

# Changing Relationship of Blood Pressure with Mortality over Time among Hemodialysis Patients

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High BP is a major risk factor for atherosclerotic cardiovascular disease mortality in the general population. Surprising, studies that have been conducted among hemodialysis (HD) patients have yielded conflicting data on the relationship between BP and mortality. This study explores two hypotheses among HD patients: (1) The relationship between BP and mortality changes over time, and (2) mild to moderate hypertension is well tolerated. Incident HD patients who were treated at Dialysis Clinic Inc. facilities between 1993 and 2003 were studied. Primary end points were atherosclerotic cardiovascular disease and all-cause mortality. The relationship between BP and mortality was analyzed in two sets of Cox proportional hazards models. Model-B explored the relationship between baseline BP and mortality in sequential time periods. Model-TV assessed the relationship between BP, treated as time-varying, and mortality. The study sample ( $n = 16,959$ ) was similar in characteristics to the United States Renal Data Systems population, although black patients were slightly overrepresented. Model-B demonstrated that the relationship between baseline BP and mortality changes over time. Low systolic BP ( $<120$  mmHg) was associated with increased mortality in years 1 and 2. High systolic BP ( $\geq 150$  mmHg) was associated with increased mortality among patients who survived  $\geq 3$  yr. Low pulse pressure was associated with increased mortality. Model-TV demonstrated that mild to moderate systolic hypertension may be relatively well tolerated. In conclusion, the relationship between baseline BP and mortality changes over time. Mild to moderate systolic hypertension was associated with only modest increases in mortality.

*J Am Soc Nephrol* 17: 513–520, 2006. doi: 10.1681/ASN.2004110921

In the general population, hypertension is associated with accelerated atherosclerotic cardiovascular disease (ASCVD) (1–3). Successful treatment of hypertension decreases ASCVD morbidity (4–7) and mortality (3,4,6,8). The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) defined hypertension among adults as systolic BP (SBP)  $\geq 140$  mmHg and/or diastolic BP (DBP)  $\geq 90$  mmHg (2). The Joint National Committee recommends a target BP  $<130/80$  mmHg in patients with existing ASCVD (2).

The high prevalence of hypertension among hemodialysis (HD) patients (9,10) may contribute to the observed excess of ASCVD morbidity and mortality (11,12). Thus, it is important to identify the ideal BP target in this high-risk group. The National Kidney Foundation's (NKF's) Kidney Disease Outcomes Quality Initiative (KDOQI) and JNC VII (2) have recommended a target BP  $<130/80$  mmHg for patients with chronic kidney disease stages I to IV (13). NKF KDOQI has recently recommended pre- ( $<140/90$  mmHg) and post-HD ( $<130/80$

mmHg) BP targets (14). The evidence supporting this recommendation was graded as weak because it was extrapolated from the general population. The only prospective study in a dialysis population demonstrated that a BP  $\leq 140/90$  was associated with a decreased risk for left ventricular hypertrophy but an increased mortality risk (15). Observational studies have provided conflicting data on the relationships between BP and mortality among HD patients (11,12,16–19).

We previously described a "U"-shaped relationship between postdialysis SBP and mortality in a prevalent cohort of HD patients in facilities operated by Dialysis Clinic Inc. (DCI) (16). Mild to moderate elevations in predialysis SBP were not associated with significant increases in ASCVD and all-cause (AC) mortality. These observations were subsequently confirmed by other investigators. Foley *et al.* (11) reported that high postdialysis SBP and low pre- and postdialysis diastolic BP (DBP) were associated with increased mortality. Port *et al.* (17) reported that predialysis SBP  $<110$  mmHg was associated with increased mortality. In contrast, other investigators did not observe an association between BP and mortality (19).

A potential explanation for these disparate results is that the relationship between baseline BP and mortality may vary over time. This study explores this hypothesis, which, if correct, suggests that the proportionality assumption underlying the Cox proportional hazards model is violated. We also explore

Received November 8, 2004. Accepted November 3, 2005.

Published online ahead of print. Publication date available at [www.jasn.org](http://www.jasn.org).

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the hypothesis that mild to moderate hypertension may be relatively well tolerated.

