Sickle Trait in African-American Hemodialysis Patients and Higher Erythropoiesis-Stimulating Agent Dose


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ABSTRACT

African Americans require higher doses of erythropoiesis-stimulating agents (ESAs) during dialysis to manage anemia, but the influence of sickle cell trait and other hemoglobinopathy traits on anemia in dialysis patients has not been adequately evaluated. We performed a cross-sectional study of a large cohort of adult African-American hemodialysis patients in the United States to determine the prevalence of hemoglobinopathy traits and quantify their influence on ESA dosing. Laboratory and clinical data were obtained over 6 months in 2011. Among 5319 African-American patients, 542 (10.2%) patients had sickle cell trait, and 129 (2.4%) patients had hemoglobin C trait; no other hemoglobinopathy traits were present. Sickle cell trait was more common in this cohort than the general African-American population (10.2% versus 6.5%–8.7%, respectively, \( P<0.05 \)). Among 5002 patients (10.3% sickle cell trait and 2.4% hemoglobin C trait) receiving ESAs, demographic and clinical variables were similar across groups, with achieved hemoglobin levels being nearly identical. Patients with hemoglobinopathy traits received higher median doses of ESA than patients with normal hemoglobin (4737.4 versus 4364.1 units/treatment, respectively, \( P=0.02 \)). In multivariable analyses, hemoglobinopathy traits associated with 13.2% more ESA per treatment (\( P=0.001 \)). Within subgroups, sickle cell trait patients received 13.2% (\( P=0.003 \)) higher dose and hemoglobin C trait patients exhibited a similar difference (12.9%, \( P=0.12 \)). Sensitivity analyses using weight-based dosing definitions and separate logistic regression models showed comparable associations. Our findings suggest that the presence of sickle cell trait and hemoglobin C trait may explain, at least in part, prior observations of greater ESA doses administered to African-American dialysis patients relative to Caucasian patients.


Sickle cell trait (HbAS) is present among 6%–8% of American Americans and historically described as a relatively benign carrier state in healthy individuals.1,2 Few studies exist on whether this variant hemoglobin might impact another existing disease. Sickle trait could be particularly influential in CKD and its associated anemia.

Renal abnormalities are the most well-recognized manifestations of HbAS and they include hematuria, altered urinary concentrating ability, papillary necrosis, and renal medullary carcinoma.3–7 With these aberrations, one might expect HbAS to be common in patients with renal disease. Although not conclusive, some epidemiologic data support this contention in CKD patients, particularly patients requiring maintenance dialysis.8–11

The anemia of CKD is a specific instance in which hemoglobinopathy traits may have an impact. Uremic toxins alter erythrocytes, and transit
through an extracorporeal hemodialysis circuit could predispose to sickling of red blood cells containing HbAS. African Americans at dialysis initiation have lower hemoglobin levels and require higher initial doses of erythropoiesis-stimulating agents (ESAs). This difference in ESA dose persists despite similarly achieved hemoglobin levels. Although reasons for ESA dose difference have not been clearly determined and are likely quite variable, sickle cell trait and other variant hemoglobins could play a role.

We sought to determine the prevalence of sickle cell trait and other hemoglobinopathy traits and their association with ESA dosing in a large cohort of African-American hemodialysis patients. We postulated that HbAS and other hemoglobinopathy traits would be common and predispose to higher ESA dosing to achieve the hemoglobin target of 10–12 g/dl in 2011.

