

Relationship among catheter insertions, vascular access infections, and anemia management in hemodialysis patients

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Background. Arteriovenous fistulas are the recommended permanent vascular access (VA) for chronic hemodialysis. However, in the United States most patients begin chronic hemodialysis with a catheter. Recent data suggest that VA type contributes to recombinant human erythropoietin (rHuEPO) resistance. We examined catheter insertions, VA infections, and anemia management in Medicare, rHuEPO-treated, chronic hemodialysis patients.

Methods. We compared hemoglobin values and rHuEPO and intravenous iron dosing with concurrent catheter insertions and VA infections in 186,348 period-prevalent patients in 2000. We studied anemia management after catheter insertions and VA infections in 67,410 incident patients from 1997 to 1999. Multiple linear regression models examined follow-up hemoglobin and rHuEPO dose per week (rHuEPO/wk) by numbers of catheter insertions and hospitalizations for VA infection.

Results. In the prevalent cohort, increasing temporary and permanent catheter insertions and VA infections were associated with slightly lower hemoglobin, higher rHuEPO doses, and higher intravenous iron doses. In the incident cohort, compared to patients with no VA infections or no catheter insertions (temporary or permanent), respectively, patients with 2+ VA infections or 2+ catheter insertions had 0.12 g/dL and 0.06 g/dL lower mean hemoglobin ($P = 0.0028$ and $P < 0.0001$), and 25.7% and 12.2% higher mean rHuEPO/wk ($P < 0.0001$).

Conclusion. Higher rHuEPO doses may be required to maintain similar or slightly lower mean hemoglobin values among chronic hemodialysis patients with higher numbers of catheter insertions and VA infections, compared to patients without any.

Arteriovenous (AV) fistulas are considered the permanent vascular access (VA) of choice for chronic hemodialysis because they are associated with higher patency rates

and lower rates of infection compared to polytetrafluoroethylene (PTFE) grafts [1]. However, in the United States (U.S.), most patients begin chronic hemodialysis with a catheter, and PTFE grafts are more common than AV fistulas. Catheters are not recommended as permanent VA because of their increased risk of luminal thrombosis [2, 3] and infection [4–6], lower delivered dose of dialysis due to unreliable blood flow [7–10], risk of central venous stenosis [11], shorter expected use life [12], and cosmetic concerns [1]. Recent studies also suggest that catheter use is associated with an increased risk of all-cause and infection-related mortality in both incident and prevalent hemodialysis patients [10, 13].

Scant data are available regarding the effect that type of VA used for chronic hemodialysis has on anemia management. In a small cohort of Spanish hemodialysis patients with no recognizable causes of resistance to recombinant human erythropoietin (rHuEPO), consistent use of PTFE grafts was associated with significantly higher rHuEPO doses to achieve the target hematocrit value compared to AV fistulas [14]. Given the high prevalence of PTFE grafts and catheters among patients undergoing chronic hemodialysis in the U.S. [15, 16], we hypothesized that catheter insertions and VA infections may be important contributors to rHuEPO resistance, and, consequently, to the overall utilization of rHuEPO therapy in these patients.

In this study, we examined the effect of catheter insertions and VA infections on anemia management in a large cohort of U.S. chronic hemodialysis patients.

METHODS

Overview

Associations among anemia management, catheter insertions, and VA infections were described in 2 patient cohorts: period-prevalent and incident hemodialysis patients. Both cohorts were used to obtain a broad view of associations in 2 diverse patient groups. In the incident

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cohort, we also performed a regression analysis of follow-up hemoglobin and rHuEPO dose, adjusting for entry-period characteristics. The incident cohort was selected for this regression because it contained patients with similar time on dialysis. This may result in less confounding than with a prevalent cohort, which has a mixture of patients with varying lengths of time on dialysis.

Concurrent anemia management, catheter insertions, and VA infections in period-prevalent hemodialysis patients

Data sources and patient population. We studied period-prevalent Medicare hemodialysis patients from the year 2000. The start of the follow-up period was defined as follows: January 1 for point-prevalent patients who were prevalent on January 1, 2000, and whose first end-stage renal disease (ESRD) service date was at least 90 days before January 1; and day 91 of ESRD for incident patients who reached day 91 of ESRD between January 1 and December 31, 2000. The follow-up period started after day 90 due to incomplete claims in the first 90 days after initiation of dialysis. Patients were followed until the earliest date of death, modality change, loss to follow-up, or December 31, 2000. Patients with Medicare as a secondary payer, with coverage from a health maintenance organization (HMO), or with dialysis payment amounts less than \$675 per month were excluded on the basis of incomplete Medicare claims [17].