## Materials and Methods

### Study Population

We studied an incident cohort of HD patients who were treated in DCI facilities between January 1, 1993, and December 31, 2003. All data were obtained from DCI's medical information system (DARWIN). Inclusion criteria were (1) age  $\geq 20$  yr; (2) initiation of chronic HD during the study period; and (3) survival  $\geq 150$  d from the first outpatient HD and before December 31, 2003. Patients had to survive 150 d so that we could exclude their first 30 d on dialysis, obtain baseline data during the subsequent 90 d, and separate baseline data from outcomes by  $\geq 30$  d. Exclusion criteria were (1) previous renal transplant or peritoneal dialysis (PD); (2) initiation of chronic HD outside DCI; and (3) missing data on gender, age, or date of onset of ESRD. Patients were censored at modality change, prolonged absence, or transfer out of DCI. For analysis of ASCVD mortality, patients were censored for other causes of death.

### End Points

Study end points were ASCVD and AC mortality. Dates and causes of death were obtained from the Centers for Medicare and Medicaid Services (CMS) Death Notification forms (2746) and coded using the *International Classification of Diseases, 9th Revision (ICD-9)*. Deaths that were attributed to ASCVD were identified by ICD-9 codes 410 to 414, 427.5, 430 to 438, and 440 to 443, which include myocardial infarction, acute cardiac ischemia, sudden cardiac death, and cerebrovascular and peripheral vascular disease. Mortality reported on the Centers for Medicare and Medicaid Services form 2746 was confirmed by direct contact with each DCI facility.

### BP Variables

SBP and DBP were measured with the participants in the sitting position, before and after each dialysis session. Allowable ranges were 50 to 300 mmHg for SBP and 10 to 150 mmHg for DBP. When a value was outside the range, the data point was coded as missing before averaging the BP over 90-d periods. Pre- and postdialysis pulse pressure (PP) was calculated.

### Covariates

Covariates included demographic data (gender, race, age at onset, and cause of ESRD), laboratory values (serum albumin concentration and hematocrit), and dialysis dose (spKt/V) (20). Allowable ranges included serum albumin concentration ( $\leq 5.0$  g/dl), hematocrit (15 to 54%), and spKt/V ( $\leq 4.0$ ). When a value was outside the specified range, it was coded as missing. Information was obtained on prescribed antihypertensive medications (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers,  $\beta$ -adrenergic blockers, calcium-channel blockers, and central  $\alpha$ -agonists), but because of the potential for incomplete data on changes in prescriptions for oral medications, patients were categorized by antihypertensive medication use in the first 120 d of ESRD.

### Statistical Analyses

The associations between BP and ASCVD and AC mortality were assessed with Cox proportional hazards models. All models included fixed (gender, race, age at onset, and cause of ESRD), potentially time-varying covariates (serum albumin concentration, hematocrit, and spKt/V), and BP. The BP variables in the models were SBP and/or DBP or only PP. Separate models were used to examine pre- and postdialy-

sis BP and ASCVD and AC mortality. To assess the potential for confounding, we examined models with SBP and DBP in separate models and added SBP to models with PP. To test for possible interactions between SBP and DBP and between SBP and PP, we added interaction terms to the corresponding models.

Two sets of models were examined to assess the relationship between BP and mortality. The first set used baseline BP (Model-B) and described the relationship of baseline BP with mortality during years 1, 2, 3, and 4+ of HD. Thus, this set forms a series of models that are conditioned on survival to the start of the follow-up period. Baseline values of BP were obtained by averaging SBP, DBP, and PP over days 31 through 120 of HD. Survival was monitored after 150 d, so the baseline value was at least 30 d before any event. Serum albumin concentration, hematocrit, and spKt/V were treated as either fixed or time-varying covariates. The second set of models (Model-TV) used time-varying BP as well as time-varying covariates (serum albumin concentration, hematocrit, and spKt/V). BP and the time-varying covariates were averaged over 90-d periods ending 30 d before an end point. To assess potential nonlinear associations, we categorized SBP, DBP, and PP into 10-, 5-, and 5-mmHg categories, respectively. The sample size after several years of follow-up was reduced, so some extreme categories were combined. The referent groups were 140 to 149 mmHg for SBP, 75 to 79 mmHg for DBP, and 70 to 74 mmHg for PP. Serum albumin concentration, hematocrit, and spKt/V were categorized to allow for nonlinear associations. Some models included linear and quadratic terms for serum albumin concentration.

To test for possible associations of gender, race, and cause of ESRD with mortality, Model-B and Model-TV included these variables as main effects. Baseline use of antihypertensive medications also was included in versions of Model-B and Model-TV. To assess the potential for interactions between these variables and BP, we also stratified models by race, cause of ESRD, and baseline antihypertensive medication use.