RESULTS

Residual blood samples from 5920 hemodialysis patients (5323 [89.9%] from African Americans) were tested. Four patients with primarily fetal hemoglobin were excluded. The study consisted of 5319 African-American patients, with 671 (12.6%) patients carrying a hemoglobinopathy trait: 542 (10.2%) patients had HbAS, and 129 (2.4%) patients had hemoglobin C trait (HbAC). No other variants were identified. Compared with prior prevalence estimates in the general population, HbAS was more common in dialysis-dependent CKD (10.2% versus 6.5%–8.6%, P<0.001; versus 8.7%, P=0.02). Comparatively observed when using weight-based ESA dosing, with a median dose of 55.5 units/kg per treatment for HbAS versus 60.5 for any trait (P=0.01), 60.0 for HbAS (P=0.03), and 61.0 (P=0.15) for HbAC. Variability in ESA dose was assessed by SEM as a proportion of monthly ESA dose. We found no difference in ESA variability between those patients without and those patients with a hemoglobinopathy trait (SEM=19.73% ±10.53% versus 18.90%±9.89%, P=0.06). With this same measure, ESA variability was just slightly lower among those patients not hospitalized (19.11%±10.22% versus 20.02%±10.61%; P=0.002). In evaluating only hospitalized patients, we found no significant difference in variability between those patients without and those patients with a hemoglobinopathy trait (19.17%±10.23% versus 18.63%±10.15%; P=0.44).

Multivariable Analyses

In a linear regression model of the log-transformed ESA dose per treatment, diabetes, hypertension, and weight were not identified as confounders. The multivariable model included age, sex, dialysis vintage, intact parathyroid hormone, albumin, Kt/V, ferritin, transferrin saturation, vascular access, iron dose per treatment, missed treatments, and hospitalization days. Vascular access was included as a binary variable (catheter versus either arteriovenous fistula [AVF] or arteriovenous graft [AVG]), because both AVG and AVF had similar association with ESA dose. Backward elimination identified all covariates as contributory, and all were retained. Compared with HbAA patients (Table 2), those patients with hemoglobinopathy traits received approximately 13.2% more ESA per treatment (95% confidence interval [95% CI], 5.2% to 21.9%; P=0.001). Within subgroups, patients with HbAS also received 13.2% more ESA (95% CI, 4.3% to 22.9%; P=0.003), whereas HbAC exhibited a familiar trend with 12.9% higher ESA (95% CI, −3.1% to 31.6%, P=0.12). Sensitivity analyses using weight-adjusted ESA dose indicated a similar pattern (Table 2); any hemoglobinopathy trait was associated with 14.9% higher ESA dose (P<0.001), with HbAS at +15.3% (P=0.001) and HbAC at +13.1% (P=0.14).
In a separate logistic regression model, we established our outcome as the likelihood of receiving the highest quartile of ESA dose. Those patients with any hemoglobinopathy trait had greater odds of receiving the highest ESA quartile (unadjusted odds ratio [OR], 1.25; 95% CI, 1.03 to 1.50; \( P =0.02 \)), with a similar trend present between subgroups of HbAS and HbAC (Table 3). The fully adjusted logistic model indicated that hemoglobinopathy trait patients remained more likely to belong in the highest quartile of ESA (OR, 1.44; 95% CI, 1.17 to 1.77; \( P =0.001 \)). This association was consistent within subgroups of HbAS (OR, 1.44; 95% CI, 1.14 to 1.80; \( P =0.002 \)) and HbAC, although predictably, the latter group (with its small sample size) failed to attain statistical significance (OR, 1.44; 95% CI, 0.93 to 2.22; \( P =0.10 \)). Backward elimination identified only transferrin saturation as the primary confounder in a simplified model, remaining consistent with prior results (Table 3).

### DISCUSSION

We found hemoglobinopathy traits, particularly sickle cell trait, to be common in a large national sample of African Americans receiving in-center hemodialysis. The presence of a hemoglobinopathy trait was associated with a 13% higher ESA dose administered to achieve nearly identical hemoglobin even after controlling for available known potential confounding factors.
Table 3. Association of hemoglobinopathy trait with being in the highest quartile of ESA dosing

