

Temporal Trends in Hemoglobin, Use of Erythropoiesis Stimulating Agents, and Major Clinical Outcomes in Incident Dialysis Patients in Canada



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Introduction: Several jurisdictions have adopted a more conservative approach to anemia in patients receiving dialysis amid safety concerns from target hemoglobin studies. It is largely unknown if this has contributed to a change in clinical outcomes.

Methods: A national registry was used to identify 35,945 adult patients who initiated and were maintained on dialysis for ≥ 90 days in Canada from January 2007 to December 2015. Outcomes were ascertained until March 2017 via linkage with hospital discharge diagnoses. Cox proportional hazards models were used to investigate the association between the era of dialysis initiation and the primary composite outcome (acute myocardial infarction [AMI], stroke, or mortality).

Results: The mean hemoglobin at dialysis initiation decreased from 102.9 g/l in 2007 to 95.5 g/l in 2015, corresponding with a higher prevalence of hemoglobin < 80 g/l (8% to 17%) and a reduction in erythropoiesis stimulating agent (ESA) use (49% to 44%). After multivariable adjustment, Era 3 (2013–2015) was associated with an 8% relative risk reduction in the primary outcome compared with Era 1 (2007–2009) (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.88–0.96), a 10% relative reduction in mortality (HR 0.90, 95% CI 0.85–0.94) but no significant change in AMI or stroke. In a model without era, neither hemoglobin nor ESA use was an independent predictor of outcome.

Conclusion: There have been modest declines in average hemoglobin values and ESA use among incident dialysis patients in Canada with no change in major cardiovascular outcomes. Patient survival has improved over time, likely for reasons other than anemia management.

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KEYWORDS: acute myocardial infarction; anemia; dialysis; erythropoiesis stimulating agent; mortality; stroke

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The optimal management strategy for anemia in individuals with kidney disease is uncertain.¹ Contemporary guidelines for the treatment of anemia in patients with end-stage kidney disease (ESKD) continue to rely on a relatively weak evidence base.² A series of landmark clinical trials conducted between 1998 and 2009 demonstrated no improvement in hard clinical endpoints when targeting higher hemoglobin values with the use of ESAs in patients with chronic kidney disease and ESKD.^{3–7} Conversely, individuals

allocated to the higher hemoglobin arm in these studies had an increased risk of all-cause mortality,^{3,4} major cardiovascular events including stroke,^{6,7} and vascular access thrombosis.³ As a consequence of these findings, international guidelines recommended against aggressive treatment of anemia with ESAs, and instead suggested more conservative hemoglobin targets with the aim of avoiding harm.² Although most of these clinical trials were conducted in patients with predialysis chronic kidney disease, the findings have been extrapolated to patients receiving chronic dialysis.

Since the publication of the most recent target hemoglobin trial in 2009,⁶ a number of studies from the United States and Europe have demonstrated a reduction in ESA use and attendant decreases in average hemoglobin values among patients starting dialysis.^{8–11}

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In the United States, the use of ESAs declined abruptly in 2011 following the introduction of a bundled payment system for hemodialysis that removed incentives for ESA prescribing.^{12,13} This coincided with a revision of the drug label for ESAs from the Food and Drug Administration, warning about the potentially detrimental consequences of using high doses of ESAs to achieve a higher hemoglobin target.¹⁴ Two studies evaluated the incidence of clinical outcomes before and after this change in funding policy in the United States.^{8,9} The investigators identified a reduction in the rate of stroke^{8,9} and venous thromboembolic disease⁹ in the post-policy period, providing counterfactual evidence in support of a causative role of high-dose ESA in the pathogenesis of vascular thrombosis. These findings should be interpreted in the context of ESA prescribing patterns in the pre-policy period in the United States, when average monthly doses of epoetin alfa exceeded 100,000 units among older patients with hemoglobin values less than 90 g/l.⁸ Outside of the United States, in jurisdictions where baseline ESA doses tended to be lower in magnitude and not under the influence of reimbursement policies, it is not known whether the adoption of a more conservative approach to anemia management has contributed to a change in the incidence of stroke or other clinical outcomes in patients receiving dialysis.

We sought to investigate temporal trends in hemoglobin distribution and ESA use among incident dialysis patients in Canada during the period 2007 to 2015, and explore the association between the era of anemia management and major clinical outcomes in this population.

METHODS

Study Design

This was a retrospective cohort study of adult patients (age ≥ 18 years) with ESKD who started chronic hemodialysis or peritoneal dialysis in Canada between January 1, 2007, and December 31, 2015. The sample was restricted to include patients who received dialysis for at least 90 days from the date of their first dialysis treatment. This was done to reduce the likelihood of including patients with acute kidney injury, in whom both the management of anemia and the risk of clinical outcomes may differ from patients receiving chronic maintenance dialysis. Patients with a previous kidney transplant were also excluded. Follow-up continued until March 31, 2017, such that all patients had a minimum of 1-year follow-up for outcome ascertainment beyond their 90th day of dialysis. Censoring events included kidney transplantation, an interruption in dialysis of >90 days (patients were censored on

the last date of dialysis before the interruption), loss to follow-up, or the end of the era-specific observation period.

Data Sources

The Canadian Organ Replacement Registry (CORR) is a national longitudinal database that captures comprehensive patient-level information from provincial programs and participating dialysis centers across Canada (except Quebec).¹⁵ Patients on renal replacement therapy are followed from their first treatment until death. The data are provided to CORR by physicians, nurses, and administrative staff from individual facilities via the use of standardized forms.¹⁶ The initial registration form for patients starting dialysis includes demographic, clinical, and laboratory data. Follow-up data for laboratory tests and outcomes (including dialysis withdrawal and death) are captured on an annual basis. Individual-level data from the CORR were linked with the Discharge Abstract Database (DAD) and/or the National Ambulatory Care Reporting System (NACRS) to capture clinical outcomes. Professional coders translate diagnoses from all inpatient hospital discharges and visits to the emergency room into International Classification of Disease codes, which are then recorded in the DAD and NACRS, respectively. The CORR, DAD, and NACRS are all housed within the Canadian Institute for Health Information, which conducted the data linkage using a unique patient identifier. Patient-level data in CORR from individuals receiving dialysis in Manitoba could not be linked to DAD/NACRS and so these patients were excluded from the analysis. The final analytical dataset included de-identified data only. The study protocol was approved by the Research Ethics Board of the University of British Columbia.

