Organizational Status of Dialysis Facilities and Patient Outcome: Does Higher Injectable Medication Use Mediate Increased Mortality?

Yi Zhang, Mae Thamer, Onkar Kshirsagar, and Dennis J. Cotter

Objective. Examine the mediating effect of injectable drugs in the relationship between dialysis facility organizational status and patient mortality.

Study Setting. Medicare dialysis population.

Study Design. Data from the U.S. Renal Data System (USRDS) were used to identify 3,884 freestanding dialysis facilities and 37,942 Medicare patients incident to end-stage renal disease (ESRD) in 2006. The role of injectable medications was evaluated during a 2-year follow-up period by mediational analyses using mixed-effect regression models.

Data Collection. USRDS data were matched with Dialysis Facility Report data from Centers for Medicare and Medicaid Services (CMS) and census data.

Principal Findings. There was a strong association found between organizational status and use of injectable drugs. Large for-profit chains used significantly higher injectable medications compared with nonprofit chains and independent facilities. However, the relationship between facility organizational status and patient mortality was not found to be mediated through the higher use of injectable drugs.

Conclusions. Large for-profit chain facilities administered higher IV epoetin, iron, and vitamin D dosages, but this did not result in improved survival. Given the associated costs and lack of a survival benefit, the overuse of injectable medications among the U.S. dialysis patients will likely end under the recent bundling of injectable medications without jeopardizing patient outcomes.

Key Words. Dialysis facility, injectable drugs, chain, profit status, mortality

Prior to 2011, dialysis facilities primarily relied on Medicare payment for intravenous (IV) erythropoiesis-stimulating agents (ESAs, mostly epoetin) for management of anemia, IV iron for low transferrin saturation, and IV vitamin D for hyperparathyroidism, collectively called “separately billable injectable end-stage renal disease (ESRD) drugs,” to subsidize the

declining Medicare composite rate payments that facilities received for provision of dialysis and routine laboratory services (Department of Health and Human Services [DHHS] 2004). In 2007, for example, these three injectable medications accounted for about 98 percent of the approximately \$2.2 billion in Medicare expenditures for injectable ESRD drugs; the average monthly Medicare expenditure per dialysis patient was \$515 for epoetin, \$102 for IV vitamin D, and \$59 for IV iron (Government Accountability Office [GAO] 2010). Notably, the average epoetin dose increased more than 4-fold between 1991 and 2005 in dialysis patients (Steinbrook 2006), reaching nearly \$2 billion in 2005 (GAO 2006; United States Renal Data System [USRDS] 2006). Large increases in doses and expenditures for IV iron and IV vitamin D have also been reported (USRDS 2011).

Earlier research (Garg et al. 1999; Irvin 2000; Devereaux et al. 2002), including our own (Zhang, Cotter, and Thamer 2011), has shown significant variation in patient mortality across different types of dialysis providers. Both facility chain and profit status (subsequently referred to as facility organizational status) were found to be independently associated with patient survival. Specifically, patients from large for-profit dialysis facilities are at increased risk of mortality. However, there is a paucity of research evaluating why patients treated in these dialysis facilities have higher mortality rates. As a potential explanatory factor, the role that injectable drugs play in the pathway between dialysis organizational status and patient outcomes is controversial. Given the neutral or deleterious results of randomized trials on the effect of injectable drugs, some postulate that beneficial effects are unproven, although an increased risk of mortality and adverse cardiovascular outcomes is likely if drugs are used aggressively (Singh et al. 2006; Palmer et al. 2007; Rozen-Zvi et al. 2008; Pfeffer et al. 2009; Szczech et al. 2010). Others suggest that higher hematocrit and better management of iron deficiency and hyperparathyroidism through higher injectable drug use might result in better survival. To test these hypotheses, we examined the mediational effect of three injectable medications, IV epoetin, IV iron, and IV vitamin D, in relation to facility organizational status and patient mortality.

Address correspondence to Yi Zhang, Ph.D., Medical Technology and Practice Patterns Institute (MTPPI), 4733 Bethesda Ave, Suite #510, Bethesda, MD 20814; e-mail: yz@mtppi.org. Mae Thamer, Ph.D., Onkar Kshirsagar, M.S., and Dennis J. Cotter, M.S.E., are also with the Medical Technology and Practice Patterns Institute (MTPPI), Bethesda, MD.

METHODS

Data Sources

The most recent Standard Analytical Files (SAFs), collected and maintained by the U.S. Renal Data System (USRDS), were used to obtain patient clinical history and dialysis facility provider characteristics. The variables included in the USRDS SAF, as well as the data source, collection methods, and validation studies, are listed at the USRDS website, <http://www.usrds.org>. Facility organizational status and characteristics were obtained from the CMS Dialysis Facility Report (DFC) data, which are updated quarterly and have facility characteristics that are not available in the USRDS database. In addition, the 2000 U.S. Census data were used to obtain information on several ecological characteristics, including race-specific median household income, percent of Caucasian population, and urbanicity status by linking zip codes.

Study Design and Sample Selection

This was a retrospective cohort study of incident hemodialysis patients and their dialysis facility providers with two main phases: (1) a 3-month *baseline period* following enrollment into the Medicare ESRD Program, during which time all patient baseline characteristics were obtained; and (2) a 2-year *follow-up period* that tracked the death and censoring events.

All Medicare-eligible, adult (>18-year-old) ESRD patients who initiated in-center (vs at home) hemodialysis in 2006 were deemed eligible for inclusion in the study sample. All patients were required to (1) have their first ESRD service date at least 90 days before the beginning of the baseline period due to the 90-day enrollment rule required by Renal Beneficiary Utilization System; (2) receive only hemodialysis services from the same provider during the 3-month baseline period; (3) survive the baseline period; and (4) use Medicare as the primary payor throughout the baseline period to ensure the completeness of clinical and treatment history data. Furthermore, because patients treated in hospital-based facilities (comprising approximately 15 percent of all dialysis facilities) might be more complex; that is, more comorbidities, compared with patients treated in freestanding facilities (USRDS 2007), patients treated in hospital-based facilities were excluded from the analysis. Each patient in the study was assigned to the facility where he/she was receiving care at the end of the baseline period. Follow-up started after 3 months of outpatient dialysis treatment and ended 24 months later; at the time of death; at

the time of censoring due to transplantation, 60 days after a switch to peritoneal dialysis, 60 days after a change in dialysis facility provider, or gap in outpatient dialysis services (defined as missing institutional claims for 60 consecutive days or longer). By cross-referencing facility data, patient-level data, and ESRD Medicare institutional claims, a patient-facility file was constructed for analysis and modeling.

