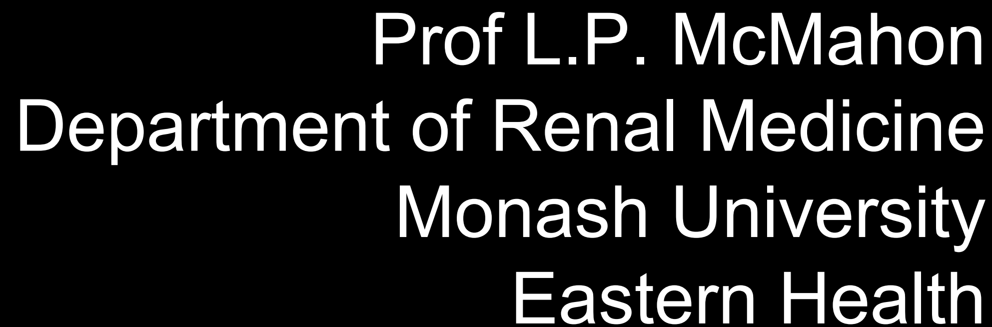
Anaemia of Chronic Kidney Disease



Prof L.P. McMahon
Department of Renal Medicine
Monash University
Eastern Health

Mandy, a 51-year old woman, presented to her local doctor complaining of fatigue and headaches.

Past history of urine infections as a child, pre-eclampsia with her two children, irritable bowel.

Found to have hypertension and persistent proteinuria 10 years earlier – not followed up (too busy).

O/E: Sallow complexion, BP 180/110, S4, mild oedema, proteinuria +++.

Na^+	136 mmol/L	Hb	92 g/L
K^+	5.6 mmol/L	MCV	88 fL
Cl^-	108 mmol/L	WCC	10.4 x 10^3/L
HCO_3^-	14 mmol/L	Platelets	263 x 10^9/L
Urea	28.4 mmol/L		
Creatinine	463 µmol/L	PTH	68 pmol/L (<7.0)
		Uric acid	0.56 mmol/L (<0.45)
Ca^{2+}	1.96 mmol/L		
PO_4^{2-}	2.63 mmol/L	Ultrasound	
Albumin	28 g/L	Scarred kidneys, 7 and 9 cm	

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Clinical Issues

HYPERTENSION

FLUID OVERLOAD

ANAEMIA

ELECTROYTE IMBALANCE

METABOLIC ACIDOSIS

BONE DISEASE

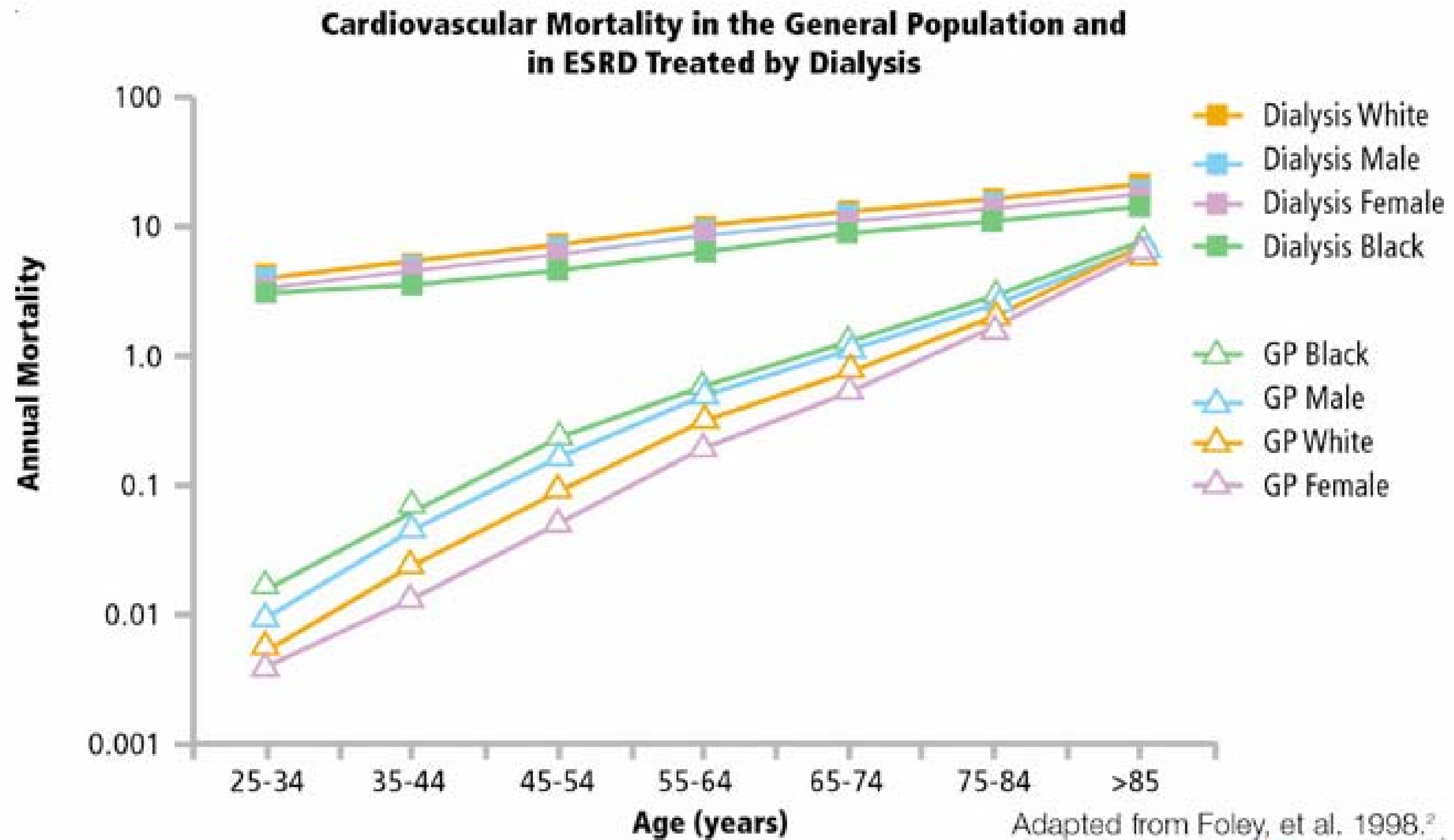
POOR NUTRITION

INFLAMMATION

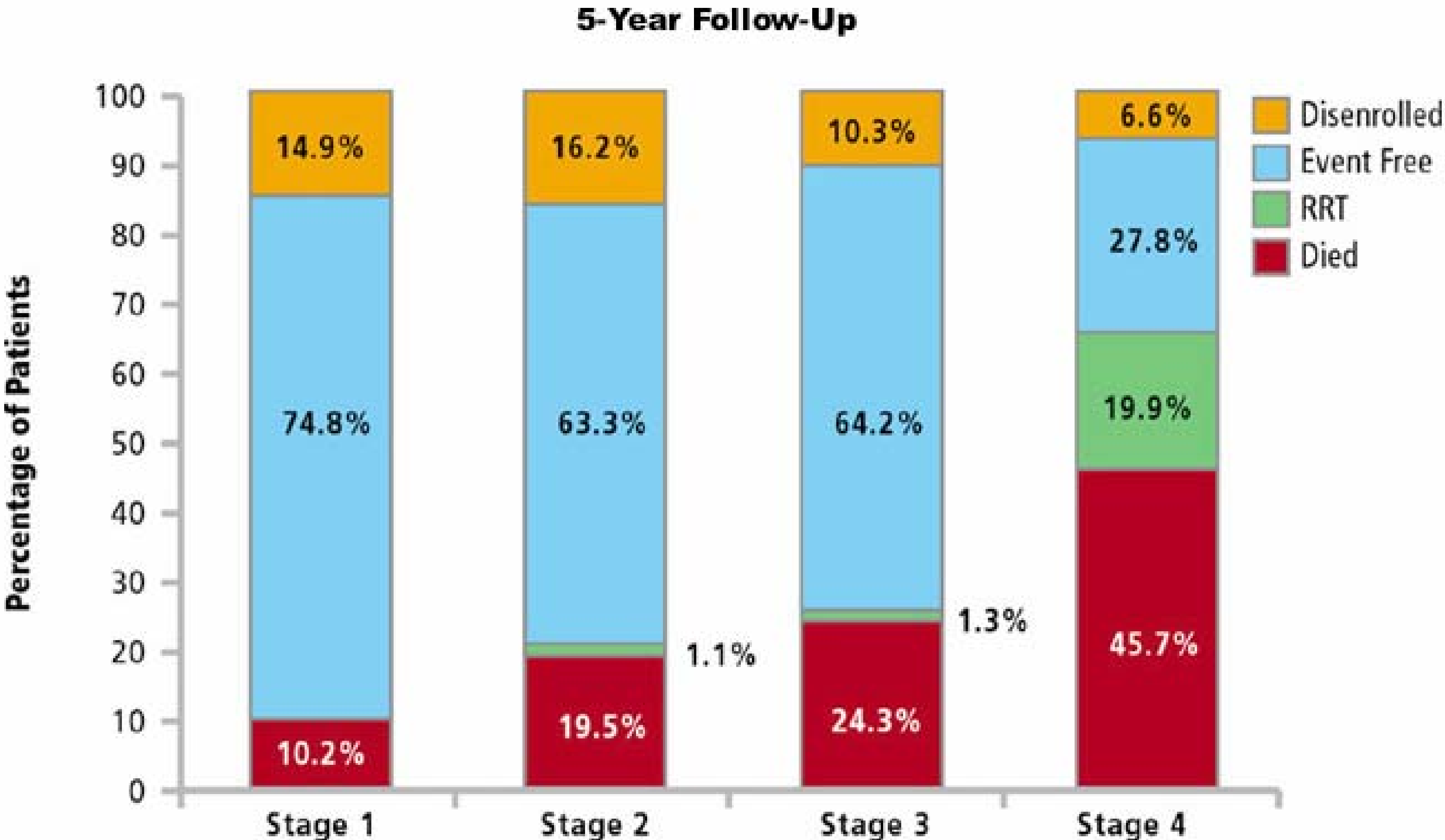
ATHEROGENIC MILIEU

OTHER . . .

Life Expectancy in Dialysis Patients



CKD patients are more likely to die than start dialysis



JASN, 2005

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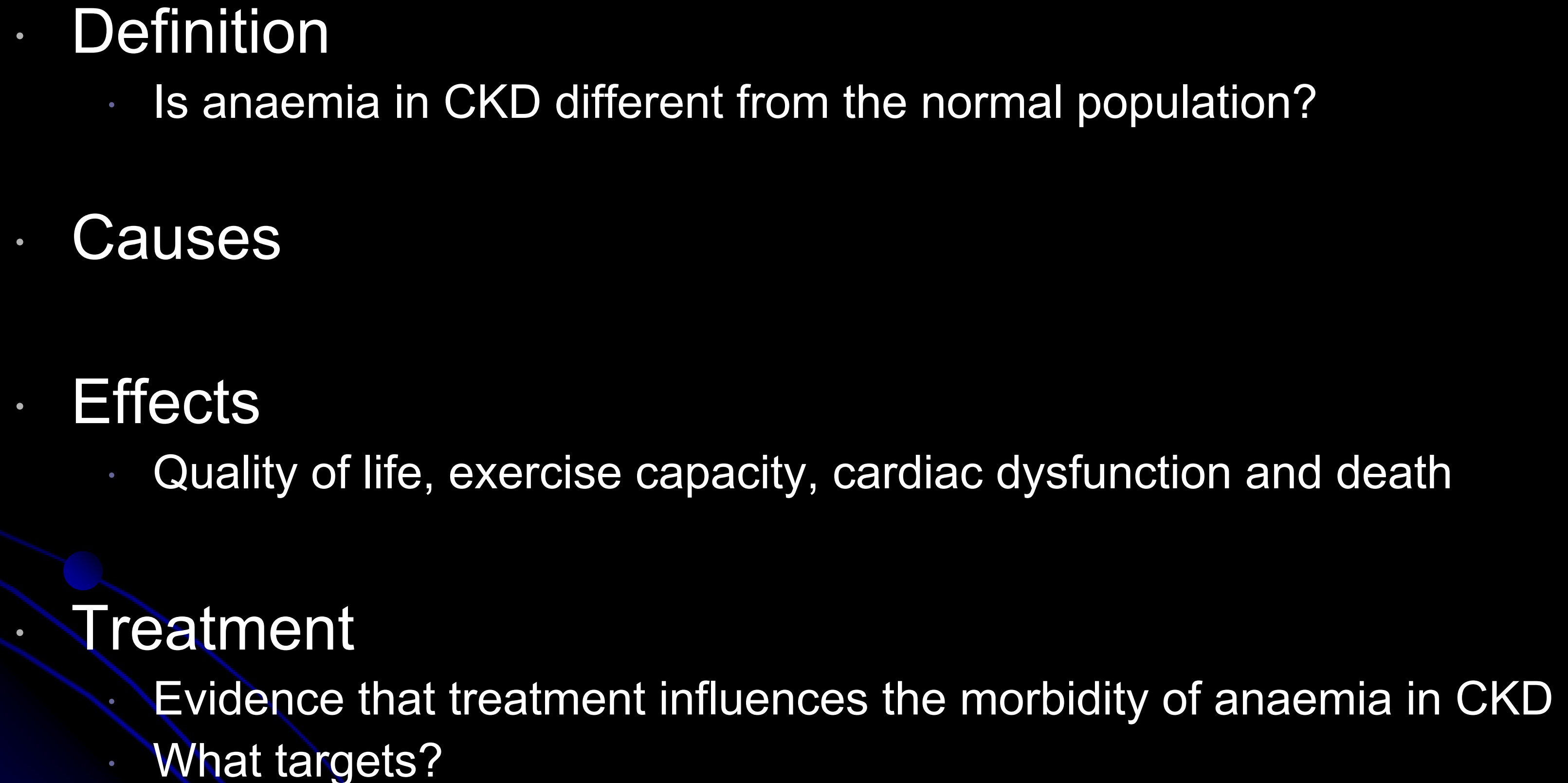
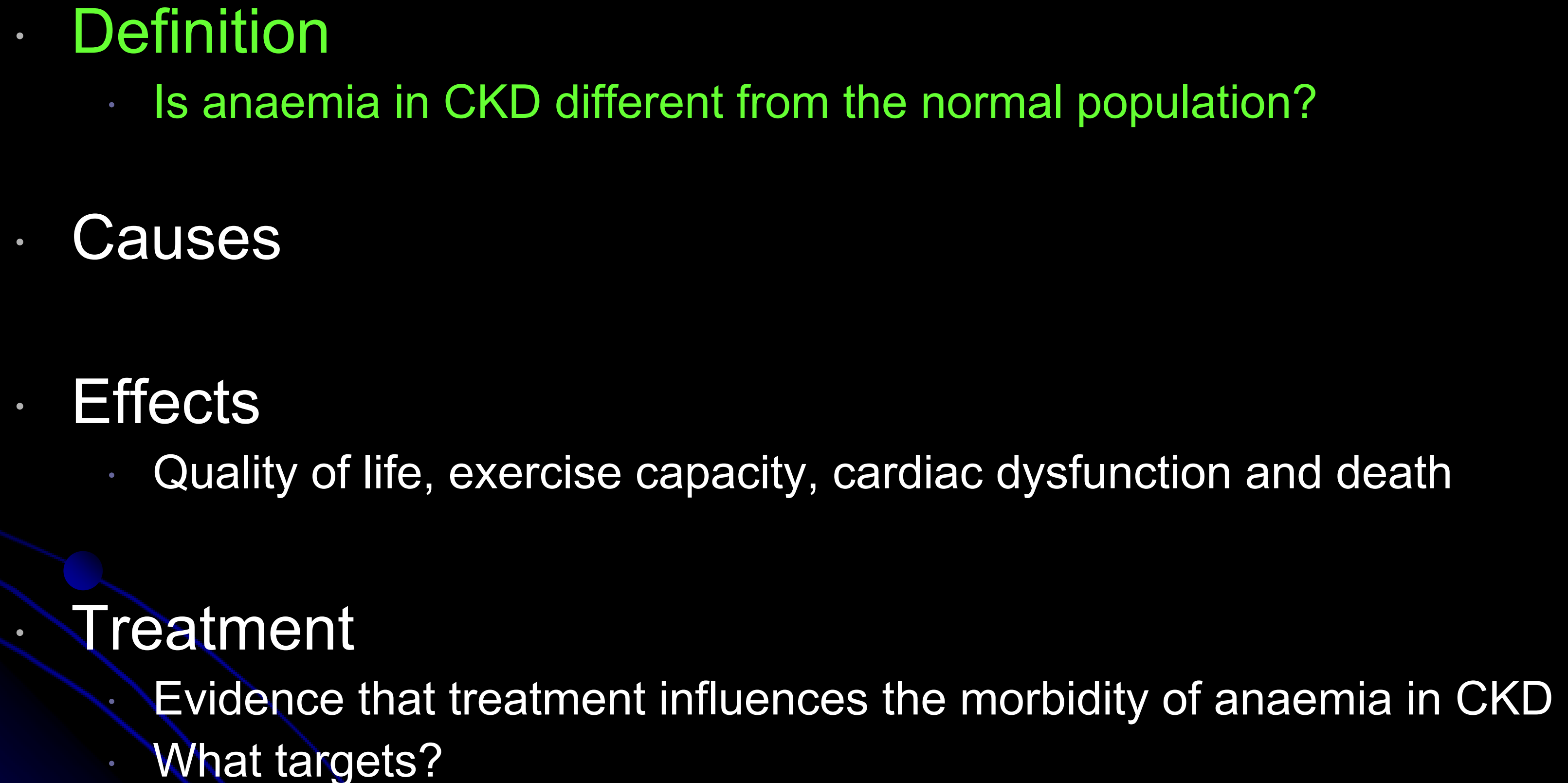
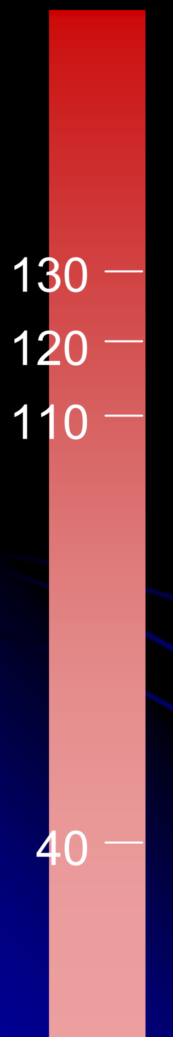
Anaemia and CKD



