Comparative Mortality Risk of Anemia Management Practices in Incident Hemodialysis Patients

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Context Controversy exists about optimal management of anemia in end-stage renal disease.

Objective To compare the mortality risk of different dialysis center–level patterns of anemia management.

Design, Setting, and Patients Using data from Medicare’s end-stage renal disease program (1999-2007), we characterized each US dialysis center’s annual anemia management practice by estimating its typical use of erythropoiesis-stimulating agents (ESAs) and intravenous iron in hemodialysis patients within 4 hematocrit categories. We used Cox proportional hazards regression to correlate center-level patterns of ESA and iron use with 1-year mortality risk in 269,717 incident hemodialysis patients.

Main Outcome Measure One-year all-cause mortality.

Results Monthly mortality rates were highest in patients with hematocrit less than 30% (mortality, 2.1%) and lowest for those with hematocrit of 36% or higher (mortality, 0.7%). After adjustment for baseline case-mix differences, dialysis centers that used larger ESA doses in patients with hematocrit less than 30% had lower mortality rates than centers that used smaller doses (highest vs lowest dose group: hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.90-0.97). Centers that administered iron more frequently to patients with hematocrit less than 33% also had lower mortality rates (highest vs lowest quintile, HR, 0.95; 95% CI, 0.91-0.98). However, centers that used larger ESA doses in patients with hematocrit between 33% and 35.9% had higher mortality rates (highest vs lowest quintile, HR, 1.07; 95% CI, 1.03-1.12). More intensive use of both ESAs and iron was associated with increased mortality risk in patients with hematocrit of 36% or higher. These findings persisted across a range of secondary analyses.

Conclusions Greater ESA and iron use were associated with decreased mortality risk at lower hematocrit levels, in which mortality rates are the highest. Although the overall mortality rate was lower at higher hematocrit levels, elevated mortality risk was associated with greater use of ESAs and iron in these patients.
lytic approach. We studied the potential natural experiment created by differences between dialysis centers in their anemia management practice.11,12 Our approach was motivated by (1) evidence suggesting that there is great variation among dialysis centers in the protocols used to make ESA and iron treatment decisions and (2) the assumption that patients are assigned to centers in a way that effectively randomizes them to different anemia management protocols. This approach is conceptually similar to most of the major trials of ESAs, where patients are not randomized to receive a specific dose of an ESA but are randomized to different treatment protocols dictating how ESAs and iron doses are to be titrated to achieve a desired hematocrit level.

Because data are not available on the anemia management protocols of individual dialysis centers, we were unable to directly estimate the mortality risk associated with different protocols. Instead, we associated characteristics of the observed anemia management practice in each dialysis center with mortality risk among patients initiating hemodialysis at the center. Using recent data from Medicare’s ESRD program, we estimated an annual anemia management profile for every US dialysis center. The profile consisted of a set of predicted ESA and iron treatments given to patients with varying degrees of anemia. We then correlated the predicted treatments with 1-year mortality risk among patients initiating hemodialysis at each center.

METHODS

Data Source

Our analysis was based on data from the United States Renal Data System (USRDS). The USRDS contains detailed data on all patients in Medicare’s ESRD program, including information collected at dialysis initiation (reported on the Medical Evidence Form) describing demographics, primary cause of ESRD, clinical data (eg, body mass index), and certain laboratory measurements (eg, serum albumin and hematocrit levels). In addition, the USRDS contains all Medicare Parts A and B claims that include information on diagnoses and procedures recorded for all hospitalizations and outpatient visits. The USRDS also contains data on total monthly ESA doses, which must be submitted with the final hematocrit laboratory recorded during the month. Most ESA use was epoetin alfa; however, there was a small amount of darbepoetin alfa use in the latter years of our study. We converted darbepoetin alfa to units of epoetin alfa using the equimolar dose conversion ratio of 200:1 (1 µg of darbepoetin = 200 units of epoetin). We identified intravenous iron administration using Healthcare Common Procedure Coding System codes from the Medicare Parts A and B claims. The Brigham and Women’s Hospital Institutional Review Board approved this research.

Study Cohort

From the USRDS, we identified all patients who began receiving maintenance hemodialysis between January 1, 1999, and August 31, 2006, and had no history of cancer indicated on the Medical Evidence Form (CMS-2728). Our study cohort consisted of a 50% random sample of all incident patients in this population. The remaining 50% of patients were placed in a “training sample” that was used to construct the anemia management profile for each US dialysis center.

