Trends in Anemia Care in Older Patients Approaching End-Stage Renal Disease in the United States (1995-2010)

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IMPORTANCE Anemia is common in patients with advanced chronic kidney disease. Whereas the treatment of anemia in patients with end-stage renal disease (ESRD) has attracted considerable attention, relatively little is known about patterns and trends in the anemia care received by patients before they start maintenance dialysis or undergo preemptive kidney transplantation.

OBJECTIVE To determine the trends in anemia treatment received by Medicare beneficiaries approaching ESRD.

DESIGN, SETTING, AND PARTICIPANTS Closed cohort study in the United States using national ESRD registry data (US Renal Data System) of patients 67 years or older who initiated maintenance dialysis or underwent preemptive kidney transplantation between 1995 and 2010. All eligible patients had uninterrupted Medicare (A+B) coverage for at least 2 years before ESRD.

EXPOSURE Time, defined as calendar year of incident ESRD.

MAIN OUTCOMES AND MEASURES Use of erythropoiesis-stimulating agents (ESA), intravenous iron supplements, and blood transfusions in the 2 years prior to ESRD; hemoglobin concentration at the time of ESRD. We used multivariable modified Poisson regression to estimate utilization prevalence ratios (PRs).

RESULTS Records of 466,803 patients were analyzed. The proportion of patients with incident ESRD receiving any ESA in the 2 years before increased from 3.2% in 1995 to a peak of 40.8% in 2007; thereafter, ESA use decreased modestly to 35.0% in 2010 (compared with 1995; PR, 9.85 [95% CI, 9.04-10.74]). Among patients who received an ESA, median time from first recorded ESA use to ESRD increased from 120 days in 1995 to 337 days in 2010. Intravenous iron administration increased from 1.2% (1995) to 12.3% (2010; PR, 9.20 [95% CI, 7.97-10.61]). The proportion of patients receiving any blood transfusions increased monotonically from 20.6% (1995) to 40.3% (2010; PR, 1.88 [95% CI, 1.82-1.95]). Mean hemoglobin concentrations were 9.5 g/dL in 1995, increased to a peak of 10.3 g/dL in 2006, and then decreased moderately to 9.9 g/dL in 2010.

CONCLUSIONS AND RELEVANCE Between 1995 and 2010, older adults approaching ESRD were increasingly more likely to be treated with ESAs and to receive intravenous iron supplementation, but also more likely to receive blood transfusions.
Anemia is a hallmark complication of advanced chronic kidney disease (CKD) and a consequence of reduced erythropoietin production by the kidneys, among other factors. Using data from the Third National Health and Nutrition Examination Survey (1988-1994), Hsu et al found that even among patients who were relatively iron replete (serum ferritin level, ≤100 ng/mL [to convert to micromoles per liter, multiply by 2.247] and serum transferrin saturation, ≥20%), 46% (95% CI, 37%-59%) of men with advanced CKD (serum creatinine clearance, ≤30 mL/min/1.73 m² [to convert to milliliters per second per meters squared, multiply by 0.0167]) had a hemoglobin concentration less than 12 g/dL and 21% (95% CI, 15%-27%) of women had a hemoglobin concentration less than 11 g/dL (to convert to grams per liter, multiply by 10). Although not specifically ascertained in that study, it is unlikely that a sizeable proportion of persons with advanced CKD in the United States received any maintenance treatment for anemia because only limited treatment options were available and used in patients with non–diabetes–requiring CKD at the time. Iron dextran of various molecular weights were the only formulations available at that time; relatively few patients with non–diabetes–requiring CKD used the iron dextran for fear of anaphylactoid reactions; even fewer used anabolic steroids, which had also been shown to increase hemoglobin concentrations in ESRD.

