Research Review
EDUCATIONAL SERIES

Treating Renal Anaemia of Chronic Kidney Disease (CKD)

Introduction

The following publication is intended as an educational resource for health professionals. It presents a short background on renal anaemia in New Zealand and a review of selected peer reviewed studies featuring medicines used to treat the condition. It is intended to help readers stay informed of developments and advancing clinical practice in the areas covered.

The Burden of Renal Anaemia

Scientific literature increasingly attests to the significant morbidity, mortality and economic burden of anaemia associated with chronic kidney disease (CKD)[1,2]. With a growing number of patients worldwide expected to be affected in the future, approaches are required to improve anaemia management without increasing the burden on healthcare professionals[1].

It has been estimated that CKD and its effects account for about one-third of New Zealand's health costs and numbers of sufferers are predicted to rise dramatically; epidemiological research has estimated that up to one in seven New Zealanders may have renal disease[3]. The current epidemic of type 2 diabetes mellitus in New Zealand will have major implications for this country's limited health resources[4]. In 2005, diabetic kidney disease accounted for 41% of the 436 new cases of end-stage renal disease[4]. Further, patients with CKD have a 3- to 5-fold higher risk of cardiovascular events; the death rate is 20-fold higher in those with diabetes and CKD compared to the healthy population[4]. Typically, CKD and renal anaemia are common in the later course of disease. Due to the public health burden caused by renal anaemia it is important to raise awareness of this condition and encourage early diagnosis and treatment[5-9].

Identifying Patients with Renal Anaemia

Factors that increase an individual's risk of developing kidney disease include:

- A family history of kidney disease
- Age >50 years
- Maori and/or Polynesian descent
- Diabetes
- Smoking
- High blood pressure[10].

The anaemia of CKD becomes increasingly prevalent at a glomerular filtration rate (GFR) of 30mL/min/1.73m^2 or lower. In the vast majority of cases, recombinant human erythropoietin (rhEPO) is initiated after the patients have been seen in the nephrology clinic or in hospital. General practitioners (GPs) may refer patients with suspected renal anaemia for further evaluation and initiation of rhEPO treatment. Any physician with vocational registration is now eligible to apply for rhEPO. GPs will be increasingly involved in starting and monitoring of rhEPO treatment of those with CKD as some patients are infrequently followed-up by clinics. Dialysis patients receiving rhEPO treatment and who are being monitored are almost exclusively managed by the renal unit.

About Research Review

Research Review is an independent medical publishing organisation producing journals including Respiratory Research Review, Diabetes & Obesity Review and Natural Health Review. These journals provide summaries of studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter in New Zealand.

About the Reviewer

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Defining Renal Anaemia

The diagnosis of renal anaemia is made after haemoglobin (Hb) falls below certain threshold levels.

These have been defined by the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF-KDOQI)[11], the World Health Organization (WHO)[12], and the European Best Practice Guidelines (EBPG) for the Management of Renal Anaemia in Patients with Chronic Renal Failure[13].

Organisation	Threshold haemoglobin concentrations for the diagnosis of anaemia (g/L)	
	Adult males	Adult females
NKF-KDOQI[11]	135	120
WHO[12]	130	120 (110*)
EBPG[13]	135 (120†)	115

* Pregnant women; † Men >70 years old.

Defining Renal Anaemia continued

Anaemia is a major complication of CKD, even affecting patients with early-stage disease. Haemoglobin levels progressively decrease with increasing degree of renal impairment[14]. Renal anaemia occurs even earlier in patients with diabetes[15]. The diagnosis of renal anaemia depends on whether there is impairment of renal function and no cause for anaemia other than CKD is detected during assessment[16]. CKD is defined as kidney damage with structural and/or functional abnormalities or a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, or both, for ≥3 months. CKD is staged as follows[11]:

Stage	Description	eGFR (mL/min/1.73 m^2)
1	Kidney damage* with normal or increased eGFR	>90
2	Kidney damage with mild decrease in eGFR	60–89
3	Moderate decrease in eGFR	30–59
4	Severe decrease in eGFR	15–29
5	Kidney failure	<15 or dialysis

* Defined by the National Kidney Foundation as 'pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies'. eGFR = estimated Glomerular Filtration Rate.

