Anaemia in CKD: Impact on Outcomes

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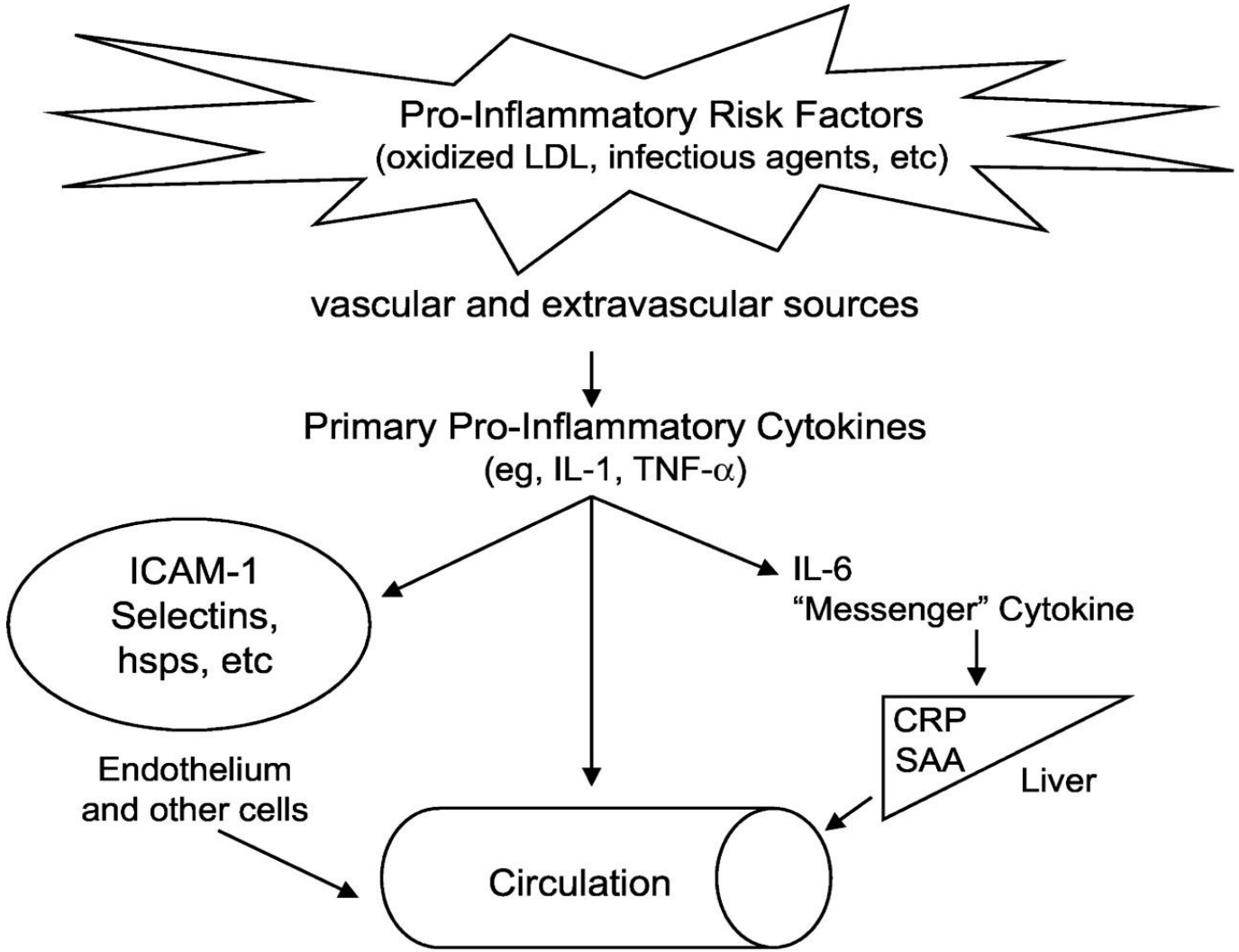
“Outcomes”

- Death
- Disability
- Transplantability
- Quality of Life

Same risk factors for CVD as for anaemia: pivotal role of chronic inflammation



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RESEARCH ARTICLE Open Access

Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anaemia

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QUALITY OF LIFE

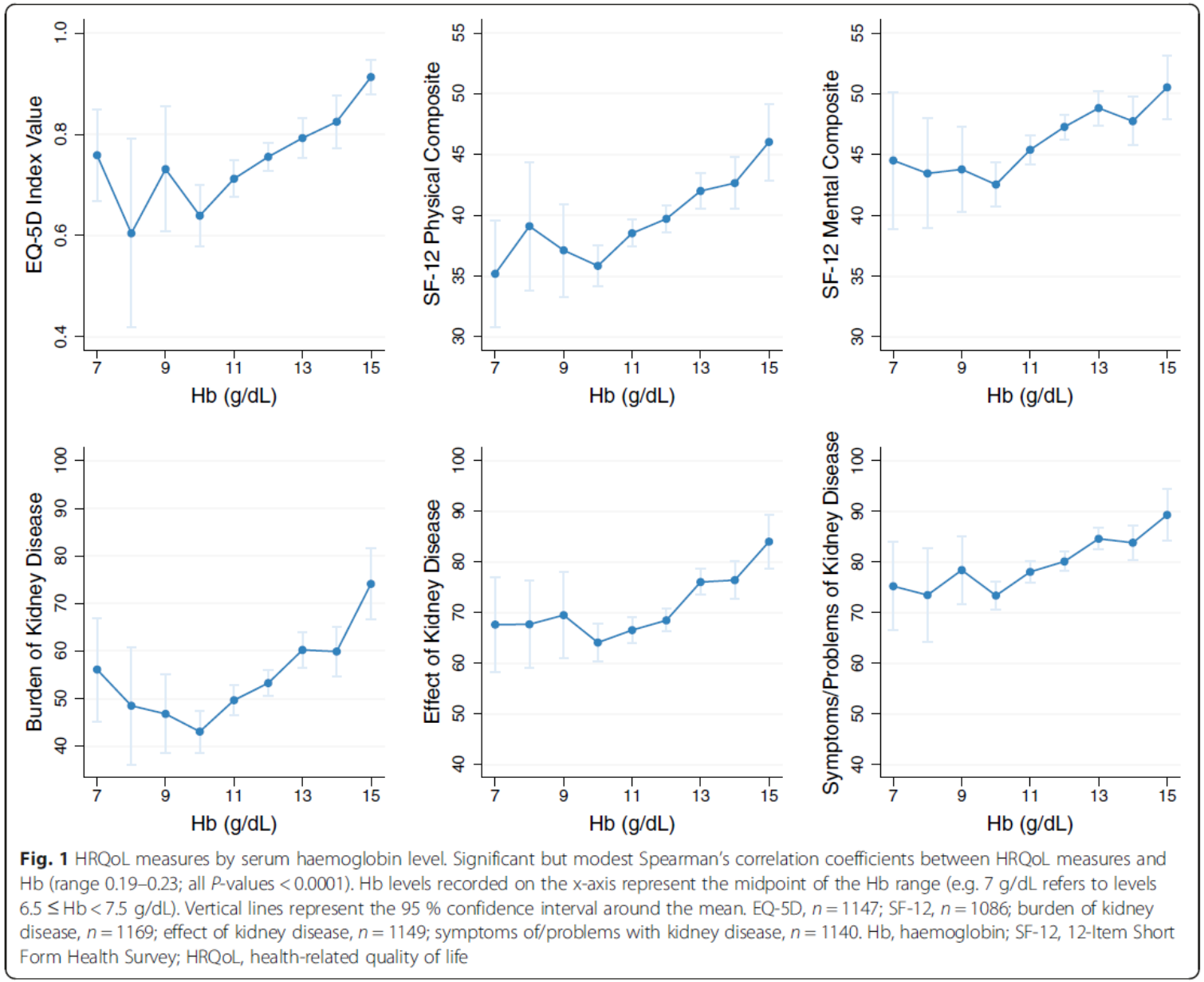


Fig. 1 HRQoL measures by serum haemoglobin level. Significant but modest Spearman's correlation coefficients between HRQoL measures and Hb (range 0.19–0.23; all *P*-values < 0.0001). Hb levels recorded on the x-axis represent the midpoint of the Hb range (e.g. 7 g/dL refers to levels 6.5 ≤ Hb < 7.5 g/dL). Vertical lines represent the 95 % confidence interval around the mean. EQ-5D, $n = 1147$; SF-12, $n = 1086$; burden of kidney disease, $n = 1169$; effect of kidney disease, $n = 1149$; symptoms of/problems with kidney disease, $n = 1140$. Hb, haemoglobin; SF-12, 12-Item Short Form Health Survey; HRQoL, health-related quality of life

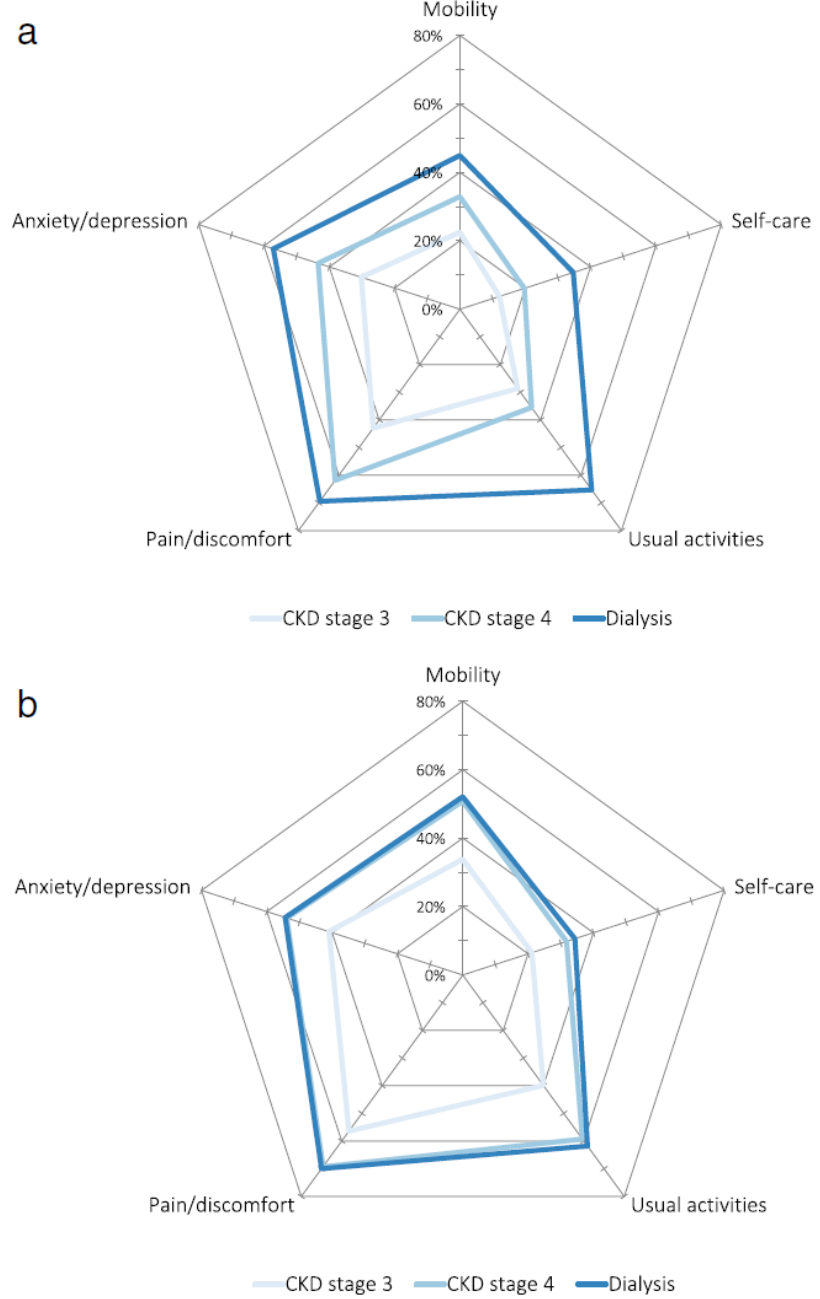
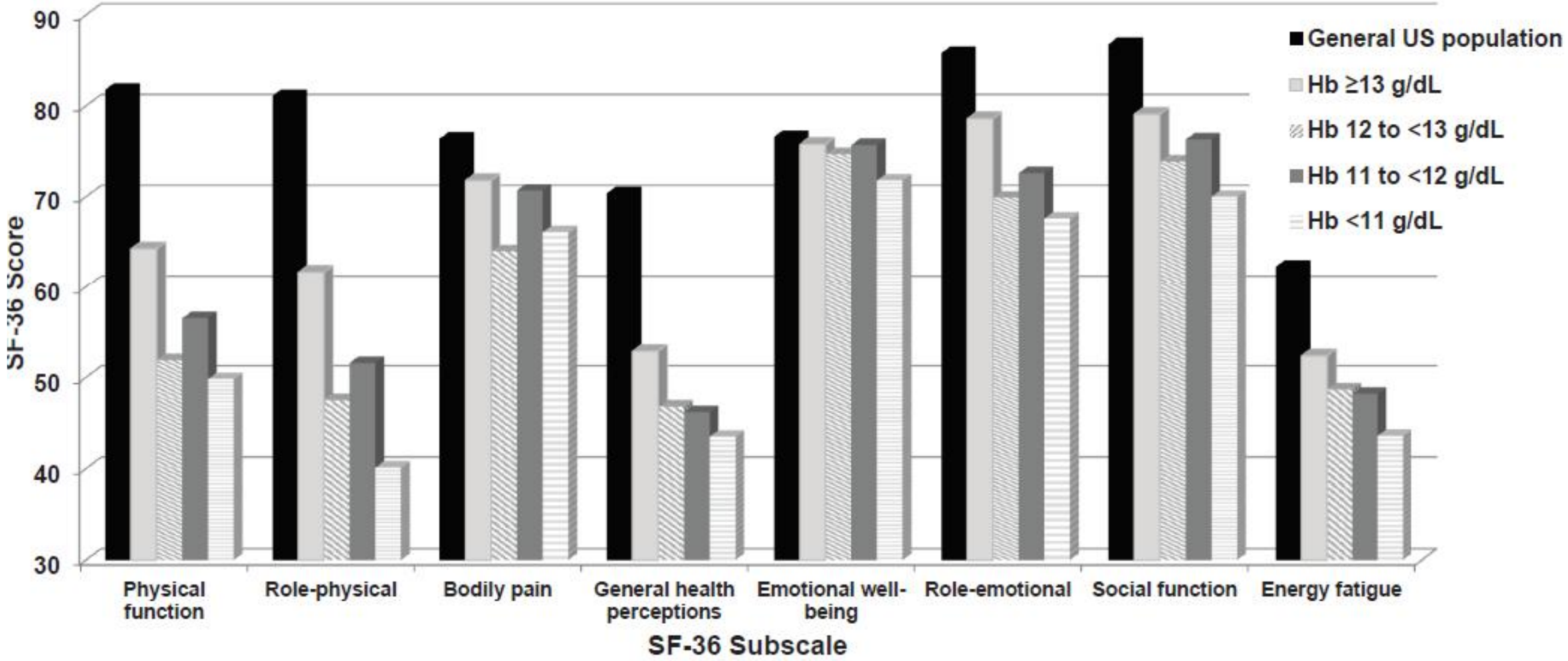


