NCGC National Clinical Guideline Centre

Anaemia Management in Chronic Kidney Disease

Rapid Update 2011

Clinical Guideline

Methods, evidence and recommendations

February 2011

Commissioned by the National Institute for Health and Clinical Excellence

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Rapid update 2011

This is a rapid partial update of the 2006 clinical guideline on Anaemia Management in Chronic Kidney Disease. The full guideline is subject to review for a complete update in 2012.
The sections updated in 2011 are:

- Guideline development group and scope
- Methodology
- Diagnostic role of Hb levels
- Optimal Hb levels
- Health economic appendix

All other sections and recommendations from the 2006 guideline remain unchanged.
The content of other sections has not been amended and we have integrated these new sections into the relevant chapters of the old publication. This has inevitably led to inconsistencies in style of write up for reviews. New recommendations (without any gradings) have been added to, or replaced, existing recommendations (which do have gradings).
New or amended sections of the guideline are highlighted in a pale orange box and have an 'Updated 2011' bar in the left hand margin.

Update 2011

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Foreword

Chronic kidney disease (CKD) is not the most common cause of anaemia in the UK, but data from different sources suggest that nationally there are around 100,000 people with the combination of CKD and a low haemoglobin level. Anaemia in this context is important because it contributes significantly to the heavy symptom burden of CKD, and because it is potentially reversible with appropriate treatment, including erythropoietin. Erythropoietin is naturally produced by the kidneys and has been available in synthetic form for the treatment of anaemia of CKD since 1989, but it remains a fairly expensive product and its usage is not straightforward. Moreover, it will not necessarily be the only therapy required for optimal treatment. Against this background, the present guideline has been commissioned to address the appropriate management of anaemia of CKD for patients in the NHS.

The guideline has been produced using standard NICE methodology[221], and is therefore explicitly evidence-linked. Following a comprehensive literature search and evaluation of research papers, a Guideline Development Group (GDG) comprising clinical experts and patient and carer representatives assessed the evidence and used it to produce a detailed set of recommendations. This was no easy task, but one which the GDG have carried out diligently, thoroughly and with patient good humour. They have been a pleasure to work with and all at the National Collaborating Centre for Chronic Conditions are grateful to them.

The guideline recommendations cover many aspects of anaemia management in CKD, but some deserve emphasis. The thresholds at which treatment should be considered receive deserved attention, as do target values for haemoglobin. The GDG were clear that treatment, including administration of erythropoiesis stimulating agents, should be considered for all ages when there is the prospect of improving physical function and quality of life. The importance of correctly managing iron status is emphasised as well as the role of erythropoiesis stimulating agents. The GDG also stressed the importance of agreeing a detailed plan with patients regarding all aspects of delivery of treatment.

There is no doubt that symptoms would be improved in many patients with CKD if anaemia were to be managed optimally. We hope and expect that this guideline will make a significant contribution to improving the lives of the patients who suffer from this debilitating condition.

Dr Bernard Higgins MD FRCP

Director, National Collaborating Centre for Chronic Conditions

Contents

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Ms Jane Alderdice was invited to contribute at a specific meeting as an expert representing the British Dietetic Association, but was not a full member of the GDG

Dr Luigi Gnudi acted as a deputy for Dr Stephen Thomas at a GDG meeting, representing the Royal College of Physicians

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Update 2011

Acknowledgments [2006]

The Guideline Development Group is grateful to the following for their valuable contributions to the development of this guideline:

- Dr Bernard Higgins, Director, NCC-CC
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- Mr Derek Lowe, Medical Statistician, Astraglobe Ltd
- Ms Jill Parnham, Manager, NCC-CC
- Mrs Susan Varney, Research Fellow, NCC-CC
- Colleagues working on the Health Technology Assessment of erythropoiesis stimulating agents for cancer treatment-induced anaemia.

Update 2011

Acknowledgments [2011]

The development of this guideline was greatly assisted by the following people:

Fatema Limbada (NCGC Project Coordinator); Vanessa Nunes (NCGC Senior Research Fellow and Project Manager); Taryn Krause (NCGC Senior Project Manager); Jill Cobb (NCGC Information Scientist); Robert Pitcher (NCGC Research fellow); Bernard Higgins (NCGC Clinical Director); Sarah Dunsdon (NICE Commissioning Manager); Linda Landells (NICE Editor); Stefanie Reken (NICE Health Economist); Andrew Gyton (NICE Guidelines Coordinator).

1 Introduction

1.1 Definition of anaemia

Internationally anaemia is defined as a state in which the quality and/or quantity of circulating red blood cells are below normal. Blood haemoglobin (Hb) concentration serves as the key indicator for anaemia because it can be measured directly, has an international standard, and is not influenced by differences in technology. However, because haemoglobin values in healthy individuals within a population show a normal distribution, a certain number of healthy individuals will fall below a given cut-off point.

Conventionally anaemia is defined as a haemoglobin concentration lower than the established cut off defined by the World Health Organization (WHO)[341], and different biological groups have different cut-off haemoglobin values below which anaemia is said to be present. This cutoff figure ranges from 11 grams per decilitre (g/dl) for pregnant women and for children between 6 months and 5 years of age, to 12 g/dl for non-pregnant women, and to 13 g/dl for men (Table 1.1). No downward adjustment for the elderly is made for age. Although there is a theoretical basis for a fall in male haemoglobin levels with age, because of reduced testosterone production, this is clearly not the case for women. Furthermore there is accumulating evidence that anaemia reflects illness and is associated with adverse outcomes in the elderly[125].

Table 1.1: Haemoglobin cut offs to define anaemia in people living at sea level[341]

Age or gender group	Haemoglobin below: (g/dl)
Children	
6 months to 5 years	11.0
5 to 11 years	11.5
12 to 14 years	12.0
Non-pregnant females >15 years	12.0
Men >15 years	13.0

In the Cardiovascular Health Study 8.5% of participants were anaemic by WHO criteria. Those who were anaemic had a greater prevalence of associated comorbidity and significantly higher 11-year death rates than those without anaemia (57% and 39% respectively, $p \leq 0.001$). The strongest correlates of anaemia were low body mass index, low activity level, fair or poor self-reported health, frailty, congestive heart failure, and stroke or transient ischemic attack. Anaemia was also associated with higher concentrations of creatinine, C-reactive protein, and fibrinogen, and lower levels of albumin and white blood cell count[345].

In addition to gender, age, and pregnancy status, other factors influence the cut-off values for haemoglobin concentration. These include altitude, race, and whether the individual smokes. Although altitude is not a factor in patients in England, ethnicity may influence the cut-off values for haemoglobin concentration.

Data from the USA show that healthy people of African extraction of all age groups at all times, except during the perinatal period, have haemoglobin concentrations 0.5–1.0 g/dl below those of white people, a difference independent of iron-deficiency and socioeconomic factors[70,116,142,243,250] Haemoglobin concentration increases in smokers because of the formation of carboxyhaemoglobin, which has no oxygen transport capacity[320].

The US Centers for Disease Control and Prevention have developed a smoking-specific haemoglobin adjustment to define anaemia in smokers (Table 1.2) and suggest that these values should be subtracted from observed haemoglobin values[287].

Table 1.2: Haemoglobin adjustment for smokers

Amount smoked	Haemoglobin adjustment (g/dl)
½–1 packs/day	0.3
1–2 packs/day	0.5
>2 packs/day	0.7
All smokers	0.3

1.2 Chronic kidney disease: definition and prevalence

The Renal National Service Framework[79,80] has adopted the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of chronic kidney disease (CKD)[299].This classification divides CKD into five stages (Table 1.3) defined by evidence of kidney damage and level of renal function as measured by glomerular filtration rate (GFR).

Table 1.3: Stages of chronic kidney disease

Stage	GFR (ml/min/1.73m2)	Description
1	>90	Normal or increased GFR, with other evidence of kidney damage
2	60–89	Slight decrease in GFR, with other evidence of kidney damage
3	30–59	Moderate decrease in GFR, with or without other evidence of kidney damage
4	15–29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure

Stage 5 CKD may be described as established renal failure (also called end stage renal failure), and is CKD which has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) will be required to maintain life. Established renal failure is an irreversible, long-term condition. A small number of people with established renal failure may choose conservative management only.

Conventionally, the total number of people receiving renal replacement therapy has been taken as a proxy measure for the prevalence of established renal failure. The National Service Framework (NSF) for renal services estimates that more than 27,000 people were receiving renal replacement therapy in England in 2001. Approximately one-half of these had a functioning transplant and the remainder were on dialysis. It is predicted that numbers will rise to around 45,000 over the next 10 years. However, the most recently published Renal Registry Report (2004) highlights that in the UK there were over 37,000 patients receiving renal replacement therapy during 2003, a prevalence of 632 per million population. Of these, 46% had a functioning transplant and the remainder were receiving dialysis treatment[265].

Data from the third US National Health and Nutrition Examination Survey (NHANES III) suggests that overall 11% of the population have some degree of kidney disease: 3.3% of the population are in stage 1 CKD, 3.0% in stage 2 CKD, 4.3% in stage 3 CKD, 0.2% in stage 4 CKD and 0.2% in stage 5 CKD[320]. A similar population prevalence of stage 3–5 CKD has recently been described for England from data derived from primary care records[73]. It is estimated that 4.9% of the population are in stage 3–5 CKD (estimated GFR less than 60 ml/min/1.73m2), although for methodological reasons this is probably an underestimate.

1.2.1 Is chronic kidney disease a natural consequence of ageing?

For many years glomerular filtration rate has been shown to decline with age. However, is is unclear to what extent these changes are a result of 'normal ageing' or a result of disease processes. The cumulative exposure of the kidney to common causes of chronic kidney disease (atherosclerosis, hypertension, diabetes, heart failure, infection and nephrotoxins) increases with age and it is difficult to separate these from the ageing process.

Only one significant longitudinal study to date has addressed the issue of decreasing GFR with increasing age. In the Baltimore Longitudinal Study of Ageing[182], 446 community-dwelling participants were followed over a period of up to 24 years. Their data suggests that the decline in GFR with increasing age is largely attributable to hypertension, possibly as a consequence of microvascular disease[182]. In the absence of hypertension or other identifiable causes of renal disease, one-third of older participants were noted to have stable GFR over a period of 20 years. In a small percentage of participants, GFR actually increased with ageing.

Similarly, Fliser et al[101] in a cross-sectional study using inulin clearance found heart failure to be a significant factor in the decline of GFR with increasing age. Additionally, both heart failure and hypertension contributed to reductions in renal plasma flow and increases in the filtration fraction and renal vascular resistance.

In a post-mortem study, Kasiske[150] has demonstrated a relationship between the prevalence of sclerotic glomeruli and atherosclerotic vascular disease. Although twice as many patients with significant atherosclerosis had a history of hypertension as those with milder atherosclerosis, hypertension was not found to be independently predictive of glomerulosclerosis.

Further evidence[102] suggests that cumulative dietary protein intake is an important determinant of the fall in GFR. Studies such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have shown that the prevalence of reduced GFR is high in older hypertensive patients. Patients with moderate or severe reduction in GFR in the ALLHAT trial were more likely to have a history of cardiovascular disease and left ventricular hypertrophy compared with those with higher levels of GFR. Even modest reductions in GFR were independently associated with a higher prevalence of cardiovascular disease and left ventricular hypertrophy[261].

The implications are that disease processes for renal disease in older people are similar to those of younger people and that a decline in renal function is not an inevitable consequence of ageing.

1.2.2 Prevalence of anaemia in patients with chronic kidney disease

The importance of anaemia in CKD has become increasingly apparent since the introduction of erythropoietin treatment into clinical practice in the late 1980s. However, until recently it has not been fully appreciated that anaemia begins to develop early in the course of CKD. NHANES III found lower levels of kidney function to be associated with lower haemoglobin levels and a higher prevalence and severity of anaemia[63].

Table 1.4: NHANES III data

eGFR (ml/min/1.73m2)	Median Hb in men (g/dl)	Median Hb in women (g/dl)	Prevalence of anaemia*
60	14.9	13.5	1%
30	13.8	12.2	9%
15	12.0	10.3	33%
* Hb ≤ 12.0 g/dl in men, Hb ≤ 11.0 g/dl in women.			

The UK information concerning the prevalence of anaemia in patients with CKD comes from two studies. The prevalence of diagnosed CKD, predicated by serum creatinine levels of ≥130 µmol/l in women and ≥180 µmol/l in men, was 5,554 per million population (pmp), median age was 82 years (range, 18 to 103 years), and median calculated GFR was 28.0 ml/min/1.73m2 (range, 3.6 to 42.8 ml/min/1.73 m2)[138]. Data for haemoglobin levels were available for 85.6% of patients. Mean haemoglobin concentration was 12.1±1.9 g/dl: 49.6% of men had haemoglobin levels less than 12 g/dl and 51.2% of women had levels less than 11 g/dl. Furthermore, in 27.5% of patients identified, the haemoglobin level was less than 11 g/dl, equivalent to nearly 90,000 of the population based on 2001 Census population figures.

In a larger cross-sectional study abstracting data from 112,215 unselected patients with an age and sex profile representative of the general population, haemoglobin level was weakly correlated with eGFR ($r=0.057$, $p<0.001$)[73]. The population prevalence of stage 3–5 CKD in this study was estimated to be 4.9%. In those patients with stage 3–5 CKD the prevalence of anaemia, defined as a haemoglobin level less than 12 g/dl in men and post-menopausal women and less than 11 g/dl in pre-menopausal women, was 12.0%, haemoglobin level was less than 11 g/dl in 3.8%, equivalent to over 108,000 of the population based on 2001 Census population figures.

1.2.3 Diabetes, CKD and anaemia

It has been known for some years that anaemia exists in patients with diabetes and CKD, and that this anaemia occurs early in the course of diabetic kidney disease and is associated with inappropriately low erythropoietin concentrations[134,160]. Ishimura et al[134] demonstrated that when those with Type 2 diabetes and CKD are compared with those with non-diabetic CKD, despite similarly advanced CKD and similar serum erythropoietin levels, those with Type 2 diabetes were significantly more anaemic.

Similar findings have also been demonstrated in people with Type 1 diabetes and CKD compared with those without diabetes[43]. More recently, in a series of articles based on cross-sectional surveys of patients with diabetes, Thomas and colleagues demonstrated that at all levels of GFR, anaemia was more prevalent in those with diabetes compared with the general population[317], that with increasing albuminuria the prevalence of anaemia was higher at each level of renal function[316], and that levels of erythropoietin were inappropriately low in those with anaemia[315].

Finally, in a report from the Kidney Early Evaluation Programme (KEEP)[88], the prevalence of anaemia in those with diabetes was significantly higher than in those without diabetes in stage 2 and 3 CKD (7.5% vs 5%, $p=0.015$ and 22.2% vs 7.9%, $p<0.001$ respectively). Although the prevalence of anaemia was also higher in those with diabetes in stages 1 and 4 CKD the differences were not significant (8.7% vs 6.9% and 52.4% vs 50% respectively).

1.2.4 Causes of anaemia other than chronic kidney disease

Not all anaemia in patients with CKD will be 'renal anaemia' and causes of anaemia other than CKD should be actively looked for and excluded before a diagnosis of anaemia associated with CKD can be made (Table 1.5)

Table 1.5: Other causes of anaemia in CKD

Chronic blood loss
Iron deficiency
Vitamin B12 or folate deficiency
Hypothyroidism
Chronic infection or inflammation
Hyperparathyroidism

Chronic blood loss
Aluminium toxicity
Malignancy
Haemolysis
Bone marrow infiltration
Pure red cell aplasia

Iron deficiency anaemia is the most common cause of anaemia worldwide, either due to negative iron balance through blood loss (commonly gastrointestinal or menstrual), or to inadequate intake which may be nutritional or related to poor gastrointestinal absorption. Studies in elderly patients (aged over 65 years) show that the 'anaemia of chronic disorders' predominates, accounting for 34% to 44% of causes[126,146,249].

Iron-deficiency is the cause in 15% to 36% of cases and recent bleeding in 7.3%. Vitamin B12 or folate deficiency is the cause in 5.6% to 8.1%, myelodysplastic syndrome and acute leukaemia in 5.6% and chronic leukaemia and lymphoma-related disorders in 5.1%. Other haematological disorders (myelofibrosis, aplastic anaemia, haemolytic anaemia) are the cause in 2.8%, and multiple myeloma in 1.5%.

1.2.5 Pathogenesis of anaemia associated with chronic kidney disease

Although anaemia in patients with CKD may develop in response to a wide variety of causes, erythropoietin deficiency is the primary cause of anaemia associated with CKD. Erythropoietin is predominantly produced by peritubular cells in the kidney and is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Loss of peritubular cells leads to an inappropriately low level of circulating erythropoietin in the face of anaemia.

Other factors in the genesis of renal anaemia include functional or absolute iron deficiency, blood loss (either occult or overt), the presence of uraemic inhibitors (for example, parathyroid hormone, inflammatory cytokines), reduced half-life of circulating blood cells, and deficiencies of folate or Vitamin B12.

1.3 How to use this guideline

The purpose of this guideline is to support clinical judgement, not to replace it. This means the treating clinician should:

- take into consideration any contraindications in deciding whether or not to administer any treatment recommended by this guideline
- consider the appropriateness of any recommended treatment for a particular patient in terms of the patient's relevant clinical and non-clinical characteristics.

Wherever possible, before administering any treatment the treating clinician should follow good practice in terms of:

- discussing with the patient why the treatment is being offered and what health outcomes are anticipated
- highlighting any possible adverse events or side-effects that have been associated with the treatment
- obtaining explicit consent to administer the treatment.

For those recommendations involving pharmacological treatment, the most recent Summary of Product Characteristics should be followed for the determination of:

- indications
- drug dosage
- method and route of administration
- contraindications
- supervision and monitoring
- product characteristics
- except in those cases where guidance is provided within the recommendation itself.

1.4 Recommendations for children with anaemia of CKD

This guideline gives recommendations for both adults and children. Where the recommendations are different for children, details are given separately, see:

- recommendations 33-37 in section 6.9
- recommendations 41-42 in section 6.12.

2 Methodology [2006]

2.1 Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) that:

- offers best clinical advice for anaemia management in chronic kidney disease (AMCKD)
- is based on best published evidence and expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of NHS care provision for anaemia of CKD
- indicates areas suitable for clinical audit
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences.

2.2 Scope

The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the Department of Health and specified those aspects of anaemia of CKD to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by the National Institute for Health and Clinical Excellence (NICE)[220,221]. The full scope is shown in Appendix B.

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The rapid update 2011 scope is also shown in Appendix B:.

2.3 Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with anaemia of CKD and their parents and carers
- patient support groups
- commissioning organisations
- service providers.

2.4 Involvement of people with anaemia of CKD

The NCC-CC was keen to ensure the views and preferences of people with anaemia of CKD and their parents and carers informed all stages of the guideline. This was achieved by:

- having a person with anaemia of CKD and a user organisation representative on the Guideline Development Group (GDG)
- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline.

2.5 Guideline limitations

These include:

- Clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.

2.6 Other work relevant to the guideline

The NCC-CC and NICE are developing a clinical guideline on chronic kidney disease (publication is expected in 2008).

NICE has published technology appraisal guidance on erythropoietin for anaemia induced by cancer treatment. This is available from www.nice.org.uk

2.7 Background

The development of this evidence-based clinical guideline draws on the methods described by the NICE Guideline development methods manual[221] and the methodology pack[217] specifically developed by the NCC-CC for each chronic condition guideline (see www.rcplondon.ac.uk/college/ncc-cc). The developers' role and remit is summarised in Table 2.1.

Table 2.1: Role and remit of the developers

National Collaborating Centre for Chronic Conditions (NCC-CC)	The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the National Institute for Clinical Excellence (NICE). A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.
NCC-CC Technical Team	The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised the following members: GDG Chair GDG Clinical Advisor Information Scientist Research Fellow Health Economist Project Manager.
Guideline Development Group	The GDG met monthly for 12 months (January to December 2005) and comprised a multidisciplinary team of professionals, service users (a person with anaemia of CKD), carers, and user organisation representatives who were supported by the technical team. The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.
Guideline Project Executive (PE)	The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.

	The PE comprised: NCC-CC Director NCC-CC Assistant Director NCC-CC Manager NICE Commissioning Manager Technical Team.
Sign-off workshop	At the end of the guideline development process the GDG met to review and agree the guideline recommendations.
Members of the GDG declared any interests in accordance with the NICE technical manual[221]. A register is available from the NCC-CC for inspection upon request: ncc-cc@rcplondon.ac.uk	

2.8 The process of guideline development

The basic steps in the process of producing a guideline are:

- developing clinical evidence-based questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- grading the evidence statements and recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in Appendix A.

Searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for supplemental papers to inform detailed health economic work (for example modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix A for literature search details.

Appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors, however, there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with:

- NICE methodology as detailed in the 'Guideline development methods – information for National Collaborating Centres and guideline developers' manual[221].
- NCC-CC quality assurance document and systematic review chart, available at: www.rcplondon.ac.uk/college/ncc-cc

Health economic evidence

Areas for health economic modelling were agreed by the GDG after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis on which to formulate recommendations[341]. The criteria for grading evidence and classifying recommendations are shown in Table 2.2.

Evidence tables are available online at www.rcplondon.ac.uk/college/NCC-CC

Table 2.2: Grading the evidence statements and recommendations

Levels of evidence			**Classification of recommendations**
Level	**Type of evidence**	**Class**	**Evidence**
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* Level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		
1−	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation	
2++	High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results.

2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.		*or* Extrapolated evidence from 1++ or 1+.
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or* Extrapolated from 2+ *or* Formal consensus.
		GPP	A good practice point (GPP) is a recommendation based on the experience of the GDG.
Diagnostic study level of evidence and classification of recommendation was also included[221].			

Agreeing the recommendations

The sign-off workshop employed formal consensus techniques[219] to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The sign-off workshop also reached agreement on the following:

- five to ten key priorities for implementation
- five key research recommendations
- algorithms.

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation[221].

Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains:

- Clinical introduction sets a succinct background and describes the current clinical context.
- Methodological introduction describes any issues or limitations that were apparent when reading the evidence base.
- Evidence statements provide a synthesis of the evidence base and usually describe what the evidence showed in relation to the outcomes of interest.
- Health economics presents, where appropriate, an overview of the cost-effectiveness evidence base.
- From evidence to recommendations sets out the GDG decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- Recommendations provide stand alone, action-orientated recommendations.
- Evidence tables are not published as part of the full guideline but are available online at www.rcplondon.ac.uk/college/NCC-CC These describe comprehensive details of the primary evidence that was considered during the writing of each section.

Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication[221]. The registered stakeholders for this guideline are detailed on the NICE website, see www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

The following versions of the guideline are available:

Table 2.3: Versions of this guideline

Full version	Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at **www.rcplondon.ac.uk/pubs/books/AMCKD/**
NICE version	Documents the recommendations without any supporting evidence. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Quick reference guide	An abridged version. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Information for the public	A lay version of the guideline recommendations. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**

Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process, allowing any relevant papers published by 28 September 2005 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately 4 years after publication[221].

2.9 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.10 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

Methodology [2011]

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009[222].

2.11 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome). This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). The PICO questions were drafted by the NCGC technical team, refined and validated by the GDG and based on the key clinical areas identified in the scope (Appendix B:). Further information on the outcome measures follows this section. See table 2.1U.

Table 2.1U: Review questions and outcomes

Chapter	Review question	Outcomes
4	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?	• All-cause mortality. • Cardiovascular mortality. • Increased hospitalisation. • Stroke. • Myocardial infarction. • Left ventricular hypertrophy/left ventricular mass index. • Quality of life indices. • Progression of CKD in non-dialysis patients.
6.9	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?	• All-cause mortality. • Cardiovascular mortality. • CKD progression (studies with non-dialysis patients). • Access thrombosis (for studies with haemodialysis patients). • Stroke. • Myocardial infarction. • Hypertension/blood pressure control. • Left ventricular hypertrophy/left ventricular mass index. • Reduction in transfusion requirements. • Haemoglobin variability. • Quality of life indices.

Update 2011

2.12 Searching for evidence

2.12.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence from 2005 onwards within the published literature in order to answer the review questions as per the Guidelines Manual 2009[222]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. Searches were conducted in core databases, MEDLINE, Embase, Cinahl and the Cochrane Library. All searches were updated on 8th July 2010. No papers after this date were considered. Search strategies were checked against search strategies in the original guideline, reference lists of relevant key papers, search strategies in other systematic reviews and asking the GDG for known studies. Searching for grey literature or unpublished literature was not undertaken. The questions, the study types applied, the databases searched and the years covered can be found in Appendix A:.

2.12.2 Health economic literature search

Update 2011

Systematic literature searches were also undertaken to identify health economic evidence within the published literature relevant to the review questions published since the original guideline. The evidence was identified by conducting a broad search relating to anaemia management in chronic kidney disease in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases from 2005 onwards (the cut-off date for the original guideline was 28th September 2005). Additionally, the search was run in Medline and Embase, with a specific economic filter, from January 2009, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix A:. All searches were updated on 8th July 2010. No papers published after this date were considered.

2.12.3 Request for additional data

Many studies in the optimal Hb review (Section 6.9) reported SF-36 results but did not provide full numerical data for all eight domains. In order to provide data for meta-analysis and mapping of SF-36 to EQ5D for use in the economic analysis, numerical data for all eight domains was requested for studies that either reported the significance of the results but did not report the numerical data or where results for only certain domains on the SF-36 were reported. In addition the authors of one study that reported that SF-36 data was collected and would be reported separately was contacted. The clinical advisor on behalf of the NCGC contacted the lead authors.

Lead authors for six studies in the predialysis population were contacted for further information:

- Four studies[84,251,270,273] that reported some results for SF-36
- One study[277] that reported results graphically at the end of a stabilisation period (4 months) and non-numerically at the end of the following maintenance phase
- One study[176] that reported that SF-36 data was collected and would be reported separately.

Data for two of these six studies[139,271] was provided by the sponsors of the studies.

Lead authors for two dialysis studies were contacted for further information:

- Both studies reported some results for SF-36[35,245]

Data for one of these two studies[15] were provided by the sponsor of the study[15].

2.13 Evidence of effectiveness

The Research Fellow identified potentially relevant studies for each review question from the search results by reviewing titles and abstracts – full papers were then obtained.

Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix G:).

Relevant studies were critically appraised using the appropriate checklist as specified in the Guidelines Manual 2009[222].

Key information about the study's methods and results was extracted into evidence tables (evidence tables are included in Appendix H:).

Summaries of the evidence by outcome were generated (and included in the relevant chapter write-ups).

Where appropriate randomised studies were meta-analysed, and reported in GRADE profiles (for clinical studies) – see below for details.

2.13.1 Inclusion/exclusion

Update 2011

See the review protocols in Appendix G: for full details.

2.13.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes. The continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data was presented as a hazard ratio using the generic invariance method on the Cochrane Review Manger (RevMan5) software. In order to enable pooling with studies that did not report the outcome as a time-to-event, an estimate of the hazard ratio was calculated from the risk ratios using a Microsoft Excel spreadsheet[319]. Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, predefined subgroup analyses for co morbidities (diabetes, heart failure) was carried out. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data (if the reason for lost to follow-up was not due to renal replacement therapy) or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analyses. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as "less than", a conservative approach was undertaken. For example, if the p value was reported as "p ≤0.001", the calculations for standard deviations was based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (September 2009)[6] 'Missing standard deviations' were applied as the last resort.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Data synthesis for prognostic factor reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95% confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5) software. Studies were not combined in a meta-analysis for cohort studies. Heterogeneity between trials was assessed by visual inspection of forest plots. Where appropriate, sensitivity analyses were carried out on the basis of study quality and results were reported as ranges.

2.14 Appraising the quality of evidence by outcomes

Update 2011

The evidence for outcomes from the included studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as two separate tables in this guideline. The "Clinical/Economic evidence- quality assessment" table includes details of the quality assessment while the "Clinical /Economic - results" table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent. Each outcome was examined separately for the quality elements listed and defined in Table 2.2U and each graded using the quality levels listed in Table.2.3U. The main criteria considered in the rating of these elements are discussed below (see section 2.14.1 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 2.4U). The GRADE toolbox is currently designed only for randomised trials and observational studies and hence does not apply to prognostic or diagnostic studies.

Table 2.2U: Descriptions of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.

Quality element	Description
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2.3U: Levels for quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 2.4U: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Update 2011

2.14.1 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

A quality rating was assigned, based on the study design. RCTs start as HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.

The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated down -1 or -2 points respectively.

The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.

The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections.

2.14.2 Study limitations

The main limitations for randomised controlled trials are listed in Table 2.5U.

Table 2.5U: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • carry-over effects in cross-over trials • recruitment bias in cluster-randomised trials

Update 2011

2.14.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

2.14.4 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

Update 2011

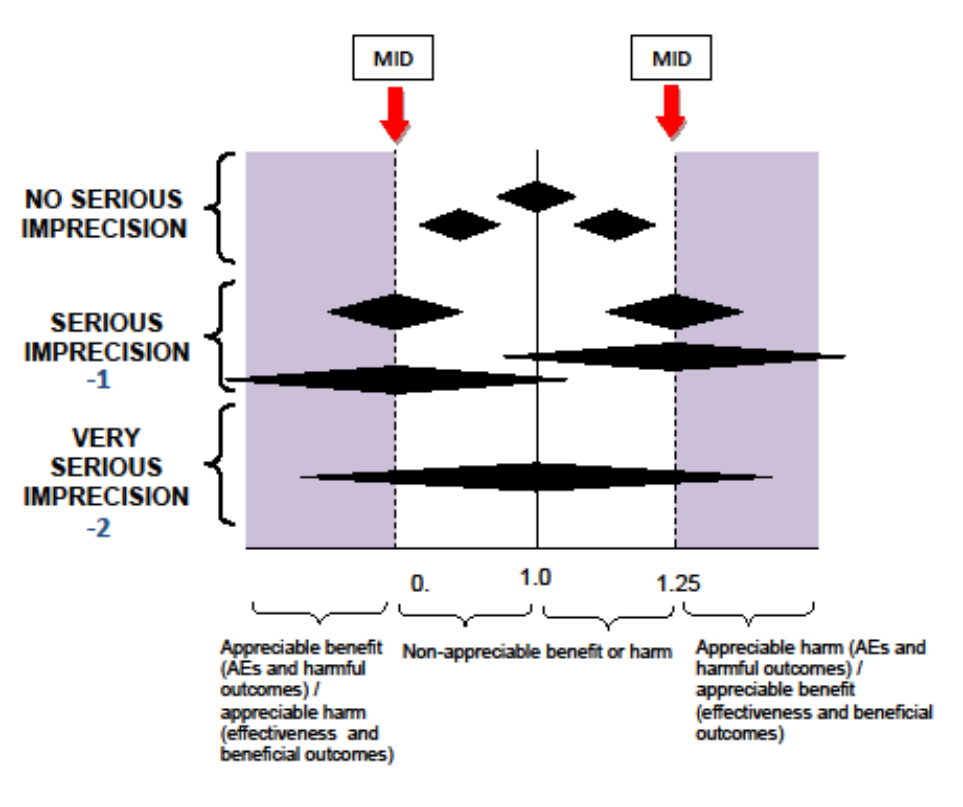
2.14.5 Imprecision

The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect as outlined in Table 2.6U, an illustrative explanation of imprecision is shown in figure 2.1U.

Table 2.6U: Criteria applied to determine precision

Dichotomous and continuous outcomes
1. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) does not cross the threshold for appreciable benefit or harm defined as precise Rating for precision: 'no serious imprecision'
2. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) If the 95% confidence interval crosses either minimal important difference (MID) threshold, defined as imprecise Rating for precision: 'serious'
3. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) crosses both the line of appreciable benefit and harm, defined as imprecise Rating for precision: 'very serious'

Figure 2.1U An illustrative explanation of imprecision



Update 2011

MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms.

The MIDs for the outcomes in the guideline are shown in table 2.7U. The MID's for the outcomes were based on the advice from the clinical advisor, Chair and GDG for the guideline.

Table 2.7U

Outcome	Relative risk reduction
All-cause mortality	5%
CV mortality	5%
Progression of CKD	5 ml/min
Access thrombosis	20%
Transfusion requirements	25%
Stroke	5%
MI	5%
Hypertension	10%
Change in LVMI	25%

For quality of life on the SF-36 there were no published studies reporting the minimal important difference for all the SF-36 domains in the CKD population. One study[41] which used a dataset of patients with chronic conditions (cardiovascular, musculo-skeletal, respiratory, uro-genital [including kidney disease], and other disorders) recommended a MID of 5 points on the vitality domain of the

SF-36 in patients groups with an average score approaching one standard deviation below the general population average. One study[35] reported an increase of 7.2 points was a clinically meaningful increase in the score on the physical-function scale. As there was limited information on MIDs for all domains of the SF-36 in the literature, a distribution-based method[267] of estimation of MID was utilised where MID is approximately 1/2 of the standard deviation or is approximately one standard error of measurement.

2.15 Evidence of cost-effectiveness [2011]

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook:

- a systematic review of the economic literature
- new cost-effectiveness analysis in priority areas.

2.15.1 Literature review [2011]

The Health Economist:

- Identified potentially relevant studies for each review question for the update from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual[222] .
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix H:).
- Generated summaries of the evidence .

Update 2011

2.15.2 Inclusion/exclusion [2011]

Full economic evaluations (cost-effectiveness, cost¬–utility, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence. The same population and intervention criteria were applied as in the clinical review.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-Organisation for Economic Co-operation and development [OECD] country).

Remaining studies were prioritised for inclusion based on their relative applicability to the current UK NHS situation and development of this guideline, and the study limitations. For example, if a high quality, directly applicable UK analysis is available other less relevant studies may not be included. Where exclusions occurred on this basis, this is noted in the relevant evidence section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix H:)[222] and the health economics research protocol in Appendix G:.

2.15.3 Undertaking new health economic analysis [2011]

Update 2011

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See the Health Economic Appendix C: for details of the health economic analysis undertaken for the guideline.

3 Key messages of the guideline

3.1 Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

When to begin treating the anaemia

Update 2011

- Consider investigating and managing anaemia in people with CKD if:
  - their Hb level falls to 11 g/dl or less (or 10.5 g/dl or less if younger than 2 years) **or**,
  - they develop symptoms attributable to anaemia(such as tiredness, shortness of breath, lethargy and palpitations). **[new 2011]**

Who should receive ESAs

- Treatment with erythropoiesis-stimulating agents (ESAs) should be offered to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function.**[2006]**

Agreeing a plan for ESA treatment

- ESA treatment should be clinically effective, consistent and safe in people with anaemia of CKD. To achieve this, the prescriber and patient should agree a plan that is patient-centred and includes:
  - continuity of drug supply
  - flexibility of where the drug is delivered and administered
  - the lifestyle and preferences of the patient
  - cost of drug supply
  - desire for self-care where appropriate
  - regular review of the plan in light of changing needs. **[2006]**

Aspirational range and action thresholds for Hb

Update 2011

- When determining individual aspirational Hb ranges for people with anaemia of CKD, take into account:
  - patient preferences
  - symptoms and comorbidities
  - the required treatment. **[new 2011]**

- The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.
  - Typically maintain the aspirational Hb range between 10 and 12 g/dl for adults, young people and children aged 2 years and older, and between 9.5 and 11.5 g/dl for children younger than 2 years of age, reflecting the lower normal range in that age group.
  - To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 0.5 g/dl of the range's limits). **[new 2011]**

Age

- Age alone should not be a determinant for treatment of anaemia of CKD. **[2006]**

Iron supplementation: aspirational ranges

- People receiving ESA maintenance therapy should be given iron supplements to keep their:
  - serum ferritin levels between 200 and 500 micrograms/l in both haemodialysis and non-haemodialysis patients, and either
    - transferrin saturation level above 20% (unless ferritin is greater than 800 micrograms/l) or
    - percentage hypochromic red cells (%HRC) less than 6% (unless ferritin is greater than 800 micrograms/l).

In practice it is likely this will require intravenous iron. **[2006]**

3.2 Complete list of recommendations

1. Consider investigating and managing anaemia in people with CKD if:
   - their Hb level falls to 11 g/dL or less (or 10.5 g/dL or less if younger than 2 years) or,
   - they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations). [new 2011]
2. An estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73m2 should trigger investigation into whether anaemia is due to CKD. When the eGFR is ≥60 ml/min/1.73m2 the anaemia is more likely to be related to other causes. [D]
3. Serum ferritin levels may be used to assess iron deficiency in people with CKD. Because serum ferritin is an acute phase reactant and frequently raised in CKD, the diagnostic cut-off value should be interpreted differently to non-CKD patients. [A(DS)]
4. Iron deficiency anaemia should be:
   - diagnosed in people with stage 5 CKD with a ferritin level of less than 100 µg/l
   - considered in people with stage 3 and 4 CKD if the ferritin level is less than 100 µg/l. [D(GPP)]
5. In people with CKD who have serum ferritin levels greater than 100 µg/l, functional iron deficiency (and hence those patients who are most likely to benefit from intravenous iron therapy) should be defined by:
   - percentage of hypochromic red cells >6%, where the test is available or
   - transferrin saturation <20%, when the measurement of the percentage of hypochromic red cells is unavailable. [B(DS)]
6. Measurement of erythropoietin levels for the diagnosis or management of anaemia should not be routinely considered for people with anaemia of CKD. [D(GPP)]
7. ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency. [D(GPP)]
8. In people with functional iron deficiency, iron supplements should be given concurrently when initiating ESA therapy. [D(GPP)]

9. In people treated with iron, serum ferritin levels should not rise above 800 µg/l. In order to prevent this, the dose of iron should be reviewed when serum ferritin levels reach 500 µg/l. [D (GPP)]

10. The pros and cons of a trial of anaemia management should be discussed between the clinician, the person with anaemia of CKD and their families and carers if applicable. [D (GPP)]

11. ESAs need not be administered where the presence of comorbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia. [D (GPP)]

12. A trial of anaemia correction should be initiated when there is uncertainty over whether the presence of comorbidities, or the prognosis, would negate benefit from correcting the anaemia with ESAs. [D (GPP)]

13. Where a trial of ESA therapy has been performed, the effectiveness of the trial should be assessed after an agreed interval. Where appropriate, a mutual decision should be agreed between the clinician, the person with anaemia of CKD and their families and carers on whether or not to continue ESA therapy. [D (GPP)]

14. All people started on ESA therapy should be reviewed after an agreed interval in order to decide whether or not to continue using ESAs. [D(GPP)]

15. Supplements of vitamin C, folic acid or carnitine should not be prescribed as adjuvants specifically for the treatment of anaemia of CKD. [A]

16. In people with anaemia of CKD, androgens should not be used to treat the anaemia. [C]

17. In people with anaemia of CKD, clinically relevant hyperparathyroidism should be treated to improve the management of the anaemia. [C]

18. People offered ESA therapy, and their GPs, should be given information about why ESA therapy is required, how it works, and what benefits and side effects may be experienced. [D]

19. When managing the treatment of people with anaemia of CKD, there should be agreed protocols defining roles and responsibilities of healthcare professionals in primary and secondary care. [D(GPP)]

20. People receiving ESA therapy should be informed about the importance of concordance with therapy and the consequences of poor concordance. [D]

21. When prescribing ESA therapy, healthcare professionals should take into account patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA and storage. [D(GPP)]

22. In order for people to self-administer their ESA in a way that is clinically effective and safe, arrangements should be made to provide ready, reasonable and uninterrupted access to supplies. [D]

23. Culturally and age-appropriate patient education programmes should be offered to all people diagnosed with anaemia of CKD and their families and carers. These should be repeated as requested, and according to the changing circumstances of the patient. They should include the following key areas:
    - practical information about how anaemia of CKD is managed
    - knowledge (eg about symptoms, iron management, causes of anaemia, associated medications, phases of treatment)
    - professional support (eg contact information, community services, continuity of care, monitoring, feedback on progress of results)

- lifestyle (eg diet, physical exercise, maintaining normality, meeting other patients)
- adaptation to chronic disease (eg previous information and expectations, resolution of symptoms). [D(GPP)]

24. Treatment with ESAs should be offered to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. [A]

25. In people with anaemia of CKD, in whom kidney transplant is a treatment option, blood transfusions should be avoided where possible. [D]

26. In people with anaemia of CKD there may be situations where a transfusion is indicated clinically. In these cases, the relevant haematology guidelines[51] should be followed. [D (GPP)]

27. The choice of ESA should be discussed with the person with anaemia of CKD when initiating treatment and at subsequent review, taking into consideration the patient's dialysis status, the route of administration and the local availability of ESAs. There is no evidence to distinguish between ESAs in terms of efficacy. [A]

28. People with anaemia of CKD should have access to a designated contact person or persons who have principal responsibility for their anaemia management and who have skills in the following activities:
    - monitoring and managing a caseload of patients in line with locally agreed protocols
    - providing information, education and support to empower patients and their families and carers to participate in their care
    - coordinating an anaemia service for people with CKD, working between secondary and primary care and providing a single point of contact, to ensure patients receive a seamless service of the highest standard
    - prescribing medicines related to anaemia management and monitoring their effectiveness. [D(GPP)]

29. ESA therapy should be clinically effective, consistent and safe in people with anaemia of CKD. To achieve this, the prescriber and patient should agree a plan that is patient-centred and includes: [D (GPP)]
    - continuity of drug supply
    - flexibility of where the drug is delivered and administered
    - the lifestyle and preferences of the patient
    - cost of drug supply
    - desire for self-care where appropriate
    - regular review of the plan in light of changing needs.

30. The patient with anaemia of CKD and the prescriber should agree (and revise as appropriate) the route of administration of ESAs, taking into account the following factors:
    - patient population (eg haemodialysis patients)
    - pain of injection
    - frequency of administration
    - the lifestyle and preferences of the patient
    - efficacy (eg subcutaneous vs intravenous administration, or long-acting vs short-acting preparations)
    - cost of drug supply. [C]

31. The prescriber should take into account that when using short-acting ESAs, subcutaneous injection allows the use of lower doses of drugs than intravenous administration. [A]

32. When correcting anaemia of CKD, the dose and frequency of ESAs should be:
    - determined by the duration of action and route of administration of the ESA [B]
    - adjusted to keep the rate of Hb increase between 1 and 2g/dl/month. [D(GPP)]

33. Age alone should not be a determinant for treatment of anaemia of CKD. (D(GPP))

34. When determining individual aspirational Hb ranges for people with anaemia of CKD, take into account:
    - patient preferences
    - symptoms and comorbidities
    - the required treatment. [new 2011]

35. The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.
    - Typically maintain the aspirational Hb range between 10 and 12 g/dl for adults, young people and children aged 2 years and older, and between 9.5 and 11.5 g/dl for children younger than 2 years of age, reflecting the lower normal range in that age group.
    - To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 0.5 g/dl of the range's limits). [new 2011]

36. Consider accepting Hb levels below the agreed aspirational range if:
    - high doses of ESAs are required to achieve the aspirational range or
    - the aspirational range is not achieved despite escalating ESA doses. [new 2011]

37. Consider accepting Hb levels above the agreed aspirational range when:
    - these develop with iron therapy alone or
    - these develop with low doses of ESAs or
    - it is thought that the person might benefit (for example, if they have a physically demanding job) or
    - the absolute risk of cerebrovascular disease is thought to be low. [new 2011]

38. Iron status should be optimised before or coincident with the initiation of ESA administration and during maintenance treatment with ESAs. [C]

39. Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists is not precluded, but if they are used, an increase in ESA therapy should be considered. [D]

40. Haemoglobin measurements should be taken into account when determining the dose and frequency of ESA administration:
    - The cause of an unexpected change in Hb level should be investigated (that is, intercurrent illness, bleeding) to enable intervention and iron status should be optimised.
    - ESA dose and/or frequency should be increased or decreased when Hb measurements fall outside action thresholds (usually below 10.5g/dl or above 11.5g/dl), or for example when the rate of change of haemoglobin suggests an established trend (eg >1g/dl/month). [D(GPP)]

41. People with anaemia of CKD who are receiving ESAs should be given iron therapy to maintain: [D(GPP)]

- serum ferritin >200 µg/l
- transferrin saturation >20% (unless ferritin >800 µg/l)
- hypochromic red blood cells <6% (unless ferritin >800 µg/l)

Most patients will require 600–1,000 mg of iron for adults or equivalent doses for children, in a single or divided dose depending on the preparation. Patients with functional iron deficiency should be treated with intravenous iron. Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron. In appropriate circumstances, iron treatment can also be administered in the community.

42. In non-dialysis patients with anaemia of CKD in whom there is evidence of absolute or functional iron deficiency, this should be corrected before deciding whether ESA therapy is necessary. [D(GPP)]

43. Once ferritin levels are greater than 200 µg/l and HRC is less than 6% or TSAT is greater than 20%, people with anaemia of CKD who are receiving ESAs should be given maintenance iron. The dosing regimen will depend on modality, for example haemodialysis patients will require the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children of 1 mg/kg/week). Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron. [D(GPP)]

44. People receiving ESA maintenance therapy should be given iron supplements to keep their:
    - serum ferritin between 200 and 500 µg/l in both haemodialysis patients and non-haemodialysis patients, and either [D]
    - the transferrin saturation level above 20% (unless ferritin > 800 µg/l) or [B]
    - percentage hypochromic red cells (%HRC) less than 6% (unless ferritin > 800 µg/l). [D(GPP)]

In practice it is likely this will require intravenous iron.

45. People with anaemia of CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. The length of time to monitoring of iron status is dependant on the product used and the amount of iron given. [C]

46. Routine monitoring of iron stores should be at intervals of 4 weeks to 3 months. [D(GPP)]

47. In people with anaemia of CKD, haemoglobin should be monitored:
    - every 2–4 weeks in the induction phase of ESA therapy
    - every 1–3 months in the maintenance phase of ESA therapy
    - more actively after an ESA dose adjustment
    - in a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local healthcare systems. [D(GPP)]

48. After other causes of anaemia, such as intercurrent illness or chronic blood loss have been excluded, people with anaemia of CKD should be considered resistant to ESAs when:
    - an aspirational Hb range is not achieved despite treatment with ≥300 IU/kg/week of subcutaneous epoetin or ≥450 IU/kg/week of intravenous epoetin or 1.5 µg/kg/week of darbepoetin, or
    - there is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range [D(GPP)]

49. In people with CKD, pure red cell aplasia (PRCA) is indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. The GDG considered that PRCA should

be confirmed when anti-erythropoietin antibodies are present and there is a lack of pro-erythroid progenitor cells in the bone marrow. [D]

50. In people with anaemia of CKD, aluminium toxicity should be considered as a potential cause of a reduced response to ESAs after other causes such as intercurrent illness and chronic blood loss have been excluded. [C]

51. In haemodialysis patients with anaemia of CKD in whom aluminium toxicity is suspected, a desferrioxamine test should be performed and the patient's management reviewed accordingly. [C]

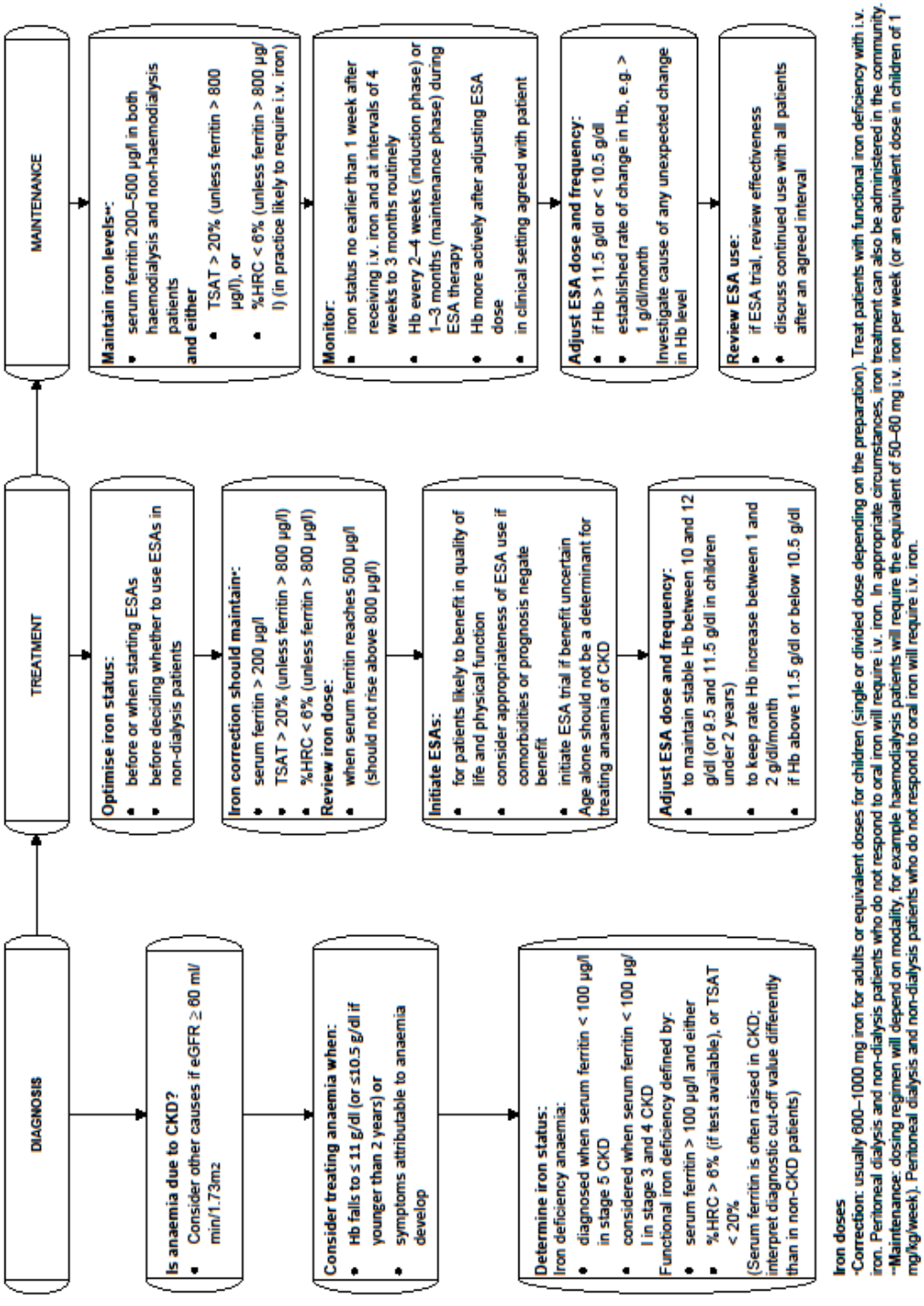
52. Consider specialist referral for ESA-induced PRCA. [2006, amended 2011]

3.3 Algorithm [2011]

Update 2011

The following algorithm replaces all the previous algorithms published in 2006.

The changes the GDG made to the aspirational ranges and the use of ESA to achieve this, meant that the algorithms published in 2006 were no longer relevant, therefore the GDG felt it was safer to delete them and replace with one summary algorithm which includes diagnosis, treatment and maintenance.


DIAGNOSIS
Is anaemia due to CKD?
Consider other causes if eGFR ≥ 60 ml/min/1.73m2
Consider treating anaemia when:
Hb falls to ≤ 11 g/dl (or ≤10.5 g/dl if younger than 2 years) or
symptoms attributable to anaemia develop
Determine iron status:
Iron deficiency anaemia:
diagnosed when serum ferritin < 100 µg/l in stage 5 CKD
considered when serum ferritin < 100 µg/l in stage 3 and 4 CKD
Functional iron deficiency defined by:
serum ferritin > 100 µg/l and either
%HRC > 6% (if test available), or TSAT < 20%
(Serum ferritin is often raised in CKD; interpret diagnostic cut-off value differently than in non-CKD patients)
TREATMENT
Optimise iron status:
before or when starting ESAs
before deciding whether to use ESAs in non-dialysis patients
Iron correction should maintain*:
serum ferritin > 200 µg/l
TSAT > 20% (unless ferritin > 800 µg/l)
%HRC < 6% (unless ferritin > 800 µg/l)
Review iron dose:
when serum ferritin reaches 500 µg/l (should not rise above 800 µg/l)
Initiate ESAs:
for patients likely to benefit in quality of life and physical function
consider appropriateness of ESA use if comorbidities or prognosis negate benefit
initiate ESA trial if benefit uncertain
Age alone should not be a determinant for treating anaemia of CKD
Adjust ESA dose and frequency:
to maintain stable Hb between 10 and 12 g/dl (or 9.5 and 11.5 g/dl in children under 2 years)
to keep rate Hb increase between 1 and 2 g/dl/month
if Hb above 11.5 g/dl or below 10.5 g/dl
MAINTENANCE
Maintain iron levels**:
serum ferritin 200–500 µg/l in both haemodialysis and non-haemodialysis patients
and either
TSAT > 20% (unless ferritin > 800 µg/l), or
%HRC < 6% (unless ferritin > 800 µg/l) (in practice likely to require i.v. iron)
Monitor:
iron status no earlier than 1 week after receiving i.v. iron and at intervals of 4 weeks to 3 months routinely
Hb every 2–4 weeks (induction phase) or 1–3 months (maintenance phase) during ESA therapy
Hb more actively after adjusting ESA dose
in clinical setting agreed with patient
Adjust ESA dose and frequency:
if Hb > 11.5 g/dl or < 10.5 g/dl
established rate of change in Hb, e.g. > 1 g/dl/month
Investigate cause of any unexpected change in Hb level
Review ESA use:
if ESA trial, review effectiveness
discuss continued use with all patients after an agreed interval
Iron doses
*Correction: usually 600–1000 mg iron for adults or equivalent doses for children (single or divided dose depending on the preparation). Treat patients with functional iron deficiency with i.v. iron. Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require i.v. iron. In appropriate circumstances, iron treatment can also be administered in the community.
**Maintenance: dosing regimen will depend on modality, for example haemodialysis patients will require the equivalent of 50–80 mg i.v. iron per week (or an equivalent dose in children of 1 mg/kg/week). Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require i.v. iron.

Update 2011

3.4 Audit criteria [2006, updated 2011]

Table 3.7: Audit criteria

Key priority for implementation	Criterion	Exception
Management of anaemia should be considered in people with anaemia of chronic kidney disease (CKD) when the haemoglobin level is less than or equal to 11 g/dl (or 10.5 g/dl if under 2 years of age) or they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations).	1. % of patients with CKD with recorded Hb ≤11 g/dl (or 10.5 g/dl if under 2 years of age) who were started on iron/ESAs at the time, or at the following appointment.	Documented refusal, contraindications.
Treatment with ESAs should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function.	2. % of patients with ACKD with recorded Hb ≤11 g/dl not on anaemia treatment, with a breakdown of the reasons for it not being offered.	
ESA therapy should be clinically effective, consistent and safe in people with anaemia of CKD. To achieve this, the prescriber and patient should agree a plan which is patient-centred and includes: • provision of a secure drug supply • flexibility of where the drug is delivered and administered • lifestyle and preferences • cost of drug supply • desire for self-care where appropriate • regular review of the plan in light of changing needs.	3. % of patients with ACKD receiving anaemia treatment who are receiving ESAs, with a plan recorded as specified.	
In people with anaemia of chronic kidney disease, treatment should maintain stable haemoglobin (Hb) levels between 10 and 12 g/dl for adults and children aged over 2 years, and between 9.5 and 11.5 g/dl in children aged under 2 years, reflecting the lower normal range in that age group. This should be achieved by: • Considering adjustments to treatment, typically when Hb levels are within 0.5 g/dl of the range's limits. • Taking patient preferences, symptoms and comorbidity into account and revising the aspirational range and action thresholds accordingly.	4. % of patients with diagnosed ACKD who have received treatment for 3 months or longer and, at the time of a cross-sectional audit, have Hb levels between 10 and 12 g/dl for adults and children aged over 2 years, or between 9.5 and 11.5 g/dl in children aged under 2 years.	Patients who have underlying causes for poor response (see section 1.2.4), patients who are in the induction phase of their treatment.

Key priority for implementation	Criterion	Exception
Patients receiving ESA maintenance therapy should be given iron supplements to keep their: • serum ferritin between 200 and 500 µg/l in both haemodialysis patients and non-haemodialysis patients, and either • the transferrin saturation level above 20% (unless ferritin > 800 ug/l) or • percentage hypochromic red cells (%HRC) less than 6% (unless ferritin > 800ug/l). In practice it is likely this will require i.v. iron.	5. % of patients with diagnosed ACKD and on maintenance therapy with ESAs who, at the time of a cross-sectional audit, have: • serum ferritin between 200 and 500 µg/l in both haemodialysis patients and non-haemodialysis patients and either • The transferrin saturation level above 20% (unless ferritin >800 ug/l) or • percentage hypochromic red cells (%HRC) less than 6% (unless ferritin >800ug/l).	

4 Diagnostic evaluation and assessment of anaemia

4.1 Diagnostic role of Hb levels

4.1.1 Clinical introduction [2011]

Update 2011

Why is the haemoglobin level important in patients with CKD? Possible adverse effects of anaemia include reduced oxygen utilisation, increased cardiac output and left ventricular hypertrophy, increased progression of CKD, reduced cognition and concentration, reduced libido and reduced immune responsiveness. How much these adverse effects translate into adverse outcomes such as impaired quality of life, increased hospitalisation, increased cardiovascular events and increased cardiovascular and all-cause mortality has been the subject of debate for several years. What is incontrovertible is that since the introduction of human recombinant erythropoietin for treatment of CKD-related anaemia over 2 decades ago we have had the tools to significantly influence anaemia management. The phenotype of the kidney patient with haemoglobin levels between 5-8 g/dL, rendered massively iron over-loaded and virtually un-transplantable as a result of multiple transfusions, has thankfully become unrecognisable. Attention has shifted from treatment of severe anaemia in dialysis patients to prevention of anaemia non-dialysis and to correction of anaemia to higher levels of haemoglobin.

It is well established that haemoglobin levels fall as kidney function declines but there is significant heterogeneity at each level of kidney dysfunction. Although normal values for haemoglobin in the general population differ by gender this has not been addressed in most study designs of anaemia in kidney disease. Observational data suggest that lower haemoglobin values are associated with increased cardiovascular abnormalities/events, increased hospitalisation, increased mortality, increased transfusion requirements and reduced quality of life. Major criticisms though have been the heterogeneity of such studies and the variation in adjustment for confounders. We do not have randomised controlled trials designed to assess the level of haemoglobin at which we should intervene with treatment but we do have treatment dilemmas. We know from clinical practice that not all patients will necessarily benefit from treatment so at what level of haemoglobin should we consider intervention with anaemia treatment? Should this level differ by age, gender or ethnicity? Should we adopt differing strategies dependent on whether patients are non-dialysis or already receiving renal replacement therapy?

The GDG agreed to address the following question: *In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?*

4.1.2 Methodological introduction

A literature search identified longitudinal,[133,257,336,340] before and after[127,202,205,285] and cohort[60,177,178,186] studies, conducted predominantly in haemodialysis patients.

Four studies[81,144,170,206] had methodological limitations and were excluded from evidence statements.

Notable aspects of the evidence base were:

- No studies were found which specifically addressed the issues of gender and ethnicity and only one study was identified which stratified the study population according to age[205].
- Only two studies included populations over 80 years old[133,178].

- Not all studies reported gender and ethnicity of the participants. Some studies included predominantly male[202,285] or predominantly white participants[60,178] or predominantly male and white participants[81,177]. One study included a population that was 67% African American[133].
- The number of study participants varied greatly, ranging between 7 and over 60,000.

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects, therefore no health economic evidence statements are given.

4.1.3 Methodological introduction [2011]

Update 2011

The GDG noted a change in terminology for the 2011 update concerning predialysis to nondialysis.

A literature search was undertaken to identify papers published from September 2005 onwards. Eight cohort studies[113,163,171,175,199,255,335,339] in nondialysis, haemodialysis and transplant patients were included. Studies not meeting the inclusion criteria were excluded.

Notable aspects of the evidence base:

- No studies were found which reported the interaction of age, gender and ethnicity with Hb/Hct levels.
  - One study[163] included only male patients with subgroup analyses for age and ethnicity. The results were only presented on a forest plot and numerical data were not reported.
- The mean age, where reported, ranged from 51 years[339] to 72 years[171]; one study[175] reported 29% of the included patients were over 75 years.
- The ethnicity of the patients included in the studies comprised mainly of those classified as white. One study[163] reported patients with higher Hb levels were likely to be 'white'.

The outcomes considered in the review are:

- Left ventricular hypertrophy
- Hospitalisation
- Mortality
- Composite outcome (all cause mortality, stroke and MI)
- Cardiac events
- Quality of life
- Stroke
- Progression of CKD

4.1.4 Evidence statements [2006, updated 2011]

These evidence statements are grouped by outcome measure per sub-population of anaemia patients.

Left ventricular hypertrophy

Predialysis patients

In a 1-year study[206] (n=318), a mean decrease in Hb of 0.5 g/dl from baseline of 12.8 ± 1.9 g/dl was found to be one of three factors (including systolic blood pressure and left ventricular (LV) mass index) that was associated with left ventricular hypertrophy (LVH) (OR 1.32, 95% CI 1.1 to 1.59, p=0.004). (Level 2+)

A decrease in LV mass index (p<0.01) was observed after raising haematocrit (Hct) from 23.6 ± 0.5% (Hb ~ 7.8 g/dl) to 39.1 ± 0.8% (Hb ~ 13 g/dl) with epoetin over a time period of 12 months in a small

sample (n=9)[127]. Similarly, in another study[257] (n=11) treatment with epoetin increased Hct levels from 26.3 ± 0.6% (Hb ~ 8.7 g/dl) to 34.4 ± 1.1% (Hb ~ 11.4 g/dl) at 3 months and 34.7 ± 1.3% (Hb ~ 11.5 g/dl) at 6 months. A reduction in LV mass index at month 6 ($p<0.05$), cardiac output ($p<0.05$), cardiac index ($p<0.05$), and an increase in total peripheral resistance ($p<0.05$) at months 3 and 6 of the study were observed. (Level 3)

In two studies,37,41 increased Hct levels with epoetin from 26.3 ± 0.6% (Hb ~ 8.7 g/dl) to 34.7 ± 1.3% (Hb ~ 11.5 g/dl) at 6 months37 and from 23.6 ± 0.5% (Hb ~ 7.8 g/dl) to 39.1 ± 0.8% (Hb ~ 13 g/dl) at 12 months41 found no changes in LV end-diastolic/systolic diameters, interventricular septum thickness, LV posterior wall thickness over 6 months37 or over 12 months.41 (Level 3)

Haemodialysis patients

In a 12 month study[285] where Hb was increased from a baseline level of 6.3 ± 0.8 g/dl to 11.4 ± 1.5 g/dl by epoetin administration, a reduction in LV mass ($p <0.001$), LV end-diastolic volume ($p=0.005$) and LV end diastole ($p=0.003$) was found in patients with baseline LV mass above 210 g. In the same study[285], no significant changes were observed in echocardiography measurements of LV posterior wall, interventricular septum or mean wall thickness. (Level 3)

In a small study[202] (n=7), an increase in Hb from 9.8 ± 1.3 g/dl to 14.2 ± 0.6 g/dl using epoetin over a period of approximately 6 months found a significant reduction in cardiac output ($p<0.01$) and stroke volume ($p<0.01$), which was accompanied with a significant increase in total peripheral resistance ($p<0.05$). However, there was no change in mean arterial pressure. (Level 3)

Update 2011

There were no new relevant studies identified reporting left ventricular hypertrophies in the rapid update review.

Hospitalisation

Haemodialysis patients

A cohort (n=66,761), with data stratified into increasing Hct levels and compared with an Hct level of 33 to 35% over a 1-year follow-up period[60] found the following:

Table 4.1 Summary data from study[60] (Level 2+)

Hct (%)	<30	30 to 32	33 to 35 (Ref)	36 to 38	≥39
Hb (g/dl)	**<10**	**10-10.7**	**11 to 11.7 (Ref)**	**12 to 12.7**	**≥13**
RR of all-cause hospitalisation	1.42	1.21	1	0.78	0.84
RR of hospitalisation from cardiac causes	1.3	1.17	1	0.75	NS
RR of hospitalisation from infections	1.76	1.3	1	0.82	0.62

RR = relative risk; NS = not significant

In a 2.5-year follow-up study[178], participants (n=50,579) were stratified into increasing Hct levels and compared with patients with the arbitrary reference of Hct 34 to 36% (n=22,192), see Tables 4.2 to 4.5.

Table 4.2 Adjusted relative risk of first hospitalisation due to any cardiac disease[178] (Level 2+)

Hct (%)	≤30	31 to 33	34 to 36 (Ref)	37 to 39	≥40
Hb (g/dl)	**≤10**	**10.3-11**	**11.3 to 12 (Ref)**	**12.3 to 13**	**≥13.3**
RR	1.18	1.07	1.00	0.92	0.79
95% CI	Not reported	Not reported	N/A	0.88 to 0.97	0.72 to 0.87

RR = relative risk

Table 4.3 Adjusted relative risk of first hospitalisation due to specific cardiac diseases[178] (Level 2+)

Hct (%)	34 to 36 (Ref)	37 to 39	≥40
Hb (g/dl)	**11.3 to 12 (Ref)**	**12.3-13**	**≥13.3**
RR due to congestive heart failure, fluid overload or cardiomyopathy	1.00	0.85 (95% CI 0.77 to 0.95)	0.80 (95% CI 0.65 to 0.97)
RR due to ischemic heart disease, cerebrovascular disease or circulatory system disease	1.00	N/S	0.81 (95% CI 0.70 to 0.93)
RR due to other cardiac diseases	1.00	N/S	0.76 (95% CI 0.62 to 0.92)

RR = relative risk; NS = not significant

Table 4.4 Adjusted relative risk of first hospitalisation for patients with cardiac comorbid conditions (n=45,166)[178] (Level 2+)

Hct (%)	34 to 36	37 to 39	≥40
Hb (g/dl)	**11.3 to 12**	**12.3-13**	**≥13.3**
Relative risk	1.00	0.93	0.79
95% CI	N/A	0.89 to 0.98	0.71 to 0.87

Table 4.5 Adjusted relative risk of hospitalisation for patients with Hct 37 to 39% without pre-existing cardiac disease (3-year follow-up)[178] (Level 2+)

	RR	P value
All-cause hospitalisation	0.78	<0.0001
Any cardiac hospitalisation	0.74	0.0005

Update 2011

There were no new relevant studies identified in the rapid update review reporting the outcome hospitalisation.

Mortality

Nondialysis patients

Evidence statements:

There is moderate to high quality evidence[163,175,199] to show that:

- low Hb levels [<11 g/dL] compared to high Hb levels [>13 to ≤14 g/dL] are associated with an increased risk of mortality
- low Hb levels [≥11 to ≤12 g/dL] compared to high Hb levels [>13 to ≤14 g/dL] are associated with an increased risk of mortality
- low Hb levels [>12 g/dL] compared to high Hb levels [≥14 g/dL] are not associated with an increased risk of mortality.

There is uncertainty concerning all of the above results.

There is moderate quality evidence[163,175] to show that a decrement in Hb level of 1 g/dL is associated with an increased risk of mortality.

There is moderate quality evidence[335] to show:

- a decrement in Hb level of 1.5 g/dL is associated with an increased risk of mortality in patients with higher Hb levels [>14.5 g/dL] this decrement is associated with a decreased risk of mortality.

There is low quality evidence[171] to show that CHD-mortality is associated with lower Hb quintiles when GFR is estimated using the Cockcroft-Gault method. This effect is not evident when GFR is estimated using the MDRD method.

Update 2011

Evidence report:

Three studies[163,175,199,339] reported the risk for mortality associated with low and high haemoglobin levels. Risk of mortality was assessed over follow-up periods ranging from 16 months[199] to 27 months[175], while overall mortality rates ranged from 0.5% [191/27153][199] to 29% [245/853][163]. Mortality rates were stratified according to Hb ranges in one study[163] [<11 g/dL: 39.0% (68/174); 11.1 to 12 g/dL: 34.2% (74/216); 12.1 to 13 g/dL: 24.9% (50/201); >13 g/dL: 20.2% (53/262)].

An emerging trend suggests that lower Hb levels are associated with an increased risk of mortality compared with higher Hb levels. At higher Hb levels, a significant difference was not observed; however, there is some uncertainty concerning the precision of these effects (figure I.1a to figure I.1c, Appendix I:).

Three studies reported the affect of incremental increases in Hb level on the risk of mortality. The overall mortality rates were: 20% [618/3028][175]; 29% [245/853][163]; 44.6% [748/1678][335].

In one study[175] an decrement of 10 g/L [1 g/dL] in Hb level was associated with a significantly increased risk of mortality in patients with: eGFR <15 mL/min [RR 0.91 (95% CI 0.84-0.99); eGFR of 15-29 mL/min [RR 0.86 (95% CI 0.81-0.92)]; eGFR of 30–59 mL/min [RR 0.81 (95% CI 0.71-0.92)] (figure 1.2a, Appendix B).

An increment of 10 g/L [1 g/dL] in Hb level was also associated with a decreased risk in mortality in a second study[163] [HR 0.86 (95% CI 0.78-0.95)] (figure I.2b, Appendix I:).

A third study[335] reported that an increment of 1.5 g/dL in Hb level was associated with a decreased risk in mortality [HR 0.86 (95% CI 0.79-0.94]. This benefit was increased in patients with Hb levels

Update 2011

<14.5 g/dL [HR 0.70 (95% CI 0.63-0.78)]. However, in patients with Hb levels >14.5, an increment of 1.5 g/dL in Hb resulted in an increased risk of mortality [HR 1.31 (95% CI 1.09-1.56)] (figure I.2c, Appendix I:).

A single study[171] reported the risk of CHD-related mortality for the lowest Hb quintiles [range: 7.6-14.6], as a continuous variable, compared with patients in higher Hb quintiles using different methods of estimating GFR. GFR estimated with the Cockcroft-Gault method reported an overall mortality rate of 11% [179/1639] and the proportion of patients who died within the groups were as follows: lower quintiles: 41% (74/179); other quintiles: 64% (115/179).

GFR estimated with the MDRD method reported an overall mortality rate of 9% [148/1639] and the proportion of patients who died within the groups were as follows: lower quintiles: 53/148; other quintiles: 95/148.

An increased risk in CHD-mortality associated with lower Hb quintiles was observed when GFR was estimated using the Cockcroft-Gault method (figure I.3, Appendix I:).

This study[171] also reported that there was no significant difference in CHD-related deaths in patients with the lowest quintiles of Hb and GFR compared with high Hb and GFR in subgroups for men and women; however, these subgroups included both CKD and non-CKD patients so the results are not presented here.

Haemodialysis patients

Data from a cohort (n=66,761) were stratified into increasing Hct levels and compared with an arbitrary Hct level of 33 to 35% over a 1-year follow-up period[60]:

Table 4.6 Adjusted relative risks (Level 2+)

Hct (%)	**<30**	**30 to 32**	**33 to 35 (Ref)**	**36 to 38**	**≥39**
Hb (g/dl)	**<10**	**10-10.7**	**11 to 11.7 (Ref)**	**12 to 12.7**	**≥13**
RR of all-cause mortality	1.74	1.25	1	NS	NS
RR of mortality from cardiac cause	1.57	1.25	1	NS	NS
RR mortality from infections	1.92	1.26	1	NS	NS

NS = not significant

In a 3-year follow-up study[178] participants (n=50,579) were stratified into Hct levels and compared with patients with the arbitrary reference of Hct 34 to 36% (n=22,192):

Table 4.7 Adjusted relative risk of mortality due to cardiac diseases[178]

Hct (%)	**34 to 36 (Ref)**	**37 to 39**	**≥40**
Hb (g/dl)	**11.3 to 12 (Ref)**	**12.3-13**	**≥13.3**
Relative risk	1.00	0.92	0.83
95% CI	N/A	0.87 to 0.98	0.74 to 0.93

Table 4.8 Adjusted relative risk of all-cause mortality[178]

Hct (%)	**34 to 36 (Ref)**	**37 to 39**	**≥40**
Hb (g/dl)	**11.3 to 12 (Ref)**	**12.3-13**	**≥13.3**
Relative risk	1.00	0.92	0.86

Hct (%)	34 to 36 (Ref)	37 to 39	≥40
95% CI	N/A	0.88 to 0.96	0.80 to 0.93

Table 4.9 Adjusted relative risk of mortality for patients with Hct 37 to 39% without pre-existing cardiac disease[178]

	RR	P value
All-cause death	0.69	0.0002
Any cardiac death	0.69	0.0137

In one study[133] (n=309), no association was found between any Hct quartile (<33.4%, ≥33.4 to 35.73%, ≥35.74% to 38.55%, and >38.55%) and survival over 18 months. (**Level 3**)

In a 4-year study[340], renal units with more than 87% of patients achieving target Hct ≥33% (Hb ≥11 g/dl) had a lower mortality rate than those with less than 64% of patients achieving target Hct (p<0.0001). A 10% point increase in the fraction of patients with Hct of more than or equal to 33% (Hb ≥11 g/dl) was found to be associated with a 1.5% decrease in mortality (p=0.003). (**Level 3**)

A retrospective cohort study with 1-year follow-up[186] (n=75,283) found an increase in the age group associated with higher all-cause and cause-specific mortality. Female patients had better outcomes. When compared with white patients, black patients and other ethnic minority patients had lower all-cause and cause-specific mortality. In the same study[186], mortality data were compared with Hct 30 to <33% (Hb 10 to <11 g/dl)[186], see Table 4.10.

Table 4.10 Adjusted relative risks[178] (Level 2+)

Hct (%)	<27 (n=9,130)	27 to 30 (n=22,217)	30 to <33 (Ref) (n=33,122)	33 to <36 (n=10,129)	1992 and 1993 data 33 to <36 (n=61,797)
Hb (g/dl)	**<9 g/dl (n=9,130)**	**9-<10 g/dl (n=22,217)**	**10 to 11 g/dl (Ref) (n=33,122)**	**11 to <12 g/dl (n=10,129)**	**1992 and 1993 data 11 to <12 g/dl (n=61,797)**
RR of all-cause death	1.33 95% CI 1.26-1.40	1.13 95% CI 1.08-1.17	1.00	NS	0.96 95% CI 0.92–0.99
RR of cardiac death	1.25 95% CI 1.15-1.35	1.11 95% CI 1.05-1.17	1.00	NS	Not reported
RR of infections death	1.53 95% CI 1.33-2.75	1.13 95% CI 1.02-1.26	1.00	NS	Not reported

NS = not significant

Update 2011

Kidney transplant patients

Evidence statement:

There is moderate quality evidence[339] showing there is no significant difference in the risk of mortality in kidney transplant patients with low Hb levels [≤10 g/dL] compared with high Hb levels [>10 to >13 g/dL] . There is some uncertainty in the result.

Evidence report:

One moderate quality study[339] examined the association between Hb level and mortality in kidney transplant patients.

Update 2011

Overall mortality rate over a median follow-up period of 8.2 years was 20% [251/825]. The proportion of patients who died within each Hb range was as follows: >10 to 11 g/dL: 31% (28/89); >11 to 12 g/dL: 27% (38/138); >12 to 13 g/dL: 30% (50/167); >13 g/dL: 30% (111/373); ≤10 g/dL : 41% (24/58).

There is uncertainty in the precision around the effect to determine whether Hb levels are associated with risk of mortality (figure I.4, Appendix I:).

MI, stroke and all-cause mortality

Predialysis patients

In one study[336] (n=2,333), the hazard ratio for the composite outcome (MI, stroke and all-cause mortality) was significantly increased in individuals with anaemia (defined as Hb <12 g/dl or Hct <36% in women and Hb <13 g/dl or Hct <39% in men) when compared with those without anaemia (hazard ratio 1.51; 95% CI 1.27 to 1.81). (Level 3)

Update 2011

Nondialysis patients

Evidence statement:

There is moderate quality evidence[335] to show an increased risk in composite outcomes [MI, stroke, all-cause mortality] with a decrease in Hb of 1.5 g/dL; however, this effect was not observed in Hb levels >14.5 g/dL.

Evidence report:

Secondary analysis of two cohorts in one study[335] reported the risk associated with composite outcome (all-cause mortality, stroke, MI) for an increase in Hb of 1.5 g/dL: HR 0.89 (95% CI 0.82 to 0.96) and for an increase in Hb of 1.5 g/dL with Hb level less than 14.5 g/dL [HR 0.75 (95% CI 0.67 to 0.84). The risk increased with Hb levels greater than 14.5 g/dL [HR 1.22 (95% CI 1.03 to 1.45)] (figure I.5, Appendix I:).

Cardiac events - MI and CHD

Nondialysis patients

Evidence statement:

There is moderate quality evidence[335] to show no significant effect of a 1.5 g/dL decrease in Hb level and risk of cardiac events.

Evidence report:

Secondary analysis of two cohorts in one study[335] reported the risk associated with 1.5 g/dL increase in Hb and cardiac events. The results show that for every 1.5 g/dL increase in Hb there was no significant effect on cardiac events [HR 0.98 (95% CI 0.87 to 1.10)]. 22.5% patients [378/1678] experienced a cardiac event. The study also reported the risk associated with a 1.5 g/dL increase when the Hb level is less than 14.5 g/dL or greater than14.5 g/dL; there was no significant difference (figure I.6, Appendix I:).

Quality of life

Update 2011

Nondialysis patients

Evidence statement:

There is low quality evidence[113] showing a 10% reduction in haematocrit levels from baseline was associated with a significant decrease in the 'vitality' domain of the SF-36 health survey.

Evidence report:

One study[113] examined associations between haematocrit levels and changes in SF-36 score at 1 year. A 10% decrement in haematocrit levels from baseline was associated with a significantly decreased score for the 'vitality' domain of the SF-36 (change in score: 4.5 points; p=0.003). There were no significant changes in the scores in the remaining 7 domains.

Haemodialysis patients

When evaluated in epoetin-treated patients[205] (n=57) whose Hct increased from 21 ± 0.3% (Hb ~ 7 g/dl) at baseline to 28 ± 0.4% (Hb ~ 9.3 g/dl) at month 3 and 29 ± 0.4% (Hb ~ 9.7 g/dl) at month 6, quality of life was shown to improve by means of the Karnofsky scale (p=0.0001) and the global (p=0.0001), physical (p=0.0001) and psychosocial (p=0.0001) dimensions of the Sickness Impact Profile (SIP) questionnaire. This was further reinforced by linear regression between improvement of the SIP global score and final achieved Hct (29 ± 0.4%) (b coefficient 0.57, $p<0.05$, R^2 0.57). (**Level 2+**)

Update 2011

Evidence statement:

There is moderate quality evidence[255] to show that a 1 g/dL increase in Hb level is associated with significantly higher QoL scores [SF-36 and CHEQ].

Evidence report:

A single study[255] assessed whether Hb concentration ≥11 g/dL at 6 months after initiation of haemodialysis was associated with better generic (SF-36) and disease-specific QoL [CHOICE Health Experience Questionnaire-CHEQ] at 1 year.

QoL scores at 1 year for patients who achieved haemoglobin concentrations of 11 g/dL at 6 months were significantly higher for the following SF-36 domains: physical functioning, role physical, bodily pain, role emotional, mental and social functions; and the following CHEQ domains: cognitive function and financial well-being. These patients also achieved a higher score for the following disease-specific domains: diet restriction and dialysis access. The effect size, ranged from 0.10 (general health) to 0.34 (mental health) in the SF-36 domains and from -0.07 (sexual function) to 0.31(finances) in the CHEQ domains.

A 1 g/dL increase in Hb (regardless of whether it fell to within 11 to 12 g/dL) was associated with significantly higher QoL scores for most of the generic and disease-specific QoL domains.

Effect of age on quality of life

Haemodialysis patients

In a subgroup analysis of epoetin-treated patients divided into age groups of more than or equal to 60 years (n=23) and less than 60 years (n=34), Hct levels were higher in the younger age group[205] (p<0.05). No differences were observed in improvements of quality of life scores using the Karnofsky scale or SIP score when these age groups were compared[205]. The same was true when patients were stratified into age groups of more than 60 years (n=34) and more than or equal to 65 years (n=15)[205]. (Level 2+)

Update 2011

Stroke

Nondialysis patients

Evidence statement:

There is moderate quality evidence[335] to show that a 1.5 g/dL decrease in Hb level is associated with an increased risk of stroke. This effect was observed in patients who had Hb levels <14.5 g/dL but not in those with Hb levels >14.5 g/dL.

Evidence report:

Secondary analysis of two cohorts in one study[335] reported the risk associated with a 1.5 g/dL increase in Hb and stroke. 13.9% patients [233/1678] experienced a stroke.

The results show that for a 1.5 g/dL increase in Hb there is a decreased risk of stroke [HR 0.85 (95% CI 0.73 to 0.99)]. This effect was observed for a 1.5 g/dL increase in the <14.5 group [HR 0.79 (95% CI 0.64 to 0.97)]. This effect was not seen in patients who had Hb>14.5 g/dL [1.02 (95% CI 0.71 to 1.46)] (figure I.7, Appendix I:).

Progression of CKD

Nondialysis patients

Evidence statement:

There is high quality evidence[163] to show that:

- lower time-averaged Hb levels [(<11 g/dL; 11.1 to 12 g/dL) compared to >13 g/dL] are associated with a significantly increased risk of progression to ESRD.
- a 10 g/L [1 g/dL] decrement in higher time-averaged Hb is associated with a significantly increased risk of progression to ESRD.

Evidence report:

One high-quality study[163] reported the risk associated with progression to end-stage renal disease (ESRD) for male nondialysis patients.

Overall rate of progression to ESRD was 23% [195/853]; the proportion of patients who progressed to ESRD for each Hb range was as follows: <11 g/dL: 40.2% (70/174); 11.1 to 12.0 g/dL: 30.0% (65/216); 12.1 to 13.0 g/dL: 17.9% (36/201); and >13 g/dL: 9.2% (24/262).

A lower time–averaged Hb (<11 g/dL; 11.1 to 12 g/dL) compared with >13 g/dL is associated with significantly higher risk of ESRD [<11 g/dL: HR 2.96 (95% CI 1.70 to 5.15); 11.1 to 12 g/dL: HR 1.81 (95% CI 1.07 to 3.06)]; however there is some uncertainty in the precision around the effects (figure I.8, Appendix I:).

The study also examined progression to ESRD associated with Hb level 12.1 to 13 g/dL compared with >13 g/dL and reported no significant difference was found; numerical data were not presented.

In addition, results showed that a 10 g/L [1 g/dL] higher time-averaged Hb is associated with a decreased risk of progression to ESRD [HR 0.74 (95% CI 0.65 to 0.84)] (figure I.9, Appendix I:).

4.1.5 Health economic methodological introduction [2011]

No economic studies were included in the 2006 guideline. A literature search was undertaken to identify papers published from September 2005 onwards.

Update 2011

One study[173] was identified that examined the association between haemoglobin level and cost in nondialysis patients with chronic kidney disease aged 65 years or older who were not receiving treatment for anaemia. This was a retrospective cohort analysis with multivariate regression (covariates: age, gender, GFR, diabetes, hypertension, liver cirrhosis, CAD, MI, LVH). Data was derived from a large US managed care database – this limits the applicability of the results to the guideline. Costs included inpatient and outpatient medical claims and pharmacy dispensing claims.

4.1.6 Health economic evidence statements [2011]

Evidence statement:

There is moderate quality evidence[173] that is partially applicable to the guideline to show that in untreated patients:

- low Hb [<11 g/dL] compared to higher Hb [>11 g/dL] is associated with increased costs.
- an decrement in Hb level of 1 g/dL is associated with increased cost.

Lefebvre and colleagues[173] reported that, in CKD patients untreated for anaemia, a haemoglobin level <11 g/dL was associated with an additional monthly cost of £320 (CI: £223, £408) compared to a haemoglobin level >11 g/dL. Every 1g/dL decrease in haemoglobin was associated with a £52 increase in cost (CI: £32-£71).

4.1.7 From evidence to recommendations

Data about the outcome of LVH were presented to the GDG[177]. Two studies which demonstrated an association between decreasing left ventricular mass and increasing haematocrit levels[127,257] were based on small sample sizes (n=9 and n=11) and the GDG weighed these studies accordingly in their deliberations.

Two studies were appraised that examined the rate of progression of renal failure but these were excluded as underpowered by the GDG[127,257] and hence, no evidence statements were presented for this outcome.

The GDG noted that the greater hospitalisation rate seen in a study based on registry data[60] could be a reflection of a sicker population and this may be another reason for the lower Hb level. It was also noted that the lowest haematocrit group required double the amount of EPO to reach this level, and as such, these participants may have a reduced health status.

The study by Moreno et al[206] was excluded by the GDG because of a highly selected population (excluding both elderly and ill patients) and a lack of intention to treat analysis. The group agreed to increase the grade of one other study[178] from 3 to 2+ as the study participants had been subdivided according to Hct levels and a multivariate analysis of risk had been performed.

The GDG agreed that the evidence supported an association between decreased haematocrit and increased risk of hospitalisation.

The group felt that the evidence presented on mortality from one study[60] suggested that there was an increase in mortality between Hct <30 to <33% (Hb levels ~ 1 –11g/dl) when compared with Hct 33 to 36% (Hb ~ 11–12g/dl). It was noted that this range spans the standard levels quoted in many guidelines. The data presented by two studies[186,340] suggest that an Hb of <11g/dl was the threshold below which there was an increased risk of mortality. However, the GDG noted that these studies may not have accounted for confounding factors such as intercurrent illness. The issue was also raised that there might be a reverse causality and that patients requiring high amounts of epoetin may be sicker and hence more likely to require hospitalisation.

One study[133] concluded that the haematocrit level was not a predictor of survival and that other markers of morbidity were more important. The data also suggested that confounding factors may be present that were not taken into account, e.g. infection. This possibility was reflected in the study as the haematocrit levels were corrected for albumin. This study also suggested that men and women require different doses of ESA: women appear to need more ESA than men.

Only one study[202] was appraised that evaluated haemodynamic parameters but this was excluded for this outcome by the GDG as it was felt to be underpowered (n=7).

Concerning quality of life in haemodialysis patients(n=57)[202], a subgroup analysis of those over and under 60 years of age found a significant increase in quality of life scores associated with higher Hb levels in both age groups.

4.1.8 Recommendation and link to evidence [2011]

1. **Consider investigating and managing anaemia in people with CKD if:**
   - **their Hb level falls to 11 g/dL or less (or 10.5 g/dL or less if younger than 2 years) or,**
   - **they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations). [new 2011]**

4.1.8.1 Relative values of different outcomes

Update 2011

The GDG noted the outcomes that were important for decision making were mortality, quality of life, hospitalisation, cardiac events, stroke and composite events. There were no new relevant studies identified reporting the outcome LVH. Outcomes reporting change in LVMI and progression of CKD were not as influential in decision making. The GDG noted that the evidence was from observation cohort studies and the relationship between Hb levels and outcomes of interest may be influenced by other confounding factors such as chronic inflammation.

4.1.8.2 Trade off between clinical benefits and harms

The GDG noted:

- the overall trend of adverse outcomes at lower Hb levels in both non-dialysis and dialysis patients. There was limited evidence in the transplant population.

- the risk of mortality appears to increase below Hb 12 g/dL for the non-dialysis population and below 11 g/dL for the dialysis population, but there is a some heterogeneity in the data.
- There was no new relevant studies identified considering children.
- more evidence is available at the 2011 update for the non-dialysis population than was available at the time of the original guideline.

The GDG also debated if there were other subgroups where different relationships between Hb levels and outcomes could be distinguished, for example sex, ethnicity or people with diabetes. However there is insufficient evidence on which to base different recommendations for these sub-groups.

4.1.8.3 Economic considerations

No cost effectiveness analyses were identified that compared initiating management of anaemia at different threshold Hb levels.

One cohort study was identified that examined the association between cost and Hb level in untreated people with CKD and reported that lower Hb was associated with higher costs in patients not treated for anaemia.

4.1.8.4 Quality of evidence

There was low to moderate quality evidence from prospective and retrospective cohort studies. The majority of the studies were adjusted for confounding factors but the GDG considered that confounding (for example the more severe the chronic kidney disease, the lower the Hb is likely to be) remained an important issue in deciding at which level of Hb to initiate management.

Update 2011

4.1.8.5 Other considerations

The GDG noted that the Hb level at which patients are at increased risk for mortality differed between non-dialysis and dialysis patients, however there was some heterogeneity in the results. The GDG debated whether to make separate recommendations for the different population groups but the level of uncertainty and the strength of the evidence did not allow firm conclusions to be drawn.

The GDG noted the complexity in deciding the level of Hb at which to start treatment, also noting that different patients become symptomatic at different levels of Hb concentration.

The GDG considered the recommendation drafted in the original guidance together with the additional evidence accruing since publication of the original guidance. The GDG unanimously agreed that the recommendation to initiate management of anaemia in people with CKD and Hb levels below 11 g/dl did not require change. The GDG's rationale for having the intervention point within the aspirational target range and not at the lower limit of the range is because investigation and management would begin before the Hb level had fallen below the lower limit of the aspirational range (see paragraph 6.9), thereby allowing time for management to maintain Hb levels within the range rather than having to raise them to within the range.

However, the GDG felt that the recommendation should be amended to read 'fallen below 11 g/dl' (original: 'less than or equal to 11 g/dl') to highlight that management and investigation was indicated when Hb levels were declining and not when they were stable.

The GDG also felt that they should recommend investigation and management of anaemia in individual patients who are thought to be symptomatic from anaemia despite higher levels of Hb or below the normal range for people with CKD, for example between 11 and 12 g/dL. The recommendation was modified to reflect this.

4.2 Diagnostic role of glomerular filtration rate

4.2.1 Clinical introduction

Data from population studies such as NHANES III in the USA and the NEOERICA study in the UK suggest an increasing prevalence of anaemia with decreasing GFR level. A similar relationship between glomerular filtration rate (GFR) and anaemia has also been demonstrated in population cohorts of people with diabetes[317]. Although anaemia is common in people with diabetes it is also commonly unrecognised and undetected[300]. The prevalence of anaemia in people with diabetes is increased at all levels of renal function in those with increased proteinuria/albuminuria[318], and it has been suggested that in people with diabetes, anaemia associated with CKD may occur earlier in the evolution of CKD when compared with people without diabetes. In investigating the evidence base, this section seeks to describe the relationship between GFR and haemoglobin levels and provide guidance for clinicians about the threshold level of GFR below which they should suspect that anaemia is associated with CKD.

4.2.2 Methodological introduction

A literature search identified five studies investigating the association between GFR or creatinine clearance (CCr) with Hb/Hct levels in non-diabetic patients[20,99,129,155,197] and four studies in diabetic patients[73,88,316,317].

Notable aspects of the evidence base were:

- Two studies were not limited to patients with CKD[20,129].
- Two studies were conducted in selected patient populations[155,197] and one study[99] was conducted in children.
- Patient populations in some studies were not stratified to diabetic and non-diabetic patients and where reported, the percentage of diabetics varied from 5%[20] to 28%[155] and to 64.4%[197]. All patients with CKD were in the untreated predialysis stage, except for one study where some patients received oral iron (26%) and epoetin (12.8%) to treat their anaemia[99].
- One study was conducted in people with Type 2 diabetes[316], and one in people with Type 1 and people with Type 2 diabetes[317].

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects, therefore no health economic evidence statements are given.

4.2.3 Evidence statements

Hb/Hct levels associated with different GFR or CCr levels in non-diabetic patients

Table 4.11: GFR vs Hb55 (Level 3)

Median Hb level in women (g/dl)	Median Hb level in men (g/dl)	eGFR (ml/min/1.73 m2)
13.5	14.9	60
12.2	13.8	30
10.3	12.0	15

Table 4.12: GFR vs Hb using >80 ml/min/1.73 m2 as the reference value56 (Level 2+)

GFR (ml/min/1.73 m2) >80=ref	Women (n=8,495)		Men (n=3,560)	
	Difference in Hb (g/dl)	p value	Difference in Hb (g/dl)	p value
>70 to ≤80	0.1	<0.0001	NS	0.44

GFR (ml/min/1.73 m2)	Women (n=8,495)		Men (n=3,560)	
	95% CI 0.1–0.2			
>60 to ≤70	0.1 95% CI 0.1–0.2	0.0009	NS	0.40
>50 to ≤60	0.1 95% CI 0.0–0.2	0.006	−0.2 95% CI −0.3–0.0	0.07
>40 to ≤50	−0.2 95% CI −0.4, −0.1	0.0004	−0.8 95% CI −1.1, −0.5	<0.0001
>30 to ≤40	−0.6 95% CI −0.8, −0.3	<0.0001	−1.4 95% CI −1.8, −1.0	<0.0001
>20 to ≤30	−1.4 95% CI −1.8, −1.1	<0.0001	−1.9 95% CI −2.3, −1.4	<0.0001
≤20	−1.9 95% CI −2.3, −1.6	<0.0001	−3.4 95% CI −3.9, −2.9	<0.0001

Table 4.13: GFR vs Hb57 (Level 3)

GFR (ml/min/1.73m2)	n	% of n with Hb ≤10 g/dl	% of n with Hb >10 to ≤12 g/dl	% of n with Hb ≤12 g/dl
≥60	116	5.2	21.6	26.7
≥30 to <60	2,832	5.6	35.9	41.6
≥15 to <30	1,968	11.0	42.6	53.6
<15	298	27.2	48.3	75.5

Table 4.14: GFR vs Hct58 (Level 2+)

Hct (%)	Estimated Hb (g/dl)	GFR (ml/min/1.73 m2)
<28	<9	16.5 ± 6.8
28.0–29.9	9–<10	17.9 ± 8.8
30.0–32.9	10–<11	20.1 ± 7.6
33.0–35.9	11–<12	22.0 ± 8.9
≥36	≥12	27.4 ± 7.9

Table 4.15: GFR vs Hct in children (<21 years old)59

	% of patients with Hct		
	≤30 %	31–32.9 %	>33 %
	% of patients with estimated Hb (g/dl)		
	≤10	>10–<11	>11
All patients	30.9 %	13.0 %	56.1 %
GFR (ml/min/1.73 m2)			
<10	62.9 %	11.3 %	25.8 %
10–25	48.1 %	16.8 %	35.1 %
25–50	25.7 %	13.3 %	61.0 %
50–75	13.1 %	8.1 %	78.7 %

2.4% of the study participants were treated with RBC transfusions after study entry. In addition, 26% of study participants received oral iron and 12.8% received epoetin during the course of the study. (**Level 2+**)

Hb levels associated with different GFR levels in diabetic patients

In a retrospective cross-sectional study (n=28,862)[73], diabetes was recorded in 15.4% of patients with GFR of more than 60 (stage 3–5 CKD). Of these, 15.3% were anaemic when defined as Hb <12 g/dl for women and <13 g/dl for men) and 3.8% were anaemic when defined as Hb <11 g/dl. (Level 3)

In a retrospective cross-sectional study in people with Type 1 and 2 diabetes (n=820)[317], GFR was found to be an independent predictor of Hb (p<0.0001). Associations between Hb and GFR were continuously significant (p<0.05) at lower levels of GFR <70 vs GFR 80–100. Hb was significantly lower in all male and female patients with GFR <70 (both p<0.0001). GFR of more than 80 ml/min/1.73 m2 was not significantly associated with anaemia defined as Hb ≤11 g/dl (irrespective of sex) and Hb <13 g/dl in men and Hb <12 g/dl in women. (Level 3)

Diabetes status and estimated GFR (eGFR) (ml/min/1.73m2) categories <30, 30–59, and 60–89 were significantly associated with an increased likelihood of anaemia, defined as Hb <12.0 g/dl for men and post-menopausal women (older than 50 years old) and Hb <11.0 for pre-menopausal women (50 years old or younger) using eGFR ≥90 as the reference[88]. (Level 3)

In the same study[88], when eGFR was divided into 10 ml/min/1.73m2 strata, the prevalence of anaemia by diabetes status was statistically significant at each of the categories between 31 and 60 ml/min/1.73m2, but did not differ for any other categories.

In addition, in men with diabetes, significantly lower Hb levels were observed at all eGFR categories <60 ml/min/1.73m2, whereas among women with diabetes and all study participants without diabetes (both men and women), significantly lower Hb levels were not apparent until more advanced levels of kidney impairment were observed (eGFR <31 ml/min/1.73m2). (Level 3)

Hb levels associated with different CCr levels in diabetic patients

Type 2 diabetic patients with mild renal impairment (CCr 60–90 ml/min/1.73 m2)[316] were approximately twice as likely to have anaemia as diabetic patients with normal renal function, defined as Hb <130 g/l in men and Hb <120 g/l in women (CCr >90 ml/min/1.73 m2) (p value not reported by the authors). (Level 3)

4.2.4 From evidence to recommendations

The comparison of diabetic and non-diabetic populations was based on a clinical perception that the diabetic population was at risk of developing anaemia of CKD at an earlier stage. The GDG felt that this perception had arisen partly because of the selected patient populations in many of the studies, the cross-sectional nature of the studies, and the lack of standardisation of estimates of renal function used in the various studies.

The current clinical perception of the GDG is that although there was a correlation between diabetes and the anaemia of CKD, the prevalence of anaemia in those with diabetes appeared greater than those without at higher levels of GFR. Within whole population studies there were similar mean haemoglobin levels between those with diabetes and those without diabetes across a range of GFRs.

It was agreed that setting a threshold value of eGFR of 60 ml/min/1.73m2 (the boundary between stage 2 and stage 3 CKD) would be of use in helping clinicians decide whether to consider anaemia of CKD as a cause of the anaemia, although there were some concerns about whether the error around a single measurement would make this a suitable recommendation.

It was felt there was some merit in an empirical statement that supported setting an eGFR of <60 ml/min/1.73m2 which should alert a clinician to consider anaemia of CKD as the cause, and that other causes were likely in patients with a eGFR > 60.

4.2.5 Recommendation

2. An estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73m2 should trigger investigation into whether anaemia is due to CKD. When the eGFR is ≥60 ml/min/1.73m2 the anaemia is more likely to be related to other causes. [D]

4.3 Diagnostic tests to determine iron status

4.3.1 Clinical introduction

The purpose of the evidence review in this section was to identify the best combination of tests to determine iron status in patients with CKD.

The aim of determining iron status is to identify which patients need iron supplementation, as well as those who do not. Although absolute iron deficiency may occur in patients with chronic kidney disease we more frequently identify what is termed 'functional iron deficiency'. Although iron stores may seem adequate when measured by conventional indices of iron status, there may be a lack of 'freely available iron' for effective erythropoiesis in the bone marrow.

There is a lack of well-accepted gold standard tests for determining iron deficiency in the setting of CKD. While bone marrow iron stores are often regarded as the best indicator of iron status, this is not universally accepted and taking a bone marrow sample is invasive, relatively time consuming and expensive. The frequent coexisting inflammatory or infective problems in patients with CKD can complicate the interpretation of iron status parameters. For example, serum ferritin is a good marker of storage iron and decreases in iron deficiency states. However, it is also an acute phase reactant, which means it is frequently raised in inflammatory conditions, such as CKD, regardless of the iron status. All the available tests of iron status are subject to similar limitations and detailed discussion is beyond the scope of this guideline. The British Committee for Standards in Haematology is producing a document 'Evaluation of iron status', which will deal comprehensively with these issues (although not specifically in the setting of CKD). It is accepted that no single parameter can determine iron status.

In patients without CKD normal serum ferritin levels are over 20 µg/l, but in those with CKD a value of 100 µg/l is considered to be the lower limit of normal to allow for the associated mild inflammatory state. The percentage of hypochromic red cells (HRC) directly reflects the number of red blood cells with suboptimal levels of haemoglobin content (<28 g/dl) and may be determined using certain analysers. HRC <2.5% is normal and HRC >10% indicates definite iron deficiency. Measurement must be on a fresh sample (<4 hours after the blood is withdrawn) because of storage artefact. Reticulocyte haemoglobin content (CHr) may also be measured by certain analysers and is derived from the simultaneous measurement of volume and haemoglobin concentration in reticulocytes. Levels indicating functional iron deficiency depend on the analyser used. Transferrin saturation (TSAT) is a derived value and may be calculated from serum iron × 100 ÷ total iron binding capacity; or serum iron (mg /dL) × 70.9 ÷ serum transferrin (mg/dl). Transferrin levels are also

influenced by inflammation and nutrition (correlating with serum albumin levels). A TSAT of <20% suggests iron deficiency.

4.3.2 Methodological introduction

A literature search identified studies which addressed the ability of tests to detect iron deficiency[67,93,147] and the ability of tests to predict the response to intravenous iron supplementation in patients with predefined iron parameters receiving epoetin[96,97,149,154,184,314].

Of the six studies looking at the response to intravenous iron, five studies predefined the patient population to whom iron was given as being iron deficient (see Table 4.16). In one study[314] the response to intravenous iron was used to define the prior iron status. No study addressed the issue of loading with iron prior to epoetin administration.

Table 4.16: Definition of detection of iron deficiency

Reference	Iron dosing regimen	Definition of positive response to iron administration, ie iron-deficient
96	1g infusion (over 2 hours)	Erythropoietic response to the iron treatment; a sustained increase in corrected reticulocyte index of one base point (ie from 1.7% to 2.7%) within 2 weeks
184	500mg to 1g infusion (over 1 hour)	>5% increase in Hct, 4 weeks after administration
314	~1g over 8 weeks	Hb response ≥15% of baseline value
149	240mg iron colloid over 2 weeks	Not reported
154	1.5g over 41.7 weeks	• Reduction in weekly epoetin dose of at least 30 U/kg/week in the subsequent 12 weeks while maintaining a target Hct of 30 to 33% • Reduction in weekly epoetin dose of at least 60 U/kg/week in the subsequent 12 weeks while maintaining a target Hct of 30 to 33%
97	1g over 10 HD treatments	• ≥5% increase in Hct or a decrease in epoetin dose if the Hct increased to more than 38%

HD = Haemodialysis.

4.3.3 Evidence statements

Studies where iron was administered

A variety of studies looked at the utility of a number of markers of iron status as indicators of iron deficiency following iron administration. Response to iron administration was variably defined by an increase in haemoglobin level and/or reduction in erythropoietin dose.

Table 4.17: Studies where iron was given

Reference	N (range)	Iron test (cut- off range in studies)	Test cut-off value	Sensitivity	Test cut-off value	Specificity	Evidence hierarchy
96,154,184,314	32–136	Serum ferritin (50	<50 µg/l	19.6%	<100 µg/l	30–78.4%	DSII[96,184,314] DSIII[154]

Reference	N (range)	Iron test (cut- off range in studies)	Test cut-off value	Sensitivity	Test cut-off value	Specificity	Evidence hierarchy
		to 400 µg/l)					
			<100 µg/l	35.3–71.4%	<50 µg/l	94.6%	
[96,314]	32 and 51	%HRC (>4% to >10%)	>4%	86.3%	>4%	78.4%	DSII[96,314]
			>10%	42.8 and 45.1%	>10%	80 and 100%	
[96,149,154,184,314]	32–136	TSAT (<12% to <28%)	<20%	57.1–74%	<20%	36–80%	DSII[96,149,184,314] DSIII[154]
[184,314]	17 and 51	Serum ferritin (<100µg/l) and TSAT (<20%)	Serum ferritin <100µg/l and TSAT <20%	33% and 68.6%	Serum ferritin (<100µg/l) and %TSAT (<20%)	67% and 60.8%	DSII[184,314]
[96,149,314]	32–94	Ret Hb (<26 pg to <32.5 pg)	<26 pg	100%	<26 pg	80%	DSII[96,149,314]
			<32.5 pg	23.1%	<32.5 pg	66.7%	
[314]	51	ZPP (>52 and >90 µmol/mol haem)	>52 µmol/mol haem	80.6%	>52 µmol/mol haem	68.7%	DSII
			>90 µmol/mol haem	13.9%	>90 µmol/mol haem	96.9%	
[314]	51	%HRC (>6%) and other tests	%HRC >6% and Ret Hb ≤29 pg	86.3%	%HRC >6% and Ret Hb ≤29 pg	93.2%	DSII
			%HRC >6% and serum ferritin <50 ng/ml	82.4%	%HRC >6% and serum ferritin <50 ng/ml	89.2%	
			%HRC >6% and TSAT <19%	96.1%	%HRC >6% and TSAT <19%	74.3%	
			%HRC >6% and ZPP >52 mmol/mol haem	94.9%	%HRC >6% and ZPP >52 mmol/mol haem	71.9%	
			%HRC >6% and STR >1.5 mg/100 ml	85.7%	%HRC >6% and STR >1.5 mg/100 ml	73.2%	

HRC = hypochromic red cells; TSAT = transferrin saturation; Ret Hb = reticulocyte haemoglobin content; ZPP

Reference	N (range)	Iron test (cut- off range in studies)	Test cut-off value	Sensitivity	Test cut-off value	Specificity	Evidence hierarchy
= erythrocyte zinc protoporphyrin; STR = serum transferrin receptor; PPV = positive predictive value; NPV = negative predictive value.							

No iron administration

Table 4.18: Studies where iron was not given

Reference	N (range)	Iron test cut-off range in studies)	Test cut-off value	Sensitivity	Test cut-off value	Specificity	Evidence hierarchy
[93]	63	STR (1.39 µg/ml to 3.5 µg/ml)	STR 1.39 µg/ml	84%	STR 1.39 µg/ml	30%	DSIb
			STR 3.5 µg/ml	38%	STR 3.5 µg/ml	90%	
[147]	25	Bone marrow examination (BME) vs other tests	BME vs Serum ferritin <200 µg/l	41%	BME vs Serum ferritin <200 µg/l	100%	DSIb
			BME vs TSAT <20%	88%	BME vs TSAT <20%	63%	
[67]	36	TSAT vs other tests	TSAT <15% vs Ret Hb <26 pg	73	TSAT <15% vs Ret Hb <26 pg	100	DSII
			TSAT <15% vs %HRC >2.5%	91	TSAT <15% vs %HRC >2.5%	54	
			TSAT <15% vs %HRC >5%	91	TSAT <15% vs %HRC >5%	62	

4.3.4 From evidence to recommendations

The group compared the tests based on the sensitivity, specificity and receiver operator characteristics. The group did not use the negative or positive predictive values as they were considered sensitive to demographics and epidemiology and therefore not generalisable.

These iron supplementation studies have dealt with iron deficiency or 'functional iron deficiency' (where storage iron may be adequate, but iron utilisation in red cell production is defective). The studies have not addressed the issues of whether iron supplementation could be beneficial in patients having erythropoietin even with apparently normal iron status, or when iron supplementation should be stopped because of a risk of iron overload.

Recticulocyte Hb content and the percentage of hypochromic red cells were also discussed. Neither of these tests are widely available and both are currently under a commercial patent. With respect to recticulocyte Hb content, the GDG felt that although this looked like a sensitive test, the cut-off for this test was a Hb content of less than 26pg. This was considered very low as the normal range is reported to be 31–33pg. The GDG noted that the percentage of hypochromic red cells provided the best sensitivity and specificity from a single test.

In general, the GDG noted that tests for serum ferritin and transferrin saturation were the most widely used but that they had poor sensitivity and specificity. The GDG took note, however, that these tests were both cheap and widely available. It was noted that serum ferritin was the only test addressing iron storage while the other tests reviewed in the evidence assessed iron utilisation. The GDG agreed that no single test was adequate to determine iron status. Serum ferritin showed the best correlation with bone marrow iron scores. Iron deficiency should be ascertained by a combination of serum ferritin (storage iron) and tests of iron utilisation (reticulocyte haemoglobin content, percentage of hypochromic red cells, transferrin saturation, ZPP).