Patient demographic data (including age, gender, race, and primary cause of ESRD) were obtained from the Identification and Medical Evidence portions of the Renal Beneficiary Utilization System of the Centers for Medicare & Medicaid Services. Data on hematocrit value, rHuEPO dose, and intravenous (IV) iron use were obtained from Medicare institutional outpatient claims. Included rHuEPO-treated patients had at least one rHuEPO claim during the year. Compared to previous years, Medicare billing for IV iron changed in the year 2000, with billing done by dosing increments (e.g., 50-mg injections of iron dextran), rather than number of vials. Consequently, the billing data included claims for both vials and doses. For patients in the year 2000, we considered two 50-mg doses to equal one 100-mg vial. Of the IV iron billed in 2000, 92% was for iron dextran, and 8% was for ferric gluconate.

Data on catheter insertions were drawn from Medicare Part B physician/supplier claims; data on hospitalizations for VA infection were taken from Part A institutional outpatient claims. Event information was obtained from the following Physicians' Current Procedural Terminology (CPT) and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: temporary catheter insertions, CPT codes 36489, 36491, and 36800; permanent catheter insertions, CPT code 36533;

and VA infection, ICD-9-CM principal diagnosis code 996.62. Additional methods excluded catheters used for purposes other than dialysis, and excluded patients with any chemotherapy or parenteral nutrition claims during the year [17]. Catheter insertions indicated by Healthcare Common Procedure Coding System (HCPCS) codes 36489, 36491, and 36533 were included only if they were associated with a line-level or claim-level principal diagnosis code related to dialysis or kidney failure.

Analysis. Hematocrit values were used to calculate estimated hemoglobin values because complete hemoglobin data are unavailable in the Medicare claims. For each patient, each hematocrit value during the year was divided by three; then, these estimated hemoglobin values were averaged to obtain the mean hemoglobin value. Mean rHuEPO dose per week (rHuEPO/wk) was calculated as total rHuEPO received divided by total outpatient weeks. Outpatient weeks were calculated as the total number of weeks of follow-up after subtracting inpatient hospital days because outpatient rHuEPO claims are not generated during hospitalizations. Patients were grouped according to number (0, 1, or 2+, where 2+ indicates ≥ 2) of catheter insertions (temporary or permanent) and hospitalizations for VA infection during the year, and the following were computed for each group: mean hemoglobin, mean rHuEPO/wk, and mean IV iron vials per month. The Wilcoxon rank-sum test compared mean values between groups (0 vs. 1 and 0 vs. 2+ catheter insertions and hospitalizations for VA infection).

Anemia management after catheter insertion and VA infection in incident hemodialysis patients

Data sources and patient population. We evaluated adult incident Medicare hemodialysis patients who were treated between January 1, 1997, and December 31, 1999. Because Medicare data may be incomplete in the 90 days following the first ESRD service date, included patients survived those 90 days plus 6-month entry and 6-month follow-up periods. Inclusion criteria followed those used in the prevalent analyses, with these additional requirements: included patients had at least three rHuEPO claims during follow-up, had a valid hematocrit measurement at initiation of dialysis, were at least 20 years old, and had complete age and gender data.

Sources for demographic data, as well as for hematocrit, rHuEPO, and IV iron, were identical to those described for the prevalent patient analysis. For each patient, the total number of entry-period months (range, 0 to 6 total months) with any IV iron claim was determined. The data sources and definitions of hospitalization for VA infection and temporary or permanent catheter insertion (characterized during the entry period) also replicated those described for prevalent patients. A hematocrit measurement at initiation of dialysis was obtained for each

patient from the Medical Evidence form, and hemoglobin at initiation was estimated by dividing this value by three. The number of hospital days and blood transfusions during the 6-month entry period were obtained from Medicare Part A and B claims files [18]. Patients were characterized by number of total hospital days during the entry period, and by number of non-VA hospital days (all hospital days except those having a principal ICD-9-CM diagnosis code 996.62, for VA infection). Comorbid conditions were determined from Part A and B Medicare claims during the 6-month entry period using CPT and ICD-9-CM codes, as previously described [19].

