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Erythropoiesis-stimulating agents and thrombotic events in dialysis patients

Marit M. Suttorp [a,*], Tiny Hoekstra [a], Gürbey Ocak [a], Anouk T.N. van Diepen [a,b], Ilka Ott [c], Moshe Mittelman [d], Ton J. Rabelink [e], Raymond T. Krediet [b], Friedo W. Dekker [a]

[a] Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Nephrology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[c] Deutsches Herzzentrum der Technischen Universität München, Munich, Germany
[d] Department of Medicine, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv, Israel
[e] Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Background: Erythropoiesis-stimulating agents (ESA) have been associated with a higher cardiovascular event and mortality rate in dialysis patients. The ESA-associated risk of arterial thrombotic events is mainly based on composite endpoints of anemia-correction trials targeting high hemoglobin levels. The ESA-associated risk of venous thromboembolism (VTE) has not been studied in dialysis patients yet. We therefore aimed to determine the association between ESA use and dose with ischemic stroke, myocardial infarction (MI) and VTE.
Materials and Methods: In NECOSAD, a Dutch cohort study of incident dialysis patients, data on ESA use and dose, comorbidities and laboratory parameters were routinely collected every 6 months. Thrombotic events were collected by chart review of all dialysis patients from 6 participating centers. Time-dependent Cox regression analysis was performed to calculate hazard ratios (HR) with 95% confidence interval (CI) for ischemic stroke, MI and VTE with updated information on ESA use and dose.
Results: Patients with ESA had a 2 times lower ischemic stroke rate than patients without ESA: adjusted HR 0.45 (95% CI 0.23-0.90), and an adjusted HR of 1.12 (95% CI 0.58-2.14) for MI. No evident ESA dose response effect was present. Unadjusted HR for VTE was 0.41 (95% CI 0.11-1.50) for patients with ESA compared to patients without, but the low event rate made further adjustments impossible.
Conclusions: In our observational cohort of dialysis patients, reflecting everyday clinical practice, ESA was not associated with an excess of thrombotic events. Further investigation is needed to enlighten the true cause of ESA-associated cardiovascular events and mortality.

Introduction

The introduction of erythropoiesis stimulating agents (ESAs) has been a breakthrough in the anemia management of patients with chronic kidney disease (CKD). Nowadays about 90% of dialysis patients are treated with ESAs[1] and various studies reported significant increases in quality of life [2]. After the successful implementation of ESA treatment, several anemia-correction trials were conducted, trying to find the optimal target hemoglobin (Hb) level. Unexpectedly, an increase in myocardial infarction (MI) and death was reported in hemodialysis patients in the high Hb arm of the normal hematocrit study (NHS) [3]. Subsequent trials also showed increases in composite endpoints of serious adverse cardiovascular events (CHOIR and CREATE) [4,5] or stroke (TREAT) [6] in CKD patients assigned to the higher Hb arm of the trial, although not always statistically significant.

This potentially higher cardiovascular event rate has led to a debate about the safety of ESA's, since patients in the higher Hb arms were treated with on average higher ESA doses. It has been hypothesized that ESAs increase arterial blood pressure, alter endothelial function and may result in pro-thrombotic changes[7], all contributing to a higher risk of cardiovascular and especially thrombotic events. These findings resulted in a series of warnings in the ESA label by the US Food and Drug Administration (FDA) starting in 2007 [8]. However, the aforementioned trials were designed to identify the optimal target Hb level and not to evaluate the safety of ESAs. By targeting higher Hb levels in a selected group of patients, the trials might not adequately reflect everyday clinical practice in the general dialysis population. Furthermore, conclusions were mainly based on composite endpoints, including all-cause mortality and a diverse spectrum of cardiovascular events.

* Corresponding author at: Department of Clinical Epidemiology C7-83, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 71 526 1510.
E-mail address: M.M.Suttorp@lumc.nl (M.M. Suttorp).

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Results from observational studies could aid to unravel the potential risk of ESA for thrombotic events. Unfortunately, observational studies mainly focused on mortality risk with high ESA doses and were unable to assess the non-fatal thrombotic events [9–12]. Furthermore, no study associated the use of ESA with venous thromboembolism (VTE) in dialysis patients yet, whereas a meta-analysis reported a 1.57 increased risk of VTE in ESA treated oncology patients with chemotherapy associated anemia [13]. Thus, it is important to evaluate whether ESA treated patients indeed experience more thrombotic events in clinical practice. We therefore conducted the present study to determine the association between ESA use and dose with ischemic stroke, MI and VTE in a cohort of incident dialysis patients.

