Blood Pressure and Mortality Among Hemodialysis Patients

Rajiv Agarwal

Abstract—Blood pressure measured before and after dialysis does not agree well with those recorded outside the dialysis unit. Whether recordings obtained outside the dialysis unit are of greater prognostic value than blood pressure obtained just before and after dialysis remains incompletely understood. Among 326 patients on long-term hemodialysis, blood pressure was self-measured at home for 1 week, over an interdialytic interval by ambulatory recording and before and after dialysis over 2 weeks. Over a mean follow-up of 32 (SD 20) months, 102 patients died (31%), yielding a crude mortality rate of 118/1000 patient years. Systolic but not diastolic blood pressure was found to be of prognostic importance. Adjusted and unadjusted multivariate analyses showed increasing quartiles of ambulatory and home systolic blood pressure to be associated with all-cause mortality (adjusted hazard ratios for increasing quartiles of ambulatory: 2.51, 3.43, 2.62; and for home blood pressure: 2.15, 1.7, 1.44). Mortality was lowest when home systolic blood pressure was between 120 to 130 mm Hg and ambulatory systolic blood pressure was between 110 to 120 mm Hg. Blood pressure recorded before and after dialysis was not statistically significant (P=0.17 for predialysis, and P=0.997 for postdialysis) in predicting mortality. Out-of-dialysis unit blood pressure measurement provided superior prognostic information compared to blood pressure within the dialysis unit (likelihood ratio test, P<0.05). Out-of-dialysis unit blood pressure among hemodialysis patients is prognostically more informative than that recorded just before and after dialysis. Therefore, the management of hypertension among these patients should focus on blood pressure recordings outside the dialysis unit. (Hypertension. 2010;55:00-00.)

Key Words: Home blood pressure ■ ambulatory blood pressure ■ prognosis ■ end-stage renal disease ■ cohort studies

Hypertension is common among patients with chronic kidney disease and often remains poorly controlled in hemodialysis patients.1 Recently, a large cohort study found that the variability of blood pressure (BP) within patients was at least as great as variability seen between patients.2 BP obtained in the dialysis unit by technicians and nurses without attention to detail differ strikingly from BP obtained using standard methods. Nearly half the systolic BP are more than 10 mm Hg different from routine BP when standard methods of measurements are used.3 BP obtained before and after dialysis, even if obtained using standardized methods, agree poorly with interdialytic ambulatory BP.4,5 Furthermore, even standardized BP recordings cannot be used to predict the presence or absence of left ventricular hypertrophy.6 In contrast, BP obtained outside the dialysis unit, whether obtained by interdialytic automatic BP measurement or self-measured BP at home is useful in diagnosing left ventricular hypertrophy.6 Thus, dialysis unit measurement is only distantly related to ambulatory BP or target organ damage. This poor relationship calls into question the use of BP obtained before and after dialysis for the diagnosis and treatment of hypertension among patients on hemodialysis.7

Large cohort studies have found that lower systolic BP obtained before or after dialysis is a determinant of mortality.8,9 On the other hand, a higher ambulatory BP is associated with increased mortality among hemodialysis patients.10 More recently, home and ambulatory BP recordings were found to be of prognostic value.11 Yet, almost all hypertension management in dialysis units uses dialysis unit BP. For treating hypertension, even the national guidelines recommend the use of BP obtained in the dialysis unit.12 The recommendation is possibly because studies that have delineated the relationship between out-of-dialysis unit BP measurement with outcomes are limited in size.

This study examines the hypothesis that out-of-dialysis unit BP measurement will be of greater prognostic significance compared to BP recorded just before and after dialysis. The purpose of this report was to evaluate the presence, strength, and shape of the relationship between BP measured using different modalities (home, ambulatory, and dialysis unit) and all-cause mortality among hemodialysis patients.

Methods

Participants

The cross-sectional data on part of this cohort has previously been reported.3,6 Patients 18 years or older who had been on chronic hemodialysis for more than 3 months, and were free of vascular, infectious, or bleeding complications within 1 month of recruitment who were dialyzed 3 times a week at 1 of the 4 dialysis units in Indianapolis affiliated with Indiana University, were enrolled in the study. Those who missed 2 hemodialysis treatments or more over 1
month, abused drugs, had chronic atrial fibrillation, or body mass index of 40 kg/m² or more were excluded. Patients who had a change in dry-weight or antihypertensive drugs within 2 weeks were also excluded. The study was approved by the Institutional Review Board of Indiana University and Research and Development Committee of the Roudebush Veterans Administration Medical Center, Indianapolis, and all subjects gave written informed consent.