Anemia Management Data

We estimated the anemia management profile using data on ESA doses and iron administrations given to the patients in the training sample. By doing so, we ensured that the patients used to characterize the dialysis center’s anemia management practice would not also be used in our assessment of outcomes.

As required by Medicare, the final hematocrit value of the month must be submitted with each claim for ESA reimbursement. We paired each ESA administration with the hematocrit laboratory value from the previous month; ie, the hematocrit level that gave rise to the ESA dosing. If no hematocrit was identified prior to a given ESA administration, that monthly ESA claim was not included in the analysis. Because ESA exposure captured in the USRDS is almost entirely from outpatient treatment at dialysis centers, we did not include months in which a patient spent 5 or more days in the hospital. We also did not include months that occurred after a patient switched to peritoneal dialysis or received a transplant. We converted the total ESA administered during the index month into units per day by dividing the total units of ESA administered during the month by the days in the month minus the time the patient spent in hospital during the month. We allowed each patient to contribute multiple observations to the analysis data set but used only ESA dosing and iron administration data that occurred 6 months after the start of dialysis.

Statistical Analysis

Dialysis Center Anemia Management Profiles. For each dialysis center, we estimated a center-level ESA dosing profile (a characterization of the center’s typical use of ESAs) using a set of linear random-effects models. To adjust for basic aspects of dialysis center case mix, we included fixed effects for race (white, black, American Indian, or other, as reported to the Centers for Medicare & Medicaid Services by the dialysis centers), age, sex, dialysis center business status (profit vs nonprofit), and cause of ESRD in each model. Other clinical variables were adjusted for in a later stage of the analysis. To capture center-specific ESA dosing practices, we included a center-level random effect that we assumed to be normally distributed. A separate model was fit for each calendar year and hematocrit value (classified as <30%, 30%-32.9%, 33%-35.9%, or ≥36%). This allowed the center’s ESA dosing profile to change each year. Using the fitted models, predicted ESA doses for
each dialysis center during each calendar year were generated for each hematocrit range. For each dialysis center, this set of predicted values represented estimates of typical ESA doses given to patients across the hematocrit groups. The models were fit using PROC MIXED in SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

For each center, we estimated typical use of intravenous iron (proportion of patients treated) using a set of logistic random-effects models that included race, age, sex, cause of ESRD, and dialysis center profit status as fixed effects and a normally distributed center-level random effect. Separate models were likewise fit for each calendar year and hematocrit range. Using the fitted models, predicted probabilities of iron administration for each dialysis center during each calendar year were generated for each hematocrit group. For each dialysis center, this set of predicted values represented the estimated probability that a patient with a given hematocrit would receive supplemental intravenous iron. These models were fit by PROC GLIMMIX using a quasi-likelihood approach maximized with the Nelder-Mead simplex algorithm.13

Association of Dialysis Center Anemia Management Profile and 1-Year All-Cause Mortality Risk. In our study cohort, we evaluated the 1-year all-cause mortality risk associated with dialysis center ESA and intravenous iron management practices. The statistical analysis was based on a Cox proportional hazards regression model of 1-year mortality. Follow-up began 60 days after the start of dialysis. Censoring occurred at the end of 1 year of follow-up, administrative end of follow-up (August 31, 2007), loss to follow-up, change to peritoneal dialysis, or renal transplantation.

We categorized predicted center-level ESA and intravenous iron use into quintiles for each hematocrit range and created indicator variables for these categories that were entered into the model, with the lowest quintile of ESA and iron use for each hematocrit range taken to be the reference category. The Cox models were stratified across calendar year and patient age (broken into 5-year age groups). This explicitly creates risk sets composed of patients of the same age, who began dialysis the same year and were receiving dialysis for the same length of time. We also made multivariable adjustments for various comorbid conditions as reported on the Medical Evidence Form (eg, history of stroke, myocardial infarction, heart failure), cause of ESRD, geographic region indicator variables (to account for regional differences in outcomes and medical practice), zip code–level measures of socioeconomic status, and several dialysis center–level variables. We computed standard errors that appropriately accounted for the clustering of patients within facility.14

Secondary Analyses. Associations between center-level practices and mortality risk could be confounded by patient characteristics or other aspects of care correlated with the center’s anemia management practice. To assess this possibility, we compared our results that were adjusted only for the stratification variables with those from the full multivariable-adjusted model. To test the validity of the anemia management profile, we examined how well it predicted the actual management of anemia in patients from the outcomes sample as well as month-to-month changes in hematocrit. The details of this analysis are provided in the eAppendix.