Fig. 2 Proportion of patients reporting problems for the five EQ-5D dimensions by stages of chronic kidney disease. **a** Non-anaemic patients and **b** anaemic patients. CKD, chronic kidney disease

SF-36 and CKD anaemia



QoL metrics comparing ESA Rx with none

Table 5 Health-related quality of life scores by erythropoiesis stimulating agent/supplemental iron use in patients with CKD stages 3 and 4 and those on dialysis

Subscales of the KDQOL-36	No ESA/supplemental iron use Mean (SD)	ESA and/or supplemental iron use Mean (SD)	*P*-value
Symptoms/problems list	83.5 (17.1)	77.1 (17.6)	<0.0001
Effect of Kidney Disease	76.9 (19.0)	64.5 (21.0)	<0.0001
Burden of Kidney Disease	61.5 (25.8)	46.9 (25.8)	<0.0001
SF-12 physical composite summary	42.4 (10.1)	37.6 (9.5)	<0.0001
CKD stage 3	44.6 (9.3)	40.8 (9.9)	0.0019
CKD stage 4	40.5 (10.3)	36.9 (8.9)	0.0007
Dialysis	39.0 (10.4)	37.1 (9.7)	0.1441
SF-12 mental composite summary	47.9 (9.3)	45.4 (10.1)	<0.0001
CKD stage 3	49.7 (8.6)	46.9 (10.0)	0.0206
CKD stage 4	46.9 (9.4)	44.9 (9.8)	0.0653
Dialysis	44.3 (10.0)	45.3 (10.3)	0.4347

Abbreviations: *CKD* chronic kidney disease, *ESA* erythropoiesis stimulating agent, *KDQOL-36* Kidney Disease Quality of Life Instrument, *SD* standard deviation, *SF-12* 12-Item Short Form Health Survey

