Which Targets in Clinical Practice Guidelines Are Associated with Improved Survival in a Large Dialysis Organization?

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ABSTRACT

Professional organizations have developed practice guidelines in the hope of improving clinical outcomes. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) has set targets for dialysis dosage (single-pool Kt/V), hematocrit, serum albumin, calcium, phosphorus, parathyroid hormone, and BP for hemodialysis (HD) patients. Several guidelines are largely based on results from observational studies. In contrast to other parameters, BP values within the KDOQI guidelines have been associated with increased mortality. Therefore, it was postulated that having multiple parameters that satisfy the current guidelines, except those for BP, is associated with improved survival among HD patients. A retrospective analysis was conducted of incident HD patients who were treated at facilities operated by Dialysis Clinic Inc., a not-for-profit dialysis provider, between January 1, 1998, and December 31, 2004 (n = 13,792). Cox proportional hazards models were used to assess the association between satisfying guidelines and mortality. Values within guidelines for single-pool Kt/V, hematocrit, serum albumin, calcium, phosphorus, and parathyroid hormone were associated with decreased mortality ($P \leq 0.0001$). The largest survival benefit was found for serum albumin (hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.24 to 0.31). Satisfying these six guidelines simultaneously was associated with an 89% reduction in mortality (HR 0.11; 95% CI 0.06 to 0.19]). Conversely, BP values satisfying the guideline were associated with increased mortality (HR 1.90; 95% CI 1.73 to 2.10). Because this target was largely extrapolated from the general population, a randomized, controlled trial is needed to identify the optimal BP for HD patients.

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Increasing attention to the delivery of high-quality care has led many professional health care organizations to develop clinical practice guidelines. These guidelines define standards of care and are intended to reduce variability in practice patterns and improve clinical outcomes. Interest in "pay-for-performance"[1] is expected to accelerate the implementation of practice guidelines.[2]

In an effort to improve clinical outcomes among patients with ESRD, the National Kidney Foundation (NKF) launched the Dialysis Outcomes Quality Initiative (DOQI) clinical practice guidelines in 1995. In 1999, the program was extended to earlier stages of chronic kidney disease and was renamed the Kidney Disease Outcomes Quality Initiative (KDOQI). Work groups composed of domain ex-

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perts formulate clinical practice guidelines on the basis of structured evidence review. In the absence of definitive published clinical data, expert opinion has influenced some guideline recommendations. This process led to the publication of KDOQI practice guidelines and target ranges for several parameters that cover many aspects of care for hemodialysis (HD) patients, including dialysis dosage,[3] anemia,[4] nutrition,[5] bone and mineral metabolism[6] and cardiovascular disease.[7] Most recently, updates on anemia,[8] dialysis adequacy, and vascular access[9] have been published.

Several investigators have reported decreased mortality among patients who satisfy KDOQI guidelines for individual parameters, including dialysis dosage, serum albumin, anemia, and mineral metabolism.[10–13] HD patients who had arteriovenous fistulas and satisfied guidelines for dialysis dosage, serum albumin, and anemia simultaneously had fewer hospitalizations and lower mortality during a 1-yr follow-up[14] than patients who did not satisfy all three of these guidelines. Similar results were recently shown in the ESRD Quality (EQUAL) study, a prospective study of process of care and outcomes in HD.[15] However, no previously published studies examined mortality among patients who simultaneously satisfied anemia, dialysis dosage, calcium, phosphorus, and parathyroid hormone (PTH) guidelines.

The evidence supporting the current KDOQI guidelines was not always derived from randomized, controlled trials in the target population. Specifically, the BP target ranges were extrapolated from the general population; therefore, the evidence was graded as weak. Despite these limitations, professional organizations and large dialysis organizations have urged health care providers to attempt to achieve the recommended BP targets. However, to our knowledge, no studies have examined the relationship between BP values that satisfy the KDOQI targets and mortality. This is an important issue, because HD patients with mild to moderate hypertension may have a lower mortality risk compared with patients whose BP satisfies the current target.[16–18] Therefore, it is reasonable to postulate that adherence to the current BP guideline may have a detrimental effect on survival. This study was designed to explore the relationships between all-cause mortality and satisfying KDOQI guidelines for dialysis dosage (single-pool Kt/V [spKt/V]), hematocrit, serum albumin, calcium, phosphorus, and PTH individually and in combination. We also assessed the relationship between BP values that satisfy the KDOQI guideline and mortality.

RESULTS

A total of 13,792 patients met the inclusion criteria. Follow-up began 120 d after start of HD and continued until death ($n = 5270$); kidney transplantation ($n = 1184$); switch to peritoneal dialysis ($n = 372$); absence from Dialysis Clinic Inc. (DCI) for >90 d ($n = 2585$); or the end of follow-up on December 31, 2005 ($n = 4381$). Median follow-up was 569 d. The study sample was representative of the United States Renal Data System incident cohort with respect to the distributions of age, gender, and cause of ESRD (Table 1). However, because of the large sample size, even small differences in age and cause of ESRD attained statistical significance. Black patients were slightly overrepresented in the study sample. Overall, the proportion of patients who satisfied guidelines at baseline was extremely low (Table 1). For instance, only 19% of participants had hematocrit ≥33% at baseline.

