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

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Summary

Background **Recombinant human erythropoietin is commonly used for treatment of anaemia. Our aim was to determine whether targeting different haemoglobin concentrations with such treatment is associated with altered all-cause mortality and cardiovascular events in patients with anaemia caused by chronic kidney disease.**

Methods **We did a meta-analysis of randomised controlled clinical trials that were identified in medical databases and trial registration websites. Trials were eligible for inclusion if they assessed the effects of targeting different haemoglobin concentrations in patients with anaemia caused by chronic disease who were randomly assigned to treatment with recombinant human erythropoietin, recruited at least 100 patients, and had a minimum follow-up of 12 weeks.**

Findings **We analysed nine randomised controlled trials that enrolled 5143 patients. There was a significantly higher risk of all-cause mortality (risk ratio 1·17, 95% CI 1·01–1·35; p=0·031) and arteriovenous access thrombosis (1·34, 1·16–1·54; p=0·0001) in the higher haemoglobin target group than in the lower haemoglobin target group in the fixed effects model without heterogeneity between studies. There was a significantly higher risk of poorly controlled blood pressure (1·27, 1·08–1·50; p=0·004) in the higher haemoglobin target group than in the lower target haemoglobin group with the fixed effects model; however, this was not significant in the random effects model (1·31, 0·97–1·78; p=0·075). The incidence of myocardial infarction was much the same in the two groups.**

Interpretation **To target higher haemoglobin concentrations when treating patients with anaemia caused by chronic kidney disease with recombinant human erythropoietin puts such patients at increased risk of death. Current guidelines do not include an upper limit for the target haemoglobin concentration; such an upper limit should be considered in future recommendations.**

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Introduction

Anaemia is commonly seen in individuals with chronic kidney disease.[1] A reduction in haemoglobin concentrations in these patients has been shown to be associated with impairment in quality of life, reduced energy, neurocognitive decline, decreased exercise capacity, and increased mortality.[2–5] The cause of anaemia in such individuals is mainly related to a deficiency in the synthesis of endogenous erythropoietin.[6] Therefore, the use of recombinant human erythropoietin represents a logical and commonly used treatment for this disorder. At present, such treatments include erythropoiesis-stimulating agents such as epoetin alfa and beta as well as the analogue of recombinant human erythropoietin, darbepoetin alfa.

Use of recombinant human erythropoietin to treat anaemia caused by chronic kidney disease has been found in some small mechanistic studies to be associated with improvements in muscle strength,[7] exercise capacity,[8] fatigue,[9] neurocognitive function,[10] and depression.[11] However, considerable controversy exists with regard to the concentration of haemoglobin at which patients should begin treatment with recombinant human erythropoietin as well as the haemoglobin concentration that should be aimed for to increase benefits to a maximum and to reduce potential adverse effects to a minimum. These adverse effects include the development or worsening of systemic hypertension, site access thrombosis in dialysis patients with arteriovenous shunts, and the apparent potential for increased cardiovascular events.[2,12] The publication of two major studies of recombinant human erythropoietin in chronic kidney disease—Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)[13] and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)[14]—has raised further the possibility that this treatment might be associated with an increase in cardiovascular events in those individuals in whom a higher haemoglobin concentration is aimed for.

Our aim was to do a meta-analysis of all available data to determine whether targeting different haemoglobin concentrations when treating anaemic patients with chronic kidney disease with erythropoiesis-stimulating agents is associated with altered all-cause mortality and cardiovascular events.

Methods

Search strategy and selection criteria

Randomised controlled clinical trials were identified via MEDLINE (source PubMed, 1966 to November, 2006), EMBASE (1974 to November, 2006), the Cochrane Controlled Clinical Trials Register Database (through November, 2006), the Cochrane Renal Group Specialised Register of Randomized Controlled Trials (through

November, 2006), and the ClinicalTrials.gov website. All searches included the keywords and corresponding MeSH terms for erythropoietin, darbepoetin, kidney disease, renal disease, and randomised controlled trial. Manual reference checking of the bibliographies of all retrieved articles was also done. To identify studies reported only at scientific meetings, we searched—both manually and electronically—the abstracts of annual scientific sessions of the American Society of Nephrology, European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA), and the International Society of Nephrology from 2000 to November, 2006.

