Heart failure and anaemia – investigation and management

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Conflict of interest:

Speaker fees and advisory boards for Vifor International and Vitaline Pharmaceuticals

Prevalence of anaemia in large CHF studies

-- sorted by CHF severity --

Study	Gender	Definition (g/dL)	Prevalence (%)
Tx assessment Horwich H et al. JACC 2002	F M	<12 <13	30.0
COPERNICUS	M + F	<12.5	19
IN CHF	F M	<11 <12	15.6
ELITE II	F M	<12 <12	16.6 7.2
Val-HeFT	F M	<11 <12	9.0

Prevalence of anaemia

- Systematic review and meta-analysis
- 34 studies
- n=153,180
- Majority WHO definition (18/34)
- Using study definition, anaemia present in:

37.2%

Groenveld et al. J Am Coll Cardiol 2008;52:818-827

Acute heart failure in the elderly

- Italian Survey on AHF – 206 departments enrolled 2,807 in 3 months
- Octogenarians (mean age 84) - 28% of cohort
- Females 50% (36% in those <80 yrs)
- Anaemia (64% vs 53%, p< 0.0001) and CKD (56% vs 43%, p<0.0001) more common in those >80 yrs
- In-hospital mortality twice as high in octogenarians (11.8% vs 5.6%, p<0.001).

Miani et al. Am Heart J 2009;158:126-32

Prevalence of anaemia increases with NYHA class in elderly CHF patients

Prospective study: 201 patients (aged >65 years)

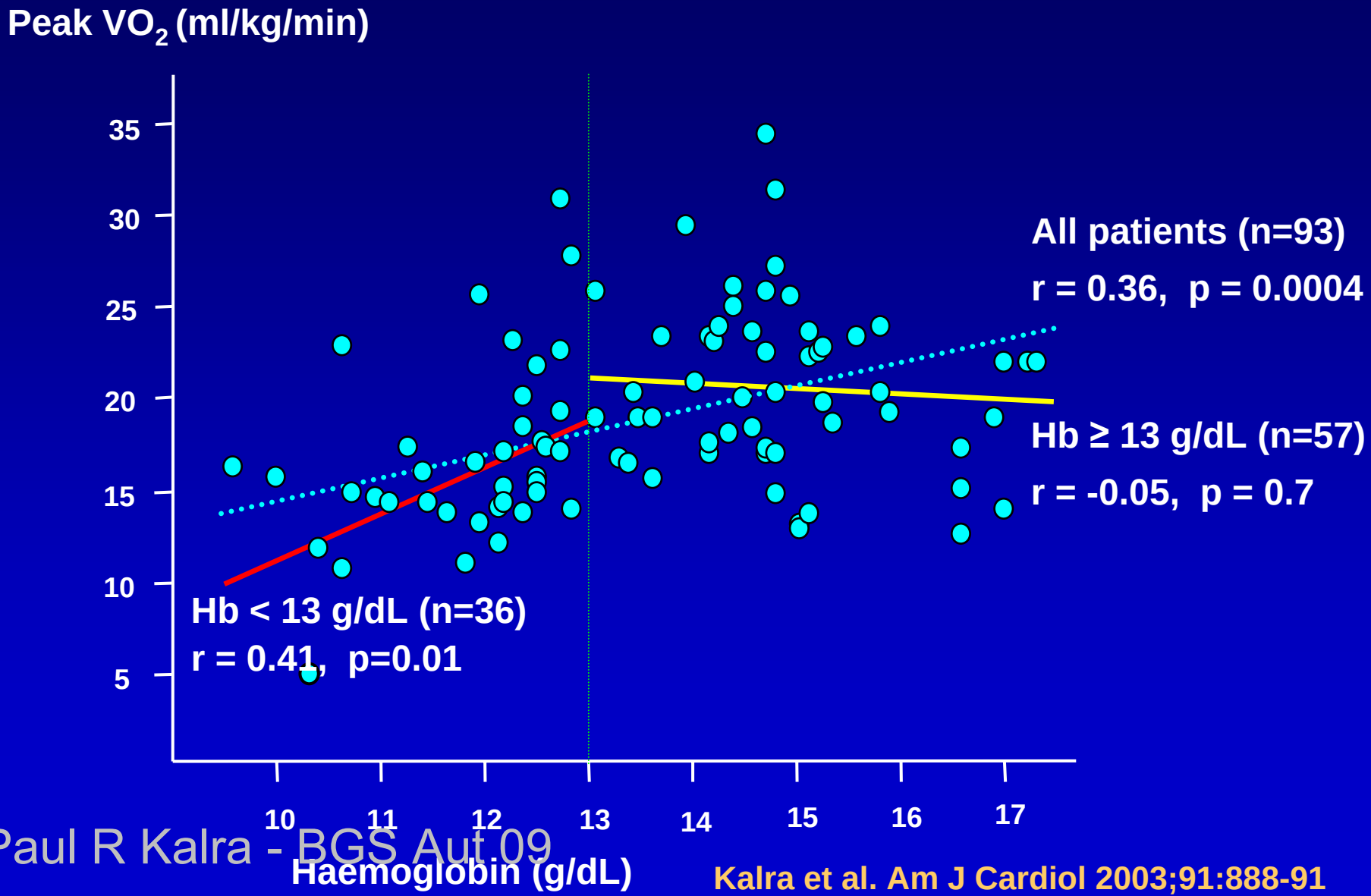
Results: 49.8% had haemoglobin (Hb) <12 g/dL

