MHRA Public Assessment Report

Epoetins for the management of anaemia in patients with chronic renal disease: mortality and cardiovascular morbidity

November 2007

EXECUTIVE SUMMARY

Epoetins are authorised for the treatment anaemia in people with chronic renal disease. Four epoetins are authorised in the UK: epoetin alfa (Eprex); darbepoetin alfa (Aranesp); epoetin beta (NeoRecormon); and epoetin delta (Dynepo).

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices work and are acceptably safe. Evidence-based judgments underpin the Agency's work to ensure that the benefits to patients and the public justify the potential risks. The MHRA keeps the safety of all medicines—including epoetins—under continual review.

The Commission on Human Medicines (CHM) advises ministers on the quality, safety, and efficacy of medicines. The Commission has recently assessed the safety of epoetins. This Public Assessment report summarises the data reviewed by CHM that suggest an increased risk of serious and potentially fatal cardiovascular events (eg, heart attack, stroke, heart failure, and sudden death) associated with epoetins for treatment of anaemia in patients with chronic kidney disease.

The results of two studies and a meta-analysis that have recently been published suggest that treatment of anaemia with epoetins in patients with chronic kidney disease to achieve relatively high target haemoglobin concentrations may be associated with increased risk of mortality and cardiovascular morbidity.

The first trial (the CHOIR study) compared risk of death and cardiovascular complications in 1432 patients with chronic renal disease who were treated with epoetin alfa to achieve either a high haemoglobin concentration (13·5 g/dL) or a low haemoglobin concentration (11·3 g/dL). Patients who were given epoetin alfa to achieve a haemoglobin concentration of 11·3 g/dL had a statistically significantly longer time to the composite endpoint of death, myocardial infarction, hospitalisation for congestive heart failure (excluding renal-replacement therapy), or stroke than did those treated to achieve a haemoglobin concentration of 13·5 g/dL. Groups did not differ in quality of life (the main marker for benefit in this trial).

The outcome of the trial tends to favour the low-haemoglobin treatment group, and suggests that the balance of risks and benefits of treatment to achieve a haemoglobin concentration of 11·3 g/dL may be more favourable than that of treatment to achieve higher haemoglobin concentrations. The outcome seems to be driven mainly by the greater proportion of deaths from any cause and of patients who developed congestive heart failure in the group treated to achieve higher haemoglobin concentrations. The frequency of serious adverse reactions was higher in the high-target haemoglobin group compared with low (1·5% *vs* 0·4%), most of which were thrombovascular complications in both treatment groups.

The second study (the CREATE study) compared cardiovascular outcomes in 603 patients with chronic kidney disease and anaemia treated with epoetin beta to achieve a haemoglobin concentration of either 10·5–11·5 g/dL or 13·0–15·0 g/dL.

Groups did not differ significantly in the frequency of death from cardiovascular causes, or in time to death from cardiovascular causes or all causes. Such trends as there were in death from any cause and cardiovascular morbidity consistently favoured the low target haemoglobin group, but differences between groups were very small. There were no differences between groups for reporting of thrombotic complications.

Both CHOIR and CREATE showed no benefit for correction of haemoglobin concentration to higher levels compared with correction to lower levels. Assuming either

the same degree of cardiovascular risk for both treatment strategies, or a slightly lower risk for the low-target haemoglobin group (as suggested by CHOIR), and given the small trends evident in CREATE, there seems to be little justification for the correction of haemoglobin concentration beyond the minimum that is compatible with good control of symptoms of anaemia in patients with chronic kidney disease.

A meta-analysis of 9 prospective randomised controlled trials (5143 patients) assessed death from any cause and cardiovascular events (ie, myocardial infarction, change in blood pressure, arteriovenous access thrombosis) and effects on left ventricular mass associated with treatment with epoetins to achieve different ranges of haemoglobin concentration in trials of patients with anaemia due to chronic kidney disease. The results suggest an increased risk of death from any cause in patients with anaemia associated with chronic kidney disease who are treated to achieve a haemoglobin concentration between 12 g/dL and 16 g/dL compared with those treated to achieve a haemoglobin concentration less than 12 g/dL. Furthermore, the risk of arteriovenous access thrombosis and poorly controlled hypertension seems to be increased in such patients. However, the risk of myocardial infarction does not seem to be affected by the choice of target haemoglobin concentration.

The meta-analysis assessed neither the risk of thrombotic complications (other than myocardial infarction and shunt thrombosis) nor the risk of congestive heart failure. The risks attributable to these and other cardiovascular events may account for the persistent trend for higher all-cause mortality that seems to be developing as more clinical study data become available for survival in relation to the target haemoglobin concentration in the management of anaemia in chronic renal disease.

The best estimate of relative risk of death associated with higher target haemoglobin concentrations is 1·17 (–0·01 to 1·35). Relative risks recorded in the studies that were included in the meta-analysis ranged from 0·17 to 1·48. These estimates are not greatly elevated and may be due to residual confounding factors, which it has not been possible to take into account in the analyses.

There is little, if any, evidence that correction of haemoglobin concentration to within the range 12–16 g/dL has any clinically meaningful benefits that cannot be gained from correction to less than 12 g/dL. Given the lack of evidence of benefit, it would be a sensible precaution to consider reducing the apparent risks to patients by avoiding the correction of anaemia to haemoglobin concentrations that are greater than may be necessary to control symptoms of anaemia, and preferably not to concentrations above 12 g/dL. Patients with pre-existing cardiovascular risk factors may need closer medical supervision than those who do not.

Members of the Commission on Human Medicines postulated that the apparent excess mortality associated with epoetin use may not be attributable solely to thrombosis and related complications, but may also be due to aggravation of hypertension in patients with chronic renal disease or sudden death due to uraemic cardiomyopathy.

The Commission advised that the evidence would support correction of anaemia to a maximum haemoglobin concentration of 12 g/dL, possibly with a lower maximum in women and children. The purpose of treatment with epoetins is to relieve symptoms of anaemia and to avoid the need for blood transfusion. The Commission advised treatment with epoetins should be appropriately adjusted when symptoms of anaemia have been adequately brought under control, irrespective of haemoglobin concentration.

The Commission also advised that the evidence of risk associated with overcorrection of haemoglobin concentration should be brought to the attention of the athletic community in order to minimise risk and discourage abuse of epoetins.

1 INTRODUCTION

Epoetins are authorised for the treatment anaemia in people with chronic renal disease. Four epoetins are authorised in the UK: epoetin alfa (Eprex); darbepoetin alfa (Aranesp); epoetin beta (NeoRecormon); and epoetin delta (Dynepo).