Models were tested for goodness of fit and the proportional hazards assumption assessed using Schoenfeld residuals and by fitting models by year of follow-up. Summaries for selected variables are shown as mean and SD or percentages. Model results are summarized by hazard ratios (HR) and 95% confidence intervals (CI). Statistical significance was defined as  $P < 0.05$ . Statistical analyses were conducted in SAS (Cary, NC).

## Results

The study sample consisted of 16,959 HD patients. Distributions of age, gender, and cause of ESRD were similar to the incident United States Renal Data System's cohort in the year 2000 (Table 1). However, the percentage of black patients was higher in DCI. At baseline, average predialysis SBP and DBP were  $151.8 \pm 18.4$  and  $78.9 \pm 1.1$  mmHg, respectively. Average postdialysis SBP and DBP were  $144.8 \pm 17.9$  and  $76.2 \pm 10.1$  mmHg, respectively. Mean baseline values for serum albumin concentration ( $3.60 \pm 0.40$  g/dl), hematocrit ( $33.2 \pm 4.1\%$ ), and spKt/V ( $1.35 \pm 0.30$ ) were computed. Total and median follow-up were 34,706 and 2.05 person-years, respectively. There were 2630 ASCVD and 6211 total deaths. Remaining patients were censored for modality change (switch to PD,  $n = 749$ ; transplant,  $n = 1361$ ; prolonged absence or transfer out of DCI,  $n = 2918$ ; and study end,  $n = 5720$ ).

### Baseline BP and Mortality (Model-B)

**SBP.** Kaplan-Meier survival curves of patients who were stratified by baseline predialysis SBP demonstrated that sur-

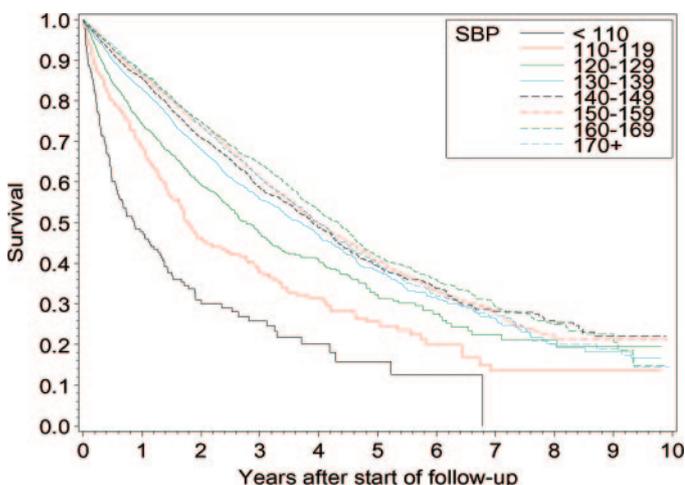
**Table 1.** Comparison of demographics between DCI study sample ( $n = 16,959$ ) and USRDS incident hemodialysis patients for year 2000<sup>a</sup>

Demographics	DCI		USRDS	
	<i>n</i>	%	<i>n</i>	% <sup>b</sup>
Age (yr)				
20 to 44	2781	16.4	11,003	13.3
45 to 64	6570	38.7	29,062	35.0
65 to 74	4387	25.9	21,587	26.0
≥75	3221	19.0	21,294	25.7
Female gender	8088	47.7	38,947	46.6
Ethnicity	9354	55.2	52,670	63.0
white				
black	6487	38.3	24,914	29.8
other/unknown	1118	6.6	6051	7.2
Cause of ESRD				
diabetes	7567	44.6	37,714	45.1
hypertension	4277	25.2	22,658	27.1
glomerulonephritis	1800	10.6	6651	8.0
other	2376	14.0	12,296	14.7
unknown/missing	939	5.6	4316	5.2
Any use of BP medication in first 120 d on dialysis	10,188	60.1	NA	NA