On the basis of its demonstrated ability to increase hemoglobin concentrations and to reduce the need for transfusions, epoetin alfa was approved for use by the US Food and Drug Administration (FDA) in 1989 for the treatment of anemia associated with chronic renal failure, including patients receiving dialysis (ESRD) and patients not receiving dialysis. Comprehensive guidelines on the anemia of kidney disease were published by the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) in 1997, in which treatment of anemia using epoetin alfa was strongly endorsed, however, mostly on the basis of expert opinion about potential clinical benefit beyond erythropoiesis alone. Data from patients with ESRD indicate increased use of ESAs between 1992 and 2005, whereas transfusion rates decreased during that time. However, clinical trials that were subsequently published raised serious concerns about more intensive treatment of anemia using ESAs in patients with CKD. Their results led to more critical assessment of targets of ESA treatment, including changes in ESA labels, and to reduced use of ESAs in patients with CKD requiring dialysis in the most recent years. However, little is known about trends in the treatment of anemia in patients with CKD not yet requiring dialysis. We conducted the present study to examine trends in the use of several types of anemia treatment before the initiation of dialysis or receipt of preemptive kidney transplantation in the continental United States, Alaska, or Hawaii between 1995 and 2010. We restricted the cohort to all patients who, per payor history file, had uninterrupted Medicare Part A and B coverage for at least 2 years prior to ESRD, the latter being the study index. The institutional review board of Stanford University approved the study.

Exposure of Interest
The exposure of interest was calendar year of initiation of treatment for ESRD.

Variables of Interest: Indicators for Anemia Treatment
From 2 years of Medicare claims prior to initiation of dialysis or receipt of preemptive kidney transplantation, we ascertained receipt of several treatments commonly used to treat anemia in patients with advanced CKD: erythropoiesis-stimulating agents (ESAs) (epoetin alfa, darbepoetin alfa), intravenous iron supplements (iron dextran, iron sucrose, sodium ferric gluconate complex, ferumoxytrol), and blood transfusions (for specific codes used, refer to eTable 1 in Supplement). The timing of the earliest recorded receipt of each of these treatments relative to the initiation of ESRD treatment was also noted. For blood transfusions, we defined the distinct number of days on which a transfusion was administered to each patient (the number of transfusions given on any single day cannot be ascertained from claims data). From the Medical Evidence Report (form CMS-2728), we ascertained the hemoglobin concentration or hematocrit reportedly present at initiation of treatment for ESRD. Hematocrit values were converted into approximate hemoglobin concentrations by dividing by 3.

Patient Characteristics
We ascertained the following characteristics from the USRDS patient file: age (on index), sex, race (white, black, Asian, other), and (dual) eligibility for Medicaid. We also ascertained reported kidney function at dialysis initiation (estimated glomerular filtration rate [eGFR]), serum albumin level, and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) from the Medical Evidence Report.

We additionally identified the following comorbidities from the Medical Evidence Report and from Medicare claims using previously published algorithms: diabetes mellitus, hypertension, heart failure, coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, and cancer. Comorbidities were ascertained in the 2-year period prior to the index date and were established by the presence of at least 1 inpatient or 2 outpatient claims not on the same day.

Statistical Analysis
We described all patient characteristics by incident year (collapsed into 3 eras: 1995-2000, 2001-2005, 2006-2010) using medians and interquartile ranges for continuous variables and percentages for categorical variables. We then tabulated and/or plotted receipt of each category of anemia treatment prior to ESRD over time. We estimated unadjusted and adjusted prevalence ratios and their corresponding 95% confidence inter-
vals (CIs) using Poisson regression with a modified variance to get proper inference. This was done (1) without any adjustment, (2) with adjustment for demographic characteristics, (3) with additional adjustment for presence of diabetes mellitus and eGFR and BMI at initiation, and (4) with adjustment for all reported comorbidities. The third model is reported in the results unless otherwise noted. Year was treated as a categorical variable to allow for nonlinear changes. The earliest year (1995) served as the referent. A priori, we anticipated an increase in use of ESAs over time but then a decrease following the publication of 2 trials questioning the benefit and indicating some harm from more aggressive anemia treatment in 2006. Therefore, we also conducted analyses that used 2007 as the referent year to quantify any changes following the year in which important safety information on ESA use in CKD became available. For the same reason, we compared the trends for any transfusion use and for number of transfusion days between the 2003 through 2006 and 2007 through 2010 eras using interrupted time-series analyses.

