Chapter 3

Trends in hemoglobin, erythropoiesis-stimulating agents and iron use in Swedish chronic kidney disease patients between 2008 and 2013

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Nephrology Dialysis Transplantation 2015; accepted for publication

Abstract

Introduction The guidelines for anemia management in Chronic Kidney Disease (CKD) patients have changed substantially during the past 10 years. We here evaluate if guideline changes are followed by subsequent modifications in physician's anemia management in Sweden.

Methods We included patients incident to the Swedish Renal Registry for Chronic Kidney Disease non-dialysis (CKD-ND, referred patients with an estimated glomerular filtration rate <45 ml/min/1.73m) and hemodialysis (HD) between 2008 and 2013. Time trends in anemia management were investigated in relation to prescribed medication, laboratory measures, and other relevant clinical characteristics. Linear and binominal regression models were used to describe trends across three predefined time periods (2008-2009, 2010-2011, and 2012-2013).

Results Erythropoiesis-stimulating agent (ESA) use decreased over time both among both CKD-ND and HD patients (Risk Ratio (RR) 2012-2013 compared to 2008-2009 for CKD-ND 0.88 (95% Confidence Interval (CI) 0.81;0.96) RR for HD 0.95 (95% CI 0.93;0.97). Mean ESA dose decreased significantly among HD patients (7% in 2010-2011 compared with 2008-2009 and another 3% during 2012-2013). Over the time periods studied, ESA doses increased slightly in the CKD-ND population. Mean hemoglobin levels decreased in CKD-ND patients, both among ESA-users and non-users, while it decreased to a lesser degree, albeit significantly, among HD ESA-users. The risk of having hemoglobin above 120 g/l decreased, especially between 2008-2009 and 2010-2011. Iron use increased over time, mainly in the HD population, but also among CKD-ND ESA-users.

Conclusion Changes in guidelines have influenced the clinical anemia practice of Swedish nephrology care, resulting in lower ESA use and lower hemoglobin levels.

Introduction

Anemia is a frequent complication of chronic kidney disease (CKD), mainly caused by a decreasing erythropoietin production by the kidney.[1] Since 1989, erythropoiesis-stimulating agents (ESAs) have been approved by the Federal Drug Agency (FDA) for treatment of anemia in patients with CKD. ESAs are effective in increasing the patients' hemoglobin (Hb) while decreasing the need for red blood cell transfusions.[2]

However, between 2006 and 2009, three anemia-correction trials in CKD patients were published, raising concerns on the safety of ESAs and high ESA dosages.[3-5] In response to these trials, along with meta-analyses and reports of ESA-related risks in oncology patients, changes in anemia management guidelines and position statements were published (Figure 1). Between 2004 and 2013 the recommended Hb target has shifted from above 110 g/l (with an upper limit of Hb 140 g/l, except for risk groups) to today's recommendation of initiating ESAs at Hb <100 g/l aiming to maintain Hb below 115 g/l for the majority of the patients.[6] In the US, the FDA currently recommends the lowest dose of ESAs sufficient to reduce red blood cell transfusion and has even removed the target Hb level from the label.[7] As a consequence, US reports have shown a decrease in ESA use, ESA dose and Hb after 2007.[8;9] Finally, a recent US study identified a marked decline in ESA prescribing after the publication of the TREAT in 2009.[10]

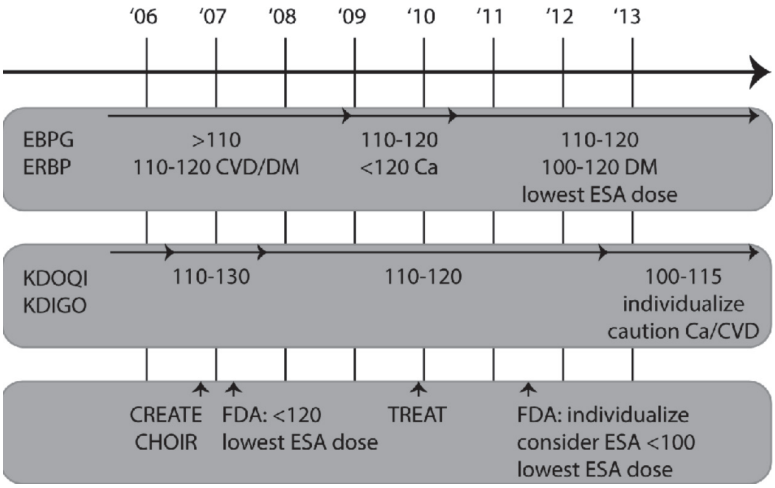
Health care policies are different in the US than in European countries like Sweden, as expressed by the higher ESA doses prescribed in the US.[11] Swedish healthcare is tax-financed with no economic incentives linked to ESA prescriptions or Hb targets. Changes in anemia management in Sweden would therefore be likely attributed to guideline changes, with the European Renal Best Practice (ERBP) as the most influential one. The latest ERBP position statements were published in 2009 and 2010, with an updated commentary in 2013.[6;12;13]