4.3.5 Recommendations

3. Serum ferritin levels may be used to assess iron deficiency in people with CKD. Because serum ferritin is an acute phase reactant and frequently raised in CKD, the diagnostic cut-off value should be interpreted differently to non-CKD patients. [A(DS)]

4. Iron deficiency anaemia should be:

- **diagnosed in people with stage 5 CKD with a ferritin level of less than 100 µg/l**
- **considered in people with stage 3 and 4 CKD if the ferritin level is less than 100 µg/l. [D(GPP)]**

5. In people with CKD who have serum ferritin levels greater than 100 µg/l, functional iron deficiency (and hence those patients who are most likely to benefit from intravenous iron therapy) should be defined by:

- **percentage of hypochromic red cells >6%, where the test is available or**
- **transferrin saturation <20%, when the measurement of the percentage of hypochromic red cells is unavailable. [B(DS)]**

4.4 Measurement of erythropoietin

4.4.1 Clinical introduction

Although anaemia in CKD may develop in response to a wide variety of causes, erythropoeitin (EPO) deficiency is the primary cause of renal anaemia. Predominantly produced by peritubular cells in the kidney, EPO is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Loss of peritubular cells leads to an inappropriately low level of circulating EPO in the face of anaemia (Figure 4.2).

We know that anaemia develops early in the course of chronic kidney disease. NHANES III found lower levels of kidney function to be associated with lower haemoglobin levels and a higher prevalence and severity of anaemia[20]. The prevalence of anaemia, defined as haemoglobin levels of less than 12 g/dl in men and less than 11 g/dl in women, increased from 1% at an estimated GFR of 60 ml/min per 1.73 m2, to 9 and 33% at estimated GFRs of 30 and 15 ml/min per 1.73 m2 respectively. Using the same definition of anaemia, it is suggested that in people with diabetes and

CKD the prevalence of anaemia in stage 2 and 3 CKD is greater than in those without diabetes[88]. In a study of 5,380 participants from the Kidney Early Evaluation

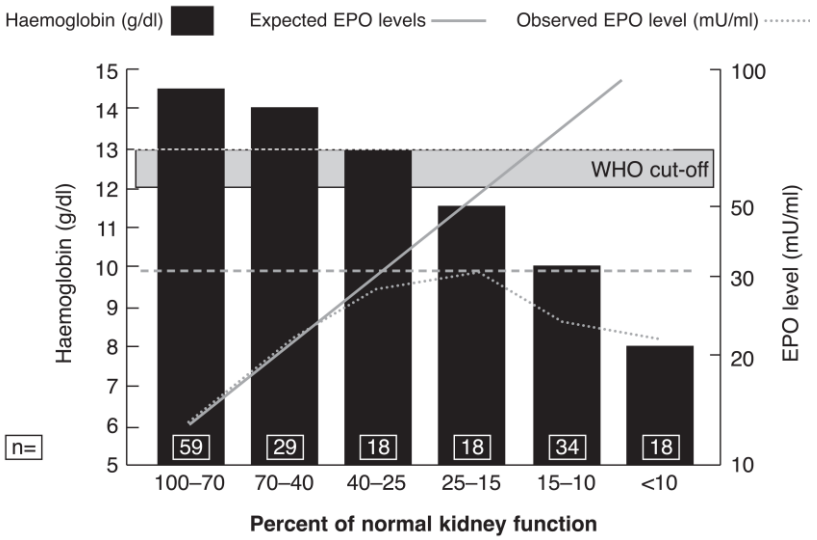


Figure 4.2 Evolution of anaemia in CKD (Reproduced with kind permission of Dr Anatole Besarab). EPO = erythropoietin; WHO = World Health Organization.

Program, 22% of those with CKD stage 3 and diabetes had anaemia, compared with 7.9% of those with stage 3 CKD alone (p<0.001). In stage 2 CKD 7.5% of those with diabetes were anaemic compared with 5.0% of those without diabetes (p=0.015). In people with diabetes the prevalence of anaemia at all levels of GFR is greater with increasing levels of albuminuria[316].

When patients with diabetes and CKD are stratified into those more likely to be iron-replete (TSAT>16%) and those less likely to be iron-replete (TSAT<16%) anaemia is associated with a relative lack of EPO response in those with TSAT>16%[315].

In patients with less advanced CKD there may be some uncertainty about whether or not the anaemia is associated with lack of EPO, and this may be particularly so in transplanted patients in whom immunosuppression may also play a role in suppressing the bone marrow response. In these patients, knowledge of serum EPO levels may be beneficial and the evidence review in this section seeks to address this.

4.4.2 Methodological introduction

One cohort study[260], six cross-sectional studies[10,43,85,91,212,315] and two longitudinal studies, prospective[50] and retrospective[64], which examined the association between serum erythropoeitin with Hb levels or renal function, were identified in a literature search.

Notable aspects of the evidence base were:

- The studies comprised selected and unselected participants.
- Of the three studies conducted in people with diabetes, the study populations consisted of people with Type 2 diabetes without nephropathy[64], selected people with Type 1 diabetes with diabetic nephropathy in the absence of advanced renal failure[43], people with Type 1 and 2 diabetes[315].
- Other causes of anaemia were explicitly ruled out in some studies[43,50,64,91,260].
- Where reported, anaemia was defined as <13 g/l for men and <11.5 g/l for women[64], Hb ≤11.5 g/dl for women and 12.0 g/dl for men[43], Hb <11 g/dl[91], Hb <12 g/dl for women and Hb <13 g/dl for men[315].

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects, therefore no health economic evidence statements are given.

4.4.3 Evidence statements

Adults with diabetes

In people with Type 2 diabetes without nephropathy (n=62) a significant negative correlation between serum EPO and Hb levels was found (r2=0.612, p=0.01)[64]. (Level 3)

In contrast to the above finding, a study in people with Type 1 diabetes with diabetic nephropathy (in the absence of advanced renal failure) (n=27), found no significant EPO response to lower Hb levels[43]. (Level 3)

A cross-sectional study conducted in people with diabetes[315] found no significant EPO response in anaemic patients (defined as Hb <12 g/dl for women and Hb <13 g/dl for men) with GFR >60 ml/min/1.73m2 or >90 ml/min/1.73m2. (Level 3)

In a subgroup of iron replete diabetic patients (transferrin saturation level >16%), from the above study[315], serum EPO levels did not change significantly with Hb level as shown below.

Table 4.19: Characteristics in anaemia and raised or normal serum EPO (Level 3)

	No anaemia, n=554	Anaemia + normal EPO, n=131	Anaemia + raised EPO, n=37
Erythropoietin (IU/l)	15 ± 8	16 ± 7	74 ± 112*#
Haemoglobin (g/dl)	14.1 ± 1.1	11.6 ± 1.0*	11.0 ± 1.1*#
GFR (ml/min/1.73m2)	79 ± 26	57 ± 28*	66 ± 28*#
TSAT <16%	15%	31%*	73%*#
* Vs no anaemia p<0.05.			
# Vs anaemia with normal levels of EPO.			

Children with chronic renal failure

No significant correlation was found between serum EPO and Hb/Hct levels in three studies conducted in children with chronic renal failure (n=7[10]; n=10[85]; n=37[50]). (Level 3)

Likewise, no significant correlation was found between serum EPO levels and renal function assessed by means of eGFR (n=37)[50] or serum creatinine (SCr) (n=30)[212] in children with chronic renal failure. (Level 3)

The results of a study which investigated Hb and serum EPO levels in children with chronic renal failure and healthy children are shown in Table 4.20.

Table 4.20: Hb and serum EPO in children (Level 3)

	N	Hb (g/dl)	Mean serum EPO (U/l)
Predialysis	30	10.7 ± 2.5	36.2 (range 7 to 235)
Post-transplant	15	11.6 ± 2.6	39.5 (range 10 to 125)
Healthy children	20	13.2 ± 0.8	35.2 (range 18 to 64)

Adults with chronic renal failure on conservative therapy

In patients with CKD of varying renal function (CCr 2 to 90 ml/min/1.73m2 (n=117)), mean serum EPO levels were significantly elevated in all patients when compared with healthy controls (n=59) ($p<0.01$). In a subgroup analysis of patients with CCr 2–40 ml/min/1.73m2 (n=88), CCr and serum EPO showed a positive correlation ($r=0.27$, $p<0.015$)[260]. (Level 2+)

Unselected population of adults

In a random sample of patients investigated by coronary angiography (n=395) stratified by renal function, a significant inverse relationship was found between serum EPO and Hb levels in participants with CCr >40 ml/min ($r=-0.35$, $p<0.0001$). No significant correlation was found, however, in participants with CCr <40 ml/min[91]. (Level 3)

4.4.4 From evidence to recommendations

Anaemia is associated with increased EPO levels in individuals without evidence of CKD but the anaemia associated with CKD is characterised by a relative lack of EPO response. However, in the clinical situation routine measurement of EPO levels is of limited value in assessing anaemia.

The GDG reached consensus on a threshold GFR of 40 ml/min, below which anaemia is most likely to be of renal aetiology and measurement of erythropoietin levels will not be required except in exceptional circumstances. At GFR levels between 40 and 60 ml/min, the utility of testing is uncertain from the existing evidence, and a research recommendation is given.

4.4.5 Recommendation

6. Measurement of erythropoietin levels for the diagnosis or management of anaemia should not be routinely considered for people with anaemia of CKD.
[D(GPP)]

5 Management of anaemia

5.1 Initiation of ESA therapy in iron-deficient patients

5.1.1 Clinical introduction

Iron management forms an essential part of the treatment of anaemia associated with CKD and availability of iron is of key importance for iron optimal erythropoiesis. Before erythropoietin treatment was available, patients with anaemia associated with CKD frequently received blood transfusions. One of the consequences of this was the progressive accumulation of iron, manifested by extremely high ferritin levels in excess of 1,500 to 5,000 µg/l. With the advent of ESA therapy this accumulated iron was rapidly mobilised, and serum ferritin levels fell accordingly. We now recognise that in order to manage the anaemia optimally, there needs to be an appropriate balance between stimulation of erythropoiesis and provision of iron as a key substrate in the manufacture of haemoglobin.

In health, iron is almost completely recycled and losses are of the order of 1 mg/day, requiring minimal replacement. Iron deficiency is the most common cause of anaemia worldwide. This is due to either negative iron balance through blood loss (commonly gastrointestinal or menstrual), or to inadequate intake (which may be nutritional or related to poor gastrointestinal absorption). Patients with CKD are particularly susceptible to gastrointestinal blood loss and additional sources of significant blood loss include routine (and non-routine) blood sampling, and blood loss on haemodialysis which may represent the need for up to an extra 3,000 mg iron per year. In the first 3 months of ESA therapy it is estimated that a haemodialysis patient needs an extra 1,000 mg of supplemental iron, underlining the importance of adequate availability of iron for optimal erythropoiesis[34].

5.1.2 Clinical methodological introduction

A comprehensive literature search did not identify any studies that were suitable to address the clinical aspects of this section, therefore no evidence statements are given.

5.1.3 Health economics methodological introduction

One study met methodological criteria[282]. This Canadian study estimated annual cost savings of intravenous iron dextran from reductions in EPO and oral iron in patients who did not tolerate or did not respond adequately to oral iron in a 6-month prospective study with an initial goal serum ferritin of 100–200 µg/l. If an increase in haemoglobin was not achieved, transferrin saturation was measured and when less than 20%, the goal serum ferritin was increased to 200–300 µg/l. EPO was used to maintain haemoglobin levels of 9.5–10.5 g/l only if ferritin targets were met[282].

5.1.4 Health economic evidence statements

The study found that intravenous iron dextran saved approximately Canadian $63 per patient ($3,016 total) from EPO savings and oral iron savings in 50 patients. However, the initial cost of i.v. iron dextran loading was $3,426 in the first year. Therefore, the loading dose of i.v. iron dextran offset the cost reduction in EPO and oral iron in the first year but would not apply in subsequent years. Intravenous iron dextran costs were $29,692 (Canadian $, 1996) per year in the 50 patients in the study with $30,120 of EPO savings per year and $2,738 from oral iron savings per year[282].

5.1.5 From evidence to recommendations

There is little evidence in this area but the GDG agreed that ESAs alone should not be administered to patients with iron deficiency (ferritin level <100 µg/l). The GDG debated whether ESAs should be administered together with iron supplements. It was noted that some patients with higher GFR had a good response to iron treatment alone but that there was no evidence to support a threshold for iron stores required prior to commencing ESAs, except in patients with iron deficiency.

5.1.6 Recommendations

7. ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency. [D(GPP)]

8. In people with functional iron deficiency, iron supplements should be given concurrently when initiating ESA therapy. [D(GPP)]

Also see recommendation 42 in section 6.12.6.

5.2 Maximum iron levels in patients with anaemia of CKD

5.2.1 Clinical introduction

Iron is crucial for survival and is necessary for erythropoiesis and the production of usable energy through oxidative phosphorylation. However, iron-overload states are harmful and the potent oxidising ability of non-transferrin bound iron makes it potentially toxic. The majority of iron not actively circulating as haemoglobin is safely sequestered in the form of ferritin and hemosiderin in macrophages of the reticuloendothelial system. Molecules that hold iron tend to be very large, containing a central core of iron with a proteinaceous envelope that insulates the body from the iron atom. We know that in iron-overload states, such as haemochromatosis, in which serum ferritin levels can increase to more than 10,000 µg/l, the body is presented with unmanageable levels of free iron leading to iron-related toxicity. The focus of debate about potential iron toxicity in patients with anaemia associated with CKD revolves around the possible increased susceptibility to infectious complications and increased cardiovascular morbidity and mortality engendered by iron administration. In vitro, iron preparations enhance bacterial growth, induce leukocyte dysfunction, inhibit phagocytosis, produce reactive oxygen species, increase oxidative stress, consume antioxidants and, at very high doses, promote lipid peroxidation and cell death. These observations have led to concern that too much iron might translate these in vitro phenomena into adverse infectious and cardiovascular in vivo effects.

5.2.2 Methodological introduction

A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.

5.2.3 From evidence to recommendations

Because of the lack of evidence, it was agreed that an upper limit of 800 µg/l of ferritin should be used in line with the current European Best Practice Guidelines[a]. This level is drawn from data on iron toxicity studies performed in the pre-ESA era that demonstrated that high ferritin levels >1,000 µg/l led to the deposition of iron in tissues. However, in practice, in order to prevent serum ferritin

a At the time of writing the current European guidelines were: European best practice guidelines for the management of anemia in patients with chronic renal failure. *Nephrology Dialysis Transplantation* 1999;14(Suppl 5):1-50.

from rising above 800 µg/l a patient's iron dose should be reviewed if their serum ferritin levels exceed 500 µg/l. It was noted that it was not known whether there are any long-term consequences related to the administration of intravenous iron as this route bypassed normal absorption routes and homeostatic mechanisms.

It should be noted that ferritin is an acute phase protein that is increased during inflammatory events, this affects the interpretation of some of the studies reviewed.

5.2.4 Recommendation

9. In people treated with iron, serum ferritin levels should not rise above 800 µg/l. In order to prevent this, the dose of iron should be reviewed when serum ferritin levels reach 500 µg/l. [D (GPP)]

5.3 Clinical utility of ESA therapy in iron-replete patients

5.3.1 Clinical introduction

Patients who are iron replete (ferritin >100 µg/l and %HRC <6% or TSAT ≥20%) yet still have anaemia associated with CKD will not achieve target haemoglobin levels without administration of ESAs. Should all patients regardless of the clinical situation and their functional status receive ESAs? Estimates of the number of people in England and Wales with significant CKD (eGFR <60 ml/min) and a haemoglobin level below 11 g/dl not currently receiving ESAs suggest that the potential number requiring anaemia management is 108,000. However, this estimate was made from an unselected population that will have included those with causes of anaemia other than CKD. A significant number may not have been iron replete, and the mean age of the cohort was 75.1 ± 11.63 years. The National Service Framework for Older People states that 'NHS services will be provided, regardless of age, on the basis of clinical need alone'. For many older patients improvement in quality of life is their paramount need, and older people should not necessarily be excluded from these treatments. Becoming able to move around your house independently and therefore not needing admission to a care home would clearly be a successful outcome in treating anaemia.

The key goals in the management of anaemia are increased exercise capacity, improved quality of life, improved cognitive function, improved sexual function, reduced transfusion requirements, regression/prevention of left ventricular hypertrophy, improved morbidity, prevention of progression of renal disease, reduced risk of hospitalisation, and reduced mortality. We do not yet have the evidence that all of these goals are achievable and there may be certain patients whose physical and mental status renders these goals unachievable from the outset. Clearly these patients will not therefore benefit from administration of ESAs.

5.3.2 Methodological introduction

A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.

5.3.3 From evidence to recommendations

The GDG expected there to be a paucity of literature in this area. The reason for investigating the evidence base in this section was to determine whether there were any subgroups of patients in whom the administration of ESAs may be of little clinical benefit.

The GDG discussed whether they considered there were any patient subgroups with a Hb level below 11 g/dl and with stage 3–5 CKD who should not be considered for treatment with ESAs. The GDG felt

that it was a matter of clinical judgement, based on a patient's individual circumstances (eg presence of comorbidities), as to whether a patient would benefit from the administration of ESAs.

The GDG considered it important to note that antibody mediated pure red cell aplasia (PRCA) does occur sporadically and this was one group of patients where epoetin administration should be very carefully considered.

The GDG felt the most relevant issue was how to best focus resources in the wider CKD population to provide the most benefit. The lack of evidence would suggest this is an area where research is required. The GDG discussed that where there is uncertainty over the benefits a patient may gain from ESA therapy, a trial of ESA therapy and assessment of response may be indicated prior to continuing long-term treatment. The GDG felt that the patient was a good judge of whether the treatment had any noticeable improvement on their quality of life and did not feel there was any need to recommend any formal tests. The GDG felt strongly that the decision to actively manage an individual patient's anaemia should be made by an experienced clinician, but that this did not necessarily have to be a renal physician.

5.3.4 Recommendations

10. The pros and cons of a trial of anaemia management should be discussed between the clinician, the person with anaemia of CKD and their families and carers if applicable. [D (GPP)]

11. ESAs need not be administered where the presence of comorbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia. [D (GPP)]

12. A trial of anaemia correction should be initiated when there is uncertainty over whether the presence of comorbidities, or the prognosis, would negate benefit from correcting the anaemia with ESAs. [D (GPP)]

13. Where a trial of ESA therapy has been performed, the effectiveness of the trial should be assessed after an agreed interval. Where appropriate, a mutual decision should be agreed between the clinician, the person with anaemia of CKD and their families and carers on whether or not to continue ESA therapy. [D (GPP)]

14. All people started on ESA therapy should be reviewed after an agreed interval in order to decide whether or not to continue using ESAs. [D(GPP)]

5.4 Nutritional supplements

5.4.1 Clinical introduction

Vitamins are essential cofactors that regulate the metabolic pathways from which lipids, proteins and carbohydrates are generated and processed. The uraemic environment is responsible for the development of significant alterations in serum levels, body stores and functions of many vitamins.

In patients with more advanced CKD (stages 4 and 5) the dietary restrictions imposed for potassium and phosphate inevitably limit the intake of some vitamins from natural sources. More recently dietary counselling has focused more on nutritional support than dietary restrictions, with people eating more liberal diets to try and optimise nutritional status. Currently there are no recommendations or guidance as to which population would benefit from vitamin supplementation and in what quantity. Much of our information about supplementation of vitamins comes from

studies with small subject numbers, over short periods of time. Many of the studies only address vitamin requirements in the dialysis-dependent population, excluding predialysis patients.

Reasons to support vitamin supplementation include dietary restrictions, uraemic toxins, drug–nutrient interactions and the dialysis process itself. Water soluble vitamins are lost during both haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). However, this may be offset by the altered kinetics caused by renal failure which may result in reduced urinary losses or renal catabolism. The fact that CKD affects the normal absorption, retention and activity of the necessary micronutrients which support all aspects of carbohydrate, protein and lipid metabolism, further strengthens the evidence in favour of supplementation.

Less is known about the nutritional requirements of fat soluble vitamins in patients with CKD. Studies report anything from subnormal through normal to enhanced levels. In practice supplementation with fat soluble vitamins is not recommended.

Data remain incomplete on individual requirements of vitamins, the handling of vitamins in uraemia, the vitamin status of uraemic patients and the effect of vitamin administration.

Carnitine is synthesised in the body from two essential amino acids, lysine and methionine, whereas glutathione is a peptide containing the amino acids glutamic acid, cysteine and glycine. Carnitine and glutathione have both been implicated in enhancing responsiveness to EPO in CKD patients but there are few studies to date. In practice, this is not done routinely.

Although much is known about the prevalence of macronutrient deficiency in renal patients, nutritional status in CKD is beyond the scope of this guideline. This section focuses on micronutrient supplementation and its effect on the treatment of anaemia due to CKD.

5.4.2 Methodological introduction

A comprehensive literature search identified eight studies. Of these, two studies addressed vitamin C: a cross-over RCT[119] and a non-randomised controlled trial[307]. One RCT addressed folic acid[236]. Five studies addressed carnitine supplementation, which consisted of three RCTs,[47,159,164] a cross-over RCT[280] and a before and after study[179].

Eleven studies had methodological limitations and were thus excluded from the evidence statements. These include four which addressed vitamin C,[156,284,308,310] one which addressed vitamin E[227], one which addressed folate[158], and five which addressed carnitine supplementation[131,195,274,295,324].

Notable aspects of the evidence base were:

- No studies addressing vitamin E or glutathione were found.
- The meta-analysis investigating carnitine supplementation[131] did not meet quality criteria, hence the studies within it[47,159,164] were individually appraised.
- One study was conducted in children[179].
- One study[119] was conducted in a pre-selected patient population.

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section.

5.4.3 Evidence statements

Vitamin C

Haemodialysis patients

A non-randomised trial (n=52)[307] where 100 mg ascorbic acid was administered i.v. three times weekly in one group (n=23) and as an adjunct to ESA and i.v. iron in another, found no significant change in Hb levels from baseline in either group after 6 months. In addition, no changes were identified in either group in any of the eight domains of quality of life assessed using the Short-Form 36 (SF 36) scale. (Level 2+)

In a randomised controlled trial (RCT) of cross-over design (n=27)[119], where ascorbic acid 1,500 mg/week was administered i.v. for 3 months, Hb increased ($p<0.01$ in group I and $p<0.005$ in group II) and TSAT increased (both group I and group II $p<0.001$), whereas ferritin decreased ($p<0.004$ in group I and $p<0.001$ in group II) when compared with baseline levels. Epoetin doses, however, remained unchanged in both groups. (Level 1+)

Folic acid

Haemodialysis patients

Reticulocyte counts (both $p<0.05$) and Hct levels (both $p<0.01$) increased from baseline levels in both sets of patients receiving folic acid 5 mg three times a week over 12 months (n=10) and patients whose folic acid supplementation had been stopped over this time period (n=10). Hct levels increased further (both $p<0.01$) in the 6-month follow-up period after folic acid supplementation had been stopped in both groups of patients. There were no differences, however, in response to epoetin between the two groups[236]. (Level 1+)

Carnitine

Haemodialysis patients

No differences were observed in any of the five domains of quality of life as assessed by the Kidney Disease Questionnaire or in overall quality of life, in a RCT of cross-over design (n=16) in which placebo or 20 mg/kg L-carnitine were administered i.v. over a 12-week period. Similarly, no differences were observed in epoetin dose or Hb levels[280]. (Level 1+)

No differences were observed in epoetin dose requirement or Hct and reticulocyte counts in a 6-month study investigating the effects of supplementation with 1 g L-carnitine three times a week in elderly patients (n=28), after which patients were followed up for 3 months[47]. (Level 1+)

No differences were found when patients treated with epoetin were supplemented with 1 g carnitine three times a week or placebo (n=24) for 6 months and compared in terms of epoetin dose, endogenous epoetin levels or Hct and iron levels[164]. (Level 1+)

No significant changes in epoetin dose requirement were observed between patients supplemented with either 5 mg/kg (n=15) or 25 mg/kg (n=5) L-carnitine vs placebo (n=20) over 8 months. However, a greater reduction in change in epoetin dose was observed in the carnitine treated group ($p<0.05$) and a higher epoetin resistance index (epoetin dose:Hb ratio) ($p<0.02$). Additionally, after 4 months, there were significant negative correlations between plasma free carnitine, plasma total carnitine and plasma free carnitine:plasma total carnitine to EPO dose and ERI in both treatment groups[159]. (Level 1+)

Paediatric haemodialysis and peritoneal dialysis patients

Total carnitine and free carnitine increased significantly from baseline (both $p<0.05$) after 26 weeks treatment with orally administered L-carnitine 20 mg/kg daily in both haemodialysis (n=8) and

peritoneal dialysis patients (n=4), with a mean age of 10.2 years. Acylcarnitine increased only in haemodialysis patients (n=8) after 26 weeks. Despite this, no changes were observed in Hb levels or epoetin dose from baseline in both sets of patients. In addition, no correlation was found between epoetin dose or Hb levels with total carnitine, free carnitine and acylcarnitine levels[179]. (Level 3)

5.4.4 From evidence to recommendations

It was concluded that there was no evidence to support the adjunctive use of vitamin C, folic acid or carnitine supplements in the treatment of anaemia of CKD. There was very little evidence available for the CKD population and no evidence in the predialysis population. It was considered acceptable to extrapolate the conclusions to the predialysis population.

With regard to vitamin C, the appraised studies administered very high doses (1,500 mg/wk, 1,000 mg/wk and 100 mg/wk). A dose of 50 mg/week was considered to be a more appropriate supplement given in clinical practice to renal patients. The biological basis for the administration of vitamin C was related to aiding the mobilisation of iron and promoting effective erythropoiesis. The evidence base was small.

In clinical practice, when patients are given folate supplements this is generally for other reasons than the correction of anaemia. The studies appraised on carnitine supplementation gave negative results.

5.4.5 Recommendation

15. Supplements of vitamin C, folic acid or carnitine should not be prescribed as adjuvants specifically for the treatment of anaemia of CKD. [A]

5.5 Androgens

5.5.1 Clinical introduction

Interest in the use of androgens as adjunctive treatment in the management of anaemia associated with CKD stems from their use prior to the availability of ESAs. A number of early studies[49,77,110,128,337] suggested a beneficial effect on renal anaemia by treatment with androgens, although notably one double blind cross-over trial of nandrolone decanoate failed to show a sustained significant effect on haemoglobin level or red cell mass[213]. However, their regular use was abandoned because of the requirement for parenteral administration and a number of adverse effects such as acne, flushing of skin, hirsutism, changes in voice, masculinisation, amenorrhoea and increasing libido, together with adverse effects related to liver function such as peliosis as well as hepatocellular adenoma and carcinoma.

The mechanism of action of androgens on erythropoiesis is still not completely understood and mechanisms proposed include increased production of endogenous erythropoietin, synergism with ESAs, enhanced sensitivity of erythroid precursors to erythropoietin, increased red cell survival, and a direct effect on erythroid precursors. There is thus a potential role for androgens in enhancing the effectiveness and reducing the dose requirements of available ESAs.

5.5.2 Methodological introduction

A literature search identified eight studies, including two RCTs[118,224], three cohort studies[26,312,313] and one before and after study[169].

Two studies[33,117] had methodological limitations and were therefore excluded from the evidence statements.

The GDG agreed that the following outcomes were priorities:

- mortality and morbidity
- improved response to ESAs
- quality of life
- Hb/Hct level
- ESA dose
- adverse effects.

Notable aspects of the evidence base were:

- The studies were investigating:
  - epoetin vs nandrolone[224,313]
  - epoetin vs epoetin and nandrolone[26,118]
  - epoetin and nandrolone (no control group)[169]
  - Nandrolone alone (no control group)[312].
- Although side effects were noted in some studies[118,169,312], the authors did not attempt to quantify all of these.
- The studies were conducted in both male and female patients except for two studies[26,224], which were conducted solely in male patients.

5.5.3 Evidence statements

Hb/Hct levels

Haemodialysis patients

In a before and after study conducted in male (n=9) and female (n=8) patients[169], Hb (p=0.001) and Hct (p=0.003) levels increased following adjuvant therapy with epoetin (3,000 U/week s.c.) and nandrolone decanoate (100 mg i.m. weekly) for 6 months. When stratified into sex of patients, Hb and Hct levels (both p=0.01) were higher only in female patients. (Level 3)

In a cohort study conducted in male (n=67) and female (n=17) patients[312], Hb and Hct levels rose (both p<0.01) following 6 months' therapy with nandrolone decanoate 200 mg i.m. weekly. Although baseline Hb levels were higher in the male patients (p<0.05), the increase with respect to baseline levels was similar in both sexes throughout the study. In order to evaluate the influence of other factors, patients were divided into the following:

- non-responders (Hb increase <1 g/dl with respect to baseline; n=28)
- mild responders (Hb increase 1–1.9 g/dl with respect to baseline; n=18)
- good responders (Hb increase 2–2.9 g/dl with respect to baseline; n=25)
- excellent responders (Hb increase >2.9 g/dl with respect to baseline; n=13).

Only age was significantly associated with response to androgen therapy (p<0.01). When the cohort was stratified into ages less than 46 years (n=29), 46–55 years (n=28) and more than 55 years (n=27), only the latter two groups showed improvement in Hb levels (both p<0.01) following androgen therapy. (Level 2+)

A 6-month cohort study conducted to compare the effect of 200 mg nandrolone decanoate i.m. once weekly in male patients aged over 50 years (n=18) vs epoetin 6,000 IU a week in male and female

patients aged less than 50 years (n=22) found an increase in Hb levels in both groups (both p<0.01), despite a drop in serum ferritin levels in the epoetin treatment group (p<0.01)[313]. (Level 2+)

In a cohort study[26] conducted over 12 weeks in male patients treated with epoetin 6,000 U i.v. 3 times a week (n=7) vs epoetin 6,000 U i.v. 3 times a week and 100 mg nandrolone decanoate i.m. once a week (n=8), Hct values increased in the group receiving adjuvant therapy (p<0.001) after 12 weeks and no transfusions were required in either group. (Level 2+)

A RCT conducted in predominantly black male and female patients administered with epoetin 4,500 U per week vs epoetin 4,500 U per week (n=10; 4 men and 6 women) and nandrolone 100 mg i.m. once a week (n=9; 7 men and 2 women) over 26 weeks found a significant increase in Hct in both treatment groups when compared with baseline values (p=0.003 and p=0.001 respectively). However, the rise in Hct was greater in the epoetin plus androgen group (p=0.012) when compared with epoetin alone[118]. (Level 1+)

CAPD patients

Hb and Hct levels increased in both treatment groups in a RCT[224] investigating influence of epoetin initiated at 50 U/kg/week and tailored to target Hb of 11–13 g/dl vs nandrolone 200 mg i.m. once weekly (both p<0.001) when compared with baseline values. However, these increases in Hb and Hct levels were not significantly different when the treatment groups were compared with each other. (Level 1+)

Epoetin dose

Haemodialysis patients

In a before and after study conducted in male (n=9) and female (n=8) patients[169], weekly epoetin doses following adjuvant therapy with nandrolone decanoate (100 mg i.m. weekly for 6 months) did not change significantly, either in the overall cohort or when stratified into male and female patients. (Level 3)

In a cohort study conducted over 12 weeks in male patients treated with epoetin (6,000 U i.v. three times a week) (n=7) vs epoetin (6,000 U i.v. three times a week) and nandrolone decanoate 100 mg i.m. once a week (n=8), no difference was observed in epoetin dose between the two treatment groups[26]. (Level 2+)

Adverse events—serum triglycerides

Haemodialysis patients

In a cohort study conducted in male (n=67) and female (n=17) patients, serum triglycerides increased (p<0.01) after therapy with nandrolone decanoate 200 mg i.m. weekly for 6 months[312]. (Level 2+)

A 6-month cohort study conducted to compare the effect of nandrolone decanoate (200 mg i.m. once weekly) in male patients aged over 50 years (n=18) vs epoetin (6,000 IU a week) in male and female patients aged less than 50 years (n=22) found an increase in serum triglycerides in the androgen group (p<0.001)[313]. (Level 2+)

5.5.4 From evidence to recommendations

The rationale for the administration of androgens to patients with anaemia of CKD was historical in that androgens were administered in the pre-ESA era. The studies had administered nandrolone

decanoate but this androgen is no longer used in clinical practice. The doses of nandrolone administered in the studies were considered to be supraphysiological. The group agreed that there was some evidence of efficacy in that the administration of androgens could reduce the dose of ESA required but were concerned about the potential side effects and considered this an outdated approach to anaemia management.

5.5.5 Recommendation

16. In people with anaemia of CKD, androgens should not be used to treat the anaemia. [C]

5.6 Hyperparathyroidism

5.6.1 Clinical introduction

Elevations in serum parathyroid hormone (PTH) concentration (secondary hyperparathyroidism) are seen early in CKD and are common when the estimated GFR is <60 ml/min (stage 3 CKD onwards)[263,296,325]. Elevation of PTH in the stage 3 and 4 CKD populations predicts the development of more severe hyperparathyroidism, which in turn is clearly associated with increased skeletal and cardiovascular morbidity and mortality[72]. Whether hyperparathyroidism causes anaemia and resistance to treatment of anaemia, and if it does, what degree of hyperparathyroidism is clinically important, remain controversial. Potential mechanisms include a direct effect of PTH on endogenous erythropoietin synthesis, on bone marrow erythroid progenitors, and on red cell survival through accelerated haemolysis, and an indirect effect through induction of bone marrow fibrosis. This section looks at whether treatment of hyperparathyroidism in people with anaemia associated with CKD improves the management of anaemia in terms of haemoglobin level achieved and dose of ESA required, and also attempts to determine when treatment should be considered.

5.6.2 Methodological introduction

A literature search identified seven studies. These consisted of a cohort study[72], a two-part study comprising a cohort study and prospective before and after study[180], a two-part study comprising a prospective longitudinal study and cohort study[121], a prospective before and after study and cohort study[344], a prospective longitudinal study[14], and two retrospective before and after studies[58,262].

Six studies[29,112,226,256,326,346] had methodological limitations and were therefore excluded from the evidence statements.

The GDG agreed that the following outcomes were priorities:

- parathyroid hormone levels
- mortality and morbidity
- quality of life
- ESA dose
- improved response to ESA
- plasma erythropoietin levels
- reduction in ESA resistance
- Hb/Hct level.

Notable aspects of the evidence base were:

- Treatment for parathyroidism was stratified into drug-based with calcitriol[121,180], alfacalcidol[14], or surgery[58,72,168,262].

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.

5.6.3 Evidence statements

Table 5.1: Summary of evidence for appraised studies

Reference	Drug-based therapy	Sample size	Baseline iPTH levels (pg/ml)	Treatment duration	Outcome	Effect	Level of evidence
[180]	Calcitriol 2 µg	n=16	778 ± 172.7	6 months	n=7 responders		Level 2+
					iPTH	↓	
					Hct	↑	
					Epoetin dose	↓	
[14]	Alfacalcidol 6 mg	n=12	~475	18 months	iPTH	↓	Level 3
					Hb	↑	
[121]	Calcitriol i.v. 2 µg	n=28	811.6 ± 327	12 months	Hb/Hct	↑	Level 3
					IPTH	↓	
[121]	Calcitriol i.v. 2 µg	n=28	811.6 ± 327	12 months	Epoetin use (n=21) vs No Epoetin (n=7) Epoetin dose	No change	Level 2+
[121]	Calcitriol i.v. 2 µg	n=28	811.6 ± 327	12 months	Responders (n=19) vs non-responders (n=9)		Level 2+
					Hct	↑	
					Epoetin dose	No change	

Author/Study ID	**Surgical procedure**	**Sample size**	**Basal iPTH levels (pg/ml)**	**Length of follow-up after surgery**	**Outcome**	**Effect**	**Level of evidence**
[262]	Subtotal parathyroidectomy (n=9) and total parathyroidectomy with forearm autotransplantati	n=10	Not reported	6 months	iPTH	↓	Level 3
					Hct	↑	
					Epoetin dose	↓	

	on (n=1)						
[180]	Total parathyroidectomy with forearm autotransplantation	n=3	976 ± 436.1	6 months	iPTH Hct Epoetin dose	↓ ↑ ↓	Level 3+
[58]	Subtotal parathyroidectomy	n=19	1,726 ± 1,347	1–2 years (n=44)	Hb	No change	Level 3
	Total parathyroidectomy and autotransplantation	n=10	913 ± 380	3–5 years (n=24)	Hb	↑	
	Total parathyroidectomy	n=10	1,006 ± 668				
	Partial parathyroidectomy (removal of 2–3 parathyroid glands)	n=6	1,176 ± 3346				
[344]	Total parathyroidectomy and forearm autotransplantation	n=29 Note n=7 underwent reoperation for recurrences in neck and forearm	873 ± 710.8	12 months	iPTH Hb Plasma erythropoietin	↓ ↑ ↑	Level 3
				12 months	Epoetin use (n=23) vs No Epoetin (n=6) Epoetin dose	No change	Level 2+
[168]	Total parathyroidectomy and forearm autotransplantation	n=32 1,338 ± 350.6	Responders Non-responders 1,228 ± 290.8	3 months	n=17 responders (≥10% Hb increase post-PTX) vs n=15 non-responder	No change No change No difference	Level 2+
					Hb Serum erythropoietin	↓ but no difference between the 2 groups	
					iPTH		
↑ = significant increase;							

↓ = significant decrease;

PTX = parathyroidectomy.

5.6.4 From evidence to recommendations

Treatment of hyperparathyroidism secondary to CKD is part of good clinical practice as is routine monitoring of PTH levels in patients with CKD. Early control of hyperparathyroidism is crucial for preventing metabolic bone disease and treating hyperparathyroidism is beneficial to anaemia management. The strategies used do not differ in patients with CKD whether they are anaemic or not. On the evidence available, it was not felt to be appropriate to recommend specific interventions and the British[266], American[194] and European[4] treatment guidelines in the management of renal osteodystrophy which are aimed at attainment of target PTH, calcium and phosphate concentrations should be followed.

5.6.5 Recommendation

17. In people with anaemia of CKD, clinically relevant hyperparathyroidism should be treated to improve the management of the anaemia. [C]

5.7 Patient-centred care: ESAs

5.7.1 Clinical introduction

The ESAs currently available in clinical practice differ in terms of frequency of administration and route of administration. The ESAs currently available in clinical practice may be administered either subcutaneously or intravenously. Darbepoetin is likely to require less frequent administration than the erythropoietins, while the erythropoietins are likely to require less frequent administration and a lower dose when administered subcutaneously vs intravenously. Logistically it is easier for patients not on haemodialysis to receive ESAs subcutaneously by self-administration or administration by their carer/practice nurse at home; patients on haemodialysis may also elect to receive their ESA either through self-administration or from dialysis staff at the end of haemodialysis.

Key considerations for patients with anaemia associated with kidney disease are that:

- ESAs are prescribed when clinically indicated.
- The ESA supply, route of supply and storage arrangements are clearly defined, secure and convenient.
- The administration and monitoring of anaemia treatment is as efficient, comfortable and least disruptive as possible.

5.7.2 Methodological introduction

Seven studies were identified, including two RCTs[123,211], one of which was of cross-over design[123], one retrospective longitudinal study[334], one retrospective case series[230], and three cross-sectional studies[19,191,223].

One study[25] had methodological limitations and was thus excluded from the evidence statements. The buffer used in the preparation in the cross-over study[123] is no longer used, and the paper was therefore not considered further.

Notable aspects of the evidence base were:

- The studies conducted using questionnaires were limited by the use of closed questions in their design[191,223,334], with the exception of one study[19], which reported the use of both closed and open questions.
- All the studies using questionnaires were cross-sectional, with the exception of one study[334], which was of longitudinal design.

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no evidence statements are given.

5.7.3 Evidence statements

Route of administration – effect on quality of life

Haemodialysis patients

In a 24-week cross-over study[211] where s.c. was compared with i.v. administration, quality of life assessed by means of the Kidney Disease Questionnaire (KDQ), which consists of five domains, found improvements from epoetin administration (both intravenous and subcutaneous) in the physical ($p<0.05$) and fatigue ($p<0.05$) domains, but no significant differences between the two modes of administration in any other domains[123]. (Level 1+)

Adherence and ESA administration

Peritoneal dialysis patients

In a retrospective longitudinal study[334], 19 of 54 (35%) patients administering s.c. epoetin in the home setting were non-concordant (defined as less than 90% of the prescribed dose used), with the most commonly reported reason being forgetfulness. Missing dialysis exchanges, completion of secondary education and younger age were found to be independent predictors of non-adherence ($r2=0.36$). (Level 3)

In a retrospective study[230], 30 of 55 (55%) patients administering epoetin s.c. in the home setting were non-concordant (defined as less than 90% of the prescribed dose used). Whether another person administered the ESA on behalf of the patient was the only significant correlation with concordance ($r=0.46$, $p=0.005$). (Level 3)

Haemodialysis and continuous ambulatory and automated peritoneal dialysis patients

In a cross-sectional study[191], concordance ranged from 24–33%, with the over-60 age group least likely to miss an epoetin dose and reduced frequency of administration associated with less missed doses. The majority of patients were likely to self-administer. Fewer injections were preferred by 72.5%, with the under-60 age group preferring once-weekly because of convenience, pain on injection and epoetin storage. (Level 3)

Predialysis, hospital and home haemodialysis and continuous ambulatory peritoneal dialysis patients

In a cross-sectional study[19], 57 of 86 (66%) patients reported they never missed doses, while 31% admitted to occasionally missing doses and 3% admitted to frequently missing doses. Following a missed dose, the majority (39%) informed the renal unit, 27% carried on as usual after the missed dose, 19% administered the missed dose as soon as they remembered. The majority (55%) of patients preferred self-administration of epoetin, with 17% reporting difficulties with injection preparation and 17% reporting pain at the injection site. (Level 3)

Communication and obtaining of ESA

Predialysis, hospital and home haemodialysis and continuous ambulatory peritoneal dialysis patients

In a cross-sectional study[19], the majority of patients (89%) reported the renal unit anaemia nurse to be the preferred source of information. However, most patients (59%) reported they did not need more information. Most requests for information were found to be about how epoetin works (31%), possible side effects (29%) and what epoetin is for (26%). Epoetin supply was found to be mostly by GPs (71%), although 20 patients (23%) reported that their GPs had refused to supply epoetin. Most patients preferred obtaining epoetin supplies from a community pharmacy (n=63). (Level 3)

Predialysis, dialysis and transplant patients

In a cross-sectional study[223], most (91%) anaemic patients received epoetin therapy. Of the 4% that were refused epoetin, the reasons given were that the GP could not pay for it (50%) and that the hospital could not pay for it (20%). (Level 3)

EPO administration – effect on quality of life

Predialysis, dialysis and transplant patients

In a cross-sectional study[223], sleep disturbance, tiredness and ability to attend a 9am to 5pm job were found to be associated with baseline Hb and post-treatment levels. Patients whose post-treatment Hb levels had increased from below 11 g/dl to above 11 g/dl were 1.8 times more likely to report an improvement in QoL. Patients with post-treatment Hb levels >11 g/dl were 1.9 times more likely to agree with the statement 'I can attend a 9am–5pm job'. (Level 3)

5.7.4 From evidence to recommendations

The evidence from seven studies contained outcome data on quality of life, pain, concordance, obtaining ESAs and communication with patients.

The data supported the view that patient preferences and experiences should be taken into account, where possible, when decisions are reached about treatment with ESAs. The patient should be given access to sufficient information about their condition and its treatment to allow them to make informed choices about the management of their condition (for example, whether to have supervised- or self-administration of ESAs). It was noted that some studies had shown an increased lack of concordance in some groups who had chosen self-administration[230,334]. Patients need to be aware of the consequences of poor concordance and one study highlighted that a reduced frequency of administration of ESAs resulted in increased concordance[191]. Currently many patients have difficulties securing a supply of ESAs. Many patients are unable to obtain ESAs from their local hospital or GP practice and have the ESAs delivered to them at home. This can cause problems in finding the capacity to refrigerate large quantities of drugs. This area needs to be addressed by healthcare providers to ensure adequate drug supply and storage facilities for patients.

5.7.5 Recommendations

18. People offered ESA therapy, and their GPs, should be given information about why ESA therapy is required, how it works, and what benefits and side effects may be experienced. [D]

19. When managing the treatment of people with anaemia of CKD, there should be agreed protocols defining roles and responsibilities of healthcare professionals in primary and secondary care. [D(GPP)]

20. People receiving ESA therapy should be informed about the importance of concordance with therapy and the consequences of poor concordance. [D]

21. When prescribing ESA therapy, healthcare professionals should take into account patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA and storage. [D(GPP)]

22. In order for people to self-administer their ESA in a way that is clinically effective and safe, arrangements should be made to provide ready, reasonable and uninterrupted access to supplies. [D]

5.8 Patient education programmes

5.8.1 Clinical introduction

Patient self-management is one of the cornerstones of chronic disease management, enabling patients some degree of control of their own disease process. The level of independence each individual achieves depends as much on the quality of the information and self-management tools provided as it does on the ability of the individual patient. Patient education programmes are therefore of paramount importance in achieving effective patient self-management.

Structured patient education involves planned education that covers all aspects of anaemia management and is flexible in content, is relevant to a person's clinical and psychological needs, and is adaptable to their educational and cultural background. A well-planned education course will provide a written outline, be delivered by trained educators (preferably someone who is both well versed in the principles of patient education and is competent to teach the programme), be quality assured, and provide the opportunity for feedback.

5.8.2 Methodological introduction

A comprehensive literature search did not identify any clinical or health economic studies that were suitable to address this section.

5.8.3 From evidence to recommendations

Patient education was considered to be hugely important and information should be available at different levels. Adequate information helps patients to make decisions about their treatment and illness, although it was noted that there might be some patients who will wish to remain passive about their condition.

Patient education should meet the individual needs of each patient and five themes drawn from recent work in the area[272] were considered to be important:

- practical management of anaemia
- knowledge (about symptoms, iron and ESA management and product delivery and storage)
- professional support (contact information, community services, continuity of care, monitoring, feedback on progress of results)
- lifestyle (diet, physical exercise, maintaining normality, meeting other patients)
- adaptation (causes of anaemia, associated medications, phases of treatment, previous information and expectations, resolution of symptoms).

5.8.4 Recommendation

23. Culturally and age-appropriate patient education programmes should be offered to all people diagnosed with anaemia of CKD and their families and carers. These should be repeated as requested, and according to the changing circumstances of the patient. They should include the following key areas:

- **practical information about how anaemia of CKD is managed**
- **knowledge (eg about symptoms, iron management, causes of anaemia, associated medications, phases of treatment)**
- **professional support (eg contact information, community services, continuity of care, monitoring, feedback on progress of results)**
- **lifestyle (eg diet, physical exercise, maintaining normality, meeting other patients)**
- **adaptation to chronic disease (eg previous information and expectations, resolution of symptoms).** **[D(GPP)]**

6 Assessment and optimisation of erythropoiesis

6.1 Benefits of treatment with ESAs

6.1.1 Clinical introduction

The introduction of ESAs into clinical practice nearly 20 years ago dramatically changed the management of anaemia associated with chronic kidney disease. Prior to ESA therapy, dialysis-dependent patients were profoundly anaemic, frequently manifesting haemoglobin levels of between 6 and 7 g/dl, the only treatments available being blood transfusions, iron or androgen therapy. The potential benefits associated with anaemia treatment are numerous. These include avoidance of blood transfusions with their attendant risks of sensitisation against future transplantation, iron overload, blood-borne disease and transfusion reactions; improved quality of life and physical functioning; improved cognitive and sexual function; cardiovascular benefits in terms of structure, function, incidence and prevalence of disease; and reduced hospitalisation, morbidity and mortality.

6.1.2 Clinical methodological introduction

Four studies were identified. A meta-analysis (epoetin vs placebo or no treatment)[57], two multisite RCTs (epoetin vs placebo)[2,231], one cohort study (epoetin vs no treatment)[56] and a retrospective longitudinal study[258]. Two studies[23,258] had methodological limitations and were therefore excluded.

The outcomes to assess the efficacy of the ESA preparations in comparison with placebo or no treatment were morbidity, left ventricular hypertrophy, left ventricular function, mortality, hospitalisation and dialysis adequacy.

Notable aspects of the evidence base:

- All studies except for two included in the meta-analysis[57] did not explicitly state if they used epoetin-alfa or epoetin-beta.
- The study durations ranged from 12 weeks to 3.5 years.
- Studies included in the meta-analysis[57] achieved a lower Hb level and excluded patients with significant comorbidities.
- In one study[231] red cell transfusions were given to placebo or treatment arms when required.

6.1.3 Clinical evidence statements

Quality of life

Predialysis patients

Of the studies in the meta-analysis[57], Kleinman (1989), by means of a visual analogue scale rating of three questions, found an improvement in quality of life after 12 weeks with a mean difference of 35 (95% CI 12.47 to 57.53). Roth (1994), by means of the Sickness Impact Profile and other validated tests, found an improvement at 48 weeks, with the control group having decreased physical function (p=0.03) and the epoetin group having increased physical function (p=0.015) as well as increased energy (p=0.045). However, the number of domains assessed in this study was not provided by the authors. (Level 1+)

Haemodialysis patients

In one study[2] an improvement in four out of five categories of the Kidney Disease Questionnaire were found (physical p<0.001; fatigue p<0.001; relationships p=0.001; depression p=0.018). In addition, the Sickness Impact Profile questionnaire found an improvement in quality of life as reflected by the reduction of the global scores (p=0.024) and the physical scores (p=0.005). Psychosocial scores did not change significantly. (Level 1+)

Mortality

There were insufficient mortality data available from the meta-analysis[57] and the RCT[231] to write evidence statements.

Hospitalisation

Study participants new haemodialysis patients

No statistically significant difference in hospitalisation between epoetin and placebo treatment groups was found, including when stratified and analysed into admission type, age group and history of cardiovascular disease[56]. (Level 2+)

6.1.4 Health economics methodological introduction

Three studies were identified[172,264,299]. One study[204] did not meet met quality criteria and therefore no evidence statements were made.

One study contained a cost-effectiveness analysis before and during epoetin therapy[299]. It was predominantly a cost-savings analysis with 1990 to 1991 UK£ and earlier costs. However, the 1990 to 1991 or earlier cost data meant that there was insufficient data from which to derive evidence statements for application to the current NHS context.

One study compared cost per QALY results in five European countries including the UK[172]. This study used QALYs as the effectiveness measure. Nevertheless, costs were derived from 1988 values, which indicates there are insufficient data from which to derive evidence statements for the current NHS context.

An additional study[264] evaluated the cost per QALY of epoetin using the same framework as the Leese study[172] (1988 values), but updated data with values from the year 2000 in the UK.

6.1.5 Health economics evidence statements

The cost per QALY of ESA therapy in the UK using data from the year 2000 was £17,067. The model was most sensitive to changes in the QALY gain. The baseline QALY gain used to derive the cost per QALY was 0.088 per year. However, if a 0.17 QALY gain occurs, the cost per QALY drops to £8,809, conversely if a 0.02 QALY gain occurred, the cost per QALY would increase to £74,876[264].

6.1.6 From evidence to recommendations

One study[57] was appraised that assessed mortality but the GDG considered the study to be underpowered to determine whether there was a clinically important difference in mortality rate. The GDG felt that the evidence was not sufficient to make a sound evidence statement.

The GDG concluded that the study of people receiving peritoneal dialysis[231] did not contribute meaningful data as the study duration was too short (12 weeks) to assess mortality.

Of the outcomes assessed, the GDG felt there was only good evidence supporting improvement in quality of life through ESA therapy. The GDG noted that the studies had small sample sizes and had concerns over the statistical validity of the evidence. The studies in the meta-analysis[57] achieved a low target haemoglobin and the patients that may have shown the greatest benefits were excluded from the studies.

The GDG noted that because highly selected populations were included in these studies, the effects reported were not as large as those observed in the unselected patient populations observed in clinical practice.

The GDG concluded on the basis of qualitative data and clinical experience that ESAs are of value.

Health economic evidence was presented to the group. The GDG agreed that one study was presented that was sufficiently robust to be included and gave useful cost per QALY information in the UK context[264]. However, as the model was sensitive to the gain in QALY, the GDG felt further economic evidence is required before definitive statements about the cost effectiveness are made. The GDG felt the other studies:

- estimated the price but underestimated the benefit of the treatment (n=24)[172]
- were based on a study design that could introduce bias[204], or
- were based on historical cost data that no longer had relevance to the current NHS context[299].

6.1.7 Recommendation

24. Treatment with ESAs should be offered to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function.
[A]

6.2 Blood transfusions

6.2.1 Clinical introduction

The potential risks of blood transfusion include transfusion reactions, immunomodulation, iron overload and transfusion transmitted infections.

Data concerning adverse transfusion events in the UK are collected by the Serious Hazards of Transfusion (SHOT) group. Their 2003 report included data from 351/415 UK hospitals (see www.shotuk.org). Since the inception of SHOT in 1996 there has been an increase in the number of adverse transfusion incidents reported with now over 2,000 recorded in the SHOT database (Table 6.1). Although the numbers of transfusion-transmitted infections reported are low, the list of infections that may be potentially transmitted is growing rapidly and includes hepatitis B, C and G, human immunodeficiency virus (HIV), human t-lymphocytotrophic virus (HTLV-1), transfusion transmitted virus (TTV), cytomegalovirus (CMV), Creutzfeld-Jakob disease (CJD), human herpes virus (HHV-8), leishmaniasis, Lyme disease, malaria, babesiosis and toxoplasmosis.

Table 6.1: Serious Hazards of Transfusion (SHOT) Report 2003

SHOT category	Reported cases 1996–2003, n (%)	Risk category	Estimated risk
Incorrect blood component transfused	1393 (66.7)	Risk of incorrect blood component transfused	1 in 16,500
Acute transfusion reaction	233 (11.2)	Risk of ABO incompatibility	1 in 102,200
Delayed transfusion reaction	213 (10.2)		

SHOT category	Reported cases 1996–2003, n (%)	Risk category	Estimated risk
Transfusion-related acute lung injury	139 (6.7)	Risk of transfusion-related acute lung injury	1 in 165,000
Transfusion-transmitted infection	45 (2.2)		
Post-transfusion purpura	44 (2.1)	Risk of serious hazard	1 in 11,000
Transfusion-associated GVHD	13 (0.6)	Risk of major morbidity	1 in 92,000
Unclassified	7 (0.3)	Risk of death	1 in 255,500

Prior to the introduction of ESAs, in addition to the immediate risks of transfusion reactions and infection, the two biggest concerns for patients with CKD were sensitisation against future transplantation and iron overload. This was complicated by the evidence suggesting that transfusion prior to transplantation may actually be beneficial in terms of future transplant outcome. This had been first suggested in 1973[238]. However, a subsequent assessment following the introduction of ciclosporin failed to confirm a benefit[237] and this subject remains controversial. Donor-specific transfusion prior to living-related transplantation appears favourable[104] but in cadaveric transplantation the picture is less clear. A multicentre randomised controlled trial of transfusion of three units of packed cells demonstrated improved graft survival at 1 and 5 years[239]. However, approximately 5% of the patients in this study became sensitised, and had not been transplanted by the end of the study period. In children, a retrospective study hinted at a beneficial effect from transfusion of 1–5 units of blood, but this beneficial effect was lost with greater numbers of units transfused[53]. A recent study looking at the causes of sensitisation of potential renal allograft recipients in Ireland in the post-EPO era demonstrated that the level of sensitisation clearly increased with the number of units transfused[294]. Non-sensitised participants (PRA <10%) received a mean of 5.65 units (SEM 1.38), sensitised participants (PRA 11–59%) a mean of 9.8 units (SEM 3.17), significantly sensitised (PRA 60–79%) a mean of 18.2 units (SEM 6.51), while highly sensitised participants (PRA ≥80%) received a mean of 37.8 units (SEM 8.4). There was a direct relationship between the waiting time for transplantation and the degree of sensitisation.

Although blood transfusion is not the only factor related to recipient sensitisation, since ESAs have become more freely available and the use of routine blood transfusion for correction of anaemia has disappeared, sensitisation has markedly reduced (Figure 6.1).

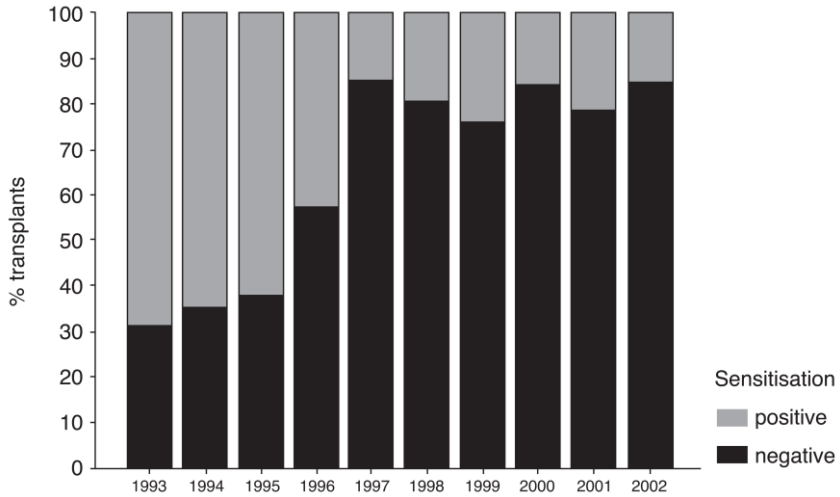


Figure 6.1 Recipient pre-transplant HLA-specific sensitisation: adult recipients of cadaver donor kidneys
(Manchester Kidney Transplants, NWKTA Audit Project, January 2003)

6.2.2 Methodological introduction

A comprehensive literature search identified two studies, a case-control study[65] and a before and after study[68].

Five studies[31,51,76,78,215,294] had methodological limitations and were therefore excluded from the evidence statements.

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.

6.2.3 Evidence statements

Immunological parameters/sensitisation

Haemodialysis patients

No significant differences were observed in the analyses of lymphocytes, monocytes, T8, T4, T11, T13, Ia and B1 cells or T4/T8 ratios in patients who had previously received five or more transfusions over 6 months (n=30) when compared with a matched lightly transfused group (n=30)[65]. (Level 2+)

Dialysis patients

More patients in the lightly transfused group developed narrowly reactive antibodies (reacting with 10–29% panel cells) in comparison with the more heavily transfused group who developed antibodies against ≥30% panel cells. Sensitisation increased waiting time for transplants both in subsequently transplanted patients ($p<0.003$) and the entire patient population regardless of transplantation ($p<0.03$)[68]. (Level 3)

6.2.4 From evidence to recommendations

The GDG noted the lack of evidence on important factors that would impact on the risks of correcting anaemia with regular blood transfusions, such as blood borne viruses and iron overload. In the late 1970s and early 1980s there was evidence that giving blood transfusions before transplantation improved transplant outcome and most units had a deliberate transfusion policy; most research focused on the risks of sensitisation which meant that certain donors would be excluded if the antibodies were directed to their lymphocytes (detected in the 'cross match test'). Around the mid-1980s transmission of blood borne viruses by transfusion (in particular HIV) became a major public health issue. At the same time ciclosporin came into regular use. Ciclosporin improved survival, and taken together with the risk of the transmission of blood borne viruses and the availability of erythropoietin for treating anaemia, deliberate transfusion was discontinued.

The GDG considered the evidence on the immunological risks of correcting anaemia with regular blood transfusions. They agreed that the evidence relating to the development of cytotoxic antibodies to lymphocytes[68] was more clinically relevant than the data on the levels of different subtypes of lymphocytes induced by transfusion[65]. It was noted that blood transfusion increased the percentage of cytotoxic antibodies in dialysis patients resulting in not only an increased waiting time for a transplant but also increased difficulty in finding a cross match negative donor.

The GDG felt it was important to stress the benefits of transfusion when clinically indicated for blood loss or in some cases the correction of anaemia (eg in some elderly patients). The GDG agreed that there were general clinical reasons to avoid blood transfusion and the relevant haematology guidelines should be followed (eg the British Committee for Standards in Haematology (BCSH) guidelines www.bcshguidelines.com).

6.2.5 Recommendations

25. In people with anaemia of CKD, in whom kidney transplant is a treatment option, blood transfusions should be avoided where possible. [D]

26. In people with anaemia of CKD there may be situations where a transfusion is indicated clinically. In these cases, the relevant haematology guidelines[51] should be followed. [D (GPP)]

6.3 Comparison of ESAs

6.3.1 Clinical introduction

Erythropoiesis stimulating agents (ESAs) are agents stimulating production of red blood cells through a direct or indirect action on erythropoietin receptors of erythroid progenitor cells in the bone marrow. There are three licensed forms of ESA currently available in England and Wales[b], two short-acting (epoetin alfa and epoetin beta) and one long-acting (Darbepoetin alfa).

Epoetin alfa is a glycoprotein manufactured by recombinant DNA technology and has the same biological effects as endogenous erythropoietin. It has an apparent molecular weight of 32,000 to 40,000 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The protein fraction of the molecule contributes about 58% and consists of 165 amino acids. Four carbohydrate chains are attached via three N-glycosidic bonds and one O-glycosidic bond to the protein moiety. Epoetin alfa obtained by gene technology is identical in its amino acid and carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients.

In both patients and normal volunteers, after intravenous administration of epoetin alfa, serum levels decline in a monoexponential manner and the volume of distribution is similar to that of the plasma volume. The half-life in normal volunteers is approximately 5 hours, but in patients with renal failure it is prolonged to approximately 9 hours. With multiple injections of epoetin alfa, half-life and clearance decrease. Measurement of epoetin alfa following multiple dose intravenous administration revealed a half-life of approximately 4 hours in normal volunteers and approximately 5 hours in renal failure patients. A half-life of approximately 6 hours has been reported in children. After s.c. administration of epoetin alfa, peak serum levels occur between 12 and 18 hours later. The peak is always well below the peak achieved using the i.v. route (approximately 1/20th of the value). The bioavailability of subcutaneous injectable epoetin alfa is approximately 20% lower than that of the intravenous drug. Elevated levels of epoetin alfa are found in the serum 48 hours after a subcutaneous dose, but not after an intravenous dose.

Epoetin beta is also identical in its amino acid and carbohydrate composition to erythropoietin that has been isolated from the urine of anaemic patients. Pharmacokinetic investigations in healthy volunteers and uraemic patients show that the half-life of intravenously administered epoetin beta is between 4 and 12 hours and that the distribution volume corresponds to one to two times the plasma volume. After subcutaneous administration of epoetin beta to uraemic patients, the protracted absorption results in a serum concentration plateau, whereby the maximum concentration is reached after an average of 12 to 28 hours. The terminal half-life is higher than after intravenous administration, with an average of 13 to 28 hours. The bioavailability of epoetin beta

b Epotein delta was granted marketing approval in March 2002 by EMEA and introduction into the UK market is pending. Prescribers should be aware of developments in the available products and should check the most recent Summaries of Product Characteristics.

after subcutaneous administration is between 23 and 42% when compared with intravenous administration.

The biological efficacy of epoetin alfa and epoetin beta has been demonstrated in various animal models in vivo (normal and anaemic rats, polycythaemic mice). After administration of epoetin alfa and epoetin beta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the Fe-incorporation rate. It has been shown in cell cultures of human bone marrow cells that epoetin alfa and epoetin beta stimulate erythropoiesis specifically and do not affect leucopoiesis.

Darbepoetin alfa is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced by recombinant DNA technology. It is a 165-amino acid protein that differs from recombinant human erythropoietin in containing five N-linked oligosaccharide chains. The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone.

Darbepoetin stimulates erythropoiesis by the same mechanism as endogenous erythropoietin and epoetin alfa and beta. Following subcutaneous administration, absorption is slow and rate limiting. The observed half-life in patients with renal failure was 49 hours (range: 27 to 89 hours) and reflects the rate of absorption. Following intravenous administration to patients with renal failure, serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal half-life of 21 hours. Following subcutaneous administration in patients with renal failure peak concentrations occur at 34 hours (range: 24 to 72 hours). Following intravenous administration, the terminal half-life of darbepoetin is approximately three times longer than epoetin alfa. The bioavailability of darbepoetin in patients with renal failure after subcutaneous administration is 37% (range: 30% to 50%).

6.3.2 Clinical methodological introduction

Epoetin alfa vs epoetin beta

There were no studies comparing epoetin alfa and epoetin beta.

Darbepoetin vs epoetin alfa

One multisite RCT[232] comparing darbepoetin and epoetin alfa was identified. One study[183] was excluded because of methodological limitations.

Notable aspects of the evidence base were:

- Of the 28-week study duration[232] the first 20 weeks were a dose titration and stabilisation period.

Darbepoetin vs epoetin beta

A comprehensive literature search identified one open-label RCT comparing darbepoetin and epoetin beta[321].

Notable aspects of the evidence base were:

- Darbepoetin dose was converted at 200 IU:1 µg according to the manufacturer's dose conversion.

The GDG agreed that the following outcomes were priorities in assessing the efficacy of the ESA preparations:

- haemoglobin level
- ESA dose

- morbidity
- mortality
- quality of life
- left ventricular hypertrophy and left ventricular function.

6.3.3 Clinical evidence statements

Darbepoetin vs epoetin alfa

Haemodialysis patients

Efficacy

A mean change in Hb level between baseline and evaluation periods of 0.13 g/dl (95% CI −0.08 to 0.33) was above the pre-defined margin of −1.0 g/dl and therefore implied that no significant difference was observed between the two treatment groups[232]. (Level 1+)

No significant difference was observed for:

- haemoglobin variability assessed as variance in haemoglobin
- percentage values within the Hb target range
- percentage values within the therapeutic range and instability of Hb levels requiring a dose change within the two treatment groups[232]. (Level 1+)

Dose change from baseline to evaluation was similar for both treatment groups[232]. (Level 1+)

The number of patients with dose changes during the titration and evaluation periods was similar for both treatment groups[232]. (Level 1+)

Safety

The type and frequency of adverse events was similar in both treatment groups, with no antibody formation to either treatment detected[232]. (Level 2+)

Darbepoetin vs epoetin beta

Haemodialysis patients

Efficacy

There was no significant difference in maintaining Hb at 11–12 g/dl between darbepoetin (n=81) and epoetin beta (n=81), both administered s.c. weekly over 9 months[321]. (Level 1+)

Dose

Over the 9-months study duration, median dose fell in the darbepoetin arm (p=0.006), but increased in the epoetin beta arm (p=0.002). When converted into the same units (IU/kg/week) using the manufacturer's dose conversion, darbepoetin dose required to achieve the same Hb outcome was significantly lower than epoetin beta dose at 9 months (95%CI 17–61 IU/kg/week, p<0.001)[321]. (Level 1+)

Blood pressure

Blood pressure did not change significantly in the course of the study in either treatment arm[321]. (Level 1+)

6.3.4 Health economics methodological introduction

Only one economic evaluation[208] was found that compared darbepoetin and epoetin alfa. However, this study had methodological limitations and therefore no evidence statements were made. [c]

6.3.5 From evidence to recommendations

The GDG agreed that the evidence statements from the multisite RCT support the summary that there is no difference between darbepoetin and epoetin alfa for the outcomes measured, in a selected group of patients who were stable[232].

Evidence statements on efficacy suggest that both darbepoetin and epoetin beta effectively maintain target haemoglobin levels. ESAs are made available to NHS trusts through a system of tendering for local supply contracts. Costs therefore vary between locations and over time. The recommendation below outlines the considerations in agreeing on a first choice ESA rather than specifying a particular agent for all patients. This is intended to allow flexibility for local units over the lifetime of the guideline while providing useful advice in selecting the best treatment for the patient.

6.3.6 Recommendation

27. The choice of ESA should be discussed with the person with anaemia of CKD when initiating treatment and at subsequent review, taking into consideration the patient's dialysis status, the route of administration and the local availability of ESAs. There is no evidence to distinguish between ESAs in terms of efficacy. [A]

6.4 Early or deferred ESA therapy

6.4.1 Clinical introduction

The patients most likely to derive the greatest long-term benefit from correction of anaemia are those with chronic kidney disease who are predialysis. Early intervention to correct anaemia has the potential to impact on the progression of chronic kidney disease and affect patient morbidity, hospitalisation rates, quality of life, and mortality. The key goals in the management of anaemia are increased exercise capacity, improved quality of life, improved cognitive function, improved sexual function, reduced transfusion requirements, regression/prevention of left ventricular hypertrophy, improved morbidity, prevention of progression of renal disease, reduced risk of hospitalisation, and reduced mortality.

6.4.2 Methodological introduction

A comprehensive literature search identified two studies[122,273].

Notable aspects of the evidence base were:

- One study[122] was conducted in a selected patient population, recruiting only patients without diabetes.
- Target Hb levels in both studies were not met. The target Hb level for one study[122] was 13 g/dl, however, the mean Hb levels achieved was 12.9 g/dl (standard deviation 0.4) in the early treatment group and 10.3 g/dl (standard deviation 1.0) in the deferred treatment group.

[c] In interpreting economic evaluation of ESAs, it should be borne in mind that different units will have developed their own pricing structures which may differ considerably from BNF list prices.

- The target Hb levels for the other study[273] were 12–13 g/dl in the early treatment group and 9–10 g/dl in the deferred treatment group, while mean levels achieved were 12.1 g/dl (standard deviation 1.4) and 10.8 g/dl (standard deviation 1.3) respectively.

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.

6.4.3 Evidence statements

Left ventricular mass index

Predialysis patients

No significant differences were observed in left ventricular mass index measurements in a 2-year study[273] conducted to maintain Hb 12–13 g/dl (n=75) vs 9–10 g/dl (n=80) using epoetin. Treatment was initiated in the latter group when Hb was <9 g/dl at two consecutive assessments 2 months apart or <8 g/dl at any one time. (Level 1++)

Renal function

Predialysis patients

No significant differences were observed in renal function (eGFR) in a 2-year study[273] conducted to maintain Hb 12–13 g/dl (n=75) vs 9–10 g/dl (n=80) using epoetin. However, eGFR progressively decreased in the two treatment arms (p<0.001). Treatment was initiated in the latter group when Hb was <9 g/dl at two consecutive assessments 2 months apart or <8 g/dl at any one time. (Level 1++)

In a study conducted over 22.5 months in patients without diabetes with similar baseline creatinine clearance levels, where initiation of epoetin treatment was early (n=45) vs deferred (n=43, Hb <9 g/dl) and administered to achieve a target Hb ≥13 g/dl, the adjusted relative hazard for doubling of serum creatinine, renal replacement or death was 0.37 (95% CI 0.18 to 0.73, p=0.004) in the early epoetin treatment arm. Additionally, the risk of an event increased 2.23-fold (95% CI 1.56 to 3.18, p<0.01) per 1 mg/dl higher serum creatinine at baseline. Similarly, the adjusted relative hazard for renal replacement or death was 0.38 (95% CI 0.19 to 0.76, p=0.006) in the early epoetin treatment arm and the risk of an event increased 2.25-fold (95% CI 1.57 to 3.23, p<0.001) per 1 mg/dl higher serum creatinine at baseline[122]. (Level 1+)

Hypertension

Predialysis patients

In a 2-year study conducted to maintain Hb 12–13 g/dl (n=75) vs 9–10 g/dl (n=80), using epoetin and initiated in the latter group when Hb was <9 g/dl at two consecutive assessments 2 months apart or <8 g/dl at any one time, no significant differences were observed in systolic and diastolic blood pressure[273]. (Level 1++)

In a study conducted over 22.5 months in non-diabetic patients with similar baseline creatinine clearance levels, whereby initiation of epoetin treatment was early (n=45) vs deferred (n=43, Hb <9 g/dl) and administered to achieve a target Hb ≥13 g/dl, no significant differences were observed in systolic and diastolic blood pressure between the 2 treatment arms[122]. (Level 1+)

Quality of life

Predialysis patients

In a 2-year study conducted to maintain Hb 12–13 g/dl (n=75) vs 9–10 g/dl (n=80), using epoetin and initiated in the latter group when Hb was <9 g/dl at two consecutive assessments 2 months apart or <8 g/dl at any one time, no significant differences were observed in quality of life domains, as assessed by the Renal Quality of Life Profile and Short Form 36 (SF 36) questionnaires[273]. (Level 1++)

6.4.4 From evidence to recommendations

Both studies presented in the evidence were considered to be methodologically sound. The GDG felt that the study by Gouva et al[122] had achieved the study aims (in terms of level of Hb achieved) and showed a significant reduction in rate of renal progression. The study by Rogers et al[273] did not achieve the study aim and showed no significant difference in any outcome. It was not considered possible to reach any sound conclusions on the basis of these papers.

The GDG felt they could not make any recommendations on this area based on these studies alone. The evidence showed no contraindication to early correction of anaemia.

6.5 Coordinating care

6.5.1 Clinical introduction

During the past decade in the UK, the management of anaemia associated with CKD has evolved into a nurse-led programme in many renal units. The introduction of specialist nurses dedicated to managing anaemia in CKD is in response to an increased number of patients receiving treatment for renal anaemia. This role may also be undertaken by other health professionals, such as pharmacists, the goal being to deliver an effective, efficient, patient-centred anaemia service. The inefficient use of ESAs, the increase in the use of intravenous iron therapy, the requirement for patient monitoring and for regular audit have also highlighted the need to have a dedicated person responsible for anaemia management. Specialist nurses are able to work within protocols, become supplementary and extended nurse prescribers, and therefore can manage this group of patients with a high degree of independence.

The exact role of these health professionals will depend on how the anaemia management programme is set up and run, and this will vary from unit to unit. For example, they may be responsible for a small case load such as haemodialysis patients and the management may be lead by a computer algorithm or clinicians, or they may be responsible for managing the entire anaemia programme across all modalities.

6.5.2 Methodological introduction

A comprehensive literature search identified a before and after study[32]. However, because of methodological limitations, it was excluded from the evidence statements.

A comprehensive literature search did not identify any health economic studies that were suitable to address this issue.

6.5.3 From evidence to recommendations

The GDG felt that there is a benefit to having a healthcare worker identified as having responsibility for the provision of care of specific patients. There are core social and professional skills that will be needed which can be delivered by people from different clinical backgrounds, for example nurses or

pharmacists. The cost effectiveness varies according to the activity of the anaemia coordinator and improves with increasingly independent activity.

6.5.4 Recommendation

28. People with anaemia of CKD should have access to a designated contact person or persons who have principal responsibility for their anaemia management and who have skills in the following activities:

- **monitoring and managing a caseload of patients in line with locally agreed protocols**
- **providing information, education and support to empower patients and their families and carers to participate in their care**
- **coordinating an anaemia service for people with CKD, working between secondary and primary care and providing a single point of contact, to ensure patients receive a seamless service of the highest standard**
- **prescribing medicines related to anaemia management and monitoring their effectiveness.**

[D(GPP)]

6.6 Providing ESAs

6.6.1 Clinical introduction

Patients with anaemia associated with CKD do not necessarily need to receive their treatment within a hospital setting. One of the core principles involved in improving health outcomes for people with long-term conditions is improved care in primary care and community settings, emphasising the patient's role in self-care and thus promoting independence and empowering patients to allow them to take control of their lives. Provision of ESA therapy is no different and can only be achieved with an appropriate infrastructure and an effective delivery system enabling the right patients to get the right ESA at the right time and in the right place.

6.6.2 Methodological introduction

A comprehensive literature search identified one cross-sectional study[19].

A comprehensive literature search did not identify any health economic studies that were suitable to address this issue.

6.6.3 Evidence statements

Predialysis, hospital and home haemodialysis and continuous ambulatory peritoneal dialysis patients

In a cross-sectional study[19] of 87 patients, ESA supply was found to be mostly by GPs (71%), followed by hospital pharmacies (29%), although 20 patients (23%) reported that their GPs had refused to supply an ESA. Of 124 patients, 51% preferred obtaining their ESA supplies from a community pharmacy, while 19% preferred a hospital pharmacy. The reasons for both community and hospital pharmacy were primarily convenience (55%), followed by easier access (16%), supply always available (13%), shorter waiting time (10%) and provision of a larger supply (6%).

6.6.4 From evidence to recommendations

One cross-sectional study showed that there were issues for patients in obtaining ESA supplies from GPs and that many patients obtained their drugs from community pharmacists or the hospital pharmacy. This study was completed prior to the introduction of home delivery schemes run by

pharmaceutical companies. However, there was often little flexibility in the day/time that companies could provide a home delivery service to patients. Hospitals source the cheapest supply of ESAs from the drug companies and cost was also an important factor in the provision of ESAs. However, every patient should have a secure supply of ESAs obtained from a source that took the patients choice and lifestyle into consideration.

It was noted that maintaining choice for patients in how ESAs are supplied and administered was vital as some patients were dependant on hospitals to administer drugs or did not have the facilities to store large quantities of drugs.

6.6.5 Recommendation

29. ESA therapy should be clinically effective, consistent and safe in people with anaemia of CKD. To achieve this, the prescriber and patient should agree a plan that is patient-centred and includes: [D (GPP)]

- **continuity of drug supply**
- **flexibility of where the drug is delivered and administered**
- **the lifestyle and preferences of the patient**
- **cost of drug supply**
- **desire for self-care where appropriate**
- **regular review of the plan in light of changing needs.**

6.7 ESAs: optimal route of administration

6.7.1 Clinical introduction

Three ESAs are currently available in the UK, two short-acting (epoetin alfa and epoetin beta) and one long-acting (darbepoetin). Short-acting ESAs are more suited to short dose intervals and long-acting ESAs are more suited to dosing intervals of at least a week or more. Intravenous administration of ESAs obviously requires intravenous access and is therefore logistically difficult in predialysis, peritoneal dialysis, and transplant patients. Patients on haemodialysis treatment may therefore easily receive ESA therapy by any route, and at varying dose intervals, whereas other patients with anaemia associated with CKD will normally require subcutaneous administration with dosing intervals largely determined by the ESA used.

6.7.2 Methodological introduction

A literature search identified 58 studies. Because of the high number of retrieved studies, studies were grouped into the various identified factors and only the studies describing clinically relevant factors of the highest level of evidence and those which used regression analysis were included in the evidence statements. These are detailed below:

Table 6.2: Studies included in the evidence statements

Route of administration	Study type
[74]	RCT
[141]	RCT, cross-over
[141]	RCT
[166]	RCT
[174]	RCT, cross-over
[211]	RCT

Route of administration	Study type
[329]	RCT
Frequency of administration	**Study type**
[111]	RCT
[185]	RCT
[240]	RCT
Patient population	**Study type**
[87]	Non-randomised study
[167]	Cohort study
[241]	Cohort study
Hypertension	**Study type**
[225]	Prospective longitudinal study
Patient preference	**Study type**
[108]	Prospective cross-sectional cross-over study

Four studies[136,198,216,298] were excluded from the evidence statements because of methodological limitations. The buffer used in the preparation in the patient preference study is no longer used, and the paper was therefore not considered further.

The GDG agreed the following outcomes were priorities:

- mortality
- morbidity
- quality of life
- pain
- Hb/Hct levels
- complications
- patient satisfaction
- patient concordance
- patient compliance
- ESA dose required.

A comprehensive literature search found no suitable health economic studies to address this issue.

6.7.3 Evidence statements

Haematocrit and arterial pressure

Haemodialysis patients

A 6-month study[225] conducted in hypertensive patients (n=13) found no significant changes in Hct after conversion of epoetin administration from the intravenous route to the subcutaneous route. However, a significant decrease in predialysis mean arterial pressure from the first month was observed ($p<0.05$). (Level 3)

Antihypertensive dose requirement

Continuous ambulatory peritoneal dialysis patients

In a 16-week RCT[166], a mean epoetin dose of 84 ± 9 U/kg/week administered subcutaneously vs a mean dose of 133 ± 7 U/kg/week administered intraperitonealy increased antihypertensive therapy in both groups, but no significant difference was found between the two groups. (Level 1+)

Pain

Haemodialysis patients

In an RCT study[108] (n=208) comparing intravenous and subcutaneous routes for three times weekly treatment[141], level of discomfort assessed using the Visual Analogue Scale found similar scores between the two modes of administration. (Level 1++)

ESA dose requirement

Haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients

In a 130-day non-randomised study investigating epoetin administration by subcutaneous vs intravenous routes (n=29)[87], the time and cumulative dose required to achieve a target Hb of 11.3 g/dl was lower in the s.c. treated HD (n=9) and CAPD groups (n=9) (both $p<0.05$) when compared with the i.v. treated HD group (n=11). In addition, once target Hb was achieved, a lower epoetin dose was required in the HD and CAPD subcutaneous groups ($p<0.05$) when compared with the intravenously treated HD group. There were no differences in epoetin dose requirement between the subcutaneously treated HD and CAPD groups. In agreement with this finding, no differences were observed in both Hb/Hct levels and epoetin requirement over 6 months in a cohort study[241] comparing epoetin administration by the subcutaneous route in CAPD (n=8) vs HD (n=7) patients. (Level 2+)

In contrast to the above findings, a 24-week cohort study[167] comparing HD (n=10) vs CAPD (n=11) when epoetin was administered by the subcutaneous route found that the epoetin requirements, both to achieve and to maintain a target Hct of 30%, were higher in the HD group (both $p<0.05$). (Level 2+)

Frequency of administration

Haemodialysis patients

Three RCTs of 12–16 weeks duration[111,185,240] investigating subcutaneous epoetin administration once weekly vs twice weekly[185] and once weekly vs three times weekly[111,240], found no significant difference in epoetin requirement or rise in Hb levels[111,185] or systolic blood pressure in both groups[111]. (Level 1+)

Efficacy

Haemodialysis patients

Four RCTs of the following durations:

- 12 months[74]
- 8 to 24-week active treatment duration with 24-week follow-up period[211]
- 48-week duration consisting of a 26-week maintenance phase[141]

- 4-months[329]

compared subcutaneous vs intravenous epoetin administration three times weekly and found no significant differences in Hb/Hct levels between the two groups[74,153,211,329], although time to reach the target Hb was higher in the intravenously treated group (p=0.037) of one study[211].

One study[74] found no significant differences between the two modes of administration of epoetin in terms of the weight-standardised epoetin doses at monthly intervals or the cumulative epoetin dose to achieve target Hct 28–36%. One other study[211] found greater epoetin requirement in the intravenous group (p=0.019) during the Hb stabilisation (correction) phase of the study, but once target Hb was achieved in both groups, no difference was observed. Two other studies[141,329] found that the epoetin requirement was less for the subcutaneously treated group (p=0.02).

In addition, one study[211] assessed quality of life using the Kidney Disease Questionnaire and showed improvement in the physical and fatigue domains of both the intravenous and subcutaneous groups. These improvements, however, did not differ between the two routes of administration at any time. (Level 1+ and 1++)

In contrast to the above findings, in a randomised cross-over study[174] patients received similar doses of subcutaneous epoetin once (A1), twice (A2) or three times (A3) weekly (n=43), and crossed over to receiving intravenous epoetin once (B1), twice (B2) or three times (B3) weekly (n=38) over 3 months (or vice versa). A significant rise (p<0.001) in Hb was noted during the subcutaneous phase, whereas the intravenous phase was associated with a fall in Hb (p<0.001). (Level 1++)

Continuous ambulatory peritoneal dialysis (CAPD) patients

In a 16-week RCT (n=19), subcutaneously administered epoetin produced a rise in Hb levels (p<0.01), whereas intraperitonealy administered epoetin did not, despite a higher mean[166]. (Level 1+)

Peritoneal dialysis patients

Similarly to the CAPD patients, in a 32-week randomised cross-over study (n=13)[141] Hb levels in patients receiving intraperitoneal epoetin fell (p=0.03) when compared with the subcutaneous route. In support of this finding, the 16-week area under the Hct response curve (p=0.001) and the mean slope of the 16-week Hct response curve (p=0.05) were greater for subcutaneous dosing. Conversely, epoetin requirement per week was greater with intraperitoneal treatment in terms of the 16-week dose-requirement area under the curve (p=0.0029) and the slope of the 16-week dose requirement curve (p=0.017). In addition, the mean total dose per week over the entire study was greater for the intraperitoneal route (p<0.01). (Level 1+)

6.7.4 Health economics: cost-minimisation analysis

A meta-analysis of trial data was conducted to compare costs for subcutaneous and intravenous administration of ESAs. Only epoetin beta had sufficient data to allow a valid comparison. Subcutaneous administration appears to save £1,100 ± £727 per patient per year, compared with intravenous administration. Full details are given in Appendix D.

6.7.5 From evidence to recommendations

Of the factors addressed, hypertension was not shown to be affected by the route of administration of ESAs. The patient population, pain of injection, frequency of administration, efficacy and cost were all important factors in determining the route of administration.

The following points were also relevant:

- It was not practicable to administer ESAs by the intravenous route in patients not on haemodialysis. Equally, patients on haemodialysis may prefer to receive their ESA via the intravenous route.
- Frequency of administration was also considered important for nursing compliance. In some units it was considered better to give ESAs routinely at all dialysis visits rather than at every third.
- The half-life of the drug also determines the frequency of administration.
- With regards to efficacy, administration via the subcutaneous route using short-acting ESAs required up to 30% less drug to be administered to achieve the same Hb/Hct.

6.7.6 Recommendations

30. The patient with anaemia of CKD and the prescriber should agree (and revise as appropriate) the route of administration of ESAs, taking into account the following factors:

- **patient population (eg haemodialysis patients)**
- **pain of injection**
- **frequency of administration**
- **the lifestyle and preferences of the patient**
- **efficacy (eg subcutaneous vs intravenous administration, or long-acting vs short-acting preparations)**
- **cost of drug supply.** **[C]**

31. The prescriber should take into account that when using short-acting ESAs, subcutaneous injection allows the use of lower doses of drugs than intravenous administration. [A]

6.8 ESAs: dose and frequency

6.8.1 Clinical introduction

Currently, the available ESAs fall into two broad classes, short- and long-acting. The characteristics of long-acting ESAs are such that when using these agents the shortest dose interval is weekly, with no appreciable difference between subcutaneous and intravenous routes of administration. With short-acting ESAs, dose intervals of a week or more are less cost effective than shorter dose intervals, and the subcutaneous route of administration is more cost effective than the intravenous route.

In patients without renal disease, studies looking at erythropoietin response to anaemia show an exponential rise in serum EPO levels with falling haemoglobin, suggesting that with increasing severity of anaemia the natural 'endogenous' EPO dose is initially high and subsequently tails off as the anaemia corrects. Although it would be logical to attempt to mimic this, the early days of ESA therapy showed that very rapid correction of anaemia was associated with significant adverse effects. The dose and frequency of administration of ESA is therefore likely to depend on haemoglobin level and rate of change of haemoglobin, the class of ESA used and (in the case of short-acting ESAs) the route of administration, the CKD population under treatment, and various patient factors and patient preferences.

6.8.2 Methodological introduction

A literature search identified nine studies[12,18,22,27,30,38,61,71,90].

Two studies[37,330] had methodological limitations and were therefore excluded from the evidence statements. As the meta-analysis[37] addressing route of administration had methodological

limitations, the 10 studies within it were individually appraised and five met quality criteria[74,153,211,248,329]. The clinically relevant factors and respective study types are detailed in Table 6.3.

Table 6.3: Summary of included studies

Route of administration	Study design
Studies included in the meta-analysis	
211	RCT
74	RCT
141	RCT
329	RCT
248	Cohort study
Study published after the meta-analysis literature search cut-off date	
30	Cohort study
Starting Hb level	**Study design**
27	Prospective longitudinal study
Hypertension	**Study design**
18	Before and after study
61	RCT (open-label)
Rate of Hb correction	**Study design**
12	Prospective longitudinal study
22	Retrospective longitudinal study
38	Cohort study
71	Prospective longitudinal study
90	RCT(open-label)

The GDG agreed that the outcomes of priority were Hb levels, rate of Hb correction and complications.

Notable aspects of the evidence base were:

- Due to methodological limitations, one RCT[61] was downgraded to Level 2 in the evidence hierarchy.
- Adjuvant red blood cell transfusions were administered in addition to epoetin during the study period in four studies[27,71,90,141].
- Two studies addressing rate of Hb correction[22,71] were conducted in children.

6.8.3 Evidence statements

Route of administration

Table 6.4: Haemodialysis patients

Study reference	Evidence hierarchy	ESA therapy arms	Outcome
30	Level 2++	Once weekly s.c. vs once weekly i.v.	The number of patients who maintained a stable Hb level (defined as a decrease of ≤1 g/dl) was similar in both groups. Decrease ($p<0.05$) in Hb concentration in the i.v. treated group when the evaluation phase of the study was compared with the dosing phase.

Study reference	Evidence hierarchy	ESA therapy arms	Outcome
			Increased (p<0.05) mean weekly dose of epoetin alfa needed to maintain individual target Hb levels in the i.v. group.
[141]	Level 1++	Three times weekly i.v. vs three times weekly s.c.	Hb and Hct were similar in both groups. Average weekly epoetin dose was lower (p=0.002) in the s.c. group.
[329]	Level 1++	s.c. vs i.v.	Mean Hb levels were stable and remained equivalent in both groups at the end of the study. Epoetin requirement was found to be less (p=0.02) when administered by the s.c. route. When the different dosing strata were studied (ie >150 U/kg/week vs 100–150 U/kg/week vs <100 U/kg/week), it was evident that this difference was only in patients with the highest epoetin needs (>150 U/kg/wk).
[248]	Level 2+	s.c. vs i.v.	Hct levels were similar over the entire study period.
[74]	Level 1+	Three times weekly s.c. vs three times weekly i.v.	Weight-standardised epoetin doses at monthly intervals and cumulative epoetin doses were similar in both groups. Hct levels were similar in both groups.
[211]	Level 1+	Three times weekly s.c. vs three times weekly i.v.	Although time to reach the target Hb was longer (p=0.037) in the i.v. treated group, mean Hb and Hct levels were similar in both groups. Epoetin requirement was greater (p=0.019) in the i.v. group during the Hb stabilisation phase of the study, but once target Hb was achieved in both groups, no difference was observed between the two groups.

A meta-analysis of the four Level 1 studies addressing epoetin dose when administered s.c. vs i.v[74,153,211,329] found a lower epoetin requirement when administered s.c. (weighted mean difference (WMD) −30.05 (95% CI −43.96 to −16.14) I2 =7%). This was in support of the findings of the excluded heterogeneous meta-analysis[37]. A sensitivity analysis excluding the study with sample size n <20[74] was also in agreement with this finding and ruled out heterogeneity (WMD −41.61 (95% CI −60.66 to −22.55) I2 =0%).

Table 6.5: Starting Hb level

Study reference	Patient population	Evidence hierarchy	Hb level at baseline	Outcome
[27]	Continuous ambulatory peritoneal dialysis (CAPD)	Level 3	≤7.5 g/dl vs >7.5 g/dl	Time to achieve Hb target was longer (p<0.001) in the lower Hb group at 6 months despite similar rate of Hb increase and epoetin dose in both groups.

Study reference	Patient population	Evidence hierarchy	Hb level at baseline	Outcome
[71]	Children on haemodialysis	Level 3 vs ≥6.8 g/dl	<6.8 g/dl	A similar proportion of each group (81% vs 80%) reached the target Hb of 9.6–11.2 g/dl. The median time to achieve target Hb was higher in the lower Hb group (median 13 weeks vs 9 weeks; p-value not reported by the authors).

Table 6.6: Hypertension: haemodialysis patients

Study reference	Evidence hierarchy	ESA therapy arms	Outcome
[18]	Level 3	i.v. three times weekly	No change in mean systolic and diastolic blood pressures was found, and only three of 24 patients who had required treatment for hypertension before epoetin therapy required an increased dose of antihypertensive medication.
[61]	Level 2+	Hct 40.8 ± 5.2% vs Hct 30 ± 4.3%	No differences were found in mean daytime systolic or diastolic BP and mean night time systolic or diastolic BP between the two groups.

Table 6.7: Rate of Hb correction

Study reference	Patient population	Evidence hierarchy	ESA therapy	Outcome
[12]	Predialysis	Level 3	s.c. twice weekly	There was a rise in Hb and Hct when compared with baseline levels after 3 months, which was sustained after 6 months and 12 months (all p<0.001). Target Hb was achieved 10–11 g/dl after 6 months.
[71]	Children on haemodialysis	Level 3	i.v. two to three times weekly with an aim to achieve a rise in Hb of 1 g/dl per 4 weeks in order to attain target Hb 9.6–11.2 g/dl	A median time to target of 11 weeks was achieved with a median dose of 150 U/kg/week in 81% of patients. The mean rate of Hb rise was 0.5 g/dl per 4 weeks in patients receiving the starting dose of 75 U/kg/week and 0.8 g/dl per 4 weeks in those whose dose had been increased to 150 U/kg/week (p value not reported by the authors).

Study reference	Patient population	Evidence hierarchy	ESA therapy	Outcome
[38]	Haemodialysis	Level 2+	Same weekly epoetin alfa dose in varying dose intervals	Patients who received 4,000 U epoetin as a bolus injection did not require increased epoetin doses, but dosing intervals significantly increased (p=0.01), unlike patients who received 10,000 U epoetin at intervals who required higher epoetin doses (p=0.002) with reduced dosing intervals (p=0.0001) to maintain Hb >11 g/dl throughout the 24-week study period.
[90]	Peritoneal dialysis patients	Level 1+	5, 10 and 20 U/kg epoetin daily s.c., to target Hct 30–35%	The differences in the mean weekly change in Hct were significant (p<0.05) over the 8 week constant-dose phase, between all three groups, in ascending order. During the correction phase, the time to achieve the target Hct in 50% of the patients (total n=72) who received 5, 10 and 20 U/kg daily s.c. was 154, 119 and 92 days respectively and the median cumulative epoetin doses to reach target Hct were calculated as 1,494, 1,523 and 1,678 U/kg respectively.
[22]	Post- transplant paediatric patients with chronic allograft dysfunction	Level 3	Thrice weekly s.c. vs twice weekly s.c. vs once weekly s.c.	There was an increased Hct in 84% of the children from 23.2% ± 3.1% to 33% ± 3.1% (p value not reported by the authors) within 7.2 ± 4.9 weeks at a mean rate of 1.98% per week. Hct increase and epoetin starting dose were linearly related (r=0.44, p<0.05).

6.8.4 Health economics methodological introduction

One study[75] was identified in a literature search. Three studies[37,193,204] did not meet quality criteria. The included study[75] estimated the increased costs of changing from s.c. epoetin to i.v. epoetin in a retrospective analysis of 99 haemodialysis patients over 7 months.

A cost-minimisation analysis was conducted at the request of the GDG to compare subcutaneous and intravenous epoetin administration. Full details are given in Appendix D.3

6.8.5 Evidence statements

The mean dose in the 's.c. switched to i.v.' patients increased significantly (46.83 + 10.20 IU/kg/week, +34.9%, p=0.001) over 7 months and was estimated to increase costs by €1,841 + €401 (Euros, 2002) per patient per year (+26.3%)[75].

The cost-minimisation analysis presented to the GDG stated in conclusion: 'The subcutaneous route of administration of epoetin vs intravenous route results in cost savings of approximately £1,100 + £727 per patient per year'.

6.8.6 From evidence to recommendations

Of the factors addressed, hypertension was not shown to have an effect in determining the dose and frequency of ESAs required to correct anaemia. But the route of administration and the rate of correction were important factors.

An acceptable rate of rise of haemoglobin was considered to be ~1–2g/dl/month. In general, it was thought that a patient's pre-treatment starting level of Hb would not influence the starting dose of ESA, but that their subsequent haemoglobin response would influence the dose thereafter.

Hypertension should be treated prior to the administration of ESAs. It was stated that episodes of severe hypertension would temporarily alter the dose of ESA, but that generally hypertension would not affect this issue.

The included health economic study supported the excluded meta-analysis[37] that intravenous administration of short-acting ESAs was more costly than subcutaneous administration.

The group concluded that in general s.c. administration leads to a reduced dose of short acting ESA. One study indicated that this was only relevant during the stabilisation phase but not during the maintenance phase of treatment.

6.8.7 Recommendation

32. When correcting anaemia of CKD, the dose and frequency of ESAs should be:

- **determined by the duration of action and route of administration of the ESA [B]**
- **adjusted to keep the rate of Hb increase between 1 and 2g/dl/month. [D(GPP)]**

6.9 Optimal Hb levels

6.9.1 Clinical introduction [2011]

Update 2011

Much of the published research in the treatment of CKD-related anaemia in the last decade has focused upon the optimum range of Hb to which patients should be treated. The prevailing research question has been 'since lower Hb is consistently associated with poor outcomes, does raising Hb to more normal levels improve outcomes?' The four largest randomised controlled trials in anaemia management in CKD that have attempted to answer this (US Normalization of Hematocrit trial[35], CREATE[84], CHOIR[291] and TREAT[251]) have generated debate and controversy in the literature. Most would at least agree that Hb is a biomarker and indeed the achieved Hb in RCTs was not related to the clinical consequences[35,305], which has raised the question of Dose Targeting Bias[244] in these studies.

The Hb achieved by any given patient is a composite of patient-related factors and co-morbidities, intercurrent events and clinical management (Table 6.1U). The time taken to achieve any desirable Hb target range is dependent on all of these, the baseline Hb level and an individual patient's responsiveness to anaemia therapy. Even in well conducted RCTs designed to achieve similar Hb ranges, where care is taken to control for as many of these factors as possible, we observe considerable variation in what can be achieved, and what it takes to do this.

Although Hb level is the quantitative measure of anaemia, the optimal treatment of renal anaemia demands consideration of what clinical results we are anticipating, and how we are going to produce them, rather than focussing only on a Hb level within a given range. Erythropoiesis stimulating agents (ESAs) have major effects on the bone marrow and red blood cell survival , but erythropoietin receptors are found also in the brain, retina, heart, skeletal muscle, kidney and endothelial cells[276]. EPO-receptor activation plays a role in cell differentiation, proliferation and apoptosis through a variety of signalling pathways and it has been suggested that high treatment doses of ESAs may be related causally to the adverse effects reported in recent randomised controlled trials[290].

In making guideline recommendations for desirable treatment ranges we need to consider patient-related outcomes (mortality, cardiovascular and renal outcomes, safety, quality of life, and transfusions) together with Hb level and ESA dose. We should keep in mind that guideline recommendations form a background to the clinical assessment of benefits and risk for individual patients.

Table 6.1U: Factors contributing to Hb variability

Patient factors and co-morbidities	Intercurrent events	Practice pattern-related
Red cell lifespan	Infection & transient inflammation	ESA dose adjustment protocol design
Chronic inflammation	Hospitalization	Iron therapy protocol
Patient adherence	Iron deficiency	Protocol compliance
Secondary hyperparathyroidism	Bleeding/haemolysis	Laboratory monitoring
Chronic viral infection	Malnutrition	Narrow target Hb range
Malignancies	Vitamin deficiency	Dialysis adequacy
Haematological disorders	Pure red cell aplasia	Water purity
Complications of diabetes	Medications eg. ACE inhibitors	Payment restrictions
Other	Interdialytic weight gain	

Reprinted from: Stevens 2008[301] (This table is reproduced with permission from Dr Anatole Besarab)

Update 2011

The GDG agreed to address the following question: *what should be the aspirational Hb (Hb) target range for patients undergoing treatment for anaemia in CKD?*

6.9.2 Clinical methodological introduction

A literature search identified one meta-analysis[303] containing 19 RCTs, which assessed the effects of lower vs higher haemoglobin collectively in predialysis, peritoneal dialysis and haemodialysis patients attained by means of ESA therapy or blood transfusion. The findings were stratified into two categories, namely studies that compared treatment to two haemoglobin ranges, higher (11.9–15.0 g/dl) vs lower (9.0–12.0 g/dl) (seven studies) and those which assessed the effects of epoetin (Hb 9.5–13.3 g/dl) vs no treatment (Hb 7.5–10.4 g/dl) (12 studies).

An additional three RCTs[200,201,245] and a prospective longitudinal study[107] were found which addressed the effects of lower vs higher Hb levels.

The different Hb levels examined and study durations need to be accounted for when evaluating the evidence and are summarised in Table 6.8.

Table 6.8 Study duration and Hb levels for the included studies

Reference	Study duration	Low Hb (g/dl)	High Hb (g/dl)
303	6 to 29 months	9.0–12.0	11.9–15.0
303	2 to 12 months	7.5–10.4	9.5–13.3
200	8 months	9.0	12.0
245	24 months	10.9 ± 0.7	12.6 ± 1.0
107	8 months	10.5 ± 0.9	12.6 ± 1.0

Notable aspects of the evidence base were:

- Although the meta-analysis[303] was of rigorous methodology leading to a systematic review of a high standard, the trials within it were of variable quality.
- The meta-analysis[303] was heavily weighted by a single study[35] conducted in haemodialysis patients with severe cardiovascular disease, which may imply unsuitability for extrapolation to the entire CKD patient population.
- Although two studies in the meta-analysis[303] enrolled children, the findings were not stratified on the basis of age.
- Due to methodology limitations, one RCT[200] was downgraded to Level 2+ of the evidence hierarchy.
- The means of achieving target Hb in the studies included the use of ESAs and/or blood transfusions.

Update 2011

Clinical methodological introduction [2011]

A literature search was undertaken to retrieve papers published from 2005 onwards for RCTs considering the aspirational Hb target range for people with anaemia in CKD. Twelve reports of eight RCTs[84,86,105,176,199,245,251,270,277,291,305,306] were identified. Systematic reviews [115,137,242,246,253,303,304] identified in the searches were cross-checked to ensure all relevant trials had been identified and included in the review.

For studies with an adult population, RCTs were included if there were at least 100 patients randomised and compared two target Hb levels. For studies in the paediatric population all RCTs, irrespective of sample size were considered for inclusion. In addition, studies examining treatment targets and drug versus placebo comparisons were included.

Results for adults and children as well as the non-dialysis and dialysis populations are presented separately.

16 reports of 12 RCTs (identified from the old guideline and update searches) with varying degrees of bias were found which addressed the question and were included in the review.

The characteristics of the included studies are reported in Appendix H:. Notable aspects of the evidence base were:

Update 2011

- 11 reports of 8 RCTs[84,86,176,190,251,270,273,277,291,305,306] included patients with non-dialysis CKD, and 4 reports of 3 RCTs[35,105,106,245] were in dialysis patients and one study[114] included both groups [results are reported separately].
- Non-dialysis dependent CKD trials stated the inclusion criteria with respect to mean GFR of ≤60 mL/min. One study[176] included patients with creatinine clearance levels between 15 to 79 mL/min.
- The baseline aspirational and achieved Hb levels for the included studies are summarised in table 6.2U and figure 6.1U (Paragraph 6.9.5).
- Patients were administered epoetin-alfa[35,106,114,176 190,245,273,277,291], epoetin-beta[84 270,277] or darbepoetin[251]. Details on dosage and mode of administration are described in figures 6.2U and 6.3U.

Update 2011

Table 6.2U. Baseline, target and achieved Hb levels for non-dialysis and dialysis populations

Study	High target				Low target		
	High target Hb (g/dL)				Low target Hb (g/dL)		
	Baseline	Target	Achieved		Baseline	Target	Achieved
Non-dialysis							
ACORD[270]	11.9 (IQR 11.3 to 12.2)	13 to 15	13.5		11.9 (IQR 11.3 to 12.0)	10.5 to 11.5	12.1
CREATE[§84]	11.6 (SD 0.6)	13 to 15	13.3 (SD 0.5)		11.6 (SD 0.6)	10.5 to 11.5	11.8 (SD 0.7)
CHOIR*[291]	10.1 (SD 0.9)	13.5	12.6		10.1 (SD 0.9)	11.5	11.3
TREAT[¶251]	10.5 (IQR 9.8 to 11.0)	13	12.5 (IQR 12.0-12.8)		10.4 (IQR 9.8 to 10.9)	>9	10.6 (IQR 9.9-11.3)
Furuland 2003[114]	10.6 (SD 1.0)	13.5 to 16	14.3 (SD 1.1)		10.9 (SD 0.7)	9 to 12	11.7 (SD 1.3)
Levin 2005[176]	11.76 (SD 0.76)	12 to 14	12.7 (SD 0.88)		11.73 (SD 0.80)	9 to 10.5	11.4 (SD 1.2)
Macdougall 2007[†190]	10.89 (SD 0.60)	10 to 12	11		10.76 (SD 0.66)	>9	10.48
Roger 2004[273]	11.2 (SD 0.9)	12 to 13	12.1 (SD 1.4)		11.2 (SD 0.8)	9 to 10	10.8 (SD 1.3)
Rossert 2006[277]	11.5 (SD 1.0)	13 to 15	13.5 (SD 1.9)		11.6 (SD 0.9)	11 to 12	11.9 (SD 1.6)
Dialysis							
Besarab 1998[35]	10.2 (SD 1.0)	13 to 15	13.2		10.2 (SD 1.0)	9 to 11	10
Foley 2000[106]	10.4 (95% CI 10.2 to 10.6)	13 to 14	12.2		12.2 (95% CI 11.9 to 12.5)	9.5 to 10.5	10.4
Furlund 2003[114]	HD: 11.0 (SD 1.1); PD: 11.2 (SD 0.9)	13.5 to 16	HD : 13.5(1.4); PD: 13.4 (1.5)		HD: 11.0 (SD 0. 9); PD: 11.2 (SD 0.9)	9 to 12	HD: 11.3 (SD 1.3); PD: 11.5 (SD 1.2)
Parfrey 2005‡[245]	11.0 (SD 1.2)	13.5 to 14.5	13.1 (SD 0.9)		11.0 (SD 1.2)	9.5 to 11.5	10.8 (SD 0.7)

§One secondary analysis[86] of the CREATE trial was identified. *Two secondary analyses[305,306] of the CHOIR trial were identified. One study reported results for diabetes and heart failure patients. However, the study did not report the mean Hb values for these groups. ‡One report[105] of the Parfrey (2005) study[245] was identified and included in the review.

¶ TREAT: patients randomised to the placebo group were assigned to receive darbepoetin alfa as rescue therapy if the Hb level fell below 9.0 g/dL. Rescue therapy continued until the Hb level increased to ≥ 9.0 g/dL, at which time placebo administration resumed.

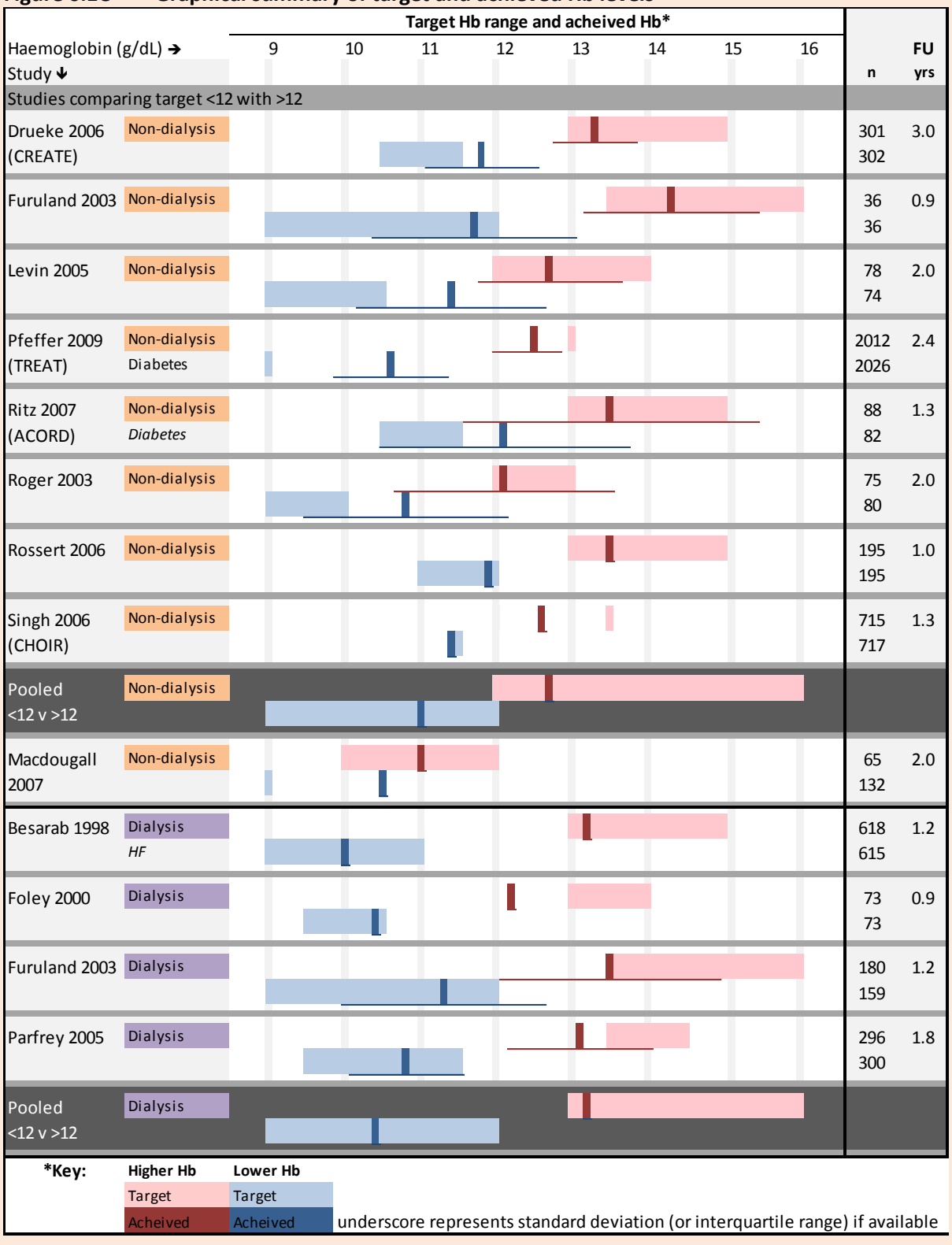
†Macdougall 2007[190]: treatment commenced when Hb had remained at ≤9.0 g/dL for 3 months or had fallen to ≤8.0 g/dL on two consecutive occasions 2 weeks apart or clinical symptoms of anaemia had developed.