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices work and are acceptably safe. Evidence-based judgments underpin the Agency's work to ensure that the benefits to patients and the public justify the potential risks. The MHRA keeps the safety of all medicines—including epoetins—under continual review.

The Commission on Human Medicines (CHM) advises ministers on the quality, safety, and efficacy of medicines. The Commission has recently assessed the safety of epoetins. The advice of CHM was fed into a Europe-wide review co-ordinated by the European Medicines Agency (Dynepo, Aranesp and NeoRecormon have centralised European licences). This Public Assessment report summarises the data reviewed by CHM that suggest an increased risk of serious and potentially fatal cardiovascular events (eg, heart attack, stroke, heart failure, and sudden death) associated with epoetins for treatment of anaemia in patients with chronic kidney disease. The results of two studies and a meta-analysis have recently been published, which suggest that treatment of anaemia with epoetins in patients with chronic kidney disease may under some circumstances be associated with an increased risk of mortality and cardiovascular morbidity.[1–3]

Table 1 shows the currently authorised renal indications for the four epoetins that are authorised in the European Union (EU).

Table 1: Authorised renal indications for the epoetins authorised in the EU

	Authorised indications in the EU
Epoetin alfa (Eprex)	• Anaemia associated with chronic renal failure in children and adults on haemodialysis and adults on peritoneal dialysis • Severe anaemia of renal origin accompanied by clinical symptoms in adults with renal insufficiency who are not yet undergoing dialysis
Epoetin beta (Neorecormon)	• Anaemia associated with chronic renal failure in patients on dialysis • Symptomatic renal anaemia in patients not yet undergoing dialysis
Darbepoetin alfa (Aranesp)	• Anaemia associated with chronic renal failure in adults and children age 11 years or older.
Epoetin delta (Dynepo)	• Anaemia in adults with chronic renal failure

2. EPOETINS FOR ANAEMIA ASSOCIATED WITH CHRONIC RENAL DISEASE

2.1 Correction of Haemogloblin and Outcomes In Renal insufficiency (CHOIR)

This US study was reported by Singh and colleagues.[1]

Objectives

To compare the risk of death and cardiovascular complications in patients with chronic renal disease treated with epoetin alfa to achieve either a high haemoglobin concentration (13·5 g/dL) or a low haemoglobin concentration (11·3 g/dL).

Trial design

Multicentre, randomised, open-label trial of adults who were not receiving dialysis. Baseline haemoglobin concentration was required to be less than 11 g/dL. Estimated glomerular filtration rate (GFR) was required to be 15–50 mL per minute per 1·73 m^2 body-surface area. Patients were excluded if they had uncontrolled hypertension, active gastrointestinal bleeding, iron-overload state, history of frequent transfusions in the previous 6 months, refractory iron-deficiency anaemia, active cancer, previous treatment with epoetin alfa, or angina pectoris that was unstable or present at rest.

The first patients to enter the study were randomly allocated epoetin alfa to attain either a high haemoglobin concentration (13·0–13·5 g/dL) or a low haemoglobin concentration (10·5–11·0 g/dL). The study protocol was amended after about 25% of the total number of patients had been recruited (at the same time the proportion of the total observation time that had accrued was only 6·8%): target haemoglobin concentrations were changed to 13·5 g/dL and 11·3 g/dL, respectively. Epoetin alfa was given subcutaneously either weekly or fortnightly to maintain a stable haemoglobin concentration.

The primary endpoint was the time to the composite of death, myocardial infarction, hospitalisation for congestive heart failure (excluding renal-replacement therapy), or stroke. Secondary outcomes included time to renal-replacement therapy, hospitalisation due to cardiovascular cause or any cause, and quality of life.

4 interim analyses were planned (only 2 of which were done). Study power was set at 80% to detect a 25% risk reduction in the composite event in the high-haemoglobin group over 3 years, assuming: a 30% event frequency in the low-haemoglobin group; the occurrence of at least 295 composite events overall during the 3-year period, a 30% frequency of early withdrawal for reasons other than the occurrence of the primary endpoint; and a type I error of 0·05. An independent Data and Safety Monitoring Board reviewed the study.

The Kaplan-Meier method was used to analyse the time to the first event during the study period. Log-rank test was used to compare the times to the first event between the two groups. Repeated-measures analysis of variance was used to assess haemoglobin measurements over time.

Results

The study was terminated prematurely on the recommendation of the Data and Safety Monitoring Board because the conditional power to show a benefit for the high-haemoglobin group by the scheduled end of the study was less than 5% for all plausible values of the true effect for the remaining data. The Board also took into account differences between groups in adverse events, biochemical data, and quality-of-life data.

1432 patients were enrolled, 715 of whom were assigned to the high target haemoglobin group. Men and women were equally represented in both treatment groups. Mean ages in both treatment groups were also similar (about 66 years). The baseline characteristics of both treatment groups were similar in all relevant respects.

Mean baseline haemoglobin concentration in both groups was 10·1 g/dL. Mean haemoglobin concentrations increased in the high-target haemoglobin group by 2·5 g/dL (mean haemoglobin achieved 12·6 g/dL), and in the low target haemoglobin group by 1·2 g/dL. The mean dose of epoetin alfa that was needed to maintain the target level in the high-haemoglobin group was nearly twice that of the low-haemoglobin group (11 215 U *vs* 6276 U per week, respectively). The median time for patients in the high-haemoglobin group to reach the target of 13·5 g/dL was 126 days (95% CI 113–139) compared with 36 days (95% CI 29–43) to reach the target level of 11·3 g/dL for patients in the low-haemoglobin group ($p<0·001$).

Table 2 shows the outcome for the study endpoints. In the primary analysis of composite events, a patient was counted only once irrespective of how many of the composite events they may have had (eg, death and myocardial infarction, whichever event occurred first). In the analysis of secondary outcomes for the components of the primary composite endpoint, every event was counted once (**table 2**). Death and hospitalisation for congestive heart failure accounted for 74·8% of the composite events. This finding is reflected in the higher risk of death and hospitalisation for congestive heart failure noted when these endpoints were analysed separately, although neither hazard ratio achieved statistical significance (**table 2**). The risk of myocardial infarction and stroke did not differ between groups.

Patients were withdrawn from the study if they needed renal-replacement therapy. There was no significant difference between groups in the proportion of patients who needed such therapy ($p=0·15$; **table 2**). Sensitivity analysis was done to assess whether the outcome could have been biased by early withdrawal due to the need for renal-replacement therapy. When the time to composite events was analysed in combination with time to renal-replacement therapy, the hazard ratio (HR) still favoured the low-target haemoglobin group (HR 1·28 [95% CI 1·07–1·54], $p=0·007$).