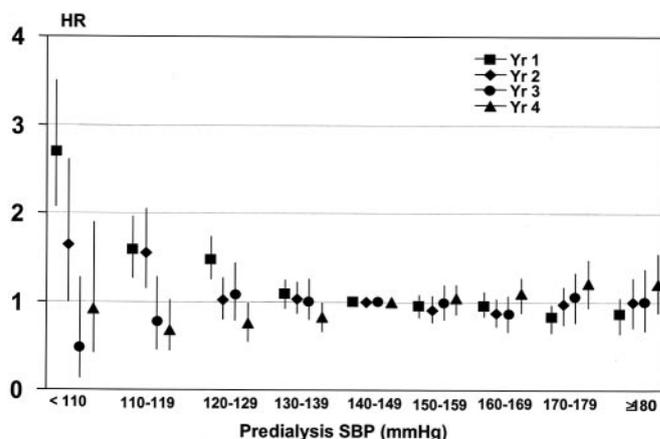
<sup>a</sup>DCI, Dialysis Clinic Inc.; USRDS, United States Renal Data System; NA, not available.

<sup>b</sup>Percentage is based on the entire USRDS incident hemodialysis population, except for age, which is restricted to those ≥20 yr of age.

vival was lower among patients with baseline SBP <130 mmHg (Figure 1). The relationships between baseline predialysis SBP with AC mortality and with adjustment for time-varying serum albumin concentration, spKt/V, and hematocrit, during successive follow-up intervals are shown (Figure 2). Predialysis baseline SBP <120 mmHg was associated with increased AC mor-



**Figure 1.** Unadjusted survival by baseline predialysis systolic BP (SBP).



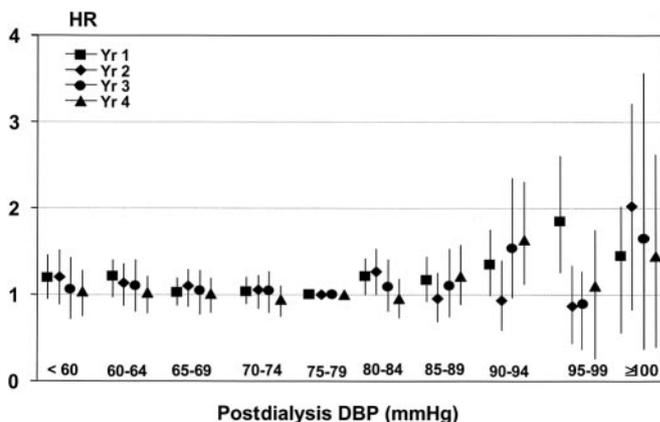
**Figure 2.** Hazard ratios (HR) for all-cause (AC) mortality from Model-B by baseline predialysis SBP.

tality in the first 2 y. The magnitude of the HR associated with predialysis SBP above the referent category (140 to 149 mmHg) tended to increase over the successive follow-up periods. Among participants with >3 yr of follow-up, baseline predialysis SBP ≥150 mmHg was associated with mortality. Results were similar for ASCVD mortality, models with postdialysis BP, and models with baseline rather than time-varying serum albumin concentration, spKt/V, and hematocrit (results not shown).

**DBP.** There were no significant associations between low baseline predialysis DBP (data not shown) or low baseline postdialysis DBP and AC (Figure 3) and ASCVD mortality, with adjustment for time-varying serum albumin concentration, spKt/V, and hematocrit. Baseline pre- or postdialysis DBP >80 mmHg tended to be associated with increased AC (Figure 3) and ASCVD mortality but did not consistently attain statistical significance. Adjusting for serum albumin concentration, spKt/V, and hematocrit using baseline rather than time-varying values did not change the results.

*Time-Varying BP and Mortality (Model-TV)*

**SBP and DBP.** Predialysis SBP <140 mmHg was associated with increased ASCVD and AC mortality, but predialysis



**Figure 3.** HR for AC mortality from Model-B by baseline predialysis diastolic BP (DBP).

SBP values above the referent category (140 to 149 mmHg) were not (Figure 4). Predialysis SBP >160 mmHg was associated with improved survival. Postdialysis SBP <110 mmHg was associated with increased ASCVD and AC mortality (data not shown). Postdialysis SBP between 110 and 119 mmHg was associated with increased AC mortality. Postdialysis SBP ≥170 mmHg tended to be associated with increased ASCVD and AC mortality but did not consistently attain statistical significance. Pre- and postdialysis DBP ≥90 mmHg were associated with increased AC (Figure 5) and ASCVD mortality. The magnitude of the HR for mortality associated with SBP and DBP, respectively, was similar in models that contained either SBP alone or both SBP and DBP. Predialysis DBP <75 mmHg was associated with increased mortality when unadjusted for SBP (Figure 5).