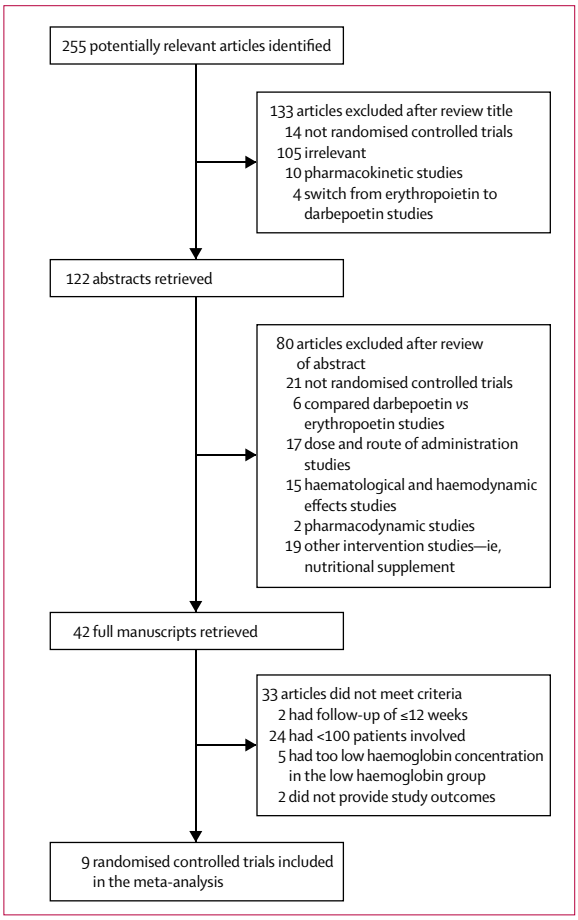

***Figure 1*: Flow chart of the search strategy and selection of trials**

Studies were assessed for data quality and validity by consensus between two investigators (AP and ME). Formal data analysis was done in a blinded manner by another investigator (SJH), in accordance with Quality of Reporting of Meta-analyses recommendations.[15]

Prospective randomised controlled trials done in adults that were published in English were considered for inclusion in this meta-analysis. Studies were included if they assessed the effects of targeting different haemoglobin concentrations when treating patients with anaemia caused by chronic kidney disease with erythropoiesis-stimulating agents. Potential therapies used to achieve target haemoglobin concentrations were epoetin alfa, epoetin beta, darbepoetin, or placebo. Studies with fewer than 100 patients or with a duration of treatment and follow-up of less than 12 weeks were excluded. Trials with very low concentrations of haemoglobin at baseline (<80 g/L) were excluded from the main analysis, but were used in sensitivity analyses.

Data extraction and quality assessment

Trials were assessed by two independent reviewers (AP and ME), who extracted data on patient characteristics, type and mode of erythropoiesis-stimulating agents, method of dialysis, co-intervention, and outcomes. Outcomes assessed were all-cause mortality, myocardial infarction, changes in blood pressure, arteriovenous access thrombosis, and

	Type of trial	Method of allocation	Outcome assessors masked?	Adjudication of adverse events	Intention-to-treat analysis?	Number of patients lost to follow-up	Early termination?	Study chair/design	Control of database
Besarab et al[21]	Open label	..	..	Investigators	Yes	..	Yes	..	..
Foley et al[22]	Open label	..	Yes	..	Yes	..	No	Author	..
Furuland et al[23]	Open label	..	..	Central coordinator*	Yes	0	No†	..	..
Roger et al[26]	Open label	Centrally computer generated	..	Investigators	Yes	1 (low haemoglobin)	No	Author	Sponsor
Parfrey et al[25]	Double blind	Centrally computer generated	Yes	Investigators	Yes	2 (1 high, 1 low haemoglobin)	No	Author	..
Levin et al[24]	Open label	Centrally computer generated	Yes	..	Yes	2 (low haemoglobin)	No	Author	..
Rossert et al[27]	Open label	Computer generated	..	Study site investigators	Yes	0	Yes	Author	..
Singh et al[14]	Open label	Computer generated	Yes	Central committee	Yes	Yes, number not stated	No‡	Authors and sponsor	Duke Clinical Research Institute
Drueke et al[13]	Open label	Centrally computer generated	Yes	Central committee	Yes	0	No	Authors and sponsor	Sponsor

..=no data. *Thrombovascular events and vascular access thrombosis. †Amended by addition of exclusion criteria. ‡Amended by change of target haemoglobin concentrations.