To further assess the robustness of our findings, we conducted the following secondary analyses: (1) we re-

Figure. Median Predicted Center-Level ESA Dose and Iron Use by Hematocrit Value and Calendar Year

Boxes indicate interquartile range (IQR); horizontal lines, median. ESA indicates erythropoiesis-stimulating agent. Each center contributed up to 2 observations per period (1 per year). For 1999-2000, there were 7387 observations; 2001-2002, 8063 observations; 2003-2004, 8740 observations; and 2005-2006, 9351 observations.

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RESULTS

We analyzed data on approximately 4500 dialysis units in the United States. For each unit, we created a unique anemia management profile for each calendar year. The FIGURE, A, shows the median predicted center-level ESA dose for 33 541 annual anemia management profiles. The plot reveals a secular trend in ESA dosing, with centers using more ESA in the later years of the study, particularly among patients with lower hematocrit. The most variability in center-level dosing occurs in patients with hematocrit less than 30%. Many centers are treating these patients with less than 3500 units/d, whereas others are using more than 6000 units/d of ESAs. For patients with hematocrit of 36% or higher, predicted center-level ESA doses were considerably lower (1000-2000 units/d). The Figure, B, depicts the distribution of center-level intravenous iron use as a monthly rate by calendar year. The graph reveals a modest secular trend toward greater use of intravenous iron in later years: centers in 2005-2006 used intravenous iron in about 62% to 68% of patient-months (depending on hematocrit level), whereas centers in 1999-2000 used iron more frequently in patients with hematocrit of 36% or higher (highest vs lowest quintile of predicted dose: hazard ratio [HR], 1.07; 95% CI, 1.03-1.12) and in those with hematocrit of 36% or higher (highest vs lowest quintile of predicted dose: HR, 1.11; 95% CI, 1.07-1.15). We observed decreased mortality in centers that used iron more frequently in patients with hematocrit less than 30% (highest vs lowest quintile of monthly rate of iron administration: HR, 0.97; 95% CI, 0.94-0.99) and in patients with hematocrit between 30% and 32.9% (highest vs lowest quintile of monthly rate of iron administration: HR, 0.95; 95% CI, 0.91-0.98). We also observed increasing mortality rates in centers that used iron more frequently in patients with hematocrit levels of 36% or higher (highest vs lowest quintile of monthly rate of iron administration: HR, 1.07; 95% CI, 1.02-1.13).

In secondary analyses, we found that the estimated effects were substantively unchanged when we removed all covariates from the Cox model (eAppendix and eTable 1; available at http://www.jama.com), when we added baseline laboratory and clinical

Table 1. Characteristics of Patients in the Sample (N=269 717)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)a</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>144 272 (53.5)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>62.5 (15.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>168 134 (62.3)</td>
</tr>
<tr>
<td>Black</td>
<td>83 836 (31.1)</td>
</tr>
<tr>
<td>American Indian</td>
<td>3455 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>14 292 (5.3)</td>
</tr>
<tr>
<td>Glomerular filtration rate, estimated, mean (SD), mL/min/1.73 m²</td>
<td>3.1 (0.7)</td>
</tr>
<tr>
<td>Serum albumin, mean (SD), g/dL</td>
<td>27.8 (7.4)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)b</td>
<td>14 292 (5.3)</td>
</tr>
</tbody>
</table>

aData are reported as No. (%) unless otherwise specified.
bBody mass index is calculated as weight in kilograms divided by height in meters squared.


Comorbidities were common: 90 005 (33%) had a history of heart failure, 25 719 (10%) had a history of ischemic heart disease, and 25 719 (10%) had a history of stroke or transient ischemic attack. The patients studied were mostly treated at for-profit dialysis centers (78%) and at centers that were not connected to a hospital (90%).