NYHA Class	Patients (%)
1	0
2	36.4
3	52.0
4	65.9

P = 0.01

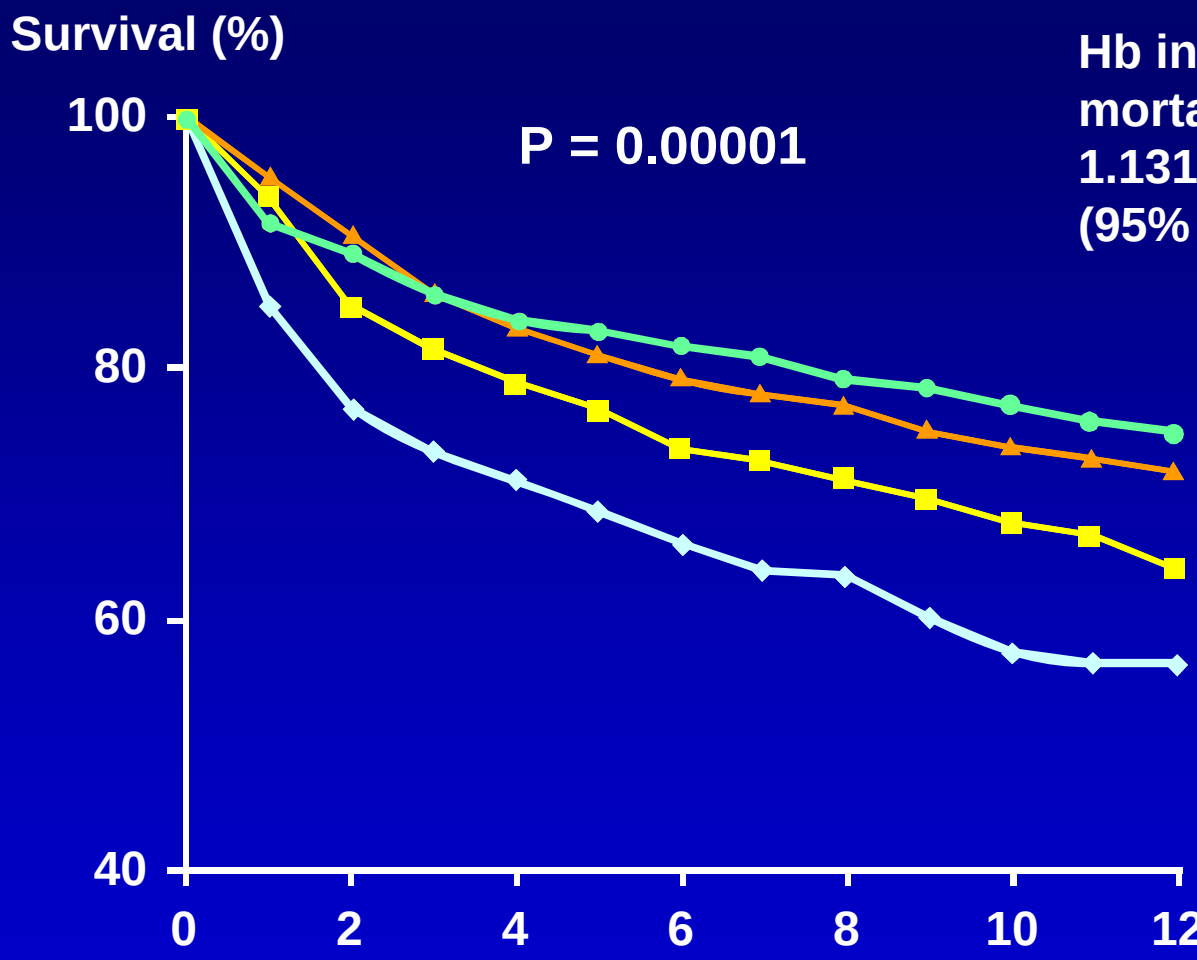
Wisniacki N et al. Heart 2001

Independent relation between peak VO_2 and Hb in males with CHF



Kalra et al. Am J Cardiol 2003;91:888-91

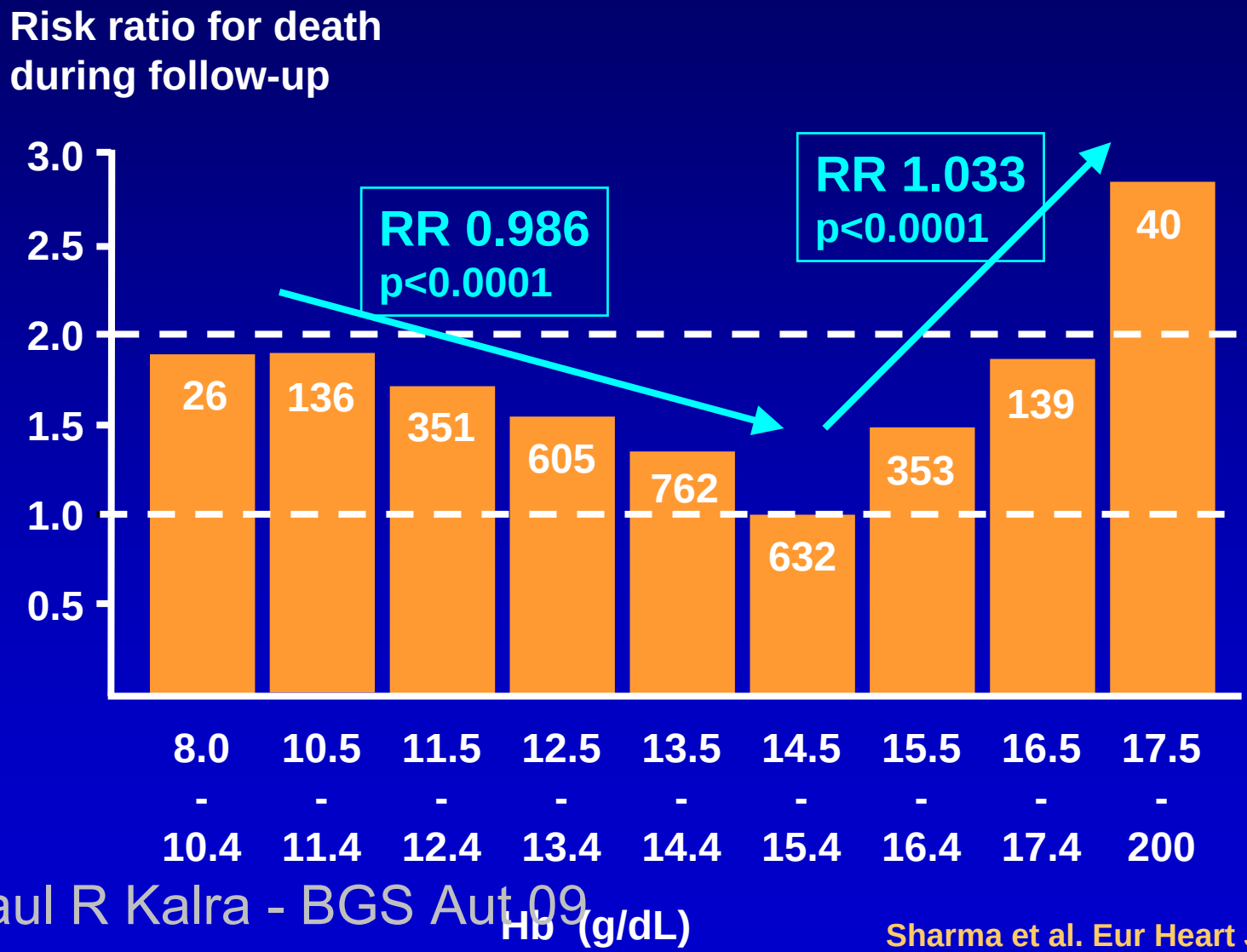
CHF: Hb level *vs* Mortality (n=1,061)



