Chapter 7

Treatment with high dose of erythropoiesis-stimulating agents and mortality: analysis with a sequential cox approach and a marginal structural model

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Abstract

Introduction Anemia-correction trials indicated higher mortality rates in chronic kidney disease patients assigned to higher hemoglobin targets. The safety of the high erythropoiesis-stimulating agent (ESA) doses that these patients received has therefore been questioned. However, no trial that directly compares treatment with different ESA doses has been published. We thus aimed to estimate the effect of high ESA dose on mortality in an observational cohort of dialysis patients.

Methods NECOSAD is a Dutch cohort study of incident dialysis patients in which ESA dose, comorbidities and laboratory parameters were collected every 6 months. Mortality in patients with a high ESA dose (above median 6,000 units/week) was compared to patients with no or a low ESA dose with Cox regression analyses. To handle time-dependent confounding, a sequential Cox approach was used conditional on baseline covariates, with inverse probability of censoring weights (IPCW) for dependent censoring. Analyses were repeated with a Marginal Structural Model (MSM) with inverse probability of treatment weights and IPCW.

Results Hazard Ratio (HR) for high ESA dose was 1.20 (95% CI 0.83-1.73) with a sequential Cox and 1.54 (95% CI 1.08-2.18) with a MSM. Truncation of weights in the MSM did not affect estimates. To compare: conventional Cox analyses indicated a baseline adjusted HR of 1.66 (95% CI 1.20-2.31).

Conclusion Patients treated with high ESA dose have a 1.2-1.5 increased risk of mortality. Our analyses support guidelines advising a conservative ESA dosing regimen, which carefully weighs the patients' benefits and risks.

Introduction

The safety of erythropoiesis-stimulating agents (ESAs) has been questioned after the publication of several anemia-correction trials in patients with chronic kidney disease. These randomized clinical trials indicated that ESA treatment with higher hemoglobin (Hb) targets was associated with an increased cardiovascular event or mortality rate.[1-3] However, these events were not only attributed to the higher Hb targets. Since patients in the high Hb arm of the trials were treated with on average higher ESA doses, the safety of ESAs and especially high ESA doses became a topic of debate. It resulted in a series of warnings by the FDA in the ESA label.[4]

In the absence of randomized controlled trials designed to evaluate the safety of high ESA doses, observational studies could aid to answer this question. Estimating the effect of ESA and ESA dose on survival in observational studies requires careful adjustment for confounding. It has been suggested that the observed association between ESA dose and mortality may be highly dependent on the analytic method used.[5;6] Since the dose of ESAs is prescribed and titrated according to achieved Hb levels, the current ESA treatment is a consequence of previous ESA treatment and Hb level. Subsequently, current ESA treatment will also affect future Hb levels and ESA treatment. This complex relation between ESA dose and Hb, even further complicated by other concurrent comorbid conditions, results in time-dependent confounding. Conventional survival analysis methods do not adequately control for time-dependent confounding.[7] Previously, a number of studies used marginal structural models (MSMs) to estimate the effect of ESA dose on mortality. In MSMs, inverse probability weights are used to adjust for time-dependent confounding.[8;9] An alternative method to handle time-dependent confounding, is a sequential Cox approach.[10] With this approach, Cox regression analyses are performed on several landmark datasets with consecutive baseline timepoints, and stacked in the overall analyses.

Previous results from MSMs were not conclusive and ranged from no effect of higher ESA doses on mortality to a possible harmful effect of higher ESA doses.[6;11-13] Furthermore, all previous analyses were performed on large cohorts of patients from the United States (US). US patients are treated with higher ESA doses than patients in most European countries. The generalizability of these results to European countries is thus questionable.[14] We therefore aimed to estimate the effect of high ESA dose treatment on mortality in a cohort of incident dialysis patients in the Netherlands. To adequately handle time-dependent confounding, two statistical models were used. We first used a sequential Cox approach and subsequently fitted a MSM.

Methods

Study design

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD-II) is a prospective multicentre cohort of dialysis patients. Between January 1997 and January 2007 incident dialysis patients from 38 dialysis centers throughout the Netherlands were enrolled. Patients were eligible if they started hemodialysis or peritoneal dialysis for the first time and were at least 18 years of age. All patients gave written informed consent before inclusion. The NECOSAD study was approved by the medical ethical committees of all participating centers. Baseline was defined as 3 months after start of dialysis since our interest is in chronic dialysis patients and patient characteristics are usually not yet stabilized immediately after start of dialysis. For the present analysis, all patients with information on ESA use and confounding factors at baseline were included.