Outcome

The primary outcome was a composite of AMI, stroke, and all-cause mortality. This composite outcome was chosen to facilitate a direct comparison with previous studies.^{8,9} Each component of the primary outcome was also examined separately. Date of death was captured from the CORR and/or discharge reporting from the DAD and NACRS. Cardiovascular outcomes were ascertained from the DAD (AMI and stroke) and NACRS (stroke) using International Classification of Diseases, 10th revision, codes according to published algorithms (see [Supplementary Appendix 1](#) for further details).

Exposure

The exposure of interest was the era of dialysis initiation categorized into 3 distinct time periods: Era 1

(January 1, 2007 to December 31, 2009), Era 2 (January 1, 2010 to December 31, 2012), and Era 3 (January 1, 2013 to December 31, 2015). These periods were chosen to reflect the timing of landmark clinical trials of target hemoglobin (last trial published in 2009⁶) and the release of Kidney Disease Improving Global Outcomes anemia guidelines in 2012.²

Covariates

ESA exposure and hemoglobin level were captured at the time of dialysis initiation. A minority of hemoglobin values were captured from longitudinal follow-up data, as long as follow-up values were within 6 months of dialysis initiation. ESA dose was ascertained from follow-up data in CORR within 12 months of dialysis initiation. Most patients were prescribed epoetin alfa during the study period. For patients receiving darbepoetin alfa, the dose was re-expressed as the equivalent monthly dose of epoetin alfa (1 μ g of darbepoetin alfa = 200 units of epoetin alfa). Demographic covariates from the time of dialysis initiation included age, sex, race/ethnicity, initial dialysis modality (hemodialysis or peritoneal dialysis), type of vascular access, and the duration of predialysis nephrology care. Clinical covariates included body mass index and comorbidities including diabetes, ischemic heart disease, congestive heart failure, stroke, and peripheral vascular disease. Baseline laboratory data at the time of dialysis initiation included phosphate, albumin, and parathyroid hormone. Due to potential under-ascertainment of comorbidities in the CORR,¹⁷ these variables were also captured from hospitalization data for all patients in the 12 months preceding the start of dialysis.¹⁸

Statistical Analysis

Rates of each outcome were calculated per 1000 person-years of follow-up. The association between era and time to the primary outcome (time to first event of interest) was visualized using Kaplan-Meier plots and evaluated using Cox proportional hazards regression. For this analysis, the time at risk started on day 90 after the date of first dialysis. Models were sequentially adjusted for demographics (age, sex, and race/ethnicity), comorbidity variables (cause of ESKD, diabetes, ischemic heart disease, congestive heart failure, prior stroke, and peripheral vascular disease), markers of predialysis care (initial dialysis access and duration of predialysis nephrology care), and clinical/laboratory risk factors (body mass index, albumin, phosphate, and parathyroid hormone). The relationship between era and each outcome was examined within the following predefined subgroups: age (<65, 65–75, >75 years), sex, race/ethnicity, dialysis modality, cause of ESKD,

diabetes; cardiovascular disease (composite of ischemic heart disease, heart failure, stroke, or peripheral vascular disease), duration of predialysis nephrology care (none, <6 months, >6 months), ESA use at dialysis initiation, and hemoglobin category (<80, 80–89, 90–109, 110–119, \geq 120 g/l). In the aforementioned analysis, the era of dialysis initiation served to represent different periods of anemia management. To interrogate this further, we replaced era as the primary exposure variable with 2 markers of anemia management: (1) the level of hemoglobin at dialysis initiation, and (2) ESA status at dialysis initiation.

Missing data for variables included in multivariable models were imputed using Markov Chain Monte Carlo algorithms. Continuous variables are presented as mean and SD or median and interquartile range (IQR), as appropriate. Categorical variables are presented as a percentage. Analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

A total of 35,945 individuals were included in the analysis (Figure 1). Their characteristics, overall and stratified by era of anemia management, are described in Table 1. In the overall cohort, the mean (SD) age at dialysis initiation was 64.1 (15) years, 61% were male and most (69%) were White. Compared with Era 1 (2007–2009), individuals who started dialysis in Era 3 (2013–2015) were more likely to have diabetes and tended to have higher body mass index. Individuals in Era 3 also had a longer duration of predialysis nephrology care, were more likely to start peritoneal dialysis than hemodialysis, and were less likely to start hemodialysis with a catheter as their first vascular access. The frequency of missing data is reported in Supplementary Table S1.

Hemoglobin Distribution and ESA Use

Figure 2 illustrates the longitudinal trend in mean hemoglobin values at the start of dialysis along with the relative proportions of individuals with hemoglobin values <80, 80–89, 90–109, 110–119, and \geq 120 g/l in each year of the study period. The mean hemoglobin at dialysis initiation demonstrated a gradual and progressive decrease from 102.9 g/l in 2007 to 95.5 g/l in 2015. The proportion of individuals with hemoglobin <90 g/l at the start of dialysis increased from 22% in 2007 to 37% in 2015, with a corresponding doubling in the proportion of patients with hemoglobin <80 g/l (8% to 17%). Figure 3 shows the proportion of individuals who were receiving an ESA at the time of dialysis initiation and the mean monthly dose of ESA for each year of the study period. The