Data are presented as mean (SD), median (IQR) or mean (95% CI).

HD= haemodialysis; PD=peritoneal dialysis

Update 2011

Figure 6.1U Graphical summary of target and achieved Hb levels



Update 2011

Evidence Profiles [2011]

The evidence profiles (tables 6.3U-6.5U) summarise the quality of the evidence and outcome data from the 15 reports of 12 RCTs included in this review, comparing two target Hb levels. Results are presented by outcomes for the non-dialysis and dialysis populations. The update work below presents the following evidence profile tables:

Table No	Population	Hb group
6.3U	Non-dialysis	>12.0 g/dL vs lower Hb
6.4U	Non-dialysis	10-12 g/dL vs lower Hb
6.5U	Dialysis	>12.0 g/dL vs lower Hb

6.9.3 Clinical evidence statements [2006, updated 2011]

Table 6.9 Summary of appraised studies

Reference	Outcome	Patient population (n)	Aiming for a high Hb	Aiming for a low Hb	Evidence grading
[303]	All-cause mortality	Predialysis, peritoneal dialysis and haemodialysis (n=1949)	11.9-15.0g/dl	9.0-12.0 g/dl ↓	Level 1++
[303]	All-cause mortality	Predialysis, peritoneal dialysis and haemodialysis (n=255)	9.5-13.3 g/dl	7.5-10.4 g/dl No difference	Level 1++
[303]	Hypertension	Predialysis, peritoneal dialysis and haemodialysis (n=1277)	11.9-15.0 g/dl	9.0-12.0 g/dl No difference	Level 1++
[201]	Hypertension	Haemodialysis (n=12)	12.0 g/dl ↑	9.0 g/dl	Level 2+
[303]	Quality of life	Predialysis, peritoneal dialysis and haemodialysis (n=unknown)	11.9-15.0 g/dl	9.0-12.0 g/dl No difference	Level 1++
[303]	Quality of life	Predialysis, peritoneal dialysis and haemodialysis (n= unknown)	9.5-13.3 g/dl	7.5-10.4 g/dl No difference	Level 1++
[200]	Quality of life	Haemodialysis (n=12)	12.0 g/dl	9.0 g/dl No difference	Level 2+
[201]	Physical performance-exercise radionuclide ventriculogram	Haemodialysis (n=12)	12.0 g/dl	9.0 g/dl No difference	Level 2+

Reference	Outcome	Patient population (n)	Aiming for a high Hb	Aiming for a low Hb	Evidence grading
[201]	Physical performance-maximal incremental exercise testing	Haemodialysis (n=12)	12.0 g/dl ↑	9.0 g/dl	Level 2+
[245]	6-minute walking distance	Haemodialysis (n=596)	12.6±1.0 g/dl	10.9±0.7 g/dl No difference	Level 1++
[201]	Left ventricular mass and mass index	Haemodialysis (n=12)	12.0 g/dl	9.0 g/dl No difference (note: short study duration)	Level 2+
[245]	Left ventricular volume index left ventricular mass index	Haemodialysis (n=596)	12.6±1.0 g/dl	10.9±0.7 g/dl No difference in either cardiovascular parameter	Level 1++
[107]	Left ventricular septal, posterior wall thickness and left ventricular mass index. Left ventricular ESD and EDD RWT parameter for left ventricular geometry		13.4±3.1 g/dl All ↓ No difference ↓	10.5±0.9 g/dl	Level 3

↑= significant increase; ↓= significant decrease.

Update 2011

Table 6.3U Non-dialysis: >12g/dL versus lower Hb

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	>12g/dL compared to lower Hb levels-non dialysis	control	Relative (95% CI)	Absolute	Quality
All cause mortality > 12 g/dL v lower Hb level (follow-up 1-4 years) 13-16 v 9-12 [12.5-14.5 v 10.6-11.9]											
6	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	501/3338 (15%)	462/3349 (13.8%) 0%	HR 1.10 (0.97 to 1.24)	13 more per 1000 (from 4 fewer to 30 more) 0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW
CV mortality 13-16 v 9-12 [13.3-14.3 v 11.7-11.8]											
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/337 (4.5%)	10/338 (3%)	RR 1.5 (0.69 to 3.3)	15 more per 1000 (from 9 fewer to 68 more)	⊕OOO VERY LOW
Composite outcome (death, MI, hospitalisation for congestive heart failure) 13-15 v 9-11.55 [12.5-13.3 v 10.6-11.8]											
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	815/3028 (26.9%)	746/3045 (24.5%)	HR 1.1 (1 to 1.21)	21 more per 1000 (from 0 more to 43 more)	⊕⊕⊕O MODERATE
Mean decrease in GFR 12-16 v 9-12 [12.1-14.3 v 10.6-11.9] (follow up 1-4 yesrs) (Better indicated by lower values)											
5	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	539	546	-	SMD 0.04 lower	⊕⊕⊕O

										(0.16 lower to 0.07 higher)	MODERATE
Change in creatinine clearance (mL/min) 12-14 v 9-10.5 [12.7 vs 11.4] (Better indicated by lower values)											
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[3]	none	78	74	-	MD 1.7 higher (1.66 lower to 5.06 higher)	⊕OOO VERY LOW
Initiation of dialysis 12-15 v 9-11.5 [12.1-13.5 v 10.8-12.1]											
4	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[3]	none	164/541 (30.3%)	137/536 (25.6%)	RR 1.2 (1 to 1.44)	51 more per 1000 (from 0 more to 112 more)	⊕OOO VERY LOW
Worsening renal function 13-15 v 11-12 [13.5 v 11.9]											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/195 (1%)	2/195 (1%)	RR 1 (0.14 to 7.03)	0 fewer per 1000 (from 9 fewer to 62 more)	⊕OOO VERY LOW
Proportion of patients transfused 13-15 v >9-11.5 [12.5-13.3 v 10.6-11.8]											
2	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	323/2313 (14%)	529/2328 (22.7%)	RR 0.61 (0.54 to 0.7)	89 fewer per 1000 (from 68 fewer to 105 fewer)	⊕⊕⊕O MODERATE
Stroke (stroke included: TIA/stroke, neurological deficit not reversible w/in 24 hours) 13-15 v 9-11.5 [12.5-13.5 v 10.6-11.8]											
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/3028 (4.2%)	72/3045 (2.4%)	HR 1.69 (1.28 to 2.24)	16 more per 1000 (from 7 more to 29 more)	⊕⊕⊕O MODERATE
MI 13-15 v 9-12 [12.5-13.5 v 10.6-11.9]											
4	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[3]	none	158/3223 (4.9%)	166/3240 (5.1%)	RR 0.88 (0.64 to 1.2)	6 fewer per 1000 (from 18	⊕OOO

										fewer to 10 more)	VERY LOW
Hypertension (definition varied: BP>160mm Hg; at least 1 recorded BP>140/90mm Hg) 12-15 v 9-12 [12.5-13.5 v 10.6-12.1]											
5	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	none	663/2674 (24.8%)	574/2679 (21.4%)	RR 1.16 (1.05 to 1.27)	34 more per 1000 (from 11 more to 58 more)	⊕⊕OO LOW
Change in LVMI [g/m2]- (follow-up 1.25 to 2 years) 12-15 v 9-11.5 [12.1-13.5 v 10.8-12.1] (Better indicated by lower values)											
4	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	very serious[3]	none	542	538	-	MD 1.08 lower (4.45 lower to 2.29 higher)	⊕OOO VERY LOW
Change in LVMI [g/m2]- (1 year) (Better indicated by lower values)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	171	186	-	MD 2.00 lower (7.19 lower to 3.19 higher)	⊕⊕⊕O MODERATE
Change in LVMI [g/m2]- (2 years) (Better indicated by lower values)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	serious[13]	none	136	146	-	not pooled	⊕⊕OO LOW
Change in LVMI[g/m2] - (3 years) (Better indicated by lower values)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74	81	-	MD 6.20 higher (4.19 lower to 17.31 higher)	⊕⊕⊕O MODERATE
CV event free survival – Concentric LVH (1 year)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	38/43 (88.4%)	35/42 (83.3%)	RR 1.06 (0.89 to 1.26)	50 more per 1000 (from 92 fewer to 217 more)	⊕OOO VERY LOW
CV event free survival– Concentric LVH (2 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											

1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	33/43 (76.7%)	29/42 (69%)	RR 1.11 (0.86 to 1.44)	76 more per 1000 (from 97 fewer to 304 more)	⊕OOO VERY LOW
CV event free survival– Concentric LVH (3 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/43 (37.2%)	18/42 (42.9%)	RR 0.87 (0.52 to 1.46)	56 fewer per 1000 (from 206 fewer to 197 more)	⊕OOO VERY LOW
CV event free survival – Eccentric LVH (3 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/61 (26.2%)	28/66 (42.4%)	RR 0.62 (0.37 to 1.03)	161 fewer per 1000 (from 267 fewer to 13 more)	⊕OOO VERY LOW
CV event free survival – Eccentric LVH (1 year) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	50/61 (82%)	61/66 (92.4%)	RR 0.89 (0.77 to 1.02)	102 fewer per 1000 (from 213 fewer to 18 more)	⊕OOO VERY LOW
CV event free survival – Eccentric LVH (2 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	33/61 (54.1%)	46/66 (69.7%)	RR 0.78 (0.59 to 1.03)	153 fewer per 1000 (from 286 fewer to 21 more)	⊕OOO VERY LOW
Change in SF-36: physical function 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
4	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	3118	3142	-	MD 0.40 higher (0.17 lower to 0.97 higher)	⊕OOO VERY LOW
physical role 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											

3	randomised trials	serious[18]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.19 higher (1.82 lower to 2.21 higher)	⊕OOO VERY LOW
pain 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.19 lower (2.32 lower to 1.93 higher)	⊕OOO VERY LOW
general health 13-15 v 10.5-12 [12.6-13.5 v 11.3-12.1] (Better indicated by lower values)											
4	randomised trials	serious[19]	no serious inconsistency	no serious indirectness	serious[13]	none	1192	1198	-	MD 3.96 higher (1.72 to 6.2 higher)	⊕⊕OO LOW
vitality 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
4	randomised trials	serious[16]	serious[17]	no serious indirectness	serious[13]	none	3318	3142	-	MD 0.88 higher (0.15 to 1.6 higher)	⊕⊕OO LOW
social function - 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.91 higher (1.26 lower to 3.08 higher)	⊕OOO VERY LOW
emotional role 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 1.70 lower (4.84 lower to 1.44 higher)	⊕OOO VERY LOW
mental health 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											

3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.44 higher (0.73 lower to 1.61 higher)	⊕OOO VERY LOW
physical health composite score 12-13 v 9-10 [12.1 v 10.8] (Better indicated by lower values)											
1	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	very serious[3]	none	75	80	-	MD 1.00 lower (5.26 lower to 3.26 higher)	⊕OOO VERY LOW
mental health composite score 12-13 v 9-10 [12.1 v 10.8] (Better indicated by lower values)											
1	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	very serious[3]	none	75	80	-	MD 3.00 higher (0.98 lower to 6.98 higher)	⊕OOO VERY LOW

[1] Studies: CHOIR, CREATE, TREAT, Furuland 2006, Levin 2005, Rossert 2006: 4/6 had unclear allocation concealment, 2/6 blinding not done; 1/6 blinding unclear; 3/6 open label trial; Three trials were powered for composite outcomes not for all-cause mortality; CHOIR and Rossert trials terminated early
[2] Moderate heterogeneity (I2=47%; p=0.09)
[3] 95% CI includes both the line of appreciable benefit and harm
[4] CREATE, Furuland 2006: unclear allocation concealment and blinding
[5] CHOIR, CREATE, TREAT: 2/3 unclear allocation concealment; 2/3 no blinding; 1/3 unclear blinding. CHOIR terminated early
[6] CREATE, Furuland 2006, Levin 2005, Roger 2004, Rossert 2006: 4/5 unclear allocation concealment; 4/5 open label; 1/5 unclear blinding. Rossert terminated early
[7] Levin 2005: open label
[8] ACORD, CREATE, Levin 2005, Roger 2004:3/4 unclear allocation concealment; 1/4:unclear blinding;3/4 blinding not done
[9] Rossert 2006- unclear allocation concealment and not blinded. Rossert terminated early
[10] CREATE, TREAT- 2/2 unclear allocation concealment; blinding unclear
[11] CREATE, CHOIR, TREAT, Rossert 2005: 4/4 unclear allocation concealment ; 1/4: unclear blinding and 3/4 not blinded
[12] ACORD, CREATE, TREAT, Levin 2005, Rossert 2006: 4/5 unclear allocation concealment; unclear if blinded/not blinded. Rossert terminated early
[13] 95% CI includes appreciable benefit/harm
[14] ACORD, CREATE, Levin 2005, Roger 2004: 3/4 unclear allocation concealment and 3/4 blinding unclear 1/4 blinding not done
[15] Eckardt 2009: secondary analysis of CREATE; results reported for patients who had echocardiogram available at baseline and at 1, 2 and 3 years
[16] CREATE, CHOIR, TREAT, Rossert 2006:3/4 unclear allocation concealment; 1/4 blinding unclear, 1/4 open label blinded and 2/4 blinding not done; CHOIR and Rossert terminated early
[17] Significant heterogeneity
[18] CREATE, CHOIR, Rossert 2006:3/3 unclear allocation concealment; 1/3 open label;3/4 blinding unclear/not done; CHOIR and Rossert terminated early
[19] ACORD, CREATE, CHOIR, Rossert 2006: 4/4 unclear allocation concealment ;1/4 open label: 3/4 unclear or not blinded
[20] Roger 2006:unclear allocation concealment and not blinded

Update 2011

Update 2011

Results for the quality of life outcome reported in table 6.3U includes unpublished data for two trials[139,271]. Data received upon request from the sponsors

Update 2011

Results for two studies[270,273] for progression of CKD are reported below in a narrative format as the studies either did not report the numerical values or were reported in a format that would not allow for analysis in RevMan or the GRADEpro programme.

One study[270] reported median (IQR) for decrease in eGFR (mL/min) [calculated using MDRD formula]: -5.1 mL/min (IQR -10.7 to -0.1) vs -3.9 mL/min (IQR -12.1 to 1.8) for the high (13-15 g/dL) and the low (10.5-11.5 g/dL) Hb target groups, respectively. It also reported median (IQR) for decrease in creatinine clearance (mL/min) [calculated using Cockcroft-Gault formula]: -5.5 mL/min (IQR -11.5 to -0.1) vs -3.4 mL/min (IQR -11.4 to 2.0) for the high (13-15 g/dL) and the low (10.5-11.5 g/dL) Hb target groups, respectively.

A second study[273] stated that creatinine clearance values would be reported but data was not shown. The study noted that calculated creatinine clearance values [Cockcroft-Gault formula] exhibited similar results to decrease in GFR.

Update 2011

Table 6.4U Non-dialysis: 10 to 12g/dL versus lower Hb levels

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	10-12 g/dL compared to lower Hb level in pre-dialysis patients	control	Relative (95% CI)	Absolute	Quality
All cause mortality - 10-12 v >9 [11 v 10.48];@21-24mo.											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/64 (1.6%)	5/132 (3.8%)	RR 0.41 (0.05 to 3.46)	22 fewer per 1000 (from 36 fewer to 93 more)	⊕OOO VERY LOW
Creatinine clearance [mL/min] - 10-12 v >9 [11 v 10.48] (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65	132	-	MD 0.86 higher (1.55 lower to 3.27 higher)	⊕⊕⊕O MODERATE
Initiation of dialysis - 10-12 v >9 [11 v 10.48]											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29/65 (44.6%)	61/132 (46.2%)	RR 0.97 (0.7 to 1.34)	14 fewer per 1000 (from 139 fewer to 157 more)	⊕OOO VERY LOW
Change in LVMI- 2 years - 10-12 v >9 [11 v 10.48] (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	111	-	MD 15.4 lower (39.69 lower to	⊕⊕⊕O

Update 2011

										8.89 higher)	MODERATE
Hypertension - 11 v >9 [11 v 10.48]											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/65 (21.5%)	9/132 (6.8%)	RR 3.16 (1.44 to 6.91)	147 more per 1000 (from 30 more to 403 more)	⊕⊕⊕O MODERATE

[1] Macdougall 2007; 1/1 had unclear allocation concealment and was open label trial
[2] 95% CI includes both the line of appreciable benefit and harm

Update 2011

Table 6.5U Dialysis: > 12 g/dL versus lower Hb

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>12g/dL compared to lower Hb levels-dialysis**	**control**	**Relative (95% CI)**	**Absolute**	**Quality**
All cause mortality (follow up 48-56 weeks) 13-16 V 9-12 [12.2-13.5 v 10-11.3]											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	223/871 (25.6%)	189/852 (22.2%)	RR 1.11 (0.88 to 1.4)	24 more per 1000 (from 27 fewer to 89 more)	⊕OOO VERY LOW
CV mortality 13-16 v 9-12 [13.1-13.5 v 10-11.3]											
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	159/1094 (14.5%)	147/1079 (13.6%)	RR 1.07 (0.87 to 1.31)	10 more per 1000 (from 18 fewer to 42 more)	⊕OOO VERY LOW
Access Thrombosis 13-16 v 9-11.5 [13.1-13.5 v 10-11.3]											

4	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	301/1144 (26.3%)	242/1124 (21.5%)	RR 1.24 (1.07 to 1.43)	52 more per 1000 (from 15 more to 93 more)	⊕OOO VERY LOW
Number of patients transfused 13-15 v 9-11.5 [13.1-13.2 v 10-10.8]											
2	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/914 (17.1%)	250/915 (27.3%)	RR 0.62 (0.52 to 0.74)	104 fewer per 1000 (from 71 fewer to 131 fewer)	⊕⊕⊕O MODERATE
MI 13-15 v 9-11.5 [13.1-13.2 v 10-10.8]											
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[2]	none	26/914 (2.8%)	18/915 (2%)	RR 1.44 (0.8 to 2.61)	9 more per 1000 (from 4 fewer to 32 more)	⊕OOO VERY LOW
Fatal MI 13-15 v 11-12 [13.2 v 10]											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[2]	none	22/618 (3.6%)	28/615 (4.6%)	RR 0.78 (0.45 to 1.35)	10 fewer per 1000 (from 25 fewer to 16 more)	⊕OOO VERY LOW
Cardiac event 13-14 v 9.5-10.5 [12.2-10.4]											
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/73 (13.7%)	10/73 (13.7%)	RR 1 (0.44 to 2.26)	0 fewer per 1000 (from 77 fewer to 173 more)	⊕OOO VERY LOW
Hypertension - 13.5-14.5 V 9.5-11.5 [13.1 v10.8]											
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	120/296 (40.5%)	110/300 (36.7%)	RR 1.11 (0.9 to 1.35)	40 more per 1000 (from 37 fewer to 128 more)	⊕OOO VERY LOW
Change in LVMI 13.5-14.5 v 9.5-11.5 [13.1 v 10.8] (Better indicated by lower values)											

1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	260	256	-	MD 2.6 lower (12.3 lower to 7.1 higher)	⊕OOO VERY LOW
Quality of life - Physical function (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	316	349	-	MD 0.13 lower (4 lower to 3.74 higher)	⊕⊕⊕O MODERATE
Quality of life - Physical role (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	349	-	MD 2.06 lower (8.96 lower to 4.84 higher)	⊕⊕⊕O MODERATE
Quality of life - Pain (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	316	350	-	MD 0.72 lower (5.23 lower to 3.79 higher)	⊕⊕⊕O MODERATE
Quality of life - General Health (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	317	351	-	MD 0.18 higher (2.95 lower to 3.31 higher)	⊕⊕⊕O MODERATE
Quality of life - Vitality (Better indicated by lower values)											
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	596	629	-	MD 3.05 higher (0.77 to 5.34 higher)	⊕⊕⊕O MODERATE
Quality of life - Social function (Better indicated by lower values)											

1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	316	350	-	MD 0.87 higher (3.85 lower to 5.59 higher)	⊕⊕⊕O MODERATE
Quality of life - Emotional role (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	309	346	-	MD 3.23 higher (4.67 lower to 11.13 higher)	⊕⊕⊕O MODERATE
Quality of life - Mental health (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	314	348	-	MD 0.43 lower (3.34 lower to 2.48 higher)	⊕⊕⊕O MODERATE
Quality of life - Mental health composite score (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	312	347	-	MD 0.89 higher (0.92 lower to 2.7 higher)	⊕⊕⊕O MODERATE
Quality of life - Physical health composite score (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	347	-	MD 0.43 lower (1.85 lower to 0.99 higher)	⊕⊕⊕O MODERATE

1 Besarab 1998, Foley 2000, Furuland 2003: 3/3unclear allocation concealment; 3/3 open label trials. Besarab trial terminated early.
2 95% CI include both the line of appreciable benefit and harm
3 Besarab 1998;Furuland 2003;Parfrey 2005: 3/3unclear allocation concealment; 2/3 not blinded and unclear in one study. Besarab trial terminated early.
4 Besarab 1998; Foley 2000; Furuland 2003; Parfrey 2005: all- unclear allocation concealment; 2/4 open label and 1/4 blinding unclear; Besarab trial terminated early
5 Significant heterogeneity: I2=63% p=0.04
6 95% confidence interval includes appreciable benefit or harm
7 Besarab 1998; Foley 2008: 1/2 unclear allocation concealment; 1/2 open label; Besarab trial terminated early

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8 Besarab 1998; Parfrey 2005; 2/2 unclear allocation concealment;1/2 open label; 1/2 unclear blinding
9 Besarab 1998; unclear allocation concealment; open label; Besarab trial terminated early.
10 Foley 2000: unclear allocation concealment; open label
11 Parfrey 2005: unclear allocation concealment and blinding

Results for the quality of life outcome reported in table 6.5U include unpublished data from one trial[15]. Data received upon request from the sponsor. One study[106] reported that the change in LVMI was similar for both Hb target groups but the numerical values were not reported. The study noted there was no correlation between the mean Hb level and the observed echocardiographic change.

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Clinical evidence statements [2011]

The evidence statements are grouped by comparisons (>12 g/dL versus lower Hb; 10 to 12 g/dL versus lower Hb) and results are given for non-dialysis and dialysis populations.

Tables 6.6U-6.8U are presented here to provide a brief overview of the results.

Table 6.6U Increased risk/benefit for high/low Hb in NON-DIALYSIS patients: Comparison: >12 g/dL versus lower Hb; [The aspirational Hb levels are noted within the square brackets]

	High Hb target g/dL	**Low Hb target**
Increased risk in the higher Hb group for :	Composite events*‡ [13-15 vs >9-11.5]	
	Stroke [13-15 vs >9-11.5]	
	Hypertension [12-15 vs 9-12]	
	Initiation of dialysis‡ [12-15 vs 9-11.5]	
	Worse CV event free survival (in patients with eccentric LVH at baseline) [13-15 vs 10.5-12.5]	
No difference	• Mortality • CV mortality • MI • Progression of CKD [mean decrease in GFR; creatinine clearance] • Change in LVMI • QoL (physical function, physical role, pain, role –emotional, social function, mental health, physical health composite score and mental health composite score)	
Increased benefit in the higher Hb group for :	Lower transfusion requirements [13-15 vs >9-11.5]	
	QoL: • General health [13-15 v 10.5-12] • Vitality [13-15 vs >9-12]	

*Composite events included: time to a first CV event, death from any cause or CV event and time to death, MI, hospitalisation for CHF and stroke ‡borderline significant

Table 6.7U Increased risk/benefit for high/low Hb in DIALYSIS patients Comparison: >12 g/dL versus lower Hb [The aspirational Hb levels are noted within the square brackets]

	High Hb target	**Low Hb target**
Increased risk in the higher Hb group for:	Access thrombosis [13-16 vs 9-12]	
No difference	• All cause mortality • CV mortality • MI	

	• Cardiac event • Hypertension • Change in LVMI • QoL (all domains with the exception of the vitality domain)	
Increased benefit in the higher Hb group for :	Lower transfusion requirements [13-15 vs 9-11.5]	
	QoL: • vitality [13-15 vs 9-11.5]	

Table 6.8U Increased risk/benefit for high/low Hb in NON-DIALYSIS patients: Comparison: 10 to 12 g/dL versus >9 g/dL
Comparison: >12 g/dL versus lower Hb
(aspirational Hb levels are noted in parenthesis)

	High Hb target	**Low Hb target**
Increased risk in the higher Hb group for:	Hypertension	
No difference	• All cause-mortality • Progression of CKD [creatinine clearance; initiation of dialysis] • Worst LVM-change from baseline	

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Comparison: >12 g/dL versus lower Hb

1. All-cause mortality

a. *Non-dialysis*

There is very low quality evidence [83,114,176,251,277,291] to show no significant difference in the risk of mortality in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 12 g/dL) groups. (Fig I.10, Appendix I:).

b. *Dialysis*

There is very low quality evidence[35,106,114] to show no significant difference in the risk of mortality in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) groups in the dialysis population. (Fig I.11, Appendix I:).

2. CV mortality

a. *Non-dialysis*

There is very low quality evidence[84,114] to show no significant difference in the risk of cardiovascular mortality in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL). (Fig I.12, Appendix I:).

b. *Dialysis*

There is very low quality evidence[35,114,245] to show no significant difference in the risk of cardiovascular mortality in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) dialysis patients. (Fig I.13, Appendix I:).

3. Progression of CKD

Non dialysis

i. Mean decrease in GFR

There is moderate quality evidence[84,114,176,273,277] to show no significant difference in the progression of CKD, as determined by the mean decrease in GFR, in the higher Hb level (12 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) group. (Fig I.14, Appendix I:).

ii. Creatinine clearance

There is very low quality evidence[176] to show no significant difference in the progression of CKD, as determined by the creatinine clearance, in the higher Hb level (12 to 14 g/dL) group compared with the lower Hb level (9 to 10.5 g/dL) group. (Fig I.15, Appendix I:).

iii. Initiation of dialysis

There is very low quality evidence[84,176,270,273] to show a borderline increased risk of initiation of dialysis in the higher Hb level (12 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group. (Fig I.16, Appendix I:).

iv. Worsening renal function

There is very low quality evidence [277] to show no difference in worsening renal function in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (11 to 12 g/dL) group. (Fig I.17, Appendix I:).

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4. Access thrombosis [*Dialysis*]

There is very low quality evidence[35,106,114,245] to show a significant increased risk of access thrombosis in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) groups. (Fig I.18, Appendix I:).

5. Transfusion

a. *Non-dialysis*

There is moderate quality evidence[84,251] to show a significantly lower number of patients transfused in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (>9 to 11.5 g/dL)(Fig I.19, Appendix I:).

(Reason for transfusions not reported).

b. *Dialysis*

There is moderate quality evidence[35,105] to show a significantly lower number of patients transfused in the higher Hb level (13 to 15g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group (Fig I.20, Appendix I:). (Reason for transfusions not reported.)

6. Stroke

a. *Non-dialysis*

There is low quality evidence[84,251,291] to show an increased risk of stroke in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (>9 to 11.5 g/dL) group. (Fig I.21, Appendix I:).

b. *Dialysis*

There were no studies reporting stroke outcome in a dialysis population.

7. MI

a. *Non-dialysis*

There is very low quality evidence[84,251,277,291] to show no significant difference in myocardial infarction in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group. (Fig I.22, Appendix I:).

b. *Dialysis*

There is very low quality evidence to show no significant difference in:

- myocardial infarction in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group (FigI.23, Appendix I:) [35,245].
- fatal myocardial infarction in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11 g/dL) group (Fig I.24, Appendix I:) [35].
- cardiac events in the higher Hb level (13 to 14 g/dL) group compared with the lower Hb level (9.5 to 10.5 g/dL) group (Fig I.25, Appendix I:) [106].

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8. Hypertension

a. *Non-dialysis*

There is low quality evidence[84,176,251,270,277] to show an increased risk of hypertension in the higher Hb level (12 to 15 g/dL) group compared with the lower Hb level (9 to 12 g/dL) group. (Fig I.26, Appendix I:).

b. *Dialysis*

There is very low quality evidence[245] to show no significant difference for the risk of hypertension in the higher Hb level(13.5 to 14.5 g/dL) group compared with the lower Hb level (9.5 to 11.5 g/dL) group. (Fig I.27, Appendix I:).

9. Change in LVMI

a. *Non-dialysis*

There is very low quality evidence[84,176,270,273] which shows no significant difference in the change in LVMI in the higher Hb level (12 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group. (Fig I.28, Appendix I:).

There is low quality evidence[86] to show:

- no significant difference in change in LVMI (at 1 and 3 years follow-up) in patients in the higher Hb level (13-15 g/dL) group compared with the lower Hb level (10.5-11.5 g/dL) group. (Fig I.28, Appendix I:).

- a significantly greater change in LVMI at 2 years in the lower Hb level (10.5-11.5 g/dL) group compared with the higher Hb level (13-15 g/dL) group. (Fig I.29, Appendix I:).

b. *Dialysis*

There is low quality evidence[245] to show no significant difference in the change in LVMI in the higher Hb level (13.5 to 14.5 g/dL) group compared with the lower Hb level (9.5 to 11.5 g/dL) group. (Fig I.30, Appendix I:).

10. Quality of Life (SF-36)

A summary of the statistical significance for each of the domains for each study is reported in tables 6.9U.

Two studies[270,273] did not report numerical values for all of the domains and one study[84] reported that there was no statistically significant difference in the QoL scores at year 3 and year 4; the numerical values were not reported.

Table 6.9U Quality of Life: Change in SF-36 scores from baseline [all domains]

Study	Physical function	Physical role	Pain	General health	Vitality	Social function	Emotional role	Mental health	Physical health composite	Mental health composite
NON-DIALYSIS										
ACORD [Ritz 2007]	-	-	-	NS	NS §	-	-	-	-	-
CREATE‡- [Drueke 2006] (year 1)	↑	↑	NS	↑	↑	↑	NS	↑	-	-
CREATE‡ (year 2)	NS	NS	NS	↑	↑	NS	NS	NS	-	-
CREATE ‡(year 3)	NS	NS	NS	NS	NS	NS	NS	NS	-	-
CREATE ‡(year 4)	NS	NS	NS	NS	NS	NS	NS	NS	-	-
CHOIR [Singh 2006]	NS	NS	NS	NS	NS	NS	↓	NS	-	-
TREAT [Pfeffer 2009] (25 weeks)	NS	-	-	-	NS	-	-	-	-	-
Roger 2004 (2 years)	-	-	-	-	-	-	-	-	NS	NS
Rossert 2006 †(4 months)	↑	↑	NS	NS	↑	NS	NS	NS	-	-
Rossert 2006 (9 months)	NS	NS	NS	NS	NS	NS	NS	NS	-	-
DIALYSIS										
Besarab * (1 year)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Besarab* (2.5 years)	↓	NS	NS	NS	NS	NS	NS	NS	↓	NS

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Study	Physical function	Physical role	Pain	General health	Vitality	Social function	Emotional role	Mental health	Physical health composite	Mental health composite
Parfrey 2005¶ (0.9 years)	-	-	-	-	NS	-	-	-	-	-

§ACORD: Study did not report numerical values for the vitality domain but stated that the difference was not significant. ‡CREATE[271]: Additional data received upon request; numerical values not reported for years 3 and 4. †Rossert: Data extracted from graph for QoL reported at end of stabilisation period – 4months; Only raw scores reported not adjusted for change from baseline. Additional data[139] received upon request - only raw scores reported not adjusted for change from baseline.

*Besarab[15]: Additional data received upon request. ¶Parfrey 2005- Study stated in the methods section that only SF-36 for vitality would be assessed.

↑=statistically significant in favour of the higher Hb group; ↓=statistically significant in favour of the lower Hb group NS = not statistically significant; - =domain not reported

a. *Non-dialysis*

There is very low quality evidence[84,84,251,270,277,277,291,291] (Fig I.31, Appendix I:) to show:

- a significant improvement in the quality of life scores in the higher Hb level (13 to 15 g/dL) group compared to the lower Hb level (>9 to 12 g/dL) group in the following domain:
  - vitality
  - general health.
- no significant difference in the quality of life scores in the higher Hb level (13 to 15 g/dL) group compared to the lower Hb level (>9 to 12 g/dL) group in the following domain:
  - physical function.

There is very low quality evidence[84,277,291] (Fig I.31, Appendix I:) to show:

- no significant difference in the quality of life scores in the higher Hb level (13 to 15 g/dL) group versus the lower Hb level (10.5 to 12 g/dL) group in the following domains:
  - physical role
  - pain
  - emotional role
  - social function
  - mental health.

There is very low quality evidence[273] to show:

- no difference in the quality of life scores in the higher Hb level (12 to 13 g/dL) group versus the lower Hb level (9 to 10 g/dL) group in the following domain:
  - physical health composite score.
- no significant difference in the quality of life scores in the higher Hb level (12 to 13 g/dL) group versus the lower Hb level (9 to 10 g/dL) group in the following domain:
  - mental health composite score.

b. *Dialysis*

There is moderate quality evidence[35] (Fig 23, Appendix B) to show no significant difference in the quality of life scores in the higher Hb level (13 to 15 g/dL) group versus the lower Hb level (9 to 11 g/dL) group in the following domains:

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- physical function
- physical role
- pain
- general health
- social function
- emotional role
- mental health
- physical health composite score
- mental health composite score.

There is moderate quality evidence[35,245] (Fig I.32, Appendix I:) to show a significant increase in the quality of life scores favouring the high Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group in the following domain:

- vitality

11. Composite events

Non-dialysis

There is moderate quality evidence[84,251,291] to show a borderline increased risk of composite events* in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (>9 to 11.5 g/dL) group. (Fig I.33, Appendix I:).

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* composite events were as follows:

- CREATE: time to a first cardiovascular event, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischaemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis),or cardiac arrhythmia resulting in hospitalisation for 24 hours or more.
- CHOIR: time to the composite outcome: of death, MI, hospitalisation for CHF (excluding RRT) or stroke.
- TREAT: time to composite outcome: death from any cause or a cardiovascular event (non fatal MI, CHF, stroke or hospitalisation of myocardial ischaemia).

12. CV event free survival

Non-dialysis

There is very low quality evidence[86] to show:

- no significant difference in CV event free survival (at 1, 2 and 3 years follow-up) in patients with concentric LVH at baseline in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (10.5 to 11.5g/dL) group. (Fig I.34, Appendix I:).
- no significant difference in CV event free survival (at 1 year and 2 years) in patients with eccentric LVH at baseline in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (10.5 to 11.5g/dL) group. (Fig I.35, Appendix I:).
- a borderline significant higher CV event free survival (at 3 years) in patients with eccentric LVH at baseline in the lower Hb level (10.5 to 11.5g/dL) group compared with the higher Hb level (13 to 15 g/dL) group. (Fig I.35, Appendix I:).

Comparison: 10 to 12 g/dL versus >9 g/dL

Non-dialysis

1. All-cause mortality

There is very low quality evidence[190] to show no significant difference in the risk of mortality in the high Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Fig I.36, Appendix I:).

2. Creatinine clearance

There is low quality evidence[190] to show no significant difference in the progression of CKD, as determined by creatinine clearance, in the high Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Fig I.37, Appendix I:).

3. Initiation of dialysis

There is very low quality evidence[190] to show no significant difference in the risk of initiation of dialysis, in the high Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Fig I.38, Appendix I:).

4. Hypertension

There is low quality evidence[190] to show an increased risk of hypertension in the higher Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Fig I.39, Appendix I:).

5. Worst LVM- Change from baseline

There is low quality evidence[190] to show no significant difference in the worst LVM (change from baseline) in the higher Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Fig I.40, Appendix I:).

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6.9.4 Health economic literature review [2011]

One cost-effectiveness model comparing the treating to different Hb targets was included in the 2006 guideline and one in the 2011 update search; these were however both excluded as they were only partially applicable to the UK NHS setting and were judged to be of limited use to decision making for the guideline due to the approaches taken to the clinical data[322,323].

6.9.5 Cost of reaching targets in RCTs [2011]

The estimated cost of erythropoiesis-stimulating agent (ESA) in the different arms of the RCTs identified in the systematic review above are summarised in Figure 6.2U and Figure 6.3U below.

The average drug dose reported for each arm of the study was obtained. Different studies reported different measures of dose; the best available measure was used with mean preferred over median, estimates over the whole study preferred over estimates at the end of the study and units/kg/week from the study (assuming 65kg in calculations) preferred over units/week from the study.

All doses were converted to epoetin for comparison. Epoetin alfa and epoetin beta doses were assumed to be equivalent; darbepoetin dose was converted using a darbepoetin:epoetin ratio of 1:200. This is the adult conversion ratio currently stated in the UK summary of product characteristics for calculating initial dose[89]. It is noted that some studies have suggested the ratio should be higher[42] – this would increase the equivalent dose estimates for the darbepoetin study.

The cost of epoetin alfa is based on the British National Formulary list price of £5.09 per 1000 units[46]; it is noted that substantial discounts are however often available for ESAs in practice. Where data is

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pooled a weighted average is used based on trial patient numbers (so larger studies contribute more to the pooled estimate than smaller studies).

It was noted that in some of the dialysis studies iv or sc dosing could be used while in others only sc could be used; when iv dosing with short acting ESAs (epo alfa and epo beta) is used the ESA dose required is generally higher than when sc dosing is used.

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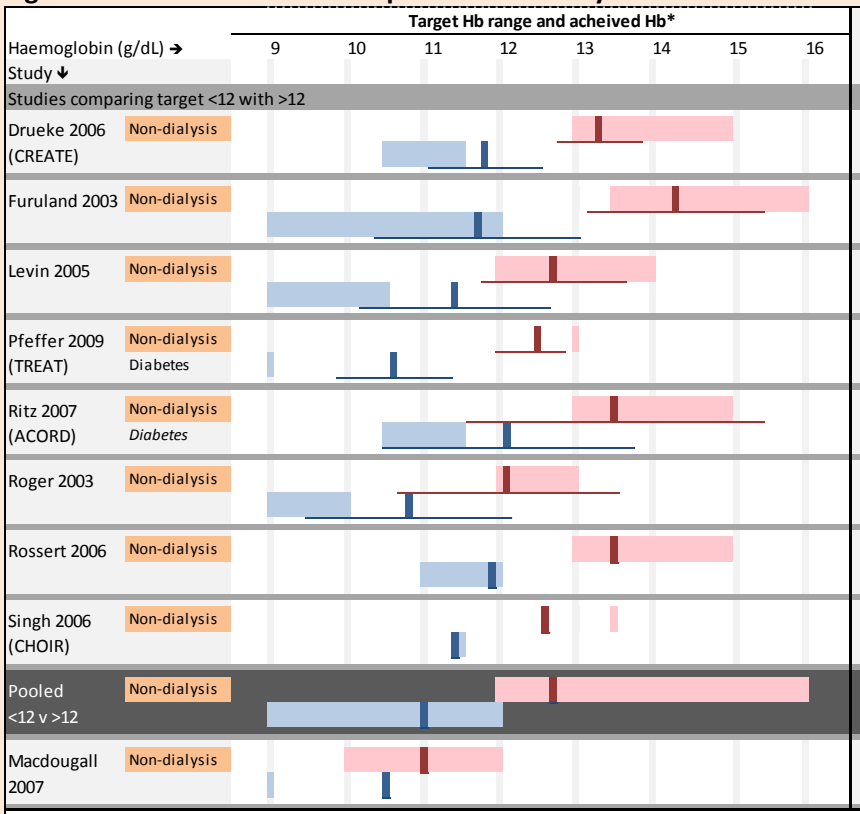
Figure 6.2U: Dose and cost comparison: non-dialysis studies



Study ↓		n	FU yrs	Drug	Dose U/wk	Measure	Eqiv. dose epo	Estimated cost/year	Difference High - Low
Studies comparing target <12 with >12									
Drueke 2006 (CREATE)	Non-dialysis	301	3.0	Epo beta (sc)	4554	Estimate based on mean dose in those receiving drug at various timepoints and % that received drug over study	4554	£1,205	£628
		302		Epo beta (sc)	2182		2182	£577	
Furuland 2003	Non-dialysis	36	0.9	Epo alfa (sc)	6955	Mean at end of study (U/kg/wk, 65kg)	6955	£1,841	£1,170
		36		Epo alfa (sc)	2535	Mean at end of study (U/kg/wk, 65kg)	2535	£671	
Levin 2005	Non-dialysis	78	2.0	Epo alfa (sc)	3106	Mean at end of study	3106	£822	£619
		74		Epo alfa (sc)	768	Mean at end of study	768	£203	
Pfeffer 2009 (TREAT)	Non-dialysis	2012	2.4	Darbo alfa	56	Mean over study	11250	£2,978	£2,911
	Diabetes	2026		Darbo alfa	1.25	Mean over study	250	£66	
Ritz 2007 (ACORD)	Non-dialysis	88	1.3	Epo beta (sc)	2997	Median over study (U/kg/wk, 65kg)	2997	£793	n/a
	Diabetes	82		Epo beta (sc)	NR	NR	NR	n/a	
Roger 2003	Non-dialysis	75	2.0	Epo beta (sc)	NR	NR	NR	n/a	n/a
		80		Epo beta (sc)	NR	NR	NR	n/a	
Rossert 2006	Non-dialysis	195	1.0	Epo alfa (NR)	4352	Estimate based on median in those receiving drug and % that received drug	4352	£1,152	£911
		195		Epo alfa (NR)	910		910	£241	
Singh 2006 (CHOIR)	Non-dialysis	715	1.3	Epo alfa (NR)	11125	Mean over study (U/kg/wk, 65kg)	11125	£2,945	£1,283
		717		Epo alfa (NR)	6276	Mean over study (U/kg/wk, 65kg)	6276	£1,661	
Pooled <12 v >12	Non-dialysis						9979	£2,641	£2,168
							1788	£473	
Macdougall 2007	Non-dialysis	65	2.0	Epo alfa (sc)	2047	Mean at end of study	2047	£542	£337
		132		Epo alfa (sc)	773	Mean at end of study	773	£205	

*Key:

Higher Hb	Lower Hb
Target	Target
Acheived	Acheived

underscore represents standard deviation (or interquartile range) if available

Equiv. dose epo: epoetin alfa and epoetin beta assumed equivalent; darbopoetin dose converted using a darbepoetin:epoetin ratio of 1:200.
Estimated cost/year: calculated using the British National Formulary list price of £5.09 per 1000 units for epoetin alfa[46].
Pooled: weighted average with weighting based on trial patient numbers
Sources: Dreuke[271,84], Furuland[114], Levin[176], Pfeffer[251,252], Ritz[270], Roger[273], Rossert[277], Singh[291], Macdougall[190]

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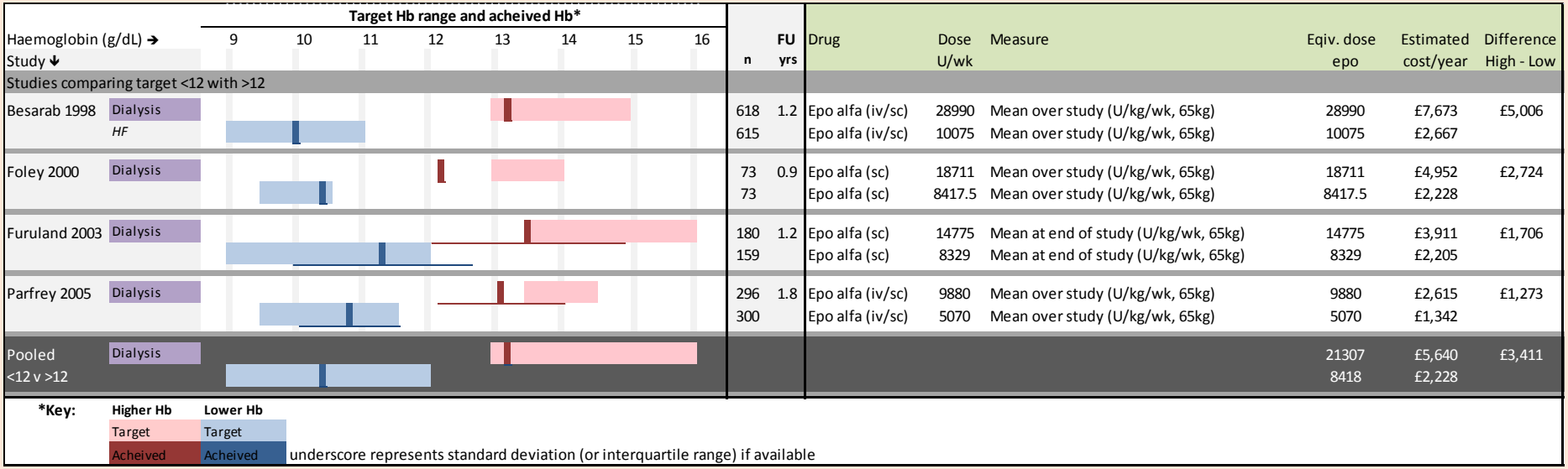
Figure 6.3U: Dose and cost comparison: dialysis studies



Study ↓		n	FU yrs	Drug	Dose U/wk	Measure	Eqiv. dose epo	Estimated cost/year	Difference High - Low
Studies comparing target <12 with >12									
Besarab 1998	Dialysis	618	1.2	Epo alfa (iv/sc)	28990	Mean over study (U/kg/wk, 65kg)	28990	£7,673	£5,006
	HF	615		Epo alfa (iv/sc)	10075	Mean over study (U/kg/wk, 65kg)	10075	£2,667	
Foley 2000	Dialysis	73	0.9	Epo alfa (sc)	18711	Mean over study (U/kg/wk, 65kg)	18711	£4,952	£2,724
		73		Epo alfa (sc)	8417.5	Mean over study (U/kg/wk, 65kg)	8417.5	£2,228	
Furuland 2003	Dialysis	180	1.2	Epo alfa (sc)	14775	Mean at end of study (U/kg/wk, 65kg)	14775	£3,911	£1,706
		159		Epo alfa (sc)	8329	Mean at end of study (U/kg/wk, 65kg)	8329	£2,205	
Parfrey 2005	Dialysis	296	1.8	Epo alfa (iv/sc)	9880	Mean over study (U/kg/wk, 65kg)	9880	£2,615	£1,273
		300		Epo alfa (iv/sc)	5070	Mean over study (U/kg/wk, 65kg)	5070	£1,342	
Pooled	Dialysis						21307	£5,640	£3,411
<12 v >12							8418	£2,228	

*Key:	Higher Hb	Lower Hb
	Target	Target
	Acheived	Acheived

underscore represents standard deviation (or interquartile range) if available

Equiv. dose epo: epoetin alfa and epoetin beta assumed equivalent; darbopoetin dose converted using a darbepoetin:epoetin ratio of 1:200.
Estimated cost/year: calculated using the British National Formulary list price of £5.09 per 1000 units for epoetin alfa[46].
Pooled: weighted average with weighting based on trial patient numbers
HF = heart failure
Sources: Besarab[35], Foley[106], Furuland[114], Parfrey[245]

6.9.6 EQ5D utility estimates [2011]

For economic evaluation, a specific measure of quality of life known as utility is required to calculate QALYs. Utility is measured on a scale of zero to one where zero is dead and one is full health. The NICE reference case prefers utility to be assessed by the EQ5D instrument. EQ5D data was not reported in the study publications for the RCTs comparing different targets but SF36 data was commonly reported. The eight domain scores from SF36 can be mapped to a single EQ5D utility score using a published algorithm[17].

Sufficient data was available to map SF36 data from three non-dialysis and one dialysis study. Full details of mapping methods are included in Appendix C:.

Table 6.10U EQ5D data: model inputs

	Study n overall	Mapped EQ5D				
		Target <12	*SE*	Difference	*SE*	*CI*
NON-DIALYSIS						
Drueke 2006 (CREATE)	603	0.82	*0.008*	0.033	*0.007*	*0.018, 0.047*
Rossert 2006	390	0.81	*0.012*	0.018	*0.018*	*-0.019, 0.052*
Singh 2006 (CHOIR)	1432	0.71	*0.008*	-0.006	*0.013*	*-0.025, 0.013*
Pooled‡ - Dreuke, Rossert, Singh		**0.75**	***0.005***	**0.008**	***0.007***	***-0.006, 0.021***
DIALYSIS						
Besarab 1998	1233	0.63	*0.01*	-0.003	*0.01*	*-0.029, 0.024*

‡ Pooled estimates are based on a weighted average of study averages; weighting based on number of patients in each study overall; CI = confidence interval; SE = standard error

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6.9.7 Health economic modelling [2011]

In the 2006 guideline a cost-effectiveness model comparing different Hb treatment targets was developed. However, the approach taken (using cohort data) was judged by the GDG to no longer be appropriate in light of new clinical data available in the 2011 update. The 2006 analysis was therefore removed from the guideline and a new analysis undertaken as part of the 2011update.

A new cost-effectiveness analysis based on the RCT data identified in the clinical review was developed. This compared treating to a target Hb of <12g/dL and to a target of >12 g/dL in a non-dialysis population.

Full details of methods, model inputs, results and sensitivity analyses, and a discussion of limitations of the analysis, can be found in Appendix C:.

Population

The non-dialysis and haemodialysis populations were considered separately by the GDG. The cost-effectiveness analysis was restricted to non-dialysis patients as there was limited SF36 quality of life data for haemodialysis patients to inform the estimate of utility for the model required to calculate QALYs.

Comparators

It was decided that the most useful and feasible option based on the available RCT data would be to compare a higher Hb target (>12 g/dL) versus a lower Hb target (<12 g/dL) based on pooled data for studies that make this comparison. Data did not allow more refined comparisons.

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Note that the studies used to inform the model all compare slightly different ranges. The lower targets were in the range 9-12 g/dL and the higher targets were in the range 12-16 g/dL. Studies also varied in their baseline Hb levels and achieved Hb levels. This information is all summarised in section 6.9 of the full guideline.

It was felt that the available RCT data was insufficient to allow a comparison to be made within the lower end of the Hb range (11-12 versus 9-11 g/dL, or similar). While one RCT reports mortality data for a comparison within this range (MacDougall; n=197; RR 0.93, 10-12 vs 9), no RCTs reported EQ5D or SF36 data within this range[190].

Model overview

Costs and quality-adjusted life-years (QALYs) were considered from a NHS and personal social services perspective. In the base case analysis a three year treatment period was considered with the impact of this extrapolated to a lifetime perspective.

The model incorporated differences between the Hb targets in terms of mortality, quality of life and ESA dose based on the RCTs identified in the clinical review of the literature.

Results

Results found that treating to a higher target of >12 was not cost effective when compared to treating to a target <12. The lower target 'dominated' the higher target with less costs and better health outcomes (higher QALYs). This conclusion was robust to various sensitivity analyses.

6.9.8 From evidence to recommendations

The GDG did not feel that increasing age should be a specific factor in setting a haemoglobin target but felt that low levels of physical activity in some individuals should be considered before setting the haemoglobin range for that individual.

The GDG highlighted that two studies within the meta-analysis[303] included children but that no outcome data were specifically reported from this population. The GDG noted that despite a lack of direct evidence relating to children, they could in general be expected to benefit from a similar Hb level to adults.

The GDG noted that the kinetics of a patient's response to epoetin vary. This means that whatever range of haemoglobin is specified as being optimal, it is inevitable that some patients will have a haemoglobin outside this range some of the time. This is because action to maintain the haemoglobin within the specified range may only be taken when a haemoglobin measurement falls outside the range and it will take time for any action to produce an effect. The GDG therefore agreed that they would specify a target range in the knowledge that this would result in most patients maintaining a haemoglobin concentration within 0.5g/dl either side of that specified range.

The GDG felt that setting a Hb range of 11.0–12.0g/dl would in effect allow the majority of patients to reach a level between 10.5 and 12.5 g/dl. It was noted from anecdotal evidence that maintaining a Hb of 12g/dl could make a large difference to a patients quality of life, exercise capacity and cognitive function; the increase in physical performance was further supported by the evidence[201]. The GDG also considered a health economic model that suggested haemoglobin ranges above 12 g/dl were not cost effective because of the high cost of epoetin and low incremental QALYs gained from higher haemoglobin ranges[323].

The consensus among the GDG was that a range of 11.0–12.0 g/dl was consistent with both the clinical and health economic evidence.

6.9.9 Recommendation

33. Age alone should not be a determinant for treatment of anaemia of CKD. (D(GPP))

6.9.10 Recommendations and link to the evidence [2011]

34. When determining individual aspirational Hb ranges for people with anaemia of CKD, take into account:

- **patient preferences**
- **symptoms and comorbidities**
- **the required treatment. [new 2011]**

35. The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.

- **Typically maintain the aspirational Hb range between 10 and 12 g/dl for adults, young people and children aged 2 years and older, and between 9.5 and 11.5 g/dl for children younger than 2 years of age, reflecting the lower normal range in that age group.**
- **To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 0.5 g/dl of the range's limits). [new 2011]**

36. Consider accepting Hb levels below the agreed aspirational range if:

- **high doses[d] of ESAs are required to achieve the aspirational range or**
- **the aspirational range is not achieved despite escalating ESA doses. [new 2011]**

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37. Consider accepting Hb levels above the agreed aspirational range when:

- **these develop with iron therapy alone or**
- **these develop with low doses of ESAs or**
- **it is thought that the person might benefit (for example, if they have a physically demanding job) or**
- **the absolute risk of cerebrovascular disease is thought to be low. [new 2011]**

6.9.10.1 Relative values of different outcomes

The GDG gave the most weight to the hard clinical outcomes of, mortality, cardiovascular events (stroke, MI) and transfusion requirements. They also acknowledged the importance of quality of life as a key goal of anaemia treatment. There were, however, limitations of the evidence on quality of life outcomes (discussed under 'quality of evidence' section).

Intermediate cardiovascular outcomes (hypertension and LV function) were given less weight but considered as important indicators of increased cardiovascular risk and future adverse outcomes.

Progression of CKD was given less weight due to difficulties in measuring and interpreting this outcome. Mean decrease in GFR, change in creatinine clearance and initiation of dialysis were all considered as indicators of progression and were considered to suggest adverse outcome.

[d] >175 international units per Kg per week, for haemodialysis population; >125 international units per Kg per week, for peritoneal dialysis population; >100 international units per Kg per week, for non-dialysis population (Data provided by the UK Renal Registry and GDG expert opinion).

The GDG also considered the impact of higher Hb levels on dialysis access thrombosis.

6.9.10.2 Trade off between clinical benefits and harms

The evidence for nondialysis and dialysis patients was considered separately as the underlying risk profile is different in these groups.

The GDG again noted that the interpretation of the evidence is complicated by the relationship between the target (aspirational) Hb levels in the different treatment groups in the trials and the achieved Hb levels. There was considerable variation in the doses of ESA used in the different trials and that no data were available that related the outcomes of interest to the dose of ESA used rather than the level of Hb achieved.

The GDG noted that a comparison of the outcomes above and below a Hb level of 12g/dL was the only analysis that the data allowed as this reflected the levels achieved in most studies, but they would have liked to have been able to compare outcomes above and below different thresholds.

The GDG considered the evidence in nondialysis patients which showed an increased risk for stroke (in patients with diabetes), hypertension and there was a borderline significant trend indicating increased risk for initiation of dialysis aspiring to correct anaemia to higher Hb levels (>12 g/dL).

For all-cause mortality there was a trend toward the higher target Hb group being at increased risk however this data was derived from studies powered for composite outcomes (not all cause mortality) and several of the trials were terminated early. The GDG were mindful that although there was no significant difference in all cause mortality being reported this was not considered robust enough evidence from which they could defer that there was no difference in mortality.

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The GDG also considered the evidence for dialysis patients which showed an increased risk of access thrombosis with higher Hb levels.

The GDG noted that in both nondialysis and dialysis patients there was a reduction in transfusion requirements and a statistically but not clinically significant improvement in quality of life outcomes in the groups with high aspirational Hb levels (>12 g/dL) to correct anaemia.

As part of an economic model undertaken for the guideline based on the clinical studies identified in the clinical review, treating people with nondialysis CKD and anaemia to a higher Hb target (>12 g/dL) was found to result in less quality-adjusted life-years (QALYs) than treating to a lower target. The model included quality of life and mortality. While cardiovascular events were excluded, this would only further lower the QALYs with the higher Hb target as these outcomes generally favoured the lower target.

The GDG concluded that the evidence of increased risk of adverse events outweighed beneficial effects of aspiring to a high Hb levels.

6.9.10.3 Economic considerations

The GDG considered the doses, and associated costs, of achieving the higher Hb targets in the RCTs included in the clinical review for nondialysis and dialysis populations. As might be expected, aiming for a higher target resulted in higher ESA doses being used which would result in higher costs.

It was noted that ESA doses varied between studies. US studies (such as CHOIR[291]) tended to have used considerably higher doses than European studies (such as CREATE[84]).

An economic model was built to assess the costs and QALYs of aiming for a higher Hb target (>12g/dL) with a lower target (<12g/dL) in nondialysis patients. This found that aiming for a higher target was associated with less QALYs (worse health outcome) and higher costs. This therefore

suggested that a lower target was both clinically and economically favourable. This conclusion was robust to a range of sensitivity analyses including scenarios favouring the higher target.

Whilst it is difficult to extrapolate from a nondialysis population to a dialysis population, the available dialysis evidence suggested no difference in quality of life, a similar difference in mortality to nondialysis patients and larger difference in ESA dose than in nondialysis patients. It was therefore considered unlikely that results would vary in dialysis patients.

6.9.10.4 Quality of evidence

The GDG noted that the quality of the evidence ranged from moderate (composite events) to very low (all-cause mortality).

The GDG recognised that the evidence for stroke was largely weighted by the TREAT[251] study in nondialysis diabetic patients and they noted that whilst the reasons why stroke may have occurred in this population were unclear the overall evidence still shows an increased risk of stroke in the high Hb group. They also debated whether the diabetic population was fundamentally different to the non-diabetic population, or whether their higher baseline risk of cardiovascular events allowed an increased risk of adverse outcome to be observed.

The GDG noted that there were limitations in the evidence on quality of life data on the SF-36 scale. Reporting was variable and data was often not reported for all domains, the quality rating was very low in the nondialysis population, and the observed improvements in quality of life scores were small. They also discussed other limitations of the evidence, for example lack of blinding in trials, which although was a source of bias may not have affected the results as the trials still showed harms and effects of adverse outcomes.

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There was no new evidence identified in young people and children and it was agreed the ranges for young people and children would be decided based on the discussions for the ranges agreed for the adult population.

6.9.10.5 Other considerations

Trials should be interpreted with care as:

- Trials were selective and baseline Hb quite high –trials did not include patients with very low Hb
  - In some studies many patients in the low Hb arm did not require treatment as they were already within the target.
- While most trials have been grouped into comparing targets of Hb >12g/dL and Hb <12 g/dL, studies were variable in terms of baseline Hb, the exact targets they compare and the Hb level achieved in each arm.
  - High (>12 g/dL) targets were all in the range of 12-16 g/dL and low (<12 g/dL) targets were in the range of 9-12 g/dL. However, high target arms systematically underachieved and low targets overachieved.

The GDG recognised that a 'one-size fits all' recommendation for an aspirational range was not practical and that recommendations should be individualised. The GDG's reasoning for this approach was based on:

- the recognition that Hb levels are not just a marker of anaemia
- some of the adverse effects observed may not necessarily be from a high Hb level in itself but may be due to using high doses of ESA to achieve the level
- acknowledgment that the evidence does not answer whether there are any benefits of a higher Hb in a young highly active patient.

The GDG were not aware of any ethnicity or diversity issues that needed to be taken into account as a result of the evidence reviewed.

In making recommendations the GDG considered:

- what the usual aspirational Hb levels should be for adults and children
- that lower levels of Hb are acceptable in patients who cannot reach the target despite treatment
- that in some situations higher levels of Hb may be acceptable and beneficial to individual patients.

Recommendation 34

The GDG debated the multi factorial elements underpinning this recommendation and considered:

- anecdotal evidence from patient representatives of the importance of the quality of life issue, especially in day-to-day living and functioning.
- that Hb is a biomarker and there are dangers in considering Hb in isolation – ESA doses required to achieve given levels of Hb are an important consideration.
- that there may be people with CKD who are at low vascular risk and low stroke risk who would derive a quality of life benefit from higher Hb levels. In these people higher Hb levels achieved with relatively low doses of ESA may be appropriate.
- that conversely people with additional co-morbidities may display different clinical indicators and signals. For example, the TREAT study was in a population of people with diabetes and CKD, a population with microvascular disease and increased risk of stroke. There is a known microvascular disease aspect to diabetes and there are pathophysiological reasons why a diabetic may be more predisposed to stroke.
- that there are elements/factors awaiting precise definition that clearly place certain groups of people with ACKD at increased risk from higher Hb levels. In these groups the evidence signals that escalating doses of ESA are associated with adverse outcome and the GDG agreed that caution should be displayed.

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Recommendation 35

The GDG noted that the evidence did not support correction of anaemia to normal levels of Hb in people with CKD. The unifying feature of the studies reviewed was that viewing Hb level in isolation whilst attempting to achieve correction of anaemia to normal healthy population Hb levels was inappropriate. The evidence clearly signalled caution in trying to push people to achieve higher levels of Hb.

The consensus of the GDG was that the evidence supported reducing the aspirational Hb treatment range to 10-12 g/dL. The Hb range was kept at 2 g/dL as patients' Hb levels naturally vary and are not at a constant level therefore it is impractical to achieve a narrower range. The action thresholds were adjusted accordingly.

Recommendations 36 and 37

A separate recommendation was drafted regarding adjustment of Hb in relation to ESA doses in both patients who fail to achieve aspirational Hb levels despite high ESA doses and those unintentionally exceeding aspirational Hb levels with low doses of ESAs.

The GDG debated what would constitute 'high doses of ESA'. No upper dose limit exists in the BNF and the upper dose limits quoted in the Summary of Product Characteristics (SPC) may be higher than the doses that were associated with worse outcomes in the clinical trials and is above that thought to be clinically appropriate.

It was suggested that the doses (the median (IQR) or mean ± 2SD) in the predominantly European trials (e.g. CREATE), could used as a guide. However it was felt that the trial populations may be

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unrepresentative of the whole population of people with anaemia of CKD. The GDG decided to refer to UK clinical practice as reflected in the UK Renal Registry data, recognising that these encompass patients with predominantly dialysis-dependent CKD.

6.9.10.6 Future research recommendation

Future research should look to stratify patients randomised to different target ranges of Hb by responsiveness to ESA in terms of maintenance EPO dose/kg body weight/maintenance Hb level achieved before analysing outcomes.

6.10 Optimum haemoglobin levels in children with anaemia of CKD

6.10.1 Methodological introduction

The two RCTs reported in the meta-analysis[303] conducted in children[44,209] – one of cross-over design[209] – were used to address the effects of lower vs higher haemoglobin and were individually appraised. An additional cross-over RCT[210] that was conducted in the same paediatric population was also appraised.

Issues for consideration were as follows:

- The two cross-over RCTs[209,210] were downgraded to Level 2+ because of methodological limitations.
- One study[44] had set out to investigate dosing requirements.
- Study duration to assess cardiovascular benefits of epoetin administration[210] may not have been sufficiently long at 48 weeks.

Table 6.11 Summary characteristics of appraised studies

Study	N	Target Hb	Study type	Study duration
44	44	Between mean and 2 standard deviations below mean for age	RCT of low dose vs high dose epoetin	12 weeks
210	7	10.5–12.0 g/dl	Cross-over RCT of epoetin vs placebo	24 weeks in each limb, 48 weeks total
209	7	10.5–12.0 g/dl	Cross-over RCT of epoetin vs placebo	24 weeks in each limb, 48 weeks total

6.10.2 Evidence statements

Table 6.12 Evidence statements for optimum Hb levels in children

Study	Hypertension and cardiovascular parameters	Patient population (n)	Achieved high Hb	Achieved low Hb	Evidence grading
44	Systolic and diastolic BP No difference	Children on haemodialysis, peritoneal dialysis and	12.9 ± 0.7; 11.9 ± 1.6; 12.7 ± 2.0 g/dl	8.4 ± 1.0; 10 ± 2.04; 11.9 ± 1.8 g/dl	Level 1+

Study	Hypertension and cardiovascular parameters	Patient population (n)	Achieved high Hb	Achieved low Hb	Evidence grading
		predialysis (n=44)			
[210]	Cardiac index (p=0.01), ventricular stroke index (p=0.03),heart rate (p=0.002), aortic stroke distance (p=0.01), minute distance (p=0.03) and left ventricular end diastolic diameter (p=0.04) all decreased. There was no change in shortening fraction, interventricular septum and left ventricular posterior wall thickness. No change was found in systolic, diastolic or mean BP.	Children on peritoneal dialysis (n=7)	11.5 g/dl (target 10.5–12.0 g/dl)	6.9 g/dl	Level 2+
[209]	No changes were found in the 2-minute walking distance (n=7) and treadmill exercise testing workload (n=3). A reduction in	Children on peritoneal dialysis (n=7)	Median 11.2 g/dl (range 9.5–14.2 g/dl)	Median 7.3 g/l (range 4.2–8.1 g/l)	Level 2+

Study	Hypertension and cardiovascular parameters	Patient population (n)	Achieved high Hb	Achieved low Hb	Evidence grading
	heart rate at rest was found after epoetin administration (p=0.02) and at each successive stage of the exercise test. No arrhythmias or ischaemic changes were found.				
[209]	Quality of life (25-part parental questionnaire, using a visual analogue scale) found an improvement in physical and general health (p<0.02), but the global score did not find an improvement in quality of life.	Children on peritoneal dialysis (n=7)	11.2 g/dl (range 9.5–14.2 g/dl)	Median 7.3 g/l (range 4.2–8.1 g/l)	Level 2+

6.10.3 From evidence to recommendations

The use of exercise testing for outcomes is not meaningful in very young children, which exacerbates the problem of the small sample size in the evidence.

6.10.4 Recommendations

Recommendations pertaining to children with anaemia of chronic kidney disease are presented in relevant sections throughout the guideline.

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Optimum haemoglobin levels in children with anaemia of CKD [2011]

Two RCTs[44,210] identified in a paediatric population in the original guideline were further assessed. One study was an RCT of low dose versus high dose epoetin and the other study was a cross-over RCT comparing rHuEPO versus placebo.

The characteristics of the included studies are reported in Appendix H:.

Evidence profile

The evidence profile summarises the quality of the evidence and outcome data for the 2 RCTs (Tables 6.13U-6.15U) included in this review. Results are presented by outcomes and results for the non-dialysis and dialysis populations are presented separately.

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Table 6.13U Non-dialysis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	8.35(SD1.1) g/dL compared to lower Hb(8.68(SD0.9)) level for children - non-dialysis	control	Relative (95% CI)	Absolute	Quality
Proportion of patients transfused - 12.7 v 11.9											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/12 (8.3%)	0/13 (0%)	RR 3.23 (0.14 to 72.46)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW

[1] Brandt 1999; 1/1 had unclear allocation concealment and no report of blinding
[2] 95% CI include both the line of appreciable benefit and harm

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Table 6.14U Dialysis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	7.23(SD) to 9.18(SD1.1) g/dL compared to lower Hb (6.78(SD1.0) to 7.68(SD1.3))evel for children - dialysis	control	Relative (95% CI)	Absolute	Quality
Proportion of patients transfused-haemodialysis - 12.9 v 8.4											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/3 (0%)	3/6 (50%)	RR 0.25 (0.02 to 3.71)	375 fewer per 1000 (from 490 fewer to 1355 more)	⊕⊕OO LOW

[1] Brandt 1999; 1/1 had unclear allocation concealment and no report of blinding
[2] 95% CI includes both the line of appreciable benefit and harm

Table 6.15U Dialysis and non-dialysis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	11-12 g/dL compared to lower Hb level for children - both dialysis and non-dialysis	control	Relative (95% CI)	Absolute	Quality
LVMI (g/m2) after first 24 weeks group 1 - treatment, group 2 - placebo - 11.5 V 6.9 (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4	3	-	MD 13.6 higher (31.51 lower to 58.71 higher)	⊕OOO VERY LOW
LVMI (g/m2) after second 24 weeks group 1 - placebo, group 2 - treatment - 11.5 v 6.9 (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4	3	-	MD 57.1 higher (7.64 to 106.56 higher)	⊕OOO VERY LOW

[1] Brandt 1999; 1/1 had unclear allocation concealment and no report of blinding
[2] 95% CI includes both the line of appreciable benefit and harm

One study[44] either did not report the numerical values (outcome: progression of CKD) or did not report the numerical value for each treatment group (outcome: hypertension). The results for progression of CKD and hypertension are summarised in the evidence statements below with evidence statements for the outcomes transfusion rates and change in LVMI.

1. Progression of CKD

a. Non-dialysis

One study[44] reported that the change in creatinine during the study was 'insignificant' between the dosing groups and within the nondialysis group. There were no numbers reported to determine whether this difference was significant or not.

b. Dialysis

One study[44] reported that the change in creatinine during the study was 'insignificant' between the dosing groups and within the haemodialysis and peritoneal dialysis groups. There were no numbers reported to determine whether this difference was significant or not.

2. Hypertension

a. Non-dialysis

One study[44] reported that the 33% (3/9) children had new or worsening hypertension.

b. Dialysis

One study[44] reported that the 66% (6/9) children had new or worsening hypertension in the haemodialysis group and 30% (3/10) had new or worsening hypertension in the peritoneal dialysis group. Results for the high dose and low dose groups were not reported separately.

3. Transfusion rate:

a. Non-dialysis

There is low quality evidence[44] to show no significant difference in the proportion of patients transfused in high dose Hb group compared with low dose Hb group (Fig I.41, Appendix I:).

b. Dialysis

There is low quality evidence[44] to show no significant difference in the proportion of patients transfused in high dose Hb group compared with low dose Hb group (Fig I.42, Appendix I:).

4. LVMI

There is very low quality evidence[210] to show :

- no significant difference in LVMI at 24 weeks between the groups that received rHuEpo versus placebo. (Fig 34, Appendix B)
- a significant increase in LVMI at 48 weeks favouring the group that received placebo followed by rHuEPO compared with the group that received rHuEPO prior to placebo (Fig I.43, Appendix I:).

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6.11 Adjusting ESA therapy

6.11.1 Clinical introduction

ESA dose adjustments are made to encourage haemoglobin levels into the recommended ranges. The details of such 'targeting' varies unit by unit, but must always involve decisions on when to make the dose change (ie at what haemoglobin level), and by how much to change the ESA dose and/or frequency. ESA therapy (even with the currently available long-acting agent) involves delivery of short, intermittent, pharmacological bursts of bioavailable EPO which bear no relation, either temporally or in magnitude, to normal physiological control of erythropoiesis. Under normal conditions, the body's oxygen sensing, EPO-producing, and erythropoietic systems are closely regulated and coordinated to maintain haemoglobin levels within a narrow range. During ESA therapy, haemoglobin levels fluctuate widely and the pattern of fluctuation varies from patient to patient[165]. This haemoglobin cycling may complicate the management of anaemia associated with CKD. Factors likely to be associated with fluctuations in haemoglobin level include changes in ESA dose, intravenous iron treatment, intercurrent illness (especially infection) and hospitalisation. Those patients experiencing more frequent fluctuations, and those with the greatest amplitude of fluctuation, have been characterised as being more responsive to ESAs[94].

Experimental and clinical studies have defined a desirable outcome range of haemoglobin and have used the limits of the range to trigger a dose change when the haemoglobin level falls above or below these limits. The extent of the dose change, whether an absolute amount or a proportion of the existing dose, has to fit the available ESA formulations or decisions are required about the dosage interval. However, because of logistical delays in responding to any current laboratory value and because of differences in the momentum of haemoglobin change, it may be necessary to alter ESA therapy pre-emptively prior to the haemoglobin level breaching the limits of the desirable range. There are also individual variations in the response to ESAs that may be taken into account from historical data. The case mix and treatment history of any patient cohort will also influence the outcome and while tailoring of the timing and dose changes may be attempted there is inevitable unpredictability of outcome.

So how then do we adjust ESA dose and dose frequency to keep haemoglobin levels within the maintenance range, and what factors determine how we do this?

6.11.2 Clinical methodological introduction

A literature search found 13 studies: an RCT[214], prospective cohort studies[13,234], retrospective cohort studies[66,196,268], cross-over studies[7,228], retrospective longitudinal studies[59,343], and cross-sectional studies[124,148,181].

One study[198] had methodological limitations and was therefore excluded from the evidence statements.

6.11.3 Clinical evidence statements

Factors affecting epoetin dose: route of epoetin administration

Haemodialysis patients

One study[59] found patients administered with epoetin by the i.v. route received significantly higher doses than those prescribed epoetin by the s.c. route (p=0.0001). (Level 3)

Iron status

Haemodialysis patients

Three studies found epoetin dose to be inversely correlated with iron status when measured by means of serum transferrin saturation (p=0.0001)[59], serum saturation ratio (r=−0.16, p=0.003)[148] and total iron binding capacity levels (r=0.27, p<0.01)[196]. (Level 3 and Level 2+)

In contrast, one study[196] did not find an association with serum transferrin saturation. Also, no association between epoetin dose and serum ferritin levels was found in two studies[59,196]. (Level 3 and Level 2+)

Dialysis adequacy

Haemodialysis patients

One study[59] found an inverse correlation between urea reduction ratio and administered epoetin dose (p<0.0001). (Level 3)

Cause of end stage renal failure

Haemodialysis patients

One study[59] found diabetes mellitus as the cause of end stage renal failure to be associated with lower epoetin doses (p=0.003). (Level 3)

Inflammation

Haemodialysis patients

One study[148] found a direct correlation between administered epoetin dose and malnutrition-inflammation score (ie increasing degree of severity) (r=0.13, p=0.03). This was reflected in the direct correlation between weekly epoetin dose and logarithmic inflammatory cytokines, IL-6 (r=0.31, p<0.001) and TNF-α (r=0.18, 0.001) as well as C-reactive protein (CRP) (r=0.18, p<0.001) and lactase (p<0.001) levels. Similarly, there was an inverse correlation observed between epoetin dose and nutritional markers (r=−0.19, p<0.001).

In another study[124], albumin (r=−0.359, p<0.001), log CRP (r=0.337, p=0.001), log ferritin (r=0.240, p=0.021) and transferrin (r=–0.264, p=0.011) all showed correlation with epoetin:Hct ratio. When patients in the lowest and highest epoetin:Hct quartiles were compared, only median CRP showed statistical significance (p=0.009). (Level 3)

Contrary to the above findings, in one study[181] C-reactive protein levels did not show any association with epoetin dose. (Level 3)

Peritoneal dialysis patients

In one study[124], albumin (r=−0.453, p=0.006) and CRP (r=0.375, p=0.024) showed correlation with epoetin/Hct ratio, but not ferritin. (Level 3)

Haemodialysis vs peritoneal dialysis patients

When compared with one another in the same study[124], haemodialysis patients had a greater epoetin/Hct ratio than peritoneal dialysis patients (p<0.001), which was matched with a higher

epoetin dose (p<0.001) and lower Hct levels (p=0.002). Also lower CRP (p<0.001), ferritin (p<0.001), transferrin (p<0.001) and aluminium (p<0.001) levels were found in the haemodialysis patients. However, no difference was observed for albumin, transferrin saturation, intact parathyroid hormone and PCRn. (Level 3)

Adjunctive medical treatment

Haemodialysis patients

Higher epoetin doses were administered to patients receiving ACE-inhibitor therapy when compared with those not treated with ACE-inhibitors (p<0.05) in one study[196]. In a 12-month study[13], patients receiving high dose enalapril (ACE-inhibitor) required a higher epoetin dose at the end of the study period (p<0.0001) and also when compared with those receiving nifedipine (calcium-channel blocker) (p<0.0001) or control (epoetin only) (p<0.0001) to maintain a Hb >10 g/dl. Similarly, in a 12-month study aimed to maintain Hb >10 g/dl[234], high dose losartan (angiotensin-II receptor blocker) required a higher epoetin dose at the end of the study period (p<0.0001) and also when compared with those receiving amlodipine (calcium-channel blocker) (p<0.0001) or control (epoetin only) (p<0.0001). (Level 2+)

In contrast to the above findings, two studies with patients receiving ACE-inhibitors[7,66] aimed to maintain Hct levels at 30–36% (Hb ~ 10–12 g/dl) did not find any association between ACE-inhibitor administration and epoetin resistance. (Level 2+)

Peritoneal dialysis patients

Weekly epoetin dose given to maintain Hct >30% (Hb ~ 10 g/dl) at the end of a 12-week study[214] was greater in patients receiving ACE-inhibitors (p<0.01) and in patients receiving angiotensin-II receptor blocker treatment (p<0.05), but not in those receiving calcium-channel blockers when compared with individual weekly doses at the beginning of the study. In addition, plasma epoetin levels were higher in the ACE-inhibitor treated group (p<0.05) but not in the angiotensin-II receptor blocker and control groups. (Level 1+)

Parathyroid hormone

Haemodialysis patients

In a study conducted in patients over the age of 65 years, whereby patients were divided into PTH >250 pg/ml and <250 pg/ml, despite similar epoetin doses and serum iron and ferritin levels, patients in the hyperparathyroid group had lower Hb and Hct levels (p=0.009 and p=0.008 respectively) as well as higher levels of alkaline phosphatase (p=0.023), phosphorus (p=0.001) and calcium x phosphorus product (p=0.009)[228]. (Level 2+)

Hospitalisation

Haemodialysis patients

In one study[343], higher epoetin doses were required in patients who were transfused during hospitalisation up to 2 months following discharge (p<0.05). (Level 3)

The same study[343] found no association between discharge diagnosis, (inflammatory vs non-inflammatory) or surgical procedure during hospitalisation and epoetin requirement up to 2 months following discharge. (Level 3)

Dialysate chloramine levels

Haemodialysis patients

One before and after study (n=72)[103] found an association between higher achieved Hb level (p<0.001) and decreased epoetin dose (p<0.001) with installation of new carbon filters, which decreased the chloramine levels from to 0.25 parts per million (ppm) to <0.1 ppm. This was supported by findings in a subgroup analysis (n=15) that showed low-grade haemolysis by a post-dialysis rise in methaemoglobins (p<0.01) and a drop in haptoglobins (p<0.01), which was not detected after the use of the carbon filters. Additionally, the water board confirmed the sustained two fold increase in chloramines levels and acceptable levels of nitrate, aluminium, bacterial counts and endotoxins in the mains water supply during the study time period. In agreement, one satellite dialysis unit[268], found decreasing Hb levels at months 10 (p<0.01) and 11 (p<0.01) of the study despite higher epoetin dose (p=0.04) when compared with other local dialysis units. These findings were associated with a high chlorine water content relative to the desirable limit (p value not given), which coincided with evidence of haemolysis as shown by higher ferritin (p<0.01) and low haptoglobin (p value not given). Furthermore, installation of an activated charcoal filter decreased chlorine concentration to <0.02, which was accompanied by an increase in Hb and a reduction in epoetin requirement. (Level 2+ and Level 3)

6.11.4 Health economics methodological introduction

The appraised study[254] performed a decision analysis comparing three dosage regimens: epoetin-6 strategy, 6,000 U (107 U/kg), epoetin-9 strategy, 9,000 U (167 U/kg) and epoetin-12 strategy, 12,000 U (211 U/kg) of subcutaneous epoetin in continuous ambulatory peritoneal dialysis to maintain the target Hct level of 0.33 (equivalent to 11 g/dl)[254]. Epoetin was given weekly for the first 2 months until a target Hct of 0.33 was reached. This was maintained for an additional 3 months with the administration frequency reduced to fortnightly or 4-weekly. Non-responders in 6,000 U and 9,000 U after 2 months entered 12,000 U regimen.

6.11.5 Health economics evidence statements

Of the three subcutaneous epoetin strategies compared, it was most cost effective in peritoneal dialysis patients to give 6,000 units weekly for 2 months, followed by a weekly or 2-weekly epoetin 6,000 unit dose for the next 3 months while maintaining the target Hct level of 0.33 and to restart non-responders after 2 months on the 12,000 unit epoetin strategy[254]. The savings from the lower administration frequency of the 9,000 unit dosage regime were offset by the higher cumulative acquisition cost[254].

Varying the parameters over the 20-week treatment period:

- Epoetin-6 strategy is always the least costly over the $0–60 range for drug administration costs. Drug administration costs must be $137 for epoetin-6 to become more costly than epoetin-12.
- Epoetin-6 is least costly over the 95% CI range for response probabilities.
- Epoetin-12 strategy becomes less costly than the Epoetin-9 as drug administration costs increase over $35.

Varying the parameters over a 1-year treatment period:

- Epoetin-6 was less costly than both epoetin-9 and epoetin-12 over the range of costs ($0–60).
- Epoetin-6 becomes more costly than epoetin-12 at $95.
- Epoetin-6 was less costly over whole range of 95% CI.
- Epoetin-9 was more costly than epoetin-12 at lower 95%CI limit.

- Epoetin-12 becomes less costly than epoetin-9 at drug administration costs of $8 per injection and above.

6.11.6 From evidence to recommendations [2006, amended 2011]

Of all of the outcomes considered in the evidence, the GDG felt that the route of ESA administration, the patient's iron status, administration of adjunctive medical treatment, and the presence or absence of inflammation were of most relevance to determine the dose and frequency of ESA required to keep haemoglobin levels within the maintenance range in all CKD patients. Dose adjustments were also likely to be influenced by:

- the patient's haemoglobin level
- the observed rate of change in haemoglobin level
- an individual patient's response to ESA therapy.

In patients on haemodialysis, chloramine levels in dialysis water were also of relevance. The outcomes of dialysis adequacy, adjunctive medical treatment, race, and parathyroid hormone levels were discussed but the evidence was either limited or would be more fully covered in separate guideline sections, the GDG therefore did not wish to make any recommendations regarding these. The outcomes of end-stage renal failure and hospitalisation were included but the GDG did not feel that they were helpful in determining the dose and frequency of ESA required to keep haemoglobin levels within the maintenance range for individual patients.

With regards to the route of administration, two studies reported that doses of short-acting ESAs could be reduced when administered subcutaneously as opposed to intravenously[59,198]. It was noted that the decision of whether to administer ESAs s.c. or i.v. was also a matter of patient choice.

Several studies supported the view that the amount of ESA required is inversely correlated with iron status[59,148,198]. The GDG felt this was an important factor to take into account when determining the dose and frequency of ESA required to keep haemoglobin levels within the maintenance range and also Unit policy in view of the need for uniform and convenient clinical procedures.

The GDG noted that there was evidence to support a correlation between the weekly dose administration of ESA and inflammatory cytokines (IL-6, TNF-alfa)[148].

The GDG noted that the evidence supported the intuitive notion that sicker patients generally require higher doses of ESAs[124]. The GDG discussed that intercurrent illness may be a cause of temporary resistance that should be assessed, and it was noted that in patients with a chronic illness, resistance to ESAs may be prolonged.

The GDG discussed the evidence with respect to adjunctive medical treatment, that patients receiving either ACE inhibitor therapy or angiotensin-II receptor antagonists required an increased dose of ESA in comparison with those patients administered a calcium-channel blocker or to control groups[196,234]. Two further studies reported no association between ACE-inhibitor administration and resistance to ESAs[7,66]. The GDG considered one study to have methodological limitations due to the non-randomised study design[7]. The GDG noted that the treatment ranges in these studies were appropriate and the doses being administered would not lead the GDG to consider that ESA resistance should be suspected. The GDG concluded that there was no evidence that ACE-inhibitors caused ESA resistance and that such treatment should not be stopped, although the dose of ESA may require adjustment.

The GDG discussed the implications of dialysis water purity on ESA administration, in particular the GDG noted that increased chloramine levels (formed by the combination of free chlorine and ammonia gas) were associated with a need for higher doses of ESAs in haemodialysis patients[103,268]. The GDG discussed that the addition of activated charcoal filters reduced the level of chlorine in the

dialysis water. However, it was noted that these filters can be prone to infection suggesting that a risk–benefit analysis would be useful. It was noted that neither study had performed such an analysis. The GDG noted that NHS Estates have produced a document covering facilities for renal services. This outlines that the required standards for water purity must be monitored and achieved (point 2.19), and specifically notes that 'carbon filters should be selected to achieve sufficient contact time to remove all chlorine and chloramines' (point 6.78)[229]. This issue was considered an issue for a dialysis unit rather than the individual patient but the information may be of use to unit managers. The GDG concluded that dialysis units should consider the use of carbon filters but that a risk–benefit analysis should be used to assess the benefits of reducing chloramines levels against the risk of infection of the carbon filters.

The GDG discussed monitoring issues around how frequently patients should be monitored and when to intervene to correct the Hb level. It was felt that there was a need to follow the trend of a patient's response to Hb but that in general, if two consecutive tests taken a month apart fell outside the target range, or if the rate of rise or fall of haemoglobin exceeded 1 g/dl/month, then intervention would be necessary to correct the Hb level.

With regards to the health economic evidence, the GDG felt that there were some issues with the transferability of the costs from a study conducted in the USA to the UK healthcare setting. However, the GDG did agree with the principal message that giving a low dose of ESA more frequently was more cost effective at the unit level.

Update 2011

This section was outside the scope of the 2011 rapid partial update. However, when reviewing the recommendations as a whole, the GDG felt that slight changes to recommendations 38 and 40 below were necessary. This was to increase patient safety through emphasising the requirement to optimise iron status before either initiating ESA therapy or escalating ESA doses. In fact, optimisation of iron status prior to administration of ESAs, and continued optimisation of iron status during maintenance treatment with ESAs is an essential part of anaemia management because it allows ESA dosages to be kept to a minimum. This avoids the risk of higher doses of ESA, which have been associated with adverse patient outcomes. In addition, these changes that emphasise the importance of iron status in recommendations 38 and 40 below are consistent with and complement the existing recommendations 41 and 44.

6.11.7 Recommendations [2006, amended 2011]

38. Iron status should be optimised before or coincident with the initiation of ESA administration and during maintenance treatment with ESAs[e]. [C]

39. Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists is not precluded, but if they are used, an increase in ESA therapy should be considered. [D]

40. Haemoglobin measurements should be taken into account when determining the dose and frequency of ESA administration:

- **The cause of an unexpected change in Hb level should be investigated (that is, intercurrent illness, bleeding) to enable intervention and iron status should be optimised[f].**
- **ESA dose and/or frequency should be increased or decreased when Hb measurements fall outside action thresholds (usually below 10.5g/dl or above 11.5g/dl), or for example when the rate of change of haemoglobin suggests an established trend (eg >1g/dl/month).**

[D(GPP)]

[e] Amended to clarify that iron status should be monitored during ESA maintenance treatment (see Recommendation 44)

[f] Amended to show iron status should be optimised following an unexpected change in Hb level.

6.12 Treating iron deficiency: correction

6.12.1 Clinical introduction

While there are many different preparations of oral iron available (see Table 6.13), there are currently only two forms of parenteral iron licensed in the UK, iron sucrose and iron dextran. The key issues are iron safety and efficacy.

Table 6.13: Iron content of different oral iron preparations

Iron salt	Dose	Content of ferrous iron
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous succinate	100 mg	35 mg
Ferrous sulphate	300 mg	60 mg
Ferrous sulphate, dried	200 mg	65 mg

Oral iron preparations contain varying amounts of ferrous iron, and the frequency of gastrointestinal side effects related to each different preparation tends to be directly related to the content of ferrous iron. Common adverse effects from oral preparations include constipation, diarrhoea, nausea, vomiting, and dyspepsia.

Iron sucrose is a complex of ferric hydroxide with sucrose containing 2% (20 mg/ml) of iron and iron dextran is a complex of ferric hydroxide with dextran containing 5% (50 mg/ml) of iron. Adverse effects from intravenous iron are mainly related to the size of dose and rate of infusion. Potential adverse effects include nausea, vomiting, abdominal pain, flushing, anaphylactoid reactions, dyspnoea, numbness, fever, urticaria, rash, arthralgia, myalgia, blurred vision, injection-site reactions including phlebitis, rarely diarrhoea, arrhythmias, hypotension, chest pain, seizures, tremor, dizziness, fatigue and sweating.

Intestinal iron absorption declines as serum ferritin increases[161,162] and ESA administration boosts iron absorption in erythropoietin deficient haemodialysis patients[293]. Patients with CKD who have anaemia, a GFR below 40 ml/min, and are not receiving ESA therapy are likely to be erythropoietin deficient[91]. The relative lack of oral iron efficacy in each of these conditions may be due to a lack of erythropoietin-stimulated iron absorption. This lack of oral iron efficacy led to the use of i.v. iron and early use of i.v. iron employed low doses given relatively frequently and administered as an infusion. Frequent administration of i.v. iron in haemodialysis patients is made feasible through use of dialysis vascular access but in peritoneal dialysis and predialysis patients venous access is required for each dose. Administration of higher doses in CKD patients not on haemodialysis offers the potential to spare venous access, but at the possible expense of increased adverse effects.

Relative to other CKD patient groups there is a wealth of information concerning iron status and response to iron administration in patients on haemodialysis. In CKD patients not on dialysis low iron indices are common. TSAT levels below 20% and ferritin levels below 100 µg/l may occur in up to 20–70% of patients, depending on CKD stage and gender [130] However, little is known about the relationship between baseline iron status, the likelihood of a response to an iron challenge, and the relative efficacy and safety of oral vs intravenous iron.

Iron therapy in haemodialysis patients is an essential adjuvant to ESA therapy and adequate iron stores are required prior to treatment with ESAs to ensure effective erythropoiesis. Virtually all haemodialysis patients will require ESA therapy to achieve target haemoglobin levels. By contrast, a significant proportion of predialysis CKD patients, and some peritoneal dialysis patients, may not

require ESA therapy to achieve target haemoglobin levels. Iron therapy in these patients may be undertaken as primary treatment of anaemia.

6.12.2 Methodological introduction

A comprehensive literature search identified one RCT[327] investigating the efficacy of oral vs i.v. iron in predialysis patients without concurrent ESA therapy and two before and after studies investigating the efficacy of i.v. iron over 6 months[289] or as a single dose[16] in iron-deficient predialysis patients who had not previously received ESA therapy. A further before and after study was identified investigating the efficacy of i.v. iron over 12 months[203].

One study[40] did not meet quality criteria and was therefore excluded from the evidence statements.

6.12.3 Evidence statements

Iron dextran: predialysis patients

Following administration of 1g iron dextran in 500 ml normal saline i.v. as a total dose infusion over 6 hours (n=56), Hb ($p<0.001$) and serum ferritin ($p<0.0001$) levels increased after 12 weeks. However, this increase in Hb was not apparent after one year (n=21); ferritin was still increased compared with baseline, although to a lesser extent than at 12 weeks ($p<0.001$). In addition, no major adverse events were found and systolic and diastolic blood pressure did not change after 12 weeks[16]. (Level 3)

Ferric saccharate (also known as ferric hydroxide sucrose or iron sucrose): predialysis patients

In one study 200 mg elemental iron (Ferric saccharate) was administered in 150 ml saline over 2 hours, once monthly for 5 months, to give a total i.v. iron dose of 1,000 mg per patient (n=33). After 3 months of i.v. iron treatment, the mean Hct and Hb values were not significantly increased, despite raised serum ferritin levels compared with baseline ($p<0.05$). At 6 months, however (ie 1 month after the last iron dose), the mean Hct ($p=0.035$) and Hb ($p=0.008$) had significantly increased. Additionally, there were no differences in those responding to i.v. iron treatment with an increase in mean Hct and Hb compared with those not responding in any of the other parameters (serum creatinine, creatinine clearance, systolic and diastolic blood pressure) either before or after onset of i.v. iron therapy. None of the patients reported side effects during the study period. Also, no correlation was found between Hb/Hct and any other of the study parameters in the responders and non-responders[289]. (Level 3)

In a study of pre-dialysed chronic renal failure patients with haemoglobin levels less than 11g/dl who were not receiving erythropoietin (n=60)[203], monthly intravenous administration of 200mg of iron sucrose for a period of 12 months was associated with a significant increase in haemoglobin from 9.7 ± 1.1 at baseline to 11.3 ± 2.5g/dl after 12 months ($p<0.05$): a mean increase of 1.6g/dl. No worsening of renal function, no increase in blood pressure and no other side effects were noted. (Level 3)

Oral vs i.v. iron sucrose: predialysis patients

In a RCT[327] investigating i.v. iron sucrose 1,000mg in divided doses over 14 days administered either as an injection or infusion vs oral ferrous sulphate 325 mg three times daily (≡195 mg ferrous iron per day) for 56 days, in patients with and without ESA use, mean adherence of 97.3 (95% CI 94.3–100.0) in the i.v. treatment group was greater than in the oral treatment group mean 88.5 (95% CI 84.8–92.3). In addition, both the proportion of patients who achieved the primary end point (ie rise

in Hb ≥1.0 g/dl) (p=0.0344) and the mean increase in Hb were higher in the i.v. group by day 42 (p=0.0298). Notably, the difference in ESA use in achieving primary end point in the i.v. and oral group was not found to be significant. Three patients in the i.v. group discontinued treatment due to adverse events attributed to the study drug (hypotension, n=2 and nausea, n=1). Transient taste disturbance (dysgeusia) was the most prominent GI complaint associated with i.v. iron administration. Constipation, diarrhoea, nausea, vomiting and dyspepsia were associated prominently with oral iron therapy, while headache, myalgia and hypotension were exclusively associated with i.v. iron administration. (Level 1++)

6.12.4 Health economics methodological introduction

One study was found but did not meet quality criteria[69]. The patient population contained three patients receiving epoetin, methodology of analysis was not stated, cost analysis was insufficiently reported and there was no estimation of uncertainty.

6.12.5 From evidence to recommendations

The available published evidence does not suggest the most effective and safest dose, frequency, preparation or route of administration of iron in ACKD patients with functional iron deficiency prior to ESA therapy. GDG consensus was that patients with anaemia associated with CKD and functional iron deficiency will require intravenous iron treatment. The published evidence did not allow the GDG to recommend a preparation. Two preparations are available in the UK and the dose and frequency will be dictated by the preparation used and by measurement and monitoring of iron indices (serum ferritin and %HRC or %TSAT).

6.12.6 Recommendations

41. People with anaemia of CKD who are receiving ESAs should be given iron therapy to maintain: [D(GPP)]

- **serum ferritin >200 µg/l**
- **transferrin saturation >20% (unless ferritin >800 µg/l)**
- **hypochromic red blood cells <6% (unless ferritin >800 µg/l)**

Most patients will require 600–1,000 mg of iron for adults or equivalent doses for children, in a single or divided dose depending on the preparation. Patients with functional iron deficiency should be treated with intravenous iron. Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron. In appropriate circumstances, iron treatment can also be administered in the community.

42. In non-dialysis patients with anaemia of CKD in whom there is evidence of absolute or functional iron deficiency, this should be corrected before deciding whether ESA therapy is necessary. [D(GPP)]

6.13 Treating iron deficiency: maintenance

6.13.1 Clinical introduction

See 6.12.1.

6.13.2 Methodological introduction

Because of the high number of retrieved studies in the literature search, these were grouped into:

- induction iron therapy for iron deficiency (both absolute and functional iron deficiency) and
- maintenance iron therapy for iron replete patients on epoetin

and thereafter further subgrouped into the various iron routes and frequencies of administration investigated. The seventeen studies included in the evidence statements were selected on the basis of evidence level hierarchy.

Two studies[8,140] did not meet quality criteria and were therefore excluded from the evidence statements.

Notable aspects of the evidence base were:

- Three studies were conducted in children[278,332,333].
- Study durations ranged from 12 weeks to 18 months, which has implications on the time required to measure stability of treatment outcomes.

The GDG agreed that the following outcomes were priorities:

- epoetin dose
- efficacy/Hb response
- compliance
- patient preference
- side effects
- safety.

Following the first consultation on the guideline drafts, the GDG also considered additional retrospective studies[24,54,55,98,100,331] on the incidence of adverse events with intravenous iron. These papers did not report whether patients had previously had ESA therapy or not and because of potential confounding were not added as evidence statements but are discussed below under 'from evidence to recommendations' (see section 6.13.6).

6.13.3 Evidence statements

Oral iron vs intravenous iron

Two RCTs[95,187] in adult dialysis patients with serum ferritin levels >100 µg/l compared i.v. and oral iron. One study[95] (n=52, all haemodialysis) administered 100 mg i.v. iron dextran twice a week and the other[187] (n=37, 15 haemodialysis and 19 peritoneal dialysis) administered 250 mg iron dextran fortnightly. Oral comparators were ferrous sulphate (200–325 mg tds) and iron polysaccharide (150 mg bd). Both studies found i.v. iron to be superior. In one study[95] haematocrit increased ($p<0.05$) and ESA dose fell ($p<0.05$); in the second study[187] haemoglobin increased ($p<0.05$) compared with those treated with oral iron. (Level 1+)

A study in predialysis patients[302] randomised patients with baseline ferritin levels of 47–155 µg/l to either oral ferrous sulphate 200 mg tds (n=23) or 300 mg intravenous iron sucrose. Over a follow-up period of 5.2 months, no significant difference in haemoglobin level or ESA requirement was observed. (Level 1++)

In a 29-day study with follow-up after 14 days[52] patients were randomised to epoetin and intermittent i.v. iron sucrose 200 mg bolus weekly (n=48) vs epoetin and ferrous sulphate (65 mg elemental iron) orally 3 times daily (n=48). Although the i.v. iron group had a greater increase in serum ferritin levels ($p<0.0001$), the rise in Hb from baseline was not statistically different between

the two treatment groups. However, when patients were stratified by a baseline serum ferritin < or ≥100 µg/l, the i.v. iron group had a greater increase in Hb at follow-up compared with oral iron patients ($p<0.05$). Also, more patients in the i.v. iron group attained Hb >11.0 g/dl compared with the oral iron group ($p=0.028$) and the percentage change from baseline to follow-up for both Hb and ferritin was significantly greater for the i.v. iron group ($p<0.0001$). Mean treatment concordance assessed by tablet counts was lower in the oral iron group (85.5%) compared with the i.v. iron group (95.0%); no p-value was reported. GI side effects were more common in the oral iron group and taste disturbances in the i.v. iron group. No patient required discontinuation of iron treatment in either group. (Level 1+)

In a study conducted in peritoneal dialysis patients[9] comparing oral and intravenous iron using a crossover design, higher haematocrit levels ($p=0.02$) and lower ESA doses ($p=0.008$) were found with intravenous iron. Nine patients received oral ferrous sulphate 325 mg tds for 4 months followed by a single bolus infusion of 1 g iron dextran after a washout period of 1 month. (Level 2+)

One study conducted in children with TSAT>20%[332] randomised them to intravenous iron dextran or oral ferrous fumarate (n=35, all haemodialysis). Doses were based on weight; ferrous fumarate varied between 4 and 6 mg/kg/day, children <20 kg received 25 mg/week iron dextran, those weighing 20–40 kg received 50 mg/week and those >40 kg received 100 mg/week. After 16 weeks, no differences in ESA requirements or haemoglobin levels were found. (Level 1+)

Intravenous iron studies in adults

Three observational studies in haemodialysis patients noted a reduction in ESA requirements with regular maintenance intravenous iron: $p<0.0005$[188], $p<0.05$[36], $p<0.001$[269]. One study[188] (n=116) used iron sucrose 100 mg post-haemodialysis. Another study[36] (n=24) used either a loading dose of 1g iron dextran given in divided doses over 10 consecutive dialyses followed by further boluses when TSAT fell below 20% or serum ferritin fell below 200 µg/l, or an initial pulse of iron dextran 300–500 mg followed by 25–100 mg every 1–2 weeks to maintain TSAT 30–50%. The third study[269] (n=396) maintained haemoglobin at a median level of 11.3 to 11.8 g/dl over a 24-month period. Patients with serum ferritin <500 µg/l were treated with concomitant i.v. iron sucrose regimen as follows: months 1–3, for ferritin <100 µg/l, 50 mg iron sucrose twice weekly, for ferritin 100–500 µg/l, 50 mg iron sucrose once weekly, months 4–9, for ferritin <100 µg/l, 50 mg iron sucrose twice weekly, for ferritin 100–500 ng/ml, iron sucrose dose depended on functional iron deficiency. Those with %HRC <5% were given 50 mg iron sucrose once weekly and those with %HRC >5%, 50 mg iron sucrose twice weekly. During months 10–24 those with ferritin <100 µg/l received 50 mg iron sucrose thrice weekly. Those with ferritin 100–500 µg/l received 50 mg iron sucrose once weekly if %HRC <2% (iron replete), or 50 mg iron sucrose twice weekly if %HRC 2–5%, or 50 mg iron sucrose thrice weekly if %HRC >5%. (Level 2+ and Level 3)

Another observational study in haemodialysis patients[286] stratified patients' responses to 20 mg intravenous iron saccharate given 3 times a week over a 6-month period by ferritin <100 µg/l (n=17) vs ≥100 <400 µg/l (n=16). Haemoglobin levels ($p<0.0001$) increased and ESA levels decreased ($p<0.003$) in all patients compared with baseline but there was no difference between groups. Four patients reported a metallic taste in association with iron but no other adverse events were reported. (Level 2+)

A further observational study[288] administered 100 mg intravenous ferric saccharate twice a month to 41 haemodialysis patients and 4 peritoneal dialysis patients who had been receiving ESAs for at least 6 months, and 11 haemodialysis patients who started ESA and intravenous iron simultaneously. In those previously on ESA, haematocrit levels were higher ($p<0.05$) and ESA doses lower ($p<0.05$) after 12 months. Those who started ESA and intravenous iron simultaneously had higher haematocrit levels ($p<0.05$) after 6 months of treatment. (Level 2+)

Four studies compared different intravenous iron dosing regimens[11,21,151,279]. In three studies conducted in haemodialysis patients the same total dose of iron was administered. One study[151] gave 400 mg saccharated ferric oxide in 10 divided doses either following 10 consecutive dialysis sessions (n=12) or weekly for 10 weeks (n=12). This study also included 11 subjects to whom iron was not administered. These patients had lower haemoglobin levels and greater ESA requirements compared with the iron–treated groups. The only difference in the iron treated groups was a lower ESA requirement compared with baseline ($p<0.01$) in those given sequential treatment after each dialysis. One study[279] gave a total of 600 mg iron dextran (n=43). Patients received either a single bolus dose, six divided doses of 100 mg following consecutive dialyses, or 100 mg/week for 6 weeks. No difference was observed in haemoglobin or ESA requirements with the different dosing regimens. (Level 1+ and Level 2+)

A further study in haemodialysis patients aiming for a target haemoglobin level of 11.8 g/dl compared three different iron dextran regimens[21]. A total dose infusion of 550–2000 mg was used in 14 patients, 12 patients received 500 mg/week as a bolus dose to a total of 400–1500 mg and 17 patients were given 100 mg/dialysis session to a total dose of 500–2100 mg. No differences in peak haematocrit or time to peak haematocrit were observed between groups. (Level 1+)

In peritoneal dialysis patients, one study[11] gave a total dose of intravenous ferric saccharate of 600 mg in divided doses with two different regimens using a crossover design (n=17). There was a greater increase in haematocrit levels in patients given 50 mg twice a week ($p<0.05$) compared with those given 100 mg/week. (Level 1+)

Intravenous iron studies in children

In a 6-month study[278] (n=40) children below 16 years of age received epoetin to target Hct ≥30% and i.v. iron dextran administered as a maintenance dose of 1 mg/kg/week following a weight-based loading dose. This was compared with an as required intermittent weight-based course of 10 doses of iron dextran if Hct was <33%, ferritin <100 µg/l and/or TSAT <20%. Despite the higher cumulative dose in the intermittent group ($p<0.001$) the average epoetin dose was similar in both groups and Hb increased to 10 g/dl, with no difference between the 2 treatment groups. (Level 1+)

A double-blind RCT in children <16 years old receiving epoetin[333] randomised patients to concomitant treatment with eight consecutive intravenous infusions of either 1.5 mg/kg (n=24) or 3.0 mg/kg (n=32) of sodium ferric gluconate complex. Mean cumulative dose in the 1.5 mg/kg group was 431 ± 168 mg and 725 ± 202 mg in the 3.0 mg/kg group ($p<0.0001$). Although increases from baseline were found in both groups at 2- and 4-week evaluation time points after the last iron dose, no difference was found in Hb levels between the two groups. Responders were defined by Hb increase ≥1.0 g/dl. No difference was found between numbers of responders in either group. Epoetin dose remained unchanged in both treatment groups. (Level 1+)

Intravenous iron safety studies

In a safety study, n=657 patients received 200 mg bolus injections of iron sucrose[189]. A total of 2,297 injections were administered, with some patients receiving multiple injections with a minimum of 1 week between injections. Mild and transient metallic taste was found for 412 injections and other adverse events for 57 injections. These were anaphylactoid reactions in seven patients, pain during injection in 31 patients, pain after injection in nine patients, with/without bruising, nausea/GI symptoms in three patients, lethargy in four patients, and light-headedness in three patients. (Level 3)

A cohort study[92] (n=32,566) sought to investigate if an apparent relationship between iron dosing and mortality was confounded by incomplete representation of iron dosing and morbidity over time. The study found doses of iron >1,000 mg over 6 months to be associated with increased risk of mortality compared with subjects not receiving iron using an adjusted proportional hazards analysis relating baseline iron dose to survival with a hazard ratio (HR) of 1.09 (95% CI 1.01–1.17). Those receiving >1800 mg of iron had HR 1.18 (95% CI 1.09–1.27). However, the association disappeared when the adjusted probability of dying in a particular month as a function of cumulative iron dose received during the previous 0 to 6 months, 6 to 12 months and 12 to 18 months was estimated. No significant association was found between mortality and any level of iron dosing >0 to >1,800 mg over 6 months. (Level 2+)

Oral iron studies

One study[192] randomised iron replete patients to polysaccharide-iron complex 150 mg elemental iron twice daily (n=12) vs placebo (n=13) over 3 months with 2 months follow-up. No difference was found in Hct levels between the two groups. The same study also randomised iron deficient patients to either polysaccharide-iron complex 150 mg elemental iron twice daily (n=14) or placebo (n=10) over 3 months and 2 months follow-up. Those receiving iron had an increase in Hct levels ($p<0.01$) (Level 1+)

Another study[338] randomised patients to a number of different oral iron preparations containing a daily dose of 200 mg elemental iron, ferrous fumarate (Chromagen, n=12 and Tabron, n=11), ferrous sulphate (n=11) and iron-polysaccharide complex (n=12). Patients were also given various doses of daily ascorbic acid (750, 1,000, 0, 100 mg respectively) over 6 months. Hct levels increased with all preparations (Chromagen and ferrous sulphate, $p<0.01$; Tabron $p<0.05$), except for the iron-polysaccharide complex. In addition, Hct/epoetin ratio decreased ($p<0.05$) in the Tabron (ferrous fumarate) treatment group only. No differences were noted in compliance. (Level 1+)

6.13.4 Health economics methodological introduction

Six studies were appraised[39,82,207,247,281,297] and one study met quality criteria[82]. Three of the studies did not report unit costs, total costs or doses adequately[39,207,281] One study was excluded because of potential bias by physician adjustment of the epoetin dose in a before and after design[247]. One study[297] was excluded as cost-savings were not based on evidence.