Key Points about CKD:

- CKD can develop from several conditions, including glomerulonephritis, diabetes mellitus, and hypertension[17-21], as a consequence of damage to the nephrons, reducing their capacity for filtration.
- These three conditions are the most common causes of end-stage renal disease, with diabetes mellitus accounting for 35.4% of cases, hypertension for 30.3% and chronic glomerulonephritis for 14.2% of cases[22].
- Other risk factors for CKD include: polycystic kidney disease, chronic kidney or urinary infections, immune disorders and obstructions (e.g. stones, tumours)[23].
- In early-stage disease, renal anaemia is experienced by up to 25% of CKD patients, increasing to 75–95% in late-stage dialysis patients[24,25].
- CKD leads to renal anaemia primarily by reducing erythropoietin production, leading to abnormally low haemoglobin concentrations[11].
- Other mechanisms by which CKD may lead to anaemia include[26]:
  1. blood loss through dialysis
  2. shortened red cell lifespan (approximately 80 days in dialysis patients compared with 120 days in healthy individuals)
  3. inefficient iron transportation
  4. vitamin B_{12} and folate deficiencies
  5. inflammation

Interpreting GFR Results

Large-scale population data from a US-based survey demonstrate a strong association between the prevalence of anaemia and a decline in GFR in patients with CKD[24]. As shown in Figure 1, the percentage of patients with Hb ≤120 g/L increased from 26.7% to 75.5% when the GFR decreased from ≥60 mL/min/1.73 m^2 to <15 mL/min/1.73 m^2. The prevalence of Hb ≤100 g/L increased substantially from 5.2% to 27.2% when the GFR diminished from ≥60 mL/min/1.73 m^2 to <15 mL/min/1.73 m^2.

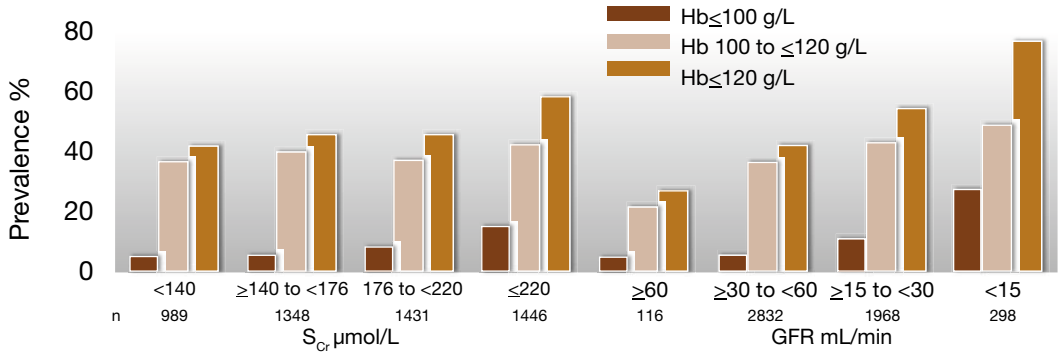

Fig 1. Relationship between level of renal function, reflected by serum creatinine (SCr) level or GFR, and prevalence of anaemia, defined at different Hb cutoff levels, among patients under the care of physicians[24].