Baseline variables and time-varying variables

Age, gender, primary kidney disease, medication and comorbidities were collected at start of dialysis treatment. Primary kidney disease was classified according to the European Renal

Association-European Dialysis and Transplant Association (ERA-EDTA) codes[15] and grouped into four categories: diabetes mellitus, glomerulonephritis, renal vascular disease and other. Data on medication, comorbidities, blood and 24-hour urine samples were collected at three and six months after start of dialysis and in subsequent 6 month intervals. Comorbidities were classified by a nephrologist. Cardiovascular disease consisted of angina pectoris, myocardial infarction, heart failure, stroke and claudication. Nutritional status was measured by trained nurses with the 7-point subjective global assessment (SGA).[16] Both hemodialysis and peritoneal dialysis patients were included in the study. Patients were not censored at modality switch, modality was measured and incorporated as a time-varying variable in the analyses. For hemodialysis patients, blood samples were taken before the dialysis session. Hb, albumin, ferritin, creatinine and urea were measured in serum. Urea and creatinine were also determined in urine samples. Residual glomerular filtration rate (rGFR) was calculated as the mean of creatinine and urea clearance corrected for body surface area (mL/min per 1.73m^2).

ESA

ESA treatment was recorded from start of dialysis and in subsequent six month intervals, with an extra measurement at three months after the start of dialysis (baseline). Dose was registered in units per week. For darbepoietin dose in micrograms was converted to units by multiplying with 200. For the analyses, an ESA dose above median (6,000 units/week) was regarded as treatment with high ESA dose. ESA dose up until median dose and no ESA treatment was considered the reference.

Outcome definition

The endpoint was all-cause mortality. Patients were followed until death, kidney transplantation or the end of follow-up in May 2009.

Statistical analyses

Baseline characteristics were stratified for patients with no or low ESA dose and high ESA dose at 3 months after start of dialysis. 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). For descriptive purposes and in analogy with the MSM analysis, stacked cumulative incidence curves of death, kidney transplant and ESA treatment switch were constructed with competing risks,[17] with mstate for the calculation of the cumulative incidences.[18] The cumulative incidence of mortality was calculated for both the low dose or no ESA treatment group and the high ESA dose group at baseline. Kidney transplant and deviation from initial ESA treatment (thus later switch from high dose ESA treatment to no or low dose ESA treatment and vice versa) were regarded as competing risks, and all cumulative incidences were stacked in one plot.

Sequential Cox approach

The effect of starting with high ESA dose treatment on survival was estimated with sequential Cox regression analyses, to adequately handle time-dependent confounding.[10] The basic idea of this approach is to mimic a sequence of clinical trials at a number of time points, providing comparison of outcomes of patients starting high ESA dose at that time point with patients who are never treated with high ESA dose. Those time points are called landmark time points. Patients with a first time recording of a high ESA dose in the month before the landmark were compared to patients not treated with high ESA doses up until the landmark. Patients already treated with high ESA dose more than a month before the landmark were thus excluded, as we wanted to compare patients who had started with high ESA dose with patients who did not start high ESA dose. In order to obtain unbiased estimates,

the comparison was adjusted for confounding factors at the landmark (confounding factors shown in the baseline table), and were artificially censored at time of later start with high ESA doses for the patients not treated with high ESA doses at the landmark. Inverse probability of censoring weights (IPCW) were used to adjust for any dependent censoring, including censoring due to kidney transplantation and the artificial censoring of patients in the no or low ESA treatment group that start with high ESA doses during follow-up. Cox regression was used to estimate the denominator of the IPCW, predicting the probability of being censored, given the patient's baseline and time-varying covariates, using last observation carried forward. The IPCW were stabilized by using as numerator the calculated probability of the observed censoring obtained from the Kaplan-Meier estimator. The analysis was performed for 21 landmark data sets with landmarks at the 4th until the 24th month after start of dialysis, each with follow-up until the end of the study. An overall analysis was obtained by stacking the 21 landmark data sets, and estimating one causal effect assumed to be constant over the landmark time points. Since the same individual may appear in more than one landmark data sets, robust sandwich estimators were used to adjust for clustering. A linear interaction between time and high ESA dose was used to test whether the effect of high ESA dose changed with follow-up time. The effect estimate of the sequential Cox model has a causal interpretation under the assumption of no unmeasured confounding and correct model specification for the hazard rate and censoring weights.[10]