**PP.** Postdialysis PP <65 mmHg and predialysis PP <70 mmHg were associated with increased AC mortality in models that did not contain SBP as a covariate (Figure 6). The largest HR were observed for PP <55 (2.1 [1.94 to 2.35] and 1.4 [1.24 to 1.51] for pre- and post-PP, respectively). No significant associations between PP above the referent category (70 to 74 mmHg) and mortality were observed. SBP was added to the model to assess potential confounding, but no changes in the overall association between PP and mortality were observed (data not shown). To test for interaction between PP and SBP, we added to the model terms for interactions between PP and SBP. This model used predialysis PP and SBP, as well as serum albumin concentration, spKt/V, and hematocrit, as time-varying (data not shown). For SBP below the referent category (140 to 149 mmHg), PP <70 mmHg was consistently associated with increased AC mortality. PP ≥75 mmHg was associated with increased mortality only among patients with an SBP <150 mmHg.

**Relationship between Covariates and Mortality.** The highest HR for AC mortality (10.2 [9.09 to 11.40]) was associated with serum albumin concentrations <3.0 *versus* ≥4.0 g/dl. Female gender (0.93 [0.88 to 0.98]), black relative to white patients (0.60 [0.57 to 0.64]), and glomerulonephritis relative to diabetes as a cause of ESRD (0.81 [0.74 to 0.88]) were associated with decreased mortality. The estimates of the effects of BP did

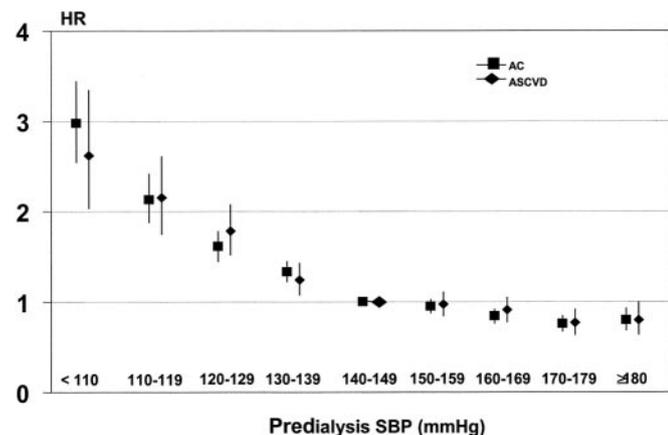


Figure 4. HR for AC and atherosclerotic cardiovascular disease (ASCVD) mortality from Model-TV by predialysis SBP.

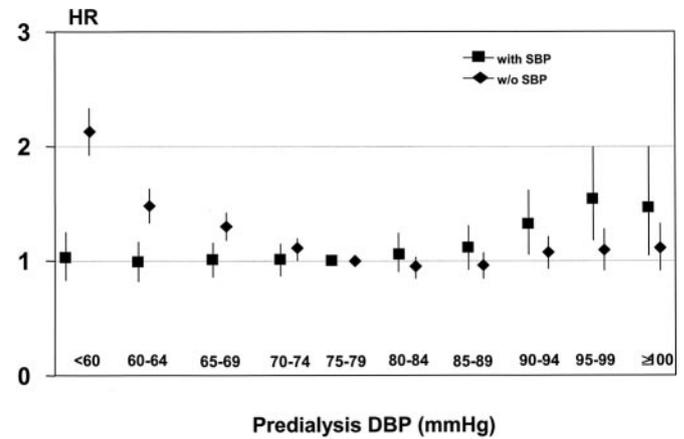


Figure 5. HR for AC mortality from Model-TV by predialysis DBP, with and without adjustment for SBP.

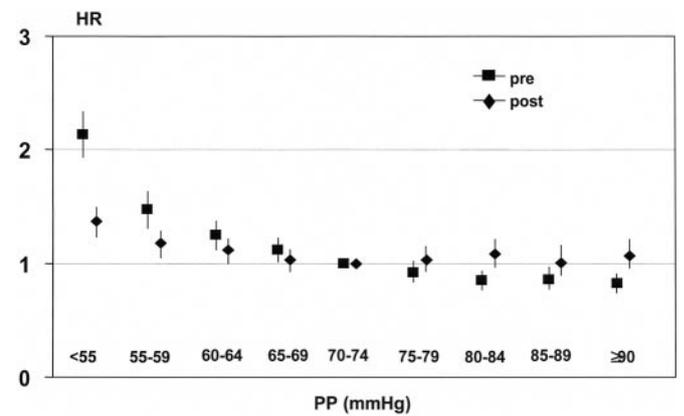


Figure 6. HR for AC mortality from Model-TV by pre- and postdialysis pulse pressure (PP).

