Anemia correction in patients with CKD – Which targets ?

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Anemia and CKD

1) **General aspects**

2) **Relation between anemia and outcome**
   - Observational studies
   - Intervention studies (RCTs)
   - Negative effects of full correction - Why ?

3) **Present anemia targets**

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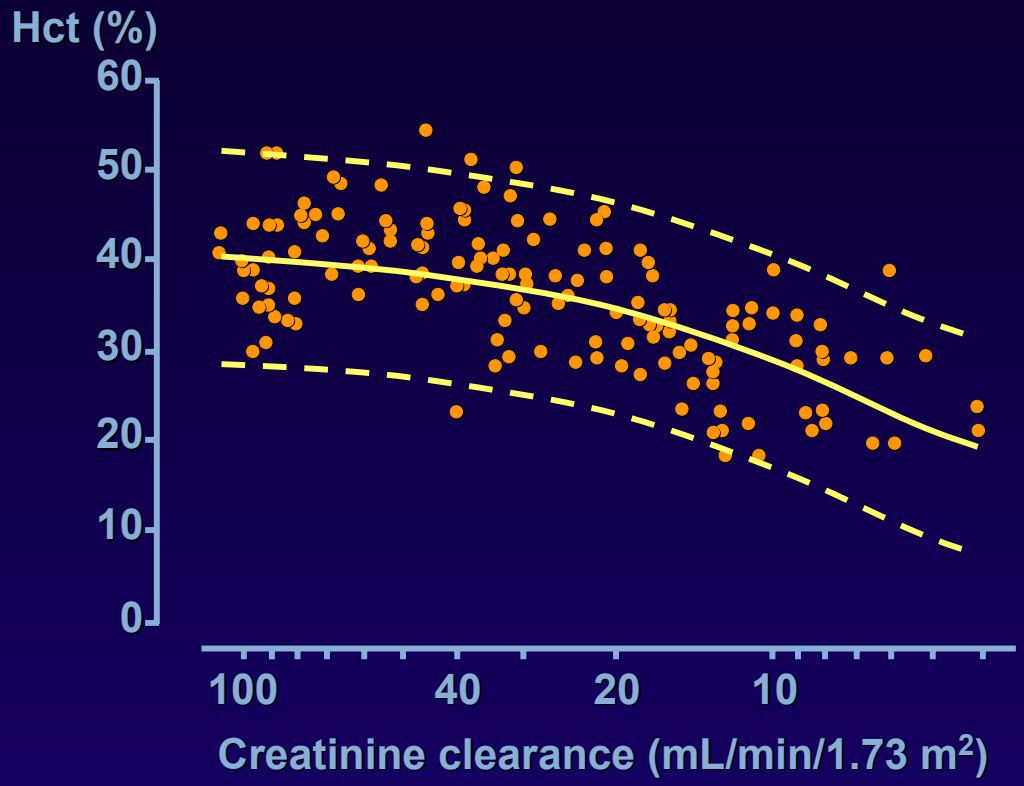
Anemia as a function of decreasing GFR

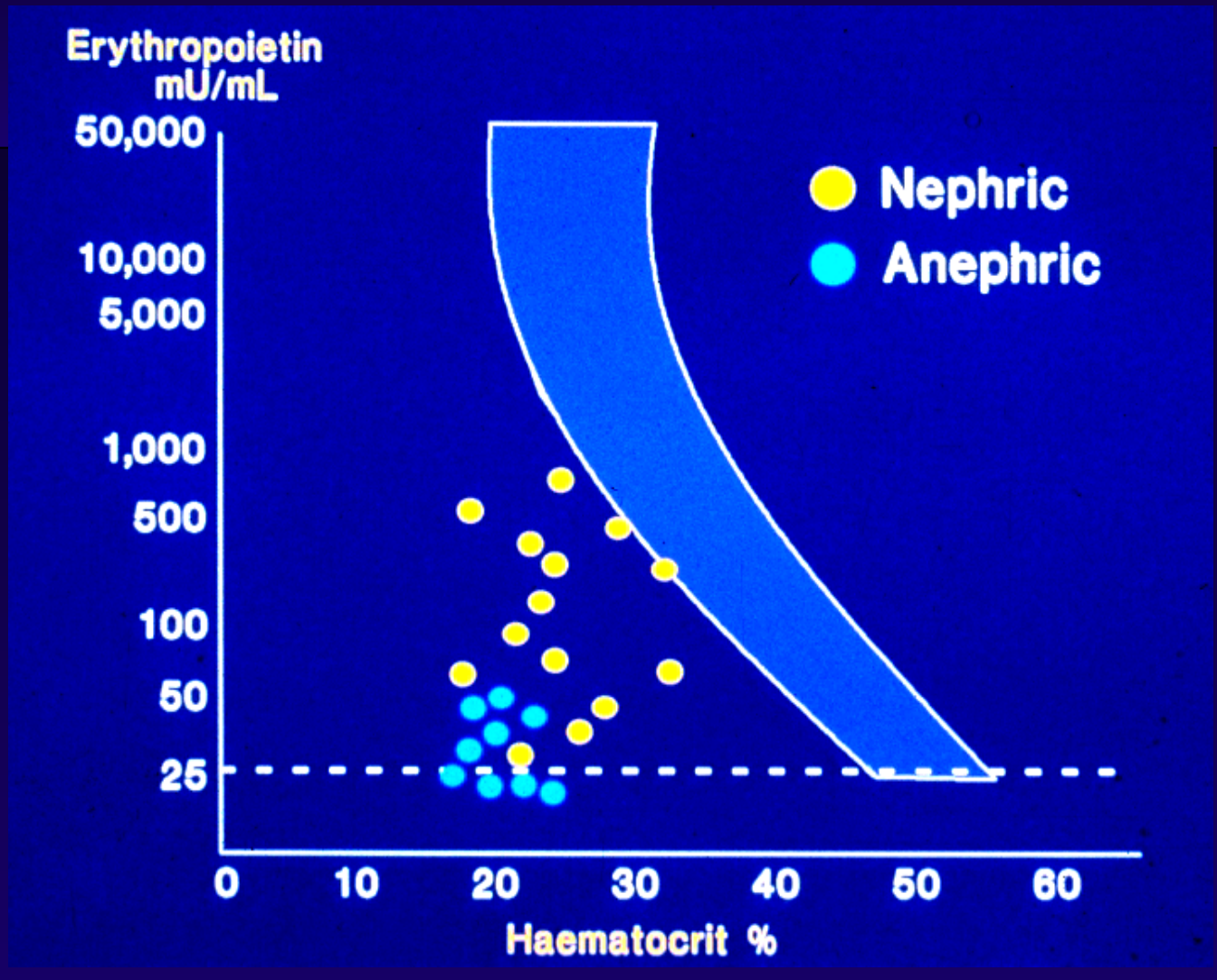


adapated from J Pediatr (1988) 113: 1015; Blood (1979) 54: 877

Causes of anemia in chronic renal failure

- **Erythropoietin deficiency**
- Deficiency states (iron, vitamins, malnutrition)
- Blood loss (G-I & vag. bleeding; blood sampling)
- Chronic inflammatory state
- Inhibition of erythropoiesis: uremic toxins (?)
- Shortening of RBC survival (hemolysis)
- Hyperparathyroidism / marrow fibrosis
- Aluminum overload
- Inadequate dialysis treatment