***Table 1*: Design of included trials**

	n	Age (years)*		Sex†		Diabetes mellitus‡		CKD caused by diabetes mellitus‡		Stage of kidney disease §	Renal function ¶	Dialysis	Number starting dialysis during study		Hypertension (%) at baseline		Cardiac inclusion criteria	Type of ESA and mode of delivery	Mean dose of ESA (U/week)		Mean study duration including follow-up (months)
		High	Low	High	Low	High	Low	High	Low				High	Low	High	Low			High	Low	
Besarab et al[21]	1233	65 (12)	61 (12)	309 (50%)	295 (52%)	334 (54%)	357 (58%)	259 (42%)	283 (46%)	5	NA	HD	NA	NA	71%	69%	CHF or IHD	Epoetin alfa, SC/IV	420 (350–520) ||	140 (90–175) ||	29
Foley et al[22]	146	62 (58–66) **	62 (57–67) **	31 (79%) ††	28 (76%) ††	NA	NA	14 (36%) ‡‡	9 (24%) ‡‡	5	NA	HD	NA	NA	NA	NA	LVH or LVD	Epoetin alfa, SC	21 049 (16 686–25 412)§§	8092 (6272–9422)§§	12
Furuland et al[23]	416	63 (12)	63 (14)	145 (67%)	126 (63%)	41 (19%)	40 (20%)	37 (17%)	32 (16%)	4–5	NA	Predialysis, HD, PD¶¶	2	0	52% ||||	48%	None	Epoetin alfa, SC	107 (117)***	39 (53) ***	12–19
Roger et al[26]	155	53 (14) (M); 54 (12) (F)	54 (12) (M); 50 (15) (F)	38 (51%)	33 (42%)	18 (24%)	26 (33%)	NA	NA	3–4	15–50	None	24	15	NA	NA	None	Epoetin alfa, SC	NA	NA	48
Parfrey et al[25]	596	52·2 (15·6)	49·4 (15·2)	178 (60%)	180 (60%)	NA	NA	56 (19%)	51 (17%)	5	NA	HD	NA	NA	82% ||||	81%	no LVD, DBP <100 mm Hg	Epoetin alfa, SC/IV	179·4 (14·7) †††	75·8 (11·8) †††	18·5
Levin et al[24]	172	56·5 (14·9)	57·3 (14·9)	55 (70·5%)	52 (70·3%)	32 (41%)	26 (35·1%)	25 (32·1%)	22 (29·7%)	2–4	15–79	None	7 HD, 4 PD	6 HD, 2 PD	NA	NA	None	Epoetin alfa, SC	3146 (2615) ‡‡‡	3552 (2562) ‡‡‡	22·6 (median)
Rossert et al[27]	390	58·5 (13·6)	57·8 (13·6)	113 (58%)	118 (61%)	67 (34%)	68 (35%)	51/192 (27%)	49/192 (26%)	3–4	25–60	None	NA	NA	72%	70%	None	Epoetin alfa, SC	4514 (658–14 655) §§§	2730 (333–7667) §§§	11·4 (high); 12·3 (low)
Singh et al[14]	1432	66·0 (14·3)	66·3 (13·5)	313 (43·8%)	329 (45·9%)	NA	NA	335 (46·8%)	364 (50·8%)	3–4	15–50	None	155	134	95·8% ¶¶¶	93·2%	None	Epoetin alfa, SC	11 215	6276	16 (median)
Drueke et al[13]	603	59·3 (14·6)	58·8 (13·7)	171 (57%)	154 (51%)	80 (27%)	77 (25%)	61 (20%)	63 (21%)	3–4	15–35	None	127 HD	111 HD	91%	89%	BP <170/95 mm Hg	Epoetin beta	5000 (3000–8000) §§§	2000 (1000–3000) §§§	36