During follow-up, 60 993 patients (22.6%) died, 5662 (2.1%) were censored by a switch to peritoneal dialysis, and 7478 (2.8%) were censored by transplantation. We found that mortality rates were highest in months following hematocrit levels less than 30% (mortality, 2.1%) and then decreased monotonically: for hematocrit levels of 30% to 32.9%, mortality was 1.3%; for 33% to 35.9%, it was 0.9%; and for 36% or higher, it was 0.7%.

TABLE 2 summarizes the multivariable-adjusted associations between anemia management practices and mortality. Centers that used larger doses of ESAs in patients with hematocrit less than 30% achieved lower mortality rates (highest vs lowest quintile of predicted dose: hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.90-0.97). We observed no association between mortality and predicted center ESA dose in patients with a hematocrit between 30% and 32.9%. However, mortality rates were increased in centers that used larger ESA doses in patients with hematocrit between 33% and 35.9% (highest vs lowest quintile of predicted dose: HR, 1.07; 95% CI, 1.03-1.12) and in those with hematocrit of 36% or higher (highest vs lowest quintile of predicted dose: HR, 1.11; 95% CI, 1.07-1.15). We observed decreased mortality in centers that used iron more frequently in patients with hematocrit less than 30% (highest vs lowest quintile of monthly rate of iron administration: HR, 0.97; 95% CI, 0.94-0.99) and in patients with hematocrit between 30% and 32.9% (highest vs lowest quintile of monthly rate of iron administration: HR, 0.95; 95% CI, 0.91-0.98). We also observed increasing mortality rates in centers that used iron more frequently in patients with hematocrit levels of 36% or higher (highest vs lowest quintile of monthly rate of iron administration: HR, 1.07; 95% CI, 1.02-1.13).

In secondary analyses, we found that the estimated effects were substantively unchanged when we removed all covariates from the Cox model (eAppendix and eTable 1; available at http://www.jama.com), when we added baseline laboratory and clinical
variables to the Cox model (eTable 2), when censoring was redefined (eTable 3), when we restricted the analysis to non–hospital-based facilities (eTable 4), and when we restricted the analysis to large dialysis centers (eTable 5). When we stratified by time period, we observed similar results during the years 1999-2002 (eTable 6), but in 2003-2006 the apparent benefit of iron in patients with low hematocrit was slightly attenuated (eTable 7). We also found that the center-level anemia management profile was strongly related to ESA dosing and iron use decisions and month-to-month changes in hematocrit. In this analysis, we observed increased center-level use of ESAs associated with increased hematocrit across all hematocrit categories and increased use of iron associated with modestly increased hematocrit in patients with hematocrit of 30% or higher (eTable 8). These results support the validity of the analysis.

COMMENT

In a large cohort of incident US hemodialysis patients, we assessed the 1-year mortality risk associated with different dialysis center–level patterns of ESA and intravenous iron use. After adjustment for a range of potential confounding factors, we found that certain patterns of ESA and iron use by dialysis centers were associated with altered mortality risk among incident patients at those centers.

We found elevated risk at centers that use larger (vs smaller) doses of ESAs in patients with hematocrit levels of 33% or higher and at centers that use more iron (vs less) in patients with hematocrit levels of 36% or higher. Several major randomized controlled trials of ESAs have found increased risk associated not directly with dose but with protocols that target normal or near-normal hematocrit levels. Besarab et al stud.

Table 2. Dialysis Center Anemia Management Practice and 1-Year Mortality Risk Among Incident Patients

