

Haemoglobin

Date written: April 2007
Final submission: February 2008
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GUIDELINE

The targeting of haemoglobin concentrations above 130 g/L has been associated with an increased mortality in chronic kidney disease (CKD) patients (dialysis and pre-dialysis) and is therefore currently considered inadvisable. (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- There is some evidence of improved quality of life, enhanced neuropsychological functioning and/or better exercise capacity at haemoglobin concentrations above 120 g/L in selected CKD patients. (Level II – IV)
- For patients in whom atheromatous or arteriosclerotic cardiovascular disease is unlikely (e.g. new-onset kidney failure in younger patients), a target between 120 and 130 g/L may be considered. (Level II and III)
- Cohort and population studies suggest morbidity and mortality begin to rise as haemoglobin concentrations fall below 110 g/L. In many patients therefore, a haemoglobin concentration of 110 g/L may be a suitable therapeutic target nadir. (Level III and IV)
- Prior to the commencement of administration of epoetin analogues, appropriate iron indices and adequate concentrations of Vitamin B12 and folate should be ensured. In addition, efforts should be made to control hyperparathyroidism, aluminium accumulation and/or significant systemic inflammation. Blood pressure levels should be controlled, preferably below 160/100 mmHg. (Level III)
- Readers should refer to the PI (Product Information) brochures for the 3 epoetin products currently available in Australia and/or New Zealand for information concerning mode and frequency of administration, and for side effects. All agents currently have approval for both intravenous and subcutaneous administration.
- Increments in dosage should be considered if there is an inadequate increase in haemoglobin concentration (<15 g/L) after a 2-month period. The haemoglobin concentration is usually checked at least monthly initially, and/or 1 month after a change in ESA dosage. Dosages in excess of 200 U/kg per week (1 mcg/kg per week for darbepoetin) in the setting of significant systemic inflammation are unlikely to elevate haemoglobin concentrations further. (Opinion)

- In normal circumstances, the rise in haemoglobin concentrations should not exceed 10 g/L per month (averaged over 3 months). The haemoglobin concentration should be checked at least every 2 months and iron stores at least every 3 months. Vitamin B12 and folate levels should be checked at least every 12 months. (Opinion)

BACKGROUND

Anaemia is an almost universal accompaniment of CKD. Several of the co-morbidities associated with kidney failure have been primarily attributed to anaemia, including the development of left ventricular dysfunction, cardiac failure, reduced exercise capacity and reduced quality of life. Prior to the synthesis of epoetin, transfusion dependence was characterised by blood-borne infection, iron overload and sensitisation to HLA antigens, which limited transplantation opportunities.

With the availability of epoetin analogues (epoetin alpha, epoetin beta, darbepoetin alpha and others), collectively known as erythropoiesis-stimulating agents (ESAs), clinicians, patients and funders of health care require information about their effectiveness as well as the clinical consequences and economic impact of an increase in haemoglobin. These guidelines were developed to present and integrate the available evidence.

Target Haemoglobin

Until relatively recently, there has been insufficient information to determine clear guidelines for appropriate haemoglobin targets in patients with CKD. Most early studies were either too small or too short to assess anything but surrogate endpoints,¹⁻⁶ and the use of patients with extensive cardiovascular disease in the large, Amgen-sponsored, study by Besarab *et al.* made it difficult to determine

whether such findings were applicable to the whole CKD community (see below).

However, the publication in the past 4 years of at least five major studies⁸⁻¹² addressing mortality and/or morbidity in both dialysis and pre-dialysis patients has substantially addressed this issue. Culminating in a meta-analysis published earlier this year by Phrommitikul *et al.*,¹³ there are now reasonable grounds to advise appropriate targets for most patients with CKD. With the provision of apparently adequate mortality data and clear directions regarding risk of arteriovenous fistula thrombosis and hypertension,^{7-11,13-18} the issues pertaining to quality of life and exercise capacity are less persuasive, particularly when the improvements in these areas with higher haemoglobin concentrations were largely transitory or marginal^{5,10} and the dosage (and associated costs) of ESA to reach and maintain near-physiological targets are so disproportionately high.

Hence, as will be evident from analysis of the evidence below, it is now necessary for protagonists of higher haemoglobin targets to justify their claim in specific individuals although it is as well to recall that such individuals do, however, exist. There are, for instance, no data to suggest that the minority of CKD patients who maintain their haemoglobin concentrations above the proposed target without the need for ESA should have their levels reduced by venesection; similarly, the appropriate haemoglobin target for patients with chronic airflow obstruction, for patients on peritoneal dialysis, the elderly, the very young, and those with sickle cell disease, thalassaemia or concurrent cyanotic cardiac disease may require specific targets yet to be determined.

Other issues remain and/or require further clarification. For haemodialysis patients, for instance, haemoglobin concentration is conventionally measured before dialysis. There are fears that excessive ultrafiltration may produce dangerously high haematocrit levels with associated intravascular red cell sludging or thrombosis if the baseline haematocrit is kept at more than 39%.¹⁹⁻²¹ Changes in haematocrit from the start to end of dialysis can vary by as much as 3-6%^{22,23} depending on the volume of ultrafiltration and the timing of the post-dialysis sample. It would seem prudent to also measure the post-dialysis haemoglobin concentration in patients when the pre-dialysis level is above 130 g/L to ensure that haemoconcentration during dialysis does not exceed physiological limits.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for haemoglobin, hematocrit, and anemia were combined with MeSH terms and text words for chronic kidney disease and renal replacement therapy. The searches were carried out in Medline (1966 to 1 May 2007) and in the Cochrane Controlled Trial Register.