BP=blood pressure. CHF=congestive heart failure. DBP=diastolic blood pressure. ESA=erythropoiesis-stimulating agents. F=female. HD=haemodialysis. IHD=ischaemic heart disease. IV=intravenous. LVD=left ventricular disease. LVH=left ventricular hypertrophy. M=male. NA=not available. PD=peritoneal dialysis. SC=subcutaneous. *Data are mean (SD) or mean (95% CI). †Data are number of men (%). ‡Data are n (%); numbers are back-calculated from percentage in Besarab et al,[21] Singh et al,[14] Parfrey et al,[25] and Furuland et al.[23] §On the basis of the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative clinical practice guidelines. ¶Glomerular filtration rate (mL per min per 1·73 m^2). ||Mean (95% CI; estimated from graph) in U/kg/week. **Data for LVD group, mean (95% CI); in LVH group, 62 (57–67) in high group *vs* 60 (56–65) in low group. ††Data for LVD group; in LVH group, 16 (47%) in high group *vs* 16 (44%) in low group. ‡‡Data for LVD group, in LVH group 9 (26%) in high group *vs* 11 (31%) in low group. §§Data are mean (95% CI) for LVD group; in LVH (high *vs* low haemoglobin 19 058 *vs* 8993). ¶¶Predialysis: 36 patients in high haemoglobin group *vs* 36 in low haemoglobin group; HD group: 157 *vs* 136; PD: 23 *vs* 23. ||||Based on the number of patients that received anti-hypertensive therapy. ***Data shown in predialysis group as U/kg/week (high *vs* low haemoglobin); HD (236 [SD 148] *vs* 140 [182]); PD (168 [118] *vs* 58 [86]). †††Estimated from graph; data are mean (2SE). ‡‡‡Data are last dose, mean (SD). §§§Data are median (range). ¶¶¶Significantly different (p=0·03) between the high haemoglobin group and the low haemoglobin group.

Table 2: **Characteristics of trials included in meta-analysis**

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

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

***Table 3*: Baseline, target, and achieved haemoglobin concentrations in included trials**

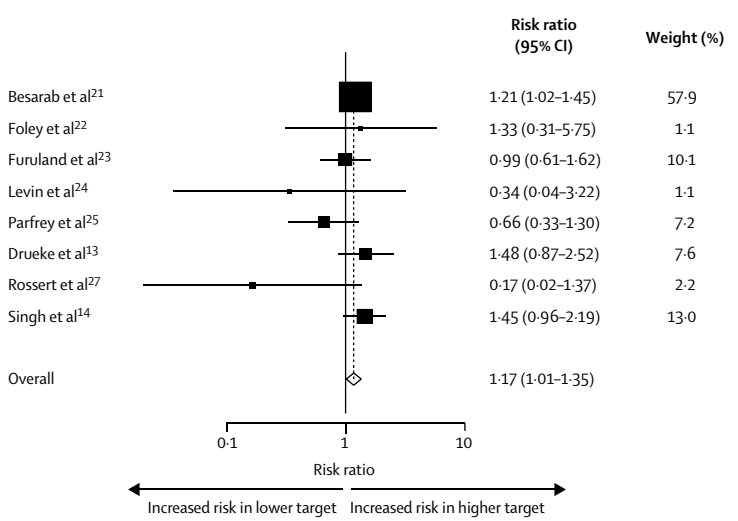

***Figure 2*: Risk of all-cause mortality in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)**
The Roger et al trial[26] is not reported because there were no deaths in either group.

See Online for webappendix

effects on left ventricular mass. We were unable to assess quality-of-life measures because of differences between studies in the scales used for such assessments, as mentioned in a previous systematic review.[2]

The quality of trials was assessed with standard criteria for allocation concealment, analysis by intention-to-treat, completeness of study and follow-up, adjudication of adverse events, study chair and design, funding source, and data-base controller.[16]

Statistical analysis

Risk ratios (RR) with 95% CI of outcomes were derived from every study. Results were pooled with Stata version 8.2 with both the Mantel-Haenszel fixed effects model and the DerSimonian and Laird random effects model for dichotomous outcomes. In the Mantel-Haenszel model, we used Stata to calculate a weighting for every study in accordance with the number of events that occurred in every study to form an average overall outcome statistic and 95% CI. The DerSimonian and Laird model also considered any observed variability between the studies included in the analysis.[17–19] Heterogeneity between studies was analysed with χ^2 and I^2 statistics.[20] Significance was tested with the fixed effects model, unless heterogeneity was shown, in which case the random effects model was used. Statistical significance was set at the 0·05 level on the basis of two-way Z-tests and the 0·1 level of χ^2 tests.

