High versus low dose erythropoiesis-stimulating agents in people with end-stage kidney disease treated with haemodialysis (C.E. DOSE): an open-label, pragmatic, multicentre, parallel-group randomised controlled trial

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Background The increased risks of death and cardiovascular complications with erythropoiesis-stimulating agent (ESA) therapy targeting a higher haemoglobin (Hb) level are established, it is thought that these may be dependent on the dose of ESA used, but the benefits and harms of a fixed high vs low ESA dose treatment approach are not established.

Methods C. E. DOSE was a multicenter, pragmatic, non-blinded, randomised controlled, parallel-group trial that randomised 656 hemodialysis patients with anemia to receive either high dose (18,000 IU epoetin alfa or beta or 90 mcg darbepoetin alfa per week) or low dose (4000 IU epoetin alfa or beta or 20 mcg darbepoetin alfa per week) ESA. Rescue dose adjustments were made when the Hb level moved outside the safety range of 9·5-12·5 g/dl. The primary outcome was the composite of death or a cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, or hospitalization for acute coronary syndrome, transient ischemic attack, unplanned percutaneous coronary intervention or peripheral revascularization). Secondary endpoints included components of the primary outcome, health-related quality of life, blood transfusions, blood pressure, and Hb levels. Analyses were by intention to treat (ClinicalTrials.gov, number NCT00827021).

Results Between July 2009 and July 2013, 332 people were randomly assigned to receive high dose ESA and 324 to low dose ESA (**Figure 1**). Enrolment ceased at 656 patients, rather than at 2104 patients as planned, because of slow recruitment and convergence of ESA dose in the two groups by 12 months (**Figure 2**). Baseline characteristics, including haemoglobin level and ESA dose, were well-balanced between groups with the exception of a history of dyslipidaemia which was higher in the high dose group (**Table 1**). All follow-up data were completed by July 19, 2014. High dose ESA compared with low dose did not change the risk of primary composite outcome (55 [17%] *vs* 46 [14%] patients; hazard ratio [HR] 1·19, 95% CI 0·81–1·77) or death alone (40 [12%] *vs* 35 [11%]; HR 1·21, 95% CI 0·77–1·91) at 12 months (**Figure 3**), and had no impact on health-related quality of life. Patients allocated to high dose therapy experienced a lower risk of red cell blood transfusions (16 patients received 46 transfusions in the high dose arm versus 31 patients had 52 transfusions in the low dose arm; hazard ratio 0·51, 95% CI 0·28–0·93).

Figure 1: Flow chart of patient progression through the trial.

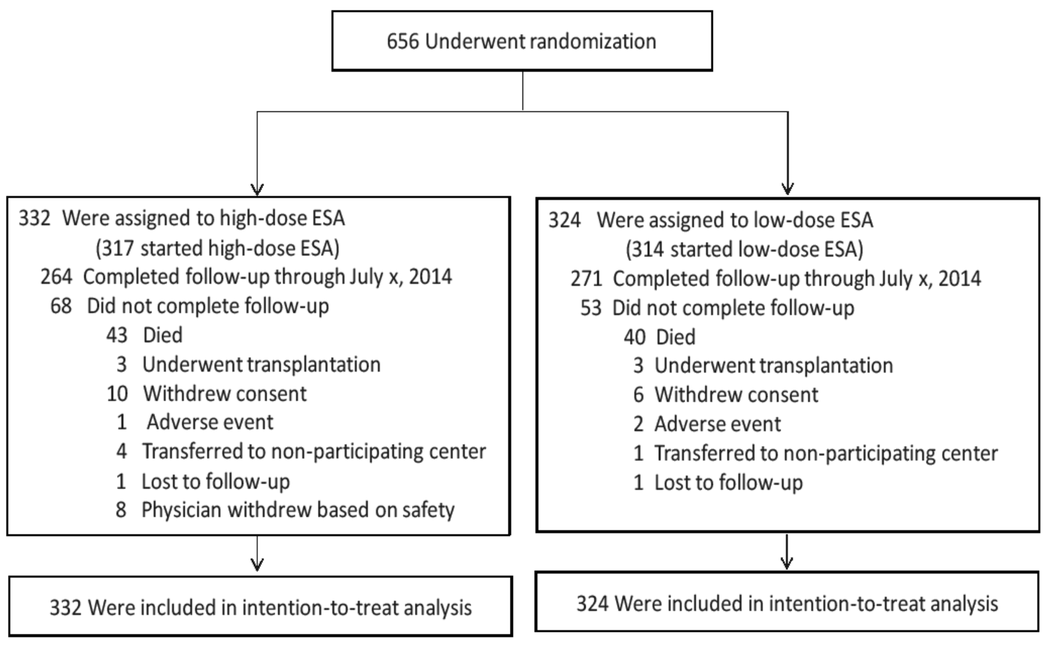


Table 1: Baseline characteristics of patients.