Information on Testing

A recent investigation by the Australasian Creatinine Consensus Working Group reports that over 69% of New Zealand's clinical laboratories report eGFR results, with most requests for plasma creatinine in adults, in support of recently published guideline recommendations; variations reflect local preferences[27]. eGFR is a more sensitive measurement of renal function and it is used in guidelines and drug dosing. Patients should have clinical and laboratory evaluations to define the cause of anaemia before considering treatment with rhEPO. A laboratory evaluation should include:

- Haemoglobin concentration, mean cell volume (MCV) and mean cell haemoglobin (MCH) to assess the type of anaemia. The anaemia of CKD is usually normocytic and normochromic.
- Serum vitamin B_{12} and red blood cell folate levels to assess stores. Deficiency should be corrected before the commencement of rhEPO. These levels should be monitored annually while on rhEPO treatment.
- Serum ferritin and transferrin saturation to assess iron stores and functional iron available for erythropoeisis. To achieve and maintain the target Hb, the serum ferritin should be >100 µg/L (target of 200–600 µg/L) and the transferrin saturation >20% (target of 30–40%). Any deficiency should also be corrected and levels should be monitored every 2 months while on rhEPO.

Treating Patients with Renal Anaemia

Optimal management of anaemia would improve CKD symptoms in many patients[13]. It is recommended that all patients with chronic anaemia associated with CKD should be investigated for possible treatment, irrespective of the stage of kidney disease and requirement for renal replacement therapy[13].

In Australia and New Zealand, national guidelines for treating patients with chronic kidney disease – the Caring for Australasians with renal impairment (CARI) guidelines – were released in March 2000, with details and updates on the CARI website (http://www.cari.org.au)[28]. They provide nephrologists, renal nurses and other health carers with an evidence base for patient management and improving outcomes. The use of rhEPO obviates the need for blood transfusions, and is now the treatment of choice for the anaemia of CKD and end stage renal failure. The two forms of rhEPO available in New Zealand are rhEPO beta (Recormon®; Roche)[29] and rhEPO alpha (Eprex®; Janssen-Cilag)[30]. These variations of rhEPO appear to have the same efficacy, although the former preparation is associated with a lower reported incidence of serious idiosyncratic adverse events (pure red cell aplasia). Both can be administered subcutaneously or intravenously. PHARMAC partially subsidises rhEPO alpha, and fully subsidises rhEPO beta.

The PHARMAC criteria for rhEPO beta allow fully funded drug therapy for patients who:

- have a haemoglobin of ≤100 g/L AND
- have an eGFR of ≤ 45 ml/min (with diabetes mellitus) OR
- have an eGFR of ≤ 30 ml/min (without diabetes mellitus) OR
- are on haemodialysis or peritoneal dialysis.

Until recently, initial application for a Special Authority for Subsidy could only be made by a renal specialist. Now, other specialists with vocational registration have the right to make an initial application[31]. Approvals are valid for 2 years. Renewal may only be made by a specialist with vocational registration.

In patients with CRF, it must be demonstrated that there is no other cause of anaemia, apart from reduced renal function.

Target haemoglobin for patients with CKD

>110 g/L	All patients with CKD
>110 g/L to 120 g/L	Patients with significant cardiovascular disease (CARI)
>110 g/L to ≤ 130g/L	Patients without significant cardiovascular disease (KDOQI)

The minimal target Hb of >110 g/L is common to all guidelines. However, the upper limit remains unclear, given the results of trials to date and such a level should be judged individually.

The starting dose should be 50–120 units/kg/week, administered subcutaneously (via the anterior abdominal wall) as 2 to 3 divided doses. The Hb concentration should be monitored fortnightly until the target Hb is reached, then monthly thereafter. The initial rate of Hb increase should be 10–20 g/month. If there is a change of <10 g/L/month over 2–3 months, the weekly rhEPO dose should be increased by 25%. If the Hb rate of increase is >20 g/L/month, the total weekly dose should be reduced by 25–50%. In the maintenance phase, once the target level is achieved, Hb monitoring should be monthly. For any change of Hb by 10 g/L, the rhEPO weekly dose should be increased or decreased by 25%.

Blood pressure should be monitored closely, especially in the initiation phase. Up to a quarter of patients will develop or exacerbate pre-existing hypertension, needing treatment. Oral iron such as ferrous fumarate should also be started concurrently with rhEPO. The target ferritin level may not be achieved with oral iron as its absorption is poor in those with significant renal dysfunction. In such cases, iron infusion is recommended. With education (hospital or community nurses), most patients are able to administer the injection which comes in pre-filled syringes. Caregivers and community nurses can administer the injection in those cases where the patient cannot manage self administration.