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariable Analysis OR (95% CI)</th>
<th>P Value</th>
<th>Multivariable Analysis OR (95% CI)</th>
<th>P Value</th>
<th>Simplified Analysis OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Hb trait</td>
<td>1.25 (1.03 to 1.50)</td>
<td>0.02</td>
<td>1.44 (1.17 to 1.77)</td>
<td>0.001</td>
<td>1.30 (1.07 to 1.58)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>&lt;0.001</td>
<td>0.98 (0.98 to 0.99)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (men)</td>
<td>0.91 (0.80 to 1.04)</td>
<td>0.17</td>
<td>0.91 (0.78 to 1.05)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis vintage (yr)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>0.65</td>
<td>1.00 (1.00 to 1.00)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact parathyroid hormone</td>
<td>1.00 (1.00 to 1.00)</td>
<td>&lt;0.001</td>
<td>1.00 (1.00 to 1.00)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Albumin</td>
<td>0.20 (0.17 to 0.24)</td>
<td>&lt;0.001</td>
<td>0.21 (0.17 to 0.27)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Kt/V</td>
<td>0.16 (0.11 to 0.22)</td>
<td>&lt;0.001</td>
<td>0.34 (0.23 to 0.51)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Ferritin</td>
<td>1.00 (1.00 to 1.00)</td>
<td>&lt;0.001</td>
<td>1.00 (1.00 to 1.00)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Transferrin saturation</td>
<td>0.92 (0.91 to 0.93)</td>
<td>&lt;0.001</td>
<td>0.94 (0.93 to 0.95)</td>
<td>&lt;0.001</td>
<td>0.92 (0.91 to 0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Access type (catheter versus AVF/AVG)</td>
<td>2.11 (1.84 to 2.41)</td>
<td>&lt;0.001</td>
<td>1.27 (1.08 to 1.48)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron dose</td>
<td>1.10 (1.08 to 1.12)</td>
<td>&lt;0.001</td>
<td>1.04 (1.02 to 1.06)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missed treatments</td>
<td>1.04 (1.03 to 1.05)</td>
<td>&lt;0.001</td>
<td>1.03 (1.02 to 1.04)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Hospitalization days</td>
<td>2.20 (1.50 to 3.23)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model stratified by trait type</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HbAS</td>
<td>1.22 (0.99 to 1.49)</td>
<td>0.06</td>
<td>1.44 (1.14 to 1.80)</td>
<td>0.002</td>
<td>1.27 (1.03 to 1.57)</td>
<td>0.03</td>
</tr>
<tr>
<td>HbAC</td>
<td>1.38 (0.93 to 2.04)</td>
<td>0.11</td>
<td>1.44 (0.93 to 2.22)</td>
<td>0.10</td>
<td>1.43 (0.95 to 2.17)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Any Hb trait, any hemoglobinopathy trait (includes HbAS and HbAC).

*Only reported to two significant digits but may be < 0.001.

*Covariates and their ORs (95% CIs) identical to the model using any Hb trait as primary exposure.

Factors. Patients with either sickle cell trait or HbAC trait have a 30% increase in the likelihood of falling in the highest quartile of ESA dosing. To our knowledge, this study is the first study to quantify the influence of hemoglobinopathy traits on anemia management in hemodialysis patients, and it may have several implications.

African Americans on hemodialysis had a higher prevalence of sickle cell trait compared with the general African-American population. A prior study of African-American dialysis patients from four North Carolina centers detected an even higher prevalence of 14.9%. This largest study to date reports a prevalence in between our prior study and the lowest prevalence (7.9%) in dialysis-dependent CKD. The study by Hicks et al. drew from a wide region, including North Carolina, South Carolina, Georgia, Virginia, and Tennessee, but used a dialysis cohort recruited for genetic studies. We speculate that this difference in participant selection could have influenced the prevalence of HbAS patients. The well-recognized renal manifestations of sickle cell trait have led to speculation that HbAS could contribute to development of CKD and progression to maintenance dialysis. The present study, which shows a higher prevalence of sickle cell trait in the ESRD population, supports this hypothesis. However, we acknowledge that the contribution of sickle cell trait to CKD progression would ideally be studied in a prospective cohort.