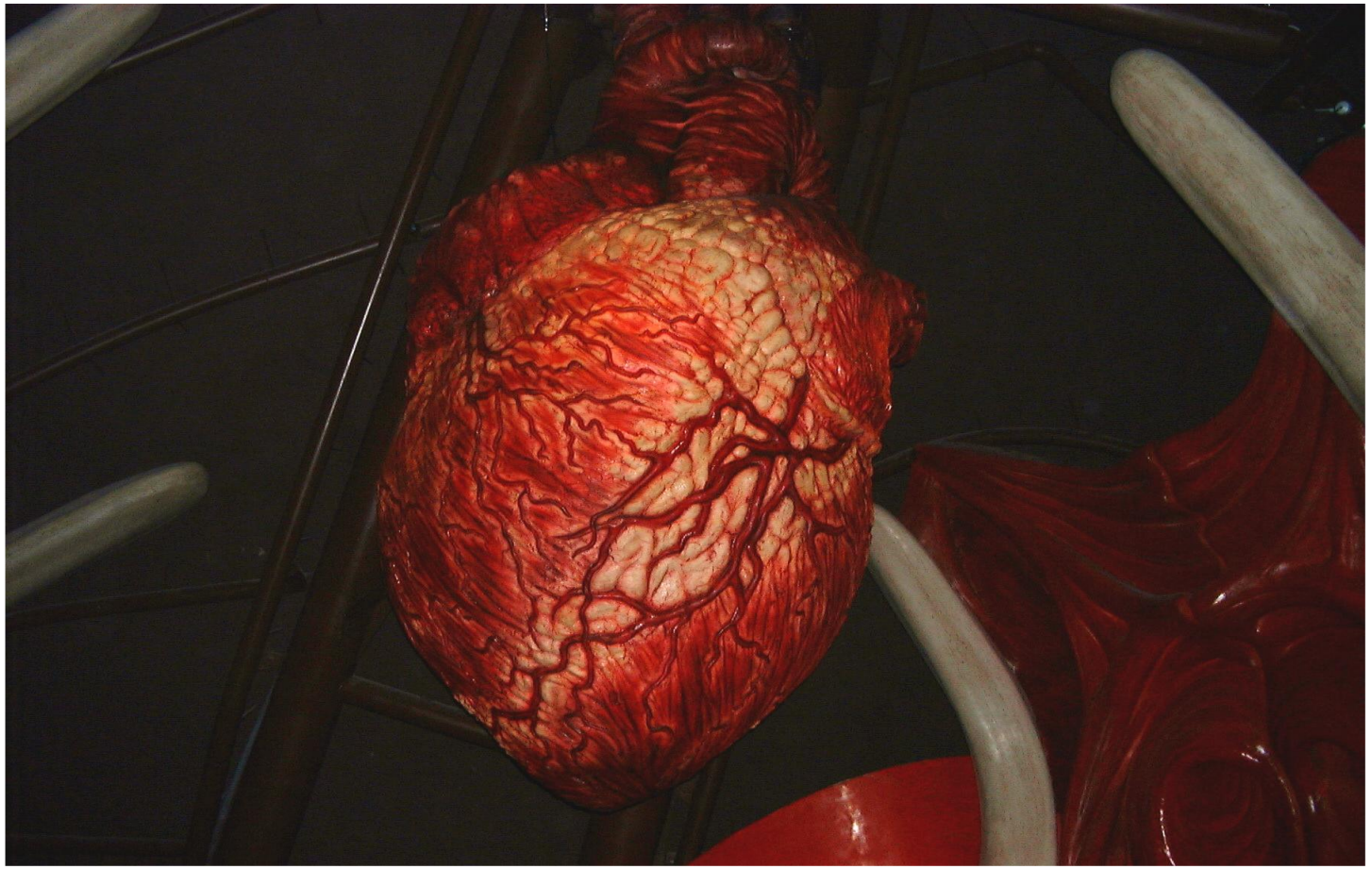
Complex outcomes of interventions for anaemia

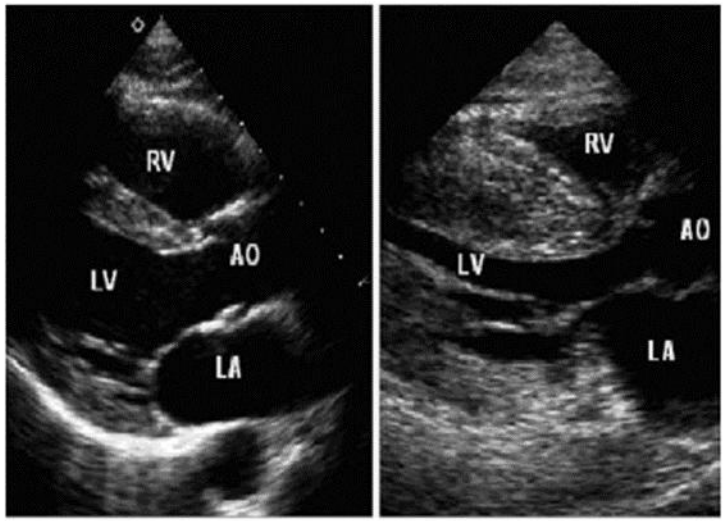
- QoL instruments are crude and insensitive
- CKD-associated loss of QoL is very significant
- ESA, Iv Iron and transfusions all can shift (INCREASE) QoL indices especially if acute, but effects may not track change in rbc mass; such improvements can be transient and rarely maintained (eg TREAT study Pfeffer et al NEJM 2009)
  - Patients often report benefit; placebo and pleasedoc effects
- Effects on mental faculties and function, and mood, less well understood
  - Depression and anxiety seen in around 20-25% of dialysis patients

Physical Outcomes

- Cardiovascular
  - LVH
  - Heart failure
  - Stroke
- Renal (GFR)

LVH





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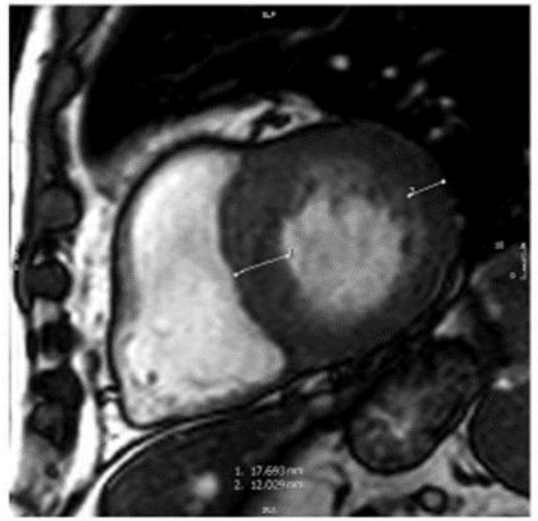

LVH - 1

- Left ventricular hypertrophy — LVH is a major risk factor for cardiovascular morbidity and mortality in ESRD patients. Among patients with ESRD or near ESRD, the reported prevalence of LVH is nearly 75 to 80 percent, with a higher prevalence among those of greatest dialysis vintage
- Anaemia has been identified as a risk factor for the development of LVH in dialysis and nondialysis CKD patients. In an observational study including 432 hemodialysis and peritoneal dialysis patients, anaemia was independently associated with an increase in left ventricular mass index [1].
- In an analysis of data from the Atherosclerosis Risk in Communities Study (ARIC), among nondialysis CKD patients, anaemia was predictive of left ventricular diameter after adjusting for kidney function and blood pressure [2].

[1] Foley RN, Parfrey PS, Harnett JD, et al. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis 1996; 28:53. 2002; 13:1928.