Materials and methods

Study design

The Netherlands Cooperative study on the Adequacy of Dialysis (NECOSAD) is a multicenter cohort study in which incident adult dialysis patients from 38 centers in the Netherlands were included. Patients without previous renal replacement therapy who started dialysis between January 1997 and January 2007 were eligible. All patients gave informed consent and the study was approved by all local medical ethics committees. For the present analysis, we conducted a review of the medical records of all patients from six dialysis centers that participated in NECOSAD to obtain more detailed information on history and occurrence of thrombotic events. These six centers were two academic hospitals and four regional hospitals and were chosen for logistic reasons, meaning they provided a large number of patients for efficient data collection. Information on thrombotic events (ischemic stroke, MI and VTE) was collected from start of dialysis until death or censoring. Censoring was defined as transfer to a non-participating dialysis center, withdrawal from the study, transplantation or end of the follow-up period, which was June 2009. Baseline of follow-up was set at three months after start of dialysis, since our interest was in chronic dialysis patients and patient characteristics are usually not yet stabilized immediately after start of dialysis.

Demographic and clinical data

Data on age, sex, primary kidney disease, comorbidities and medication were collected at the start of dialysis treatment. Primary kidney disease was classified according to the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) codes and grouped into four categories: diabetes mellitus, glomerulonephritis, renal vascular disease, and other kidney diseases [14]. Data on comorbidities and medication were updated three and six months after start of dialysis and in subsequent six month intervals. Comorbid conditions were classified by the patients' nephrologist and verified by chart review. Nutritional status of the patients was measured by trained nurses with the 7-point subjective global assessment (SGA) [15]. A score of 1 or 2 was classified as severe malnourished and 6 or 7 as well-nourished. Blood and 24-hour urine samples were obtained three and six months after start of dialysis and then in subsequent six month intervals. For hemodialysis patients, blood samples were taken before the dialysis session. Hb, albumin, ferritin, creatinine and urea were routinely measured in serum. Urea and creatinine were also determined in urine samples and residual glomerular filtration rate (rGFR) was calculated as the mean of creatinine and urea clearance corrected for body surface area and expressed as mL/min per 1.73 m^2.

ESA

ESA use was recorded at start of dialysis, three and six months after start of dialysis and in subsequent six month intervals. ESA dose was registered in units per week. For darbepoietin the dose in micrograms was converted to units by multiplying with 200. ESA dose was divided into tertiles of ≤4000, 4001-8000 and >8000 units per week.

Thrombotic events

Endpoints were fatal and non-fatal thrombotic events during five years of dialysis. Symptomatic ischemic stroke, MI and VTE (deep vein thrombosis and pulmonary embolism (PE)) were identified from hospital diagnosis registration systems and review of medical records with a pre-specified standardized check list. In general, thrombotic events were scored when diagnosed by a treating physician, implicating that only clinically relevant symptomatic events were recorded. Additionally, ischemic stroke had to be diagnosed by computed tomography or magnetic resonance imaging. MI was scored in the presence of typical angina with elevated levels of cardiac enzymes and/or electrocardiogram changes. VTE was considered confirmed when diagnosed by compression ultrasound for deep vein thrombosis or by spiral computed tomography or ventilation-perfusion scanning for PE. In addition, information about the occurrence of thrombotic events was completed with the causes of death as classified by the ERA-EDTA codes [14].

Statistical analysis

Baseline characteristics were stratified for patients with and without ESA. Continuous data were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), as appropriate, and categorical data as percentages. Differences in baseline characteristics were tested with an unpaired Student's t-test, Mann-Whitney (continuous data) or chi-square test (categorical data). Incidence rates were calculated for ischemic stroke, MI and VTE. Time-dependent Cox regression analysis was performed to calculate hazard ratios (HR) with 95% confidence interval (CI) for ischemic stroke, MI and VTE with updated information on ESA use. Analyses were adjusted for baseline confounders, namely age, sex, primary kidney disease, comorbidities, dialysis modality, nutritional status, ferritin, rGFR and albumin. Missings were present for the following parameters: Hb 1.2%, rGFR 23.3%, SGA 24.2%, albumin 6.5%, ferritin 5.6% and ESA dose 8.7%. Missing data were imputed with standard multiple imputation techniques in SPSS with 10 imputation sets, based on the Markov Chain Monte Carlo (MCMC) method [16].

Sensitivity analysis

To test the robustness of our results, several sensitivity analyses were performed. In the main analyses we adjusted for baseline confounders to avoid the risk of adjusting within the causal pathway. However, to account for the potential influence of changes in covariates we repeated the analyses with time-dependent confounders. In addition, analyses were performed with additional adjustment for Hb, systolic and diastolic blood pressure. These factors might also be intermediates in the causal pathway and are therefore not included in the main analyses. To further validate our results, baseline was set at the start of dialysis and analyses including the first 3 months on dialysis were done. Furthermore, our analyses were repeated in patients with diabetes mellitus or cardiovascular comorbidity. Last, in analogy with the anemia-correction trials, we performed an analysis according to Hb categories in ESA treated patients, to explore the association with achieved Hb.

Results

A total of 808 NECOSAD-patients were identified from six hospitals. Three patients from three different hospitals were excluded because the charts could not be retrieved. Of the remaining 805 patients, 755 reached baseline measurement at three months after start of dialysis (35 patients died, 4 recovery of renal function, 1 renal transplant and 10 other).