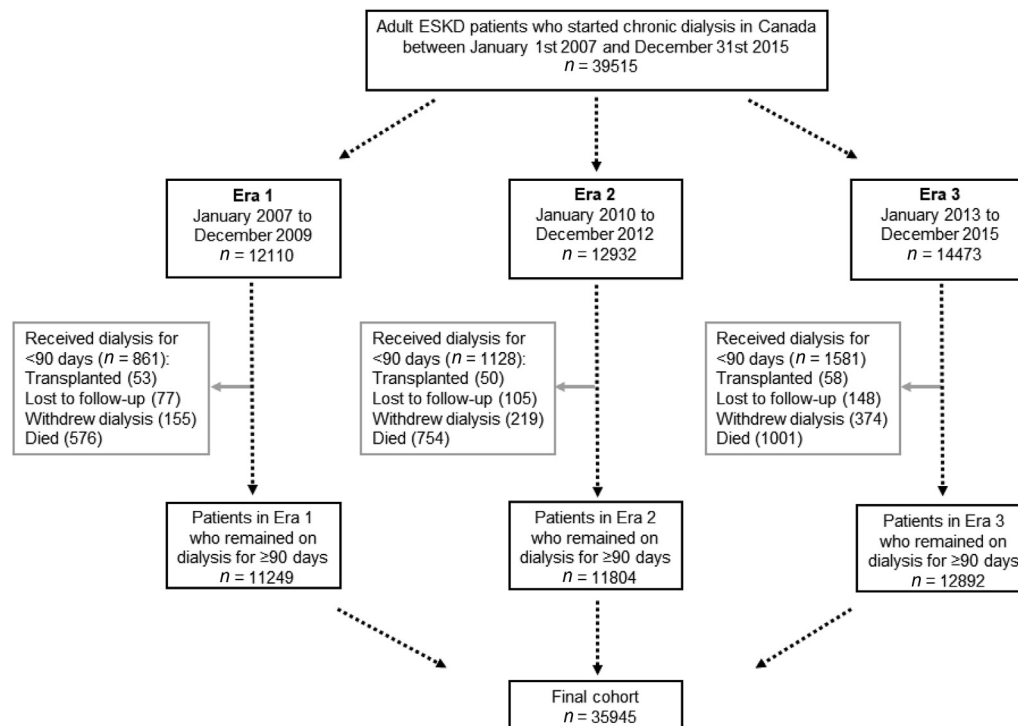


Figure 1. Flowchart of case ascertainment. ESKD, end stage kidney disease.

use of ESA at dialysis initiation dropped after 2009 from 49% to a nadir of 42% in 2011 to 2014, and was 44% in 2015. The mean monthly dose of ESA demonstrated an early decline between 2007 and 2009 and fluctuated thereafter.

Association Between Dialysis Era and Outcomes

A total of 11,810 primary outcome events were observed in the cohort overall during 66,844 person-years at risk. The median follow-up time was 21.1 months in Era 1, 21.3 months in Era 2, and 21.4 months in Era 3. All-cause mortality accounted for most events (69.8%) compared with AMI (20.9%) or stroke (9.3%). The rate of the primary composite outcome (per 1000 person-years) decreased steadily from 196.3 in Era 1 to 176.6 in Era 3 (Table 2), representing a 10% relative risk reduction (unadjusted HR 0.90, 95% CI 0.86–0.94). There was a consistent reduction in the rate of all-cause mortality from 160.3 in Era 1 to 139.1 in Era 3 (unadjusted HR 0.87, 95% CI 0.83–0.91). In contrast, rates of AMI and stroke did not demonstrate a consistent pattern across eras (Table 2 and Figure 4). Compared with Era 1, Era 3 was not associated with a difference in the risk of AMI (unadjusted HR 0.94, 95% CI 0.85–1.03) or stroke (unadjusted HR 1.07, 95% CI 0.94–1.22). After adjusting for demographics, cause of ESKD, comorbidities, metrics of care, and laboratory markers, Era 3 was associated with an 8% relative reduction in the risk of the primary outcome (HR 0.92,

95% CI 0.88–0.96) and a 10% reduction in the risk of all-cause mortality (HR 0.90, 95% CI 0.85–0.94) compared with Era 1 (Table 2). The multivariable model for the primary outcome is shown in Table 3. The multivariable models for AMI (Supplementary Table S2), stroke (Supplementary Table S3) and all-cause mortality (Supplementary Table S4) are provided in the Supplementary Material.

The multivariable-adjusted relationship between era and the primary outcome was consistent across hemoglobin categories and comorbidities, including cause of ESKD, diabetes, and preexisting cardiovascular disease (Figure 5). The lower risk observed in Era 3 (vs. Era 1) was more pronounced among patients older than 75 years compared with younger patients ($P = 0.04$ for interaction). We repeated the analysis with hemoglobin category and ESA status at dialysis initiation as the exposure variables of interest, and with era removed from the model (Table 4). In an unadjusted model, both a higher hemoglobin level and being on ESA therapy were associated with lower risk of both the primary composite outcome and all-cause mortality. After multivariable adjustment, neither hemoglobin nor ESA was an independent predictor of the primary outcome or all-cause mortality.

DISCUSSION

In this national cohort of patients who initiated and were maintained on dialysis for at least 90 days in Canada from 2007 to 2015, we observed a gradual