[20333] Astor BC, Arnett DK, Brown A, Coresh J. Association of kidney function and hemoglobin with left ventricular morphology among African Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am J Kidney Dis 2004; 43:836

LVH - 2

PATHOPHYSIOLOGY —

Potential mechanisms that may explain the relationship between anaemia and the development of LVH among CKD patients include:

- Effects of reduced oxygen delivery to the myocardium, perhaps leading to increased myocyte necrosis and apoptosis
- Anaemia-related increased cardiac output and reduced systemic vascular resistance
- Increased oxidative stress
- Activation of the sympathetic nervous system

A decrease in circulating endogenous erythropoietin caused by kidney disease may contribute to LVH among CKD patients. Erythropoietin receptors are present in cardiac tissue, and erythropoietin may have direct effects on myocardial function [3]

[3] van der Meer P, Voors AA, Lipsic E, et al. Erythropoietin in cardiovascular diseases. Eur Heart J 2004; 25:285

LVH - 3

TREATMENT OF ANAEMIA

- The treatment of severe anaemia with ESAs is associated with improvement of LVH.
- The best data are from a 2009 meta-analysis of 15 studies including 1731 patients [4]. Among patients with baseline severe anaemia (defined as haemoglobin [Hb] levels <10 g/dL with mean baseline Hb levels as low as 5.9 g/dL in individual studies), ESA treatment to increase Hb levels to ≤12 g/dL was associated with significant reductions in left ventricular mass index (-32.7 g/m2, 95% CI -49.4 to -16.1).
- *The treatment of moderate anaemia (ie, Hb ≥10 g/dL) to either Hb levels >12 g/dL or ≤12 g/dL was not associated with significant changes in the left ventricular mass index*.

[4] Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P. Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. Clin J Am Soc Nephrol 2009; 4:755

LVH - 4

- HOWEVER - The effects of administered ESAs on myocardial function may be independent of effects on anaemia. Erythropoietin may have direct effects on myocardial function.
- ESA administration reduced cellular damage and myocyte apoptosis and lowered infarct size and subsequent left ventricular dilatation and functional decline in some animal and in vitro models of ischemic reperfusion.
- Additionally, a systematic review and meta-analysis concluded that short-term administration of ESAs (ie, immediately before or within three days after percutaneous coronary intervention) did not improve cardiac function, infarct size, or mortality in patients with myocardial infarction [5].

[5] Ali-Hassan-Sayegh S, Mirhosseini SJ, Tahernejad M, et al. Administration of erythropoietin in patients with myocardial infarction: does it make sense? An updated and comprehensive meta-analysis and systematic review. Cardiovasc Revasc Med 2015; 16:179

“Heart Failure” – reduced FSI or LVEF (“systolic”)

- Severe anaemia is an important, independent risk factor for the development of HF.

- Prior to the availability of ESAs, one study of 432 dialysis patients (mean baseline Hb level of 8.8 g/dL) found that each 1 g/dL lower Hb was associated with an higher odds of left ventricular dilatation (odds ratio [OR] 1.46), de novo HF (OR 1.28), and recurrent HF (OR 1.20) [6].

Foley RN, Parfrey PS, Harnett JD, et al. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis 1996; 28:53

Heart Failure – treatment with ESA

- EFFECT OF TREATMENT OF ANAEMIA — Uncontrolled studies, none very recent, have described improvement in the clinical manifestations of HF after prolonged treatment of anaemia in CKD patients.
- As an example, in one study of 126 CKD patients with HF, an increase in the mean Hb level from 10.3 to 13.1 g/dL (with intravenous iron and ESAs) over a mean period of 12 months was associated with a rise in the mean left ventricular ejection fraction (33 to 40 percent), falls in the mean New York Heart Association (NYHA) class (3.8 to 2.7), and number of hospitalizations (3.7/patient to 0.2/patient) [7]. An index of fatigue and shortness of breath also fell significantly.
- Similar results were noted in another uncontrolled study that included 179 CKD patients with severe HF studied over a mean of nearly 12 months [8].

[7] Silverberg DS, Wexler D, Blum M, et al. Aggressive therapy of congestive heart failure and associated chronic renal failure with medications and correction of anemia stops or slows the progression of both diseases. Perit Dial Int 2001; 21 Suppl 3:S236.

[8] Silverberg DS, Wexler D, Blum M, et al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dial Transplant 2003; 18:141.

Heart Failure – treatment with ESA

- A systematic review of nine randomized trials of ESAs in HF, not all specifically in patients with CKD, concluded that anaemia treatment improved exercise duration and capacity, ejection fraction, NYHA class, quality-of-life indicators, and HF-related hospitalizations [9].
- Another, more recent meta-analysis of randomized, controlled trials found that ESA treatment improved dyspnoea and NYHA class; there was no significant improvement in mortality or hospitalization, but there was increased risk of thromboembolic events [10].
- Increased morbidity and/or mortality has been associated with attaining normal or near-normal Hb levels with ESAs.

[9] Kotecha D, Ngo K, Walters JA, et al. Erythropoietin as a treatment of anemia in heart failure: systematic review of randomized trials. Am Heart J 2011; 161:822.

[10] Kang J, Park J, Lee JM, et al. The effects of erythropoiesis stimulating therapy for anemia in chronic heart failure: A meta-analysis of randomized clinical trials. Int J Cardiol 2016; 218:12

Mortality in general:

- The combination of anaemia and LVH may be associated with an even higher risk of adverse cardiovascular outcomes [11]. Among 2423 CKD patients in four population-based studies, the presence of anaemia and LVH was correlated with the risk of the primary composite outcome of myocardial infarction, stroke, and death [11].
- LVH was associated with an increased risk for composite and cardiac outcomes (hazard ratio [HR] 1.67, 95% CI 1.34-2.07 and HR 1.62, 95% CI 1.18-2.24, respectively), while anaemia was associated with increased risk for only the composite outcome (HR 1.51, 95% CI 1.27-1.81). The combination was associated with a higher increased risk for both study outcomes compared with individuals with neither risk factor (HR 4.15, 95% CI 2.62-6.56 and HR 3.92, 95% CI 2.05-7.48).
- In a more recent study of 415 CKD patients, the combination of anaemia and LVH also increased the risk of a cardiovascular event (defined as cardiovascular death, hospitalization for unstable angina or HF, nonfatal myocardial infarction, ventricular arrhythmia, or transient ischaemic attack/stroke) (HR 4.3, 95% CI 1.4 to 13) [12].

[11] Weiner DE, Tighiouart H, Vlagopoulos PT, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. J Am Soc Nephrol 2005; 16:1803.

[12] Chang JM, Chen SC, Huang JC, et al. Anemia and left ventricular hypertrophy with renal function decline and cardiovascular events in chronic kidney disease. Am J Med Sci 2014; 347:183.