Role of the funding source

There was no source of external funding for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 255 potentially eligible articles, 246 of which were excluded (figure 1). Nine trials with 5143 patients met the specified criteria.[13,14,21–27] Table 1 shows the design of the trials; table 2 shows the characteristics of these trials. Briefly, the trials differed in terms of the population studied, duration of intervention, and primary outcomes. The number of patients in each study ranged from 146 to 1432. All studies were done in patients with moderately to severely reduced glomerular filtration rate or kidney failure, except that by Levin and collegues,[24] which also included patients with mildly reduced glomerular filtration rates. Age was fairly homogeneous, ranging between 50 to 65 years. Participants were mainly men, with the exception of Singh and colleagues' study[14] and those by Besarab and colleagues[21] and Roger and co-workers[26] (webappendix). Duration of follow-up ranged from 12 to 48 months. Two studies were terminated prematurely because of safety issues. Besarab and colleagues[25] halted their study after an interim analysis raised concerns about safety, whereas Rossert and co-workers[27] terminated their study after two cases of red cell aplasia. Singh and colleagues' study[14] was terminated because of the unlikelihood of showing a benefit in the higher haemoglobin target group. The studies differed in terms of cardiac co-morbidities in the recruited patients (table 2). Besarab and colleagues[21] and Singh and co-workers[14] both enrolled a higher proportion of diabetic patients than did the other trials. Table 3 shows the target and achieved haemoglobin concentrations in the trials. Reporting of cardiovascular outcomes and criteria for defining such outcomes (especially hypertension and left ventricular mass) varied between the trials. A detailed discussion of the differences between the included trials, can be found in the webappendix.

Four trials[28–31] comparing recombinant human erythropoietin with placebo were excluded because of very low

haemoglobin concentrations at baseline, with the achieved haemoglobin concentration in the placebo group (about 70–80 g/L) being considerably lower than the currently recommended target.[12,32] One further low baseline haemoglobin trial, with three treatment arms—one arm that used recombinant human erythropoietin to aim for a high haemoglobin concentration, another that targeted a low haemoglobin concentration, and a placebo group—was excluded since the number of patients in the two active treatment groups did not meet the minimum patient number inclusion criteria.[33] The effect of addition of these five excluded trials[28–31,33] on the outcomes assessed in the meta-analysis was examined in sensitivity analyses.

The risk of all-cause mortality was significantly higher in the higher haemoglobin target group (RR 1·17, 95% CI 1·01–1·35; p=0·031; figure 2) than in the lower haemoglobin target group. This effect was dominated by Besarab and colleagues' study,[21] which contributed about 58% of the weight. There was no significant heterogeneity between the trials (heterogeneity χ^2 9·59, p=0·213, I^2=27%; figure 2).

A subgroup analysis was done with the studies that included patients with chronic kidney disease both predialysis[13,14,23,24,26,27] and undergoing dialysis.[21–23,25] RR of all-cause mortality was 1·33 (95% CI 0·98–1·81; p=0·067) in those not receiving dialysis and 1·11 (0·94–1·31; p=0·22) in the dialysis subgroup. A sensitivity analysis including the five trials that were excluded from the main analysis because baseline haemoglobin concentrations were too low, resulted in a RR for all-cause mortality of 1·14 (0·99–1·32; p=0·07).

Seven studies provided data on myocardial infarction.[13,14,21,24–27] No difference was seen in the effect of recombinant human erythropoietin on myocardial infarction between the two groups (0·98, 0·73–1·31; p=0·88; figure 3). Again, this effect was dominated by Besarab and colleagues' study,[21] which contributed about 49% of the weight. There was no heterogeneity between the trials (heterogeneity χ^2 1·42, p=0·965, I^2=0%; figure 3). A subgroup analysis done with the predialysis patients[13,14,24,26,27] resulted in an RR of 0·90 (95% CI 0·58–1·41; p=0·66) between the two haemoglobin target groups. We were not able to analyse this outcome in the haemodialysis subgroup because relevant data were available in only two trials. A sensitivity analysis, which included the two trials that were excluded from the main analysis in which myocardial infarction was reported,[29,30] resulted in an RR of 0·97 (95% CI 0·72–1·29; p=0·82).

The risk of poorly controlled blood pressure was significantly higher in the higher haemoglobin target group than it was in the lower haemoglobin target group (RR 1·27, 95% CI 1·08–1·50; p=0·004; figure 4) with the fixed effects model. There was no heterogeneity across the trials with χ^2 but low to moderate heterogeneity by I^2 (heterogeneity χ^2 5·86, p=0·119, I^2=48%; figure 4). The effect was not significant when a random effects model was used (RR 1·31, 95% CI 0·97–1·78; p=0·075), with the analysis widening the CI by placing a higher weighting on the study by Rossert and colleagues,[27] which had just over half the number of patients of each of the trials by Parfrey and colleagues and Drueke and co-workers.[13,25] A sensitivity analysis, which included the four excluded trials that had reported poorly controlled blood pressure[28–30,33] introduced significant heterogeneity (χ^2 16·94, p=0·018) with an RR of 1·42 (95% CI 1·22–1·66; p<0·0001) with the fixed effects model and 1·62 (1·16–2·26; p=0·005) with the random effects model.