6.13.5 Health economics evidence statements

One study found iron dextran did not reduce the average dose of ESA in 33 patients but improved the number of patients with 'successful treatment' (10 vs 27). Successful treatment was defined as Hct 33–36%, TSAT >20%, ferritin concentration of >100ng/ml and no blood administered except for acute blood loss. The study estimated the incremental cost effectiveness of iron dextran to be $41.61 (US$, 1998) per successful treatment[82]. No sensitivity analysis was performed.

6.13.6 From evidence to recommendations

The published evidence was very limited in peritoneal dialysis and predialysis patients. It did not provide data to allow the GDG to specify a test dose of iron in the recommendations, nor a route or frequency of administration.

Caution is required because of the potential side-effect profile (particularly anaphylaxis) when administering both test and maintenance doses of iron. The GDG considered additional retrospective studies of adverse events in patients receiving intravenous iron to inform the recommendations:

- Baillie et al[24] investigated tens of millions of 100mg dose equivalents (the exact sample size is not given in the paper) from the American Food and Drug Administration (FDA) 'freedom of information surveillance database'. They considered all adverse events between January 1997 and September 2002 and found rates per million 100mg dose equivalents of 29.2 for iron dextran, 10.5 for sodium ferric gluconate and 4.2 for iron sucrose (which had the lowest rates for all clinical categories of adverse event).
- Chertow et al[54,55] investigated 30,063,800 doses in FDA data from 2001 to 2003 and found significantly lower rates among people who received sodium ferric gluconate or iron sucrose, compared with those who received higher molecular weight iron dextran. Rates of 'life-threatening' events per million doses were 11.3 for higher molecular weight iron dextran, 3.3 for lower molecular weight iron dextran, 0.9 for sodium ferric gluconate, and 0.6 for iron sucrose.
- Fishbane et al[98] investigated all patients (n=573) receiving intravenous iron dextran at any of four USA haemodialysis centres between July 1993 and June 1995 and found 27 patients (4.7%) had related adverse events. History of drug allergy (OR 2.4, p=0.03) and multiple drug allergy (OR 5.5, p<0.001) were found to be significant risk factors for adverse events.
- Fletes et al[100] investigated the Fresenius Medical Care North America (FMCNA) clinical variance reports from October 1998 to March 1999 for iron dextran only and found an adverse event rate of 196.1 per million doses. The study reported higher rates in patients receiving higher molecular weight iron dextran, but this was not statistically significant.
- Walters and van Wyck[331] investigated 1,066,099 doses of intravenous iron dextran from the Gambro Healthcare US database between January 1999 and April 2000. They found a rate of 316.1 adverse events per million doses for all severities, and reported in detail on seven patients who had adverse events requiring resuscitation, all of whom were receiving test doses or first therapeutic doses. Significance testing to compare molecular weights of iron dextran was only reported for these seven patients.

Adverse event rates for intravenous iron are very low for both preparations in use in the UK (circa 3.3 events per million doses for low molecular weight iron dextran, and 0.6 per million doses for iron sucrose), and the GDG therefore did not distinguish between them in the recommendation.

The GDG acknowledged the cost-effectiveness evidence of predialysis anaemia treatments is limited as there is little data to make comparisons to alternative treatments and insufficient effectiveness data of patient benefit such as quality of life. The GDG noted that collecting quality of life data that could be converted into utility scores and resource data in all future randomised controlled trials would be useful, especially in predialysis patients.

6.13.7 Recommendation

43. Once ferritin levels are greater than 200 µg/l and HRC is less than 6% or TSAT is greater than 20%, people with anaemia of CKD who are receiving ESAs should be given maintenance iron. The dosing regimen will depend on modality, for example haemodialysis patients will require the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children of 1 mg/kg/week). Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron. [D(GPP)]

6.14 ESAs: monitoring iron status during treatment

6.14.1 Clinical introduction

Measurement of ferritin together with %HRC or %TSAT provides an indication of iron stores and availability of iron for erythropoiesis. We know that in patients with anaemia associated with CKD

who are under treatment with ESAs, an adequate supply of iron is essential for effective erythropoiesis and cost-efficient use of ESAs. We also know that too much iron may expose patients to risk of infectious complications and may also increase cardiovascular risk through oxidative stress. What then are the most desirable levels of these parameters of iron status to be maintained during treatment with ESAs?

6.14.2 Clinical methodological introduction

A literature search identified four studies consisting of a RCT[34], a cohort study[143], a prospective longitudinal study[269] and a prospective longitudinal study in children[311].

One study[145] did not meet quality criteria and was therefore excluded from the evidence statements.

Notable aspects of the evidence base were:

- In the study comparing TSAT 20–30% and 30–50%[34], achieved TSAT levels were 27.6% and 32.6% in the respective groups at the end of the 6-month study period.

6.14.3 Clinical evidence statements

Serum ferritin

Haemodialysis patients

Intravenous iron supplementation which led to an increase in mean ferritin to 395 ± 206 mg/100 ml (p-value not given) in children aged 10–17 years (n=8) lead to an increase in the Hb (p=0.0117) and Hct (p=0.0024), despite a fall in epoetin dose from 6,500 U to 6,150 U with no side effects noted, particularly hypertension[311]. (Level 3)

In a 24-month study (n=396)[269] Hb was maintained at a median level of 11.3 to 11.8 g/dl and median epoetin dose decreased to 72 (inter-quartile range 33–134) (p<0.001) when compared with baseline, when patients with serum ferritin <500 ng/ml were treated with concomitant i.v. iron sucrose regimen. (Level 3+)

Transferrin saturation (TSAT)

Haemodialysis patients

In a study comparing the effects of TSAT 20–30% vs 30–50% on epoetin dose required to maintain Hb 9.5–12.0 g/dl, epoetin dose progressively decreased in the TSAT 30–50% group, with ~40% dose reduction in months 4, 5 and 6 when compared with the 20–30% group (p=0.0038). This change in epoetin dose was independent of baseline dose in both the TSAT 30–50% group and TSAT 20–30% group[34]. (Level 1+)

Percentage of hypochromic red cells (%HRC)

Haemodialysis patients

In an 8-week study whereby patients stratified by baseline %HRC 0–3%, 4–9% and ≥10% received a fixed epoetin dose and i.v. iron saccharate 200 mg once weekly up to serum ferritin 250 µg/l, although mean Hb and ferritin levels significantly increased in all 3 groups (P≤0.001 for all), mean Hb increase was greater with increasing %HRC at baseline (p=0.02). In addition the proportion of patients with >1 g/dl increase in Hb was greater as %HRC at baseline increased (p=0.02)[143]. (Level 2+)

6.14.4 Health economic methodological introduction

Three studies were appraised[34,132,281] and two met quality criteria[34,132]. The study that did not meet quality criteria estimated cost-savings based on average reduced EPO dosages[281]. However, with no inclusion of the prices used, the costing was not sufficiently transparent to warrant inclusion.

An American study estimated the cost-savings per patient per year over a 6-month period while maintaining TSAT between 30 and 50% vs 20 to 30% using maintenance intravenous iron dextran[34].

One American study was a cost analysis of ESAs using percent reduction of urea (PRU) as an index of dialysis adequacy and transferrin saturation as a measure of iron stores. The study investigated two comparisons: the total dose of ESA received during the 4-week study by the 20 participants with the highest transferrin saturation to the 20 participants with the lowest transferrin saturation, and the total dose of ESA administered during the 4-week study to the 20 patients with the highest PRU to the 20 participants with the lowest PRU[132].

6.14.5 Health economic evidence statements

The study estimated intravenous iron dextran saves approximately $109 per month or $1,308 per year per patient when maintaining the TSAT between 30 and 50% (n=23) (vs 20 to 30% in control group; n=19)[34]. Cost difference between the intervention and control group was statistically significant by the third month of study and remained significant until the end of the study at 6 months ($p<0.02$)[34].

At $10 per 1,000 units of ESA, it costs $45 (10.2%) more per month per patient in the 20 patients with the lowest transferrin saturation compared with the 20 patients with the highest transferrin saturation[132].

6.14.6 From evidence to recommendations

The GDG agreed that there was very little long-term effectiveness data to determine the most appropriate maintenance levels. The GDG based their recommendation on the European Best Practice Guidelines[3].

6.14.7 Recommendations

44. People receiving ESA maintenance therapy should be given iron supplements to keep their:

- **serum ferritin between 200 and 500 µg/l in both haemodialysis patients and non-haemodialysis patients, and either [D]**
  - **the transferrin saturation level above 20% (unless ferritin > 800 µg/l) or [B]**
  - **percentage hypochromic red cells (%HRC) less than 6% (unless ferritin > 800 µg/l). [D(GPP)]**

In practice it is likely this will require intravenous iron.

7 Monitoring treatment of anaemia of CKD

7.1 Monitoring iron status

7.1.1 Clinical introduction

Monitoring of iron status should be aimed at ensuring that patients undergoing treatment with ESAs maintain levels of iron that ensure maximally effective erythropoiesis. The frequency of monitoring must take account of the stage of anaemia treatment, ie initial correction of anaemia or maintenance of target range of haemoglobin, the frequency and mode of iron supplementation, CKD status (haemodialysis patients have an unavoidable loss of iron through the dialysis process), clinical situations likely to result in depletion of iron stores such as bleeding and surgery, clinical situations likely to result in misinterpretation of iron parameters (for example, co-existent infection leads to falsely elevated ferritin levels and depressed %TSAT), and pre-existing iron-overload states. The frequency of monitoring may also be dictated by the availability of the patient and by trend analysis of changes in iron status over time.

7.1.2 Methodological introduction

A comprehensive literature search identified a cohort study[36].

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.

7.1.3 Evidence statements

Monitoring after intermittent iron dosing

Haemodialysis patients

Table 7.1: Time profile of intermittent i.v. iron dextran dosing regimen (n=14) (Level 2)

Treatment with 1,000 mg iron dextran over 10 doses	T=0	T=3 days	Time averaged value over 4 months after completion (trapezoid method)
TSAT (%)	20.6 ± 2.0 (range 15–37)	93 ± 6 (range 63–134)	30.1
	T=0	T=2 months (peak value)	
Ferritin (ng/ml)	197 ± 31 (range 27–424)	351	
	T=0	T=3 months	T=4 months
TIBC (µg/ml)	210 ± 7 (166–246)	180 ± 7	192 ± 11

Monitoring after single iron dose

Haemodialysis patients

Table 7.2: Time profile of single dose i.v. iron dextran 50 mg or 100 mg (n=16) (Level 2+)

	T=0	Time averaged over 2 weeks
TSAT (%)	Mean 34.6 ± 3.1 (n=16)	35.5 for 50 mg group (n=8) 36.7 for 100 mg group (n=8)
	T=0	
Ferritin (ng/ml)	231 ± 29 (n=16)	T=1 week, 297 ± 44 (n=16)
		T=2 weeks, 276 ± 35 (n=16)
	T=0	**Time averaged over 2 weeks**
TIBC (µg/ml)	Not reported	No change (data not reported)

7.1.4 From evidence to recommendations

The GDG agreed on a range of possible intervals for iron stores monitoring, which will allow practice to be tailored to the individual patient and to local systems. It is clear from the evidence that monitoring soon after intravenous iron is not helpful, and the GDG felt that a minimum time elapsed of 1 week would be appropriate.

7.1.5 Recommendations

45. People with anaemia of CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. The length of time to monitoring of iron status is dependant on the product used and the amount of iron given. [C]

46. Routine monitoring of iron stores should be at intervals of 4 weeks to 3 months. [D(GPP)]

7.2 Monitoring haemoglobin levels

7.2.1 Clinical introduction

The initial step in clinical management of the CKD patient maintained in an anaemia programme must be the acquisition of laboratory and treatment data at specified intervals. The frequency of acquisition of data has been driven by anaemia treatment algorithms and decision matrices designed to achieve the required rate of rise of haemoglobin during the correction phase, and the desired haemoglobin level during the maintenance phase. However, the effectiveness of such algorithms and decision matrices is difficult to evaluate because there is a lack of published clinical outcomes related to their use. Furthermore, there is inherent variability in haemoglobin levels within a given population, and there are several components of this variability. One component is population or interpatient variability. Biological variability is found with nearly all laboratory measurements and in the case of haemoglobin levels in patients with CKD multiple factors contribute including gender and race, environmental factors, assay or sampling differences, the patient's state of hydration and other related physiological determinants. Another component of haemoglobin level variability is individual or intraindividual variability. Here there is variation with repeated measurements over time in the same individual. Again there are multiple factors contributing to this variability including seasonal variations, sampling methods, comorbid conditions such as nutritional status, inflammation,

gastrointestinal bleeding, and bone marrow fibrosis. Two major factors are under control of the anaemia management team: ESA and iron therapy, and these are also determinants of haemoglobin level and factors in population variability. The physiological characteristics of erythropoiesis are such that there is a time required for the bone marrow to react to changing ESA stimulus and that reaction time varies widely among patients with CKD, ranging from a few weeks to a few months. It requires 1 to 2 months to induce red blood cell production and 1 to 3 months after removal of ESA stimulus for patients to experience turnover of red blood cells to cease production. Data from a 1-year study demonstrates that haemoglobin levels may change from less than 11 g/dl to greater than 12 g/dl (or vice versa) in more than 28% of patients[165]. Haemoglobin synthesis, red blood cell production and destruction are not processes that can be controlled instantaneously and haemoglobin level undershooting or overshooting should be expected when health professionals react to single haemoglobin values. We should therefore react to trends in haemoglobin levels but how frequently should the haemoglobin level be monitored to determine the trend?

7.2.2 Methodological introduction

A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.

7.2.3 From evidence to recommendations

Monitoring is part of care in ESA induction and maintenance, including consideration of the rate of haemoglobin change. The GDG felt that a range of intervals would allow monitoring to be tailored to the patient and the local systems, and agreed on 2–4 weeks in induction and 1–3 months in maintenance.

7.2.4 Recommendation

47. In people with anaemia of CKD, haemoglobin should be monitored:

- **every 2–4 weeks in the induction phase of ESA therapy**
- **every 1–3 months in the maintenance phase of ESA therapy**
- **more actively after an ESA dose adjustment**
- **in a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local healthcare systems. [D(GPP)]**

7.3 Detecting ESA resistance

7.3.1 Clinical introduction

The physiological characteristics of erythropoiesis are such that there is a time required for the bone marrow to react to ESA stimulus and that reaction time varies widely among patients with CKD, ranging from a few weeks to a few months. The magnitude of reaction to ESA stimulus is also variable. In determining resistance to ESA therapy it is important to distinguish between true resistance, a lack of bone marrow response to ESA therapy, and apparent resistance where increased red cell destruction or red cell loss offsets ESA stimulated red cell production. It is also important to determine a dose threshold of ESA above which resistance to therapy is defined and a duration of therapy beyond which resistance to therapy should be suspected.

7.3.2 Methodological introduction

A literature search identified a case series[48] and a cohort study[309].

Five studies[28,120,152,283,292] did not meet quality criteria and were therefore excluded from the evidence statements.

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no evidence statements are given.

7.3.3 Evidence statements

Pure red cell aplasia (PRCA)

Haemodialysis patients

In a study of patients predominantly receiving subcutaneous epoetin alfa, serum from all epoetin-treated patients (n=13) inhibited growth of erythroid cells and addition of epoetin to their serum samples reversed inhibitory effects. Also serum from all patients was shown to bind to epoetin and Scatchard analysis suggested presence of homogeneous binding sites[48]. (Level 3)

Aluminium toxicity

Haemodialysis patients

In a study conducted to maintain Hct 30% (Hb ~10 g/dl), where patients were divided into 2 groups on the basis of response to epoetin treatment, the poor responders received a higher epoetin dose ($p<0.05$), yet had lower Hb and Hct levels (both $p<0.001$). Of the haematological parameters investigated, basal aluminium and aluminium levels following challenge with desferrioxamine were higher in the poor responders (both $p<0.01$). In addition, mean corpuscular volume showed inverse correlation with basal aluminium (data not provided), post-desferrioxamine aluminium ($r=-0.617$, $p=0.005$) and change in aluminium levels ($r=-0.711$, $p<0.001$) in the poor responders. In the good responders, mean corpuscular volume only showed correlation with change in aluminium levels ($r=-0.476$, $p=0.03$)[309]. (Level 2+)

7.3.4 From evidence to recommendations

In considering when resistance to ESAs should be suspected and what conditions lead to ESA resistance, the GDG reviewed evidence on two outcomes, PRCA and aluminium toxicity.

The GDG considered the definition of resistance and agreed on the definition suggested by the Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure[5]. It was agreed to suspect resistance when a patient does not achieve the target Hb level after receiving an epoetin dose more than 300 U/kg/week s.c. (approximately 20,000 units/week) or equivalent or 1.5 mg/kg darbepoetin alfa s.c. or i.v. (approximately 100 mg/week) or has a continued need for the administration of high doses of ESAs to maintain the target Hb level.[5] It was noted that 300 U/kg/week is used as this value is two standard deviations above the mean value used. The GDG considered that resistance should be suspected after 3 months of failure to respond to ESAs, after exclusion of other causes of a temporary lack of response (eg intercurrent illness or other causes of chronic bleeding).

With regards to conditions that lead to ESA resistance the GDG reviewed evidence on PRCA. The GDG agreed their working definition of PRCA to be the presence of a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. The GDG considered PRCA to be confirmed where anti-erythropoietin antibodies are present (as shown by an appropriate laboratory assay) and there was a lack of pro-erythroid progenitor cells in the bone marrow. The GDG noted that PRCA can be induced by other causes aside from sensitisation to erythropoietin. This has since been addressed by using a fluoro-resin coating, which forms a barrier between the rubber stopper and erythropoietin

in some pre-filled syringes. The evidence presented specifically addressed PRCA induced by sensitisation to erythropoietin and demonstrated that the inhibition of the erythroid cells was correlated with the presence of anti-erythropoietin antibodies[48].

The GDG noted that the issue of aluminium toxicity was of clinical importance but the incidence is now very rare. The GDG noted that there was a current source of aluminium from the responsible use of aluminium hydroxide capsules (Alu-caps, used as phosphate binders to reduce the absorption of dietary phosphate). However, it was considered unlikely that the use of Alu-caps would lead to aluminium toxicity. The issue of toxicity originally stemmed from a lack of water purity which has improved. It was noted that the trial[309] did not report either the use of aluminium-based phosphate binders or whether any water purification system was being used. The GDG noted that aluminium levels are routinely measured in their haemodialysis patients but that the need to continue doing so was under question.

7.3.5 Recommendations

48. After other causes of anaemia, such as intercurrent illness or chronic blood loss have been excluded, people with anaemia of CKD should be considered resistant to ESAs when:

- **an aspirational Hb range is not achieved despite treatment with ≥300 IU/kg/week of subcutaneous epoetin or ≥450 IU/kg/week of intravenous epoetin or 1.5 µg/kg/week of darbepoetin, or**
- **there is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range [D(GPP)]**

49. In people with CKD, pure red cell aplasia (PRCA) is indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. The GDG considered that PRCA should be confirmed when anti-erythropoietin antibodies are present and there is a lack of pro-erythroid progenitor cells in the bone marrow. [D]

50. In people with anaemia of CKD, aluminium toxicity should be considered as a potential cause of a reduced response to ESAs after other causes such as intercurrent illness and chronic blood loss have been excluded. [C]

7.4 Managing ESA resistance

7.4.1 Clinical introduction

Management of ESA resistance will clearly depend on the underlying cause. The Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD-2) identified an incidence of inadequate ESA response of 16.7 per 1,000 patients years on ESA while on dialysis.[157] Fifty-seven of 1,677 patients with incident end stage renal disease in the NECOSAD-2 study had an inadequate ESA response. Table 7.3 shows the various causes identified.

Table 7.3: Possible causes for ESA resistance from the NECOSAD-2 study (n=57)

Causes for inadequate ESA response	Number*	Causes for inadequate ESA response	Number*
Infection/inflammation	41	Haemolysis	0
Blood loss	16	Pure red cell aplasia	1
Hyperparathyroidism/aluminium toxicity	10	Malignancy	7
Haemoglobinopathy	2	Graft/shunt problems	14
Folate/vitamin B12 deficiency	1	Operation	8

Causes for inadequate ESA response	Number*	Causes for inadequate ESA response	Number*
Multiple myeloma/myelofibrosis/myelodysplastic syndrome	6	Suspected noncompliance	9
Malnutrition	5	Medication (≥bone marrow suppress)	4
Inadequate dialysis	2	Unknown	2
* Some patients fell into more than one category (ie there was more than one possible cause for their inadequate ESA response).			

7.4.2 Methodological introduction

The literature search identified three studies: a 2-part study with a prospective cohort group and a subsequent before and after study in a subgroup[342], a retrospective case series[328] and a before and after study[62].

A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no evidence statements are given.

7.4.3 Evidence statements

Treatment of aluminium toxicity with desferrioxamine

Dialysis patients

Patients receiving epoetin with no concurrent or prior treatment for aluminium toxicity (n=5) had a low mean rise of Hb above baseline and did not achieve target Hb 9 g/dl over 20 weeks, unlike the control groups with treatment prior to the study (n=4) ($p<0.05$) and no aluminium toxicity (n=8) ($p<0.05$), which reached target Hb within 12 weeks of the study[342]. This was supported by the correlation between baseline serum aluminium levels and the mean rise of Hb ($r=-0.51$, $p=0.03$) and between Hb rise during epoetin therapy and aluminium increment following challenge with desferrioxamine. (Level 2+)

In addition, concurrent treatment with desferrioxamine in this group led to a mean Hb rise when compared with previous treatment with epoetin only ($p<0.01$)[342]. (Level 3)

Reduced T-cell production of inflammatory markers TNF-α and IFN-γ with low dose pentoxifylline

Patient population not specified

Hb levels in poor responders to epoetin (n=12) significantly improved after 4 months treatment with low dose pentoxifylline ($p=0.0001$). This was associated with a decrease in TNF-α ($p=0.0007$) and IFN-γ ($p=0.0002$) production 6–8 weeks following pentoxifylline therapy, and no change in white blood cell production after 4 months. This suggestive evidence was supported by a correlation between change in Hb and TNF-α production ($rs=0.7145$, $p=0.0118$), however, no correlation was found between change in Hb and IFN-γ ($rs=0.4406$, $p=0.1542$)[62]. (Level 3)

Treatment of ESA-induced pure red cell aplasia (PRCA) with immunosuppressants/immunoglobulins/kidney transplant

Not on dialysis, haemodialysis and peritoneal dialysis patients

In a group of patients with epoetin-induced PRCA (n=43 epoetin alfa ± epoetin beta or darbepoetin and n=4 epoetin beta exclusively), 37 patients received treatment which consisted of one treatment (n=26), two consecutive treatment regimens (n=10) or five different regimens (n=1). Of these, 29 patients recovered (ie reticulocyte counts >20,000/µl and not requiring red cell transfusions), however, no patient was challenged with ESA. As the treatments are not comparable for superiority, the data from the study is presented in the Table 7.4.

Table 7.4: Summary data from Verhelst (2004)290 (Level 3)

PRCA treatment	n	Number of patients who recovered	Time before recovery (months)	Follow-up (months)
Corticosteroids alone (n=14) ± high dose i.v. immunoglobulins	18	10 (56%)	1†, 2†, 2†, 3†, 3†, 3†, 3†, 3†, 6†, 18†	3, 3, 3, 3, 5†, 13†, 20, 30†
High dose i.v. immunoglobulins alone	9	1 (11%)	3†	3, 3, 4, 4, 4, 9, 10†, 19
Corticosteroids + cyclophosphamide	8	7 (87%)	1†, 2, 2, 3†, 4, 5, 7	3
Ciclosporin	6	4 (67%)	1†, 1†, 1†, 1	3, 9†
Kidney transplant*	6	6 (100%)	<1†, <1†, <1†, <1†, <1, <1	–
Antibodies to CD20	2	0	–	3†, 3
Corticosteroids + high dose i.v. immunoglobulins + plasma exchange	1	1 (100%)	3†	–
Mycophenolate motefil	1	0	–	12
Note: for patients who did not recover, follow-up was length of time between start of treatment and last visit or start of new treatment.				
† Received only 1 kind of treatment.				
* Received induction treatment followed by triple immunosuppressive therapy.				

7.4.4 From evidence to recommendations

When considering how ESA resistance should be managed the GDG reviewed evidence on three outcomes, aluminium toxicity, markers of inflammation and the treatment of PRCA.

The GDG noted that with regard to treating aluminium toxicity that desferrioxamine was considered the treatment of choice. If aluminium toxicity was suspected, a patient should be administered a bolus of desferrioxamine and the amount of aluminium flushed into the blood stream determined. Treatment with desferrioxamine should be administered until aluminium toxicity is no longer present. The GDG noted that it was rare to find patients with toxic levels of aluminium and that this should be considered a special circumstance that would be most likely to occur in haemodialysis patients managed by renal physicians.

With regard to inflammatory markers, the GDG reviewed one study that suggested that in poor responders to ESAs, treatment with low-dose pentoxifylline reduced the production of inflammatory markers (TNF-α and IFN-γ) by T-cells[62]. However, the GDG cautioned that this was an academic scientific study that, although interesting, did not reflect current clinical practice and noted that pentoxifylline was not licensed for this use. The GDG felt that clinical trials were needed to support this data.

The GDG reviewed evidence on the treatment of ESA-mediated PRCA. The GDG felt this was a specialised area with few annual cases. Because of this, the GDG acknowledged that the treatment of this condition was not fully established and that the most up-to-date information was available online and was written by the PRCA Global Scientific Advisory Board (GSAB: www.prcaforum.com/treatment.php) [259] and this should be accessed to determine the current best

practice to treat this condition. The GDG noted that immunosuppressive therapies have been shown to reverse antibody-mediated PRCA. However, it was noted that the total number of patients with this condition was so small that they felt unable to recommend this treatment. The GDG noted that the GSAB suggested ciclosporin as the treatment of choice.

7.4.5 Recommendations [2006, Updated 2011]

51. In haemodialysis patients with anaemia of CKD in whom aluminium toxicity is suspected, a desferrioxamine test should be performed and the patient's management reviewed accordingly. [C]

52. Consider specialist referral for ESA-induced PRCA. [2006, amended 2011]

8 Research recommendations

The Guideline Development Group has made the following recommendations for research, on the basis of its review of the evidence. The Group regards these recommendations as the most important research areas to improve NICE guidance and patient care in the future.

Intravenous iron in children

A prospective study of adequate duration of i.v. iron preparations in children with anaemia of CKD, including safety, dosing and efficacy outcomes.

Why this is important

There is very little evidence relating to anaemia of CKD in children. It is known that there is a range of iron levels for adults outside which adverse outcomes become more likely and this helps guide monitoring and treatment adjustment over anaemia correction and maintenance. In children, there is likely to be much greater variation between individuals.

Trials of ESAs in children

Trials of ESAs in children with anaemia of CKD (including darbepoetin, which is currently unlicensed in children younger than 12 years), including safety, dosing and efficacy outcomes.

Why this is important

As above, there is very little evidence relating to anaemia of CKD in children. ESAs are a key therapy and therefore more data are needed in order to define suitable treatment regimens.

Haemoglobin levels in older people

An observational study of Hb levels and adverse outcomes in older people.

Why this is important

Evidence suggests that anaemia due to reduced erythropoiesis occurs even in early stages of CKD. This may be undetected, and is associated with adverse outcomes in older people. A better understanding of the haemoglobin levels associated with adverse outcomes in older people would enable improved detection of anaemia of CKD and reduction of risk.

ESA tolerance test

A trial of an ESA tolerance test including collection of data on ESA regimens and Hb levels achieved.

Why this is important

A better understanding of the practical impact of ESA tolerance testing on treatment and outcomes would clarify whether such tests are useful, particularly in terms of tailoring ESAs and optimal Hb levels for individual patients depending on their response.

Iron levels in predialysis patients

An RCT to assess Hb level as an outcome in predialysis patients treated to serum ferritin levels <200 µg/l vs those treated to 300–500 µg/l.

Why this is important

The ferritin level up to which predialysis patients should be treated to achieve acceptable Hb (and at which ESAs are considered if Hb is still inadequate) is not well addressed in the evidence base.

Implementation of management algorithm

An observational study of patient management in line with the initial management and maintenance algorithms given in this guideline, with the aim of formally piloting and validating them, or providing evidence for amendments when the guideline is updated.

Why this is important

Protocols and prescribing algorithms for ESAs are in use, including computerised decision support systems. Some of these have been piloted and validated, and it is important that the NICE guideline's algorithms match this standard to provide additional support at the broader scale of management strategies.

Other potential research topics

Optimal Hb levels to be achieved with ESAs in children with ACKD.

Are the same levels of serum ferritin, %HRC and %TSAT that define functional iron deficiency in dialysis patients applicable to the predialysis population?

The value of endogenous erythropoietin testing in the diagnosis of anaemia associated with CKD.

Which patients would most benefit from ESA therapy in the wider CKD population?

Does the co-administration of ESAs with physiological doses of androgens reduce the dose of ESA administered?

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Appendices

Appendix A: Evidence-based clinical questions and literature searches

A.1 Evidence-based clinical questions and literature searches [2006]

Question ID	Question wording	Study type filters used	Databases and years
PROG1	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
DIAG1	In patients with chronic kidney disease, what is the association between glomerular filtration rate (GFR) and haemoglobin levels in a) diabetic and b) non-diabetic patients?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
DTEST2	What are the best tests, or combination of tests, to determine iron status in patients with chronic kidney disease?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
DTEST1	What is the role of erythropoietin testing in the assessment of anaemia in patients with chronic kidney disease?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MGTFE1	Up to what levels of serum ferritin, percentage transferrin saturation and percentage hypochromic red cells should patients with ACKD be treated with iron without adverse events?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MGTFE2	In patients with ACKD what, if any, are the serum	Systematic reviews,	Medline

Question ID	Question wording	Study type filters used	Databases and years
	ferritin, transferrin saturation and percentage hypochromic red cells thresholds for commencing treatment with ESAs?	RCTs and comparative studies	1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MGTFE3	In patients with ACKD what, if any, are the optimal serum ferritin, transferrin saturation and percentage hypochromic red cells levels to be maintained during treatment with ESAs?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MGTN1	What is the benefit of vitamin C, vitamin E, folic acid, carnitine or glutathione supplementation in the treatment of anaemia due to chronic kidney disease?	Systematic reviews and RCTs	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MGTN2	What is the benefit of androgens in the treatment of anaemia due to chronic kidney disease?	Systematic reviews and RCTs	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
HYP1	When does treating hyperparathyroidism improve the management of anaemia caused by chronic kidney disease?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
PAT1	What are the patient preferences and experiences when receiving ESAs for the treatment of ACKD?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005 BNI 1985–2005
PAT2	Is the effectiveness of anaemia management of CKD improved by patient education programmes?	All study types	Medline 1966–2005

Question ID	Question wording	Study type filters used	Databases and years
			Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005 BNI 1985–2005 PsycInfo 1806–2005
MGTHB1	What haemoglobin range should be maintained during anaemia treatment in CKD?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MGTHB2	In patients with chronic kidney disease what are the risks and benefits of early vs deferred correction of anaemia?	Systematic reviews and RCTs	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXFE1	What is the most effective and safest dose, frequency, preparation and route of administration of iron in ACKD patients with functional iron deficiency prior to ESA treatment?	Systematic reviews and RCTs	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXFE2	What is the most effective and safest dose, frequency, preparation and route of administration of iron in ACKD patients with functional iron deficiency receiving ESA treatment?	Systematic reviews and RCTs	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXEF1	In patients with ACKD what are the benefits and risks of correcting anaemia with epoetin alfa compared to epoetin beta in reducing morbidity and mortality and improving quality of life?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005

Question ID	Question wording	Study type filters used	Databases and years
TXEF2	In patients with ACKD what are the benefits and risks of correcting anaemia with epoetin alfa compared to darbepoetin in reducing morbidity and mortality and improving quality of life?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXEF3	In patients with ACKD what are the benefits and risks of correcting anaemia with epoetin beta compared to darbepoetin in reducing morbidity and mortality and improving quality of life?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXEF4	In patients with ACKD what are the benefits and risks of correcting anaemia with ESAs compared to placebo or no treatment in reducing morbidity and mortality and improving quality of life?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MGTE1	Which iron replete patients with ACKD should receive ESAs?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXEF5	In patients with ACKD what are the benefits and risks of correcting anaemia with blood transfusions in reducing morbidity and mortality and improving quality of life?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXDF1	In patients with ACKD, what factors (including patient factors) determine the dose and frequency of ESA required to correct anaemia?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
TXDF2	In patients with ACKD, what factors determine the dose and frequency of ESA required to keep the haemoglobin level within the maintenance range?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005

Question ID	Question wording	Study type filters used	Databases and years
			Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
ESAD1	In patients with ACKD, what factors determine the provision of ESAs?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
ESAD2	In patients with ACKD, what factors determine the route of administration of ESAs?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
NURS1	Is the effectiveness of anaemia management in chronic kidney disease improved by the involvement of anaemia nurse specialists/coordinators?	All study types including qualitative	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MON1	In patients with ACKD treated with ESAs, how frequently should iron status be checked?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
MON2	In patients with ACKD treated with ESAs, how frequently should haemoglobin levels be checked a) during Hb correction and b) during Hb maintenance?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
ESAR1	When should resistance to ESAs be suspected and what conditions lead to ESA resistance?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane

Question ID	Question wording	Study type filters used	Databases and years
			1800–2005 Cinahl 1982–2005
ESAR2	How should ESA resistance be managed?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
NOTE: The final cut-off date for all searches was 28 September 2005.			

A.2 Literature search strategies [2011]

Search strategies used for the AMCKD guideline are outlined below and were run as per the NICE Guidelines Manual 2009
http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf

Searches for the clinical reviews were run in Medline (OVID), Embase (OVID), the Cochrane Library and Cinahl (EBSCO).

Searches for the health economic reviews were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessments database (HTA) and the Health Economic Evaluation Database (HEED). NHSEED and HTA were searched via The Cochrane Library. Searches in NHS EED, HTA and HEED were constructed only using population terms. For Medline and Embase an economics filter (instead of a study type filter) was added to the population search strategy.

Searches were based on those done for the original 2006 guideline. All searches were run from the original search date (2005) to 8th July 2010. The Cochrane Library was searched to Issue 3, July 2010 with the exception of the Cochrane Database of Systematic Reviews which was searched to Issue 7, July 2010.

Update 2011

The full searches are presented below.

A.2.1 Diagnostic search strategies

The following searches for chapter 4.1 relate to the clinical question:

In patients with chronic kidney disease, at what haemoglobin (Hb)/haematocrit (Hct) levels should treatment commence?

Medline search terms

No.	Search terms
1	kidney failure, chronic/
2	exp renal insufficiency, chronic/
3	(chronic adj2 (renal or kidney)).ti,ab.
4	((endstage or (end adj1 stage)) adj2 (renal or kidney)).ti,ab.
5	esrd.ti,ab.
6	exp renal replacement therapy/

Update 2011

No.	Search terms
7	kidney diseases/ and (chronic$ or end-stage or endstage).ti,ab.
8	kidney failure/ and (chronic$ or end-stage or endstage).ti,ab.
9	((renal adj3 insufficienc$) not (acute adj2 renal)).ti,ab.
10	(predialysis or hemodialysis or haemodialysis or dialys*).ti,ab.
11	or/1-10
12	(anemi* or anaemi*).ti,ab.
13	exp anemia/
14	or/12-13
15	11 and 14
16	hematocrit/
17	exp hemoglobins/
18	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*).ti,ab.
19	(hb or hct).ti,ab.
20	or/16-19
21	11 and 20
22	exp mortality/
23	mo.fs.
24	quality of life/
25	quality-adjusted life years/
26	treatment outcome/
27	exp prognosis/
28	exp cardiovascular diseases/
29	exp stroke/
30	exp blood transfusion/
31	exp "outcome and process assessment (health care)"/
32	(adverse adj (outcome* or event*)).ti,ab.
33	or/22-32
34	21 and 33
35	limit 34 to english language
36	letter.pt.
37	letter/
38	letter$/
39	editorial.pt.
40	historical article.pt.
41	anecdote.pt.
42	commentary.pt.
43	note.pt.
44	case report/
45	case report$.pt.
46	case study/
47	case study.pt.
48	exp animal/ not human/
49	nonhuman/

No.	Search terms
50	exp animal studies/
51	animals, laboratory/
52	exp experimental animal/
53	exp animal experiment/
54	exp animal model/
55	exp rodentia/
56	exp rodents/
57	exp rodent/
58	or/36-57
59	35 not 58

Embase search terms

No.	Search terms
1	chronic kidney failure/
2	chronic kidney disease/
3	(chronic adj2 (renal or kidney)).ti,ab.
4	((endstage or (end adj1 stage)) adj2 (renal or kidney)).ti,ab.
5	esrd.ti,ab.
6	exp renal replacement therapy/
7	kidney disease/ and (chronic$ or end-stage or endstage).ti,ab.
8	kidney failure/ and (chronic$ or end-stage or endstage).ti,ab.
9	((renal adj3 insufficienc$) not (acute adj2 renal)).ti,ab.
10	(predialysis or hemodialysis or haemodialysis or dialys*).ti,ab.
11	or/1-10
12	(anemi* or anaemi*).ti,ab.
13	exp anemia/
14	or/12-13
15	11 and 14
16	hematocrit/
17	exp hemoglobin/
18	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*).ti,ab.
19	(hb or hct).ti,ab.
20	or/16-19
21	11 and 20
22	exp mortality/
23	exp "quality of life"/
24	exp treatment outcome/
25	prognosis/
26	exp cardiovascular disease/
27	exp stroke/
28	exp blood transfusion/
29	(adverse adj (outcome* or event*)).ti,ab.
30	or/22-29
31	21 and 30

Update 2011

Update 2011

No.	Search terms
32	letter.pt.
33	letter/
34	letter$/
35	editorial.pt.
36	historical article.pt.
37	anecdote.pt.
38	commentary.pt.
39	note.pt.
40	case report/
41	case report$.pt.
42	case study/
43	case study.pt.
44	exp animal/ not human/
45	nonhuman/
46	exp animal studies/
47	animals, laboratory/
48	exp experimental animal/
49	exp animal experiment/
50	exp animal model/
51	exp rodentia/
52	exp rodents/
53	exp rodent/
54	or/32-53
55	31 not 54

Cinahl search terms

No.	Search terms
S16	S10 and S15
S15	S11 or S12 or S13 or S14
S14	hb or hct
S13	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*)
S12	(MH "Hemoglobins+")
S11	(MH "Hematocrit")
S10	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9	(predialysis or hemodialysis or haemodialysis or dialys*)
S8	((renal and insufficienc*) not (acute and renal))
S7	(MH "Kidney Failure") and (chronic* or end-stage or endstage)
S6	(MH "Kidney Diseases") and (chronic* or end-stage or endstage)
S5	(MH "Renal Replacement Therapy+")
S4	esrd
S3	((endstage or (end stage) or end-stage) and (renal or kidney))
S2	(chronic and (renal or kidney))
S1	(MH "Kidney Failure, Chronic")

Update 2011

Cochrane search terms

No.	Search terms
#1	MeSH descriptor Kidney Failure, Chronic explode all trees
#2	MeSH descriptor Renal Insufficiency, Chronic explode all trees
#3	(chronic near/2 (renal or kidney)):ti,ab,kw
#4	((endstage or (end near/1 stage)) near/2 (renal or kidney)):ti,ab,kw
#5	esrd:ti,ab,kw
#6	MeSH descriptor Renal Replacement Therapy explode all trees
#7	((renal near/3 insufficienc*) not (acute near/2 renal)):ti,ab,kw
#8	(predialysis or hemodialysis or haemodialysis or dialys*):ti,ab,kw
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10	MeSH descriptor Kidney Diseases, this term only
#11	MeSH descriptor Kidney Failure, this term only
#12	(chronic* or end-stage or endstage):ti,ab,kw
#13	(#10 AND #12)
#14	(#11 AND #12)
#15	(#9 OR #13 OR #14)
#16	(anemi* or anaemi*):ti,ab,kw
#17	MeSH descriptor Anemia explode all trees
#18	(#16 OR #17)
#19	(#15 AND #18)
#20	MeSH descriptor Hematocrit, this term only
#21	MeSH descriptor Hemoglobins explode all trees
#22	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*):ti,ab,kw
#23	(hb or hct):ti,ab,kw
#24	(#20 OR #21 OR #22 OR #23)
#25	(#15 AND #24)

A.2.2 Optimal search strategies

The following searches for chapter 4.1 relate to the clinical question:

What should be the optimum Haemoglobin target range for patients undergoing treatment for anaemia in CKD?

Medline search terms

No.	Search terms
1	kidney failure, chronic/
2	exp renal insufficiency, chronic/
3	(chronic adj2 (renal or kidney)).ti,ab.
4	((endstage or (end adj1 stage)) adj2 (renal or kidney)).ti,ab.
5	esrd.ti,ab.
6	exp renal replacement therapy/
7	kidney diseases/ and (chronic$ or end-stage or endstage).ti,ab.
8	kidney failure/ and (chronic$ or end-stage or endstage).ti,ab.
9	((renal adj3 insufficienc$) not (acute adj2 renal)).ti,ab.

Update 2011

No.	Search terms
10	(predialysis or hemodialysis or haemodialysis or dialys*).ti,ab.
11	or/1-10
12	(anemi* or anaemi*).ti,ab.
13	exp anemia/
14	or/12-13
15	11 and 14
16	exp hemoglobins/
17	hematocrit/
18	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*).ti,ab.
19	(hb or hct).ti,ab.
20	or/16-19
21	15 and 20
22	(range* or target* or level* or maintain* or maintenance).ti,ab.
23	21 and 22
24	letter.pt.
25	letter/
26	letter$/
27	editorial.pt.
28	historical article.pt.
29	anecdote.pt.
30	commentary.pt.
31	note.pt.
32	case report/
33	case report$.pt.
34	case study/
35	case study.pt.
36	exp animal/ not human/
37	nonhuman/
38	exp animal studies/
39	animals, laboratory/
40	exp experimental animal/
41	exp animal experiment/
42	exp animal model/
43	exp rodentia/
44	exp rodents/
45	exp rodent/
46	or/24-45
47	23 not 46

Embase search terms

No.	Search terms
1	chronic kidney failure/
2	chronic kidney disease/
3	(chronic adj2 (renal or kidney)).ti,ab.

Update 2011

No.	Search terms
4	((endstage or (end adj1 stage)) adj2 (renal or kidney)).ti,ab.
5	esrd.ti,ab.
6	exp renal replacement therapy/
7	kidney disease/ and (chronic$ or end-stage or endstage).ti,ab.
8	kidney failure/ and (chronic$ or end-stage or endstage).ti,ab.
9	((renal adj3 insufficienc$) not (acute adj2 renal)).ti,ab.
10	(predialysis or hemodialysis or haemodialysis or dialys*).ti,ab.
11	or/1-10
12	(anemi* or anaemi*).ti,ab.
13	exp anemia/
14	or/12-13
15	11 and 14
16	hematocrit/
17	exp hemoglobin/
18	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*).ti,ab.
19	(hb or hct).ti,ab.
20	or/16-19
21	15 and 20
22	(range* or target* or level* or maintain* or maintenance).ti,ab.
23	21 and 22
24	letter.pt.
25	letter/
26	letter$/
27	editorial.pt.
28	historical article.pt.
29	anecdote.pt.
30	commentary.pt.
31	note.pt.
32	case report/
33	case report$.pt.
34	case study/
35	case study.pt.
36	exp animal/ not human/
37	nonhuman/
38	exp animal studies/
39	animals, laboratory/
40	exp experimental animal/
41	exp animal experiment/
42	exp animal model/
43	exp rodentia/
44	exp rodents/
45	exp rodent/
46	or/24-45

No.	Search terms
47	23 not 46

Cinahl search terms

No.	Search terms
S22	S20 and S21
S21	(range* or target* or level* or maintain* or maintenance)
S20	S16 and S19
S19	S17 or S18
S18	anaemi* or anemi*
S17	(MH "Anemia+")
S16	S10 and S15
S15	S11 or S12 or S13 or S14
S14	hb or hct
S13	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*)
S12	(MH "Hemoglobins+")
S11	(MH "Hematocrit")
S10	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9	(predialysis or hemodialysis or haemodialysis or dialys*)
S8	((renal and insufficienc*) not (acute and renal))
S7	(MH "Kidney Failure") and (chronic* or end-stage or endstage)
S6	(MH "Kidney Diseases") and (chronic* or end-stage or endstage)
S5	(MH "Renal Replacement Therapy+")
S4	esrd
S3	((endstage or (end stage) or end-stage) and (renal or kidney))
S2	(chronic and (renal or kidney))
S1	(MH "Kidney Failure, Chronic")

Cochrane search terms

No.	Search terms
#1	MeSH descriptor Kidney Failure, Chronic explode all trees
#2	MeSH descriptor Renal Insufficiency, Chronic explode all trees
#3	(chronic near/2 (renal or kidney)):ti,ab,kw
#4	((endstage or (end near/1 stage)) near/2 (renal or kidney)):ti,ab,kw
#5	esrd:ti,ab,kw
#6	MeSH descriptor Renal Replacement Therapy explode all trees
#7	((renal near/3 insufficienc*) not (acute near/2 renal)):ti,ab,kw
#8	(predialysis or hemodialysis or haemodialysis or dialys*):ti,ab,kw
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10	MeSH descriptor Kidney Diseases, this term only
#11	MeSH descriptor Kidney Failure, this term only
#12	(chronic* or end-stage or endstage):ti,ab,kw
#13	(#10 AND #12)
#14	(#11 AND #12)
#15	(#9 OR #13 OR #14)

Update 2011

No.	Search terms
#16	(anemi* or anaemi*):ti,ab,kw
#17	MeSH descriptor Anemia explode all trees
#18	(#16 OR #17)
#19	(#15 AND #18)
#20	MeSH descriptor Hematocrit, this term only
#21	MeSH descriptor Hemoglobins explode all trees
#22	(hemoglobin* or haemoglobin* or hematocrit* or haematocrit*):ti,ab,kw
#23	(hb or hct):ti,ab,kw
#24	(#20 OR #21 OR #22 OR #23)
#25	(#19 AND #24)
#26	(range* or target* or level* or maintain* or maintenance):ti,ab
#27	(#25 AND #26)

A.2.3 Economics search strategies

The following searches relate to health economics.

Medline search terms

Update 2011

No.	Search terms
1	kidney failure, chronic/
2	exp renal insufficiency, chronic/
3	(chronic adj2 (renal or kidney)).ti,ab.
4	((endstage or (end adj1 stage)) adj2 (renal or kidney)).ti,ab.
5	esrd.ti,ab.
6	exp renal replacement therapy/
7	kidney diseases/ and (chronic$ or end-stage or endstage).ti,ab.
8	kidney failure/ and (chronic$ or end-stage or endstage).ti,ab.
9	((renal adj3 insufficienc$) not (acute adj2 renal)).ti,ab.
10	(predialysis or hemodialysis or haemodialysis or dialys*).ti,ab.
11	or/1-10
12	(anemi* or anaemi*).ti,ab.
13	exp anemia/
14	or/12-13
15	11 and 14
16	exp "costs and cost analysis"/
17	economics/
18	exp economics, hospital/
19	exp economics, medical/
20	exp economics, nursing/
21	exp economics, pharmaceutical/
22	exp "fees and charges"/
23	exp budgets/
24	ec.fs.
25	(economic$ or pharmacoeconomic$ or price$ or pricing$ or cost$ or budget$).ti,ab.
26	(value adj2 (money or monetary)).ti,ab.

Update 2011

No.	Search terms
27	(expenditure not energy).ti,ab.
28	or/16-27
29	((metabolic or energy or oxygen) adj1 cost$).ti,ab.
30	28 not 29
31	exp quality-adjusted life years/
32	quality adjusted life.tw.
33	exp "quality of life"/
34	value of life/
35	(qaly$ or qald$ or qale$ or qtime$).tw.
36	disability adjusted life.tw.
37	daly$.tw.
38	health status indicators/
39	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
40	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
41	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
42	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
43	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
44	(euroqol or euro qol or eq5d or eq 5d).tw.
45	(hql or hqol or h qol or hrqol or hr qol).tw.
46	(hye or hyes).tw.
47	health$ year$ equivalent$.tw.
48	health utilit$.tw.
49	(hui or hui1 or hui2 or hui3).tw.
50	disutili$.tw.
51	rosser.tw.
52	quality of well?being.tw.
53	qwb.tw.
54	willingness to pay.tw.
55	standard gamble$.tw.
56	time trade off.tw.
57	time tradeoff.tw.
58	tto.tw.
59	or/31-58
60	30 or 59
61	15 and 60

Embase search terms

No.	Search terms
1	chronic kidney failure/
2	chronic kidney disease/
3	(chronic adj2 (renal or kidney)).ti,ab.

Update 2011

No.	Search terms
4	((endstage or (end adj1 stage)) adj2 (renal or kidney)).ti,ab.
5	esrd.ti,ab.
6	exp renal replacement therapy/
7	kidney disease/ and (chronic$ or end-stage or endstage).ti,ab.
8	kidney failure/ and (chronic$ or end-stage or endstage).ti,ab.
9	((renal adj3 insufficienc$) not (acute adj2 renal)).ti,ab.
10	(predialysis or hemodialysis or haemodialysis or dialys*).ti,ab.
11	or/1-10
12	(anemi* or anaemi*).ti,ab.
13	exp anemia/
14	or/12-13
15	11 and 14
16	health economics/
17	exp economic evaluation/
18	exp health care cost/
19	exp pharmacoeconomics/
20	exp fee/
21	budget/
22	(economic$ or pharmacoeconomic$ or cost$ or price$ or pricing$ or budget$).ti,ab.
23	(value adj2 (money or monetary$)).ti,ab.
24	(expenditure not energy).ti,ab.
25	or/16-24
26	((metabolic or energy or oxygen) adj1 cost$).ti,ab.
27	25 not 26
28	quality adjusted life year/
29	quality of life/
30	(qaly$ or qald$ or qale$ or qtime$).tw.
31	daly$.tw.
32	quality adjusted life.tw.
33	disability adjusted life.tw.
34	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
35	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
36	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
37	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
38	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
39	(euroqol or euro qol or eq5d or eq 5d).tw.
40	(hql or hqol or h qol or hrqol or hr qol).tw.
41	(hye or hyes).tw.
42	health$ year$ equivalent$.tw.
43	health utilit$.tw.

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No.	Search terms
44	(hui or hui1 or hui2 or hui3).tw.
45	disutili$.tw.
46	rosser.tw.
47	quality of well?being.tw.
48	qwb.tw.
49	willingness to pay.tw.
50	standard gamble$.tw.
51	time trade off.tw.
52	time tradeoff.tw.
53	tto.tw.
54	or/28-53
55	27 or 54
56	15 and 55

Cochrane search terms (NHSEED/HTA)

No.	Search terms
#1	MeSH descriptor Kidney Failure, Chronic explode all trees
#2	MeSH descriptor Renal Insufficiency, Chronic explode all trees
#3	(chronic near/2 (renal or kidney)):ti,ab,kw
#4	((endstage or (end near/1 stage)) near/2 (renal or kidney)):ti,ab,kw
#5	esrd:ti,ab,kw
#6	MeSH descriptor Renal Replacement Therapy explode all trees
#7	((renal near/3 insufficienc*) not (acute near/2 renal)):ti,ab,kw
#8	(predialysis or hemodialysis or haemodialysis or dialys*):ti,ab,kw
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10	MeSH descriptor Kidney Diseases, this term only
#11	MeSH descriptor Kidney Failure, this term only
#12	(chronic* or end-stage or endstage):ti,ab,kw
#13	(#10 AND #12)
#14	(#11 AND #12)
#15	(#9 OR #13 OR #14)
#16	(anemi* or anaemi*):ti,ab,kw
#17	MeSH descriptor Anemia explode all trees
#18	(#16 OR #17)
#19	(#15 AND #18)

HEED search terms (Compound search)

All Data	(chronic or endstage or end-stage)	OR
All Data	(renal or kidney)	OR
All Data	(predialys* or hemodialys* or haemodialys* or dialys*)	OR
All Data	anemi* or anaemi*	AND

Appendix B: Scope

Guideline title

Anaemia management in people with chronic kidney disease (CKD)

Short title

Anaemia in chronic kidney disease

Background

The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on the management of anaemia in chronic kidney disease (CKD) for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see below). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework. The NSF for Renal Services (2004) is of particular relevance to this guideline.

Clinical need for the guideline

The NSF for Renal Services (2004) defines chronic kidney disease (CKD) as kidney (renal) disease that is irreversible and progressive. Established renal failure (also called end stage renal failure) is CKD that has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) is needed to maintain life.

Established renal failure is an irreversible, long-term condition. A small number of people with established renal failure may choose conservative management only. Conventionally the total number of people receiving renal replacement therapy has been taken as a proxy measure for the prevalence of established renal failure. The NSF for Renal Services estimates that more than 27,000 people received renal replacement therapy in England in 2001. Approximately one-half of these had a functioning transplant and the remainder were on dialysis. It is predicted that numbers will rise to around 45,000 over the next 10 years. However, the most recent Renal Registry Report (2003) states that 32,500 patients received renal replacement therapy with 46% having a renal transplant.

The UK Renal Registry Report (2003) highlights that 43% of patients newly receiving dialysis had a haemoglobin level of <10 g/dl in 2002. This is despite the fact that patients receiving dialysis treatment during 2002 had haemoglobin concentrations that continued to improve. The Registry demonstrated that 82% of haemodialysis patients and 88% of peritoneal dialysis patients had a haemoglobin concentration >10 g/dl.

The clinical need for the guideline is supported by the wide variation in practice and lack of agreement on the optimal management of renal anaemia. The UK Renal Registry Report (2003) draws attention to the fact that it was not possible to provide accurate information about

erythropoietin because of variations in the recording of erythropoietin data and also the provision of erythropoietin from primary care in some parts of the UK. An evidence-based guideline should improve the standards of care across renal units and aid appropriate commissioning of cost-effective treatments.

The guideline

The guideline development process is described in detail in two publications which are available from the NICE website (see further information below). Guideline development process – an overview for stakeholders, the public and the NHS describes how organisations can become involved in the development of a guideline. The Guideline development methods – information for national collaborating centres and guideline developers provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see below).

The areas that will be addressed by the guideline are described in the following sections.

Population

- Groups that will be covered
  a. The guideline will offer best practice advice on the care of people who have a clinical diagnosis of anaemia associated with CKD.
  b. The guideline will encompass the care of people with predialysis CKD, people with established renal failure receiving renal replacement therapy, people with established renal failure receiving conservative management, and people after renal transplant surgery.
  c. The guideline will cover children (aged <16 years).
- Groups that will not be covered

Where CKD is not the principal cause of the anaemia it will be excluded, for example:

- anaemia caused by haematological disease
- anaemia caused by acute and chronic inflammatory disease states
- anaemia caused by malignancy
- anaemia caused by acquired immunodeficiency syndrome
- anaemia caused by acute renal failure.

Healthcare setting

The guideline will cover the care provided by healthcare professionals in direct contact with patients with anaemia associated with CKD and make decisions about their care. This will include healthcare professionals in primary, secondary and tertiary NHS care settings.

Clinical management

The guideline will include recommendations in the following areas.

(a) Detection and diagnosis of anaemia in people with CKD:

- exclusion of other causes of anaemia

- diagnostic evaluation of anaemia in CKD
- assessment of anaemia.

(b) Criteria for the threshold levels of haemoglobin concentration for initiating the treatment of anaemia.

(c) Factors which have an impact on anaemia in renal disease and their management including:

- nutritional status including haematinics
- dialysis adequacy (peritoneal and haemodialysis)
- hyperparathyroidism
- assessment and optimisation of erythropoiesis to include iron stores, iron supplements and erythropoiesis stimulating agents
- monitoring of treatment of anaemia associated with people with CKD.

Guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the Summary of product characteristics to inform their decisions for individual patients.

Status

- Scope

This is the final version of the scope.

- Guideline

The development of the guideline recommendations will begin in October 2004.

Further information

Information on the guideline development process is provided in:

- *Guideline development process – an overview for stakeholders, the public and the NHS*
- *Guideline development methods – information for national collaborating centres and guideline developers*

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health and Welsh Assembly Government

The Department of Health and Welsh Assembly Government asked the Institute:

'To develop a guideline for the NHS in England and Wales for the management of anaemia in people with poor renal function, including chronic kidney disease and established renal failure, based on evidence of clinical and cost effectiveness of interventions available for treating anaemia in such people. The interventions should be all those factors that have an impact on anaemia including nutritional status, dialysis effectiveness, iron stores and the use of recombinant human erythropoietin. The purpose of the guideline will be to take renal staff and patients through the most cost-effective set of investigations and procedures which will optimise haemoglobin and if possible keep it above the accepted international standard, for example European and K-DOQI of 11 g/dl.'

Scope [2011]

The Scope is now a retrospective document and sets the scene for what the guidelines amendment covered.

B.1 Guideline title

Anaemia management in people with chronic kidney disease (rapid partial update of NICE clinical guideline 39)

B.2 Short title

Anaemia in chronic kidney disease (rapid partial update)

B.3 The remit

This is a partial update of 'Anaemia management in people with chronic kidney disease', NICE clinical guideline 39 (2006), available from www.nice.org.uk/guidance/CG39. This update is being undertaken because new evidence has emerged on haemoglobin target levels and the published recommendations in this area will be considered for amendment. See "Key clinical issues that will be covered" for details of which sections will be updated.

This partial update does not alter the scheduled review date for the guideline and all other areas of the original scope will be considered for review then.

Update 2011

B.4 Clinical need for the guideline

B.4.1 Epidemiology

a) The National Service Framework for Renal Services (2004) defines chronic kidney disease (CKD) as kidney (renal) disease that is irreversible and progressive. Epidemiological studies suggest that between 10.2 and 11.7% of the adult population have CKD, roughly half of whom have stage 3-5 CKD (defined by a glomerular filtration rate of less than 60 ml/minute/1.73m^2). Established renal failure, also called end stage renal failure, is CKD that has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) is needed to maintain life.

b) Established renal failure is defined in the Renal National Service Framework as a glomerular filtration rate (GFR) below 15 ml/minute (CKD stage 5) and is an irreversible, long-term condition. A small number of people with established renal failure may choose conservative management only, but the total number of people receiving renal replacement therapy has generally been taken as a proxy measure for the prevalence of established renal failure. The UK Renal Registry records that at the end of 2008 there were 47,525 adults receiving renal replacement therapy for established renal failure (774 per million population). Of these, 47% had a functioning kidney transplant, 43% were receiving centre-based haemodialysis, 1% home haemodialysis and 9% peritoneal dialysis. Significant trends include a plateauing of incident end stage renal disease rates but a continued annual increase in prevalence of approximately 4.4%.

c) Many people with CKD or established renal failure also develop associated anaemia. The prevalence of anaemia associated with CKD increases progressively with stage of CKD.

d) UK population data show the prevalence of haemoglobin levels below 11 g/dl is 2.7% in those with a glomerular filtration rate (GFR) above 60 ml/minute. This increases to 2.9% in those with a GFR between 45 and 59 ml/minute (CKD stage 3A), 4.1% in those with a GFR between 30 and 44 ml/minute (CKD stage 3B) and 10% in those with a GFR below 30 ml/minute (CKD stages 4 and 5).

B.4.2 Current practice

a) The UK Renal Registry Report (2009) highlights that the median haemoglobin level (Hb) of patients in the UK in 2008 was 10.2 g/dl at the time of starting dialysis, with 57% of patients having Hb levels above 10.0 g/dl (compared with 58% in the 2008 report). The variation between centres remained high (29–84%).

b) The median Hb of patients on haemodialysis in the UK was 11.6 g/dl with an interquartile range (IQR) of
10.6–12.5 g/dl, 85% of haemodialysis patients had Hb levels of at least 10.0 g/dl and 54% were within the current target range of 10.5–12.5 g/dL.

c) The median Hb of peritoneal dialysis patients in the UK was 11.7 g/dl (IQR 10.8–12.6 g/dl), 89% of peritoneal dialysis patients had Hb levels of at least 10.0 g/dl, and 55% were within the recommended range of 10.5–12.5 g/dL.

d) In haemodialysis patients receiving erythropoiesis stimulating agents, the median dose was 8000 iu/week. In peritoneal dialysis patients receiving erythropoiesis stimulating agents the median dose was 4000 iu/week.

e) At the time of publication of the 2006 NICE guideline, guidance on limiting the upper level of haemoglobin was primarily driven by health economics and a lack of evidence of additional benefit in patients treated to achieved Hb levels above 12.5 g/dL. Studies published since the guidance was released highlight a lack of benefit and possible harm related to higher Hb levels; we are therefore reviewing the published recommendations.

Update 2011

B.5 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

The areas that will be addressed by the guideline are described in the following sections.

B.6 Population

B.6.1 Groups that will be covered

a) Adults and children with a clinical diagnosis of anaemia associated with CKD, including:
   i. those with pre-dialysis CKD
   ii. those with established renal failure receiving renal replacement therapy
   iii. those with established renal failure receiving conservative management, and
   iv. after renal transplant surgery.

b) No patient subgroups have been identified as needing specific consideration.

B.6.2 Groups that will not be covered

a) People with anaemia not principally caused by CKD, for example anaemia caused by:
   i. haematological disease

ii. acute and chronic inflammatory disease states
iii. malignancy
iv. acquired immunodeficiency syndrome
v. acute kidney injury.

B.7 Healthcare setting

Care provided by healthcare professionals who are in direct contact with patients with anaemia associated with CKD and who make decisions about their care. This will include healthcare professionals in primary, secondary and tertiary NHS settings.

B.8 Clinical management

B.8.1 Key clinical issues that will be covered

a) The level of haemoglobin at which treatment should commence, and the optimal haemoglobin target range.
b) Update of recommendations 1.1.1.1 (diagnostic role of Hb levels) and 1.3.8.1 (optimal Hb levels) from NICE clinical guideline 39:
   i. 1.1.1.1 Management of anaemia should be considered in people with anaemia of chronic kidney disease (CKD) when their haemoglobin (Hb) level is less than or equal to 11 g/dl (or 10 g/dl if younger than 2 years of age).
   ii. 1.3.8.1 In people with anaemia of CKD, treatment should maintain stable Hb levels between 10.5 and 12.5 g/dl for adults and children older than 2 years of age, and between 10 and 12 g/dl in children younger than 2 years of age, reflecting the lower normal range in that age group. This should be achieved by:
      - adjusting treatment, typically when Hb rises above 12.0 or falls below 11.0 g/dl.
      - taking patient preferences, symptoms and comorbidities into account and revising the aspirational range and action thresholds accordingly.

Update 2011

B.8.2 Clinical issues that will not be covered

All other issues considered in NICE clinical guideline 39.

B.9 Main outcomes

B.9.1 Diagnostic role of Hb levels review

- All-cause mortality.
- Cardiovascular mortality.
- Increased hospitalisation.
- Stroke.
- Myocardial infarction.
- Left ventricular hypertrophy/left ventricular mass index.
- Quality of life indices.
- Progression of CKD in non-dialysis patients.

B.9.2 Optimal Hb level review

- All-cause mortality.
- Cardiovascular mortality.
- CKD progression (studies with non-dialysis patients).
- Access thrombosis (for studies with haemodialysis patients).
- Stroke.
- Myocardial infarction.
- Left ventricular hypertrophy/left ventricular mass index.
- Reduction in transfusion requirements.
- Haemoglobin variability.
- Quality of life indices.
- Hypertension/blood pressure control.

B.10 Economic aspects

Developers will take into account both clinical and cost effectiveness when considering the update of the two recommendations. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

B.11 Status

B.11.1 Scope

This is the final scope.

B.12 Timing

The development of the guideline recommendations will begin in June 2010.

B.13 Related NICE guidance (Published guidance)

B.13.1 NICE guidance to be updated

This guideline will partially update and replace the following NICE guidance.

- Anaemia management in chronic kidney disease. NICE clinical guideline 39 (2006). Available from www.nice.org.uk/guidance/CG39

B.13.2 Other related NICE guidance

- Chronic kidney disease. NICE clinical guideline 73 (2008). Available from www.nice.org.uk/guidance/CG73
- Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia. NICE technology appraisal guidance 142 (2008). Available from www.nice.org.uk/guidance/TA142

B.13.3 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Update 2011

Appendix C: Cost-effectiveness analysis of optimal treatment target for the 2011 rapid update

C.1 Introduction

In the 2006 guideline a cost-effectiveness model looking at the optimal Hb (Hb) target was undertaken. However, the approach taken (using cohort data) was judged by the GDG to no longer be appropriate in light of new clinical data available in the 2011 update. On this basis this analysis was removed from the guideline in the 2011 update.

The preferred approach was to undertake a new cost-effectiveness analysis based on the available randomised clinical trial (RCT) data comparing different treatment targets identified in the systematic literature review for the guideline (see Section 6.9 in the full guideline).

C.2 Methods

C.2.1 Model overview

Update 2011

A cost-utility analysis was undertaken where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance[222].

C.2.1.1 Population

The population included for the analysis is non-dialysis CKD patients requiring anaemia management.

The non-dialysis and haemodialysis populations were considered separately by the GDG. The cost-effectiveness analysis was restricted to non-dialysis patients as there was limited SF36 quality of life data for haemodialysis patients to inform the estimate of utility for the model required to calculate QALYs.

C.2.1.2 Comparators

The comparators selected for the model were treating with erythropoiesis stimulating agent (ESA) to:

2. Lower Hb target (<12 g/dL)
3. Higher Hb target (>12 g/dL)

It was decided that the most useful and feasible option based on the available RCT data would be to compare a higher Hb target (>12 g/dL) versus a lower Hb target (<12 g/dL) based on pooled data for studies that make this comparison.

Data did not allow more refined comparisons. Note that the studies used to inform the model all compare slightly different ranges. The lower targets were in the range 9-12 g/dL and the higher targets were in the range 12-16 g/dL. Studies also varied in their baseline Hb levels and achieved Hb levels. This information is all summarised in Section 6.9 of the full guideline.

It was felt that the available RCT data was insufficient to allow a comparison to be made within the lower end of the Hb range (11-12 g/dL versus 9-11 g/dL, or similar). While one RCT reported

mortality data for a comparison within this range (MacDougall; n=197; RR 0.93, 10-12 g/dL vs 9 g/dL), no RCTs reported EQ5D or SF36 data within this range[190].

C.2.1.3 Differences between comparators incorporated into the model

Following review of the clinical evidence and GDG discussion, it was decided to include mortality and quality of life (EQ5D utility mapped from SF36) in the model. The clinical review suggested some other health impacts – mainly increased cardiovascular risk with a higher target Hb >12 g/dL versus <12 g/dL suggested by an increased risk of hypertension and stroke. There was some debate within the GDG about the stroke outcome and it was recognised that the evidence was largely weighted by a study in diabetic patients. Following GDG discussion these effects were excluded due to these issues, and also to keep the model manageable within the timeframe of the rapid update. This was noted as a potential limitation *a priori* and one that needed to be considered when interpreting the model results, possibly biasing the model in favour of the >12 g/dL target.

C.2.1.4 Treatment period and analysis time horizon

A treatment period of three years was examined in the basecase. This matches the longest mean follow-up of the clinical trials that inform the comparisons in this model. During this period a difference in terms of ESA dose, mortality rate and utility (quality of life) are applied between the higher and lower target Hb groups based on RCT data.

Although a three-year treatment period was used in the basecase, the time horizon of the analysis was a lifetime (50 cycles). A lifetime horizon is most appropriate to capture the full impact of treatment when a mortality difference is incorporated in the model. Restricting the analysis will underestimate the QALYs gained when mortality is reduced. People will also continue to consume healthcare resources during the time they are alive – it is appropriate to take these costs into account when calculating cost effectiveness.

Update 2011

After the initial three-year treatment period the same ESA dose, mortality rate and utility were applied to both groups; the inputs associated with the lower Hb target group were used. When mortality is impacted differentially between treatment groups there are different numbers of people alive at the end of the treatment period. Due to this total QALYs therefore vary between treatment options beyond 3 years, even assuming no further differences in dose, mortality and quality of life for each alive patient.

As a sensitivity analysis, we also examined the effect of using a longer treatment duration of a lifetime which might be considered more realistic although also requires greater extrapolation away from the data observed in the RCTs. A shorter treatment period of one year (with a lifetime analysis horizon) was also examined.

C.2.2 Approach to modelling

The model quantifies the trade-off between increased mortality and improved quality of life of treating to a higher Hb target by calculating QALYs (quality adjusted life years) and so will identify whether the quality of life benefits of a higher Hb target outweigh the increased mortality risk. If it does (and there are higher QALYs with a higher target), it will also assess whether the additional benefit is worth the additional cost of aiming for that target due to the higher ESA dose required.

C.2.2.1 Model structure

A simple Markov model was constructed with two states: alive and dead. A cycle length of one year was used. People entered the model aged 65 years and the model was run for 50 cycles (by when the majority of people in the model will have died). A mortality rate defines how quickly people in the

cohort move from the alive state to the dead state. Quality of life weights are applied to time spent in the alive state in order to calculate QALYs. Costs for ESA and other anaemia management are applied to time spent in the alive state in order to calculate costs.

The model was populated with mortality, quality of life and ESA dose data for the lower target Hb group (baseline data). The model is run and total costs and QALYs are calculated for that group.

To compare the impact of treating the same population to a higher target Hb relative treatment effect data was applied to the baseline model inputs (the hazard ratio for mortality, mean difference in quality of life, mean difference in dose). The model is then rerun and total costs and QALYs recalculated.

Comparing the results for the two different targets allows us to identify which group is the most cost-effective.

Update 2011

C.2.2.2 Uncertainty

The model was built probabilistically in order to take account of the uncertainty around input parameter point estimates. A probability distribution is defined for each model input parameter. When the model is run a value for each input is randomly selected from its respective probability distribution simultaneously and mean costs and mean QALYs are calculated using these values. The model is run repeatedly – in this case 10,000 times – and results are summarised. Probability distributions in the analysis were parameterised by error estimates from data sources, for example confidence intervals around relative risk estimates.

In addition, various sensitivity analyses were undertaken to test the robustness of model assumptions and data sources. In these one or more inputs were changed and the probabilistic analysis rerun to see the impact on results.

C.2.3 Model inputs

C.2.3.1 Summary table of model inputs

Model inputs were based on the RCTs identified by the systematic review of the literature supplemented by additional data sources where necessary. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the basecase (primary) analysis is provided in Table C.1 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table. Details of the probability distributions used for the probabilistic analysis are also included in subsequent sections.

Table C.1: Summary of basecase model inputs

Input	Data		Sources
Comparators	Hb target <12 g/dL Hb target >12 g/dL		
Population	Non-dialysis chronic kidney disease patients with anaemia		
Perspective	UK NHS and PSS		
Time horizon	Lifetime		
Initial cohort settings	Age Female	65 years 54%	Mean across relevant RCTs [84,114,176,251,270,273,277,291]
Baseline inputs (when target <12 g/dL)			
Annual mortality rate	Years 1-3 Year 4+	0.065 (SE 0.003) Lifetables + CKD HR	Pooled RCT data[84,114,176,251,277,291] ONS, NICE CG73 CKD[218,235]
Utility (quality of life)	0.75 (SE 0.005)		Pooled RCT data – SF36 mapped to EQ5D[84,139,271,277,291]
Epoetin alfa dose	1788 U/wk (SE 37)		Pooled RCT data[84,114,176,251,252,271,277,291]
Difference when target higher (>12 g/dL)			
Mortality	HR: 1.10 (CI: 0.97, 1.24)		Pooled RCT data[84,114,176,251,277,291]
Utility (QoL)	Additional: 0.01 (SE 0.007)		Pooled RCT data – SF36 mapped to EQ5D[84,139,271,277,291]
Epoetin alfa dose	Additional: 8198 U/wk (SE 162)		Pooled RCT data[84,114,176,251,252,271,277,291]
Duration differences applied	3 years		Based on longest mean follow-up of relevant RCTs[84]
Costs			
Epoetin alfa	£5.09 per 1000 units		BNF 59[46]
Other anaemia management costs	£1000 annually		Assumption

CI = 95% confidence interval; CKD = chronic kidney disease; Hb = haemoglobin; HR = hazard ratio; PSS = personal social services; RCT = randomised clinical trial; SE = standard error; U/wk = units per week

C.2.3.2 Overview of how RCT data was used from clinical review

Where possible model inputs were based on pooled data from RCTs identified in the clinical review comparing different treatment targets. Studies in a non-dialysis population comparing a higher Hb target >12 g/dL with a lower Hb target <12 g/dL were used.

Update 2011

Eight RCTs fell into this category. Studies were used to inform the pooled estimate if data was available. Which studies informed which input are summarised in Table C.2.

Table C.2: RCT data available to inform pooled estimates for model inputs

Study	Cohort settings	Mortality	Quality of Life	Epoetin dose
Drueke 2006 (CREATE)[84]	✓	✓	✓	✓
Furuland 2003[114]	✓	✓	×	✓
Levin 2005[176]	✓	✓	×	✓
Pfeffer 2009 (TREAT)[251]	✓	✓	×	✓
Ritz 2007 (ACORD)[270]	✓	×	×	×
Roger 2003[273]	✓	×	×	×
Rossert 2006[277]	✓	✓	✓	✓
Singh 2006 (CHOIR)[291]	✓	✓	✓	✓

C.2.3.3 Initial cohort settings

A starting age of 65 years was used for people entering the model. The starting age of the cohort was based on a weighted average of the mean ages in the non-dialysis RCTs comparing targets >12 g/dL with <12 g/dL, with weighting based on study size[84,114,176,251,270,273,277,291]. The cohort was assigned to be 54% female also based on a weighted average of data from the same RCTs. Table C.3 below summarises the RCT data used.

Update 2011

Table C.3: Age and % female in RCTs comparing a target of >12 g/dL with one of <12 g/dL in non-dialysis CKD patients with anaemia

Study	Age (per arm)	% female (per arm)	N (per arm)
Drueke 2006 (CREATE)[84]	59.3	43%	301
	58.8	49%	302
Furuland 2003[114]	57	47%	36
	60	53%	36
Levin 2005[176]	56.5	30%	78
	57.3	30%	74
Pfeffer 2009 (TREAT)[251]	68	59%	2012
	68	56%	2026
Ritz 2007 (ACORD)[270]	58	49%	88
	57	50%	82
Roger 2003[273]	53	62%	75
	54	67%	80
Rossert 2006[277]	58.5	42%	195
	57.8	39%	195
Singh 2006 (CHOIR)[291]	66	56%	715
	66.3	54%	717

C.2.3.4 Mortality

Mortality rate with lower target Hb <12 g/dL

In the model an annual mortality rate of 0.07 (SE 0.003) based on pooled RCT data was used for an initial 3-year period (based on the longest mean follow-up in the available RCTs) [84,114,176,251,277,291].

After this England and Wales life tables were used to model declining mortality over time; these were adjusted with hazard ratios for CKD to reflect the increased mortality risk in this population[218,235]. More details are provided below.

Pooled RCT mortality rate:

Mortality rates from the lower Hb target arms of relevant RCTs were pooled by summing the number of deaths over all the trials, summing the estimated number of patient years over all the trials (estimated using the number of patients and mean study follow-up) and dividing one by the other[84,114,176,251,277,291]. If the mean study follow-up was not reported the available data was used to provide the best available estimate of the mean follow-up. For example, the median was used if reported. The standard error of the pooled estimate was calculated as √(total deaths)/total patient years. Table C.4 summarises the RCT mortality data used and resultant pooled rate.

Table C.4: Mortality data from RCTs in arm where Hb target <12 g/dL

Study	Deaths	Study arm N	Best estimate of mean follow-up	Patient years**
Drueke 2006 (CREATE)[84]	21	301	3.0†	903
Furuland 2003[114]	1	36	0.9§	32
Levin 2005[176]	3	74	2.0‡	148
Pfeffer 2009 (TREAT)[251]	395	2026	2.4*	4913
Rossert 2006[277]	6	195	1.0*	192
Singh 2006 (CHOIR)[291]	36	717	1.3†	956
Total	**462**			**7144**
Annual mortality rate (SE)				**0.065 (0.003)**

*†Mean; §Actual weeks in study were reported however study stated that some outcomes were reported at 48 weeks and so mortality was assumed to be reported at 48 weeks and therefore this is used as best available estimate of mean; ‡Only planned study duration reported therefore used as best available estimate of mean; *Only median reported therefore used as an best available estimate of mean; **Based on 'best estimate of mean follow-up' multiplied by n number.*

Update 2011

This input was incorporated into the probabilistic analysis. A gamma distribution was used initially to reflect the feasible range of a rate (bounded by zero) but as the standard error is small relative to the mean the software often returned an error (a programming issue with Excel). Therefore a normal distribution was used instead – a normal distribution is not bounded by 0 but as the standard error of the estimate is small the distribution will be tight and not vary far from the point estimate, and therefore will not go below zero. This was parameterised using the mean and standard error.

Population life table mortality rates adjusted to reflect increased mortality in a CKD population:

After the initial 3 years of the model, England and Wales lifetables (2006-08) were used to incorporate increasing mortality over time[235]. CKD hazard ratios for mortality were applied to adjust these to a more relevant mortality rate for the population of the model. Standardised mortality ratios by CKD stage were available from the NICE CKD guideline modelling[218]. These hazard ratios were based on a large US cohort analysis (n=2,583,911, 20% stage 3 and above)[233]. Stage of CKD was not incorporated in this model and the pooled ratios reported for stage 3a/3b/4 CKD patients by age were used (Table C.5). This approach was considered a reasonable simplification for modelling purposes in this analysis. Lifetables go up to 100 years of age, in the model beyond 100 years of age the mortality rate for 100 years of age is applied. These inputs were not varied probabilistically.

Table C.5: CKD stage 3a/3b/4 hazard ratios for mortality

Age	Hazard ratio CKD stage 3a/3b/4
18–44	2.14

Age	Hazard ratio CKD stage 3a/3b/4
45–54	1.83
55–64	1.64
65–74	1.32
75–84	1.22
85+	1.14

Source: NICE CG73 CKD[218]

Difference in mortality with higher target Hb >12 g/dL

A hazard ratio for mortality with a target Hb >12 g/dL versus <12 g/dL of 1.10 (CI: 0.97, 1.24) was applied in the model. This was based on the meta analysis of RCTs undertaken as part of the systematic clinical review (see chapter 6.9 of full guideline) [84,114,176,251,270,273,277,291].

This difference was applied in the higher target Hb >12 g/dL group for the differential treatment duration being modelled – three years in the basecase analysis (as described in Section C.2.1.4).

This input was incorporated into the probabilistic analysis using a lognormal distribution parameterised using the log hazard ratio and SE calculated using the log confidence interval.

C.2.3.5 Quality of life (utilities)

Update 2011

For economic evaluation, a specific measure of quality of life known as utility is required to calculate QALYs. The NICE reference case specifies that the preferred way for this to be assessed is by the EQ5D instrument. EQ5D data was not reported in the study publications for the RCTs comparing different targets. However, SF36 data was commonly reported (see Chapter 6.9 of full guideline) and SF36 summary data can be mapped to EQ5D using a published algorithm[17].

In order to map SF36 to EQ5D, mean scores for each of the eight SF36 domains are required. Where insufficient numerical data were reported in study publications lead authors were contacted to request mean scores for each SF36 domain (as described in the Methods chapter in the full guideline). Sufficient data was available from three of the seven non-dialysis studies that reported collecting SF36 data: the CREATE study, the CHOIR study and the study reported by Rossert and colleagues[84,139,271,277,291].

Of two dialysis studies that reported collecting SF36 data, sufficient data for mapping was available from one; the study reported by Besarab and colleagues[15,35]. This was mapped for comparison with the non-dialysis data but was not incorporated into the cost-effectiveness analysis.

Some studies had data available at different time points during the study. Where this occurred the measurement closest to one year was used (as was done in the meta analysis of SF36 data in Chapter 6.9 of full guideline).

Quality of life (utility score) with lower target Hb <12 g/dL

In the model a utility score of 0.75 (SE 0.005) was used for the group with an Hb target of <12 g/dL. The mean EQ5D utility for the lower Hb target group was estimated by pooling the EQ5D utility estimates from each RCT as a weighted average with weighting based on the total number of patients in each study. Results for baseline utility are summarised in Table C.6.

For each study, the mean scores for the SF36 domains with a lower Hb target (data summarised in Table C.7 of this report) were used to map to an EQ5D utility estimate for the lower Hb target group. In studies that reported change from baseline, mean scores for each SF36 domain were calculated by adding the reported change from baseline to the reported baseline score.

This difference was applied in the higher target Hb >12 g/dL group for the differential treatment duration being modelled – three years in the basecase analysis (as described in Section C.2.1.4).

The baseline utility in the lower Hb target group was incorporated into the probabilistic analysis using a beta distribution parameterised by the mean pooled EQ5D and SE (using method of moments[45]).

Update 2011

Table C.6: Results of EQ5D mapping from SF36 data

	Study n overall	Mapped EQ5D				
		Target <12	*SE*	Difference	*SE*	*CI*
NON-DIALYSIS						
Drueke 2006 (CREATE)	603	0.82	*0.008*	0.033	*0.007*	*0.018, 0.047*
Rossert 2006	390	0.81	*0.012*	0.018	*0.018*	*-0.019, 0.052*
Singh 2006 (CHOIR)	1432	0.71	*0.008*	-0.006	*0.013*	*-0.025, 0.013*
Pooled‡ - Dreuke, Rossert, Singh		**0.75**	***0.005***	**0.008**	***0.007***	***-0.006, 0.021***
DIALYSIS						
Besarab 1998	1233	0.63	*0.01*	-0.003	*0.01*	*-0.029, 0.024*

‡ Pooled estimates are based on a weighted average of study averages; weighting based on number of patients in each study overall; CI = confidence interval; SE = standard error

Update 2011

Table C.7: SF36 data used in mapping to EQ5D

Study		Lower target mean								*SE*								Mean difference (Higher - Lower)§								SE							
		GH	MH	PF	PR	SF	V	BP	ER	*GH*	*MH*	*PF*	*PR*	*SF*	*V*	*BP*	*ER*	GH	MH	PF	PR	SF	V	BP	ER	GH	MH	PF	PR	SF	V	BP	ER
NON-DIALYSIS																																	
Drueke 2006 (CREATE)	Baseline*	46.5	68.8	71.9	65.3	78.7	53.6	71.6	73.1	*1.2*	*1.2*	*1.6*	*2.3*	*1.7*	*1.3*	*1.6*	*2.5*																
	Change (1 yr)*†	-0.1	-2.1	-2.1	-5.5	-3.0	-0.6	-2.1	-4.3	*1.0*	*1.0*	*1.3*	*2.5*	*1.7*	*1.2*	*1.5*	*2.8*	4.2	4.8	5.6	8.1	4.8	4.5	1.9	4.7	1.4	1.4	1.6	3.1	1.7	1.4	1.9	3.1
	Score (BL+Change)	46.4	66.7	69.8	59.8	75.7	53.0	69.5	68.8									50.6	71.5	75.4	67.9	80.5	57.5	71.4	73.5								
Rossert 2006																		1.4	1.1	-2.5	9.8	0.7	5.0	6.2	4.7	3.0	2.5	3.9	6.2	3.6	3.2	4.3	5.7
	Mean score (end FU ~0.75 yrs)‡	52.9	74.0	68.6	58.7	78.6	53.0	62.4	71.8	*2.1*	*1.7*	*2.5*	*4.4*	*2.4*	*2.1*	*2.9*	*4.0*	54.3	75.1	66.1	68.5	79.3	58.0	68.6	76.5								
Singh 2006 (CHOIR)	Baseline‡	42.6	70.2	42.4	32.5	63.7	36.6	58.0	57.4	*0.8*	*0.8*	*1.0*	*1.5*	*1.1*	*0.8*	*1.0*	*1.6*																
	Change (end FU mean 1.3 yrs)‡	1.8	2.4	2.1	7.5	3.5	8.2	2.4	5.9	*0.7*	*0.7*	*0.9*	*1.6*	*1.1*	*0.8*	*1.0*	*1.8*	1.2	-0.7	1.1	-1.1	-2.2	1.8	-2.0	-5.1	7.3	0.7	1.6	1.1	1.6	3.3	1.4	2.0
	Score (BL+Change)	44.4	72.6	44.5	40.0	67.2	44.8	60.4	63.3									45.6	71.9	45.6	38.9	65.0	46.6	58.4	58.2								
DIALYSIS																																	
Besarab 1998	Baseline	42.9	69.1	38.5	33.2	65.1	44.1	58.2	58.7	*0.9*	*0.8*	*1.1*	*1.6*	*1.1*	*0.9*	*1.2*	*1.8*																
	Change (1 yr)	-2.5	-1.3	-4.1	3.6	-0.3	-2.5	-1.6	-0.1	*1.1*	*1.1*	*1.3*	*2.4*	*1.7*	*1.1*	*1.6*	*2.7*	0.2	-0.4	-0.1	-2.1	0.9	3.1	-0.7	3.2	1.6	1.5	2.0	3.5	2.4	1.8	2.3	4.0
	Score (BL+Change)	40.4	67.8	34.4	36.7	64.8	41.6	56.6	58.7									40.6	67.3	34.3	34.7	65.6	44.7	55.9	61.9								

SF 36 domains: GH = general health; MH = mental health; PF = physical function; PR = physical role; SF = social function; V = vitality; BP = bodily pain; ER = emotional role

*Standard errors not reported; estimated assuming standard deviation equal to Singh and dividing by the square root of the n number for the lower target arm of study.

†Change from baseline with lower target reported as from ANCOVA with baseline score as covariate.

‡Standard errors estimated by dividing reported standard deviations by the square root of the n number for the lower target arm of study.

§Mean difference and standard error as reported for clinical review in chapter 6.9

Source: Drueke[84,271], Rossert[139,277], Singh[291], Besarab[15,35]

Difference in quality of life (utility score) with higher target Hb >12 g/dL

In the model, a mean difference in utility score of 0.01 (SE 0.007) was used for the group with an Hb target of >12 g/dL compared to the group with a target <12 g/dL. The mean difference in EQ5D utility (higher target versus lower) was estimated by calculating the mean EQ5D utility difference for each study and then pooling these as a weighted average with weighting based on the total number of patients in each study. Results are summarised in Table C.6 above.

For each study, the mean difference for each SF36 domain with a higher Hb target (mean and SE as reported in the clinical review in Chapter 6.9; data also summarised in Table C.7 of this report) was added to the domain score for the lower Hb target to give mean domain scores for the higher Hb target group. These new mean scores where then used to map to an EQ5D utility estimate for the higher Hb target group. The mean difference in EQ5D utility was then calculated for each study as the difference between the estimate for the higher target group minus that for the lower target group.

The mean difference in EQ5D utility was incorporated into the probabilistic analysis using a normal distribution parameterised by the pooled mean difference and standard error.

Mapping SF36 mean domain scores to a EQ5D utility score

Summary data from the eight SF36 domains were mapped to a single EQ5D utility score using the algorithm published by Ara and Brazier[17]. Regression model 1 was used.

Update 2011

The SF36 input parameters used (described above) were varied probabilistically to reflect uncertainty in the estimates. The distributions used are summarised in Table C.8.

Table C.8: Probabilistic parameters in EQ5D estimation

Parameter	Distribution	Data used
Mean baseline score if change from baseline reported	Beta	Mean, SE
Mean change from baseline in lower Hb target arm	Normal	Mean, SE
Mean SF36 domain score with lower Hb target (in studies where change from baseline not used)	Beta	Mean, SE
Mean difference in mean score or mean change in score with higher Hb target	Normal	Mean, SE

10,000 simulations were run and the mean and standard error of the pooled EQ5D estimate for the lower Hb arm and the difference with the higher Hb arm were calculated based on the results.

C.2.3.6 Resource use and costs

ESA drug doses and costs

Dose and cost estimate with lower target Hb <12 g/dL:

In the model a mean epoetin dose of 1788 U/wk (SE 37) was used for the group with an Hb target of <12 g/dL based on pooled RCT data[84,114,176,251,252,271,277,291]. Using a unit cost of £5.09 per 1000 units epoetin alfa this is an annual cost of £473. More detail on the derivation of this estimate is given below.

Difference in dose and cost with higher target Hb >12 g/dL:

In the model a difference in epoetin dose of 8198 U/wk (SE 162) was used for the group with an Hb target of <12 g/dL based on pooled RCT data[84,114,176,251,252,271,277,291]. Using a unit cost of £5.09 per 1000 units epoetin alfa this is an additional annual cost of £2,170. More detail on the derivation of this estimate is given below.

This difference was applied in the higher target Hb >12 g/dL group for the differential treatment duration being modelled – three years in the basecase analysis (as described in Section C.2.1.4). The additional cost was added to the cost in the lower target group giving a total cost of £2,643. Following the differential treatment period (for the remainder of the lifetime of the cohort) the difference was no longer applied – this means that the total cost was the same as in the lower target group during this time.

Data and calculations:

Pooled dose estimated were calculated based on data available from relevant non-dialysis RCTs[84,114,176,251,252,271,277,291]. This is summarised in Table C.9 below. Note that Section 6.9 of the full guideline includes a summary of available dose data for all RCTs included in the clinical review for both non-dialysis and dialysis population including those not used in the model.

Table C.9: Dose and standard error

Study	Target	Dose/wk epoetin§	SE‡	Difference dose/wk Higher - Lower	SE†	Cost/year*	Difference cost/yr Higher - Lower
Drueke 2006 (CREATE)	Higher	4554	224	2373	294	£1,205	£628
	Lower	2182	189			£577	
Furuland 2003	Higher	6955	1268	4420	1391	£1,841	£1,170
	Lower	2535	574			£671	
Levin 2005	Higher	3106	296	2338	420	£822	£619
	Lower	768	298			£203	
Pfeffer 2009 (TREAT)††	Higher	11250	232	11000	232	£2,978	£2,911
	Lower	250	12			£66	
Rossert 2006	Higher	4352	545	3442	598	£1,152	£911
	Lower	910	247			£241	
Singh 2006 (CHOIR)	Higher	11125	284	4849	312	£2,945	£1,283
	Lower	6276	129			£1,661	
Pooled**	Higher			8196	162		£2,169
	Lower	1788	37			£473	

§Best available estimate of dose. Drueke = estimate based on mean dose in those receiving drug at various timepoints and % that received drug over study; Furuland = mean at end of study (U/kg/wk, 65kg); Levin = mean at end of study; Pfeffer = mean over study; Rossert = estimate based on median in those receiving drug and % that received drug; Singh = Mean over study (U/kg/wk, 65kg)
‡Dreuke, Furuland, Levin, Pfeffer SEs caluclated from SDs = SD/SQRT(n); Rossert, Singh SEs estimated as SDs not reported or calculatable = Furuland SD/SQRT(study lower arm n), Furuland SD used as a conservative estimate as it is the largest of the available standard deviations.
*Calculated based on an epoetin unit cost of £5.09 per 1000 units.
†SE difference calculated: SQRT(SElower^2+SEhigher^2).
††Doses converted from darbepoetin to epoetin using a ratio of 1:200.
**Pooled mean calculated as weighted average, with weighting based on study size. Mean and SE above reported based on 10,000 probabilistic simulations where Lower dose/week and difference dose/week for each studiy varied probabilsitically.

Source: Drueke[84,271], Furuland[114], Levin[176], Pfeffer[251,252], Rossert[277], Singh[291].

The average drug dose reported for each arm of the study was obtained. Different studies reported different measures of dose; the best available measure was used with mean preferred over median, estimates over the whole study preferred over estimates at the end of the study and units/kg/week from the study (assuming 65kg in calculations) preferred over units/week from the study.

Update 2011

All doses were converted to epoetin for comparison. Epoetin alfa and epoetin beta doses were assumed to be equivalent; darbepoetin dose was converted using a darbepoetin:epoetin ratio of 1:200. This is the adult conversion ratio currently stated in the UK summary of product characteristics for calculating initial dose[89]. It is noted that some studies have suggested the ratio should be higher[42] – this would increase the equivalent dose estimates for the darbepoetin study. The use of a 1:200 darbepoetin:epoetin dose ratio is therefore potentially favourable for the higher Hb target.

The cost of epoetin alfa is based on the British National Formulary list price of £5.09 per 1000 units[46]; it is noted that substantial discounts are however often available for ESAs in practice. Where data is pooled a weighted average is used based on trial patient numbers (so larger studies contribute more to the pooled estimate than smaller studies).

In the probabilistic analysis the mean dose in the lower target Hb arm and the mean difference (high - low) from each study were varied using gamma distributions parameterised using the mean and SEs as calculated above. When the standard error was small relative to the mean the software returned an error (due to a programming issue in Excel), a normal distribution was therefore used instead.

Other costs of managing anaemia in chronic kidney disease

It is appropriate to include other disease-related costs in a lifetime cost-effectiveness analysis where mortality is impacted. In these circumstances, even if these costs do not vary between groups per alive patient, the total costs vary because different numbers of people are alive at each time point when mortality is different.

Update 2011

Additional costs specific to anaemia management rather than CKD management were included. This was considered a reasonable interpretation of the NICE reference case given that the guideline is about anaemia management not CKD management.

It was assumed that all patients, whilst alive, will have additional anaemia management costs on top of their erythropoietin costs. This will include things such as additional healthcare visits to monitor Hb levels and adjust erythropoietin treatment and also potentially iv iron and blood transfusions. This was assumed to be constant and not to vary with Hb target. In GDG discussion it was noted that other costs could also be higher with a higher target but the assumption was considered a reasonable simplification. The assumption is therefore potentially favourable for the higher target.

Data was not identified to inform this input and a value of £1000 was used in the basecase analysis. Sensitivity analysis was done where this value was varied from £0 to £10,000.

C.2.4 Computations

The model was constructed in Microsoft Excel and was evaluated by cohort simulation.

Patients start in cycle 0 in the alive health state. Patients moved to the dead health state each 1 year cycle as defined by the annual mortality rate. Life years for the cohort are computed each cycle. A half-cycle correction is applied.

To calculate QALYs for each cycle, Q(t), the time spent (i.e. 1 year) in the alive state of the model was weighted by the utility value. QALYs were then discounted to reflect time preference (discount rate = r). QALYs during the first year were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle.

$$Total \quad discounted \quad QALYs = \sum_{t=1}^{i} \frac{Q(t)}{(1+r)^{t-1}}$$

Where: t = cycle number; i = maximum cycle number; Q(t) = QALYs in cycle t; r = discount rate

The costs per cycle, C(t), were calculate in the same way as QALYs apart from the time spent in the alive state was multiplied by annual cost of ESA therapy and other anaemia management costs. These were also discounted to reflect time preference (discount rate = r). Costs during the first year were not discounted. The total discounted costs were the sum of the discounted costs per cycle.

$$Total \quad discounted \quad costs = \sum_{t=1}^{i} \frac{C(t)}{(1+r)^{t-1}}$$

Where: t = cycle number; i = maximum cycle number; C(t) = Costs in cycle t; r = discount rate

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs\ (B) - Costs\ (A)}{QALYs\ (B) - QALYs\ (A)}$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X

- Cost-effective if: ICER < Threshold

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net benefit (NB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NB is used to identify the optimal strategy in the probabilistic analysis simulations.

Update 2011

$$Net\ Benefit\ (X) = QALYs\ (X) \times D - Costs\ (X)$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X; D = threshold

The probabilistic analysis was run for 10,000 simulations. Each simulation, total discounted costs and total discounted QALYs were calculated for each treatment option. The net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest net benefit), at a threshold of £20,000 and £30,000 per QALY gained.

The results of the probabilistic analysis were summarised in terms of mean discounted costs and QALYs with confidence intervals, where means were the average of the 10,000 simulated estimates and the 95% confidence intervals are the 2.5 and 97.5 percentiles. If appropriate, a cost-effectiveness ratio was calculated from the mean costs and QALYs. The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

C.2.5 Sensitivity analyses

C.2.5.1 Mortality rate sensitivity analyses

In the model, a baseline mortality rate is established for the lower target group and then the relative difference with the higher group is modelled by applying a hazard ratio. The baseline mortality rate applied for the lower target in the model is the pooled RCT rate for the first 3 years. After this life tables for England and Wales were used to model increasing mortality with age; these were adjusted to reflect the additional mortality in the CKD population compared with the general population (see Section C.2.3.4.)

The mortality rate in the TREAT study[251] was considerably higher than the other studies. This is likely to be because it is in an exclusively diabetic population. The higher the baseline mortality rate, the ess favourable the analysis is to the >12 g/dL group which has a hazard ratio of greater than 1 for mortality compared to the <12 g/dL group. Therefore two sensitivity analyses were run with lower baseline mortality rates (note: the hazard rate for the difference between groups remained the same).

- A sensitivity analysis was undertaken where the pooled RCT mortality rate was recalculated excluding the TREAT data (SA1). This reduced the baseline mortality rate over the first 3 years to ~3% per year.
- A second sensitivity analysis was run where the pooled RCT data was not used at all and the CKD-adjusted population life table rates were applied throughout the whole model duration (SA2). This lowered the baseline mortality rate over the first 3 years even further to ~2% per year.

In the clinical review the hazard ratio for mortality with the higher Hb group >12 g/dL was found to be non-significant and so there was some uncertainty as to whether the trend observed was real. Therefore a third, very conservative, sensitivity analysis was undertaken where both the baseline mortality rate (for the lower target Hb <12 g/dL group) was reduced (as per SA1 above) and the hazard ratio for mortality with the higher target Hb >12 g/dL group was set to 1 (that is no difference in mortality).

C.2.5.2 Treatment period sensitivity analyses

Update 2011

In the model, the treatment period in the basecase analysis was three years (differences in mortality, quality of life and ESA dose are applied during this time). After this both groups have the same mortality rate, quality of life and ESA dose. 3 years was selected as this was the longest mean follow up in the RCTs being used to inform the analysis.

A sensitivity analysis was undertaken where the treatment period was set to a lifetime (the pooled RCT mortality rate remains only applied for 3 years as increasing this would mean that the increasing mortality with age would be lost). This models what may be the real world case for patients, however extrapolates beyond the available data. A sensitivity analysis was also undertaken using a shorter treatment period of 1 year only (the pooled RCT mortality rate was also only applied for 1 year).

C.2.5.3 Quality of life sensitivity analyses

In the basecase constant utility over time is assumed. In reality utility is likely to decrease as CKD progresses and patients age. A sensitivity analysis was undertaken to incorporate an annual utility decline of 2%.

C.2.5.4 Cost of ESA sensitivity analyses

The BNF list price for epoetin alfa was used in the basecase. It was noted that substantial discounts are often available in practice and so a series of sensitivity analysis were undertaken where these costs were reduced in 10% increments up to 50%.

C.2.5.5 Other costs of managing anaemia sensitivity analyses

The other costs of managing anaemia were assumed to be £1000 in the basecase. A series of sensitivity analyses were undertaken where these annual costs were varied between £0 and £10,000.

C.2.5.6 CREATE study scenario analysis

Drug doses varied between studies with US studies generally using higher doses than European studies. The population and dosing of the CREATE study was considered by the GDG to be most

similar to a UK population and so a sensitivity analysis was undertaken where mortality, quality of life and dose inputs were based only on the CREATE study[84]. Inputs are summarised in Table C.10 below. Details of any necessary calculations are described in the preceding model input sections.

Table C.10: Sensitivity analysis inputs: CREATE study scenario analysis

Baseline inputs (when target <12 g/dL)			
Annual mortality rate	Years 1-3 Year 4+	0.023 (SE 0.005) Lifetables + CKD HR	CREATE study[84] ONS, NICE CG73 CKD[218,235]
Utility (quality of life)	0.82 (SE 0.008)		CREATE study – SF36 mapped to EQ5D[17,84,271]
Epoetin alfa dose	2182 U/wk (SE 189)		CREATE study[84,271]
Difference when target higher (>12 g/dL)			
Mortality	HR: 1.52 (CI: 0.87, 2.64)		CREATE study[84]
Utility (QoL)	Additional: 0.03 (SE 0.007)		CREATE study – SF36 mapped to EQ5D[84,271]
Epoetin alfa dose	Additional: 2373 U/wk (SE 294)		CREATE study[84,271]
Duration differences applied	3 years		Mean follow-up of CREATE study[84]

CI = 95% confidence interval; CKD = chronic kidney disease; Hb = haemoglobin; HR = hazard ratio; SE = standard error; U/wk = units per week

Update 2011

C.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation. In addition the model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of all the model calculations.

C.2.7 Interpreting results

This analysis replaced the analysis in the existing 2006 guideline on the basis that the GDG felt the approach taken (using cohort data) no longer be appropriate in light of new clinical data available in the 2011 update.

The aim was to help the GDG assess whether the trade-off of improved quality of life with higher Hb targets is offset by the increased risk of mortality – that is, is aiming for a target of Hb >12 g/dL associated with less QALYs than <12 g/dL. If not, are the increased QALYs worth the additional cost of achieving a higher Hb target.

It was not designed to inform what the exact target range should be. This was considered to be a matter of interpretation of the studies, which all use slightly different ranges, and have different baseline and achieved Hb levels, using expert clinical knowledge and experience.

C.3 Results

C.3.1 Basecase results (probabilistic analysis)

The basecase analysis found that a lower target Hb of <12 g/dL was associated with more QALYs and lower costs than a higher target Hb of >12 g/dL. This means that a lower target Hb of <12 g/dL is the 'dominant' option. A higher target Hb of >12 g/dL was cost-effective in 0% of the simulations of the probabilistic analysis suggesting low uncertainty about this conclusion within this analysis. Results are summarised in Table C.11. The distribution of the simulations from the probabilistic analysis are shown in Figure C.1.

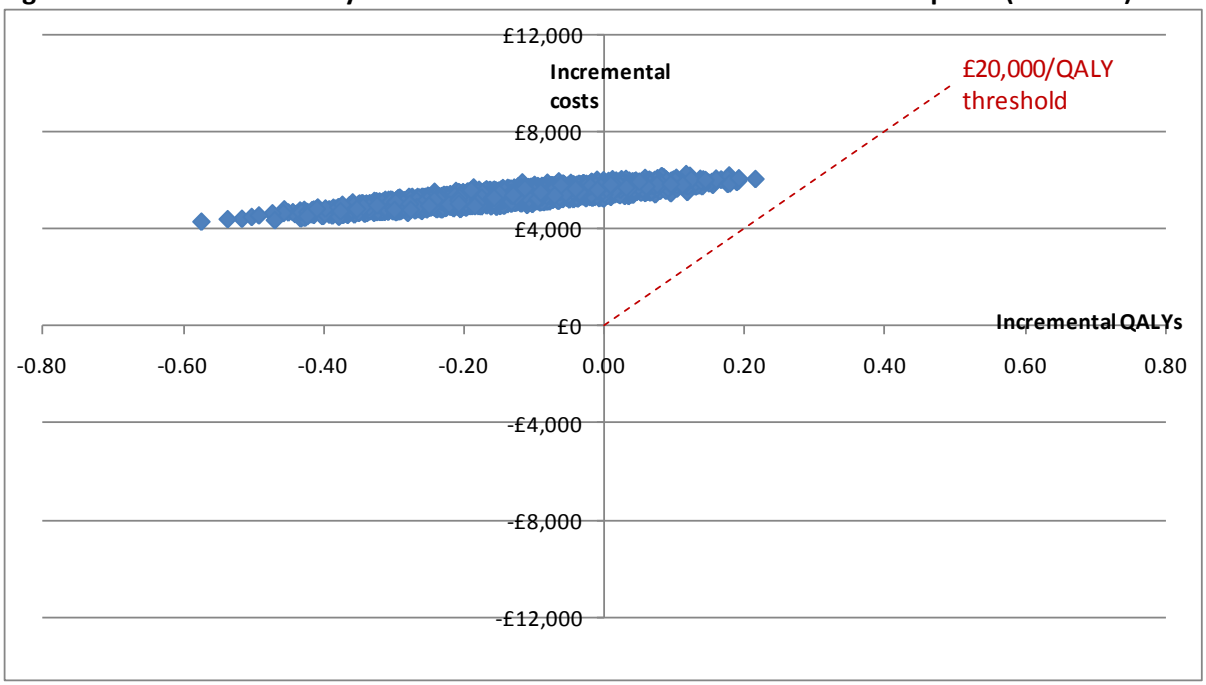
Table C.11: Basecase results (probabilistic analysis)

Mean costs and QALYs per person (base case - probabilistic analysis)			
Resource item:	**Target <12**	**Target >12**	**Difference >12 - <12**
ESA (epoetin alfa)	£7,176	£12,911	£5,735
Other anaemia management costs	£15,160	£14,893	-£267
Total cost	£22,336	£27,804	£5,468
Total cost (discounted)	**£16,311**	**£21,708**	**£5,397** ***(CI: £4,884, £5,874)***
Deaths at end year 3 (per 1000 people)	176	192	16
Life years	15.16	14.89	-0.27
QALYs	11.40	11.22	-0.18
QALYs (discounted)	**8.33**	**8.21**	**-0.12** ***(CI: -0.32, 0.06)***
Incremental cost-effectiveness ratio (ICER)			**<12 dominant**
% simulations >12 cost-effective (£20K/QALY)			0%
% simulations >12 cost-effective (£30K/QALY)			0%

QALYs = quality-adjusted life year

Update 2011

Figure C.1: Probabilistic analysis simulation results on the cost-effectiveness plane (basecase)



Incremental costs and QALYs for higher target (>12 g/dL) compared with lower target (<12 g/dL)

C.3.2 Sensitivity analyses

Uncertainty around model inputs or assumptions was also explored through a series of sensitivity analyses. For each sensitivity analysis an input or selection of inputs were changed and the probabilistic analysis was rerun. A summary of these analyses and the results are presented in Table C.12. The rationale for the selected sensitivity analyses are described in the methods section C.2.5 above.

Conclusions were not sensitive to any of the sensitivity analyses undertaken.