Marginal structural model

Subsequently, a MSM was created by calculating inverse probability of treatment weights (IPTW).[19] Patients received a weight inversely proportional to the chance of receiving their actual ESA treatment. Patients who were unlikely to receive a high ESA dose, but did in reality, received a relatively large weight. Patients who were treated as predicted, contributed less to the analysis. In this way a pseudo-population is

created in which there is no association between confounding and ESA treatment and confounding is thus controlled for. The treatment effect has a causal interpretation under several assumptions: exchangeability, positivity, consistency and correct model specification.[9] The data was organized in 10 day intervals, with last observation carried forward. Logistic regression and Cox regression were used to estimate the denominator of the IPTW, given the patient's baseline and time-varying covariates (covariates shown in baseline table). First, logistic regression was used to estimate the probability of starting treatment with high ESA dose. Subsequently, Cox regression was used to estimate the probability of continuing the initial ESA treatment. In addition, IPCW were created with Cox regression based on baseline and time-varying covariates. IPCW were used to correct for dependent censoring due to kidney transplant and ESA treatment switch. IPTW and IPCW were stabilized by using the observed population probability of treatment or censoring as the numerator, so independent of individual covariates. These observed probabilities were obtained from Kaplan-Meier curves or proportions. The final weights for the marginal structural model were calculated as the product of IPTW and IPCW. To reduce the effect of few patients with extremely large weights, a sensitivity analysis was performed in which weights were truncated at the 1st and 99th percentiles. 95% Confidence intervals (CI) were calculated using bootstrap with 100 replications.

Additional analyses

For comparison, conventional Cox regression analyses were also performed with time-updated ESA treatment. Analyses were adjusted for baseline confounders, not taking changes in covariates into account, thus expecting to contain residual confounding. Analyses were repeated adjusting for time-updated confounding, which probably adjusts in the causal pathway and could introduce collider-stratification bias.[20] Furthermore, we performed multiple sensitivity analyses. First, hospitalization in the previous 6 months (yes/no) was

included as a covariate to evaluate the impact of hospitalization in addition to our other covariates. Furthermore, to compare only ESA treated patients, patients that were not treated with ESA were excluded from start of the analysis or censored when they switched from treatment to no ESA treatment. Last, to explore the influence of last Hb carried forward, analyses with interpolation of Hb between two measurements was performed with the sequential Cox analysis.

R version 2.15.1 was used for the analyses, and mstate for calculation of the cumulative incidences.[18]

Results

Table 1 depicts the descriptive characteristics of 1463 patients with complete baseline information at three months after start of dialysis, stratified by ESA treatment. At baseline, 536 patients were treated with high ESA dose. Patients treated with high ESA dose at baseline were older and more often treated with hemodialysis. Furthermore, patients treated with high ESA dose at baseline had more comorbidities and a lower Hb.

The total number of person-years of follow-up was 4282. During follow-up, 627 deaths were observed and 494 patients were censored due to a kidney transplant. To illustrate, in the first landmark analysis, 67 patients were first recorded with a high ESA dose and 1072 were not treated with high ESA dose up until that landmark. Of these 1072 patients, 441 patients switched to treatment with high ESA dose at a later landmark (and were then analyzed in the high ESA dose treatment group). In total, 35% of patients received a kidney transplant. For the MSM analysis, the cumulative incidence of death, kidney transplant and censoring due to ESA treatment switch are shown stacked in Figure 1. Of the 536 patients that received high ESA dose treatment at baseline, 327 switched

Table 1. Characteristics of patients at baseline (3 months after start of dialysis)

	low or no ESA	high ESA	p
Number	**927**	**536**	
Sex (% male)	63.2	60.1	0.233
Age	57.6 (15.2)	61.1 (14.3)	<0.001
Primary cause of kidney disease (%)			0.028
Diabetes Mellitus	14.7	15.1	
Glomerulonephritis	16.2	11.4	
Renal Vascular Disease	16.8	21.3	
Other	52.3	52.2	
Modality (% hemodialysis)	50.9	79.7	<0.001
Davies comobidity score (%)			<0.001
low	50.8	37.1	
intermediate	41.0	51.3	
severe	8.2	11.6	
Malignancy (%)	7.1	14.4	<0.001
Cardiovascular disease (%)	31.7	41.2	<0.001
Diabetes mellitus (%)	19.7	23.7	0.075
Nutritional status (SGA), (%)			<0.001
severe malnourished	1.2	1.3	
mild-moderate	20.9	31.3	
well nourished	77.9	67.4	
rGFR (ml/min/1.73m2)	3.8 (2.0-5.7)	2.8 (1.3-4.7)	<0.001
Albumin (g/L)	36.7 (4.9)	35.6 (5.2)	<0.001
Ferritin (µg/L)	125 (60-248)	158 (73-308)	<0.001
Hb (g/dl)	11.4 (1.6)	10.9 (1.5)	<0.001
Iron medication (%)	58.7	71.5	<0.001
ESA dose (units/week)	4000 (4000-4000)	10000 (8000-12000)	

