Age, Race, Diabetes, Blood Pressure, and Mortality among Hemodialysis Patients

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ABSTRACT

Observational studies involving hemodialysis patients suggest a U-shaped relationship between BP and mortality, but the majority of these studies followed large, heterogeneous cohorts. To examine whether age, race, and diabetes status affect the association between systolic BP (SBP; predialysis) and mortality, we studied a cohort of 16,283 incident hemodialysis patients. We constructed a series of multivariate proportional hazards models, adding age and BP to the analyses as cubic polynomial splines to model potential nonlinear relationships with mortality. Overall, low SBP associated with increased mortality, and the association was more pronounced among older patients and those with diabetes. Higher SBP associated with increased mortality among younger patients, regardless of race or diabetes status. We observed a survival advantage for black patients primarily among older patients. Diabetes associated with increased mortality mainly among older patients with low BP. In conclusion, the design of randomized clinical trials to identify optimal BP targets for patients with ESRD should take age and diabetes status into consideration.


Studies of the general population have consistently demonstrated the benefits of aggressive antihypertensive therapy.

Published guidelines for the treatment of hypertension have been widely circulated and applied to heterogeneous patient groups; however, the risks associated with hypertension vary considerably across patients. The majority of patients with hypertension experience normal health and longevity. Some studies indicated that age, race, and diabetes status may influence the relationship between BP and clinical outcomes. There is a U-shaped relationship between BP and mortality among patients who are older than 85 years. The very old may be at increased risk from aggressive antihypertensive therapy. A given increase in BP may carry a higher risk for adverse outcomes among black versus white individuals. On the basis of results of several studies, including Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Steno type 2, the American Heart Association and the American Diabetes Association have issued guidelines calling for lower BP targets among patients with versus without diabetes.

Among hemodialysis (HD) patients, observational studies have often demonstrated a U-shaped relationship between BP and mortality; however, the majority of these studies were conducted in large, heterogeneous cohorts of HD patients. This study explored the hypothesis that...
the relationship between BP and mortality among incident HD patients is modified by age, race, and diabetes status.

RESULTS

The study cohort consisted of 16,283 incident HD patients with 32,042 person-years of follow-up (median 1.5 years). There were 6250 deaths. Demographics of the study cohort are shown in Table 1. Diabetes was the cause of ESRD in 36.1, 56.7, and 40.4% of patients who were aged <50, 50 to 69, and ≥70 years, respectively. The ages of patients with and without diabetes were similar. White patients (64.8 ± 14.4 years) were older than black patients (57.3 ± 14.9 years). Isolated systolic hypertension was more common among patients with versus without diabetes (P < 0.001). Combined systolic and diastolic hypertension was more common among black versus white patients. Isolated diastolic hypertension was uncommon (≤0.3%).

Combined Effects of Systolic and Diastolic BP on Mortality

Hazard ratios (HRs) for mortality risks, associated with increasing levels of systolic BP (SBP) at given diastolic BP (DBP) values are shown in Figure 1. Mortality associated with a given SBP tended to increase as DBP rose (P < 0.001, SBP × DBP interaction). Low SBP levels were associated with increased mortality over the range of DBP. Regardless of DBP, increasing levels of SBP, up to 180 mmHg, were not associated with increased mortality. The addition of DBP to models that already contained SBP increased rather than decreased the Bayesian Information Criterion (BIC; Table 2); therefore, SBP was much stronger than DBP as a predictor of mortality. Although...
Table 2. Relative fit of models for predicting mortality of incident HD patients