Date of searches: Medline and CCTR – 1 May 2007.

WHAT IS THE EVIDENCE?

Level I evidence (Meta-analysis and Systematic Review)

Evidence regarding the benefits and risks of low (haemoglobin <100 g/L) versus high (haemoglobin 140 g/L) haemoglobin targets was initially reviewed in a Cochrane systematic review of randomised controlled trials.²⁴ The review was published in early 2003 and recently updated to include an additional trial by Furuland *et al.*¹² This systematic review included 16 randomised controlled trials and evaluated the effect of low versus high haemoglobin targets on mortality, serious cardiovascular events, access thrombosis, renal function, seizures, hypertension and quality of life (see Table 1).

The authors concluded that the benefits associated with higher haemoglobin targets (reduced seizures) are outweighed by the risks (increased risk of hypertension and increased mortality) in patients with cardiovascular impairment. Haemoglobin targets >133 g/L at best implied no reduction in deaths and at worst, implied an increase in the number of deaths. The evaluation of quality of life that was performed in this review was problematic because five of eight trials in which this measure was evaluated did not use validated scales for the assessment of quality of life²⁵⁻²⁹ (see Table 2).

Recently, a meta-analysis of nine randomised trials,¹³ each of at least 100 patients and lasting over 12 weeks, examined the effects of different target haemoglobin concentrations on mortality and morbidity. The study included 5143 patients. It is worth noting that the Besarab study,⁷ because of its high mortality, dominates the statistical trends. The authors identified a higher risk of all-cause mortality (RR 1.17, 95% CI 1.01, 1.35; $P = 0.031$) and arteriovenous access thrombosis (RR 1.34, 95% CI 1.16, 1.54, $P = 0.0001$) in the higher haemoglobin target group compared to the lower. There was a higher risk of poorly controlled blood pressure (RR 1.27, 95% CI 1.08, 1.5, $P = 0.004$) in the higher target group in the fixed effects but not random effects model. The incidence of myocardial infarction did not differ between groups. The authors proposed that higher target haemoglobin concentrations place patients at an increased rate of death.

Examination of the respective studies involved in the meta-analysis indicates certain similarities in both pre-dialysis and dialysis patients, according to their inclusion criteria. Comparing those studies where the mortality was clearly increased in the group targeted to a higher haemoglobin concentration,^{7,9} with those where little difference was identified between the two targets,^{8,10} patients in the former two studies at enrolment were older, had worse heart disease, a higher incidence of diabetes, required treatment for rather than prevention of anaemia, and used a higher dose of epoetin to achieve target concentrations.

To what extent such differences affect survival and therefore a different target haemoglobin is uncertain, however the potential benefits of a higher target appear restricted to some improvement in the quality of life, as evidenced by numerous smaller studies^{10,12} (see also Tables 1 and 2), and

possibly an enhanced but still suboptimal, exercise performance.^{5,30} Such benefits come at a substantially increased cost. The potential risks and costs from a higher haemoglobin concentration therefore appear to outweigh substantially whatever benefits might be gained.

Level II evidence (Individual Trials)

An outline of the characteristics of the populations and interventions used in the available randomised trials is presented in Table 1. Two groups of trials are available in the literature. In one, patients are randomised to two different doses of the same ESA to achieve and maintain two different haemoglobin targets. In the other, patients are randomised to an ESA versus a placebo or no treatment (Table 1).

The largest single trial for the first group (ESA versus ESA) was published by Besarab *et al.* in 1998.⁷ In this trial, patients were randomised to a high ('normal') haemoglobin target (140 ± 16 g/L) versus a lower haemoglobin target of 100 ± 3 g/L. Patients with significant cardiovascular disease were specifically selected because it was assumed that these would benefit from the raised haemoglobin target. However, the trial showed reduced survival in the group with the higher haemoglobin target (RR 0.82, 95%CI 0.68, 0.99).

Another trial, which included both ESA versus ESA and ESA versus no treatment groups was published in 2003.¹² The authors concluded that there was an improvement in the quality of life of patients treated with 'normal' haemoglobin targets but no difference was found between the lower and higher targets in terms of overall mortality, incidence of thrombovascular events and incidence of vascular access thrombosis. This trial included both pre- and post-dialysis patients. However, the authors of the Cochrane systematic review²⁴ found the study quality of both these studies to be suboptimal because of unclear allocation concealment and no blinding of study participants.

The Australian and New Zealand pre-dialysis study was published in 2004.¹¹ This study enrolled 155 patients with CKD, with a creatinine clearance of 15 to 50 mL/min and an entry haemoglobin of 110 to 120 g/L (female) or 110 to 130 g/L (male); 28% of patients were diabetic. Target haemoglobins were 90 to 100 g/L (low) and 120 to 130 g/L. Achieved haemoglobin concentrations were 108 ± 13 g/L and 121 ± 14 g/L for low and high target groups respectively. The primary endpoint was change in left ventricular mass index. There was no difference between the target groups for the primary endpoint on an intention to treat analysis, although for those patients who did achieve protocol target ($n = 15$ and 37 , respectively), a significant difference in the left ventricular mass index was found favouring the higher target group. There was no apparent benefit in quality of life in the higher target group. No patients died.