The *study endpoint* was all cause mortality during the 2-year follow-up period. Independent covariates included facility- and patient-level characteristics and are listed in Tables 2 and 3. Dialysis organizational status was categorized into eight groups by (1) chain size (four largest chains [100 or more facilities], medium chains [10–99 facilities], small [less than 10 facilities], and/or nonchain-affiliated facilities subsequently referred to as non-chain facilities); and (2) profit status (for-profit or nonprofit). Facility-level injectable drug dosing was estimated based on the average facility use of injectable drugs in 2006. Specifically, the monthly doses were first calculated for each patient, and then average doses per patient per month were calculated for patients from the same dialysis facility. Because analyzing injectable drug practices is the key aspect of this research, special considerations were implemented. The analyses first modeled the facility use of epoetin and other injectable drugs with cubic splines (with knots located at the 5th, 25th, 50th, 75th, and 95th percentiles). The use of cubic splines allows for a nonlinear association between continuous variable and probability of death without strong parametric assumptions about the shape of the nonlinear relation. These variables were then grouped and modeled according to quartile values of their distributions. In addition, because the use of injectable practices might be closely interrelated leading to *collinearity* concerns, separate regression models were conducted using a single drug as the independent variable. Finally, summary measure profiling the use of all services was also generated based on the sum of the dose distribution quartile scores. For example, if all doses of epoetin, iron, and vitamin D are in the 4th quartile of distribution, the summary measure for injectables would equal 12. Only one type of ESA is included in our study, epoetin alfa. However, all formulations of IV iron and vitamin D were included to calculate the total dosage based on dose equivalents.

Mediated Regression Analysis

Tests of the mediating role of injectable medications in the relationship between organizational status and patient mortality followed the guidelines

outlined by Baron and Kenney (1986). Three regression equations, comprising so-called mediational analyses, were estimated. First, the dependent variable (mortality) was regressed on the independent variable of facility chain status (*Model 1*); second, the mediator (injectable drugs) was regressed on the facility chain status (*Model 2*); and third, the dependent variable (mortality) was regressed on both the independent variable (chain status) and the mediator (injectable drugs, *Model 3*). All patient characteristics and other facility variables were adjusted for in all three models. To establish mediation, the effect of organizational status must be significant in both Models 1 and 2, and the mediator effect of injectable drugs must affect patient mortality in Model 3. If in Model 3, the effect of organizational status on patient mortality is smaller than results found in Model 1 by the likelihood ratio test (Sobel tests) (Sobel 1982), mediation is established. To disentangle the facility-level factors from patient determinants that might influence patient mortality, all three models were built using three-level pooled regression modeling (random-effects regression or hierarchical regression modeling) (Rice and Leyland 1996; Christiansen and Morris 1997; Singer 1998; Austin, Tu, and Alter 2003) with facilities at the third level, patients at the second level, and patient months at the first level. Specifically, observations over 24 monthly intervals were pooled into a single sample and a random intercept model that treats the dialysis facility effects as random effects was fit with patient months during follow-up as the unit of analyses. Models 1 and 3 applied pooled logistic regression using GLIMMIX procedure in SAS software to estimate the probability of death at each month of follow-up, also called discrete-time hazard modeling and has been shown to be asymptotically equivalent to the Cox regression model (D'Agostino et al. 1990).

Linear mixed-effects modeling was used to estimate least-square mean of facility-level dosages of IV epoetin, IV iron, and IV vitamin D using MIXED procedure in SAS software (Model 2). To determine whether there was a differential impact of patient characteristics on facility-level injectable drug dosing, we analyzed the effect of the patient demographic and clinical characteristics, including patient age, gender, race, diabetic status, and response to epoetin therapy (often viewed as a surrogate of patient underlying health state), on facility drug use. Interaction effects between facility organizational status and patient demographic and clinical characteristics were also examined. All analyses were performed using SAS, version 9.1.3 for Linux. Statistical significance is defined as a *p* value less than .05 unless otherwise noted.

RESULTS

Distribution of Facilities and Patients by Organizational Status

The study included 37,942 patients receiving dialysis at 3,884 facilities. During the follow-up period, 44 percent of all patients survived, 31 percent died, and 25 percent were censored due to change in dialysis facility provider (9 percent), gap in outpatient dialysis services (7 percent), change in modality (6 percent), and kidney transplantation (3 percent). Mean follow-up time was 16 months. In 2006, more than 70 percent of patients received dialysis from the four largest chain facilities; all were for-profit except for nonprofit Chain 4, which accounted for 4.7 percent of all dialysis facilities and was the nation’s largest nonprofit dialysis chain (Table 1).

Patient Characteristics by Organizational Status

Among the study cohort, more than 57 percent were older than 65 years, 54 percent were male, 63 percent were white, and 13 percent were Hispanic (data not shown). Patient characteristics are significantly different by organizational status using ANOVA analyses ($p < .0001$, Table 2). Compared with other facilities, patients from nonprofit Chain 4 tended to be younger, male, black, non-Hispanic, and from lower income areas. Patients from Chain 4 and other nonprofit facilities had the highest proportion of patients who used predialysis epoetin, but the lowest average

Table 1: Distribution of Facilities and Patients by Facility Organizational Status

<i>Facility Type</i>	<i>Facilities (N = 3,884)</i>		<i>Patients (N = 37,942)</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
Large chain (≥ 100 units)				
For-profit chain 1	1,150	29.6	11,186	29.5
For-profit chain 2	1,099	28.3	10,752	28.3
For-profit chain 3	372	9.6	3,503	9.2
Nonprofit chain 4	183	4.7	1,535	4.1
Medium chain (10 to ≤ 99 units)				
For-profit	347	8.9	3,579	9.4
Nonprofit	84	2.2	885	2.3
Small/nonchain (<10 units or independent)				
For-profit	559	14.4	5,484	14.5
Nonprofit	90	2.3	1,018	2.7

Table 2: Patient Characteristics by Facility Organizational Status (N = 37,942)