Relation between hematocrit und erythropoietin



Caro J, J Lab Clin Med 1979;93:449-58

Anemia and CKD

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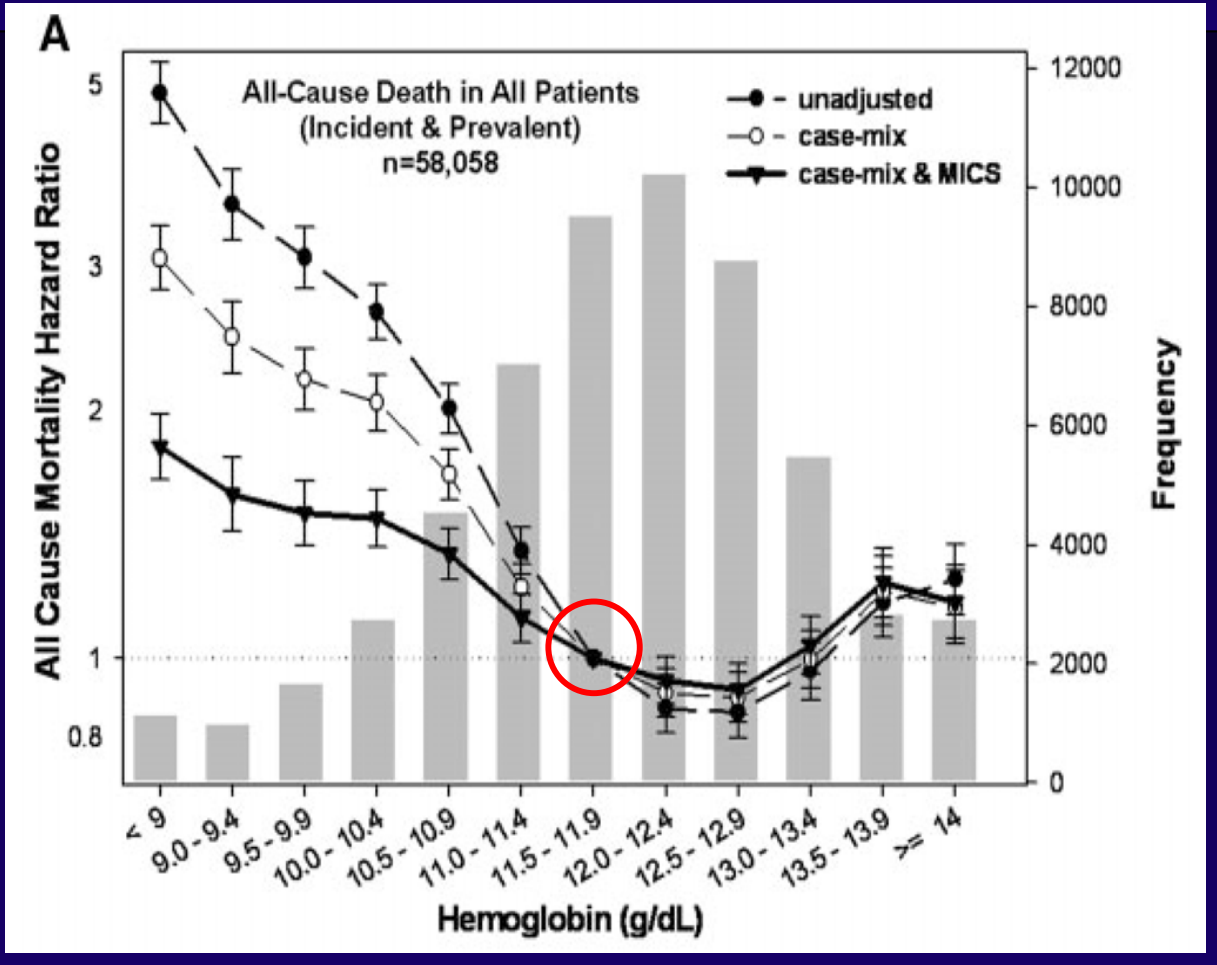
Time varying Hb values and relative risk for death in chronic HD patients *(Observational study, 58 058 pts)*



Regidor DL et al, JASN 2006; 17: 1181-91

Observational studies: implications and limitations

- Implications:
  - Hb values >11 g/dL are associated with improved survival
- Limitations:
  - Relationship between Hb and outcomes may not be causally determined
  - Increasing Hb levels >11 g/dL may not improve outcomes

Hb, haemoglobin

Anemia and CKD

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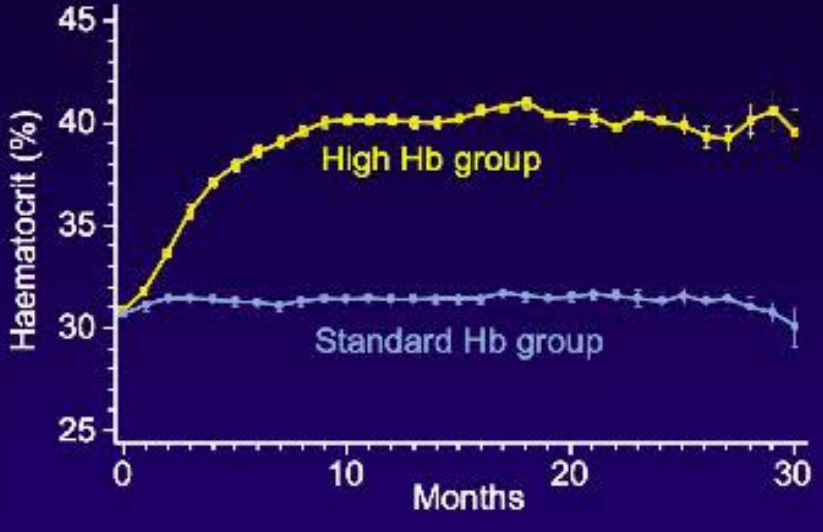
Major published randomized controlled trials of anaemia therapy and CV outcomes in CKD

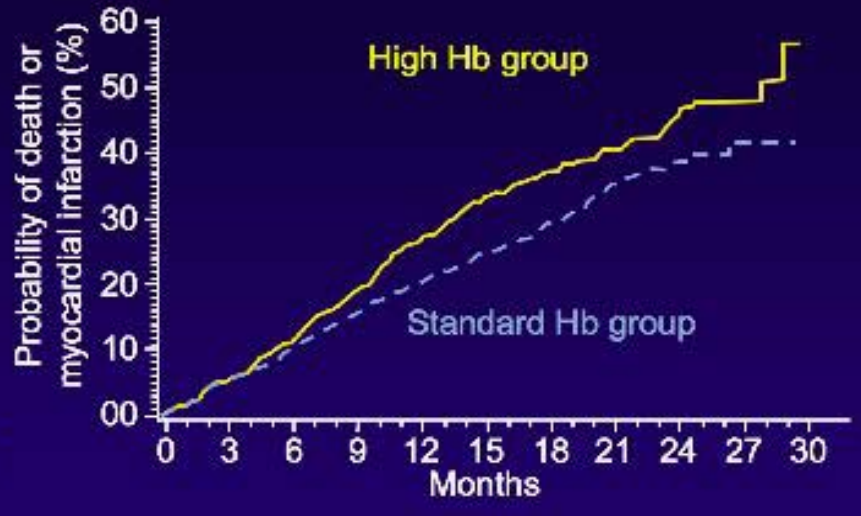
Study	N	Design	Study population	Hb (g/dL) target	Primary endpoint	Follow-up (months)
Besarab *NEJM* 1998;339: 584–590	1233	Open Label	HD + CHF/CAD	10 14	Death, MI	29
Foley *KI* 2000;58: 1325–1325	146	Open Label	HD – CHF/CAD	9.5–10.5 13–14	LVMI LVVI	12
Roger *JASN* 2004;15: 148–156	155	Open Label	CKD 3–5	9–10 12–13	Δ LVMI	24
Parfrey *JASN* 2005;16: 2180–2109	596	Double Blind	HD – CHF/CAD	9.5–11.5 13.5–14.5	LVVI	22
Levin *AJKD* 2005;46: 799–811	172	Open Label	CKD 2–5	9–10.5 12–14	LVMI	22
Singh *NEJM* 2006;355: 2085–2098	1432	Open Label	CKD 3–4	11.3 13.5	Death, CV event	16
Drüeke *NEJM* 2006;355: 2071–2084	603	Open label	CKD 3–4	11–11.5 13–15	Sudden death, CV event	36

CV, cardiovascular; CKD, chronic kidney disease; HD, haemodialysis; CHF, congestive heart failure; CAD, coronary artery disease; MI, myocardial infarction; LVMI, left ventricular myocardial infarction; LVVI, left ventricular volume index

Besarab trial: Hb levels and primary endpoint

- Primary endpoint: time to death of non-fatal MI
  Risk ratio: 1.3 (95% CI, 0.9–1.9)





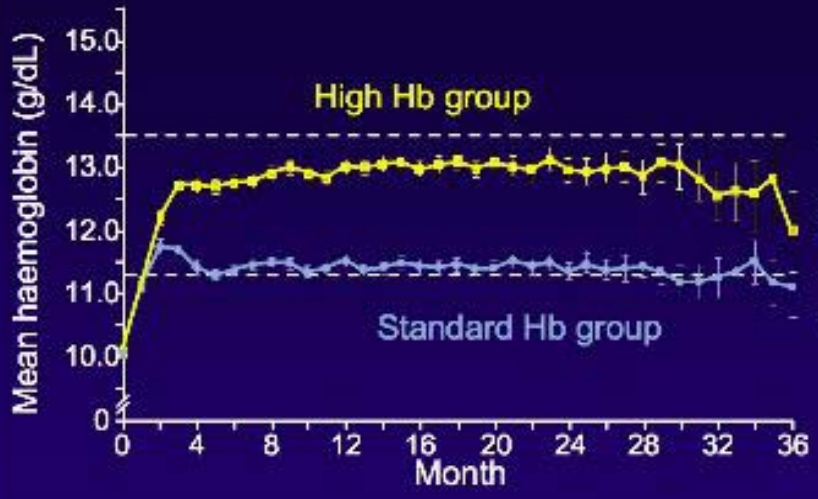
- Normal haematocrit group (43%): 183 deaths, 19 non-fatal MIs
- Low haematocrit group (30%): 150 deaths, 14 non-fatal MIs