Values Satisfying KDOQI Guidelines over Time after Initiation of HD

The proportion of patients who satisfied guidelines during each quarter after the start of HD is shown for the subset of patients who were followed for at least 12 quarters ($n = 4002$; Figure 1). Overall, the proportion of patients who satisfied guidelines increased over the 12 quarters ($P < 0.001$). However, the proportion who satisfied the serum calcium guideline declined ($P < 0.001$) and the proportion who satisfied the phosphorus guideline did not change significantly. To rule out

Table 1. Demographic and clinical characteristics of the study sample and USRDS 1999 to 2002 incident cohort aged ≥20 yr[a]

Characteristic	Study Population (%) ($n = 13,792$)	USRDS (%) ($n = 366,907$)
Age (yr)[b]		
20 to 44	15.2	13.9
45 to 64	38.4	35.6
65 to 74	24.8	25.5
≥75	21.6	25.0
Gender		
female	46.5	46.4
male	53.5	53.6
Race[b]		
white	57.5	66.1
black	36.0	29.2
other	6.4	4.6
Cause of ESRD[b]		
diabetes	46.7	44.7
hypertension	24.1	27.3
glomerulonephritis	9.7	8.4
other/unknown	19.5	19.6
Satisfying KDOQI guidelines at baseline[c]		
spKt/V (≥1.2)	56.7	
hematocrit (33 to 36%)	19.2	
albumin (≥4.0 g/dl)	12.0	
calcium (8.4 to 9.5 mg/dl)	57.0	
phosphorus (3.5 to 5.5 mg/dl)	53.2	
PTH (150 to 300 pg/ml)	25.7	
predialysis BP (≤140/90 mmHg)	38.2	

[a]KDOQI, Kidney Disease Outcomes Quality Initiative; PTH, parathyroid hormone; spKt/V, single-pool Kt/V; USRDS, US Renal Data System.
[b]$P < 0.001$ *versus* USRDS incident cohort.
[c]Baseline defined as first value within 60 d of initiating hemodialysis (HD).

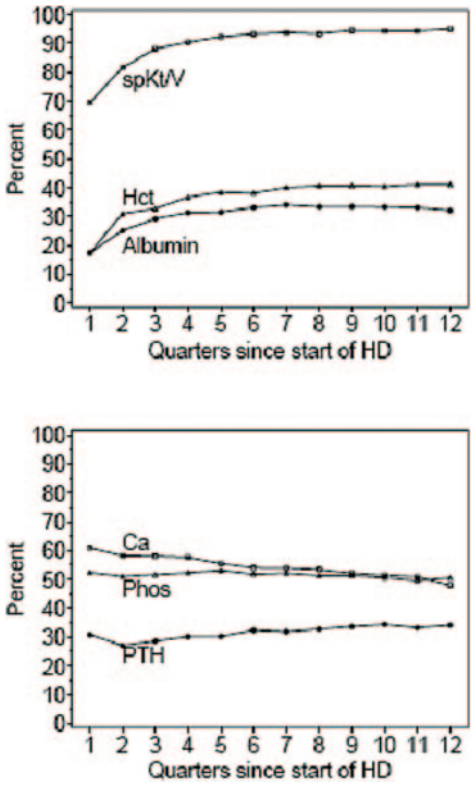

Figure 1. Proportion of patients with values satisfying Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (parameters were defined as satisfying the KDOQI guideline when at least 67% [100% for parathyroid hormone [PTH]) of measurements in the quarter were within the guidelines) over time since first hemodialysis treatment. The analysis was restricted to a cohort of participants who survived ≥3 yr ($n = 4002$). The proportion of patients with values within guidelines for single-pool Kt/V (spKt/V), hematocrit (Hct), albumin, and PTH was significantly higher after 12 quarters on hemodialysis. Values within guideline for serum calcium declined over time ($P < 0.001$ for all parameters). Value within guidelines for phosphorus did not change significantly.

potential selection bias as a result of survival, we conducted similar analyses in the entire study population ($n = 13,792$) and among patients who were followed for at least four quarters ($n = 10,556$). Results were almost identical to those shown in Figure 1 (data not shown).

Associations between Values Satisfying KDOQI Guidelines and Mortality

Hazard ratios (HR) for mortality associated with guideline adherence are shown for each parameter (Table 2). An increase in the proportion of values satisfying the guideline during a 90-d period was associated with decreased mortality for serum albumin, calcium, phosphorus, PTH, spKt/V, and hematocrit. The greatest reduction in mortality was seen in patients who satisfied the serum albumin guidelines for 100% of measurements in the 90-d period (HR 0.27; 95% confidence interval [CI] 0.24 to 0.31). Conversely, satisfying the guideline for at least 75% of predialysis BP measurements was associated with increased mortality (HR 1.90; 95% CI 1.73 to 2.10). Satisfying the guideline for 100% of BP measurements was associated with an HR of 2.32 (95% CI 2.06 to 2.60), although this occurred only 5.2% of the time (data not shown).