Anaemia and CKD



Anaemia



- Physiological range of haemoglobin:

  males: 130 – 180 g/L

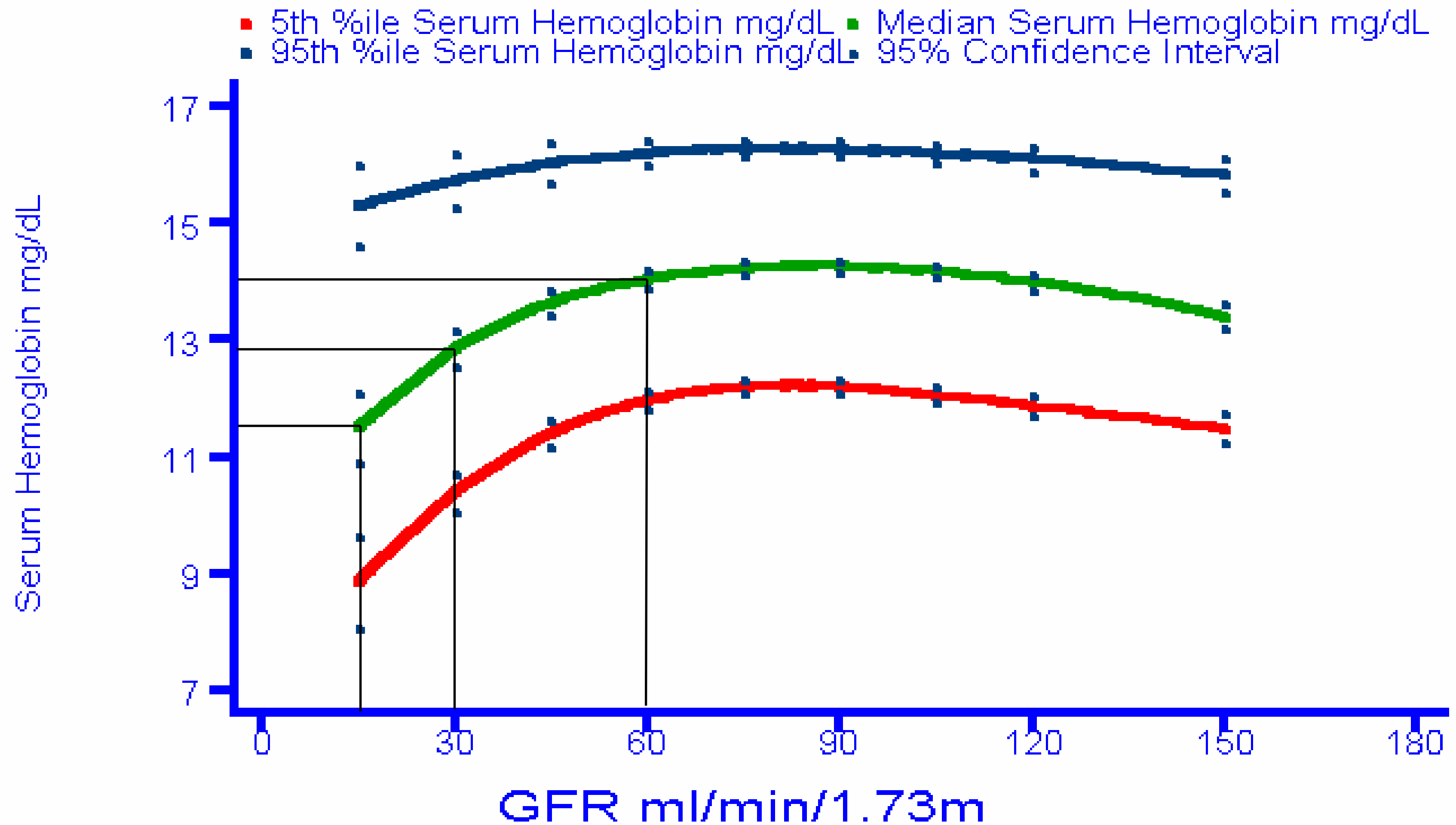
  females: 120 – 140 g/L

  (NHANES II, 2001)

- Anaemia is also a relative condition which progressively affects symptomatic and objective parameters of well-being as it becomes more severe.

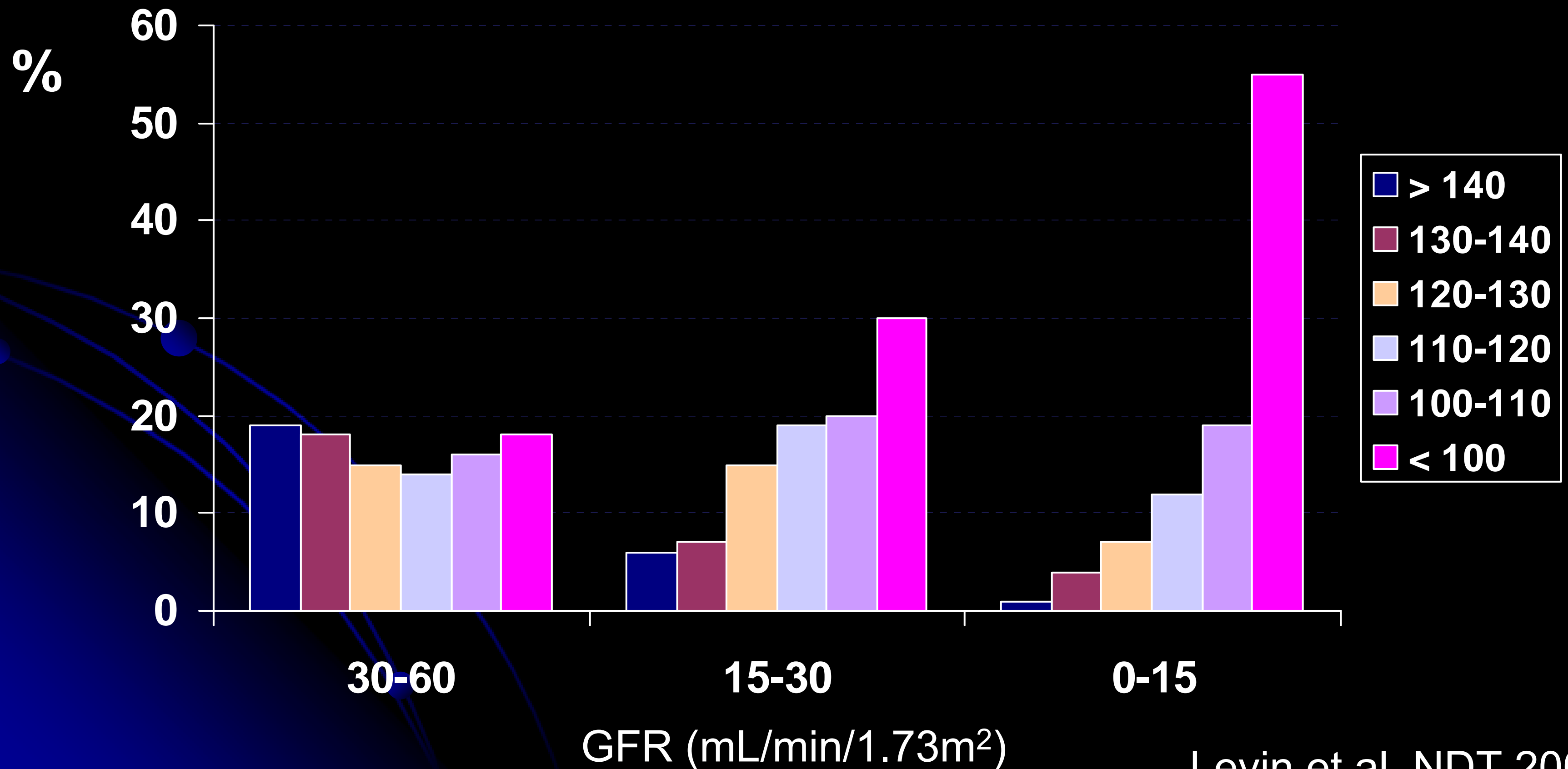
- Clinical tolerance to anaemia does not mean that it has no effect.

Haemoglobin Percentile Curves by GFR Adjusted to Age 60 – NHANES III



Prevalence of Anaemia at Different Levels of GFR in Outpatient CKD Cohort

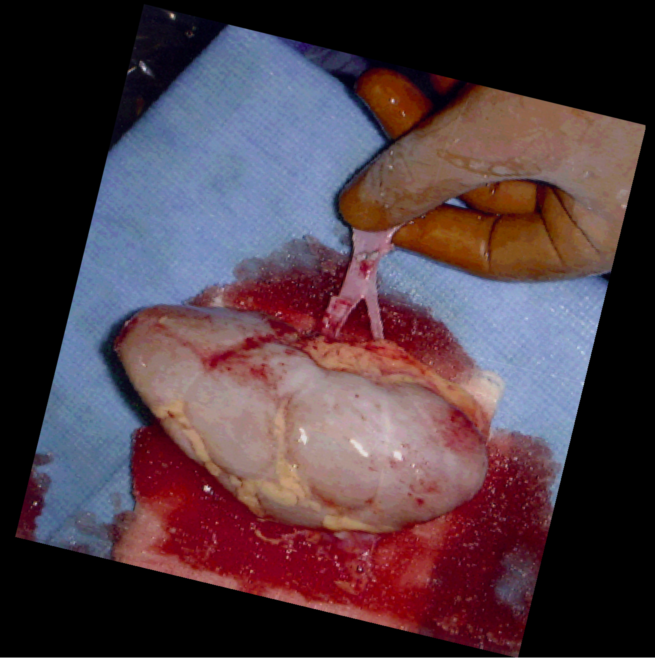
N= 3028 CKD Patients in BC Canada, referred to nephrologists, prior to initiation of anaemia therapy



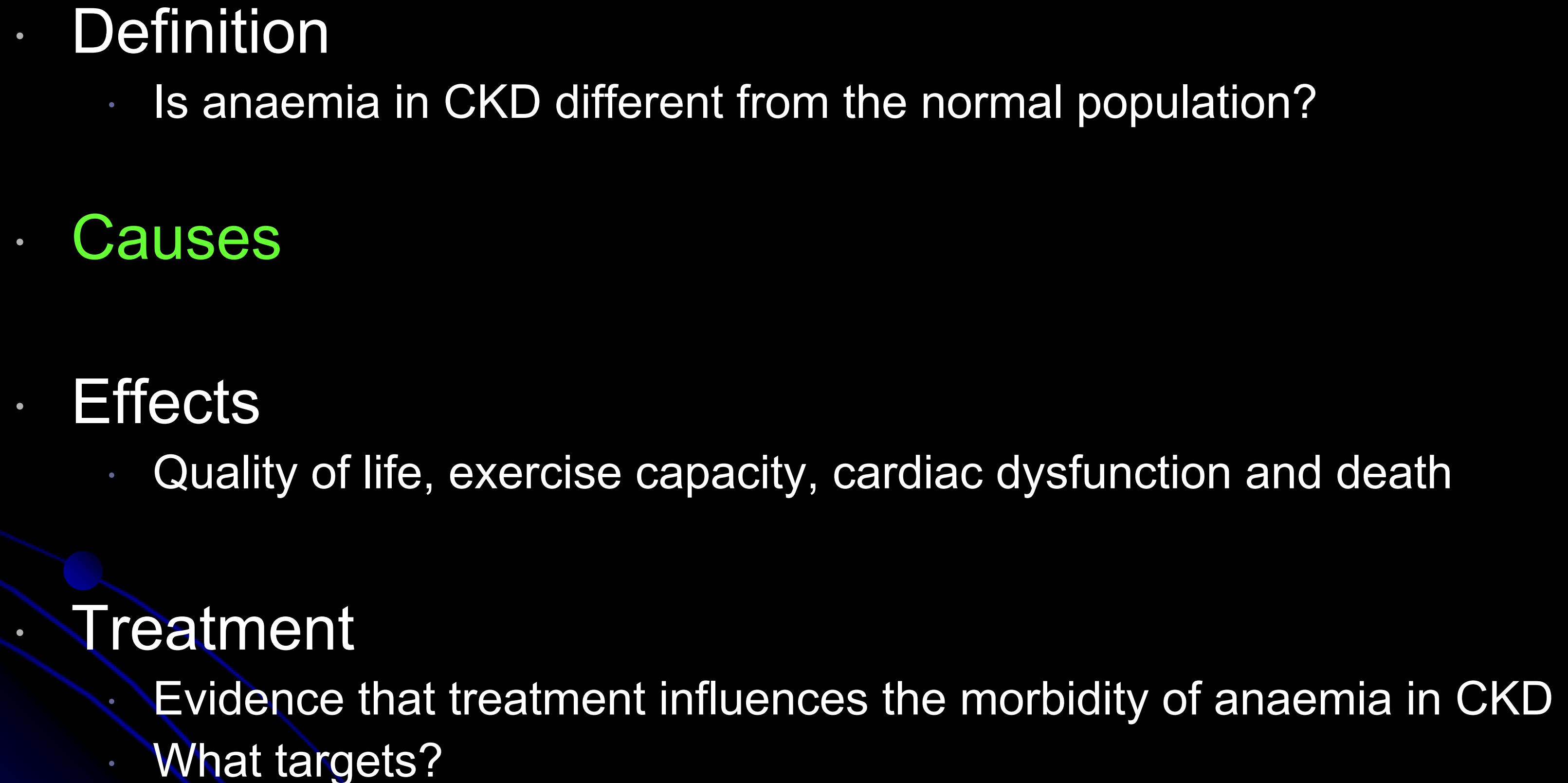
Levin et al, NDT 2005

Failing Transplants: CKD

- Anaemia evident in > 50%
- [Hb] independently predicts graft loss (Gill et al, ASN 2000)
- [Hb] predicts CHF & mortality (Rigatto et al, JASN 2002)
- At risk group
  - Impact of uremic milieu
  - Impact of immunosuppressive agents
  - Impact of anaemia per se



Anaemia and CKD



- Definition
  - Is anaemia in CKD different from the normal population?
- Causes
- Effects
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- Treatment
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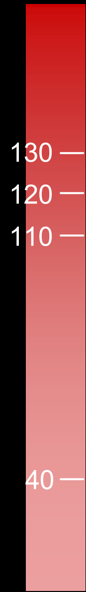
  - What targets?