Values are presented as mean (standard deviation), median (interquartile range) or percentage.
ESA: erythropoiesis-stimulating agent, rGFR: residual glomerular filtration rate, Hb: hemoglobin, SGA: subjective global assessment.

Figure 1. Stacked cumulative incidences of death, kidney transplant and ESA treatment switch

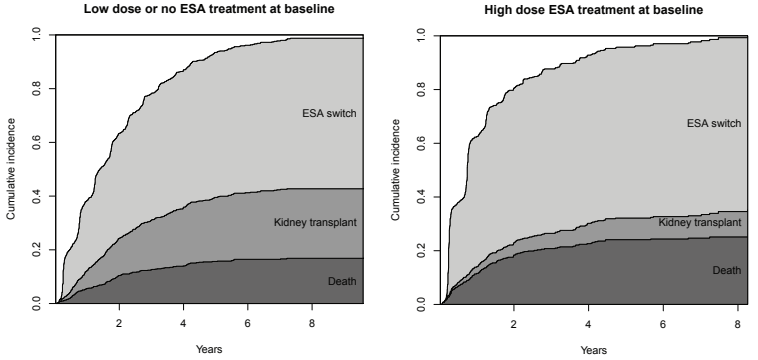
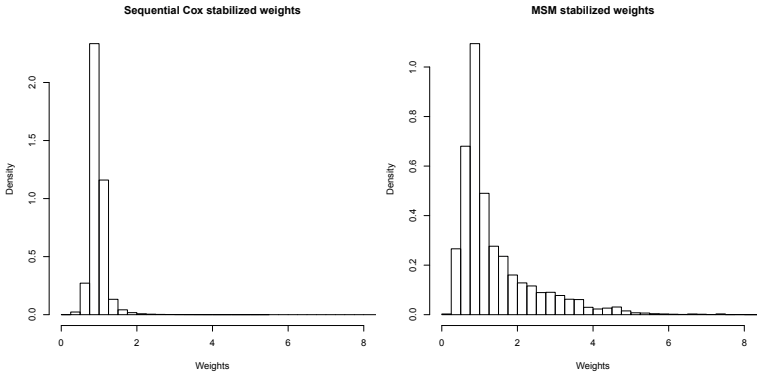


Figure 2. Distribution of inverse probability weights in Sequential Cox (left) and Marginal Structural Model (right)



to low ESA dose. 472 patients who were treated with no or low dose ESA at baseline switched to high ESA dose during follow-up.

Distribution of weights

The distribution of the final stabilized weights for both models are shown in Figure 2. In the sequential Cox model, mean and median of weights was 1.0, with a minimum weight of 0.1 and a maximum weight of 12.1. Since weights were not excessively large in this model, weights were not truncated. For the MSM, final weights had a mean of 1.4 and a median of 0.99. Minimum weight was 0.0 and maximum weight was 45.2. Truncation at the 1st and 99th percentile resulted in a minimum weight of 0.35 and a maximum weight of 5.20, with a similar mean.

High ESA dose and mortality

Table 2 shows hazard ratios (HR) with 95% CI for the effect of treatment with high ESA dose on mortality compared to no or low dose ESA treatment. The sequential Cox approach indicated an overall HR of 1.20 (95% CI 0.83-1.73). The interaction term between time and ESA treatment was not significant, indicating no change in effect over time. The results for the MSM were more or less in line with the sequential Cox approach. The MSM estimated a HR of 1.54 (95% CI 1.08-2.18) for patients with high ESA treatment, which was somewhat higher than the sequential Cox method, and statistically significant. Truncation of weights only changed the effect estimate minimally. To compare, we also performed conventional Cox analyses. Unadjusted analyses indicated a HR of 2.27 (95% CI 1.78-2.89). HRs attenuated with adjustment as shown in Table 3. Estimates ranged from 1.66 to 1.39 for patients treated with high ESA dose, depending on adjustment.