To evaluate whether baseline guideline adherence modifies the association between guideline adherence and mortality, we constructed models stratified by the value of the parameter at the beginning of HD (satisfying guidelines *versus* not satisfying guidelines). There was little difference between the two strata, indicating that baseline values do not significantly change the relationship between guideline adherence and mortality.

Satisfying guidelines for multiple laboratory parameters simultaneously was associated with decreased mortality. The HR for mortality decreased as the number of parameters for which guidelines were satisfied increased from one to six (Table 3). Compared with patients who satisfied guidelines on zero parameters, patients who satisfied guidelines for all six parameters simultaneously experienced an 89% reduction in mortality (HR 0.11; 95% CI 0.06 to 0.19). However, only a small proportion of patients satisfied guidelines for all six parameters. The median number of parameters satisfying guidelines was three, and the associated HR was 0.39 (95% CI 0.31 to 0.49).

The associations of mortality with guideline adherence were generally homogeneous across categories of age, gender, race, cause of ESRD, and year of diagnosis. However, a few significant differences were observed (Table 4). Satisfying guidelines for spKt/V was more strongly associated with improved survival for patients who were 65 yr or older than for patients who were 45 to 64 yr of age. The association between guideline adherence for hematocrit and improved survival was stronger for patients who began HD in 2001 to 2004 than among those who began HD in 1998 to 2000. Guideline adherence for hematocrit and PTH were more strongly associated with improved survival among patients with glomerulonephritis than among those in whom diabetes or hypertension caused ESRD. BP values satisfying guidelines were associated with increased mortality in all groups except among patients aged 20 to 45 yr. This association was stronger among patients with diabetes than among patients whose ESRD was due to glomerulonephritis or hypertension.

DISCUSSION

This study confirms a previous report that simultaneous achievement of dialysis dosage, anemia, and serum albumin targets was associated with a marked reduction in mortality[14,15] and extends these observations to include serum calcium, phosphorus, and PTH targets. We show that for all parameters, the proportion of patients who satisfied guidelines was low at the beginning of HD. Over time, the proportion of patients who satisfied the guidelines increased for some (spKt/V, hematocrit, albumin, and PTH) but not all (calcium and phosphorus) parameters. Although it occurred infre-

Table 2. HR (95% CI) for mortality associated with satisfying KDOQI guidelines stratified by baseline value (outside *versus* within guideline)[a]

No. of Values Satisfying KDOQI Guidelines	Frequency (%)	All Patients (HR [95% CI])	Outside Guideline at Baseline (HR [95% CI])	Within Guideline at Baseline (HR [95% CI])
spKt/V (≥1.2)				
0 of 3	4.3	1.00	1.00	1.00
1 of 3	5.9	0.89 (0.76 to 1.05)	0.92 (0.76 to 1.12)	0.74 (0.54 to 1.00)
2 of 3	13.5	0.77 (0.67 to 0.89)	0.72 (0.61 to 0.87)	0.70 (0.54 to 0.91)
3 of 3	76.3	0.60 (0.53 to 0.69)	0.59 (0.50 to 0.70)	0.52 (0.40 to 0.66)
Hematocrit (33 to 36%)				
0 of 3	28.1	1.00	1.00	1.00
1 of 3	36.5	0.88 (0.82 to 0.94)	0.86 (0.80 to 0.93)	0.95 (0.81 to 1.11)
2 of 3	25.4	0.81 (0.75 to 0.87)	0.80 (0.74 to 0.87)	0.85 (0.71 to 1.01)
3 of 3	10.0	0.68 (0.61 to 0.76)	0.65 (0.58 to 0.74)	0.80 (0.63 to 1.02)
Albumin (≥4.0 g/dl)				
0 of 3	56.2	1.00	1.00	1.00
1 of 3	15.4	0.51 (0.47 to 0.56)	0.50 (0.45 to 0.55)	0.68 (0.53 to 0.86)
2 of 3	12.4	0.41 (0.36 to 0.46)	0.43 (0.38 to 0.48)	0.40 (0.30 to 0.53)
3 of 3	16.0	0.27 (0.24 to 0.31)	0.30 (0.26 to 0.34)	0.24 (0.18 to 0.32)
Calcium (8.4 to 9.5 mg/dl)				
0 of 3	25.7	1.00	1.00	1.00
1 of 3	20.3	0.96 (0.89 to 1.04)	0.97 (0.86 to 1.08)	0.97 (0.88 to 1.08)
2 of 3	24.1	0.90 (0.83 to 0.97)	0.86 (0.77 to 0.97)	0.92 (0.83 to 1.02)
3 of 3	29.9	0.80 (0.74 to 0.86)	0.83 (0.73 to 0.93)	0.78 (0.71 to 0.86)
Phosphorus (3.5 to 5.5 mg/dl)				
0 of 3	24.2	1.00	1.00	1.00
1 of 3	25.7	0.95 (0.88 to 1.03)	0.95 (0.86 to 1.06)	0.96 (0.86 to 1.07)
2 of 3	28.1	0.88 (0.81 to 0.95)	0.84 (0.75 to 0.94)	0.92 (0.83 to 1.02)
3 of 3	22.0	0.67 (0.62 to 0.73)	0.70 (0.62 to 0.79)	0.66 (0.58 to 0.74)
PTH (150 to 300 pg/ml)				
0 of 1	69.4	1.00	1.00	1.00
1 of 1	30.6	0.89 (0.83 to 0.95)	0.93 (0.86 to 1.02)	0.85 (0.76 to 0.96)
Predialysis BP (≤140/90 mmHg)				
0 of 12	18.4	1.00	1.00	1.00
1 to 4 of 12	41.9	1.20 (1.09 to 1.32)	1.22 (1.10 to 1.36)	1.13 (0.93 to 1.37)
5 to 8 of 12	21.5	1.40 (1.26 to 1.54)	1.34 (1.19 to 1.51)	1.45 (1.19 to 1.76)
9 to 12 of 12	18.2	1.90 (1.73 to 2.10)	1.76 (1.56 to 2.00)	1.97 (1.64 to 2.37)

