin is Not an accurate marker in CHF
 - Grote Beverborg, (Circ Heart Fail 2018)
 - 42pts with LVEF <38%
 - 17 No bone marrow iron
 - Ferritin ranged from 44–162ng/ml
 - Nanas, (JACC 2006)
 - 37 pts with NYHA Class III–IV CHF
 - 73% No bone marrow iron
 - 2pts had low ferritin

Associations

▶ ACE Inhibitors

- SOLVD Trial (enalapril vs placebo)
 - At 1 year follow up, HCT < 39%:
 - 11.3% of enalapril group
 - 7.9% of placebo group
- Mechanism:
 - Tetrapeptide Goralatide inhibits erythropoiesis
 - Goralatide is metabolized by ACE

Clinical Correlates of Anemia in CHF

- ▶ Horwich et al, (JACC 39: 2002)
 - 1061 pts with NYHA Class III–IV, LVEF >40%
 - Hb <13.6: Increased BUN,Creat; decreased albumen
 - Worse hemodynamics
 - Higher incidence in Class IV pts
 - Lower peak O₂ consumption
 - Independent predictor of mortality

Clinical Correlates of Anemia in CHF

- ▶ SOLVD Trial
 - Low Hb independent predictor of mortality
 - Each 1% reduction in Hb associated with 3% increased mortality in either arm of study
 - Criticism is lack of assessment of comorbidities

Clinical Correlates of Anemia in CHF

- ▶ Kosiborod et al, (Arch Int Med: 2005)
 - Observational study of 50,000 CHF hospital admits
 - Anemia associated with statistically significant increase in mortality at 1 year
 - When adjusting for comorbidities, no difference between Hct > 40% and Hct < 24%

Clinical Correlates of Anemia in CHF

- ▶ Limited prospective data
- ▶ Armand, et al, (Circ 112, 2005) VAL-HEFT trial
 - Subgroup analysis of Hb changes over 1 year
 - Quartile with largest decrease in Hb
 - MACE increased with HR 1.6
 - Quartile with increase in Hb
 - MACE decreased with HR 0.79

Iron Deficiency

- ▶ TSAT is reduced in inflammation and iron deficiency
- ▶ Okonko et al, (JACC 58: 2011)
 - 157pts with systolic heart failure
 - TSAT < 20% in
 - 16% NYHA Class I-II
 - 72% NYHA Class III
 - 100% NYHA Class IV

Iron Deficiency

- ▶ TSAT < 20% Associated with
 - Decreased O₂ consumption
 - Increased mortality at 2 years, HR 3.4
 - Again, predicted mortality independent of hb

Iron and Muscle Energetics

- ▶ Finch, et al (JClinInvest:58)
 - Work performance in iron deficient rats
 - Hemoglobin reduced but controlled
 - Performance normalized only in group with iron replacement
 - Marked decrease in performance persisted in rats with low iron even when Hb normalized
 - Mitochondrial phosphorylation improved in rats treated with iron

Iron and Muscle Energetics

- ▶ Willis, et al (J Nutr:120)
 - Iron deficient rats, Hb 4.1–5.2
 - Walking duration increased 6–10fold for 12–18 hours after iron repletion

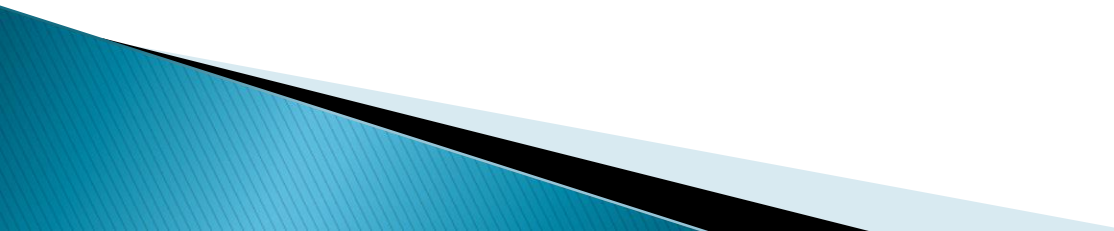
Therapeutic Trials

- ▶ **FAIR-HF Trial** Anker, et al, NEJM 361:2009
 - 459 pts with
 - NYHA Class II and EF <40%
 - NYHA Class III and EF < 45%
 - Ferritin <100
 - TSAT <20
 - Hb 9.5–13.5

FAIR-HF Trial

- ▶ Randomized DB to 200mg IV iron weekly vs placebo
- ▶ Endpoint: Global Assessment score
 - Self reported

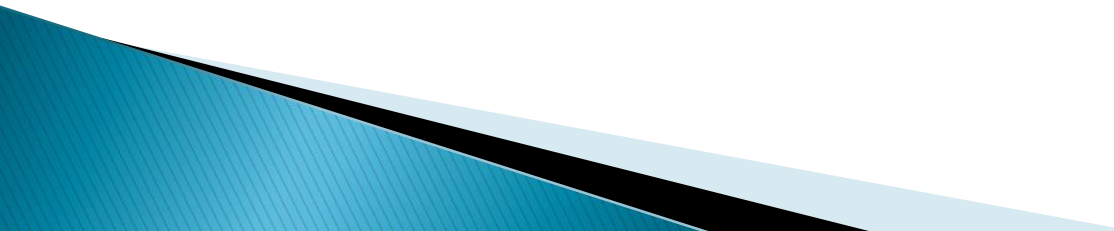
FAIR-HF Trial

- ▶ Moderate/Much improved:
 - 50% in active arm
 - 28% in placebo
 - ▶ Improvement to NYHA I:
 - 47% in active arm
 - 30% in placebo
 - ▶ Ferritin increased 246ng/ml
 - ▶ Hb increased 0.5mg/dl
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Oral Iron Replacement

- ▶ **IRONOUT HF Trial** Lewis et al, JAMA 317:2017
 - 299 pts, EF <40%
 - Ferritin <100
 - TSAT <20%
 - Hb 9–15
 - 16 week follow up
 - Result: No difference in Peak VO₂, 6 minute walk, or Quality of Life assessment

Summary

- ▶ Iron Deficiency is very common in CHF, and nearly universal in Class IV patients
 - ▶ Ferritin level alone is NOT an accurate marker of iron deficiency in CHF
 - ▶ Muscle energetics impaired with iron deficiency
 - ▶ Iron deficiency appears to be an independent predictor of adverse outcome in CHF
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Summary

- ▶ Repletion of iron improves function, quality of life and possibly mortality **INDEPENDENT** of anemia
- ▶ Limited data on therapy suggests that intravenous iron replacement may be effective, but oral replacement has not been shown to achieve similar endpoint

Remaining Questions

- ▶ Safety of long term treatment with infused iron
 - ▶ Very limited data on prospective primary endpoint of MACE with treatment
 - ▶ Effect of iron replacement on myocardial energetics and function is unknown
 - ▶ Is iron deficiency a factor independent of inflammation markers?
 - ▶ Why is oral iron possibly ineffective in achieving clinical benefit?
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