Certain variables had incomplete data, especially those on eGFR and BMI at ESRD incidence. Because missingness for the variables considered for multivariable adjustment affected fewer than 10% of patients, we conducted complete case analyses. However, we also conducted sensitivity analyses that used multiple imputation using chained equation (MICE package in R) with 5 imputations to test the robustness of our findings; findings were not materially different and are reported in eTables 2, 3, and 4 in the Supplement.

Analyses were performed using SAS software, version 9.2 (SAS Institute, Inc) and R (R Project for Statistical Computing).

Results

We identified 702,192 patients 67 years or older who initiated treatment for ESRD between 1995 and 2010. Of those, 471,083 had 2 years of uninterrupted Medicare fee-for-service (Parts A and B) coverage prior to the index date. An additional 4280 patients were excluded who resided outside the continental United States, yielding the final cohort of 466,803. Trends in patient characteristics over time are illustrated in the Table. Pertinent to this study of anemia and its treatment, patients initiating treatment for ESRD in more recent years did so with more preserved kidney function (ie, higher eGFR), higher BMI, and a more substantial degree of comorbidity (diabetes mellitus, cerebrovascular disease, peripheral artery disease). Patients initiating dialysis in more recent years also had received more and earlier care by a nephrologist, as previously reported.

Use of ESAs increased from 3.2% in patients approaching ESRD in 1995 to 40.8% among those who did so in 2007; thereafter, ESA use plateaued or decreased slightly to 35.0% in 2010 (Figure 1A). The proportion using darbepoetin alfa, after its FDA approval in 2001 and availability of a specific billing code in 2003, increased swiftly and exceeded 47% in 2007 (Figure 1A). Among patients who received an ESA, median time from first recorded ESA use to ESRD increased from 120 days in 1995 to 337 days in 2010 (Figure 1B).

When temporal trends in pre-ESRD ESA use were modeled (Figure 1B; eTable 2 in Supplement), compared with 1995, patients initiating treatment for ESRD in 2010 were almost 10 times (PR, 9.85 [95% CI, 9.04-10.74]) more likely to have received an ESA. The findings were similar after adjustment for demographic characteristics and for eGFR, BMI, and the prevalence of diabetes mellitus at ESRD incidence (eTable 2 in Supplement).

Use of intravenous iron supplementation was low while iron dextran remained the only treatment option (eg, 1.2% in 1995) and increased rapidly once sodium ferric gluconate and iron sucrose became available (Figure 2A), which were approved by the FDA in 1999 and 2000, respectively. The specific intravenous iron formulation used in patients’ earliest recorded intravenous iron supplementation claim is shown in Figure 2B. Among patients initiating treatment for ESRD in 2010, 12.3% had received intravenous iron supplementation in the 2 years before ESRD treatment, a more than 9-fold increase over the 15-year study period (PR, 9.20 [95% CI, 7.97-10.61]) (Figure 2C; eTable 3 in Supplement).

Despite more frequent use of ESAs and intravenous iron supplementation, the proportion of patients receiving at least 1 transfusion also increased considerably over time (Figure 3A). Whereas 20.6% of patients reaching ESRD in 1995 had received at least 1 blood transfusion in the 2 years prior to their first ESRD treatment, the proportion increased steadily, reaching 40.3% among patients approaching ESRD in 2010. The PR comparing receipt of transfusion in patients approaching ESRD in 2010 vs 1995 was 1.88 (95% CI, 1.82-1.95) (Figure 3C; eTable 4 in Supplement) and was unaffected by differences in case mix or multivariable adjustment. These findings were consistent with increases in the cumulative number of transfusion days (Figure 3B). Of note, the slope of the increase in any transfusion use or in number of transfusion days was statistically steeper after 2007 (when compared with 2003-2006; P < .001 and P = .04, respectively). The proportions of all possible combinations of anemia treatments received prior to ESRD in 2010 are shown in Figure 4 (comparisons with other years are shown in eFigure 1 in Supplement).