not differ between models that were stratified by race or cause of ESRD, respectively. A 10-yr increase in age (1.37 [1.33 to 1.40]), hematocrit <33% relative to 33 to 36% (1.41 [1.33 to 1.50]), and use of baseline antihypertensive medications (1.10 [1.04 to 1.16]) were associated with increased AC mortality. The direction and magnitude of the HR for ASCVD mortality were similar among patients with and without a history of antihypertensive medication use.

We considered the possibility that baseline BP might affect subsequent changes in serum albumin concentrations, hematocrit, spKt/V, and BP. Thus, we stratified patients by baseline BP and assessed changes in these parameters among patients who survived ≥3 yr (Figure 7). At baseline, patients with SBP <120 mmHg had lower serum albumin concentrations *versus* those with a higher SBP ( $P < 0.0001$ ). Although serum albumin concentrations increased during the first 6 mo ( $P < 0.0001$ ), followed by a plateau and an eventual gradual decline in all patients, they tended to remain lower among patients with baseline SBP <120 mmHg ( $P < 0.0001$ ). To determine whether a possible incomplete adjustment for serum albumin concentration may have led to biased estimates of association between BP and mortality, we examined a model with linear and qua-

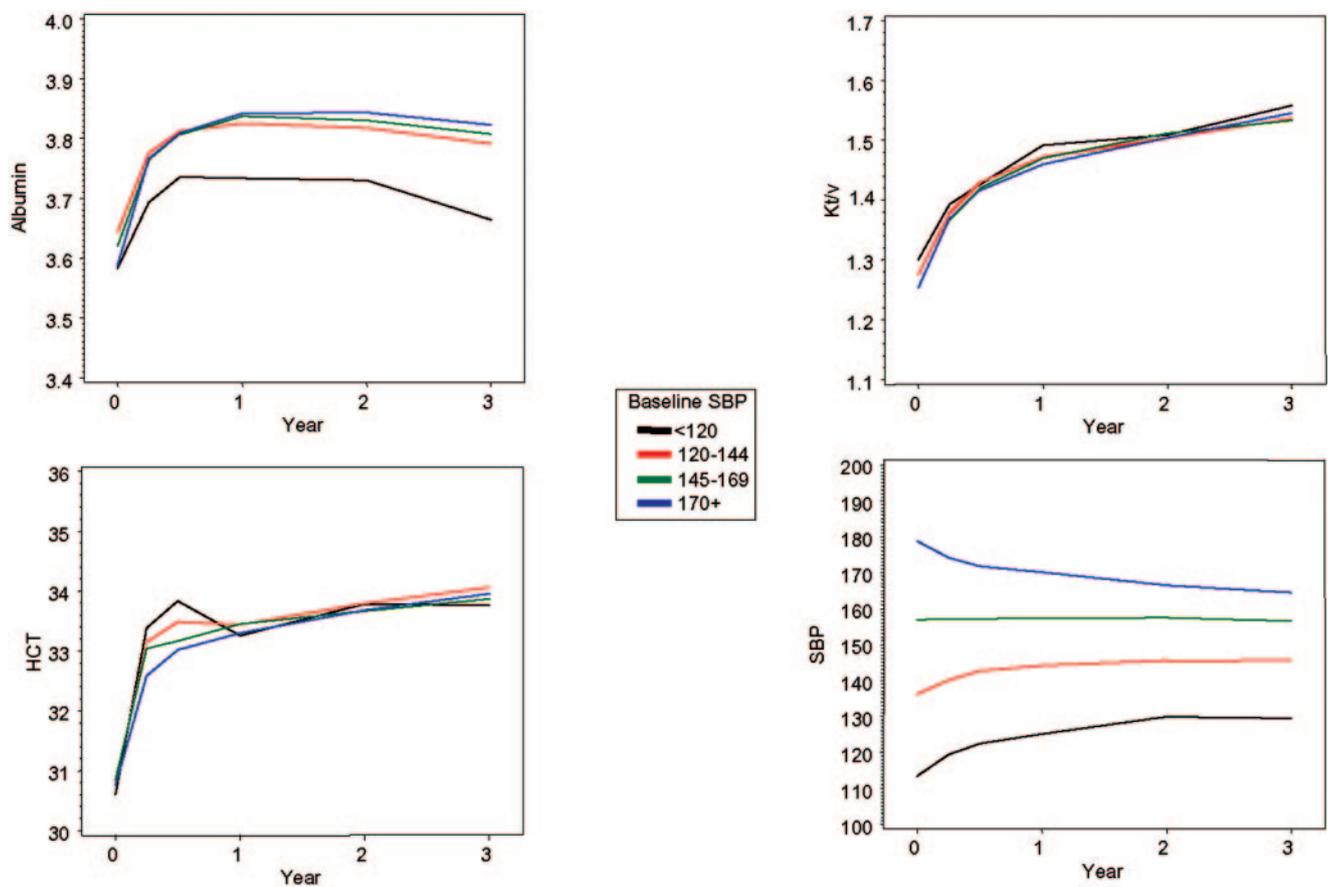


Figure 7. Mean albumin, spKt/V, hematocrit (HCT), and SBP over time since diagnosis of ESRD by baseline SBP.

dratic terms for albumin. However, no differences in the estimates for BP were discerned. Values for hematocrit and spKt/V tended to increase progressively over time, and the patterns did not differ by baseline SBP. The relationships of baseline SBP to SBP at subsequent time points resembled regression to the mean, and the patterns did not differ by baseline SBP.

**Model Assessment.** Assessment of the Schoenfeld residuals demonstrated that the proportional hazard assumption was valid in the 1-yr observation periods in Model-B and for the time periods used in Model-TV. We fit Model-TV for the time period used in Model-B (*i.e.*, separately for years 1, 2, 3, and later). The HR remained similar throughout these time periods, indicating that the proportional hazards assumption is valid for the time-varying BP variables used in Model-TV.