Parfrey *et al.* published the results of a study of 596 relatively new-onset (mean duration 10 months) haemodialysis patients in 2005.¹⁰ The study was double-blinded and examined left ventricular volume index (echocardiogram) and quality of life over 2 years. The mean age of patients was

50.8 years and 18% were diabetic. Targeted haemoglobins were 9.5 to 11.5 g/dL (low group) and 13.5 to 14.5 g/dL (high group). Target concentrations were achieved by week 24. No advantage was found in being randomised to the higher target, however, vitality was improved. Greater rates of pain, surgery and dizziness were seen in the lower target group and headache and cerebrovascular events were more frequent in the higher group. Vascular access loss was not significantly different between the two groups.

Two CKD studies, recognised by the acronyms CHOIR and CREATE, were published simultaneously in 2006.^{8,9} CHOIR enrolled 1432 patients with a mean age of 66 ± 13 years, of whom 55% had significant cardiovascular disease. The mean eGFR was 27 ± 9 mL/min and almost 50% of patients were diabetic. Patients were followed for 30 months. Anaemia was treated with epoetin alfa and mean doses were approximately 5000 Units (low haemoglobin target, 11.3 g/dL) and 12,000 Units (high haemoglobin target, 13.5 g/dL) per week. CREATE enrolled 603 patients with a mean age of 59 ± 14 years. Significant cardiovascular disease at baseline was 36% and 26% of patients had diabetes. The eGFR was between 15 and 35 mL/min. Patients were followed for 36 months and anaemia was largely prevented with target haemoglobins of 11 and 14 g/dL. Epoetin beta was used with weekly doses of 2000 and 5000 Units per week (low versus high target). CHOIR demonstrated an increased mortality and higher rate of congestive cardiac failure (CCF) in the higher target haemoglobin group without a quality of life benefit. CREATE found no benefit in the higher target group with respect to a first cardiovascular event but general health and physical fitness was improved. Hypertension and headaches were also more prevalent in this group.

Level III evidence (Cohort and Case Control Studies)

Data in pre-dialysis CKD patients is less comprehensive and mostly cohort based. Various studies³¹⁻³⁴ have demonstrated that most patients have developed left ventricular hypertrophy by the time end stage kidney disease is reached. In dialysis patients, all-cause and cardiac mortality was lowest at a haematocrit between 33% and 36% both before and after adjusting for severity of disease, in a retrospective database analysis of over 75,000 patients although higher haematocrits were not assessed.³⁵ Similar findings have been reported in other epidemiological studies.³⁶⁻³⁸

Summary of the evidence

Substantial evidence now indicates that targeting (without necessarily achieving) haemoglobin concentrations above 130 g/L with ESA in patients with CKD results in an increased mortality and morbidity with little benefit (compared to targeting concentrations below 120 g/L) and at a higher cost. Older patients and those with more advanced cardiovascular disease and/or diabetes are at highest risk, which appears to pertain to both dialysis and pre-dialysis patients. In addition, there appears to be an increased risk of

hypertension and arteriovenous access thrombosis in patients targeted for higher haemoglobin concentrations without substantial evidence of benefit in quality of life or normalisation of exercise capacity. The ESA dosage and associated cost of achieving and maintaining higher haemoglobin concentrations is significantly greater.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative (KDOQI) 2007: The Hb target is the intended aim of ESA therapy for the individual patient with CKD. In clinical practice, achieved Hb results vary considerably from the Hb target.

- In the opinion of the Work Group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life threatening adverse events). (Clinical Practice RECOMMENDATION)
- In the opinion of the Work Group, in dialysis and non-dialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. (Clinical Practice RECOMMENDATION)
- In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL. (Clinical Practice GUIDELINE – MODERATELY STRONG EVIDENCE)

UK Renal Association 2006:

- Patients with CKD should achieve an outcome distribution of haemoglobin of 10.5–12.5 g/dl. (Evidence).
- Adjustments to ESA doses should be considered when Hb is <11 or >12 g/dl in order that the population distribution has the maximum proportion of patients in the range 10.5–12.5 as is possible (Evidence)

Canadian Society of Nephrology (CSN) 1999:

- The target haemoglobin during epoetin therapy is advised to be between 110 and 120 g/L for both men and women. It is suggested that epoetin be used before and after initiation of dialysis as well as in patients with failing transplants, if necessary.

European Best Practice Guidelines (EBPG) 2004:

- Patients with chronic kidney disease (CKD) should maintain a target haemoglobin (Hb) concentration of >11 g/dl [haematocrit (Hct) >33%] (Level B) (*Target Rationale*) – Exact target Hb concentrations >11 g/dl should be defined for individual patients, taking gender, age, ethnicity, activity and co-morbid conditions into account. In HD patients, pre-dialysis Hb concentrations above 14 g/dl are not desirable due to the risks associated with the effects arising from post-dialysis haemoconcentration. (Level C) –
- Hb concentrations >12 g/dl are not recommended for patients with severe cardiovascular disease [defined as class III and above of the New York Heart Association Classification of Congestive Heart Failure unless continuing severe symptoms (e.g. angina) dictate otherwise. (Level A)]
- Until data become available, it seems prudent to recommend a cautious approach to raising Hb concentrations to

levels >12 g/dl in patients with diabetes, especially with concurrent peripheral vascular disease. (Level C)

International Guidelines (KDIGO) 2008:

- No recommendation.