<table>
<thead>
<tr>
<th>Model</th>
<th>ΔBIC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>496.23</td>
</tr>
<tr>
<td>SBP + age</td>
<td>8.07</td>
</tr>
<tr>
<td>DBP + age</td>
<td>264.32</td>
</tr>
<tr>
<td>SBP + DBP + age</td>
<td>27.71</td>
</tr>
<tr>
<td>SBP × age (Figure 2A)</td>
<td>8.16</td>
</tr>
<tr>
<td>DBP × age (Figure 2B)</td>
<td>272.51</td>
</tr>
<tr>
<td>PP × age (Figure 2C)</td>
<td>108.60</td>
</tr>
<tr>
<td>Race × SBP + age (Figure 3A)</td>
<td>53.05</td>
</tr>
<tr>
<td>Race × DBP + age (Figure 3B)</td>
<td>310.43</td>
</tr>
<tr>
<td>Diabetes × SBP + age (Figure 3C)</td>
<td>0.00</td>
</tr>
<tr>
<td>Diabetes × DBP + age (Figure 3D)</td>
<td>292.93</td>
</tr>
<tr>
<td>SBP × DBP + age (Figure 1)</td>
<td>40.01</td>
</tr>
<tr>
<td>SBP × age + DBP</td>
<td>34.34</td>
</tr>
<tr>
<td>Race × SBP × age (Figure 4, A through C)</td>
<td>94.50</td>
</tr>
<tr>
<td>Race × DBP × age</td>
<td>365.83</td>
</tr>
<tr>
<td>Diabetes × SBP × age (Figure 4, D through F)</td>
<td>76.95</td>
</tr>
<tr>
<td>Diabetes × DBP × age</td>
<td>388.83</td>
</tr>
<tr>
<td>SBP × DBP × age</td>
<td>88.64</td>
</tr>
<tr>
<td>Race × SBP × DBP × age</td>
<td>289.08</td>
</tr>
<tr>
<td>Diabetes × SBP × DBP × age</td>
<td>278.95</td>
</tr>
</tbody>
</table>

Smaller values of the relative fit measure, ΔBIC, indicate greater empirical support for the model. All models adjusted for age; gender; race; cause of ESRD; and time-varying serum albumin, hemoglobin, creatinine, dialysis dosage, and postdialysis weight. Analyses for table were restricted to black and white patients (n = 15,228 and 5,975 events).

*Change in criteria relative to model with smallest value.

DBP parameters may have a statistically significant relationship to mortality, its clinical impact seems to be modest.

Age, BP, and Mortality

The relationship between SBP and mortality varied with age (P < 0.001; Figure 2A). Among patients who were older than 50 years, SBP <140 mmHg was associated with an increased mortality. SBP values ≥160 mmHg were not associated with increased mortality. Among patients who were younger than 50 years, SBP values <140 mmHg were not associated with increased mortality, and values >160 mmHg were associated with increased mortality. Low DBP values were associated with an increased mortality only among older patients (P < 0.001; Figure 2B). The relationship among pulse pressure (PP), age, and mortality (Figure 2C) was similar to that of SBP. Older patients with low PP had the highest mortality.

Race, BP, and Mortality

Overall, black patients had lower mortality than white patients (HR 0.70 [95% confidence interval [CI] 0.59 to 0.82] at 150 mmHg SBP; Figure 3A and B). Race did not significantly modify the relationships of either SBP or DBP with mortality. Curves representing the HRs at different levels of SBP among black and white patients were nearly parallel except at lowest levels of SBP (Figure 3A). The relationships between DBP and mortality were similar among black and white patients (Figure 3B).

Diabetes, BP, and Mortality

The greater mortality among patients with versus without diabetes was largely restricted to those with SBP <140 mmHg (P < 0.001; Figure 3C). In contrast, among patients with SBP >140 mmHg, mortality was similar among patients with and without diabetes. The diagnosis of diabetes also modified the relationship between DBP and mortality (P = 0.001; Figure 3D).

We conducted sensitivity analyses to ascertain whether the mortality, SBP, and diabetes association was affected by increasing the lag between events/censoring and the time-varying covariate window from 30 to 90 days. This reduced the number of eligible patients by 590 and the number of events by 261; however, the relationship among diabetes, SBP, and mortality was similar using either the 30- or 90-day lag (data not shown).

Joint Association of Race, BP, and Age with Mortality

Among patients who were older than 40 years, mortality at any given SBP was lower among black versus white patients. In contrast, among patients who were younger than 40 years, mortality was similar among black and white patients at any given SBP (P < 0.001; Figure 4, A through C); however, the percentage of patients with SBP <120 mmHg was smaller among black (3.6%) versus white (7.1%) patients. Although statistically significant, the clinical relevance of the effect was

Figure 2. Age interacts with BP so that (A) mortality among incident HD patients is highest for older patients with lower SBP. Only patients <40 years old have increased mortality risk with increasing SBP. (B) Mortality is highest for older patients with lower DBP. (C) Mortality risk and PP show higher mortality risk for older patients with low PP. Models adjusted for age; gender; race; cause of ESRD; and time-varying serum albumin, hemoglobin, creatinine, dialysis dosage, and postdialysis weight. Error bars are point-wise 95% CIs. Referent: SBP = 140 mmHg, DBP = 80 mmHg, PP = 73 mmHg.
modest, as reflected in the 86-unit increase in ∆BIC value over the SBP × age model (Table 2).