Table C.12: Sensitivity analyses

Mean costs and QALYs per person (probabilistic analysis)				
	Mean cost difference (>12 - <12)	Mean QALY difference (>12 - <12)	Incremental cost effectiveness ratio (ICER)	% simulations >12 cost-effective (£20K/QALY)
Basecase analysis				
Basecase	£5,397	-0.12	<12 dominant	0%
Sensitivity analysis: baseline mortality rate in target <12 group (basecase = 7% years 1-3)				
SA1: mortality rate years 1-3 reduced to 3%	£5,849	-0.05	<12 dominant	0%
SA2: mortality rate years 1-3 reduced to 2%	£6,046	-0.02	<12 dominant	0%
Sensitivity analysis: treatment period duration (basecase = 3 years)				
SA3: treatment period 1 year	£1,984	-0.05	<12 dominant	0%
SA4: treatment period lifetime	£22,305	-0.27	<12 dominant	0%
Sensitivity analysis: baseline utility assumption (basecase = constant utility)				
SA5: declining utility over time	£5,395	-0.10	<12 dominant	0%
Sensitivity analysis: no mortality difference				

Mean costs and QALYs per person (probabilistic analysis)				
SA8: no mortality difference	£5,730	0.02	£286,542	0%
Sensitivity analysis: ESA cost reduction (basecase = 0%)				
SA9: 10% reduction in ESA cost	£4,842	-0.12	<12 dominant	0%
SA10: 20% reduction in ESA cost	£4,277	-0.12	<12 dominant	0%
SA11: 30% reduction in ESA cost	£3,719	-0.12	<12 dominant	0%
SA12: 40% reduction in ESA cost	£3,162	-0.12	<12 dominant	0%
SA13: 50% reduction in ESA cost	£2,605	-0.12	<12 dominant	0%
Sensitivity analysis: other costs of managing anaemia (basecase = £1000)				
SA14: cost set to £0	£5,585	-0.12	<12 dominant	0%
SA15: cost set to £500	£5,492	-0.12	<12 dominant	0%
SA16: cost set to £5000	£4,635	-0.12	<12 dominant	0%
SA17: cost set to £10,000	£3,689	-0.12	<12 dominant	0%
Sensitivity analysis: CREATE study scenario				
SA18: CREATE mortality, utility and dose data	£1,047	-0.26	<12 dominant	7%

QALYs = quality-adjusted life years

C.4 Discussion

C.4.1 Summary of results

In the 2006 guideline a cost-effectiveness model looking at the optimal Hb (Hb) target was undertaken. However, the approach taken was judged by the GDG to no longer be appropriate in light of new clinical data available in the 2011 update. On this basis this analysis was removed from the guideline in the 2011 update.

A new cost-effectiveness analysis based on the RCT data identified in the clinical review was developed. This compared treating to a target Hb of <12 g/dl and >12 g/dl. Costs and quality-adjusted life years (QALYs) were considered from a NHS and personal social services perspective. In the basecase analysis a 3-year treatment period was considered with the impact of this extrapolated to a lifetime perspective.

The model incorporated differences between the Hb targets in terms of mortality, quality of life and ESA dose based on the RCTs identified in the clinical review of the literature.

Results found that treating to a higher target of >12 g/dL was not cost effective when compared to treating to a target <12 g/dL. The lower target 'dominated' the higher target with lower costs and improved health outcomes (higher QALYs). This conclusion was robust to various sensitivity analyses.

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C.4.2 Limitations & interpretation

The analysis reflects the clinical studies that go into it and therefore issues concerning the interpretation of the clinical studies also apply to the interpretation of the economic analysis based on these studies. A decision was made for the guideline to pool clinical studies to aid decision making but it should be noted that the studies used to inform the model all compare slightly different ranges. The lower targets were in the range 9-12 g/dL and the higher targets were in the range 12-16 g/dL. Studies also varied in their baseline Hb levels, achieved Hb levels and the ESA doses used to achieve Hb levels. There was also variation in complication rates in the studies, such as mortality. This information is all summarised in Section 6.9 of the full guideline. Sensitivity analysis was used to explore these issues where possible.

The analysis suggested that aiming for a higher target would not improve overall health outcomes, taking into account mortality risk and quality of life improvement on a population level. As mentioned above the lower targets were in the range 9-12 g/dL. The mean achieved Hb in the lower arms of the studies ranged from 10.6 to 11.9 g/dL, with an average across studies of 11.0 g/dL. The cost-effectiveness analysis was not designed to inform what the exact target range should be. This was considered to be a matter of interpretation of the studies, which all use slightly different ranges, and have different baseline and achieved Hb levels, using expert clinical knowledge and experience.

Not all studies reported mortality, SF36 and dose data – all the available data was used for model inputs but this meant that different numbers of studies informed each input. An alternative would have been to only use studies that reported data for these key inputs. However, this would mean restricting to only three studies (Drueke, CREATE[84,271]; Rossert[139,277]; Singh, CHOIR[291]). Comparing the pooled estimates based only on these studies would result in less favourable outcomes in the higher group in terms of mortality (HR 1.41; 95% CI: 1.01, 1.97 vs HR: 1.10; CI: 0.97, 1.24) and a smaller difference in epoetin dose (~4000 vs ~8000). This is considered unlikely to impact conclusions given that the sensitivity analysis using only the CREATE data with an even smaller difference in dose did not find the higher target to be cost effective.

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As described in the model inputs section, data was not identified to inform the input for other costs of anaemia management and so an estimate was used. However, this was varied through a wide range in sensitivity analysis and did not impact conclusions.

The model assumed a dose conversion ratio for darbepoietin:epoetin of 1:200 as described in summary of product characteristics for initial dose[89]. It is noted that some studies have suggested the ratio should be higher[42] – this would increase the equivalent dose estimates for the darbepoetin study. Using a dose ratio of 1:200 therefore potentially biases the model in favour of treating to higher Hb targets. This would therefore not impact conclusions from this analysis.

The model structure was kept simple and did not incorporate CKD progression over time. This was largely a pragmatic decision to keep the model manageable within the timeframe of the rapid update but was considered a reasonable simplification for this analysis. Increasing mortality over time was incorporated and a sensitivity analysis looked at adding in declining utility over time.

As described in the methods section (C.2.1.3) the model did not include some potential cardiovascular health effects that were identified by the systematic clinical review. However given the results of the analysis this was not considered a serious limitation as the incorporation of stroke and hypertension would further favour the lower target and would most likely make the results even more unfavourable for the higher target group in terms of both health outcomes and costs.

C.4.3 Generalisability to other populations/settings

Whilst it is difficult to extrapolate from a non-dialysis population to a dialysis population, the available dialysis evidence did not suggest an overall improvement in quality of life over a dialysis population (as based on difference in EQ5D utility score where SF36 data was available be mapped – see Section C.2.3.5 for details), suggests a similar difference in mortality to non-dialysis patients and suggests a larger difference in ESA dose than in non-dialysis patients. It was therefore considered unlikely that conclusions would vary in dialysis patients.

Appendix D: Health economic calculation: route of administration of ESAs

D.1 Background

D.1.1 Aim

To perform a cost-minimisation analysis based on equivalent effectiveness between intravenous (i.v.) and subcutaneous (s.c.) epoetin. ESAs are made available to NHS trusts through a system of tendering for local supply contracts. Costs therefore vary between locations and over time, and this should be borne in mind in applying the findings of this analysis.

D.1.2 Methods

A cost-minimisation model was constructed from the perspective of the NHS. Cost analysis included epoetin, iron, administration and potential wastage. A meta-analysis of randomised controlled trials comparing i.v. and s.c. doses required to maintain target haematocrit or haemoglobin levels was performed to derive the average dose difference of i.v. and s.c. Other resource use was estimated by expert opinion and the trials used in the meta-analysis.

Incremental cost = (C_1-C_2)

Where:

C_1 = Estimated cost of i.v. epoetin therapy

C_2 = Estimated cost of s.c. epoetin therapy

D.2 Data sources

D.2.1 Costs

Subcutaneous epoetin

Table D.1: Unit cost of subcutaneous epoetin beta[BNF49]

Subcutaneous epoetin beta	Units	Price (£)
	10,000	77.93
	20,000	155.87
	60,000	467.61

The average cost per unit of s.c. epoetin used in cost calculation was £0.007793.

D.2.2 Other costs

Iron

Only one of the three studies included in the meta-analysis reported the average total amounts of iron administered per patient during all phases[141]. No significant differences in average total amount of parenteral iron dextran were found between the i.v. and s.c. groups within the study (1,683 +

1,280 vs 1,765 + 1,342, p=0.65). Expert opinion indicated there would be an equivalent iron strategy in clinical practice regardless of the route of administration of epoetin. Therefore the cost difference of iron with i.v. or s.c. epoetin was assumed to be negligible.

Administration

Expert opinion suggested the same health professional would administer i.v. or s.c. epoetin, the healthcare setting would not need to be changed and wastage would be similar with either i.v. or s.c. administration. Two studies reported there was no significant difference in mean dialysis time[211,329]. Therefore the cost difference of administration with i.v. or s.c. epoetin was assumed to be negligible.

Dose differences

Three randomised controlled trials[153,211,329] were used to derive the mean difference and 95% confidence interval of i.v. and s.c. dose in a fixed meta-analysis. Only studies receiving a 1++ or 1+ in the NICE levels of evidence hierarchy in the clinical effectiveness review and with n >7 were included. The average dose difference of patients treated with s.c. vs i.v. epoetin was 41.61 IU/kg/wk (95% CI 22.55 – 60.66) (p=0.000). Drug cost differences were calculated using the median unit cost in the base-case and the 95% confidence interval to calculate the range of cost savings per week and per year.

D.3 Results

Based on a unit cost of £0.007793 per unit of epoetin and a 65 + 10 kg patient, the average cost savings per patient with s.c. epoetin vs i.v. epoetin was £21.08 + £13.93 per week. The average yearly cost savings with s.c. epoetin was £1,100 + £727 per patient.

D.3.1 Discussion

There are potential drug cost savings when using s.c. epoetin instead of i.v. epoetin to maintain target haematocrit or haemoglobin levels. These savings occur in supervised healthcare settings; however, self-administration in the patient's home with s.c. epoetin is an alternative anaemia management strategy. Further evidence including delivery costs, gaining health professional time and treatment-related outcomes during self-management would be needed to assess different service provision strategies.

Darbepoetin is an alternative drug used in the management of anaemia in chronic kidney disease. Darbepoetin can be used by both the s.c. and i.v. routes of administration. However, because of the lack of data it was not included. When further data is available, this analysis could include the cost effectiveness of darbepoetin s.c. vs i.v. and darbepoetin vs epoetin.

A potential consideration of s.c. vs i.v. administration of epoetin that may vary on an individual level is patient preference due to potential pain at the injection site. One of the included randomised trials measured the discomfort during treatment[141]. Of 96 patients who had received both routes of administration, 74% preferred i.v. and 26% had no preference or preferred s.c. Eight of 24 (33%) at the start of treatment with s.c. epoetin had pain at the injection site, however, only one of these patients had pain at the end of study (4 months)[329]. 31% of patients reported pain during placebo subcutaneous injection during the run-in period and only 18% reported pain during epoetin subcutaneous injection[211].

D.3.2 Conclusion

The subcutaneous route of administration of epoetin vs intravenous route results in cost savings of approximately £1,100 + £727 per patient per year.

Appendix E: Glossary

E.1 Guide to assessment scales

Health related quality of life (HRQL)	A combination of a person's physical, mental and social well-being; not merely the absence of disease.
Renal Quality of Life Profile	A quality of life scale developed and validated specifically for people with renal disease.
Short Form 36 (SF-36)	The SF-36 assesses functioning and well-being in chronic disease. Thirty-six items in eight domains are included, which cover functional status, well- being, and overall evaluation of health.
Sickness Impact Profile (SIP)	SIP is a general quality of life scale. It consists of 136 items, which measure 12 distinct domains of quality of life. Participants identify those statements, which describe their experience. Higher scores represent greater dysfunction.
Visual Analogue Scale (VAS)	A non-graduated 100 mm vertical line ranging from '0=no pain' to '100=pain as bad as could be'. Patients indicate pain sensation by scoring on the vertical line with a horizontal dash.
Verbal Descriptive Scale (VDS)	Divided into the following six categories: no pain, hardly any pain, mild pain, moderate pain, severe pain, unbearable pain. Patients tick the appropriate category on a questionnaire

E.2 Stages of chronic kidney disease

Stage	GFR (ml/min/1.73m2)	Description
1	>90	Normal or increased GFR, with other evidence of kidney damage
2	60–89	Slight decrease in GFR, with other evidence of kidney damage
3	30–59	Moderate decrease in GFR, with or without other evidence of kidney damage
4	15–29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure

E.3 Abbreviations and Definitions of terms

ACKD

Anaemia of chronic kidney disease

bd

Twice daily

CAPD

Continuous ambulatory peritoneal dialysis

CCr

Creatinine clearance

CI

Confidence interval

CKD

Chronic kidney disease

DM

Diabetes mellitus

DS

Diagnostic study

eGFR

Estimated glomerular filtration rate

EPO

Erythropoietin

ESA

Erythropoiesis stimulating agent

FID

Functional iron deficiency

GI

Gastrointestinal

GFR

Glomerular filtration rate

GPP

Good practice point

Hb

Haemoglobin

Hct

Haematocrit

HD

Haemodialysis

HR

Hazard ratio

HRC

Hypochromic red cells

IP

Intraperitoneal

i.v.

Intravenously

LVH

Left ventricular hypertrophy

MCV

Mean corpuscular volume

MI

Myocardial infarction

NHS

National Health Service

NICE

National Institute for Health and Clinical Excellence

NSF

National service framework

PD

Peritoneal dialysis

PRCA

Pure red cell aplasia

PTX

Parathyroidectomy

RCT

Randomised controlled trial

RES

Reticuloendothelial system

ROC

Receiver-operator curve

RR

Relative risk

s.c.

Subcutaneous

s.c.r

Serum creatinine

tds

Three times daily

TSAT

Transferrin saturation

WMD

Weighted mean difference

ZPP

(Erythrocyte) zinc protoporphyrin

E.4 Definition of terms

Absolute iron deficiency

Depletion in iron body stores.

Adverse events

A harmful, and usually relatively rare, event arising from treatment.

Algorithm (in guidelines)

A flow chart of the clinical decision pathway described in the guideline.

Allocation concealment

The process used to prevent advance knowledge of group assignment in an RCT, and potential bias that may result.

Anaemia coordinator

A healthcare professional who is a central point of contact for patients with ACKD – see recommendation R28 in section 6.5.3 for details.

Audit

See 'clinical audit'.

Before and after study

See 'observational study'.

Bias

The effect that the results of a study are not an accurate reflection of any trends in the wider population. This may result from flaws in the design of a study or in the analysis of results.

Blinding (masking)

A feature of study design to keep the participants, researchers and outcome assessors unaware of the interventions that have been allocated.

Carer (caregiver)

Someone other than a health professional who is involved in caring for a person with a medical condition, such as a relative or spouse.

Case-control study

Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Class of recommendation

All recommendations are assigned a class (A, B, C, D, A(DS), B(DS), C(DS), or D(GPP)) according to the level of evidence the recommendation is based on (see 'level of evidence').

Clinical audit

A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.

Clinician

In this guideline, the term clinician means any healthcare professional.

Cochrane review

A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.

Cohort study

A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Concordance

Concordance is a concept reflecting agreement between clinicians and patient on the best course of managing a disease, and adherence to that course until alternatives are agreed on and adopted.

Confidence interval

A range of values which contains the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.

Cost-effectiveness analysis

An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness model

An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost-utility analysis

A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life years (QALYs).

Cycling

See 'haemoglobin cycling'.

Diagnostic study

Any research study aimed at evaluating the utility of a diagnostic procedure.

Erythropoiesis

Red blood cell production.

Evidence-based healthcare

The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.

Follow up

An attempt to measure the outcomes of an intervention after the intervention has ended.

Functional iron deficiency

Inadequate iron mobilisation, which is incapable of meeting demands of erythropoiesis.

Generalisability

The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

Gold standard

See 'reference standard'**.**

Good Practice Point

Recommended good practice based on the clinical experience of the Guideline Development Group.

Grade of recommendation

See 'class of recommendation'.

Guideline development group (GDG)

An independent group set up on behalf of NICE to develop a guideline. They include healthcare professionals and patient and carer representatives.

Haematocrit

Relative volume of blood occupied by red blood cells.

Haemoglobin cycling

Fluctuation of haemoglobin levels which may vary from patient to patient.

Hazard ratio

A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates.

Heterogeneity

In systematic reviews, heterogeneity refers to variability or differences between studies in estimates of effect.

Homogeneity

In a systematic review, homogeneity means there are no or minor variations in the results between individual studies included in a systematic review.

Inclusion criteria

Explicit criteria used to decide which studies should be considered as potential sources of evidence.

Incremental cost

The cost of one alternative less the cost of another.

Incremental cost-effectiveness ratio (ICER)

The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.

Intention-to-treat analysis (ITT analysis)

An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Level of evidence

A code (eg 1++, 1+,2++) linked to an individual study, indicating where it fits into the NICE hierarchy of evidence and how well it has adhered to recognised research principles.

Meta-analysis

A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.

Methodological limitations

Features of the design or reporting of a clinical study, which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.

Multivariate model

A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

National Collaborating Centre for Chronic Conditions (NCC-CC)

A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the NICE Patient and Public Involvement Programme, the Royal College of General

Practitioners, the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians' Patient Involvement Unit, the Royal College of Surgeons of England, and the Royal Pharmaceutical Society of Great Britain. Set up in 2001 to undertake commissions from NICE to develop clinical guidelines for the NHS.

National Health Service

This guideline is written for the NHS in England and Wales.

National Institute for Health and Clinical Excellence

NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

Negative predictive value

The proportion of people with a negative test result who do not have the disease.

Observational study

Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.

Odds ratio

A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

Outcome

Measure of the possible results that may stem from exposure to prevention or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints.

p-values

The probability that an observed difference could have occurred by chance. A p-value of less than 0.05 is conventionally considered to be 'statistically significant'.

Placebo

An inactive and physically indistinguishable substitute for a medication or procedure, used as a comparator in controlled clinical trials.

Positive predictive value (PPV)

The proportion of people with a positive test result who actually have the disease.

Pure red cell aplasia

Transitory arrest of erythropoiesis.

Quality of life

Refers to the level of comfort, enjoyment, and ability to pursue daily activities.

Quality-adjusted life year (QALY)

A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1

corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.

Randomisation

Allocation of participants in a study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to reduce sources of bias.

Randomised controlled trial

A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.

Reference standard (or gold standard)

An agreed desirable standard, for example a diagnostic test or treatment, against which other interventions can be compared.

Relative risk

An estimate for the number of times more likely or less likely an event is to happen in one group of people compared with another, based on the incidence of the event in the intervention arm of a study, divided by the incidence in the control arm.

Sample size

The number of participants included in a trial or intervention group.

Sensitivity (of a test)

The proportion of people classified as positive by the gold standard, who are correctly identified by the study test.

Sensitivity analysis

A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.

Single blind study

A study where the investigator is aware of the treatment or intervention the participant is being given, but the participant is unaware.

Specialist

A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.

Specificity (of a test)

The proportion of people classified as negative by the gold standard, who are correctly identified by the study test.

Stakeholder

Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.

Statistical power

In clinical trials, the probability of correctly detecting an underlying difference of a pre-specified size due to the intervention or treatment under consideration. Power is determined by the study design, and in particular, the sample size. Larger sample sizes increase the chance of small effects being correctly detected as statistically significant, though they may not be clinically significant.

Statistical significance

A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).

Systematic review

Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Washout period

The stage in a crossover trial when one treatment is withdrawn before the second treatment is given.

Withdrawal

When a trial participant discontinues the assigned intervention before completion of the study.

Appendix F: Declarations of interest [2011]

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required actions.

Dr David Halpin

GDG meeting	Declaration of Interests
Chair recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Dr Penny Ackland

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Dr Samir Agrawal

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Ms Carol Anderson

GDG meeting	Declaration of Interests
GDG recruitment	Personal pecuniary interest: Current member of Anaemia Nurse Specialist Association (ANSA). Previously on Executive Committee and previously Treasurer of ANSA. Non-paid. Non-personal pecuniary interest:

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GDG meeting	Declaration of Interests
	Participating in FIND-CKD study FER-CKD-01 – Vifor Other: Filmed by Virgo Health on process of switching patients onto Mircera Jan 2010 - Roche
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Miranda Dodwell

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

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Bob Dunn

GDG meeting	Declaration of Interests
GDG recruitment	Personal pecuniary interest: Member of the Dept of Health Renal advisory group. Serving as a patient advocate, living donor and carer. All renal matters are discussed by this group in their advisory role to the Dept of Health. Non-personal pecuniary interest: I am employed by the National Kidney Federation who receives sponsorship and donations from the renal pharma and equipment companies. The NFK has clearly defined written statements of policy covering their relationship with these companies.
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Dr Jonathan Evans

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting	No change to declarations

GDG meeting	Declaration of Interests
(09 June 2010)	
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Ms Karen Jenkins

GDG meeting	Declaration of Interests
GDG recruitment	Personal pecuniary interest: - CKD Consultant - European Dialysis and transplant nurses association (EDTNA/ERCA) - End of Life Care in CKD - NHS Kidney Care End of Life Board for Advanced Kidney Disease - Member of CKD Forum - British Renal Society - Founder member - Anaemia Nurse Specialist Association Other: - Guest Speaker at Annual BRS Conference 2009 honorarium received - Vifor Pharmaceuticals - Anaemia Advisory Board April 2009 - honorarium received - Roche Products Ltd
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Dr Mick Kumwenda

GDG meeting	Declaration of Interests
GDG recruitment	Personal pecuniary interest: Sponsorship to attend: 1- Renal Association - Liverpool 2009. Abbot UK Ltd 2 - American Society of Nephrology - San Diego 2009 - Orthobiotec 3 - European Cardiology Society - Barcelona 2009 - Pfitzer Dahchi Sawkyo Personal non-pecuniary interest: - Sharp Study (multicentre) - Marck Shering Plough - Aurora Study (multicentre) - Astrazeneca
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Update 2011

Update 2011

Professor Alison MacLeod

GDG meeting	Declaration of Interests
GDG recruitment	Personal pecuniary interest: - Member Executive - European Renal Beat Practice (ERBP) - Member Executive - Kidney Disease Improving Global Outcomes (KDIGO)
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Dr Shelagh O'Riordan

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Professor Paul Roderick

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Dr Paul Stevens

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Update 2011

Dr Stephen Thomas

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Dr Eric Will

GDG meeting	Declaration of Interests
GDG recruitment	None
First GDG meeting (09 June 2010)	No change to declarations
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Declarations of interests of the NCGC members

GDG meeting	Declaration of Interests of NCGC members
First GDG meeting (09 June 2010)	None
Second GDG Meeting (18 August 2010)	No change to declarations
Third GDG Meeting (12 November 2010)	No change to declarations

Appendix G: Review protocols [2011]

G.1 Review protocol for the diagnostic role of Hb levels

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Objectives	This review will examine Hb/Hct level as an independent predictor of adverse outcomes. Where reported, the interaction between age, gender, ethnicity and Hb/Hct levels on the adverse outcomes will be examined. This review, in conjunction with the findings of the optimal Hb level review will inform at which Hb/Hct level treatment could commence and determine the upper threshold at which further correction may be unnecessary or harmful.
Criteria	Population- Patients [adults and children] with chronic kidney disease not undergoing treatment Intervention(s): Levels of Hb/Hct; Interactions with age, gender, ethnicity Comparator(s): Reference level of Hb/Hct Outcome (s): All-cause mortality LVH MI Stroke Increased hospitalisation Progression of CKD QoL- overall score
Search Strategy	See appendix A.
Review Strategy	Study design: Cohort studies that have undertaken multivariable regression analysis adjusting for confounding factors. Prospective cohorts will be examined and where there are areas of limited evidence retrospective cohorts may be considered. Confounding factors: Age, gender, comorbidity, underlying diseases, infection, comorbidities, intercurrent illness, stage of CKD , iron status, smoking status [not considered as a confounder for the outcome: progression of CKD] If patients received treatment, the intervention status should be taken into account in the multivariable analysis. Taking into consideration the advice on prognostic reviews in the NICE guidelines manual, meta-analysis or GRADE will not be undertaken.

Update 2011

G.2 Review protocol for the optimal Hb levels

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Objectives	To review studies which examine to what Hb levels patients should be treated to and not what interventions are used, i.e. we are not looking at efficacy of individual interventions. The finding of this review will be interpreted in conjunction with results from the diagnostic role of Hb levels review.
Criteria	Population- Patients [Adults and children] with anaemia in chronic kidney disease Patients- non-dialysis and dialysis (peritoneal and haemodialysis)

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
	The intervention and comparator are the different Hb target levels. In relation to the drugs: Interventions: ESA epoetin-alpha epoetin-beta darbepoetin-alfa Mircera Comparators: placebo no treatment standard treatment ESA Concomitant treatment(s) may include iron supplementation and/or blood transfusions Outcomes: All cause mortality CV mortality Quality of life- overall score Progression of CKD (non-dialysis patients)/Access thrombosis (haemodialysis patients) Reduction in transfusion requirement Hb variability Stroke LVMI/LVH MI Hypertension
Search Strategy	See appendix A
Review Strategy	Study design: RCTs N≥100 (no minimum number of participants for studies investigating children) Studies which consider two target Hb ranges (except in children where comparison of drug and placebo will be included) Where appropriate, meta-analysis will be undertaken. Considering non-dialysis and dialysis patients separately. If looking at Hb variability outcome, considering class effect. Sensitivity analysis will be carried out based on methodological quality if significant heterogeneity exists. Overall assessment of the quality (for each outcome) will be undertaken using GRADE.

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G.3 Health economics update literature review protocol

Health economics literature review protocol	
Objectives	The aim is to identify economic studies relevant to the review questions for the 2011 update set out above (Appendix 2A and 2B).

Health economics literature review protocol	
Criteria	Populations, interventions and comparators as specified in the review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search Strategy	See appendix A
Review Strategy	Study assessment: NICE economic evaluation checklistg Inclusion/exclusion criteria If a study is rated as both 'Directly applicable' and 'Minor limitations' (by economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile (see Training session on the economic profile). If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline. Also exclude: unpublished reports abstract-only studies letters editorials reviews of economic evaluationsh foreign language articles Where there is discretion The health economist should be guided by the following hierarchies. Setting: UK NHS OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) Non-OECD settings (always be 'Not applicable') Economic study type: Cost-utility analysis Other type of full economic evaluation (cost-benefit analysis or cost-effectiveness analysis) Comparative cost analyses Cost of illness studies (always be 'Not applicable') Year of analysis:

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[g] Note that a quality assessment for cohort regression cost analyses were presented in the guideline on the same basis as for the clinical cohort regression analyses for consistency.

[h] Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Update 2011

Health economics literature review protocol	
	The more recent the study, the more applicable it is Quality of effectiveness data used in the economic analysis: The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

Appendix H: EVIDENCE TABLES

H.1 EVIDENCE TABLES [2006]

H.1.1 Section 4: Diagnostic evaluation and assessment of anaemia

PROG1: In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of (a) age (b) gender (c) ethnicity?

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Jones M, Schenkel B, Just J. Epoetin alfa's effect on left ventricular hypertrophy and subsequent mortality. *International Journal of Cardiology* 2005;**100**:253-65.
Study type	Meta analysis of before and after studies
Evidence level	3-
Study objective	(i) To examine the association between improving anaemia using Epoetin alpha in patients with CKD and

<table>
<tr><td></td><td>congestive heart failure and improvement in left ventricular hypertrophy

(ii) To examine the association between LVH and mortality in patients with CKD and congestive heart failure- not reported here as not answering the clinical question</td></tr>
<tr><td>Number of patients</td><td>Effects of Epoetin alpha on anaemia and LV function - Meta analysis of 26 studies consisting of 28 Epoetin alpha-treated cohorts

Effects of Epoetin alpha on anaemia and LV function - sample sizes (number of cohorts) for each clinical parameter in the 26 studies
<table>
<tr><th></th><th>Hb</th><th>Hct</th><th>LVM</th><th>LVMi</th><th>EF</th><th>LVEDV</th><th>LVESV</th></tr>
<tr><td>Sample size (no. of cohorts)</td><td>407 (22)</td><td>344 (19)</td><td>194 (10)</td><td>224 (13)</td><td>368 (19)</td><td>121 (6)</td><td>84 (4)</td></tr>
</table></td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria for studies used in the meta analysis for Epoetin alpha and LV function
➢ Epoetin alpha in N≥10 patients per study group
➢ Reported on ≥1 of the following parameters: Hb, Hct, LVM, LVMi, EF, LVEDV and LVESV

➢ Studies which met inclusion criteria were included in the analysis if they reported findings in a manner enabling comparison to other studies

The 4 components of the data analyses were:
➢ Simple combined estimates of findings across the studies
➢ Analysis of potential publication bias
➢ Analysis of between-study variability in all clinical outcomes
➢ Analysis of the sources of variability in finding between the studies</td></tr>
</table>

Baseline demographic and clinical parameters for all patient cohorts in MA of Epoetin alpha-induced changes in anaemia and LV function

	Mean (95% CI)	No. of cohorts
Age (years)	47 (40,53)	27
% female	48 (42,55)	25
Creatinine (µmol/l)	792 (596,989)	4
Creatinine clearance (ml/min)	13 (10,16)	1
Systolic BP (mmHg)	142 (136,147)	20
Diastolic BP (mmHg)	81 (78,84)	19
Weight (kg)	59 (54,64)	11
Target Hb (g/dl)	11	13
Target Hct (%)	31	14
Duration of disease (years)	13	19

Baseline clinical parameters in MA of Epoetin alpha-induced changes in anaemia and LV function

	Mean (CIL)	Homogeneity (P value)*
Hb (g/dl)	7.67 (7.23,8.10)	<0.001

	Hct (%)	21.68 (20.79,22.57)	<0.001
	LVM (g)	289.03 (246.00,332.06)	<0.001
	LVMi (g/m^2)	179.95 (157.32,202.58)	<0.001
	EF (%)	61.60 (54.69,68.50)	<0.001
	LVEDV (ml)	143.24 (133.08,153.40)	0.008
	LVESV (ml)	54.32 (42.66,65.99)	<0.001
	CIL = confidence interval limit *Cochrane test of homogeneity, <0.05 indicates significant between-study variation		
Intervention	Epoetin alpha to target Hb ~11 g/dl and Hct 30%		
Comparison	N/A- observational studies		
Length of follow-up	N/A		
Outcome measures	➢ LV function- left ventricular mass (LVM), left ventricular mass index (LVMi), ejection fraction (EF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV)		
Effect size	Epoetin alpha, anaemia and LVH ➢ These studies were of the "pre-post" design (i.e. before and after studies) Estimates of changes in anaemia with Epoetin alpha Tx and LVH ➢ Mean increase in Hb and Hct (**heterogeneous** findings) ➢ Decrease in LVM was observes in the 10 studies that reported this outcome (**heterogeneous** findings) ➢ LVMi (standardised for body surface area) decreased (**heterogeneous** findings) ➢ LVEDV and LVESV decreased (**homogenous** findings)		

	<table><tr><th></th><th>Mean change (95% CI)</th><th>Homogeneity P value*</th><th>Bias P value</th></tr><tr><td>Hb (g/dl)</td><td>3.22 (2.9,3.55)</td><td><0.001</td><td>0.3</td></tr><tr><td>Hct (%)</td><td>9.85 (8.89,10.73)</td><td><0.001</td><td>>0.99</td></tr><tr><td>LVM (g)</td><td>-42.03 (-65.92,-18.14)</td><td>0.04</td><td>0.4</td></tr><tr><td>LVMi (g/m^2)</td><td>-26.68 (-40.17,-13.19)</td><td><0.001</td><td>0.7</td></tr><tr><td>EF (%)</td><td>1.49 (-0.54,3.52)</td><td><0.001</td><td>0.7</td></tr><tr><td>LVEDV (ml)</td><td>-23.26 (-29.36,-17.15)</td><td>0.9</td><td>0.2</td></tr><tr><td>LVESV (ml)</td><td>-12.52 (-19.51,-5.54)</td><td>0.2</td><td>0.8</td></tr></table> ***Cochrane test of homogeneity, <0.05 indicates significant between-study variation** ➢ Meta-regression analyses to examine the relationships between the 7 outcome parameters (changes in Hb, Hct, LVM, LVMi, EF, LVEDV, LVESV) and 5 independent clinical variables (patient follow-up, systolic BP, duration of disease, Hb target, Hct target) were conducted ➢ Only 3 statistically significant relationships were found: between change in Hb and Hb target (P=0.04); change in Hct and duration of disease (P=0.02) and change in EF and duration of follow-up (P=0.02)
Source of funding	Pharmaceutical company
Citation	
NCC CC ID (Ref Man)	1728

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Wolfe RA, Hulbert-Shearon TE, Ashby VB, Mahadevan S, Port FK. Improvements in dialysis patient mortality are associated with improvements in urea reduction ratio and hematocrit, 1999 to 2002. *American Journal of Kidney Diseases* 2005;**45**:127-35.
Study type	Retrospective longitudinal study (1999-2002)
Evidence level	3+
Study objective	To investigate if changes in achieving K/DOQI guidelines URR ≥65% and Hct ≥33% are associated with changes in mortality in patients with ESRD
Number of patients	Multisite study in 2,858 dialysis centres in USA
Patient characteristics	Exclusion criteria: ➢ Patient claims with Hct <14% or >60% were excluded ➢ <4 claims ➢ Non-Medicare certificated ➢ Facilities with <5 patients included in Hct, URR, SMR or with <1 expected death for any year 1999-2002 ➢ Facilities with <70% HD patients

<table>
<tr><td></td><td></td></tr>
<tr><td>Intervention</td><td>URR ≥65% and Hct ≥33%</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>4 years (1999-2002)</td></tr>
<tr><td>Outcome measures</td><td>➢ Standardised mortality ratio – compares observed death rate for a group of patients with expected national death rate for patients with same characteristics. Adjusted for age, sex, race, diabetes as a cause of ESRD, years of dialysis Tx, facility comorbidity index and facility average BMI</td></tr>
<tr><td>Effect size</td><td>➢ Facilities were divided into quintiles according to fraction of patients achieving K/DOQI guidelines for Hct and for URR in 1999 and in 2002
➢ Poisson regression was used to model the no. of expected deaths based on the 10 resulting categories of Hct/URR grouping (5 quintiles for 1999 and for 2002)
➢ Standardised mortality ratio was calculated as total observed deaths divided by total expected deaths for each group
➢ Associations between changes in practice and mortality were assessed at the facility level; the association of average change per year in SMR with average change per year in % patients with URR ≥65% and Hct ≥33% was analysed using linear regression models weighted by facility size

Trends in URR and Hct in the 4 year period 1999-2002 in N=2,858 facilities
➢ Improvements in URR and Hct were ~2%/year and ~4%/year respectively

<table>
<tr><th>Year</th><th>% patients with URR ≥65%</th><th>% patients with Hct ≥33%</th></tr>
<tr><td>1999</td><td>85.5</td><td>74.3</td></tr>
<tr><td>2000</td><td>87.9</td><td>79.5</td></tr>
<tr><td>2001</td><td>89.1</td><td>83.0</td></tr>
</table>
</td></tr>
</table>

2002	90.2	86.2

SMR

Quintiles for % patients with URR ≥65%	1999	2000
0-78.1	1.15 (N=574)	1.19 (N=197)
78.2-85.7	1.11 (N=587)	1.08 (N=413)
85.8-90.5	1.04 (N=565)	1.03 (N=539)
90.6-95.1	1.00 (N=562) (REF)	0.96 (N=772)
95.2-100	0.93 (N=570)	0.93 (N=937)

N refers to no. of dialysis facilities

- Relative mortality risk for facilities in highest quintile of % patients with URR ≥65% compared with lowest quintile =0.93/1.19 = 0.78 (P<0.0001) for 2002. I.e. facilities with >95% of patients achieving URR ≥65% had 22% lower mortality rate than those with 78% achieving target URR

Quintiles for % patients with Hct ≥33%	1999	2000
0-64.5	1.10 (N=572)	1.09 (N=83)
64.6-74.3	1.03 (N=574)	1.13 (N=183)

	<table><tr><td>74.4-81.1</td><td>1.05 (N=575)</td><td>1.03 (N=373)</td></tr><tr><td>81.2-87.1</td><td>1.00 (N=566) (REF)</td><td>0.99 (N=650)</td></tr><tr><td>87.2-100</td><td>0.96 (N=571)</td><td>0.94 (N=1569)</td></tr></table> N refers to no. of dialysis facilities ➢ Relative mortality risk for facilities in highest quintile of % patients with Hct ≥33% compared with lowest quintile =0.94/1.09 = 0.86 (P<0.0001) for 2002. I.e. facilities with >87% of patients achieving Hct ≥33% had 14% lower mortality rate than those with <64% achieving target Hct ➢ Multiple regression analysis showed compliance with K/DOQI guideline for URR and Hct independently had an effect on mortality ➢ A 10% point increase in fraction of patients with URR ≥65% was associated with a 2.2% decrease in mortality (P=0.0006) ➢ A 10% point increase in fraction of patients with Hct ≥33% was associated with a 1.5% decrease in mortality (P=0.003) ➢ There was no significant interaction between effects of URR and Hct slopes on SMR slope (P=0.75)
Source of funding	Insurance company who provided the data
Citation	
NCC CC ID (Ref Man)	1899

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS *et al*. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. *J Am Soc Nephrol* 2005;**16**:1803-10.
Study type	Secondary evaluation of 4 community-based longitudinal studies to evaluate CKD
Evidence level	3+
Study objective	To examine i) The relationship between anaemia and left ventricular hypertrophy (LVH) and adverse events ii) The interaction between these 2 risk factors in a pooled cohort of patients with CKD
Number of patients	N=2,333; predialysis
Patient characteristics	Baseline characteristics of CKD cohort

Mean (median) GFR (ml/min/1.73 m^2)	51.0 (53.1) ± 8.3
Mean calibrated serum creatinine (median) (mg/dl)	1.3 (1.3) ± 0.3
Mean age (years)	69.4

Male (%)	38.3
No. with history of CVD	759 (31.3%)
No. with diabetes (%)	17.1
No. with history of hypertension (%)	69.1
Mean Hct for men (%)	43.8
Mean Hct for women (%)	41.1
No. with anaemia	**275 (11.8%)**
No. with LVH (by ECG criteria)	130 (5.6%)
No. with anaemia and LVH	25 (1.1%)

- Anaemia was defined by WHO definition: Hb <12 g/dl or Hct <36% in women and Hb <13 g/dl in or Hct <39% in men
- LVH criteria was defined by voltage, S-T segment and T wave characteristics

Baseline characteristics of individuals stratified by anaemia and LVH status

	LVH		Anaemia	
	Absent (N=2,228)	Present (N=131)	Absent (N=2,112)	Present (N=287)
Age (years)	69.0 ± 11.0	73.1 ± 9.0	69.1 ± 10.8	72.1 ± 11.2
Male	37.9[b]	43.5[b]	37.5	46.0
White	91.1	77.1	93.2	69.0

	CVD	29.3	59.5	30.8[c]	36.9[c]
	Diabetes	16.8[b]	20.6[b]	16.2	24.7
	Hypertension	67.4	93.1	67.9	78.0
	Currently smokes	15.2[b]	16.0[b]	15.9	9.4
	Currently drinks	50.0[b]	50.0[b]	51.0	38.9
	BMI (kg/m^2)	27.1 ± 4.6	25.9 ± 3.6	27.1 ± 4.5[c]	26.4 ± 5.0[c]
	Systolic BP	134.6 ± 22.3	150.6 ± 26.7	135.1 ± 22.6	139.9 ± 25.6
	Diastolic BP	72.9 ± 11.7[b]	73.8 ± 13.8[b]	73.2 ± 11.6	71.0 ± 13.4
	LVH (%)	-	-	5.1[c]	8.7[c]
	Creatinine (mg/dl)	1.3 ± 0.3	1.5 ± 0.5	1.3 ± 0.3	1.6 ± 0.6
	GFR (ml/min/1.73 m^2)	51.2 ± 8.1	47.5 ± 10.6	51.7 ± 7.5	45.9 ± 11.5
	Total cholesterol (mg/dl)	222.3 ± 45.9[b]	218.5 ± 44.0[b]	223.2 ± 45.0	211.5 ± 50.4
	HDL	50.4 ± 15.8[b]	49.4 ± 16.8[b]	50.2 ± 15.5[b]	51.5 ± 17.8[b]
	Hct (%)	42.2 ± 4.6[c]	41.3 ± 5.1[c]	43.2 ± 3.8	34.6 ± 2.9
	Anaemia (%)	11.4	18.5[c]	-	-
	Clinical outcomes (%) Cardiac Stroke	17.2	34.4	17.5[c]	23.3[c]

	Mortality Composite Follow-up (months)	10.0 33.3 41.9 91.9 ± 31.5	22.9 65.6 74.0 68.0 ± 37.3	10.5 32.6 41.4 93.1 ± 30.8	14.3[d] 56.4 63.1 69.1 ± 35.9
	Values are mean ± SD. All P values are <0.01 when compared within the LVH or anaemia status except for [b]P>0.05; [c]P<0.05; [d]P=0.05				
Intervention	N/A				
Comparison	N/A				
Length of follow-up	Median 102 months (8.5 years) ➢ ARIC, 107 months ➢ CHS, 99 months ➢ FHS, 120 months ➢ Offspring, 120 months				
Outcome measures	➢ Primary study outcome: a composite of MI, stroke and all-cause mortality ➢ Secondary study outcomes: cardiac events (fatal coronary heart disease and MI) stroke and all-cause mortality				
Effect size	Primary outcome Distribution of events by anaemia and LVH status*				

	Composite	Cardiac	Stroke	Mortality

	(N=1,022)	(N=423)	(N=252)	(N=821)
+LVH, +anaemia (N=25)	22 (88.0%)	11 (44.0%)	9 (36.0%)	20 (80.0%)
+LVH, -anaemia (N=130)	74 (56.9%)	33 (25.4%)	21 (16.2%)	65 (50.0%)
-LVH, +anaemia (N=250)	152 (60.8%)	52 (20.8%)	30 (12.0%)	135 (54.0%)
-LVH, -anaemia (N=1,928)	774 (40.1%)	327 (17.0%)	192 (10.0%)	601 (31.2%)

* No. of individuals with composite outcome is smaller than the total of cardiac, stroke and mortality because some individuals had more than 1 outcome, and composite outcome was counted only once

- Adjusted analysis found hazard for composite outcome (MI, stroke and all-cause mortality) was significantly increased in individuals with anaemia when compared to those without anaemia (hazard ratio 1.51; 95% CI 1.27 to 1.81) and in individuals with LVH compared to those without (hazard ratio 1.67; 95% CI 1.34 to 2.07)
- Adjustment for interaction between black people in CHS and ARIC was not statistically significant

Secondary outcomes

- LVH was an independent risk factor for cardiac events, stroke and death
- Anaemia was an independent risk factor for all-cause mortality, but cardiac events and stroke was NS

Hazard ratios and CI from adjusted multivariate analysis (age, gender, race, history of CVD, hypertension and diabetes, smoking, alcohol use, high school graduation status, systolic BP, total cholesterol, HDL, GFR and study terms) for primary and secondary outcomes in individuals with CKD

	Composite[b]	Cardiac[b]	Stroke[b]	Mortality[c]
Without interaction				

	LVH	1.67 (1.34 to 2.07)	1.62 (1.18 to 2.24)	1.78 (1.20 to 2.65)	1.74 (1.38 to 2.20)
	Anaemia	**1.51 (1.27 to 1.81)**	**1.21 (0.90 to 1.61)**	**1.30 (0.89 to 1.89)**	**1.68 (1.39 to 2.04)**
	With interaction				
	+LVH, +anaemia	4.15 (2.62 to 6.56)	3.92 (2.05 to 7.48)	4.2 (2.00 to 8.99)	3.30 (2.04 to 5.34)
	+LVH, -anaemia	1.43 (1.18 to 1.72)	1.36 (0.94 to 1.97)	1.47 (0.92 to 2.34)	1.68 (1.29 to 2.18)
	-LVH, +anaemia	1.48 (1.16 to 1.89)	1.08 (0.79 to 1.48)	1.14 (0.75 to 1.71)	1.65 (1.35 to 2.02)
	-LVH, -anaemia	Reference	Reference	Reference	Reference

[b]P<0.05 for interaction between LVH and anaemia

[c]The interaction term for anaemia and LVH with mortality was NS (P>0.20)

Interaction of anaemia and LVH with outcomes

Primary outcome:

- Interaction term LVH x anaemia was statistically significant (P=0.02)
- Individuals with both anaemia and LVH had a nearly 4-fold increase in risk (HR 4.15, 95% CI 2.62 to 6.56) for the composite outcome compared to individuals with neither anaemia nor LVH
- Anaemia without LVH and LVH without anaemia increased the risk for composite outcomes by ~40% compared with the risk in individuals with neither anaemia nor LVH

	Secondary and other outcomes: ➢ Interaction term LVH x anaemia was significant for secondary (cardiac) outcome (P=0.01) and stroke (P=0.04) but not all-cause mortality (P>0.20) ➢ Individuals with both anaemia and LVH had a nearly 4-fold increase in risk (HR 3.92, 95% CI 2.05 to 7.48) for the cardiac outcome compared with individuals with neither anaemia nor LVH ➢ In individuals who had LVH and did not have anaemia, however, and in individuals who had anaemia and did not have LVH, there was no significant risk for cardiac outcomes
Source of funding	
Citation	
NCC CC ID (Ref Man)	1900

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 1999;**10**:610-9.
Study type	Retrospective cohort study

<table>
<tr><td>Evidence level</td><td>2+</td></tr>
<tr><td>Study objective</td><td>To assess the effect of Hct levels up to 36% on mortality, with adjustment for comorbidity and disease severity in HD patients receiving EPO</td></tr>
<tr><td>Number of patients</td><td>N=75,283</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
➢ Survive at least 90 days prior to follow-up period (1st July to 31st December, 1993)
➢ Patients with 4 or more EPO claims (i.e. average 5.1 months EPO coverage)

Exclusion criteria:
Hct >36%

Patient characteristics stratified to Hct levels

<table>
<tr><th>N=75,283</th><th><27%
N=9,130</th><th>27 to <30%
N=22,217</th><th>30 to <33%
N=33,122</th><th>33 to <36%
N=10,129</th><th>≥36%
N=685</th><th>P</th></tr>
<tr><td>Age</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Under 45</td><td>27.2</td><td>19.8</td><td>16.5</td><td>15.1</td><td>18.0</td><td>0.001</td></tr>
<tr><td>45-64</td><td>38.5</td><td>36.5</td><td>34.3</td><td>33.2</td><td>38.0</td><td></td></tr>
<tr><td>65-74</td><td>23.4</td><td>28.4</td><td>30.8</td><td>32.2</td><td>29.2</td><td></td></tr>
<tr><td>≥74</td><td>10.9</td><td>15.2</td><td>18.5</td><td>19.5</td><td>15.0
39.7</td><td></td></tr>
</table>
</td></tr>
</table>

	Female	52.6	53.4	51.5	46.0	53.6	0.001
	Race						
	White	37.1	45.4	52.6	57.7	53.6	0.001
	Black	54.7	45.2	37.6	32.5	33.7	
	Native American	1.4	1.4	1.4	1.7	4.1	
	Other	6.8	8.1	8.1	8.1	8.6	
	ESRD exposure						
	<1 year	21.6	22.9	23.5	23.0	20.0	0.001
	1-2 years	19.0	19.6	19.8	19.5	17.2	
	2-5 years	34.1	34.3	33.7	33.5	32.6	
	≥5 years	25.3	23.2	23.1	240.	30.2	
	Renal diagnosis						
	Diabetes mellitus	27.2	31.2	32.1	31.3	31.4	0.001
	Hypertension	32.6	31.6	30.8	29.8	27.6	
	GN	16.2	16.2	16.2	17.6	19.1	
	Other	24.0	21.0	20.9	21.4	21.9	
	Comorbidities						
	ASHD	35.4	57.6	55.4	53.1	43.1	0.001
	CVA/TIA	28.8	30.0	29.1	28.1	24.8	0.002

	PVD	61.8	63.0	61.2	60.0	60.2	0.001
	CHF	59.2	57.6	55.4	53.1	55.6	0.001
	Cardiac other	68.0	67.8	65.2	63.6	64.1	0.001
	COPD	21.9	23.9	23.3	23.3	22.5	0.002
	Cancer	24.1	25.4	25.3	26.0	20.4	0.024
	Liver	26.7	23.3	22.2	21.1	24.7	0.001
	Gallbladder	11.2	11.8	10.7	9.7	10.1	0.001
	GI	34.1	31.2	27.5	25.0	27.2	0.001
	No. access procedures						
	0	61.1	63.9	70.2	74.8	73.3	0.001
	1-3	24.1	22.6	19.5	17.0	18.4	
	≥4	14.8	13.6	10.3	8.2	8.3	
	No. transfusions						
	0	74.9	84.1	91.3	94.5	96.1	0.001
	1-2 pints	11.3	8.5	4.7	3.0	2.2	
	≥3 pints	13.8	7.4	4.0	2.1	1.8	
	Length of hospital stay						
	0	42.4	48.4	58.2	67.5	67.7	0.001

	1-3 days	11.4	12.1	11.7	10.3	10.4	
	3-10 days	19.4	17.8	15.5	12.3	11.5	
	11-20 days	13.0	11.1	7.8	5.7	5.8	
	>20 days	13.9	10.7	6.9	4.3	4.5	
	Hct (mean ± SD)	25.04 ± 2.06	28.69 ± 0.84	31.40 ± 0.84	33.88 ± 0.72	37.57 ± 1.62	0.001
Intervention	Epoetin						
Comparison	N/A						
Length of follow-up	1 year (1st January to 31st December, 1994) ➢ Patients were censored at time of dialytic modality switch or transplantation, when lost to follow-up, or on 31st December 1994, whichever occurred first						
Outcome measures	End points were all-cause mortality and cause-specific mortality (incl cardiac death and infectious death)						
Effect size	Mortality adjusted for risk factors (demographics and comorbidity), <u>without</u> severity of disease (incl. no. of access procedures, blood transfusions and prior hospital days) ➢ Increase in age group associated with higher all-cause and cause-specific mortality ➢ Female patients had better outcomes ➢ When compared to white patients, black and other minorities had lower all-cause and cause-specific mortality ➢ When Hct 30 to <33% was used as reference, patients with Hct <27% and 27 to <30% had a higher risk for all-cause death. In contrast, patients with Hct 33 to <36% had a lower risk ➢ For cardiac death, Hct <27%, 27 to <30% had a higher risk, whilst Hct 33 to <36% had a lower risk ➢ For infectious death, Hct <27%, 27 to <30% had a higher risk, whilst Hct 33 to <36% had no significant beneficial impact						

Impact of patient characteristics and Hct levels on mortality without adjusting for severity of disease

	All-cause death		Cardiac death		Infectious death	
	RR	95% CI	RR	95% CI	RR	95% CI
Age						
Under 45 (REF)	1.00	-	1.00	-	1.00	-
45-64	1.67	1.56-1.78	1.67	1.51-1.85	1.77	1.46-2.13
65-74	2.21	2.07-2.37	2.17	1.96-2.40	2.21	1.83-2.68
≥74	3.11	2.90-3.34	2.90	2.61-3.23	3.29	2.70-3.99
Female	0.94	0.91-0.97	0.86	0.82-0.91	1.02	0.93-1.12
Race						
White (REF)	1.00	-	1.00	-	1.00	-
Black	0.73	0.70-0.76	0.66	0.63-0.70	0.81	0.73-0.89
Native American	0.83	0.72-0.97	0.82	0.65-1.02	0.55	0.33-0.92
Other	0.87	0.82-0.92	0.89	0.81-0.97	0.80	0.67-0.95
Hct						
<27%	1.51	1.44-1.59	1.40	1.30-1.52	1.82	1.59-2.08
27 to <30%	1.20	1.16-1.25	1.18	1.12-1.25	1.25	1.12-1.39
30 to <33% (REF)	1.00	-	1.00	-	1.00	-
33 to <36%	0.90	0.85-0.95	0.92	0.85-0.99	0.94	0.81-1.10

Mortality adjusted for risk factors (demographics and comorbidity), with severity of disease (incl. no. of access procedures, blood transfusions and prior hospital days)

- Impact of patient demographics was similar to data in table above

Impact of Hct levels on mortality risk

- Adjustments for disease severity decreased the absolute values of RR of Hct level on mortality
- Patients with Hct <30% still had significantly higher risks of death when compared to patients with Hct 30 to <33%, but with reduced magnitude of impact to unadjusted values
- The reduced effect of Hct levels on mortality especially in the 33 to <36% group may be due to complex confounding effect of interactions between Hct level, comorbidity and severity of disease and adjustments for these effects may require more patients to detect a true effect. A sensitivity analysis was therefore conducted
- Hence a 1992 & 1993 cohort was used (N=61,797) and demonstrated sample size could mask the true effect of Hct levels on patient mortality

	All-cause death		Cardiac death		Infectious death	
	RR	95% CI	RR	95% CI	RR	95% CI
Hct						
<27%	1.33	1.26-1.40	1.25	1.15-1.35	1.53	1.33-2.75
27 to <30%	1.13	1.08-1.17	1.11	1.05-1.17	1.13	1.02-1.26
30 to <33% (REF)	1.00	-	1.00	-	1.00	-
33 to <36%	0.96	0.91-1.01 (P≤0.0956)	0.97	0.90-1.05	1.02	0.88-1.19

	1992 & 1993 33 to <36%	0.96	0.92-0.99 (P=0.0385)				
Source of funding	Not reported						
Citation							
NCC CC ID (Ref Man)	1915						

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Collins AJ, Li S, St Peter W, Ebben J, Roberts T, Ma JZ et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. Journal of the American Society of Nephrology 2001;**12**:2465-73.
Study type	Cohort study

<table>
<tr><td>Evidence level</td><td>2+</td></tr>
<tr><td>Study objective</td><td>To assess the risks of death and hospitalisation associated with hematocrit values of >36% in incident hemodialysis ESRD patients</td></tr>
<tr><td>Number of patients</td><td>Total N=66,761

➢ Treated in 1996, N=26,443
➢ Treated in 1997, N=24,910
➢ Treated during half of 1998, N=15,408</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
➢ Survived first 90 days and a full 6 month entry period
➢ Follow up for a minimum of 6 months, up to 1 year

Exclusion criteria:
➢ Less than 4 EPO and hematocrit claims during the 6-month entry period
➢ Secondary-pay insurance
➢ Payments of < $675 per month for dialysis due to incomplete data ion comorbidity, hematocrit values and EPO dosing

<table>
<tr><th>Characteristics</th><th>N=26,443</th></tr>
<tr><td>Mean age</td><td>65y</td></tr>
<tr><td>Male</td><td>51.2%</td></tr>
<tr><td>Race

White</td><td>

58.3%</td></tr>
</table>
</td></tr>
</table>

Black	35.4%
Primary diagnosis of diabetes mellitus	44.8%
Mean no. of hospital days	5.94
Vascular access procedures	49.3%
Received blood transfusions	5.8%
Hematocrit values <30% 30 to <33% 33 to <36% 36 to <39% ≥39%	 13.1% (N=8,760) 36.6% (N=24,465) 43% (N=28,674) 6.5% (N=4,307) 0.8% (N=555)

- Due to significant differences in patient characteristics when grouped into hematocrit levels (see table below), an adjustment was made for these differences in survival and hospitalisation models

Characteristics	Hct <30%	Hct 30 to <33%	Hct 33 to <36%	Hct 36 to <39%	Hct ≥39%	P value
No. of patients	8,760	24,465	28,674	4,307	555	

	Age (y)	61.4	64.7	66.0	65.6	66.5	<0.0001
	Male (%)	48.1	49.5	52.8	55.3	53.5	<0.001
	Race						
	White (%)	48.7	57.5	61.6	60.9	61.4	<0.001
	Black (%)	45.4	36.4	32.1	31.9	31.9	<0.001
	Diabetes mellitus (%)	42.3	46.0	44.7	43.6	38.7	<0.001
	Hospital days	10.7	6.8	4.2	3.8	4.0	<0.0001
	Mean EPO (U/month)	66,980	53,746	42,820	38,538	40,702	<0.0001
	Mean iron (vials/month)	2.08	2.203	2.359	2.488	2.645	<0.0001
Intervention	EPO to different Hct levels						
Comparison	N/A						
Length of follow-up	Minimum of 6 months for 1998 patients and up to 1 year follow-up for 1996/1997 patients						
Outcome measures	➢ Mortality ➢ Hospitalisation						
Effect size	*Adjusted mortality and hospitalisation rates*						

- Using the reference population of Hct 33 to <36%, statistically significant differences were observed when confidence intervals of relative risk (RR) did not include 1

Relative risk of death and hospitalisation from all causes in the 1 year follow-up period

- There was a higher risk of death in patients in Hct <30% and Hct 30 to <33%, but no significant difference in mortality for patients in Hct 36 to <39% and Hct ≥39% when compared to the reference population of Hct 33 to <36%
- A similar pattern was observed in this category for hospitalisation risks. However, patients in Hct 36 to <39% and Hct ≥39% showed significantly lower risk of hospitalisation when compared to the reference population of Hct 33 to <36%

	Hct <30%	Hct 30 to <33%	Hct 33 to <36%	Hct 36 to <39%	Hct ≥39%
RR of death	1.74*	1.25*	1	0.99 (NS)	1.05 (NS)
RR of hospitalisation	1.42*	1.21*	1	0.78*	0.84*

* significant

Relative risk of death and hospitalisation from cardiac causes in the 1 year follow-up period

- Again, there was a higher risk of death in patients in Hct <30% and Hct 30 to <33%, but no significant difference in mortality for patients in Hct 36 to <39% and Hct ≥39% when compared to the reference population of Hct 33 to <36%
- A similar pattern was observed in this category for hospitalisation risks. However, only patients in Hct 36 to <39% showed significantly lower hospitalisation risk when compared to the reference population of Hct 33 to <36%

	Hct <30%	Hct 30 to <33%	Hct 33 to <36%	Hct 36 to <39%	Hct ≥39%
RR of death	1.57*	1.25*	1	0.96 (NS)	0.93 (NS)
RR of hospitalisation	1.3*	1.17*	1	0.75*	0.88 (NS)

* significant

Relative risk of death and hospitalisation from infectious causes in the 1 year follow-up period

- Again, there was a higher risk of death in patients in Hct <30% and Hct 30 to <33%, but no significant difference in mortality for patients in Hct 36 to <39% and Hct ≥39% when compared to the reference population of Hct 33 to <36%
- Again, there was a higher risk of hospitalisation in patients in Hct <30% and Hct 30 to <33%. In contrast, patientswith Hct >36% (in Hct 36 to <39% and Hct ≥39%) showed significantly lower hospitalisation risk when compared to the reference population of Hct 33 to <36%

	Hct <30%	Hct 30 to <33%	Hct 33 to <36%	Hct 36 to <39%	Hct ≥39%
RR of death	1.92*	1.26*	1	1.08 (NS)	0.96 (NS)
RR of hospitalisation	1.76*	1.3*	1	0.82*	0.62*

* significant

Source of funding	In part by a research foundation and a pharmaceutical company

Citation	
NCC CC ID (Ref Man)	52

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. Journal of the American Society of Nephrology 2000;**11**:335-42.
Study type	Longitudinal study
Evidence level	3-
Study objective	To determine whether use of EPO to increase the hematocrit to “near normal” levels improves functional status and quality of life in stable hemodialysis patients
Number of patients	N=156 Multicenter study in 34 hemodialysis centers in Spain

<table>
<tr>
<td>Patient characteristics</td>
<td>
Inclusion criteria:
➢ Received EPO for at least 3 months prior to study entry
➢ Stable Hb ≥9 g/dl and hematocrit ≥28%
➢ Non-diabetic
➢ Age 18 to 65 years

Exclusion criteria:
➢ Diabetes
➢ Uncontrolled hypertension
➢ Malfunction of vascular access (hemodialysis blood flow <300 ml/min, high return venous pressure and/or recirculation >15%)
➢ History of stroke
➢ Seizures
➢ Symptomatic ischemic heart disease or congestive heart failure
➢ Presence of severe associated disease (Friedman Comorbidity Index >7)
➢ Anemia unrelated to chronic renal failure
➢ Received a kidney transplant or experienced complications possibly related to EPO treatment or to increased hematocrit

<table>
<tr><th>Characteristic</th><th>Mean</th></tr>
<tr><td>Age (years) (SD)</td><td>44 ± 15</td></tr>
<tr><td>Male</td><td>60 %</td></tr>
<tr><td>Months on dialysis (SD)</td><td>37 ± 40</td></tr>
<tr><td>Friedman Comorbidity Index* (SD)</td><td>3 ± 2</td></tr>
<tr><td>Kt/V (SD)</td><td>1.17 ± 0.3</td></tr>
<tr><td>PCR (SD)</td><td>1.2 ± 0.3</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Hb (g/dl) (SD)</td><td>10.2 ± 0.7</td></tr>
<tr><td>Hct (%) (SD)</td><td>31 ± 2</td></tr>
<tr><td>Previous failed transplant</td><td>19 %</td></tr>
<tr><td>Hemodialysis technique</td><td>HD 92%/HDF 8%</td></tr>
<tr><td>Hemodialysis buffer</td><td>Bicarbonate 82%/Acetate 18%</td></tr>
<tr><td>Dialyzer membrane</td><td>Cellulosic 60%/Synthetic 40%</td></tr>
<tr><td>Vascular access</td><td>PTFE graft 30%/Native fistula 70%</td></tr>
</table>

* Friedman Comorbidity Index was used to evaluate comorbidity. 13 pathology groups are evaluated by a physician, on a 4-point scale (0 absent; 1 slight; 2 moderate; 3 severe) and scores added up. Other collated information includes social, professional and economic status and education level.
</td></tr>
<tr><td>Intervention</td><td>Epoetin to Hb 12.5 ± 0.9 g/dl and Hct 38.5 ± 2.5 % at 6 months</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>Study duration 6 months</td></tr>
<tr><td>Outcome measures</td><td>➢ Quality of life using the Karnofsky scale (KS) and Sickness Impact Profile (SIP) questionnaires. KS is an indicator of self-sufficiency and functional capacity. It is a 10-level scale, with scores ranging from 100 (no limitations) to 10 (moribund). SIP is a behaviour-based questionnaire consisting of 136 statements grouped into 12 categories. These are further grouped into physical dimension (body care & movement, mobility and ambulation) and psychosocial dimension (emotional behaviour, social interaction, alertness and communication), leaving 5 independent categories. All partial categories give the global dimension. Scores vary from 0 (absence of dysfunction) to 100 (maximum dysfunction)
➢ Adverse effects
➢ Hospitalization – no. of admissions and length of hospital stay</td></tr>
</table>

Effect size

Quality of life

Indicator	Mean (SD)	Median	P value
SIP physical dimension			
Baseline	5.4 ± 1.2	3.3	<0.005
Final	4.1 ± 1.12	1.2	
SIP pscychosocial dimension			
Baseline	9.2 ± 1.8	6.8	<0.001
Final	7 ± 1.7	4.6	
SIP global score			
Baseline	8.9 ± 1.39	7.9	<0.001
Final	7.25 ± 1.3	5.5	
Karnofsky scale			
Baseline	75.6 ± 2.7	80	<0.01
Final	78.4 ± 2.8	80	

Adverse Effects

- No patient died during the 6 months
- 9 patients were censored from the study due to vascular access thrombosis
- 3 patients were censored for hypertension that was difficult to control, 1 of which had a hypertensive emergency with cardiac failure
- No significant changes were observed in the prevalence of arterial hypertension or mean BP in the 115 patients who completed

the study

Category	Baseline	3 months	6 months	X^2
Hypertensive	68	62	66	P = NS
Normotensive	47	53	49	

Hospitalisation

Variable	6 previous months		6 months of study		P value
	Total	Mean per patient	Total	Mean per patient	
No. of hospitalisations	19	0.17	8	0.07	<0.05
Length of hospital stay (days)	152	1.3	47	0.4	<0.05

Source of funding	Pharmaceutical company
Citation	
NCC CC ID (Ref	76

Man)	

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Djamali A, Becker YT, Simmons WD, Johnson CA, Premasathian N, Becker BN. Increasing hematocrit reduces early posttransplant cardiovascular risk in diabetic transplant recipients. Transplantation 2003;**76**:816-20.
Study type	Retrospective longitudinal study
Evidence level	3-
Study objective	To evaluate the impact of ESRD-related anemia on post transplant cardiovascular events and peripheral vascular disease in early post transplant type I diabetic recipients
Number of patients	N=404
Patient characteristics	➢ All type I diabetic ESRD patients who received transplant between January, 1997 and August, 2000

Characteristics	Value
Number	404
Average age (years ± SD)	39.8 ± 7.7

<table>
<tr><td></td><td>
<table>
<tr><td>Gender F/M</td><td>158 (39%) / 246 (61%)</td></tr>
<tr><td>Race

African American

White

Other</td><td>

40 (10%)

351 (87%)

13 (3%)</td></tr>
<tr><td>Kidney transplant alone (KA) or simultaneous pancreas-kidney (SPK)</td><td>81 / 323</td></tr>
<tr><td>Pretransplant dialysis</td><td>299 (74%) (72 KTA and 227 SPK)</td></tr>
<tr><td>Pretransplant tobacco use</td><td>87 (21.5% out of 176))</td></tr>
<tr><td>ACE-inhibitor or angiotensin receptor blocker use</td><td>68 (16.8%)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Kidney transplant alone (KA) or simultaneous pancreas-kidney (SPK)</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>1 year</td></tr>
<tr><td>Outcome measures</td><td>➢ Post transplant cardiovascular (CV) event rate – defined as post transplant CV death, myocardial infarction, hospitalisation secondary to congestive heart failure or angina
➢ Post transplant peripheral vascular (PV) event rate – defined as post transplant stroke (cerebrovascular accident), lower extremity amputation or lower extremity vascularisation procedure</td></tr>
<tr><td>Effect size</td><td>Pretransplant cardiac screening
➢ Pretransplant ischemic heart disease was present in 73 patients (18%)
➢ Cardiac event rates were more frequent post transplant (P=0.001)</td></tr>
</table>

	➢ A positive post transplant stress test or angiogram was predictive of post-SPK or KTA cardiovascular events (P<0.015) ➢ A pretransplant CV event increased the risk for a post-SPK transplant CV events (relative risk, RR 5.52, P=0.02) ➢ Pretransplant PV disease was associated with an increased risk for post-SPK transplant CV enets (RR 2.12, P=0.01) ➢ Pretransplant CV events in the KTA patients did not increase risk for post transplant CV events **Post transplant hematocrit** ➢ Rolling Hct values improved during the first post transplant year Month 1 Hct 26.3 ± 3.7 % Month 6 Hct 33.4 ± 2.6% (P=0.001) ➢ Initial decrease in post transplant Hct was 5.9 ± 5.6%. There was no association between the change in Hct and rolling Hct (P=0.6, NS) ➢ Leukopenia (white cell count <3,800/µl) affected 69 (17.1%) of study subjects during the first month post transplant ➢ There was no association between the leukopenia and rolling Hct <30% in subsequent months (P=0.3, NS) **Post transplant cardiovascular (CV) event rate** ➢ Study participants with an average rolling Hct ≤30% experienced significantly more CV events during the first 6 months post transplant At least 1 post transplant CV event during the first 6 month Hct ≤30% (N=42) vs. Hct >30% (P<0.002) ➢ Using a univariate analysis: Increasing Hct levels significantly decreased the risk for a CV event when compared to

the reference Hct level of 30% (RR 0.237, 95% CI 0.062 to 0.904, P=0.015)

Number of patients within each category not provided by the authors

Hct (%)	RR	P value
31 to 33	0.237	0.015
34 to 36	0.108	0.0029

- Using a multivariate analysis: Increasing Hct levels significantly decreased the risk for a CV event when compared to the reference Hct level of 30% (RR 0.65, 95% CI 0.33 to 0.91, P=0.022)

Number of patients within each category not provided by the authors

Hct (%)	RR	95% CI	P value
31 to 33	0.78	0.062 to 0.904	0.04
34 to 36	0.59	0.51 to 1.14	0.026

- Using a multivariate analysis in the SPK transplant population alone: Hct levels above 30% were associated with a significant reduction in CV events post transplant (RR 0.6, 95% CI 0.46 to 0.69, P=0.001

Post transplant peripheral vascular (PV) event rate

- 64 study participants experienced a PV event
- A history of pretransplant ischemic heart diease was associated with an increased risk of a post transplant PV event (RR 3.2, P=0.002)
- No significant effect of increasing Hct levels was found on risk reduction for a post transplant PV event

Source of funding	Government and transpantation society grants
Citation	
NCC CC ID (Ref Man)	281

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Ifudu O, Uribarri J, Rajwani I, Vlacich V, Reydel K, Delosreyes G et al. Low hematocrit may connote a malnutrition/inflammation syndrome in hemodialysis patients. Dialysis & Transplantation 2002;**31**.
Study type	Prospective data analysis (non-analytical study)
Evidence level	3+
Study objective	To determine (i) the univariate relation between Hct and mortality and (ii) the effect of Hct on mortality after adjusting for nutrition and other variables in hemodialysis ESRD patients
Number of patients	N=309

<table>
<tr><td></td><td>2 haemodialysis centres in Brooklyn & New York</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
➢ Maintenance hemodialysis 3 times weekly for at least 3 months
➢ Age 18 years+
➢ Absence of severe comorbidity known to cause anemia (i.e. sickle cell disease, active gastrointestinal bleeding, malignancy)

Exclusion criteria:
➢ Known blood dyscrasia or hemoglobinopathy
➢ HIV positive status
➢ On treatment for or being evaluated for any infection
➢ Treatment with drugs known to affect erythropoiesis, including androgens

<table>
<tr><th>Variable</th><th>N=309</th></tr>
<tr><td>Mean age (years) (±SD)</td><td>55.4 ± 15.6 (range 19-91 years)</td></tr>
<tr><td>Gender M/F</td><td>144/165</td></tr>
<tr><td>Race

Blacks

Hispanics

Whites

Asians</td><td>

207 (67%)

74 (24%)

23 (7%)

5 (2%)</td></tr>
<tr><td>Diabetes mellitus</td><td>108 (35%)</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>Mean duration of ESRD at study onset (months)</td><td>50 ± 51.4 (range 4-357 months)</td></tr><tr><td>Mean Hct (%)</td><td>36.3 ± 3.6</td></tr><tr><td>Mean urea reduction ratio (%)</td><td>72.7 ± 6.4</td></tr><tr><td>Mean serum albumin concentration (g/dl)</td><td>3.9 ± 0.4</td></tr><tr><td>Mean i.v. iron over 3-month period (mg)</td><td>376 ± 401</td></tr><tr><td>Mean EPO dose given i.v. 3 times weekly (U/kg)</td><td>79 ± 63</td></tr></table>
Intervention	N/A
Comparison	N/A
Length of follow-up	18 months
Outcome measures	Survival
Effect size	**Survival** ➢ 64 patients died during the 18-month observational period ➢ By univariate analysis: a low Hct was associated with shortened survival (relative hazard = 0.94, 95% CI 0.89 to 0.99, P=0.04) ➢ Kaplan-Meier estimates of 18-month survival by Hct quartile:

	Hct <33.4% 72% Hct ≥ 33.4 to 35.73% 76% Hct ≥ 35.74% to 38.55% 80% Hct >38.55% 89% Log-rank test P=0.0270 ➢ However, after adjustment for serum albumin concentration, diabetes mellitus, dry weight and gender, Hct as a survival predictor was not significant (P=0.55) Cox regression analysis: Variable = Hct (relative hazard 0.98, 95% CI 0.92 to 1.04, P=0.5513)
Source of funding	Academic research grant and non-profit organisation
Additional comments	➢ Intention-to-treat analysis ➢ No subjects were lost to follow-up ➢ Monthly values for Hct, urea reduction ratio, serum albumin, transferring saturation and ferritin were extracted from patients records and a mean obtained for each patient over 3 months during study entry period
Citation	
NCC CC ID (Ref Man)	307

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Lee S-Y, Lee H-J, Kim Y-K, Kim S-H, Kim L, Lee MS et al. Neurocognitive function and quality of life in relation to hematocrit levels in chronic hemodialysis patients. Journal of Psychosomatic Research 2004;**57**:5-10.
Study type	Cohort study
Evidence level	2-
Study objective	To examine the association between hematocrit levels and improvement of cognitive function and quality of life in hemodialysis end stage renal disease patients
Number of patients	N=56 2 site study in Korea
Patient characteristics	Inclusion criteria: ➢ Age 20-70 years ➢ On hemodialysis for 3months+ ➢ Clinically stable, based on patient history ➢ Ambulant ➢ Literate

Exclusion criteria:

- Evident cerebrovascular disease
- Major psychiatric illness
- Major visual or hearing impairment
- Unstable coronary heart disease
- Uncontrolled hypertension during 3 months prior to study entry
- Collagen vascular disease or vasculitis
- Use of glucocorticoids or other neurocognitive funvtion affecting medication during previous 3 months

Characteristic	Hct <27.2% N=28		Hct >27.2% N=28		P value
	No. (%)	Mean ± SD	No. (%)	Mean ± SD	
Age (y)		53.46 ± 10.83		51.35 ± 11.37	0.68
Male Female	15 (53.6) 13 (46.4%)		16 (57.1%) 12 (42.9%)		0.78
Months on dialysis		35.75 ± 39.80		48.14 ± 35.73	0.23
Diabetic patients	7 (25.0)		6 (21.4)		0.75
Hypertensive patients	14 (50.0)		12 (42.9)		0.59

	Hematocrit (g%)		23.26 ± 2.66		32.42 ± 4.29	<0.001
	Albumin (g/dl)		3.40 ± 0.45		4.00 ± 0.39	0.95
	Creatinine (mg/dl)		9.77 ± 2.32		9.83 ± 2.03	0.93
	Kt/V		1.35 ± 0.35		1.33 ± 0.20	0.42
	Education (y)		12.79 ± 2.41		13.89 ± 2.94	0.13
	Socioeconomic status (level)		3.50 ± 1.10		2.40 ± 1.08	0.018
Intervention	N/A					
Comparison	N/A					
Length of follow-up	N/A; measurements were taken as a one-off once patients had been grouped into either Hct group					
Outcome measures	➢ Neurocognitive function using 4 tests i. Trail-making test, where 25 randomly distributed numbers are connected in a correct (part A) or alternating (part B) order. The score is recorded in time taken (seconds) to complete the task ii. Stroop test, where subjects are required to read randomised printed word names of coloured ink and note the ink colour while disregarding the contradictory verbal content (e.g. the word red printed in blue ink). The score is the no. of words or colours read correctly in 60s iii. Digit-span test, an auditory verbal short-term memory test, requires the subject to repeat a spoken string of digits, with two trials each of 3-9 digits in forward order and 2-8 digits in reverse order. The score is the no. of correct trials iv. Digit-symbol test, assess sustained attention, visual searching, visual sequencing and new-learning abilities. Subjects are given 9 different symbols that were matched to numbers and are required to change the number					

	with its matched symbol. The score is the no. of symbols correctly changed within 90s ➢ Quality of life using 3 tests i. Karnofsky scale, a global indicator of self-sufficiency and functional capacity. It is a 10-point scale, with scores ranging from 100 (no limitations) to 10 (moribund) ii. Index of well-being, a self-rating scale which allows patients to assess their sense of well being and consists of 2 parts; the sum of the average score for the index of general affect and life satisfaction, with the final score ranging from 0 (lowest) to 14.7 (highest) iii. The 36-item short-form health survey (SF-36), a self-rating test, is used to assess functional status and sense of well being of patients with chronic disease. It consists of the following 8 scales: general health (GH), physical functioning (PF), role physical (RP), role emotional (RE), mental health (MH), social functioning (SF), bodily pain (BP) and vitality (VT). Each scale is worth 100 points, with a higher score representing a better quality of life ➢ Inapparent depression assessed by means of the Beck depression inventory (BDI) scale; a self-rating scale consisting of 21 items
Effect size	*Neurocognitive function* ➢ Hct >27.2% performed better in the forward digit-span (t= -2.17, P=0.34) and the digit-symbol test (t= -2.34, P=0.023) ➢ In part A of the trail-making test, although the lower Hct group (<27.2%) took longer, the difference was not statistically significant (P=0.098) ➢ There were no differences in the results of part B of the trail-making test, the stroop test and the backward digit-span test *Quality of life and depression* ➢ No significant differences were observed between the 2 groups in BDI score ➢ No significant differences were observed between the 2 groups in any of the 3 scales assessing quality of life

Test	Hct <27.2% N=28 Mean ± SD	Hct >27.2% N=28 Mean ± SD	P value
Karnofsky score	66.42 ± 11.93	70.00 ± 13.05	0.29
Index of well-being	9.20 ± 1.92	8.72 ± 1.59	0.31
Index of general affect	4.37 ± 1.20	4.31 ± 1.03	0.85
Life satisfaction	4.39 ± 1.20	4.04 ± 1.23	0.28
SF-36 (total)	409.41 ± 136.82	433.85 ± 138.51	0.51
GH	40.17 ± 22.30	43.21 ± 23.14	0.62
PF	52.14 ± 24.70	58.21 ± 22.20	0.34
RF	33.93 ± 30.59	53.57 ± 41.23	0.10
RE	39.28 ± 36.35	51.19 ± 37.93	0.24
SF	55.80 ± 28.76	50.89 ± 28.85	0.53
MH	62.71 ± 19.68	57.57 ± 14.75	0.27
BP	65.71 ± 30.56	66.34 ± 28.99	0.94
VT	59.64 ± 22.85	52.32 ± 19.36	0.20
BDI score	11.10 ± 4.12	9.82 ± 5.14	0.30

Source of funding	Not reported
Citation	
NCC CC ID (Ref Man)	328

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Hayashi T, Suzuki A, Shoji T, Togawa M, Okada N, Tsubakihara Y et al. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. American Journal of Kidney Diseases 2000;**35**:250-6.
Study type	Before and after (non-analytical) study
Evidence level	3+
Study objective	To evaluate the rate of progression of left ventricular (LVH) on echocardiography in 9 predialysis patients with CRF after partial correction (Hct 30%) and normalisation (Hct 40%) with EPO
Number of patients	N=9

<table>
<tr>
<td>Patient characteristics</td>
<td>
Inclusion criteria:
➢ Hct <25%

Exclusion criteria:
➢ Presence of valvular disease
➢ Arrythmia
➢ Active ischaemic heart disease
➢ History of seizures
➢ Cerebrovascular disease
➢ Severe or uncontrolled hypertension
➢ Malignancy

<table>
<tr><th>Characteristic</th><th>N=9</th></tr>
<tr><td>Male/female</td><td>5/4</td></tr>
<tr><td>Mean age (years)</td><td>62.4 ± 3.3</td></tr>
<tr><td>Baseline Hct (%)</td><td>23.6 ± 0.5</td></tr>
<tr><td>Cause of renal failure
Glomerulonephritis
Diabetic nephropathy</td><td>
8
1</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td>Intervention</td><td>Epoetin i.v.</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>Study duration 12 months; Partial correction (Hct 30%) maintained for 2 months and subsequently normalisation (Hct 40%) was maintained for 10 months</td></tr>
<tr><td>Outcome measures</td><td>➢ Echocardiography
➢ 24 hour ambulatory blood pressure monitoring
➢ Haematological parameters</td></tr>
<tr><td>Effect size</td><td>Haematological parameters
➢ Only hematocrit significantly changed from baseline (see table below). There were no significant changes observed in platelet count, serum creatinine, potassium, phosphate, plasma rennin activity, atrial natriuretic peptide, systolic and diastolic blood pressure, body weight and heart rate
➢ After the 10-month normalisation period, hematocrit was 40.4 ± 0.6% in men and 37.6 ± 0.8% in women
➢ The EPO dose averaged 6,000 U/week during the partial correction period and 7,700 U/week during the normalisation period
➢ A comparison of the slopes of linear progression plots of the reciprocoal value of the serum creatinine level vs. time did not show any difference before or after EPO therapy, indicating there was no change in the progession of renal failure

<table>
<tr><th></th><th>Baseline</th><th>Partial correction
(time = 2 months)</th><th>Normalisation
(time = 12 months)</th><th>P value</th></tr>
<tr><td>Hematocrit (%)
Mean ± SEM</td><td>23.6 ± 0.5</td><td>32.1 ± 0.6</td><td>39.1 ± 0.8</td><td><0.0001</td></tr>
<tr><td>Creatinine (mg/dl)
Mean ± SEM</td><td>6.2 ± 0.7</td><td>5.7 ± 0.7</td><td>5.5 ± 0.7</td><td>NS</td></tr>
</table>
</td></tr>
</table>

Clinic systolic blood pressure (mmHg) Mean ± SEM	147.8 ± 7.7	151.3 ± 7.6	148.2 ± 7.4	NS
Clinic diastolic blood pressure (mmHg) Mean ± SEM	74.2 ± 4.9	76.5 ± 2.6	72.7 ± 3.2	NS

Echocardiography

- A significant decrease in left ventricular mass index (LVMI) was seen at normalisation
- No changes were observed in the remaining measurements of the left ventricle

	Baseline	Partial correction (time = 4 months)	Normalisation (time = 12 months)	P value
Left ventricular end-diastolic diameter (mm)	50.1 ± 1.9	48.0 ± 1.2	47.2 ± 1.3	NS
Left ventricular end-systolic diameter (mm)	33.0 ± 1.7	31.6 ± 1.4	30.8 ± 1.1	NS
Stroke volume (ml)	97.3 ± 9.0	87.5 ± 4.1	84.8 ± 6.6	NS
Cardiac index (l/min/m^2)	4.9 ± 0.5	4.4 ± 0.2	3.9 ± 0.3	NS
Ejection fraction (%)	68.0 ± 2.4	68.0 ± 1.6	68.0 ± 1.6	NS

	<table><tr><td>Interventricular septum thickness (mm)</td><td>9.0 ± 0.3</td><td>8.7 ± 0.4</td><td>8.3 ± 0.4</td><td>NS</td></tr><tr><td>Left ventricular posterior wall thickness (mm)</td><td>9.5 ± 0.5</td><td>9.3 ± 0.4</td><td>8.4 ± 0.3</td><td>NS</td></tr><tr><td>Left ventricular mass index (g/m^2)</td><td>140.6 ± 12.1</td><td>126.9 ± 10.0</td><td>111.2 ± 8.3</td><td><0.01</td></tr></table> All data is expressed as Mean ± SEM **24 hour ambulatory blood pressure monitoring** ➢ All patients received blood pressure medication before EPO administration and additional medication was required in 4 patients during the course of the study ➢ No differences were seen in the 24-hour day time, night time and sleeping time blood pressure between baseline and partial correction or normalisation ➢ Circadian blood pressure was maintained through the entire 24-hour period
Source of funding	Not reported
Citation	
NCC CC ID (Ref Man)	1553

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of a) Age b) Gender c) Ethnicity	
Bibliographic reference	Silberberg J, Racine N, Barre P, Sniderman AD. Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. Canadian Journal of Cardiology 1990;**6**:1-4.
Study type	Before and after study
Evidence level	3+
Study objective	To evaluate hemodialysis patients before and after correction of anemia with EPO, by echocardiography
Number of patients	N=22 Patients derived from multisite (13 hospitals) RCT of N=118 in Canada. This was a sub-study of the Canadian Erythropoetin Study
Patient characteristics	Inclusion criteria: ➢ Aged 18-75 years ➢ Receiving hemodialysis 3 times weekly ➢ Clinically stable with an average Hb <90 g/l for at least 3 months ➢ Maintained Hb at 30 g/l above baseline for at least 6 months ➢ Technically adequate echocardiograms were obtained at baseline and at 12 months following initial randomisation Exclusion criteria: ➢ Insulin-dependent diabetes mellitus

<table>
<tr><td></td><td>
Inability to perform a 6 min exercise test
<table>
<tr><th>Variable</th><th>Baseline</th></tr>
<tr><td>Age (years)</td><td>45 ± 16</td></tr>
<tr><td>Sex (male/female)</td><td>14/8</td></tr>
<tr><td>Time on dialysis (years)</td><td>5 ± 5</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>EPO to Hb 30 g/l above baseline</td></tr>
<tr><td>Comparison</td><td>Placebo (for 6 months only)</td></tr>
<tr><td>Length of follow-up</td><td>Follow-up was 9.9 ± 0.9 months after achieving target Hb</td></tr>
<tr><td>Outcome measures</td><td>Echocardiography – left ventricular mass, left ventricular end diastole, left ventricular posterior wall, interventricular septum, mean wall thickness, left ventricular end diastolic volume</td></tr>
<tr><td>Effect size</td><td>
Echocardiography
<table>
<tr><th>Variable</th><th>Baseline</th><th>Follow-up</th><th>P value</th></tr>
<tr><td>Hemoglobin (g/l)</td><td>63 ± 8</td><td>114 ± 15</td><td>0.0001</td></tr>
<tr><td>Systolic blood pressure (mm Hg)</td><td>141 ± 19</td><td>144 ± 16</td><td>0.15</td></tr>
</table>
</td></tr>
</table>

Diastolic blood pressure (mm Hg)	76 ± 12	81 ± 9	0.01
Weight (kg)	65.8 ± 13	66.3 ± 13	0.33
Echocardiography			
Left ventricular mass (g)	253 ± 77	215 ± 71	0.0004
Left ventricular end diastole (cm)	5.5 ± 0.6	5.14 ± 0.6	0.003
Left ventricular posterior wall (cm)	0.97 ± 0.1	0.96 ± 0.1	0.82
Interventricular septum (cm)	1.0 ± 0.2	0.95 ± 0.2	0.16
Mean wall thickness (cm)	0.99 ± 0.1	0.96 ± 0.1	0.32
Left ventricular end diastolic volume (ml)	173 ± 60	138 ± 48	0.005

- In study participants with a left ventricular mass above 210g at baseline, LV mass decreased
- Similarly, LV end diastolic volume decreased for study participants in this category

	Baseline	Follow-up	P value
Baseline LV mass >210 g			
Left ventricular mass (g)	292 ± 57	234 ± 72	<0.001
Left ventricular end diastolic volume (ml)	193 ± 61	142 ± 46	<0.001
Baseline LV mass <210 g			
Left ventricular mass (g)	170 ± 39	171 ± 37	NS

	Left ventricular end diastolic volume (ml)	129 ± 30	129 ± 53	NS
Source of funding	Not indicated			
Citation				
NCC CC ID (Ref Man)	1576			

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis 1999;**34**:125-34.
Study type	Retrospective cohort study
Evidence level	2+
Study objective	To describe the prevalence and incidence of left ventricular hypertrophy (LVH) and left ventricular growth (LVG) in patients with renal insufficiency and to identify clinical or laboratory variables that predict LVG
Number of patients	N=246

<table>
<tr><td></td><td>Multicenter study in 8 academic centers in Canada</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
➢ Impaired renal function defined as ceratinine clearance 25-75 ml/min
➢ Clinically established chronicity by biopsy or clinical course and/or ultrasound showing small kidneys

Exclusion criteria:
➢ Unable to commit for follow-up
➢ Not expected to live for duration of study (1 year)
➢ Receiving immunosuppressive therapy for renal disease
➢ Likely to require dialysis therapy during study period (1 year)

<table>
<tr><th>Variables</th><th>Patients with baseline and 12-month follow-up data and second echocardiogram (N=246)</th></tr>
<tr><td>Sex (male)</td><td>166 (67.5%)</td></tr>
<tr><td>Race

White

Asian

Black</td><td>

215 (89%)

14 (5.8)

6 (2.5%)</td></tr>
<tr><td>Age (y)</td><td>56.7 ± 13.8</td></tr>
<tr><td>Creatinine clearance (ml/min)</td><td>36.8 ± 15</td></tr>
</table>
</td></tr>
</table>

Haemoglobin (g/dl)	12.8 ± 1.9
Duration of renal disease (y)	4 (2-10)
Diabetes all	63 (25.8%)
Diabetes insulin dependent	28 (52.8%)
Angina	41 (16.8%)
Past history of myocardial infarction	31 (12.8%)

Patient characteristics continued…

Variables	Patients with baseline and 12-month follow-up data and second echocardiogram (N=246)
Past history of congestive heart failure	18 (7.5%)
Any cardiovascular disease	96 (39%)
Use of ACE inhibitors	127 (52%)
Use of Calcium channel blockers	105 (43.2%)
Systolic BP (mm Hg)	143.6 ± 23.8
Diastolic BP (mm Hg)	84.6 ± 11.4
Weight (kg)	75.5 ± 16.7
Posterior wall thickness (mm)	10.5 ± 2.1

<table>
<tr><td></td><td>
<table>
<tr><td>Intraventricular septal thickness (mm)</td><td>10.8 ± 2.5</td></tr>
<tr><td>Left ventricular end diastolic diameter (mm)</td><td>51.2 ± 6.9</td></tr>
<tr><td>Left ventricular mass index (g/m^2)</td><td>113.2 ± 37.2</td></tr>
<tr><td>Left ventricular hypertrophy</td><td>84 (34.2%)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>N/A</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>Study duration 12 months</td></tr>
<tr><td>Outcome measures</td><td>1° outcome measure = change in left ventricular mass index (LVMI) over 12 months

2° outcome measures = number of hospitalisations and change in cardiac status class (New York Heart Association or Canadian Cardiovascular Society classification)</td></tr>
<tr><td>Effect size</td><td>Prevalence of LVH and growth of LVM
➢ 34% of the patient population had LVH at the start of the study, with a greater prevalence with decreasing renal function

<table>
<tr><th></th><th>Patients with LVH</th><th>Patients without LVH</th><th>P value</th></tr>
<tr><td>Mean creatinine clearance (ml/min)</td><td>32.1</td><td>37.7</td><td>0.001</td></tr>
<tr><td>Mean Hb level

(g/dl)</td><td>12.08</td><td>13.0</td><td><0.0001</td></tr>
<tr><td>Mean systolic blood pressure (mmHg)</td><td>141.3</td><td>150.3</td><td><0.0003</td></tr>
</table>
</td></tr>
</table>

- 38% of the patient population had LVH at 12-month follow-up and were analysed according to renal function categories

	CCr >50 ml/min		CCr 25-50 ml/min		CCr <25 ml/min	
	LVH-	LVH+	LVH-	LVH+	LVH-	LVH+
Number	40	10	88	44	26	36
Mean Hb level (g/dl)	14.5 ± 1.5	13.3 ± 0.97	13 ± 1.8	12.5 ± 1.92	12 ± 1.6	11.5 ± 1.5
P value	0.003		0.189		0.213	
Mean change Hb	-0.16 ± 0.8	0.03 ± 0.6	-0.21 ± 1.2	-0.31 ± 1.5	-0.23 ± 0.92	-0.63 ± 1.3
P value	0.426		0.679		0.163	

CCr = creatinine clearance

- Decrease in Hb level was significant in groups with and without LVG over the 12-month period. Multivariate logisitic analysis showed decrease in Hb level [OR 1.32 (95% CI 1.1 to 1.59)] was one of three factors, including systolic blood pressure and baseline LVMI that predicted LVG.
- The robustness of this analysis was tested and confirmed by repeating the analysis with the 158 patients who did

not have a high LVH at baseline (OR 1.35 for 0.5- g/l decrease; 95% CI 1.08 to 1.70; P=0.01).

	Without LVG N=191	With LVG N=55	P value
Baseline Hb (g/dl)	12.9 ± 0.17	12.8 ± 0.21	0.719
Hb at 12-month follow up (g/dl)	-0.11 ± 0.12	-0.85 ± 0.11	0.001
Baseline LVMI (g/m^2)	116 ± 39.2	103.5 ± 29.9	0.012
LVMI at 12-month follow up (g/m^2)	-9.27 ± 21.8	35.2 ± 20.8	<0.001

Progression of cardiac symptoms

- 31 of 206 patients who had evaluations at baseline and at 12-month follow up had progression of cardiac symptoms.
- However, no significant changes in Hb levels were found. Without cardiac symptoms (N=175) –0.28 ± 1.25 vs. with cardiac symptoms (n=31) –0.33 ± 1.13 (P=0.828)

Hospitalisations

- There were 55 hospitalisations in 238 patients of the 246 patients who assessable echocardiograms and 12-month follow up (some were multiple admissions).
- Mean Hb level at baseline (12.4 ± 2.0 vs 13.0 ± 1.8 g/dl; P=0.029) predicted subsequent hospitalisations, along with mean creatinine clearance (P=0.01) and median serum parathyroid hormone levels (P=0.008)

Source of funding	A national kidney foundation

Citation	
NCC CC ID (Ref Man)	1590

Evidence Table PROG1 In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit are associated with adverse outcomes and what are the effects of a) Age b) Gender c) Ethnicity	
Bibliographic reference	Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis 1997; **29**:541-8.
Study type	Descriptive (non-analytical) study
Evidence level	3+
Study objective	To evaluate changes in blood pressure and left ventricular hypertrophy in predialysis ESRD patients after correction of anaemia with EPO
Number of patients	N=11
Patient characteristics	Exclusion criteria: ➢ requirement of dialysis within 8 months ➢ difficult to control hypertension or arrhythmia, valvular disease or any other condition that might complicate the echocardiogram follow-up

Variable	Baseline (N=11)
Age (years) (Mean ± SD)	53.8 ± 12.9; range 21 to 68 years
No. of men	6
Renal disease	
Nephroangiosclerosis	2
Glomerulonephritis	2
Interstitial nephropathy	2
Polycyctic disease	1
Diabetes mellitus	1
Undefined	3
No. on antihypertensive medication	8
Haemoglobin (g/dl)	9.0 ± 0.3
Hematocrit (%)	26.3 ± 0.6
Systolic blood pressure (mm Hg)	144.0 ± 9.8
Diastolic blood pressure (mm Hg)	76.0 ± 6.9
Creatinine (mg/dl)	6.3 ± 1.3
Creatinine clearance (ml/min)	13.3 ± 1.5

<table>
<tr><td></td><td></td></tr>
<tr><td>Intervention</td><td>Epoetin to a target Hct of 35%</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>Study duration 6 months</td></tr>
<tr><td>Outcome measures</td><td>➢ Continuous 24-hour ambulatory blood pressure (CABP) monitoring
➢ Echocardiography</td></tr>
<tr><td>Effect size</td><td>Haematocrit
➢ Increased to 34.4 ± 1.1% at 3 months and remained stable, 34.7 ± 1.3% at 6 months

Rate of progression of renal failure
➢ No differences were observed when comparing the slope of 1/serum creatinine vs. time before and after EPO treatment, indicating there was no change in rate of progression of renal failure

Continuous 24-hour ambulatory blood pressure monitoring
➢ No significant changes were observed in the mean BP recordings

<table>
<tr><th>CABP Monitoring</th><th>Baseline</th><th>3 months</th><th>6 months</th><th>P value</th></tr>
<tr><td>Daytime</td><td></td><td></td><td></td><td></td></tr>
<tr><td>SBP</td><td>142.1 ± 8.1</td><td>140.0 ± 7.0</td><td>144.2 ± 9.5</td><td>NS</td></tr>
<tr><td>DBP
% SBP > 140 mmHg</td><td>80.7 ± 5.5</td><td>82.1 ± 4.0</td><td>81.7 ± 4.8</td><td>NS</td></tr>
<tr><td>% DBP > 90 mmHg</td><td>48.9 ± 12.9</td><td>50.9 ± 12.3</td><td>59.2 ± 13.7</td><td>NS</td></tr>
</table></td></tr>
</table>

	31.1 ± 11.6	29.3 ± 7.8	29.7 ± 9.8	NS
Night time				
SBP	132.7 ± 7.8	127.5 ± 7.1	137.0 ± 9.5	NS
DBP	71.4 ± 4.9	72.3 ± 3.5	73.5 ± 4.0	NS
% SBP > 140 mmHg	36.7 ± 13.7	34.6 ± 12.2	50.6 ± 16.4	NS
% DBP > 90 mmHg	17.9 ± 10.5	12.0 ± 5.5	8.12 ± 5.5	NS

Echocardiography

- A trend was found in decreasing LVEDD and thickening of posterior wall and inter-ventricular septum in the LVPWT and IVST
- No changes were observed in the remaining left ventricle measurements
- The cardiac output decreased by month 3 of EPO treatment (i.e. improvement in anemia)
- An increase in total peripheral resistance was observed after month 3 and month 6 of EPO treatment (i.e. improvement in anemia)
- No significant changes were observed in the myocardial contractility parameters (expressed as ejection time, ejection fraction, fractional shortening and velocity of circumferential fibre shortening)

Parameter	Baseline	3 months	6 months	P value
LVEDD (mm)	48.7 ± 1.4	47.3 ± 1.8	47.1 ± 2.7	NS
LVESD (mm)	32.9 ± 2.1	30.9 ± 2.3	31.2 ± 2.5	NS
IVST (mm)	14.8 ± 1.4	14.4 ± 1.5	13.6 ± 1.4	NS

LVPWT (mm)	12.2 ± 1.1	11.8 ± 0.9	11.3 ± 1.3	NS
LVMi (g/m^2)	178.2 ± 20.6	161.7 ± 20.8	147.3 ± 20.6	<0.05*
CO (l/min)	4.75 ± 0.39	4.0 ± 0.5	4.1 ± 0.5	<0.05†
Coi ($l/min/m^2$)	3.02 ± 0.3	2.66 ± 0.20	2.7 ± 0.5	<0.05†
TPR ($dyne/cm^6/sec$)	1,896 ± 165	2,119 ± 144	2,117 ± 0.3	<0.05†
EF (%)	62.9 ± 10	60.1 ± 13.4	61.2 ± 208	NS
ET (sec)	0.33 ± 0.06	0.32 ± 0.05	0.31 ± 10.9	NS
FS (%)	34.0 ± 7.6	34.5 ± 8.7	35 ± 0.03	NS
VCF (s)	1.04 ± 0.2	1.04 ± 0.10	1.10 ± 0.29	NS

* baseline vs. 6 months

† baseline vs. 3 and 6 months

Abbreviations

LVEDD	Left ventricular end-diastolic diameter
LVESD	Left ventricular end-systolic diameter
IVST (mm)	Inter-ventricular septum thickness
LVPWT (mm)	Left ventricular posterior wall thickness
LVMi (g/m^2)	Left ventricular mass index
CO (l/min)	Cardiac output

	COi (l/min/m^2)	Cardiac output index
	TPR (dyne/cm^6/sec)	Total peripheral resistance
	EF (%)	Ejection fraction
	ET (sec)	Ejection time
	FS (%)	Fractional shortening
	VCF (s)	Velocity of circumferential fibre shortening
Source of funding	Not reported	
Citation		
NCC CC ID (Ref Man)	1594	

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Moreno F, Aracil FJ, Perez R, Valderrabano F. Controlled study on the improvement of quality of life in elderly hemodialysis patients after correcting end-stage renal disease-related anemia with erythropoietin. American Journal of Kidney Diseases 1996;**27**:548-56.

<table>
<tr><td>Study type</td><td>Presented as a matched-cohort study but data analysis is presented as a before and after (non-analytical) study</td></tr>
<tr><td>Evidence level</td><td>3+</td></tr>
<tr><td>Study objective</td><td>Primary objective: To evaluate if EPO treatment for anemia of ESRD improves the quality of life of elderly patients receiving hemodialysis when compared to younger hemodialysis patients

Secondary objective: To identify factors associated with quality of life improvement after treatment of ESRD-related anemia</td></tr>
<tr><td>Number of patients</td><td>Treatment group N=57

Control group N=29

➢ Multisite study; 7 dialysis centres in Madrid, Spain
➢ Age-matched control group consisted of hemodialysis patients not requiring EPO treatment</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
➢ Clinically stable for more than 3 months and on chronic hemodialysis
➢ Required EPO treatment

Exclusion criteria:
➢ Diabetes
➢ Uncontrolled hypertension
➢ Non-ESRD-related anemia
➢ Contraindications to EPO treatment
➢ Associated severe disease
➢ Changed dialysis modality to peritoneal dialysis or discontinued hemodialysis for renal transplant

<table>
<tr><th>Variable</th><th>EPO group</th><th>Control</th><th>P value</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><th></th><th>N=57</th><th>N=29</th><th></th></tr>
<tr><td>Mean age (years)</td><td>50 ± 2</td><td>53 ± 2</td><td>NS</td></tr>
<tr><td>Sex (M % /F %)</td><td>56 / 44</td><td>79 / 21</td><td><0.05</td></tr>
<tr><td>Baseline Hct (%)</td><td>21 ± 0.3</td><td>30 ± 0.8</td><td><0.0001</td></tr>
<tr><td>Years on dialysis</td><td>2.9 ± 0.4</td><td>5.6 ± 0.8</td><td><0.005</td></tr>
<tr><td>Previous renal transplant (%)</td><td>14</td><td>28</td><td>NS</td></tr>
<tr><td>Friedman’s comorbidity index</td><td>1.5 ± 0.2</td><td>1.6 ± 0.2</td><td>NS</td></tr>
<tr><td>Arterial hypertension (%)</td><td>50</td><td>66</td><td>Not given</td></tr>
<tr><td>Chronic liver disease (%)</td><td>0</td><td>27</td><td>Not given</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>EPO</td></tr>
<tr><td>Comparison</td><td>Primary objective: N/A

Secondary objective: no EPO</td></tr>
<tr><td>Length of follow-up</td><td>Study duration 6 months</td></tr>
<tr><td>Outcome measures</td><td>Primary objective:

Quality of life – assessed by the following questionnaires:
i. Karnofsky performance scale (KS), which is an indicator of self-sufficiency and functional capacity. It is a 10-level scale, with scores ranging from 100 (no limitations) to 10 (moribund).
ii. The Sickness Impact Profile (SIP), which is a non-disease specific behaviour-based questionnaire consisting of 136 statements grouped into 12 categories. These are further grouped into physical dimension (body</td></tr>
</table>

<table>
<tr><td></td><td>care & movement, mobility and ambulation) and psychosocial dimension (emotional behaviour, social interaction, alertness and communication), leaving 5 independent categories. All partial categories give the global dimension. Scores vary from 0 (absence of dysfunction) to 100 (maximum dysfunction)</td></tr>
<tr><td>Effect size</td><td>
EPO treatment
➢ The mean initial dose was 96 ± 8 U/kg/wk which reduced to 75 ± 10 U/kg/wk at the end of the study
➢ Onset of hypertension was observed in 4 patients (7%), worsening of previous hypertension in 7 patients (12%) and one patient suffered vascular access thrombosis

Quality of Life
➢ Mean KS and SIP scores significantly increased in the EPO-treatment group when scores at 3 months and 6 months were compared to those at baseline
➢ However, no differences in QoL were seen between month 3 and month 6 in the EPO-group
➢ No changes in QoL were seen in the control group

<table>
<tr><th></th><th>Baseline
Mean ± SEM</th><th>Month 3
Mean ± SEM</th><th>Month 6
Mean ± SEM</th><th>P value</th></tr>
<tr><td colspan="5">EPO group (N=57)</td></tr>
<tr><td>Hematocrit (%)</td><td>21 ± 0.3</td><td>28 ± 0.4</td><td>29 ± 0.4</td><td>0.0001</td></tr>
<tr><td>KS</td><td>68.4 ± 1.8</td><td>78.6 ± 1.6</td><td>81 ± 1.4</td><td>0.0001</td></tr>
<tr><td>SIP- physical dimension</td><td>15.4 ± 1.8</td><td>11.3 ± 1.6</td><td>9.6 ± 1.4</td><td>0.0001</td></tr>
<tr><td>SIP - psychosocial dimension</td><td>19 ± 1.9</td><td>12.2 ± 1.3</td><td>10.8 ± 1.3</td><td>0.0001</td></tr>
<tr><td>SIP- global score</td><td>19.8 ± 1.6</td><td>14.8 ± 1.4</td><td>13.5 ± 1.2</td><td>0.0001</td></tr>
</table>
</td></tr>
</table>

Control group (N=29)				
Hematocrit (%)	30 ± 0.8	31 ± 0.8	31 ± 0.8	NS
KS	79.7 ± 2.6	77.2 ± 2.7	76.9 ± 2.6	NS
SIP- physical dimension	11.6 ± 2.4	10.5 ± 2.5	10.6 ± 2.5	NS
SIP - psychosocial dimension	16 ± 3	14 ± 2.7	14.3 ± 2.9	NS
SIP- global score	16.6 ± 2.4	14.9 ± 2.2	15.1 ± 2.2	NS

Factors associated with improvement of quality of life indicators

- *Final Hct was positively related to improvement in the SIP global score by linear regression (β coefficient 0.57; P<0.05; R^2 0.57)*

Effect of age on the evolution of QoL indicators after EPO treatment

- Patients were distributed into 2 age groups and patients with diabetes or other severe associated disease excluded from the analysis

	≥60 years	*<60 years*	*P value*
No. of patients	*23*	*34*	*NS*
Mean age	*67 ±1*	*38 ±2*	*NS*
Sex (M/F)	*52%/48%*	*59%/41%*	*NS*
Years on dialysis	*2 ±0.4*	*3.5 ±0.6*	*NS*

	<table><tr><td>*Hypertension*</td><td>*52%*</td><td>*53%*</td><td>*NS*</td></tr><tr><td>*Previous transplant*</td><td>*4%*</td><td>*20%*</td><td>*NS*</td></tr><tr><td>*Friedman's comorbidity index*</td><td>*2.26 ±0.31*</td><td>*1.03 ±0.16*</td><td>*<0.001*</td></tr></table> ➢ Improvement in Hct levels was parallel in aged (≥60 years) and younger patients (<60 years), with no significant differences at baseline or month 3. However, at month 6, Hct levels were lower in the older age group (P<0.005) ➢ The older age group had poorer baseline quality of life as assessed by KS (P<0.0001) and SIP (P<0.0001), which was maintained throughout the 6-month study period ➢ No differences were observed in the improvement of QoL scores in the older group vs. the younger age group ➢ To assess consisitency of results, comparisons of QoL scores for patients receiving EPO aged <60 years (N=34) vs. ≥65 years (N=15) were made. Although QoL scores significantly improved using both KS and SIP, no interaction was found between age and QoL scores
Source of funding	Not reported
Citation	
NCC CC ID (Ref Man)	1599

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

<table>
<tr><td>Bibliographic reference</td><td>Li S., Collins AJ. Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients.[see comment]. Kidney International 2004;65:626-33.</td></tr>
<tr><td>Study type</td><td>Cohort study</td></tr>
<tr><td>Evidence level</td><td>2+</td></tr>
<tr><td>Study objective</td><td>To assess the relationship between hematocrit levels above 36% and morbidity and mortality due to cardiovascular disease (congestive heart failure, ischemic heart disease, cerebrovascular disease, etc.) in incident hemodialysis patients with ESRD</td></tr>
<tr><td>Number of patients</td><td>N=50,579

Selected from 1998 data = 26,207

Selected from 1999 data = 24,372</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
➢ Consistently received hemodialysis for 9 months after the onset of ESRD

Exclusion criteria:
➢ Patients who dies during the 9 months after inititation of hemodialysis
➢ Patients who changed modality to peritoneal dialysis or had a transplant during the 9 months after inititation of hemodialysis
➢ Incomplete demographic and baseline characteristics data (e.g. date of birth, gender, race, creatinine level at onset of ESRD)
➢ Fewer than 4 EPO claims during the 6-month entry period

<table>
<tr><th>Variable</th><th></th></tr>
<tr><td>Mean age (years)</td><td>65.4 ± 14.3</td></tr>
<tr><td>Male gender (%)</td><td>50.6</td></tr>
</table>
</td></tr>
</table>

Race (%) White Black	 61.0 33.0
Diabetes as a primary cause of ESRD (%)	48.1
Mean GFR at ESRD onset (ml/min)	8.6 ± 3.9
Mean hospital stay (days)	6.1 ± 11.8
Patients with urea reduction ratio (URR) ≥ 70%	54.3
Mean hematocrit value (%)	34.1 ± 3.0

- Due to significant differences in patient characteristics and comorbid conditions when grouped into hematocrit levels between the >33% to ≤36% and other groups (see table below), an adjustment was made for these differences in data analysis

Variable	Hct ≤30%	Hct >30 to ≤ 33%	Hct >33 to ≤ 36%	Hct >36 to ≤39%	Hct >39%	P value
No. of patients	4308	11,558	22,192	10,265	2,256	<0.0001
Mean age (years)	61.3 ± 15.5	64.6 ± 14.4	66.1 ± 13.9	66.2 ± 14.1	66.1 ± 14.2	<0.0001
Male (%)	48.3	48.0	50.8	53.1	54.8	<0.0001

	Race (%) White Black	 51.6 44.2	 59.9 34.8	 63.1 30.7	 62.1 31.1	 59.2 34.1	<0.0001
	Diabetes as primary cause of ESRD (%)	45.4	50.6	48.4	46.4	46.3	<0.0001
	Mean GFR at ESRD onset (ml/min)	8.4 ± 4.0	8.6 ± 3.9	8.6 ± 3.9	8.7 ± 4.0	8.6 ± 4.1	<0.0001
	Mean hospital stay (days)	13.0 ± 17.6	8.6 ± 13.8	4.9 ± 9.9	3.7 ± 8.7	4.0 ± 9.7	<0.0001
	Mean no. of vascular access procedures	3.9 ± 5.8	3.4 ± 5.6	2.6 ± 8.3	2.3 ± 4.5	2.4 ± 5.3	<0.0001
	Mean hematocrit (%)	28.0 ± 2.0	31.8 ± 0.8	34.5 ± 0.8	37.2 ± 0.8	40.6 ± 1.5	<0.0001
Intervention	EPO						
Comparison	N/A						

<table>
<tr><td>Length of follow-up</td><td>➢ Hospitalisation 2.5 years
➢ Mortality 3 years</td></tr>
<tr><td>Outcome measures</td><td>The Hct >33 to 36% was used as a reference from which all outcomes were adjusted. I.e. all relative risks and 95% CI for specific Hct groups were compared to those of >33 to ≤36% Hct group

➢ First hospitalisation due to cardiac disease
➢ First hospitalisation for patients with cardiac comorbid conditions
➢ Death due to cardiac diseases and all-cause death
➢ First hospitalisation and death for patients without pre-existing cardiac disease</td></tr>
<tr><td>Effect size</td><td>Adjusted relative risk of first hospitalisation due to any cardiac disease (2.5 year follow up)

<table>
<tr><th>Hematocrit value (%)</th><th>Relative risk</th><th>95% CI</th><th>P value</th></tr>
<tr><td>10 to 30</td><td>1.18</td><td></td><td></td></tr>
<tr><td>>30 to 33</td><td>1.07</td><td></td><td></td></tr>
<tr><td>>33 to 36</td><td>1.00</td><td>N/A</td><td>N/A</td></tr>
<tr><td>>36 to 39</td><td>0.92</td><td>0.88 to 0.97</td><td>*</td></tr>
<tr><td>>39</td><td>0.79</td><td>0.72 to 0.87</td><td>*</td></tr>
</table>
* significant (i.e. 95% CI did not include 1.00)

Adjusted relative risk of first hospitalisation due to specific cardiac diseases (2.5 year follow up)</td></tr>
</table>

Hematocrit (%)	Relative risk due to congestive heart failure, fluid overload or cardiomyopathy	P value	Relative risk due to ischemic heart disease, cerebrovascular disease or circulatory system disease	P value	Relative risk due to other cardiac diseases	P value
>33 to 36	1.00	N/A	1.00	N/A	1.00	N/A
>36 to 39	0.85 (95% CI 0.77 to 0.95)	*	0.94 (95% CI 0.88 to 1.01)	NS	0.95 (95% CI 0.87 to 1.05)	NS
>39	0.80 (95% CI 0.65 to 0.97)	*	0.81 (95% CI 0.70 to 0.93)	*	0.76 (95% CI 0.62 to 0.92)	*

* 95% CI did not include 1.00

Adjusted relative risk of first hospitalisation for patients with cardiac comorbid conditions (2.5 year follow up)

- A sub-group was identified, N=45,166 with one or more of the following: artheroscelrotic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack and other cardiac diseases
- A similar pattern to that seen with hospitalisation and Hct in all selected hemodialysis patients was seen in patients with cardiac comorbid conditions

Hematocrit value (%)	Relative risk	95% CI	P value
>33 to 36	1.00	N/A	N/A

>36 to 39	0.93	0.89 to 0.98	*
>39	0.79	0.71 to 0.87	*

* 95% CI did not include 1.00

Adjusted relative risk of death due to cardiac diseases (3 year follow up)

Hematocrit value (%)	Relative risk	95% CI	P value
>33 to 36	1.00	N/A	N/A
>36 to 39	0.92	0.87 to 0.98	*
>39	0.83	0.74 to 0.93	*

* 95% CI did not include 1.00

Adjusted relative risk of all-cause death (3 year follow up)

- All-cause death encompassed cardiac disease, infection and other causes
- The same pattern to that observed in risk of death due to cardiac causes was seen

Hematocrit value (%)	Relative risk	95% CI	P value
>33 to 36	1.00	N/A	N/A
>36 to 39	0.92	0.88 to 0.96	*
>39	0.86	0.80 to 0.93	*

* 95% CI did not include 1.00

Adjusted relative risk of hospitalisation and death for patients without pre-existing cardiac disease (3 year follow up)

- Evaluated in patients without pre-exisiting cardiac disease (number of patients not given by the authors) with Hct >36% to ≤ 39% and compared to the reference population (Hct > 33% to ≤ 36%)
- These patients had a lower adjusted risk of death and hospitalisation during the follow-up period
- The authors state analysis performed using 3-month entry period after 90 days of ESRD, with follow-up period of 1, 2 and 3 months as well as on the basis of broader enrolment criteria, increasing the sample size from 50,579 patients with 3 or more EPO claims to 52,473 patients with 2 or more EPO claims both obtained similar results

	Relative risk	P value
All-cause death	0.69	0.0002
Any cardiac death	0.69	0.0137
All-cause hospitalisation	0.78	<0.0001
Any cardiac hospitalisation	0.74	0.0005
Hospitalisation due to cardiac disease	0.71	0.026
Hospitalisation due to CHF, fluid overload and cardiomyopathy	0.68	0.045
Hospitalisation due to other cardiac disease	0.79	0.07

Source of funding	In part by a research foundation and pharmaceutical company
Citation	
NCC CC ID (Ref Man)	1603

Evidence Table

PROG1

In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of

a) Age
b) Gender
c) Ethnicity

Bibliographic reference	Metry G, Wikstrom B, Valind S, Sandhagen B, Linde T, Beshara S et al. Effect of normalization of hematocrit on brain circulation and metabolism in hemodialysis patients. Journal of the American Society of Nephrology 1999;**10**:854-63.
Study type	Presented as a cohort study, but using healthy control subjects. As results are presented as a before and after study, it was appropriate to downgrade the study to a non-analytical study
Evidence level	3+
Study objective	To investigate the effects of Hct normalisation and related change in blood rheology in hemodialysis ESRD patients on brain circulation and oxygen metabolism by means of positron emission topography (PET)
Number of patients	N=7
Patient characteristics	Inclusion criteria: ➢ Anemia of renal origin ➢ Baseline Hb <12 g/dl in men and <11 g/l in women ➢ Adequate iron stores, s-ferittin ≥50 µg/l ➢ Exclusion criteria: ➢ Uncontrolled hypertension (diastolic BP >110 mmHg ➢ Co-existing major disease e.g. liver or cardiac insufficiency, malignancy, etc.