We here evaluate whether the publications and ERBP position statements have influenced the anemia management in Europe. In addition, it is unknown if practice pattern changes differ between chronic kidney disease non-dialysis (CKD-ND) and hemodialysis (HD) patients. The aim of this study was to estimate trends in ESA and iron treatment, ESA dose and achieved Hb levels in a Swedish representative sample of CKD-ND and HD patients from 2008 onwards.

Methods

Patients were those included in the Swedish Renal Registry (SRR), which is a nation-wide registry of patients on renal replacement therapy (RRT) or CKD Stage 3-5 followed at any nephrology clinic in Sweden. The SRR keeps two parallel but reciprocally linked registers: The first register is SRR-CKD, in which nephrology clinics report information on out-patient visits in patients followed at the clinic (referred cohort) with an eGFR <30 ml/min/1.73m^2. The involved centers are also given the option to report patients already with their first diagnosed/referred eGFR <45 ml/min/1.73m^2. The register started on a national level in 2008, but registries were already established regionally in the two largest regions since 1999. Patients are followed until they start RRT. From that point, the second SRR cohort registers yearly information on all patients with chronic dialysis. The yearly cross-sectional measurements are performed in all dialysis patients in Sweden since 2002, and consist of a randomly-selected dialysis session between September 15 and October 15. The national coverage (proportion of patients taking part in the cross-sectional investigation compared to all HD patients in Sweden) was 96.4% in 2013. For the SRR-CKD, the proportion of patients with at least one pre-dialysis visit before starting RRT increased from 59% in 2008-2009 to 70% in 2010-2011 and 76% in 2012-2013.[14] In the current analysis, we included all CKD-ND patients older

Figure 1. Overview of changes in general anemia practice guidelines



Chronology of published guideline changes by institution and important trials between 2006-2013.

than 18 years of age with an estimated GFR (eGFR) <45 ml/min/1.73m^2 (CKD stage 3b – 5) who had not yet started RRT and who had a baseline visit from 2008 onwards. We then selected the first recorded visit to an outpatient clinic during the time period 2008-2013. In the analysis of HD patients we included all incident patients >18 years of age taking part in the yearly cross-sectional dialysis investigation between 2008 and 2013. Thus, patients who were recorded in the national registry before 2008 were excluded from further analyses and each patient only contributed once to the analyses. The study was approved by the regional ethics committee in Stockholm.

Information on demographic data (age, sex, place of residence, and type of nephrology clinic) was obtained as entered into the SRR on the visit date by the local administrators. Current medication (ESA use, type of ESA, ESA dose, iron use and route

of administration) was also registered on the date of the visit together with clinical data (height, weight (dry weight for HD patients), and primary renal disease was classified according to the European Renal Association- European Dialysis and Transplant Association (ERA-EDTA) new coding system). All ESA doses were converted to a weekly epoetin equivalent dose using a 200 IU conversion factor. The laboratory parameters of interest (Blood-Hb, and Serum-ferritin (analyzed by either Dxl or ModE)) were also used as entered into the SRR for the date of the visit (before the dialysis session for HD patients). Information used to calculate standard Kt/V[15] was obtained from the registered dialysis session together with information on current HD access. We linked the CKD-ND cohort to the National Patient Registry (NPR) using the unique patient identification number given to all Swedish citizens to obtain information on comorbidity (ICD codes). Since the information in the NPR is lagging behind, we could only receive comorbidity data for patients included in the SRR before 2012. Trends were analyzed by two-year intervals; 2008-2009, 2010-2011, and 2012-2013, based upon the approximate release of important changes in ERBP guidelines. The first time period (2008-2009) was considered to reflect the 2004 ERBP[16] and 2007 Kidney Disease Outcomes Quality Initiative (KDOQI) update on Hb target,[17] while the second (2010-2011) covers the periods after the TREAT study[5] (November 2009) and the ERBP position statements in 2009 and 2010.[12;13] The last period (2012-2013) reflects the impact of Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines.[18]