Measurements

Ambulatory BP Monitoring
Ambulatory BP monitoring was performed either after the first or midweek hemodialysis session for 44 hours. Ambulatory BP was recorded every 20 minutes during the day (6 AM to 10 PM) and every 30 minutes during the night (10 PM to 6 AM) using a Spacelab 90207 ambulatory blood pressure monitor (Spacelabs Medical, Inc) in the nonaccess arm, as reported previously.13 Awake and sleep readings were calculated for each patient by self-reported sleep and wake times by means of a diary. Even limited number of ambulatory BP are useful for prognostic purposes in the general population; therefore, we did not exclude any patients based on the number of ambulatory BP recordings.14

Dialysis Unit Blood Pressures
The "reverse epidemiology" of hypertension and mortality among dialysis patients has been described using BP measured in the dialysis unit using oscillometric technique and without adherence to standardized BP measurement methods. To reflect this practice and allow comparisons with larger cohorts, BP was measured by routine oscillometric technique in the dialysis unit. Accordingly, dialysis unit BP recordings were obtained by the dialysis unit staff using the sphygmomanometer equipped with hemodialysis machines without a specified technique and were averaged over 2 weeks surrounding the ambulatory BP measurement. Thus, each patient had 6 predialysis and 6 postdialysis BP recordings to provide routine dialysis unit BP.

Home BP Monitoring
Home BP monitoring was performed over 1 week using a validated self-inflating automatic oscillometric device (HEM 705 CP or 790 TT; Omron Healthcare). Patients were instructed in the use of this monitor and asked not to share this monitor with others. Patients were asked to record their BP 3 times daily—on waking up, between noon and 6 PM, and at bedtime—and log this on a chart provided for this purpose. In some participants, home BP was recorded twice daily in triplicate for 4 days after the midweek dialysis. The average of all readings by day was taken as those representing the overall home BP. Because this monitor is equipped with a memory and printer, only those recordings that were recorded in the memory of the monitor were used.

Outcomes
All-cause mortality was the primary focus of this study, and this outcome was available in every patient. Patients were censored on the date that they had the last dialysis visit if they were transplanted or left the dialysis unit.

Data Analysis
Kaplan–Meier survival curves were created and the log-rank test performed to test the equality of survival by quartiles of BP. Cox proportional hazards regression was used to determine the significance and strength of association of factors associated with mortality outcomes. The proportionality assumption was tested both by evaluating the log minus log plot as well as by testing the Schoenfield residuals. Initially, model fits for mortality were compared between BP without adjustment. To directly compare the BP types (home versus ambulatory) on their impact on all-cause mortality, the hazards ratio for each BP type and the nested model was compared with the likelihood ratio test. We then created multivariate-adjusted models. Adjustments were made for the following variables: age, ethnicity, sex, diabetes mellitus, cardiovascular disease, antihypertensive medications, serum albumin, hemoglobin, and dialysis vintage. Adjusted hazard ratios were calculated with continuous covariates (age, albumin, hemoglobin, dialysis vintage) at their group means for male sex and categorical variables treated as present between quartiles of BP. To ascertain the BP level associated with the best survival, restricted cubic splines of BP were generated, and the association of these splines with mortality was tested using the Cox model.

All analyses were conducted using Stata 11.0 (Stata Corp). The probability values reported are 2-sided and taken to be significant at <0.05.

Results
Between September 2003 and September 2009, 326 patients from 4 dialysis units staffed by the nephrology faculty of Indiana University, Indianapolis, Ind, were recruited. The study flow is outlined in Figure 1. Most patients were excluded because of absence of ambulatory BP recordings; only 2 patients were dropped because ambulatory BP recording was inadequate.

The clinical characteristics of patients by quartiles of systolic ambulatory BP are shown in Table 1. The population was predominantly black, with average age of 55 years. All patients were on 3 times weekly dialysis and were prescribed a dialysis time of 4 hours and blood flow rate of 400 mL/min. Serum albumin and hemoglobin reflect the general hemodialysis population. Cardiovascular disease defined as previous history of myocardial infarction, coronary bypass surgery or angioplasty, or stroke was present in 33% of patients. A majority (74%) of the patients received antihypertensive drugs; β-blockers were used in approximately half, and ACE inhibitors or angiotensin receptor blockers in two-thirds. As expected, those who were in the upper quartiles of hypertension also took more antihypertensive drugs.