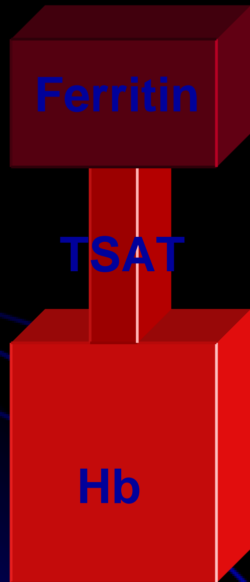
Anaemia – Causes in CKD



- Iron deficiency (functional & absolute)
- Inflammation and malnutrition
- Folate deficiency
- GIT blood loss
- Dialysis
- Uraemic milieu
- Relative erythropoietin deficiency
- Vitamin B12 deficiency
- Haemodilution
- Haemolysis
- Aluminium toxicity
- Hyperparathyroidism
- Other
  - thalassaemia
  - past transplantation
  - sickle cell disease

Stages of Iron Deficiency in CKD

Normal Iron Status



Hb > 110
TSAT > 20
Ferritin > 100

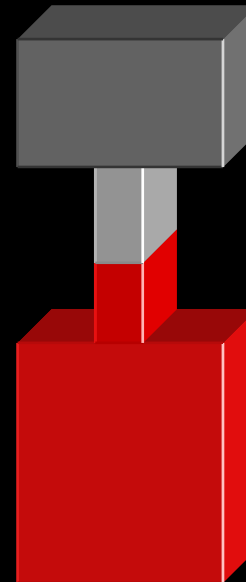
Negative Iron Balance

Ferritin falling

Storage Iron Depletion

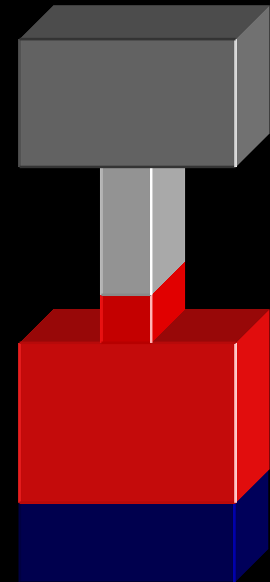
Ferritin < 100 ng/ml

Iron Deficient Erythro-poiesis



TSAT < 20
Epo ⇑

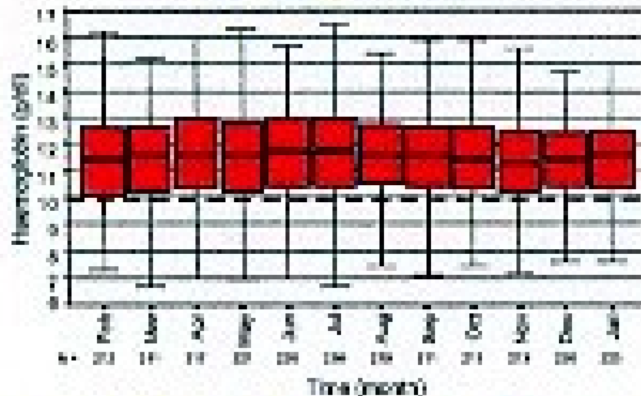
Iron Deficiency Anemia

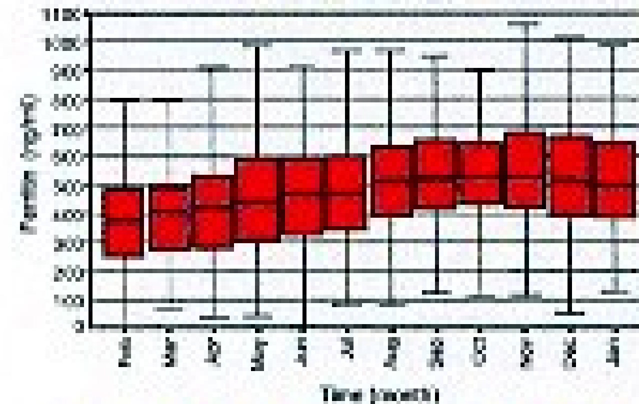


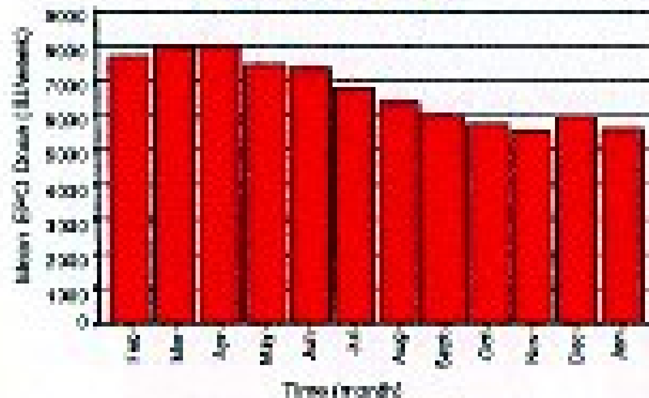
Hb < 110 g/L,
Epo ⇑

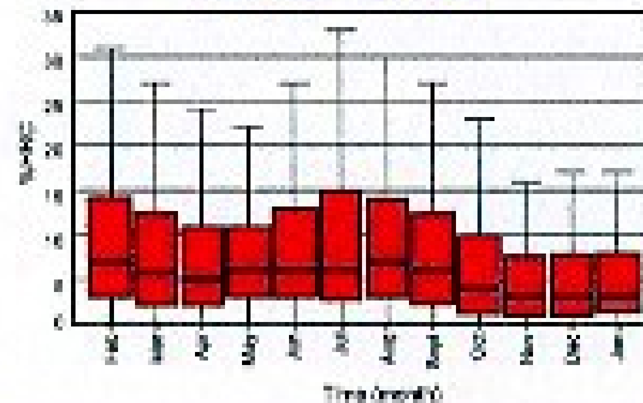
Source: Adapted from Danielson BG, Iron Therapy (1996

Effect of increasing ferritin levels on epoetin dosage whilst maintaining a stable haemoglobin





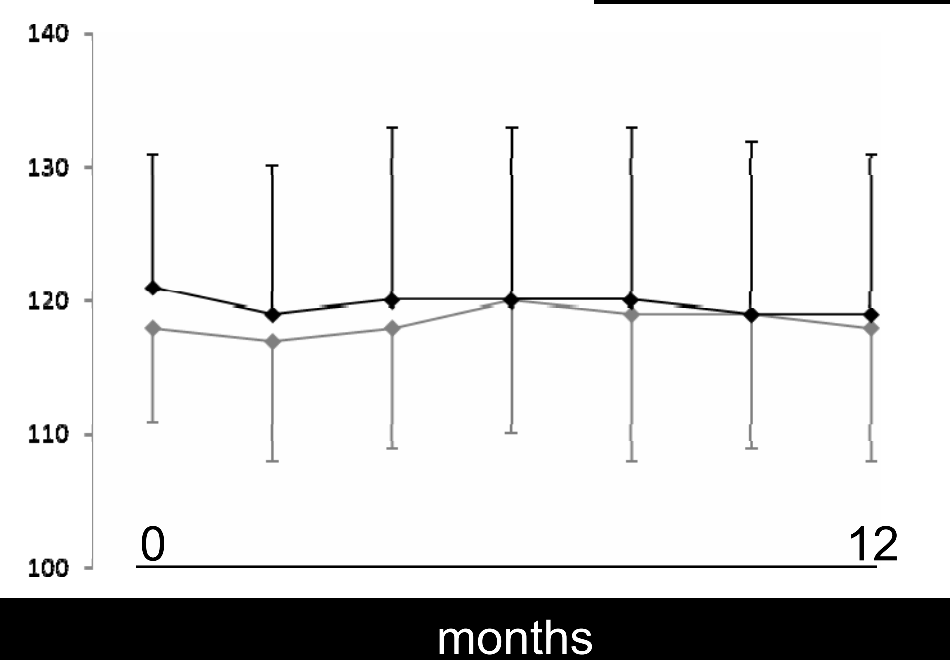




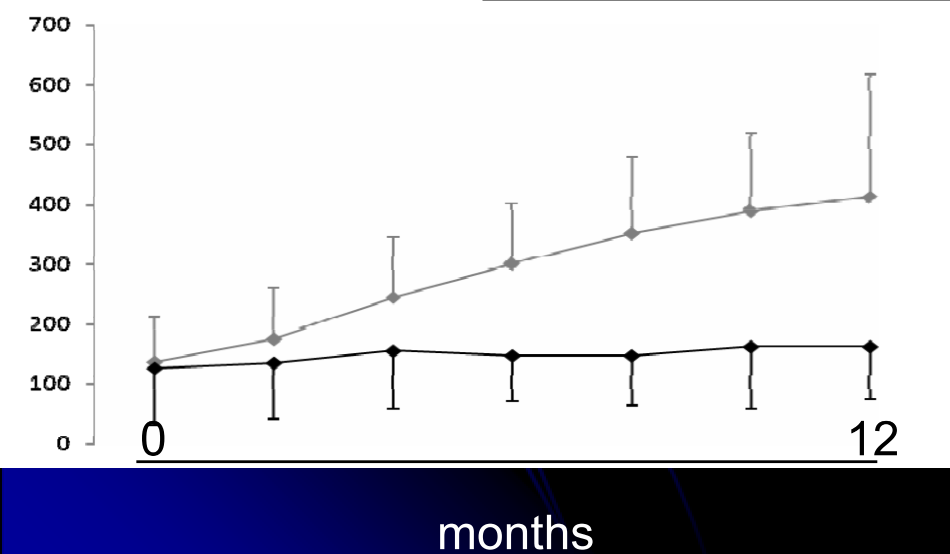
Richardson et al, NDT, 2001

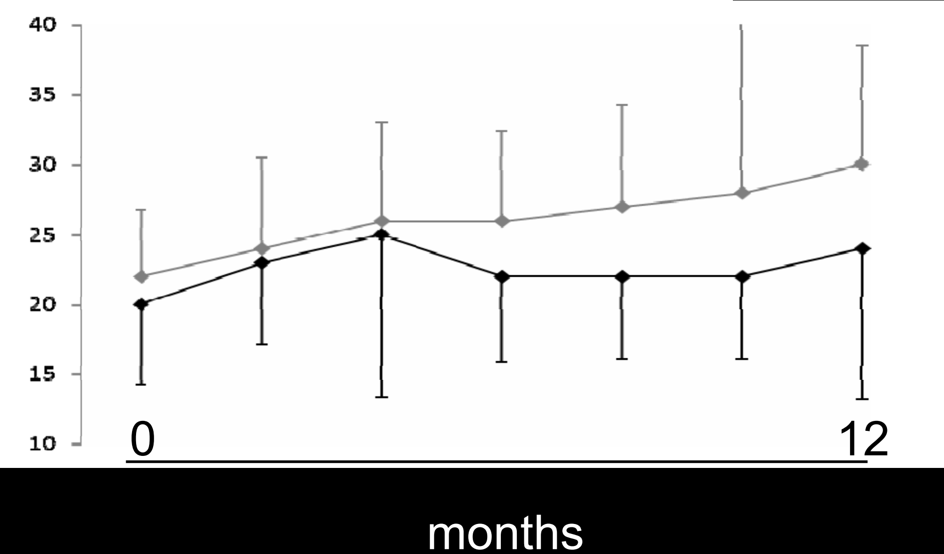
Iron supplementation in CKD (non-dialysis) patients

McMahon LP et al, NDT 2010



months





months

months

Causes of Anaemia in CKD

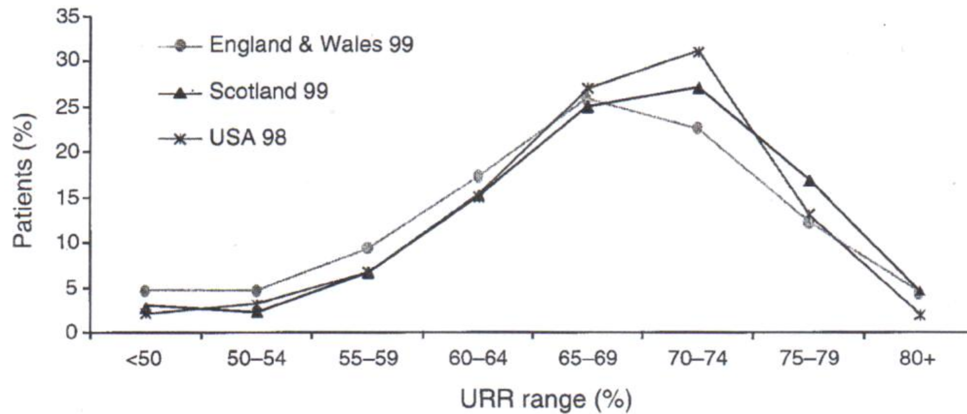


Fig. 3. Distribution of the urea reduction ratio (URR) in the UK and USA.

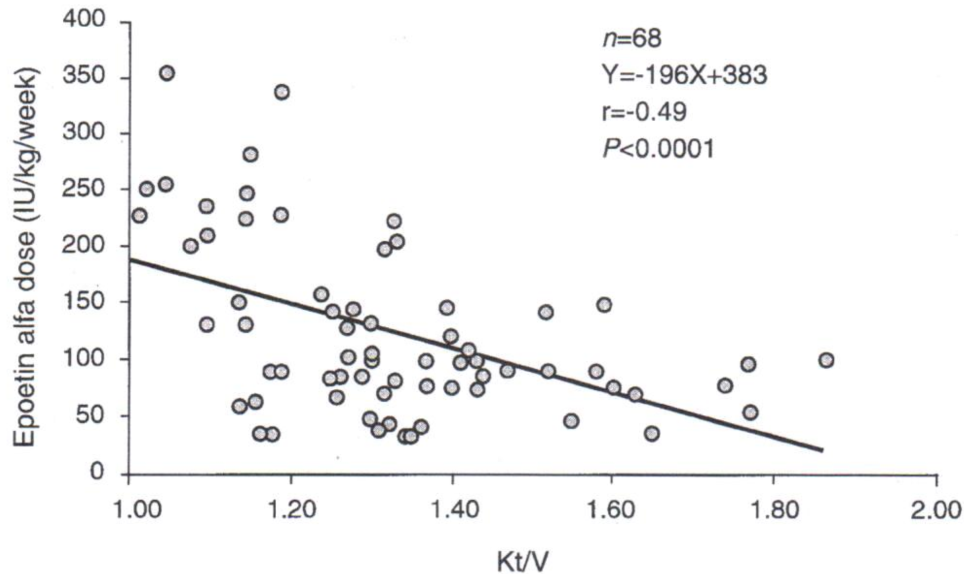


Fig. 4. Correlation between dialysis adequacy (Kt/V) and epoetin alfa dose.

Richardson D et al, NDT 2002

Causes of Anaemia in CKD

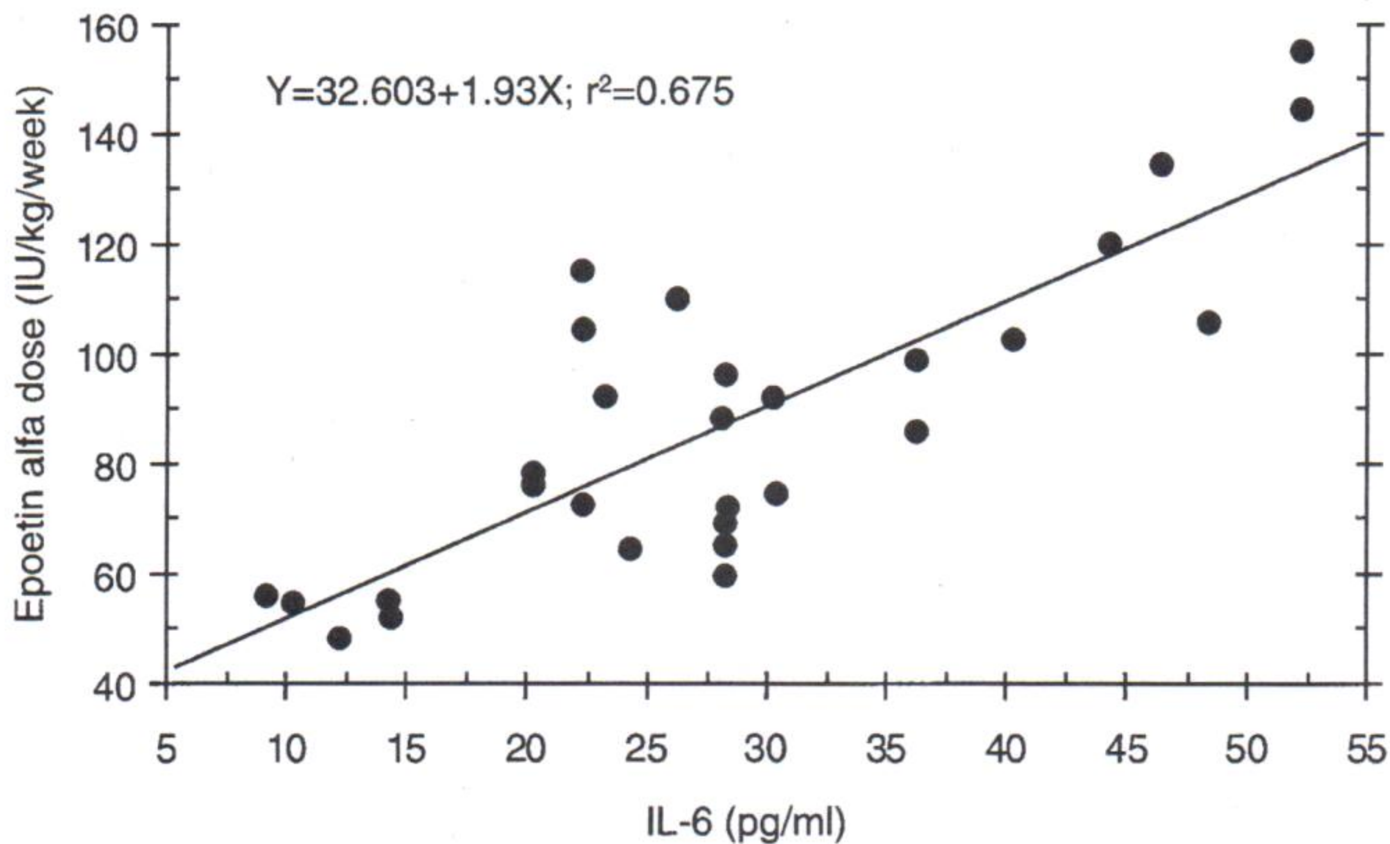


Fig. 5. Correlation between inflammatory response (IL-6) and epoetin alfa dose.