<table>
<tr><td></td><td>
<table>
<tr><th>Patient</th><th>Gender</th><th>Age (y)</th><th>Original renal disease</th></tr>
<tr><td>1</td><td>F</td><td>58</td><td>Chronic glomerulonephritis</td></tr>
<tr><td>2</td><td>M</td><td>65</td><td>Nephrosclerosis</td></tr>
<tr><td>3</td><td>M</td><td>51</td><td>Cardiolipin antibody syndrome</td></tr>
<tr><td>4</td><td>F</td><td>64</td><td>Diabetic nephropathy</td></tr>
<tr><td>5</td><td>M</td><td>60</td><td>IgA nephritis</td></tr>
<tr><td>6</td><td>M</td><td>50</td><td>Diabetic nephropathy</td></tr>
<tr><td>7</td><td>M</td><td>49</td><td>Chronic glomerulonephritis</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>EPO to a target Hb 14-15 g/dl for men and 13-14 g/dl for women</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>Not indicated, however, measurements were performed once at the basal level and repeated when target Hb level had been stable for 2 months</td></tr>
<tr><td>Outcome measures</td><td>

Hemodynamic measurements – cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR), mean arterial pressure (MAP)
Positron emission topography (PET) measuerments – regional cerebral blood flow (rCBF), fraction of oxygen in arterial blood extracted by the brain (rOER), cerebral metabolic rate of oxygen ($rCMRO_2$)
Blood gas analyses – blood pH, arterial CO_2 saturation (PCO_2), arterial O_2 tension (PO_2), arterial O_2 saturation (SaO_2), arterial O_2 content (caO_2), carboxyhemoglobin (COHb) and methemoglobin (MetHb)
Blood rheology – whole blood viscosity, plasma viscosity, erythrocyte fluidity and erythrocyte aggregability
Blood chemistry

</td></tr>
</table>

Effect size

Hb and Hct

- Hb and Hct rose from 9.8 ± 1.3 to 14.2 ± 0.6 g/dl and 29.3 ± 3.3 to 42.4 ± 2.2% respectively over a period of 5-6 months

Hemodynamic measurements

- Cardiac output and stroke volume both significantly decreased
- Total peripheral resistance increased significantly
- MAP did not change

	Cardiac output (CO) (l/min)	Stroke volume (SV) (ml)	Total peripheral resistance (TPR) ($dyn.s.cm^{-5}.m^{-2}$)	Mean arterial pressure (MAP) (mmHg)
Baseline	5.99 ± 1.21	79 ± 11	2,635 ± 907	102 ± 19
After Hb target	4.32 ± 1.16	64 ± 10	3,632 ± 1,058	105 ± 16
P value	<0.01	<0.01	<0.05	NS

Blood gas analyses

- Arterial blood pH, PCO_2, PO_2 and SaO_2 were not altered by EPO treatment and increase in Hb
- caO_2 significantly increased after anemia correction

	pH	PCO_2 (kPa)	PO_2 (kPa)	SaO_2 (%)	caO_2	Hb	COHb (%)	MetHb (%)

					(mmol/l)	(g/dl)		
Baseline	7.41±0.03	4.85±0.44	9.10±1.96	94.0±2.9	5.7±0.7	9.8±1.3	2.8±1.0	0.8±0.2
After Hb target	7.41±0.03	4.88±0.56	9.81±0.61	94.6±1.1	8.0±0.4	14.2±0.6	3.0±0.8	0.9±0.2
P value	NS	NS	NS	NS	<0.001	<0.001	NS	NS

Blood rheology

- Only whole blood viscosity increased significantly after anemia correction

	Blood viscosity ($mPa.s^{-1}$)	Plasma viscosity ($mPa.s^{-1}$)	Erythrocyte fluididty ($Pa^{-1}.s^{-1}$)	Erythrocyte aggregability	Hct (%)
Baseline	3.72 ± 0.38	1.51 ± 0.19	85.8 ± 4.8	1.2 ± 0.1	29.3 ± 3.3
After Hb target	4.57 ± 0.16	1.46 ± 0.13	79.9 ± 7.4	1.22 ± 0.02	42.4 ± 2.2
P value	<0.005	NS	NS	NS	<0.001

Blood chemistry

- *Serum aluminium remained within the normal range before and after EPO administration*
- Plasma parathyroid increased after EPO treatment. However, both values were higher than normal
- Both plasma fibrinogen and serum total cholesterol did not significantly increase with EPO treatement

	Baseline	After anaemia correction	P value
Serum aluminium (μg/l)	6.3 ± 2.2	7.5 ± 2.4	NS
Plasma parathyroid hormone (pmol/l)	54 ± 13	84 ± 11	<0.05
Plasma fibrinogen (g/l)	6.55 ± 1.38	6.10 ± 1.03	NS
Serum cholesterol (mol/l)	7.37 ± 1.04	6.39 ± 1.13	NS

PET measurements

Cerebellum		Deep Nuclei		Cerebral cortices				White matter	Total cortices
		Putamen	Thalamus	Parietal	Frontal	Occipital	Temporal		
Regional cerebral blood flow (rCBF) (ml.min^{-1}.100ml^{-1})									
Baseline	76 ± 12	87 ± 16	94 ± 15	65 ± 11	56 ± 13	78 ± 13	51 ± 11	29 ± 7	65 ± 11
After	56 ± 11[c]	61 ± 14[d]	66 ± 18[d]	51 ± 13[e]	46 ± 11[e]	61 ± 15[e]	36 ± 9[e]	26 ± 6	48 ± 12[e]
Normal	60 ± 11	65 ± 12	71 ± 14	51 ± 9	53 ± 9	64 ± 9	39 ± 8	23 ± 3	51 ± 9
Regional cerebral blood volume (rCBV) (ml/100ml cc brain tissue)									
Baseline	3.7 ± 0.9	3.1 ± 0.6	2.9 ± 0.7	3.5 ± 0.1	2.6 ± 0.2	4.6 ± 0.8	3.3 ± 0.5	1.3 ± 0.1	3.5 ± 0.5

After	4.8 ± 0.9 [e]	3.7 ± 0.8 [e]	4.8 ± 0.9 [d]	4.4 ± 0.5 [e]	3.5 ± 0.4 [e]	5.8 ± 0.8 [c]	4.1 ± 0.4 [c]	1.7 ± 0.2 [e]	4.6 ± 0.6 [c]
Normal	4.1 ± 1.1	2.6 ± 0.5	3.7 ± 0.8	3.6 ± 0.7	3.1 ± 0.8	4.6 ± 0.9	3.1 ± 0.7	1.2 ± 0.3	3.6 ± 0.8
Regional oxygen extraction ratio (rOER) (%)									
Baseline	44 ± 3.0	44 ± 7.0	37 ± 9	45 ± 3	43 ± 2	42 ± 3	45 ± 5	40 ± 4	44 ± 3
After	50 ± 2.0 [e]	55 ± 3.0 [c]	40 ± 5	52 ± 6 [e]	50 ± 6 [e]	48 ± 6	52 ± 5 [e]	47 ± 2 [e]	51 ± 6 [e]
Normal	43 ± 3.0	43 ± 8.0	39 ± 3	44 ± 2	43 ± 3	44 ± 6	42 ± 6	40 ± 1	43 ± 4
Regional cerebral metabolic rate of oxygen ($rCMRO_2$) ($ml.min^{-1}.100ml^{-1}$)									
Baseline	4.83± 0.81	5.22± 0.70	4.36± 0.79	3.94± 0.70	3.49± 0.50	4.52± 0.90	3.49± 0.43	1.41± 0.29	3.86± 0.60
After	4.68± 0.72	5.35± 0.69	4.86± 0.81	4.23± 0.76	3.48± 0.60	4.77± 0.80	3.54± 0.79	1.68± 1.02	4.01± 0.77
Normal	5.52± 0.82	5.75± 0.82	5.10± 0.68	4.90± 0.72	4.77± 0.67	5.99± 0.57	4.46± 0.71	1.54± 0.27	5.03± 0.68

Normal = healthy control subjects

P values when compared to pre-treatment [c] P<0.01; [d] P<0.001; [e] P<0.05

The following are comparisons made between measurements at baseline and after Hb/Hct targets were reached in the haemodialysis patients:

	➢ Regional cerebral blood flow (rCBF) decreased (P<0.05) as regional cerebral blood volume (rCBV) increased (P<0.01) ➢ The cerebral hemodynamic perfusion reserve (rCBF/rCBV) decreased significantly from 18.2 ± 3.0 to 11.3 ± 2.3 (P<0.01) ➢ A significant correlation was found between Hct and rCBF (r= -0.87, P<0.001) ➢ Regional oxygen extraction ratio (rOER) increased significantly (P<0.05) after Hb correction ➢ There was no significant change in regional cerebral metabolic rate of oxygen ($rCMRO_2$) after Hb correction
Source of funding	Not indicated
Citation	
NCC CC ID (Ref Man)	1608

H.2 EVIDENCE TABLES [2011] (Diagnostic evaluation and assessment of anaemia)

H.2.1 Clinical studies

Evidence table

Update 2011

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	Fukuhara 2007 Ref ID: 724
Study type	Cohort
Number of patients	N=471 predialysis CRF patients
Patient characteristics	Included: Patients clinically diagnosed with CRF by nephrologists based on serum creatinine value of 1.5 mg/dL or greater and had completed a baseline SF-36 Excluded if patients: • were receiving dialysis or erythropoietin for anaemia • had clinical dementia as judged by the attending physician • had a visual disturbance that left the patient unable to read the questionnaire.

Baseline characteristic	Patients responding to baseline survey only (n=177)	Patients responding to at least 1 but not all follow-up survey	Patients responding to all follow-up survey (n=126)	Reported p-value

			(n=168)		
	Age (years)	57.2 ± 15.0	55.7± 14.3	59.1 ± 13.2	0.15
	Sex (female)	37.9	32.1	34.1	0.56
	Haematocrit	29.5± 5.7	29.9± 5.0	31.6 ± 5.2	0.004
	Serum creatinine (mg/dL)	4.7 ± 1.8	4.9 ± 1.6	4.0 ± 1.1	<0.001
	Original diabetic disease	14.1	15.5	7.1	0.08
	Original chronic glomerulonephritis	63.3	62.5	65.1	0.90
	Data are reported as mean ± SD or %.				
	Domain of SF36 (mean score± SD)				
	Physical functioning:	68.2 ± 23.3	75.7 ± 20.5	74.2 ± 21.3	0.004
	Role-physical	48.4 ± 41.6	61.9 ± 37.8	61.4 ± 41.0	0.003
	Bodily pain	74.2 ± 25.1	76. ± 24.9	78.3 ± 23.9	0.34
	General health perceptions	35.5 ± 19.4	38.6 ± 17.3	41.1 ± 18.2	0.03
	Vitality	54.0 ± 23.9	60.2 ± 21.4	60.6 ± 23.1	0.02
	Social functioning	72.9 ± 26.1	75.9 ± 23.5	79.8 ± 24.3	0.06
	Role-emotional	58.9 ± 43.1	66.1 ± 40.5	67.7 ± 39.5	0.14
	Mental health	66.8 ± 21.6	69.9 ± 20.0	70.5 ± 19.6	0.23

Follow-up	48 weeks or until dialysis, erythropoietin treatment, death or other dropout.
Outcome	Outcome measured: • Quality of life (SF-36)

Factors adjusted for in the multivariate analysis	Hb/Hct values	Ref Hb/Hct	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
age, sex, serum creatinine, baseline HQoL, number of follow-ups , haematocrit	10% increment of haematocrit		QoL (SF-36) [Change in score per 10% increment]	-	Overall quality: Low; Representative sample; Key factors: 2 (age,sex); Ratio: 49 (294/6); One or more follow-ups obtained for 60% of the patients; Valid method of assessment; QoL measurements taken at baseline

Domain	Change in domain score of the SF-36 per 10% increment of haematocrit	p value
Physical functioning:	0.25	0.86
Role-physical	1.57	0.60
Bodily pain	0.56	0.75
General health perceptions	-0.39	0.72
Vitality	4.45	0.003
Social functioning	2.78	0.13

	Role-emotional	1.34	0.66	
	Mental health	1.17	0.35	
Additional information	Funding: non industry grants			

Evidence table

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	Kovesdy 2006 Ref ID: 911
Study type	Cohort study
Number of patients	N =960 patients with CKD not yet on dialysis identified. N=853 patients available for analysis <11.0 g/dL=174; 11.1-12.0 g/dL=216; 12.1-13.0=201; >13.0 g/dL = 262
Patient characteristics	Included: Male patients with CKD stages 3-5 not yet on dialysis. Excluded: After patients with a kidney transplant, patients on dialysis and patients referred for problems other than CKD were excluded. Patients with CKD stage 1 and 2 (n=99) Female patients excluded from further analysis.(n=8)

Baseline characteristics- stratified by categories of time-averaged Hb level

	<11.0 g/dL	**11.1-12.0 g/dL**	**12.1-13.0 g/dL**	**>13.0**	**Reported p-value**
Age (years)	68.6 ± 10.6	68.9± 10.3	68.3± 10.5	67.0± 10.8	0.1
Race (% 'black')	55(31.6)	61(28.2)	46(22.9)	47(17.9)	0.005
DM	102(58.6)	128(59.3)	108(53.7)	112(42.7)	0.001
HT	161(92.5)	205(94.9)	193(96.0)	246(93.9)	0.5
ASCVD	113(64.9)	133(61.6)	123(61.2)	152(58.0)	0.5
GFR (mL/min/1.73m^2)	27.3 ±12.5	21.3± 11.4	33.9± 10.2	37.0± 9.8	<0.0001
Smoking	48(30.8)	46(23.6)	55(28.3)	66(26.5)	0.4
BMI (kg/m^2)	28.7± 6.6	28.0 ± 5.5	29.0 ± 5.2	29.1 ± 5.5	0.2
MAP (mm Hg)	102.1 ± 18.6	102.1± 15.9	99.9 ± 17.7	101.1± 17.2	0.5
Albumin (g/L)	34 ± 6	35 ± 5	36 ± 5	38 ± 4	<0.0001
Cholesterol (mmol/l)	4.52 (4.33-4.72)	4.90(4.73-5.08)	4.83(4.65-5.02)	4.96(4.81-5.12)	0.004
Proteinuria (g/24h)	1.4(1.2-1.8)	1.1(0.8-1.4)	0.7(0.5-0.9)	0.4(0.3-0.5)	<0.0001

Data are presented as mean ±SD, number (% of total) or geometric means (95%C I); Comparisons are made by ANOVA, Fisher's exact test or X^2 test.

<table>
<tr><td>Follow-up</td><td>Duration of follow-up:2.1 years. Patients considered lost to follow-up if no contact for more than 6 months. 4.2% (n=36) lost to follow-up.</td></tr>
<tr><td>Outcome</td><td>Outcomes reported:
Composite (all-cause mortality and ESRD)
Death before dialysis
Dialysis
<table>
<tr><td></td><td>Composite (n=440)</td><td>Death before dialysis (n=245)</td><td>Dialysis (n=195)</td></tr>
<tr><td><11.0</td><td>139 (79.3)</td><td>68(39.0)</td><td>70(40.2)</td></tr>
<tr><td>11.0-12.0</td><td>139(64.3)</td><td>74(34.2)</td><td>65(30.0)</td></tr>
<tr><td>12.1-13.0</td><td>86(42.8)</td><td>50(24.9)</td><td>36(17.9)</td></tr>
<tr><td>>13.0</td><td>77(29.4)</td><td>53(20.2)</td><td>24(9.2)</td></tr>
</table>
Data reported as numbers (% of total).

Adjusted HR of the composite endpoint, all-cause mortality and ESRD associated with 1 g/dL higher time-averaged Hb level by subgroups (age, ethnicity, DM, ASCVD, BMI, proteinuria, GFR, albumin and cholesterol) reported graphically.
<table>
<tr><th>Factors adjusted for in the multivariate analysis</th><th>Hb/Hct values</th><th>Ref Hb/Hct</th><th>Outcomes</th><th>Comments</th><th>Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

	age, race, diabetes mellitus, atherosclerotic CV disease, BMI, smoking status, mean arterial pressure, eGFR,serum albumin, blood cholesterol, 24h urine protein level, Hb [3 levels]	Patients in each Hb level: <11g/dL:20% [174/853];11.1 to 12g/dL: 25% [216/853];12.1 to 13g/dL: 24% [201/853]	>13: 31% [262/853]	**ESRD** **HR (95% CI)**	ESRD was defined as the start of dialysis [haemodialysis or peritoneal]	Overall: high quality; male patients only; Key factors: 5 [age,race,DM, ASCVD, eGFR]; Ratio: 14 [195/14]; ESRD ascertained from local medical records
		<11 g/dL [progressed to dialysis: 70 patients]	>13 g/dL [progressed to dialysis: 24 patients]	2.96 (1.70 to 5.14)		
		11.1 to 12 g/dL [progressed to dialysis: 65 patients]		1.81 (1.07 to 3.05)		
		12.1 to 13g/dL [progressed to dialysis:36 patients]		Study reported NS difference found. Numerical data not reported. Presented on graph.		

	age, race, diabetes mellitus, atherosclerotic CV disease, BMI, smoking status, mean arterial pressure, eGFR,serum albumin, blood cholesterol, 24h urine protein level, Hb [1 level]	Hb [continuous variable]		0.74 (0.65 to 0.84)		Ratio: 16[195/12]

Factors adjusted for in multivariate analysis	**Hb/Hct values**	**Ref Hb/Hct**	**Outcomes**	**Comments**	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
age, race, diabetes mellitus, atherosclerotic CV disease, BMI, smoking status, mean arterial pressure, eGFR,serum ,	Patients in each Hb level: <11g/dL:20% [174/853];11.1 to 12g/dL: 25% [216/853];12.1 to 13g/dL: 24% [201/853]		**Pre-dialysis All-cause mortality : HR (95%CI)**	Data on cause of death not available, hence study reported all-cause mortality. Overall mortality: 29% [245/853]	Overall: High quality; Selected population; Key factors: 6 [age, race, DM, ASCVD, eGFR, smoking status]; Ratio: 18 [245/14]. All patients followed up until death, or lost to follow up or until 06.2005. 4.2% patients lost to follow-up

	albumin, blood cholesterol, 24h urine protein level, Hb [3 levels]					
		<11 g/dL[68 patients died]	>13g/dL: [262 died]	2.06 (1.35 to 3.13)		
		11.1 to 12g/dL [74 died]		1.80 (1.23 to 2.63)		
		12.1 to 13g/dL [50 died]		Study reported NS difference found. Numerical data not reported.		
Additional information	Funding: not reported					

Evidence table

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	Leeder 2006 Ref ID 926

<table>
<tr><td>Study type</td><td>Cohort</td></tr>
<tr><td>Number of patients</td><td>N=3654

CKD patients: Lower Hb quintile: n=352; Other Hb quintile: n=1287</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
All residents born before Jan 1 1943 invited to attend a local clinical for a detailed interview and physical examination.
CKD and non-CKD patients
Excluded:
People who lived in nursing homes.
<table>
<tr><td></td><td>Lowest Hb quintile; n=352</td><td>Other Hb quintile; n=1287</td><td>Reported p-value</td></tr>
<tr><td>Age (years)</td><td>73.9 (0.46)</td><td>70.8 (0.22)</td><td>0.0001</td></tr>
<tr><td>Male [n(%)]</td><td>131(37.2)</td><td>519 (40.3)</td><td>0.29</td></tr>
<tr><td>BMI</td><td>25.0 (0.21)</td><td>25.0 (0.11)</td><td>0.77</td></tr>
<tr><td>Mean Hb (g/dL)1</td><td>13.1 (0.05)</td><td>15.2 (0.03)</td><td><0.0001</td></tr>
<tr><td>Anaemia2</td><td>50 (14.2)</td><td>0</td><td><0.0001</td></tr>
<tr><td>Mean GFR[3] (mL/min/1.73m^2)</td><td>44.7(0.56)</td><td>49.2 (0.23)</td><td><0.0001</td></tr>
<tr><td>Severe HT[4]</td><td>200 (56.8)</td><td>675 (52.5)</td><td>0.15</td></tr>
</table>
</td></tr>
</table>

Diabetes	25(7.1)	114 (8.9)	0.29
Pre-existing CHD	67(19.0)	258(20.1)	0.67
Mean arterial BP (mm Hg)	105.2 (0.74)	105.1 (0.35)	0.93
Total serum cholesterol(mmol/L)	5.9 (0.06)	6.1 (0.03)	0.0002
Current smoker	23 (6.5)	181 (14.1)	0.0001
Alcohol consumption – standard drinks per week	4.3(0.52)	5.8(0.27)	0.01
Fibrinogen (mg/dL)	4.6(0.07)	4.1(0.03)	<0.0001

Data reported as mean (SE) or number (%)

[1]Mean Hb for men and women combined. For women, Hb in the 'lowest quintile' ranged from 8.4 to 13.5 g/dL and in 'other 372uintile' ranged from 13.6 to 22.4 g/dL. For men, Hb in the 'lowest quintile' ranged from 7.6 to 14.5 g/dL and in 'other 372uintile' ranged from 14.7 to 19.3 g/dL.

[2]Anaemia defined as <12 g/dL for women and <13 g/dL for men.

[3]GFR estimated using the Cockroft-Gault equation. CKD defined as GFR <60 mL/min/1.73m^2

[4] Defined according to WHO/International Society of Hypertension category grade 2 or 3 i.e. a previous diagnosis of HT and current use of antihypertensive medication or systolic BP≥ 160 mm Hg or diastolic BP≥ 100mm Hg at baseline examination.

Follow-up	9 years
Outcome	Outcome reported: • CHD related mortality

Factors adjusted for in the multivariate analysis:	Hb/Hct values	Ref Hb/Hct	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes, self-reported health status; Hb [continuous]	Low quintile mean Hb (SE): 13.1 g/dL (0.05); Hb-treated as continuous variable	other quintiles [mean Hb (SE): 15.2 g/dL (SE 0.03)	**CHD-related mortality:** **HR (95% CI)**	580 patients excluded from analyses due to missing data; Cause of death collected from death certificates by NDI and ICD-10; CHD-deaths defined according to ICD-9	Overall quality: Low. Only 3% patients with ACKD; Key factors: 5 (age; gender; diabetes; pre-existing CHD; smoking status);

		Hb [lowest quintile]; [64 patients died]	other quintiles ; [115 patients died]	eGFR estimated with Cockcroft-Gault:1.49 (1.08 to 2.06)		Ratio: 18 [179/11]
		Hb [lowest quintile]; [53 died];	other quintiles ; [95 patients died]	eGFR estimated with MDRD:1.36 (0.95 to 1.94)		Ratio: 15 [148/11]
Additional information	Funding: non industry grant					

Evidence table

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	Levin 2006 Ref ID:917
Study type	Cohort
Number of patients	N=3028
Patient characteristics	Patients registered in a CKD database. Entry criteria for the database included calculated GFR <60 mL/min/1.73m^2 or diagnosis of kidney disease, presumed to be chronic on the basis of biopsy diagnosis, ultrasound or clinical history of deterioration, and having been referred to nephrologists. Patients were not on dialysis at time of referral.

	GFR <15 (n=974)		GFR 15-29 (n=1452)		GFR 30-59 (n=602)	
	≥ 11(n=245)	<11 (n=729)	≥ 11 (n=719)	<11 (n=733)	≥ 11 (n=394)	<11 (n=208)
Age	62.9 (14.4)	64.7 (15.4)	65.1(15.0)	66.2(15.8)	61.1 (16.2)	67.6(16.3)
Male	165(68)	332 (45)	469(65)	391(53)	295 (75)	131 (63)
Race						
'Caucasian'	121 (75)	274(59)	256(66)	225(56)	139(73)	71(70)
'Asian'	34(21)	161(5)	117(30)	155(39)	43(23)	30(29)
Other	6(4)	29(6)	15(4)	20(5)	9(5)	2(2)
eGFR (mL/min)	11.4(2.5)	10.2(2.9)	22.0(4.2)	20.9 (4.1)	39.3(7.6)	37.1(6.8)
Hb	12.7(1.02)	9.16(1.08)	12.53(1.20)	9.54(0.98)	13.23(1.47)	9.75(0.86)
Iron use	67(49.6)	259(69)	175(50)	248(78)	95(47)	63(81)
Diabetes	54(22)	258(35)	469(65)	391(53)	295(75)	131(63)

Follow-up	Median : 27 months
Outcome	Outcome reported: • Mortality

Update 2011

Factors adjusted for in the multivariate analysis	Hb/Hct values [proportion of patients]	Ref Hb/Hct	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
age (5 years), gender, diabetes, eGFR, Hb[5 levels]	Proportion of patients in each quintile not reported;<11: 55% [1670/3028]; ≥11:45% [1358/3028]		**Mortality: RR (95% CI)**	Study reported 14% patients died in those without anaemia (≥11 g/dL); 26% among those with anaemia (<11g/dL) at time of registration	Overall: Moderate quality; Representative population; Key factors: 3(age; gender; diabetes); Ratio: 77 [617/8]
Erythropoietin therapy was included as an explanatory variable only if it was initiated immediately after the baseline Hb.	<10	≥14 g/dL	1.904 (1.197 to 3.027)	Number of patients lost to follow-up unclear but study reported patients who moved out of the province were classed as lost to follow-up	Data on death validated using vital statistics record
	10 to 10.9		1.770 (1.104 to 2.838)	Proportion of patients who died within each Hb level not reported	
	11 to 11.9		1.500 (0.926 to 2.430)		

		12 to 12.9		1.126 (0.673 to 1.884)			
		13 to 13.9		0.992 (0.568 to 1.731)			

Additional information	Funding: study reported work was not supported by any industry funding nor requested by any organisation.

Evidence table

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	McCullough 2005 Ref ID: 625
Study type	Cohort
Number of patients	N=37,153
Patient characteristics	Inclusion criteria: Eligible patients were men or women At least 18 years old With DM, hypertension or family history of DM, HT or kidney disease

	N=37,153
Age (years)	52.9 ± 16.9
Male	11,163 (31%)

Update 2011

Update 2011

	Race/ethnicity		
	White	15,477 (41.7)	
	African American	13,744(37.0)	
	Hispanic	4332(11.7)	
	Native American	2405(6.5)	
	Asian Pacific Islander	1679(4.5)	
	Other	3848(10.4)	
	Family history of HT, DM or kidney disease	34,596(93.1)	
	BMI	30.2 ±6.8	
	DM	9738 (26.2)	
	HT[1]		
	Normal	14,253(38.4)	
	High Normal	6735 (18.1)	
	Stage I	10,325 (27.8)	
	Stage II	4026 (10.8)	
	Stage III	1412 (3.8)	
	eGFR		
	Missing	1663 (4.5)	

Update 2011

	<30 | 310 (0.8) 30-59 | 5194(14.0) 60-89 | 17,885 (48.1) ≥90 | 5504 (14.8) <60 | 4588 (12.3) Hb quartile | Missing | 2170(5.8) ≤12.8 | 9411(25.3) 12.9-13.5 | 8176 (22.0) 13.7-14.6 | 9004 (24.2) >14.6 | 8392 (22.6) Data are presented as mean ±SD or number (%) [1]Normal: systolic blood pressure(SBP):<130 mmHg; diastolic blood pressure (DBP)<85 mm Hg; high normal: SBP: 130-139 mm Hg; DPB: 85-89 mm Hg; stage I: SBP:140-159 mm Hg; DBP:90-99 mm Hg; Stage II: SBP:160-179 mm Hg; DBP:100-109 mm Hg; Stage III: SBP≥ 180 mm Hg; DBP: ≥110 mm Hg;
Follow-up	Median: 16 months (range 0.2 to 47.5 months)
Outcome	Outcome reported: • All-cause mortality

Factors adjusted for in the multivariate analysis	Hb/Hct values [proportion of patients]	Ref Hb/Hct	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;

Update 2011

		sex [male], race/ethnicity[2 levels],education, smoking status, health insurance coverage, family history of DM, HT, or kidney disease, BMI, DM, HT, Microalbuminuria category[3 levels], eGFR [3 levels], Hb[3 levels],prevalentCKD xCVD [3 levels]	Patients in each Hb level: ≤12.8 : 25.3%; 12.9 to 13.6:22%;13.7 to 14.6:24.2%; >14.6:22.6%; Missing: 5.8%		**All cause-mortality: HR (95% CI)**	Overall number of deaths: 0.5% [191/27153]; Missing data:28%	Overall quality: Moderate; Majority of patients in Stage 2 CKD; Key factors: 7 [sex, race/ethnicity, smoking status, DM, CVD, HT, eGFR]; Ratio: 8 [191/23];
			≤12.8 g/dL	>14.6 g/dL	1.62 (0.87 to 2.99)	Proportion of patients who died within each Hb level not reported	
			12.9 to 13.6 g/dL		1.43 (0.88 to 2.32)		

		13.7 to 14.6 g/dL		1.03 (0.64 to 1.67)		All-cause mortality determined using a previously validated multilevel tracking system- Nephrology Analytical Service Division Division cross checks against US Medicare Database and Social Security Administration Death Files)
Additional information	Funding: none					

Update 2011

Evidence table

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	Plantinga 2007 Ref ID: 655
Study type	Cohort
Number of patients	N=767 incident haemodialysis patients
Patient characteristics	Included: • Cohort assembled form the Choices for Healthy Outcomes in Caring for End Stage Renal Disease (CHOICE) • All patients initiating dialysis during the enrolment period were recruited. • Patients >18 years of age and speak either English or Spanish. Excluded:

Update 2011

- Patients who did not have:
  - a 1-year QoL (n=313)
  - 6 month haemoglobin (n=16)
  - Reasons for missing measurements: death (n=77), transplant (n=39), study closeout (n=74) or unknown reasons (n=139)

Baseline patient characteristics by haemoglobin concentration at 6 months

Baseline characteristic	<11 g/dL (n=169)	≥ 11 g/dL (n=269)	Reported p-value[a]
Demographic			
Age (years)	57.5 ± 14.2	60.1 ± 13.8	0.062
Sex (male)	46.8	58.4	0.018
Race (white)	56.8	65.1	0.212
Clinical			
BMI	28.9 ± 7.7	26.9 ± 5.9	0.004
Kt/V	1.21 ± 0.31	1.27 ± 0.30	0.066
Index of Coexisting Diseases (ICED) (% score of 3)	30.8	28.3	0.846
Laboratory			
Albumin (g/dL)	3.62 ± 0.34	3.66 ± 0.33	0.249
Creatinine (mg/dL)	7.46 ± 2.34	7.13 ± 2.34	0.151
CRP (µg/dl)	4.3 (1.8,12.7)	3.8 (1.6,6.4)	0.053
Haemoglobin			
Baseline Hb (g/dL)	10.1 ± 1.2	10.8 ± 1.1	<0.001

Baseline Hb <11 g/dL	130 (76.9)	144 (53.5)		
Baseline Hb >11 g/dL	29 (23.1)	125 (46.5)		
Data reported as mean SD; n(%); % or median (IQR); [a]By t-test (continuous variables) or X^2 (categorical variables)				

Follow-up: 1 year

Outcome: Outcomes reported:

Generic (SF-36) and disease specific (CHOICE Health Experience Questionnaire) QoL at 1 year

Factors adjusted for in the multivariate analysis	Hb/Hct values	Ref Hb/Hct	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
baseline QoL score, age, race, sex, ICED, albumin, creatinine,Hb[continuous]	1g/dl increase in Hb from baseline to 6 mo	n/a	Change in QoL score (1 year)- see table below	Results not available for 42% [313/738 patients] ; n=438	Overall quality: Moderate Representative sample; Key factors: 4 (age, race,sex, ICED)
Baseline QoL score, age, race,sex,ICED,albumin and creatinine	≥11 g/dL	<11 g/dL	Change in QoL score (1 year)- see table below	Analysis adjusted for BMI and epo use as well. Study reported this did not change the results-data not reported.	Ratio: 15 [438/30]

Domain	Adjusted difference (95% CI)- 1-year QoL score for 6 month haemoglobin ≥11 g/dL vs <11 g/dL	Adjusted difference (95% CI)- in QoL score at 1 year associated with 1 g/dL greater 6-month haemoglobin concentration

Update 2011

	Generic domains		1.51(0.39,2.62)
	Physical functioning	5.02 (1.44,8.60)	2.72(1.03,4.40)
	Role physical	6.07 (0.69,11.5)	1.33(0.41,2.26)
	General health	2.63 (-2.12,7.38)	1.57(0.20,2.94)
	Bodily pain	6.16 (2.37,9.96)	3.06(1.01,5.10)
	Role emotional	9.99 (-0.64,20.6)	1.13(0.21,2.04)
	Mental health	5.12 (2.31,7.93)	2.56(1.20,3.92)
	Social functioning	5.72 (0.33,11.1)	1.59(0.55,2.62)
	Vitality	2.39(-0.51,5.29)	1.59(0.55,2.62)
	PCS	1.56 (0.16,2.96)	0.64(0.16,1.11)
	MCS	2.49(0.35,4.62)	0.80(0.27,1.33)
	Cognitive function	3.42(0.25,6.58)	0.58(-0.45,1.62)
	Sexual function	0.55(-7.53,8.63)	0.86(-0.86,2.57)
	Sleep	3.62(-2.54,9.77)	1.30(0.10,2.50)
	Work	4.52(-0.01,9.05)	0.43(-1.31,2.17)
	Recreation	2.05(-3.45,7.55)	0.48(-1.07,2.03)
	Travel	0.76(-4.11,5.63)	1.17(-0.53,2.86)
	Finances	3.85(-2.67,10.4)	1.44(-0.15,3.04)
	General QoL	1.71(-1.49,4.91)	0.91(-0.11,1.92)

	Disease-specific domains		
	Diet restriction	5.96(2.14,9.78)	0.88(-0.61,2.37)
	Freedom	2.61(-3.04,8.26)	1.33(0.02,2.63)
	Time	2.58(-2.37,7.53)	-0.07(-1.30,1.15)
	Body image	1.66(-3.36,6.68)	0.99(-0.35,2.34)
	Dialysis access	7.77(3.20,12.3)	2.02(0.68,3.37)
	Symptoms	0.06(-2.99,3.10)	0.22(-0.56,1.00)
Additional information	Funding: non industry grants.		

Update 2011

Evidence table

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	Weiner 2008 Ref ID: 474
Study type	Cohort
Number of patients	N=1678 patients
Patient characteristics	Stage 3 to 4 CKD patients ; secondary analysis of 2 cohorts: ARIC &CHS; ARIC: participants aged 45 to 65 years;

Update 2011

CHS: patients 65 years or older randomly selected from Medicare eligibility file;

Baseline descriptive data for the pooled cohort with eGFR of 15 to 60 mL/min/1.73 m^2

Characteristic	Percent or Mean SD	Median (range)
Age (y)	70± 10	72 (45-91)
Women	56	-
African American	14	-
Study origin: ARIC	26	
Current smoking	13	-
Current alcohol	47	-
Medical history		
Cardiovascular disease	34	-
Diabetes	15	-
Hypertension	74	-
Medication use		
Antihypertensive	62	-
Antihyperglycemic	11	-
Lipid-lowering	6	-
Examination findings		

Update 2011

BMI (kg/m^2)	27 5	27 (17-53)
Systolic BP (mm Hg)	135 ± 24	132 (74-228)
Diastolic BP (mm Hg)	72 ± 12	72(24-136)
Left ventricular hypertrophy *using electrocardiographic criteria)	6	-

Laboratory results		
Total cholesterol (mg/dL)	215 ± 44	212 (86-465)
HDL cholesterol (mg/dL)	51 ± 16	48 (15-132)
LDL cholesterol (mg/dL)	133 ± 40	130 (14-387)
Triglycerides (mg/dL)	153 ± 88	130 (24-954)
Haemoglobin (g/dL)	13.8 ± 1.6	13.8 (7.0-25.4)
Uric acid (mg/dL)	6.8 ± 1.8	6.7 (1.7-15.9)
Albumin (g/dL)	4.0 ± 0.3	4.0 (2.0 -5.2)
Fibrinogen (mg/dL)	334 ± 72	328 (132-854)
Creatinine (mg/dL)	1.3 ± 0.4	1.3 (1.0-4.8)
eGFR (mL/min/1.72m^2)	51 ± 9	53 (16-60)

Update 2011

Follow-up	Median (IQR)follow up:108 months (IQR53)
Outcome	Outcomes reported: • Mortality • Stroke • Cardiac events [fatal CHD and MI]

Factors adjusted for in the multivariate analysis	Hb/Hct values	Ref Hb/Hct	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
age, sex, race,Hx of CV disease, Hx diabetes, LVH, smoking, total cholesterol level, high-density lipoprotein cholesterol level, systolic BP, GFR, study of origin, Hb[continuous]			**Mortality** **HR (95% CI)**	Study reported the composite outcome [mortality, stroke, MI] as the primary outcome; mortality secondary outcome; Number of deaths: 44.6% (748/1678)	Overall quality: moderate; Mainly Stage 3 CKD patients; Key factors:7 (age, sex, race, CV disease, diabetes, smoking, GFR); Ratio:58 [748/13]
	Hb 1.5g/dL increase <14.5 g/dL	n/a	0.70 (0.63 to 0.79)		

Update 2011

		Hb 1.5g/dL increase >14.5 g/dL	n/a	1.31 (1.09 to 1.56)		

Factors adjusted for in the multivariate analysis	Hb/Hct values	Ref Hb/Hct	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
age, sex, race, history of CV disease, history diabetes, LVH, smoking, total cholesterol level, high-density lipoprotein cholesterol level, systolic BP, GFR, study of origin, Hb[continuous]			**Stroke** **HR (95% CI)**	Study reported the composite outcome [mortality, stroke, MI] as the primary outcome; Stroke-secondary outcome	Overall quality: moderate; Mainly Stage 3 CKD patients; Key factors:7 (age, sex, race, CV disease, diabetes, eGFR, smoking) ; Ratio:18 [233/13]

Update 2011			Hb 1.5g/dL increase <14.5 g/dL	n/a	0.79 (0.64 to 0.97)	Number of patients who experienced a stroke:13.9 % (233/1678)	Definition of stroke and confirmation of event not reported in this study- as per in the ARIC[1] and CHS[109] study. ARIC study-adequate method of confirmation of stroke; CHS study-reported stroke confirmed.
			Hb 1.5g/dL increase >14.5 g/dL	n/a	1.02 (0.71 to 1.46)		
			Hb 1.5 g/dL increase	n/a	0.85 (0.73 to 1.00)		
					Cardiac Events [fatal CHD & MI] HR (95% CI)	Number of patients with cardiac events: 22.5% (378/1678)	Overall: Moderate quality; Mainly Stage 3 CKD patients; Key factors:4 (age, sex, CV, diabetes); Ratio: 29 [378/13]
			Hb 1.5g/dL increase <14.5 g/dL	n/a	0.94 (0.79 to 1.11)		Method of CHD assessment chest x-ray; echo or diagnosed by physician MI ascertained with ECG
			Hb 1.5g/dL increase >14.5	n/a	1.05 (0.81		MI- both clinically recognised and silent

		g/dL		to 1.35)		infarctions
Additional information	Funding: non-industry grants					

Evidence table

Review question	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?
Bibliographic reference	Winkelmayer 2006 Ref ID:762
Study type	Cohort
Number of patients	N=825
Patient characteristics	Patient level data of two cohorts of kidney transplant recipients

Variable	Anaemia (n=339; 41.1%)	No anaemia (n=486; 58.9%)	p-value
Recipient age (years)	49.1± 13.9	53.4 ±12.7	<0.001
Recipient gender (male)	206 (60.8)	285 (58.6)	0.54
Time since transplantation (years)	4.3 ± 4.1	4.8 ± 4.0	0.08

Update 2011

Serum creatinine (mg/dL)	2.0 ± 1.0	1.5 ± 0.4	<0.001
Creatinine clearance (mL/min/1.73m^2)	46.8 ± 17.9	58.4 ± 17.0	<0.001
BMI (kg/m^2)	24.7 ± 4.0	25.8 ± 4.2	<0.001
Serum iron (mg/dL)	75.8 ± 32.1	84.2 ± 34.2	<0.001
C-reactive protein (mg/dL)			
≤0.5	278 (82)	379 (78.0)	
0.5-1.0	25 (7.4)	61 (12.6)	
>1.0	36 (10.6)	46 (9.5)	0.53

Variable	Anaemia (n=339; 41.1%)	No anaemia (n=486; 58.9%)	p-value
Underlying renal disease			
Diabetic nephropathy	16 (4.7)	37 (7.6)	
Glomerulonephritis	127 (37.5)	141 (29.0)	
Interstitial nephritis	33 (9.7)	54 (11.1)	
Polycystic kidney disease	35 (10.3)	75 (15.4)	
Various other, specified	37 (10.9)	54 (11.1)	
Unspecified/unknown	91 (26.8)	125 (25.7)	
Number of previous transplants			

Update 2011

0	257 (75.8)	414 (85.2)	
1	66 (19.5)	64 (13.2)	
2+	16 (4.7)	8 (1.7)	<0.001

Data reported as mean ± SD or n(%)

Follow-up	Median 8.2 years
Outcome	Outcomes reported: • All-cause mortality

Factors adjusted for in the multivariate analysis	Hb/Hct values [n/N]	Ref Hb/Hct [n/N]	Outcomes	Comments	Representative population? Key factors; ratio=events/factors; Outcome at b/l if relevant; Outcome assessment valid?;
age [continuous], gender, BMI[continuous & squared], estimated creatinine clearance [continuous & squared],serum iron[quartiles] , C-	>10 to 11g/dL: 11% [89/825]; >11 to 12g/dL: 17% [138/825]; >12 to 13: 20%; 45% [373/825]	≤10: 7% [58/825]	**All-cause mortality HR (95% CI)**	Overall mortality: 30% [251/825]	Overall: Moderate quality; Representative population; Key factor: 3 (age, gender, serum iron ; Ratio: 14[251/13]

Update 2011

	reactive protein [2 levels?], immunosuppressive therapy [2 levels], native kidney disease [5 levels?], Hb [4 levels]					
		>10 to 11 [28 patients died]	≤10 [24 patients died]	0.80 (0.45 to 1.42)		
		>11 to12 [38 patients died]		0.78 (0.45 to 1.34)		
		>12 to 13: [50 died]		0.80 (0.46 to 1.40)		
		>13 [111 died]		0.76 (0.44 to 1.31)		
Additional information	Funding: not reported					

H.2.2 Economic studies

P. Lefebvre, M. S. Duh, S. Buteau, B. Bookhart, and S. H. Mody. Medical costs of untreated anemia in elderly patients with predialysis chronic kidney disease. *J Am Soc Nephrol* 17 (12):3497-3502, 2006.				
Study details	**Population & comaprison**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: Cost analysis **Study design:** Retrospective cohort analysis with multivariate regression (covariates: age, gender, GFR, diabetes, hypertension, liver cirrhosis, CAD, MI, LVH) (moderate quality cohort study) **Perspective:** USA direct medical costs **Observation period:** Mean 2.1 years (SD1.0) **Discounting:** Costs: none Outcomes: none	**Population:** Predialysis CKD patients of 65 years or over, untreated for anaemia • N=2001 • Patients with stage 3 CKD = 1435 • Age= 76.0 (SD2.7) • Female = 46.5% • Baseline Hb = 12.8 (SD1.6) • Baseline GFR = 40.0 (SD12.2) • Comorbidities: Hypertension=87.9%; Diabetes = 49.4%; CAD=23.3%; LVH=18.7%; MI=13.2%; Liver cirrhosis = 1.0% **Group 1:** Time when people had anaemia (Hb<11g/dl) **Group 2:** Time when people did not have anaemia (Hb≥11g/dl)	N/a	**Monthly costs :** ***All patients*** Group 1: NR; Group 2: NR *Incremental (1-2):£320 (CI:£233 ,£408 p<0.001)* Hb continuous variable model: -£52 for every 1g/dl increase in Hb (CI: -£71, -£32 p<0.001) ***Patients with stage 3 CKD*** Group 1: NR; Group 2: NR *Incremental (1-2):£352(CI:£240 ,£464 p<0.001)* Hb continuous variable model:-£48 for every 1g/dl increase in Hb (CI: -£71, -£25 p<0.001) **Cost components incorporated:** Inpatient and outpatient medical claims, pharmacy dispensing claims	N/a

Update 2011

			Currency & cost year: 1999-2005 USA dollars – (presented here as 2005 UK pounds†)	
Data sources				
Health outcomes: n/a; **Quality-of-life weights:** n/a; **Cost sources:** Large US managed care database				
Comments				
Source of funding: Ortho Biotech Clinical Affairs (epoetin alfa manufacturer). **Limitations:** Uncertainty about applicability of US costs and resource use to UK NHS setting; claims data; retrospective study design; not a cost-effectiveness analysis. **Other:**				
Applicability*: Partially applicable **Cohort study quality: Moderate****				

Abbreviations: CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; Hb = haemoglobin; LVF = left ventricular hypertrophy; MI = myocardial infarction; NR = not reported; SD = standard deviation

* Directly applicable / Partially applicable / Not applicable; ** Representative sample; Key factors: all key confounding factors taken into account; Ratio: n/a; Follow-ups n/a; Valid method of assessment for outcome (cost)

†Converted using 2005 Purchasing Power Parities

H.2.3 Evidence tables [2011] (Optima Hb lelevs)

Evidence table

Update 2011

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Besarab 1998. Ref id 213
Study type	Randomised prospective open label trial
Number of patients	N=1233 enrolled; N (normal-haematocrit group)= 618 patients received increasing doses epoetin-alfa to achieve and maintain haematocrit levels of 42% [±3% points] ;and N (low-haematocrit group)= 615 patients received epoetin-alfa sufficient to achieve haematocrit levels of 30% [±3% points] Multisite study in 51 haemodialysis centers in USA
Patient characteristics	Inclusion criteria: • Patients with congestive heart failure [CHF: defined as the need for hospitalisation or nonroutine ultrafiltration for CHF in preceding two years] or ischaemic heart disease [defined as angina pectoris requiring medication in the preceding two years, coronary artery disease documented by cardiac catheterisation, or prior MI] and a serum transferring saturation of 20% or higher. • End stage renal disease • Undergoing long term haemodialysis • Haematocrit level to 27 to 33%

- Receiving epoetin during the 4 weeks before enrolment.

Exclusion criteria:

- Diastolic blood pressure of 100 mm Hg or more
- Life expectancy of less than 6 months
- Severe cardiac disability (New York Heart Association class IV)
- MI, percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting in the previous 3 months before the study began
- Pericardial disease
- Cardiac calvular disease likely to require surgery
- Cardiac amyloidosis; and
- Androgen therapy

All patients had documented congestive heart failure or ischaemic heart disease

Characteristic	Normal haematocrit level (42%± 3%) (N=618)	Low haematocrit level (30% ± 3%) (N=615)
Age (years)	65±12	64±12
Female sex (%)	50	52
Race or ethnic group (%)		

Update 2011

	White	45	42	
	Black	41	44	
	Hispanic	8	9	
	Other	6	5	
	Duration of dialysis (years)	3.2±3.6	3.1±3.3	
	Cause of renal failure (%)			
	Diabetes mellitus	42	46	
	Hypertension	28	27	
	Glomerulonephritis	7	8	
	Other	23	19	
	Type of vascular access			
	Graft	66	67	
	Natural fistula	23	23	
	Catheter	10	10	
	Not specified	2	0	
	Hypertension (%)	71	69	
	Diabetes mellitus (%)	54	58	
	Peripheral vascular disease (%)	39	38	
	Cardiac-related hospitalisation (%)			

	Angina pectoris		
	Congestive heart failure	32	28‡
	MI	44	47
	Coronary-artery bypass graft	25	23
	Percutaneous transluminal coronary angioplasty	20	19
		10	9
	New York Heart Association class (%)		
	I		
	II	29	31
	III	51	52
		19	15
	Haematocrit (%)	30.5±3.0	30.5±2.9
	Epoetin dose (U/kg/wk)	146±103	153±119
	All values reported as mean ± SD unless otherwise indicated.‡p=0.04		
Intervention	• Intravenous or subcutaneous epoetin-alfa (depending on route of administration at baseline; and same frequency per week as before the study) to achieve and maintain haematocrit levels of 42% [± 3%]. • Mean Hb achieved:13.2 g/dL • Dose increased by a factor of 1.5 on study entry. Subsequently, doses were increased by 25% of the baseline dose if the Hct had not increased by at least 2% during the preceding two weeks. If Hct increased by more than 4% in two-week period, the dose was reduced by 25U/kg of body weight. • Mean dose (over study): 28990 U/kg/wk		

	• IV iron dextran administered to 85% [526/618] patients; During 6 months before death or censoring patients who survived received an average of 152 mg (SD 150) per four-week period and those who died received an average of 214 mg (SD 190) per four-week period.
Comparison	• Intravenous or subcutaneous epoetin-alfa (depending on route of administration at baseline) to achieve haematocrit levels of 30% [± 3%] • Mean Hb achieved:10 g/dL • Dose adjusted by 10 to 25 U/kg at 2-week intervals, when needed, to maintain Hct of 30%. • Mean dose (over study): 10075 U/kg/wk • IV iron dextran administered to 75% [464/615] patients; During 6 months before death or censoring patients who survived received an average of 119 mg (SD 133) per four-week period and those who died received an average of 145 mg (SD 179) per four-week period.
Length of follow-up	Study period ranged from 4 days to 30 months, with a median of 14 months. Study was terminated due to concern about safety.
Outcome measures and effect size	The study stated the following were the primary outcomes: • Time to death or a first non fatal MI The study stated the following were the secondary outcomes: • CHF requiring hospitalisation, • Angina pectoris requiring hospitalisation • Coronary-artery bypass grafting • Percutaneous transluminal coronary angiolplasy • Hospitalisation for all causes • Change in CV drugs • Red-cell transfusions • Changes in QoL scores NB: With the exception of QoL scores all other secondary outcomes were not relevant to the review. Other events recorded: • All cause mortality • CV death

- Access thrombosis
- Proportion of patients receiving red-cell transfusion
- Hypertension

Results:

Outcome	Normal haematocrit level (42%± 3%) (N=618)	Low haematocrit level (30%± 3%) (N=615)
All cause mortality	32% [195 / 618]	26% [160/ 615]
Mortality (29 mo.) excl fatal MI	30% [183/618]	24% [150/615]
CV death	20% [125/618]	18% [112/615]
Access thrombosis	39% [243/ 618]	29% [176/ 615]
Proportion of patients receiving red cell transfusion	21% [129 /618]	31% [192/ 615]

	Non-fatal MI	3% [19 / 618]	2% [14 / 615]
	Fatal and non-fatal MI	7% [41/618]	7% [42/615]
	Hypertension	There was no significant difference between the two groups in blood pressure. Mean values were 150 mm Hg for systolic and 78 mm Hg for diastolic blood pressure.	
	QoL (SF-36)	Physical-function score at 12 months increased by 0.6 point (p=0.03) for each percentage-point increase in the haematocrit. The study reported 'no significant changes in the scores on the other seven scales'. Unpublished data[15] received upon request from the sponsor reported QoL scores at 1 year (see table below):	

QoL scores-all domains at 1 year

General Health	Mental Health	Physical Function	Physical Role	Social Functions	Vitality	Bodily Pain	Emotional Role	PCS	MCS
317	314	316	313	316	314	316	309	313	312
-2.31	-1.74	-4.22	1.52	0.55	0.65	-2.33	3.18	-1.21	0.56
21.07	18.66	25.98	46.17	30.76	23.71	30.12	52.58	9.61	11.8
351	348	349	349	350	347	350	346	347	347
-2.49	-1.31	-4.09	3.58	-0.32	-2.47	-1.61	-0.05	-0.7	-0.33

										8	
		20.09	19.51	24.75	44.19	31.32	21.19	29.17	50.29	8.94	11.92
Source of funding	Supported by Amgen. Study reported Dr. Schwab and Dr.Nissenson (co-authors) have served as consultants to Amgen.										

Evidence table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Brandt 1999. Ref id 226
Study type	RCT
Number of patients	N= 44 patients enrolled sequentially and randomised N (high dose)= 21 patients (13 predialysis, 6 peritoneal dialysis, 3 haemodialysis) N (low dose)=23 patients (12 predialysis, 4 peritoneal dialysis, 6 haemodialysis) N= 25 patients were predialysis (12 received low dose erythropoietin, 13 received high dose erythropoietin), N= 10 on peritoneal dialysis (4 received low dose erythropoietin, 6 received high dose erythropoietin), N=9 on haemodialysis (6 received low dose erythropoietin, 3 received high dose erythropoietin)

<table>
<tr>
<td>Patient characteristics</td>
<td>
Inclusion criteria:

< 21 years old
Chronic renal failure
< -2 SD below the mean Hb for age

Exclusions criteria:

Poorly controlled hypertension
Poorly controlled seizure disorder
Severe iron deficiency
Pregnancy

Patients were in 3 groups predialysis, peritoneal dialysis and haemodialysis

Predialysis patients
<table>
<tr><td>Characteristic</td><td>High dose erythropoietin (N=12)</td><td>Low dose erythropoietin (N=13)</td></tr>
<tr><td>Mean age (years)</td><td>10.1±5.8</td><td>7.2±5.6</td></tr>
</table>

Peritoneal dialysis patients
<table>
<tr><td>Characteristic</td><td>High dose erythropoietin (N=6)</td><td>Low dose erythropoietin (N=4)</td></tr>
<tr><td>Mean age (years)</td><td>3.8±5.1</td><td>9.7±8.6</td></tr>
</table>
</td>
</tr>
</table>

Update 2011

<table>
<tr><td></td><td>Haemodialysis patients
<table>
<tr><th>Characteristic</th><th>High dose erythropoietin (N=3)</th><th>Low dose erythropoietin (N=6)</th></tr>
<tr><td>Mean age (years)</td><td>10.5±2.2</td><td>15.5±4.3</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>• High dose 450 U/kg per week erythropoietin (rHuEPO) divided thrice weekly for 12 weeks.
• Mean Hb achieved (at 12 weeks): Predialysis: 12.7 g/dL (SD 2.0); HD: 12.9 (SD 0.7); PD: 11.9 (SD1.6)
• Dose reduced after attainment of target Hb, but if not attained by 12 weeks, dose increased by 150 U/kg/week.
• Administered by s.c. for predialysis or peritoneal dialysis patients and i.v. for haemodialysis patients.
• 95% of patients reached target within 12 weeks.
• For those who eventually reached and maintained the target Hb (n=20/36) mean dose 157 (SD 108) U/kg/week; median: 150 U/kg/week- Final dose at target [results reported per anaemia CKD subgroup not by high versus low dose groups]: Predialysis: 143 U/kg/wk (SD 102); HD: 243 (SD 156); PD: 188 (SD 88)
• Fe therapy initiated for a ferritin <100 ng/mL and/or transferring saturation <20%.</td></tr>
<tr><td>Comparison</td><td>• Low dose 150 U/kg per week erythropoietin(rHuEPO) divided thrice weekly for 12 weeks.
• Mean Hb achieved (at 12 weeks): Predialysis: 11.9 g/dL (SD 1.8); HD: 8.4 (SD 1.0); PD: 10 (SD2.04)
• Administered by s.c. for predialysis or peritoneal dialysis patients and i.v. for haemodialysis patients.
• 66% of the patients reached target Hb within 12 weeks.
• For those who eventually reached and maintained the target Hb (n=16/36) mean dose 157 (SD 108) U/kg/week; median: 150 U/kg/week-
• Final dose at target [results reported per anaemia CKD subgroup not by high versus low dose groups]: Predialysis: 143 U/kg/wk (SD 102); HD: 243 (SD 156); PD: 188 (SD 88)</td></tr>
<tr><td>Length of follow-up</td><td>Study length of 12 weeks</td></tr>
<tr><td>Outcome measures and</td><td>Outcomes:</td></tr>
</table>

<table>
<tr><td>effect size</td><td>

- Transfusion rate
- New or worsening hypertension
- Creatinine clearance

Results:

Predialysis patients

<table>
<tr><td>Result</td><td>High dose erythropoietin
Mean Hb level reached: 12.7±2 g/dL
(N=13)</td><td>Low dose erythropoietin
Mean Hb level reached: 11.9±1.8 g/dL
(N=12)</td></tr>
<tr><td>Transfusion rate</td><td>1 / 13</td><td>0 /12</td></tr>
<tr><td>New or worsening hypertension</td><td colspan="2">4 out of 25 patients (study does not state results for each treatment group) within the predialysis population</td></tr>
</table>

Peritoneal dialysis patients

<table>
<tr><td>Result</td><td>High dose erythropoietin
Mean Hb level reached: 11.9±1.6 g/dL
(N=6)</td><td>Low dose erythropoietin
Mean Hb level reached: 10±2.04 g/dL
(N=4)</td></tr>
</table>

</td></tr>
</table>

Transfusion rate	0 / 6	0 / 4
New or worsening hypertension	3 out of 10 patients (study does not state results for each treatment group) within the peritoneal dialysis population	

Haemodialysis patients

Result	High dose erythropoietin Mean Hb level reached: 12.9±0.7 g/dL (N=3)	Low dose erythropoietin Mean Hb level reached: 8.4±1 g/dL (N=6)
Transfusion rate	0 / 3	3 / 6
New or worsening hypertension	6 / 9 patients (study does not state results for each treatment group within the haemodialysis population	

Result	High dose erythropoietin	Low dose erythropoietin

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		Mean Hb level reached: 11.9±1.6 g/dL (N=21)	Mean Hb level reached: 10±2.04 g/dL (N=23)
	New or worsening hypertension	38% (8/21)	22% (5/23)
Source of funding	Not reported		

Evidence table

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Drueke 2006. Ref id 20143 [CREATE]
Study type	RCT Open label and parallel group design.
Number of patients	N(enrolled)=605 N(randomised)= 603 N(early treatment group1; target level 13.0 to 15.0 g/dL)=301 N(delayed partial correction group 2; patients treated when Hb levels declined to<10.5: target : 10.5 to 11.5 g/dL)=302
Patient	Inclusion criteria:

characteristics

Patients:

- Were older than 18 years of age
- Had an estimated GFR of 15.0 to 35.0mL/min/1.73m^2 of body surface area [calculated using Cockcroft-Gault formula]
- Had mild to moderate chronic anaemia related to their kidney disease defined as a haemoglobin level of 11.0 to 12.5g/dL
- Had blood pressure of 170/95 mm of Hg or less (use of antihypertensives to achieve target level of blood pressure was encouraged)

Exclusion criteria:

Patients were excluded from the study if:

- There was an anticipated need for renal replacement therapy within 6 months
- They had advanced cardiovascular disease defined as diagnosis of clinically significant valvular disease, congestive heart failure, myocardial infarction, unstable angina, or stroke within the preceding 3 months.
- They had nonrenal causes of anaemia
- They had received blood transfusions within the preceding 3 months
- They had a serum ferritin level of less than 50ng/mL
- They had a C-reactive protein level exceeding 15mg/L
- They had previous treatment with erythropoietin.

Baseline characteristics of patients:

Characteristic	Group 1: High Hb (N= 301)	Group 2 : Low Hb (N=302)	P-value
Age in years	59.3±14.6	58.8±13.7	0.36
Male sex	171(57)	154 (51)	0.16
Body mass index	26.6±4.5	26.2±4.8	0.42

	Weight in kg	74.7±15.6	71.8±14.2	0.05
	Diabetes mellitus	80 (27)	77 (25)	0.64
	Hypertension‡	275 (91)	269 (89)	0.38
	Blood pressure (in mm Hg)			
	Systolic	139±17	139±16	0.87
	Diastolic	79±10	80±9	0.28
	Pre existing cardiovascular disease- no. of patients	280 (93)	278 (92.1)	0.71
	Estimated GFR- mL/min	24.9±6.3	24.2±6.0	0.30
	Haemoglobin- g/dL	11.6±0.6	11.6±0.6	0.89
	Serum ferritin- ng/mL	174.4±148.3	189.4±157.7	0.56
	Transferrin saturation-%	25.6	38.1	0.59
	NB-Values are reported as mean ± SD or number of patients (%) unless otherwise indicated. ‡Defined as Systolic BP of more than 160 mm of Hg			
Intervention	• Early immediate treatment of anaemia (in patients with haemoglobin levels of 11.0-12.5g/dL at the beginning of the study) to achieve a target level of 13.0-15.0 g/dL with starting dose of 2000 IU of subcutaneous epoetin-beta administered with Reco pen. • Mean Hb achieved: 13.3g/dL (SD 0.52) • Dose was reviewed every 4 weeks; if Hb levels had increased by less than 0.5 g/dL, dose was increased by more than 25 to 50% if level had increased by more than 1.0 g/dL, dose was reduced by 25 to 50%. • Median dose: 5000IU (range 3000 to 8000)			

	• Iron supplementation (iv or oral) was recommended at investigators discretion.
Comparison	• Delayed partial correction of anaemia (in patients only when their haemoglobin levels declined to <10.5g/dL) to achieve a target level of 10.5-11.5g/dL with starting dose of 2000 IU subcutaneous epoetin-beta administered with Reco pen. • Mean Hb achieved: 11.8 g/dL (SD 0.70) • Dose was reviewed every 4 weeks; if Hb levels had increased by less than 0.5 g/dL, dose was increased by more than 25 to 50% ad if level had increased by more than 1.0 g/dL, dose was reduced by 25 to 50%. • Median dose: 2000 IU (range 1000 to 3000) • Iron supplementation (iv or oral) was recommended at investigators discretion.
Length of follow-up	Mean duration for observation of primary end point was approximately 3 years. (1044 days for group 1 and 1092 days for group 2, P=0.42)
Outcome measures and effect size	Primary outcome measures (as stated in paper): • Time to first cardiovascular event Secondary outcome measures (as stated in paper): • Death from any cause • Death from cardiovascular causes • Changes in left ventricular mass index from baseline • Changes in quality of life (according to SF-36) • Need for dialysis • Need for transfusion • Decrease in estimated GFR • MI

Effect size:

End point	Group 1 Hb level = 10.5-11.5 g/dL (N=301)	Group 2 Hb level= 13-15 g/dL (N=302)	Hazard ratio	P-value
Primary outcome:				
Time to first cardiovascular event	58 (19%)	47 (16%)	0.78 (0.53 to 1.14)	P=0.20
Death from any cause	31 (10%)	21 (7%)	0.66 (0.38-1.15) [as reported in the paper- comparing group 2 vs group 1];	0.14
			group 1 vs 2: 1.48 (0.87 to 2.52)	
Incidence of death from cardiovascular causes	12 (4%)	9(3%)	0.74 (0.33-1.70) as reported in paper comparing group 2 vs group 1;	0.48
			group 1 vs group 2: 1.34 [0.57 to 3.13]	0.15
Change in left ventricular mass index at year 2	-6.4g/m^2	-7.8g/m^2	Not reported	0.65
Quality of life scores:				

The study reported the following for SF-36 score (at year 1)

General health	Group 1 significantly better than group 2	N/A	N/A	0.003
Mental health	Group 1 significantly better than group 2	N/A	N/A	<0.001
Physical function	Group 1 significantly better than group 2	N/A	N/A	<0.001
Physical role	Group 1 significantly better than group 2	N/A	N/A	0.01
Social function	Group 1 significantly better than group 2	N/A	N/A	0.006
Vitality	Group 1 significantly better than group 2	N/A	N/A	<0.001

Significant difference between above groups was maintained at year 2 with a p- value for general health being equal to 0.008 and for vitality being equal to 0.01.

Unpublished data[271] received upon request reported the following scores:

time point: 1 year	High Hb; n=301	Low Hb; n=302	
	High Hb-mean§	Low Hb- mean§	p value‡
Physical function	3.5	-2.1	0.0004
Physical role	2.6	-5.5	0.0097
Pain	-0.2	-2.1	0.3155
General health	4.1	-0.1	0.0029

Vitality	3.9	-0.6	0.0009
Social function	1.8	-3	0.0058
Emotional role	0.4	-4.3	0.1291
Mental health	2.7	-2.1	0.0005
Physical health composite	NR	NR	NR
Mental health composite	NR	NR	NR

§ Least square mean;

‡ F test

NR=not reported

End point	Group 1 Hb level = 10.5-11.5 g/dL (N=301)	Group 2 Hb level= 13-15 g/dL (N=302)	Effect size	P-value
Mean decrease in estimated GFR				
Year 1	3.6±6.7 mL/min	3.1±5.3 mL/min	Not reported	0.40
End of study	18.1± 11.5	19.2± 19.0	Not reported	0.36
After 18 months, time to initiation of dialysis was shorter in group 1 than in group 2. P= 0.03				

	Need for blood transfusion				
	Blood transfusion	26 patients	33 patients	Not reported	Not reported
	Adverse events (as stated in paper)‡:				
	Myocardial infarction	14 (5)	15(5)	Not reported	0.94
	Hypertension	89 (30)	59 (20)	Not reported	0.005
	Transient ischemic attack	5(2)	2(<1)	Not reported	0.34
	Arteriovenous fistula				
	Thrombosis	12 (4)	8(3)	Not reported	0.42
	Complications	8(3)	3(1)	Not reported	0.17
	Progression of CKD	166 (55)	163(54)	Not reported	0.77
	Results reported: No of patients (%)				
Source of funding	F. Hoffmann-La Roche				

Evidence table

Review question	What should be the aspirational haemoglobin target range/ level for patients undergoing treatment for anaemia in CKD with ESA/ blood transfusion compared with those receiving placebo/ standard treatment/ESA (different dosage or class)?

<table>
<tr><td>Bibliographic reference</td><td>Eckhardt 2007; Ref id 20152</td></tr>
<tr><td>Study type</td><td>Secondary analysis of CREATE [Drueke 2006]</td></tr>
<tr><td>Number of patients</td><td>N(enrolled)=605

N(randomised)= 603 [included in the intention to treat analysis in CREATE]

N (baseline echocardiograms)=580

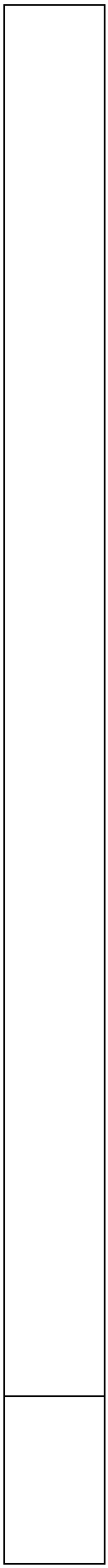
N (assessable for LVMI)= 451
• N(group 1) =219;
• N(group 2)=232)</td></tr>
<tr><td>Patient characteristics</td><td>Demographics and baseline characteristics of the population iwth baseline echocardiograms
<table>
<tr><th>Characteristic</th><th>Group 1: High Hb (N= 219)</th><th>Group 2 : Low Hb (N=232)</th></tr>
<tr><td>Age in years</td><td>57.8±14.5</td><td>56.6±13.5</td></tr>
<tr><td>Sex (male)</td><td>128(58)</td><td>113 (49)</td></tr>
<tr><td>Body mass index</td><td>26.2±4.2</td><td>26.2±4.8</td></tr>
<tr><td>Weight in kg</td><td>73.7±15.2</td><td>71.4±14.1</td></tr>
<tr><td>Diabetes</td><td>55(25)</td><td>60(26)</td></tr>
<tr><td>Hypertension</td><td>205 (94)</td><td>207 (89)</td></tr>
<tr><td>Systolic (mm Hg)</td><td>139±17</td><td>139±16</td></tr>
</table></td></tr>
</table>

	Diastolic (mm Hg)	79±10	80±9
	Pre existing cardiovascular disease- no. of patients	209 (95)	212(91)
	Estimated GFR- mL/min¶	25.0±6.1	24.3±6.0
	Haemoglobin- g/dL	11.5±0.6	11.5±0.6
	Serum ferritin- µg/L	174.1±151.0	193.5±163.0
	Transferrin saturation-%	25.9 ±9.6	42.5 ±22.5
	¶Percentages and numbers are based on available data with single data missing Data are reported as mean± SD, n(%)		
Intervention	Early immediate treatment of anaemia (in patients with haemoglobin levels of 11.0-12.5g/dL at the beginning of the study) to achieve a target level of 13.0-15.0 g/dL with starting dose of 2000 IU of subcutaneous epoetin-beta administered with Reco pen.		
Comparison	Delayed partial correction of anaemia (in patients only when their haemoglobin levels declined to <10.5g/dL) to achieve a target level of 10.5-11.5g/dL with starting dose of 2000 IU subcutaneous epoetin-beta administered with Reco pen.		
Length of follow-up	3 years.		
Results	Change in LVMI [in patients who had echocardiograms at baseline]	Group 1: High Hb	Group 2 : Low Hb (N=232)
	Year 1	-3.3 ± 26.5	-1.3 ± 23.2
	Year 2	-3.3 ± 27.5	-11.1± 27

Year 3	-1.3 ± 36	-7.4 ± 34.4

CV event free survival [patients with concentric LVH]	Group 1: High Hb N=43	Group 2 : Low Hb N=42
Year 1	38	35
Year 2	33	29
Year 3	16	18

CV event free survival [patients with eccentric LVH]	Group 1: High Hb N=61	Group 2 : Low Hb N=66
Year 1	50	61
Year 2	33	46
Year 3	16	28



Update 2011

Evidence table

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Foley 2000. Ref id 225
Study type	RCT
Number of patients	N (randomised)=146 N(concentric LV hypertrophy group)=70; ○ N9.5-10.5 g/dL)= 36 ○ N13.0-14.0 g/dL)=34 N(LV dilation group)= 76; ○ N(9.5-10.5 g/dl)= 37 ○ N(13.0-14.0 g/dl)=39
Patient characteristics	Inclusion criteria included: • Age greater than 17 years • Maintenance haemodialysis for greater than three months • LV hypertrophy(LV mass indexed to a body surface area of greater than 131 g/m^2in males and 100g/m^2in females or LV dilation (defined as LV cavity volume indexed to a body surface area of greater than 90mL/m^2 • A haemoglobin concentration between 9 and 11 g/dL in the month prior to randomisation • Stable vascular access for the previous three months • Life expectancy greater than 18 months Exclusion criteria included: • Angina pectoris, myocardial infarction, coronary artery bypass surgery, percutaneous transluminal angioplasty or congestive heart failure within the previous 12 months • Active bleeding

- Uncorrected iron deficiency
- Valvular heart disease for which surgical intervention was planned within one year
- Intravenous iron dextran intolerance

Baseline characteristics of patients:

Target Haemoglobin				
	Concentric LV hypertrophy N=70		LV dilation N=76	
	9.5-10.5 g/dL N=36	13.0-14.0 g/dL N=34	9.5-10.5g/dL N=37	13.0-14.0g/dL N=39
Age	60(56,65)	62(57,67)	62(57,67)	62(58,66)
Male	16(44%)	16(47%)	28(76%)	31(79%)
Caucasian	24(67%)	25(74%)	28(76%)	31(79%)
Renal disease				
Glomerulonephritis	11(31%)	9(26%)	10(27%)	11(28%)
Diabetes mellitus	11(31%)	9(26%)	9(24%)	14(36%)
Renovascular	5(14%)	7(21%)	8(22%)	7(18%)
Other	9(25%)	9(26%)	10(27%)	7(18%)

	Body surface area m^2	1.73(1.66,1.80)	1.75(1.67,1.83)	1.79(1.72,1.85)	1.82(1.75,1.90)
	Duration of dialysis therapy in years	5.6(3.7,7.5)	5.6(3.7,7.5)	3.7(2.4,5.0)	3.3(2.2,4.4)
	Dialysis time in hours/week	11.3(10.9,11.6)	11.2(10.5,11.8)	11.4(10.8,12.0)	11.6(11.1,12.1)
	Kt/V	1.47(1.36,1.59)	1.45(1.34,1.56)	1.51(1.36,1.66)	1.44(1.34,1.53)
	LV mass index in g/m^2	139(132,149)	147(138,156)	165(149,182)	172(161,184)
	LV cavity volume index in mL/m^2	69(63,75)	63(57,69)	123(113,133)	122(113,132)
	Haemoglobin in g/dL	10.4(10.2,10.6)	12.2(11.9,12.5)	10.4(10.2,10.6)*	12.3(12.0, 12.5)*
	Systolic blood pressure in mm of Hg	157(153,161)	162(157, 166)	155(150,160)*	154(148,160)*
	Diastolic blood pressure in mm of Hg	81(78,84)	82(79,84)	82(79,85)*	84(81,87)*
	Figures are reported as n(%) in parenthesis represent 95% CI. *N=36				
Intervention	• Partial correction of anaemia with target haemoglobin of 9.5-10.5g/dL achieved by administering epoetin-alfa subcutaneously, a ramping phase of 24 weeks followed by 24week maintenance period. Median time to reach target Hb was 14.5 weeks.				

	• Mean Hb : 12.2 g/dL. Mean Hb 1.8g/dL higher in the intervention group. Predialysis Hb:12.3 (11.9 to 12.5) • Patients were stratified on the basis of their baseline LV morphology (Concentric LV hypertrophy: n=36 and LV dilation:36) and study site • Dose U/kg/week [Mean (95% CI)]: Concentric LV hypertrophy group: 139 (102,176); L dilation group: 120 (97,144) • i.v. iron dextran use (mg/week): Concentric LV hypertrophy group: 44 (29,58); L dilation group: 46 (34,58)
Comparison	• Normalisation of haemoglobin with target haemoglobin of 13-14g/dL achieved by administering epoetin-alfa subcutaneously. • Patients were stratified on the basis of their baseline LV morphology (Concentric LV hypertrophy:n=34 and LV dilation: n=36) and study site. • Mean Hb :10.4 g/dL; Predialysis Hb:10.4 (10.2 to 10.6) • Dose U/kg/week [Mean (95% CI)]: Concentric LV hypertrophy group: 293 (208,377); LV dilation group: 283 (229,337) • i.v. iron dextran use (mg/week): Concentric LV hypertrophy group: 64 (43,85); LV dilation group: 68 (51, 84)
Length of follow-up	The length of the study was 48 weeks.
Outcome measures	Primary outcome variables reported were:

and effect size

- Change in LV mass and cavity volume index in those with concentric LV hypertrophy and in those with LV dilation

Secondary outcome variables reported were:

- Major vascular events (arteriovenous access thrombosis, cardiac events and death)
- QoL (KDQ; HUI, SF-36)

Effect sizes:

Primary outcomes:

- Concentric LV hypertrophy group:

  The changes in LV mass index were similar in both haemoglobin target groups and there was a statistically significant correlation between mean haemoglobin level achieved and change in mass index(p=0.075)

  The change in cavity volume was inversely correlated with mean haemoglobin level (p=0.009)- more data in graph.
- LV dilation group:

  The changes in LV mass and cavity volume index were similar in both groups and there was no correlation between mean haemoglobin level and observed echocardiographic changes.

Secondary outcomes:

Major vascular events:

	Target Haemoglobin		
	13-14g/dL N=73	9.5-10.5 g/dL N=73	P[a]
Arteriovenous access thrombosis	6(8%)	10 (14%)	0.4
Cardiac event[b]	10(14%)	10(14%)	0.6

	Death	4(5%)	3(4%)	1.0
	Hypertension (number of hypertensive drugs per patient)	1.2 per patient	2 per patient	

[a] Fisher's exact test

[b]Angina pectoris, myocardial infarction, pulmonary oedema or cardiac failure.

Study reported no clinically important or statistically important differences between scores according to Hb group on the SF-36.

Source of funding	Janssen-Ortho inc. Toronto Canada

Evidence table

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Foley , 2008. Ref id 20196
Study type	Secondary analysis of Parfrey 2005
Number of patients	N=596 patients randomised; N(13.5 to 14.5 g/dL) =296 N(9.5 to 11.5 g/dL) = 300
Patient characteristics	Inclusion criteria: • Aged 18 years or over

- Inception of maintenance haemodialysis within previous 3 to 18 months
- Predialysis haemoglobin between 8 and 12 g/dL
- Left ventricular volume index < 100 mL/m^2
- Predialysis diastolic BP < 100 mmHg

Exclusion criteria:

- Clinical evidence or history of symptomatic cardiac failure or ischaemic heart disease
- Daily prednisone dose ≤ 10 mg
- Medical conditions likely to reduce epoetin responsiveness, including uncorrected iron deficiency
- Concurrent malignancy
- Blood transfusion in preceding month
- Therapy with cytotoxic agents
- Seizure in preceding year
- Hypersensitivity to intravenous iron
- Current pregnancy or breastfeeding

Characteristic	Haemoglobin 13.5 to 14.5 g/dL (N=296)	Haemoglobin 9.5 to 11.5 g/dL (n=300)
Haemoglobin (g/dL)	11 (10.9 to 11.2)	11 (10.8 to 11.1)
Epoetin dose (IU per week)	7009 (6528 to 7490)	6183 (5698 to 6667)
Transferrin saturation (%)	35.8 (33.8 to 37.7)	36.8 (34.9 to 38.8)
Age	52.2 (50.4 to 53.9)	49.4 (47.7 to 51.2)
Female sex (%)	39.5	39.7
Race White	91.2	87.7

Black	4.4	5.7
Asian	1.7	4.3
Other	2.7	2.3
Dialysis duration (months)	10 (9.4 to 10.5)	10.2 (9.6 to 10.8)
BMI (kg/m^2)	26.5 (25.9 to 27.1)	26.3 (25.7 to 26.9)
Primary cause of renal disease		
Glomerulonephritis		
Diabetes	28.4	29.0
Hypertension	18.9	16.7
Polycystic kidney disease	6.8	9.3
Other / unknown	10.5	7.7
	35.5	37.3
Dialysis access (%)		
Fistula	85.8	82.7
Graft	6.1	5
Catheter	8.11	12.3
Serum albumin (mg/dL)	4 (3.9 to 4)	4 (3.9 to 4)

Data are reported either as percent or as mean (95% confidence interval).

<table>
<tr><td>Intervention</td><td>

High target haemoglobin level of 13.5 to 14.5 g/dL
Mean Hb at end of initial 24-week titration phase: 13.3 g/dL and maintenance phase from 24 to 96 weeks: 13.1 g/dL.
Patients received a 25% dose escalation or an initial dose of 150 U/kg/wk if epoetin naïve. If Hb deviated from target, epoetin doses changed by 25% of the previous dose or 25 U/kg. Mean initial on-study epoetin dose: 7009 U/wk.

</td></tr>
<tr><td>Comparison</td><td>

Low target haemoglobin level of 9.5 to 11.5 g/dL
Mean Hb at end of initial 24-week titration phase: 10.9 g/dL and maintenance phase from 24 to 96 weeks: 10.8 g/dL.

Patients remained on their prestudy epoetin dose. If Hb deviated from target, epoetin doses changed by 25% of the previous dose or 25 U/kg. Mean/median doses not reported. Mean initial on-study epoetin dose 6183 U/wk.
</td></tr>
<tr><td>Length of follow-up</td><td>Study length was 96 weeks</td></tr>
<tr><td>Outcome measures and effect size</td><td>
Outcome: Transfusion rates
<table>
<tr><th>Parameter</th><th>High Hb targetlevel 13.5 to 14.5 g/dL
N=296</th><th>Low Hb target level: 9.5 to 11.5 g/dL
N=300</th><th>Reported p-value</th></tr>
<tr><td>Transfusions per patients</td><td>0.37 (0.20, 0.37)</td><td>0.94 (0.62, 1.26)</td><td>0.00</td></tr>
<tr><td>Transfusion rate (per patient per year)</td><td>0.26 (0.22, 0.32)</td><td>0.66 (0.59, 0.74)</td><td><0.0001</td></tr>
<tr><td>Transfusion rate ratio</td><td>0.4 (0.32, 0.50)</td><td>1 (reference category)</td><td></td></tr>
<tr><td>Time to first transfusion</td><td></td><td></td><td></td></tr>
<tr><td>Proportion transfused (%)</td><td>9.1 (27/296)</td><td>19.3 (58/300)</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>HR (95% CI) reported unless otherwise stated.

Adverse events occurring within 4 weeks before the first transfusion –classified by World Health Adverse Reactions Terminology

Study reported 12 clinical manifestations e.g. infection, respiratory, neurologic. AEs not relevant to the reviews not reported below.
<table>
<tr><td>Clinical manifestation</td><td>High target Hb level
13.5 to 14.5g/dL
N=27</td><td>Low target Hb
9.5 to 11.5 g/dL
N=58</td></tr>
<tr><td>Vascular access problems</td><td>5.0 (4/27)</td><td>4.0 (9/58)</td></tr>
<tr><td>Cardiovascular</td><td>11.3 (9/27)</td><td>10.3 (23/58)</td></tr>
</table>
Figures reported are % (n/N).</td></tr>
<tr><td>Source of funding</td><td>Johnson and Johnson Pharmaceutical Research and Development</td></tr>
</table>

Evidence table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Furuland 2003 Ref id 224
Study type	RCT
Number of patients	N(randomised)=416 Patients were stratified into 3 groups: Predialysis, Haemodialysis(HD) and Peritoneal dialysis(PD)

	N(N-Hb group)= 216; patients were randomised to reach a normal haemoglobin range of 135-160 g/L N(S-Hb group)=200; patients were randomised to reach a subnormal haemoglobin value of 90-120 g/L Hospital centres in Sweden (48), Norway (8), Finland (5) and Iceland (1).
Patient characteristics	Inclusion criteria Patients were included if they had: • Renal anaemia and were either in predialysis, haemodialysis or peritoneal dialysis; predialysis patients were not expected to become dialysis dependant within 1 year(serum creatinine>300mmol/l and creatinine clearance<30 mL/min) • Haemoglobin values in the subnormal range (90-120 g/L) for at least 3 months with or without epoetin therapy prior to entering the study. Exclusion criteria included: • Anaemia from other causes other than chronic renal failure • Diastolic blood pressure repeatedLy≥100 mm of Hg • Uncontrolled diabetes (HbA1c>10%) • Clinically relevant abnormal liver function • Severe secondary hyperparathyroidism(cystic bone disease, parathyroid hormone>300 ng/L) • Clinical signs of aluminium intoxication(serum aluminium>100 mg/L) or treatment with desferrioxamine • Uncontrolled over hydration in HD patients (requiring repeated ultrafiltration of ≥4 l) • Presence of active infection, inflammation or malignancy. An amendment in 1996 added the following exclusion criteria: • Angina pectoris and/or congestive heart failure corresponding to New York Heart Association classes III or IV • History of coronary artery bypass grafting and/or percutaneous transluminal coronary angioplasty<2 years ago • History of transmural myocardial infarction<3 years ago • Permanent atrial fibrillation or uncontrolled arterial hypertension. NB. Due to addition of new exclusion criteria later, 33 patients were excluded from the study.

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Baseline characteristics of patients:

Characteristic	Predialysis		HD		PD		Total	
	N-Hb N=36	S-Hb N=36	N-Hb N=157	S-Hb N=136	N-Hb N=23	S-Hb N=23	N-Hb N=216	S-Hb N=200
Age in years	57±13	60±12	65±12	64±15	60±9	60±13	63±12	63±14
Females (%)	47	53	31	32	26	39	33	37
Caucasian (%)	100	100	99	98	100	100	99	99
Weight in kg	73±17	75±14	73±14	72±15	77±13	75±15	73±15	73±15
Serum creatinine in µmol/l	373±123	349±117						
Time on dialysis in years			2.6±3.3	3.0±3.9	1.1±1	2.4±4.4		
Previously transplanted (%)	6	3	12	14	0	18	10	13
Antihypertensive medication (%)	89	78	57	60	78	57	52	48
Diabetes (%)	25	17	18	20	22	25	19	20
Congestive Heart Failure (%)	3	0	17	12	0	0	13	8
Ischaemic Heart Disease (%)	17	19	36	32	13	32	30	30
Haemoglobin in g/L	106±10	109±7	110±11	110±9	112±9	112±9	109±11	110±9

Plus-minus values indicate means ± SD.

Intervention	• A target level haemoglobin level of 135-150 g/L in females and 145-160 g/L in males achieved by administration of subcutaneous epoetin alfa (Eprex®). • Mean Hb achieved at week 48: predialysis: 14.3 g/dL (SD 0.11); HD: 13.5g/dL (SD0.14); PD: 13.4 g/dL(SD 0.15) • Epoetin alfa administered s.c. and the dose was adjusted in response to haemoglobin values and reticulocyte count. • In patients not already receiving epoetin, initially received 50 U/kg 3 times weekly. In patients already receiving epoetin, initial dose increment was 50%. • Mean dose [U/kg/wk]: Predialysis: 107 (SD 117); HD: 236 (SD148); PD: 168 (SD 118) • Patients also received iron supplementation with oral ferrous sulphate or i.v iron sucrose to keep transferring saturation>20% and serum ferritin levels between 400 and 800 mg/L during the correction phase and >250 mg/L during the maintenance phase.
Comparison	• A target haemoglobin level of 90-120 g/L with or without epoetin alfa treatment. • In patients who received epoetin alfa, the dose was adjusted in response to haemoglobin values and reticulocyte count. Mean Hb achieved at week 48: predialysis: 117 (SD 13); HD: 113 (SD13); PD: 115(SD 12) • In patients not already receiving epoetin, initially received 50 U/kg 3 times weekly. In patients already receiving epoetin, initial dose increment was 50%. • Mean dose [U/kg/wk]: Predialysis: 39(SD 53); HD: 140 (SD182); PD: 58 (SD 86) • Patients also received iron supplementation with oral ferrosulphate or i.v iron sucrose to keep transferring saturation>20% and serum ferritin levels between 400 and 800 mg/L during the correction phase and >250 mg/L during the maintenance phase.
Length of follow-up	The study duration was extended from 48 to 76 weeks in 48 study centres due to a lower increase in Hb values than anticipated. The study stated 'since withdrawal rates was high, results at week 48 are presented for many of the variables'.
Outcome measures and effect size	**Primary outcomes:** • Renal function assessed by GFR measurements • Adverse events **Effect size:** **Renal Function assessed by GFR measurements in predialysis patients:**

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	N-Hb group		S-Hb group		P- value
	Baseline N=24	Week 48 N=19	Baseline N=22	Week 48 N=21	
GFR measured in mL/min/1.73m^2	16±9	13±10	17±6	16±7	0.43

Adverse events:

Mortality

	Predialysis		HD		PD		Total	
	N-Hb N=36	S-Hb N=36	N-Hb N=157	S-Hb N=136	N-Hb N=23	S-Hb N=28	N-Hb N=216	S-Hb N=200
Cardiovascular causes	3	1	18	10	3	5	24*	16
All cause mortality	4	1	21	20	3	6	29(13.4%)	27(13.5%)
Blood pressure 12 weeks	147±21	148±24	No significant difference at any time point		143 ±23	144 ±28	NA	NA
per protocol analysis]	90±6	83±11			88 ±12	80 ±10		

		Sig difference at 48 weeks (p=0.02) for diastolic b.p. Study reported no significant differences in b.p. at 12,24 and 76 weeks.		Sig difference at 12 weeks (p=0.04) for diastolic b.p.. Study reported no significant differences in b.p. at 24,48 and 76 weeks.		
	*P=not significant for N-Hb vs S-Hb					
Source of funding	Janssen-Cilag AB, Sollentuna, Sweden					

Evidence table

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Levin 2005 Ref id 20174
Study type	RCT Open label
Number of patients	N(assessed for eligibility)= 363 N (Randomised)= 172 N (Randomised to treatment group with Hb target levels 12-14 g/dL±0.5 g/dL)=85 N (Randomised to control group with Hb target levels levels 9.0-10.5 g/dL)=87 Reasons for exclusion of 191 patients from randomisation include technically difficult 2D echo (n=64), no decline in Hb over 12 months (n=59), other reversible causes of anaemia (n=25), refusal to participate(n=12) and other reasons(n=31).

<table>
<tr><td></td><td>N (Analysed for treatment group with Hb target levels 12-14 g/dL±0.5 g/dL)=74

N (Analysed for control group with Hb target levels levels 9.0-10.5 g/dL)=78</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:

Patients:
• Were aged between 18-75 years
• Had a calculated creatinine clearance between 15-79 mL/min;
• and had either:
1. A documented progressive decline in Hb level of 1.0 g/dL or greater within previous 12 months to a current Hb level between 11.0 and 13.5 g/dL for men and 10.0 and 13.5 g/dL for women
2. Current Hb level between 11.5 and 12.5 g/dL for men and 11.0 and 12.0 g/dL for women.

Exclusion criteria:

Patients were excluded if they:
• Had known reversible causes of anaemia or decline in Hb levels (including iron insufficiency, serum ferritin level<60 ng/mL and/or transferring saturation<20%)

Baseline characteristics:
<table><tr><td>Characteristics</td><td>Treatment group (Hb target level 12-14 g/dL±0.5 g/dL) N=78</td><td>Control group (Hb target level 9.0-10.5 g/dL) N=74</td></tr><tr><td>Age</td><td>56.5±14.9</td><td>57.3±14.9</td></tr><tr><td>Male sex</td><td>55(70.5)</td><td>52(70.3)</td></tr><tr><td>Race</td><td></td><td></td></tr></table></td></tr>
</table>

	White	65 (83.3)	67 (90.5)
	Asian	10 (12.8)	4 (5.4)
	Other	3 (3.9)	3 (4.1)
	Weight	78.2±13.4	78.0±15.5
	Body surface area	1.89±0.19	1.89±0.21
	Diabetes	32(41.0)	26(35.1)
	Primary kidney disease		
	Diabetes	25 (32.1)	22 (29.7)
	Polycystic kidney disease, nephropathy, congenital	19 (24.4)	13 (17.6)
	Glomerulonephropathy, renal vascular disease	29 (37.2)	33 (44.6)
	Cause uncertain	5 (6.4)	6 (8.1)
	Systolic BP(mm of Hg)	137.1±17.5	140.5±18.6
	Diastolic BP(mm of Hg)	75.8±11.5	79.6±10.5
	Cholesterol (mg/dL)	197±46	201±46
	Creatinine clearance (mL/min)	37.4±13.6	35.1±13.0
	eGFR (mL/min)	29.7±11.1	27.8±9.3
	Albumin (g/dL)	3.89±0.43	3.86±0.55
	Homocysteine (µmol/dL)	16.9±5.9	18.1±6.8
	Haemoglobin (g/dL)	11.76±0.76	11.73±0.80

	<table><tr><td>Ferritin (ng/mL)</td><td>100(60-172)</td><td>99(63-155)</td></tr><tr><td>Transferrin saturation (%)</td><td>27.8±10.5</td><td>26.6±9.7</td></tr></table> NB. Values are expressed as mean ± SD, number (percent), or median (25th to 75th percentiles).
Intervention	• A target haemoglobin level of 12-14 g/dL ± 0.5 g/dL was maintained with subcutaneous administration of erythropoietin alfa (Eprex®) at 2000 IU once weekly. Target levels were not to exceed 14 g/dL. Only 28% patients (22/78) had all Hb values within the target range. • Mean change of Hb from baseline [11.76 (SD0.76)] at end of follow up: 0.98± 1.13; mean Hb achieved at end of follow-up: 12.7 ±0.87 (11.83 to 13.57) • 99% (77/78) patients in this group received erythropoietin alfa therapy. • Study reported mean doses were similar in both groups. Last dose: Mean (SD) :3146 U/wk (SD 2615); Median (25th to 75th percentile): 2000 (2000 to 4000) • 7/78 (73.1%) patients in this group received oral iron and 10 (12.8%) received iv or im iron.
Comparison	• Haemoglobin levels were allowed to progressively decline to 9.0 g/dL or less at which point erythropoietin alfa was administered subcutaneously at 2000 IU once weekly to maintain the haemoglobin levels between 9.0 and 10.5 g/dL. • 24% patients (18/ 74) had a decrease in Hb level greater than 1.0 g/dL from baseline to last follow-up. Out of these, 21% (12/58) were from the group which was not started on ESA therapy and 38% (6/16) were from the group who were started on ESA therapy. Only a total of 23 patients in the comparison group actually had target levels of Hb below 11.0 g/dL (of these 7 did not receive ESA and 16 received ESA therapy). • Mean change of Hb from baseline [11.73 (SD 0.80); range:10.9 to 12.53] at last measure: -0.3 ± 1.15 - the last mean Hb level 11.4 g/dL (SD 1.2); Study reported mean Hb was stable at end of follow-up: • 22% (16/74) patients in this group received erythropoietin alfa therapy. • Study reported mean doses were similar in both groups. Last dose: Mean (SD):3552 U/wk (SD 2562); Median (25th to 75th percentile): 3000 (1500 to 6000) • 67.6% (50/74) patients in this group received oral iron and 10.8% (8/74) received i.v or i.m iron.
Length of follow-up	Both the groups were followed up for 24 months. In the treatment group, 7/85 randomised patients, were excluded (4 patients withdrew, 1 had an adverse event and 2 were not analysed for other reasons) from analysis and 78 were analysed as ITT. In the control group, 13/87 randomised patients, were excluded from analysis (7 patients withdrew, 3 had adverse events, 2

<table>
<tr><td></td><td>were lost to follow-up and 1 was not analysed for other reasons) and 74 were analysed as ITT.</td></tr>
<tr><td>Outcome measures and effect size</td><td>

Primary outcome measures:

- Change in LVMi from baseline to 24 months measured by means of 2D targeted M-mode echocardiography.

Secondary outcome measures:

- Change in renal function
- Change in quality of life.(data not reported)
- Adverse events (Defined as: death, dialysis, vascular access creation, other serious AEs included: arteriovenous fistula thrombosis, CHF and bascular blockage; CHF; chest pain requiring coronary angiography; thoracic pain requiring angiogram which showed negative results and angina pectoris followed by coronary bypass surgery)

Effect sizes:

Change in LVMi

<table>
<tr><td colspan="2">**Baseline** LVMi</td><td colspan="2">**Mean change** in LVMi during trial period</td></tr>
<tr><td>Treatment group

(Hb target level=12-14g/dL±0.5 g/dL)</td><td>Control group

(Hb target level=9-10.5 g/dL)</td><td>Treatment group

(Hb target level=12-14g/dL±0.5 g/dL)</td><td>Control group

(Hb target level=9-10.5 g/dL)</td></tr>
<tr><td>100.6±22.2g/m^2</td><td>98.3±25.0g/m^2</td><td>0.4±25.0g/m^2</td><td>5.2±30.3g/m^2</td></tr>
<tr><td colspan="4">Absolute LVMi change was not statistically significant between the two groups. P= 0.28</td></tr>
<tr><td colspan="4">Absolute mean difference between control and treatment groups in LVMi changes from baseline to 24 month echocardiogram measurement was 4.85 g/m^2 (95% CI, -4.0to 13.7); SD 28 g/m^2</td></tr>
</table>

Secondary outcome measures:

</td></tr>
</table>

Change from baseline to last measure

Characteristic	Treatment group (Hb target level 12-14 g/dL±0.5 g/dL) N=78	Control group (Hb target level 9.0-10.5 g/dL) N=74	P value
Creatinine clearance (mL/min)	-7.4±11.1	-9.1±10.0	0.315
eGFR (mL/min)	-4.9±7.5	-7.2±8.4	0.086

NB. Values are expressed as mean ± SD, number (percent), or median (25^{th} to 75^{th} percentiles).

Outcomes reported as adverse events[g]:

Outcome	Treatment group (Hb target level 12-14 g/dL±0.5 g/dL) N=78	Control group (Hb target level 9.0-10.5 g/dL) N=74	P value
Death (number of patients)	1	3	Not reported
Dialysis started			0.563
Haemodialysis	7	6	
Peritoneal dialysis	4	2	

	<table><tr><td>Hypertension*</td><td>51%</td><td>54%</td><td>0.733</td></tr><tr><td>Heart failure and MI</td><td>0</td><td>1</td><td></td></tr></table> º The study reported that data for adverse events was provided for all 172 randomised patients and not only for those in the intention to treat analysis *Hypertension defined as 1 recorded BP greater than 140/90 mm of Hg. 4 episodes reported as an AE but none related to study drug and all resolved.
Source of funding	Ortho Biotech

Evidence table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	MacDougall 2007.Ref id 20159
Study type	RCT Open label
Number of patients	N(randomised)= 197
	N (Group A, Hb maintained at 11.0±1.0g/dL with SC-EPO therapy)=65 [completed 3 years= 20, withdrew= 44, missing= 1] N (Group B, Hb allowed to fall to ≤9.0 g/dL before starting SC-EPO therapy) = 132; 55 progressed to receiving treatment. [completed 3 years= 20, withdrew= 112] 24 sites in the UK.
Patient characteristics	Inclusion criteria:

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	Patients: • Were aged between 18-25 years • Had a diagnosis of progressive renal failure within 1-5 years of study enrolment • Had a serum creatinine level of 150-500µmol/l • Had a haemoglobin concentration of 11.0±0.5g/dL • Had no evidence of iron deficiency i.e. serum ferritin ≥60µg/L, transferrin saturation≥20% and hypochromic red cells<10% • From baseline values of 150 to 500 µmol/l for creatinine and 11.0± 0.5g/dL for Hb, had to have deteriorating levels of haemoglobin and serum creatinine as determined by a series of three readings over at least 3 months before treatment showing decreasing levels of Hb concentrations and increasing levels of serum creatinine concentrations Exclusion criteria: Patients who had: • previously received renal replacement therapy including renal transplant • received prior treatment with erythropoietin or blood transfusion • taken androgens or erythropoiesis-suppressing medications within 1 month of enrolment or blood transfusion for other reasons within 3 months of enrolment Patients with: • unstable or poorly controlled angina or severe congestive cardiac failure (NYHA Grade III or IV) • gross cardiomyopathy/LVH determined by screening echocardiogram • surgically placed arteriovenous fistula, • poorly controlled hypertension defined as blood pressure>160/90mm of Hg • severe chronic respiratory disease • severe symptomatic peripheral vascular disease, 'severe' as determined by investigator • With haemoglobinopathies, marrow disorders or other conditions known to cause anaemia, inflammatory or infectious diseases which might impair the response to erythropoietin • Patients In whom LVM could not be deduced from an echocardiogram • Patients who were pregnant, lactating and women without adequate contraception.

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Baseline characteristics:

Characteristics	Group A (N=65)[1] Hb maintained at 11.0±1.0g/dL	Group B (N=132) , Hb allowed to fall to ≤9.0 g/dL
Males	41 (64.1)	82 (62.1)
Females	23 (35.9)	50 (37.9)
Age in years	55.6±13.6	54.5±14.4
Body weight in kg	78.9±17.5	77.6±15.6
Height in cm	168.8±9.6	170.4±10.0
Blood pressure in mm of Hg		
Systolic	140.4±19.4	142.2±19.1
Diastolic	78.7±10.2	80.2±9.9
Medical history(≥50% patients)[2]		
Cardiovascular	61 (95.3)	122 (92.4)
Hypertension	59 (92.2)	120 (90.9)
Ischaemic heart disease	7 (10.9)	16(12.1)
Diabetes	15 (23.4)	29 (22.0)
Haemoglobin in g/dL	10.89±0.60	10.76±0.66
Serum creatinine in µmol/l	325.8±100.5	349.3±88.4
Creatinine clearance in mL/min	25.75±12.23	23.26±10.15

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	GFR in mL/min	21.44±9.69	19.91±7.72
	Serum ferritin in µg/L	165.55±138.93	144.70±83.30
	Serum iron in µmol/l	13.48±4.55	13.75±3.87
	Transferrin saturation (%)	30.07±15.60	29.94±16.03
	Stages of CKD		
	Stage 1: ≥90	0(0)	0(0)
	Stage 2 : 60 to >90	1(1.5)	1(0.8)
	Stage 3: 30 to >60	9(13.8)	13 (9.8)
	Stage 4: 15 to >30	42 (64.6)	86 (65.2)
	Stage 5: <15	13 (20.0)	32 (24.2)

NB. Values reported indicate number(percent) or mean ± SD unless otherwise indicated. P values not reported. Calculated by reviewer and no statistically significant difference found.

[1]Data was missing for the first four variables for one patient.