Table 1. Patient characteristics overall and by era of dialysis initiation

	Overall	Era 1 2007–2009	Era 2 2010–2012	Era 3 2013–2015
<i>n</i>	35,945	11,249	11,804	12,892
Age (y)	64.1 (15)	64.3 (15.2)	64 (15)	64 (14.9)
Male sex, %	61.3	60.2	61.7	62
Race/ethnicity, %				
White	68.9	71.2	69.2	66.7
Asian	7	7	6.7	7.1
Black	4.1	3.8	4.6	3.9
Indian subcontinent	6	4.7	6.1	7
Other	14	13.3	13.4	15.2
Cause of ESKD, %				
Diabetes	38.2	36.2	38.8	39.7
Vascular disease	17.4	20	17.5	14.9
Glomerular disease	13.1	12.7	13.4	13.0
Other	31.3	31.1	30.4	32.4
Modality, %				
Hemodialysis	78.9	79.3	80.2	77.3
Peritoneal dialysis	21.1	20.7	19.8	22.7
Dialysis access, %				
Catheter	63.1	63.4	64.2	61.9
AVF/AVG	14.6	14.3	14.6	14.9
PD catheter	21.1	20.7	19.8	22.7
Unknown	1.2	1.6	1.4	0.6
Body mass index (kg/m ²)	28.2 (6.8)	27.8 (6.6)	28.2 (6.7)	28.6 (6.9)
Comorbidities, %				
Diabetes	48.1	45.3	48	50.7
Ischemic heart disease	31.8	33.4	32.2	30
Heart failure	33.8	33.3	34	34
Prior stroke	13.6	13.7	14	13.3
PVD	16.2	16.6	16.6	15.3
Predialysis care, %				
None	21.6	23.5	21.6	20
<6 months	14	16.4	13.9	11.8
≥6 months	64.4	60	64.4	68.2
Calcium (mmol/l)	2.09 (0.35)	2.11 (0.33)	2.07 (0.37)	2.09 (0.35)
Phosphate (mmol/l)	1.93 (0.69)	1.9 (0.7)	1.93 (0.68)	1.97 (0.68)
PTH (pmol/l), median (IQR)	28.2 (15.6–47.2)	26.2 (14.1–43.7)	28.2 (15.7–47.2)	30.1 (16.8–50.1)
Albumin (g/l)	32.6 (6.9)	32.8 (7.1)	32.6 (6.9)	32.3 (6.8)

AVF, arteriovenous fistula; AVG, arteriovenous graft; ESKD, end-stage kidney disease; IQR, interquartile range; PD, peritoneal dialysis; PVD, peripheral vascular disease; PTH, parathyroid hormone.

Data presented as mean (SD) unless otherwise stated.

downward trend in the mean hemoglobin level at dialysis initiation from 2007 onward, with a corresponding modest reduction in the use of ESAs. This more conservative trend in anemia management was not temporally associated with a change in the incidence of stroke or AMI. We observed an improvement in patient survival; however, this was not explained by either ESA use or the hemoglobin value at dialysis initiation, suggesting that other factors have contributed to the reduction in all-cause mortality in this population.

Previous trials of target hemoglobin identified a higher risk of stroke in the intervention group exposed

to higher doses of ESA.^{6,7} A causal association between high-dose ESA and stroke is biologically plausible. Among dialysis patients in the United States, the rate of stroke decreased after the introduction of a bundling payment policy for dialysis care that culminated in a sharp decline in ESA prescribing.^{8,9} Taken together, these data present convincing evidence that high-dose ESA is directly implicated in the mechanism of stroke. So, why did we not observe a change in the rate of stroke in this cohort of incident dialysis patients? First, the baseline use of ESA was substantially lower in Canada compared with the United States. In Canada the proportion of patients receiving ESA at the time of dialysis initiation had a peak of 49% in 2007, compared with 90% to 95% in the United States.⁹ Second, temporal changes in ESA use among Canadian patients were comparatively modest, both in terms of the frequency of ESA use at dialysis initiation and the average doses prescribed. Third, the baseline event rate was substantially higher among US patients. For example, among individuals aged 66 years and older, the rate of stroke (per 1000 person-years) was 39.9 in the United States pre-policy period, compared with 26.2 in Canada between 2007 and 2009. Finally, the reduction in stroke risk observed in the US dialysis population was most pronounced in Black patients,⁸ who represent a minority (4%) of Canadian incident dialysis patients.

The most important finding from this study was the consistent improvement in overall patient survival across the 10-year observation period. In our study design, the era of dialysis initiation represented a distinct period of anemia management, anchored to the publication of landmark clinical trials and the release of international guidelines. In the primary analysis, the era of dialysis initiation was a strong predictor of mortality, and this finding was robust to adjustment for other risk factors. In contrast, in a model without era, neither the level of hemoglobin nor the use of ESA at dialysis initiation were independent predictors of mortality. This suggests that the improvement in mortality was not related to anemia management per se. All-cause mortality was part of the composite outcome used in previous clinical trials of target hemoglobin,^{3–6} some of which identified a higher risk of death in the higher hemoglobin arm.^{3,4} Unlike the case of stroke, the underlying mechanism for the association between ESA and mortality risk is not clear, and may be related to some combination of the level of hemoglobin achieved, the dose of ESA required, and underlying multimorbidity of the patients enrolled in these studies. This degree of confounding cannot be disentangled in an observational context. Nevertheless, in this large and representative dialysis cohort, the level of hemoglobin was not independently associated with