IMPLEMENTATION AND AUDIT

1. The percentage of patients reaching the target haemoglobin concentration should be calculated.
2. The number of patients not requiring ESA should be monitored and patients followed for access thrombosis and mortality.
3. The percentage of patients requiring more than 20,000 units of epoetin alpha or epoetin beta or 100 mcg of darbepoetin per week should be assessed.
4. The percentage of patients exceeding physiological haemoglobin concentrations (both pre- and post-dialysis in haemodialysis patients) should be calculated.
5. The percentage of patients requiring cessation or reduction in epoetin dosage because of uncontrolled hypertension or an excessively rapid rise in haemoglobin levels should be assessed.

SUGGESTIONS FOR FUTURE RESEARCH

1. Agents and therapeutic modulations that may augment the effects or efficacy of epoetin such as carnitine, anabolic steroids, exercise, testosterone, increased dialysis and increased iron administration should be assessed.
2. Further delineation of patient subgroups in whom optimal target haemoglobin concentrations may differ from those currently advocated should be done.
3. A randomized controlled trial comparing mortality, quality of life and exercise capacity in patients with and without known cardiovascular disease at haemoglobin concentrations of 100–110 g/dL and 120–130 g/dL is required.

CONFLICT OF INTEREST

Lawrence McMahon has a Level IIc conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Study design breakdown of randomised controlled trials evaluating the effects of low versus high haemoglobin targets on key outcomes

Study ID	Stage of kidney failure	Randomised intervention	Cointerventions	Follow up (months)	Experimental group		Control group	
					N	Target Hematocrit (%)	N	Target Hematocrit (%)
Erythropoietin (high dose) vs erythropoietin (low dose)								
Berns <i>et al.</i> 1999 ³⁹	Hemodialysis*	EPO vs EPO	None indicated	12	14	42.0 ± 1.1	17	30.0 ± 1.0
Besarab <i>et al.</i> 1998 ⁷	Hemodialysis*	EPO vs EPO	Intravenous iron dextran	29	618	42.0 ± 3.0	618	30.0 ± 3.0
Brandt <i>et al.</i> 1999 ⁴⁰	Pre-dialysis Peritoneal dialysis Hemodialysis	EPO vs EPO	Oral (3 mg/kg/day) or intravenous iron 2 mg/kg/x 3 weekly if ferritin <100 ng/mL and or transferrin saturation <20%	20	21	>36.0	22	<36.0
Erythropoietin vs placebo								
Conlon <i>et al.</i> 2000 ⁴¹	Hemodialysis*	EPO vs EPO	None indicated	6	15	42.0 ± 3.0	16	30.0 ± 3.0
Foley <i>et al.</i> 2000 ⁴²	Hemodialysis*	EPO vs EPO	None indicated	12	73	39.0-42.0	73	28.5-31.5‡
Abraham & Macres 1991 ⁴³	Pre-dialysis	EPO vs standard†	Iron (dose and route not indicated) if serum iron <50 mcg/dL or transferrin saturation <20%; folic acid 1 mg/day	3	4	37.0-40.0‡	4	<30.0
Bahlmann <i>et al.</i> 1991 ²⁷	Hemodialysis	EPO vs standard†	None indicated	3	63	30.0-35.0‡	66	<30.0
Canadian Erythropoietin Study Group 1991 ¹⁷	Hemodialysis	EPO vs placebo	Oral or intravenous iron (dose not indicated) if serum ferritin <250 mg/L	6	78	28.5-33.0‡ 24.5-36.0‡	40	<30.0

Clyne & Jøgestrand 1992 ²⁹	Pre-dialysis	EPO vs standard†	3	12	31.8–35.1‡	10	25.2–31.2‡	Oral iron
								200–300 mg/day or intravenous iron 100 mg/week to all patients with normal range ferritin
Furuland <i>et al.</i> 2003 ¹²	Pre-dialysis Hemodialysis Peritoneal dialysis	EPO vs EPO or no treatment	12–19	216	40.5–45	200	27–36	Oral iron or intravenous iron to keep transferrin saturation >20% and serum ferritin 400–800 mg/L (correction phase) and >250 mg/L (maintenance phase)
								Oral iron 300 mg thrice a day and oral folic acid 1 mg/day to all patients except those with excess iron stores
Kleinman <i>et al.</i> 1989 ²⁵	Pre-dialysis	EPO vs placebo	3	7	38.0–40.0‡	7	<30.0	Iron supplementation
								Iron 'at investigator's discretion'
Kuriyama <i>et al.</i> 1997 ⁴⁴	Pre-dialysis	EPO vs no treatment	9	42	35.5 ± 4.0	31	25.3 ± 1.9	Iron 'at investigator's discretion'
								Oral iron 300 mg thrice a day and oral folic acid 1 mg/day to all patients except those with excess iron stores
Morris <i>et al.</i> 1992 ⁴⁵	Peritoneal dialysis	EPO vs placebo	6	6	31.5–36.0‡	5	<30.0	None indicated
								Iron <200 mg/die (route not indicated) if transferrin saturation <20%
Revicki <i>et al.</i> 1995 ⁴⁶	Pre-dialysis	EPO vs no treatment	12	43	36.0	40	26.8 ± 3.6	Iron <200 mg/die (route not indicated) if transferrin saturation <20%
								None indicated
Sikole <i>et al.</i> 1993 ⁴⁷	Hemodialysis	EPO vs no treatment	12	19	30.0–35.0‡	19	<30.0	None indicated
								None indicated
Teehan <i>et al.</i> 1990 ²⁸	Pre-dialysis	EPO vs placebo	6	86	40.0	31	30.0	None indicated
								None indicated
Watson <i>et al.</i> 1990 ⁴⁸	Pre-dialysis	EPO vs placebo	3	5	35 ± 2	6	26 ± 2	None indicated
								None indicated

*Known cardiovascular abnormality; †no treatment or blood transfusion; ‡range.