During the period when these marked changes in the use of ESAs, intravenous iron supplementation, and transfusion were taking place, mean hemoglobin concentrations were 9.5 g/dL in 1995, increased to a peak of 10.3 g/dL in 2006, and then decreased to 9.9 g/dL in 2010 (Figure 5). The corresponding fractions of patients with hemoglobin concentrations less than 8.0 g/dL (the upper value of the 7-8 g/dL range suggested by the AABB [formerly the American Association of Blood Banks] for hospitalized patients with relevant symptoms or preexisting cardiovascular disease) were 17.3%, 5.5%, and 7.0%, respectively.

Discussion

We studied treatment patterns for anemia, a common complication of advanced CKD, in a national registry of older patients approaching ESRD in the United States between 1995 and 2010. We found that the use and duration of ESA treatment prior

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to ESRD increased considerably during that era (at least until 2007) along with increasing use of intravenous iron supplementation, which jointly contributed to significantly but modestly higher hemoglobin concentrations by the time patients reached ESRD. However, almost twice as many patients received blood transfusions prior to reaching ESRD, even when accounting for changes in case mix and comorbidity over time. Thus, the main objective of ESA treatment that gave rise to its original approval—transfusion avoidance—was not consistently met at the population level. These findings are in contrast with declining transfusion trends in older patients without diagnosed CKD and older patients with diagnosed CKD (mostly of lesser stages), as well as in patients of any age receiving dialysis, in whom transfusion rates decreased between 1992 and 2004 or 2005.8,19 The observed doubling over time of the proportion of older patients approaching ESRD who received a transfusion may be a consequence of an upward drift in practitioners’ hemoglobin thresholds for transfusion over the 15 years we studied, which was previously shown in patients receiving dialysis,8 or a function of increasing attention to the correction of anemia or responsiveness to patients’ reported symptoms. Our findings are also compatible with a study of younger patients with CKD insured by United Healthcare (Ingenix database) in which patients who tran-