Richardson D et al, NDT 2002

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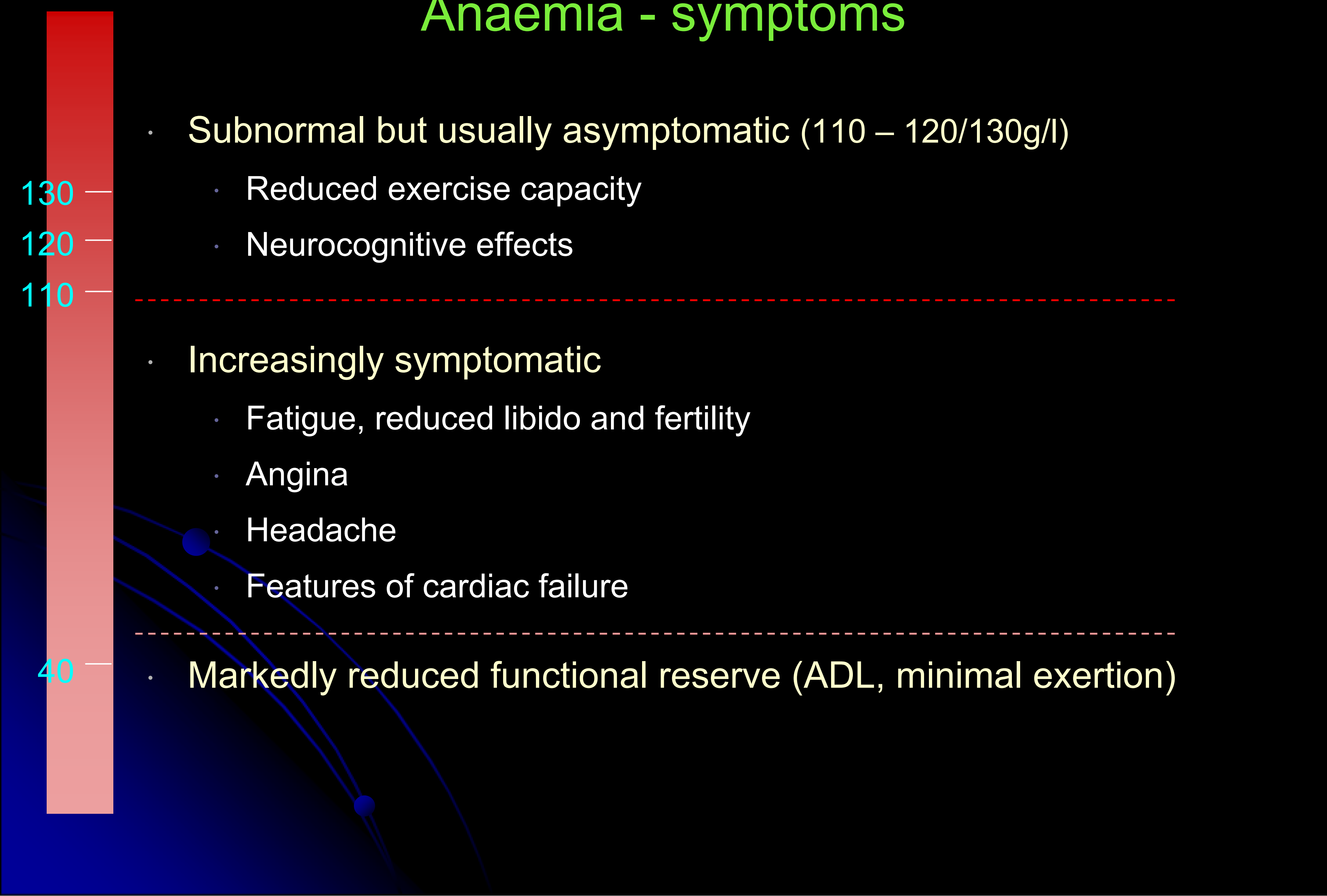
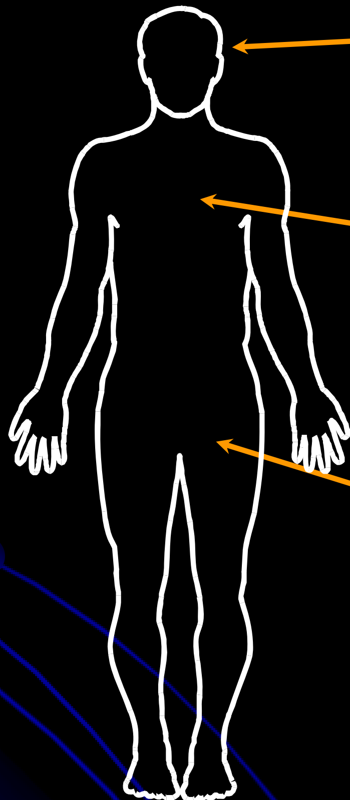


Anaemia - symptoms
Subnormal but usually asymptomatic (110 – 120/130g/l)
Reduced exercise capacity
Neurocognitive effects
Increasingly symptomatic
Fatigue, reduced libido and fertility
Angina
Headache
Features of cardiac failure
Markedly reduced functional reserve (ADL, minimal exertion)
130
120
110
40

Adverse Sequelae Associated With Anaemia



Cognitive function

- Confusion[1]
- Impaired cognition[6]

Cardiovascular

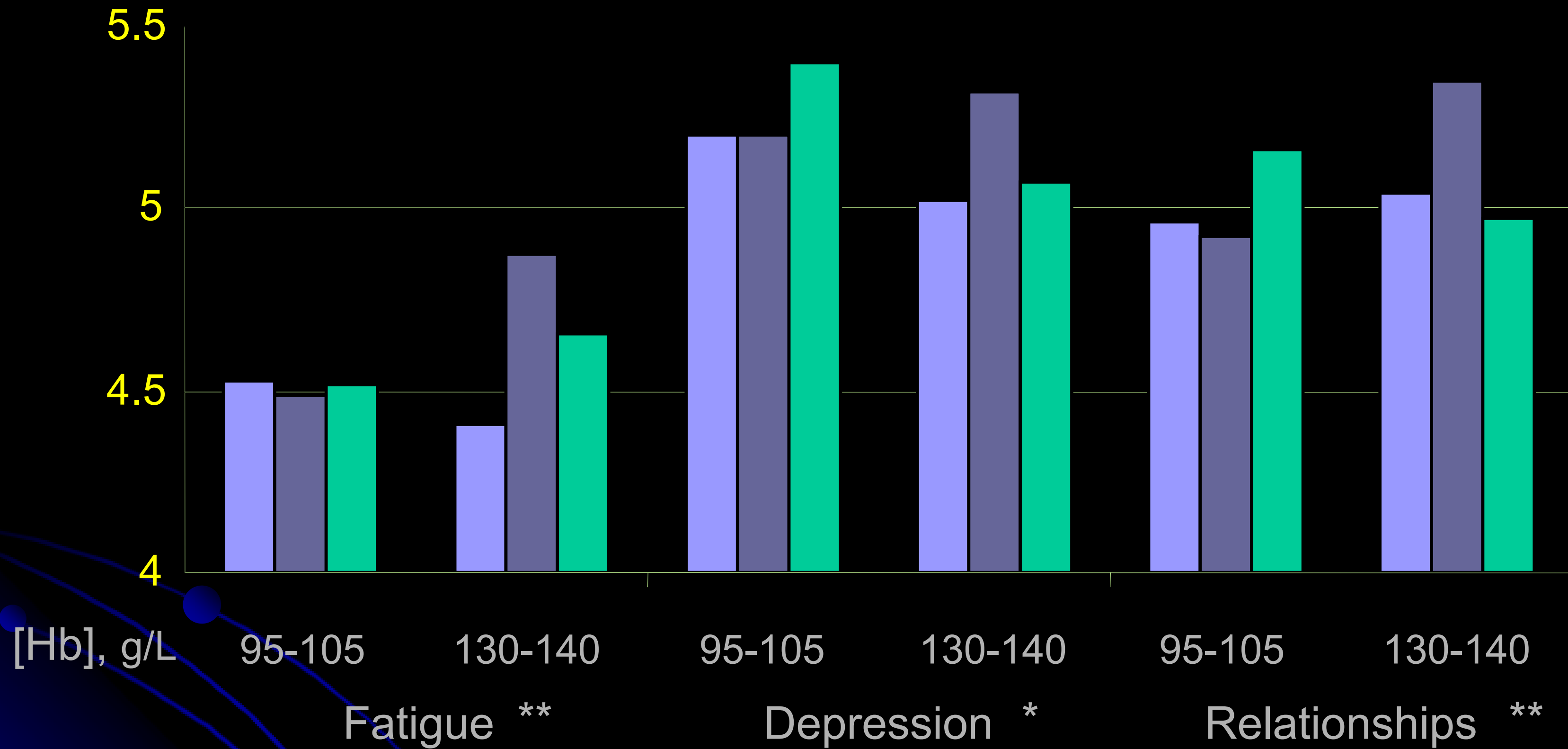
- Cardiac enlargement, CCF[2,3]
- Angina[1,5]
- Palpitations[5]

Quality of life

- Reduced exercise capacity[4]
- Impaired libido/impotence[7]

[1]**Hoffbrand AV et al. *Essential Hematology*.1993. [2]Levin A et al. *Am J Kidney Dis.* 1999;34:125-134. [3]Foley RN et al. *Am J Kidney Dis.* 1998;28:53-61. [4]Mayer G et al. *Kidney Int*. 1998;34:525-528. [5]Mackie MJ et al. In: Edwards CRW et al, eds. *Davidson's Principles and Practice of Medicine*, 1995. [6]Nissenson AR. *Am J Kidney Dis*. 1992;20:21-24. [7]Schaefer RM et al. *Contrib Nephrol*. 1989;76:273-81.**