Table 2 Means of Quality of Life assessment in randomised controlled trials evaluating the effects of low versus high haemoglobin targets on key outcomes

Study ID	Scale or tool	Validated*	Time of assessment	Result
Erythropoietin (high dose) vs erythropoietin (low dose)				
Besarab <i>et al.</i> 1998 ⁷	Short Form 36	Yes	Baseline and every 6 months	Significant increase of physical function score; no significant changes in other scores of the scale with higher targets
Foley <i>et al.</i> 2000 ⁴²	Kidney Disease Quality of Life tool Short Form 36	Yes Yes	Baseline, 3, 6 and 7 months	Improvement in fatigue, depression and relationship with others measures with higher targets No changes with Short Form 36
Erythropoietin vs placebo				
Bahlmann <i>et al.</i> 1991 ²⁷	Study specific	No	Baseline and end of treatment	Angina, dyspnea, 'other' cardiovascular symptoms and sexuality improved with higher targets
Canadian Erythropoietin Study Group 1991 ¹⁷	Kidney Disease Quality of Life tool Sickness Impact Profile	Yes Yes	Baseline, 2 and 6 months	Improvement in fatigue, physical symptoms, depression and relationship with other measures with higher targets Overall improvement with Short Form 36 with higher targets
Clyne & Jogestrand 1992 ²⁹	Standardised symptom-limited exercise test and electrically-braked bicycle ergometer	No	Baseline and end of treatment	Significant increase in exercise capacity with higher targets
Furuland <i>et al.</i> 2003 ¹²	Kidney Disease Questionnaire (KDQ) part 1 and part 2	Yes	Baseline and 12 months	Improvement of main physical symptoms in the normal hematocrit group compared with the lower hematocrit group. Change in KDQ score for main physical symptoms, fatigue, depression and frustration favoured the normal compared with the lower hematocrit group.
Kleinman <i>et al.</i> 1989 ²⁵	Model developed for patients with advanced cancer	No	Baseline and end of treatment	Improvement in level of energy, ability to do work and overall quality of life with higher targets
Lim <i>et al.</i> 1989 ²⁶	Study specific	No	Baseline and end of treatment	Improvement in exercise capacity with higher targets
Teehan <i>et al.</i> 1990 ²⁸	Study specific	No	Baseline and end of treatment	Improvement in energy level and work capacity with higher targets

*SA codified scale for the standard assessment of quality of life or exercise capacity in patients with kidney disease.

Table 3 Quality of randomised controlled trials

Study ID	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Abraham & Macres, 1991 ⁴³	Not specified	Yes	No	Not stated	No	0.0
Bahlmann <i>et al.</i> , 1991 ²⁷	Not specified	No	No	Not stated	No	23.2
Berns <i>et al.</i> , 1999 ³⁹	Not specified	No	No	No	No	50.9
Besarab <i>et al.</i> , 1998 ⁷	Not specified	No	No	Not stated	Yes	2.5
Brandt <i>et al.</i> , 1999 ⁴⁰	Not specified	No	No	Not stated	No	2.2
Canadian Erythropoietin Study Group, 1991 ¹⁷	Not specified	Yes	Yes	Not stated	No	16.1
Clyne & Jogestrand, 1992 ²⁹	Not specified	No	No	Not stated	No	15.0
Conlon <i>et al.</i> , 2000 ⁴¹	Not specified	No	No	No	Unclear	0.0
Drueke <i>et al.</i> (CREATE), 2006 ⁸	Central	No	No	Yes	Yes	21.0
Foley <i>et al.</i> , 2000 ⁴²	Central	No	No	Not stated	Yes	21.1
Furuland <i>et al.</i> , 2003 ¹²	Not specified	No	Not stated	Not stated	Yes	49.5
Kleinman <i>et al.</i> , 1989 ²⁵	Not specified	No	No	Not stated	No	17.1
Kuriyama <i>et al.</i> , 1997 ⁴⁴	Central	No	No	Not stated	Yes	49.5
Lim <i>et al.</i> , 1989 ²⁶	Not specified	Yes	No	Not stated	No	7.1
Morris <i>et al.</i> , 1993 ⁴⁵	Not specified	No	No	Not stated	No	31.4
Parfrey <i>et al.</i> , 2005 ¹⁰	Central	Yes	Yes	No	Yes	0.7
Revicki <i>et al.</i> , 1995 ⁴⁶	Not specified	Yes	Yes	Not stated	No	15.0
Roger <i>et al.</i> , 2004 ¹¹	Central	No	No	Yes	Yes	0.6
Sikole <i>et al.</i> , 1993 ⁴⁷	Not specified	Yes	No	Not stated	No	36.3
Singh <i>et al.</i> (CHOIR), 2006 ⁹	Central	No	No	Yes	No	Not stated
Teehan <i>et al.</i> , 1990 ²⁸	Central	Yes	No	Yes	Yes	6.4
Watson <i>et al.</i> , 1990 ⁴⁸	Not specified	No	No	Not stated	Yes	57.8