Hb independent predictor of mortality with relative risk 1.131 per 1 g/dL decrease (95% CI 1.045 to 1.224)

Horwich et al. J Am Coll Cardiol 2002;39:1780-6

Hb and survival in ELITE II (n=3044)



Sharma et al. Eur Heart J 2004;25:1021-8

Possible mechanisms of anaemia in CHF

Haemodilution
- Plasma Volume ↑

Decreased CO
- Bone Marrow (BM) dysfunction

Iron deficiency
- Fe^{++} uptake ↓
- malabsorption
- chronic bleeding (aspirin)

Chronic immune activation (TNF)
- production of Epo ↓
- Epo activity in BM ↓
- Impaired release and utilization of Fe

Drugs
- ACE-I: Epo synthesis ↓
- Epo activity in BM ↓

Chronic kidney failure
- Production of Epo ↓
- Loss in urine ↑

Aetiology of anaemia in CHF

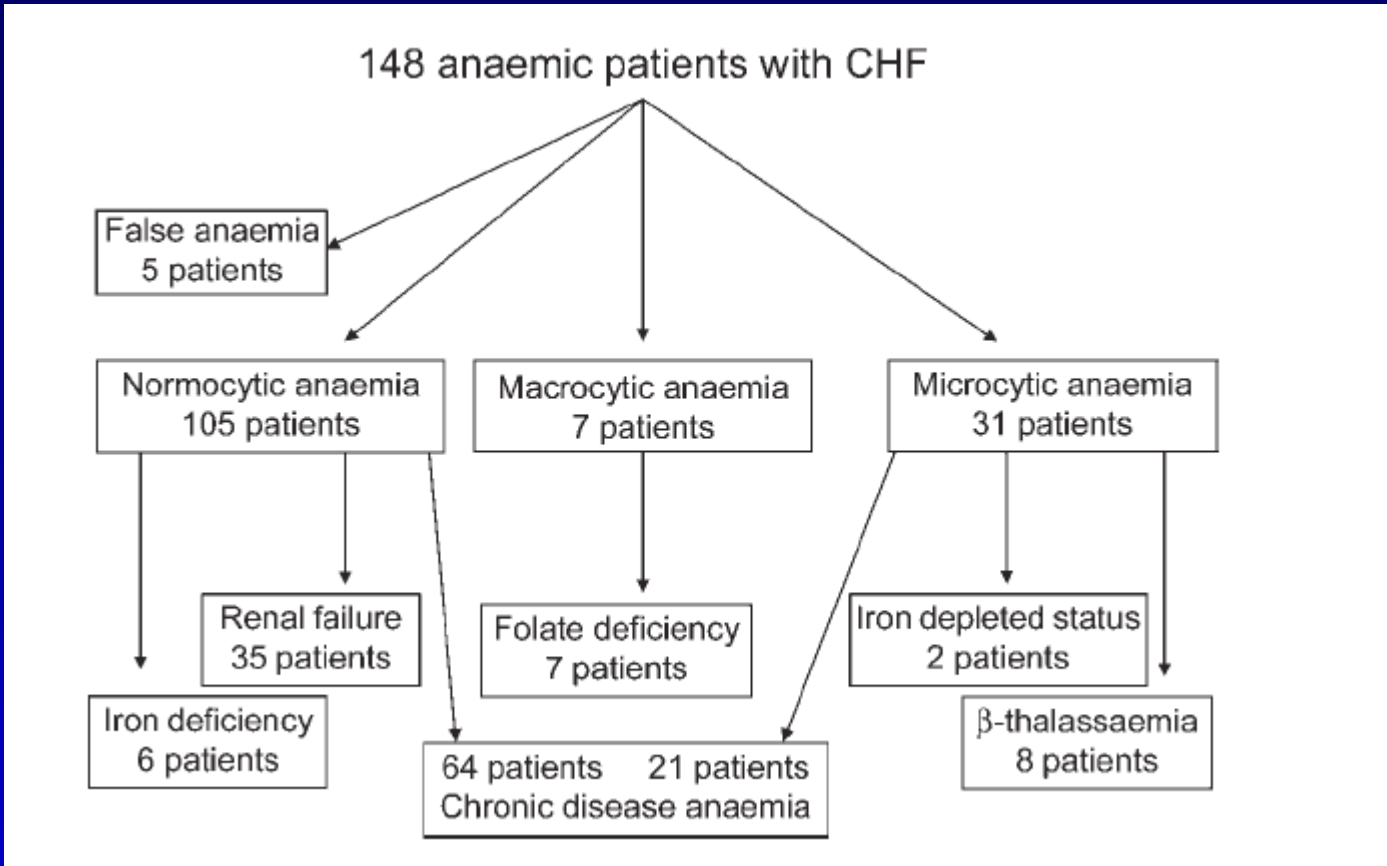
- n=173 LVSD, n=123 preserved LV
- anaemia <12.5 g/dL: 35% LVSD, 33% preserved LV
- 6% Vit B12 and 8% folate deficient