Stroke

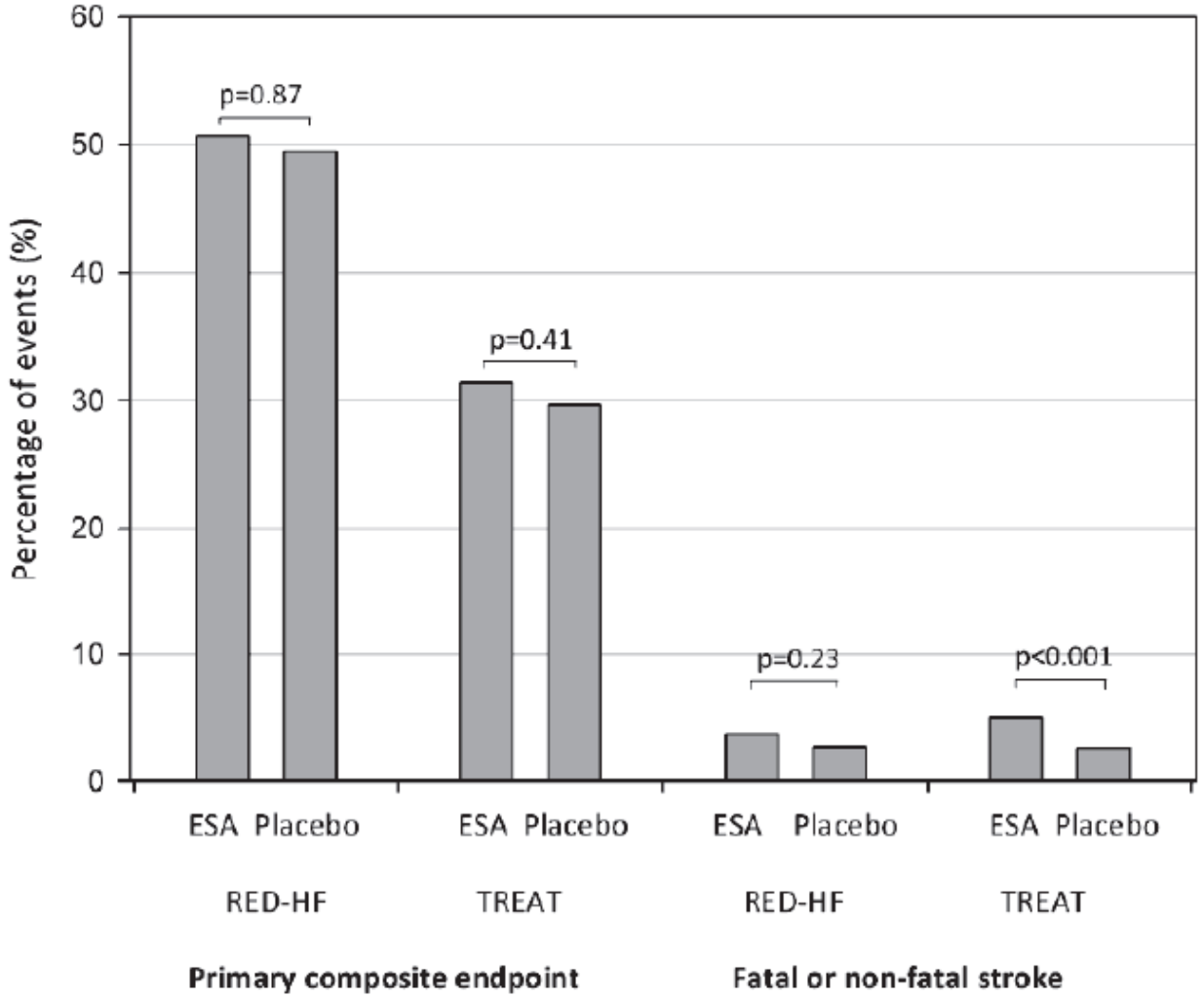

Fig 1. Percentage of primary composite endpoint and fatal and non fatal stroke in RED-HF and TREAT.

Stroke in TREAT

- UN-related to ESA dose, Hb, BP, platelets, CRP

- Biggest risk factor for CVA is prior history of CVA (“stroke prone”)

Anaemia and CKD progression - 1:

- Anaemia may be a risk factor for progression of kidney dysfunction to end-stage renal disease (ESRD).
- As an example, one four-year study of over 1500 patients with diabetic nephropathy found that, compared with patients with the highest baseline hemoglobin (Hb) levels (>13.8 g/dL), patients with lower Hb levels had a nearly twofold increase in the adjusted risk of developing ESRD [13].
- In a more recent study of 415 CKD patients, the combination of anaemia and left ventricular hypertrophy (LVH) was also associated with faster renal decline compared with patients with no anaemia and no LVH (estimated glomerular filtration rate [eGFR] slope -2.66±0.23 versus -0.59±0.23 mL/min/1.73 m^2 per year) and compared with patients with LVH but no anemia (eGFR slope -1.05±0.26 mL/min/1.73 m^2 per year) [14].
- From animal models of ischaemic and nephrotoxic renal injury, various mechanisms by which erythropoietin might have renoprotective effects have been proposed. These include reduced apoptosis, increased tubular regeneration, decreased caspase activity, and decreased interstitial fibrosis.

[13] Mohanram A, Zhang Z, Shahinfar S, et al. Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. Kidney Int 2004; 66:1131.

[14] Chang JM, Chen SC, Huang JC, et al. Anemia and left ventricular hypertrophy with renal function decline and cardiovascular events in chronic kidney disease. Am J Med Sci 2014; 347:183

Anaemia and CKD progression – 2:

- The most recent clinical trial data are from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial, in which 4038 patients with type 2 diabetes and CKD (eGFR between 20 to 60 mL/min/1.73 m2) were randomly assigned to receive darbepoetin alfa to achieve a target Hb level of 13 g/dL or to placebo, with darbepoetin administered if the Hb level was <9 g/dL [15].
- The mean achieved Hb level was 12.5 g/dL and 10.6 g/dL in the darbepoetin and placebo groups, respectively.
- At a median follow-up of 29 months, there was no difference between groups in the risk of ESRD (16.8 versus 16.3 percent in placebo, hazard ratio [HR] 1.02, 95% CI 0.87 to 1.18).
- In my opinion these are more reliable data than Gouva et al (KI 2004) or a secondary analysis of CHOIR (Singh et al (NEJM 2006))

Inrig JK, Barnhart HX, Reddan D, et al. Effect of hemoglobin target on progression of kidney disease: a secondary analysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial. Am J Kidney Dis 2012; 60:390

In-Depth Topic Review

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Erythropoiesis-Stimulating Agents (ESA) for Preventing the Progression of Chronic Kidney Disease: A Meta-Analysis of 19 Studies