	Large Chain				Medium Chain		Small/Nonchain	
	FP Chain 1	FP Chain 2	FP Chain 3	NP Chain 4	For-Profit	Nonprofit	For-Profit	Nonprofit
Sociodemographics								
Age (years)	65.2	64.6	65.8	63.7	65.8	67.0	65.3	65.1
Male gender (%)	54.1	52.4	55.3	55.4	52.4	54.9	54.0	54.6
% White	61.3	63.1	64.3	61.2	61.6	64.0	66.7	67.2
Hispanic ethnicity (%)	13.4	13.8	8.8	5.7	17.0	7.2	14.8	8.8
Median white household income	42,746	41,322	40,493	39,592	42,743	46,203	42,252	41,890
Median black household income	33,536	31,641	30,194	28,730	35,285	37,596	33,913	34,118
ESRD clinical history								
Body mass index (kg/m)	28.7	29.3	29.6	29.0	29.1	28.2	29.1	29.3
Total inpatient days	3.8	4.2	3.5	3.5	4.0	3.7	4.2	4.1
Predialysis GFR (ml/min)	10.5	10.2	10.9	10.2	10.4	11.2	10.7	10.5
Predialysis creatinine (mg/dl)	6.5	6.7	6.3	6.7	6.5	6.1	6.4	6.4
Predialysis albumin (g/dl)*	3.1	3.1	3.2	3.1	3.1	3.2	3.2	3.2
Anemia management								
Predialysis epoetin use*	29.4	31.9	29.7	32.6	31.5	37.5	31.0	40.6
Predialysis hemoglobin (gm/dl)	10.1	10.1	10.1	10.0	10.4	10.3	10.1	10.1
Baseline average epoetin (units/administration)	8,020	8,084	7,495	7,160	6,915	6,573	6,515	6,070
Baseline average HCT (%)								
<33%	10.6	13.1	11.0	12.5	28.7	16.9	25.0	29.7
33 to <36%	22.5	22.8	18.8	26.8	24.6	22.4	24.8	19.9
36 to <39%	36.5	35.1	29.9	39.4	26.8	30.3	28.5	28.9
≥ 39%	30.5	29.0	40.3	21.3	19.9	30.4	21.7	21.5
Comorbidities (% yes) [†]								
Charlson index	3.1	3.2	3.1	3.5	3.1	3.1	3.0	3.3

continued

Table 2. Continued

	Large Chain				Medium Chain		Small/Nonchain	
	FP Chain 1	FP Chain 2	FP Chain 3	NP Chain 4	For-Profit	Nonprofit	For-Profit	Nonprofit
Diabetes	60.5	62.1	58.4	59.9	61.6	59.8	59.4	58.6
Congestive heart failure	35.3	36.6	35.8	37.7	38.4	38.6	37.8	34.9
Atherosclerotic heart disease (ASHD)	21.6	24.7	22.4	24.6	25.0	30.4	26.3	28.4
CVA/TIA	9.7	10.7	10.7	12.6	9.9	14.0	11.4	14.0
Peripheral vascular disease	14.3	16.4	14.9	15.4	17.4	16.7	16.7	18.5
Cardiac disease other than CHF and ASHD	15.7	15.5	15.5	20.7	15.3	16.5	18.3	17.7
Hypertension	86.0	86.1	85.5	87.8	84.7	87.0	87.2	87.0
Cancer	7.4	6.3	6.5	8.2	6.5	5.8	7.1	9.9
Chronic obstructive pulmonary disease	8.7	9.1	10.9	11.5	8.4	9.9	9.7	12.5
Current smoker	5.8	7.1	6.0	10.8	4.7	7.9	6.0	7.3
Alcohol/drug dependence	2.4	2.4	2.6	4.2	1.7	2.6	2.0	3.1
Other severe conditions*	8.3	8.6	7.7	11.0	8.9	10.5	10.4	10.0
Pre-ESRD care (% yes)								
Initial vascular access type								
AV fistula	14.5	15.5	17.2	18.2	14.2	20.3	13.5	20.1
Graft	5.4	5.2	5.5	4.7	5.4	4.2	4.8	4.5
Catheter	78.9	78.5	75.6	76.7	78.6	74.4	80.3	75.0
Other	1.3	0.8	1.7	0.3	1.8	1.1	1.4	0.4
Predialysis care under a kidney dietitian*	10.4	10.3	9.2	8.8	9.7	16.3	13.5	17.5
Predialysis care under a nephrologist*	63.8	69.0	70.8	74.5	65.8	75.9	66.4	70.3

*Contains missing values and is adjusted for in multivariate analysis by having a separate category.
†All comorbidities are collected from Medical Evidence form except for Charlson Index, which is measured during baseline period.
‡Includes amputation, inability to ambulate, and inability to transfer.
CHF, congestive heart failure; ESRD, end-stage renal disease; FP, for-profit; NP, nonprofit.

epoetin doses during study baseline. Chain 4 had the largest proportion of patients (62.3 percent) who had achieved hematocrit in the recommended target range (33 to <36 percent) during the baseline period, whereas patients from Chain 3 followed by Chain 1 had the largest proportion of patients who had hematocrit beyond the recommended target of 36 percent. Pre-ESRD care also differed by organizational status. Nonprofit facilities cared for patients who were best prepared for the rigors of permanent dialysis; these facilities had the highest rates of patients with AV-fistulas (widely promoted as the best vascular access method) and a higher proportion of patients cared for by a nephrologist and dietitian prior to ESRD.

Comorbid conditions were highly prevalent among dialysis patients. Before the start of dialysis, 61 percent had diabetes (as a primary diagnosis or comorbidity), 37 percent had congestive heart failure, 86 percent had hypertension, and 9 percent had traumatic conditions such as an amputation. During the 3-month study baseline, approximately 60 percent of the patients had a calculated Charlson Index score of 3 or more, indicating a higher burden of comorbid disease. Patients from Chain 4 had the highest Charlson Index scores, the highest proportion of patients with hypertension (88 percent), and the highest rate of preexisting severe conditions (11 percent).

Facility Characteristics by Organizational Status

Facility characteristics are significantly different by organizational status ($p < .0001$, Table 3). Medium-sized chain facilities generally had larger individual facility sizes compared with the four largest chains. Chain 4 and nonprofit nonchain facilities had the greatest number of nurses per patients and a lower ratio of technicians to nurses, both shown to improve patient care. All large chains were more likely to be found in the Southeast U.S. region. Chain 4 facilities were more likely to be located in rural areas compared with all other chain-operated facilities.

In general, for-profit dialysis chains, regardless of size, used significantly higher epoetin, vitamin D, and iron doses compared with their nonprofit counterparts ($p < .0001$, Table 3). To test whether facilities that used higher average epoetin doses also tended to use higher iron and vitamin D doses, Pearson correlation coefficient results confirmed that the use of epoetin is positively associated with both use of iron and vitamin D ($p < .0001$, data not shown). In addition, iron doses are also positively associated with vitamin D doses ($p < .0001$, data not shown).