[a]Baseline defined as first value within 60 d of initiating HD. Models adjusted for demographic characteristics plus spKt/V for all models other than that for spKt/V and serum albumin for all models other than that for serum albumin. CI, confidence interval; HR, hazard ratio.

quently, satisfying guidelines for all six parameters simultaneously was associated with a marked reduction in mortality.

Table 3. HR (95% CI) for mortality associated with satisfying KDOQI guidelines for multiple laboratory parameters simultaneously[a]

No. of Parameters Satisfying KDOQI Guidelines	Frequency (%)	HR (95% CI)
0	1.1	1.00
1	10.2	0.74 (0.59 to 0.93)
2	26.5	0.52 (0.42 to 0.65)
3	32.6	0.39 (0.31 to 0.49)
4	21.1	0.30 (0.24 to 0.37)
5	7.5	0.19 (0.15 to 0.25)
6	1.0	0.11 (0.06 to 0.19)

[a]A parameter was defined as satisfying the KDOQI guideline when at least two thirds of the individual values during the 90-d period were within the guidelines. Laboratory parameters include hematocrit, serum albumin, calcium, phosphorus, and PTH.

In contrast, having BP values within guidelines was associated with significantly increased mortality.

The relationship between mortality and adherence to guidelines for anemia, dialysis dosage, and serum albumin observed in this study is in concert with a recent report.[14] In both studies, mortality decreased as the number of parameters satisfying guidelines increased. However, Rocco *et al.*[14] examined measurements from a single 3-mo period and the follow-up period was limited to 1 yr. The results of this study are also in agreement with recent studies that examined achievement of guidelines for bone mineral metabolism.[10–13] However, previous studies largely relied on single baseline laboratory values rather than longitudinal monthly data. Using Centers for Medicare and Medicaid data, Wolfe *et al.*[19] demonstrated that facilities in the lowest quintile of guideline adherence for spKt/V and hematocrit had 22 and 14% greater mortality, respectively, compared with facilities in the highest quintile ($P < 0.001$). In the Dialysis Outcomes Practice Pattern Study

Table 4. HR (95% CI) for mortality associated with satisfying KDOQI guidelines stratified by patient characteristics