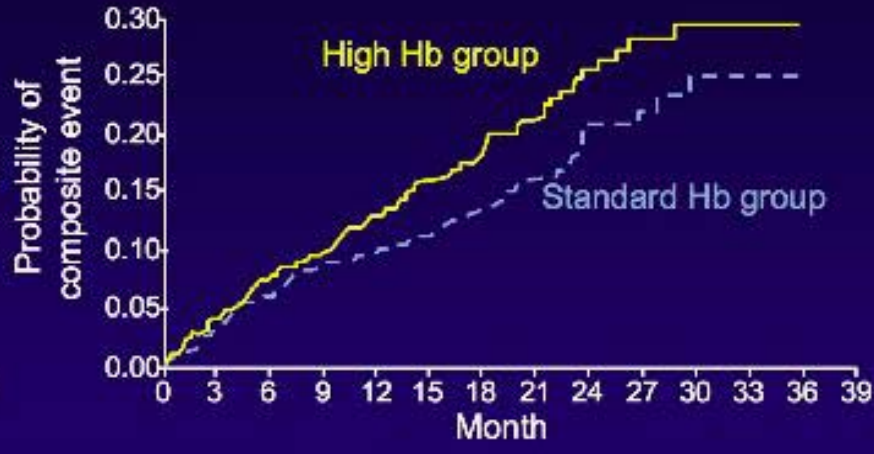
Hb, haemoglobin; MI, myocardial infarction

Besarab A et al *N Engl J Med* 1998;339:584–590

CHOIR: Hb levels and primary endpoint

- Primary endpoint: time to death or CV event
  Hazard ratio: 1.34; 95% CI, 1.03 to 1.74; p=0.03



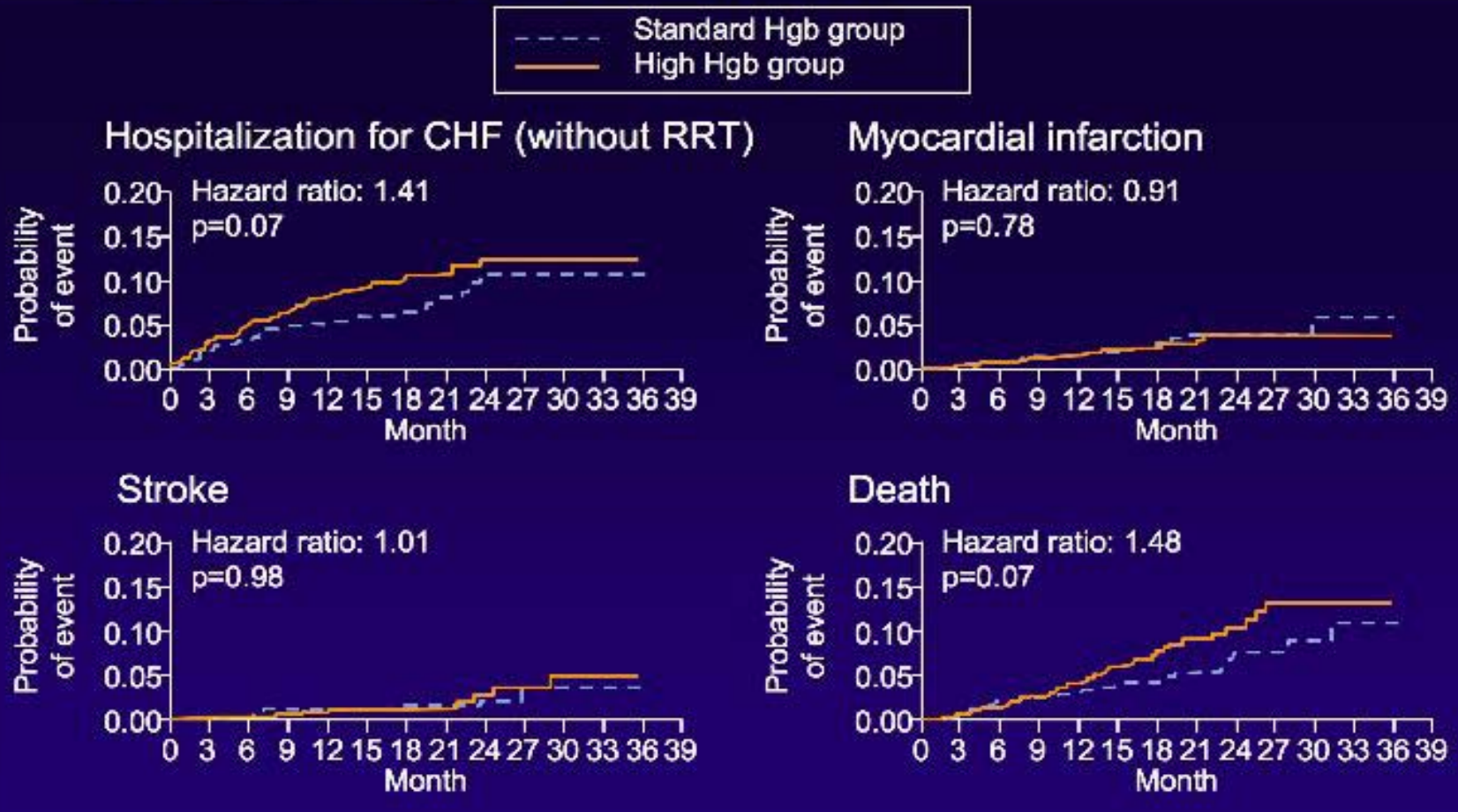


- 125 events (high Hb) versus 97 events (low Hb)

Hb, haemoglobin; CV, cardiovascular

Singh AK et al *N Engl J Med* 2006;355:2085–2098

CHOIR: secondary endpoints



CHF, coronary heart failure; RRT, renal replacement therapy

Singh AK et al *N. Engl. J. Med.* 2006;355:2085–98

CHOIR: difference in baseline CV disease

	High Hb group Target Hb 13.5 g/dL	Standard Hb group Target Hb 11.3 g/dL
Hypertension (% patients)	95.8	93.2*
CABG (% patients)	17.4	13.5**

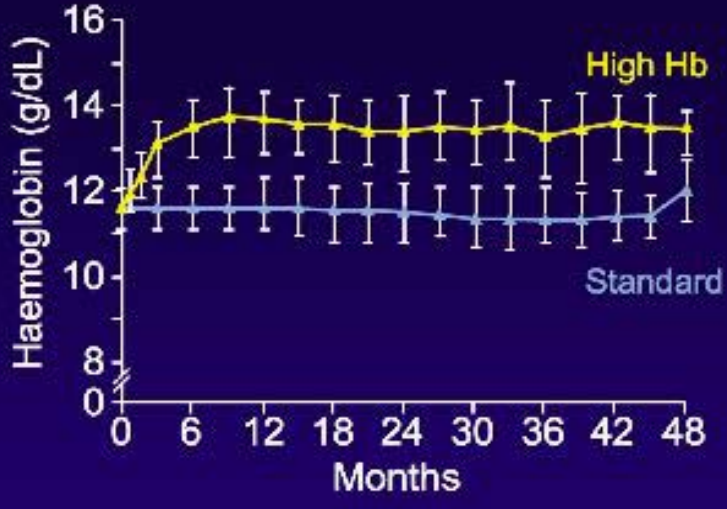
*p = 0.03
**p = 0.05

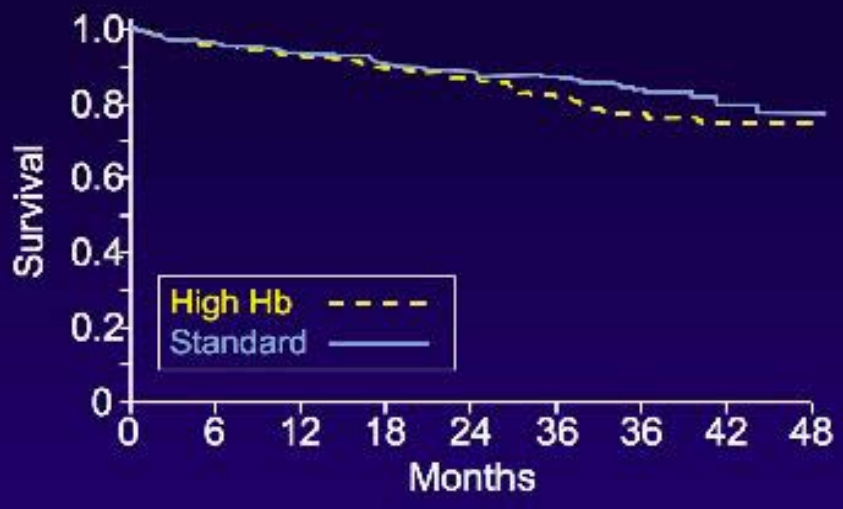
Hb, haemoglobin; CABG, coronary artery bypass grafting