Table 2. Estimated effect of high ESA dose with Sequential Cox and Marginal Structural Model

Model	weights	no/low ESA dose	high ESA dose
Sequential Cox	stabilized	ref	1.20 (0.83-1.73)
MSM	stabilized	ref	1.54 (1.08-2.18)
MSM	stabilized, truncated	ref	1.53 (1.10-2.12)

Estimates are presented as hazard ratios with 95% confidence interval. Weights were based on age, sex, primary cause of kidney disease, Hb, dialysis modality, Davies comorbidity score, malignancy, diabetes mellitus, cardiovascular disease, iron medication, nutritional status, rGFR, ferritin and albumin.
MSM: marginal structural model, ref: reference, ESA: erythropoiesis-stimulating agent.

Table 3. Estimated effect of high ESA dose with conventional Cox analyses

Model	adjustment	no/low ESA dose	high ESA dose
Baseline ESA	unadjusted	ref	2.27 (1.78-2.89)
Baseline ESA	baseline confounding	ref	1.66 (1.20-2.31)
Time updated ESA	baseline confounding	ref	1.59 (1.25-2.03)
Time updated ESA	time updated confounding	ref	1.39 (1.09-1.77)

Estimates are presented as hazard ratios with 95% confidence interval. Analyses are adjusted for age, sex, primary cause of kidney disease, Hb, dialysis modality, Davies comorbidity score, malignancy, diabetes mellitus, cardiovascular disease, iron medication, nutritional status, rGFR, ferritin and albumin. Ref: reference, ESA: erythropoiesis-stimulating agent.

Sensitivity analyses

Several sensitivity analyses were performed to test the robustness of our results. Adding hospitalization as a covariate to the analyses did not materially change the results, with a HR of 1.10 (95% CI 0.75-1.61) in the sequential Cox analyses and a HR of 1.48 (95% CI 0.99-2.23) in the MSM with stabilized and truncated weights. Also, analyses excluding patients without ESA treatment yielded similar results. Last, analyses with interpolation of Hb between two measurements resulted in a HR of 1.14 (95% CI 0.76-1.52) with the sequential Cox analyses.

Discussion

In this study we used two approaches to evaluate the effect of high ESA dose on survival in incident dialysis patients in the Netherlands. With both methods, we found an indication for an increased risk of mortality with high ESA doses, but stronger and significant with the MSM.

Estimating the causal effect of ESA dose on mortality from observational data is complicated by time-dependent confounding, since the current ESA treatment is a consequence of previous ESA and Hb and the current ESA treatment affects future ESA and Hb. Conventional analyses cannot adequately address time-dependent confounding and will probably result in biased estimates.[7] In our study, sequential Cox and MSM analyses indicated a 20%-50% increase in mortality rate for patients with above median ESA doses. Conventional Cox analyses showed a 39%-66% increase in mortality rate.

Previous studies using MSM or pooled logistic models to control for time-dependent confounding, showed conflicting results. Zhang *et al.* first reported no harmful effect of high ESA doses on mortality in elderly hemodialysis patients.[6] However, a few years later they showed a 10-30% increased

risk of mortality with higher ESA doses in elderly and specially diabetic hemodialysis patients, which is in line with our results.[12] Weinhandl *et al.* associated high ESA doses with increased mortality in patients with an Hb above 10 g/dL.[13] Wang *et al.* concluded no association of ESA dose with mortality and also showed that results are sensitive to model specification and truncation.[11] Bradbury *et al.* reported a positive association between ESA dose and mortality with conventional Cox analyses, but a near null though imprecise effect estimate with an instrumental variable approach.[21] Last, Yang *et al.* showed a possible beneficial effect of high ESA dose in severely anemic patients, but possible harmful effect in patients with higher hematocrit levels.[22]

All previous studies that used adequate methods to account for time-dependent confounding were US studies, mostly using USRDS data. Median ESA doses were 8,900-30,000 units/week, also depending on Hb level. This is considerably more than in the Netherlands and most of Europe. Compared to US standards, all Dutch patients were treated with low ESA doses. It is therefore questionable whether results from US studies are generalizable to European countries with different ESA dosing patterns.[14] Also in cancer patients, in whom ESA treatment is related to mortality, most likely due to cancer progression, angiogenesis and thromboembolic events, weekly ESA doses are usually around 30,000 units per week.[23;24] Unfortunately, as in our study in dialysis patients, non-US studies generally have a lower sample size and therefore less power to perform adequate analyses. Previous non-US studies with conventional Cox models showed either no increase in mortality with high ESA dose or increases up to 1.9-fold.[25;26]