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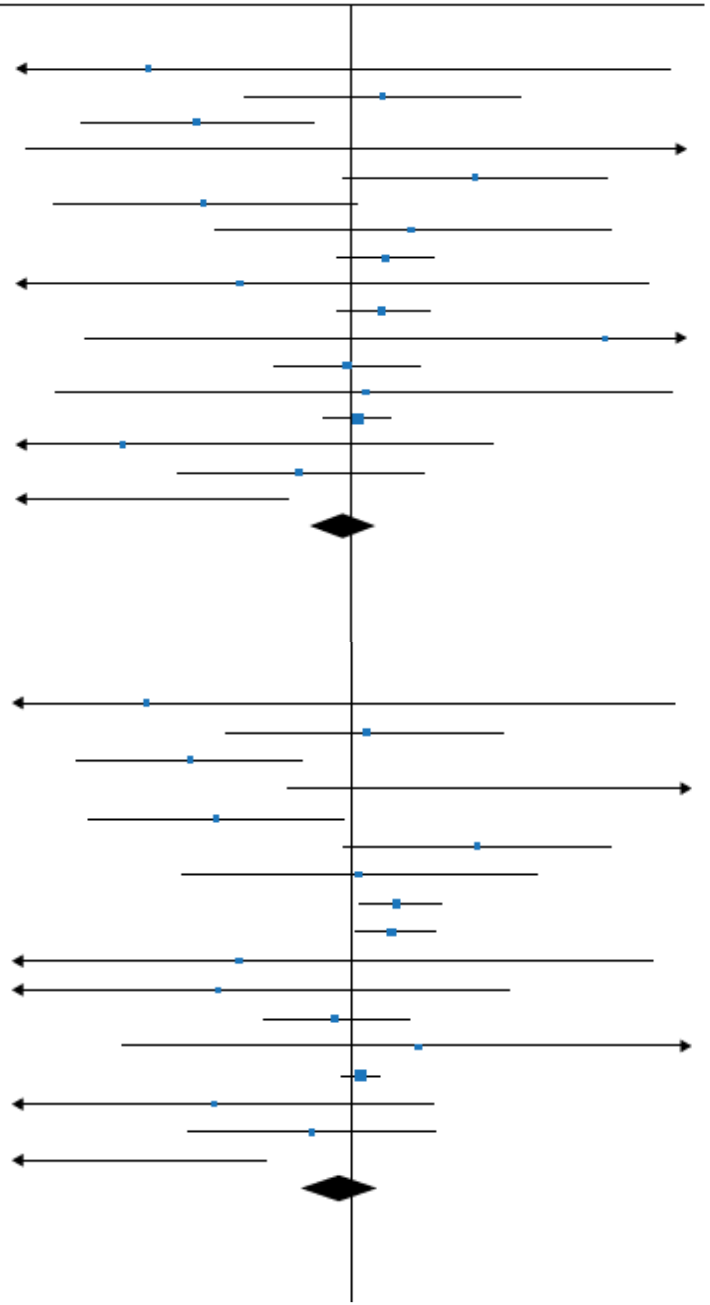
Study or Subgroup	Favours high-Hb group Events	Total	Low-hemoglobin group Events	Total	Weight	Risk ratio M–H, Random, 95% CI	Year
1.2.1 Number of patients starting RRT during study period							
Clyne 1992	1	12	2	10	0.5%	0.42 [0.04, 3.95]	1992
Revicki 1995	16	43	13	40	5.5%	1.14 [0.63, 2.07]	1994
Kuriyama 1997	14	42	20	31	7.0%	0.52 [0.31, 0.85]	1997
Furuland 2003	2	36	0	36	0.3%	5.00 [0.25, 100.63]	2003
Roger 2004	24	75	15	80	5.9%	1.71 [0.97, 3.00]	2004
Gouva 2004	10	45	18	43	4.8%	0.53 [0.28, 1.02]	2004
Levin 2005	11	78	8	74	3.1%	1.30 [0.56, 3.06]	2005
CHOIR 2006	155	715	134	717	15.6%	1.16 [0.94, 1.43]	2006
ACORD 2007	2	88	3	82	0.8%	0.62 [0.11, 3.62]	2006
CREATE 2006	127	301	111	302	15.9%	1.15 [0.94, 1.40]	2006
ECAP 2006	3	195	1	195	0.5%	3.00 [0.31, 28.59]	2007
Macdougall 2007	30	64	63	132	11.6%	0.98 [0.72, 1.35]	2007
Cianciaruso 2008	4	46	4	49	1.4%	1.07 [0.28, 4.01]	2008
TREAT 2009	338	2,012	330	2,026	18.1%	1.03 [0.90, 1.18]	2009
NEPHRODIAB2 2011	2	46	5	43	1.0%	0.37 [0.08, 1.83]	2011
Akizawa 2011	21	161	26	160	6.4%	0.80 [0.47, 1.37]	2011
CAPRIT 2012	3	63	13	62	1.7%	0.23 [0.07, 0.76]	2012
Subtotal (95% CI)		4,022		4,082	100.0%	0.97 [0.83, 1.15]	
Total events	763		766				
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 28.59$; df = 16 (p = 0.03); $I^2 = 44\%$							
Test for overall effect: Z = 0.32 (p = 0.75)							
1.2.3 Starting RRT and all cause mortality: composite outcome							
Clyne 1992	1	12	2	10	0.5%	0.42 [0.04, 3.95]	1992
Revicki 1995	16	43	14	40	5.4%	1.06 [0.60, 1.89]	1994
Kuriyama 1997	15	42	22	31	7.1%	0.50 [0.32, 0.80]	1997
Furuland 2003	6	36	1	36	0.6%	6.00 [0.76, 47.36]	2003
Gouva 2004	13	45	22	43	5.8%	0.56 [0.33, 0.97]	2004
Roger 2004	24	75	15	80	5.5%	1.71 [0.97, 3.00]	2004
Levin 2005	12	78	11	74	3.6%	1.30 [0.49, 2.20]	2005
CHOIR 2006	207	715	170	717	14.6%	1.22 [1.03, 1.45]	2006
CREATE 2006	158	301	132	302	14.8%	1.20 [1.02, 1.42]	2006
ACORD 2007	2	88	3	82	0.8%	0.62 [0.11, 3.62]	2006
ECAP 2006	4	195	7	195	1.6%	0.57 [0.17, 1.92]	2007
Macdougall 2007	31	64	68	132	10.8%	0.94 [0.70, 1.27]	2007
Cianciaruso 2008	5	46	4	49	1.5%	1.33 [0.38, 4.66]	2008
TREAT 2009	750	2,012	725	2,026	16.9%	1.04 [0.96, 1.13]	2009
NEPHRODIAB2 2011	6	46	10	43	2.3%	0.56 [0.22, 1.41]	2011
Akizawa 2011	22	161	26	160	6.1%	0.84 [0.50, 1.42]	2011
CAPRIT 2012	4	63	16	62	2.1%	0.25 [0.09, 0.69]	2012
Subtotal (95% CI)		4,022		4,082	100.0%	0.95 [0.81, 1.12]	
Total events	1,276		1,248				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 38.23$; df = 16 (p = 0.001); $I^2 = 58\%$							
Test for overall effect: Z = 0.59 (p = 0.56)							