Conclusions – Dr Tutone:

A large amount of observational data and cumulative clinical experience suggests that Hb concentrations of >110 g/L are associated with improved quality of life in CKD populations. To date, despite the strong and consistent associations between anaemia, CKD, and mortality, the cardioprotective benefit of anaemia correction has not been elucidated in trials, including CHOIR and CREATE. Almost all of the large multicentre randomised trials in the CKD population have shown that raising the Hb concentration (achieving normalisation in some cases) with rhEPO significantly improves patients' quality of life. However, controversy surrounds the issue as to whether the improved quality of life is achieved at the expense of increased cardiovascular morbidity, mortality, and a faster progression of kidney disease to end-stage kidney failure. Complicating the issue is the fact that some of the trials are flawed in their methodology and are unbalanced in their randomisation, making their findings suspect. The minimal target Hb of >110 g/L is common to all of the guidelines. The upper limit, however, remains unclear, given the results of trials to date and such levels should be judged individually and with caution, to avoid causing possible harm in those with pre-existing cardiovascular disease. It should be noted that in the clinical trials, everyone had exemplary care and the control groups had a Hb of >110 g/L. The exemplary care of blood pressure, haemoglobin A1c, iron status and mineral metabolism may have ameliorated the effect of anaemia on cardiovascular status. In real life, such exemplary care is lacking and patients may be more vulnerable to the adverse effects of anaemia, given that the other aspects of care are not perfect. While there is uncertainty, do not let patients become anaemic.

Relevant Clinical Trial Summaries – Commentary by Dr Tutone

Correction of anemia with epoetin alfa in chronic kidney disease

Authors: Singh AK et al

Summary: In the US-based CHOIR study, 1432 patients with CKD not on dialysis were randomised to receive a dose of epoetin alpha targeted to achieve a haemoglobin level of 135 g/L (high-haemoglobin group; n=715) or 113 g/L (low-haemoglobin group; n=717). The median study duration was 16 months. The primary end point was a composite of death, myocardial infarction, hospitalisation for congestive heart failure (other than for renal replacement therapy), and stroke. Patients in the high-haemoglobin group did not reach the 135g/L target but achieved a mean haemoglobin level of 126 g/L and did not show any additional quality of life benefits over patients in the low-haemoglobin group. A total of 125 primary composite endpoint events occurred in the high-haemoglobin group versus 97 such events in the low-haemoglobin group (hazard ratio, 1.34; p=0.03). More patients in the high-haemoglobin group had at least one serious adverse event (54.8% vs 48.5% of the low-haemoglobin group). The authors conclude that use of a high target haemoglobin level is associated with increased risk and no incremental improvement in the quality of life. Thus, they recommend the use of a target haemoglobin level of 110 to 120 g/L to correct anaemia in chronic kidney disease.

Comment: This study sample had more comorbidities and were older aged compared to the CREATE sample (see page 5) although their designs are similar. There are significant limitations to this trial. About half of the original cohort dropped out during the study, leaving a smaller number for the final analysis. The baseline characteristics of the two groups that completed the trial were not documented as with the original cohort, previous coronary heart disease and hypertension were significantly over-represented in the higher haemoglobin group. These baseline differences could account for the difference in the composite outcome. The trial was unjustifiably terminated. With all these limitations, opinion leaders refer to the conclusion as problematic.