Statistical analyses

Differences between patient characteristics according to time period were described using both mean and medians (together with standard deviations and interquartile range), and tested by one-way analysis of variance for continuous variables and chi-square statistics for categorical variables. Age, body mass index (BMI), eGFR according to modification of diet in renal disease (MDRD) equation,[19] and standard-Kt/V

were analyzed and categorized into quartiles. Albumin was entered in the models as a dichotomous variable (above and below the median), while c-reactive protein (CRP) was entered as continuous. Time period was included in the model as continuous variable and also as a categorical factor, based on the above categorization in periods. We used linear regression models to investigate the association between either Hb, log ESA dose or log serum ferritin (the log transformation was necessary due to skewness in the underlying distribution) and time period, adjusting for all relevant clinical variables. We used binomial regression models for estimating the relative risk (risk ratio; RR) to investigate the association between ESA use, Hb >120 g/L and time period. The first period, 2008-2009 was taken as the reference. To better appreciate the changes between 2010-2011 and 2012-2013, the analyses were also shown with the second period as the reference (2010-2011). In few instances the relative risk models could not converge and no estimates were provided. The final models included age, sex, BMI, primary renal disease, albumin and iron use (no use, any iron (oral or intravenous)). In addition, we included eGFR in the final model for the CKD-ND patients and standard Kt/V, use of hemodiafiltration versus hemodialysis, CRP and type of access (catheter versus permanent fistula/graft) for the HD patients. In all statistical models complete case data were used. The proportion of missing information was low, except for BMI and CRP among CKD-ND patients, and ferritin. In the CKD-ND models the introduction of the BMI did not materially change the estimate of the dependent variable. To explore if our results were robust or subject to changes in case-mix, we additionally adjusted for comorbidity (diabetes mellitus, cerebrovascular disease, ischemic heart disease, congestive heart failure and pulmonary disease) during the first two time periods in a sensitivity analysis of the CKD-ND population. Furthermore, we also included CRP into the CKD-ND analyses.

All analyses were performed with Stata 13.1 (StataCorp LP).

Results

Chronic Kidney Disease Stage 3b-5

Between 2008 and 2013 we identified 15,458 eligible CKD-ND patients. Almost two out of three patients were men (64 %) and mean age was 69.6 years. Baseline characteristics are described across the different time periods in Table 1a. Mean age, mean eGFR and the proportion of patients with nephrosclerosis increased during the study period. The observed proportion of patients using ESAs declined from 25.9% in 2008-2009 to 18.6% in 2012-2013, while the mean overall ESA dose did not change. While the mean Hb declined from 123.1 g/l in 2008 to 121.8 g/l in 2013, the mean Hb per time period was stable. The overall unadjusted proportion of patients using either oral or intravenous iron declined during the study period.

In Table 2a we present the adjusted RR of ESA use by time period. The RR of ESA use declined significantly over time; the RR for ESA use was 0.93 (95 % Confidence Interval (CI) 0.86;1.00) for 2010-2011 and 0.88 (95% CI 0.81;0.96) for 2012-2013 (Figure 2a) compared with 2008-2009. The largest decline in ESA use was between the first two time periods, while there was no significant change between 2010-201 and 2012-2013. For the CKD-ND population the mean ESA dose fluctuated, with an increase by 7% from 2008-2009 to 2010-2011, and a slight decrease thereafter (Figure 2b). Also the mean adjusted Hb among ESA-users decreased between the first two time periods (-3.34 g/l (95% CI -4.8;-1.9) in 2010-2012 compared with 2008-2009) while further changes after that were minor (0.24 g/l (95% CI -1.4;1.9) in 2012-2013 compared with 2010-2011) (Table 3a). The mean Hb declined significantly among ESA non-users, but to a lesser extent. Compared with 2008-2009, there was a lower chance for an ESA-treated patient to have an Hb >120g/l (RR 0.86 (95% CI 0.73;1.01) in 2012-2013).