## Discussion

Our study demonstrates that the relationship between baseline BP and mortality changes over time. Low SBP was associated with increased mortality in the first 2 yr. The adverse effects of high SBP on survival became apparent after 3 yr of HD. Thus, when assessing the long-term effects of baseline BP, the assumption of proportionality inherent in Cox proportional hazards models is violated. Previous studies that assessed the relationships between baseline BP and mortality using Cox proportional hazard models should be interpreted with caution (11,16,17,19).

The changing relationship of BP with mortality over time observed in this study is in concert with a report by Mazzuchi *et al.* (18). These investigators observed that low BP was associated with increased mortality during the early years of dialysis, whereas high BP was associated with mortality in later years. Their study population, however, had a low prevalence of diabetes and few black patients.

The magnitude of the HR for mortality associated with BP was modest compared with that associated with hypoalbuminemia but similar to those for the other covariates. The magnitude of the HR for ASCVD mortality associated with BP may be smaller among HD patients *versus* the general population. Among participants in the Multiple Risk Factor Intervention Trial aged 45 to 57 yr, SBP  $\geq 142$  mmHg and DBP  $\geq 92$  mmHg were associated with HR for ASCVD mortality of 2.79 and 2.25, respectively (21). The modest HR associated with high BP observed in our study are consistent with the hypothesis that a significant portion of the excess ASCVD mortality among HD patients may be attributable to nontraditional risk factors (22–24).

In Model-B for the first 3 yr and in Model-TV, moderate predialysis systolic hypertension (150 to 179 mmHg) was not associated with increased mortality. The Hemodialysis Study also found no association between predialysis SBP and ASCVD mortality (25). Previous reports described a U-shaped relationship between postdialysis SBP and mortality among HD pa-

tients (16,18). In this study, Model-TV demonstrated that a predialysis SBP <140 mmHg and a postdialysis SBP <120 mmHg each were associated with increased mortality. The relationship between DBP and mortality observed in this study is similar to that in the general population (26). Previous reports have shown associations between mortality and low predialysis DBP (11), low postdialysis DBP (11), and elevated postdialysis DBP (17).