Table 4 Results for continuous outcomes

Study ID	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Abraham & Macres, 1991 ⁴³	Blood pressure MAP	Low target 100.00 (7.00)	High target 98.00 (7.00)	2.00 (95%CI: -7.70, 11.70)
	Serum creatinine	Low target 4.00 (0.80)	High target 5.70 (2.00)	-1.70 (95%CI: -3.81, 0.41)
	Creatinine clearance	Low target 20.00 (7.00)	High target 18.00 (11.00)	2.00 (95%CI: -10.72, 14.78)
Besarab <i>et al.</i> , 1998 ⁷	Systolic blood pressure	Low target 151.50 (25.70)	High target 150.70 (19.80)	0.80 (95%CI: -4.78, 6.68)
	Diastolic blood pressure	Low target 75.90 (13.30)	High target 77.30 (10.40)	-1.40 (95%CI: -4.37, 1.57)
	Blood pressure MAP	Low target 104.80 (10.20)	High target 105.60 (12.80)	-0.80 (95%CI: -12.39, 10.79)
Bahlmann <i>et al.</i> , 1991 ²⁷	Blood pressure MAP	Low target 73.50 (13.60)	High target 67.30 (11.20)	6.20 (95%CI: -12.19, 24.59)
Berns <i>et al.</i> , 1999 ³⁹	Hematocrit (%)	42.0 (2.91)	30.4 (2.83)	11.60 (95%CI: 8.69, 14.51)
	24-hour SBP (mmHg)	158.7 (20.64)	150.7 (12.16)	8.00 (95%CI: -9.46, 25.46)
	24-hour DBP (mmHg)	74.7 (4.76)	77.8 (7.35)	-3.10 (95%CI: -9.29, 3.09)

Table 4 Continued

Study ID	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Canadian Erythropoietin Study Group, 1991 ¹⁷	Systolic blood pressure	Low target 139.90 (19.10)	High target 143.40 (18.70)	-3.50 (95%CI: -12.69, 5.69)
	Diastolic blood pressure	Low target 81.40 (8.50)	High target 84.50 (9.90)	-3.10 (95%CI: -7.58, 1.38)
Clyne & Jogestrand, 1992 ²⁹	Systolic blood pressure	Low target 151.00 (15.00)	High target 146.00 (19.00)	5.00 (95%CI: 9.95, 19.95)
	Diastolic blood pressure	Low target 85.00 (7.00)	High target 90.00 (9.00)	-5.00 (95%CI: -12.39, 2.39)
	Serum creatinine	Low target 8.98 (2.16)	High target 8.04 (3.28)	0.94 (95%CI: -1.44, 3.32)
Conlon <i>et al.</i> , 2000 ⁴¹	Mean hematocrit (%)	40.8 (5.2)	30 (4.3)	10.80 (95%CI: 7.43, 14.17)
Drueke <i>et al.</i> (CREATE), 2006 ⁹	Systolic blood pressure	Low target 135 (19)	High target 136 (21)	-1.00 (95%CI: -4.20, 2.20)
	Diastolic blood pressure	Low target 77 (12)	High target 79 (11)	-2.00 (95%CI: -3.84, -0.16)
	Estimated GFR (mL per min)	Low target 19.2 (19.0)	High target 18.1 (11.5)	1.10 (95%CI: -1.41, 3.61)
Furuland <i>et al.</i> , 2003 ¹²	Estimated GFR at wk 48 in predialysis patients (mL/min/1.73 m ²)	Low target 16 (7)	High target 13 (10)	3.00 (95%CI: -2.40, 8.40)
	Systolic blood pressure in predialysis patients	Low target 148 (24)	High target 147 (21)	1.00 (95%CI: -12.95, 14.95)
	Diastolic blood pressure in predialysis patients	Low target 83 (11)	High target 90 (6)	-7.00 (95%CI: -12.42, -1.58)
Morris <i>et al.</i> , 1992 ⁴⁵	Blood pressure mean arterial pressure	Low target 67.30 (11.22)	High target 73.50 (13.60)	-6.20 (95%CI: -24.61, 12.21)
Parfrey <i>et al.</i> , 2005 ¹⁰	Systolic blood pressure	Low target 139 (22)	High target 141 (22.14)	-2.00 (95%CI: -5.55, 1.55)
	Diastolic blood pressure	Low target 79 (14)	High target 80 (12.57)	-1.00 (95%CI: -3.14, 1.14)
Roger <i>et al.</i> , 2004 ¹¹	Systolic blood pressure 2 yr mean	Low target 138(13)	High target 141 (14)	-3.00 (95%CI: -7.70, 1.70)
	Diastolic blood pressure 2 yr mean	Low target 79 (9)	High target 80 (6)	-1.00 (95%CI: -3.68, 1.68)
	GFR 2 yr mean (ml/min/1.73 m ²)	Low target 24(9)	High target 23 (9)	1.00 (95%CI: -2.13, 4.13)
	Creatinine (mM) 2 yr mean	Low target 0.34 (0.15)	High target 0.38 (0.19)	-0.04 (95%CI: -0.10, 0.02)
	Changes in LV mass index (g/m ²)	Low target 4.5 (20)	High target 2.5 (20)	2.00 (95%CI: -4.96, 8.96)
	Systolic blood pressure	Low target 152.10 (18.10)	High target 151.10 (25.60)	1.00 (95%CI: -13.10, 15.10)
Sikole <i>et al.</i> , 1993 ⁴⁷	Diastolic blood pressure	Low target 92.90 (12.40)	High target 93.90 (10.50)	-1.00 (95%CI: -8.31, 6.31)
	Blood pressure mean arterial pressure	Low target 112.30 (16.50)	High target 113.30 (12.60)	-1.00 (95%CI: -10.34, 8.34)
	Serum creatinine	Low target 8.98 (2.16)	High target 8.04 (3.28)	0.94 (95%CI: -1.44, 3.32)
	Serum creatinine	Low target 7.80 (1.30)	High target 6.50 (1.80)	1.30 (95%CI: -0.59, 3.19)
Watson <i>et al.</i> , 1990 ⁴⁸	Serum creatinine	Low target 7.80 (1.30)	High target 6.50 (1.80)	1.30 (95%CI: -0.59, 3.19)
	Creatinine clearance	Low target 10.30 (2.90)	High target 12.90 (4.00)	-2.60 (95%CI: -6.80, 1.60)