Table 1a. Characteristics of CKD-ND patients

Time period Number	2008-2009 4985	2010-2011 5672	2012-2013 4801
Age	68.6 (14.4)	69.7 (13.8)	70.3 (13.4)
Sex (% men)	64.3	64.1	62.8
Primary renal disease (%)			
Glomerulonephritis	10.3	9.7	8.0
Diabetic nephropathy	19.1	20.7	19.2
Renovascular/nephrosclerosis	22.5	28.9	32.4
Other specified	12.3	11.3	12.2
Unknown	28.7	21.7	21.3
Polycystic kidney disease	4.6	5.2	4.4
Interstitial nephritis	2.6	2.6	2.7
BMI (kg/m^2)	27.5 (5.6)	28.1 (5.7)	27.9 (5.8)
eGFR (ml/min/1.73m2)	21.7 (8.7)	28.1 (5.7)	27.9 (5.8)
Ferritin (µg/l)	155 (80-290)	146 (71-280)	139 (71-261)
C-reactive protein (mcg/l)	5 (3-10)	5 (2-10)	5 (2-10)
Albumin (g/l)	36.9 (4.9)	36.6 (4.9)	36.8 (4.7)
Iron use (%)	19.0	17.1	16.4
intravenous	3.8	5.6	5.5
oral	15.1	11.6	11.0
ESA use (%)	25.9	21.7	18.6
ESA dose (iU/week)	4,000 (2,500-6,000)	4,000 (2,500-6,000)	4,000 (2,660-6,000)
Hemoglobin (g/l)	122.7 (15.5)	121.9 (15.9)	122.8 (16.4)
University hospital (%)	36.1	19.0	25.2

Values are presented as mean (sd), median (interquartile range) or percentages, as appropriate.

CKD-ND: chronic kidney disease non-dialysis, BMI: body mass index, ESA: erythropoiesis-stimulating agent, eGFR: estimated glomerular filtration rate (by MDRD equation). Hemoglobin: to convert g/l to g/dl divide by 10.

Table 2a. Trends in the use of erythropoiesis-stimulating agents in a referred CKD-ND population

	2008-2009	2010-2011		2012-2013		
		adj. RR	95% CI	Adj. RR	95% CI	p-value trend
ESA use*	ref	0.93	0.86;1.00	0.88	0.81;0.96	<0.01
		ref		0.95	0.87;1.04	
		adj. Coef.[1]	95% CI	adj. Coef.[1]	95% CI	p-value trend
ESA dose*	ref	0.08	0.01;0.14	0.05	-0.03;0.12	0.16
		ref		-0.03	-0.11;0.05	

*model adjusted for age, sex, primary renal disease, body mass index, estimated GFR (MDRD) and use of iron (yes/no).

[1] adjusted coefficient interpreted as the percentage change per period.

ESA dose expressed as the log of epoetin-equivalent dose (a conversion factor of 200 iU was used).

CKD-ND: chronic kidney disease non-dialysis, ESA: erythropoiesis-stimulating agent, adj.: adjusted, RR: risk ratio, CI: confidence interval, Coef: coefficient.

Figure 2a. Probability of ESA use among referred CKD-ND patients

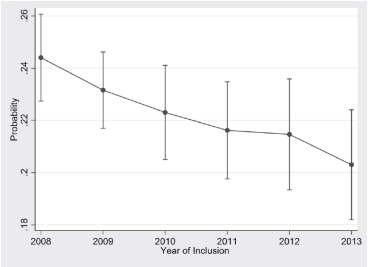
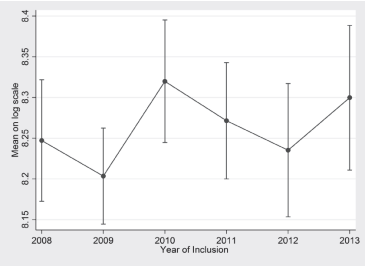