This study also shows higher ESA dosing requirements to meet a standard hemoglobin target in chronic hemodialysis patients with hemoglobinopathy traits and quantifies this association. Several potential mechanisms exist to explain these findings. Both HbAS and HbAC mutations alter the β-globin chain of hemoglobin, and they can lead to precipitation of the hemoglobin molecule and in the case of HbAS, alter the shape of the red blood cell. As blood travels through extracorporeal hemodialysis circuits, erythrocytes are exposed to lower temperature, lower partial pressure of oxygen, and physical stressors of the hemodialysis filter. Possibly, these factors could induce sickling or dehydration and subsequent injury to red cells. Transient sickling events may lead to increased phosphatidylserine exposure on erythrocytes and reduced life span. Our group previously reported that HbAS hemodialysis patients exhibit an increase in red cell phosphatidylserine exposure. Antibodies to erythropoietin have been observed in individuals with hemoglobinopathies, and although not specifically studied in ESRD patients with hemoglobinopathy traits, they could reduce the effect of erythropoietin and ESAs. Inflammation is a feature of overt sickle cell diseases, and in ESRD it contributes to ESA resistance by blunting iron use and erythropoiesis. If inflammation in ESRD is modified or augmented by sickle cell trait, it could explain the observed need for increased ESA.

The association between hemoglobinopathy traits and higher ESA dose raises other questions as well. Data have emerged that suggest that high doses of ESAs and perhaps, overcorrection of anemia are associated with higher cardiovascular risk. Several studies, including the Normal Hematocrit Study, Correction of Hemoglobin and Outcomes in Renal Insufficiency study, Cardiovascular Risk Reduction by
Early Anemia Treatment with Epoetin-β study, and Trial to Reduce Cardiovascular Events with Aranesp Therapy, showed that higher hemoglobin levels in CKD offered no significant benefit, but use of higher doses of ESA to achieve these targets may have contributed to cardiovascular and thrombotic risks.\textsuperscript{32–36} We do not have specific data on the safety of higher ESA dosing in our population, but we observed no difference in hospitalization rates among those patients with hemoglobinopathy traits. Although this finding may suggest no significant difference in morbidity or by extension, mortality, future studies are warranted to specifically evaluate this issue.

If no significant increase in morbidity or mortality exists, our findings must also be addressed in perspective of the recent dialysis bundled payment system. The Centers for Medicare and Medicaid Services have incorporated case-adjustment comorbid illness variables to the bundled payment system—three acute and three chronic conditions.\textsuperscript{37} The three chronic modifiers include hereditary hemolytic or sickle cell anemia, myelodysplastic syndromes, and monoclonal gammopathy.\textsuperscript{37} Presently, neither race nor hemoglobinopathy traits are included in this case adjustment, but the latter are much more common than hemolytic or sickle cell anemia. Many suggest that race should be included in the bundle because of prior observations that African Americans receive more ESA.\textsuperscript{38,39}

We attempted a post hoc analysis to determine whether hemoglobinopathy traits could explain racial differences in ESA. Among 504 non–African-American patients with HbAA from the same dialysis centers, this group had similar hemoglobin levels (11.3±0.7) but differed in other clinical and demographic characteristics (Supplemental Table 1). ESA doses, both whole and weight-adjusted, were no different from the African-American population (median=4569.2 versus 4420.6 units/treatment, \(P=0.97\) and 60.5 versus 56.3 units/kg per treatment, \(P=0.23\)). A linear regression model, which included these non–African-American patients and a covariate for race, did not identify race to be a significant contributor to ESA dose; hemoglobinopathy trait, however, retained nearly an identical effect size (13.1%; 95% CI, 5.1% to 21.8%; \(P=0.001\)) when this total population of non–African Americans and all African Americans was evaluated. We must emphasize that conclusions drawn from these post hoc analyses are limited. This comparator group of non–African-American patients is of relatively small number and drawn from dialysis centers with predominantly African-American patients. As such, these patients may not be truly representative of non–African-American hemodialysis patients as a whole.