[2] Data presented for intention to treat population

Intervention	• A target haemoglobin concentration of 11.0±1.0 g/dL maintained with subcutaneous epoetin-alfa (dose: 1000 U twice weekly) started on day 1 of randomisation. • Maintenance of target Hb levels was by titration of epoetin-alfa at 1000 U weekly until start of renal replacement therapy, death or until patients continued the study until 3 years. • Mean Hb achieved: 11 g/dL; Change from baseline (10.89 g/dL(SD 0.60) to final visit: 0.11g/dL (SD 1.24). • Total administered dose: 190,211U (SD 127,216). Mean weekly dose at 1 year: 1470.6 U/wk (1021.8) [n=51]; 2 years:

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	1640.6 (1219.7) [n=32]; 2047 (SD 2355.3) [n=21];final dose [including zero doses]: 1992.2 (1787.3); final dose [patient's last zero dose take for group A]:2281.3 U (SD 1747.7);
Comparison	• Group monitored every 2 months until haemoglobin fell to a trigger level of ≤9.0 g/dL.Treatment commenced with subcutaneous epoetin-alfa(dose: 2000 U three times weekly) once the haemoglobin levels had fallen to a trigger level of ≤9.0 g/dL and had remained at that level for 3 months or had fallen to ≤8.0 g/dL on two consecutive occasions ≥2 weeks apart, or when patients developed clinical symptoms of anaemia. Hb concentration was subsequently maintained at 11 g/dL (SD 1). • Maintenance of target Hb levels was by titration of epoetin-alfa at 1000 U weekly until start of renal replacement therapy, death or until patients continued the study until 3 years. 42% (55/165) patients progressed to treatment. • Mean Hb achieved: 10.48 g/dL. Change from baseline (10.76 g/dL(SD 0.66) to final visit: -0.28 g/dL (SD 1.63). • Time to trigger initiation of epoetin(i.e. when Hb fell ≤9.0 g/dL) was 13.2 (SD 7.9) months. • Total administered dose: 152,146 U (SD 139,951). Mean weekly dose at 1 year:820 U/wk (2071.4) [n=100]; 2 years: 836.5 (1792.5) [n=52]; 3 years: 772.7 (2091.5) [n=22]; final dose [includes some 0 doses]: 1772.7 (SD 3035.6); final dose [patient's last zero dose taken for group A]: 2098.5 (3166.8)
Length of follow-up	Patients were recruited over 3 years and continued the study until 3 years of start of renal replacement or death. Study prematurely terminated due to contraindication of s.c. administration route but on discontinuation of the study, patients were continued on a different epoetin preparation to maintain their well-being. 197 patients were randomised. 79% (156/197) withdrew prematurely (44/65 in Group A (68%) and 112/132 in Group B (85%). Reasons for withdrawal included adverse events, commencement of dialysis, renal transplant and others. Mean time to completion/withdrawal from study: Group A: 24.1±10.8 months Group B: 21.1±10.8 months;

<table>
<tr><td>Outcome measures and effect size</td><td>
Primary outcome measures(as stated in paper):
• Greatest (Worst) Left Ventricular Mass (LVM) according to Penn Convention method.

Secondary outcome measures (as stated in paper):
• Progression of renal failure (measured by serial blood creatinine measurements, creatinine clearance, and yearly isotopic GFR measurement)
• Hypertension
• Death

Effect Size:
<table>
<tr><td>End point</td><td>Group A Hb target 11.0±1.0 g/dL</td><td>Group B: Hb allowed to fall to ≤9.0 g/dL</td><td>Reported p-value (unless indicated otherwise)</td></tr>
<tr><td colspan="4">Primary efficacy variables:</td></tr>
<tr><td colspan="4">LVM (g)</td></tr>
<tr><td>Baseline</td><td>266.5±99.2;
n= 63</td><td>253.0±85.1;
n=130</td><td>Not statistically significant</td></tr>
<tr><td>At 1 year</td><td>237.9 ±74.6
n=49</td><td>230.4 ±78.8
n=84</td><td>Not statistically significant</td></tr>
<tr><td>At 2 years</td><td>234.7 ±71.1
n=29</td><td>208.7 ±61.4
n=47</td><td>Not statistically significant</td></tr>
<tr><td>At final visit</td><td>218.5±67.9;
n= 40</td><td>228.2±68.4;
n= 84</td><td>Not statistically significant</td></tr>
</table>
</td></tr>
</table>

Worst LVM	254.8±80.9; n=59	250.0±72.8; n= 111	0.829
Worst LVM-change from baseline	-15.2±80.2; P=0.154 [within group comparison]	0.2±70.3; P=0.981 [within group comparison]	p=0.19 [calculated]
Secondary efficacy variables:			
No of dialysis deaths (% patients)	31 (48.4)	68 (51.5)	0.686
Progression of renal failure			
Creatinine clearance in mL/min			
Baseline	25.75±12.23	23.26±10.15	
Change	-6.96±8.28	-7.82±7.80	0.486
Hypertension			
Number of patients with Hypertension	22% (14 /65)	7% (9/132)	

Reason for withdrawal:

	Group A Hb target 11.0±1.0 g/dL	Group B: Hb allowed to fall to ≤9.0 g/dL
Patients commenced dialysis	29(44.6)	61(46.2)
Renal transplant	0(0)	9(6.8)
Adverse event	29(44.6)	61 (46.2)
Other	13(19.9)[a]	34 (25.8)[b]

Values reported indicate mean ± SD or number (percent) unless otherwise indicated.

	[a]Included one patient through choice and one patient lost to follow-up [b]Included seven patients through choice.
Source of funding	Ortho Biotech

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Morris , 1993. Ref id 1724
Study type	Single blind placebo controlled crossover trial
Number of patients	N=11 children in total, N (group 1: rHuEpo/placebo)=6 N (group 2: placebo/rHuEpo)= 5 Only 7 patients completed both arms of the trial
Patient characteristics	Inclusion and exclusion criteria not explicitly reported. • 11 children • 9 boys and 2 girls • Median age: 6.7 years (range 2.3 to 12.3 years) • Median Hb concentration 73 g/L (range 42 to 81) • 10 children were on dialysis, 9 on peritoneal rapid overnight dialysis, 1 on haemodialysis • 5 children were receiving treatment for hypertension, but were normo-tensive Only 7 children completed both arms of the study. 3 children withdrew because they underwent renal transplantation and 1

	child died of hepatic fibrosis, related to underlying polycystic disease.
Intervention	r-HuEpo for 6 weeks administered s.c. followed by placebo. Injections were fixed at 0.5mL, r-HuEpo was commenced at 50 U/kg/week and increased step-wise to a maximum of 400 U/kg/week to maintain a target Hb concentration of 105-120 g/L
Comparison	Placebo followed by r-HuEpo.
Length of follow-up	24 weeks of each treatment
Outcome measures and effect size	Outcome: • LVMI • Mean blood pressure Other outcomes reported but not relevant to the review were: cardiac index, stroke index, heart rate, LVEDD, LVESD, interventricular septum, LVPM, peripheral vascular resistance, shortening fraction, cardiothoracic ratio, aortic stroke distance, minute distance. The mean Hb level reached while treated with placebo was 6.9 g/dL, the mean Hb level reached while treated with r-HuEpo was 11.5 g/dL

Results:

Outcomes	Group 1: r-HuEpo, Placebo N=4		Group 2: placebo, r-HuEpo N=3		Overall mean effect (% change) of r-HuEpo minus effect of placebo
	After 24 weeks of r-HuEpo	After 24 weeks of placebo	After 24 weeks [48 week time point] of placebo	After 24 weeks [48 week time point] of r-HuEpo	
LVMI (g/m^2)	101.2 (41.9)	120 (48.2)	87.6 (16.5)	62.9 (11.8)	-21.3 (-20); p=0.16
Mean blood	73.5 (13.6)	65.3 (8.4)	67.3 (11.2)	59.3 (11.8)	+1.3 (+2); p=0.96

	pressure (mm Hg)					
Source of funding	Boehringer Mannheim UK					

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Parfrey , 2005. Ref id 1825
Study type	RCT
Number of patients	N=596 patients enrolled. N= 296 in target Hb level 13.5-14.5 g/dL. N=300 in target Hb level 9.5-11.5 g/dL. 70% patients enrolled in Europe and 30% in Canada. 95 treatment centres in 10 European countries and Canada.
Patient characteristics	Inclusion criteria: • Aged ≥18 years • Haemodialysis started within previous 3 to 18 months • Predialysis haemoglobin between 8 and 12 g/dL • Left ventricular volume index < 100 mL/m^2 on screening echocardiography, with normal being < 90 mL/ $m^{2,}$ • Predialysis diastolic BP < 100 mmHg

Exclusion criteria:

- symptomatic cardiac failure or ischemic heart disease
- Angiographic critical coronary artery disease
- Current treatment ≥ 10 mg dose of daily prednisone for a failed renal transplant
- Medical conditions that are likely to reduce response to epotein-alfa, including uncorrected iron deficiency
- Concurrent malignancy
- Blood transfusion within the preceding month
- Therapy with cytotoxic agents
- Seizure within preceding year
- Hypersensitivity to intravenous iron
- Current pregnancy or breastfeeding

Characteristic	Haemoglobin 13.5 to 14.5 g/dL (N=296)	Haemoglobin 9.5 to 11.5 g/dL (n=300)
Age (years)	52.2 ± 15.6	49.4 ± 15.2
Duration of dialysis (months)	10±4.9	10.2±5.1
Weight (kg)	75±16	74±17
Height (m)	1.68±0.09	1.68±0.1
Haemoglobin (g/dL)	11±1.2	11±1.2

	Transferrin saturation (%)	35.7±16.7	36.8±17.8
	Urea reduction ratio (%)	65.7±10.1	66±11.3
	Serum albumin (mg/dL)	3.9±0.3	4±0.3
	Male	60	60
	Previous epotein use	93	91
	Race White Black	 91 4	 88 6
	Primary cause of renal failure glomerulonephritis Diabetic neophropathy Polycystic kidney disease Hypertension Unknown Other	 28 19 10 7 9 27	 29 17 8 9 10 27
	Dialysis access (%) Fistula		 83

	Graft Catheter	86 6 8	5 12
	Systolic BP (mmHg)	144±21.65	140±20
	Diastolic BP (mmHg)	81±11.48	80±12
	Number of hypertensive drugs	2.0 ±1.5	1.8±1.4
	Number with transferring saturation <20%	12% [35/293]	14% [40/294]
	Number receiving intravenous iron	47% [139/296]	43% [129/300]
	Number receiving antihypertensives	82% [244/296]	81% [242/300]
Intervention	• The following Hb targets was used: Predialysis Hb levels of 9.5 to 11.5 g/dL throughout in the lower target group and increments of 0.5 to 1.0 g/dL biweekly, until achieving stability between 13.5 to 14.5 g/dL (measured weekly for 24 wk then biweekly). • Mean Hb at end of initial 24-week titration phase: 13.3 g/dL and maintenance phase from 24 to 96 weeks: 13.1 g/dL. • Dose: Epoetin naive patients in the higher target group 150 IU/kg per week; For Hb levels that deviated from target, epoetin-alfa doses were changed by 25% of the previous dose or 25 IU/kg. • Dose: approximate mean dose at 96 weeks (approximate time point): 185 (extracted from graph-units unclear) • Initially epoetin-alfa were administered s.c. or i.v. Study amendment in August 2002 limited administration to the i.v. route.		
Comparison	• The following Hb targets was used: Predialysis Hb levels of 9.5 to 11.5 g/dL throughout in the lower target group and increments of 0.5 to 1.0 g/dL biweekly, until achieving stability between 13.5 to 14.5 g/dL (measured weekly for 24		

<table>
<tr><td></td><td>wk then biweekly).
• Haemoglobin target of 9.5 to 11.5 g/dL.
• Mean Hb at end of initial 24-week titration phase: 10.9 g/dL and maintenance phase from 24 to 96 weeks: 10.8 g/dL.
• Dose: approximate mean dose at 96 weeks: 76 (extracted from graph- units unclear)

• Initially epoetin-alfa were administerd s.c. or i.v. Study amendment in August 2002 limited administration to the i.v. route.</td></tr>
<tr><td>Length of follow-up</td><td>Study length was 96 weeks [24-wk titration phase, which was used to achieved Hb targets, and a 72-wk maintenance period].</td></tr>
<tr><td>Outcome measures and effect size</td><td>Primary outcome:
• Left ventricular size [powered for left ventricular cavity volume]

Secondary outcomes:

• 6 min-walking test
• LVMI
• QoL [FACIT-Fatigue; SF-36: vitality; KDQOL quality of social interaction]
• Occurrence of AEs [treatment-emergent AE that occurred in ≥10% of patients; CV death, vascular, access loss that occurred in ≥2% of patients with cardiac events]

<table>
<tr><td>Outcome</td><td>Haemoglobin 13.5 to 14.5 g/dL

(n=296)</td><td>Haemoglobin 9.5 to 11.5 g/dL(n=300)</td></tr>
<tr><td>CV death</td><td>4% [13/ 296]</td><td>7% [20/300]</td></tr>
<tr><td>LVMI (g/m^2)</td><td>Baseline: 116.6 ± 35.5

Last value: 126.8 ± 42.4

Change: 10.2</td><td>Baseline: 111.9 ± 33.2

Last value: 126.3 ± 40.9

Change: 14.4</td></tr>
</table>
</td></tr>
</table>

	MI	2% (7/296)	1% (4/ 300)
	HT	41% [120/296]	37% [110/300]
	QOL SF-36 – Vitality (Estimated treatment difference ± SE)	Week 24: 59.2 ±1.1 Week 96: 55.3 ± 1.5 Mean follow-up minus baseline: 1.21 ±1.08	Week 24: 55.1 ±1.1 Week 96: 52.4 ± 1.5 Mean follow-up minus baseline: -2.31 ±1.08
	Arteriovenous fistula thrombosis	15% [45/296]	12% [36/300]
	Non-site specific embolism thrombosis	5% [14/296]	4% [12/300]
	Permanent catheter thrombosis	3% [8/296]	3% [9/300]
	Number of hypertensive drugs	Baseline: 2 ± 1.5 Last value: 2 ± 1.7	Baseline: 1.8 ± 1.4 Last value: 1.7 ± 1.5
Source of funding	Johnson and Johnson Pharmaceuticals Research and Development		

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Pfeffer 2009. Ref id 20142 TREAT
Study type	RCT
Number of patients	N (Enrolled patients)=4047

	9 patients excluded (4 randomised to darbepoetin-alfaand 5 randomised to placebo) for not adhering to good practice guidelines. N (Included in study report)= 4038 N (darbepoetin-alfa-to maintain Hb at 13.0 g/dL)= 2012 N (Placebo; darbepoetin-alfa as rescue agent if Hb fell below 9.0 g/dL)= 2026 Study conducted at 623 sites in 24 countries; enrolment occurred over 3 years 5 months [2004 to 2007].
Patient characteristics	Inclusion criteria: Patients with • Type 2 Diabetes • Chronic kidney disease eGFR 20-60 mL/min per 1.73m^2 of body surface area • Anaemia i.e. Hb ≤ 11g/dL • Transferrin saturation of 15% or more Exclusion criteria: Patients with • Uncontrolled hypertension • Previous kidney transplantation or scheduled receipt of a kidney transplant from a living related donor • Current use of antibiotics, chemotherapy or radiation therapy • Cancer (except basal cell or squamous cell carcinoma of the skin) • Diagnosed HIV infection • Active bleeding, hematologic disease or pregnancy • History of cardiovascular event or grand mal seizure or major surgery • History of receiving ESA in 12 weeks prior to randomisation Baseline characteristics of patients:

Characteristic	Darbepoetin-alfa N= 2012	Placebo N=2026
Age in years [median (IQR)]	68 (60-75)	68 (60-75)
Female sex (%)	58.5	56
Race or ethnic group (%)- self reported		
White	63.1	64.2
Black	20.6	19.8
Hispanic	13.6	13.1
Other	2.7	3.0
Body –mass index [median(IQR)]	30.5(26.3-35.5)	30.1(26.2-34.9)
Known duration of diabetes in years [median(IQR)]	15.3(8.2-21.8)	15.5(8.4-21.7)
History of cardiovascular disease (%)- (p value 0.05)	64	66.9
Blood pressure		
Systolic [median(IQR)]	136 (122-149)	135(123-148)
Diastolic [median(IQR)]	71 (64-80)	70 (64-80)
Serum creatinine [median(IQR)]	1.8	1.9
Estimated GFR(mL/min/1.73 m^2)	34	33
Ratio of total protein (in mg/dL) to creatinine (in mg/ dL) in urine	0.4	0.4
Glycated Haemoglobin (%)	7	6.9

<table>
<tr><td></td><td>
<table>
<tr><td>Haemoglobin (g/dL)</td><td>10.5</td><td>10.4</td></tr>
<tr><td>Transferrin saturation (%)</td><td>23</td><td>23</td></tr>
<tr><td>Serum Ferritin (µg/L)</td><td>131</td><td>137</td></tr>
<tr><td>Total Cholesterol (mg/dL)</td><td>169</td><td>170</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
N.B Patients in both the groups were on oral and intravenous iron therapy prior to start of the trial; Placebo group (42.7% on oral and 1.6% on i.v iron); darbepoetin-alfa group (41.8% on oral and 1.4% on i.v iron)
</td></tr>
<tr><td>Intervention</td><td>

Darbepoetin- alfa with a median monthly dose of 176 µg (IQR 104-305);
Mean dose 225 ±208 µg[252]
66.8% of the patients received oral iron and 20.4% received i.v. iron and 14.8% received red-cell transfusions
From 3 months to end of treatment, median Hb achieved: 12.5 g/dL [IQR 12.0 to 12.8]

</td></tr>
<tr><td>Comparison</td><td>Placebo

Patients in placebo group were assigned to receive darbepoetin-alfa if the Hb levels fell below 9.0g/dL with a return to placebo once the Hb levels was 9.0 g/dL or higher.
Over the course of the study, 46% of patients in placebo group received at least 1 dose of darbepoetin-alfa [median monthly dose 0µg (IQR 0-5)];
Mean dose: 5±11 µg[252]
68.6% received oral iron, 14.8% i.v iron (compared with 20.4% in the intervention group; p<0.001) and 24.5% received red cell transfusions (HR 0.56 (95% CI 0.49 to 0.65; p<0.001 darbepoetin vs placebo).
From 3 months to end of treatment, median Hb achieved: 10.6 g/dL [IQR 9.9 to 11.3]

</td></tr>
</table>

<table>
<tr><td>Length of follow-up</td><td>Median follow up duration of the study was 29.1 months</td></tr>
<tr><td>Outcome measures and effect size</td><td>Primary outcome measures (as reported in paper):
Composite outcome of time to death from any cause or a cardiovascular event (non-fatal myocardial infarction, congestive cardiac failure, stroke, or hospitalisation for myocardial ischaemia)
Time to Death or ESRD
MI
Stroke
Secondary outcome measures (as stated in paper):
Time to death
Death from cardiovascular causes
Components of the primary outcome
Rate of decline in GFR
QOL (SF-36 and FACT-Fatigue)
Adverse events: Hypertension
Effect size:
<table>
<tr><td>End Point</td><td>Darbepoetin alfa
Hb level – 13.0 g/dL
(N=2012)
number (%)</td><td>Placebo
Hb level – >9 g/dL
(N=2026)
Number (%)</td><td>Hazard ratio
(95% CI)</td><td>P-value</td></tr>
<tr><td colspan="5">Primary end points</td></tr>
<tr><td>Cardiovascular</td><td></td><td></td><td>1.05 (0.92-</td><td>0.41</td></tr>
</table></td></tr>
</table>

	composite end point[¶]	632(31.4)	602(29.7)	1.17)	
	Death from any cause	412 (20.5)	395 (19.5)	1.05 (0.92-1.21)	0.48
	Myocardial infarction[‡]	124(6.2)	129(6.4)	0.96(0.75-1.22)	0.73
	Stroke‡	101 (5.0)	53 (2.6)	1.92 (1.38-2.68)	<0.001
	Secondary end points (as reported in the paper)				
	Death from cardiovascular causes	259 (12.9)	250 (12.3)	1.05 (0.88-1.25)	0.61
	Hypertension (reported as an adverse event in paper)	491 (24.5)	446 (22.1)		0.07
	36-Item Short-Form General Health Survey				
	Mean change in score for energy (mean ± SD score)	2.6±9.9 points	2.1±9.7 points		0.20
	Mean change in score for physical functioning (mean ± SD score)	1.3±9.2 points	1.1±8.8 points		0.51
	[¶]A patient may have had multiple cardiovascular events of different types. The cardiovascular composite end point reflects only the first occurrence of any of the components. [‡]This category includes both fatal and non-fatal events.				
Source of funding	Authors received consultancy fees from pharmaceutical companies				

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?

Bibliographic reference	Ritz , 2007. Ref id 706
Study type	RCT
Number of patients	N=172 patients randomised; N= 88 in target Hb 13 to 15 g/dL; N= 82 in target Hb 10.5-11.5 g/dL 64 centres in 16 countries (Austria, China, Czech republic, Denmark, Finland, France,Germany,Ireland, Italy,Mexico, Poland, Portugal, Russia, Spain, Sweden, Taiwan, Thailand, turkey, U.K)
Patient characteristics	Inclusion criteria: • Adults (≥18 years) not yet requiring renal replacement therapy • Hb level of 10.5 to <13 g/dL at screening • Creatinine clearance ≥30 mL/min at screening • Diabetes mellitus (type 1 or 2) with stable glycemic control for at least 3 months • One serum creatinine determination ≥3 months before enrolment (in addition to screening) • Documented diabetic nephropathy (i.e. by proteinuria, renal biopsy, or albuminuria and target-organ microangiopathy) • SBP ≤ 140 mm Hg, DBP ≤ 90 mmHg at screening Exclusion criteria: • Rapid progression of chronic renal failure (e.g. >20% increase in serum creatinine in the 3 months before enrolment) • Need for renal replacement therapy expected within 6 months after enrolment • Documented evidence of nondiabetic renal disease, nephrotic syndrome • Chronic heart failure (New York Association class III-IV) • Myocardial infarction, unstable angina, or stroke in the 3 months before enrolment • Evidence of clinically significant valvular disease

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- Haemolysis
- Vitamin B_{12} or folic acid deficiency
- Serum ferritin <50 ng/mL
- Blood transfusions within the 3 months before enrolment

Characteristic	high target Hb 13-15 g/dL N=88	Low target Hb 10.5-11.5 g/dL N=82
Sex (% men)	51	50
Age (years)	58 (49-69)	57 (47-66)
Weight (kg)	75.6 (50-106.1)	70 (41.5-110.0)
BMI (kg/m_2)	28.5 (24.9-30.7)	25.6 (23.1-29.5)
SBP (mmHg)	134 (126-140)	133 (126-139)
DBP (mmHg)	78 (70-80)	80 (71-80)
Type 1 diabetes (%) Time since diagnosis (years)	27 20 (17-30)	35 24 (21-31)
Type 2 diabetes (%) Time since diagnosis (years)	73 16 (11-21)	65 14 (9-19)
Diabetic retinopathy (%)	84	83
HbA_{1c} (%)	8.2 (7.2-9.2)	7.9 (6.8-8.7)
Haematology/iron variables Hb (g/dL)	 11.9 (11.3-12.2)	 11.7 (11.3-12.0)

Ferritin (ng/mL)	99 (69-163)	125 (62-212)	
Transferrin saturation (%)	22 (17-31)	22 (18-29)	
Renal function			
Urine protein excretion (g/24h)	1.3 (0.5-3.1)	0.8 (0.4-2.9)	
Creatinine clearance (mL/min)	51 (39-67)	46 (35-55)	
Serum creatinine (mg/dL)	1.58 (1.21-1.93)	1.63 (1.26-2.17)	
Lipid variables			
LDL (mg/dL)	116 (89-143)	124 (104-159)	
HDL (mg/dL)	50 (39-66)	50 (43-62)	
Total cholesterol (mg/dL)	197 (166-236)	201 (174-232)	
Triglycerides (mg/dL)	151 (97-204)	133 (97-213)	
Statin treatment (%)	46	35	
Fibrate treatment (%)	7	9	
Chronic heart failure (%)	5	2	
Ischemic heart disease (%)	25	14	
Previous MI	17	7	
Coronary artery disease	5	7	
Cerebrovascular disease, stroke (%)	6	5	
LVH (%)	5	4	

	<table><tr><td>Peripheral vascular disease (%)</td><td>11</td><td>6</td></tr><tr><td>Valculopathies (%)</td><td>1</td><td>4</td></tr><tr><td>Electrocardiogram abnormalities (%)</td><td>5</td><td>1</td></tr><tr><td>Other vascular diseases (%)</td><td>13</td><td>12</td></tr></table>
Intervention	• Patients started immediately on s.c. epoetin-beta treatment to reach target Hb of 13-15 g/dL within 3 months. • Starting dose: 2000 IU once weekly, self-administered using Reco-pen. • Median Hb achieved: 13.5 g/dL • Median weekly epoetin-betadose to maintain within protocol specified Hb range: 46.1 IU/wk/kg (@ 3,500 IU/wk).
Comparison	• Patients started on s.c. epoetin-beta treatment when their Hb level had decreased to less than 10.5 g/dL on 2 consecutive visits at an interval of 2 weeks or if Hb level decreased to less than 10g/dL at a signle determinationation. Partial Hb of 10.5-11.5 g/dL. • Starting dose: 2000 IU once weekly, self-administered using Reco-pen. • Median Hb achieved: 12.1 g/dL • Median epoetin-beta dose: not reported.
Length of follow-up	Study length was 15 months
Outcome measures and effect size	**Primary Outcome: (as reported in paper)** LVH assessed by echocardiographic measurement of LVMI. **Secondary outcomes: (as reported in paper)** • Left ventricular volumes • Left ventricular function • Renal function • QOL (SF-36) • Hypertension

- Number of patients referred for dialysis
- Ischaemic stroke

Results:

Outcome	Hb level 13-15 g/dL N=88	Hb level 10.5-11.5 g/dL N= 82
LVMI (g/m^2)		
At baseline	113.5 ± 30.6	116 ± 34.6
Month 6	115.2 ± 34.8	116 ± 40.1
Month 15	112.3 ± 32.9	116.5 ± 35.6
Change after 15 months	1.2	-0.5
Decrease in creatinine clearance (mL/min) Cockcroft-Gault formula	-5.5 [IQR -11.5 to -0.3]	-3.4 [IQR -11.4 to 2.0)
Estimated glomerular filtration rate (decrease, mL/min) MDRD formula	-5.1 [IQR -10.7 to -0.1]	-3.9 [IQR -12.1 to 1.8]
Number of patients referred for dialysis	2/ 88	3/ 82
Hypertension	17% [15/ 88]	11% [9/ 82]
MI	2% [2/88]	No events reported
Ischemic stroke	No events reported	1.2% [1/82]

All values reported as mean± SD or median with the respective range or IQR.

	<table><tr><td>Outcome</td><td>Hb level 13-15 g/dL N=88</td><td>Hb level 10.5-11.5 g/dL N= 82</td><td>Reported p-value</td></tr><tr><td>QoL – SF-36</td><td></td><td></td><td></td></tr><tr><td>General health</td><td>+ 5.33 from baseline [baseline scores not reported]</td><td>-0.33 from baseline [baseline scores not reported]</td><td>0.04</td></tr><tr><td>Vitality</td><td>Study reported a greater improvement from baseline for vitality in patients who received early treatment to target Hb level of 13-15 g/dL. Numerical values not reported.</td><td>Numerical values not reported.</td><td>Reported ‘difference was not significant.’</td></tr></table>
Source of funding	F. Hoffmann-La Roche Ltd, Basel, Switzerland

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Roger 2004 Ref id 1620

Study type	RCT open label.
Number of patients	N randomised= 155 N Group A (Hb maintained between 120 to 130 g/L)= 75, N received epoetin-alfa= 74 N Group B (Hb maintained between 90 to 100 /L)= 80, N received epoetin-alfa=8
Patient characteristics	Inclusion criteria: Patients : • Were between 18-75 years of age • to have demonstrated a decrease in Hb concentration of ≥10g/L within 12 months before enrolment and to have reached levels of 110-130g/L (male patients) and 100-120g/L (female patients). • Had estimated creatinine clearances of 15-50mL/min adjusted for gender and BMI Exclusion criteria: Patients : • With unstable or poorly controlled angina • With severe congestive cardiac failure (NYHA Grade 3 or 4) • With severe chronic respiratory disease • With symptomatic peripheral vascular disease • With created arteriovenous fistula

The study reported patients did not exhibit iron deficiencies, with serum ferritin levels of >100µg/L and /or transferring saturation values of >20% before entry into the study.

Baseline characteristics:

Characteristics	Group A [Hb 120 to 130 g/L] N= 75	Group B [Hb between 90 and 100 g/L] N=80
Age in years	53±14 (M), 50±14 (F)	54±12(M),50±15(F)
Males	38 (51)	33(42)
Weight in kg	78±17	76±14
Diabetes mellitus	18 (24)	26(33)
Use of ACE inhibitors		
initial	53(74)	58(74)
final	47 (71)	43 (70)
Use of other antihypertensives		
initial	20 (27)	24(31)
final	15 (23)	19 (31)
Patients commencing dialysis	24 (32)	15(19)*
Causes of renal failure		

Values reported indicate mean ± SD or number (percent) unless otherwise indicated

	*P=0.08
Intervention	• Group A:A target Hb concentration of 120-130g/L maintained throughout the study period by initiation of subcutaneous epoetin-alfa therapy with a weekly regimen (upto 2 years after enrolment and/or the onset of RRT). • Mean Hb achieved at 2 years/within 3 months end of the study: 123 (SD 5); n=37 in patients who reached their target; Mean Hb at 2 years for all patients: 12.1 g/dL (SD 0.14) • Dosage regimen not reported. • Patients received orally or occasionally i.v. administered iron polymaltose as required to maintain these levels.
Comparison	• Group B- A target Hb concentration of 90-100g/L maintained for the remainder of the study period after initiation of subcutaneous epoetin-alfa therapy if the Hb concentration was <90g/L at 2 consecutive clinic visits 2 months months apart or was <80g/L at any visit without a cause other than CKD. • Mean Hb at 2 years/within 3 months end of the study : 101 (SD 4); n=15 in patients who reached their target; Mean Hb at 2 years for all patients: 10.8 g/dL (SD 0.13) • Dosage regimen not reported. • Patients received orally or occasionally i.v. administered iron polymaltose as required to maintain these levels.
Length of follow-up	Patients evaluated every 4 months. 2 years; In Group A, 9 discontinued intervention and data not used for 1. 10/75 ie 13.3% lost to follow-up. In Group B, 18 discontinued intervention and data not used for 2. 20/80 ie 25% lost to follow-up.
Outcome measures and effect size	**Primary outcome measures:** • Change in LVMi in 2 years. LVH defined as LVMi of >125g/m^2 for male patients or >100g/m^2 for female patients. **Secondary outcome measures:** • Renal function deterioration determined by time to onset of renal replacement therapy, calculated creatinine clearance (data not reported), and estimations of GFR • QoL assessed by SF-36 Health survey and Renal QoL profile questionnaires.

Effect Size:

End point	Group A (High Hb 12 to 13 g/dL)	Group B (Low Hb 9 to 10 g/dL)	P-value
Primary end points			
Change in LVMi over 2 years (g/m^2)	2.5±20	4.5±20	P=0.44
Initial LVMi (g/m^2)	105±23	101±23	
2-year LVMi in (g/m^2)	107±25	105±24	
P=0.019 for 2 year change in LVMi (Group A vs Group B) for "protocol objective-achieved" patients in respective groups.			
Secondary end points			
Decrease in GFR in 2 years	8±9mL/min per1.73m^2	6±8mL/min per 1.73m^2	NS
Creatinine clearance:	The study did not report the data but stated that the calculated creatinine clearance values exhibited similar results to decreases in GFR.		
Patients commencing dialysis	24 (32)	15 (19)	0.08
A significant overall positive correlation was observed between [Hb] an GFR (r=0.299, P=0.002, data not reported			
Quality of life	Mean score	Mean score	95% CI
Change in SF-36 health for physical health	-2±14	-1±13	(-5.4 to 3.0)
Change in SF-36 health for	0±14	-3±13	(-1.7 to 6.4)

	mental health | | | NB. Values reported indicate mean ± SD or number(percent) unless otherwise indicated
Source of funding	Janssen-Cilag Pty. Ltd, Australia

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Rossert 2006 Ref id 20173
Study type	RCT Open label
Number of patients	N (randomised)= 390 N (High Hb target group; Hb level range13-15g/dL)= 195 N (Low Hb target group; Hb level range 11-12g/dL)= 195 Patients enrolled at 93 centres in 22 countries [Europe: n=252; Australia: n=54; Canada: n=68; Israel: n=16]
Patient characteristics	Inclusion criteria: Patients • Were adults aged 18-75 years of age with CKD • Had an estimated GFR (eGFR) of 25-60 mL/min • Had at least 6 months of follow up • Had anaemia defined as Hb<13g/dL for men and <12.5g/dL for women without active blood loss or iron deficiency. Iron

	deficiency defined as transferring saturation <20% [or >10% hypochromic red blood cells] or serum ferritin level <100 ng/mL. • Had eGFR decrease less than 0.6mL/min/mo (<0.01 mL/s/mo) • Had blood pressure of 160/100 mm of Hg or less with or without anti hypertensive therapy Exclusion criteria: Patients were excluded if they had: • autosomal dominant polycystic kidney disease • current treatment with ESAs for anaemia secondary to CKD with a Hb level greater than 12g/dL • blood pressure of 180/110 mm Hg or greater within 3 months before study entry • red blood cell transfusion within the preceding 30 days • a history of renal transplant • NYHA Class III or IV congestive heart failure or ischaemic heart disease within the preceding 2 years • a chronic inflammatory condition • a seizure within the preceding year • a malignancy other than non melanoma skin cancer • a medical condition likely to affect the response to epoetin. **Baseline characteristics:**

Characteristic	High Hb target group Hb range 13-15 g/dL	Low Hb target group Hb range 11-12g/dL
Mean age in years	N=195	N=194
	58.5±13.6	57.8±113.6
Sex	N=195	N=195
Male [n (%)]	113(58)	118(61)
Race	N=193	N=191
White	181 (94)	179 (94)
Black	6 (3)	6 (3)
Mean Hb level(g/dL)	N=192	N=193
Total	11.5±1.0	11.6±0.9
Males	11.7±1.0	11.9±0.8
Females	11.4±1.0	11.2±0.9
Comorbid disease	N=195	N=195

	<table><tr><td>Diabetes</td><td>67(34)</td><td>68(35)</td></tr><tr><td>Hypertension</td><td>140(72)</td><td>137(70)</td></tr><tr><td>Cardiovascular disease¶</td><td>154(80)</td><td>158(81)</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Mean eGFR (mL/min/1.73m^2)*</td><td>N=107</td><td>N=131</td></tr><tr><td></td><td>30.3±10.5</td><td>28.3±8.9</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Mean blood pressure (mm Hg)</td><td>N=190</td><td>N=193</td></tr><tr><td></td><td>139/76±17/10</td><td>138/78±17/10</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Mean proteinuria (g/d)</td><td>N=177</td><td>N=172</td></tr><tr><td></td><td>1.79±5.01</td><td>1.68±3.82</td></tr></table> NB. Values are expressed as mean ± SD and number (percent) *eGFR based on the Modification of Diet in Renal Disease equation. A significant difference in noted between groups,p=0.05 ¶Data was available for only 192 patients in high Hb group and 194 patients in low Hb group.
Intervention	• A haemoglobin target level of 13 to 15 g/dL: 14-15 g/dL for males and 13-14g/dL for females achieved by treatment with epoetin-alfa. Treatment consisted of an initial 4-month Hb stabilisation phase followed by a 36-month maintenance phase. • Mean Hb achieved: 13.5 (SD 1.9). Mean change in Hb from baseline for men: 2.7 g/L (1.19); women:2.0 (SD 1.08) • Epoetin-alfa was administered subcutaneously once per week at initial doses of 25-100 IU/kg. • Dose adjustments were permitted in steps of 4 weeks to achieve target levels with a permitted weekly increase in dose of 25

	IU/kg. • During stabalisation phase, 12% [24/195] required epoetin doses of 1000 IU/kg/wk or greater • Median doses 4,514 IU/wk (range 658 to 14,655 IU/wk) [n=188 patients]
Comparison	• A haemoglobin target level of 11-12 g/dL which, if required, may be achieved, by treatment with epoetin-alfa. • Mean Hb achieved:11.8 (SD 1.6). Mean change in Hb from baseline for men: 0.2g/L (0.83); women: 0.93 (SD 0.93) • Epoetin-alfa was administered subcutaneously once per week at initial doses of 25-100 IU/kg. • Dose adjustments were permitted in steps of 4 weeks to achieve target levels with a permitted weekly increase in dose of 25 IU/kg. • During stabilisation phase, 2% [3/195] required epoetin doses of 1000 IU/kg/wk or greater • Median doses 2,730 IU/wk (range 333 to 7,667 IU/wk) [n=65 patients]
Length of follow-up	Planned length of follow-up was 40 months consisting of 4 month stabilisation phase and 36 months maintenance phase. However, the study was terminated by the sponsor earlier due to safety concerns related to risk of epoetin-induced pure red cell aplasia and subsequent labelling changes for with subcutaneous administration of epoetin (Eprex®). Median durations of maintenance therapy were 7.0 months (range 0.03 to 18.60) in the high-Hb group and 8.6 months (range 0.10 to 16.83) in the low-Hb group.
Outcome measures and effect size	**Primary outcome measures: (as stated in paper)** • The primary end point was the rate of GFR decline determined by measuring plasma iohexol clearance. **Secondary outcome measures:** • GFR<10mL/min/1.73m^2 • Need for renal replacement therapy • Occurrence of cardiovascular and thrombotic adverse events and death • Quality of life measured using the Medical Outcome Study 36-item Short-Form Health Survey(SF-36) • Blood pressure control

- Safety of long term epoetin therapy to normalize Hb concentrations

Effect Sizes:

Primary outcome:

Mean monthly rate of GFR decrease

	High Hb		Low Hb	
	No of patients	Mean ±SD	No. of patients	Mean±SD
Arithmetic mean GFR decrease(mL/min/1.73m^2/mo)				
Total*	75	+0.058±0.898	88	+0.081±1.167
Males	47	+0.069±0.951	54	+0.146±1.235
Females	28	+0.040±0.818	34	-0.023±1.059
Rate of mGFR decline was numerically higher for men compared with women, but statistical testing was not performed as the study was not performed for subgroup analysis.				
Least square mean GFR decrease (mL/mon/1.73m$^{2/}$mo)				
Total¶	75	+0.066±0.12	88	+0.071±0.11
Males	47	+0.045±0.15	54	+0.077±0.14
Females	28	+0.088±0.20	34	+0.066±0.17

*P= 0.699 for comparison of low Hb versus High Hb group, Wilcox-Mann-Whitney test, controlling for sex

¶P= 0.976 for comparison of least square means between low Hb and High Hb group, from analysis of covariance model with treatment (P=0.049), sex(P=0.926), baseline mGFR (P<0.001), treatment-by-sex interaction (P=0.873 and treatment-by-mGFR (P=0.034)

Secondary outcomes:

Quality of life:

During stabilisation:

- Mean and SE for QoL scores at end of stabilisation phase (i.e. at the end of 4 months following the commencement of treatment) reported graphically.
    - SF- 36 scores favoured High Hb target groups with significant differences seen in domains of physical function (P=0.083), Role-physical (P=0.055) and Vitality (P=0.042).
    - QoL assessment available for only 177 patients and median duration between assessments was 5.8 months (range 0.25 to 12.8 months)
    - Mean (SE) [raw scores not adjusted for baseline at end of stabilisation period-4 months] extracted from graph are as follows:

Domain	High Hb (n=102)	Low Hb (n=122)	Reported p-value
Physical-function	71.31(SE 2.71)	65.12 (2.32)	0.083
Role Physical	68.13 (3.87)	56.13 (3.68)	0.055
Bodily pain	70.36 (2.71)	65.72 (2.52)	0.302
General health	56.34 (27.01)	53.25 (1.74)	0.322
Vitality	59.35(27.03)	52.77(1.74)	0.042
Social function	81.72(32.43)	79.78 (1.55)	0.598
Role Emotional	75.05(51.35)	70.02 (3.48)	0.380
Mental Health	74.58(24.34)	73.81 (0.97)	0.658

During the maintenance phase:

- Study reported that there were no significant between-group differences in changes in QoL except for the physical function

domain, which showed deterioration in the high-Hb group (mean change: -4.3 2.8

- Spearman correlation coefficients calculated for changes in individual SF-36 domains and changes in mGFR or Hb levels during first 9 months of maintenance phase. The role-physical domain correlated with change in mGFR (r= +0.18;P=0.041) and rate of mGFR decline(r= -0.19;P=0.025).
- Positive correlation coefficients between final SF-36 domain score and final Hb value were identified for Role-physical, Vitality, Bodily pain, Social function and and Role Emotional(P<0.05)
- Positive correlations between final SF-36 measures and final mGFRs were identified for Physical function, Role-physical, General Health and Role-Emotional(P<0.05)

Unpublished data[139] received reported QoL scores at end of phase b(maintenance period)-approximately 9 months. Results are presented below.

time point: end of phase b	High Hb; n=88		Low Hb n=97	
	Mean	SD	Mean	SD
Physical function	66.10	27.82	68.60	24.44
Physical role	68.50	40.79	58.70	43.12
Pain	68.60	29.72	62.40	28.09
General health *	54.30	19.76	52.90	20.46
Vitality	58.00	21.81	53.00	21.12
Social function	79.30	25.35	78.60	23.8
Emotional role	76.50	37.54	71.80	39.48

Mental health	75.10	17.49	74.00	16.65
Physical health composite	NR		NR	
Mental health composite	NR		NR	

*n=87 for the high target group for this domain

Outcomes reported as adverse events in the study*:

Serious adverse events	High Hb target group N=195	Low Hb target group N=195	Reported Odds ratio	P-value
Death	1(0.5)	6(3)	0.16 (95% CI,0.02-1.36)	0.121
Myocardial Infarction	2(1)	2(1)	Not reported	Not reported
Worsening of renal function°	2(1)	2(1)	Not reported	Not reported
Uncontrolled hypertension^	17(6)	8 (4)		0.096
Hypertension	1(0.5)	1(0.5)	Not reported	Not reported

* Values are expressed as mean ± SD or number (percent) unless otherwise stated.

°As reported by investigator

^Uncontrolled hypertension was defined as a sitting diastolic blood pressure of >100 mm of Hg occurring at any time during the study period.

Source of funding	Ortho Biotech, Europe

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Singh et al, 2006. Ref id 20144
Study type	RCT (Open label)
Number of patients	N(enrolled)= 1432 patients N (High Hb initial target level of 13.0 to 13.5g/dL; post protocol amendment: 13.5 g/dL)=715 N (Low Hb initial target level of 10.5 to 11.0 g/dL; post protocol amendment:11.5 g/dL)=717 At time of protocol amendment 24.2% patients enroled [347/1432] and 132 of 1939 patient-years had been accrued. 130 sites in the US.
Patient characteristics	Inclusion criteria: Patients had: • to be above 18 years of age • haemoglobin levels less than 11.0 g/dL • chronic kidney disease defined by an estimated GFR of 15-50 mL per min per 1.73m^2 of body surface area using the Modification of Diet in Renal Disease formula. Exclusion criteria:

Patients were excluded if they had:

- presence of uncontrolled hypertension
- active gastrointestinal bleeding
- an iron overload state
- a history of frequent transfusions in the previous 6 months
- refractory iron deficiency anaemia
- active cancer
- previous therapy with epoetin-alfa
- angina pectoris that was unstable or present at rest

Baseline characteristics of patients:

Characteristic	High Hb target(13.5g/dL) N= 715	Low Hb target (11.3 g/dL) N=717
Age in years	66.0±14.3	66.3±13.5
Female sex (%)	56.2	54.1
Race (%)		
White	62.3	61.1
Black	28.6	29.3
American Indian or Alaskan Native	0.1	0.4
Asian or Pacific Islander	3.4	3.2
Other	5.6	6.0
Hispanic ethnic background		

	Cause of chronic kidney disease (%)		
	Diabetes	46.8	50.8
	Hypertension	29.9	27.5
	Other	23.3	21.6
	History of Cardiovascular disease (%)		
	Myocardial infarction, Stroke, PCI, CABG, or amputation of a lower limb	36.3	34.5
	Congestive Heart Failure	24.4	22.9
	Myocardial Infarction	16.4	15.0
	Stroke	9.8	10.0
	Hypertension	95.8	93.2*
	Body Mass Index	30.4±7.7	30.4±7.5
	Blood Pressure (mm Hg)		
	Systolic	136.7±19.7	135.6±20.0
	Diastolic	71.6±11.6	70.9±11.2
	Mean arterial	93.3±12.1	92.5±12.0

	GFR (mL/min) [calculated according to MDRD]	27.0±8.7	27.3±9.1
	Creatinine clearance (mL/min/1.73m^2) [calculated according to Cockroft-Gault formula]	36.7±17.0	37.1±17.9
	Ratio of total protein to creatinine in urine	1.6±2.3	1.5±2.3
	Haemoglobin (g/dL)	10.1±0.9	10.1±0.9
	Haematocrit (%)	31.4±2.9	31.4±2.9
	Transferrin saturation (%)	25.2±11.8	24.6±10.1
	Ferritin (ng/mL)	167.8±157.2	179.2±171.5
	N.B- Values reported indicate mean±SD unless otherwise indicated. * p=0.03 for comparison with High Hb group		
Intervention	• Target level of haemoglobin=13.5g/dL with epoetin-alfa (initial Hb target of 13.0 -13.5 g/dL prior to protocol amendment). • Mean change in Hb from baseline [10.1(SD0.9)]to final measurement: 2.5 g/dL; Achieved Hb:12.6 g/dL • Protocol specified a maximum total dose of epoetin-alfa for each group of 20,000 units per week. • All randomised patients received an initial epoetin alfa dose of 10,000 units subcutaneously once per week for three consecutive weeks. Based upon Hb levels on subsequent visit 2 week after first dose, subsequent doses were administered weekly based on pre-specified dosing algorithm to achieve randomised Hb target. • Mean dose for patient who reached target level: 10,694 U /wk; those who did not reach target 12,844 U/wk		
Comparison	• Target level of haemoglobin=11.5g/dL with Epoetin alfa (initial Hb target of 10.5-11.0 g/dL prior to protocol amendment). • Mean change in Hb from baseline [10.1 (SD 0.9)]to final measurement: 1.2 g/dL; Achieved Hb:11.3 g/dL • Protocol specified a maximum total dose of epoetin alfa for each group of 20,000 units per week. • All randomised patients received an initial epoetin alfa dose of 10,000 units subcutaneously once per week for three		

<table>
<tr><td></td><td>consecutive weeks. Based upon Hb levels on subsequent visit 2 week after first dose, subsequent doses were administered weekly based on pre-specified dosing algorithm to achieve randomised Hb target.
• Mean dose for patient who reached target level: 6,057 U /wk; those who did not reach target 11,098 U/wk</td></tr>
<tr><td>Length of follow-up</td><td>Mean and median duration of follow-up :16 months. Originally the study was to have been conducted over a period of 36 months but was terminated earlier on the advice of the data and safety monitoring board.</td></tr>
<tr><td>Outcome measures and effect size</td><td>Primary outcome measures (as stated in paper):
• Composite of death, myocardial infarction, hospitalisation for congestive heart failure (without renal replacement therapy) and stroke.

Secondary outcome measures (as stated in paper):
• Components of the primary end point were analysed separately. If a patient had more than one event, each event was counted the first time it occurred; therefore a patient could be included in more than one category.
• Other secondary outcomes included were time to renal replacement therapy and quality of life.

Effect size:
<table>
<tr><th>End point</th><th>High target Haemoglobin group (N=715)</th><th>Low target Haemoglobin group (N=717)</th><th>Hazard ratio (95% CI)</th><th>P-value</th></tr>
<tr><td colspan="5">Primary end points (as reported in paper):</td></tr>
<tr><td rowspan="2">Composite of death, myocardial infarction, hospitalisation for congestive heart failure without renal replacement therapy, or stroke</td><td rowspan="2">125 (17.5)</td><td rowspan="2">97 (13.5)</td><td>1.34 (1.03 to 1.74)</td><td>0.03</td></tr>
<tr><td>1.30 (1.01-1.68)*</td><td>0.04*</td></tr>
</table>
</td></tr>
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				1.30 (1.01 to 1.66)‡	0.04‡
	Secondary end points (as reported in paper):				
	Components of the primary outcome:				
	Death	52 (7.3)	36 (5.0)	1.48 (0.97-2.27)	0.07
	Myocardial infarction	18 (2.5)	20 (2.8)	0.91 (0.48-1.73)	0.78
	Stroke	12 (1.7)	12 (1.7)	1.01 (0.45-2.25)	0.98
	Quality of life				
	Change in score from baseline -domains on SF-36				
	physical function	3.2±24.0	2.1±23.3		0.49
	physical role	6.4±40.7	7.5±43.2		0.32
	pain	0.4±28.1	2.4±26.7		0.15
	general health	3.0±19.2	1.8±17.8		0.87
	vitality from	10.0±23.8	8.2±20.6		0.58
	social function	1.3±33.1	3.5±28.7		0.16
	emotional role	0.8±48.3	5.9±48.1		0.01
	mental health	1.7±18.7	2.4±18.2		0.31
	Adverse event (as reported in paper):†				
	Myocardial infarction	10 (1.5)	19 (2.8)		0.09

	NB- All results reported indicate number(percentage) or mean ± SD unless otherwise indicated *Analysis was on the basis of data from intention to treat population but included all events from randomisation to study termination or 30 days after last administration of study medication. ‡Analysis included all events from randomisation to 90 days after study termination †Analysis included 1374 patients in the two study groups who received at least one dose of epoetin-alfa and for whom data were collected regarding adverse events.
Source of funding	Ortho Biotech clinical Affairs and John &Johnson Pharmaceutical Research and Development

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Szczech 2008. Ref id 20162
Study type	Secondary analysis of CHOIR trial, Singh et al 2006
Number of patients	N=1432 included in original CHOIR trial N= 1260 at 4 month time point; n=627 High Hb group ; n=633 low Hb group N=1057 at 9 month time point; n=519 High Hb group; n=538 Low Hb group
Patient characteristics	Inclusion criteria of CHOIR trial: • to be above 18 years of age • haemoglobin levels less than 11.0 g/dL • chronic kidney disease defined by an estimated GFR of 15-50 mL per min per 1.73m^2 of body surface area using the

Modification of Diet in Renal Disease formula.

Exclusion criteria of CHOIR trial:

- uncontrolled hypertension
- active gastrointestinal bleeding
- an iron overload state
- a history of frequent transfusions in the previous 6 months
- refractory iron deficiency anaemia
- active cancer
- previous therapy with epoetin-alfa
- angina pectoris that was unstable or present at rest

Baseline characteristics of patients at 4 months:

Characteristic	High Hb target13.5g/dL N= 627	Low Hb target 11.5 g/dL N=633
Age in years	65.9 (14.2)	66.6 (13.2)
Female sex (%)	56.5	54
Race (%)		
White	62.7	61.6
Black	28	29.5
American-Indian or Alaskan native	0.2	0.5
Asian or Pacific Islander	3.7	2.8
Other	5.4	5.5
Hispanic ethnic background	12.3	13.1

	History of smoking tobacco (%)	46.6	43.8
	Cause of chronic kidney disease (%)		
	Diabetes	46.4	49.7
	Hypertension	30.2	28.3
	Other	23.4	22.1
	History of Cardiovascular disease (%)		
	Hypertension	95.8	92.9
	Myocardial infarction	14.8	14.6
	CABG	17.9	13.2
	PCI	9.4	10.8
	Congestive heart failure	22	20.7
	Atrial fibrillation	8.1	8.8
	Stroke	9.5	9.0
	Lower-extremity amputation	3.2	2.8
	MI, CABG or PCI	26.3	25
	Body Mass Index	30.5 (7.8)	30.4 (7.5)
	GFR (mL/min/m^2)	27.1 (8.7)	27.6 (9.1)
	Baseline Hb (g/100mL)	10.1 (0.86)	10.1 (0.85)
	Week 3 Hb (g/100mL)	10.7 (0.94)	10.6 (0.94)

Baseline albumin (g/10mL)	3.8 (0.51)	3.8 (0.46)
Baseline phosphorus (mg/100mL)	4.1 (0.73)	4.1 (0.74)
Baseline cholesterol (mg/100mL)	184.6 (50.2)	183.5 (47.9)
Ratio of total protein/creatinine in urine	1.5 (2.10)	1.4 (2.1)
Ferritin (ng/mL)	167.8 (157.2)	178.5 (173.1)
Transferrin saturation (%)	25.3 (11.7)	24.6 (10.1)
Transferrin saturation <20% (%)	36.1	33.9
Iron (%)		
Intravenous	2.9	1.8
Oral	27.1	25.8
Not specified	3.4	1.6

Baseline characteristics of patients at 9 months:

Characteristic	High Hb target13.5g/dL N= 519	Low Hb target 11.5 g/dL N=538
Age in years	65.7 (14.3)	66.4 (13.2)
Female sex (%)	57.4	54.1
Race (%)		
White	63.5	60.8

	Black	28.6	30.5
	American-Indian or Alaskan native	0.2	0.6
	Asian or Pacific Islander		
	Other	3.1	2.2
	Hispanic ethnic background	4.6	5.9
		12.6	13.4
	History of smoking tobacco (%)	45.1	43.3
	Cause of chronic kidney disease (%)		
	Diabetes	45.8	48.6
	Hypertension	30.9	29.1
	Other	23.3	22.3
	History of Cardiovascular disease (%)		
	Hypertension	95.2	92.4
	Myocardial infarction	14.6	13.6
	CABG	16.7	12.5
	PCI	9.6	10.9
	Congestive heart failure	21	18.9
	Atrial fibrillation	8.2	7.8
	Stroke	9.8	9.2

	Lower-extremity amputation MI, CABG or PCI	3.2 26.1	2.5 23.7
	Body Mass Index	30.5 (7.6)	30.7 (7.7)
	GFR (mL/min/m^2)	27.5 (8.7)	28.3 (9.1)
	Baseline Hb (g/100mL)	10.1 (0.85)	10.1 (0.84)
	Week 3 Hb (g/100mL)	10.7 (0.95)	10.6 (0.94)
	Baseline albumin (g/10mL)	3.8 (0.47)	3.8 (0.45)
	Baseline phosphorus (mg/100mL)	4.1 (0.73)	4 (0.73)
	Baseline cholesterol (mg/100mL)	184.5 (48.9)	183.9 (47.7)
	Ratio of total protein/creatinine in urine	1.3 (1.84)	1.2 (1.84)
	Ferritin (ng/mL)	165.9 (158.1)	172.5 (157)
	Transferrin saturation (%)	25.2 (11.8)	24.7 (10.2)
	Transferrin saturation <20% (%)	36.1	33.9
	Iron (%) Intravenous	 3.1	 2.1

<table>
<tr><td></td><td>
<table>
<tr><td>Oral</td><td>26.8</td><td>24.1</td></tr>
<tr><td>Not specified</td><td>3.3</td><td>2.4</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Target level of haemoglobin=13.5g/dL with epoetin-alfa (initial Hb target of 13.0 -13.5 g/dL prior to protocol amendment).

All randomised patients received an initial epoetin-alfa dose of 10,000 units subcutaneously once per week for three consecutive weeks. Based upon Hb levels on subsequent visit 2 week after first dose, subsequent doses were administered weekly based on pre-specified dosing algorithm to achieve randomised Hb target. Protocol specified a maximum total dose of epoetin-alfa for each group of 20,000 units per week.</td></tr>
<tr><td>Comparison</td><td>Target level of haemoglobin=11.5g/dL with epoetin-alfa (initial Hb target of 10.5-11.0 g/dL prior to protocol amendment).

All randomised patients received an initial epoetin-alfa dose of 10,000 units subcutaneously once per week for three consecutive weeks. Based upon Hb levels on subsequent visit 2 week after first dose, subsequent doses were administered weekly based on pre-specified dosing algorithm to achieve randomised Hb target. Protocol specified a maximum total dose of epoetin-alfa for each group of 20,000 units per week.</td></tr>
<tr><td>Length of follow-up</td><td>Results at 4 and 9 months during the 16 month trial</td></tr>
<tr><td>Outcome measures and effect size</td><td>Outcome: Composite of death, myocardial infarction, hospitalisation for congestive heart failure, or stroke (as stated in the paper)

At 4 months:
<table>
<tr><td>Outcome</td><td>Hazard ratio (95% CI)</td><td>P-value</td></tr>
<tr><td>Composite of death, myocardial infarction, hospitalisation for congestive heart failure, or stroke</td><td>1.44 (1.05, 1.97)</td><td>0.02</td></tr>
</table>
At 9 months:</td></tr>
</table>

	Outcome	Hazard ratio (95% CI)	P-value
	Composite of death, myocardial infarction, hospitalisation for congestive heart failure, or stroke	1.62 (1.09, 2.40)	0.02
Source of funding	Ortho Biotech clinical Affairs and John &Johnson Pharmaceutical Research and Development		

Evidence Table:

Review question	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?
Bibliographic reference	Szczech 2010. Ref id 20161
Study type	Secondary analysis of CHOIR study, Singh et al 2006
Number of patients	N=1432 in original CHOIR trial, N= 375 had a history of heart failure, N=894 had diabetes mellitus
Patient characteristics	Inclusion criteria of CHOIR trial: • to be above 18 years of age • haemoglobin levels less than 11.0 g/dL • chronic kidney disease defined by an estimated GFR of 15-50 mL per min per 1.73m^2 of body surface area using the Modification of Diet in Renal Disease formula. Exclusion criteria of CHOIR trial: • uncontrolled hypertension • active gastrointestinal bleeding • an iron overload state • a history of frequent transfusions in the previous 6 months

- refractory iron deficiency anaemia
- active cancer
- previous therapy with epoetin alfa
- angina pectoris that was unstable or present at rest

Baseline characteristics of patients with heart failure:

Characteristic	High Hb target=13.5g/dL N= 192	Low Hb target 11.5 g/dL N=183
Age in years	70.2 (11.71)	689.5 (11.26)
Male sex	89/192 (46.4%)	103/183 (56.3%)
Race: black (vs non-white/black)	56/191 (29.3%)	50/183 (27.3%)
Hispanic ethnic background	18/191 (9.4%)	22/183 (12%)
Diabetes mellitus	138/192 (71.9%)	143/183 (78.1%)
Previous CVA or TIA	31/192 (16.1%)	38/183 (20.8%)
Previous coronary artery disease	118/192 (61.5%)	116/183 (63.4%)
Previous peripheral vascular disease	51/192 (26.6%)	44/183 (24%)
Previous atrial fibrillation/flutter	43/192 (22.4%)	34/183 (18.6%)
History of solid organ malignancy	25/191 (13.1%)	24/183 (13.1%)
Inflammation / malnutrition (albumin ≤ 3.6 g/dL or ferritin >600 ng/mL)	83/192 (43.2%)	68/179 (38%)
Baseline albumin (g/dL)	3.7 (0.55)	3.7 (0.48)

Baseline ferritin (ng/mL)	159.5 (142.08)	193.5 (186.05)
Baseline eGFR (mL/min)	26.9 (8.94)	26 (8.35)
Baseline cholesterol (mg/100mL)	172.5 (50.08)	178.5 (51.52)
Baseline TSAT (%)	22.1 (9.84)	24.1 (9.47)
Baseline Hb	10 (0.96)	10 (0.96)

Baseline characteristics of patients with diabetes mellitus:

Characteristic	High Hb target=13.5g/dL N= 436	Low Hb target 11.3 g/dL N=458
Age in years	65.6 (12.37)	65.9 (11.42)
Male sex	193/436 (44.3%)	224/458 (48.9%)
Race: black (vs non-white/black)	136/435 (31.3%)	141/458 (30.8%)
Hispanic ethnic background	64/434 (14.7%)	75/457 (16.4%)
Previous Hr composite	138/419 (32.9%)	143/432 (33.1%)
Previous CVA or TIA	60/420 (14.3%)	67/430 (15.6%)
Previous coronary artery disease	163/420 (38.8%)	153/432 (35.4%)
Previous peripheral vascular disease	88/419 (21%)	88/431 (20.4%)
Previous atrial fibrillation/flutter	32/419 (7.6%)	34/432 (7.9%)

	History of solid organ malignancy	45/414 (10.9%)	52/431 (12.1%)
	Inflammation / malnutrition (albumin ≤ 3.6 g/dL or ferritin >600 ng/mL)	190/436 (43.3%)	190/453 (41.9%)
	Baseline albumin (g/dL)	3.7 (0.53)	3.7 (0.46)
	Baseline ferritin (ng/mL)	169.9 (154.62)	178 (167.38)
	Baseline eGFR (mL/min)	27 (8.81)	27.5 (8.84)
	Baseline cholesterol (mg/100mL)	183.9 (54.57)	183.3 (49.95)
	Baseline TSAT (%)	23.9 (10.17)	24.3 (9.61)
	Baseline Hb	10 (0.87)	10.1 (0.88)
Intervention	Target level of haemoglobin=13.5g/dL with epoetin-alfa (initial Hb target of 13.0 -13.5 g/dL prior to protocol amendment). All randomised patients received an initial epoetin-alfa dose of 10,000 units subcutaneously once per week for three consecutive weeks. Based upon Hb levels on subsequent visit 2 week after first dose, subsequent doses were administered weekly based on pre-specified dosing algorithm to achieve randomised Hb target. Protocol specified a maximum total dose of epoetin alfa for each group of 20,000 units per week. No mean Hb or mean doses reported for the subgroups.		
Comparison	Target level of haemoglobin=11.5g/dL with epoetin-alfa (initial Hb target of 10.5-11.0 g/dL prior to protocol amendment). All randomised patients received an initial epoetin alfa dose of 10,000 units subcutaneously once per week for three consecutive weeks. Based upon Hb levels on subsequent visit 2 week after first dose, subsequent doses were administered weekly based on pre-		

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<table>
<tr><td></td><td>specified dosing algorithm to achieve randomised Hb target. Protocol specified a maximum total dose of epoetin-alfa for each group of 20,000 units per week.

No mean Hb or mean doses reported for the subgroups.</td></tr>
<tr><td>Length of follow-up</td><td>16 months. Originally the study was to have been conducted over a period of 36 months but was terminated earlier on the advice of the data and safety monitoring board.</td></tr>
<tr><td>Outcome measures and effect size</td><td>Outcome: Composite of death, myocardial infarction, hospitalisation for congestive heart failure without renal replacement therapy, or stroke

Patients with heart failure:

<table>
<tr><th>Outcome</th><th>Hazard ratio (95% CI)</th><th>P-value</th></tr>
<tr><td>Composite of death, myocardial infarction, hospitalisation for congestive heart failure without renal replacement therapy, or stroke</td><td>4.08 (3.09, 5.37)</td><td><0.001</td></tr>
</table>

Patients with diabetes mellitus:

<table>
<tr><th>Outcome</th><th>Hazard ratio (95% CI)</th><th>P-value</th></tr>
<tr><td>Composite of death, myocardial infarction, hospitalisation for congestive heart failure without renal replacement therapy, or stroke</td><td>1.31 (0.98, 1.76)</td><td>0.067</td></tr>
</table>
</td></tr>
</table>

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Source of funding	Ortho Biotech clinical Affairs and John &Johnson Pharmaceutical Research and Development

Appendix I: FOREST PLOTS

I.1 Diagnostic role of Hb levels

RESULTS

Results for outcomes identified in the update review are presented on forest plots:

1. LVH [no new evidence]
2. Increased hospitalisation [no new evidence]
3. All-cause mortality
4. Composite outcome [MI, stroke, mortality]
5. Cardiac events [MI and CHD]
6. QoL- overall score
7. Stroke
8. Progression of CKD

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Figure I.1a Low [<10 to 13] Hb to High Hb levels: risk of mortality in predialysis patients

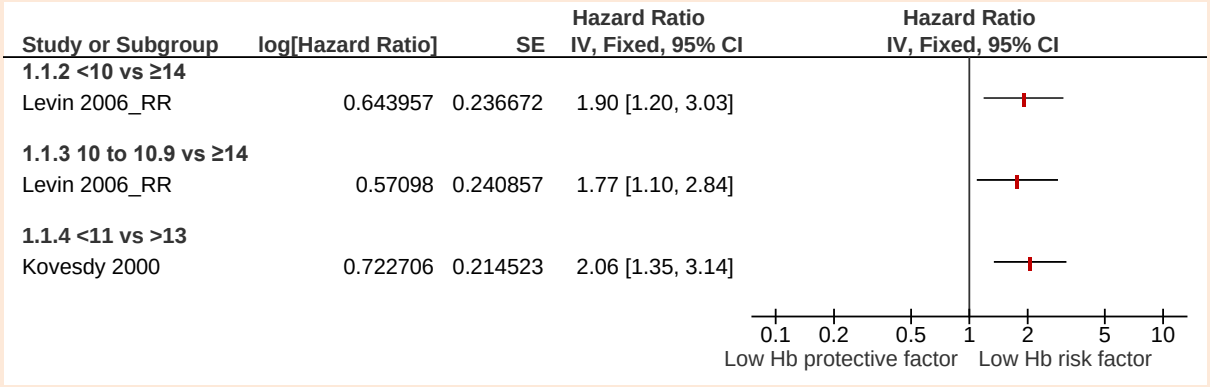

Figure I.1b Low [≥11 to 12] Hb vs High Hb [≥13] levels: risk of mortality in predialysis patients

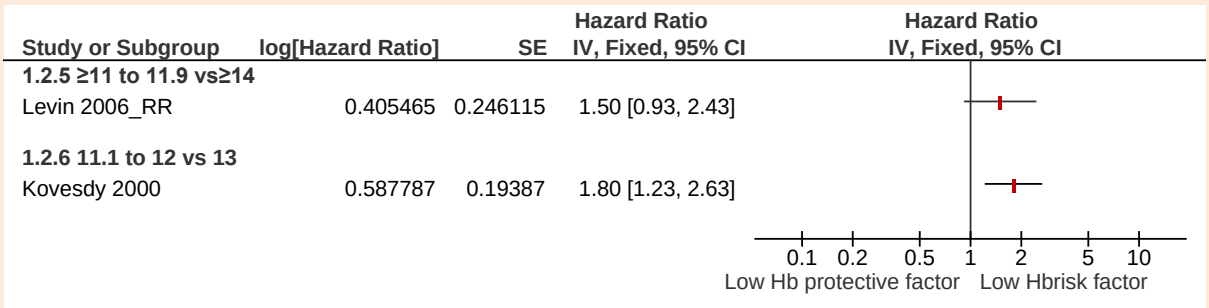

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Figure I.1c Low Hb [12 to 14.6] vs High Hb levels [>14.6]: risk of mortality in predialysis patients

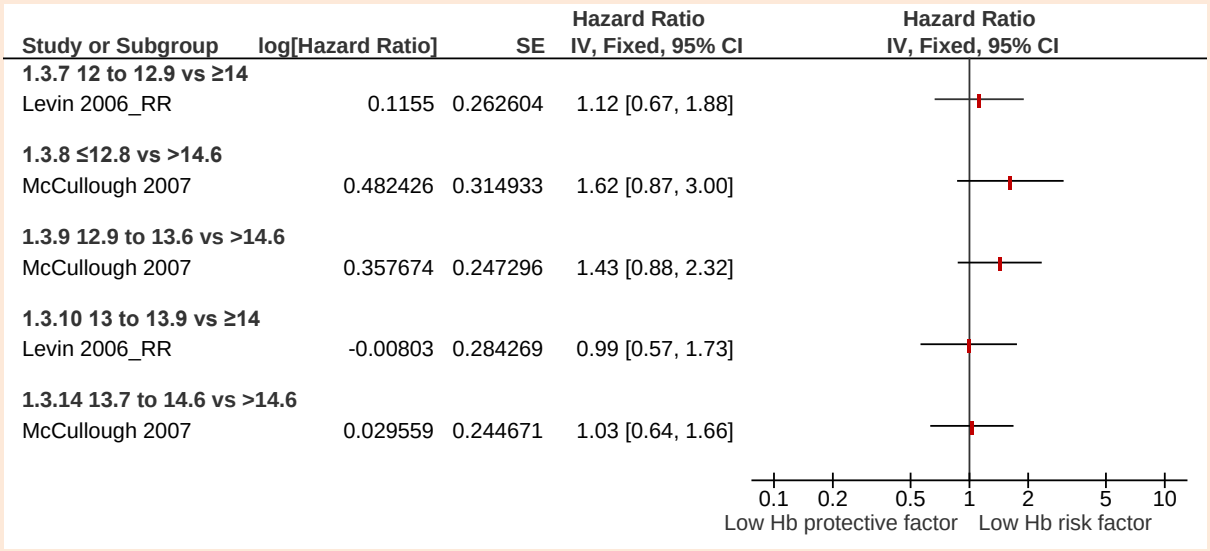
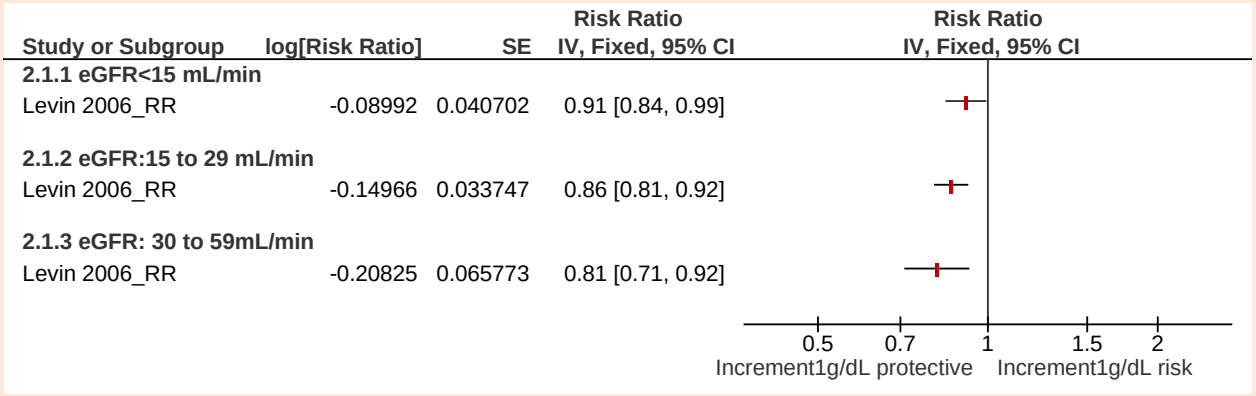


Figure I.2a Increment of 10g/L [1 g/dL] in Hb level: risk of mortality in predialysis patients



NB: Scale 0.5 to 2.0

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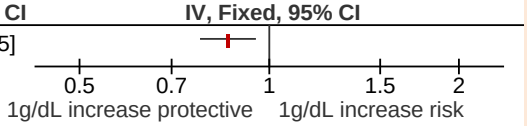
Figure I.2b Increment of 10g/L [1 g/dL] in Hb level: risk of mortality in predialysis patients

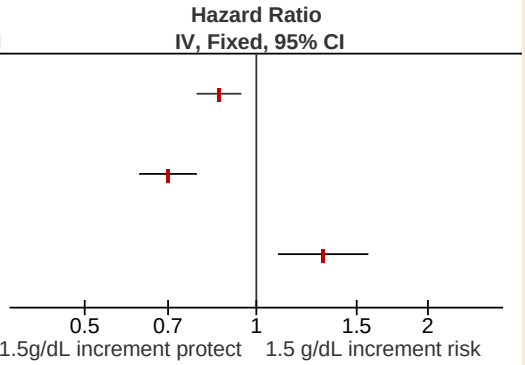
Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
Kovesdy 2000	-0.15082	0.050298	0.86 [0.78, 0.95]



NB: Scale 0.5 to 2.0

Figure I.2c Increment of 1.5g/dL in Hb level: risk of mortality in predialysis patients

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
3.1.1 1.5 g/dL increment			
Weiner 2008	-0.15082	0.044349	0.86 [0.79, 0.94]
3.1.2 1.5 g/dLincrement <14.5g/dL			
Weiner 2008	-0.35667	0.057733	0.70 [0.63, 0.78]
3.1.3 1.5 g/dL increment >14.5 g/dL			
Weiner 2008	0.270027	0.091456	1.31 [1.10, 1.57]



NB: Scale 0.5 to 2.0

Figure I.3 Lower Hb quintiles: risk of CHD-mortality in predialysis patients

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
4.1.1 eGFR: Cockcroft-Gault			
Leeder 2006	0.398776	0.164731	1.49 [1.08, 2.06]
4.1.2 eGFR:MDRD			
Leeder 2006	0.307485	0.182138	1.36 [0.95, 1.94]

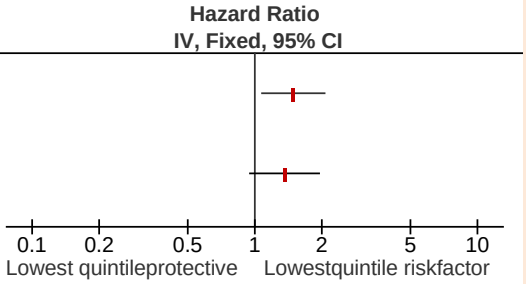


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Figure I.4 High Hb level vs Low Hb level: risk of mortality in kidney transplant patients

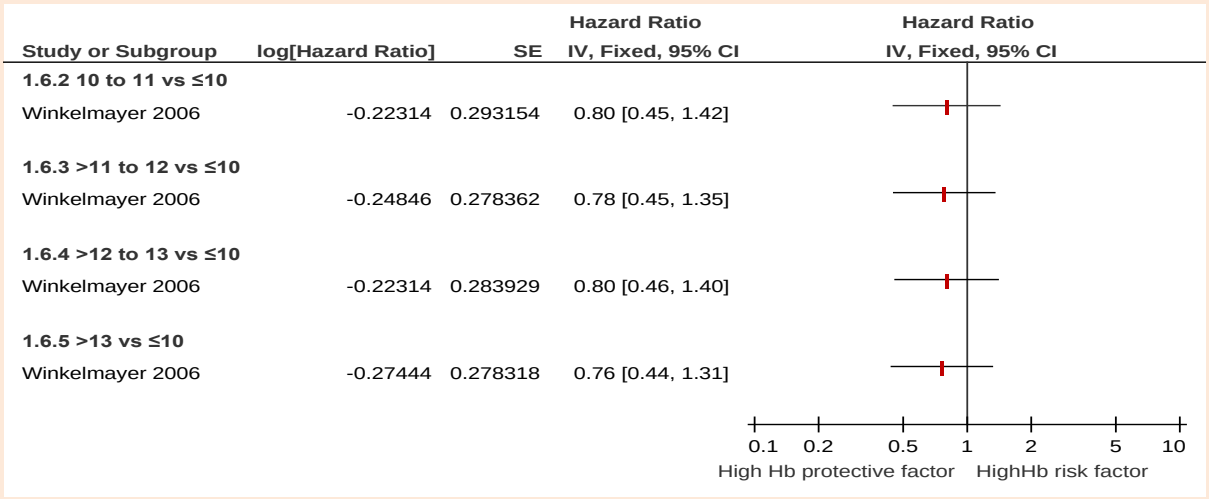
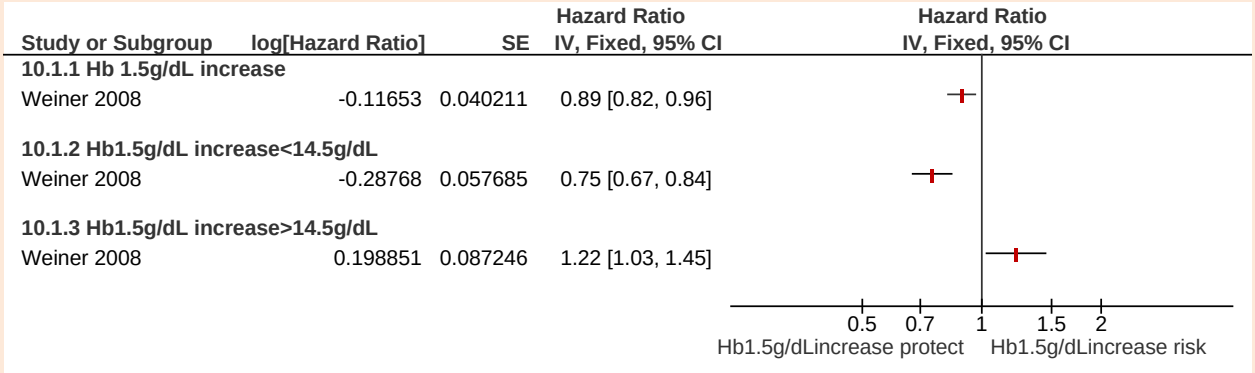


Figure I.5 Increment of 1.5g/dL in Hb level: risk of composite outcomes [MI, stroke, mortality] in predialysis patients



NB: Scale 0.5 to 2.0

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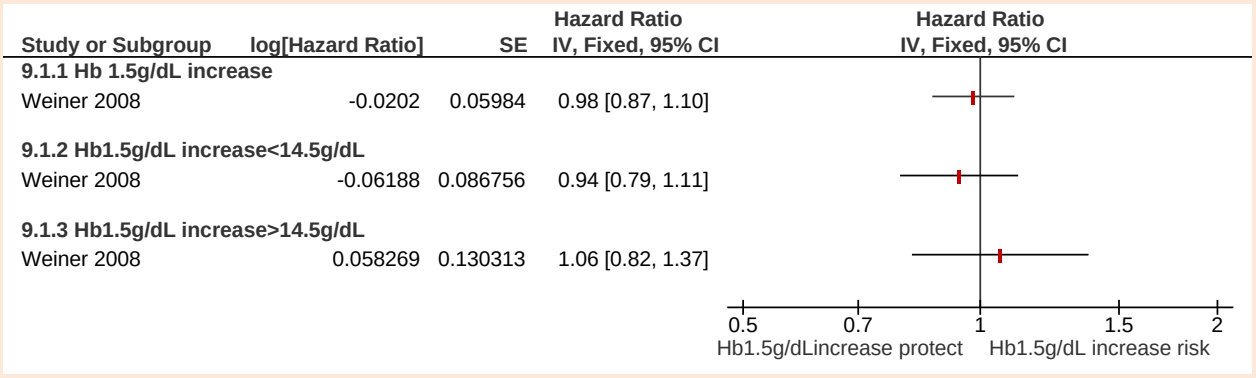
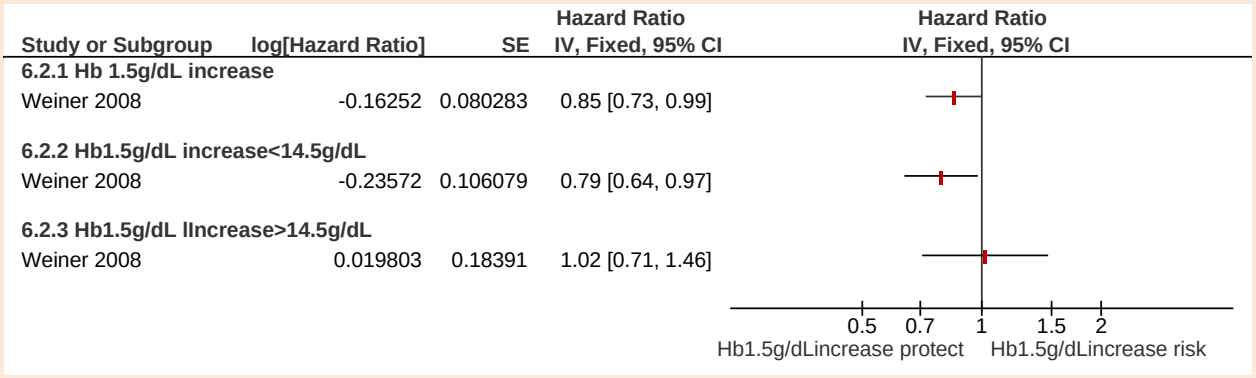
Figure I.6 Increment of 1.5g/dL in Hb level: risk of cardiac events in predialysis patients



NB: Scale 0.5 to 2

Figure I.7 Increment of 1.5g/dL in Hb level: risk of stroke in predialysis patients



NB: Scale 0.5 to 2.0

Figure I.8 Lower Hb levels vs High Hb level: progression to ESRD in predialysis patients

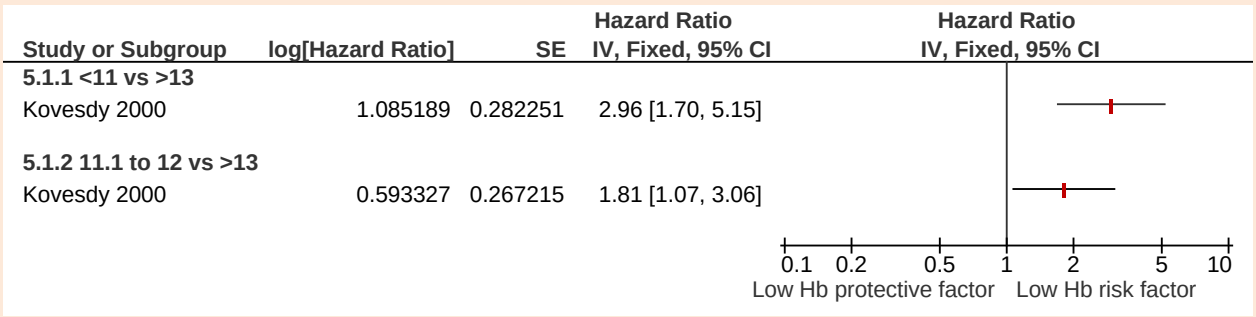
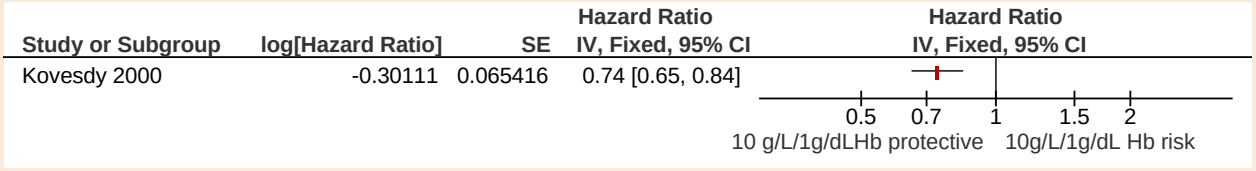


Figure I.9 Increment of 10 g/L (1 g/dL) in Hb level: progression to ESRD in predialysis patients



NB: Scale 0.5 to 2.0

I.2 Optimal Hb levels

I.2.1 ADULTS

Comparisons:

I.2.1.1 A. >12 g/dL compared with lower Hb level

Outcomes:

1. All-cause mortality
   a. Non-dialysis
   b. Dialysis
2. CV mortality
   a. Non-dialysis
   b. Dialysis
3. Progression of CKD[Non-dialysis]
   a. Mean decrease in GFR
   b. Creatinine clearance
   c. Initiation of dialysis
   d. Worsening renal function
4. Access thrombosis [Dialysis]
5. Transfusion
   a. Non-dialysis
   b. Dialysis
6. Stroke
   a. Non-dialysis
   b. Dialysis [no studies reported this outcome]
7. MI
   a. Non-dialysis
   b. Dialysis
8. Hypertension
   a. Non-dialysis
   b. Dialysis
9. Change in LVMI
   a. Non-dialysis
   b. Dialysis

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10. Quality of Life (SF-36)
    a. Non-dialysis
    b. Dialysis
11. Composite events
12. CV event free survival (Concentric LVH and Eccentric LVH)

I.2.1.2 B. 10 to 11 g/dL compared with lower Hb level[one study in non-dialysis patients]

1. All-cause mortality
2. CV mortality– study did not report this outcome
3. Progression of CKD
    a. Creatinine clearance
    b. Initiation of dialysis
4. Transfusion – study did not report this outcome
5. Stroke – study did not report this outcome
6. MI– study did not report this outcome
7. Hypertension
8. Worst LVM- change from baseline
9. Quality of Life (SF-36) – study did not report this outcome

Update 2011

I.2.2 CHILDREN

1. Progression of CKD
2. Hypertension
3. Transfusion rate
4. LVMI

Note:

Forest plots for undesirable outcomes (e.g. mortality, stroke): the axis for the forest plot is presented with 'favours intervention' (e.g. favours >12 g/dL) on the left hand side of the axis.

Forest plots for desirable outcomes (e.g. improvement in quality of life): the axis for the forest plot is presented with the 'favours intervention' (e.g. favours >12 g/dL) on the right hand side of the forest plot.

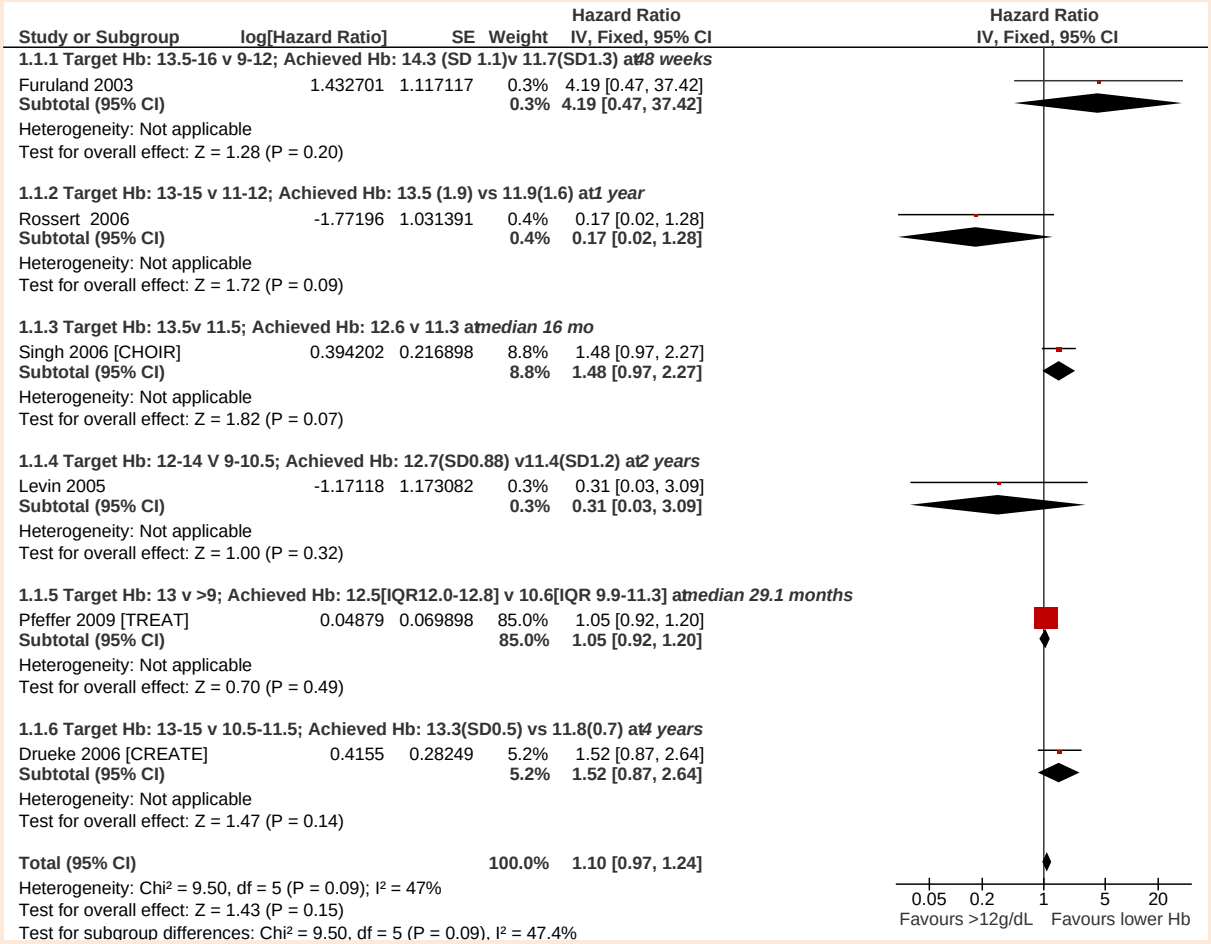
Update 2011

A. >12 g/dL Hb level compared with lower Hb level

1. All-cause mortality

1a. Non-dialysis

Figure I.10: >12 g/dL versus lower Hb level: All-cause mortality

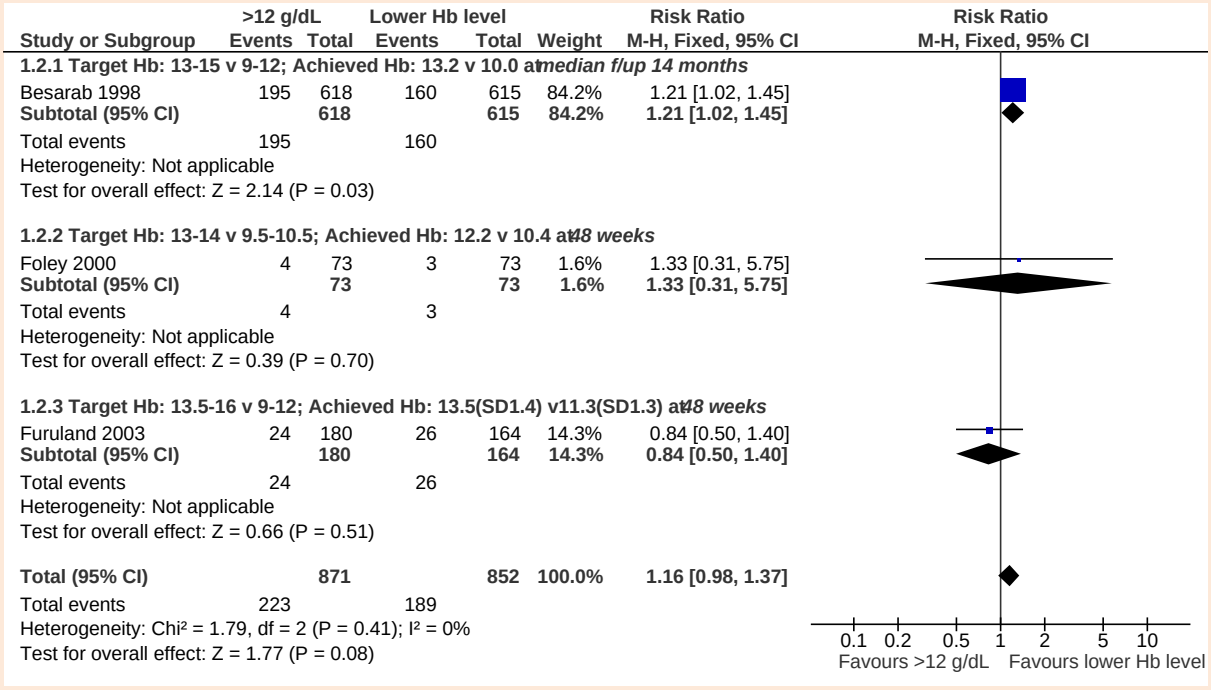


NB: Scale 0.05 to 20

Update 2011

1b. Dialysis

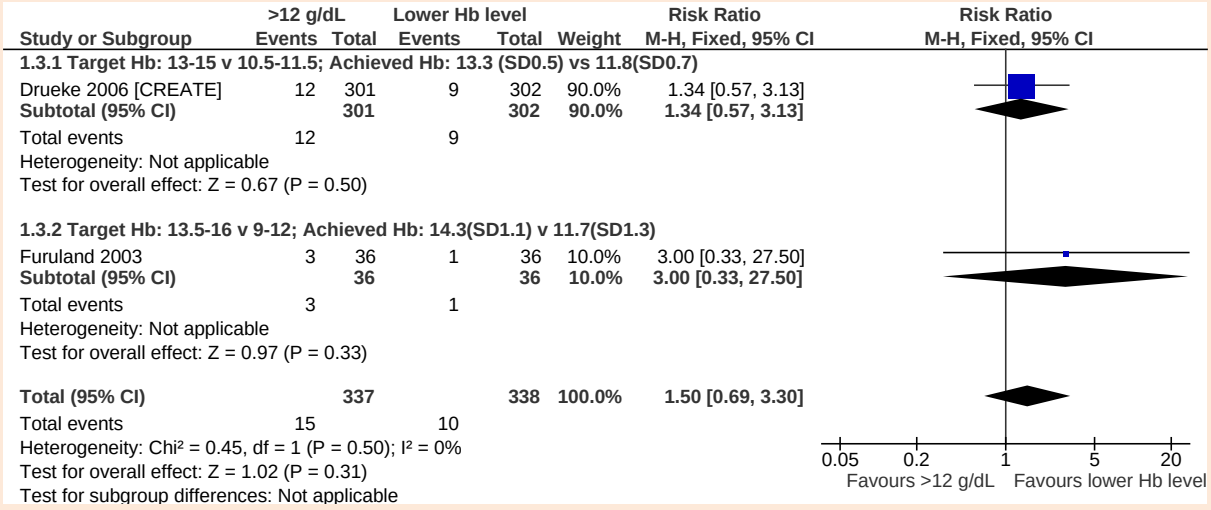
Figure I.11: >12 g/dL versus lower Hb level: All-cause mortality



2. CV MORTALITY

2a. Non-dialysis

Figure I.12: >12 g/dL versus lower Hb level: CV mortality

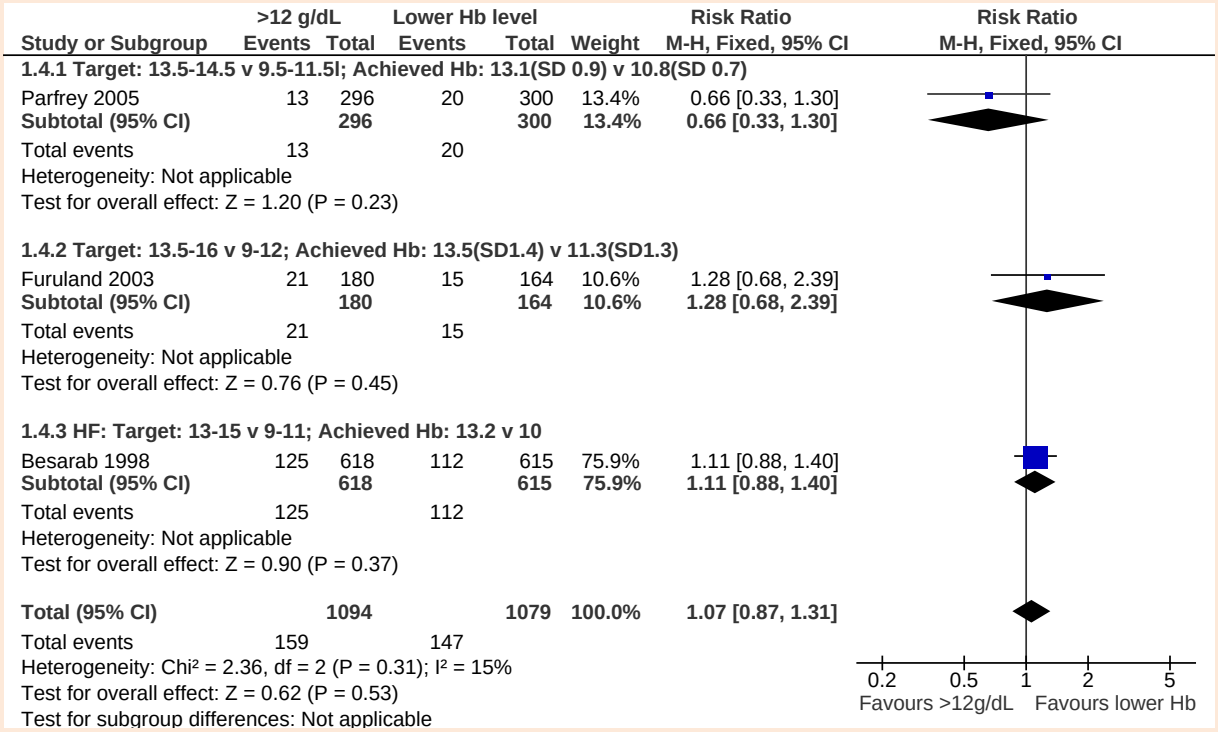


NB: Scale 0.05 to 20

Update 2011

2b. Dialysis

Figure I.13: >12 g/dL versus lower Hb level: CV mortality



NB: Scale 0.2 to 5

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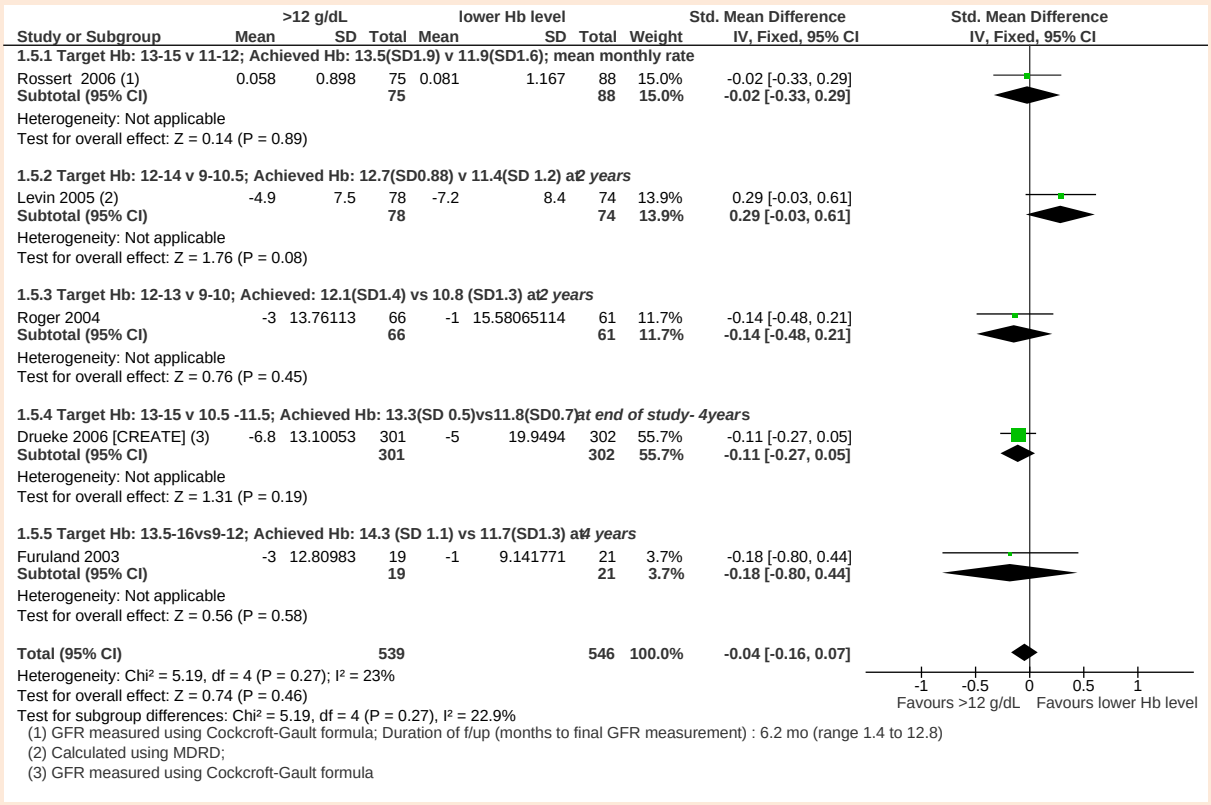
3. Progression of CKD

(i) Mean decrease in GFR

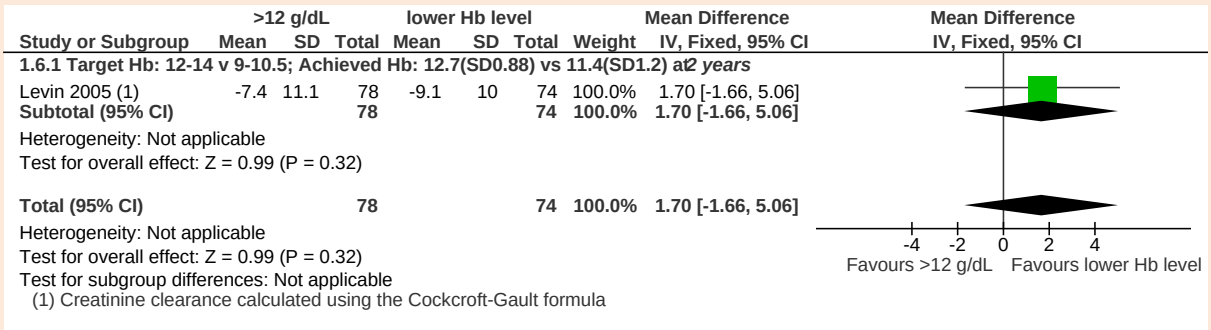
Figure I.14: >12 g/dL versus lower Hb level: Mean decrease in GFR (mL/min)



Ritz (2005): Reported median (IQR) for decrease in eGFR (mL/min) [calculated using MDRD formula]: -5.1 mL/min (IQR -10.7 to -0.1) vs -3.9 mL/min (IQR -12.1 to 1.8) for the high and the low Hb target groups, respectively.

(ii) Creatinine clearance

Figure I.15: >12 g/dL versus lower Hb level: Creatinine clearance (mL/min)



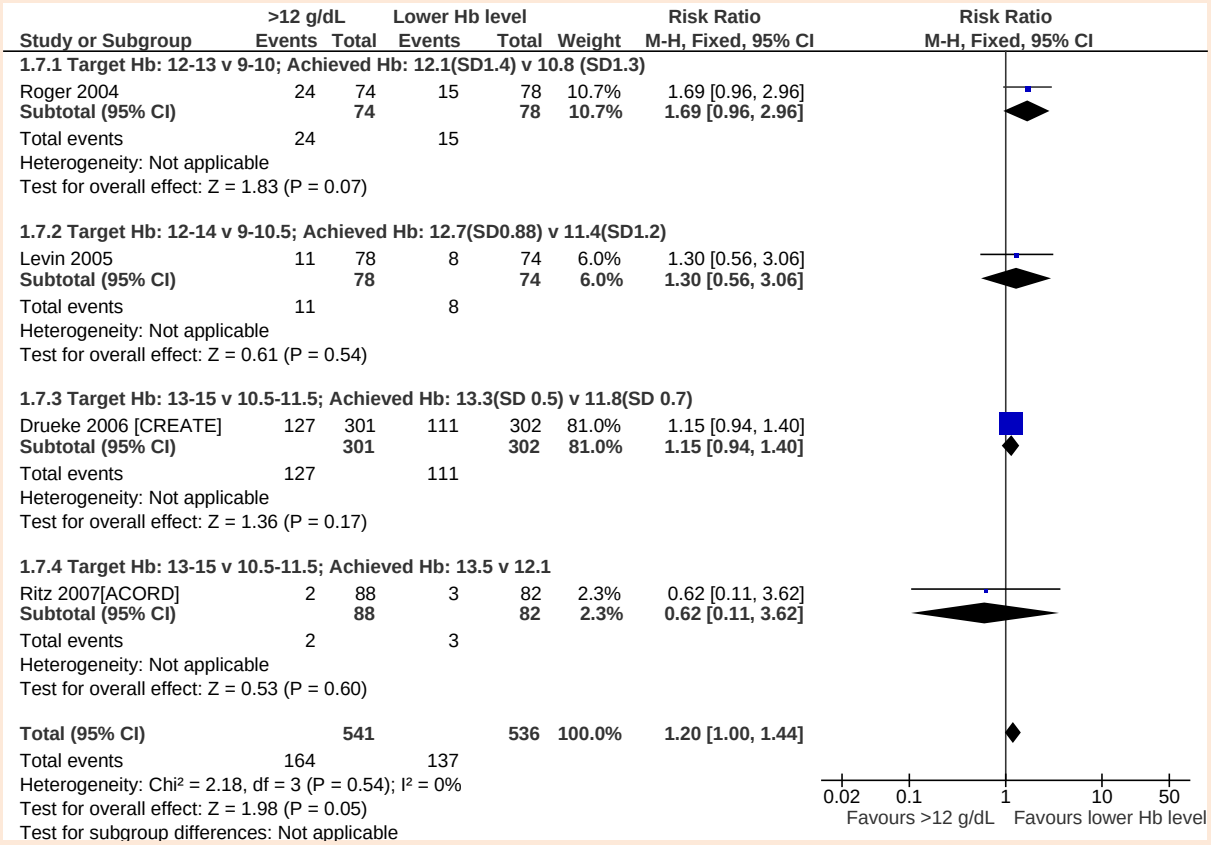
NB: Scale -4 to 4

Roger (2004): stated that creatinine clearance values would be reported but data was not shown. Study noted that calculated creatinine clearance values [Cockcroft-Gault formula] exhibited similar results to decrease in GFR.

Ritz (2005) [13-15 vs 10.5 to 11.5 (13.5 vs 12.1)]: Reported median (IQR) for decrease in creatinine clearance (mL/min) [calculated using Cockcroft-Gault formula]: -5.5 mL/min (IQR -11.5 to -0.1) vs -3.4 mL/min (IQR -11.4 to 2.0) for the high and the low Hb target groups, respectively.

(iii) Initiation of dialysis

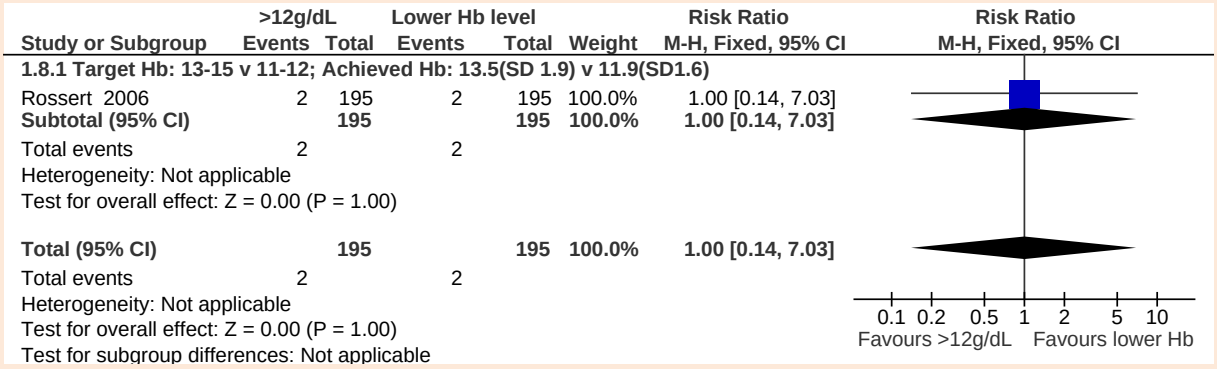
Figure I.16: >12 g/dL versus lower Hb level: initiation of dialysis



NB: Scale 0.02 to 50

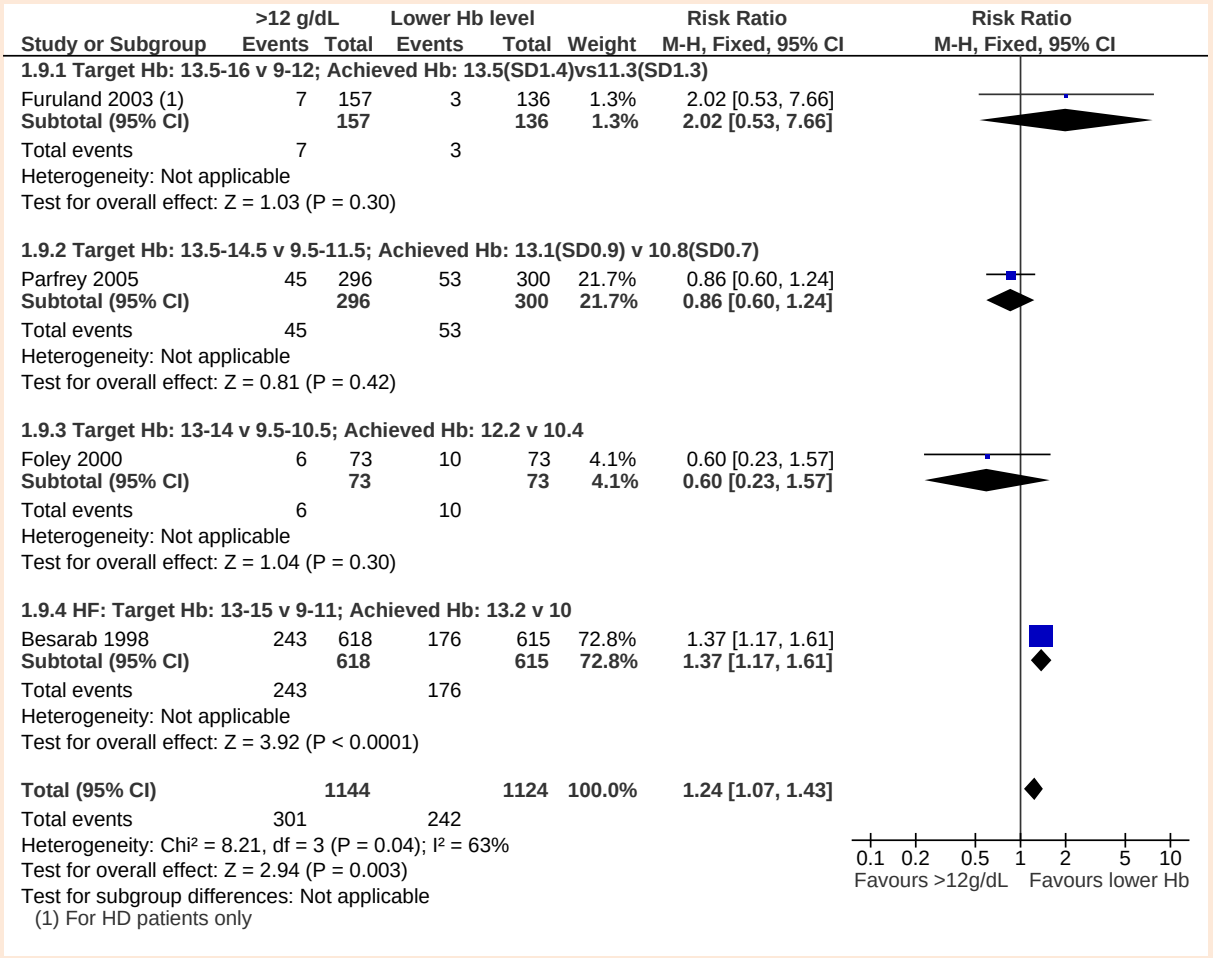
(iv)Worsening renal function

Figure I.17: >12 g/dL versus lower Hb level: worsening renal function



4. Access thrombosis

Figure I.18: >12 g/dL versus lower Hb level: access thrombosis



Predefined subgroup analysis (by co morbidities) was not carried out as there were varying proportions of patients with history/presence of cardiovascular disease. Heterogeneity may also be attributed to the variations in type of access (graft or fistula). Sensitivity analysis based on methodological quality was not undertaken as studies were at similar risk of bias.