<table>
<thead>
<tr>
<th>Hematocrit Range, %</th>
<th>Predicted Center-Level ESA Dose (for Hematocrit Range), Units/d</th>
<th>Hazard Ratio (95% CI)</th>
<th>Center-Level Probability of Iron Use per Month (for Hematocrit Range), %</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>Q1 (&lt;3744) 1 [Reference] Q2 (3745-4381) 0.97 (0.95-1.00) Q3 (4382-5039) 0.97 (0.94-1.00) Q4 (5040-5896) 0.98 (0.95-1.02) Q5 (&gt;5896) 0.94 (0.90-0.97)</td>
<td>Q1 (&lt;50.1) 1 [Reference] Q2 (50.1-58.8) 0.97 (0.94-0.99) Q3 (58.9-65.1) 0.97 (0.95-1.00) Q4 (65.2-71.4) 0.98 (0.95-1.01) Q5 (&gt;71.4) 0.97 (0.94-0.99)</td>
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<tr>
<td>30-32.9</td>
<td>Q1 (&lt;2780) 1 [Reference] Q2 (2781-3224) 1.01 (0.98-1.03) Q3 (3225-3689) 0.99 (0.96-1.02) Q4 (3690-4343) 1.00 (0.96-1.03) Q5 (&gt;4343) 0.99 (0.95-1.04)</td>
<td>Q1 (&lt;45.5) 1 [Reference] Q2 (45.5-55.4) 0.98 (0.96-1.01) Q3 (55.5-63.3) 0.99 (0.96-1.02) Q4 (63.4-71.1) 0.97 (0.94-1.00) Q5 (&gt;71.1) 0.95 (0.91-0.98)</td>
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<tr>
<td>≥33-35.9</td>
<td>Q1 (&lt;1927) 1 [Reference] Q2 (1927-2241) 1.01 (0.98-1.04) Q3 (2242-2662) 1.04 (1.01-1.07) Q4 (2563-3017) 1.04 (1.01-1.08) Q5 (&gt;3017) 1.07 (1.03-1.12)</td>
<td>Q1 (&lt;40.2) 1 [Reference] Q2 (40.2-51.5) 1.01 (0.98-1.04) Q3 (51.6-61.5) 1.01 (0.98-1.05) Q4 (61.6-71.5) 0.99 (0.96-1.03) Q5 (&gt;71.5) 1.00 (0.96-1.03)</td>
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<tr>
<td>≥36</td>
<td>Q1 (&lt;1392) 1 [Reference] Q2 (1392-1628) 1.04 (1.01-1.07) Q3 (1629-1836) 1.05 (1.02-1.08) Q4 (1837-2141) 1.06 (1.03-1.10) Q5 (&gt;2141) 1.11 (1.07-1.15)</td>
<td>Q1 (&lt;39.1) 1 [Reference] Q2 (39.1-52.6) 1.01 (0.99-1.04) Q3 (52.7-63.0) 1.02 (0.98-1.05) Q4 (63.7-73.5) 1.02 (0.99-1.06) Q5 (&gt;73.5) 1.07 (1.03-1.12)</td>
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</table>

Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; Q, quintile.

*Model is stratified on age (in 5-year groups) and calendar year. Multivariable adjustments were made for all variables listed in Table 1 in addition to geographic region indicator variables.
compared with conservative treatment of severe anemia. The existing trials were designed only to compare the effect of treating patients to achieve normal or near-normal vs relatively lower hematocrit.

The observational studies of the effect of ESA and iron dosing on mortality risk are conflicting. Earlier studies have linked higher ESA and iron doses to mortality, but several recent observational studies, including some that attempted to address limitations of previous work, found no evidence of increased mortality risk related to ESA or iron dosing. However, only 1 of these studies examined dose effects within strata of hematocrit, and it observed only patients with low hematocrit, in whom it found a near-null effect associated with larger ESA doses.

The degree to which the apparent risks of ESAs and iron are mediated through their effect on hematocrit or are a result of dose-related toxicities is unclear. Erythropoiesis-stimulating agents are known to increase platelet count and reactivity under certain circumstances, which may increase risk of thrombosis. Erythropoiesis-stimulating agents can also increase arterial pressure, possibly affecting cardiovascular risk. Iron may also have important toxic effects. Excessive use of iron could theoretically increase the risk of sepsis and infection-related mortality, worsen atherosclerosis, and increase the risk of cardiovascular disease events. Iron dextran has also been linked to hypersensitivity reactions including anaphylaxis, although fatalities attributable to these events are rare. Although there are plausible biological mechanisms, it seems unlikely that altered mortality risk would be solely attributable to dose-related effects because the largest ESA doses were given to patients in the lowest hematocrit category and were associated with lower mortality rates. However, we also found that mortality rates were inversely associated with hematocrit, suggesting that high hematocrit alone is not harmful. Whatever the mechanism, our study suggests that greater use of ESAs and iron in patients with higher hematocrit is problematic.