Still, even if limited to African Americans with hemoglobinopathy traits, a 13% increase in mean ESA dose is not trivial. With the average wholesale price of ESA reported at $1.518/100 units\textsuperscript{40} and the mean ESA dose of 6100 units/treatment in the HbAA subgroup, these trends would account for a $12.10 increase in cost of each dialysis treatment. With a conservative average of 140 treatments yearly, this increase amounts to an incremental expense of over $1 million annually in this study cohort. Extrapolating our findings to the US national hemodialysis population of over 140,000 African Americans\textsuperscript{41} and approximating a range of 7%–14% of hemoglobinopathy traits in African Americans, the annualized cost of ESA attributable to these traits is between $16.8 and $33.5 million. If this marginally higher ESA use to attain target hemoglobin is unassociated with adverse events, a strong case can be made for hemoglobinopathy traits to be evaluated as case adjustors for bundled payment.

The results of our analyses must be interpreted in the context of certain considerations. Although we note higher prevalence of HbAS, we selected dialysis centers with large proportions of African Americans, possibly biasing our results. Nonetheless, we can say that hemoglobinopathy traits, specifically sickle cell trait, are common in African-American CKD patients on hemodialysis. Despite the robust association between ESA dosing and hemoglobinopathy trait, the study was cross-sectional, and this relationship should also be evaluated prospectively from ESA initiation. Nevertheless, limiting the cohort to prevalent patients (dialysis ≥3 months) and evaluating clinical data over an averaged 6-month period rendered the initial ESA response and differences in initiation hemoglobin to be less of an issue. Although comprehensive, our observational study cannot account for residual confounding, which results from unmeasured variables, including gastrointestinal bleeding and blood transfusions; however these events would likely have occurred in the inpatient setting and may have been partially captured by hospitalization days. Our analyses may have been affected if some patients had more laboratory values captured because of more frequent measurement or fewer values captured because of hospitalizations or missing data. However, we believe that these additional or missing data were likely balanced between those patients with and without hemoglobinopathy traits, which is evidenced by the similarities in missed treatments and hospital days. Also, adjusting for these latter two factors in our analyses probably minimized any influence.

In summary, we show in a large national population of African-American hemodialysis patients that hemoglobinopathy traits, especially sickle cell trait, are relatively common and associated with greater ESA dose administration while maintaining similar hemoglobin levels. These patients receive approximately 13% more ESA, which may currently translate to approximately $30 million annually in differential unrecognized costs. Future work must identify whether this increase in dose is associated with an increase in morbidity and mortality and whether anemia management and dialysis therapy can be further optimized for patients with hemoglobinopathy traits.

\textbf{CONCISE METHODS}

\textbf{Study Population}

In total, 117 in-center hemodialysis clinics in the United States with predominantly African Americans managed by Fresenius Medical
Care North America (FMCNA) participated (Figure 1). All adult patients (age ≥ 18 years) with ≥3 months of maintenance hemodialysis and without sickle cell disease as documented by comorbid International Classification of Diseases, Ninth Revision, diagnosis codes were included, with the exception of a single patient who opted out of the study. For analyses of ESA dosing, we included all patients with at least one documented ESA dose during the study period. The study protocol and performance of the study by FMCNA were approved by the New England Institutional Review Board. Approval for analysis of the deidentified data was also obtained from the Institutional Review Board of the University of North Carolina at Chapel Hill.

**Exposure**

Residual blood samples for participants’ monthly laboratory parameters were used for hemoglobin electrophoresis (MINICAP capillary electrophoresis; Sebia Electrophoresis, Norcross, GA), which was performed by Spectra Laboratories, Inc. (Milpitas, CA), and they were tested between August of 2011 and October of 2011. Heterozygosity (trait) for any hemoglobinopathy was defined as presence of hemoglobin A (HbA) and any variant hemoglobin (e.g., hemoglobin S). Heterozygosity was then further separated by specific variant hemoglobin. Sickle cell trait was defined as presence of HbA and hemoglobin S, and HbAC trait was defined as presence of HbA and hemoglobin C.