Median follow-up was 29 months (interquartile range: 16 to 48 months) with the longest follow-up of 6 years. During this follow-up period, 102 (31%) patients died. The crude mortality rate was 118/1000 patient-years.

Figure 2 shows the Kaplan–Meier survival curves depicting the relationship between all-cause mortality and quartiles of blood pressure measured using ambulatory or BP measurements. A significant relationship between increasing levels of systolic blood pressure and all-cause mortality was seen with home (Figure 3) and ambulatory blood pressure. On the other hand, dialysis unit BP recordings were of no prognostic importance.
Table 1. Clinical Characteristics of the Study Population by Quartiles of 44-Hour Ambulatory Systolic BP

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Overall</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of ambulatory systolic BP</td>
<td>79.2–199.7</td>
<td>79.2–119.2</td>
<td>119.4–134.6</td>
<td>134.6–146.1</td>
<td>146.3–199.7</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>326 (100%)</td>
<td>82 (25%)</td>
<td>81 (25%)</td>
<td>82 (25%)</td>
<td>81 (25%)</td>
<td></td>
</tr>
<tr>
<td>Ambulatory systolic BP, mm Hg</td>
<td>134.2±20.5</td>
<td>108.9±9.0</td>
<td>127.7±4.6</td>
<td>139.9±3.5</td>
<td>160.5±12.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ambulatory diastolic BP, mm Hg</td>
<td>77.0±14.0</td>
<td>63.8±8.2</td>
<td>75.0±10.0</td>
<td>80.7±9.6</td>
<td>88.7±14.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, years</td>
<td>54.9±12.9</td>
<td>53.5±14.2</td>
<td>55.5±12.7</td>
<td>54.7±13.2</td>
<td>56.0±11.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Men</td>
<td>216 (66%)</td>
<td>56 (68%)</td>
<td>49 (60%)</td>
<td>63 (77%)</td>
<td>48 (59%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>White</td>
<td>37 (11%)</td>
<td>9 (11%)</td>
<td>6 (7%)</td>
<td>14 (17%)</td>
<td>8 (10%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>283 (87%)</td>
<td>72 (88%)</td>
<td>74 (91%)</td>
<td>65 (79%)</td>
<td>72 (89%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (2%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Predialysis weight, kg</td>
<td>84.2±20.2</td>
<td>85.4±20.8</td>
<td>87.9±21.2</td>
<td>81.0±18.4</td>
<td>82.3±19.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Postdialysis weight, kg</td>
<td>81.4±19.6</td>
<td>82.7±20.3</td>
<td>85.0±20.5</td>
<td>78.0±17.8</td>
<td>79.5±19.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Years of end-stage renal disease</td>
<td>3.8±4.2</td>
<td>4.5±4.7</td>
<td>3.3±2.9</td>
<td>3.1±2.7</td>
<td>4.2±5.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>159.0 (49%)</td>
<td>28.0 (34%)</td>
<td>36.0 (44%)</td>
<td>48.0 (59%)</td>
<td>47.0 (58%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Past cardiovascular disease</td>
<td>106.0 (33%)</td>
<td>24.0 (29%)</td>
<td>27.0 (33%)</td>
<td>26.0 (32%)</td>
<td>29.0 (36%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Antihypertensive medications</td>
<td>240.0 (74%)</td>
<td>53.0 (65%)</td>
<td>52.0 (64%)</td>
<td>60.0 (80%)</td>
<td>69.0 (85%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ACE inhibitors or angiotensin receptor blockers</td>
<td>209.0 (64%)</td>
<td>43.0 (52%)</td>
<td>53.0 (65%)</td>
<td>55.0 (67%)</td>
<td>58.0 (72%)</td>
<td>0.04</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>170.0 (52%)</td>
<td>30.0 (37%)</td>
<td>33.0 (41%)</td>
<td>53.0 (65%)</td>
<td>54.0 (67%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.7±0.4</td>
<td>3.7±0.4</td>
<td>3.8±0.4</td>
<td>3.7±0.4</td>
<td>3.6±0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.2±1.4</td>
<td>12.4±1.5</td>
<td>12.1±1.4</td>
<td>12.4±1.4</td>
<td>12.0±1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean home BP, mm Hg</td>
<td>149.6±24.1</td>
<td>127.2±18.9</td>
<td>146.5±16.0</td>
<td>152.6±16.5</td>
<td>172.1±20.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>84.6±14.9</td>
<td>75.2±11.5</td>
<td>85.4±13.0</td>
<td>85.4±12.4</td>
<td>92.4±16.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

± indicates SD. Parenthesis have percentage of patients. Continuous variables P values computed through ANOVA. Categorical variables P values computed through χ² test.