### Table. Characteristics of Older Patients Initiating Treatment for End-Stage Renal Disease (ESRD), by Era

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1995-2000 (n = 157,492)</th>
<th>2001-2005 (n = 159,726)</th>
<th>2006-2010 (n = 149,585)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>75 (71-80)</td>
<td>76 (72-81)</td>
<td>77 (72-82)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>50.1</td>
<td>48.7</td>
<td>45.9</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>75.8</td>
<td>76.6</td>
<td>78.0</td>
</tr>
<tr>
<td>Black</td>
<td>21.1</td>
<td>20.0</td>
<td>18.1</td>
</tr>
<tr>
<td>Asian</td>
<td>2.0</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Other</td>
<td>1.1</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Missing</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Medicaid “dual” beneficiary, %</td>
<td>18.2</td>
<td>19.7</td>
<td>18.8</td>
</tr>
<tr>
<td><strong>Cause of ESRD, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38.3</td>
<td>39.8</td>
<td>38.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35.4</td>
<td>36.2</td>
<td>36.8</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>8.0</td>
<td>5.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Other</td>
<td>15.8</td>
<td>16.5</td>
<td>17.7</td>
</tr>
<tr>
<td>Missing</td>
<td>2.5</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Preemptive kidney transplantation, %</td>
<td>0.1</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Pre-ESRD nephrology care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earliest outpatient visit prior to ESRD, %, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>47.4</td>
<td>39.5</td>
<td>31.7</td>
</tr>
<tr>
<td>&gt;18</td>
<td>16.6</td>
<td>24.5</td>
<td>34.8</td>
</tr>
<tr>
<td>18 to &gt;12</td>
<td>7.3</td>
<td>8.5</td>
<td>8.6</td>
</tr>
<tr>
<td>12 to 6</td>
<td>9.1</td>
<td>9.3</td>
<td>8.8</td>
</tr>
<tr>
<td>&lt;6</td>
<td>19.6</td>
<td>18.3</td>
<td>16.2</td>
</tr>
<tr>
<td>Outpatient visits in 2 y prior to ESRD, median IQR</td>
<td>7 (3-17)</td>
<td>8 (3-19)</td>
<td>9 (4-23)</td>
</tr>
<tr>
<td><strong>Comorbidities, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>56.1</td>
<td>61.2</td>
<td>64.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>94.2</td>
<td>96.6</td>
<td>98.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>72.0</td>
<td>71.5</td>
<td>70.1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>46.4</td>
<td>45.5</td>
<td>44.0</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>33.6</td>
<td>34.9</td>
<td>36.9</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>41.9</td>
<td>42.9</td>
<td>43.6</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>10.1</td>
<td>11.8</td>
<td>13.3</td>
</tr>
<tr>
<td>Cancer</td>
<td>20.9</td>
<td>22.3</td>
<td>24.6</td>
</tr>
<tr>
<td>Estimated GFR at ESRD, median (IQR), mL/min/1.73 m²</td>
<td>8.2 (6.2-11.0)</td>
<td>9.8 (7.3-13.3)</td>
<td>11.1 (9.3-14.6)</td>
</tr>
<tr>
<td>Missing, %</td>
<td>7.3</td>
<td>3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>BMI at ESRD, median (IQR)</td>
<td>24.1 (21.1-27.8)</td>
<td>25.4 (22.2-29.5)</td>
<td>26.4 (23.0-30.9)</td>
</tr>
<tr>
<td>Missing, %</td>
<td>15.0</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Serum albumin level at ESRD, median (IQR), g/dL</td>
<td>3.2 (2.8-3.6)</td>
<td>3.2 (2.7-3.6)</td>
<td>3.2 (2.7-3.6)</td>
</tr>
<tr>
<td>Missing, %</td>
<td>28.9</td>
<td>27.0</td>
<td>24.8</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GFR, glomerular filtration rate; IQR, interquartile range.

SI conversion factors: To convert GFR to to milliliters per second per meters squared, multiply by 0.0167. To convert serum albumin to grams per liter, multiply by 10.

* Percentages may not total 100% because of rounding.
tioned to ESRD in a given year experienced a 2.5-fold increase in transfusion rates between 2002 and 2008.20

Transfusion avoidance is an important clinical goal, especially in patients with advanced CKD or ESRD. These patients are particularly prone to hyperkalemia and fluid overload resulting in heart failure, both known complications of blood transfusions. Furthermore, repeated transfusions can lead to iron overload (in extreme cases, hemosiderosis), which was a challenging clinical problem in the ESRD population before the approval of epoetin alfa in 1989.21 In addition, receipt of blood transfusions markedly increases the likelihood of allosensitization in patients eligible for kidney transplantation.22 In addition to increasing the odds of a positive cross-match, disqualifying potential donors,23 allosensitization is associated with accelerated graft loss, even among patients lucky enough to cross-match negative and receive a kidney.24 With waiting times for kidney transplantation exceeding life expectancy in most geographic regions for most middle-aged and older patients with ESRD, we can ill afford the provision of unnecessary transfusions because doing so will virtually ensure that these patients live out their lives receiving dialysis.

Although transfusion avoidance provided the formal reason for the approval and use of ESAs, the enthusiastic adoption and use of ESAs may have been mostly grounded in the expectation of other clinical benefits. As stated in the introduction to the 1997 KDOQI anemia guidelines, “effective treatment of the anemia of [CKD] improves survival, decreases mortality, and increases quality of life.”7(ppS194-S195) The citations listed in support of that statement or in the guideline on target hemoglobin concentration (recommending a target range of 11-12 g/dL) referred either to studies of (unproven) surrogate endpoints (eg, left ventricular hypertrophy, exercise capacity) or to observational studies associating hemoglobin concentration with outcomes whose ability to control for confounding of inherent characteristics that differed between individuals who achieved a higher vs a relatively lower hemoglobin concentration was limited. In 2006, revised KDOQI anemia guidelines changed their language, indicating that “in patients with CKD, [hemoglobin concentration] should be 11.0 g/dL or greater. (Moderately strong recommendation)µ25(µ1533) In addition, without providing any convincing evidence, a new recommendation suggested that “there is insufficient evi-
dence to recommend routinely maintaining [hemoglobin] levels at 13.0 g/dL or greater in ESA-treated patients, which was widely interpreted as an expansion to an 11 to 13 g/dL hemoglobin concentration target range. Thus, throughout this era ESA use was driven by expectation of benefit that was unproven in any high-quality trials of hard study end points.