We analysed data from four studies with haemodialysis patients[21–23,25] and two studies in patients who began haemodialysis during the study.[13,24] There was a significantly higher risk of arteriovenous access thrombosis in the higher haemoglobin target group than in the lower haemoglobin target group (RR 1·34, 95% CI 1·16–1·54, p=0·0001; figure 5). Besarab and colleagues' study

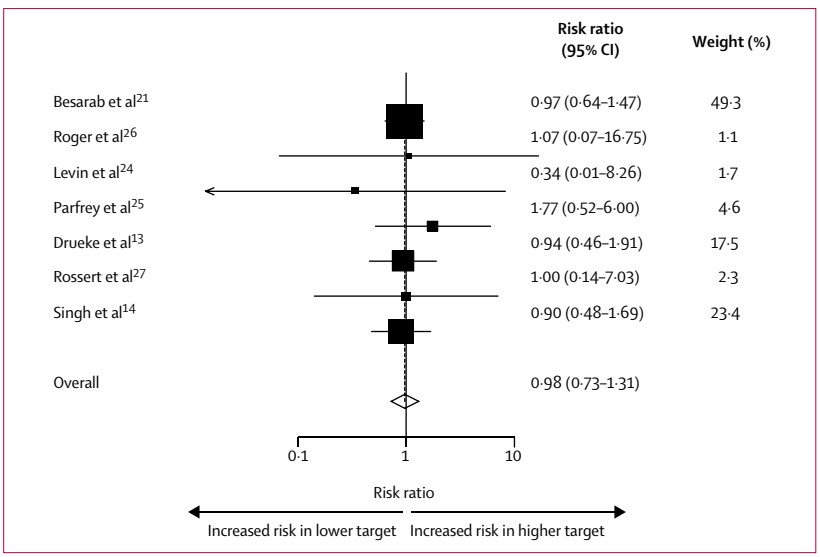

Figure 3: **Risk of myocardial infarction in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)**

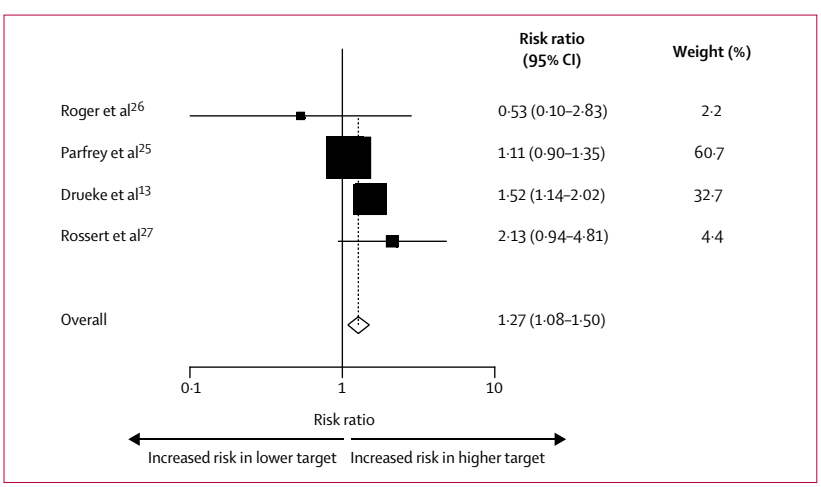

Figure 4: **Risk of poorly controlled blood pressure in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)**

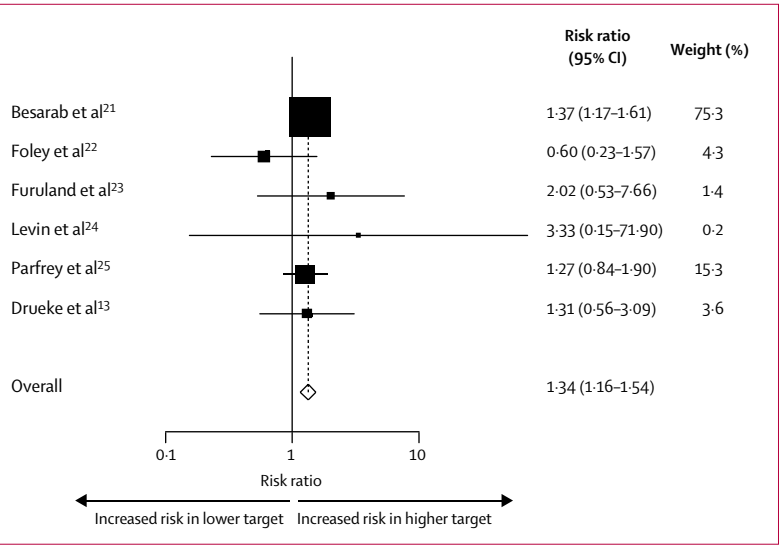

Figure 5: **Risk of arteriovenous access thrombosis in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)**