Figure 2b. Adjusted mean log weekly epoetin equivalent ESA dose among referred CKD-ND patients



▾ **Table 3a.** Trends in hemoglobin levels in a referred CKD-ND population

		2008-2009	2010-2011		2012-2013		
			adj. Coef.	**95% CI**	**adj. Coef.**	**95% CI**	**p-value trend**
Hemoglobin*	ESA	ref	-3.3	-4.8;-1.9	3.1	-4.7;1.5	<0.01
			ref		0.2	-1.4;1.9	
Hemoglobin*	no ESA	ref	-0.9	-1.8;-0.1	-1.3	-2.2;-0.4	<0.01
			ref		-0.4	-1.2;0.4	
			adj. RR	**95% CI**	**Adj. RR**	**95% CI**	**p-value trend**
Hb >120 g/l*	ESA	ref	0.87	0.74;1.01	0.86	0.73;1.01	0.08
			ref		0.99	0.83;1.18	

*model adjusted for age, sex, primary renal disease, body mass index, estimated GFR (MDRD) and use of iron (yes/no).

Hemoglobin: to convert g/l to g/dl divide by 10. CKD-ND: chronic kidney disease non-dialysis, ESA: erythropoiesis-stimulating agent, adj.: adjusted, RR: risk ratio, CI: confidence interval, Coef: coefficient.

▾ **Table 4a.** Trends in the use of iron medication and ferritin in a referred CKD-ND population

		2008-2009	2010-2011		2012-2013		
			adj. RR	**95% CI**	**Adj. RR**	**95% CI**	**p-value trend**
Iron medication*	ESA	ref	1.09	0.97;1.23	1.06	0.93;1.21	0.29
			ref		0.98	0.86;1.11	
Iron medication*	no ESA	ref	1.25	1.07;1.45	1.18	1.00;1.38	0.05
			ref		0.95	0.82;1.09	
			adj. Coef.[1]	**95% CI**	**adj. Coef.[1]**	**95% CI**	**p-value trend**
Ferritin (µg/l)		ref	0.05	-0.04;0.13	-0.03	-0.13;0.07	0.52
			ref		-0.08	-0.17; 0.01	

*model adjusted for age, sex, primary renal disease, body mass index and estimated GFR (MDRD)

[1] adjusted coefficient interpreted as the percentage change per period.

CKD-ND: chronic kidney disease non-dialysis, ESA: erythropoiesis-stimulating agent, adj.: adjusted, RR: risk ratio, CI: confidence interval, Coef: coefficient.

The adjusted RR of iron use differed according to ESA use (Table 4a). Patients not treated with ESAs had higher chance of iron treatment after 2008-2009 (RR 1.18 (95% CI 1.00;1.38) in 2012-2013). However, iron use did not increase significantly in ESA-treated patients over time. Serum ferritin levels did not change significantly over the investigated time periods. In two sensitivity analyses, further adjustments for comorbidity and CRP did not materially change the results for any of the investigated outcomes.

Hemodialysis

As many as 4585 incident HD patients were eligible between 2008 and 2013, of which 65% were male. The mean age was 64.5 years. Across the time periods, BMI and use of hemodiafiltration increased, whereas age and the use of dialysis catheters decreased (Table 1b). The overall proportion of patients using ESAs declined from 96.0 % in 2008 to 82.6 % 2013, while the mean proportion of ESA users decreased markedly in 2009 and stabilized at a lower level thereafter (Figure 3a). Mean ESA dose decreased from 9,393 iU/week to 8,228 iU/week, while the median ESA dose was stable. Across the time periods considered, mean Hb declined from 115.4 g/l in 2008-2009 to 113.6 g/l in 2012-2013.

As shown in Table 2b, the adjusted RR of ESA use did not differ significantly between the first and second time period, while it was lower during the last period 2012-2013 (RR 0.95 (95% CI 0.92;0.98) compared with 2008-2009). ESA dose on the other side, decreased significantly between the first two periods, but not significantly in 2012-2013 compared with 2010-2011 (Figure 3b). Mean adjusted Hb only decreased among ESA users (Table 3b), where there was a decreasing trend during both time periods (-1.29 g/l (95% CI -2.33;0.25) in 2010-2011 and additionally -0.44 g/l (95% CI -1.51;0.64) in 2012-2013, p-value for trend <0.01). The RR of having an Hb >120 g/l also decreased significantly over time.