There were no meaningful differences between groups for quality-of-life scores.

Table 2: Study endpoints—outcome (intent to treat analysis)

	High haemoglobin group	Low haemoglobin group	Hazard Ratio (95% CI)	p
	n=715	**n=717**		
Primary composite endpoint				
(death, myocardial infarction, hospitalisation for congestive heart failure [excluding renal-replacement therapy], or stroke)	125 (17·5%)	97 (13·5%)	1·34 (1·03–1·74)	0·03
Secondary endpoints				
Components of primary endpoint				
Death	52 (7·3%)	36 (5·0%)	1·48 (0·97-2·27)	0·07
Hospitalisation for congestive heart failure (excluding renal-replacement therapy)	64 (9·0%)	47(6·6%)	1·41 (0·97–2·05)	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
Renal-replacement therapy				
Any renal-replacement therapy	155 (21·7%)	134 (18·7%)	1·19 (0·94–1·49)	0·15
Hospitalisation for renal replacement therapy	99 (13·8%)	81 (11·3%)	1·25 (0·93–1·68)	0·13
Hospitalisation				
Cardiovascular causes	233 (32·6%)	197 (27·5%)	1·23 (1·01–1·48)	0·03
Any cause	369 (51·6%)	334 (46·6%)	1·18 (1·02–1·37)	0·03

The reporting of adverse events was compared between treatment groups by use of the χ^2 test (**table 3**). Overall reporting of adverse events, thrombovascular events, and clinically relevant thrombovascular events did not differ between treatment groups. There were statistically significantly more serious adverse events in the high-haemoglobin treatment group, and serious adverse reactions were of borderline statistical significance for this group. There were statistically significantly more reports of congestive heart failure in the high-haemoglobin treatment group compared with the low-haemoglobin group. Incidence of myocardial infarction was higher in the low-haemoglobin group than in the high-haemoglobin group (2·8% *vs* 1·5%, p=0·09).

Table 3: Adverse events

	High-haemoglobin group	Low haemoglobin group	p
	n=686*	**n=688***	
Any event	607 (88·5%)	589 (85·6%)	0·11
Thrombovascular events			
Any thrombovascular event	126 (18·4%)	120 (17·4%)	0·65
Clinically relevant events (myocardial infarction, stroke, angina pectoris, transient ischaemic attack, deep-vein thrombosis, pulmonary embolism, and retinal-vein occlusion)	74 (10·8%)	82 (11·9%)	0·51
Serious adverse events	376 (54·8%)	334 (48·5%)	0·02
Serious adverse reactions (treatment-related)	10 (1·5%)†	3 (0·4%)‡	0·05
Serious adverse events			
Congestive cardiac failure	77 (11·2%)	51 (7·4%)	0·02
Myocardial infarction	10 (1·5%)	19 (2·8%)	0·09
Renal failure	95 (13·8%)	73 (10·6%)	0·07

*Patients who received at least one dose of study drug for whom adverse-event data were actually collected. †Deep-vein thrombosis (two cases) and one case each of: pulmonary embolism; retinal-vein occlusion; transient ischaemic attack; deep-vein thrombosis and pulmonary embolism; priapism; rash; allergic dermatitis; and unstable angina. ‡One case each of: hypertension; pulmonary embolism; and stroke.

Summary

CHOIR shows that patients with renal failure who are not yet receiving dialysis and who were treated with epoetin alfa to achieve a haemoglobin concentration of 11·3 g/dL had a statistically significantly longer time to the composite endpoint of death, myocardial infarction, hospitalisation for congestive heart failure (excluding renal-replacement therapy), or stroke than did those treated to achieve a haemoglobin concentration of 13·5 g/dL. Groups did not differ significantly for individual components of the composite endpoint, although there was a trend for increased risk of death and congestive heart failure (excluding renal-replacement therapy) in the high-haemoglobin group.

There were no meaningful differences between the two treatment groups in terms of quality-of-life scores (the main marker for benefit in this trial).

The outcome of the trial tends to favour the low-haemoglobin treatment group, and suggests that the balance of risks and benefit of epoetin treatment to achieve a haemoglobin concentration of 11·3 g/dL may be better than that of epoetin treatment to achieve higher haemoglobin concentrations. The outcome seems to be driven mainly by a greater proportion of deaths from any cause and of patients who developed congestive heart failure in the group treated to achieve higher haemoglobin concentrations.

MHRA Assessor's comment: Evidence for a clinically significant difference in the frequency of thrombovascular events between treatment groups in this trial is not strong. There was no difference between groups in the frequency of thrombovascular events overall. The proportion of patients who had myocardial infarction in the low-haemoglobin group was higher than in the high-haemoglobin group. The strongest suggestion for a difference in the frequency of thrombovascular complications is a higher number of serious adverse reactions in the high-haemoglobin group (1·5% *vs* 0·4%), most of which were thrombovascular complications in both treatment groups.

CHOIR was an open-label study and therefore the possibility that the observations may have been influenced by observation bias cannot be excluded, particularly for the reporter's assessment of the causal association between reported events and the treatment given. Caution should be exercised in the drawing of inferences from differences in the reporting of serious adverse reactions between treatment groups.

There are discrepancies between the numbers of events reported for myocardial infarction in **table 2** and **table 3**: the numbers reported are higher in **table 2**, which may be due to the criteria used to define myocardial infarction for inclusion in the composite endpoint. For the composite endpoint, myocardial infarction was defined on the basis of any two of the following: chest pain lasting for 15 minutes; abnormal cardiac enzyme levels; or new findings on electrocardiography that suggested myocardial infarction. Furthermore, some myocardial infarctions that were diagnosed on the basis of this definition may not have fulfilled the criteria for the definition of serious (ie, life-threatening; resulting in death, hospitalisation, or substantial disability; or leading to a congenital anomaly or birth defect), which would also account for the discrepancy.

2.2 Cardiovascular Risk reduction by Early Anemia Treatment with Epoetin beta (CREATE)

This study was reported by Drueke and colleagues.[2] The study was conducted in 94 centres in 22 countries worldwide, excluding the USA.

Objective

To compare cardiovascular outcomes in patients with stage 3 or 4 chronic kidney disease and mild to moderate anaemia who were treated with epoetin beta to achieve a haemoglobin concentration of either 10·5–11·5 g/dL or 13·0–15·0 g/dL.