Parameter	Kt/V (HR [95% CI])[a]	Hematocrit (HR [95% CI])[a]	Albumin (HR [95% CI])[a]	Calcium (HR [95% CI])[a]	Phosphorus (HR [95% CI])[a]	PTH (HR [95% CI])[b]	BP (HR [95% CI])[c]
Age							
20 to 44	0.82 (0.76 to 0.91)[d]	0.71 (0.65 to 0.78)	0.56 (0.50 to 0.62)	0.97 (0.89 to 1.06)	0.91 (0.82 to 1.00)	0.74 (0.57 to 0.95)	0.99 (0.88 to 1.11)[d]
45 to 64	0.88 (0.84 to 0.93)	0.82 (0.78 to 0.85)	0.64 (0.60 to 0.68)	0.94 (0.90 to 0.98)	0.93 (0.88 to 0.97)	0.95 (0.85 to 1.06)	1.32 (1.25 to 1.39)
65 to 74	0.79 (0.74 to 0.83)	0.78 (0.75 to 0.82)	0.65 (0.61 to 0.69)	0.94 (0.90 to 0.98)	0.87 (0.83 to 0.91)	0.91 (0.81 to 1.02)	1.32 (1.25 to 1.38)
≥75	0.79 (0.75 to 0.84)	0.79 (0.76 to 0.83)	0.63 (0.59 to 0.68)	0.90 (0.87 to 0.94)	0.86 (0.82 to 0.90)	0.84 (0.75 to 0.95)	1.22 (1.16 to 1.28)
Gender							
male	0.84 (0.80 to 0.87)	0.80 (0.77 to 0.83)	0.61 (0.58 to 0.64)[d]	0.92 (0.89 to 0.95)	0.86 (0.83 to 0.89)[d]	0.85 (0.78 to 0.93)	1.28 (1.23 to 1.33)
female	0.81 (0.77 to 0.85)	0.78 (0.75 to 0.81)	0.67 (0.63 to 0.70)	0.94 (0.91 to 0.97)	0.92 (0.88 to 0.95)	0.93 (0.85 to 1.02)	1.24 (1.19 to 1.29)
Race							
white	0.84 (0.80 to 0.87)	0.80 (0.78 to 0.83)	0.63 (0.60 to 0.66)	0.93 (0.90 to 0.96)	0.87 (0.85 to 0.90)	0.92 (0.84 to 1.00)	1.28 (1.24 to 1.32)
black	0.82 (0.77 to 0.86)	0.77 (0.74 to 0.81)	0.63 (0.60 to 0.67)	0.93 (0.89 to 0.97)	0.90 (0.86 to 0.94)	0.87 (0.78 to 0.97)	1.22 (1.16 to 1.28)
other	0.81 (0.71 to 0.92)	0.74 (0.67 to 0.83)	0.60 (0.51 to 0.70)	0.95 (0.85 to 1.06)	0.96 (0.86 to 1.08)	0.71 (0.54 to 0.93)	1.27 (1.13 to 1.43)
Cause of ESRD							
diabetes	0.82 (0.78 to 0.85)	0.81 (0.78 to 0.84)[d]	0.66 (0.62 to 0.69)	0.93 (0.90 to 0.96)	0.86 (0.83 to 0.89)	0.95 (0.87 to 1.04)[d]	1.35 (1.30 to 1.41)[d]
hypertension	0.84 (0.79 to 0.90)	0.82 (0.78 to 0.87)	0.63 (0.59 to 0.67)	0.92 (0.88 to 0.97)	0.93 (0.88 to 0.98)	0.94 (0.83 to 1.07)	1.24 (1.18 to 1.31)
glomerulonephritis	0.89 (0.80 to 1.00)	0.77 (0.70 to 0.84)	0.57 (0.50 to 0.64)	0.92 (0.84 to 1.00)	0.95 (0.86 to 1.04)	0.71 (0.55 to 0.91)	1.22 (1.11 to 1.34)
other	0.82 (0.76 to 0.88)	0.72 (0.68 to 0.76)	0.61 (0.57 to 0.66)	0.93 (0.88 to 0.98)	0.88 (0.83 to 0.93)	0.73 (0.62 to 0.85)	1.10 (1.03 to 1.17)
Year of diagnosis							
1999 to 2000	0.83 (0.79 to 0.86)	0.81 (0.78 to 0.84)[d]	0.63 (0.60 to 0.66)	0.93 (0.90 to 0.96)	0.90 (0.86 to 0.93)	0.89 (0.81 to 0.98)	1.27 (1.22 to 1.31)
2001 to 2004	0.83 (0.79 to 0.87)	0.77 (0.74 to 0.79)	0.63 (0.60 to 0.66)	0.93 (0.90 to 0.96)	0.87 (0.84 to 0.91)	0.88 (0.81 to 0.97)	1.26 (1.21 to 1.31)

[a]HR associated with a 33% increase in the proportion of values satisfying KDOQI guidelines. For example, the same hazard would apply for an increase from 0 to 1, from 1 to 2, or from 2 to 3 values within guidelines.
[b]HR associated with 100% of values satisfying KDOQI guidelines.
[c]HR associated with a 33% increase in proportion of values satisfying KDOQI guidelines. For example, the same hazard would apply for an increase from 0 to 4, from 4 to 8, or from 8 to 12 values within guidelines.
[d]HR vary significantly across categories ($P < 0.05$).

(DOPPS), a two-fold increase in mortality was demonstrated among patients with a baseline serum albumin concentration <3.3 g/dl.[11] Noordzij *et al.*[13] demonstrated that elevations in serum phosphorus and calcium-phosphate product were associated with increased mortality.

As in previous studies, the strongest association with reduced mortality was observed for serum albumin ≥4.0 g/dl.[10,11,20,21] The magnitude of the HR associated with satisfying the serum albumin guideline was similar to that observed for satisfying guidelines for serum calcium, phosphorus, PTH, hematocrit, and spKt/V simultaneously. The independent predictive ability of these variables is supported by the multiplicative reduction of HR to a level of 0.11 when all were combined. Although satisfying guidelines for multiple parameters presents a therapeutic challenge, we observed significant increases in guideline adherence for spKt/V, hematocrit, and serum albumin over time. This may reflect in part improved clinical practice patterns and in part survivor bias. Because results of models stratified by baseline values were identical, it is not likely that patient selection contributed to our findings.

Mortality was increased among patients who satisfied guidelines for predialysis BP. These results are in concert with previous studies describing the association between BP and mortality among HD patients.[16,17,22,23] Surprising, despite the current recommended BP target of <130/80 mmHg for patients with diabetes,[7,24] BP values in this range were associated with a greater mortality risk in participants with than without diabetes. This may reflect the likely higher prevalence of cardiac and/or autonomic dysfunction among patients with diabetes.[25] Unfortunately, data on these conditions were not routinely collected in DCI's medical information system during the study period.