Singh AK et al *N Engl J Med* 2006;355:2085–2098

CREATE: Hb levels and primary endpoint

- Primary endpoint: time to first CV event
  Hazard ratio: 0.78 (0.53, 1.14; p = 0.20)





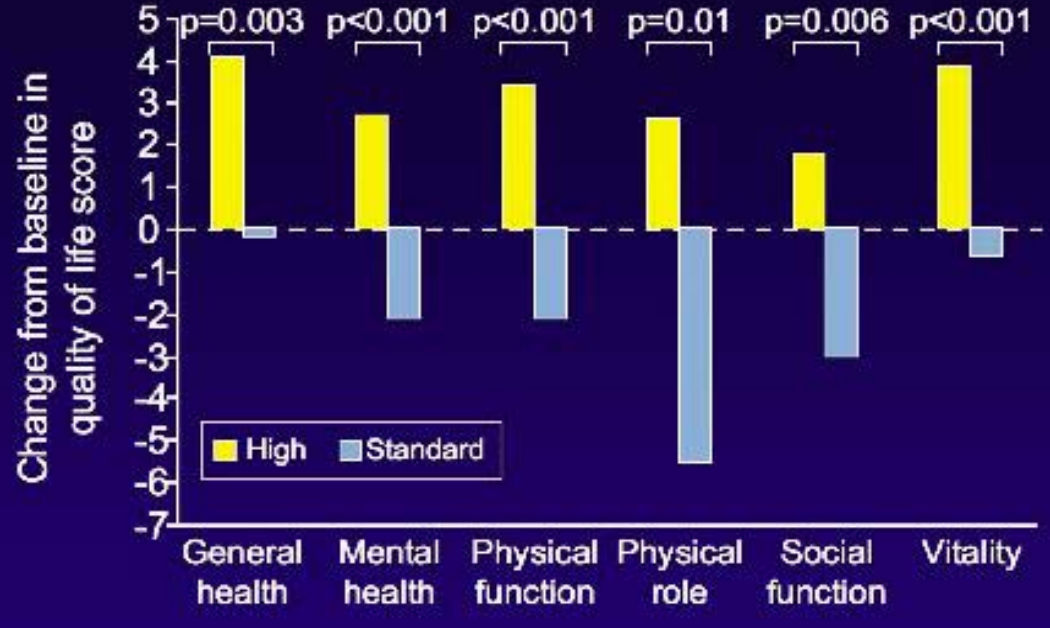
- 58 events (high Hb) vs 47 events (low Hb)

Hb, haemoglobin; CV, cardiovascular

Drüeke TB et al *N Engl J Med* 2006;355:2071–2084

CREATE : Secondary endpoints

Quality of life



Change from baseline to year 1 in SF-36 quality of life score

Drüeke TB et al *N Engl J Med* 2006;355:2071–2084

CREATE: implications and limitations

- Implications:

  "*In patients with CKD early complete correction of anaemia does not reduce the risk of cardiovascular events.*"

- Limitations:
  - Underpowered to demonstrate a difference between the groups due to lower than expected event rate (6% vs 15%)

CKD, chronic kidney disease

Drüeke TB et al *N Engl J Med* 2006;355:2071–2084

Differences between CREATE, CHOIR and the Besarab trial

	CREATE[1]		CHOIR[2]		Besarab[3]	
Target Hb (g/dL)	Strd Hb 10.5–11.5	High Hb 13–15	Strd Hb 11.3	High Hb 13.5	Strd Hb ~10	High Hb ~14
Baseline						
Hb (g/dL)	11.6	11.6	10.1	10.1	10.2	10.2
GFR (ml/min/1.73m^2)	24.2	24.9	27.3	27.0	–	–
Age	58.8	59.3	66.3	66.0	64	65
DM as cause of CKD	21%	20%	51%	47%	46%	42%
Hypertension as cause of CKD	19%	23%	28%	30%	27%	28%
Treatment						
Hb (g/dL)	11.6	13.5	~11.3	12.6	~10.5	~13.5
Epo Dosing (U/wk)	2,000	5,000	6,276	11,215	146*	153*

*U/kg/wk

Hb, haemoglobin; GFR, glomerular filtration rate; DM, diabetes mellitus; CKD, chronic kidney disease

1. Drüeke TB et al *N Engl J Med* 2006;355:2071–2084
2. Singh AK et al *N Engl J Med* 2006;355:2085–2098
3. Besarab et al *N Engl J Med* 1998;339:584–590

Conclusions on the safety and efficacy of ESAs

- Data from observational studies indicate that Hb levels >11 g/dL are associated with improved outcomes, although relationship may not be causally determined.
- Hb levels >13 g/dL should be avoided as data from RCTs showed a trend towards increased CV events, no CV benefit and uncertain improvement in QoL.

ESAs, Erythropoiesis-stimulating agents; Hb, haemoglobin;
RCTs, randomised controlled trials; CV, cardiovascular; QoL, quality of life

Anemia and CKD

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   - Negative effects of full correction - Why ?

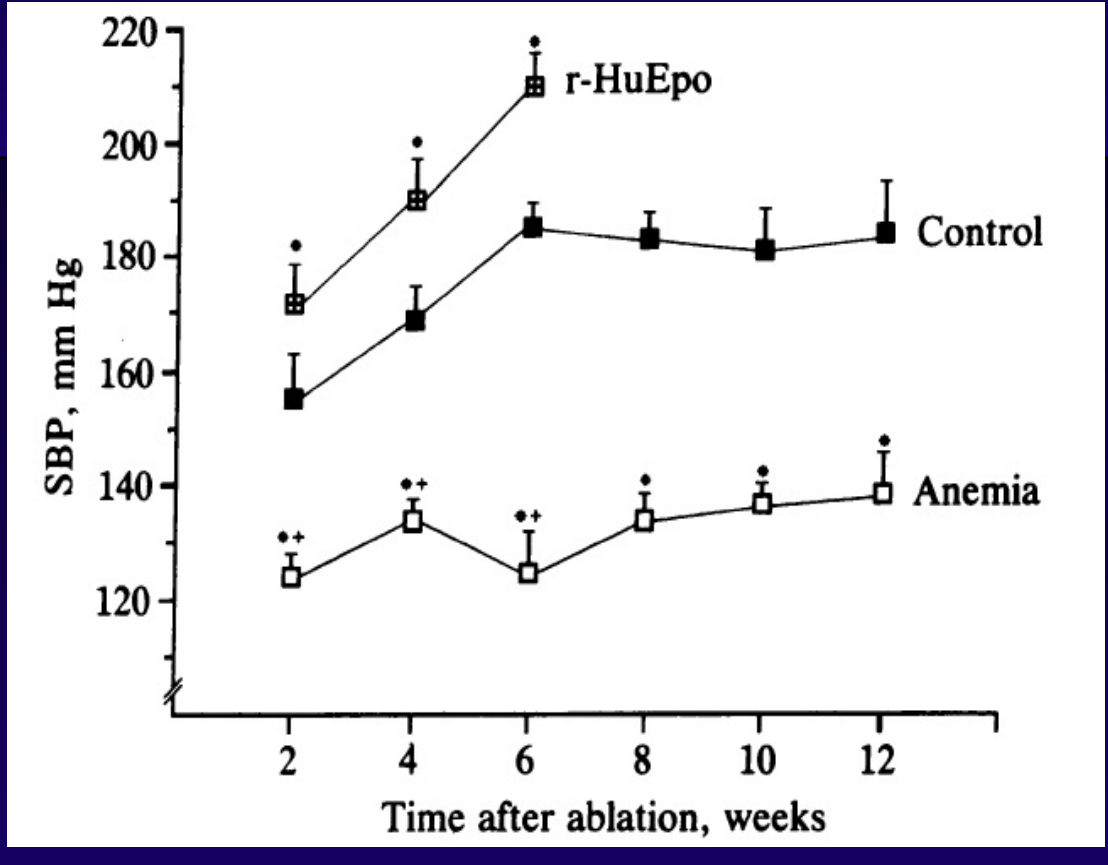
3) **Present anemia targets**

Negative effects of complete anemia correction despite better tissue oxygenation with higher Hb – Why ?