Trial design

Open-label, randomised, group-comparative study. The trial recruited adults with chronic anaemia due to renal disease (ie, haemoglobin concentration 11·0–12·5 g/dL), GFR 15·0–35·0 mL/min/1·73 m^2 body surface area, and a blood pressure of 170/95 mmHg or less. Patients were excluded if there was an anticipated need for renal-replacement therapy in the next 6 months, or if they had advanced cardiovascular disease (ie, clinically significant valvular disease, congestive heart failure, myocardial infarction, unstable angina, or stroke in the past 3 months). Patients were not allowed to have had a blood transfusion within 3 months of starting the trial and should not have been treated previously with an epoetin.

Patients were randomly assigned to epoetin beta subcutaneously once weekly to correct anaemia to the target range 13·0–15·0 g/dL (high-target haemoglobin group), or to epoetin beta only when haemoglobin concentration had declined to less than 10·5 g/dL to correct anaemia to the target range 10·5–11·5 g/dL (low-target haemoglobin group). Randomisation was stratified according to study site, previous cardiovascular risk, and estimated GFR. The dose of epoetin was adjusted as necessary every 4 weeks. The planned duration of the study was 2 years after the final patient had been randomised or after 200 cardiovascular events had occurred.

The primary endpoint was the time to first cardiovascular event, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalisation for at least 24 hours or prolongation of hospitalisation, complication of peripheral vascular disease (ie, amputation or necrosis), or cardiac

arrhythmia resulting in hospitalisation for 24 hours or more. Secondary endpoints included death from any cause; death from cardiovascular causes; congestive heart failure (according to New York Heart Association [NYHA] class); need for cardiovascular intervention; hospitalisation for any cause; hospitalisation for cardiovascular reasons for at least 24 hours or prolongation of hospitalisation; changes in left ventricular mass index, left ventricular volume, and left ventricular fractional shortening; time to initiation of renal-replacement therapy; changes in body-mass index, serum albumin level, and C-reactive protein level; changes in quality of life (SF-36); changes in haemoglobin concentration; changes in the weekly epoetin dose; need for dialysis; need for transfusion; and decrease in estimated GFR.

The primary endpoint was adjusted for the presence or absence of underlying cardiovascular disease at baseline and analysed by use of the log-rank test. A Cox proportional-hazards model was used to estimate HR with 95% CI. Times to events were expressed as Kaplan-Meier curves. A similar method was used to analyse secondary endpoints, time to death from cardiovascular causes, time to death from any cause, and time to dialysis. Analysis of covariance was used for secondary efficacy endpoints that were continuous variables, with baseline value and treatment as covariates.

Results

603 patients were randomised to treatment, 476 (79%) of whom completed the study (**table 4**). 2 patients were excluded before randomisation because of non-compliance with Good Clinical Practice at the centre where they were recruited. The study observation period was around 3 years.

Table 4: Patient disposition

	High-target haemoglobin group	**Low-target haemoglobin group**
	n (%)	**n (%)**
Randomised	301	302
Completed study	226 (75%)	250 (83%)
Withdrew prematurely	75 (25%)	52 (17%)
Died	21 (7%)	17 (6%)
Withdrew because of adverse event	17 (6%)	10 (3%)
Withdrew consent/co-operation	23 (8%)	14 (5%)

Patient demographics and baseline characteristics were generally similar between groups. However, there were small differences between groups in the mean weight (lower in the low-target haemoglobin group: 71·8 *vs* 74·7, p=0·05) and in the proportion of males (higher proportion in the high-target haemoglobin group: 57% *vs* 51%, p=0·16). These two observations are probably linked: males are on average heavier than females. Moreover, the use of beta-blockers was more common at baseline in the high-target haemoglobin group compared with the low-target group (43% *vs* 34%, p=0·02).

Both groups satisfactorily achieved the treatment objective (ie, achievement of intended target haemoglobin concentration).

At the end of the study, 58 patients in the high-target haemoglobin group and 47 in the low-target haemoglobin group had had a cardiovascular event (**table 5**). There was no statistically significant difference in the likelihood of a cardiovascular event (ie, primary endpoint) between the two treatment groups (HR 0·78 [95% CI 0·53–1·14]; adjusted p=0·2). The censoring of data at the time of initiation of dialysis did not significantly affect the HR for the primary endpoint (1·04 [95% CI 0·66–1·65]).

There were no significant differences between the two groups in: the incidence of death from any cause; incidence of death from cardiovascular causes; mean time to worsening of NYHA class heart failure; the proportion of patients undergoing cardiovascular intervention; incidence of hospital admission; or in mean duration of hospitalisation for cardiovascular reasons (**table 5**).

Table 5: Summary of results—CREATE

	Intervention		**Hazard ratio**	**95% CI**		**p**
	High target haemoglobin group	**Low target haemoglobin group**		**Lower**	**Upper**	
	n=301	n=302				
Primary endpoint						
Time to first cardiovascular event	58 (19%)	47 (16%)	0·78	0·53	1·14	0·20
Secondary endpoints						
Death (any cause)	31 (10%)	21 (7%)	0·66	0·38	1·15	0·14
Death (cardiovascular)	NS (4%)	NS (3%)	0·74	0·33	1·70	0·48
Mean time to worsening of NYHA class cardiac failure	NS	NS	NS	NS	NS	0·97
Cardiovascular intervention	NS (7%)	NS (6%)	NS	NS	NS	NS
Hospital admission	NS (61%)	NS (59%)	NS	NS	NS	NS
Mean duration of hospitalisation for cardiovascular reasons (days)	33·0	28·2	NS	NS	NS	NS

NS=not stated.

There were no significant differences between the two treatment groups in left ventricular mass index at any timepoint.

During the first year of the study, quality-of life assessments statistically significantly favoured the high-target haemoglobin group for general health, mental health, physical function, physical role, social function, and vitality. During the second year, a significant difference between groups was maintained for general health and vitality.

There were no substantial differences in adverse events between the two groups. There were statistically significantly more vascular disorders in the high-target haemoglobin group compared with low-target ($p<0·001$), mainly because of a greater frequency of hypertension, and there were more headaches (**table 6**). Arteriovenous fistula thrombosis occurred in 12 of 127 patients who underwent dialysis in the high-target haemoglobin group, and in 8 of the 111 patients who underwent dialysis in the low-target haemoglobin group (130 and 108 patient-years spent receiving dialysis, respectively).