contributed about 75% of the weight.[21] There was no heterogeneity between the trials (heterogeneity χ^2 3·58; p=0·612; I^2=0%; figure 5). A sensitivity analysis that included the two excluded trials that reported this outcome[29,30] showed a RR of 1·36 (95% CI 1·18–1·56; p<0·0001).

We were unable to do a formal meta-analysis for the effect of erythropoiesis-stimulating agents on left ventricular mass because of differences in the presentation of data. However, there was no difference in the change of left ventricular mass index over the study period between the higher and the lower haemoglobin groups in each individual study.[13,22,24–26]

Discussion

Our results show an increase in the risk of all-cause mortality in anaemic patients with chronic kidney disease in whom a higher haemoglobin target (in the normal physiological range) is aimed for with treatment with recombinant human erythropoietin. Such patients are also at an increased risk of arteriovenous access thrombosis and poorly controlled hypertension, which could contribute to the increased risk of mortality. Furthermore, there seems to be no beneficial effect on left ventricular mass in such patients, at least from individual study data. Our findings do not seem to be affected by the stage of advanced chronic kidney disease, or by dialysis. The most important of our findings is the significant increase in the risk of all-cause mortality seen when a target haemoglobin concentration of 120–160 g/L is achieved. This increase is observed despite these targets being considered to be within the physiologically normal range.

The mechanisms that underlie this excess in mortality are unclear, but could relate to an increased propensity to cardiovascular thrombosis or raised blood pressure, which might contribute to increases in lethal cardiovascular events. This contention is lent support by considerable mechanistic data;[34,35] however, the risk of myocardial infarction seemed to be much the same in the two haemoglobin target groups. Furthermore, whether the increased risk of mortality noted in the higher haemoglobin target group in this meta-analysis relates to the achieved higher haemoglobin per se or to the means by which this was achieved—ie, higher haemoglobin concentrations due to the use of (in most cases) higher doses of erythropoiesis-stimulating agents interacting with erythropoietin receptors—is unclear. Recombinant human erythropoietin not only increases blood viscosity as a result of increased erythrocyte mass[36] but also increases thrombotic risk via increased inflammation and anti-fibrinolytic activity, which can occur irrespective of haemoglobin concentration.[34,37] Other possible mechanisms are stimulation of vascular growth and the dysregulation of production and responsiveness of vasoactive factors.[38] Of interest is that Levin and colleagues[24] and Rossert and co-workers[27] used lower mean doses of recombinant human erythropoietin in the high haemoglobin group than did the other studies, and a trend toward fewer deaths was seen in these groups than in the other studies.

Sensitivity analyses showed that the inclusion of trials that began at very low haemoglobin concentrations somewhat attenuated the excess of deaths recorded with higher haemoglobin targets in individual studies. However, this finding is not surprising, since the use of recombinant human erythropoietin in these excluded studies raised very low haemoglobin concentrations to levels much the same as those in the lower haemoglobin target concentration groups in our main analysis.

Epidemiological studies of patients with chronic kidney disease have shown increased mortality at lower haemoglobin concentrations.[3,39–41] However, such studies could be confounded by several forms of bias, including treatment-by-indication bias in the presence of co-morbid disease. Previous systematic reviews and meta-analyses of randomised controlled trials have been limited with regard to the risks and benefits of therapy with recombinant human erythropoietin, in particular by fewer trials and patients able to contribute to such analyses. Thus such analyses are underpowered to comprehensively address risks at higher haemoglobin target concentrations with these agents.[2,5] Furthermore, questions have been raised with regard to the methods used (eg, combining observational studies—including registry data—with data from randomised controlled trials),[42,43] as well as the source of funding of some earlier studies.[44]

Our findings have several implications for ongoing clinical research. There remains a paucity of evidence regarding the optimum haemoglobin target concentration in anaemic patients with chronic kidney disease. The Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) will partly address this issue.[45] The effect of darbepoetin versus placebo on mortality and non-fatal cardiovascular events (ie, myocardial infarction, myocardial

ischaemia, stroke, and heart failure) in anaemic (ie, haemoglobin concentration <110 g/L) patients with chronic kidney disease and diabetes is currently being explored in this study, which involves 4000 patients. Interestingly, the target haemoglobin concentration of 130 g/L for the darbepoetin group is in the range of that achieved in the higher haemoglobin group used here (ie, 120–140 g/L), and will prospectively address whether this concentration might be too high for such patients, as suggested by our results.