Table 3: Facility Characteristics by Facility Organizational Status (N = 3,884 Facilities)

	Large Chain				Medium Chain		Small/Nonchain	
	FP Chain 1	FP Chain 2	FP Chain 3	NP Chain 4	For-Profit	Nonprofit	For-Profit	Nonprofit
Facility size (average no. of patients/facility)	79	73	70	66	81	99	72	84
Ratio of technicians to RNs	1.5	1.7	1.5	1.0	1.4	1.5	1.3	1.0
Staff intensity (no. of of RNs/100 patients)	7.3	7.0	7.9	11.5	10.0	8.3	9.8	11.7
Patients wait-listed for kidney transplant (%)	22.0	20.7	19.9	19.1	23.2	27.4	19.5	21.8
% white based on facility zip code	69	70	73	74	67	75	70	73
Region (%)								
Northeast (Networks 1–5)	20.1	21.3	9.1	21.3	26.5	6.0	22.5	28.9
Southeast (Networks 6–8, 13, 14)	38.9	47.3	37.9	42.6	33.4	17.9	41.5	18.9
Midwest (Networks 9–12)	21.9	20.6	35.8	23.0	17.0	33.3	19.5	30.0
West (Networks 15–18)	19.1	10.8	17.2	13.1	23.1	42.9	16.5	22.2
Urban/rural status, % rural	26.5	32.8	34.9	40.4	24.5	27.4	28.6	30.0
Facility use of injectables								
All three injectable medications*	9	8	7	5	7	7	6	5
Epoetin (average units/month) [†]	93,598	86,610	86,896	73,414	82,051	71,186	69,628	57,323
Use of iron (average mg/month) [†]	302	250	214	230	230	225	235	193
Vitamin D (average mcg/month) [†]	53	48	40	21	40	35	33	31
Adherence to clinical guidelines								
Patients with HCT >33% (%)	94	92	93	91	92	93	88	89
Patients with URR >65% (%)	95	96	96	91	95	94	93	94

*Summarized based on the dose quartile distributions with a minimum of 3 and a maximum of 12.

[†]Summarized for every certified facility based on 2006 outpatient dialysis claims.

FP, for-profit; HCT, hematocrit; NP, nonprofit; RN, registered nurse; URR, urea reduction ratio.

Mediating Role of Injectable Drugs

Relationship between Facility Organizational Status and Use of Injectable Drugs. For epoetin, iron, and vitamin D to be deemed as mediators, they must be affected (predicted) by facility chain status (*Model 2*). Under *Model 2*, the *difference* in the estimated doses across facilities was constant, regardless of the adjustment by patient characteristics. Figure 1a–d presents differences in mean doses between all facility types and Chain 4 based on four regression models for overall use of injectables, and separately for epoetin, iron, and vitamin D adjusted for the patient and facility characteristics included in Table 2. Results from Figure 1a indicate that Chain 4 facilities had the lowest overall injectable drug use among all facility organizational status, regardless of size and/or profit status ($p < .0001$ except for the difference between NP nonchain and Chain 4, which was 0.21), whereas Chain 1 had the highest score for the summary injectable drug measure and for all three injectable medications separately ($p < .0001$). The adjusted facility average epoetin dose and iron dose

Figure 1: Adjusted Difference in Mean Dose between All Facility Types and Chain 4 with Ninety-Five Percent Confidence Interval (*Model 2* Results)

Note. FP, for-profit; NP, nonprofit. Grid line across zero can be considered as reference line (Chain 4). Points above the line indicate higher doses than Chain 4. Points below the line indicate lower doses than Chain 4.

were lowest among nonprofit nonchain facilities and the adjusted vitamin D dose was lowest among Chain 4 facilities. No differences by patient demographics (age, race, and gender), presence of diabetes, or epoetin responsiveness were found in facility use of all injectable medications (*p* values close to 1). The interaction effect between these patient characteristics and facility organizational status was found to be nonsignificant as well.

Relationship between Facility Organizational Status, Use of Injectable Drugs, and Patient Mortality. Table 4 shows the results based on both unadjusted and adjusted results for patient mortality (*Models 1 & 3*). The unadjusted analysis indicates that, compared with patients in Chain 4, patients from all other facilities had significantly higher mortality hazard rates. After adjusting for patient and facility characteristics (*Model 1*), a more elevated risk for mortality was shown for all other facilities compared with Chain 4, reflecting the fact that patients treated in Chain 4 were more likely to have characteristics unfavorable for patient survival.

Model 3 examined whether the use of injectables is a significant factor in predicting mortality after adjusting for other patient and facility characteristics

Table 4: Hazard Ratios for Mortality by Dialysis Facility Organizational Status Based on Random-Effect Models*

Facility Type	Unadjusted Model			Model 1†			Model 3‡		
	HR	Lower CI	Upper CI	HR	Lower CI	Upper CI	HR	Lower CI	Upper CI
Large chain									
FP chain 1	1.13	1.01	1.25	1.27	1.12	1.43	1.24	1.09	1.41
FP chain 2	1.14	1.02	1.26	1.29	1.14	1.45	1.27	1.12	1.44
FP chain 3	1.17	1.04	1.32	1.32	1.16	1.51	1.31	1.15	1.50
NP chain 4	Ref			Ref			Ref		
Medium chain									
For-profit	1.19	1.05	1.34	1.29	1.13	1.47	1.27	1.11	1.45
Nonprofit	1.22	1.03	1.44	1.28	1.07	1.53	1.27	1.06	1.52
Small/nonchain									
For-profit	1.25	1.11	1.40	1.36	1.20	1.54	1.35	1.19	1.53
Nonprofit	1.18	1.01	1.39	1.23	1.04	1.46	1.23	1.04	1.46

Note. *All models are based on SAS GLIMMIX procedure to account for within facility correlations.

†Model 1 adjusted for patient and facility characteristics, not including injectable use.

‡Model 3 adjusted for patient and facility characteristics, including injectable use.

FP, for-profit; HR, hazard ratio; NP, nonprofit.

Table 5: Hazard Ratios for Mortality by Dialysis Facility Organizational Status Based on Model 3 Controlling for Individual Injectable Drugs

Facility Type	Epoetin			Iron			Vitamin D		
	HR	Lower CI	Upper CI	HR	Lower CI	Upper CI	HR	Lower CI	Upper CI
Large chain									
FP chain 1	1.27	1.12	1.43	1.25	1.11	1.42	1.26	1.10	1.44
FP chain 2	1.29	1.14	1.45	1.28	1.13	1.44	1.29	1.13	1.48
FP chain 3	1.32	1.16	1.51	1.32	1.15	1.50	1.35	1.17	1.55
NP chain 4	Ref			Ref			Ref		
Medium chain									
For-profit	1.29	1.13	1.47	1.28	1.12	1.46	1.30	1.13	1.49
Nonprofit	1.24	1.04	1.48	1.28	1.07	1.53	1.30	1.09	1.56
Small/Nonchain									
For-profit	1.32	1.17	1.49	1.35	1.19	1.52	1.37	1.21	1.56
Nonprofit	1.17	0.99	1.39	1.23	1.04	1.46	1.24	1.05	1.47