- Hypertension
- Increased blood viscosity
  - post-HD hemoconcentration
- Increased platelet number & adhesiveness, thrombosis
- Impaired endothelial NO activity
  - high Epo dose → harmful effects
- Increased iron needs → oxidative stress

Increase in BP_{syst} by Epo in rats with 5/6th Nx

Epoetin vs no Rx (control) vs iron depletion (anemia)



Garcia DL et al, PNAS 1988:85:6142-6

Decrease in GFR by Epo in rats with 5/6th Nx

Epoetin vs no Rx (control) vs iron depletion (anemia)

Table 1. Summary of renal cortical microcirculation studies

Group	*n*	BW, g	Hct, vol/dl	$\overline{AP}$, mmHg	SNGFR, nl/min
C. Control	6	279 ± 9	42 ± 1	143 ± 8	80 ± 5
A. Anemia	7	263 ± 1	27 ± 1	123 ± 2	88 ± 4
E. r-HuEpo	7	260 ± 7	50 ± 1	166 ± 9	72 ± 3
P value					
C vs. A		NS	<0.05	<0.05	NS
C vs. E		NS	<0.05	<0.05	NS
A vs. E		NS	<0.05	<0.05	<0.05

Garcia DL et al, PNAS 1988:85:6142-6

Effect of EPO treatment on arterial function in chronic hemodialysis patients

	Control	rHuEpo
Forearm Blood Flow *(ml/100 ml.min)*	**6.3 ± 1.0**	**4.6 ± 1.4****
Forearm Vasc. Resistance *(Units)*	**14.2 ± 4.2**	**21.2 ± 7.0****

London et al, Kidney Int 1989; 36: 878-82

Negative effects of complete anemia correction despite better tissue oxygenation with higher Hb – Why ?

- Hypertension
- Increased blood viscosity
  - post-HD hemoconcentration
- Increased platelet number & adhesiveness, thrombosis
- Impaired endothelial NO activity

CREATE : Increase in first CV events in group 1 after start of dialysis, *not predialysis*

	High Hgb Target Hb 13-15 g/dL	Standard Hgb Target Hb 10.5-11.5 g/dL
Total number of patients	58	47
Pre-dialysis	34	39
On dialysis	24	8

Negative effects of complete anemia correction despite better tissue oxygenation with higher Hb – Why ?

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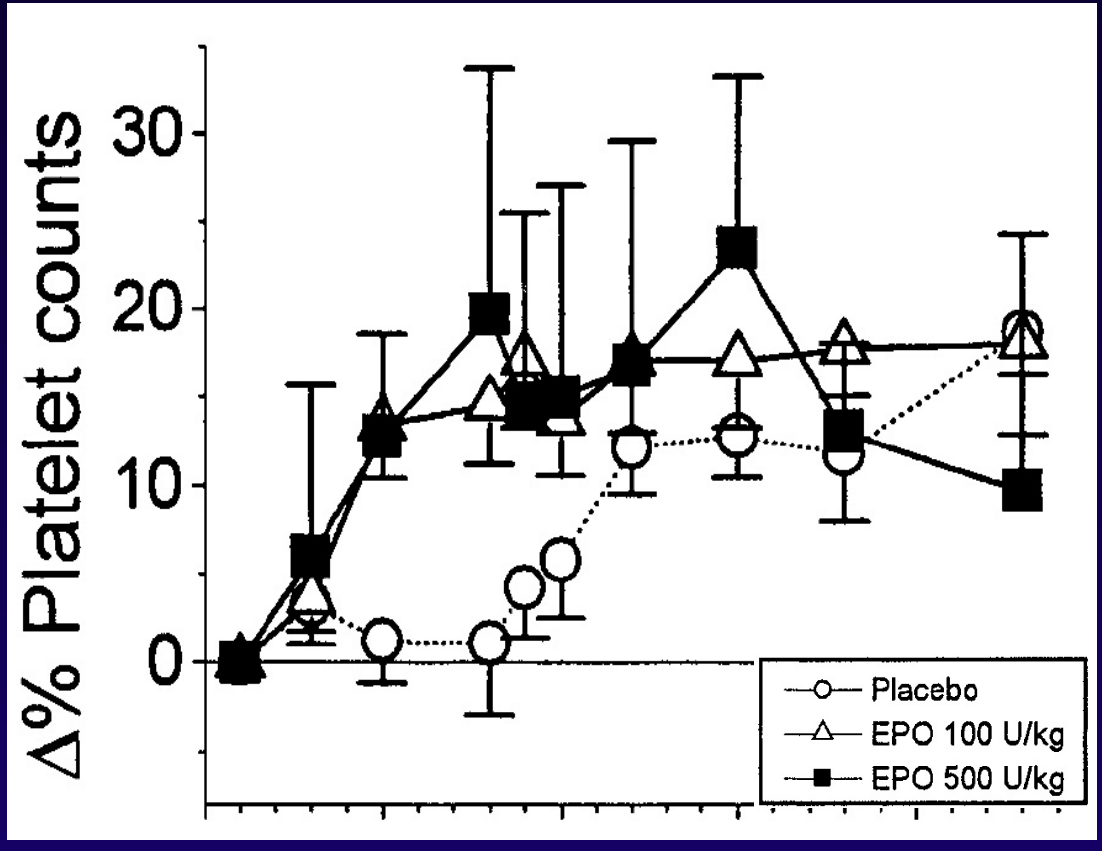
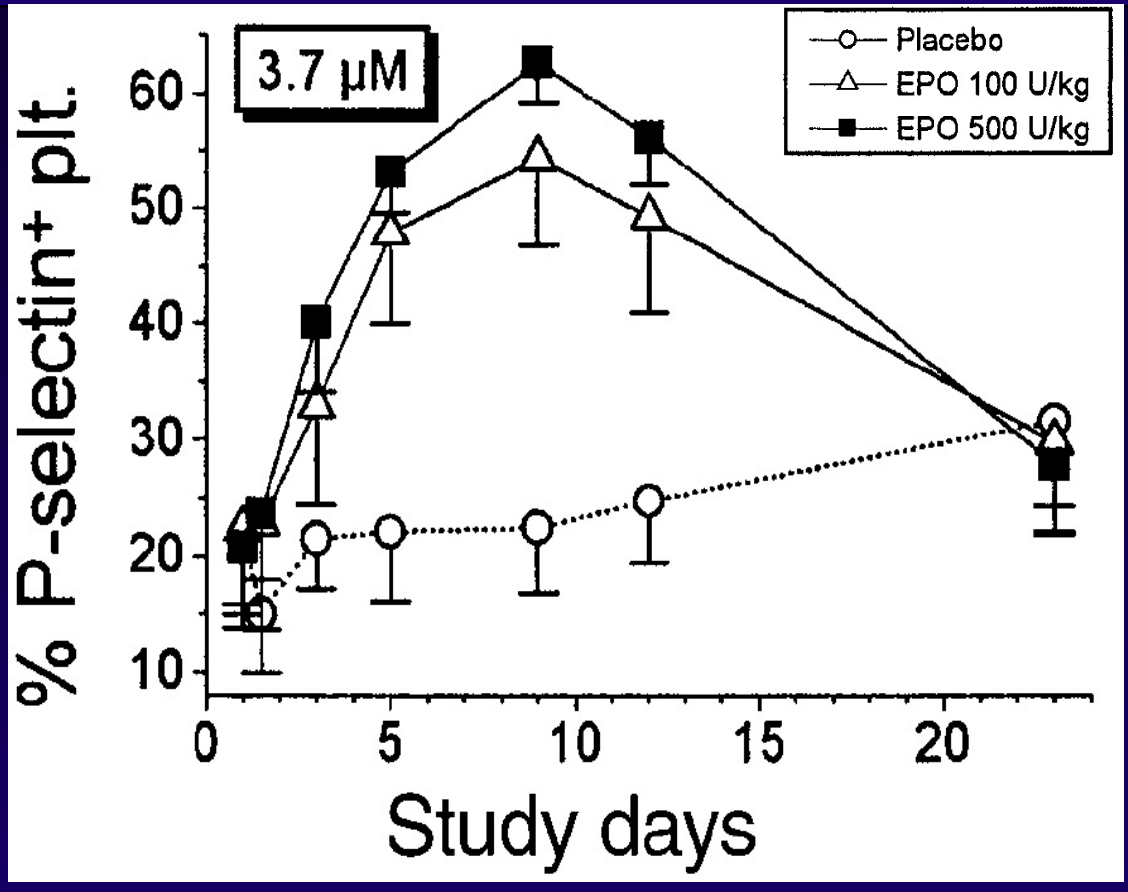
Effect of epoetin on platelet number in humans before/after phlebotomy



Stohlwetz PJ et al, Blood 2000; 95: 2983-9

Effect of epoetin on platelet reactivity in humans before/after phlebotomy



Stohlwetz PJ et al, Blood 2000; 95: 2983-9

No effect of full anemia correction on hemostasis in chronic hemodialysis patients

Haemostasis parameter (normal range)	Mean values ± SD (range) number
Platelets baseline (125–340 × 10^9/l)	215 ± 65 (98–376) $n = 24$
Platelets after 3 months	211 ± 60 (83–328) $n = 24$
Platelets after 1 year	206 ± 63 (70–338) $n = 22$
Bleeding time (Ivy) baseline (230–630 s)	591 ± 225 (375–1040) $n = 9$
Bleeding time after 3 months	593 ± 269 (378–1080) $n = 8$
Bleeding time after 1 year	558 ± 250 (270–890) $n = 6$

Christensson AG et al, NDT 2001; 16: 313-19

Negative effects of complete anemia correction despite better tissue oxygenation with higher Hb – Why ?