Our study shows that initiation of ESA treatment prior to ESRD reached a peak in 2007 and then plateaued or even decreased, with hemoglobin concentrations at ESRD also declining during that time. This reversion in the long-term upward trend reflected providers' reactions to the sobering results from 3 relatively large randomized trials in patients with moderate to advanced (non-dialysis-requiring) CKD, published in late 2006, and 2009, respectively, of which 1 failed to demonstrate any benefit and the other 2 found significant (albeit distinct) cardiovascular risks from more aggressive ESA treatment. Interestingly, it appears that the rate of transfusion prior to ESRD accelerated after 2007, compared with the slope prior to 2007. This change probably indicates the dueling effects of increasingly lenient transfusion thresholds while less aggressive ESA treatment provided less of a hemoglobin reserve to these patients. Apparently, health care providers (nephrologists, internists, hospitalists) consider hemoglobin concentration the single most important factor in their decisions to transfuse, with clinical factors such as functional status and cardiovascular comorbidities playing a much lesser role. In patients receiving dialysis, increases between 2006 and 2010 in the proportion of patients whose hemoglobin concentration was below 10 g/dL have been linked to increased transfusion rates during the same period, which was independent of any other recorded clinical factors.

Although we found a more than 10-fold increase in the use of intravenous iron supplementation over the 15 years of the study, the proportion of patients who received it remained small, at roughly 10% in 2010. The modest use of intravenous iron supplementation in CKD contrasts starkly with the almost universal use of intravenous iron supplementation in ESA-treated patients receiving dialysis, more than 95% of whom receive intravenous iron supplementation within the first 6 months after initiating dialysis. Most clinicians prefer oral

Figure 2. Trends in Treatment With Intravenous Iron Supplements Prior to End-Stage Renal Disease (ESRD)

A. Proportion of patients receiving any intravenous iron supplementation.
B. Specific intravenous iron formulation used in the earliest available claim.
C. Adjusted prevalence ratios of intravenous iron use prior to ESRD (referent: 1995). Multivariable model adjusted for age, sex, race, Medicaid (“dual”) eligibility, comorbid diabetes mellitus, estimated glomerular filtration rate, and body mass index at ESRD. Circles indicate prevalence ratio; error bars, 95% confidence interval.
Iron supplementation in patients with non-dialysis-requiring CKD despite evidence that intestinal iron absorption is poor in these patients. Intravenous iron supplementation is far less convenient in patients with non-dialysis-requiring CKD than in patients with ESRD, particularly those receiving hemodialysis, because venous cannulation and, often, admission to an infusion center is required. Moreover, several sessions are required to give “repletion” doses of intravenous iron supplementation for patients with frank iron deficiency, and these repeated venous cannulations may compromise creation of arteriovenous fistulas or grafts.