Also, because VA infections may occur in both inpatient and outpatient settings, an additional indicator of “any VA infection” used data from any institutional (inpatient, outpatient, home health, and skilled nursing) or physician/supplier Medicare claim. This indicator classified patients as with or without any VA infection (1+ or 0).

Analysis. During the follow-up period, mean hemoglobin, mean rHuEPO/wk, and number of months with IV iron were calculated for each patient; mean hemoglobin and mean rHuEPO/wk were computed as previously described. Patients were categorized by number (0, 1, or 2+) of entry-period hospitalizations for VA infection and entry-period catheter insertions (temporary or permanent). The Wilcoxon rank-sum test compared mean hemoglobin, mean rHuEPO/wk, and mean number of months with IV iron between groups (0 vs. 1 and 0 vs. 2+ catheter insertions and hospitalizations for VA infection).

Using multiple linear regression models, hemoglobin and rHuEPO/wk during follow-up were compared among groups by entry-period catheter insertions and VA infections. The independent predictors included incident year, age (20–44, 45–64, 65–74, and 75+ years), race (white, black, other), gender, primary cause of ESRD (diabetes and nondiabetes), hemoglobin at initiation of dialysis, number of months with IV iron during the entry period, number of blood transfusions, and comorbid conditions (atherosclerotic heart disease, congestive heart failure, other cardiac disease, peripheral vascular disease, cerebrovascular accident/transient ischemic attack, cancer, chronic obstructive pulmonary disease, and gastrointestinal disease with bleeding). Because catheter insertions were correlated with VA infections, to reduce multicollinearity, these two predictors were not included in the same model. Therefore, two multiple linear regression models were used with follow-up hemoglobin as the dependent variable, including the independent predictors listed above, in addition to the following predictors during the entry period: model 1, total hospital days (0, 1–4, 5–12, and 13+) and catheter insertions (0, 1, and 2+); and model 2, non-VA hospital days (0, 1–4, 5–12, and 13+) and hospitalizations for VA infection (0, 1, and 2+).

To assess rHuEPO/wk during follow-up, models 1 and 2 were repeated using natural logarithmically transformed rHuEPO/wk as the dependent variable. To reduce multicollinearity, non-VA hospital days (rather than total hospital days) were included in the models with VA infections. Also, model 2 was repeated using the indicator for any VA infection (0 and 1+) rather than hospitalization for VA infection.

Assumptions of linear regression were checked by examining residuals from the data fitted to the model. The variance inflation factor and correlation matrix suggested that multicollinearity among independent variables was not a problem. The patient-level data were trimmed to improve normality: the lower 0.25% and upper 0.25% of mean hemoglobin and lower 0.25% and upper 0.25% of mean rHuEPO/wk. A natural log transformation of rHuEPO/wk was used to satisfy the normality assumption of linear regression [20]. The modified Levene test [21] was used to test for nonconstant variance (heteroscedasticity). Significant heteroscedasticity was found only in the models with hemoglobin as the dependent variable. Weighted least-squares regression was used for the hemoglobin models as a remedial measure for nonconstant variance. Consistent results obtained from the weighted and ordinary-least-squares regression models supported use of the ordinary-least-squares results.

RESULTS

Concurrent anemia management, catheter insertions, and VA infections in period-prevalent hemodialysis patients

The study included 186,348 rHuEPO-treated prevalent patients; Table 1 displays their characteristics. Of these, 76.4% had mean hemoglobin ≥ 11 g/dL, and 80.7% were treated with IV iron. Increasing numbers of temporary catheter insertions, permanent catheter insertions, and hospitalizations for VA infection were associated with decreasing mean hemoglobin, increasing mean rHuEPO/wk, and increasing mean IV iron vials per month (Fig. 1). Among patients with 2+ compared to no catheter insertions, mean values of hemoglobin, rHuEPO/wk, and IV iron vials per month were 0.35 g/dL lower, 4987 units higher, and 0.22 vials higher ($P < 0.0001$), respectively. Similarly, among patients with 2+ compared to no hospitalizations for VA infection, respective values were 0.46 g/dL lower, 6789 units higher, and 0.24 vials higher ($P < 0.0001$). Comparisons among patients with one compared to no catheter insertions and hospitalizations for VA infection also were statistically significant ($P < 0.0001$; see Fig. 1 for mean values). Similar results were found when temporary and permanent catheters were analyzed separately (results not shown).