- Hypertension
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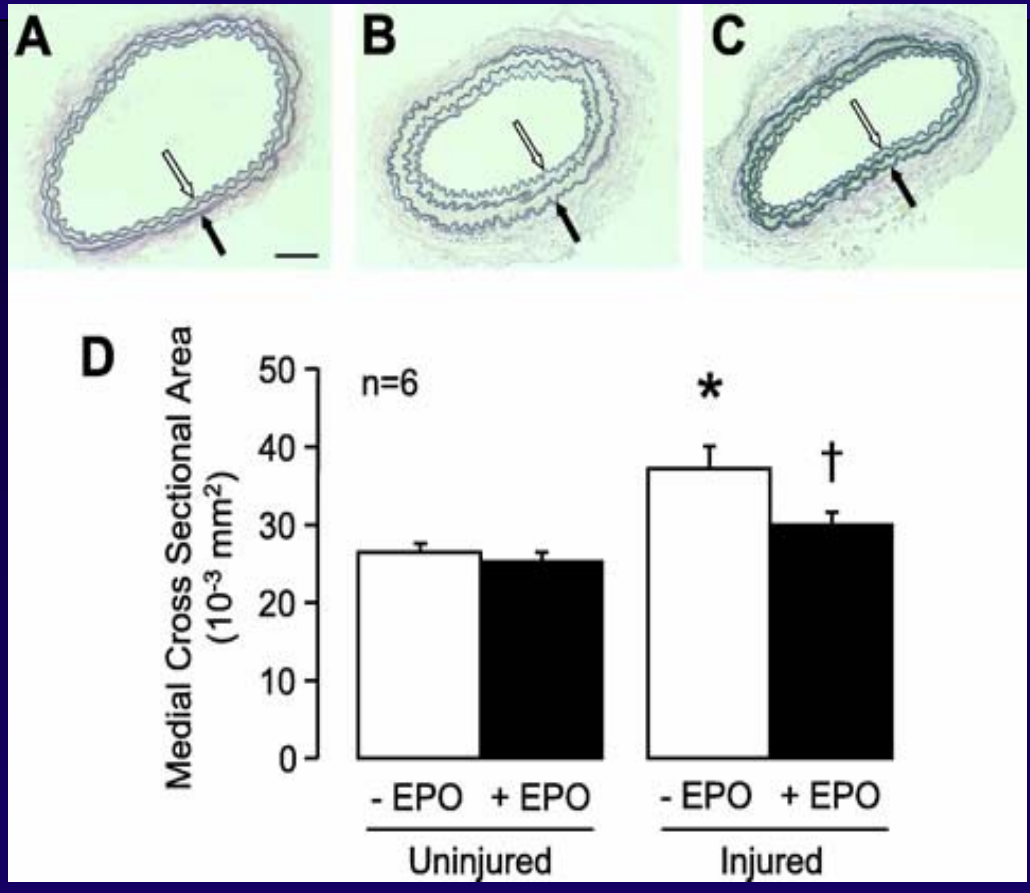
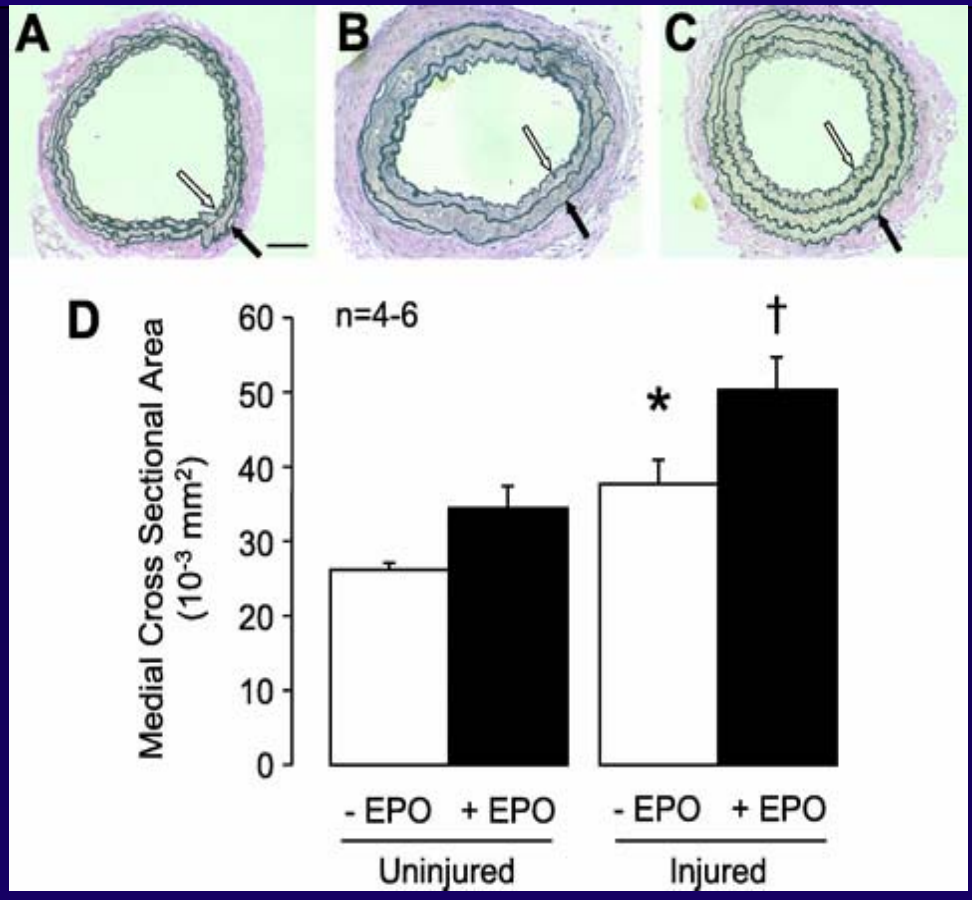
  - post-HD hemoconcentration
- Increased platelet number & adhesiveness, thrombosis
- Impaired endothelial NO activity

Effect of EPO on carotid arteries of wild-type mice
(14 days ± injury)



D'Uscio LV et al, Hypertension 2007;49:1142-8

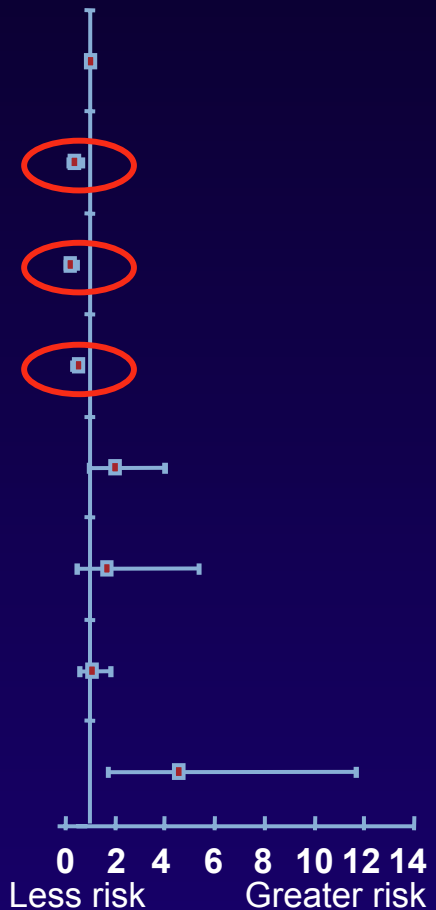
Effect of EPO on carotid arteries of eNOS-/- mice
(14 days ± injury)



D'Uscio LV et al, Hypertension 2007;49:1142-8

Time to overall C-V mortality for covariates in group 1 *(post-hoc analysis)*

Covariate	Patient #	RR	95% CI	P
Max weekly dose (per 1000 IU/week)	301	1.00	0.95–1.04	0.849
Max Hb (>15 vs. ≤15 g/dL)	295	0.32	0.14–0.72	0.006
Max Hb (>13 vs. ≤13 g/dL)	295	0.19	0.07–0.49	0.0006
Max Hb (g/dL)	295	0.47	0.34–0.64	<0.0001
Baseline Hb (≥12 vs. <12 g/dL)	301	1.97	0.97–4.03	0.0617
Baseline Hb (≥11 vs. <11 g/dL)	301	1.63	0.50–5.37	0.420
Baseline Hb (g/dL)	301	1.04	0.59–1.84	0.880
Age (≥60 vs. <60 years)	301	4.05	1.73–11.7	0.0021



Hb, haemoglobin; RR, relative risk; CI, confidence interval

Negative effects of complete anemia correction despite better tissue oxygenation with higher Hb – Why ?