Witte et al. Am Heart J 2004;147:924-930

- Advanced HF n=37,extensive Ix including bone marrow biopsy: 73% iron deficient

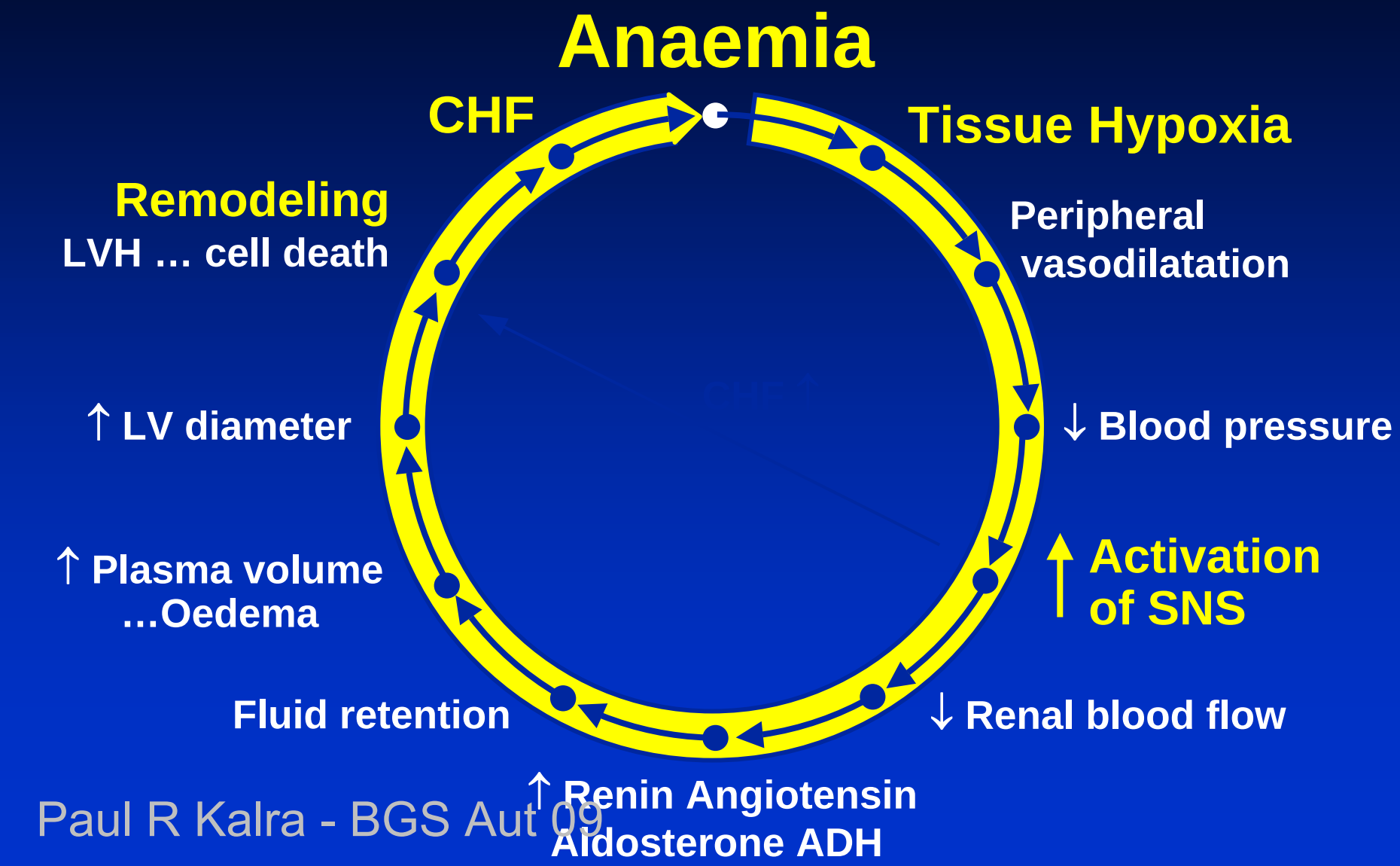
Nanas et al. J Am Coll Cardiol 2006

Opasich et al. Eur Heart J 2005;26:2232-7



92% of patients with anaemia of chronic disease exhibited iron deficiency for erthropoiesis and/or defective endogenous EPO production

Impact of anaemia on cardiac function



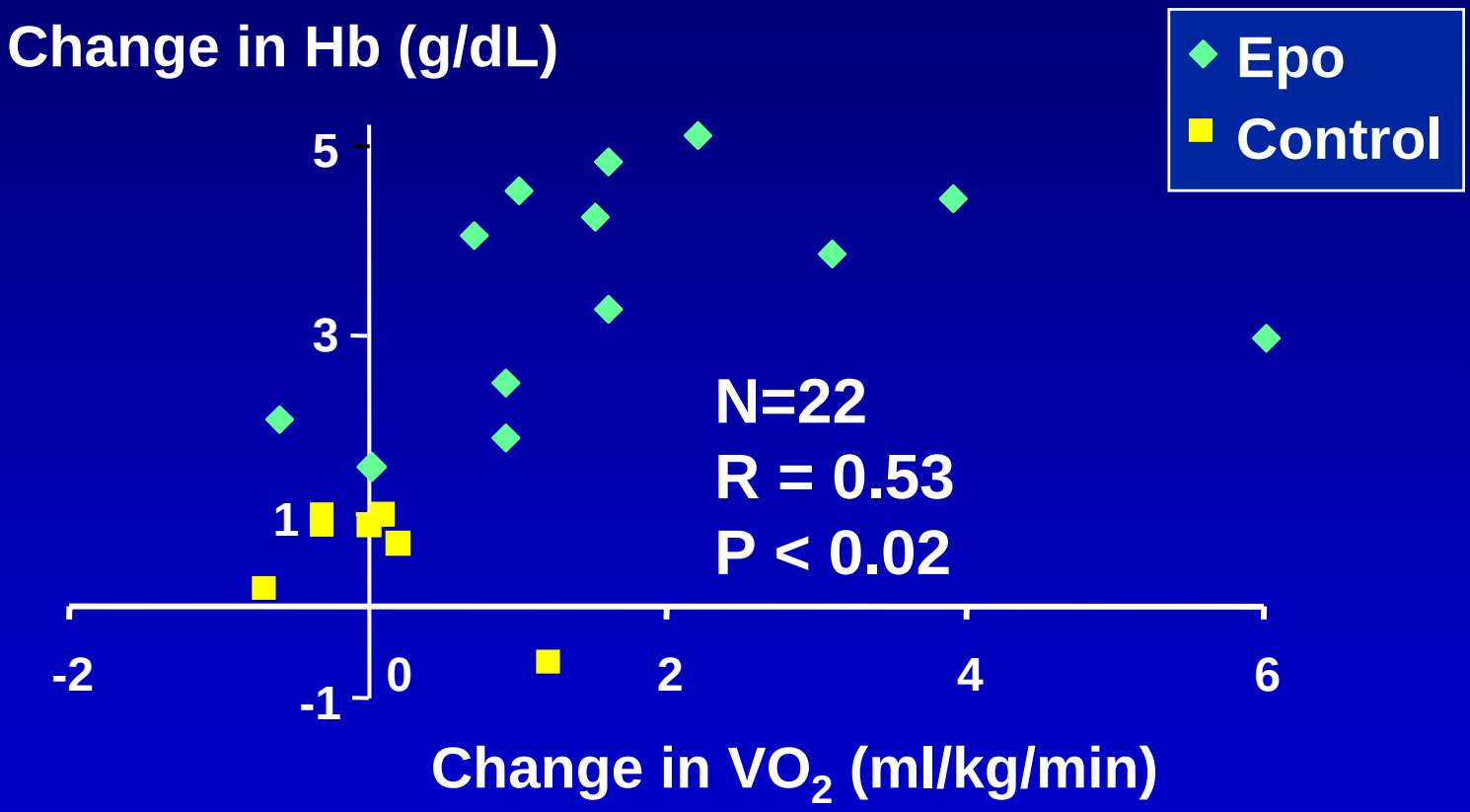
Placebo controlled study confirms benefit of anaemia Rx in CHF patients

32 patients (NYHA Class III/IV) on maximal medical therapy randomized to placebo or EPO + iv iron (goal Hb 12.5) with mean follow-up of 8.2 months.