FP, for-profit; HR, hazard ratio; NP, nonprofit.

and whether the use of injectable drugs mediates the effect of facility organizational status on patient mortality. Notably, the reduction in hazard ratios for organizational status from *Model 1* to *Model 3* was not statistically significant as determined by the Sobel test ($p = .63$). The nonsignificant results of the Sobel test were anticipated as in *Model 3*; the relationship between use of injectable drugs and patient mortality was not found to be significant based on both the summary measure and each of the injectable drugs separately analyzed (Appendix Table A1). The only exception is vitamin D use, which was found to be inversely associated with patient mortality but was found to be only marginally significant. Similarly, the model was run separately by adjusting for *each* of the injectable medication individually (Table 5). Again, the change in the point estimate (regression coefficient) associated with facility organization status from *Model 1* to *Model 3* was small and nonsignificant. In summary, Tables 4 and 5 show that use of injectables (though predicted by facility organizational status) was not a significant mediator in the relationship between facility organizational status and patient mortality. Appendix Table S2 presents the significant associations between covariates adjusted in Model 3 and patient mortality. Although these factors are not the primary interests of the study, they provide a risk profile related to commonly used case mix adjustment to account for imbalances in the ESRD population. Predictably, the largest HRs in this model were associated with age; other factors that were

associated with at least 30 percent increase or decrease in risk of death included patient race, Hispanic ethnicity, BMI, baseline hospitalizations, baseline epoetin dose and achieved hematocrit, and patient's Charlson Index score. Among all the facility characteristics, geographic region was found to have the largest impact on mortality.

To add flexibility to the GLIMMIX model, cubic spline functions for continuous epoetin, iron, and vitamin D doses with knots located at 5th, 25th, 75th, and 95th percentiles were used and the results did not change. We performed an analysis to test the proportional hazards assumption by examining the interaction effect between organizational status and follow-up time (cubic splines). Results were not found to be significant, so the proportional hazards model assumption is justified. We also considered the possibility that the survival advantage of Chain 4 might have been due to informative censoring. Frequency of censoring was not found to be different by facility organizational status. To test the potential effect of informative censoring, however, analyses were repeated without censoring, that is, assuming all patients survived until the end of the study. Results were similar to our main findings (data not shown). Finally, we performed analyses to address potential endogeneity introduced by adjusting for endogenous variables that might be affected by facility organizational status and also affect patient outcomes. Specifically, we removed all comorbidity variables measured *after dialysis was initiated* (e.g., Charlson Index, total inpatient days, and baseline hematocrit values) and retained only those comorbid variables measured prior to dialysis (e.g., cause of ESRD, predialysis lab values, and cardiovascular and other comorbidities existing at the time of dialysis initiation). Similar results to those presented in Table 4 were observed.

DISCUSSION

Variations in treatment practice patterns across more than 4,000 U.S. dialysis facilities are well established (Fink et al. 2001; Thamer et al. 2007; Hirth et al. 2010; Tangri et al. 2010). Determining which dialysis practices are associated with the best patient outcomes has been the focus of recent research in ESRD (Port and Eknoyan 2004; Robinson and Port 2009). In an earlier study, we found significant variations in mortality rates while controlling for injectable drug use (Zhang, Cotter, and Thamer 2011). In this study, we extended our analysis to further examine the role of dialysis facility-level patterns of IV epoetin, IV iron, and IV vitamin D use, which has been and continues to be a

subject of considerable controversy. Practice patterns for all three injectable drugs were found to be significantly different based on dialysis facility organizational status. Consistent with a 2007 *JAMA* study by the same authors (Thamer et al. 2007), the current research also showed that large for-profit chain facilities administered higher epoetin dosages and in addition higher vitamin D dosages, compared with all other facilities. The nation's largest two for-profit dialysis chains administered the largest amount of iron. Notably, facilities that used higher epoetin doses tended to use higher vitamin D and iron doses. Because of the ability of iron and vitamin D to enhance the response to epoetin (Albitar et al. 1997; Coyne et al. 2007), it was posited that epoetin doses would have been inversely associated with iron and vitamin D doses. In other words, it does not make clinical sense to use higher doses of all three injectable drugs.

Why do large for-profit chains prescribe higher doses of injectables than not-for-profit chain and nonchain facilities? Financial incentives are thought to have played a large role in the practice patterns observed in our study. Prior to 2011, outpatient dialysis was billed at a fixed (and deemed by many), stagnant composite rate (Hirth 2007; Public Law), whereas intravenous medications were billed separately on the basis of dose. Facilities administering higher than average doses of injectable drugs could earn greater profit, creating a financial incentive toward greater use of IV medications to enhance the profitability of dialysis facilities (Medicare Payment Advisory Commission [MedPAC] 2001; Wish 2006). For example, Medicare payments for epoetin, \$1.8 to \$2.0 billion each year between 2004 and 2009, were the second largest source of facility income, comprising approximately 22 percent (Office of Inspector General 2004; USRDS 2011). Medicare IV iron and IV vitamin D expenditures both rose to new high levels of \$286 million and \$509 million in 2009, respectively. Consequently, the extent of injectable medication use can be seen as a measure of susceptibility to financial incentives of a dialysis facility (Hirth 2007).

In contrast to financial incentives, an alternative explanation of these findings is that patients from for-profit chains might have characteristics that are associated with a greater need for injectable medications. However, the adjusted analyses controlling for a wide range of patient- and facility-level factors did not explain the observed differences in the use of injectable medications. In fact, previous analyses by Szczech et al. suggest that patients in for-profit facilities have characteristics that would make them *more responsive* to epoetin and iron (requiring smaller doses of both) (Szczech et al. 2006). Specifically, patients treated in for-profit facilities had higher adequacy of dialysis,

serum albumin, transferrin saturation, and ferritin levels, known factors to increase anemia treatment response (Kanbay et al. 2010).