Table 6: Summary of adverse events reported with a frequency of 5% or more

	High-target haemoglobin group		Low-target haemoglobin group		p
	n=300		n=302		
Cardiac disorders	73	24%	70	23%	0·78
Acute cardiac failure	13	4%	23	8%	0·11
Arrhythmia	18	6%	16	5%	0·78
Myocardial infarction	14	5%	15	5%	0·94
Angina pectoris	16	5%	7	2%	0·07
Vascular disorders	135	45%	89	29%	<0·001
Hypertension (systolic blood pressure >160 mmHg)	89	30%	59	20%	0·005
Peripheral vascular disorder	17	6%	8	3%	0·08
Nervous system disorders	77	26%	53	18%	0·02
Headache	31	10%	16	5%	0·03
Referral for unplanned investigation	45	15%	30	10%	0·07
Increased blood pressure	21	7%	13	4%	0·18
Other relevant adverse events					
Cerebrovascular accident	8	3%	5	2%	0·48
Transient ischaemic attack	5	2%	2	<1%	0·34
Arteriovenous fistula thrombosis	12	4%	8	3%	0·42
Arteriovenous fistula complication	8	3%	3	1%	0·17

Summary

The CREATE study gives no convincing evidence of an excess risk of death or cardiovascular morbidity attributable to correction of haemoglobin concentration to 10·5–11·5 g/dL compared with correction of haemoglobin concentration to 13·0–15·0 g/dL in patients with chronic kidney disease who are not receiving renal-replacement therapy. There were no significant differences between the two groups in the frequency of death from cardiovascular causes, or in the time to death from cardiovascular causes or all causes. Such trends as there were in all-cause mortality and cardiovascular morbidity consistently favoured the low-target haemoglobin group, but differences between groups were very small.

There were no differences between treatment groups in the reporting of thrombotic complications.

MHRA Assessor's comment: The sample size calculation for the CREATE trial assumed that 200 events would have to occur in order to detect, with a statistical power of 80%, a reduction in the hazard ratio for a first cardiovascular event by one third. However, only half the predicted number of cardiovascular events (ie, 105 actual events) had occurred, which would have affected the power of the study to discriminate between treatment effects.

There are important differences between CHOIR and CREATE. The CHOIR study was larger than the CREATE study. Data were also handled differently: in CHOIR, observations were censored when patients needed renal-replacement therapy, whereas in CREATE they were not. The proportion of patients who received dialysis in the two

studies differed: at the end of CREATE, about 50% of patients were receiving dialysis compared with 20% in CHOIR. However, the effect of these differences on the outcomes of the two studies does not seem to be large on the basis of sensitivity analyses.

Irrespective of the differences in conduct and outcomes of the CHOIR and CREATE studies, both show that there is no benefit associated with correction of haemoglobin concentration to higher levels compared with correction to lower levels (the CREATE study showed a short-lived improvement in quality of life in the high target haemoglobin group). Assuming either the same degree of cardiovascular risk for both treatment strategies, or a slightly lower risk for the low-target haemoglobin group (as suggested by CHOIR), and given the small trends noted in CREATE, there seems to be little justification for the correction of haemoglobin concentration beyond the minimum that is compatible with good control of symptoms of anaemia in patients with chronic kidney disease who have symptomatic anaemia.

2.3 Mortality and target haemoglobin concentrations in patients with chronic kidney disease treated with epoetin for anaemia: meta-analysis

This meta-analysis was reported by Phrommintikul and colleagues[3] and includes data from the two studies discussed above.[1–2]

Objective

To compare all-cause mortality and cardiovascular events associated with epoetin treatment to achieve different ranges of haemoglobin concentration in trials that enrolled patients with anaemia due to chronic kidney disease.

Method

The meta-analysis included prospective randomised controlled trials that assessed epoetin alfa, epoetin beta, or darbepoetin alfa to treat anaemia in adults with chronic kidney disease. Trials were included if they assessed the effects of targeting different haemoglobin concentrations. Studies were excluded if they enrolled fewer than 100 patients or if duration of treatment and follow-up was less than 12 weeks. Trials that enrolled patients with very low concentrations of haemoglobin at baseline (ie, <80 g/L) were excluded from the main analysis, but were used in sensitivity analyses.

Outcomes assessed were all-cause mortality, myocardial infarction, change in blood pressure, arteriovenous access thrombosis, and effects on left ventricular mass.

Results

The meta-analysis included 9 trials with 5143 patients. The number of patients in every study ranged from 146 to 1432. 8 studies included patients with moderately to severely reduced GFR or kidney failure; 1 study included patients with mildly reduced GFR. Age of participants ranged between 50 years and 65 years. Duration of follow-up ranged from 12 months to 48 months. 2 studies terminated prematurely for safety reasons: 1 because an interim analysis raised concerns about safety, and 1 because 2 cases of pure-red-cell aplasia occurred (see **section 2.1** for reasons of the termination of CHOIR).

Table 7 shows the target and achieved haemoglobin concentrations in the trials.

Table 7: Baseline, target, and achieved haemoglobin concentrations in included trials

	Baseline haemoglobin concentration (g/L)	Target haemoglobin concentration (g/L)		Achieved haemoglobin (g/L)	
		High	Low	High	Low
Besarab et al[5]	90–110*	140 (10)*	100 (10)*	12·7–133·3†	10·0†
Foley et al	90–110	130–140	95–105	123 (120–125)‡	104 (102–106)‡
Furuland et al	90–120	145–160 (M), 135–150 (F)	90–120	143 (11)§	113 (13)§
Roger et al	110–130 (M), 100–120 (F)	120–130	90–120	121 (14)§	108 (13)§
Parfrey et al	80–120	135–145	95–115	131 (9)¶	108 (7)¶
Levin et al	110–135	120–140	90–105	126–130‖	115–117‖
Rossert et al	<130 (M), 125 (F)	130–150	110–120	NA**	NA**
Singh et al	<110	135	113	126‡‡	113‡‡
Drueke et al	110–125	130–150	105–115	NA§§	NA§§

*Data are target (range) calculated from haematocrit results. †Data are range from Kidney Disease Outcomes Quality initiative clinical practice guidelines and clinical practise recommendation for anaemia in chronic kidney disease. ‡Data are mean (95% CI) for group with left ventricular disease; level achieved in group with left ventricular hypertrophy was 122 g/L (119–125). §Data are mean (SD). ¶Data are mean (2SE). ‖Data are range. **Change in haemoglobin for men was 27 (SE 11·9) and for women 20 (10·8) in the high-target group; in the low-target group it was 2 (8·3) for men and 2 (9·3) for women. ‡‡Data are mean. §§Target haemoglobin concentration achieved and difference in median haemoglobin concentration between groups was 15 g/L at end of study. M=Male. F=female.