Change in Haemoglobin and QoL



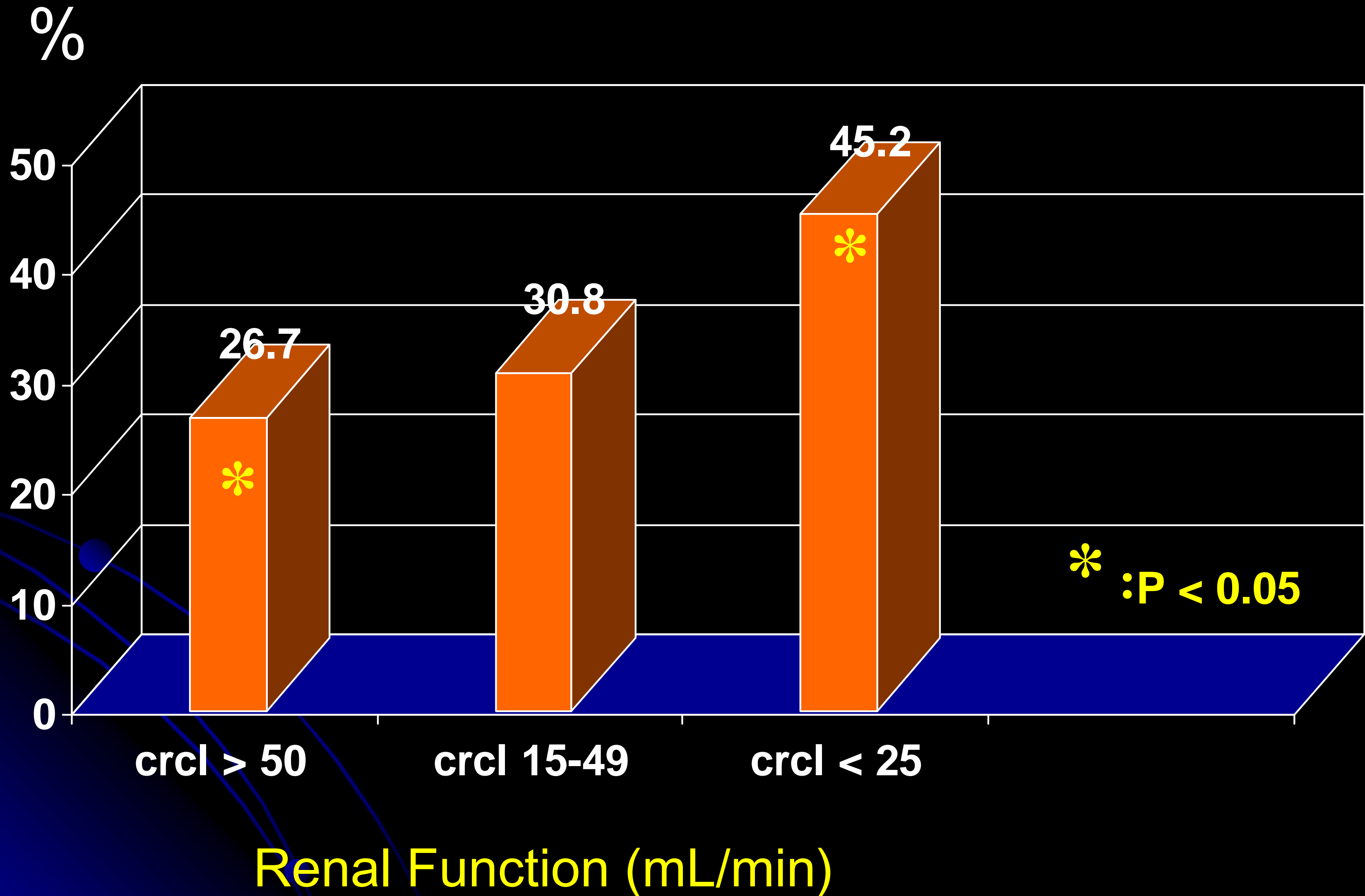
Kidney Disease Questionnaire

**: P<0.01, *: P<0.05 (for trend)

: Baseline : 6 months : 12 months

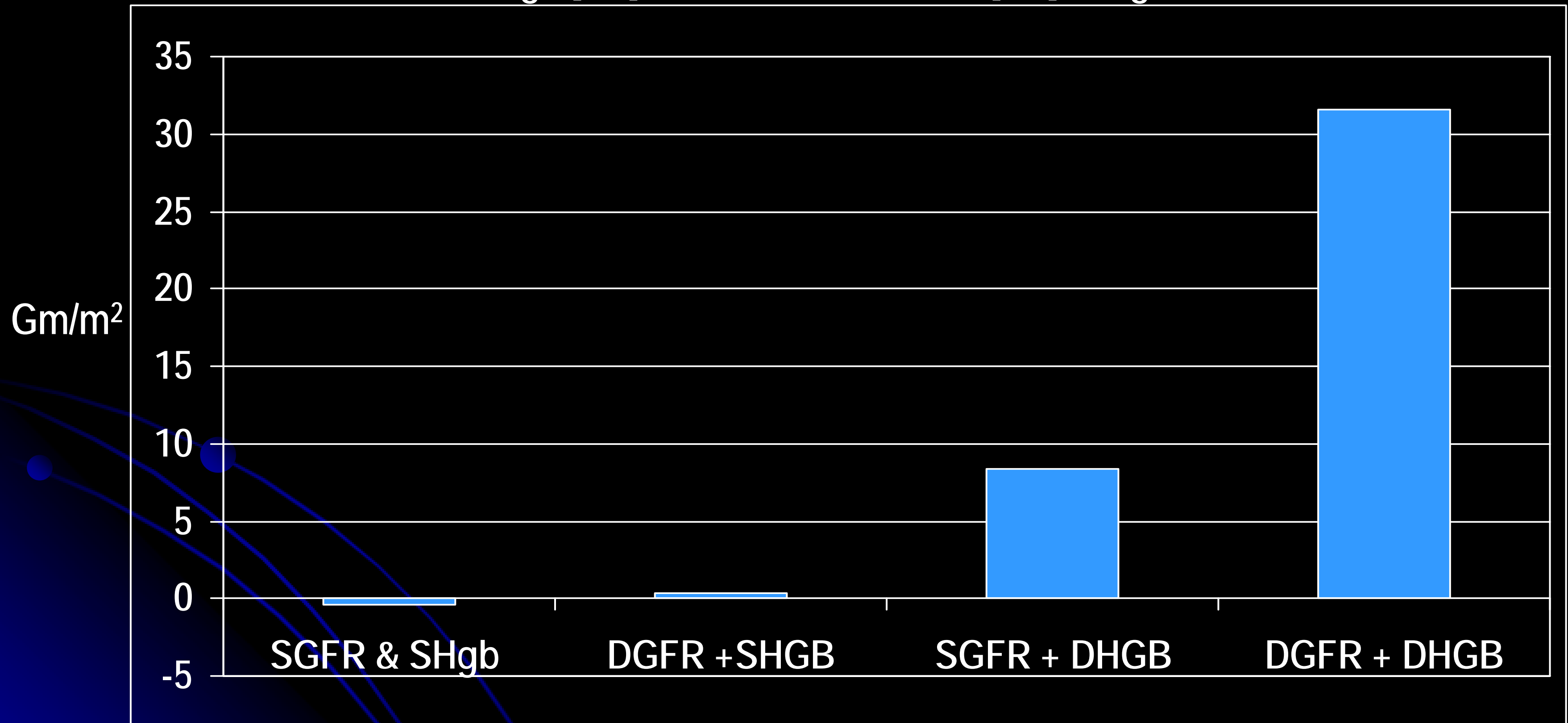
Foley RN, KI, 2000

CKD and Left Ventricular Hypertrophy



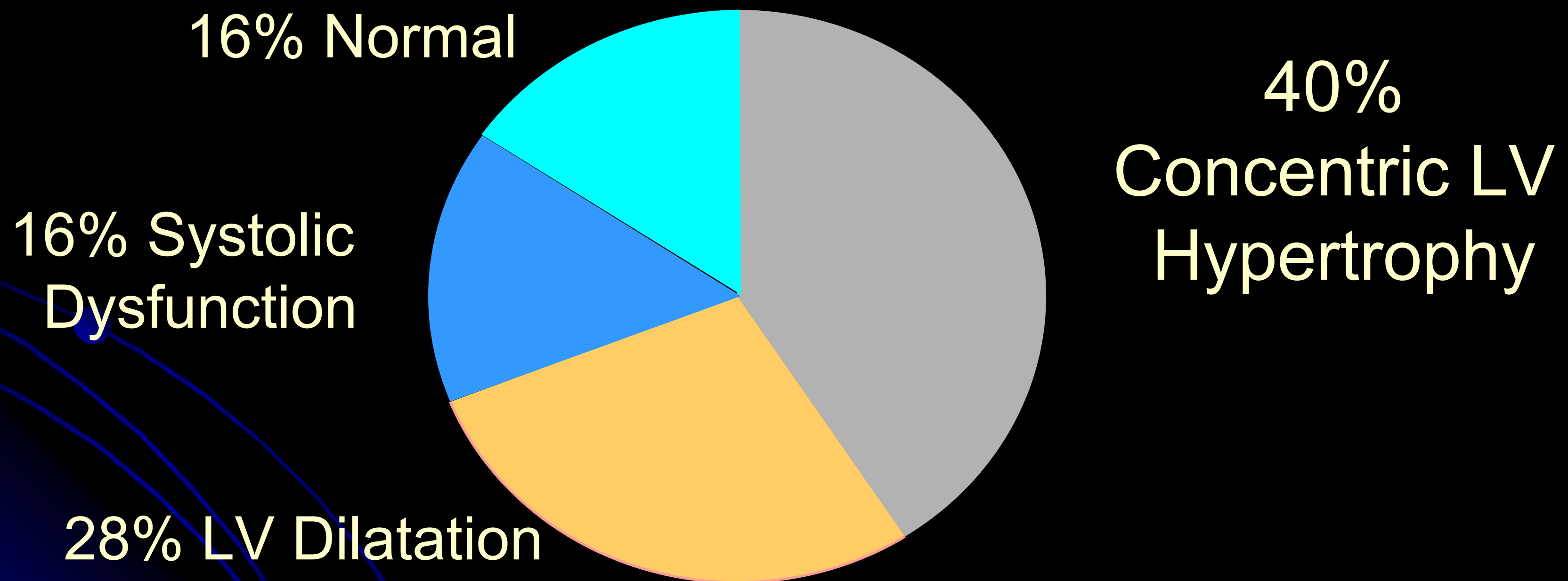
(Levin A et al, AJKD, 1996)

There appears to be an amplification effect of decline in [Hb] and GFR on LVMI growth

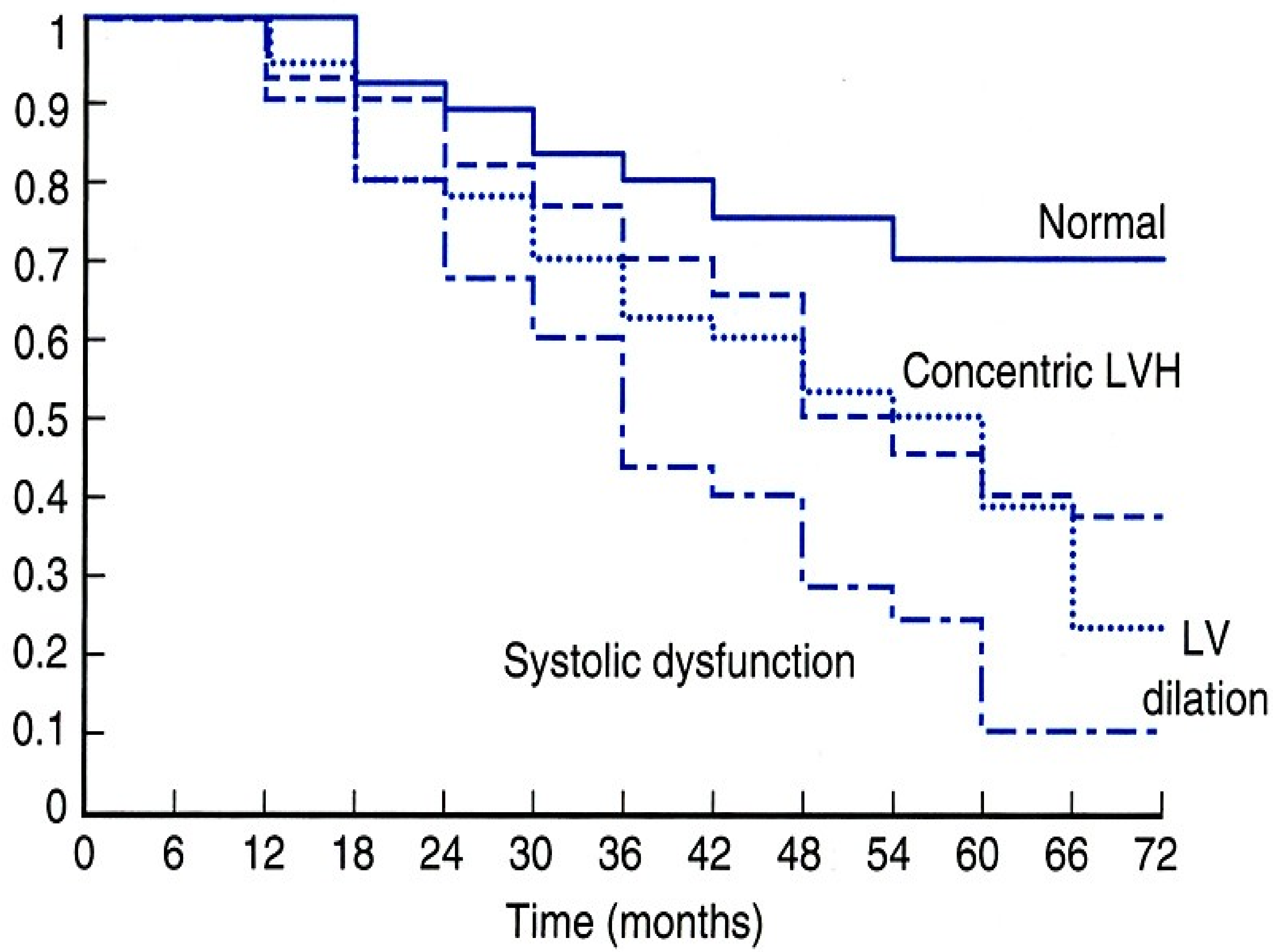


P=.002

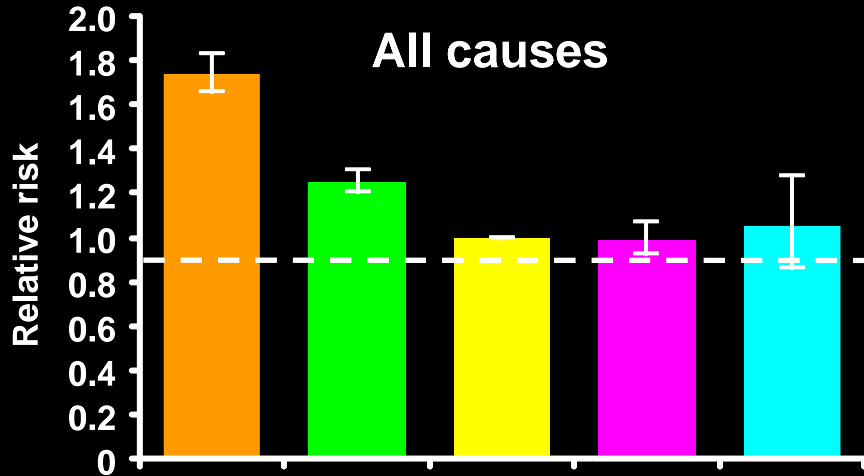
Echocardiograms of 432 incident hemodialysis patients

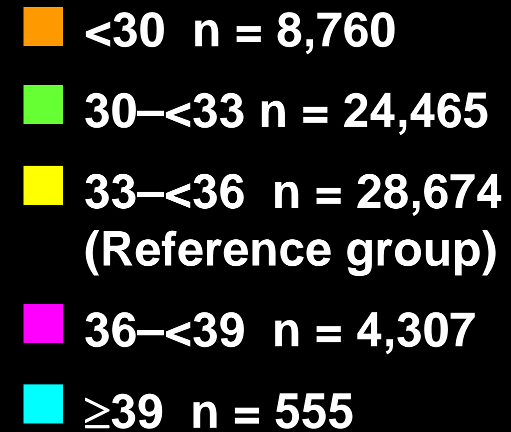


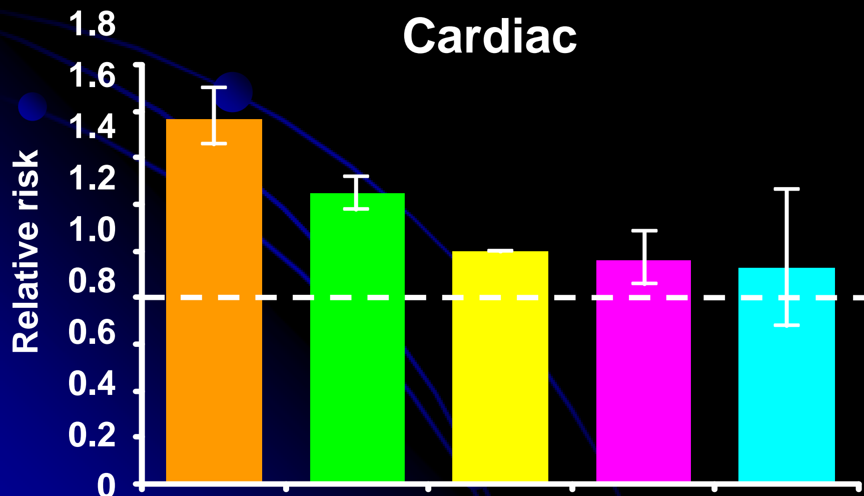
P. Parfrey. *Nephrol Dial Transplant*. 1996;11:1277.

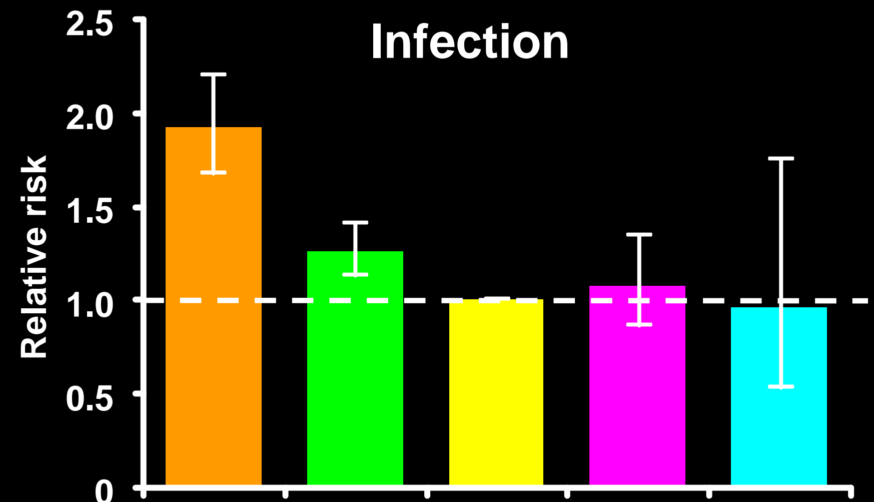

A
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
6
12
18
24
30
36
42
48
54
60
66
72
Time (months)
Normal
Concentric LVH
LV
dilation
Systolic dysfunction