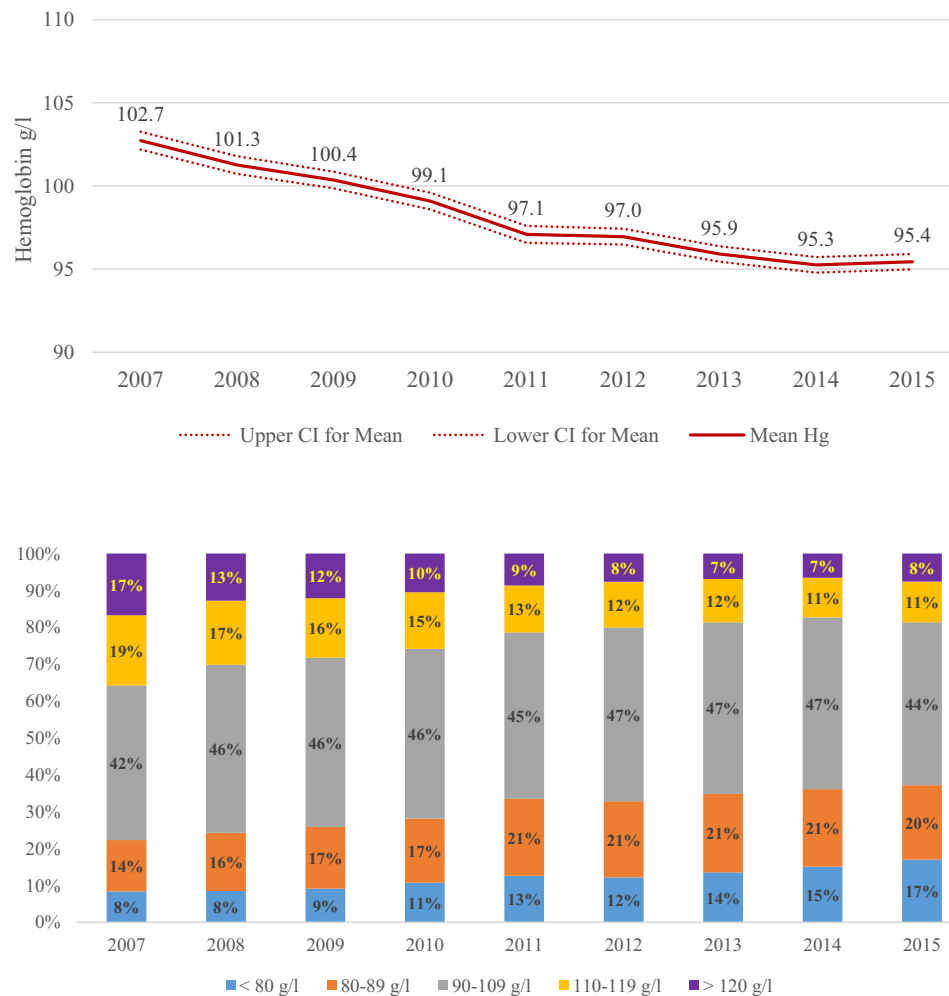


Figure 2. Mean (95% confidence interval [CI]) hemoglobin (top) and the proportion of patients in each hemoglobin category (bottom) for each year of the study period.

mortality risk. This begs the question of whether the absolute value of hemoglobin, at least in the range observed in this cohort, directly contributes to the risk of clinical outcomes. If not, then continuing to focus on changing the hemoglobin value, without considering the underlying disease mechanism(s), is unlikely to advance our understanding of the role of current or future therapies for anemia in patients receiving dialysis.

Considering the complexity of care provided to patients receiving dialysis, the observed improvement in patient survival is likely multifactorial. The prevalence of diabetes increased over time in incident dialysis patients but this was not accompanied by higher rates of cardiovascular outcomes or death, perhaps suggesting that improvements in diabetes outcomes in the general population are extending to patients with ESKD.¹⁹ Duration of predialysis care and arteriovenous fistula use both increased over time and were independent predictors of a reduced risk of all-cause mortality. These variables alone do not necessarily capture

the full spectrum of the quality of care delivered to patients, perhaps explaining why their inclusion in the multivariable model did not fully explain the change in mortality across eras. Patients older than 75 years had a larger reduction in mortality risk over time compared with younger patients, suggesting that the mortality improvement could reflect patient selection and perhaps an increased uptake of conservative care among older patients with multimorbidity. Among Canadian patients who develop kidney failure, approximately 50% choose not to receive renal replacement therapy, and this proportion is much higher in older individuals.²⁰ This pattern appears to be different from that in the United States where most patients with kidney failure go on to receive dialysis, a finding that extends to older patients with comorbidities.²¹

The downward trend we observed in the mean hemoglobin value at dialysis initiation is consistent with trends observed in the United States and in Europe.^{10,11,13} The mean hemoglobin decreased

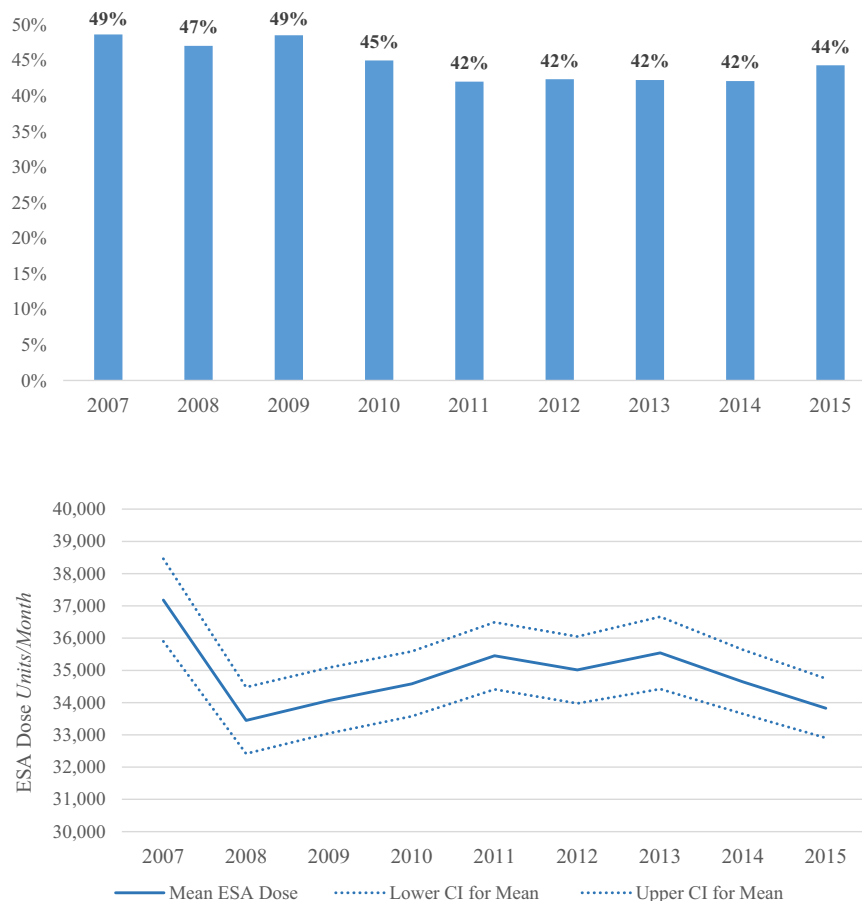


Figure 3. Proportion of patients on erythropoiesis stimulating agent (ESA) therapy at dialysis initiation (top) and the mean (95% confidence interval [CI]) monthly dose of ESA (bottom) for each year of the study period.