Table 1. Characteristics of prevalent Medicare hemodialysis patients in 2000^a

Characteristic	N	%
All patients	186,348	100.0
Age years		
0–44	27,772	14.9
45–64	61,852	33.2
65–74	51,974	27.9
75+	44,730	24.0
Missing	20	0.0
Gender		
Female	90,598	48.6
Male	95,750	51.4
Race		
White	99,549	53.4
Black	74,661	40.1
Native American	3502	1.9
Asian	6122	3.3
Other/missing	2514	1.3
Primary cause of ESRD		
Diabetes	75,948	40.8
Hypertension	54,102	29.0
Glomerulonephritis	20,790	11.2
Other/missing	35,508	19.1
Mean hemoglobin g/dL		
<10.0	11,764	6.3
10.0–10.9	32,292	17.3
11.0–11.9	92,346	49.6
12.0–12.9	41,678	22.4
13.0+	8268	4.4
Intravenous iron-treated	150,342	80.7

ESRD, end-stage renal disease; rHuEPO, recombinant human erythropoietin.

^aIncludes rHuEPO-treated patients with no chemotherapy or parenteral nutrition claims during the year.

Anemia management after catheter insertion and VA infection in incident hemodialysis patients

The study included 67,410 incident Medicare hemodialysis patients; Table 2 displays their characteristics. Mean age was 65 years, 50.5% were male, 59.6% were white, 47.6% had diabetes as primary cause of ESRD, mean hemoglobin at initiation was 9.5 g/dL, 46.6% had at least one hospital day, 44.8% had at least one non-VA hospital day, 5.0% had at least one hospitalization for VA infection, 82.8% had at least one entry-period month with IV iron, 4.7% had at least one blood transfusion, and 19.7% had at least one catheter insertion.

As in the prevalent cohort, increasing numbers of entry-period catheter insertions or hospitalizations for VA infection were associated with slightly decreased mean hemoglobin, increased mean rHuEPO/wk, and inconsistently increased mean number of months with IV iron during follow-up (see Fig. 2 for mean values; $P < 0.0001$ for all comparisons, except for mean number of months with IV iron between patients with 2+ catheter insertions and those with none, for which the P value was 0.11).

Regression analyses showed that higher numbers of catheter insertions and hospitalizations for VA infection