**Joint Association of Diabetes, BP, and Age with Mortality**

Among younger patients, the relationships of SBP with mortality were similar among patients with and without diabetes (Figure 4, D through F); however, with increasing age, the mortality risk associated with low SBP was greater among patients with versus without diabetes ($P < 0.001$). The mortality risk associated with higher SBP levels was similar among patients with and without diabetes in all age groups. Although statistical tests indicated that the association among SBP, age, and mortality was modified by diabetes and race, the BIC values for these models were 77 and 95, respectively (Table 2), suggesting that models this complex may not be needed to predict mortality. The model with the smallest BIC was the diabetes SBP age model (Figure 3C). Two other models had BIC within 10 units (SBP age [Figure 2A] and SBP age) of this model, and another four models had BIC values within 27 to 53 units.

**DISCUSSION**

This study is in concert with previous reports that described an association between low SBP and increased mortality among HD patients.13–15 It extends previous observations by demonstrating (1) that the increased mortality associated with low SBP was more pronounced among older patients and those with diabetes; (2) high SBP values among younger patients were associated with increased mortality, regardless of race or diabetes status; (3) among older patients, higher SBP values were not associated with increased mortality; and (4) increased mortality among white versus black patients was largely confined to older patients.

In this study, SBP was more powerful than DBP as a predictor of mortality. This finding is in concert with the greater predictive power of SBP in the general population16; however, our results are in contrast to a report by Bakris et al.,17 which demonstrated that the inclusion of DBP in a model containing SBP informed the risk for future mortality among patients with type 2 diabetes in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study. Recently, Agarwal18 reported that the addition of DBP to models containing SBP significantly improved the prediction of all-cause mortality among patients with chronic kidney disease (CKD). Although we found an association between DBP and mortality, it was quantitatively much less than that between SBP and mortality. The following factors may have contributed to these disparate findings: (1) Agarwal studied patients who had CKD and had not yet reached ESRD; (2) women composed only 4% of his study cohort; and (3) the covariates differed significantly.

**Age, BP, and Mortality**

The relationship between SBP and mortality among HD patients resembles that of older patients in the general population19; however, the relationship of BP to mortality was not uniform across age groups, suggesting that among HD patients, optimal BP targets may differ by age. Only in the youngest cohort (30-year-olds) of HD patients studied was the relationship of SBP to mortality similar to that observed in the general population.20,21 Thereafter, each 10-year increment in age was accompanied by an increase in the HR for mortality associated with low SBP and attenuation of the HR for mortality associated with hypertension. High SBP values were associated with increased mortality only among younger patients.
Among HD patients who were older than 40 years, isolated systolic hypertension similar to that seen in the elderly general population was common. This may reflect the presence of accelerated atherosclerosis and arteriosclerosis, which are common among HD patients. Previous studies conducted of HD patients demonstrated that hypertension was associated with increased mortality among those who survived the first 3 years of dialysis.\textsuperscript{14,22}

The association of low SBP with mortality among HD patients is in concert with observations in the general population,\textsuperscript{8} patients with CKD,\textsuperscript{23} and patients with heart failure.\textsuperscript{24} The reasons for this relationship among HD patients may be multifactorial. Untreated patients with low to normal BP may have severe cardiac disease.\textsuperscript{25} Patients with low to normal BP may have significant intradialytic reductions in myocardial perfusion during HD.\textsuperscript{26,27} Elderly patients and patients with diabetes, with stiff, noncompliant vessels and occlusive arterial disease, may experience significant reductions in organ perfusion during dialysis.

The commonly observed U-shaped relationship between SBP and mortality among HD patients may reflect the wide age spread of patients in our study cohort. Among younger patients, there is a reverse L-shaped curve, reflecting the increased mortality associated with high SBP. In contrast, among older patients, there is an L-shaped curve, reflecting increased mortality at lower SBP values. Middle-aged patients may exhibit either pattern or a U-shaped curve. Combining all age groups results in the commonly cited U-shaped curve.\textsuperscript{13,15}

**Diabetes, BP, and Mortality**

We observed effect modification of diabetes status on the relationship between SBP and mortality. The increase in mortality among patients with diabetes was largely restricted to patients with SBP \( <140 \text{ mmHg} \). The observed interaction related mainly to the higher mortality among patients who had diabetes with SBP \( <140 \text{ mmHg} \); however, low SBP values were also associated with increased mortality among HD patients without diabetes. Age, therefore, was the only analyzed variable that was associated with a qualitative change in the shape of the association curves between SBP and mortality.