In contrast with recent reports by Klassen *et al.* (25) and Tozawa *et al.* (27), increased PP was not associated with increased mortality. There are several important differences in experimental design that may have contributed to the disparate results. We studied only incident patients who were followed for several years. In contrast, Klassen *et al.* (12) studied a prevalent cohort followed for 1 yr, and Tozawa *et al.* (27) also studied a prevalent cohort. Klassen *et al.* observed that high PP was associated with mortality only in patients with a postdialysis SBP  $\leq$ 140 mmHg (12). Tozawa *et al.* reported that the observed association between PP and mortality disappeared when diabetes was included as a covariate. In our study, low PP, rather than high, was associated with mortality in models with and without SBP as a covariate. The reason for this finding is, in part, mathematical given the strong correlation between SBP and PP. However, models that contain SBP as a covariate demonstrated that low PP was a risk factor among patients with a low SBP. In these models, PP is largely driven by DBP and, not surprising, patients with a higher DBP have an increased mortality risk.

We considered the possibility that the effect of BP on clinical outcomes may have resulted from unrecognized associations between BP and important covariates. Patients with low BP had lower baseline serum albumin concentrations, which may have introduced significant bias. However, the patterns for change in serum albumin concentrations, hematocrit, spKt/V, and BP, respectively, did not differ among patients who were stratified by baseline SBP values. Thus, it is unlikely that the outcomes among groups with different baseline BP values were driven by BP-induced changes in these variables.

Our study has several limitations. First, BP measurements were obtained in the routine care of HD patients rather than with the standard K/DOQI protocol. There may be significant differences between “usual” and standardized BP measurements among HD patients (28). Second, echocardiograms were not available, and adjustment for comorbidity other than diabetes was not performed. However, serum albumin concentration is a valuable surrogate marker of comorbidity (29). The absence of formal comorbidity assessment, including the prevalence of malignancies and end-stage heart failure, may have introduced significant bias. For example, Model-B presents a series of conditional HR. For the third year of dialysis, the results from this model are conditioned on patients’ surviving the first 2 yr. The comorbidity of the cohort at baseline may be very different from that in year 3. Third, the transfer rate out of DCI (9.2% per patient-year) may have introduced bias. However, this transfer rate is in concert with that observed among the US cohort in, Dialysis Outcomes and Practice Patterns Study (DOPPS) phase II (8.1% patients in year 1) (Port F,

University Renal Research and Education Association, Ann Arbor, MI; personal communication, May 2005). According to the US Census Bureau, 14% of the entire US population moved during 2002 (30). Thus, the observation that 17.2% of our study sample (median follow-up >2 yr) was censored as a result of transfer out of a DCI facility is in concert with the mobility of the US population. Fourth, limited data on the use of oral antihypertensive medications may have caused unrecognized bias or confounding. Fifth, use of multiple models increased the probability of a spurious result. However, because the models had similar characteristics and similar results, this approach provided additional support for our conclusions.

Predialysis SBP may correlate best with left ventricular hypertrophy (31). However, postdialysis BP may correlate best with mean interdialytic BP assessed by ambulatory BP monitoring (32). In our study, HR for postdialysis SBP above the referent category tended to be higher than the corresponding predialysis values, suggesting that hypertension postdialysis may be a stronger predictor of mortality compared with predialysis hypertension. Baseline SBP values from 150 to 169 mmHg were not associated with an increased mortality risk. SBP values  $\geq$ 170 mmHg were associated with an increased mortality risk in patients only after 3 yr. Moreover, when SBP was treated as time varying, even SBP values  $\geq$ 180 mmHg were not associated with increased mortality. Low predialysis SBP was the strongest predictor of mortality in the early years. In contrast, the results for DBP from Model-B demonstrated a tendency for DBP >90 mmHg to be associated with increased mortality. In summary, our study demonstrates conclusively that, with regard to baseline BP, the assumption of proportional hazards is violated. This may have contributed to the varying findings observed in previous studies (11,16,17,19). Our study provides strong evidence that a randomized controlled trial using novel statistical methods that do not require the proportional hazards assumption should be performed to identify optimal BP targets for HD patients.

This study did not identify the ideal BP target. Current NKF K/DOQI guidelines recommend a BP <130/80 for chronic kidney disease stages I through IV (13). NKF K/DOQI recently released their guidelines for BP targets pre- (<140/90 mmHg) and post-HD (<130/80 mmHg). Our study should not be interpreted as providing strong evidence to disregard these guidelines. In contrast, the authors believe that, in the absence of symptomatic intradialytic hypotension, clinicians should adhere to these guidelines until such time as results from a randomized, controlled trial become available.

## Acknowledgments

This study was funded by DCI, a not-for-profit corporation. We thank all DCI patients and DCI health care professionals.

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