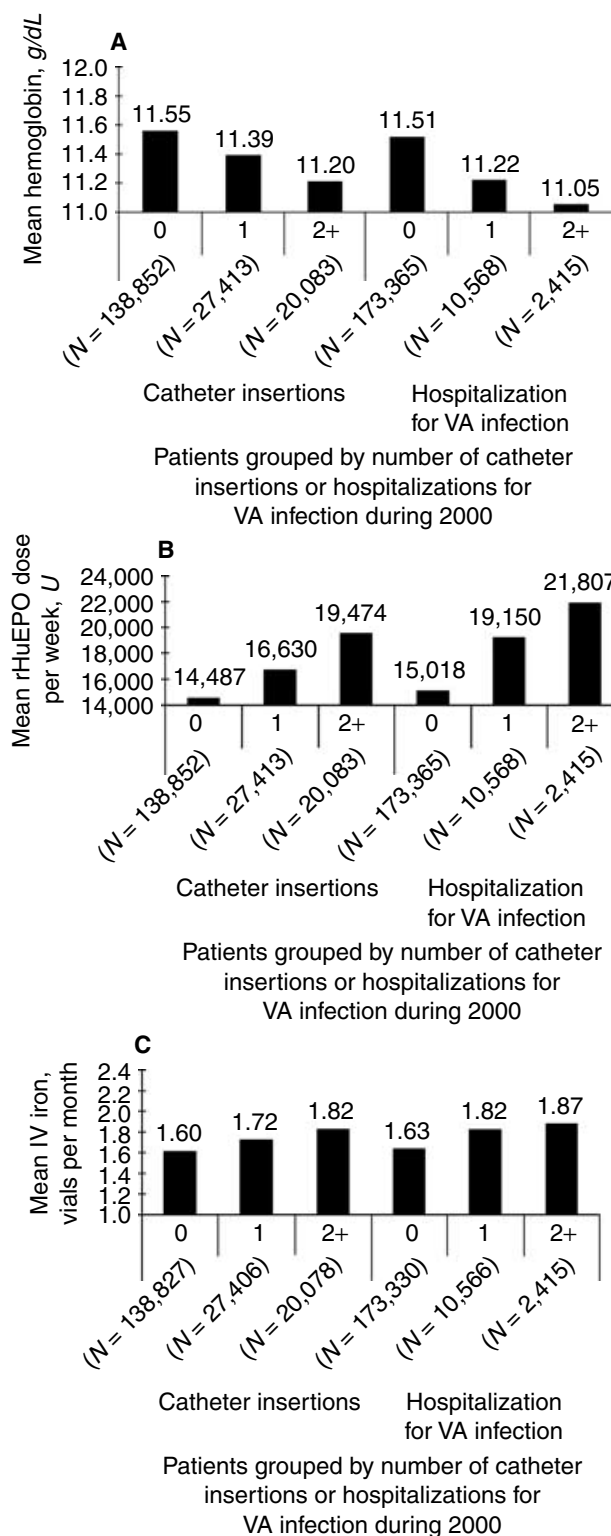


Fig. 1. Mean hemoglobin (A), mean rHuEPO dose/wk (B), and mean monthly vials of IV iron (C) by number of catheter insertions (temporary or permanent) and hospitalizations for vascular access (VA) infection during 2000. Includes prevalent rHuEPO-treated hemodialysis patients in 2000.

Table 2. Characteristics of 1997–1999 (combined) incident Medicare hemodialysis patients^a

Characteristic	N	%
All patients	67,410	100.0
Incident year		
1997	21,014	31.2
1998	22,860	33.9
1999	23,536	34.9
Age years		
20–44	7138	10.6
45–64	18,341	27.2
65–74	23,452	34.8
75+	18,479	27.4
Gender		
Female	33,363	49.5
Male	34,047	50.5
Race		
White	40,210	59.6
Black	23,059	34.2
Other/missing	4141	6.1
Primary cause of ESRD		
Diabetes	32,085	47.6
Nondiabetes	35,325	52.4
Hemoglobin at initiation g/dL		
<9.0	26,196	38.9
9.0–9.9	16,274	24.1
10.0–10.9	12,756	18.9
11.0–11.9	7216	10.7
12+	4968	7.4
Total hospital days		
0	35,996	53.4
1–4	11,610	17.2
5–12	10,456	15.5
13+	9348	13.9
Non-VA hospital days		
0	37,216	55.2
1–4	11,696	17.4
5–12	9947	14.8
13+	8551	12.7
Hospitalizations for VA infection		
0	64,010	95.0
1	2967	4.4
2+	433	0.6
Any VA infection (from any data source)		
0	52,793	78.3
1+	14,617	21.7
No. of entry-period months with IV iron		
0	11,583	17.2
1–4	31,103	46.1
5–6	24,724	36.7
Blood transfusions		
0	64,264	95.3
1+	3146	4.7
Temporary catheter insertions		
0	58,020	86.1
1	6100	9.0
2+	3290	4.9
Permanent catheter insertions		
0	61,338	91.0
1	4794	7.1
2+	1278	1.9
Catheter insertions (temporary or permanent)		
0	54,101	80.3
1	8041	11.9
2+	5268	7.8
Comorbid conditions		
ASHD	39,885	59.2
CHF	43,421	64.4
Other cardiac disease	48,440	71.9
PVD	38,907	57.7
CVA/TIA	22,889	34.0
Cancer	14,484	21.5
COPD	20,361	30.2
GI disease	16,700	24.8
Liver disease	20,120	29.8

Abbreviations are: ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; ESRD, end-stage renal disease; GI, gastrointestinal; IV, intravenous; PVD, peripheral vascular disease; rHuEPO, recombinant human erythropoietin; VA, vascular access.

^aIncludes rHuEPO-treated patients with no chemotherapy or parenteral nutrition claims.