Perhaps the most striking of our findings is the steady increase in transfusion despite the broad and consistent use of pharmaceutical agents effective at raising hemoglobin concentrations. Ironically, these agents were approved with the goal of reducing dependence on blood transfusion, mainly in the ESRD population where the need for such a therapy was clear. Indeed, in the ESRD population transfusions have markedly decreased since the introduction of ESAs. For a variety of reasons, the treatment paradigm for anemia management in patients receiving dialysis was extended to the pre-ESRD population until evidence from randomized trials challenged these practices. As our study demonstrates, the goal of transfusion avoidance has not been consistently met in patients with CKD who do not require dialysis, perhaps at least in part as a result of increasingly liberal transfusion practices or sicker patients approaching dialysis. Furthermore, the use of transfusion in the ESA era was likely driven more by a hemoglobin concentration target than by the prevalence of symptomatic anemia. Given these other factors, the increasing use of transfusion was not necessarily a failure of ESAs. Although clinicians may individualize transfusion practices on the basis of patients’ underlying conditions, including attempting to balance risks associated with uncorrected anemia and those associated with transfusion (as outlined in this article), clinical practice guidelines, including those from the AABB, suggest that transfusion may be used far too liberally in this population.

There are certain limitations of our study that require consideration. We studied a survivor cohort of patients who...
reached and started treatment for ESRD; patients with advanced CKD who died of other causes before reaching ESRD or who reached ESRD and declined dialysis or transplantation were not captured in the database. Our cohort was further restricted to older patients who possessed Medicare fee-for-service prior to reaching ESRD because information on drug use and transfusion was available only for patients who had qualified for Medicare on age or disability grounds prior to reaching ESRD. Generalizability to younger patients reaching ESRD is uncertain. The data that we had available covered only 2 years prior to treatment for ESRD, so we cannot rule out any additional use of ESAs, intravenous iron supplementation, and transfusion earlier in patients’ lifetimes. We were unable to define and examine trends in the hemoglobin concentration that gave rise to initiation of ESA or intravenous iron therapy (or to blood transfusion) because this information was not required to be submitted to Medicare with the corresponding billing claims. Because all transfusions given on any single day are subsumed in a single procedural code, we were only able to study transfusion days but could not ascertain the actual number of transfusions given. New anemia medications approved during the study period had variably short periods of availability without a dedicated Healthcare Common Procedure Coding System code. However, these periods were short (a few weeks to months) and the degree of underascertainment is likely small given their new introduction into clinical practice. Finally, the strongest response to the accumulating safety concerns with ESA use by the FDA did not occur until mid-2011, when ESA labels were revised to no longer include a target hemoglobin concentration range and suggested that ESA initiation be considered only in patients whose hemoglobin concentrations were below 10 g/dL.29 We were unable to study the impact of this FDA action because of the lag time in availability of data.

Conclusions

Over 15 years of study, we found a pronounced trend toward more aggressive treatment of anemia in older patients approaching ESRD, which included ESA use, intravenous iron supplementation, and broad-based use of red blood cell transfusions. All of these were weakly reflected in an increase in hemoglobin concentrations at the time of onset of ESRD. While ESA use plateaued and ensuing hemoglobin concentrations decreased after 2007, following safety concerns about ESA use in patients with CKD, transfusion use seemed to increase even more rapidly. In light of the costs of anemia treatments and the safety concerns of currently available anemia treatments, safe, effective, and economical anemia treatment strategies in patients with CKD and anemia need to be identified.

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Author Contributions: Dr Winkelmayer 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: Winkelmayer, Mitani, Goldstein.
Acquisition of data: Winkelmayer.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Winkelmayer, Goldstein.
Critical revision of the manuscript for important intellectual content: Mitani, Brookhart, Chertow.
Statistical analysis: Winkelmayer, Mitani, Goldstein.
Obtained funding: Winkelmayer.
Administrative, technical, and material support: Winkelmayer, Chertow.
Study supervision: Winkelmayer.

Conflict of Interest Disclosures: Dr Winkelmayer has served as a scientific advisor to Amgen, Bayer, GlaxoSmithKline, and Keryx Biopharmaceuticals and on data safety monitoring boards for Medgenics and Medtronics. Dr Chertow serves on the Board of Directors of Satellite Healthcare and on the Scientific Advisory Board for DaVita Clinical
Trends in Predialysis Anemia Care

Original Investigation Research

REFERENCES

2012; San Diego, California. The work was presented at the 2012 Kidney Week of the American Society of Nephrology; November 2, 2012, San Diego, California.

Disclaimer: 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.

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