The evidence in support of the current BP guidelines was largely extrapolated from the general population and graded as weak.[7] However, in view of the complex pathophysiology of ESRD, the ideal BP target among HD patients may differ from that in the general population.[26–28] Furthermore, clinical practice guidelines extrapolated from the general population may not be applicable to specific groups of patients with multiple comorbidities. Boyd *et al.*[29] recently demonstrated that adhering to guidelines that were developed for the general population may have undesirable effects when applied to the elderly. Therefore, professional associations should exercise caution when promulgating specific guidelines that are not based on evidence obtained in the target population.

This study contains several limitations inherent to retrospective analyses. First, because of the lack of consistently high-quality data, our modeling procedures did not include some potentially important covariates (*e.g.*, medication use, fasting serum lipid profiles, presence or absence of symptomatic intradialytic hypotension).[30–36] Second, it may be argued that our results simply reflect a higher case-mix burden among patients with values that failed to satisfy the guidelines. Our models were adjusted for several case-mix factors that have been shown to be strong determinants of mortality, including age,

race, cause of ESRD, and serum albumin. However, data on comorbid conditions were not available. Although comorbidity has been shown to be significantly associated with mortality even after accounting for serum albumin and other case-mix factors,[37] a recent study showed that its contribution to a survival model is not as large as expected. In this analysis of the European Renal Association Registry, comorbidity explained only 1.9% of the variance in mortality, whereas 14.4% was explained by age, gender, primary renal disease, treatment modality, and country.[38] These observations suggest that although the absence of these data is a limitation, it is unlikely that our results would significantly change if comorbidity were accounted for. Third, as in other large dialysis organizations, BP was measured in accordance with standard clinical practice rather than American Heart Association guidelines.[39] Finally, the study period did not coincide with the widespread implementation of KDOQI guidelines.

This study also has several strengths. First, all laboratory parameters were measured longitudinally in the same central laboratory, reducing a significant component of variability. Second, use of the DCI medical information system ensured high-quality data as a result of electronic data transfer, built-in range checks, and ongoing data monitoring. Third, participating facilities were geographically dispersed and included patients who were treated both by academic and by private practitioners. Therefore, the study had a diverse and representative patient population.

We demonstrated significant reductions in mortality associated with adherence to KDOQI guidelines for spKt/V, hematocrit, serum albumin, calcium, phosphorus, and PTH. Therefore, clinical practice patterns associated with increased adherence should be identified and implemented throughout large dialysis organizations. In contrast, BP values satisfying the KDOQI guideline were associated with increased mortality. It is reasonable to postulate that arterial and cardiac structure and function vary significantly among HD patients with different BP values. Therefore, the ideal BP target may differ on the basis of these clinical characteristics. Because even a well-designed retrospective study can demonstrate only associations, a prospective, randomized, controlled trial is necessary to establish the optimal BP target among HD patients.

CONCISE METHODS

Study Sample

We studied all incident patients who were aged ≥20 yr and began HD at a DCI clinic between January 1, 1998, and December 31, 2004, and had survived at least 120 d after the first outpatient HD treatment. Patients were excluded when they had previously been treated by peritoneal dialysis or had received a kidney transplant; when they began maintenance HD outside DCI; or when gender, age, or date of diagnosis of ESRD was missing. Follow-up began 120 d after the first outpatient HD treatment and continued until death; kidney transplantation; switch to peritoneal dialysis; absence from DCI for >90 d; or the end of follow-up on December 31, 2005.

Data Sources

Data were obtained from DCI's proprietary computerized medical information system (DARWIN). DARWIN has been used to support DCI's participation in previous multicenter studies, including the Hemodialysis (HEMO)[40] and Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) studies.[41] Dates of death were obtained from the Centers for Medicare and Medicaid Services Death Notification forms (form 2746) and confirmed by directly contacting the clinics.

Laboratory Methods

All laboratory parameters were measured monthly, except for PTH, which was measured quarterly. Venous blood samples for routine laboratory determinations were obtained immediately before the dialysis treatment and shipped to the DCI central laboratory (Nashville, TN) for analysis. Blood urea nitrogen was measured by Enzymatic Urease (Roche, Nutley, NJ), hematocrit by Advia (Bayer, Tarrytown, NY), serum albumin by bromocresol green (Roche), calcium by Cresolphthalein Complexone (Roche), serum phosphorus by Phosphomolybdate-UV (Roche), and PTH by N-tact PTH SP IRMA (DiaSorin, Stillwater, MN). spKt/V was computed using formal urea kinetic modeling. Serum calcium concentrations were corrected using the concomitant serum albumin concentrations.[42] BP was measured in accordance with standard clinical practices in place at each facility.