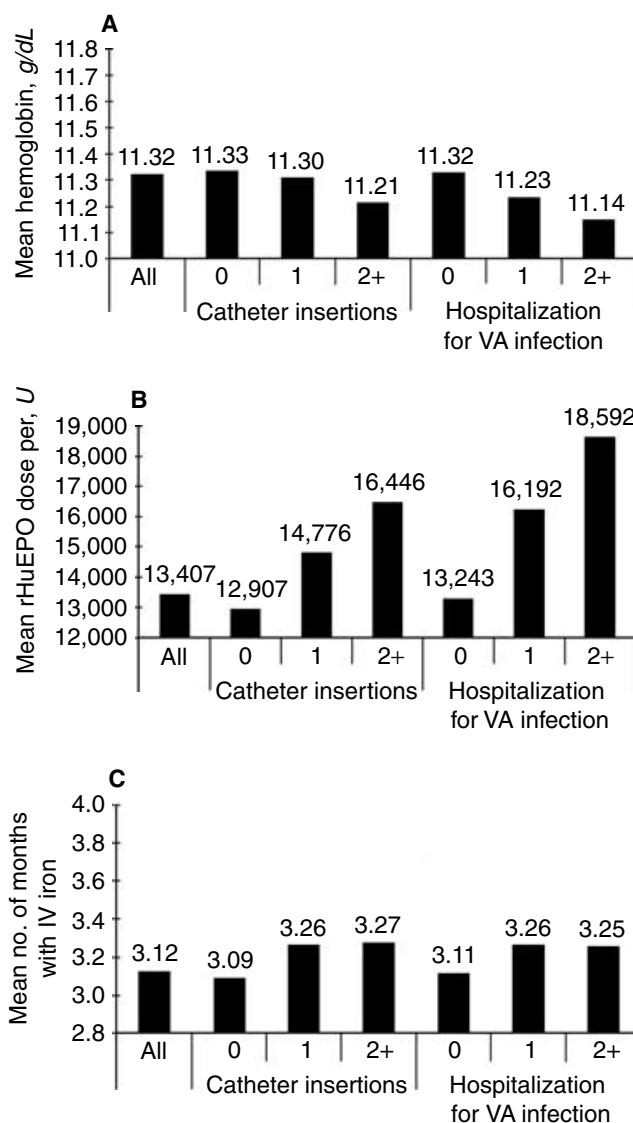


Fig. 2. Mean hemoglobin (A), mean rHuEPO dose/wk (B), and mean number of months with IV iron during 6-month follow-up (C), by number of entry-period catheter insertions (temporary or permanent) and hospitalizations for vascular access (VA) infection. Includes 1997 to 1999 incident rHuEPO-treated hemodialysis patients.

were associated with slightly, yet significantly, lower mean hemoglobin and significantly higher mean rHuEPO/wk after controlling for other factors (Table 3). Compared to those with no hospitalizations for VA infection, patients with 1 and those with 2+ VA infections had, respectively, 0.07 and 0.12 g/dL lower mean hemoglobin ($P < 0.0001$ and $P = 0.0028$), and 12.9% and 25.7% higher mean rHuEPO/wk ($P < 0.0001$). Compared to patients with no catheter insertions, patients with 1 and those with 2+ catheter insertions had, respectively, similar and 0.06 g/dL lower mean hemoglobin ($P = 0.9544$ and $P < 0.0001$), and 6.9% and 12.2% higher mean rHuEPO/wk ($P < 0.0001$). Also, compared to patients without any VA

Table 3. Differences in mean hemoglobin and rHuEPO dose/wk from reference groups in 1997 to 1999 incident Medicare hemodialysis patients^a