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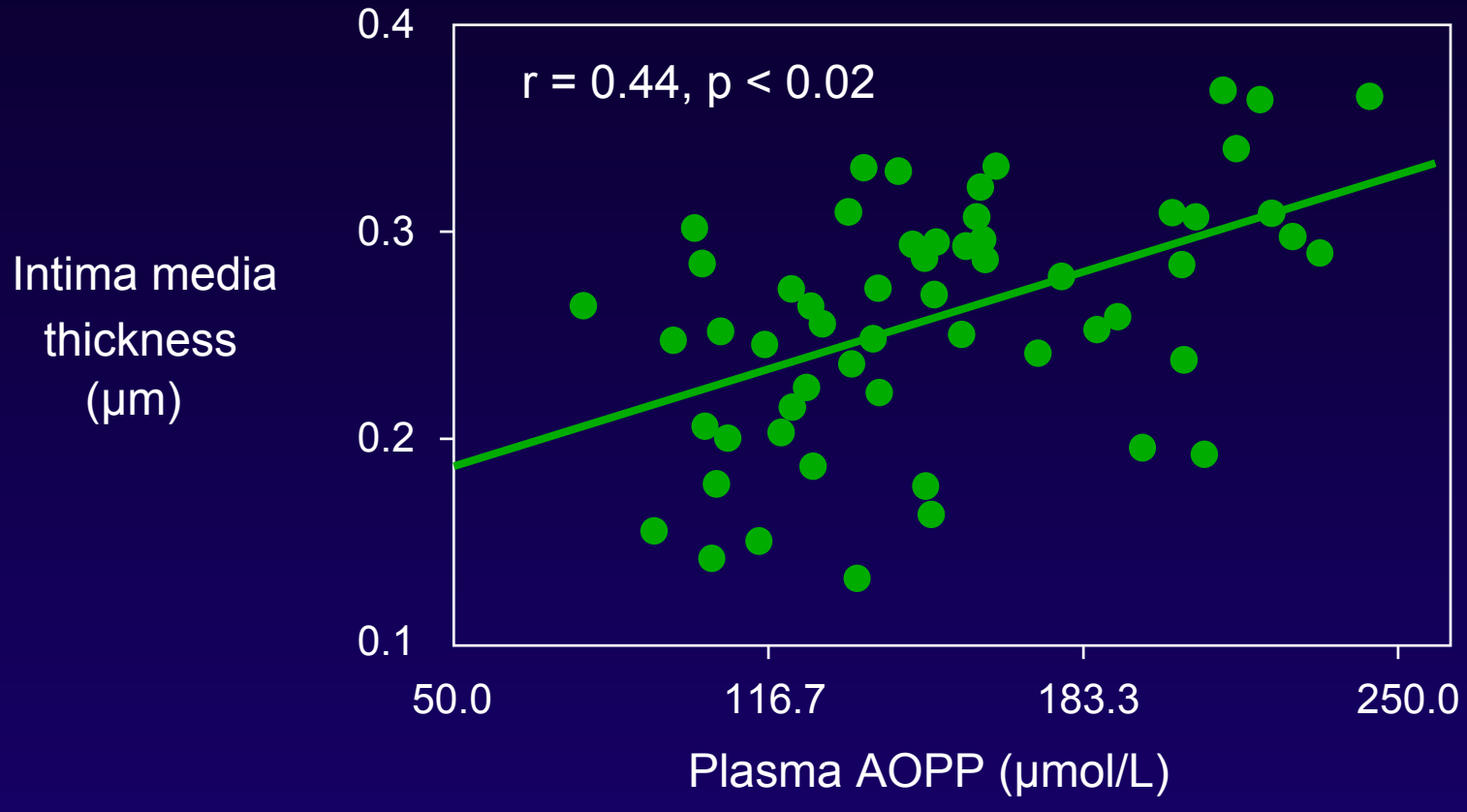
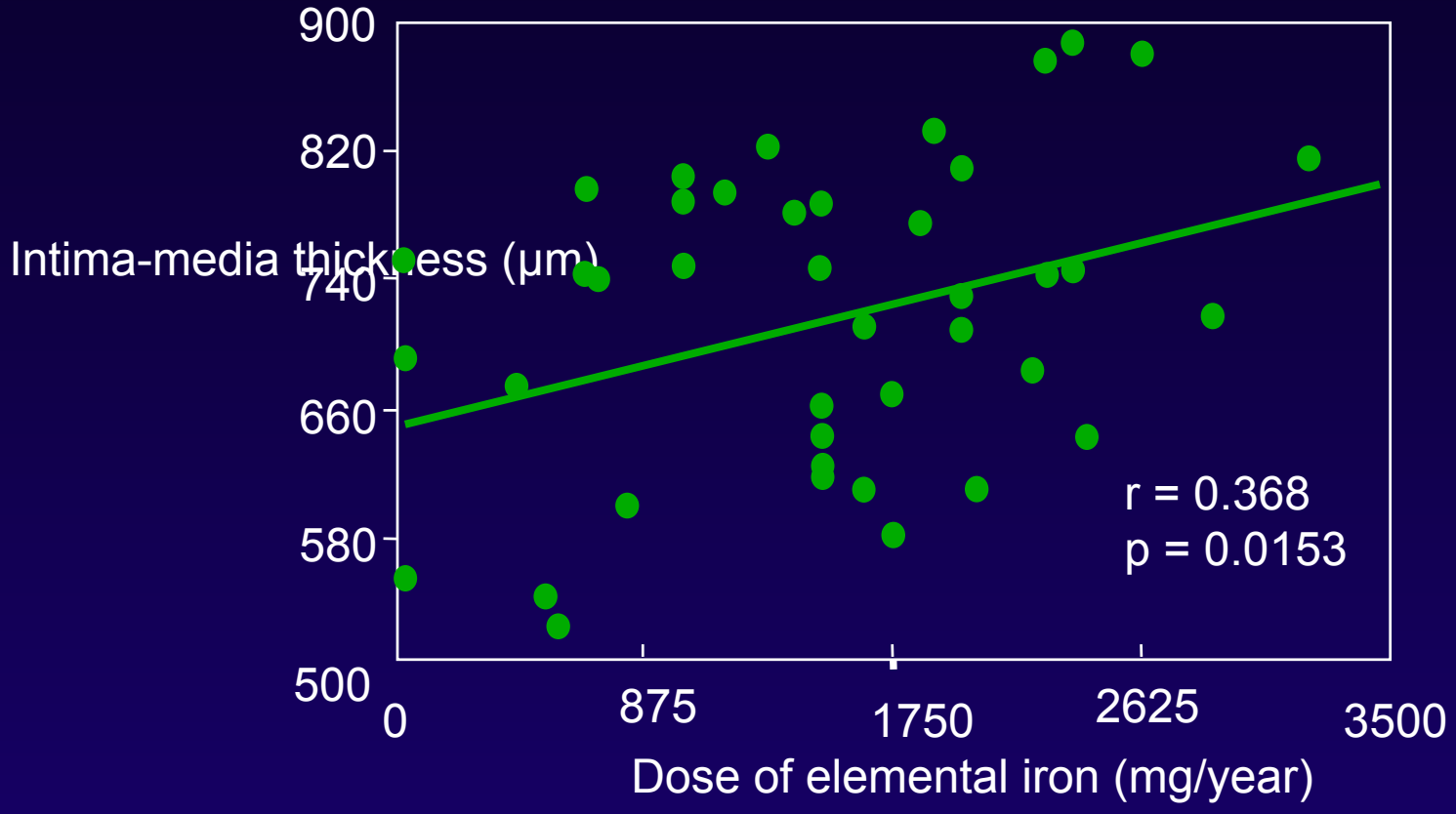
Correlation between plasma AOPP and carotid wall thickness in chronic HD patients



Drüeke T et al, Circulation 2002;106:2212-7

Correlation between yearly dose of elemental iron and carotid artery wall thickness