SUMMARY AND CONCLUSIONS

(1) Among dialysis patients, severe anaemia is a risk factor for the development and progression of left ventricular hypertrophy (LVH), heart failure (HF), and mortality.

(2) The treatment of severe anaemia with erythropoiesis-stimulating agents (ESAs) is associated with improvement of LVH and clinical manifestations of HF. *However, increased morbidity and/or mortality have been associated with attaining normal or near-normal haemoglobin (Hb) levels with ESAs*.

(3) Among non-dialysis chronic kidney disease (CKD) patients while anaemia may be a risk factor for progression of kidney dysfunction to end-stage renal disease (ESRD) *the treatment of moderate anaemia with ESAs has not been shown to decrease progression to ESRD*.

(4) Most of what we think we know is extrapolation from the era of Hb 5-8 g/dL, which is not relevant to the era of Hb 10-13 g/dL.

(J Am Heart Assoc. 2016;5:e002850 doi: 10.1161/JAHA.115.002850)

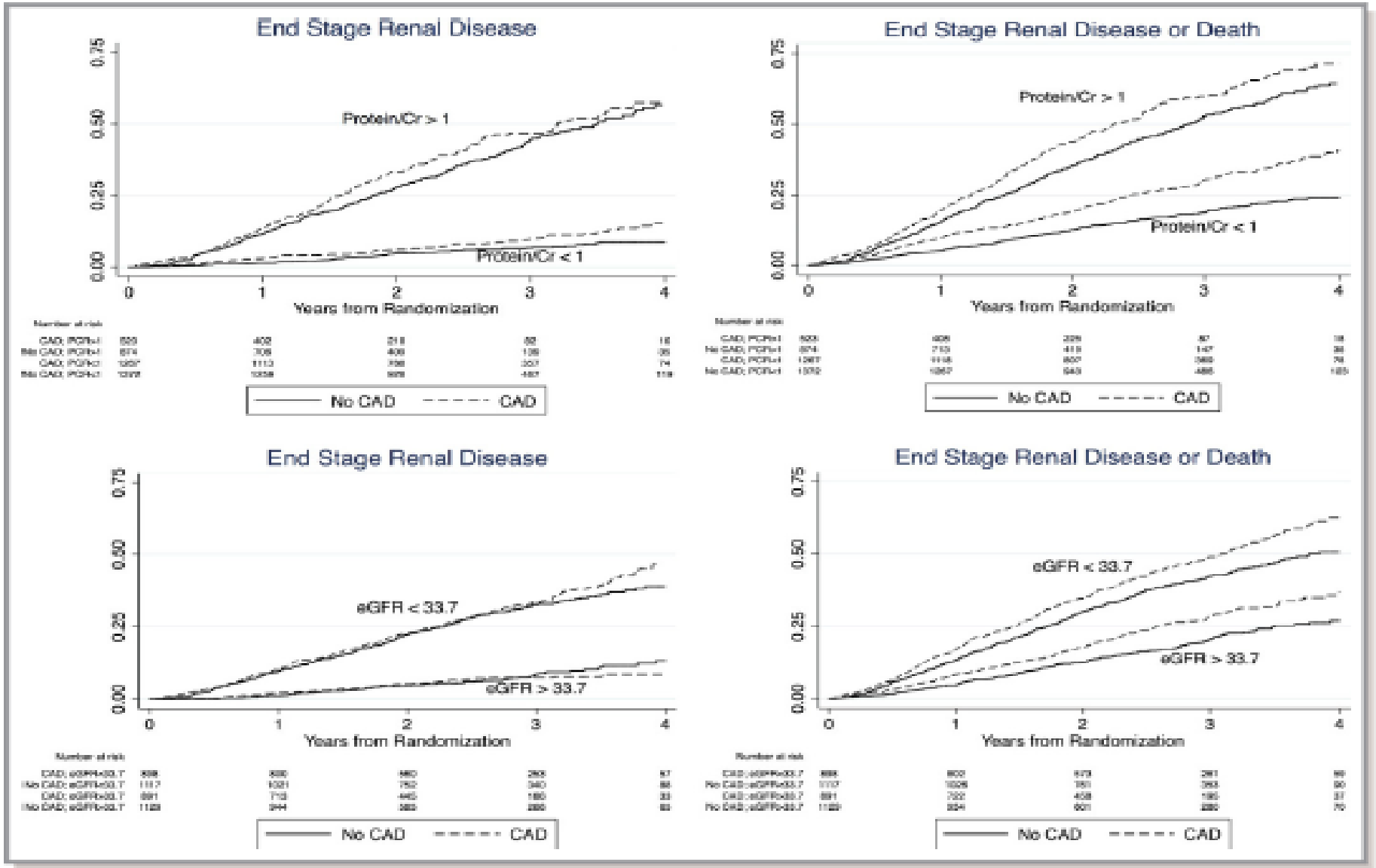


Figure. The association between CAD, proteinuria, eGFR and renal outcomes. A history of known CAD contributes to proteinuria and eGFR as a risk factor for progression to ESRD and ESRD or death. Proteinuria is represented as a categorical variable divided at a PCR of 1. eGFR is represented as a categorical variable divided at the median, 33.8 mL/min per 1.73 m^2. An interaction term for CAD and proteinuria was added to the final renal multivariable model and found to be nonsignificant for the outcomes of ESRD (P=0.23) and ESRD or death (P=0.10). Similarly, the interaction terms for eGFR and CAD were found to be nonsignificant in the final multivariable model for both outcomes (ESRD, P=0.44; ESRD or death, P=0.59). CAD indicates coronary artery disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PCR, protein/creatinine ratio.