▾ **Table 1b.** Characteristics of stable hemodialysis patients

Time period Number	2008-2009 4985	2010-2011 5672	2012-2013 4801
Age	65.9 (14.5)	64.4 (15.0)	63.3 (15.4)
Sex (% men)	64.2	66.1	66.0
Primary renal disease (%)			
Glomerulonephritis	11.7	14.3	13.8
Diabetic nephropathy	26.5	24.5	24.9
Renovascular/nephrosclerosis	20.3	20.8	20.3
Other specified	13.1	11.2	10.7
Unknown	14.2	13.3	14.5
Polycystic kidney disease	8.0	8.9	9.3
Interstitial nephritis	6.2	6.9	6.6
BMI (kg/m^2)	25.9 (5.6)	25.8 (5.5)	26.5 (5.7)
Ferritin (µg/l)	401 (230-639)	446 (253-700)	380 (210-655)
C-reactive protein (mg/ml)	7.3 (3.0-17.0)	7.0 (3.0-16.0)	5.8 (2.8-14.0)
Albumin (g/l)	34.9 (5.4)	34.2 (5.1)	34.4 (5.2)
Iron use (%)			
intravenous	65.9	70.5	69.0
oral	0.4	0.9	1.3
ESA use (%)	87.9	89.1	84.7
ESA dose (iU/week)	8,000 (4,000-12,000)	8,000 (4,000-12,000)	8,000 (4,000-10,000)
Hemoglobin (g/l)	115.4 (13.6)	113.9 (13.9)	113.6 (14.2)
Standard Kt/V	2.12 (0.44)	2.12 (0.43)	2.15 (0.45)
Hemodiafiltration (%)	17.5	22.3	29.5
Vascular access (% fistula/graft)	49.9	50.3	52.1
University hospital (%)	30.0	32.1	31.3

Values are presented as mean (sd), median (interquartile range) or percentages, as appropriate.

HD: hemodialysis, BMI: body mass index, ESA: erythropoiesis-stimulating agent, eGFR: estimated glomerular filtration rate (by MDRD equation).

Hemoglobin: to convert g/l to g/dl divide by 10.

Table 2b. Trends in the use of erythropoiesis-stimulating agents in stable hemodialysis patients

	2008-2009	2010-2011		2012-2013		
		adj. RR	**95% CI**	**Adj. RR**	**95% CI**	**p-value trend**
ESA use^	ref	1.00	0.97;1.02	0.95	0.92;0.97	<0.01
		ref		0.95	0.92;0.98	
		adj. Coef.[1]	**95% CI**	**adj. Coef.[1]**	**95% CI**	
ESA dose^	ref	-0.07	-0.12;-0.01	-0.09	-0.15;-0.04	<0.01
		ref		-0.03	-0.08;0.03	

^model adjusted for age, sex, primary renal disease, body mass index, use of iron, type of dialysis access and standard Kt/V.

[1]adjusted coefficient interpreted as the percentage change per period.

ESA dose expressed as the log of epoetin-equivalent dose (a conversion factor of 200 iU was used).

ESA: erythropoiesis-stimulating agent, adj.: adjusted, RR: risk ratio, CI: confidence interval, Coef: coefficient.

Figure 3a. Probability of ESA use among stable hemodialysis patients

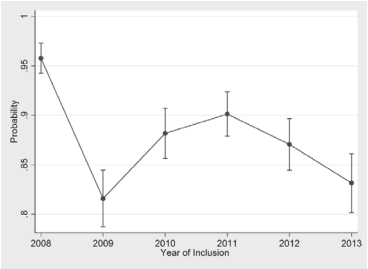


Figure 3b. Adjusted mean log weekly epoetin-equivalent ESA dose among stable hemodialysis patients