Table 2 shows the relationship between BP and mortality outcomes by quartiles of systolic ambulatory BP and home BP. The relationship between quartiles of systolic BP obtained by various methods and the hazard ratio for all-cause mortality showed a strong relationship for ambulatory and less strong relationship for home BP measurements. No such relationship between dialysis-unit BP and mortality was seen (model χ²: 4.97, P=0.17 for predialysis; and model χ²: 0.04, P=0.997 for postdialysis). The relationship between BP and mortality was limited to systolic BP; no such relationship was demonstrated for diastolic BP. The relationship between wake and sleep BP
and mortality was similar to that seen for overall 44-hour ambulatory systolic BP (Table 3).

Time on dialysis (dialysis vintage) significantly influenced survival. In case of ambulatory systolic BP, the hazard ratio per year on dialysis was 1.066 ($P=0.002$). In case of home systolic BP, the hazard ratio per year on dialysis was 1.048 ($P=0.019$). Prevalent cardiovascular disease also influenced survival (for ambulatory hazard ratio [HR]: 1.69, $P=0.017$; for home HR: 1.62, $P=0.031$) as did ethnicity (for ambulatory HR for blacks: 0.41, $P=0.013$; for home HR for blacks: 0.48, $P=0.037$; whites being the reference group).

To directly compare dialysis-unit BP with out-of-dialysis unit BP, 3 models were created. Model 1 was created with quartiles of all 4 types of BP: ambulatory, home, predialysis, and postdialysis. Two nested models were generated next. Model 2 contained only quartiles of dialysis unit BP, and model 3 contained only out-of-dialysis unit BP. The 2 nested models (models 2 and 3) were compared to the model with all 4 types of BP (model 1) using the likelihood ratio test. Model 2 was inferior to model 1 (likelihood ratio test, $P=0.009$), but model 3 was similar to model 1 (likelihood ratio test, $P=0.3$). Models containing ambulatory and home BP showed similar fits by the likelihood ratio test.

Figure 4 shows the nonlinear nature of the relationship between BP and mortality seen for ambulatory and home BP measurements and outcomes. In general, systolic ambulatory BP associated with least mortality was between 110 to 120 mm Hg. The “best” systolic home BP was between 120 to 130 mm Hg.

### Discussion

The results of this study demonstrate the following: (1) the prognostic information of BP measurements obtained in outside the dialysis unit either by the patient or by an automatic monitor is greater than that obtained in the dialysis unit; (2) the prognostic information is nearly all contained in the systolic component of BP, rather than the diastolic component.
component; (3) the relationship of BP to mortality is independent of conventional and unconventional cardiovascular risk factors (Table 2); and (4) the relationship of BP recordings and mortality followed a W-shaped curve for out-of-dialysis unit recordings (Figure 4).

Patients who were recently hospitalized or sick were excluded. Thus, patients who may have been more hypotensive were not studied. Thus, this study differed in its recruitment criteria compared to epidemiological studies which have analyzed all patients in the dialysis unit regardless of their level of illness. These large cohort studies report the consistent higher mortality for lower blood pressures and do not find increase in mortality for increasing the level of BP. Perhaps this may be because of a stronger signal of low BP for mortality reflecting the poor health of these patients. Similar to what has been reported by large cohort studies using dialysis unit measurements, we found a higher mortality among patients in the lowest quartile of home and ambulatory BP. However, in sharp contrast to the cohort studies, out-of-dialysis unit BP recordings demonstrated a clear trend of increasing all-cause mortality among patients in increasing home or ambulatory BP quartiles. These findings suggest that BP recorded outside the dialysis unit may contain greater prognostic information compared to BP measured in the dialysis unit.