Previous research has not examined the potential mediating effect of injectable drugs in the relationship between dialysis facility organizational status and patient mortality. Therefore, whether the observed differences among dialysis units in the use of injectable drugs might explain survival differences in the ESRD population remains unknown. In our study, injectable drugs were *not* found to mediate the relationship between organizational status and mortality. In other words, higher use of injectable drugs did not *further* explain the higher mortality rates among large- and medium-sized for-profit chains compared with the sole large nonprofit chain. There are several potential explanations for this finding. First, our findings are, in part, due to the lack of association between injectable drug use and patient outcomes. Direct causal effect of epoetin, iron, and vitamin D has not been evaluated in large randomized trials and thus issues regarding the effects of aggressive versus conservative dosage of injectable drugs remain unclear and controversial. Existing observational studies of the effect of epoetin, and iron dosing on mortality risk are conflicting (Feldman et al. 2004; Zhang et al. 2004; Kalantar-Zadeh et al. 2005; Messina et al. 2009; Brookhart et al. 2010). Our analysis is supported by recent studies using causal methodologies to control for confounding that suggest higher epoetin (Zhang et al. 2009), iron (Feldman et al. 2004), and vitamin D doses (Tentori et al. 2009) do not confer additional mortality risk or survival benefit in hemodialysis patients. Second, use of higher injectable drug doses might be a surrogate for unmeasured factors that are associated with both worse outcomes and larger doses. These unmeasured factors could include the patient's disease state and/or other unobserved facility characteristics. Third, mediating effects might be diluted by combining vitamin D and iron treatment doses from different analogs; mortality was shown to be higher for patients on calcitriol compared with paricalcitol (different vitamin D analogs) (Tentori et al. 2006).

The finding of a lack of a survival benefit with the use of higher injectable medications is noteworthy. In the absence of a survival benefit, other justifications for injectable drug use are necessary. In the case of epoetin therapy, the Food and Drug Administration (FDA) has removed all quality-of-life benefits previously found on the product label. Currently, the only accepted benefit for epoetin therapy is avoidance of transfusions, which requires an achieved hematocrit of approximately 30 percent (FDA 2012). For most patients, achieving a approximately 30 percent hematocrit requires relatively small epoetin doses. The significant additional costs—both to the patient as a copay

and the taxpayer in additional Medicare expenditure—for drugs that are not improving survival requires yet-to-be-established justifications.

After two decades of relative stability in the ESRD payment system, a new Prospective Payment System (PPS) has bundled separately billable items (primarily injectable medications and nonroutine laboratory tests) into the composite rate for dialysis services. Under PPS, facilities have no financial incentive to use more drugs or higher doses than are clinically necessary, generating greater savings for taxpayers (GAO 2007). However, a bundled prospective payment raises concerns that some providers might furnish fewer services than might be medically needed (Meyer and Kassirer 2002). Thus, patient care might be compromised for the sake of profit margins (in this case, profits associated with underdosing) (Medicare Payment Advisory Commission [MedPAC] 2003a,b). Based on our study findings, and the caveat that providers will not excessively lower doses, it appears that Medicare ESRD patients are not at risk for diminished survival of lowered doses already evident post-PPS (DOPPS Practice Monitor [DPM] 2012).

The findings reported herein should be considered in the context of an observational study and its inherent limitations. In particular, selection bias likely still exists, despite our considerable efforts to control for numerous patient- and facility-level characteristics. For-profit facilities tend to locate in certain economically advantageous areas, instead of locating randomly (Norton and Staiger 1994; Hirth 1997), and this is difficult to adjust for, although it is reflected in our finding that geographic region is the most important predictor of mortality. Similarly, adjusting for income differences as we did might not fully address differences in available medical resources and other amenities found outside the dialysis unit. Several factors that might affect quality differences across the various dialysis facilities, such as length of dialysis treatment time (Fan et al. 2005), adherence to prescribed dialysis time (Leggat 2005), affiliation of dialysis units with academic medical centers (Kalantar-Zadeh, Mehrotra, and Kopple 2003), physicians' bed-side time and patient counseling (Ronco and Marcelli 1999), vascular access and nutritional management, and patient education (Mehrotra and Kopple 2001), are not observed.

The current research examined whether differences in the use of injectable drugs provides one explanation of variation in patient mortality among dialysis facilities. Although there is a strong association between dialysis organizational status and use of injectable drugs, neither harm nor benefit in terms of survival was found to be mediated through the use of injectable drugs. Given the patients from certain dialysis providers had significantly increased

mortality, other practice patterns need to be examined to provide an improved understanding of the relationship between dialysis facility chain status, ownership, and outcomes. In particular, the practice patterns of Chain 4 that are potentially beneficial to patients need to be further explored and identified.

ACKNOWLEDGMENTS

Joint Acknowledgment/Disclosure Statement: The research for this article was supported by the Agency for Healthcare Research and Quality grant R03-HS018697-01. AHRQ had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the study for publication. The data reported here have been supplied by the U.S. Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as the official policy or interpretation of the U.S. government.

Disclosures: None.

Disclaimers: None.

REFERENCES

- Albitar, S., R. Genin, M. Fen-Chong, M. O. Serveaux, D. Schohn, and C. Chuet. 1997. "High-dose Alfacalcidol Improves Anaemia in Patients on Haemodialysis." *Nephrology, Dialysis, Transplantation* 12 (3): 514–8.
- Austin, P. C., J. V. Tu, and D. A. Alter. 2003. "Comparing Hierarchical Modeling with Traditional Logistic Regression Analysis among Patients Hospitalized with Acute Myocardial Infarction: Should We Be Analyzing Cardiovascular Outcomes Data Differently?" *American Heart Journal* 145 (1): 27–35.
- Baron, R. M., and D. A. Kenny. 1986. "The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations." *Journal of Personality and Social Psychology* 51 (6): 1173–82.
- Brookhart, M. A., S. Schneeweiss, J. Avorn, B. D. Bradbury, J. Liu, and W. C. Winkelmayr. 2010. "Comparative Mortality Risk of Anemia Management Practices in Incident Hemodialysis Patients." *Journal of the American Medical Association* 303 (9): 857–64.
- Christiansen, C. L., and C. N. Morris. 1997. "Improving the Statistical Approach to Health Care Provider Profiling." *Annals of Internal Medicine* 127 (8 Pt 2): 764–8.
- Coyne, D. W., T. Kapoian, W. Suki, A. K. Singh, J. E. Moran, N. V. Dahl, A. R. Rizkala, and D. S. Group. 2007. "Ferric Gluconate Is Highly Efficacious in Anemic Hemodialysis Patients with High Serum Ferritin and Low Transferrin Saturation:

- Results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study." *Journal of the American Society of Nephrology* 18 (3): 975–84.
- D'Agostino, R. B., M. L. Lee, A. J. Belanger, L. A. Cupples, K. Anderson, and W. B. Kannel. 1990. "Relation of Pooled Logistic Regression to Time Dependent Cox Regression Analysis: The Framingham Heart Study." *Statistics in Medicine* 9 (12): 1501–15.
- Department of Health and Human Services (DHHS), Office of Inspector General. 2004. *Medicare Reimbursement for Existing End-Stage Renal Disease Drugs*. OEI-03-04-00120. Washington, DC: DHHS, OIG.
- Devereaux, P. J., H. J. Schunemann, N. Ravindran, M. Bhandari, A. X. Garg, P. T. Choi, B. J. Grant, T. Haines, C. Lacchetti, B. Weaver, J. N. Lavis, D. J. Cook, D. R. Haslam, T. Sullivan, and G. H. Guyatt. 2002. "Comparison of Mortality between Private for-Profit and Private Not-for-Profit Hemodialysis Centers: A Systematic Review and Meta-Analysis." *Journal of the American Medical Association* 288 (19): 2449–57.
- DOPPS Practice Monitor (DPM). 2012. "Emerging Trends in Clinical Dialysis Care" [accessed on August 2010 to August 2011]. Available at http://www.dopps.org/DPM/DPM_highlights.pdf
- Fan, Q., J. Liu, J. P. Ebben, and A. J. Collins. 2005. "Reuse-Associated Mortality in Incident Hemodialysis Patients in the United States, 2000 to 2001." *American Journal of Kidney Diseases* 46 (4): 661–8.
- Feldman, H. I., M. Joffe, B. Robinson, J. Knauss, B. Cizman, W. Guo, E. Franklin-Beccker, and G. Faich. 2004. "Administration of Parenteral Iron and Mortality among Hemodialysis Patients." *Journal of the American Society of Nephrology* 15 (6): 1623–32.
- Fink, J. C., S. A. Blahut, A. E. Briglia, J. F. Gardner, and P. D. Light. 2001. "Effect of Center- versus Patient-Specific Factors on Variations in Dialysis Adequacy." *Journal of the American Society of Nephrology* 12 (1): 164–9.
- Food and Drug Administration (FDA). 2012. "FDA Drug Safety Communication: Modified Dosing Recommendations to Improve the Safe Use of Erythropoiesis-Stimulating Agents (ESAs) in Chronic Kidney Disease" [accessed on November 8, 2012]. Available at <http://www.fda.gov/drugs/drugsafety/ucm259639.htm>
- Garg, P. P., K. D. Frick, M. Diener-West, and N. R. Powe. 1999. "Effect of the Ownership of Dialysis Facilities on Patients' Survival and Referral for Transplantation." *New England Journal of Medicine* 341 (22): 1653–60.
- Government Accountability Office (GAO). 2006. "Report to the Chairman, Committee on Ways and Means, House of Representatives. End-Stage Renal Disease: Bundling Medicare's Payment for Drugs with Payments for All ESRD Services Would Promote Efficiency and Clinical Flexibility." GAO Publication No. GAO-07-77.
- Government Accountability Office (GAO). 2007. "End-stage Renal Disease: Medicare Should Pay a Bundled Rate for All ESRD Items and Services." GAO Publication No. GAO-07-1050T.

- Government Accountability Office (GAO). 2010. "CMS Should Monitor Access to and Quality of Dialysis Care Promptly after Implementation of New Bundled Payment System." GAO Publication No. GAO-10-295.
- Hirth, R. A. 1997. "Competition between for-Profit and Nonprofit Health Care Providers: Can It Help Achieve Social Goals?" *Medical Care Research and Review* 54 (4): 414–38.
- . 2007. "The Organization and Financing of Kidney Dialysis and Transplant Care in the United States of America." *International Journal of Health Care Finance and Economics* 7 (4): 301–18.
- Hirth, R. A., M. N. Turenne, J. R. Wheeler, Y. Ma, and J. M. Messana. 2010. "Do Resource Utilization and Clinical Measures Still Vary across Dialysis Chains after Controlling for the Local Practices of Facilities and Physicians?" *Medical Care* 48 (8): 726–32.
- Irvin, R. A. 2000. "Quality of Care Differences by Ownership in United States Renal Dialysis Facilities." *ASAIO Journal* 46 (6): 775–8.
- Kalantar-Zadeh, K., R. Mehrotra, and J. D. Kopple. 2003. "Quality of Care in Profit vs Not-for-Profit Dialysis Centers." *Journal of the American Medical Association* 289 (23): 3089; author reply 89–90.
- Kalantar-Zadeh, K., D. L. Regidor, C. J. McAllister, B. Michael, and D. G. Warnock. 2005. "Time-Dependent Associations between Iron and Mortality in Hemodialysis Patients." *Journal of the American Society of Nephrology* 16 (10): 3070–80.
- Kanbay, M., M. A. Perazella, B. Kasapoglu, M. Koroglu, and A. Covic. 2010. "Erythropoiesis Stimulatory Agent- Resistant Anemia in Dialysis Patients: Review of Causes and Management." *Blood Purification* 29 (1): 1–12.
- Leggat Jr, J. E. 2005. "Adherence with Dialysis: A Focus on Mortality Risk." *Seminars in Dialysis* 18 (2): 137–41.
- Medicare Payment Advisory Commission (MedPAC). 2001. *Report to the Congress: End-stage Renal Disease Payment Policies in Traditional Medicare*, pp. 123–38. Washington, DC: MedPAC.
- Medicare Payment Advisory Commission (MedPAC). 2003a. *Report to the Congress: End-stage Renal Disease Payment Policies in Traditional Medicare*, pp. 91–98. Washington, DC: MedPAC.
- Medicare Payment Advisory Commission (MedPAC). 2003b. *Report to the Congress: Medicare Payment Policy. Chapter 6: Quality of Dialysis Care and Providers' Costs*. Washington, DC: MedPAC.
- Mehrotra, R., and J. D. Kopple. 2001. "Nutritional Management of Maintenance Dialysis Patients: Why Aren't We Doing Better?" *Annual Review of Nutrition* 21: 343–79.
- Messana, J. M., C. C. Chuang, M. Turenne, J. Wheeler, J. Turner, K. Sleeman, P. Tedeschi, and R. Hirth. 2009. "Association of Quarterly Average Achieved Hematocrit with Mortality in Dialysis Patients: A Time-Dependent Comorbidity-Adjusted Model." *American Journal of Kidney Diseases* 53 (3): 503–12.
- Meyer, K. B., and J. P. Kassirer. 2002. "Squeezing More Cost and Care Out Of Dialysis: Our Patients Would Pay the Price." *American Journal of Medicine* 112 (3): 232–4.