**Outcome**

The primary measures of interest were (1) prevalence of hemoglobinopathy trait among African Americans and (2) average per-treatment dose of ESA administered. Prevalence was calculated as the proportion of patients with hemoglobinopathy traits. ESA dose was determined for a 6-month period centered on the date of a participant’s electrophoresis—3 months before and 3 months after electrophoresis. The total ESA received over the 6-month period was divided by the total treatments received to determine ESA dose per treatment. For sensitivity analyses, we performed regression models using

![Figure 1.](image-url) Distribution of participant in-center hemodialysis facilities. Symbols represent approximate location of dialysis centers from which patients were drawn for inclusion in the study.
average ESA per treatment divided by average postdialysis weight (units per kilogram per treatment). Variability in ESA dosing was also assessed for each individual by calculating the SEM of monthly ESA dose. SEMs were then normalized to the patient’s mean ESA dose over the study period to allow for comparison across the population. Variability was compared by presence or absence of hemoglobin variant and history of hospitalization.

Covariates
We extracted information from the FMCNA Knowledge Center for age, sex, weight, hypertension, diabetes mellitus, dialysis adequacy (equilibrated Kt/V), intact parathyroid hormone, hemoglobin, iron saturation, ferritin, intravenous iron dose received, vascular access type (catheter, AVG, or AVF), albumin, hospitalization days, blood transfusions, and missed treatments. Laboratory data were aggregated into the per-patient average of all available values over 6 months. Hospitalization days and missed treatments for each patient were calculated as proportions of total prescribed treatments.

Statistical Analyses
Baseline characteristics were described using means and SDs or medians with interquartile ranges, with categorical variables depicted by counts with percentages. We compared groups by hemoglobin status (HbAA versus any hemoglobinopathy trait) using Fisher exact test for categorical variables and t tests or Kruskal–Wallis testing for continuous variables. Identical approaches were used to compare HbA with HbAS and HbAC subgroups, substituting ANOVA for testing continuous variables with normal distributions. The prevalence of any hemoglobinopathy trait and each specific variant (i.e., HbAS or HbAC) was compared with several published values from the general African-American population, hospitalized African-American patients, and two prior cohorts of African-American dialysis patients using Fisher exact test.1,2,9,15–18

Covariates associated with the exposure (hemoglobinopathy trait) or the outcome (ESA dose) in univariable analyses were evaluated for inclusion as potential confounders in multivariable analyses (many were identified in prior observations for ESA hyporesponsiveness).43 Log transformation of ESA dose was performed to produce a parametric distribution for linear regression.44 Output of this model allowed for attribution of a percentage change in ESA dose compared with the referent population.44 Using backward elimination of covariates, we removed only variables with P > 0.15 in the fully adjusted model. Sensitivity analyses were performed in a similar fashion using weight-based ESA dose as the outcome. In alternative analyses, we defined a dichotomous variable with the outcome as the highest quartile of ESA dosing and constructed a logistic regression model with hemoglobinopathy trait as the exposure. After inclusion of all covariates identified in univariable analyses, we used backward elimination and retained only confounders resulting in greater than 10% change in estimate of the full model. All regression models were repeated using specific hemoglobinopathy traits as the exposure (i.e., evaluated the association between ESA dose and HbAS and HbAC individually).

Sample size was calculated based on the first model using prior study data.14 Assuming 10% prevalence of hemoglobinopathy traits in African Americans, we required 5000 patients to detect a 12% difference in ESA dosing with 90% power using a two-sided \( \alpha = 0.05 \). All analyses were conducted with Stata 12.1 for Mac (StataCorp LP, College Station, TX). The statistical analysis of data for this study was performed independently by V.K.D., who had access to the full dataset.

ACKNOWLEDGMENTS

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Fresenius Medical Care North America participated in the design, conduct, and management of the study; all analyses were performed independent of Fresenius Medical Care North America.

DISCLOSURES

E.K.L., R.M.H., A.M., and J.I.M.L. were employed by Fresenius Medical Care North America (the sponsor) at the time of the study. C.M.J. and C.J. are employed by Spectra Laboratories, Inc.

REFERENCES