steadily from 2007 onward, indicating that Canadian physicians were “course-correcting” as safety signals were emerging from clinical trials. A similar pattern

was demonstrated in a recent study from the United Kingdom using ESKD registry data.¹⁰ In the present study, between 2007 and 2015, the proportion of

Table 2. Association between era of dialysis initiation and outcomes

	Number of events	Rate per 1000 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR ^a (95% CI)
Primary outcome				
Era 1	3890	196.3 (190.2–202.6)	1.0 (reference)	1.0 (reference)
Era 2	3867	185.3 (179.6–191.2)	0.94 (0.90–0.99) ^b	0.95 (0.91–1.0) ^b
Era 3	4053	176.6 (171.2–182.1)	0.90 (0.86–0.94) ^c	0.92 (0.88–0.96) ^c
Acute myocardial infarction				
Era 1	823	40.9 (38.2–43.8)	1.0 (reference)	1.0 (reference)
Era 2	939	44.4 (41.6–47.3)	1.09 (0.99–1.19)	1.07 (0.97–1.17)
Era 3	893	38.3 (35.8–40.9)	0.94 (0.85–1.03)	0.93 (0.84–1.02)
Stroke				
Era 1	388	19.0 (17.2–20.9)	1.0 (reference)	1.0 (reference)
Era 2	380	17.5 (15.9–19.4)	0.93 (0.80–1.07)	0.92 (0.80–1.06)
Era 3	480	20.3 (18.5–22.2)	1.07 (0.94–1.22)	1.08 (0.95–1.24)
All-cause mortality				
Era 1	3338	160.3 (155.0–165.9)	1.0 (reference)	1.0 (reference)
Era 2	3175	144.4 (139.5–149.5)	0.90 (0.86–0.95) ^c	0.91 (0.87–0.96) ^c
Era 3	3352	139.1 (134.5–143.9)	0.87 (0.83–0.91) ^c	0.90 (0.85–0.94) ^c

CI, confidence interval; HR, hazard ratio

^aMultivariable model adjusted for age, sex, race/ethnicity, cause of end-stage kidney disease, diabetes, ischemic heart disease, heart failure, previous stroke, peripheral vascular disease, predialysis nephrology care, dialysis access, body mass index, albumin, calcium, phosphate, and parathyroid hormone.

^bP < 0.05.

^cP < 0.001.

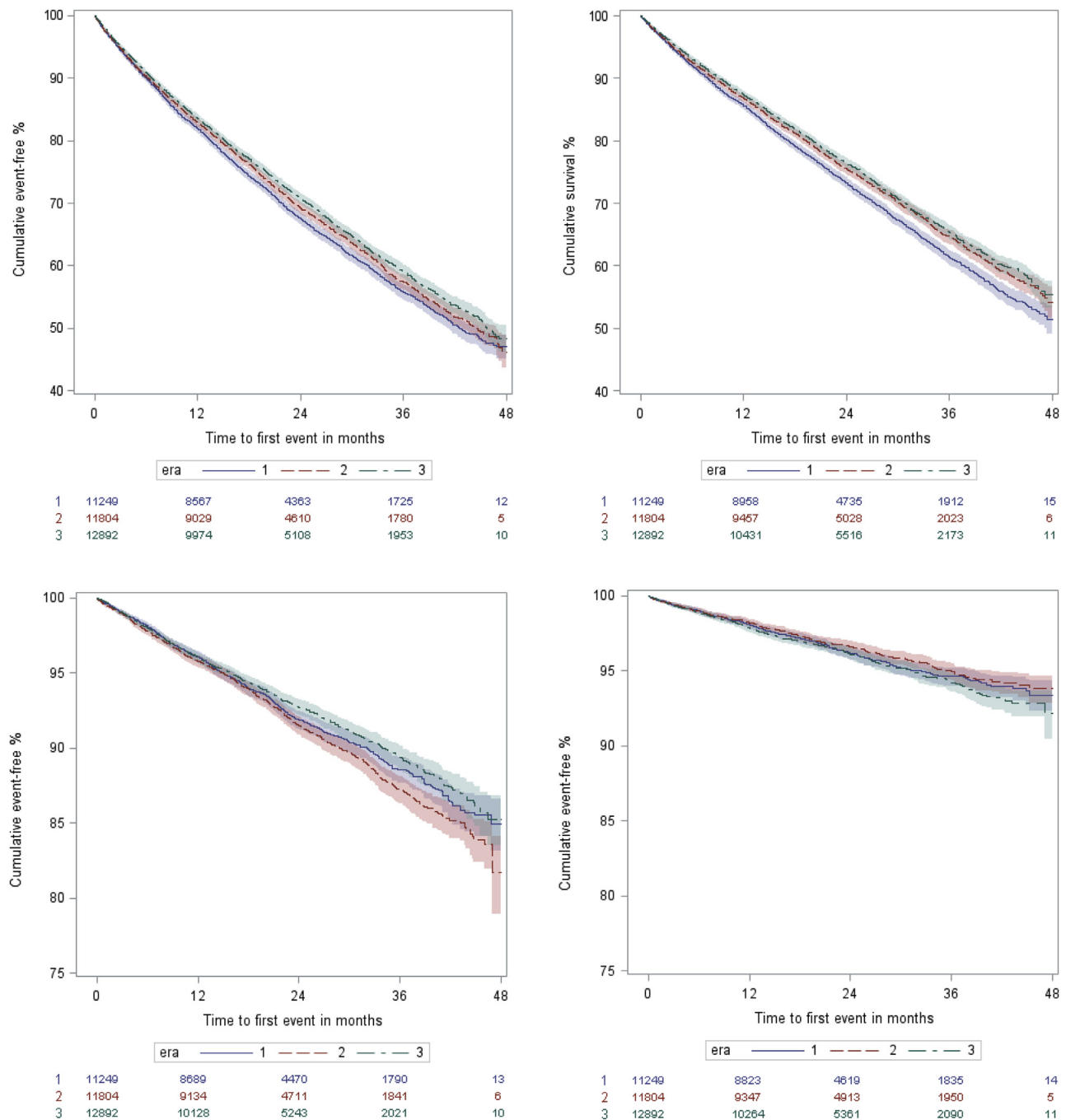


Figure 4. Kaplan-Meier curves showing the association between era of anemia management and time to first composite outcome (top left), all-cause mortality (top right), acute myocardial infarction (bottom left), and stroke (bottom right).

