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Comparison of two treatment strategies for treating anaemia with erythropoiesis stimulating agent therapy among haemodialysis patients: findings from a marginal structural model

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Introduction: Erythropoiesis stimulating agents (ESAs), with intravenous iron supplementation, are the main treatment for anaemia in patients with chronic kidney disease (CKD). Although observational studies suggest better outcomes for patients who achieve higher haemoglobin (Hb) levels, randomized controlled trials (RCTs) in haemodialysis patients with cardiac disease (1) and patients with CKD (2-4) have shown poorer outcomes with higher target Hb, leading to changes in treatment guidelines (5). The aim of this study was to use electronic health record data to simulate a trial of a higher versus lower target Hb strategy in haemodialysis patients, to investigate associations of strategy with mortality, whilst taking account of time-dependent confounding by Hb levels.

Methods: Data were obtained from electronic records, from selected hospitals that record and submit ESA doses to the UK Renal Registry. The observational data were used to emulate a pseudo RCT to compare the effect of two target Hb strategies: 95-115 g/L (low Hb strategy) and 105-125 g/L (high Hb strategy). Protocol restrictions were applied to dosing decisions (e.g. by how much doses could be increased/decreased) and doses of up to 150 micg/week darbepoetin were allowed in both strategies. Patients were eligible if they were aged over 18 years and were on haemodialysis for at least 3 months. People were excluded if they had a high ESA dose (≥120 micg/week) and low Hb (<80 g/L) at the start of their eligibility. The outcome of interest was all-cause mortality. Inverse-probability weighting of a marginal structural model was used to control for measured baseline covariates of patient age, hospital, cause of end-stage renal disease and time-dependent covariates of Hb, previous ESA dose, ferritin and c-reactive protein. Each patient's follow-up was duplicated, with one copy of follow-up data assigned to the low Hb strategy and the other copy assigned to the high Hb strategy. Everyone was eligible for both strategies at baseline and follow-up was censored when a dosing decision deviated from protocol (6). We used inverse probability of censoring weights to account for protocol deviation and modality changes to peritoneal dialysis and transplantation.

Results: A total of 8,119 patients from 11 hospitals were eligible for the pseudo RCT, with follow-up from 2014-2016. There were 637 deaths from 72,782 patient months in the low Hb strategy and 641 deaths from 88,339 patient months in the high Hb strategy. The median weekly dose in both strategies was 30 micg/week darbepoetin. The hazard ratio (HR) (95% confidence interval; CI) for the high versus low Hb strategy was 0.66 (0.48–0.91) for all-cause mortality, when truncating weights at the 95th percentile (Figure 1). Truncating at the 90th percentile of weights gave a HR (95% CI) of 0.71 (0.58-0.88).

Conclusions: We did not find evidence of harm from a higher Hb target when examining all-cause mortality. Haemodialysis patients may benefit from a higher Hb under a dosing strategy that limits changes in dose and maximum dose. However, this observational study cannot exclude the possibility of unmeasured confounding.