Variable	High-Dose Group (N = 332)	Low-Dose Group (N = 324)
Age (years)	66·6 ± 12·9	65·2 ± 15·2
Female	135 (40·7)	117 (36·1)
Primary cause of end-stage kidney disease		
Primary glomerulonephritis	58 (16·7)	54 (16·7)
Hypertension/diabetes/vascular disease	147 (44·3)	133 (41·0)
Congenital including cystic disease	23 (6·9)	25 (7·7)
Interstitial nephritis	6 (1·8)	5 (1·5)
Pyelonephritis	19 (5·7)	16 (4·9)
Hereditary disorder	5 (1·5)	5 (1·5)
Other	10 (3·0)	17 (5·2)
Coexisting conditions		
Hypertension	244 (73·5)	237 (73·1)
Dyslipidaemia	109 (32·8)	78 (24·1)
Diabetes	90 (27·1)	70 (21·1)
Ischemic heart disease	80 (24·1)	60 (18·5)
Transient ischemic attack	16 (4·8)	13 (4·0)
Heart failure	25 (7·5)	27 (8·3)
Wait-listing for kidney transplantation	30 (9·0)	39 (12·0)
Previous kidney transplantation	36 (10·8)	35 (10·5)
Erythropoiesis-stimulating agent	313 (94·3)	303 (93·5)
Epoetin alfa or beta (IU/week)	9000 (6000–16,000)	8000 (5000–15,000)
Darbepoetin alfa (µg/week)	30 (20–60)	40 (25–60)
Dialysis characteristics		
Time treated with dialysis (months)	51 (11–83)	47 (15–80)
Duration per dialysis treatment (minutes)	232 (21·0)	232 (23·5)
Kt/V urea	1·43 (0·38)	1·40 (0·35)

Data are mean (SD) or median (IQR), or frequency (percentage).

Figure 2: Haemoglobin levels and erythropoietin-stimulating agent doses during treatment

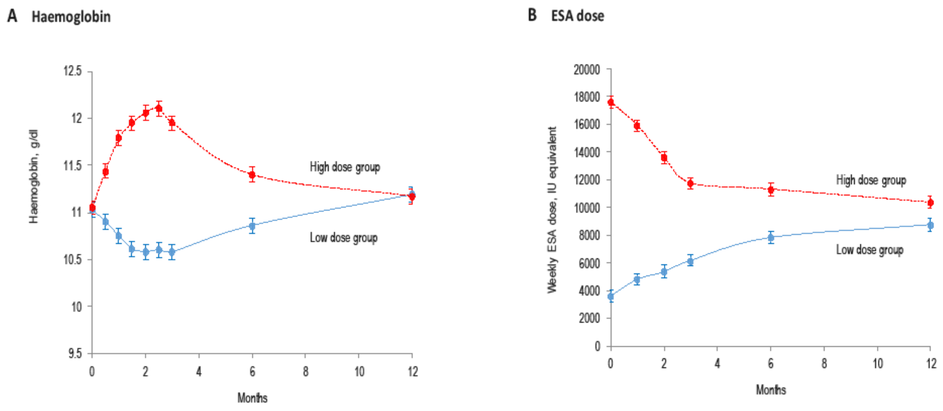
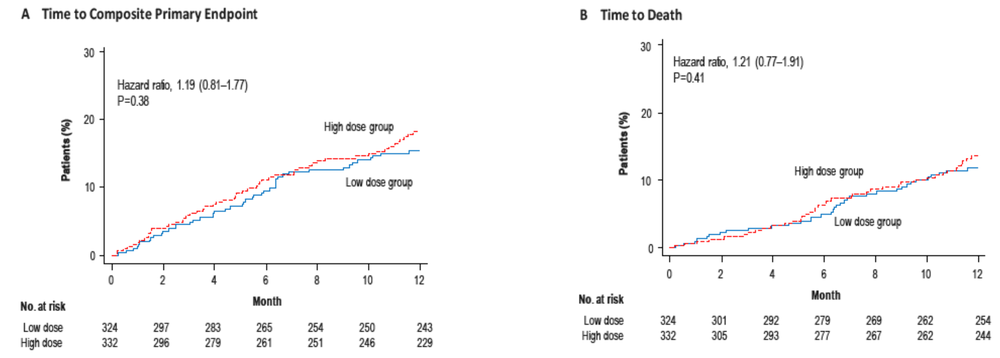


Figure 3: Effects of high versus low dose ESA on primary composite endpoint and death at 12 months.



Conclusion

In this trial of erythropoiesis-stimulating agent treatment for anaemia in haemodialysis patients, a high dose strategy (18,000 IU) had uncertain effects on mortality, cardiovascular disease, and health-related quality of life while offering lower risk of blood transfusion compared to low dose (4000 IU). For many patients, the uncertain risks of fixed high dose treatment may outweigh this clinical benefit.

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