Values Satisfying KDOQI Guidelines

We selected the last measurement in each calendar month for spKt/V, hematocrit, serum albumin, calcium, phosphorus, and PTH and the last BP measurement in each calendar week. Each individual value was classified as to whether it satisfied the guidelines using the following criteria: spKt/V ≥1.2,[3,9] hematocrit ≥33%,[4,8] serum albumin ≥4.0 g/dl,[5] calcium 8.4 to 9.5 mg/dl,[6] phosphorus 3.5 to 5.5 mg/dl,[6] PTH 150 to 300 pg/ml,[6] and predialysis BP ≤140/90 mmHg.[7]

Statistical Analyses

We used a Cox proportional hazards model to investigate the association between mortality and satisfying the guideline for a given parameter. Satisfying the guideline at a specific point in time was defined in a time-varying manner using all measurements taken during a 90-d window beginning 120 and ending 30 d before death.

There were typically three measurements of spKt/V, hematocrit, serum albumin, calcium, and phosphorus; a single measurement of PTH; and 12 measurements of predialysis BP in the 90-d window. When there were fewer, the window was extended, up to a maximum of 180 d, until the desired number of measurements was included. The desired number of measurements was generally obtained within the 90-d period for each parameter (81 to 94%) and almost always within 120 d (96 to 99%). We treated the number of values within each window satisfying the guidelines as a categorical variable. A missing value indicator was used when there was fewer than the desired number of measurements in the window. Additional covariates in the

Cox models included demographic characteristics (age, gender, race, cause of ESRD, and year HD was started) and, when appropriate, spKt/V and serum albumin, defined as the average value during the same 90-d window used for the parameter of interest. Separate models were constructed for each parameter considered.

To identify potential modifying effects, we constructed an additional series of models with interactions between values satisfying the guidelines and age, gender, race, cause of ESRD, and year of diagnosis (1998 to 2000 *versus* 2001 to 2004). In these models, the number of measurements satisfying guidelines was treated as a linear effect. We also considered the possibility that baseline status might influence the associations: The association of guideline adherence and mortality among patients whose values satisfied guidelines at baseline might differ from the associations among patients whose values did not satisfy guidelines at baseline. To explore this possibility, we stratified the models on whether the baseline parameter values satisfied guidelines. Baseline was defined as the first measurement within 60 d of initiating HD. Finally, we looked at the association of mortality with the number of parameters that satisfied guidelines during the 90-d window. A parameter was defined to satisfy guidelines during the 90-d period when at least two thirds of the individual measurements satisfied guidelines.

For each parameter considered, we constructed plots showing the proportion of patients who satisfied guidelines during time since the start of HD. A patient was classified as satisfying guidelines for a 3-mo period when at least two thirds of the measurements satisfied guidelines. We constructed plots for participants who were followed for at least 3 yr. To evaluate whether the observed trends were due to survivor bias, we also constructed plots for patients who were followed for at least 1 yr and for all participants.

Summaries for demographic variables are shown as percentages. A two-tailed t test was used to compare the DCI population with the United States Renal Data System HD population. McNemar test was used to compare the proportion of patients who satisfied guidelines between the first and 12th quarters after the start of HD. Model results are summarized by HR and 95% CI. Statistical analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC). Statistical significance was defined as $P < 0.05$.

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DISCLOSURES

None.

REFERENCES

1. Epstein AM, Lee TH, Hamel MB: Paying physicians for high-quality care. *N Engl J Med* 350: 406–410, 2004
2. Garber AM: Evidence-based guidelines as a foundation for performance incentives. *Health Aff (Millwood)* 24: 174–179, 2005
3. National Kidney Foundation: K/DOQI clinical practice guidelines for hemodialysis adequacy, 2000. *Am J Kidney Dis* 37: S7–S64, 2001
4. National Kidney Foundation: K/DOQI clinical practice guidelines for anemia of chronic kidney disease, 2000. *Am J Kidney Dis* 37: S182–S238, 2001
5. National Kidney Foundation: Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 35: S17–S104, 2000
6. National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42: S1–S202, 2003
7. National Kidney Foundation: K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 45: S16–S153, 2005
8. National Kidney Foundation: KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 47: S1–S146, 2006
9. National Kidney Foundation: KDOQI clinical practice guidelines and clinical practice recommendations for 2006 updates: Hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. *Am J Kidney Dis* 48: S1–S322, 2006
10. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329: 1001–1006, 1993
11. Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, Young EW: Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. *Kidney Int* 62: 2238–2245, 2002
12. Combe C, McCullough KP, Asano Y, Ginsberg N, Maroni BJ, Pifer TB: Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): Nutrition guidelines, indicators, and practices. *Am J Kidney Dis* 44: 39–46, 2004
13. Noordzij M, Korevaar JC, Boeschoten EW, Dekker FW, Bos WJ, Krediet RT: The Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline for bone metabolism and disease in CKD: Association with mortality in dialysis patients. *Am J Kidney Dis* 46: 925–932, 2005
14. Rocco MV, Frankenfield DL, Hopson SD, McClellan WM: Relationship between clinical performance measures and outcomes among patients receiving long-term hemodialysis. *Ann Intern Med* 145: 512–519, 2006
15. Plantinga LC, Fink NE, Jaar BG, Sadler JH, Levin NW, Coresh J, Klag MJ, Powe NR: Attainment of clinical performance targets and improvement in clinical outcomes and resource use in hemodialysis care: A prospective cohort study. *BMC Health Serv Res* 7: 5, 2007
16. Zager PG, Nikolic J, Brown RH, Campbell MA, Hunt WC, Peterson D, Van Stone J, Levey A, Meyer KB, Klag MJ, Johnson HK, Clark E, Sadler JH, Teredesai P: "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int* 54: 561–569, 1998
17. Stidley CA, Hunt WC, Tentori F, Schmidt D, Rohrscheib M, Paine S, Bedrick EJ, Meyer KB, Johnson HK, Zager PG: Changing relationship of blood pressure with mortality over time among hemodialysis patients. *J Am Soc Nephrol* 17: 513–520, 2006
18. Port FK, Pisoni RL, Bragg-Gresham JL, Satayathum SS, Young EW, Wolfe RA, Held PJ: DOPPS estimates of patient life years attributable to modifiable hemodialysis practices in the United States. *Blood Purif* 22: 175–180, 2004
19. Wolfe RA, Hulbert-Shearon TE, Ashby VB, Mahadevan S, Port FK: Improvements in dialysis patient mortality are associated with im-