The risk of death from any cause was significantly higher in the higher-target haemoglobin group (relative risk 1·17 [95% CI 1·01–1·35]; p=0·031) than in the lower-target haemoglobin group (**table 8**). There was no significant heterogeneity between the trials (heterogeneity χ^2 9·59, p=0·213, I^2=27%). There was a statistically non-significant trend toward higher risk of death from any cause in the high-target haemoglobin group subgroup analyses of patients (**table 8**). Effects were dominated by 1 study that contributed more than 50% of the weight to the meta-analysis.

7 studies had data for myocardial infarction. There was no difference in risk between high-target and low-target haemoglobin groups for all patients and for the subgroup of patients who were not receiving dialysis (**table 8**). Patients on dialysis could not be analysed because data were available in only two studies.

The effect of epoetins on blood pressure varied with the analysis model. The risk of poorly controlled blood pressure was greater in the high-target haemoglobin group than in the low-target group in the fixed-effects model, but not in a random-effects model (**table 8**).

6 studies had data for risk of venous access thrombosis and overall a statistically significantly greater risk of thrombotic shunt complications was noted for the high-target haemoglobin group compared with low (**table 8**).

Table 8: Summary of results—meta-analysis

	Hazard Ratio	95% CI		p
		Lower	Upper	
Death from any cause	1·17	0·01	1·35	0·031
Death from any cause in dialysis patients only	1·33	0·98	1·81	0·067
Death from any cause in patients not on dialysis	1·11	0·94	1·31	0·220
Sensitivity analysis: Death from any cause, including 4 trials excluded because target haemoglobin concentration was <8 g/dL and 1 trial with <100 patients	1·14	0·99	1·32	0·07
Myocardial infarction	0·98	0·73	1·31	0·88
Myocardial infarction in pre-dialysis patient subgroup	0·90	0·58	1·41	0·66
Poor blood-pressure control (fixed-effects model)	1·27	1·08	1·50	0·004
Poor blood-pressure control (random-effects model)	1·31	0·97	1·78	0·075
Arteriovenous access thrombosis	1·34	1·16	1·54	0·0001

Summary

The meta-analysis[3] compares mortality and cardiovascular morbidity associated with target haemoglobin concentrations that are either greater than or less than 12 g/dL. The results suggest an increased risk of death from any cause in patients with anaemia due to chronic kidney disease who are treated with epoetin to achieve a haemoglobin concentration between 12 g/dL and 16 g/dL compared with patients treated to achieve a haemoglobin concentration less than 12 g/dL. The risk of arteriovenous access thrombosis and poorly controlled hypertension may be similarly increased in such patients.

The choice of target haemoglobin concentration does not seem to affect the risk of myocardial infarction.

MHRA Assessor's comment: The meta-analysis does not assess the risk of thrombotic complications other than myocardial infarction and shunt thrombosis. Moreover, it does not address the risk of congestive heart failure. The risks attributable to these and other cardiovascular events may account for the persistent trend for higher all-cause mortality that seems to be developing as more clinical study data become available for survival in relation to targeted haemoglobin concentration in the management of anaemia in chronic renal disease.

The outcome for all-cause mortality in the meta-analysis is heavily weighted by the contribution of 1 study. Furthermore, estimates for relative risk are not greatly elevated and it is possible that the apparent elevated risk may be due to residual confounding factors, which it has not been possible to take into account in the analysis.

2.4 Systematic review of epoetin treatment in chronic kidney disease

A Cochrane systematic review of target haemoglobin concentrations in the treatment of anaemia due to chronic kidney disease was published in October 2006.[4] The Cochrane review precedes the publication of the CHOIR[1] and CREATE[2] studies.

The review aimed to assess the benefits and risks of different haemoglobin and haematocrit targets in patients with anaemia due to chronic kidney disease. The review includes 22 trials involving 3707 patients. It includes all studies included in the meta-analysis by Phrommintikul and colleagues[3] with the exception of the CHOIR[1] and CREATE[2] studies. Many studies included in the systematic review analysed very few patients. About a third of patients included in the review participated in 1 clinical trial.[5]

The review concluded that there was a benefit associated with higher target haemoglobin concentration in terms of a reduced incidence of epileptic seizures, but that there was an increased risk of hypertension. There were no data to suggest significant improvements in the risk of death from any cause or from cardiovascular causes in association with higher target haemoglobin concentrations. The results of the largest study in the systematic review suggest that there may be an increased risk of death and cardiovascular morbidity associated with higher target haemoglobin concentrations.[5] The reviewers suggested that a lower-target haemoglobin concentration (ie, 12 g/dL) may therefore be appropriate for patients with pre-existing cardiovascular risk factors.

MHRA Assessor's comments: The Cochrane systematic review contains more trials but fewer patients than the more recent meta-analysis by Phrommintikul and colleagues,[3] reflecting the state of knowledge before publication of the CHOIR[1] and CREATE[2] trials. The Cochrane review suggests that serious cardiovascular risks potentially associated with higher haemoglobin targets are limited to hypertension. The findings for all-cause mortality in this systematic review are superseded by the more-recent meta-analysis.[3]

3. SUMMARY AND CONCLUSIONS

The results of two studies[1,2] and a meta-analysis[3] have recently been published, which suggest that treatment of anaemia with epoetins in patients with chronic kidney disease to achieve high-target haemoglobin concentrations may be associated with an increased risk of mortality and cardiovascular morbidity.

The first trial (the CHOIR study)[1] compared the risk of death and cardiovascular complications in patients with chronic renal disease treated with epoetin alfa to achieve either a high haemoglobin concentration (13·5 g/dL) or a low haemoglobin concentration (11·3 g/dL). The trial terminated prematurely because an interim analysis showed that it was unlikely that that trial would have shown a benefit for patients allocated the high-target haemoglobin concentration. At the time of termination, 1432 patients had been enrolled.

Patients in this study with renal failure who were not receiving dialysis, but who were treated with epoetin alfa to achieve a haemoglobin concentration of 11·3 g/dL had a statistically significantly longer time to the composite endpoint of death, myocardial infarction, hospitalisation for congestive heart failure (excluding renal-replacement therapy), or stroke than did those treated to achieve a haemoglobin concentration of 13·5 g/dL. The individual components of the composite endpoint were not statistically significantly different between groups, although there was a trend for increased risk of death and congestive heart failure (excluding renal-replacement therapy) for the high-target group.