Reasons for the increased mortality with low SBP among patients with versus without diabetes include the following: \( 1) \) Diabetes is associated with the aging process\textsuperscript{28–30} such that HD patients who have diabetes and are of a given age may experience an increase in the mortality associated with low SBP comparable to that experienced by older HD patients without diabetes; \( 2) \) patients with diabetes may not tolerate low SBP as well as patients without diabetes do; \( 3) \) patients with diabetes and low SBP may have more comorbidities than patients without diabetes. Ishida \textit{et al.}\textsuperscript{31} reported that after dialysis, the reduction in middle cerebral arterial flow in response to a tilt test is much greater among patients with versus without diabetes.
Nevertheless, current clinical guidelines for patients without ESRD recommend lower BP targets for patients with diabetes; however, we are not aware of published guidelines that call for different BP goals for HD patients with versus without diabetes. Unfortunately, the optimal BP targets in both patients with and without diabetes and with CKD have not been defined. Follow-up data from the Modification of Diet in Renal Disease (MDRD) study demonstrated that a 32% reduction in risk for ESRD associated with lower than usual BP among patients with nondiabetic CKD. In contrast, both the African American Study of Kidney Disease and Hypertension (AASK) and Remipril Efficacy in Nephropathy (REIN-2) trials failed to demonstrate that intensive BP control slows the progression of nondiabetic CKD. Moreover, in Action to Control Cardiovascular Risk in Diabetes (ACCORD), intensive control of BP among patients with type 2 diabetes failed to reduce the annual rate of the primary outcome, a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

Race, BP, and Mortality
The observation that the lower mortality among black versus white patients was primarily restricted to older patients warrants further investigation. Several studies have noted an apparent paradox among black patients who are on dialysis. Despite lower values for dialysis dosage (single-pool Kt/V) and hemoglobin, mortality is lower among black versus white patients. In this study, black patients had lower mortality than white patients despite having higher BP values. Parekh et al. showed that, among dialysis patients, white patients had a higher risk for atherosclerotic cardiovascular disease; therefore, underlying atherosclerotic cardiovascular disease may be an important confounder, which may contribute to lower BP and increased mortality among white HD patients. Bellasi et al., however, found no significant differences in aortic pulse wave velocity, augmentation index, and coronary and thoracic arterial calcification scores, respectively, between black and white patients with ESRD.

Should Mild to Moderate Hypertension Be Treated in HD Patients?
In this study, the relationship between SBP and mortality among HD patients resembles that of much older patients in the general population; however, the relationship of BP to mortality was not uniform across age groups, suggesting that among HD patients, optimal BP targets may differ by age. Only in the youngest cohort (30-year-olds) of HD patients studied did the curvilinear relationship between SBP and mortality resemble that observed in the general population. However, even among young HD patients, the increase in mortality risk associated with increases in SBP was significantly less steep than that observed in the general population, as reported in a meta-analysis conducted by the Prospective Studies Collaboration.

No large randomized, controlled trials targeting tight versus usual control of BP, powered for mortality, have been conducted of HD patients. Recently Heerspink et al. conducted a meta-analysis of randomized, controlled trials that assessed the effect of different antihypertensive medications on all-cause mortality, cardiovascular mortality, and cardiovascular events among HD patients. The majority of patients had only modest hypertension, and the average baseline SBP ranged from 134 to 155 mmHg. Nevertheless, antihypertensive therapy was associated with significant reductions in mortality and cardiovascular events, even though the absolute reductions in BP were small; therefore, at least a portion of the observed beneficial effect may be attributed to medication rather than a reduction in BP.

The Study of Isolated Systolic Hypertension in the Elderly demonstrated that treatment of isolated systolic hypertension in the elderly led to significant reductions in stroke, myocardial infarction, and all-cause mortality. Because HD patients experience acceleration of the aging process, antihypertensive therapy may have a similar beneficial effect among HD patients. In contrast, however, a retrospective cohort analysis of veterans who were older than 80 years and had hypertension demonstrated that among patients whose SBP was judged to be controlled (SBP <140 mmHg), those with higher SBP values were less likely to die than those with lower SBP values. Chronic heart failure is another condition for which a higher SBP may be associated with an improved prognosis. Recently, Raphael et al. published a meta-analysis that assessed the relationship between SBP and mortality among 80,888 patients with chronic heart failure. A 10-mmHg increase in SBP was associated with decreased mortality (13.0%; 95% CI 10.6 to 15.4%).