Drüeke T et al, Circulation 2002;106:2212-7

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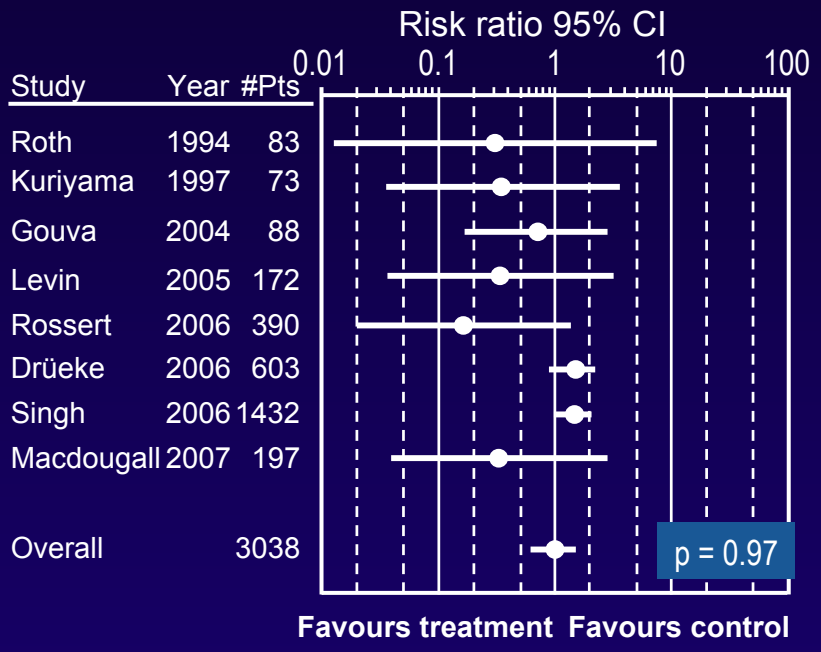
Complete correction of anemia in CKD ?

- Greater risk of cardiovascular events and mortality ?
- Improved quality of life ?

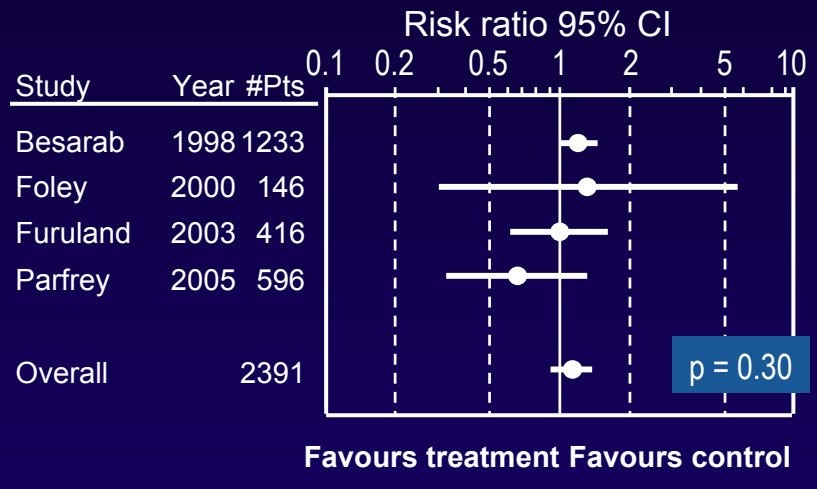
No association between higher Hb targets and relative mortality risk

Recent meta-analysis from KDOQI™

Patients not on dialysis



Patients on dialysis



CI, confidence interval

www.kidney.org KDOQI™ anemia guidelines, 2007 update

Complete correction of anemia in CKD ?

- Greater risk of cardiovascular events and mortality ?
- Improved quality of life ?

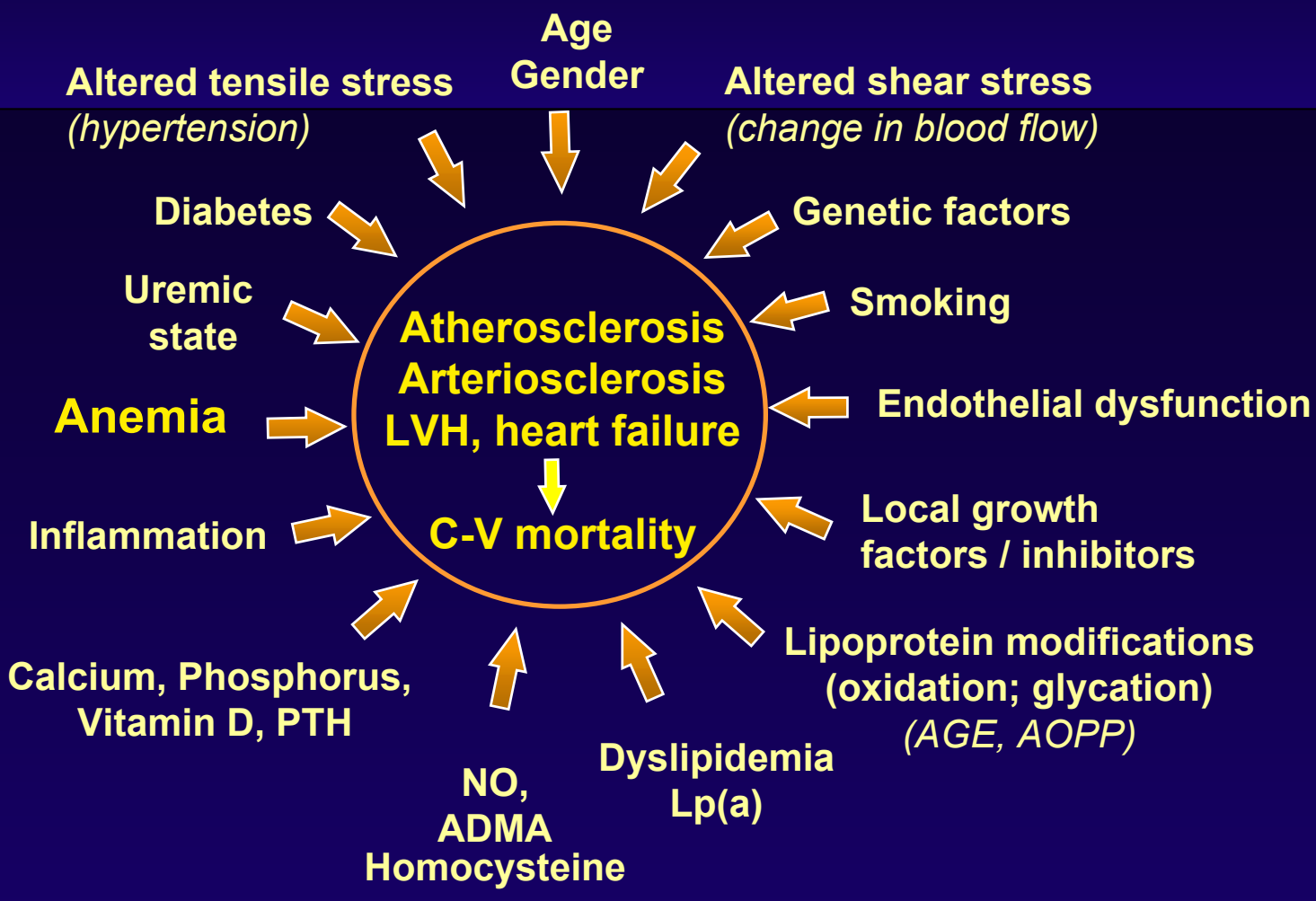
Hemoglobin target 2007 in CKD patients (KDOQI)

- ESAs have a favorable safety and efficacy profile when used to **achieve Hb target levels of 11 to 12 g/dL, not to exceed 13 g/dL**.
- Important clinical questions regarding the impact of anemia treatment on cardiovascular outcomes remain unanswered. Additional RCTs are needed.

www.kidney.org KDOQI™ anemia guidelines, 2007 update

Hemoglobin correction in CKD patients – additional common sense statements

- Correct anemia slowly.
- Don’t start with high epoetin doses.
- Adapt anemia correction to individual patient needs and comorbidities.


Age
Gender
Altered tensile stress
(hypertension)
Altered shear stress
(change in blood flow)
Diabetes
Genetic factors
Uremic
state
Smoking
Atherosclerosis
Arteriosclerosis
LVH, heart failure
Anemia
Endothelial dysfunction
C-V mortality
Inflammation
Local growth
factors / inhibitors
Calcium, Phosphorus,
Vitamin D, PTH
Lipoprotein modifications
(oxidation; glycation)
(AGE, AOPP)
NO,
ADMA
Homocysteine
Dyslipidemia
Lp(a)