Reference: N Engl J Med. 2006;355:2085-98

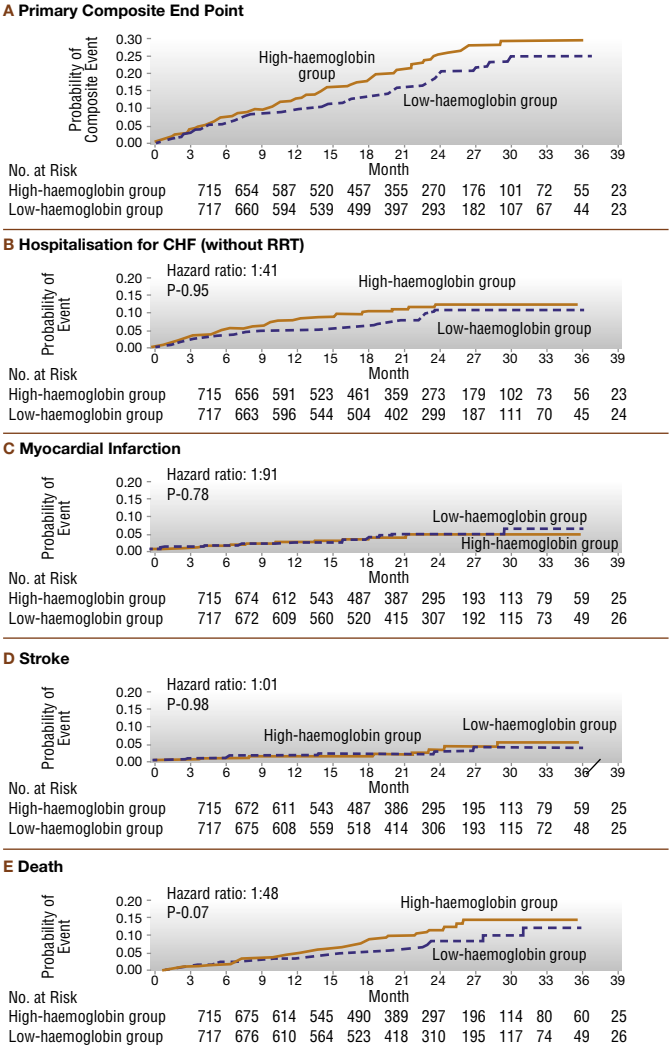

Fig. 2. Kaplan–Meier Estimates of the Probability of the Primary Composite End Point and Secondary End Points of Individual Components — Hospitalisation for Congestive Heart Failure (CHF) without Renal Replacement Therapy (RRT), Myocardial Infarction, Stroke, and Death.

Panel A shows that the largest separation between the two groups in the primary composite end point occurred at 15 months. At that time, the Kaplan–Meier estimate of the difference in cumulative event rates between the two groups reached 4.7 percentage points (15.8% in the high-haemoglobin group vs. 11.1% in the low-haemoglobin group). After 15 months, the difference between the two groups remained constant, with 752 patients (52.5%) remaining in the study (355 in the high-haemoglobin group and 397 in the low-haemoglobin group). There were no significant differences between the two groups in the four individual components of the primary composite end point (Panels B, C, D, and E). However, the hazard ratios for death and hospitalisation for CHF had strong trends toward a higher risk in the high-haemoglobin group than in the low-haemoglobin group.

Normalisation of haemoglobin level in patients with chronic kidney disease and anemia

Authors: Drüeke TB et al

Summary: The multinational CREATE study involved 603 patients with stage 3 to 4 CKD and mild-to-moderate anaemia (haemoglobin 110 to 125 g/L), who were randomised to treatment with epoetin beta to a target haemoglobin of either 130 to 150 g/L (group 1) or 105 to 115 g/L (group 2). The primary endpoint was a composite of eight cardiovascular events. In a 3-year follow-up, there were no significant differences in cardiovascular event rates or in all-cause mortality between the 2 treatment groups. A greater number of patients required dialysis in group 1 than in group 2 (127 vs 111), but patients in group 1 achieved significantly better quality of life outcomes (particularly with regard to physical function, vitality, and mental health). Overall, there were no significant differences in adverse events between the two groups, but vascular disorders were more prevalent in group 1, mainly because of a greater incidence of hypertension and more headaches. The authors conclude that CREATE *"adds direct evidence to confirm the current best practice guidelines, which recommend partial correction of anaemia and not routine normalization of haemoglobin levels".*