Table 5 Results for dichotomous outcomes

Study ID	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Abraham & Macres, 1990 ⁴³	Hypertension	Low target 2/4	High target 2/4	1.00 (95%CI: 0.25, 4.00)	0.00 (95%CI: -0.67, 0.69)
Bahlmann <i>et al.</i> , 1991 ¹⁷	Serious CV events	Low target 11/46	High target 5/53	2.53 (95%CI: 0.95, 6.76)	0.14 (95%CI: 0.00, 0.29)
	Overall mortality	Low target 2/46	High target 2/53	1.15 (95%CI: 0.17, 7.86)	0.01 (95%CI: -0.07, 0.08)
	Stroke	Low target 1/53	High target 0/53	3.00 (95%CI: 0.12, 72.02)	0.02 (95%CI: -0.03, 0.07)
	Hypertension	Low target 5/46	High target 15/53	0.38 (95%CI: 0.15, 0.98)	-0.17 (95%CI: -0.33, -0.02)
	Access thrombosis	Low target 4/46	High target 5/53	0.92 (95%CI: 0.26, 3.23)	-0.01 (95%CI: -0.12, 0.11)
Besarab <i>et al.</i> , 1998 ⁷	Overall mortality	Low target 150/615	High target 183/618	0.82 (95%CI: 0.68, 0.99)	-0.05 (95%CI: -0.10, 0.00)
	Fatal myocardial infarction	Low target 28/615	High target 22/618	1.28 (95%CI: 0.74, 2.21)	0.01 (95%CI: -0.01, 0.03)
	Non-fatal myocardial infarction	Low target 14/615	High target 19/618	0.74 (95%CI: 0.37, 1.46)	-0.01 (95%CI: -0.03, 0.01)
	All myocardial infarctions	Low target 42/615	High target 41/618	1.03 (95%CI: 0.68, 1.56)	0.00 (95%CI: -0.03, 0.03)
	Stroke	Low target 9/615	High target 14/618	0.65 (95%CI: 0.28, 1.48)	-0.01 (95%CI: -0.02, 0.01)
	Seizures	Low target 26/615	High target 23/618	1.14 (95%CI: 0.66, 1.97)	0.00 (95%CI: -0.02, 0.03)
	Hyperkalaemia	Low target 2/615	High target 3/618	0.67 (95%CI: 0.11, 4.00)	0.00 (95%CI: -0.01, 0.01)
	Access thrombosis	Low target 176/615	High target 243/618	0.73 (95%CI: 0.62, 0.85)	-0.11 (95%CI: -0.16, -0.05)
	Hypertension	Low target 116/618	High target 112/615	1.03 (95%CI: 0.82, 1.30)	0.01 (95%CI: -0.04, 0.05)
	Hyperkalaemia	Low target 1/21	High target 2/23	0.55 (95%CI: 0.05, 5.61)	-0.04 (95%CI: -0.19, 0.11)
	Hypertension	Low target 5/23	High target 8/21	0.57 (95%CI: 0.22, 1.47)	-0.16 (95%CI: -0.43, 0.10)
	Number with silent ischaemia	4/15	3/16	1.42 (95%CI: 0.38, 5.33)	0.08 (95%CI: -0.22, 0.37)
	Access thrombosis	Low target 1/40	High target 7/38	0.14 (95%CI: 0.02, 1.05)	-0.16 (95%CI: -0.29, -0.03)
	Hypertension	Low target 3/40	High target 10/38	0.29 (95%CI: 0.08, 0.96)	-0.19 (95%CI: -0.35, -0.03)
	Hypertension	Low target 3/8	High target 8/12	0.56 (95%CI: 0.21, 1.50)	-0.29 (95%CI: -0.35, -0.03)
Conlon <i>et al.</i> , 2000 ⁴¹	CV event	Low target 47/302	High target 58/300	0.80 (95%CI: 0.57, 1.14)	-0.04 (95%CI: -0.10, 0.02)
Canadian Erythropoietin Study Group, 1991 ¹⁷	Progression of CKD	Low target 163/302	High target 166/300	0.98 (95%CI: 0.84, 1.13)	-0.01 (95%CI: -0.09, 0.07)
Clyne & Jogestrand, 1992 ²⁹	Hypertension	Low target 59/302	High target 89/300	0.66 (95%CI: 0.49, 0.88)	-0.10 (95%CI: -0.17, -0.03)
	Nervous system disorders	Low target 53/302	High target 77/300	0.68 (95%CI: 0.50, 0.93)	-0.08 (95%CI: -0.15, -0.02)
Druke <i>et al.</i> , 2006 ⁸	CV event	Low target 47/302	High target 58/300	0.80 (95%CI: 0.57, 1.14)	-0.04 (95%CI: -0.10, 0.02)
	Progression of CKD	Low target 163/302	High target 166/300	0.98 (95%CI: 0.84, 1.13)	-0.01 (95%CI: -0.09, 0.07)
	Hypertension	Low target 59/302	High target 89/300	0.66 (95%CI: 0.49, 0.88)	-0.10 (95%CI: -0.17, -0.03)
	Nervous system disorders	Low target 53/302	High target 77/300	0.68 (95%CI: 0.50, 0.93)	-0.08 (95%CI: -0.15, -0.02)