This study has several important strengths: (1) Use of an incident cohort, which reduced the likelihood of survivor bias and allowed for longer follow-up time; (2) adjustment for important case-mix determinants; (3) large HD sample representative of the US Renal Data System population except for a slight overrepresentation of black patients, studied under “real-world” conditions, thereby ensuring external validity; (4) an excellent database with <1% of all time-varying covariate values missing; and (5) the consistency of the results regarding effect modification for age and diabetes status on predialysis SBP. The study also has important significant limitations: (1) Like all observational studies, we cannot exclude unidentified covariates, and we cannot infer causality; (2) we lacked reliable comorbidity data on baseline cardiovascular disease and congestive heart failure; and (3) use of routine in-center BP measurements may be inferior to measurement of home BP and ambulatory BP monitoring as a way to assess hypertension control and predict clinical outcomes among HD patients.

In summary, this study demonstrates that the relationships between BP and mortality among HD patients may be influenced by age, race, and diabetes status. In conclusion, a prospective, randomized, controlled trial is required to determine optimum BP targets in subgroups of HD patients. Future Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines may need to consider different BP targets for subgroups of HD patients.
CONCISE METHODS

Study Participants
We studied incident patients who began dialysis at facilities operated by Dialysis Clinic Incorporated (DCI) from January 1, 2000, through December 31, 2006. Inclusion criteria were age ≥20 years at start of HD and patient survival for ≥150 days from the first outpatient HD. We restricted the cohort to patients with ≥150 days of follow-up to allow a 30-day lag from the study outcome and to exclude the first 30 days of HD. Exclusion criteria were (1) previous renal transplant or peritoneal dialysis; (2) initiation of long-term HD outside DCI; and (3) missing data on gender, age, or onset of ESRD. Follow-up for death continued until change in modality (renal transplant or peritoneal dialysis), transfer from DCI or withdrawal from dialysis, or study end on December 31, 2007. Patients who transferred from DCI or withdrew from dialysis were followed for vital status for an additional 30 days.

Laboratory and Clinical Parameters
Laboratory measurements were performed monthly at the DCI Laboratory (Nashville, TN). Dialysis dosage, expressed as single-pool Kt/V, was computed using variable-volume urea kinetic modeling. Patient age, gender, race, cause of ESRD, and start date of HD were obtained from DCI’s computerized medical information system (DARWIN). Laboratory data were transferred electronically into DARWIN, using range checks to ensure quality. The study was conducted using predialysis BP measured with participants in the sitting position in accordance with standard clinical practice. Date and cause of death were obtained from Centers for Medicare and Medicaid Services Death Notification form #2746.

Statistical Analysis
Cox proportional hazards models were constructed to investigate the association between predialysis BP and PP and all-cause mortality. Fixed covariates included gender, race, cause of ESRD, and the age and year of HD initiation. Time-varying covariates, including hemoglobin, albumin, creatinine, dialysis dosage, and postdialysis weight, were defined by quintiles. We used 30- and 90-day lag periods to decrease bias from possible secondary influence of the terminal event. Age, BP, and PP were assessed as continuous variables, centered at their sample medians and divided by 10 to reduce collinearity. These variables were added to analyses as cubic polynomial splines with one to four interior knots to model potentially nonlinear relationships with mortality. Splines with two interior knots fit well without inducing clinically uninterruptable changes in the shape of the hazard functions. Additional models included statistical interactions among BP, age, race, and diabetes status to determine whether these factors modified the relationship between BP and mortality.

BP among younger and older HD patients is not the same48; therefore, graphic summaries of HRs were limited to plausible age and BP combinations defined by the bivariate 5th and 95th percentiles of 90-day BP averages. Data are presented as means ± SD. Statistical analyses were conducted in SAS 9.2 (SAS Institute, Cary, NC). Statistical significance was defined as $P < 0.05$. We used the BIC to evaluate the strength of empirical support for the importance of BP as a risk factor for mortality. The BIC combines information on lack of fit (−2 times the maximized log-likelihood) with a penalty for an increased number of parameters: [number of parameters times log(number of events)]. Smaller BIC values represent greater empirical support for a given model.51,52 We used the difference between the BIC for each model and the model with the smallest BIC to summarize support for each model.

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DISCLOSURES
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