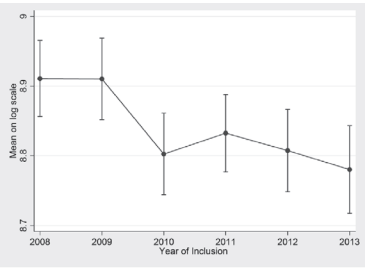


Table 3b. Trends in hemoglobin levels in stable hemodialysis patients

		2008-2009	2010-2011		2012-2013		
			adj. Coef.	95% CI	adj. Coef.	95% CI	p-value trend
Hemoglobin^	ESA	ref	-1.3	-2.3;-0.3	-1.7	-2.8;-0.6	<0.01
			ref		-0.4	-1.5;0.6	
Hemoglobin^	no ESA	ref	-0.5	-3.9;3.0	0.1	-3.2;3.4	0.94
			ref		0.6	-2.7;3.8	
			adj. RR	95% CI	Adj. RR	95% CI	p-value trend
Hb >120 g/l^	ESA	ref	0.88	0.80;0.97	0.89	0.81;0.99	<0.01
			ref		1.01	0.91;1.12	

^model adjusted for age, sex, primary renal disease, body mass index, use of iron, type of dialysis access and standard Kt/V.
Hemoglobin: to convert g/l to g/dl divide by 10.
ESA: erythropoiesis-stimulating agent, Hb: hemoglobin, adj.: adjusted, RR: risk ratio, CI: confidence interval, Coef: coefficient.

Table 4b. Trends in hemoglobin levels in stable hemodialysis patients

		2008-2009	2010-2011		2012-2013		
			adj. RR	95% CI	Adj. RR	95% CI	p-value trend
Iron medication^	ESA	ref	1.04	0.99;1.09	1.05	1.00;1.10	0.05
			ref		1.01	0.96;1.06	
Iron medication^	no ESA	ref	1.40	1.11;1.77	1.42	1.14;1.77	<0.01
			ref		1.02	0.85;1.22	
			adj. Coef.[1]	95% CI	adj. Coef.[1]	95% CI	p-value trend
Ferritin (µg/l)^		ref	0.05	-0.03;0.13	-0.06	-0.14;0.02	0.18
			ref		-0.11	-0.19;-0.03	

^model adjusted for age, sex, primary renal disease, body mass index, type of dialysis access and standard Kt/V.
[1] adjusted coefficient interpreted as the percentage change per period.
Iron medication is both oral and intravenous, ferritin expressed in log of µg/l.
ESA: erythropoiesis-stimulating agent, Hb: hemoglobin, adj.: adjusted, RR: risk ratio, CI: confidence interval, Coef: coefficient.

The chance for being prescribed iron increased over time particularly among non-ESA users (RR 1.40 (95% CI 1.11;1.77)), as shown in Table 4b. In spite of increasing iron use, serum ferritin decreased by approximately 6% in 2012-2013 compared with 2008-2009.

Discussion

During the last decade, changes in anemia guidelines have occurred after the publication of mainly three influential randomized controlled trials. Figure 1 provides a general overview of the recommended Hb targets by subsequent guidelines. The debate about the safety of ESAs and Hb targets started after the publication of Correction of epoetin alfa in Chronic Kidney Disease (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) in 2006,[3;4] followed by a FDA warning and label revisions in 2007.[20] Our study starts with the period thereafter, in which the 2009 ERBP position statement first underlined the KDOQI upper target Hb limit of 12 g/dL without intentionally exceeding 13 g/dL.[12] At the end of 2009, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT),[5] including CKD patients with type 2 diabetes mellitus, showed no significant effect of darbepoetin on the combined cardiovascular endpoint, but instead an almost twice higher stroke rate among darbepoetin treated patients in the upper Hb target arm of the trial. The 2010 ERBP position statement consequently responded with a reinforcement of the 110-120 g/L Hb target[13] and the recommendation to take the dose of ESAs into consideration, especially in patients with a history of diabetes mellitus and cardiovascular disease. During that same time, a number of additional publications discussed the ESA-related risks and Hb targets in both patients with CKD[21-23] and cancer.[24;25] In 2011 the FDA launched the latest update in the ESA label, removing the target Hb and recommending to individualize dosages.[7] The 2012 KDIGO clinical practice

guidelines recommended using ESAs with caution, if at all, in CKD patients with (a history of) malignancy or stroke,[18] together with the proposal to individualize ESA treatment decisions, not to initiate ESA therapy when Hb >100 g/L and generally not to use ESAs to maintain Hb >115 g/l.