Our observations have implications for other disease states that are associated with low haemoglobin concentrations. In particular, studies of recombinant erythropoietin (or erythropoiesis-stimulating agents) have begun in patients with chronic heart failure who also have low haemoglobin concentrations caused by multiple mechanisms, including impaired erythropoiesis. The largest of such studies—the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial[46]—also has a target haemoglobin concentration in the same range as the higher haemoglobin target concentrations in the studies assessed here. RED-HF has a primary endpoint of all-cause death and hospitalisation due to heart failure, and will therefore contribute important information with regard to target haemoglobin concentrations in a separate but overlapping disease process to that of chronic kidney disease.

Of interest is that the active erythropoiesis-stimulating agent in both RED-HF and TREAT is darbepoetin. Whether our findings can be extrapolated to this agent is unclear, since no long-term trial data regarding its use and safety in patients with chronic kidney disease were able to contribute to our analysis.

Our meta-analysis has several limitations, related both to meta-analyses in general and to this study in particular. Meta-analyses are not a substitute for a properly done, adequately powered randomised controlled trial. However, to appropriately address all-cause mortality outcomes in this patient population, a commitment to a massive trial would be required and is unlikely to occur. Thus, well-conducted meta-analyses are of considerable importance in addressing these clinical questions. Furthermore, all meta-analyses are affected by the variation in reporting methods used by different investigators. An inconsistency in key definitions and reporting style—eg, with respect to blood pressure and what is meant by uncontrolled hypertension—has the potential to affect the integrity and validity of the presented data. Such an inconsistency was also evident with respect to reported changes in left ventricular mass, which prevented us from doing a meta-analysis for this outcome. Similarly, the various composite endpoints reported by studies were not able to be combined formally because of inconsistencies in endpoint components.

Bias towards reporting of positive trials can also affect the findings of meta-analyses. We have sought to minimise publication bias by ensuring that our literature search was as rigorous as possible, in accordance with recommendations by experts in analyses of this nature.[17,47] Additionally, heterogeneity in outcomes should also be taken into account when interpreting the results of meta-analyses. However, there was, in general, very little heterogeneity in the outcomes examined here. Issues specific to the agent studied—eg, masking both patient and investigator to a clearly identifiable injectable agent—could be relevant to the internal validity of blinded randomised controlled trials and thus of this meta-analysis.

Pooling of studies that involved patients on dialysis with studies that included patients who are deemed to be predialysis could also be a source of bias. However, we feel that the combined data is the best possible summation of the current database regarding this issue. This is supported by both the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) clinical practice guidelines[12] and the ERA-EDTA guidelines,[32] which used combinations of these studies in the development of their recommendations. Our subgroup analyses, which assessed predialysis and dialysis patients with chronic kidney disease separately, supports this contention, with generally concordant results in both subgroups.

Our results raise important questions with regard to the appropriateness of current target haemoglobin concentrations in anaemic patients with chronic kidney disease who are being treated with recombinant human erythropoietin. Current guidelines[12,32] for anaemia management in chronic kidney disease recommend the maintenance of haemoglobin concentrations at 110 g/L or more, which is based mainly on evidence of benefit with regard to some quality-of-life measures. However, although the 2006 NKF-KDOQI clinical practice guidelines suggest that there is little evidence of benefit of maintaining haemoglobin concentrations above 130 g/L, they do not specifically recommend any strict upper limit of target haemoglobin concentration for anaemic patients with chronic kidney disease being treated with recombinant human erythropoietin.[12] This meta-analysis shows an excess risk of major adverse events—including death—when haemoglobin is raised to 120–160 g/L in such individuals. Although such a concentration of haemoglobin is within the normal physiological range, any putative clinical benefits seem to come at the expense of reduced survival in these patients. Therefore, an upper limit for target haemoglobin concentrations should be considered in future revisions of guideline recommendations.

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