The estimates reported herein are similar to intention-to-treat estimates; they describe the effect of a treatment practice on mortality rates in all patients at the center. The expected mortality rate in a dialysis center depends on the average risk among the patients beginning dialysis there and the product of the HRs that represent the center’s anemia management practice. To assess public health relevance, the composite relative hazard can be converted into an approximate change in absolute risk. For example, assuming a first-year mortality rate in the hemodialysis population of about 23%, a relative decrease in hazard of 5% corresponds to a decrease of approximately 1 death per 100 patients during the first year of treatment. Similarly, a 10% relative increase in hazard corresponds to an increase of approximately 2 deaths per 100 patients.

The analytic approach used in this study was motivated by evidence suggesting that standard epidemiologic methods would be subject to strong confounding by indication and information bias. By adopting a center-level analytic approach, we attempted to estimate treatment effects using differences in anemia management practices between dialysis centers as a natural experiment. Other studies of patients with ESRD have used facility-level measures of treatment patterns as a proxy for actual exposure when unmeasured confounding may be intractable. This approach has also been used in studies of inpatient procedures and prescription medications. Despite their connection to a natural experiment, these analyses are still observational in nature and can result in incorrect inferences. For example, the center-level anemia management profile could be confounded by differences in patient case mix. This could cause the anemia management profile to be more reflective of the ESA requirements of the center’s case mix rather than the center’s anemia management practice. For example, patients with greater ESA requirements because of higher levels of inflammation may be at greater risk of mortality. If higher center-level use of ESAs reflects the prevalence of treatment-resistant anemia in the center’s case mix, center-level ESA use could be associated with mortality even if ESAs have no effect on mortality. The anemia management profile could also be spuriously associated with mortality if anemia management practices are correlated with other aspects of care that might affect mortality, such as intravenous vitamin D use or dialysis adequacy. We explored the possibility of confounding by conducting both an unadjusted analysis and an analysis that included a richer set of clinical and demographic variables than were included in the main analysis. We found nearly identical results across all analyses. We also observed similar associations within subgroups defined by center characteristics. This suggests that our anemia management profiles are not confounded by patient case mix or other aspects of medical practice.

Center-level analyses may be consistent with different hypotheses about patient-level treatment effects. For example, we observed higher mortality rates in centers that used larger doses of ESAs in patients with hematocrit levels in the range of 33% to 35.9%. Centers using more ESAs in these patients could either be attempting to keep patients who are poorly responsive in the target range or may be treating all patients to a hematocrit higher than 36%. Our analysis is unable to distinguish which of these 2 practices might be potentially harmful.

Our study was limited in that we studied the incident dialysis patient population who make up only 20% of the overall hemodialysis population but have the highest mortality rates. Therefore, our results may not completely generalize to prevalent patients. Our study of iron use was subject to 2 additional limitations. First, during the period of our study,
the data could be used reliably only to identify whether iron had been given, not the dose of iron administered. Second, measures of iron availability, the primary indications for iron therapy, are not reported to the Centers for Medicare & Medicaid Services. Therefore, high or low center-level iron use may not reflect overuse or underuse, respectively. Additional studies using more reliable iron dosing information and measures of iron availability are warranted to further evaluate any potential risks or benefits related to iron dosing.

In conclusion, we found evidence of decreased mortality risk associated with greater use of ESAs and more frequent use of iron at lower hematocrit levels where mortality is the highest. While lower overall mortality risk occurs at higher hematocrit levels, elevated mortality risk was associated with greater use of ESAs and iron in these patients. Further observational and experimental studies are needed to help identify optimal treatment algorithms for both ESAs and iron that maximize clinical benefit while minimizing adverse outcomes.

Author Contributions: Dr Brookhart had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Brookhart, Schneeweiss, Avorn, Bradbury, Winkelmayer. Acquisition of data: Brookhart, Winkelmayer. Analysis and interpretation of data: Brookhart, Schneeweiss, Avorn, Bradbury, Liu, Winkelmayer. Drafting of the manuscript: Brookhart, Winkelmayer. Critical revision of the manuscript for important intellectual content: Brookhart, Schneeweiss, Avorn, Bradbury, Liu, Winkelmayer. Statistical analysis: Brookhart, Schneeweiss, Bradbury, Liu, Winkelmayer. Obtained funding: Brookhart, Bradbury. Study supervision: Brookhart, Schneeweiss, Avorn, Winkelmayer.

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Disclaimer: Data reported herein were supplied by the USDRS. Interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

Online-Only Material: The eAppendix and eTables 1 through 8 are available at http://www.jama.com.

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