This is the first study that used two approaches to account for time-dependent confounding in a non-US cohort of incident dialysis patients. Both our analyses result in comparable effect estimates, but should be interpreted slightly differently. The MSM estimates what would happen if a dialysis patient

always receives high dose ESA treatment versus never, which is perhaps difficult to interpret and imagine in clinical practice. The sequential Cox approach estimates the relative mortality risk of patients with first recorded high dose ESA treatment versus patients that are never treated with high ESA doses, conditional on baseline characteristics. Although this analysis therefore ignores patients already treated with high ESA dose, the interpretation seems more intuitive. In clinical practice patients usually start with lower ESA doses and it is questioned whether they will benefit from treatment with higher ESA doses. Furthermore, IPCWs tend to be more stable than IPTWs.[10] This was indeed confirmed by our findings (Figure 2).

Results from both analyses can be interpreted causally under the assumptions exchangeability, positivity, consistency and correct model specification. Exchangeability implies no unmeasured confounding. Given the prospectively collected detailed information on comorbidities, laboratory investigations and nutritional status, we believe that most important confounding should be controlled for. Also, our sensitivity analyses did not materially change results. However, as with all observational studies, residual confounding or confounding by indication cannot be excluded. More specifically, no detailed information on vascular access problems, inflammation or infection (other than serum albumin, e.g. measured by CRP), and iron status (besides ferritin and use of iron supplementation) could be included, which could potentially cause residual confounding. Since patients treated with high ESA doses are in general more sick and have a higher mortality risk, any residual confounding would probably lead to an overestimation of the harmful effect of high ESA dose. Also, the frequency of data collection in 6-month intervals may in itself introduce misclassification and residual confounding. In general, this misclassification would lead to less predictive power and thus less extreme weights. In theory, this would lead to an overestimation of

the harmful ESA effect, with remaining residual confounding. Our sensitivity analysis with interpolation of Hb did not materially change results. Based on descriptive statistics we believe that the range of confounding variables overlaps enough to assume positivity, thus that both levels of exposure occur within all subgroups. Furthermore, the fact that anemia guideline changes with restrictions on Hb targets in CKD patients and warnings for specific patient populations were only introduced after the inclusion of our cohort, limits the chance of confounding by indication and non-positivity. However, more confounding factors and smaller sample size raise the chance of non-positivity. Furthermore, models for the hazard ratios and weights should be correctly specified. We have some evidence to support that the sequential Cox model was well-specified, because the mean of the stabilized weights was close to one.[9] For the MSM, mean weight was 1.4, which is reasonably close to one, but not exactly. This could indicate a slight suboptimal model specification or some non-positivity. However, the best behaved weights would simply be a constant (one), but would completely fail to adjust for confounding.[9] Last, we believe we can assume consistency since ESA treatment and dose is a rather well-defined intervention.

Other limitations should be considered in interpreting our results. Although information on ESA use and dose was collected routinely, updates were only every 6 months. Fluctuations in ESA treatment in between are therefore not taken into account. On the other hand, these prospectively collected data are therefore probably less sensitive to missing ESA doses due to hospitalizations.[11] Due to the relatively limited sample size for this kind of analysis, further categorizations of ESA doses or stratification by Hb were not feasible. More contrast between ESA dose categories, i.e. very high versus very low ESA dose, could have resulted in a more pronounced ESA effect, as a dose response effect can be assumed. Although robust sandwich estimators were used to adjust for

clustering, this cannot resolve any possible systematic error. But with these remarks in mind, the present study provides insight in the effect of high ESA dose on mortality in a non-US cohort of incident dialysis patients, both HD and PD, including information on the patients' comorbidities, laboratory values and nutritional status.

To conclude, estimating the causal relation between ESA dose and mortality is challenging due to the strong correlation between patient health status, ESA dose requirements and time-dependent confounding of Hb in clinical practice. With two analytical approaches considering time-dependent confounding the excess mortality risk for patients with high ESA dose decreased, but did not fully disappear. In the absence of a randomized controlled trial comparing the effect of different ESA doses, the ideal ESA dosing strategy remains uncertain. Hopefully the currently conducted C.E. DOSE trial will give further guidance.[27] Meanwhile, our analysis also suggests that a conservative ESA dosing regimen is advisable, which carefully weighs the patients' benefits and risks.

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