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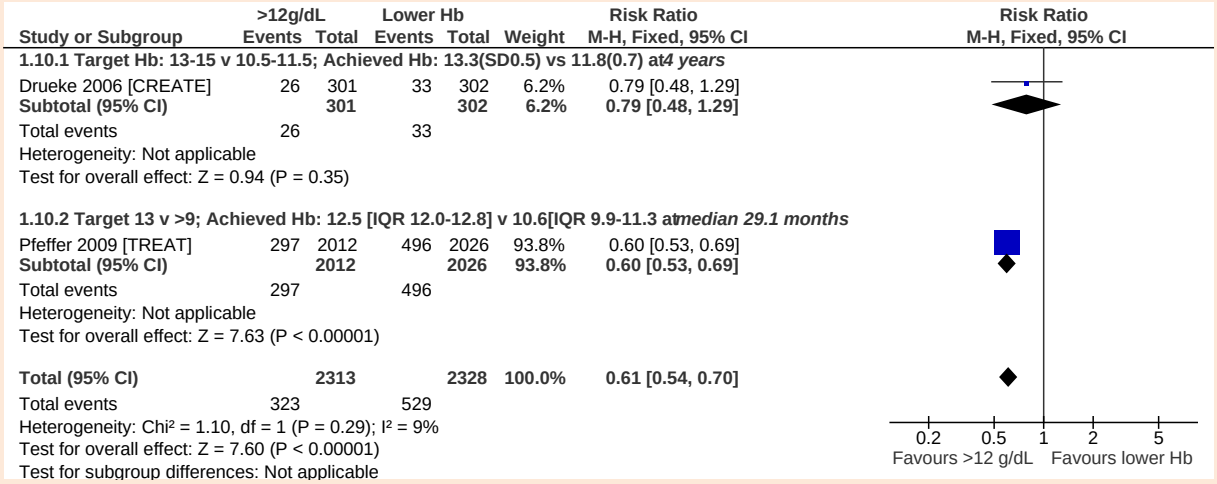
5. Transfusion requirements

5a. Non dialysis

Proportion of patients transfused

Figure I.19: >12 g/dL versus lower Hb level: proportion of patients transfused



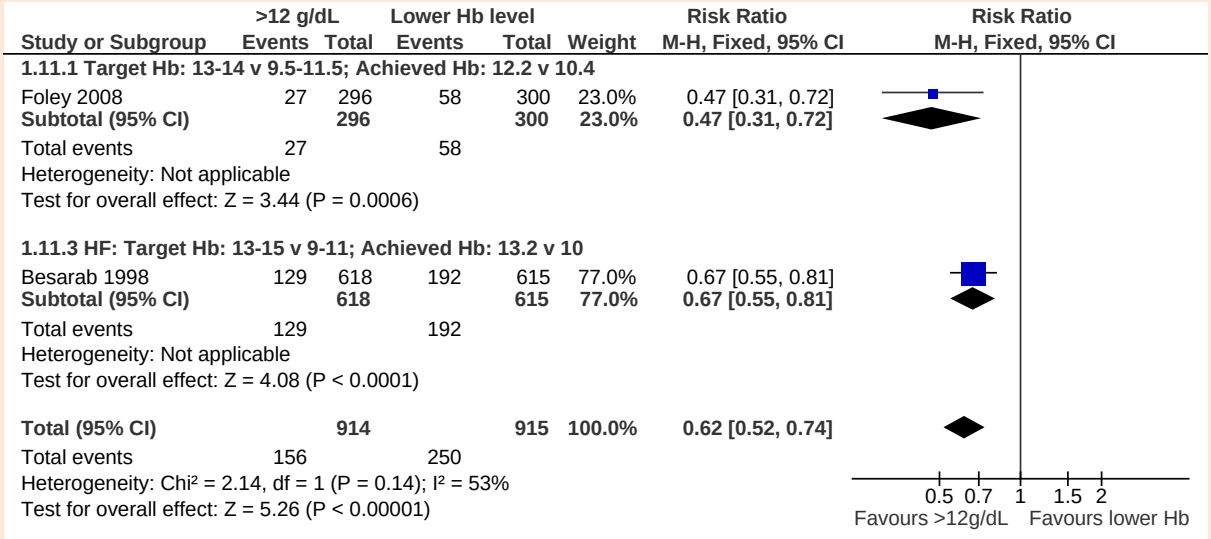
Reasons for transfusion not reported.

NB: Scale 0.2 to 5

Rossert (2003) reported no patients were administered blood transfusions during the study.

5b. Dialysis

Figure I.20: >12 g/dL versus lower Hb level: proportion of patients transfused



Reasons for transfusion not reported.

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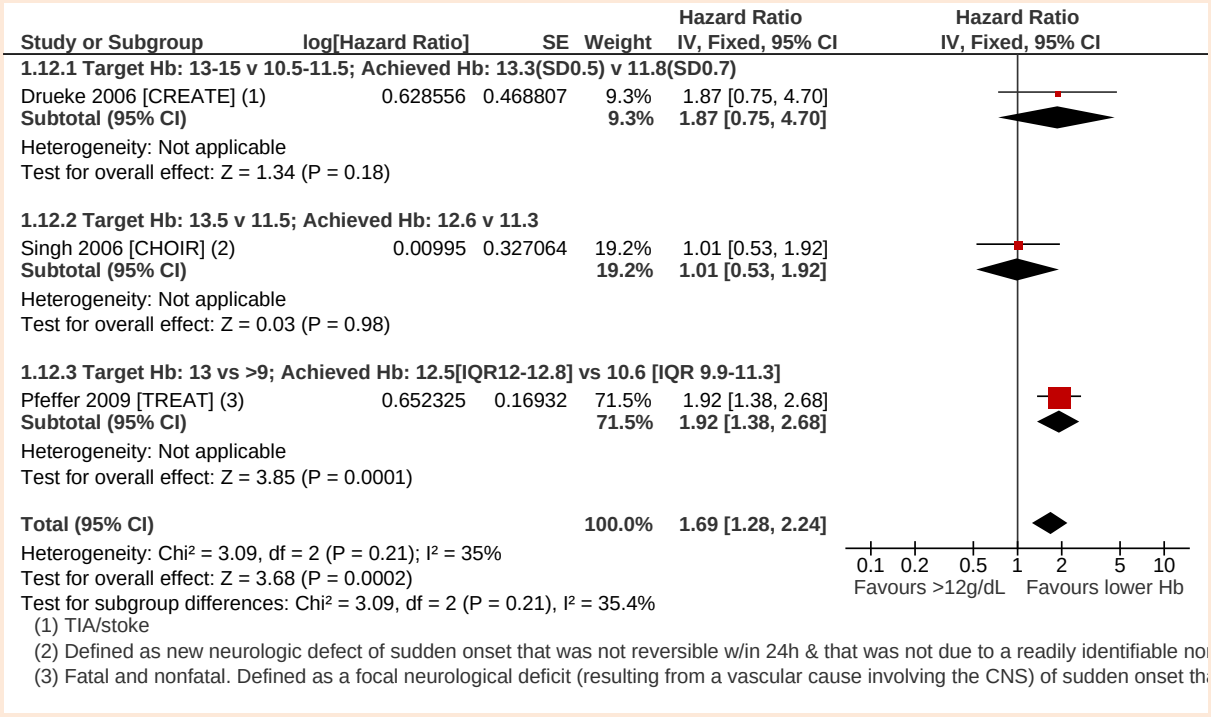
NB: Scale 0.5 to 2

Update 2011

6. Stroke

6a. Non-dialysis

Figure I.21: >12 g/dL versus lower Hb level: stroke



One additional study reported incidence of ischaemic stroke [Ritz 2007:0/88 vs 1/82 in the >12 g/dL vs lower Hb groups, respectively. RR 0.31 (95% CI 0.01 to 7.52)]. Data could not be transformed to HR.

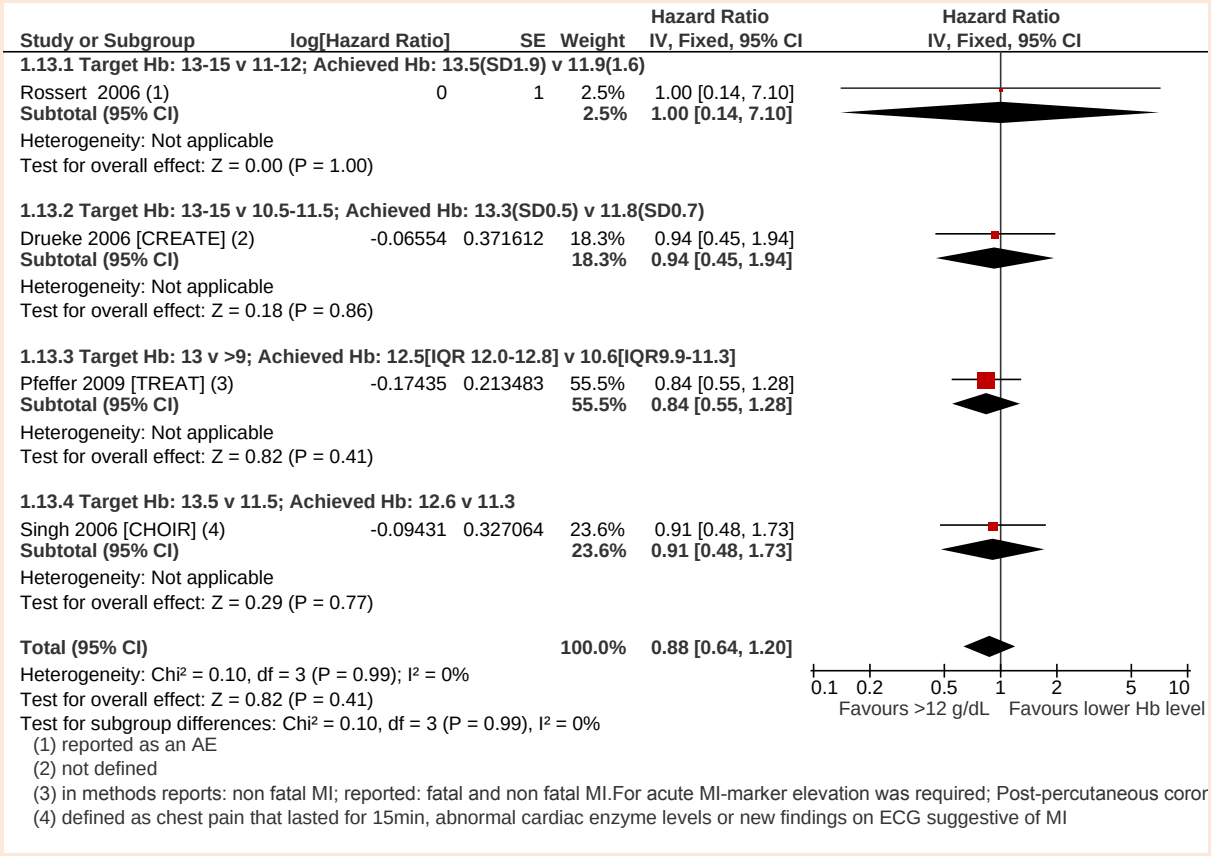
If overall RR calculated including Ritz 2007 data: RR 1.66 (95% CI 1.25 to 2.20)

Update 2011

7. MI

7a. Non-dialysis

Figure I.22: >12 g/dL versus lower Hb level: MI



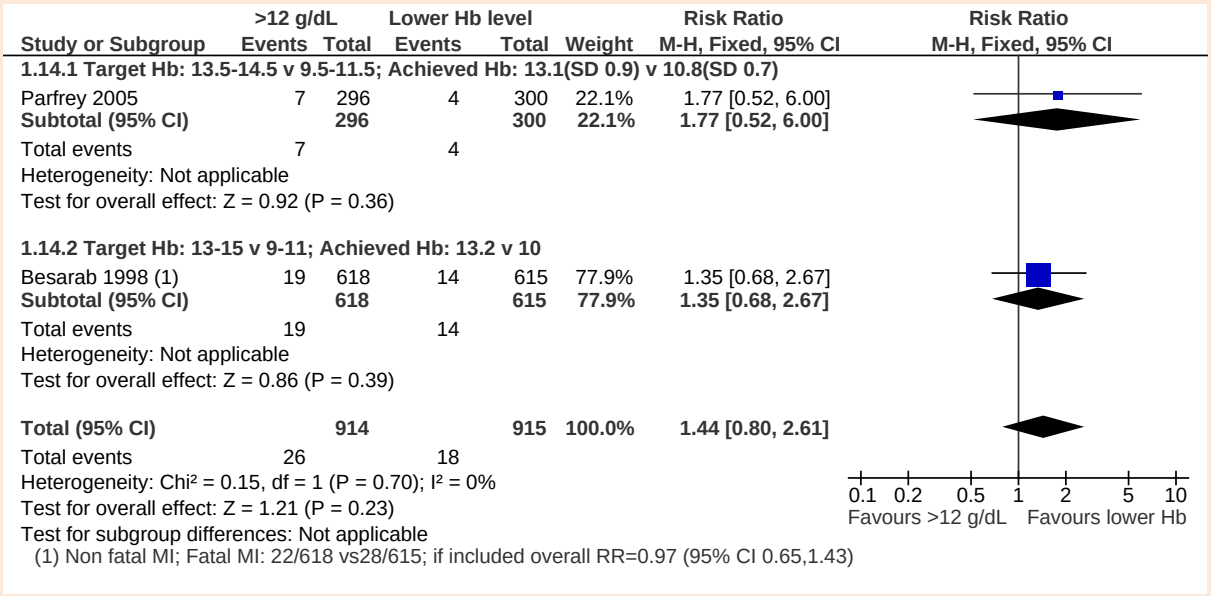
(1) reported as an AE
(2) not defined
(3) in methods reports: non fatal MI; reported: fatal and non fatal MI.For acute MI-marker elevation was required; Post-percutaneous coror
(4) defined as chest pain that lasted for 15min, abnormal cardiac enzyme levels or new findings on ECG suggestive of MI

One additional study reported incidence of MI [Ritz 2007: 2/88 vs 0/82, in the >12 g/dL and lower Hb groups, respectively; RR 4.66 (95% CI 0.23 to 95.70)]. Data could not be transformed to HR. If calculating RR including Ritz 2007 data, overall RR 0.97 (95% CI 0.79 to 1.20).

Update 2011

7b. Dialysis

Figure I.23: >12 g/dL versus lower Hb level: MI



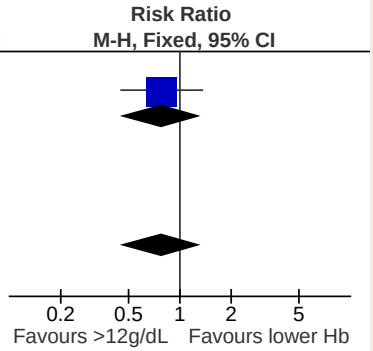
(1) Non fatal MI; Fatal MI: 22/618 vs28/615; if included overall RR=0.97 (95% CI 0.65,1.43)

Update 2011

Fatal MI

Figure I.24: >12 g/dL versus lower Hb level: fatal MI

Study or Subgroup	>12 g/dL Events	Total	lower Hb level Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 Target Hb: 13-15 v 9-11; Achieved Hb: 13.2 v 10						
Besarab 1998	22	618	28	615	100.0%	0.78 [0.45, 1.35]
Subtotal (95% CI)		**618**		**615**	**100.0%**	**0.78 [0.45, 1.35]**
Total events	22		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**618**		**615**	**100.0%**	**0.78 [0.45, 1.35]**
Total events	22		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Not applicable						



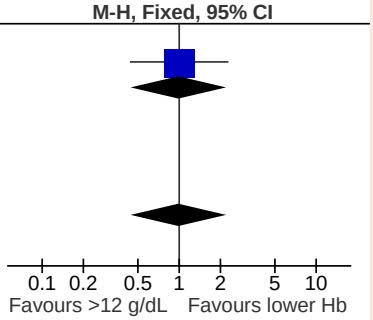
NB: Scale 0.2 to 5

(ii) Cardiac event

Figure I.25: >12 g/dL versus lower Hb level: cardiac event

Study or Subgroup	>12 g/dL Events	Total	Lower Hb level Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Target Hb: 13-14 V 9.5-10.5; Achieved Hb: 12.2 vs10.4						
Foley 2000 (1)	10	73	10	73	100.0%	1.00 [0.44, 2.26]
Subtotal (95% CI)		**73**		**73**	**100.0%**	**1.00 [0.44, 2.26]**
Total events	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**73**		**73**	**100.0%**	**1.00 [0.44, 2.26]**
Total events	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						

(1) Cardiac events:angina pectoris, MI, pulmonary oedema or cardiac failure



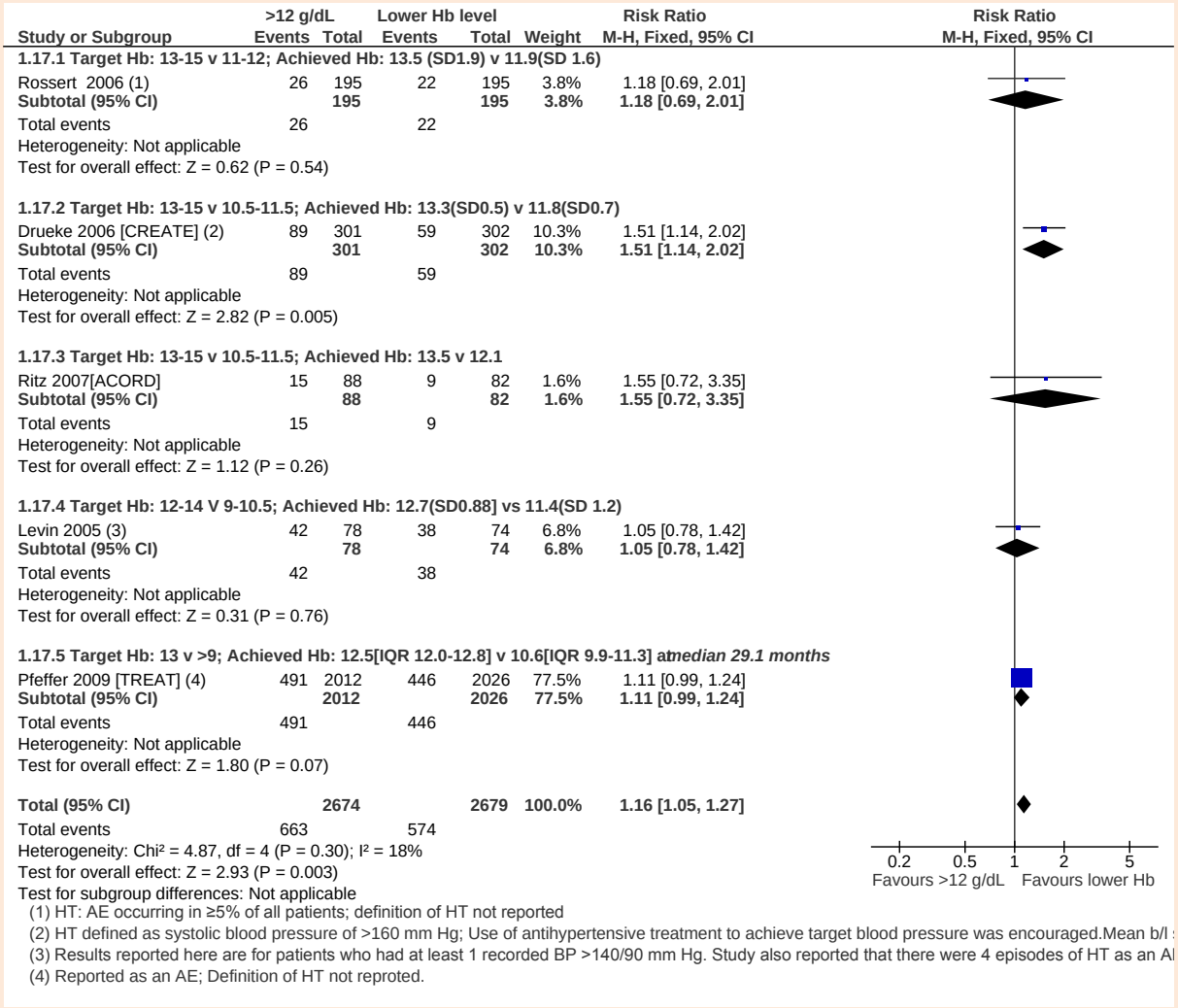
Update 2011

8. Hypertension

8a. Non-dialysis

(i) Hypertension

Figure I.26: >12 g/dL versus lower Hb level: hypertension



(1) HT: AE occurring in ≥5% of all patients; definition of HT not reported
(2) HT defined as systolic blood pressure of >160 mm Hg; Use of antihypertensive treatment to achieve target blood pressure was encouraged.Mean b/l
(3) Results reported here are for patients who had at least 1 recorded BP >140/90 mm Hg. Study also reported that there were 4 episodes of HT as an AI
(4) Reported as an AE; Definition of HT not reproted.

NB: Scale 0.2 to 5

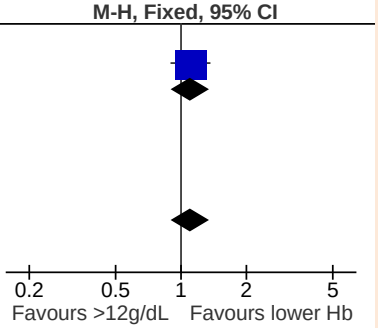
Update 2011

8b. Dialysis

Figure I.27: >12 g/dL versus lower Hb level: hypertension

Study or Subgroup	>12 g/dL Events	Total	Lower Hb Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Target Hb: 13.5-14.5 V 9.5-11.5; Achieved Hb: 13.1 (SD0.9) v 10.8 (SD 0.7)						
Parfrey 2005 (1)	120	296	110	300	100.0%	1.11 [0.90, 1.35]
Subtotal (95% CI)		**296**		**300**	**100.0%**	**1.11 [0.90, 1.35]**
Total events	120		110			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**296**		**300**	**100.0%**	**1.11 [0.90, 1.35]**
Total events	120		110			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Not applicable						

(1) Treatment emergent AE in ≥10% or patients;



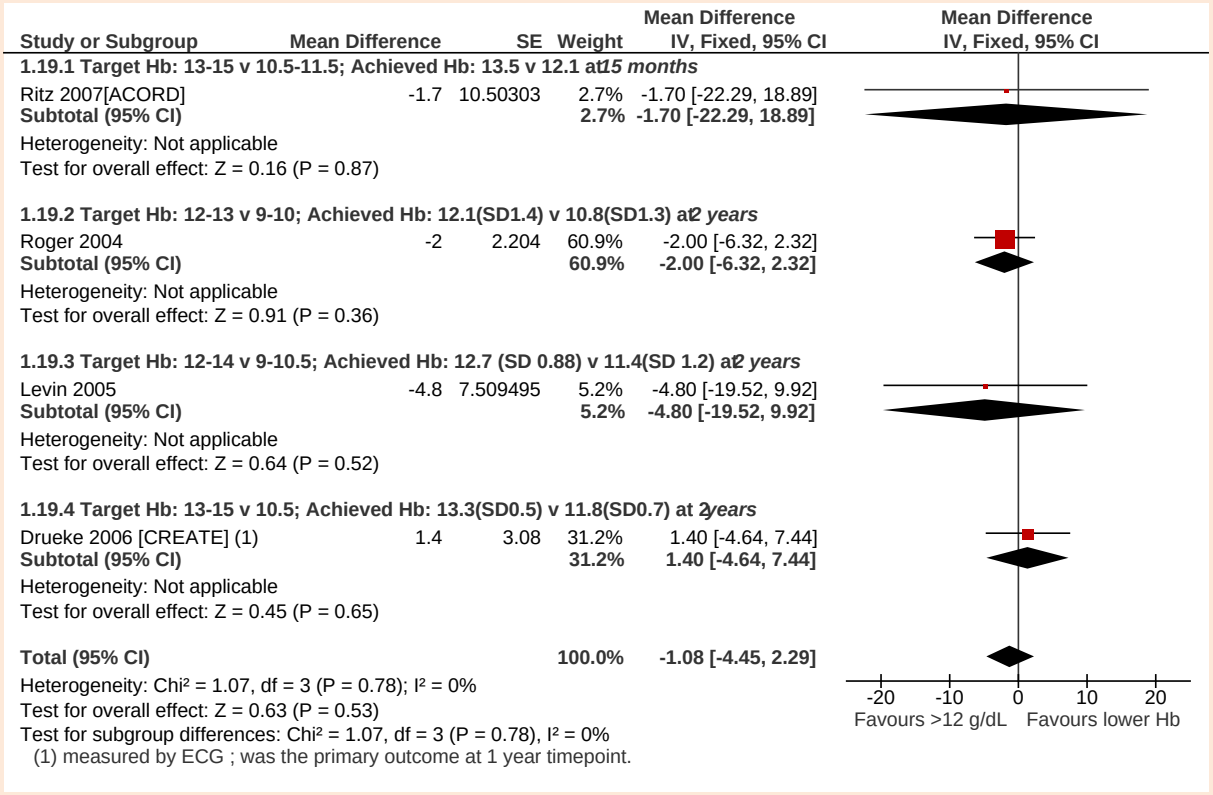
NB: Scale 0.2 to 5

Update 2011

9. Change in LVMI [g/m^2]

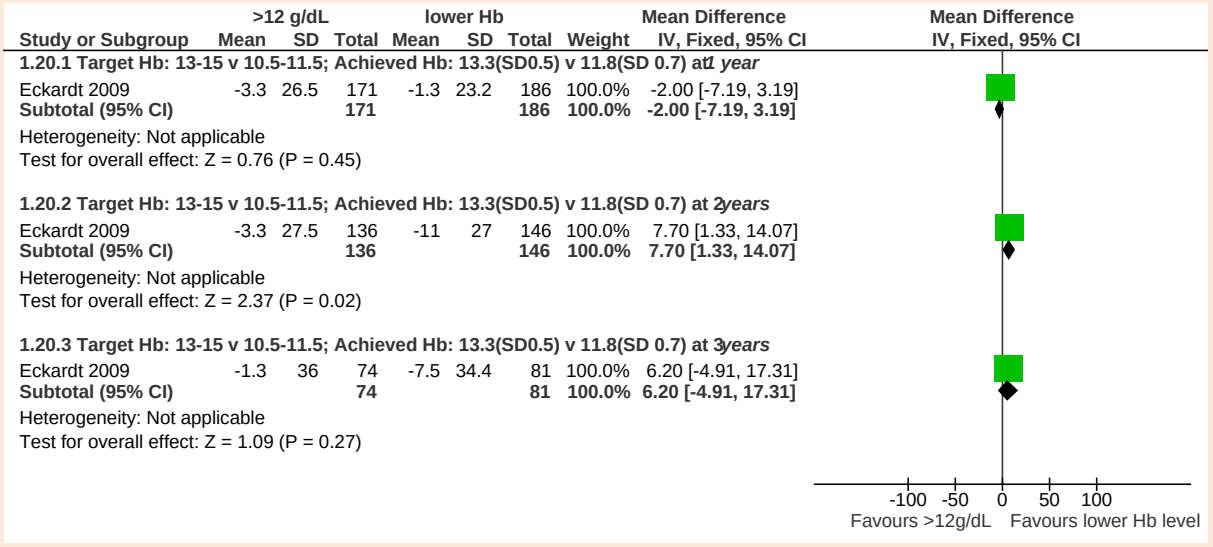
9a. Non-dialysis

Figure I.28: >12 g/dL versus lower Hb level: change in LVMI



NB: Scale -20 to 20

Figure I.29: >12 g/dL versus lower Hb level: change in LVMI over time (in patients who had echocardiograms at baseline)

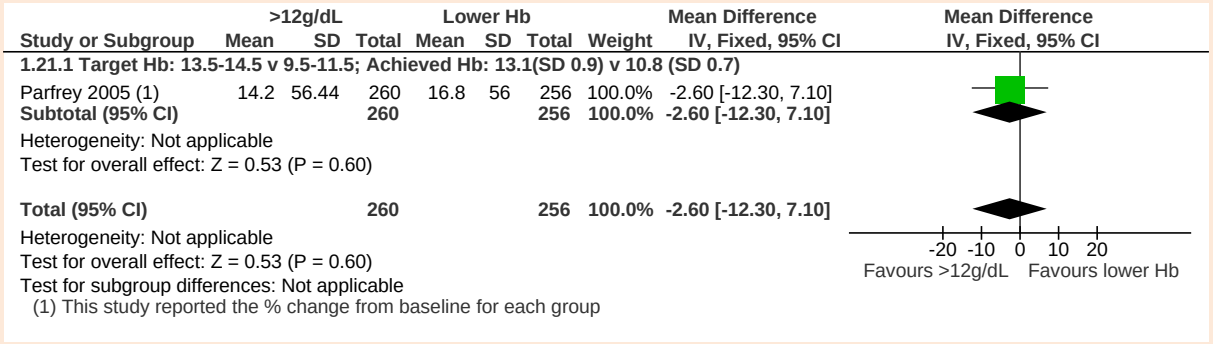


NB: Scale -20 to 20

Update 2011

9b. Dialysis

Figure I.30: >12 g/dL versus lower Hb level: change in LVMI [% change from baseline]



NB: Scale -20 to 20

One study (Foley 2000) reported the changes in LVMI was similar both Hb target groups and there was no correlation between the mean Hb level and the observed echocardiographic change.

Update 2011

10. Quality of life (SF-36)

Note: The forest plots for quality of life outcomes are presented with the 'favours intervention' i.e. 'favours >12 g/dL' on the right hand side of the forest plot to indicate an 'improvement in QoL' for the high Hb target group.

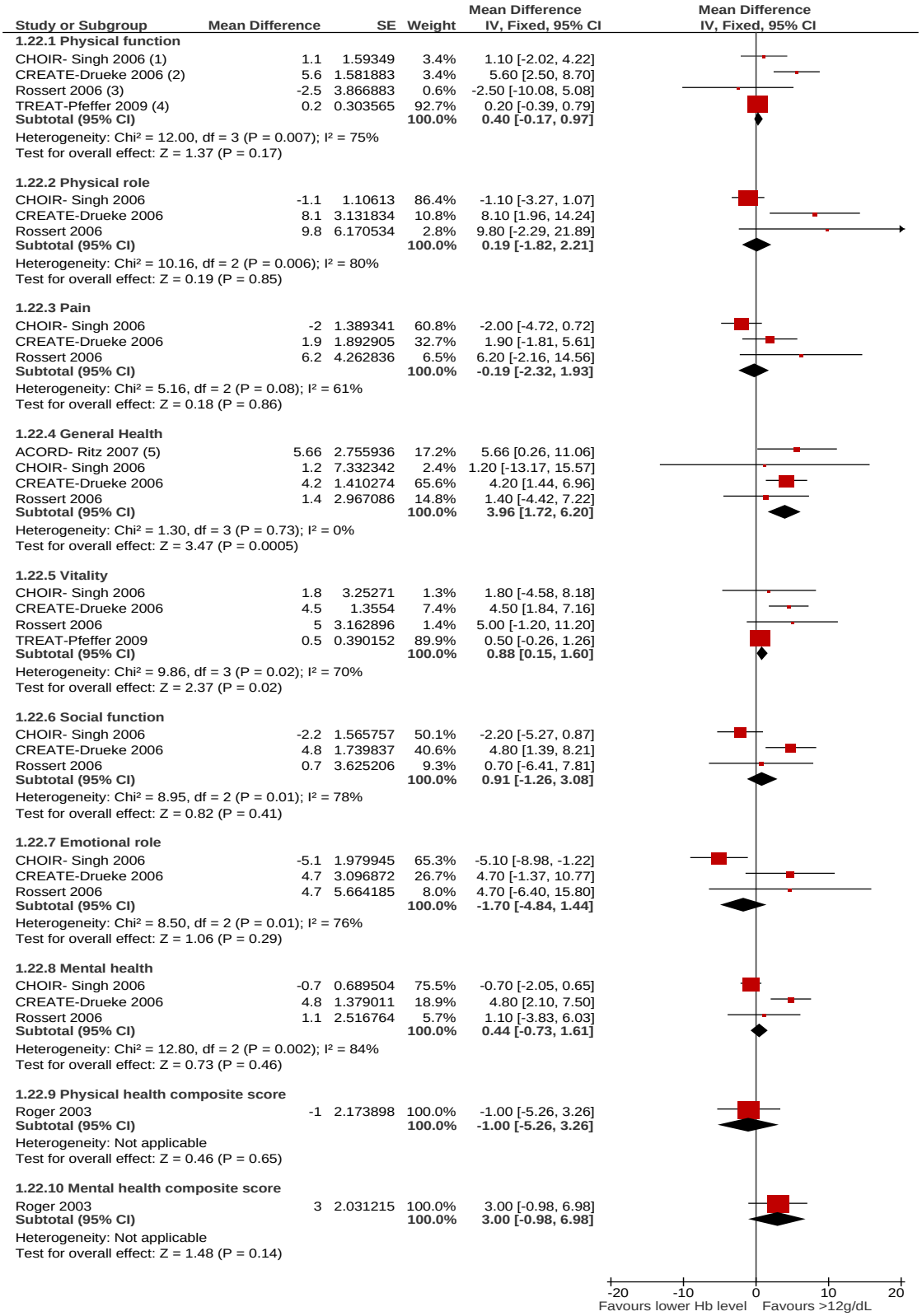
It was agreed that the meta-analysis would include QoL scores at 1 year (or at a nearest time point).

There was significant heterogeneity observed for the following domains: physical functioning, physical role, pain, vitality, social function, emotional role and mental health. The studies included varying proportions of patients with cardiovascular disease and diabetes so predefined subgroup analysis was not undertaken. Sensitivity analysis based on methodological quality was not undertaken as all of the included studies were considered to be at similar risk of bias.

10a. Non-dialysis

Quality of Life (SF-36) – all domains

Figure I.31: >12 g/dL versus lower Hb level: SF-36



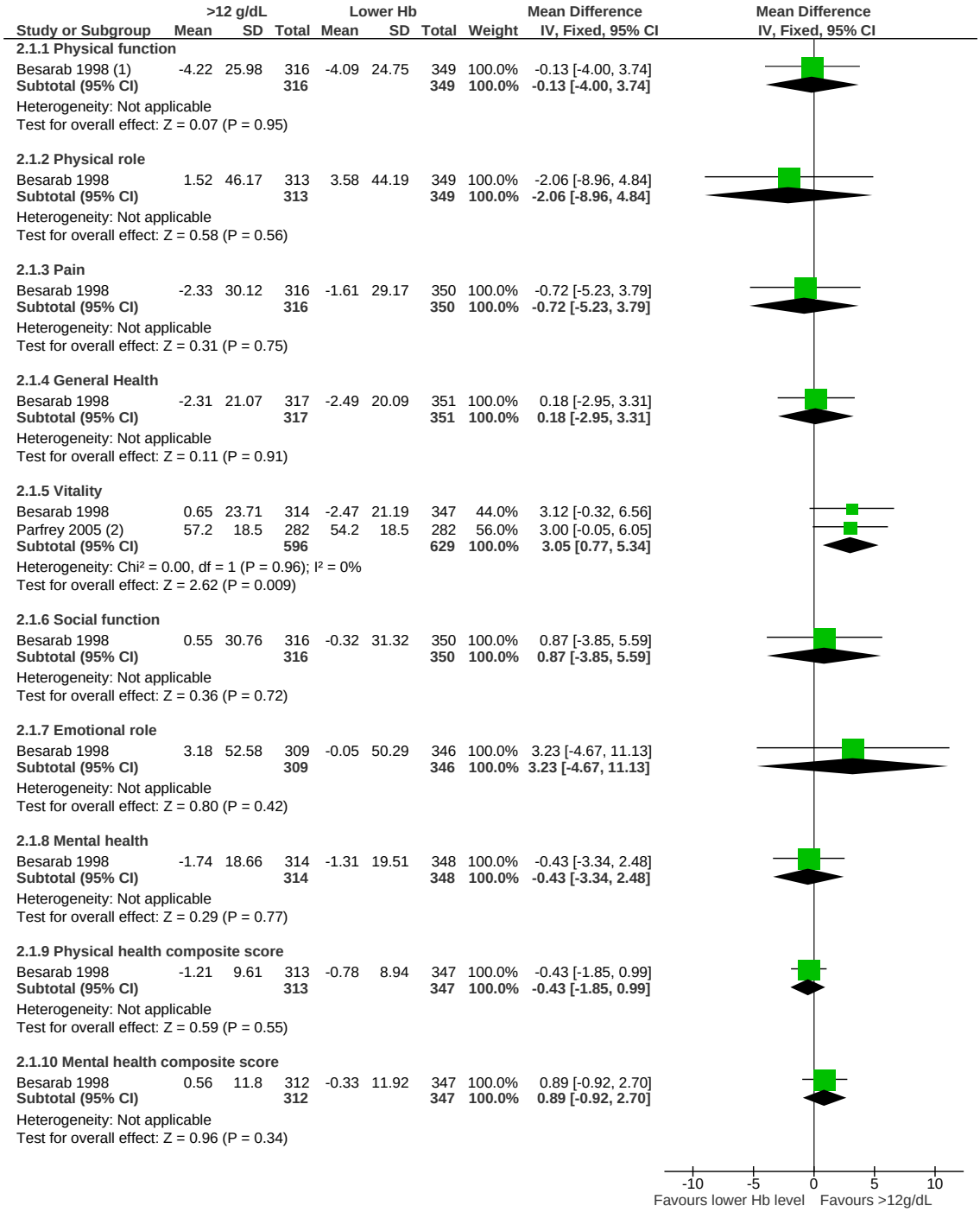
(1) time point QoL measured unclear; median follow-up:16 months
(2) 1 year
(3) Reported at 'end of phase b' @9 months
(4) 25 weeks
(5) end of study-@15 months

NB: Scale -20 to 20

10b. Dialysis

Quality of life (SF-36)- all domains

Figure I.32: >12 g/dL versus lower Hb level: SF-36



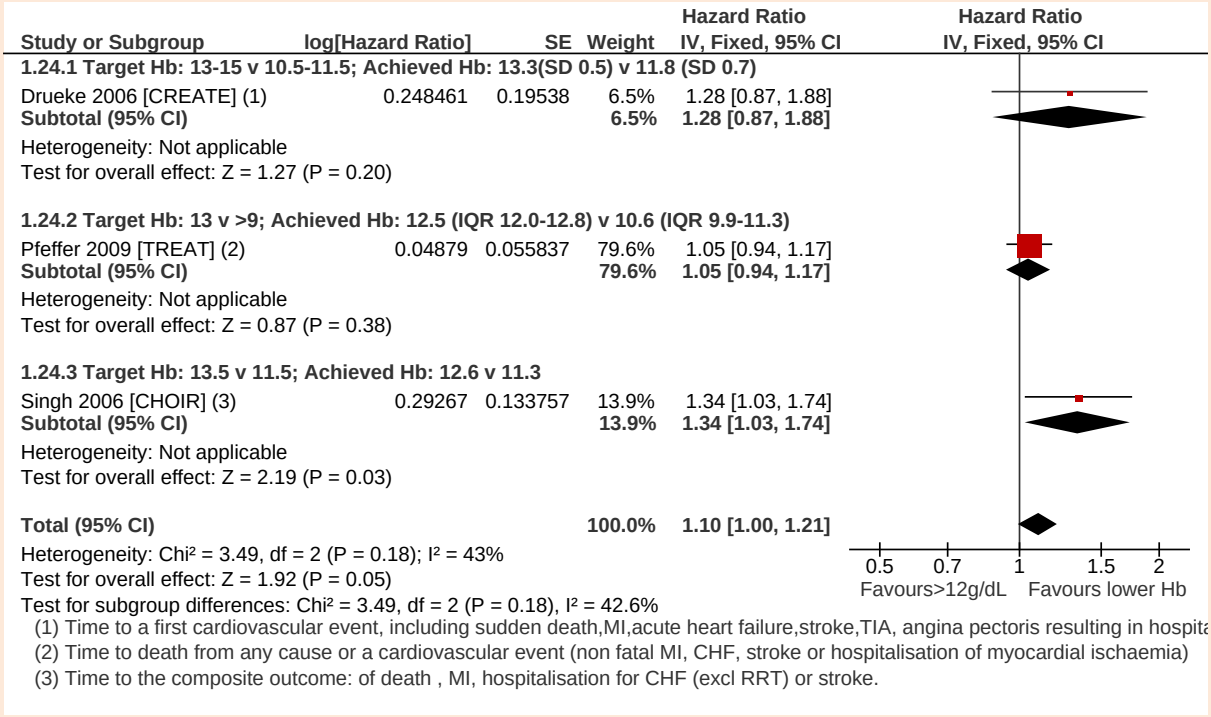
(1) at 1 year
(2) at week 48

NB: Scale -10 to 10**11. Composite outcome**

Update 2011

11a. Non-dialysis

Figure I.33: >12 g/dL versus lower Hb level: composite outcome



NB: Scale 0.5 to 2

Update 2011

12. CV event free survival

12a. Non-dialysis

Figure I.34: >12 g/dL versus lower Hb level: CV event free survival (concentric LVH)

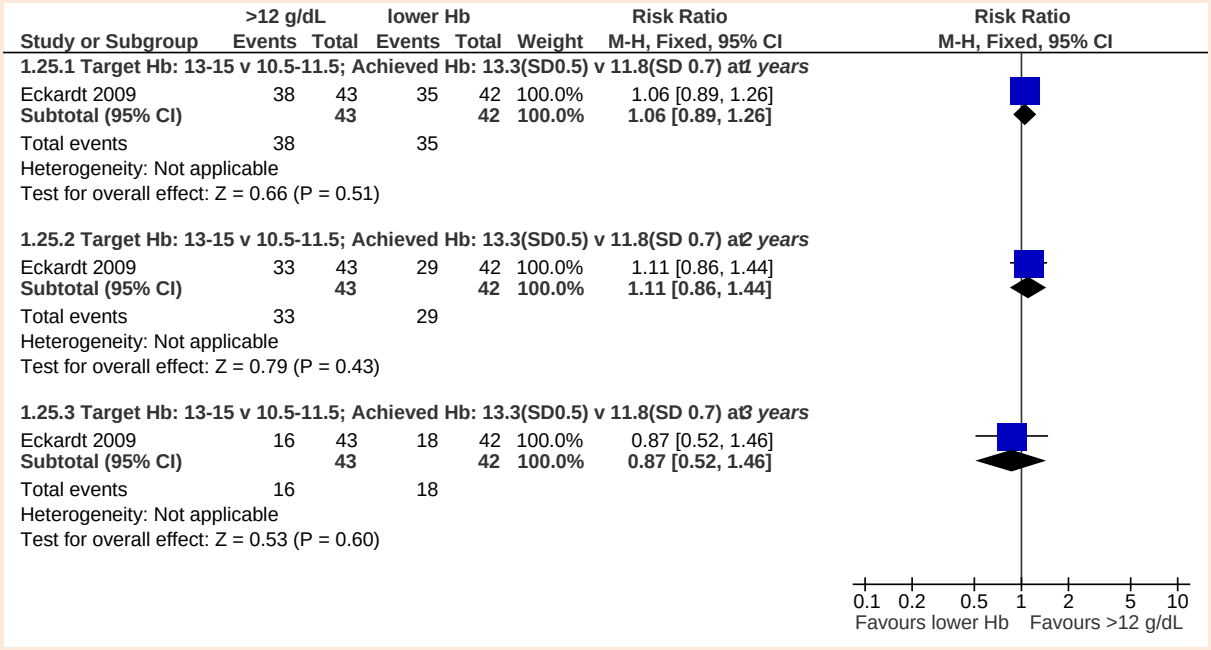
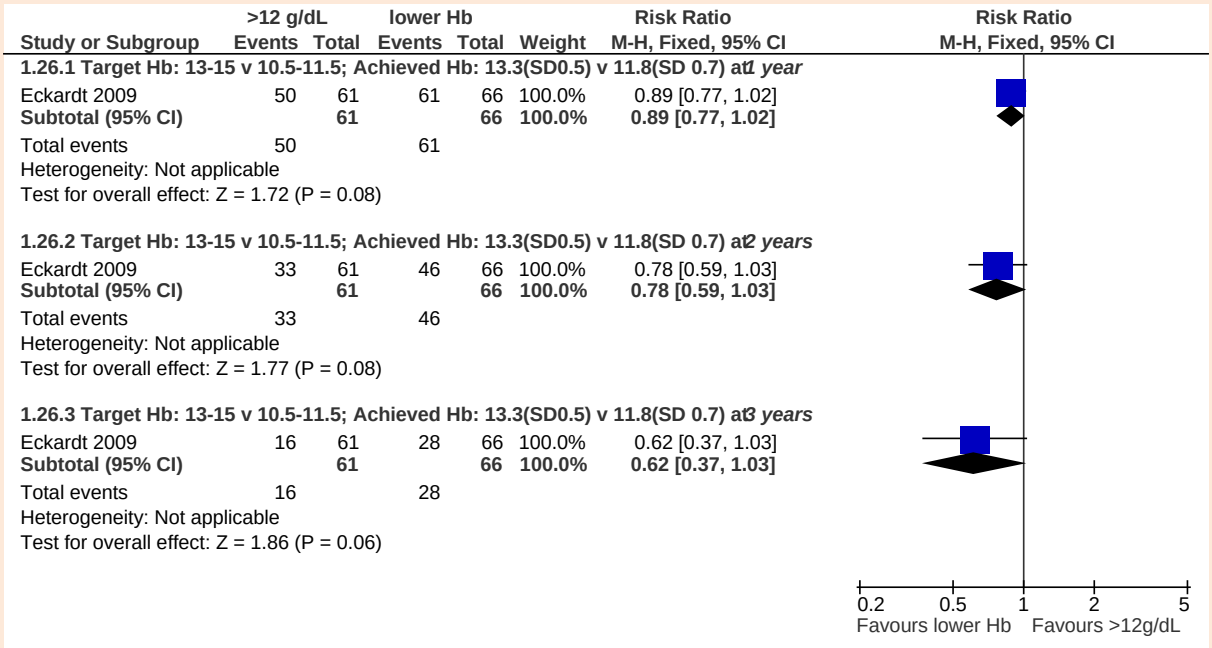


Figure I.35: >12 g/dL versus lower Hb level: CV event free survival (eccentric LVH)



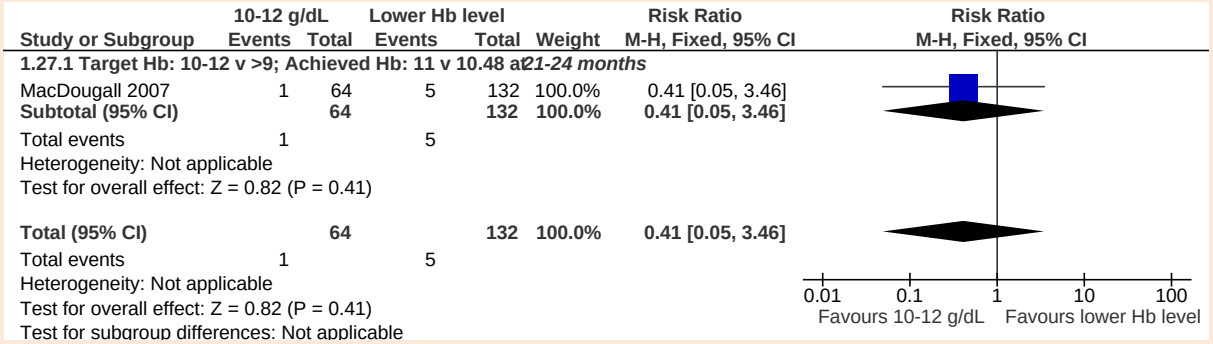
NB: 0.2 to 5

B. 10 to 12 g/dL compared with lower Hb level

1. All-cause mortality

Non-dialysis

Figure I.36: 10 to 12 g/dL versus lower Hb level: all-cause mortality



NB: Scale 0.01 to 100

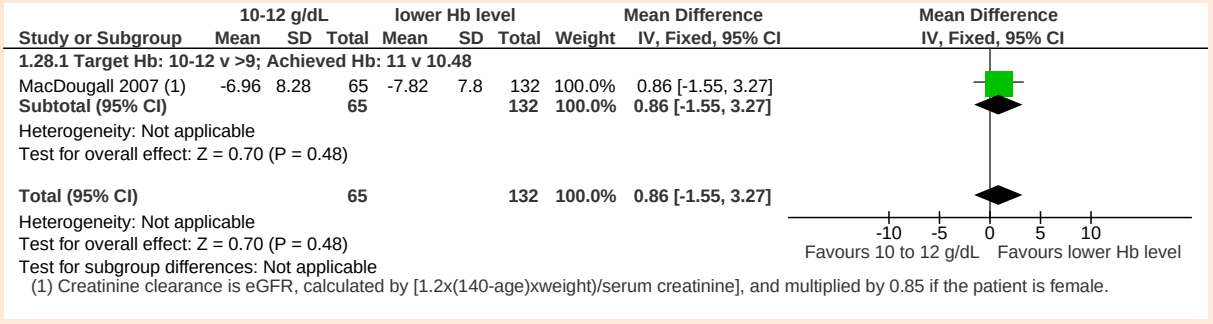
2. CV mortality

For this comparison there were no studies reporting this outcome.

3. Progression of CKD

(i) Creatinine clearance

Figure I.37: 10 to 12 g/dL versus lower Hb level: creatinine clearance



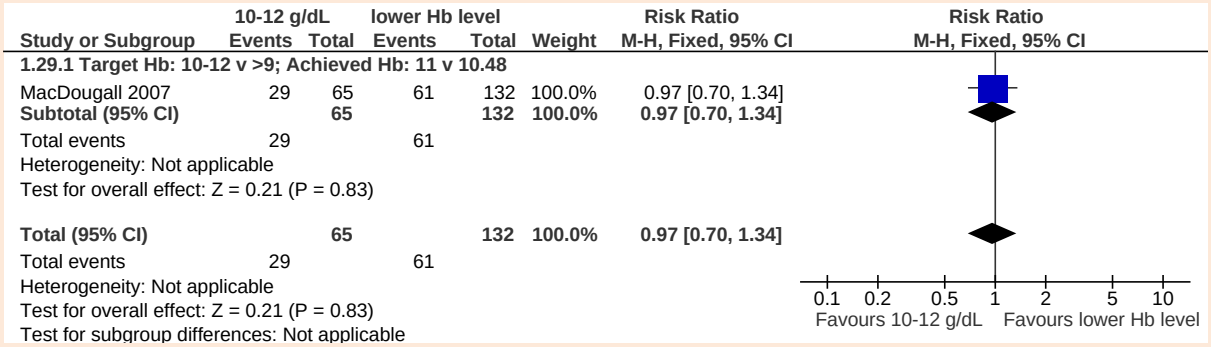
NB: Scale -10 to 10

Update 2011

Update 2011

(ii) Initiation of dialysis

Figure I.38: 10 to 12 g/dL versus lower Hb level: initiation of dialysis



4. Transfusion requirements.

For this comparison there were no studies reporting this outcome.

5. Stroke

For this comparison there were no studies reporting this outcome.

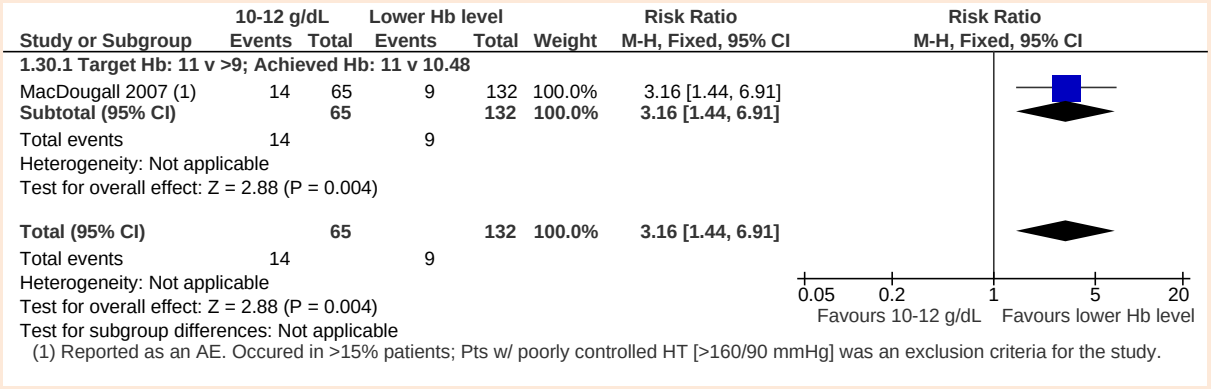
Update 2011

6. MI

For this comparison there were no studies reporting this outcome.

7.Hypertension

Figure I.39: 10 to 12 g/dL versus lower Hb level: hypertension

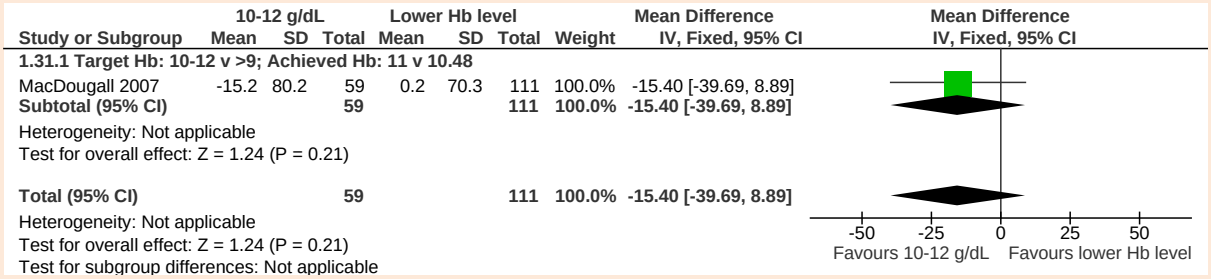


(1) Reported as an AE. Occured in >15% patients; Pts w/ poorly controlled HT [>160/90 mmHg] was an exclusion criteria for the study.

NB: Scale 0.05 to 20

8. Worst LVMI [g/m^2] - change from baseline

Figure I.40: 10 to 12 g/dL versus lower Hb level: Worst LVMI- change from baseline



Study reported in the methods that LVM calculated from an echocardiogram. The greatest (worst) LVM and change from baseline to greatest LVM were determined for each patient.

NB: Scale -50 to 50

Update 2011

Paediatric Forest plots

1. Progression of CKD

No forest plot available.

2. Hypertension

2a. Predialysis

No forest plot available.

2b. Dialysis

No forest plot available.

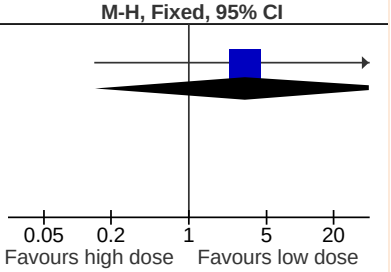
Update 2011

3. Transfusion

3a. Non-dialysis

Figure I.41: High dose vs Low dose: number of patients transfused

Study or Subgroup	High dose Events	Total	Low dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.32.1 Achieved Hb: 12.7 v 11.9						
Brandt 1999	1	12	0	13	100.0%	3.23 [0.14, 72.46]
Subtotal (95% CI)		**12**		**13**	**100.0%**	**3.23 [0.14, 72.46]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						

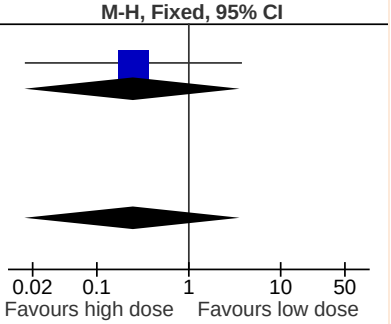


NB: Scale 0.05 to 20

3b. Dialysis

Figure I.42: High dose vs Low dose: number of patients transfused

Study or Subgroup	High dose Events	Total	Low dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.33.1 Achieved Hb: 12.9 v 8.4						
Brandt 1999 (1)	0	3	3	6	100.0%	0.25 [0.02, 3.71]
Subtotal (95% CI)		**3**		**6**	**100.0%**	**0.25 [0.02, 3.71]**
Total events	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**3**		**6**	**100.0%**	**0.25 [0.02, 3.71]**
Total events	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Not applicable						
(1) No transfusions in the periotenal dialysis group.						

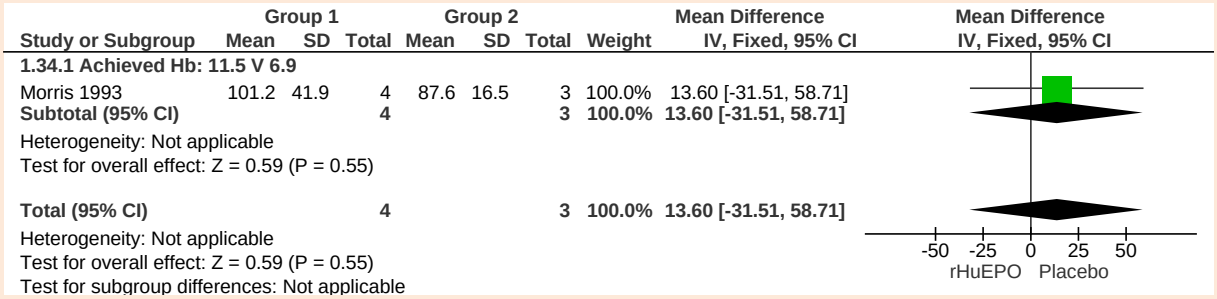


NB: Scale 0.02 to 50

4. LVMI [g/m^2]

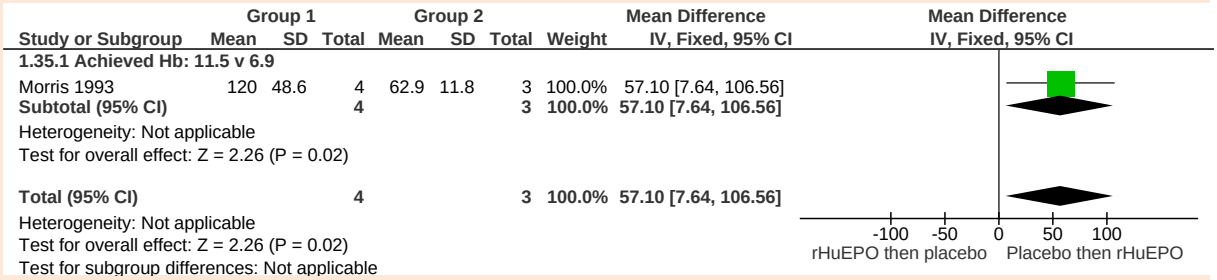
Dialysis and non-dialysis

Figure I.43: rHuEpo vs placebo- 24 weeks: LVMI



NB: Scale -50 to 50

Figure I.44: Placebo following rHuEpo vs rHuEpo following placebo - 48 weeks: LVMI



NB: Scale -100 to 100

Update 2011

I.3

Appendix J: Deleted parts from the 2006 guideline (no longer relevant)

3.2 Algorithms [2006, deleted]

An algorithm is any set of detailed instructions which results in a predictable end-state from a known beginning, ideally presented in an easy-to-follow decision tree format. Algorithms are only as good as the instructions given, however, and the result will be incorrect if the algorithm is not properly defined. The algorithms presented in this section are suggested management algorithms based on the known literature but importantly they have not been tested and should be used as guides to aid development of local practice.

3.2.1 Algorithm for diagnosis of anaemia of CKD in adults [2006, deleted]

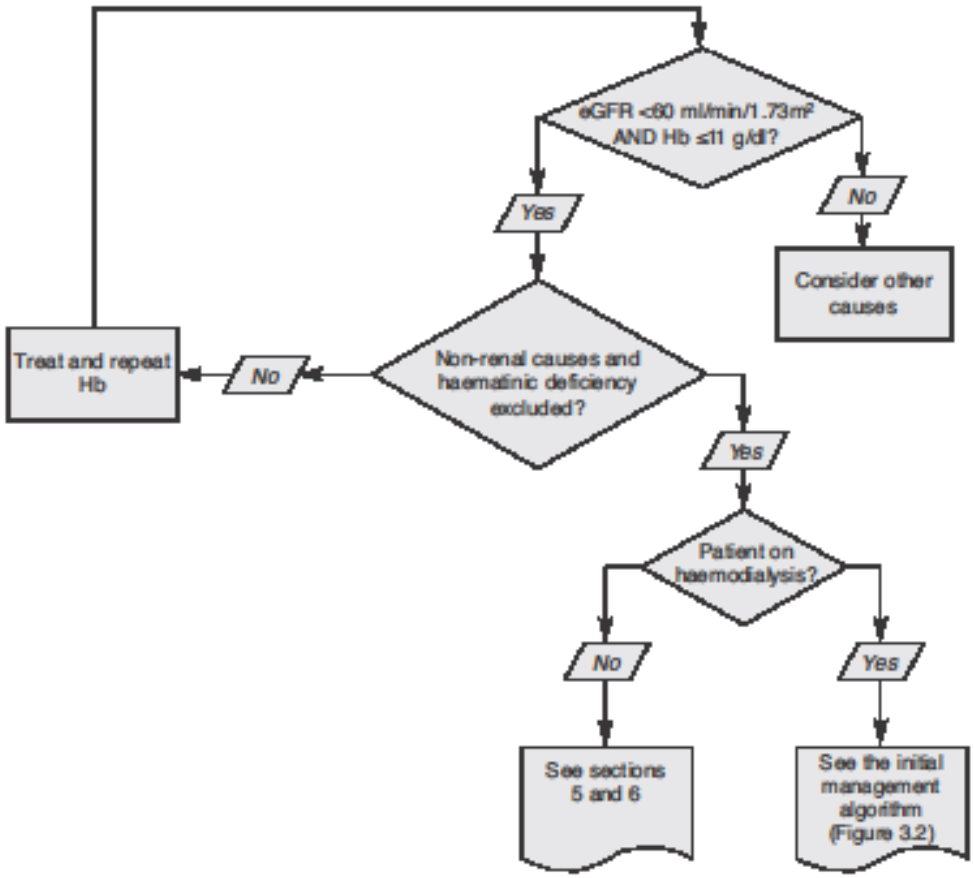


Figure 3.1 Diagnosis of anaemia of CKD in adults

Table 3.1: Test for functional iron deficiency with ferritin and TSAT or ferritin and %HRC

	Ferritin	TSAT %	MCV	HRC %
Functional iron deficiency	>100 µg/l	<20	Normal range	>6
Absolute iron deficiency	<100 µg/l	<20	Low	>6
TSAT = transferrin saturation; MCV = mean corpuscular volume; HRC = hypochromic red cells.				

3.2.2 Initial management algorithm for adult patients (assumes Hb < 11g/dl) [2006, deleted]

This algorithm is an example strategy for adult haemodialysis patients. Treatment should be tailored to individual patients according to the guideline recommendations.

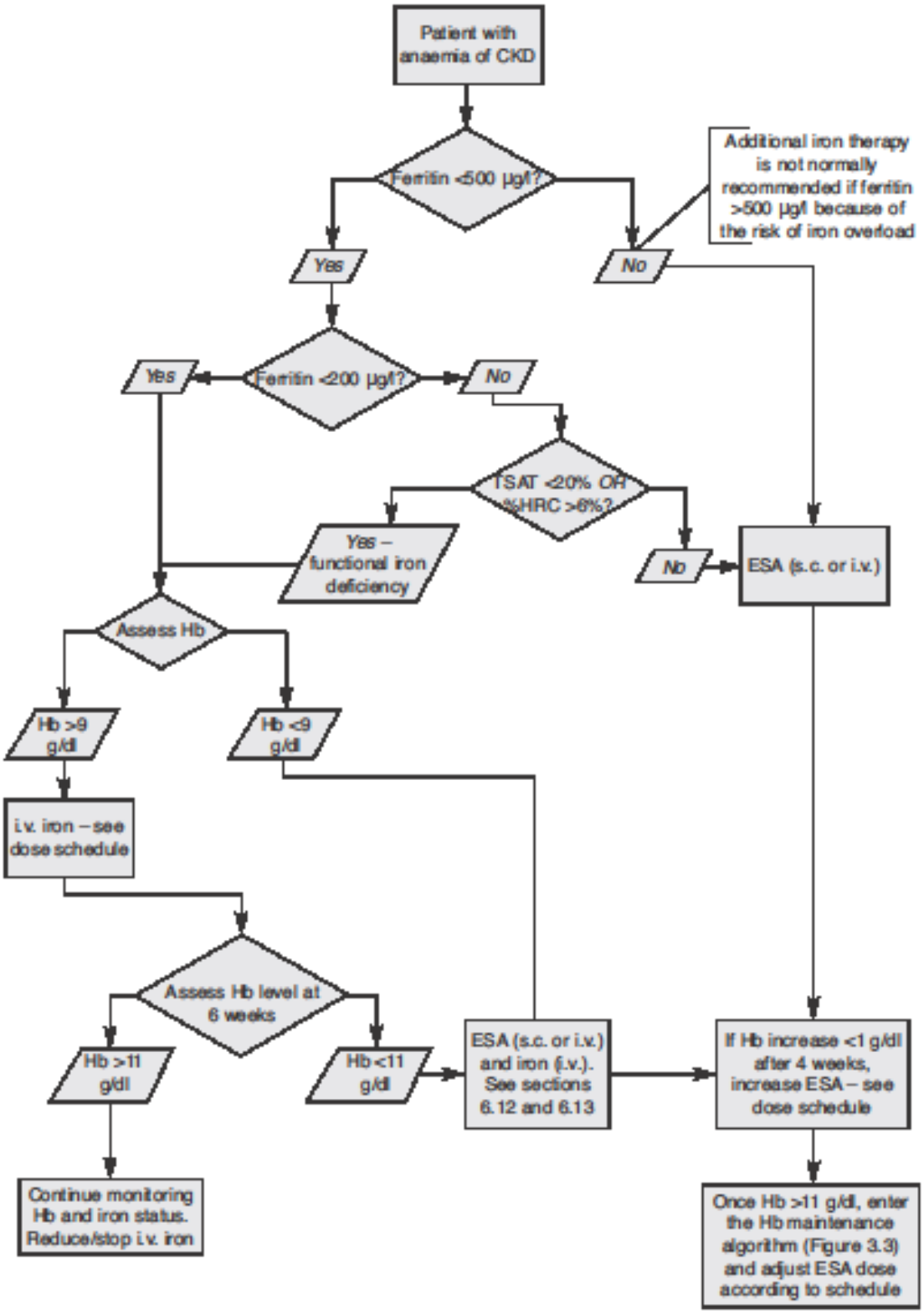


Figure 3.2 Initial management for adult patients (assumes Hb <11g/dl)

Iron dosage schedule

This is an example strategy for adult haemodialysis patients weighing over 50 kg. Treatment should be tailored to individual patients according to the guideline recommendations.

Table 3.2: Iron dosage schedule

Haemodialysis patients		Non-haemodialysis patients
Induction/loading dose	Maintenance dose	Iron sucrose 200 mg/fortnight × 3 doses or low molecular weight iron dextran 1g
Either iron sucrose 200 mg/week for 5 weeks or low molecular weight iron dextran 1g	Iron sucrose 50 mg/week or 100 mg/fortnight	
Throughout ESA induction:		
In people with anaemia of chronic kidney disease, haemoglobin should be monitored: every 2–4 weeks in the induction phase of ESA therapy every 1–3 months in the maintenance phase of ESA therapy more actively after an ESA dose adjustment in a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local healthcare systems.		
Be aware of side effects and comorbidities		

3.2.3 Haemoglobin maintenance algorithm (assumes patient is receiving ESA and maintenance i.v. iron) [2006, deleted]

This is an example strategy for adult patients. Treatment should be tailored to individual patients according to the guideline recommendations.

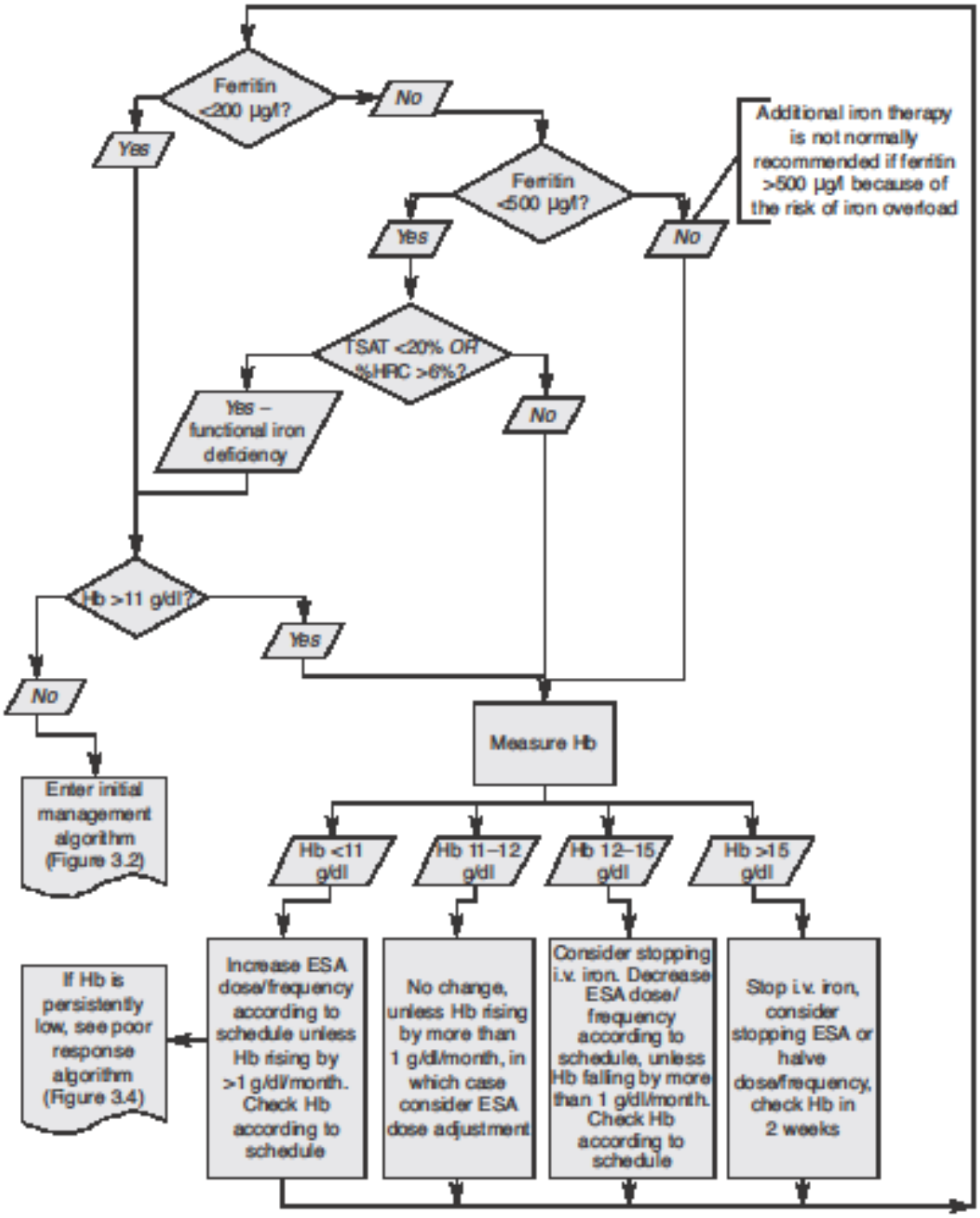


Figure 3.3 Haemoglobin maintenance algorithm (assumes patient is receiving ESA and maintenance i.v. iron)

ESA adjustment schedule for adult patients – make adjustments based on absolute Hb level and/or rate of change of Hb >1g/dl/month

Table 3.3: Erythropoietins

Current dose (units/week)	Increased dose (if single dose consider increasing dose frequency)	Decreased dose (consider reducing dose frequency, minimum weekly)
1,000	2,000	Suspend
2,000	3,000	1,000
3,000	4,000	2,000
4,000	6,000	3,000
6,000	9,000	4,000
9,000	12,000	6,000
12,000	Seek advice	9,000
>12,000	Seek advice	Seek advice

Table 3.4: Darbepoetin

Current dose (µg/week)	Increased dose (consider increasing dose frequency)	Decreased dose (consider reducing dose frequency, minimum monthly)
10	15	Suspend
15	20	10
20	30	15
30	40	20
40	50	30
50	60	40
60	80	50
80	Seek advice	60
>80	Seek advice	Seek advice

Frequency of haemoglobin monitoring in adults

Table 3.5: Haemodialysis patients

Haemoglobin level and rate of change	Monitoring frequency
<11 g/dl, rate of change ≤1 g/dl/month	4 weeks
<11 g/dl, rate of change >1 g/dl/month	2 weeks
11–12 g/dl, rate of change >1 g/dl/month	4 weeks
11–12 g/dl, rate of change ≤ g/dl/month	2 weeks
>12–15 g/dl, rate of change >1 g/dl/month	4 weeks
>12–15 g/dl, rate of change ≤1 g/dl/month	2 weeks
>15 g/dl	2 weeks

Table 3.6: Peritoneal dialysis and predialysis (including transplant) patients

<11 g/dl, rate of change ≤1 g/dl/month	**4 weeks**
<11 g/dl, rate of change >1 g/dl/month	2 weeks
11–12 g/dl, rate of change ≤1 g/dl/month	4–12 weeks
11–12 g/dl, rate of change >1 g/dl/month	2 weeks
>12–15 g/dl, rate of change ≤1 g/dl/month	4–12 weeks
>12–15 g/dl, rate of change >1 g/dl/month	2 weeks
>15 g/dl	2 weeks

3.2.4 Algorithm for adult patients with poor response to ESAs [2006, deleted]

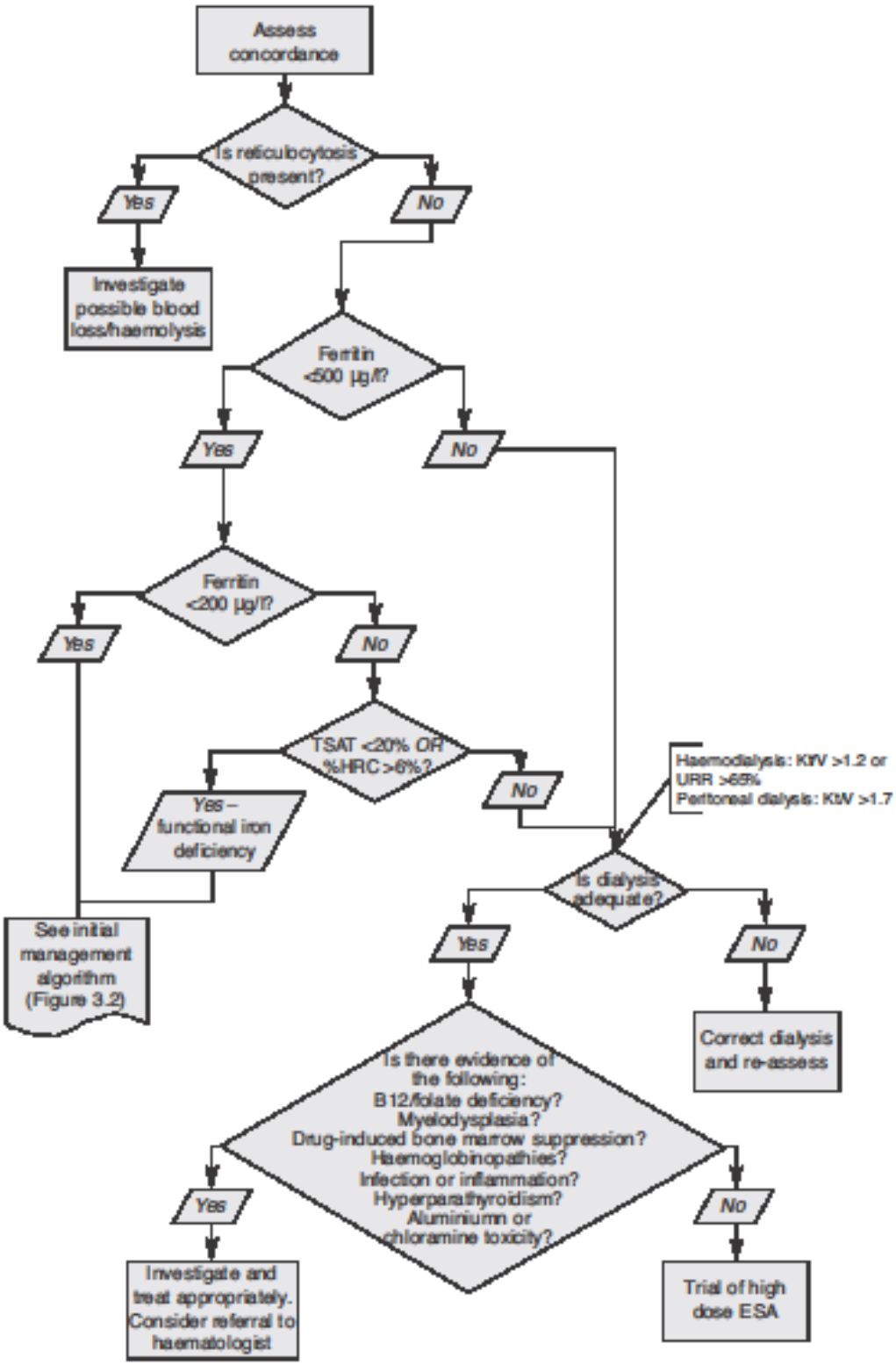


Figure 3.4 Algorithm for adult patients with poor response to ESAs

4.1.1 Clinical introduction [2006, deleted]

Possible adverse effects of anaemia in patients with CKD include reduced oxygen utilisation, increased cardiac output and left ventricular hypertrophy (cardiac dilatation ± increased wall thickness). The relationships between these are set out in Figure 4.1.

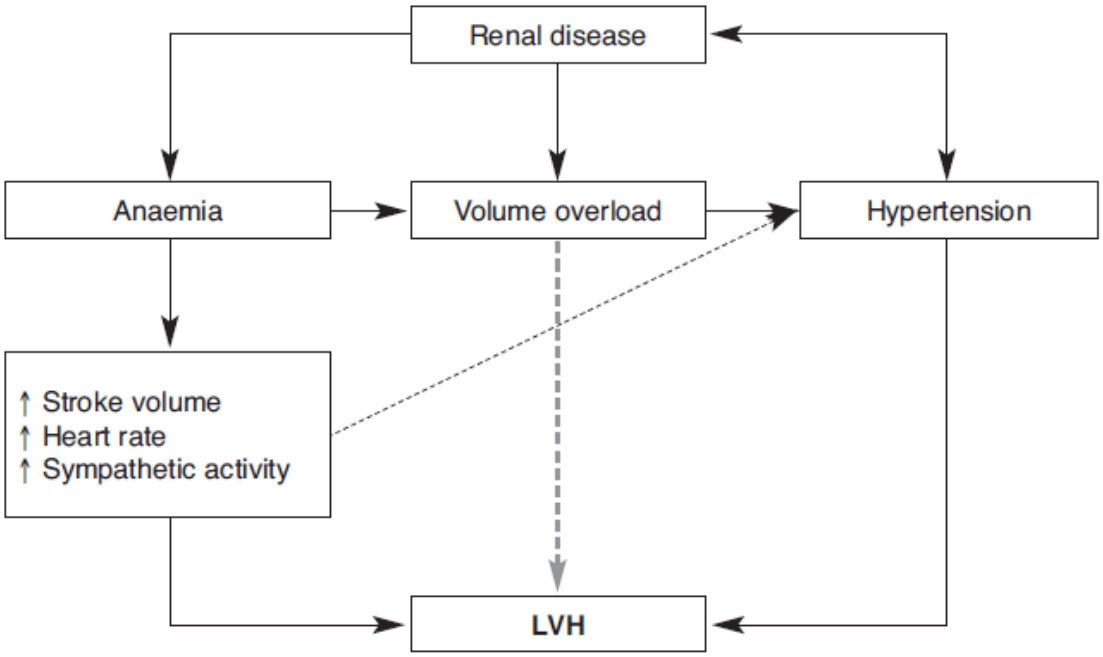


Figure 4.1 Left ventricular hypertrophy (LVH) in CKD patients (Mann JF, *Nephrol Dial Transplant* 1999; 14(Suppl 2):29-36)

It is also suggested that anaemia is associated with increased progression of CKD, reduced cognition and concentration, reduced libido and reduced immune responsiveness. How much these adverse effects translate into adverse outcomes such as impaired quality of life, increased hospitalisation, increased cardiovascular events and increased cardiovascular and all-cause mortality has been the subject of debate for several years.

Large observational studies show an inverse association between haemoglobin levels and adverse outcomes but randomised controlled trial (RCT) evidence of an improvement in these outcomes with correction of anaemia is lacking. Part of the problem is that the available studies do not compare 'no treatment of anaemia' with treatment, but rather partial correction of anaemia to better correction.

Is it likely that adverse outcomes associated with anaemia are influenced by age, gender or ethnicity? The implications of this question are that we might adopt a differing strategy when correcting anaemia if there is evidence to dictate such an approach.

RECOMMENDATION [2006, deleted]

R1 Management of anaemia should be considered in people with anaemia of chronic kidney disease (CKD) when their haemoglobin level is less than or equal to 11 g/dl (C) (or 10 g/dl if younger than 2 years of age). (D)

See 3.2.1 for the associated algorithm.

6.9.1 Clinical introduction[2006, deleted]

The optimal haemoglobin range to be maintained following correction of anaemia associated with CKD is that which confers the most benefit and least adverse effect in the most cost-effective way.

The key questions are:

- Do patients with higher haemoglobin levels do well because they are less sick, and is it because they are less sick that they attain higher haemoglobin levels?
- Or is there a causal relationship between higher haemoglobin levels and lower risks of morbidity and mortality, and if so what is the optimal haemoglobin range to be maintained?

6.9.4 Health economics methodological introduction [2006, deleted]

A cost-utility analysis study was appraised, which estimated the incremental cost per QALY of treating haemodialysis patients with epoetin doses adjusted to attain haemoglobin target ranges of 9.5 to 10.5 g/dl, 11.0 to 12.0 g/dl, 12.0 to 12.5 g/dl and 14.0 g/dl.208

An economic model was constructed to evaluate the cost effectiveness of various haemoglobin ranges in haemodialysis patients. Full details are given in Appendix C.

6.9.5 Health economics evidence statements [2006, deleted]

An additional $55,295 per additional QALY gained (95% CI: $51,404–$59,822) was required to achieve the target haemoglobin range of 11.0–12.0 g/dl vs a 9.5–10.5 g/dl haemoglobin target range[323].

An additional $613,015 per additional QALY gained (95% CI: $569,884–$663,210) was required to achieve the target haemoglobin range of 12.0–12.5 g/dl vs a 11.0–12.0 g/dl haemoglobin target range[323].

An additional $828,215 per additional QALY gained (95% CI: $769,942–$896,030) was required to achieve the target haemoglobin of 14.0 g/dl vs a 12.0–12.5 g/dl haemoglobin target range[323].

The dose of epoetin and the estimate of health-related quality of life had the largest effect on results in the sensitivity analysis, assuming 32% (base-case assumes 14%) lower dose requirement for subcutaneous epoetin than intravenous epoetin:

Health economic modelling

The economic model presented to the GDG stated in conclusion: 'The results suggest that treating anaemia with a target Hb 11–12 g/dl is cost effective in haemodialysis patients based on a £30,000 (incremental cost-effectiveness ratio) threshold. However, there is uncertainty in the results of the model from lack of certainty in the input parameters. Nevertheless, the results are relatively robust based on one-way sensitivity analyses and threshold analyses. This analysis is a simplified model of the costs and benefits of treating anaemia in the haemodialysis population and a variety of assumptions have been used in the baseline analysis'. See Appendix C for details.

6.9.6 From evidence to recommendations [2006, deleted]

The GDG noted that the largest meta-analysis considered was heavily skewed by one study that influenced the data on mortality[303]. This study of patients with cardiovascular disease was terminated early because of a trend towards increased mortality in the high target haemoglobin group. Thus statistical significance between the two groups could not be achieved. The GDG accepted that most of the studies it contained did not state their method of randomisation and were not adequately blinded; only two were carried out on an intention to treat basis[303]. It was noted that a target Hb level of 14 ± 1 g/dl (converted from Hct) was associated with higher mortality in a study

of patients with congestive heart failure and ischaemic heart disease. The GDG thought this may have related to the large doses of iron and epoetin that had to be administered in order for a sicker patient to achieve a haemoglobin in this range[303]. It was considered unhelpful both clinically and economically to administer increasing doses of epoetin and iron to a patient who was not responding adequately to the treatment. The GDG agreed with the authors of the meta-analysis that it would be prudent to ensure that patients with cardiovascular impairment maintain a Hb below 12.0 g/dl.

Recommendations [2006, deleted]

R33 In people with anaemia of CKD, treatment should maintain stable haemoglobin (Hb) levels between 10.5 and 12.5 g/dl for adults and children older than 2 years of age, and between 10 and 12 g/dl in children younger than 2 years of age, reflecting the lower normal range in that age group. This should be achieved by:

- Adjusting treatment, typically when Hb rises above 12.0 or falls below 11.0 g/dl.
- Taking patient preferences, symptoms and comorbidities into account and revising the aspirational range and action thresholds accordingly. (C)

R34 In people who do not achieve a haemoglobin level above 10.5g/dl (or 10.0 g/dl in children younger than 2 years of age) despite correction of iron deficiency and exclusion

of the known causes of resistance to ESA therapy (defined as treatment with≥300 IU/kg/week of subcutaneous epoetin or ≥450IU/kg/week of intravenous epoetinor 1.5µg/kg/week of darbepoetin), lower levels of haemoglobin may have to be accepted. (D(GPP))

See 3.2.3 for the associated algorithm.

Appendix C: Health economic model: target haemoglobin in haemodialysis patients [2006, deleted]

Background

The treatment of anaemia in CKD helps increase the health-related quality of life of patients. However, the optimal haemoglobin target continues to be debated. While there is an economic evaluation on the cost effectiveness of different targets based on US data, the lack of cost-effectiveness data in the UK warranted further investigation.

Aim

The aim of the model is to compare three alternative haemoglobin (Hb) targets in the anaemia management of haemodialysis patients over a 2-year period. The haemoglobin targets evaluated were: <11 g/dl, 11–12 g/dl and >12 g/dl. The cost per quality-adjusted life year gained was calculated.

Methods

A cost-effectiveness model was constructed from the perspective of the NHS. The effectiveness outcome measure used was quality-adjusted life years (QALYs) and the incremental cost per QALY was calculated. Point estimates are derived from probabilistic results.

Incremental cost per QALY = $(C_1 – C_2) / (Q_1 – Q_2)$

Where:

C1 = Estimated cost of anaemia treatment to reach Hb target

C2 = Estimated cost of anaemia treatment to reach higher Hb target

Q1 = Estimated quality-adjusted life years from Hb target

Q2 = Estimated quality-adjusted life years from higher Hb target

The data sources of the costs and benefits are described in further detail in Tables C.1–C.4. All costs and benefits were discounted at an annual rate of 3.5% in accordance with current NICE recommendations in their Guideline development methods 2005. Costs and benefits were accrued monthly over the 2-year period. A 1-month cycle was chosen as blood tests are routinely taken monthly in haemodialysis patients. A 2-year time horizon was chosen as it was considered a clinically relevant time period of treatment considering transplantation rates and survival on dialysis. The 11–12 g/dl haemoglobin target was selected based on the GDG's interpretation of the clinical data. This alternative was compared with below 11 g/dl and above 12 g/dl to assess the cost effectiveness of these alternative strategies. All costs are in pound sterling with base-year 2005. One-way sensitivity analysis and a cost-effectiveness acceptability curve were constructed to assess the impact of uncertainty on the incremental cost-effectiveness ratio (ICER). Threshold analyses were performed to investigate the value of the utility of Hb target 11–12 g/dl for which the ICER becomes £30,000.

Data sources and assumptions

Tables C.1–C.4 list the baseline cost and effectiveness outcomes along with the sources of data. Assumptions and methods of calculating estimates are described in further detail below.

Table C.1: Dose of ESA for each Hb target range

Model target Hb (g/dl)	Hb target in source study (g/dl)	Type of ESA	IU/wk	Source
<11	10 + 1	Epoetin-alfa	10,671 (SD 7,236, n=18)	[275]
11–12	>11.0	Epoetin-alfa/beta s.c. and i.v.	10,831 (n=189)*	[135]
>12	13.5–16.0	Epoetin-alfa s.c.	236 (U/kg/wk) (SD 148, n=157)	[114]
			15,340** (SD 148.3, n=157)	(Estimate)
* No standard deviation given in study. Assumed same %SD of IU/wk as <11. (67.8%, estimated SD 7,344).				
** Assuming 65 + 10 kg average weight.				

Mean epoetin values in Table C.1 were derived from RCT data where possible and selected based on the target haemoglobins in the studies being the closest to <11, 11–12 and >12 g/dl.

The cost of epoetin was calculated using a unit cost of £7.96 for 1,000 units of epoetin alfa and pre-filled syringe from the British national formulary (BNF) 49

Table C.2: Calculations per month

IU/month of ESA	Cost per month (£)
46,398.80	369.33
47,094.50	374.87
66,700.18	530.93

Table C.3: All-cause mortality46

Hb (g/dl)	Deaths/1,000 treatment-yr (adjusted)*	RR (adjusted) per month cycle: (mortality rate, standard error)	Deaths/1,000 treatment-yr (unadjusted)
< 11	249	1.25 (.021, .0045)	259
11–12	199	1 (.016, .0040)	199
>12	197	0.99 (.016, .0040)	192
* Calculated using unadjusted rate and RR.			

Table C.4: Utility score

Model target Hb (g/dl)	Hb target in source study (g/dl)	Value	Measurement technique	n	Source
< 11	9.5–11.0 (10.2 + 1.0)	0.51	Time trade off	34	[2]
11–12	-	0.545	–		(estimate)*
>12	11.5–13.0 (11.7 + 1.4)	0.58	Time trade off	33	[2]
* Estimated the utility score of the Hb target 11–12 g/dl as the midpoint between the values for target Hb<11 and Hb>12. (.545).					

Model target Hb (g/dl)	Hb target in source study (g/dl)	Value	Measurement technique	n	Source
Note: no standard deviation given in study. Standard error of .02 (~10%SD) for each utility value.					

Explanation of assumptions and data used

Costs

Only costs specific to anaemia treatment rather than haemodialysis care and those that are different between the treatment strategies were included.

Hb target <11 g/dl

The monthly cost of reaching the Hb target was derived from the mean dose of ESA per week used in a randomised open-label trial comparing target Hb of 10 + 1 g/dl and 14 + 1 g/dl in 35 dialysis patients[275] and the unit cost of epoetin alfa in a pre-filled syringe. The total cost of care per patient was considered stable for the 2-year period.

Hb target 11–12 g/dl

The monthly cost of Hb target 11–12 g/dl was derived from the mean epoetin dose from the Results of the European Survey on Anaemia Management in 2003 (ESAM)[135] based on 189 haemodialysis, haemofiltration and haemofiltration patients in the UK and the unit cost of epoetin alfa in a pre-filled syringe.

Hb target >12 g/dl

The monthly cost of Hb target >12 g/dl was derived from the mean U/kg/week of epoetin from a randomised controlled trial of 157 haemodialysis patients treated to a target Hb range of 13.5–16.0 g/dl and the unit cost of epoetin alfa in a pre-filled syringe. It was assumed an average patient would be 65 + 10 kg in order to calculate the mean units/week.

Other cost drivers that were assumed to be the same regardless of the Hb target range were:

- consultation time and type of health professional responsible for anaemia management
- iron strategy
- haemodialysis treatment (considered part of standard care).

Quality-adjusted life years

Hb target <11 g/dl, Hb target >12 g/dl

The quality of life in Hb target <11 g/dl and Hb target >12 g/dl were derived from a randomised study comparing placebo, 9.5–11.0 g/dl and 11.5–13.0 g/dl achieved Hb ranges in 118 haemodialysis. The results from the time trade off technique were used as the QALY weight in the estimation of QALYs. Although these were achieved Hb ranges, it was assumed that a target of >12 g/dl or <11 g/dl would have achieved haemoglobin levels similar to these ranges. Total QALY gain in each month cycle was added with a 3.5% annual discount rate.

Hb target 11–12 g/dl

The quality of life in target Hb 11–12 g/dl was estimated as the midpoint between the values for target Hb <11 and Hb >12. (.545) This method of estimation was chosen on the following reasoning from the clinical evidence:

In quality of life studies > 6 months in duration there is statistically significant quality of life improvement in certain dimensions such as physical functioning.

There is significant improvement between 9.0–12.0 and 13.5–16.0 g/dl[114], 10 and 14 g/dl[35] and 10.2 and 12.5 g/dl[206]. There is improvement (but not significant) between 9.5–11.0 and 11.5–13.0[2]. This suggests that the quality of life between 11 and 12 is probably not the same as >12, and probably is slightly less than it is in Hb >12 and more than <11, suggesting a linear estimation is reasonable.

Additional assumptions

- There is no increased risk of access failure or hypertension with higher haemoglobin targets.
- Concordance.
- Rate of transplantation is equivalent in each treatment strategy.
- Dialysis adequacy is equivalent in each treatment strategy.
- Mean epoetin doses remain representative of costs over a 2-year period.
- There is no difference in hospitalisation rates with different haemoglobin targets.

Observational studies suggest a difference in the number of hospitalisations and reduction in duration of stays[60,206], however, it is very possible these values were not adjusted sufficiently for confounders. Two RCTs[35,114] and the meta-analysis[303] indicate there is no significant difference in rate and days of hospitalisation. Therefore, the rate of hospitalisation was not used in the model to differentiate between Hb targets.

Mortality rates

The mortality rates used in the model were derived from the adjusted relative risk of death and all-cause mortality rates in patients in an observational study of 66,761 patients[60]. The GDG felt the evidence on mortality in the meta-analysis[303] may be more biased by the weight given to one study on patients with cardiovascular disease[35] than the observational study.

Results

Table C.5: Probabilistic model results: 2-year time horizon

Hb range (g/dl)	Cost (£)	QALYs
<11	7,202	0.79
11–12	7,750	0.90
>12	10,993	0.97

Table C.6: Probabilistic incremental results of baseline values

Hb range (g/dl)	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
11–12 vs <11	548	0.11	4,985
>12 vs 11–12	3,242	0.07	47,458
Note: differences due to rounding.			

Sensitivity analysis

The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables used in the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at baseline values. The variables included reflect the mortality rates, costs, utilities and hospitalisation rates used in the deterministic model. Results for the upper and lower estimates are given in Tables C.7 and C.8.

Table C.7: One-way sensitivity analysis

Variable	Baseline value	Range evaluated	Hb comparison	ICER range estimate (dominant strategy)
RR death Hb <11	1.25	1.20 1.30	11–12 vs <11	4,369 4,999
RR death Hb >12	0.99	0.92 1.07	>12 vs 11–12	46,906 69,224
Cost per month cycle Hb <11 (£)	369.33	118.89 619.78	11–12 vs <11	55,808 Hb11–12
Cost per month cycle Hb 11–12 (£)	374.87	120.67 629.07	11–12 vs <11	Hb11–12 59,007
			>12 vs 11–12	143,557 Hb>12
Cost per month cycle Hb >12 (£)	530.93	525.80 536.07	>12 vs 11–12	53,026 56,617
Utility Hb <11	0.51	0.46 0.56	11–12 vs <11	2,589 26,632
Utility Hb 11–12	0.55	0.49 0.60	11–12 vs <11	61,140 2,454
			>12 vs 11–12	21,856 Hb11–12
Utility Hb>12	0.58	0.52 0.64	>12 vs 11–12	Hb 11–12 21,018

Table C.8: Sensitivity analysis of hospitalisation risks and costs

	Baseline Estimates (No difference)	Observational Study Estimates	Cost of hospitalisation (£)
RR of hospitalisation Hb <11	1.0	1.21	2,190
RR of hospitalisation Hb 11–12	1.0	1.0	
RR of hospitalisation Hb >12	1.0	0.78	
ICER Hb11–12 vs Hb<11	4,719	1,444	
ICER Hb>12 vs Hb11–12	54,822	41,481	
ICER Hb11–12 vs Hb<11		3,719	863 (lower estimate)
ICER Hb>12 vs Hb11–12		46,750	
ICER Hb11–12 vs Hb<11		84	2,983 (upper estimate)
ICER Hb>12 vs Hb11–12		38,333	

The extent of uncertainty in the probabilistic model is displayed in Figure C.1.

Figure C.2 summarises into probabilities the uncertainty that an alternative is cost effective for a range of willingness-to-pay thresholds.

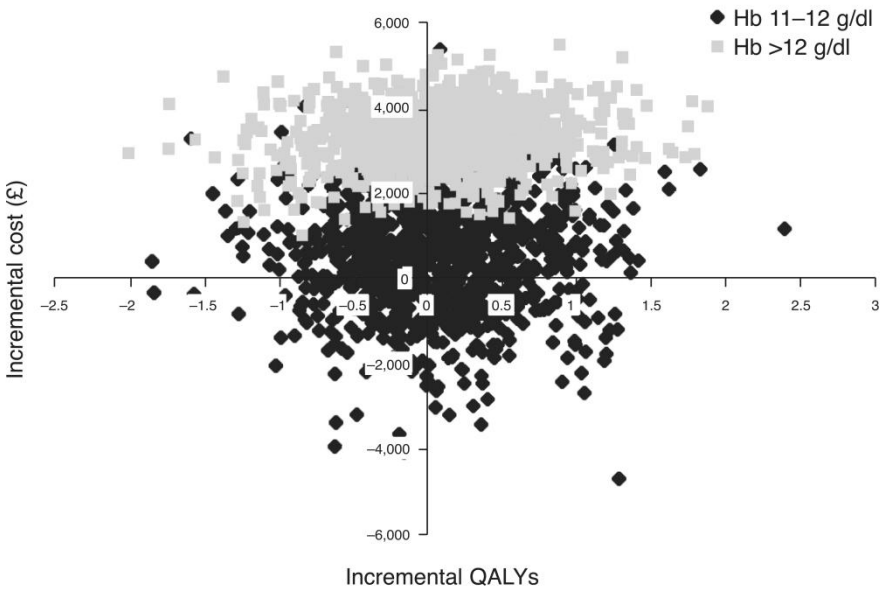


Figure C.1 Probabilistic sensitivity analysis results: incremental cost-effectiveness plane

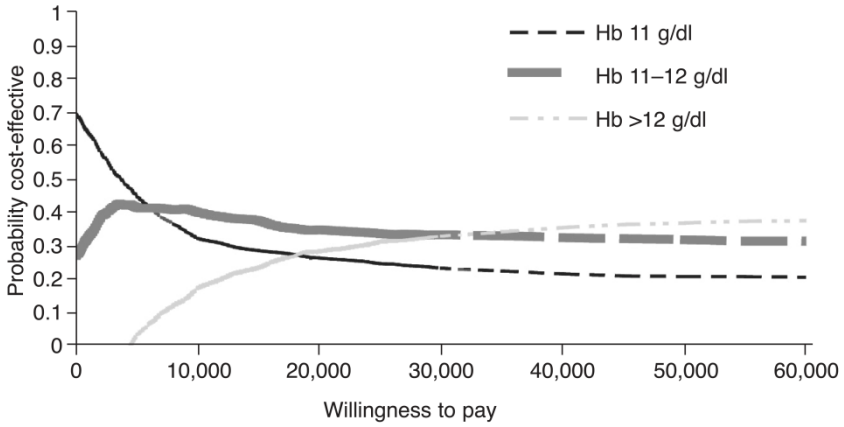


Figure C.2 Cost-effectiveness acceptability curve (£)

Discussion

Point estimates suggest Hb target 11–12 g/dl is the optimal strategy with a £20,000–30,000 threshold. Uncertainty was assessed in the deterministic results in a one-way and two-way sensitivity analyses (Tables C.7 and C.8). At the upper estimate of the monthly cost of Hb 11–12 (£629.07), target Hb 11–12 is dominated by Hb >12: the total costs in Hb 11–12 are higher than Hb >12 but results in less QALYs. While the upper estimate is a plausible estimate of Hb 11–12, it would mean the unlikely situation, in the absence of hospitalisation costs saved, where the monthly cost to reach Hb >12 is less than the monthly cost to reach Hb 11–12 (£530.93).

At the lower estimate of Hb 11–12 utility, the Hb 11–12 vs Hb<11 ICER increased to £61,140 and the Hb >12 vs Hb 11–12 ICER increased to £21,856. The lower estimate of Hb 11–12 (0.49) is less than the baseline estimate of Hb <11 (0.51), contrary to clinical evidence. Rather than make an assumption about the utility of Hb target 11–12 g/dl per month, if we allow the utility to vary, the value at which the ICER of 11–12 g/dl vs <11 g/dl target is £30,000 is 0.50. This would mean the utility

of target Hb 11–12 g/dl would have to be less than the utility of target Hb <11 g/dl (0.51) in order for the target Hb 11–12 g/dl not to be cost effective as defined by an ICER of £30,000 or less.

At the higher estimate of Hb 11–12 utility, Hb 11–12 vs Hb <11 ICER decreased to £2,454 and the Hb 11–12 dominates Hb >12 (in this case Hb 11–12 costs less with more QALYs gained). This is reasonable as the same costs and more QALYs gained in Hb 11–12 will result in more favourable ICERs.

At the lower estimate of the utility of Hb >12, the Hb 11–12 strategy dominates Hb >12 (in this case Hb 12 costs more with less QALYs gained), however, at the upper estimate, the Hb >12 vs Hb 11–12 ICER decreased to £21,018.

Similarly, if we allow the utility of target Hb 11–12 g/dl to vary, the value at which the ICER of >12 g/dl vs 11–12 g/dl is £30,000 is 0.52. This would mean the utility of target Hb 11–12 g/dl would be much closer to the Hb <11 g/dl (0.51) rather than the utility of target Hb >12 g/dl (0.58) in order for the target Hb >12 g/dl to be cost effective as defined by an ICER of £30,000 or less.

If the baseline rates of hospitalisations are changed from the assumption that rates are equivalent in each Hb target to the adjusted rates in the observational study[60], hospitalisation requires a cost. The national average unit cost of acute renal failure (£2,190) with upper (£2,983) and lower (£863) ranges of this unit cost was used in the sensitivity analysis of hospitalisation rates. ICERS with the lower and upper range of this unit cost were calculated to assess if there was an effect of the size of the cost of hospitalisation on the results. The Hb 11–12 vs Hb <11 ICER decreased from 4,719 to 1,444 (hospitalisation cost £2,190), 3,719 (hospitalisation cost £863) and 84 (hospitalisation cost £2,983) further in favour of Hb 11–12. The ICER Hb >12 vs Hb 11–12 also decreased 54,822 to 41,481 (£2,190), 46,750 (£863), 38,333 (£2,983). However these remain above a £30,000 cost-effectiveness threshold.

In probabilistic analysis, each parameter is assigned a distribution such as beta, normal, gamma and so on, and random values from these distributions are used to derive cost-effectiveness results. The extent of uncertainty in the model is displayed in Figure C.1. The scatter of the estimates indicates a high degree of uncertainty over the four quadrants. The cost-effectiveness acceptability curve (CEAC) (Figure C.2) summarises the uncertainty of the results. For every value on the x-axis third-party payers are willing to pay, the probability the alternative is cost effective is indicated on the y-axis. Between £20,000 to £30,000 willingness-to-pay threshold, the Hb target 11–12 g/dl has the highest probability of cost effectiveness (0.378 to 0.365), suggesting Hb 11–12 g/dl is the best choice of the three alternatives. Even though the strategy has the highest probability of cost effectiveness, there still is a large amount of uncertainty that could be improved with better data, especially compared with >12 g/dl.

The benefits in this model were assessed for a 2-year period only. This means life-time costs and benefits of treatments were not analysed. Also, the results were based on haemodialysis patients, rather than all CKD patients. If possible, randomised studies with target haemoglobin ranges corresponding to <11, 11–12 and >12 g/dl were selected. However, individuals will clinically respond differently to epoetin and there may be different distributions of achieved haemoglobin across the haemodialysis population with particular haemoglobin targets. The number of people who achieved the target was not taken into account in the selection of the data sources because of the limited reporting in the literature. The mean epoetin value for the <11 g/dl was based on an appropriate study target range, but there was a small number of patients[275]. The 11–12 g/dl epoetin value was based on a European survey where guidelines suggest an 11–12 g/dl target. The target haemoglobin range in the[114] study was 1.5 g/dl higher than 12, which may have increased the amount of epoetin needed to reach higher than 12 while the quality of life data was from a lower haemoglobin (11.5–13.0 g/dl). The mean epoetin data sources combined three haemodialysis populations from the USA, UK and Scandinavia potentially reducing the generalisability to the UK population. Therefore this is a preliminary analysis until further economic and clinical outcomes are measured.

The results are similar to the US study[323] that found dosing epoetin to Hb >12.0 g/dl had unfavourable cost-effectiveness ratios. However, comparative target Hb ranges, costs included, such as cost of hospitalisation, haemodialysis care, renal transplantation, epoetin dosages and time horizon (life-time of patient) were different between the studies which may make comparing direct results inappropriate. Of note, the incremental cost per QALY gained in the 12.0–12.5 vs 11.0–12.0 g/dl comparison was approximately 11 times greater than the 11.0–12.0 vs 9.5–10.5 g/dl in the US study, whereas in this UK analysis the >12 vs 11–12 is approximately 9.5 times greater than the 11–12 vs <11 g/dl incremental cost per QALY gained.

Conclusion

The results suggest treating anaemia with a target Hb 11–12 g/dl is cost effective in haemodialysis patients based on a £30,000 threshold. However, there is uncertainty in the results of the model from lack of certainty in the input parameters. Nevertheless, the results are relatively robust based on one-way sensitivity analyses and threshold analyses. This analysis is a simplified model of the costs and benefits of treating anaemia in the haemodialysis population and a variety of assumptions have been used in the baseline analysis. Therefore, the results should be interpreted correspondingly.