- Norton, E. C., and D. O. Staiger. 1994. "How Hospital Ownership Affects Access to Care for the Uninsured." *RAND Journal of Economics* 25 (1): 171–85.
- Office of Inspector General. 2004. *Medicare Reimbursement for Existing End-stage Renal Disease Drugs*. Washington, DC: OIG Publication. Publication no. OEI-03-04-00120.
- Palmer, S. C., D. O. McGregor, P. Macaskill, J. C. Craig, G. J. Elder, and G. F. Strippoli. 2007. "Meta-Analysis: Vitamin D Compounds in Chronic Kidney Disease." *Annals of Internal Medicine* 147 (12): 840–53.
- Pfeffer, M. A., E. A. Burdmann, C. Y. Chen, M. E. Cooper, D. de Zeeuw, K. U. Eckardt, J. M. Feyzi, P. Ivanovich, R. Kewalramani, A. S. Levey, E. F. Lewis, J. B. McGill, J. J. McMurray, P. Parfrey, H. H. Parving, G. Remuzzi, A. K. Singh, S. D. Solomon, R. Toto, and T. Investigators. 2009. "A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease." *New England Journal of Medicine* 361 (21): 2019–32.
- Port, F. K., and G. Eknoyan. 2004. "The Dialysis Outcomes and Practice Patterns Study (DOPPS) and the Kidney Disease Outcomes Quality Initiative (K/DOQI): A Cooperative Initiative to Improve Outcomes for Hemodialysis Patients Worldwide." *American Journal of Kidney Diseases* 44 (5 Suppl 2): 1–6.
- Public Law. No.108-173, 623(a), 117 Stat. 2066:2315.
- Rice, N., and A. Leyland. 1996. "Multilevel Models: Applications to Health Data." *Journal of Health Services Research and Policy* 1 (3): 154–64.
- Robinson, B. M., and F. K. Port. 2009. "International Hemodialysis Patient Outcomes Comparisons Revisited: The Role of Practice Patterns and Other Factors." *Journal of the American Society of Nephrology* 4 (Suppl 1): S12–7.
- Ronco, C., and D. Marcelli. 1999. "Options Regarding Outcome Differences in European and US Haemodialysis Patients." *Nephrology, Dialysis, Transplantation* 14: 2616–20.
- Rozen-Zvi, B., A. Gafter-Gvili, M. Paul, L. Leibovici, O. Shpilberg, and U. Gafter. 2008. "Intravenous versus Oral Iron Supplementation for the Treatment of Anemia in CKD: Systematic Review and Meta-Analysis." *American Journal of Kidney Diseases* 52 (5): 897–906.
- Singer, J. D. 1998. "Using SAS PROC MIXED to Fit Multilevel Models, Hierarchical Models, and Individual Growth Models." *Journal of Educational and Behavioral Statistics* 23 (4): 323–55.
- Singh, A. K., L. Szczech, K. L. Tang, H. Barnhart, S. Sapp, M. Wolfson, D. Reddan, and C. Investigators. 2006. "Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease." *New England Journal of Medicine* 355 (20): 2085–98.
- Sobel, M. E. 1982. "Asymptotic Confidence Intervals for Indirect Effects in Structural Equation Models." In *Sociological Methodology 1982*, edited by S. Leinhardt, pp. 290–312. Washington, DC: American Sociological Association.
- Steinbrook, R. 2006. "Haemoglobin Concentrations in Chronic Kidney Disease." *Lancet* 368 (9554): 2191–3.
- Szczech, L. A., P. S. Klassen, B. Chua, S. S. Hedayati, M. Flanigan, W. M. McClellan, D. N. Reddan, R. A. Rettig, D. L. Frankenfield, and W. F. Owen Jr. 2006. "Associations between CMS's Clinical Performance Measures Project Benchmarks,

- Profit Structure, and Mortality in Dialysis Units." *Kidney International* 69 (11): 2094–100.
- Szczzech, L. A., H. X. Barnhart, S. Sapp, G. M. Felker, A. Hernandez, D. Reddan, R. M. Califf, J. K. Inrig, U. D. Patel, and A. K. Singh. 2010. "A Secondary Analysis of the CHOIR Trial Shows that Comorbid Conditions Differentially Affect Outcomes during Anemia Treatment." *Kidney International* 77 (3): 239–46.
- Tangri, N., R. Moorthi, H. Tighiouhart, K. B. Meyer, and D. C. Miskulin. 2010. "Variation in Fistula Use across Dialysis Facilities: Is It Explained by Case-Mix?" *Journal of the American Society of Nephrology* 5 (2): 307–13.
- Tentori, F., W. C. Hunt, C. A. Stidley, M. R. Rohrscheib, E. J. Bedrick, K. B. Meyer, H. K. Johnson, and P. G. Zager, and I. Medical Directors of Dialysis Clinic. 2006. "Mortality Risk among Hemodialysis Patients Receiving Different Vitamin D Analogs." *Kidney International* 70 (10): 1858–65.
- Tentori, F., J. M. Albert, E. W. Young, M. J. Blayney, B. M. Robinson, R. L. Pisoni, T. Akiba, R. N. Greenwood, N. Kimata, N. W. Levin, L. M. Piera, R. Saran, R. A. Wolfe, and F. K. Port. 2009. "The Survival Advantage for Haemodialysis Patients Taking Vitamin D Is Questioned: Findings from the Dialysis Outcomes and Practice Patterns Study." *Nephrology, Dialysis, Transplantation* 24 (3): 963–72.
- Thamer, M., Y. Zhang, J. Kaufman, D. Cotter, F. Dong, and M. A. Hernan. 2007. "Dialysis Facility Ownership and Epoetin Dosing in Patients Receiving Hemodialysis." *Journal of the American Medical Association* 297 (15): 1667–74.
- United States Renal Data System (USRDS). 2006. *USRDS 2008 Annual Data Report: Atlas of End-stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
- United States Renal Data System (USRDS). 2007. *USRDS 2008 Annual Data Report: Atlas of End-stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
- United States Renal Data System (USRDS). 2011. *USRDS 2008 Annual Data Report: Atlas of End-stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
- Wish, J. B. 2006. "The Economic Realities of Erythropoiesis-Stimulating Agent Therapy in Kidney Disease." *Kidney International* 70: S21–5.
- Zhang, Y., D. J. Cotter, and M. Thamer. 2011. "The Effect of Dialysis Chains on Mortality among Patients Receiving Hemodialysis." *Health Services Research* 46 (3): 747–67.
- Zhang, Y., M. Thamer, K. Stefanik, J. Kaufman, and D. J. Cotter. 2004. "Epoetin Requirements Predict Mortality in Hemodialysis Patients." *American Journal of Kidney Diseases* 44 (5): 866–76.
- Zhang, Y., M. Thamer, D. Cotter, J. Kaufman, and M. A. Hernan. 2009. "Estimated Effect of Epoetin Dosage on Survival among Elderly Hemodialysis Patients in the United States." *Journal of the American Society of Nephrology* 4 (3): 638–44.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.

Appendix SA2: Adjusted Hazard Ratios for Mortality Based on Different Injectable Drug Measures.