

# The Administration of Subcutaneous Erythropoietin in Elderly Patients with Heart Failure and Normal Ejection Fraction over Three Months is Safe and Effective.



Cohen, R, Wajahat, R, Titova, I, Karlin, P, Mancini D, Maurer, M

Columbia University Medical Center, New York, USA

## Background

- Anemia is a significant co-morbidity among patients with heart failure and a normal ejection fraction (HFNEF), commonly called “diastolic heart failure” (DHF).
- Data in subjects with HFNEF are emerging to suggest a relationship between anemia, clinical symptoms, left ventricular structure, hemodynamics, morbidity, and renal function.
- In hospitalized patients with HFNEF, >50% are anemic with a mean hemoglobin of  $11.8 \pm 2.2$  g/dL (*JACC*. 2004; 43: 1432 – 38).
- To date, little is known about the safety and efficacy of subcutaneous erythropoietin injection in the subset of elderly patients with HFNEF and anemia.

## Methods

- **Study Design**
  - Open label, prospective experimental study over three months
- **Study Subjects**
- **Inclusion Criteria**
  - Anemia
    - All patients met criteria for anemia defined as hemoglobin < 12 g/dL
  - Heart Failure and a Normal Ejection Fraction (HFNEF)
    - All patients in the HFNEF group met criteria for *diastolic heart failure* as defined by the European Society of Cardiology: signs and symptoms of congestive heart failure, a normal LV ejection fraction (we specifically required ejection fraction  $\geq 50\%$  by three dimensional echocardiography) and evidence of abnormal diastolic function
    - NHANES criteria were employed to define the signs and symptoms of heart failure which include symptoms of dyspnea, resting heart rate, rales, JVD, and evidence of fluid on chest x-ray. Patients met criteria with NHANES score of  $\geq 3$
- **Exclusion Criteria**
  - Anemia from known GI blood loss
  - Infiltrative cardiac disease such as hemochromatosis and amyloidosis
  - Hypertrophic Cardiomyopathy
  - Chronic Pulmonary Disease ( $FEV_1 < 60\%$  Predicted)
  - History of DVT or PE within 12 months of study entry
  - Known hypercoagulable state
  - History of stroke or TIA within 6 months of study entry
  - Allergy to human serum albumin or mammalian cell derived products
  - History of Acute Coronary Syndrome within 6 months of study entry
- **Intervention**
  - Weekly subcutaneous erythropoietin injections were administered to each study participant over a three month period .
  - Supplemental oral ferrous sulfate was administered to all patients.
  - Weekly hemoglobin levels were measured and erythropoietin dosing was adjusted based on a dosing algorithm designed for use in this study not to exceed a rate of rise of hemoglobin of 0.4 g/dL per week.

## Endpoints of Study

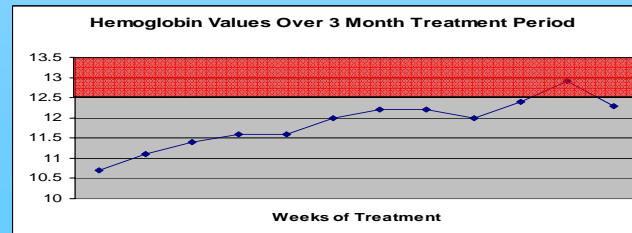
Multiple physiological endpoints were measured at baseline and follow up. These endpoints included:

1. Primary Endpoint: Exercise Capacity as measured by
    - **6 Minute Walk Test**
    - **Bicycle Ergometer Cardiopulmonary Exercise Testing**
  2. Secondary Endpoints:
    - **Three Dimensional Echocardiography: LV Volumes and Mass**
    - **Blood Volume Analysis of Plasma Volume by Tagged Albumin Method**
    - **Quality of Life Measures by Kansas City Cardiomyopathy Questionnaire**
- **Statistical Analysis**
    - Differences between baseline and treatment were evaluated by paired Student’s t test.
    - A  $p \leq 0.05$  was considered significant.

## Baseline Characteristics

Parameter (n=11)	Value
Age (years)	$68 \pm 10$
Percent Female	91%
Race (W, B, H, O)	36% Black 64% Hispanic
BMI (kg/m <sup>2</sup> )	$35 \pm 5$
Percent Diabetic	73%
Percent CAD	73%
Creatinine (mg/dL)	$1.4 \pm 0.6$
Estimated GFR (mL/min)	$59 \pm 22$

## Results



	Baseline (n=10)	Follow Up (n=10)
Adverse Events	N/A	0
Hemoglobin (g/dL)	$10.8 \pm 0.9$	$12.2 \pm 0.9^*$
Blood Pressure Parameters (mmHg)		
Systolic Blood Pressure	$144 \pm 18$	$134 \pm 21$
Diastolic Blood Pressure	$69 \pm 13$	$64 \pm 9^*$
Mean Arterial Pressure	$94 \pm 13$	$88 \pm 8$
Pulse Pressure	$75 \pm 15$	$70 \pm 26$
Medication Use (no. pts (%))		
Loop Diuretic	5(56)	6(67)
Thiazide	3 (33)	2 (22)
ACE Inhibitor	7 (78)	7 (78)
Beta Blocker	6 (67)	6 (67)
Calcium Channel Blocker	6 (67)	7 (78)
Brain Type Natriuretic Peptide (pg/mL)	$187 \pm 128$	$133 \pm 119$
Plasma Volume (mL)	$2865 \pm 532$	$2866 \pm 600$
Red Cell Volume (mL)	$1169 \pm 169$	$1735 \pm 350^*$
Six Minute Walk Test (m)	$289 \pm 81$	$321 \pm 69^*$
Bicycle Ergometer Exercise Time (s)	$434 \pm 196$	$583 \pm 193^*$
VO <sub>2</sub> (mL/min)	$628 \pm 170$	$774 \pm 260^*$
VO <sub>2</sub> (mL/kg/min)	$8.5 \pm 2.3$	$9.4 \pm 2^*$
Peak Exercise HR (bpm)	$96 \pm 20$	$110 \pm 18$
EDV (mL)	$109 \pm 11$	$100 \pm 10^*$
LV Mass (g)	$174 \pm 25$	$168 \pm 22$

## Limitations

- Single center, uncontrolled, un-blinded clinical trial.

## Conclusions

- Erythropoietin administration dosed to effect a rate of rise of <4 gm/dL to elderly anemic patients with HFNEF is associated with significant increases in hemoglobin and red cell volume, without any adverse effect on systemic blood pressure if appropriately followed and treated.
- Preliminary data suggests that such therapy is associated with significant improvement in submaximal exercise capacity, and significant reduction in left ventricular end diastolic volumes.