provements in urea reduction ratio and hematocrit, 1999 to 2002. *Am J Kidney Dis* 45: 127–135, 2005
20. Culp K, Flanigan M, Lowrie EG, Lew N, Zimmerman B: Modeling mortality risk in hemodialysis patients using laboratory values as time-dependent covariates. *Am J Kidney Dis* 28: 741–746, 1996
21. Kalantar-Zadeh K, Kopple JD, Humphreys MH, Block G: Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. *Nephrol Dial Transplant* 19: 1507–1519, 2004
22. Port FK, Hulbert-Shearon TE, Wolfe RA, Bloembergen WE, Golper TA, Agodoa LY, Young EW: Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. *Am J Kidney Dis* 33: 507–517, 1999
23. Foley RN, Herzog CA, Collins AJ: Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int* 62: 1784–1790, 2002
24. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 289: 2560–2572, 2003
25. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int* 49: 1379–1385, 1996
26. Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 340: 677–684, 1999
27. Staessen JA, Wang JG, Thijs L: Cardiovascular protection and blood pressure reduction: A meta-analysis. *Lancet* 358: 1305–1315, 2001
28. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288: 2981–2997, 2002
29. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW: Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. *JAMA* 294: 716–724, 2005
30. London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, Metivier F, Adda H, Safar ME: Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: Follow-up of an interventional study. *J Am Soc Nephrol* 12: 2759–2767, 2001
31. Efrati S, Zaidenstein R, Dishy V, Beberashvili I, Sharist M, Averbukh Z, Golik A, Weissgarten J: ACE inhibitors and survival of hemodialysis patients. *Am J Kidney Dis* 40: 1023–1029, 2002
32. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, Russo PE, Golino P, Calabro R: Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: A prospective, placebo-controlled trial. *J Am Coll Cardiol* 41: 1438–1444, 2003
33. Tepel M, Giet MV, Park A, Zidek W: Association of calcium channel blockers and mortality in haemodialysis patients. *Clin Sci (Lond)* 103: 511–515, 2002
34. Mason NA, Bailie GR, Satayathum S, Bragg-Gresham JL, Akiba T, Akizawa T, Combe C, Rayner HC, Saito A, Gillespie BW, Young EW: HMG-coenzyme a reductase inhibitor use is associated with mortality reduction in hemodialysis patients. *Am J Kidney Dis* 45: 119–126, 2005
35. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, Tracy RP, Powe NR, Klag MJ: Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. *JAMA* 291: 451–459, 2004
36. Shoji T, Tsubakihara Y, Fujii M, Imai E: Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int* 66: 1212–1220, 2004
37. Miskulin DC, Meyer KB, Martin AA, Fink NE, Coresh J, Powe NR, Klag MJ, Levey AS: Comorbidity and its change predict survival in incident dialysis patients. *Am J Kidney Dis* 41: 149–161, 2003
38. van Manen JG, van Dijk PC, Stel VS, Dekker FW, Cleries M, Conte F, Feest T, Kramar R, Leivestad T, Briggs JD, Stengel B, Jager KJ: Confounding effect of comorbidity in survival studies in patients on renal replacement therapy. *Nephrol Dial Transplant* 22: 187–195, 2007
39. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ: Recommendations for blood pressure measurement in humans and experimental animals: Part 1—Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 45: 142–161, 2005
40. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347: 2010–2019, 2002
41. Miskulin DC, Meyer KB, Athienites NV, Martin AA, Terrin N, Marsh JV, Fink NE, Coresh J, Powe NR, Klag MJ, Levey AS: Comorbidity and other factors associated with modality selection in incident dialysis patients: The CHOICE Study. Choices for Healthy Outcomes in Caring for End-Stage Renal Disease. *Am J Kidney Dis* 39: 324–336, 2002
42. Portale AA: Blood calcium, phosphorus, and magnesium. In: P*rimer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, edited by Favus MJ, Philadelphia, Lippincott Williams & Wilkins, 1999, pp 115–118