patients with hemoglobin values below 80 g/l doubled from 8% to 17%, a finding that is not in keeping with clinical guidelines and represents a substantial shift in practice. Although this pattern was not temporally associated with an increased risk of hard outcomes, there could be unintended consequences from this magnitude of anemia for more proximal outcomes. These may include a higher risk of vascular access bleeding, an outcome that is not routinely captured in dialysis patient registries, or reduced exercise tolerance and physical functioning,

which have been shown to improve with partial correction of anemia in patients receiving maintenance hemodialysis.²² The most concerning complication is the need for blood transfusion, the rate of which has increased in recent years among dialysis patients,^{23,24} with potentially negative implications for future transplantation due to immune sensitization. Remembering that the advent of ESA therapy was revolutionary for patients with severe anemia requiring transfusions, it appears as though this aspect of anemia therapy has come full circle.

Table 3. Series of nested multivariable models for the primary outcome

	Model 1	Model 2	Model 3	Model 4	Model 5
Era 1	1.0	1.0	1.0	1.0	1.0
Era 2	0.944 (0.903–0.987)	0.951 (0.910–0.995)	0.946 (0.904–0.989)	0.948 (0.907–0.992)	0.953 (0.912–0.997)
Era 3	0.90 (0.861–0.941)	0.913 (0.873–0.954)	0.907 (0.868–0.948)	0.919 (0.879–0.961)	0.918 (0.878–0.961)
Age (per 5 y)		1.174 (1.166–1.83)	1.147 (1.138–1.156)	1.15 (1.142–1.159)	1.15 (1.14–1.159)
Male sex		1.016 (0.979–1.055)	0.985 (0.949–1.023)	0.992 (0.956–1.03)	0.99 (0.953–1.028)
Race/ethnicity					
White		1.0	1.0	1.0	1.0
Asian		0.54 (0.497–0.588)	0.622 (0.571–0.677)	0.628 (0.576–0.684)	0.585 (0.537–0.638)
Black		0.573 (0.509–0.645)	0.586 (0.520–0.660)	0.582 (0.517–0.656)	0.566 (0.502–0.638)
Indian subcontinent		0.769 (0.706–0.837)	0.748 (0.687–0.815)	0.758 (0.696–0.826)	0.735 (0.675–0.802)
Other		1.009 (0.955–1.065)	1.002 (0.948–1.058)	0.994 (0.941–1.05)	0.965 (0.913–1.02)
Cause of ESKD					
Glomerular disease			1.0	1.0	1.0
Diabetes			1.313 (1.216–1.418)	1.367 (1.265–1.476)	1.394 (1.29–1.506)
Vascular disease			1.242 (1.145–1.346)	1.269 (1.170–1.376)	1.308 (1.206–1.418)
Other			1.439 (1.334–1.553)	1.398 (1.296–1.509)	1.431 (1.326–1.545)
Comorbidities					
Diabetes			1.249 (1.198–1.303)	1.216 (1.165–1.269)	1.20 (1.149–1.253)
IHD			1.281 (1.23–1.333)	1.279 (1.228–1.331)	1.299 (1.247–1.352)
Heart failure			1.383 (1.329–1.440)	1.321 (1.269–1.376)	1.299 (1.247–1.353)
Stroke			1.168 (1.114–1.225)	1.169 (1.115–1.226)	1.160 (1.106–1.216)
PVD			1.325 (1.267–1.386)	1.325 (1.267–1.386)	1.308 (1.251–1.368)
Predialysis care					
None				1.0	1.0
<6 months				0.84 (0.79–0.894)	0.891 (0.837–0.948)
≥6 months				0.819 (0.781–0.859)	0.899 (0.856–0.944)
Dialysis access					
Catheter				1.0	1.0
AVF/AVG				0.687 (0.647–0.730)	0.737 (0.694–0.784)
PD catheter				0.908 (0.862–0.957)	0.991 (0.939–1.045)
Unknown				1.064 (0.908–1.247)	1.086 (0.927–1.273)
BMI, per 1 kg/m ²					0.990 (0.987–0.994)
Albumin, per 1 g/l					0.976 (0.973–0.979)
PTH, per log unit change					0.958 (0.938–0.978)
Phosphate, per 1 mmol/l					1.035 (1.006–1.064)

AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; ESKD, end stage kidney disease; IHD, ischemic heart disease; PD, peritoneal dialysis; PTH, parathyroid hormone; PVD, peripheral vascular disease.

Our study has some limitations. Perhaps most importantly, data were not available for other aspects of anemia management that may have changed over time, such as the administration of iron, or an increase in the frequency of blood transfusions. The dose of ESA was unknown at the time of dialysis initiation and was instead captured from follow-up data within the first year of dialysis. The ascertainment of outcomes from administrative data is susceptible to misclassification, and the analysis assumes that coding procedures for events have not changed over time. We elected not to investigate vascular access thrombosis as an outcome because it was not captured in CORR and would likely have been under-captured in DAD because patients may not necessarily have been admitted to hospital for management. Data were missing for some variables; however, the degree of missingness was generally low and adjustment for these variables after multiple imputation did not

change the results. There remains the possibility of measured and unmeasured confounding. Strengths of our study include the large sample size of both hemodialysis and peritoneal dialysis adult patients of all ages from a national database, data linkage for more complete capture of baseline comorbidities, and longer follow-up time compared with previous studies.