	Change from Baseline During Study	
Parameter	EPO + iv Fe (n=16)	Placebo (n=16)
Mortality	0 deaths	4 deaths
Ejection Fraction (%)	+ 18%	– 19%
Hospitalization (days)	– 78%	+ 57%
Oral Furosemide (mg/d)	– 51%	+ 28%
iv. Furosemide (mg/wk)	– 91%	+ 27%

Silverberg et al. J Am Coll Cardiol 2001;37:1775-80

Change in peak VO_2 vs change in Hb



Mancini et al. Circulation 2003;107:294-9

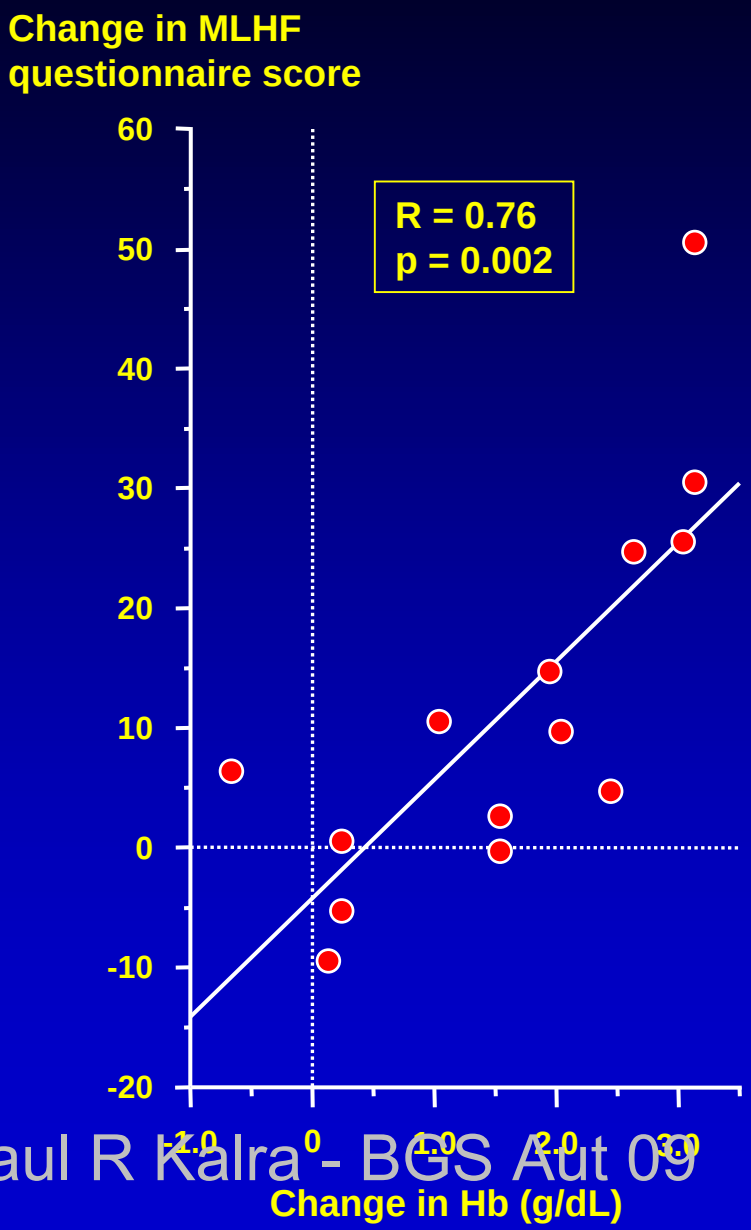
Intravenous iron alone for the treatment of anaemia in patients with chronic heart failure