Lower [Hb] Levels Associated with Higher Mortality Risk in ESRD Patients



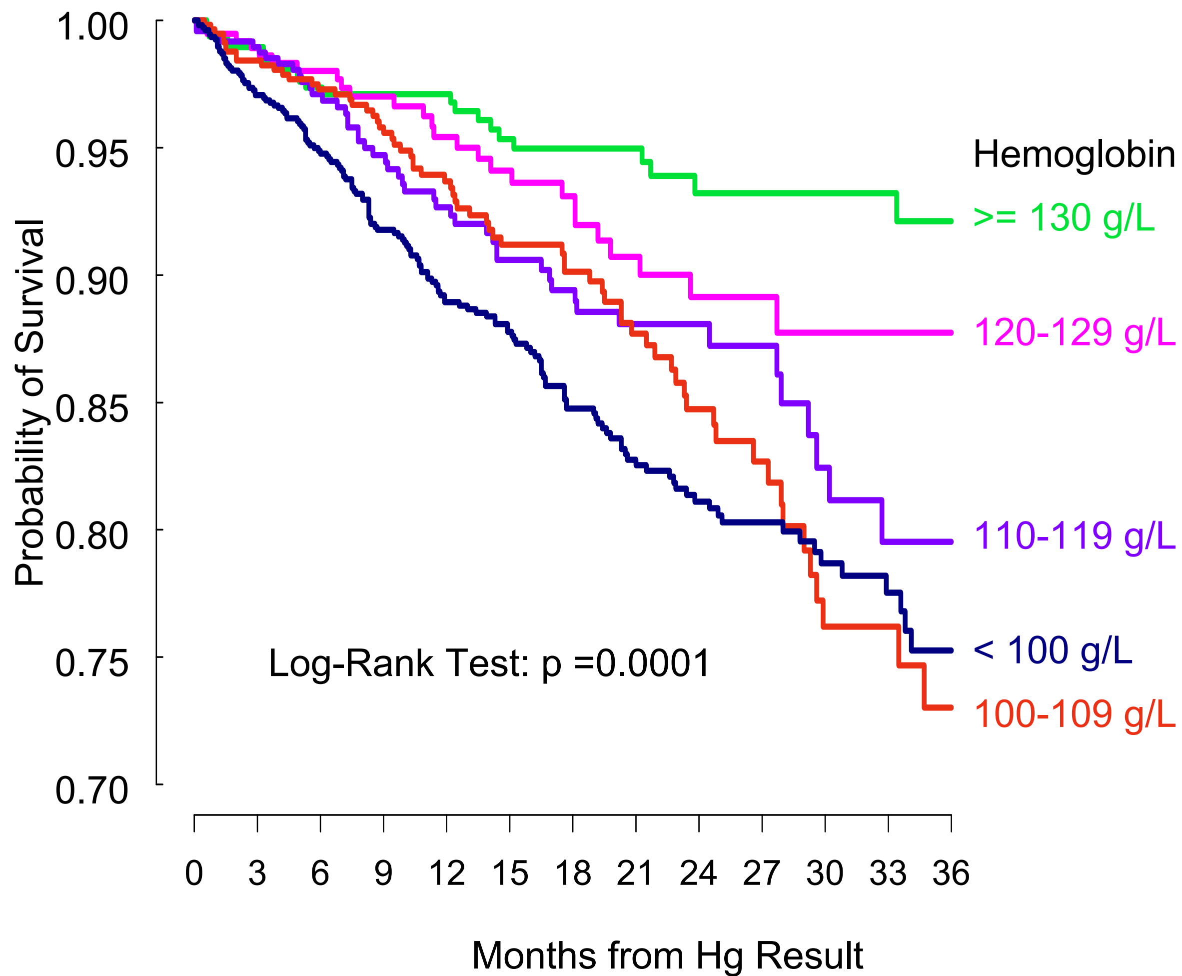






Collins AJ et al. *J Am Soc Nephrol.* 2001;12:2465-2473

Survival of CKD Patients by Hemoglobin Level



Levin et al, NDT, 2006

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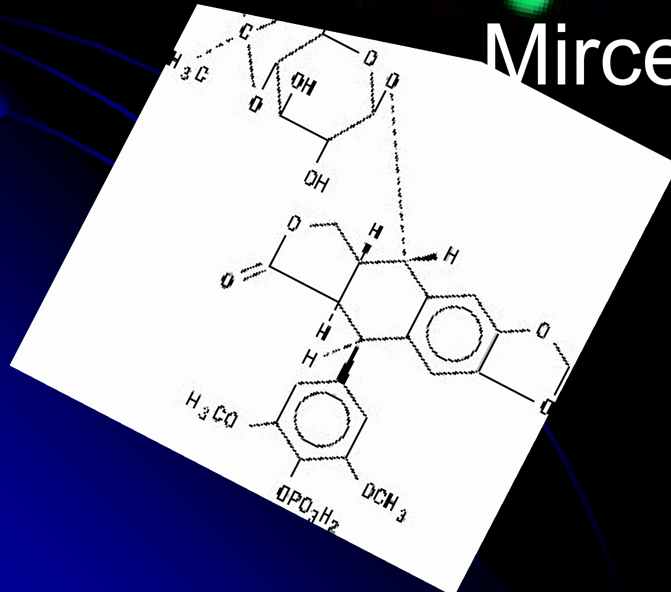
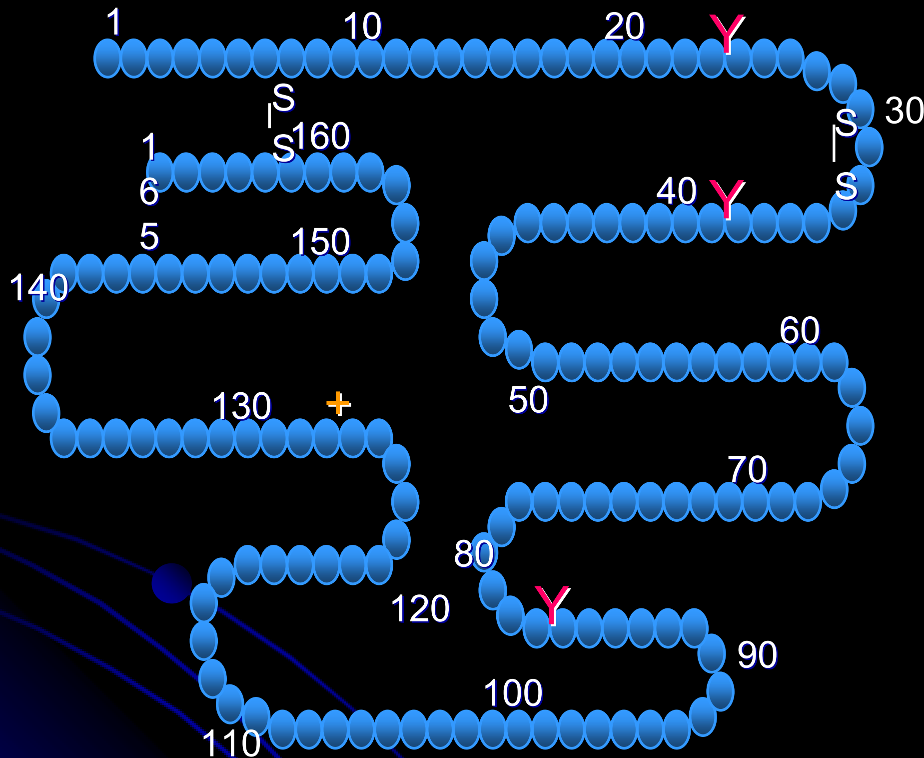
Erythropoietin Family

- Epoetin Alfa
- Epoetin Beta
- Darbepoetin Alfa
- Epoetin Omega
- Epoetin Delta
- Mircera (pegylated epoetin beta)



Erythropoietins: Structure



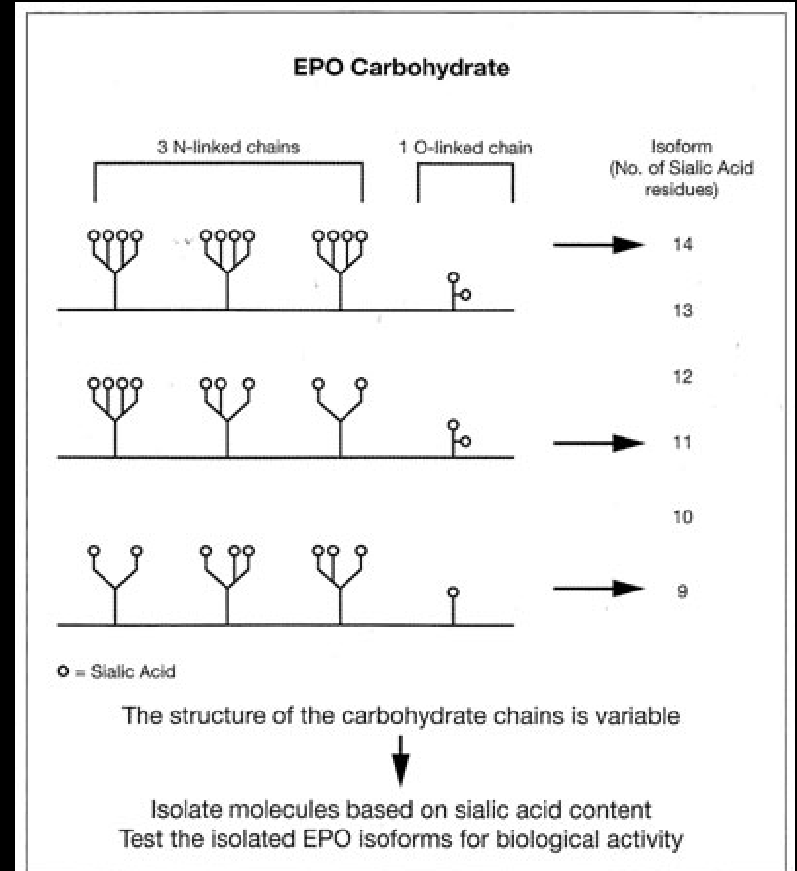


Figure 1: Schematic of EPO Carbohydrate Structure and EPO Isoform Designation. EPO = erythropoietin.

Darbepoetin Alfa versus Epoetin

- 3 N-linked CHO chains
- Up to 14 Sialic Acid Residues
- 30,400 Daltons
- 40% Carbohydrate

- 5 N-linked CHO chains
- Up to 22 Sialic Acid Residues
  (eight additional)
- 37,100 Daltons
- 51% Carbohydrate

MacDougall, Seminars in Nephrology, 2000, 20:375

What Haemoglobin?

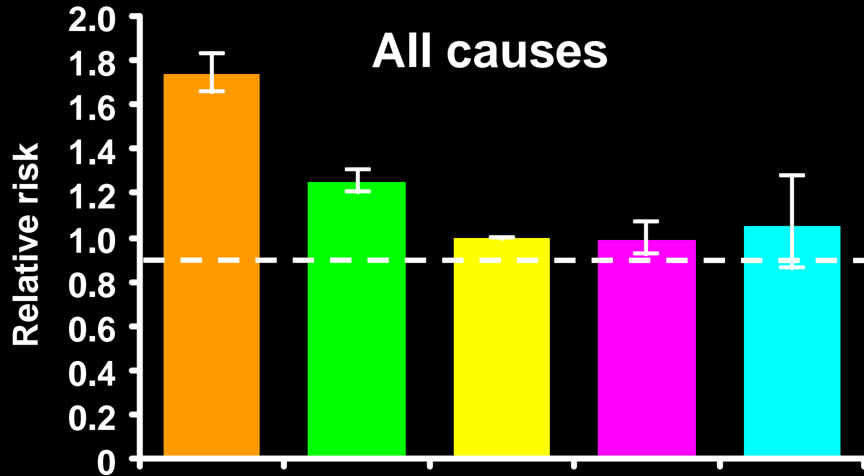
"Say … what's a mountain goat doing way up here in a cloud bank?"

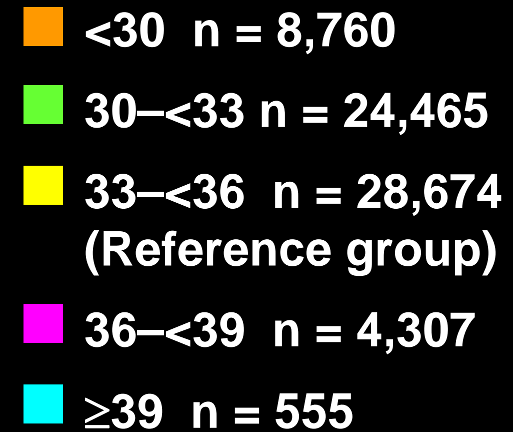
Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis

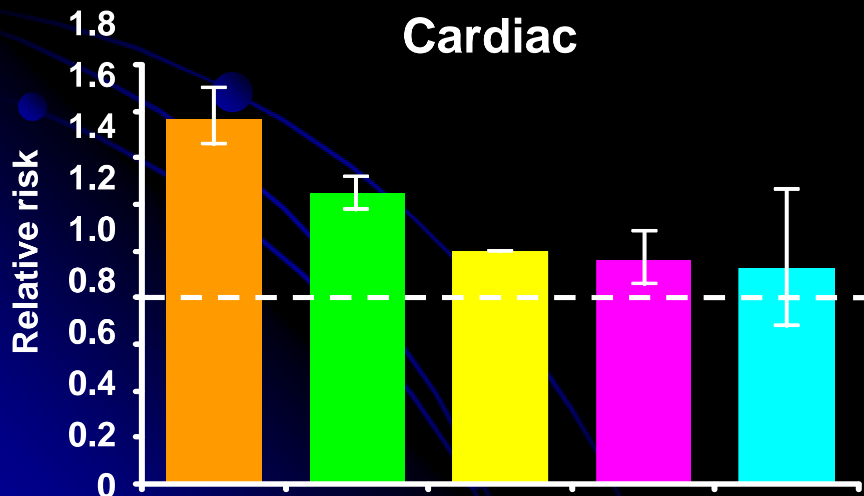
Arintaya Phrommintikul, Steven Joseph Haas, Maros Elsik, Henry Krum

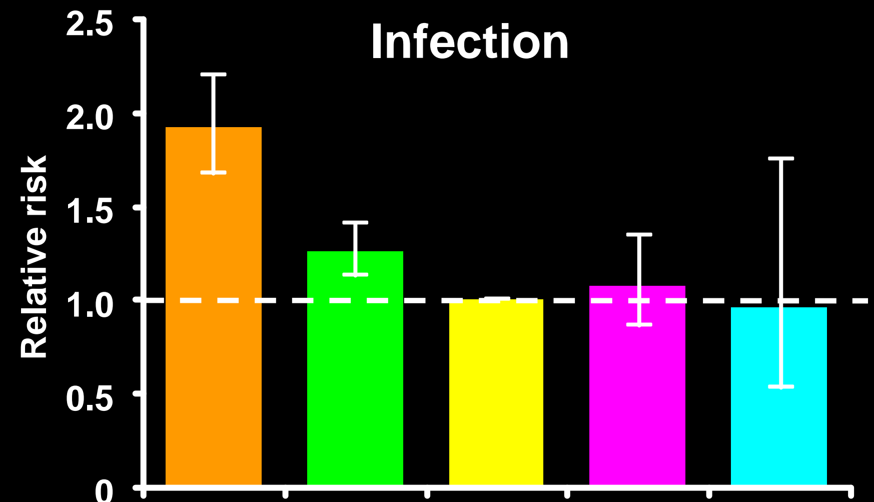
Lancet, 2007

Lower [Hb] Levels Associated with Higher Mortality Risk in ESRD Patients



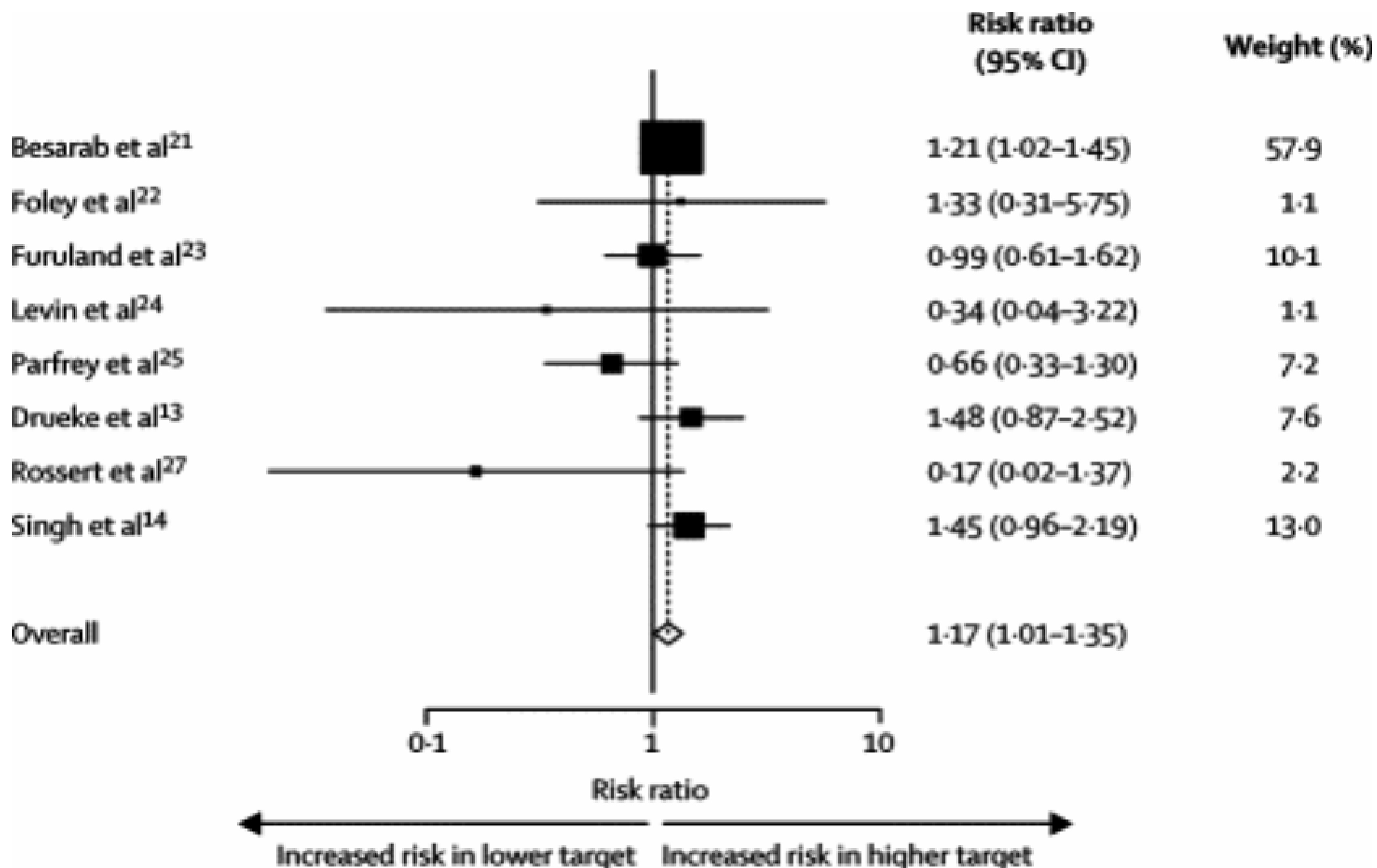






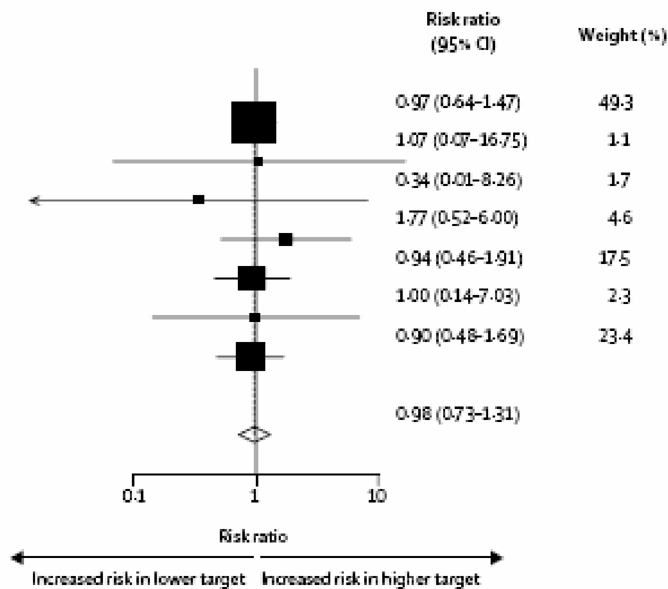
Collins AJ et al. *J Am Soc Nephrol.* 2001;12:2465-2473