Characteristic	Mean hemoglobin difference g/dL	P value	rHuEPO dose/wk difference %	P value
Hospitalizations for VA infection				
1	-0.07	<0.0001	12.9	<0.0001
2+	-0.12	0.0028	25.7	<0.0001
Any VA infection (from any data source)				
1+	-0.03	0.0002	6.7	<0.0001
Catheter insertions (temporary or permanent)				
1	0.00	0.9544	6.9	<0.0001
2+	-0.06	<0.0001	12.2	<0.0001
Age years				
45-64	0.09	<0.0001	2.1	0.0415
65-74	0.16	<0.0001	-5.7	<0.0001
75+	0.21	<0.0001	-11.6	<0.0001
Race				
Black	-0.06	<0.0001	11.0	<0.0001
Other	0.03	0.0552	-5.6	<0.0001
Male	0.05	<0.0001	-4.7	<0.0001
Diabetes as primary cause of ESRD	-0.01	0.2418	1.2	0.0340
Hemoglobin at initiation g/dL				
<9.0	-0.17	<0.0001	25.9	<0.0001
9.0-9.9	-0.11	<0.0001	14.9	<0.0001
10.0-10.9	-0.06	<0.0001	5.9	<0.0001
12+	0.04	0.0124	-4.6	0.0002
Incident year				
1998	0.40	<0.0001	11.3	<0.0001
1999	0.55	<0.0001	13.8	<0.0001
Total hospital days				
1-4	-0.04	0.0001	8.6	<0.0001
5-12	-0.04	<0.0001	14.7	<0.0001
13+	-0.07	<0.0001	24.8	<0.0001
No. of entry-period months with IV iron				
1-4	0.18	<0.0001	-3.8	<0.0001
5-6	0.26	<0.0001	-4.9	<0.0001
1+ blood transfusions	-0.19	<0.0001	27.6	<0.0001
Comorbid conditions				
ASHD	0.01	0.1388	-0.3	0.6812
CHF	-0.06	<0.0001	7.5	<0.0001
Other cardiac disease	-0.04	<0.0001	4.1	<0.0001
PVD	0.00	0.5373	3.6	<0.0001
CVA/TIA	0.01	0.0721	-3.3	<0.0001
Cancer	-0.06	<0.0001	8.9	<0.0001
COPD	-0.02	0.0095	-0.1	0.9097
GI disease	-0.08	<0.0001	9.0	<0.0001
Liver disease	0.05	<0.0001	1.5	0.0093

Abbreviations are: ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; ESRD, end-stage renal disease; GI, gastrointestinal; IV, intravenous; PVD, peripheral vascular disease; rHuEPO, recombinant human erythropoietin; VA, vascular access.

^a Includes rHuEPO-treated patients with no chemotherapy or parenteral nutrition claims. Reference groups include no hospitalizations for VA infection, no VA infection from any data source, no catheter insertions, age 20 to 44 years, white, female, nondiabetes, hemoglobin of 11.0 to 11.9 g/dL at initiation, incident year of 1997, no hospital days, no IV iron use, no blood transfusions, and no comorbid conditions during the entry period.

infections (as recorded in any data source), patients with 1+ VA infection had 0.03 g/dL lower mean hemoglobin ($P = 0.0002$) and 6.7% higher mean rHuEPO/wk ($P < 0.0001$). Results and P values for other independent predictors are displayed in Table 3, and were obtained from the multiple linear regression models with predictors as described for model 1 in the **Methods** section. These results included significantly higher mean hemoglobin and lower rHuEPO/wk among patients with hemoglobin at initiation of 12.0+ g/dL versus 11.0 to 11.9 g/dL, and among patients with 1 to 4 or 5 to 6 versus those with 0 entry-period months with IV iron.

DISCUSSION

Our results demonstrate that higher numbers of catheter insertions and hospitalizations for VA infection are associated with slightly lower hemoglobin values and higher weekly rHuEPO requirements in both prevalent and incident dialysis patients. In multivariate analyses that adjusted for some factors that can influence hemoglobin values and/or rHuEPO requirements, such as hospitalizations, comorbidity, blood transfusions, and iron use, the differences in weekly rHuEPO requirements were 26% and 12% higher among those with 2+ hospitalizations for VA infection or 2+ catheter insertions,

respectively, compared to those without any. These results indicate that considerably more rHuEPO is needed to achieve the same or a slightly lower hemoglobin value in these patients. Also, when VA infections were characterized from any data source, rather than only from hospitalizations, and patients with and without any VA infections were compared, we still found clinically similar, yet significantly lower, mean hemoglobin values, and 7% higher weekly rHuEPO requirements.

Several mechanisms may account for the association of higher numbers of catheter insertions with lower hemoglobin values and higher weekly rHuEPO requirements, including higher incidence of infection with catheters [22–30], surgical inflammation due to concomitant procedures for placement of a permanent VA [1], and lower dialysis dose due to reduced blood flow with catheters [7–10]. However, the literature regarding the effect of dialysis dose and type of membrane on rHuEPO responsiveness is inconclusive [1]. Additional mechanisms underlying the association include blood loss from surgery or the catheter site, as well as clotted dialysis circuits.