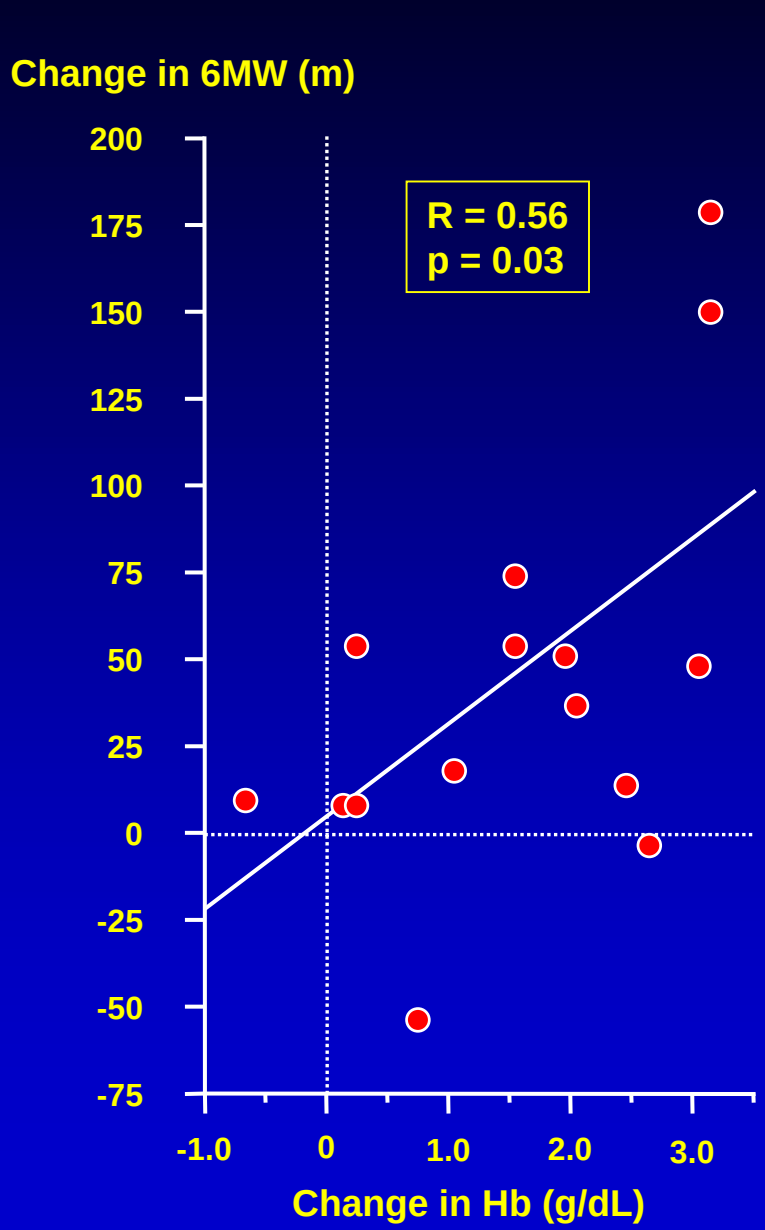
Open label study n=16, Hb<12

	Baseline (Hb 11.2)	Completion (Hb 12.6)	*P*-value
NYHA functional class (II/III)	9/7	16/0	0.02
MLHF Questionnaire (0-105)	32.9 (19.0)	19.4 (14.3)	0.02
6-minute walk test (m)	242 (78)	286 (72)	0.01
LVEF (%)	26 (13)	27 (12)	0.81

Bolger et al. J Am Coll Cardiol 2006;48:1225-7

Relationship between changes in quality of life and exercise capacity and change in Hb



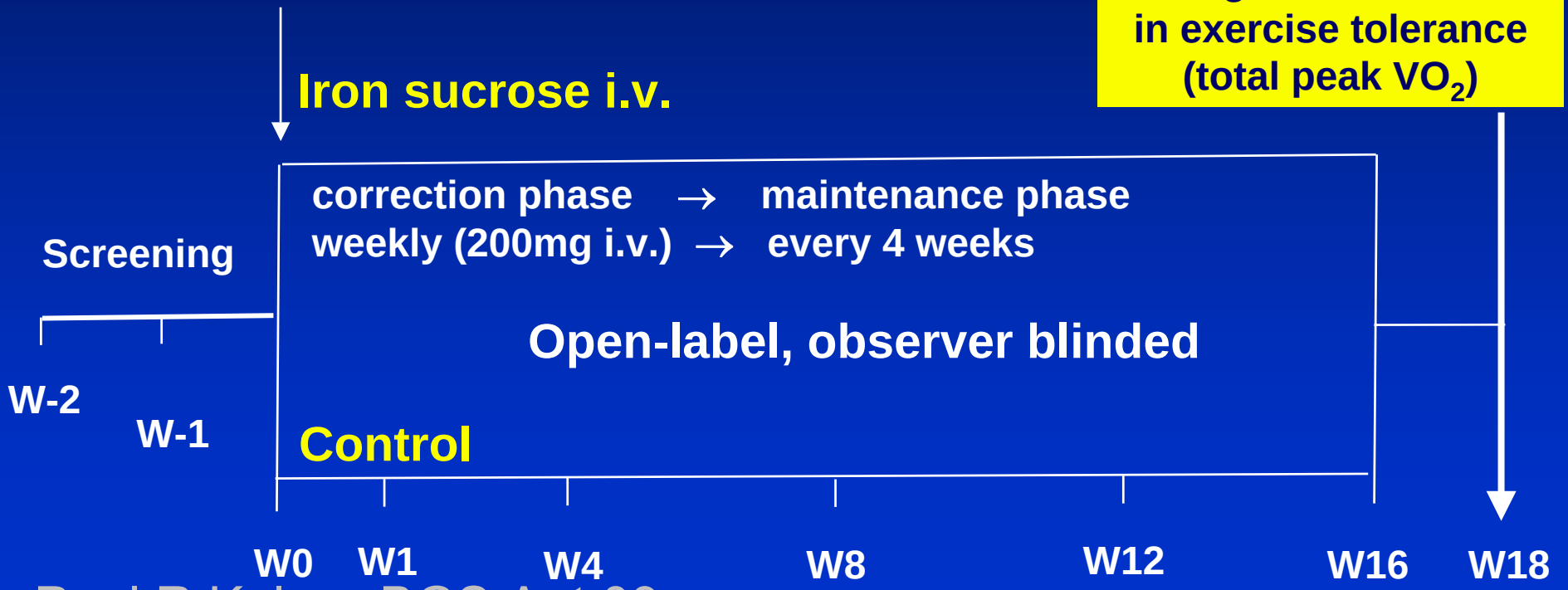


FERRIC-HF (n=35)

(mean age 63, peak VO_2 14.0, LVEF 30%, Ferritin 75, Hb 12.4)

Randomization – 2 : 1
active vs control

Primary endpoint:
Change from baseline in exercise tolerance (total peak VO_2)