Table 5 Continued

Study ID	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Foley <i>et al.</i> , 2000 ⁴²	Overall mortality	Low target 3/73	High target 4/73	0.75 (95%CI: 0.17, 3.23)	-0.01 (95%CI: -0.08, 0.06)
	Serious CV events	Low target 3/73	High target 4/73	0.75 (95%CI: 0.17, 3.23)	-0.01 (95%CI: -0.08, 0.06)
	Access thrombosis	Low target 10/73	High target 6/73	1.67 (95%CI: 0.64, 4.35)	0.05 (95%CI: -0.05, 0.16)
Furland <i>et al.</i> , 2003 ¹²	All-cause mortality	Low target 27/200	High target 29/216	1.01 (95%CI: 0.62, 1.64)	0.00 (95%CI: -0.06, 0.07)
Kleinman <i>et al.</i> , 1989 ²⁵	Cardiovascular-related mortality	Low target 16/200	High target 24/216	1.72 (95%CI: 0.39, 1.32)	-0.03 (95%CI: -0.09, 0.03)
	Non-fatal myocardial infarction	Low target 0/7	High target 1/7	0.33 (95%CI: 0.02, 7.02)	-0.14 (95%CI: -0.46, 0.18)
	Hyperkalaemia	Low target 0/7	High target 1/7	0.33 (95%CI: 0.02, 7.02)	-0.14 (95%CI: -0.46, 0.18)
Kuriyama <i>et al.</i> , 1997 ⁴⁴	Overall mortality	Low target 2/31	High target 1/42	2.71 (95%CI: 0.26, 28.56)	0.04 (95%CI: -0.06, 0.14)
	Fatal myocardial infarction	Low target 1/31	High target 0/42	4.03 (95%CI: 0.17, 95.76)	0.03 (95%CI: -0.05, 0.11)
	Stroke	Low target 1/31	High target 0/42	4.03 (95%CI: 0.17, 95.76)	0.03 (95%CI: -0.05, 0.11)
Parfrey <i>et al.</i> , 2005 ¹⁰	All-cause mortality	Low target 20/300	High target 13/296	1.52 (95%CI: 0.77, 2.99)	0.02 (95%CI: -0.01, 0.06)
	Hypertension	Low target 110/300	High target 120/296	0.90 (95%CI: 0.74, 1.11)	-0.04 (95%CI: -0.12, 0.04)
	Any adverse events	Low target 281/300	High target 284/296	0.98 (95%CI: 0.94, 1.01)	-0.02 (95%CI: -0.06, 0.01)
	Arteriovenous fistula thrombosis	Low target 23/300	High target 30/296	0.76 (95%CI: 0.45, 1.27)	-0.02 (95%CI: -0.07, 0.02)
Revicki <i>et al.</i> , 1995 ⁴⁶	All cause mortality	Low target 1/40	High target 0/43	3.22 (95%CI: 0.13, 76.82)	0.03 (95%CI: -0.04, 0.09)
	Fatal myocardial infarction	Low target 1/40	High target 0/43	3.22 (95%CI: 0.13, 76.82)	0.03 (95%CI: -0.04, 0.09)
	Hypertension	Low target 4/40	High target 11/43	0.39 (95%CI: 0.14, 1.13)	-0.16 (95%CI: -0.32, 0.00)
Singh <i>et al.</i> , 2006 ⁹	Composite events (death, MI, hospitalisation for congestive heart failure without RRT, stroke)	Low target 97/717	High target 125/715	0.73 (95%CI: 0.57, 0.93)	-0.05 (95%CI: -0.08, -0.01)
	Mortality	Low target 36/717	High target 52/715	0.69 (95%CI: 0.46, 1.04)	-0.02 (95%CI: -0.05, 0.00)
	Myocardial infarction	Low target 20/717	High target 18/715	1.11 (95%CI: 0.59, 2.08)	0.00 (95%CI: -0.01, 0.02)
	Stroke	Low target 12/717	High target 12/715	1.00 (95%CI: 0.45, 2.20)	0.00 (95%CI: -0.01, 0.01)
	Thrombovascular events	Low target 120/688	High target 126/686	0.95 (95%CI: 0.76, 1.19)	-0.01 (95%CI: -0.05, 0.03)
Teehan <i>et al.</i> , 1990 ³⁸	Hypertension	Low target 6/31	High target 20/68	0.66 (95%CI: 0.29, 1.48)	-0.10 (95%CI: -0.28, 0.08)