Regarding the association of higher numbers of VA infections with lower hemoglobin values and higher weekly rHuEPO requirements, it is well known that infections induce an inflammatory state that can markedly impair responsiveness to rHuEPO [31]. The mechanism underlying the association appears to involve increased production of inflammatory cytokines, such as tumor necrosis factor, interleukin-1, and interferon-gamma [32, 33]. In support of this hypothesis, two recent studies have shown that an elevated C-reactive protein value, which often is associated with infection and/or inflammation, predicts rHuEPO resistance in patients undergoing dialysis [34, 35].

Our finding of an association between higher numbers of catheter insertions and VA infections with increased rHuEPO requirements has important clinical and economic implications, particularly in view of the high prevalence of catheter use and synthetic graft placement for chronic hemodialysis in the U.S. In the Wave 2 of the Dialysis Morbidity and Mortality Study, among 1805 incident patients in 1996, 65% began in-center chronic hemodialysis with a catheter, 24% with a PTFE graft, and 11% with an AV fistula [15]. Two months after the start of hemodialysis, 32% of patients still had a catheter as their primary access, 50% a PTFE graft, and 18% an AV fistula. In the Dialysis Outcomes and Practice Patterns Study, VA was compared in a random cohort of European and U.S. incident and prevalent hemodialysis patients [16]. Among incident patients, 66% of European patients began chronic hemodialysis with an AV fistula, 2% with a graft, and 31% with a catheter. In contrast, only 15% of U.S. patients began hemodialysis with an AV fistula, 24% with a graft, and 60% with a catheter. Among prevalent

patients, 80% of European patients had an AV fistula, 10% an AV graft, and 8% a catheter, whereas 24% of U.S. patients had an AV fistula, 57% an AV graft, and 17% a catheter. These differences in VA might partially explain why mean rHuEPO doses for European patients undergoing chronic hemodialysis are lower than those used in their U.S. counterparts [36].

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Guidelines recommend that 40% of prevalent chronic hemodialysis patients should have an AV fistula (guideline 29), and that less than 10% of chronic hemodialysis patients should be maintained on catheters, defined as use of catheters for more than three months in the absence of a maturing access (guideline 30). The NKF-K/DOQI Guidelines also recommend that primary AV fistulas should be constructed in at least 50% of all new kidney failure patients [1]. Given the results of our study, implementation of these guidelines may have the additional benefit of reducing rHuEPO requirements and, consequently, cost, which currently exceeds \$1 billion in the U.S. [37].

Our results should be interpreted with awareness of the following limitations. First, relationships are associations and do not show causality. Second, Medicare claims provide complete data on catheter insertions only after day 90 of dialysis. The exclusion of catheter insertions in the first 90 days of dialysis is likely to have resulted in underestimation of the effect size of the associations. Third, Medicare claims do not directly indicate which type of vascular access is being used for dialysis. However, the number of catheter insertions provides an indication of catheter placement and general indication of catheter use. The focus of our analysis was the effect of catheter insertions on anemia management, not the effect of the type of VA in use for dialysis. Fourth, no information was available regarding other potential confounding factors, such as ferritin, transferrin saturation, parathyroid hormone, C-reactive protein, and some oral medications. However, these factors may influence baseline hemoglobin at initiation of dialysis, and adjustment for baseline hemoglobin may help to reduce potential confounding due to these and other unavailable factors.

CONCLUSION

We found a direct association of higher numbers of catheter insertions and VA infections with increased rHuEPO requirements. Higher rHuEPO doses may be required to maintain the same or slightly lower mean hemoglobin values among chronic hemodialysis patients with higher numbers of catheter insertions and VA infections, compared to those without any. In the U.S., the increasing use of dialysis catheters and the widespread placement of PTFE grafts put hemodialysis patients at high risk of serious VA-related infection. Implementation

of the NKF-K/DOQI Clinical Practice Guidelines for Vascular Access may result in reduced infectious complications, rHuEPO requirements, and, consequently, cost among patients undergoing chronic hemodialysis.

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