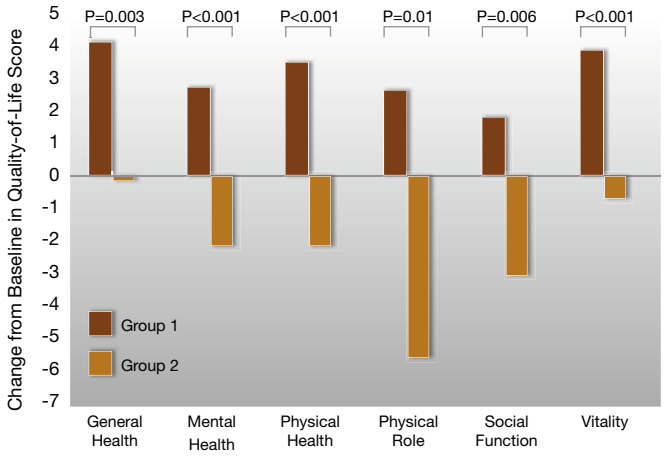

Fig 3. Changes from Baseline to Year 1 in SF-36 Quality-of-Life Scores: Values are expressed as least-square means. Positive changes indicate improvement in, and negative changes worsening of, the quality of life.

Comment: The significant improvement in the quality of life of those with higher haemoglobin is the most consistent result in almost all trials investigating normalisation of haemoglobin levels. This trial was well designed with a large sample size and few dropouts. However, CREATE was underpowered to demonstrate the difference in the primary outcome and this is perceived as its major weakness. The primary outcome, actual annual event rate (6%), was significantly lower than that expected (15%). As such, most opinion leaders air caution in the interpretation and application of the results. The mean GFR at baseline (25 ml/min) and the mean rate of decline were the same in both groups. The difference in the number of patients on dialysis could be explained by the absence of protocol dictating the timing of dialysis initiation.

Reference: N Engl J Med. 2006;355:2071-84

Left ventricular mass index increase in early renal disease: impact of decline in haemoglobin

Authors: Levin A et al

Summary: The aim of this prospective, multicentre Canadian cohort study was to identify the factors associated with left ventricular growth (LVG) measured with two-dimensional-targeted M mode echocardiography in patients with mild-to-moderate renal impairment. A total of 446 such patients were enrolled, 246 of whom were included in the final analysis, with echo results available and assessable at both baseline and at 12 months. The overall prevalence of LVH was 36%. The left ventricular mass index (LVMI) increased significantly in 25% of the population, by more than 20% from baseline to 12 months. Comparing the groups with and without LVG, significant differences were seen in the decline of Hb level (–8.54 vs –1.08 g/L) and change in systolic blood pressure (+6.50 vs –1.09 mm Hg). In the multivariate analysis, the significant independent predictive factors for LVG were a decrease in Hb level (odds ratio [OR], 1.32 for each 5.0g/L decrease), increase in systolic blood pressure (OR, 1.11 for each 5mm Hg increase), and lower baseline LVMI (OR, 0.85 for each 10g/m^2). Thus, after adjusting for baseline LVMI, Hb level and systolic blood pressure remain independent predictors of LVG. The authors conclude that their study defined the important modifiable risk factors and that *"there remains a critical need to establish optimal therapeutic strategies and targets to improve clinical outcomes".*

Comment: This trial showed that anaemia in patients with CKD is associated with left ventricular growth and hypertrophy, which are strong surrogate markers of cardiac morbidity and mortality. Within the limitation of retrospective and observational studies, the strengths of this trial are that all patients are accounted for and that all the data needed for the analysis were available. Numerous observational studies have also confirmed this association, as well as an improvement in quality of life, when the haemoglobin level is raised towards normal. These observational studies form the basis of particular endpoints and event rates needed for the designing of prospective interventional trials involving anaemia correction in CKD.