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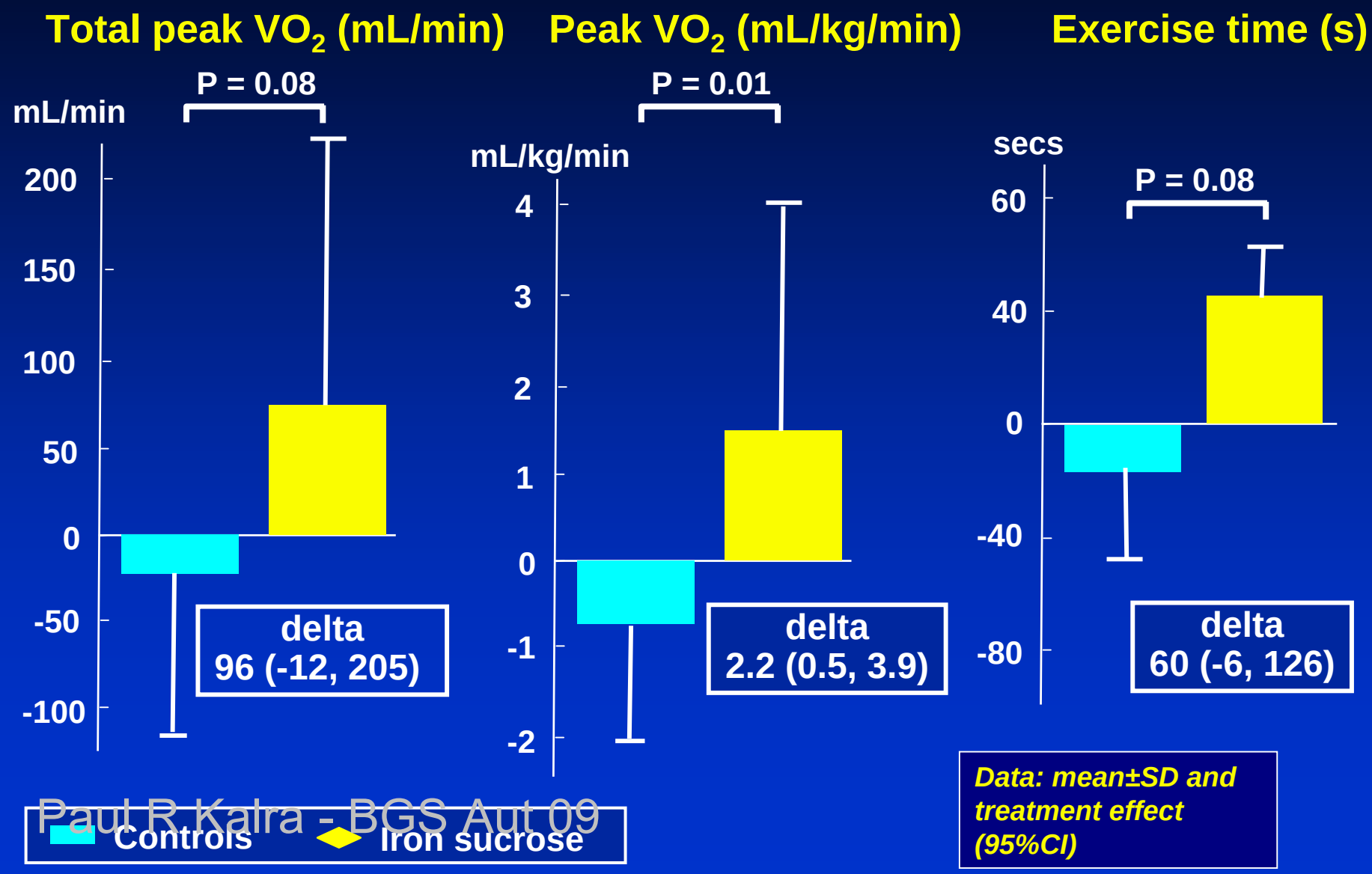
Okonko D et al. J Am Coll Cardiol 2008;51:103-12

FERRIC-HF: Results

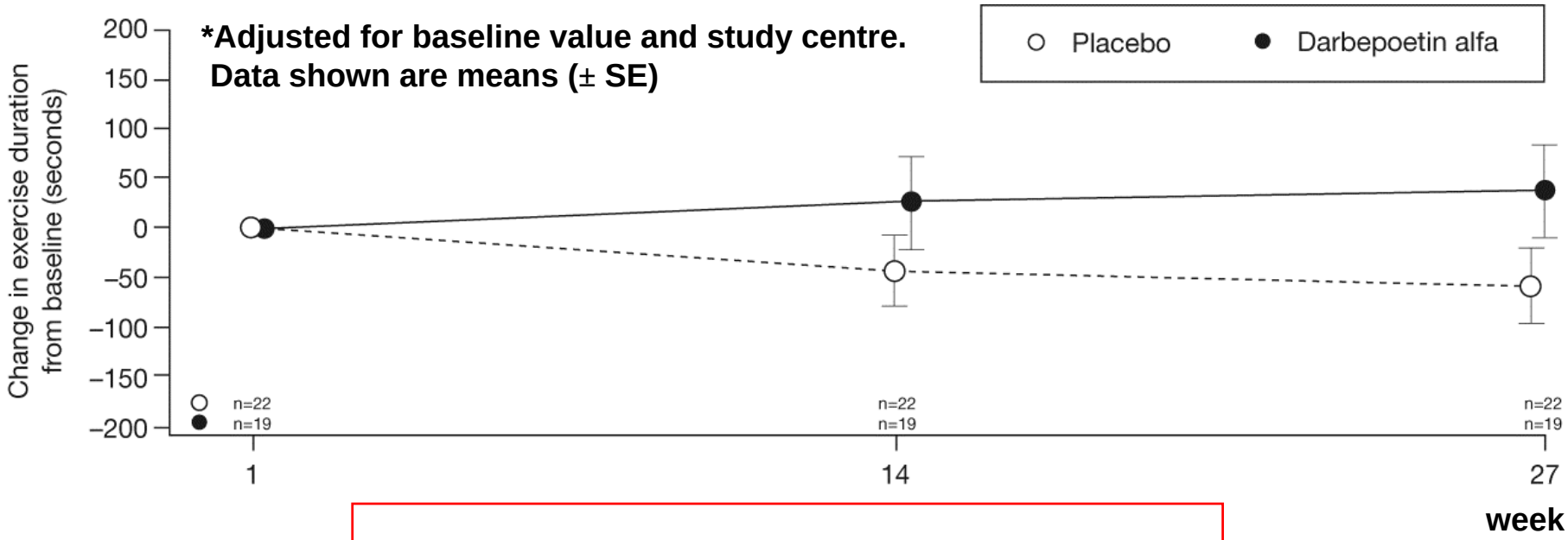
change in exercise capacity



Darbepoetin in CHF: n=41
exercise time – treadmill

Difference in adjusted* mean (95% CI) change of exercise duration from baseline to week 27 between darbepoetin alfa and placebo groups:

109 sec (-11 to 228); *P* = 0.07



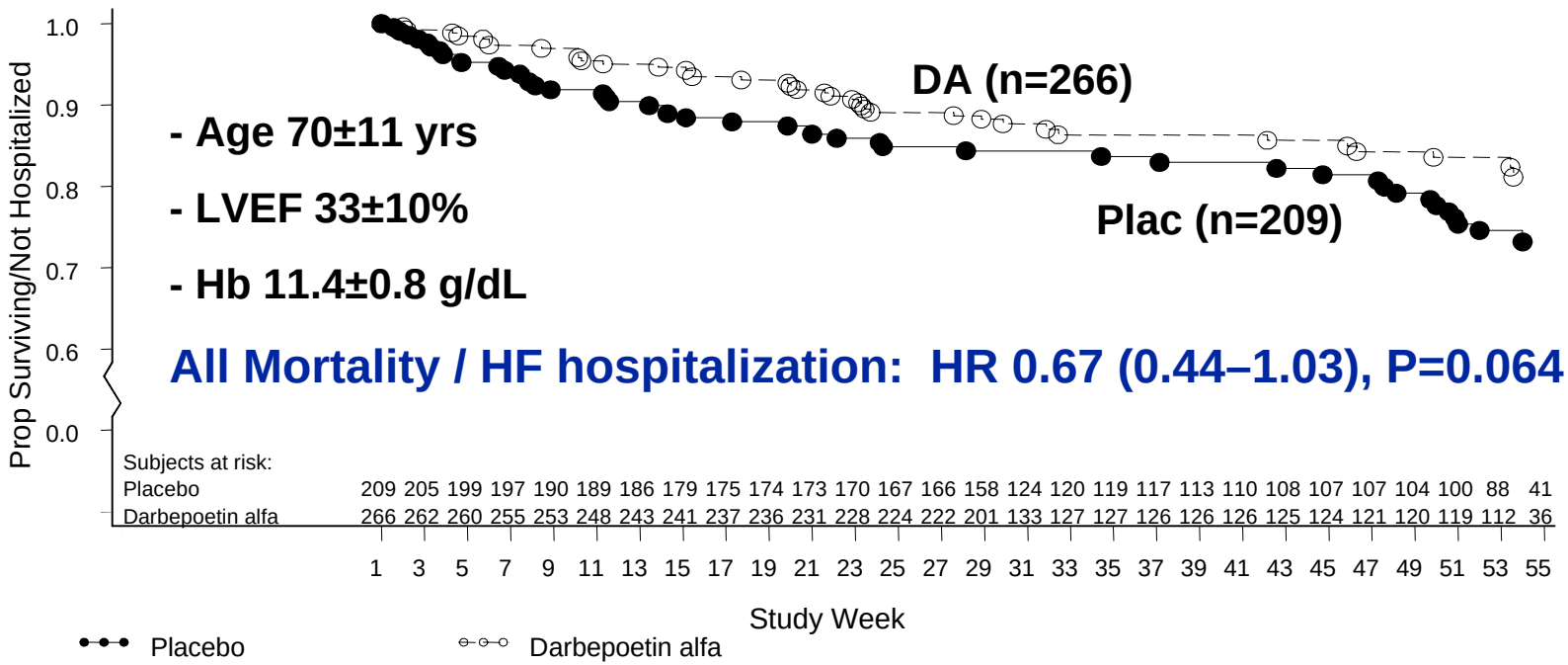
Improved PGA with Darbe: p=0.03

Ponikowski et al. J Am Coll Cardiol 2007;49:753-62

Pre-specified Pooled Analysis, Darbepoetin Alfa and Morbidity and Mortality Events

as reported by Abraham et al, ESC 2006

K-M Plot of All-cause Mortality or First Hospitalization for Worsening Heart Failure*
Integrated Analysis from Two Studies



ESA and po iron vs po iron alone (n=40)

Table III. Comparison of the initial and final (3-month) heart rate, blood pressure, walking distance with exercise, oxygen consumption during exercise, NYHA class, and BNP levels between the 2 groups

	Initial	Final	Initial	Final
Heart rate (beat/min)	84 ± 8	80 ± 8	82 ± 8	84 ± 10
Systolic BP (mm Hg)	134 ± 10	136 ± 10	130 ± 10	128 ± 12
Diastolic BP (mm Hg)	82 ± 6	85 ± 8	82 ± 5	80 ± 8
Distance walked (m)	278 ± 55	356 ± 88*	285 ± 68	266 ± 45
Exercise duration (min)	5.8 ± 2.2	7.8 ± 2.5	5.8 ± 2.4	6.0 ± 2.4
$V \cdot O_2$ (mL/kg per min)	12.8 ± 2.8	15.1 ± 2.8†	12.5 ± 3.1	12.0 ± 2.5
$V \cdot O_2$ AT (mL/kg per min)	9.2 ± 2.0	13.2 ± 3.6*	9.0 ± 2.5	8.7 ± 2.7
Respiratory rate (breath/min)	21.2 ± 4.8	31.1 ± 6.3†	20.8 ± 4.5	21.5 ± 5.2
RER ($V \cdot CO_2/V \cdot O_2$)	0.96 ± 0.20	1.15 ± 0.18	0.99 ± 0.18	1.0 ± 0.21
NYHA class	3.5 ± 0.6	2.8 ± 0.5†	3.4 ± 0.6	3.6 ± 0.4
BNP pg/mL	568 ± 320	271 ± 120*	585 ± 342	496 ± 320

$V \cdot O_2$, Oxygen consumption during maximal exercise; $V \cdot O_2$ *AT*, is oxygen consumption at anaerobic threshold; *BP*, blood pressure; *RER*, respiratory exchange rate.
*$P < .01$ (intergroup and intragroup).
†$P < .05$ (intragroup and intergroup).

ESA and po iron Hb 10.4 → 12.4, NO change with po iron

Palazzuoli et al. Am Heart J 2006;152:1096

Outstanding questions

- Need large-scale efficacy and safety data (RED-HF and FAIR-HF ongoing)
- What level of haemoglobin to initiate treatment
- Target haemoglobin
- What constitutes ‘best practice’ for investigation
- Iron or ESA or both

Investigation of CHF and anaemia

- History (including drugs) and examination – fundamental
- FBC, U&Es, LFTs, TFTs, CRP
- B12, folate, ferritin
- Simple markers of changes in RBCs that accompany iron deficiency:
  - decrease in mean cell Hb (MCH)
  - hypochromia (% hypochromics)
  - reduced mean cell volume (MCV)

- **Serum markers of iron deficiency:**

  - low ferritin (<12-15µmg/L) – very good if no co-existent disease

  - with co-existent disease ferritin <50 – suggestive of iron deficiency (<200 in severe CKD)

  - low iron

  - increase in total iron binding capacity (TIBC)

  - reduction in transferrin saturation (TSAT, <16%, <20%)

  - soluble transferrin binding receptor

- **Erythropoietin level**
- **Some → GI and/or haematological revue**

Case

- 77 year old female
- CHF secondary to IHD, previously stable NYHA II
- Rx: loop diuretic, ACE inhibitor, beta-blocker, aspirin
- Presents to GP with fatigue and exertional dyspnoea (NYHA III)
- Clinically euvolaemic
- Sinus rhythm 60 BP 100/60

Case

- ECG SR QRSd 118 ms
- Ix: eGFR 45 CRP 7

  Hb 10.8 g.dL MVC 80

  B12 & folate normal Ferritin 50

  TSAT 15%
- Who would treat with:

(i) po iron (ii) iv iron (iii) ESA +/- iron

(iv) Transfusion (v) no further options