There were no meaningful differences between the two treatment groups in terms of quality-of-life scores (the main marker for benefit in this trial).

The outcome of the trial tends to favour the low-haemoglobin treatment group, and suggests that the balance of risks and benefits of treatment to achieve a haemoglobin concentration of 11·3 g/dL may be better than that of treatment to achieve higher haemoglobin concentrations. The outcome seems to be driven mainly by a greater proportion of deaths from any cause and of patients who developed congestive heart failure in the group treated to achieve higher haemoglobin concentrations.

Evidence for a clinically significant difference between groups in CHOIR[1] in the frequency of thrombovascular events is not strong. The most robust data for a difference between groups in the frequency of thrombovascular complications are the higher numbers of serious adverse reactions reported in the high-haemoglobin group compared with low (1·5% *vs* 0·4%), most of which were thrombovascular complications in both treatment groups.

The second study (CREATE)[2] compared cardiovascular outcomes in 603 patients with chronic kidney disease and anaemia treated with epoetin beta to achieve a haemoglobin concentration of either 10·5–11·5 g/dL or 13·0–15·0 g/dL.

There were no significant differences between the two groups in the frequency of death from cardiovascular causes or the time to death from cardiovascular causes or all causes. Such trends as there were in all-cause mortality and cardiovascular morbidity consistently favoured the low-target haemoglobin group, but differences between groups were very small. There were no differences between groups for reporting of thrombotic complications.

Both the CHOIR[1] and CREATE[2] studies show no sustained benefit associated with correction of haemoglobin concentration to higher levels compared with correction to lower levels. Assuming either the same degree of cardiovascular risk for both treatment strategies, or a slightly lower risk for the low-target haemoglobin group (as suggested by CHOIR), and given the small trends noted in CREATE, there seems to be little justification for the correction of haemoglobin concentration beyond the minimum that is compatible with good control of symptoms of anaemia in patients with chronic kidney disease.

A meta-analysis[3] of 9 prospective randomised controlled trials (5143 patients) assessed death from any cause and cardiovascular events associated with epoetin treatment to achieve different ranges of haemoglobin concentration in trials of patients with anaemia due to chronic kidney disease. Outcomes assessed were death from any cause, myocardial infarction, change in blood pressure, arteriovenous access thrombosis, and effects on left ventricular mass. The results of the meta-analysis suggest an increased risk of death from any cause in patients with anaemia due to chronic kidney disease who are treated to achieve a haemoglobin concentration between 12 g/dL and 16 g/dL compared with patients treated to achieve a haemoglobin concentration less than 12 g/dL. The risk of arteriovenous access thrombosis and poorly controlled hypertension may be similarly increased in such patients. The choice of target haemoglobin concentration does not seem to affect the risk of myocardial infarction.

The meta-analysis does not address the risk of thrombotic complications other than myocardial infarction and shunt thrombosis. Moreover, it does not address the risk of congestive heart failure. The risks attributable to these and other cardiovascular events may account for the persistent trend for higher all-cause mortality that seems to be developing as more clinical study data become available for survival in relation to target haemoglobin concentration in the management of anaemia in chronic renal disease.

The best estimate of relative risk of death associated with higher target haemoglobin concentrations is 1·17 (–0·01 to 1·35). This relative risk ranges from 0·17 to 1·48 in the studies on which the meta-analysis is based. The outcome for death from all causes is heavily weighted by the contribution of 1 study in the meta-analysis. Moreover, estimates of relative risk are not greatly elevated and the apparent elevated risk may be due to residual confounding factors, which it has not been possible to take into account in the analysis.

Table 9 summarises the target haemoglobin concentrations recommended in the SPCs for the authorised epoetins.

Table 9: Target haemoglobin concentrations in renal anaemia recommended in SPCs

	Epoetin alfa	**Epoetin beta**	**Darbepoetin alfa**	**Epoetin delta**
Haemoglobin target range (g/dL)	10–12	··	11–14	10–12
Haematocrit target range (%)	··	30–35	··	··
Haemoglobin/haematocrit not to be exceeded	Not stated	35%	14 g/dL	Not stated

There is little, if any, evidence that correction of haemoglobin concentration to within the range 12 g/dL to 16 g/dL has any clinically meaningful benefits that can not be gained from correction to less than 12 g/dL. Given the lack of evidence of benefit, it would be a sensible precaution to consider reducing the apparent risks to patients by avoiding the correction of anaemia to haemoglobin concentrations greater than may be necessary to control symptoms of anaemia, and preferably not to concentrations above 12 g/dL. Patients with pre-existing cardiovascular risk factors may need closer medical supervision than those who do not.

Members of the Commission on Human Medicines hypothesised that the apparent excess mortality associated with epoetin use may not be attributable solely to thrombosis and related complications, but may also be due to aggravation of hypertension in patients with chronic renal disease or sudden death due to uraemic cardiomyopathy.

The Commission advised that the evidence would support correction of anaemia to a maximum haemoglobin concentration of 12 g/dL, possibly with a lower maximum in women and children. The purpose of treatment with epoetins is to relieve symptoms of anaemia and to avoid the need for blood transfusion. The Commission advised treatment with epoetins should be appropriately adjusted when symptoms of anaemia have been adequately brought under control, irrespective of haemoglobin concentration.

The Commission also advised that the evidence of risk associated with overcorrection of haemoglobin concentration should be brought to the attention of the athletic community in order to minimise risk and discourage abuse of epoetins.

4. REFERENCES

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5. GLOSSARY

Allergic dermatitis

Inflammation of the skin as a result of an allergy

Anaemia

The circulation of too few red blood cells in the bloodstream, leading to reduced oxygen supply to tissues and organs

Analysis of covariance

A method of statistical analysis that can help reduce experimental error

Angina pectoris

Chest pain that usually occurs during exertion or excitement

Arrhythmia

An abnormal heart rhythm

Arteriovenous access thrombosis

A blood clot where an artery to a vein

Arteriovenous fistula thrombosis

A blood clot in an abnormal connection between an artery and a vein; the connection may be abnormal as a result of a birth defect, undergoing dialysis, or disease

Baseline

The time at the start of the study

Beta-blocker

A class of medicines that are used to treat some types of heart and circulatory disease

Cardiovascular

Of the heart and circulatory system

Cardiovascular intervention

Treatment, surgical or medical, of a disorder of the heart and circulatory system

Censoring

A term in **randomised controlled trials** that describes the timepoint at which the patient was last followed up in the study

Cerebrovascular accident

Severe and sudden rupturing of the blood vessels of the brain, which can lead to a stroke