In this large national study of incident dialysis patients in Canada, we observed a gradual decline in average hemoglobin values at dialysis initiation, consistent with data from other countries and representing a paradigm shift as a reaction to the adverse outcomes observed in clinical trials of target hemoglobin. In contrast to the United States, we did not observe a temporal reduction in the rate of stroke in this population, potentially explained by differences in patterns of ESA use. Survival of incident dialysis patients has improved in Canada, a finding that is unlikely to be directly attributable to anemia management. Although

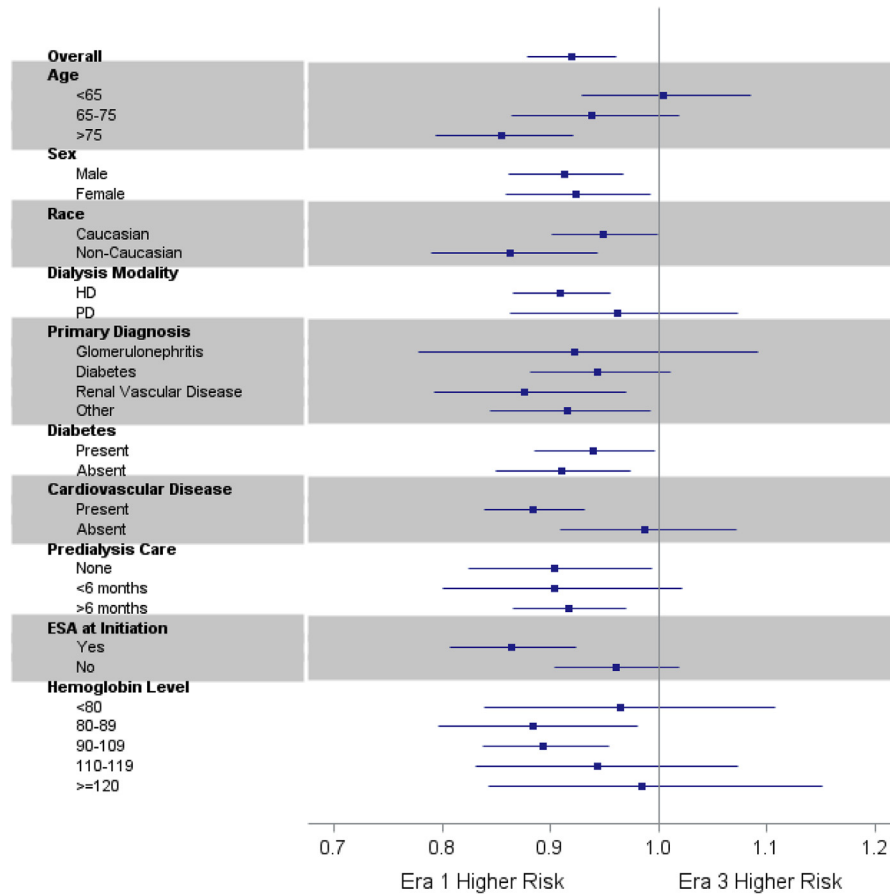


Figure 5. The association between era (Era 3 versus Era 1) and the primary outcome (acute myocardial infarction, stroke, or all-cause mortality) in demographic and clinical subgroups. Estimates are hazard ratios and associated 95% confidence intervals. HD, hemodialysis; PD, peritoneal dialysis.

recommendations to avoid excessively high hemoglobin values in dialysis patients are well-founded, this applies to only a small minority of patients in Canada. For most patients with hemoglobin values within a range deemed acceptable by guidelines, further lowering of the hemoglobin value has not contributed to a meaningful change in clinical outcomes for patients. Although not temporally associated with hard outcomes, the rising prevalence of severe anemia (hemoglobin <80 g/l) at the onset of dialysis merits further investigation in terms of patient-centered outcomes.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Appendix 1. Ascertainment of acute myocardial infarction and stroke.

Table S1. Frequency of missing data for covariates.

Table S2. Multivariable model for acute myocardial infarction.

Table 4. Association between hemoglobin level and ESA status at dialysis initiation and outcomes

Variable	Unadjusted model	P value	Multivariable model ^a	P value
Primary outcome				
Hemoglobin (g/l)		<0.001 ^b		0.48 ^b
<80	1.02 (0.96–1.08)	0.49	1.05 (0.99–1.11)	0.14
80–89	1.07 (1.02–1.12)	0.009	0.99 (0.94–1.04)	0.73
90–109	1.0 (reference)	-	1.0 (reference)	-
110–119	0.89 (0.84–0.94)	<0.001	0.99 (0.93–1.05)	0.63
≥120	0.88 (0.82–0.94)	<0.001	1.02 (0.95–1.09)	0.62
On ESA therapy	0.91 (0.88–0.95)	<0.001	0.99 (0.95–1.03)	0.64
All-cause mortality				
Hemoglobin (g/l)		<0.001 ^b		0.18 ^b
<80	1.05 (0.98–1.12)	0.16	1.07 (1.01–1.15)	0.04
80–89	1.07 (1.02–1.13)	0.008	0.99 (0.94–1.05)	0.78
90–109	1.0 (reference)	-	1.0 (reference)	-
110–119	0.88 (0.93–0.94)	<0.001	0.98 (0.92–1.04)	0.5
≥120	0.88 (0.82–0.95)	<0.001	1.02 (0.95–1.10)	0.6
On ESA therapy	0.87 (0.84–0.91)	<0.001	0.97 (0.93–1.02)	0.23

ESA, erythropoiesis stimulating agent.

^aMultivariable model adjusted for hemoglobin level, ESA status, age, sex, race/ethnicity, cause of end-stage kidney disease, diabetes, ischemic heart disease, heart failure, previous stroke, peripheral vascular disease, predialysis nephrology care, dialyses access, body mass index, albumin, calcium, phosphate, and parathyroid hormone

^bChi-square test for overall significance of categorical hemoglobin variable.

Table S3. Multivariable model for stroke.

Table S4. Multivariable model for all-cause mortality.

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