Reference: Am J Kidney Dis.1999;34:125-34

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

Authors: Phrommintikul A et al

Summary: This meta-analysis aimed to determine whether different haemoglobin targets in patients with CKD are associated with different mortality and cardiovascular event rates. A total of nine randomised controlled trials in adults with anaemia caused by CKD (n=5143) met inclusion criteria: the trials investigated the effects of epoetin alpha and beta, darbepoetin, or placebo, used to achieve different target levels of haemoglobin; recruited ≥100 patients; and had a minimum follow-up of 12 weeks. Target haemoglobin levels ranged between 90 and 120 g/L for the low group and 120 to 160 g/L for the high group. Analyses revealed that patients in the higher target group had significantly higher overall mortality than those in the lower target group (relative risk [RR] 1.17) and a significantly higher risk of arteriovenous access thrombosis (RR 1.34). There was an indication of a higher risk of poorly controlled blood pressure in the higher target group (RR 1.27), but the risk of myocardial infarction was similar in the two groups. The authors conclude that targeting a higher haemoglobin level in the treatment of patients with chronic renal disease puts them at increased risk of death. They consider that any possible benefits of achieving a normal haemoglobin level in such patients is outweighed by the harm and that guideline should therefore reflect this by stating an upper limit for target haemoglobin levels.

Comment: The strength of this meta-analysis is the inclusion of well designed trials with a large cohort for analysis. The perceived weakness is the inclusion of patients with CKD and those on dialysis who have higher cardiovascular risk and mortality. The inherent limitations of each individual trial (such as CHOIR and CREATE mentioned earlier) are carried through to the meta-analysis. There is accumulating evidence that there might be potential harm in normalising Hb, particularly in certain groups such as those with significant cardiovascular disease. The upper level of the target Hb is far from clear in trials to date. A well designed trial with a large cohort allowing subgroup analysis may be able to tease out this information. The TARGET trial, with a similar trial design to CHOIR and CREATE, is still on-going and has recruited more than 4000 patients to date. The interim analysis reveals no excess harm in comparison of the two groups. Hopefully, this will cast some light on the upper Hb level but in the meantime, caution should be exercised.

Reference: Lancet. 2007;369:381-8

Related comment: Strippoli G et al. Haemoglobin targets: we were wrong, time to move on. Lancet. 2007;369:346-50

Table 1: Baseline, target, and achieved haemoglobin concentrations in included trials

	Baseline haemoglobin concentration (g/L)	Target haemoglobin concentration (g/L)		Achieved haemoglobin concentration (g/L)	
		High	Low	High	Low
Besarab et al[21]	90–110*	140 (10)*	100 (10)*	12·7– 13·3†	10·0†
Foley et al[22]	90–110	130–140	95–105	123 (120–125)‡	104 (102–106)‡
Furuland et al[23]	90–120	145–160 (M), 35–150 (F)	90–120	143 (11)§	113 (13)§
Roger et al[26]	110–130 (M), 100-120 (F)	120–130	90–120	121 (14)§	108 (13)§
Parfrey et al[25]	80–120	135–145	95–115	131 (9)¶	108 (7)¶
Levin et al[24]	110–135	120–140	90–105	126–130‖	115–117‖
Rossert et al[27]	<130 (M), 125 (F)	130–150	110–120	NA**	NA**
Singh et al[14]	<110	135	113	126††	113††
Drueke et al[13]	110–125	130–150	105–115	NA¶	NA¶

*Target (range); calculated from haemocrit results. †Data are range; from Kidney Disease Outcomes Quality Initiative clinical practice guidelines and clinical practice recommendation for anaemia in chronic kidney disease.2 ‡Data are mean (95% CI); data for LVD group; level achieved in LVH group was 122 g/L (119–125). §Data are mean (SD). ¶Data are mean (2 SE). ‖Data are range. ††Data are mean. **Change in haemoglobin for men was 27 (SE 11·9), for women 20 (10·8) in the high group; in the low group it was 2 (8·3) for men and 2 (9·3) for women. ¶Target haemoglobin concentration achieved and diff erence in median haemoglobin concentration between the two groups was 15 g/L at the end of the study.

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