Composite

Grouping together of more than one factor

Congenital

Present at birth

Congestive heart failure

Disease of the heart such that it has impaired pumping ability, leading to accumulation of fluid in organs such as the lungs; can lead to difficulty breathing, high blood pressure, and a heart attack

Cox proportional-hazards model

A statistical method of analysing survival

C-reactive protein

A substance produced by the liver that can be used to measure inflammation

Deep-vein thrombosis

A blood clot in the legs

Electrocardiography

The recording of electrical activity of the heart

Endpoint

An event that a study aims to measure

Enzyme

A protein in the body that helps to speed up chemical reactions

Fixed-effects model

A method of statistical analysis that assumes that studies use identical methods, patients, and measurements; that they should produce identical results; and that differences are only due to within-study variation

Glomerular filtration rate (GFR)

A measure of the kidneys' ability to filter and remove waste products from the body

Haematocrit

A measure of the volume of blood that is filled by red blood cells

Haemodialysis

The process of filtering blood

Haemoglobin

The iron-containing component of red blood cells that carries oxygen around the body

Hazard ratio (HR)

A method of measuring the risk of an event. A hazard ratio of more than 1 suggests an increased risk; a hazard ratio of less than 1 suggests decreased risk. Hazard ratios are usually accompanied by a 95% CI (confidence interval)—a statistical method of assessing the true difference between two groups: the range covered by this interval gives a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is regarded as statistically significant

Heterogeneity

The extent of difference between two or more comparisons

Hypertension

High blood pressure

Independent Data and Safety Monitoring Board

A group who has responsibility for continual analysis of an ongoing clinical trial and the results that are emerging from it

Iron-overload state

Accumulation of too much iron in the body

Kaplan-Meier

A measure of estimating survival of patients in a study over time since treatment

Left ventricular disease

Disease of the muscular chamber of the heart that pumps blood around the circulation

Left ventricular fractional shortening

A measure of the performance of the left ventricle of the heart (the muscular chamber of the heart that pumps blood around the circulation)

Left ventricular hypertrophy

The thickening of muscle in the left ventricle of the heart (the muscular chamber of the heart that pumps blood around the circulation), the presence of which suggests heart disease

Left ventricular mass

The weight of the muscle in the left ventricle of the heart (the muscular chamber of the heart that pumps blood around the circulation)

Left ventricular volume

A measure of the amount of blood that can occupy the left ventricle of the heart to be pumped around the body

Log-rank test

A statistical method of comparing survival between groups

Mean (SE)

An average, calculated by dividing the sum of all values by the total number of values. Means are sometimes accompanied by a standard error (SE), which estimates the representativeness of the mean value each side of the estimate

Median

An average: the middle value of a range of values in a sample

Meta-analysis

A study that combines the results from several similar clinical trials that asked the same study question and applies new statistical analysis

Morbidity

A diseased condition

Mortality

Death

Myocardial infarction

Injury to heart muscle as a result of reduced oxygen supply, leading to a heart attack

Necrosis

The death of cells that make up an organ

Non-compliance

A situation in which guidelines (eg, treatment schedule or study conditions) are not followed

Open label

A study in which patients and healthcare professionals who are involved know the treatment to which the patients have been assigned (compare with a blinded study).

Peripheral vascular disease

Disease of the blood vessels that supply the extremities of the body

Peritoneal dialysis

A particular type of kidney dialysis that runs dialysis fluid through the stomach

Priapism

Abnormal erection

Prospective

A study in which people are recruited and subsequently followed over time

Pulmonary embolism

A blood clot in the lungs

p value

A measure of the statistical probability of an event occurring by chance. Usually, a p value of less than 0·5 suggests the event is statistically significant and did not occur by chance, whereas a p value of more than 0.5 suggests the event is not statistically significant and arose by chance

Random-effects model

A method of statistical analysis that considers variability in a study and between studies

Randomised controlled trial

A study technique, regarded as robust, in which participants are enrolled onto the study and randomly assigned a treatment or treatment technique. In a **placebo** controlled trial, some patients are allocated the drug or technique of interest, whereas some are allocated **placebo** as a control group to identify the effects of the drug of interest. In a double-blind study, neither the trial participants nor the trial investigators are aware of who has been assigned to a particular treatment group, thus minimising bias

Refractory iron-deficiency anaemia

The circulation of too few red blood cells in the bloodstream as a result of a lack of iron; the resulting anaemia can be unresponsive to treatment

Relative risk

A measure of risk for one group compared with another (eg, risk for patients given epoetin compared with those given **placebo**). A relative risk of more than 1 suggests an increased risk; a relative risk of less than 1 suggests decreased risk. Relative risks are usually accompanied by a 95% CI (confidence interval)—a statistical method of assessing the true difference between two groups: the range covered by this interval gives a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is regarded as statistically significant

Renal

Of the kidneys

Renal-replacement therapy

Vital treatment for people with kidney failure; can include **haemodialysis** and **peritoneal dialysis**

Residual confounding factors

Features of a patient or study condition that may bias the outcome of a study

Retinal-vein occlusion

Blockage of a vein in the retina of the eye

Serum albumin

The clear portion of body fluid that is present in albumin, an important product of the liver; low serum albumin can cause liver disease and malnutrition

SF-36

A survey that measures quality of life in terms of: physical functioning, role limitations due to physical health and emotional problems, body pain, general health perceptions, vitality, social functioning, and mental health.

Shunt thrombosis

A blood clot at a passage between two blood vessels

Stratified

A method of separating patients in a clinical trial into groups on the basis of their characteristics

Subcutaneously

A method of giving a medicine under the skin

Summaries of Product Characteristics (SPCs)

Detailed information that accompanies any licensed medicine. The Summary of Product Characteristics details the composition, clinical characteristics, pharmacological properties, pharmaceutical characteristics

Systematic review

An overview and appraisal of the current literature on a topic

Thrombosis/thrombotic/thrombovascular

Events leading, or related, to a blood clot

Transient ischaemic attack

Temporary disruption to the circulatory system in the brain, which can lead to temporary paralysis, numbness, or difficulty in speech; symptoms usually recover within 24 hours

Type I error

A statistical error that concludes that treatment is effective when it is not

Uraemic cardiomyopathy

Damage to the heart as a result of thickening of the left ventricle (the muscular chamber of the heart that pumps blood around the circulation) and ultimately disorders in the pumping of blood around the body

Valvular

Of the heart valves

Venous access thrombosis

A blood clot at the junction between veins

χ^2 test (chi-squared test)

A statistical method of assessing whether a difference between groups in a study is true