This is the first European nation-representative study providing insights into anemia management of both CKD-ND and HD patients during the recent years. Our results show that among CKD-ND patients there has been a shift towards lesser use of ESAs already noticeable since 2010-2011. The decline in Hb for both ESA users and non-ESA users in our study suggests that nephrologists both aim for lower Hb among ESA-treated patients, but also for initiating ESAs later (hence the lower mean Hb for non-ESA users). We found no significant reduction in ESA dose for CKD-ND patients, but a small increase in the dose the second period. For HD patients, however, with a majority of them being treated with ESAs, the first practice trend observed after the change in guidelines was a lower ESA dose, resulting in lower mean Hb. During the second study period, this was also followed by a decline in the proportion of ESA-users, together with further declines in ESA dose. Altogether, the changes in anemia management as described herein are most likely caused by the different trials reported, guideline changes and position statements. This notion may be reinforced by the fact that healthcare in Sweden is tax-financed and there are no economic incitements linked to ESA prescriptions or Hb targets. In line with this, a Dialysis Outcomes and Practice Patterns Study (DOPPS) survey reported that no Swedish physician felt that drug companies had contributed substantially to anemia management protocols.[26]

Similar trends to our study have previously been reported among US patients, where mean monthly Hb and ESA dose in HD patients increased from 2002-2006 and then declined in 2007-2008.[9] In CKD-ND patients, less frequent ESA use and lower achieved Hb was reported between 2005 and 2009,

with the most notable change in Hb in 2007 after CHOIR and CREATE.[8] The same US study also reported a decline in ESA dose, but doses were still considerably higher than in our cohort of CKD patients. More recently, the declining trend in ESA prescriptions has been reported to continue in the two subsequent years after the publication of TREAT, which is in line with our study.[10]

Nevertheless, anemia management practices among Europe and US differ as reflected by the generally observed higher ESA doses among US patients.[11] Although an earlier DOPPS report indicated that ESA use increased between 2002-2008 in HD patients of almost all DOPPS countries, including US and Sweden, the Hb levels remained stable in Sweden, whereas Hb rose substantially in patients from all other DOPPS countries.[26] In line with our results, a recent report showed a comparable decline in Hb levels after 2006 in dialysis patients in Germany and the UK.[27]

The strength of this study includes the use of a national registry with information of both referred CKD-ND patients and virtually all incident HD-patients. As with all observational studies there are, however, limitations. First, we used only cross-sectional information at the inclusion into either SRR-CKD or SRR-HD registers in order not to have individual trends obscure the general trend over time. Since the SRR-CKD first started in 2008 on a national level more patients were included the first years as can be observed both in numbers and in a generally lower mean eGFR. Although adjusting for eGFR in our analyses and excluding patients prevalent in the national CKD registries before 2008, we cannot rule out the possibility that a slightly different case-mix of incident/prevalent patients during the first years may have affected our results in the CKD-ND cohort. However, among the HD patients we excluded prevalent patients who started RRT before 2008. Also, not all facilities provided information on all covariates in all patients. Missing data was less than 3% for all studies variables except for

BMI, CRP and ferritin, which was missing in a frequency higher than 20% in the CKD-ND cohort. Therefore, only complete-cases are reported. We believe that the reason for missingness lies locally, as many centers choose to enter only mandatory laboratory values such as Hb. However, if the non-registered patients differed meaningfully in from the patients who were registered, results for ferritin may not be totally generalizable. Furthermore, our results did not substantially change with case-mix adjustments, indicating that findings were robust.

To conclude, our study demonstrates that nephrology care in Sweden adapted its practice to the European anemia management guidelines between 2008 and 2013. According to these guideline recommendations, less ESA use and lower Hb levels were subsequently observed.

Acknowledgements

JJC Acknowledges support from the Martin Rind Foundation, the Stockholm County Council (Dept. of Evidence-Based Medicine) and the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet. ME acknowledges support from the Stockholm County Council for post-doctoral research and the Swedish Renal Registry for their provision of data.

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