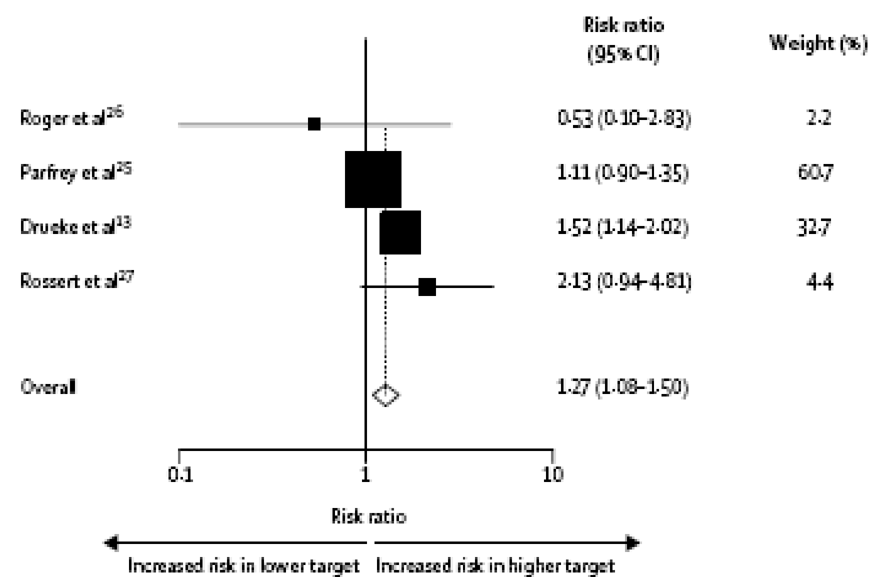
Mortality Risk in CKD (dialysis and pre-dialysis)



Phrommintikul A et al, Lancet, 2007

Target Hb - Myocardial Infarction and Hypertension

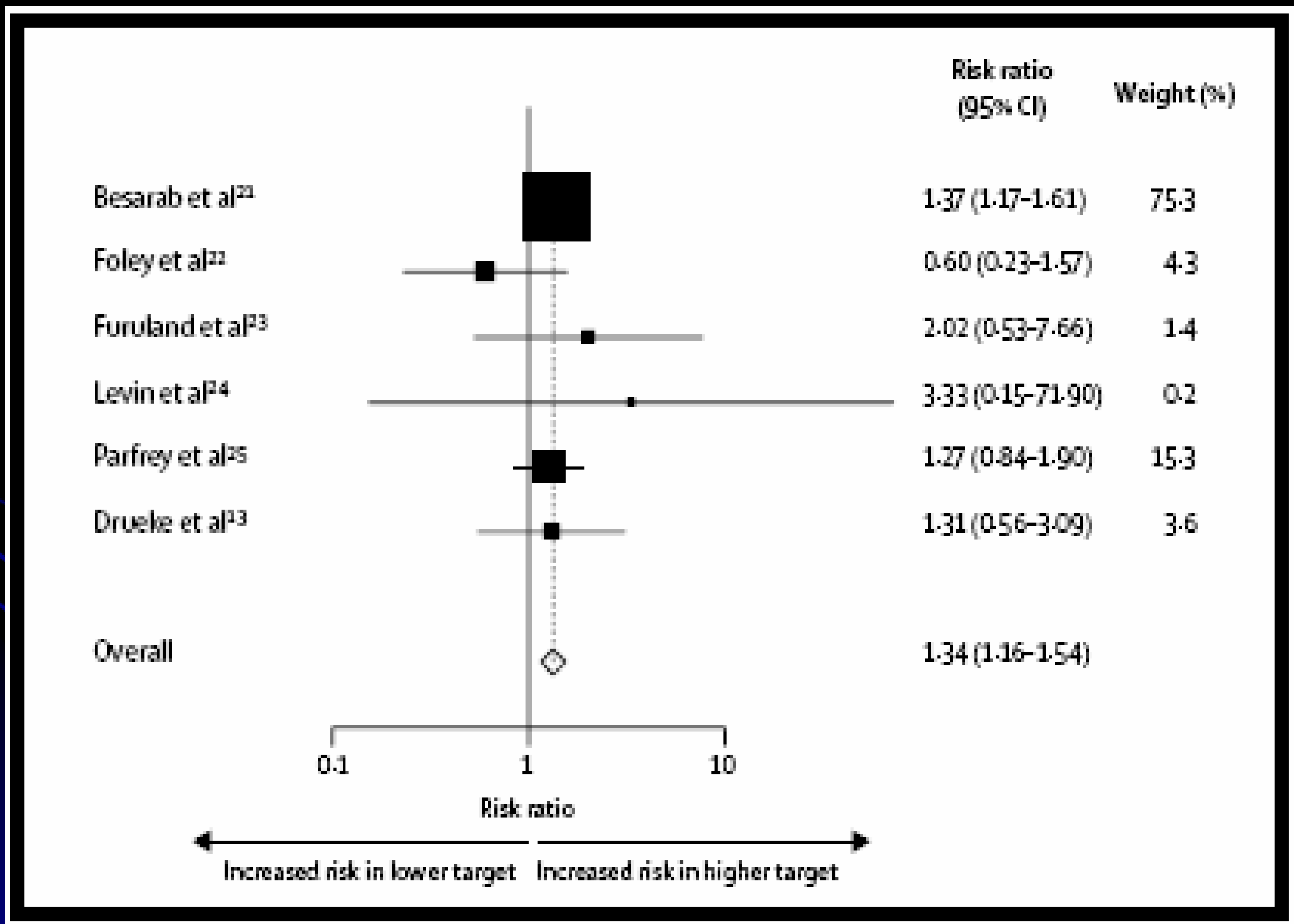




Myocardial Infarction

Blood Pressure

Target Hb and arteriovenous access thrombosis



The NEW ENGLAND JOURNAL of MEDICINE

The Effects of Normal as Compared with Low Hematocrit Values in Patients with Cardiac Disease Who Are Receiving Hemodialysis and Epoetin

Besarab, Anatole; Bolton, W. Kline; Browne, Jeffrey K.; Egrie, Joan C.; Nissenson, Allen R.; Okamoto, Douglas M.; Schwab, Steve J.; Goodkin, David A.

versus

Double-Blind Comparison of Full and Partial Anemia Correction in Incident Hemodialysis Patients without Symptomatic Heart Disease

Patrick S. Parfrey,* Robert N. Foley,† Barbara H. Wittreich,‡ Daniel J. Sullivan,§ Martin J. Zagari,‡ and Dieter Frei;‡ for the Canadian European Study Group

*Memorial University of Newfoundland, St. John's, Newfoundland, Canada; †Chronic Disease Research Group, Minneapolis, Minnesota; ‡Ortho Biotech, Bridgewater, New Jersey; and §Johnson and Johnson, Pharmaceutical Research, LLC, Raritan, New Jersey

J Am Soc Nephrol 16: 2180–2189, 2005. doi: 10.1681/ASN.2004121039

Comparators in Besarab versus Parfrey Studies

- Haemodialysis
  - 3.2 ± 3.6 years
- **Significant** cardiac disease (ischaemic or congestive)
  - c. 70% ≥ Stage II NYHA
- Diabetes: 55%
- Reversal of anaemia
  - [Hb] ≈ 10 vs 14 g/dL
- N = 1233
- Mean epoetin-α dose:
  - 10,500 vs 35,000 U/wk
  - (150 vs 500 U/kg/week)
- Age: 65 ± 12 years
- 30 months

- Haemodialysis
  - 10.1 ± 5.0 months
- **No** significant cardiac disease (ischaemic or congestive)
- Diabetes: 18%
- Reversal of anaemia (high gp)
  - [Hb] ≈ 11 vs 13 g/dL
- N = 596
- Mean epoetin-α dose:
  - 5,600 vs 12,750 U/wk
  - (75 vs 170 U/kg/week)
- Age: 51 ± 15 years
- 24 months

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2006 VOL. 355 NO. 20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*

‘CREATE Study’

The NEW ENGLAND JOURNAL of MEDICINE

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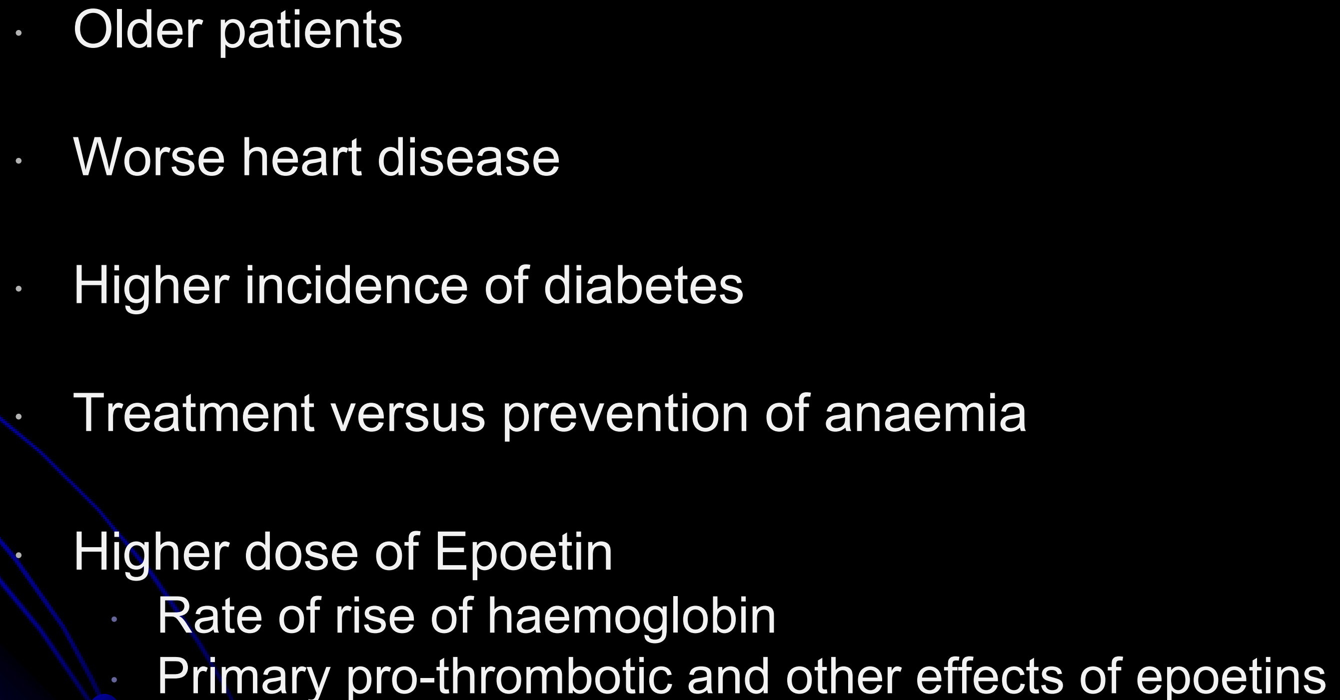
ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

‘CHOIR Study’

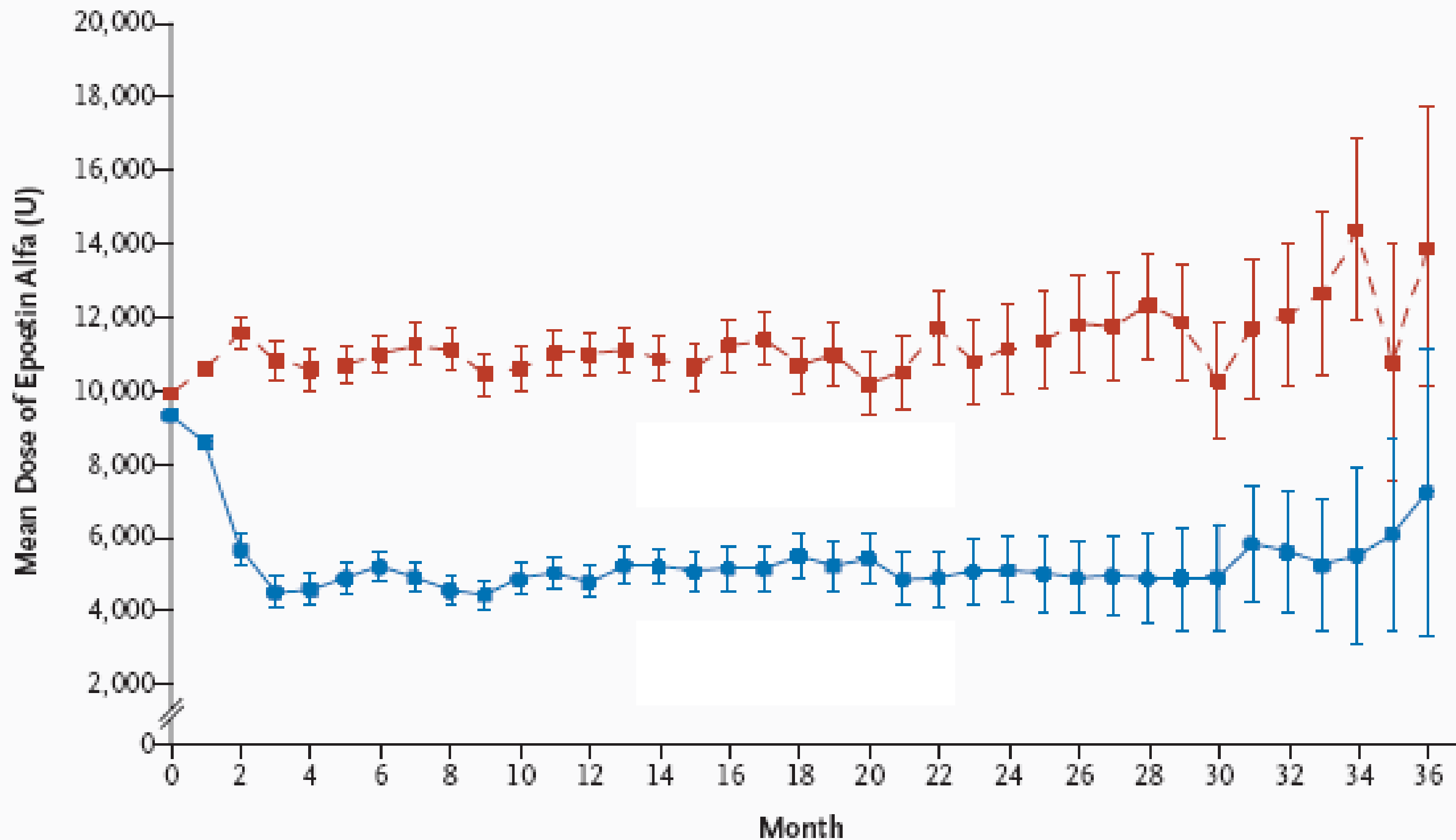
Common elements of Besarab and CHOIR studies compared with Parfrey and CREATE studies?



Mortality increased at higher ‘Target Hb’:

- Older patients
- Worse heart disease
- Higher incidence of diabetes
- Treatment versus prevention of anaemia
- Higher dose of Epoetin
  - Rate of rise of haemoglobin
  - Primary pro-thrombotic and other effects of epoetins

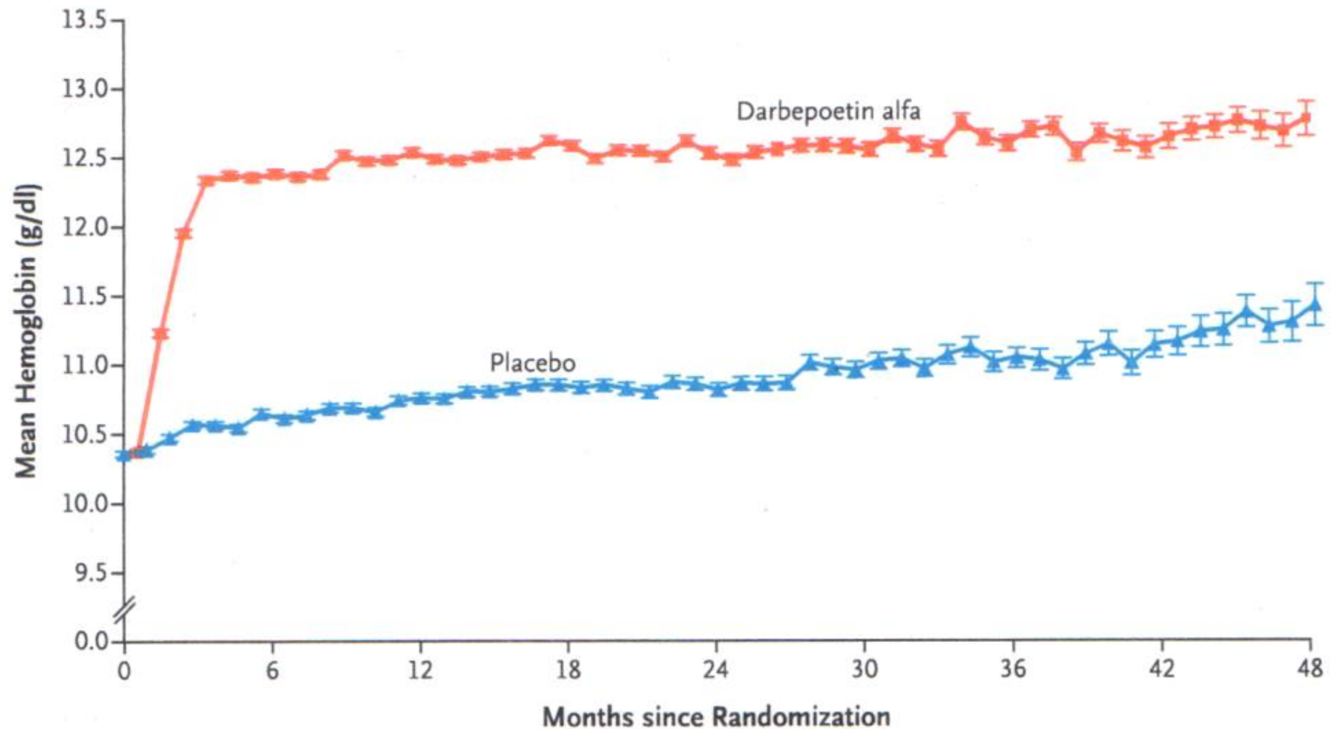
CHOIR and CREATE: Comparative doses of epoetin-α and epoetin-β



CHOIR

CREATE

TREAT Study (NEJM 2010)

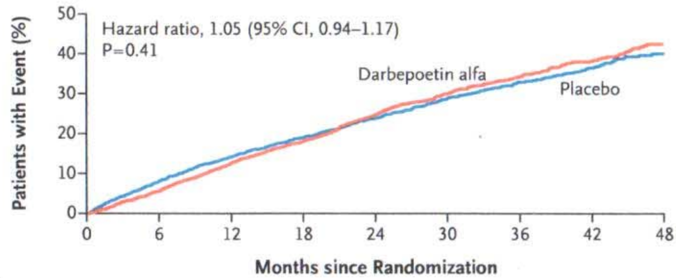


No. of Patients									
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

Figure 1. Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo.