Three studies using ambulatory BP monitoring in hemodialysis patients support the notion that ambulatory BP and mortality are strongly related. Among 57 treated French hypertensive hemodialysis patients, Amar et al. reported that at follow-up of 34±20 months, 10 patients died of cardiovascular causes. Nocturnal systolic BP was associated with increased risk of cardiovascular death (risk ratio: 1.41; 95% CI 1.08 to 1.84). The largest study to date among hemodialysis patients reporting the relationship between 24-hour ambulatory BP and cardiovascular outcomes comprised of 168 patients. Among these nondiabetic patients without preexisting cardiovascular events, Tripepi et al. reported the ratio of the average systolic BP during the night and day (night/day systolic ratio) used to indicate the nocturnal fall in BP or the dipping phenomenon was associated with all-cause and cardiovascular mortality on both univariate and multivariate analyses. In contrast to Tripepi et al., this study included blacks (who had a lower mortality compared to whites) and those with cardiovascular disease (who had a higher mortality as expected). A previous report by Alborzi et al. reported that ambulatory BP was of greater prognostic value compared to dialysis unit BP recordings, but these analyses were unadjusted for cardiovascular risk factors. An important aspect of the current report is that the effect of ambulatory and home BP on survival persisted even after adjustments for cardiovascular disease, as well as conventional and unconventional cardiovascular risk factors for mortality. Furthermore, the current study extends the above reports to a cohort nearly twice as large as the largest study reported to date and with a longer follow-up.
The present study found that home systolic BP threshold for optimal survival was 10 mm Hg higher than ambulatory systolic BP. When compared to ambulatory systolic BP among hemodialysis patients, home systolic BP is on average 12.2 mm Hg higher.\(^5\) Thus, it is not surprising to find a higher threshold for optimal outcome with home systolic BP. A shorter follow-up from a subgroup of this cohort has also found a link between increased home BP to mortality among long-term hemodialysis patients.\(^1\) The results of this study are also consistent with previously published cohort studies examining the influence of home BP with clinic BP among patients without kidney disease.\(^{17,18}\) Similarly, compared to clinic BP among patients with chronic kidney disease not on dialysis, the risk for end-stage renal disease is increased to a greater extent when home BP recordings are considered.\(^{19}\)

The W-shaped relationship for home BP and mortality was unexpected. A similar though less pronounced W pattern was discernable for ambulatory BP. It is possible that when home BP (or ambulatory BP) was found to be high, patients were treated leading to a subsequent improvement in survival. Thus, treatment with antihypertensive medications (that may have a cardioprotective effect) or dry-weight reduction may modify the relationship of the initial measurement of BP and the final outcome. Given that the analysis is limited to a single occasion of BP measurement, the time-dependent relationships cannot be explored.

There are several possibilities why out-of-dialysis unit measurements may have provided better prognostic information. First, multiple blood pressure measurements over the course of the day, as done with home or ambulatory blood pressure monitoring, can average out the troughs and peaks in BP swings, which predialysis and postdialysis BP recordings are unable to provide.\(^{20}\) Second, dialysis unit blood pressures are influenced by the white coat effect—elevated BP only in the dialysis setting—which is less pronounced with home blood pressures and eliminated by ambulatory blood pressure monitoring.\(^{21}\) Third, masked hypertension—elevated BP at home but normal in the dialysis unit—is potentially detected with home BP monitoring and ambulatory blood pressure monitoring and may be of prognostic significance.\(^{22}\) Finally, blood pressures sampled from a broader pool of situations may make them more representative of the person’s typical blood pressure.\(^{14}\)

There are several strengths and limitations of this report. This study was largely limited to black people, and excluded were certain patients such as those with morbid obesity and atrial fibrillation because of difficulties with accurate blood pressure assessment in this group. Whether the same results would hold in people of other ethnicities and of broader clinical characteristics is not known and will require verification in future cohorts. Although this is the largest study among dialysis patients reported to date, the sample size of this study was still relatively small. Some strengths of this study are as follows: (1) by using cubic splines, the threshold of BP that is associated with a better prognosis could be tested, instead of using arbitrary definitions of normotension and hypertension which are debatable in the hemodialysis population; (2) the home blood pressure monitor used was a validated device equipped with a memory device and printer, so there was a mechanism in place to confirm the authenticity of the patient reports.\(^{23}\)

**Perspective**

Dialysis unit blood pressures neither predict target organ damage\(^*\) nor all-cause mortality in relatively healthy dialysis patients. Thus, in dialysis patients more so than in the general population, blood pressure measurement and treatment should occur with recordings made outside the clinic. The results of the study support the view out of dialysis unit BP being important for prognostication of mortality even after adjustment for nonconventional risk factors. Causality cannot be implied in a cohort study; however, this study may offer some guidelines with respect to BP goals. Self-measured systolic BP of \(\approx\)120 to 130 mm Hg and of \(\approx\)110 to 120 mm Hg by ambulatory BP are associated with the best prognosis. These thresholds may be used to test the hypothesis if controlling hypertension in hemodialysis patients using out-of-dialysis unit blood pressure recordings would make a difference to cardiovascular mortality.\(^{24}\)

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**Disclosures**

None.

**References**

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