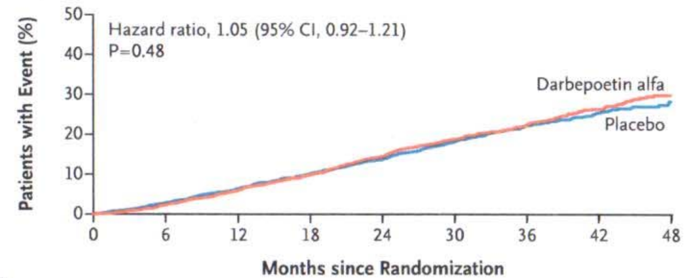
I bars represent standard errors.

A Cardiovascular Composite End Point



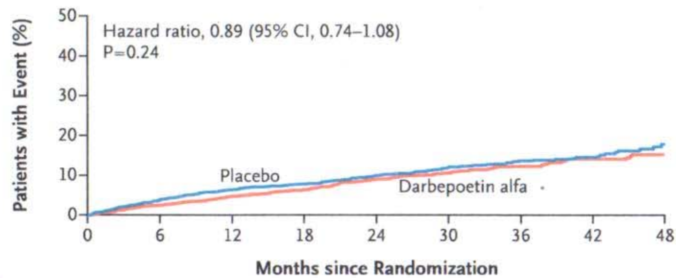
No. at Risk									
Darbepoetin alfa	2012	1882	1717	1515	1180	817	551	318	130
Placebo	2026	1836	1687	1487	1178	834	529	319	122

B Death from Any Cause



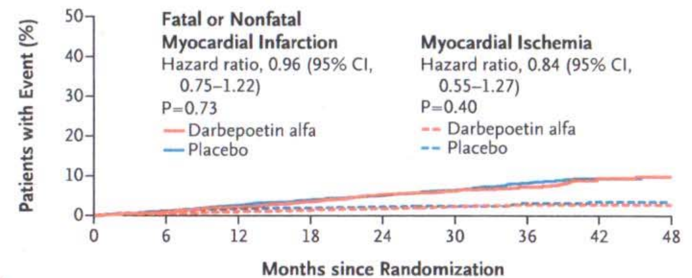
No. at Risk									
Darbepoetin alfa	2012	1947	1847	1659	1337	945	655	386	164
Placebo	2026	1943	1839	1652	1345	970	636	385	156

C Fatal or Nonfatal Congestive Heart Failure



No. at Risk									
Darbepoetin alfa	2012	1890	1742	1525	1191	819	555	319	136
Placebo	2026	1859	1702	1495	1187	835	519	307	115

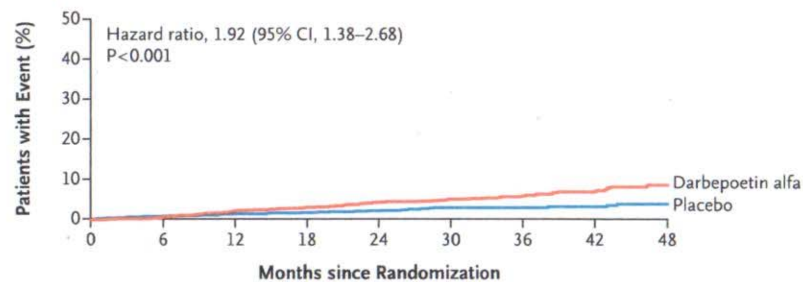
D Fatal or Nonfatal Myocardial Infarction and Myocardial Ischemia



No. at Risk									
Fatal or Nonfatal Myocardial Infarction									
Darbepoetin alfa	2012	1920	1785	1566	1232	851	577	325	137
Placebo	2026	1907	1765	1550	1235	863	539	324	123
Myocardial Ischemia									
Darbepoetin alfa	2012	1924	1794	1583	1255	869	597	347	146
Placebo	2026	1906	1767	1561	1251	880	556	338	132

E Fatal or Nonfatal Stroke

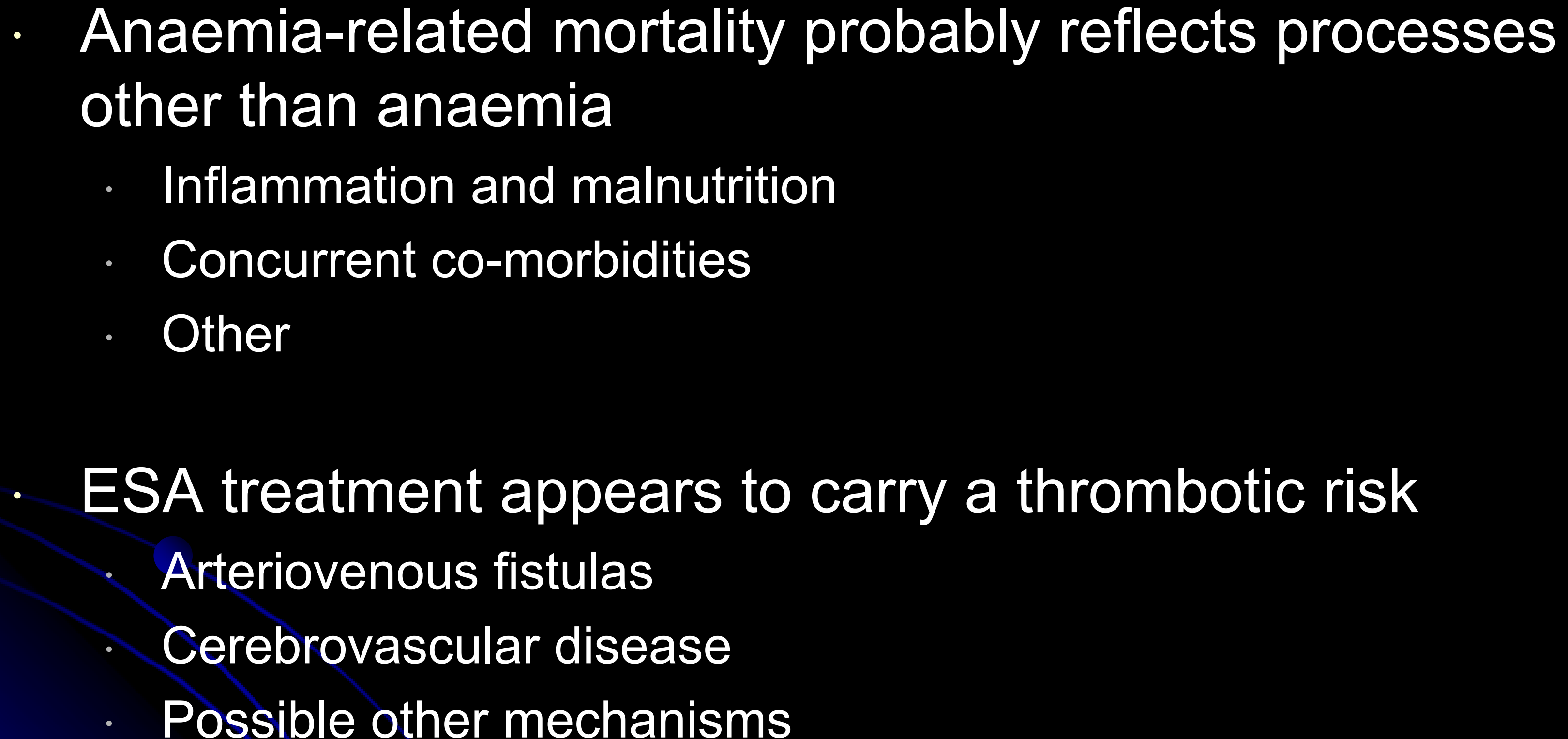
Figure 2



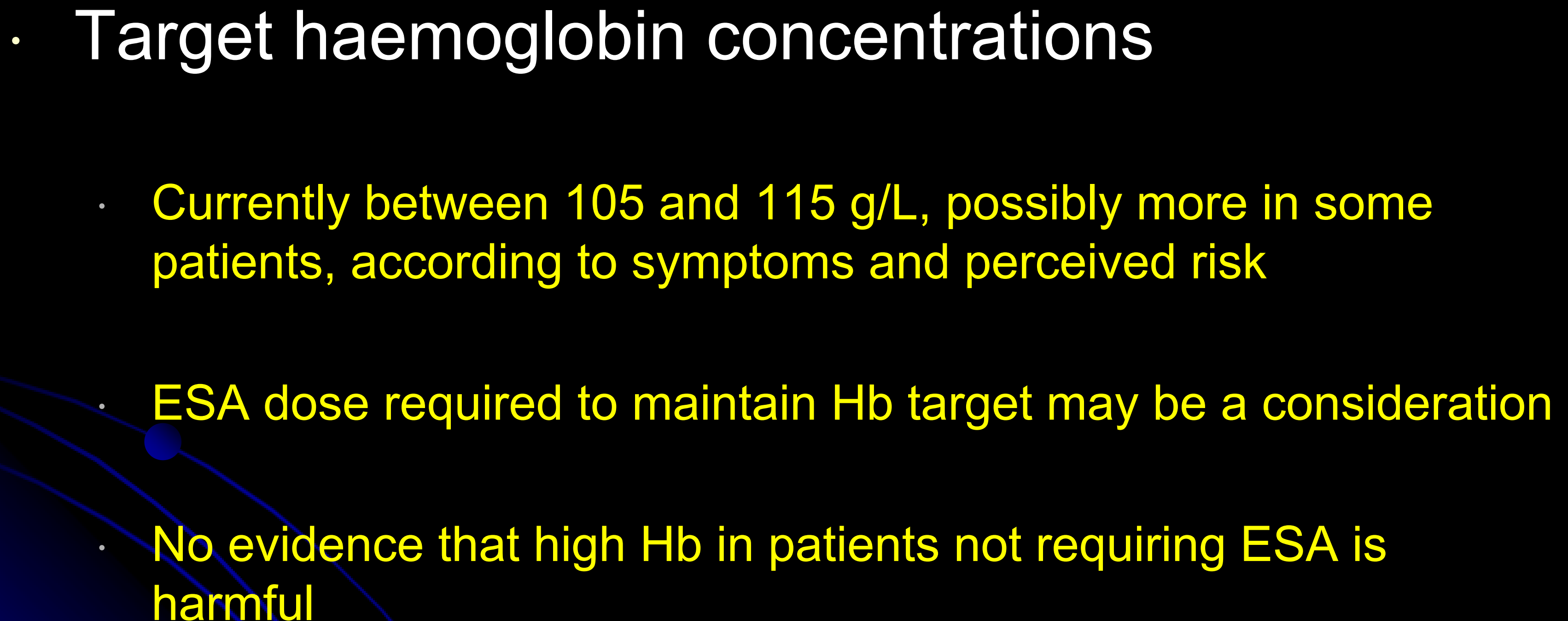
No. at Risk									
Darbepoetin alfa	2012	1923	1787	1581	1247	863	590	341	141
Placebo	2026	1914	1783	1575	1262	886	561	338	132

Trials Summary

- Anaemia-related mortality probably reflects processes other than anaemia
  - Inflammation and malnutrition
  - Concurrent co-morbidities
  - Other
- ESA treatment appears to carry a thrombotic risk
  - Arteriovenous fistulas
  - Cerebrovascular disease
  - Possible other mechanisms

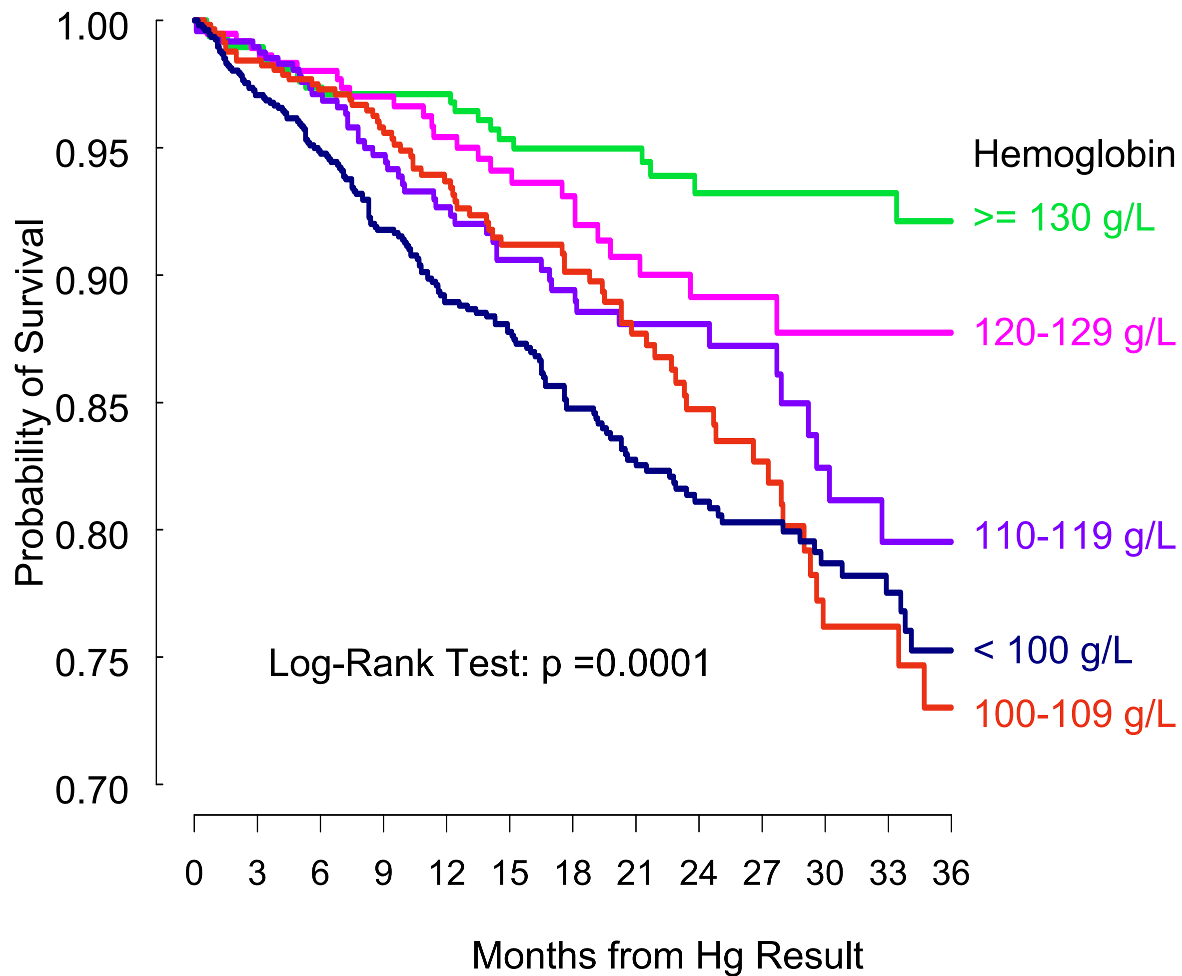


Trials Summary



- Target haemoglobin concentrations
  - Currently between 105 and 115 g/L, possibly more in some patients, according to symptoms and perceived risk
  - ESA dose required to maintain Hb target may be a consideration
  - No evidence that high Hb in patients not requiring ESA is harmful

Survival of CKD Patients by Hemoglobin Level



Levin et al, NDT, 2006

What haemoglobin for Mandy?

1. Is anaemia due to CKD?
    - eGFR < 40 mL/min

2. Ensure no other causes of anaemia
    - Coeliac disease: iron and folate deficient

3. Control blood pressure and fluid status

4. Start low dose ESA
    - 0.5-0.7 μg/kg/fortnight darbepoetin (x 100 U/kg/wk for epoetin)

5. Aim for 110-120 g/L, monitor ESA dose