Effect of Blood Pressure on Early Decline in Kidney Function Among Hypertensive Men

Suma Vupputuri, Vecihi Batuman, Paul Muntner, Lydia A. Bazzano, John J. Lefante, Paul K. Whelton, Jiang He

Abstract—Few cohort studies have examined the longitudinal association between change in blood pressure and decline in kidney function among treated hypertensive patients without chronic kidney disease. We conducted a nonconcurrent cohort study to examine the effects of blood pressure on estimated glomerular filtration rate and early kidney function decline (rise in serum creatinine ≥0.6 mg/dL during follow-up) among 504 African-American and 218 white hypertensive patients. Our results showed that each standard deviation higher treated systolic (18 mm Hg) and diastolic (10 mm Hg) blood pressure was associated with an average annual decline in estimated glomerular filtration rate of −0.92 (−1.49 to −0.36) P = 0.001) and −0.83 (−1.38 to −0.28) P = 0.003) mL · min⁻¹ · 1.73 m⁻², respectively, after adjustment for race, age, education, income, use of antihypertensive drugs, body mass index, and history of diabetes and dyslipidemia. Likewise, each standard deviation higher systolic and diastolic blood pressure was associated with relative risks (95% CIs) of 1.81 ([1.29 to 2.55] P < 0.001) and 1.55 ([1.08 to 2.22] P = 0.046), respectively, for early kidney function decline. Compared with patients with a blood pressure level <140/90 mm Hg, those with a blood pressure level ≥160/95 mm Hg had a −2.67 (−4.01 to −1.32) P < 0.001) mL · min⁻¹ · 1.73 m⁻² greater annual decline in estimated glomerular filtration rate and a 5.21-fold ([2.06 to 13.21] P < 0.001) greater risk of early kidney function decline. Our study found that higher levels of treated blood pressure were positively and significantly related to early decline in kidney function among hypertensive men. These results indicate that better blood pressure control might prevent the onset of chronic kidney disease among hypertensives. (Hypertension. 2003; 42:1144-1149.)

Key Words: blood pressure ■ kidney failure ■ hypertension, detection and control ■ glomerular filtration rate ■ longitudinal studies

Chronic kidney disease is an underrecognized and undertreated condition despite its high prevalence, clinical significance, and economic cost in the United States. The exact prevalence of chronic kidney disease is unknown, but current estimates based on the Third National Health and Nutrition Examination Survey indicate that 3.0% of the US population aged 17 years or older has an elevated level of serum creatinine (defined as ≥1.6 mg/dL in men and ≥1.4 mg/dL in women). This corresponds to 5.6 million persons with impaired kidney function, 70% of whom have hypertension. Of those with an elevated serum creatinine and hypertension, 27% had their blood pressure (BP) reduced to <140/90 mm Hg, and only 11% had their BP reduced to <130/85 mm Hg. One of the most significant health consequences of chronic kidney disease is end-stage renal disease (ESRD), of which 23% of cases in 1999 were judged by nephrologists to be caused by hypertension. Despite the availability and widespread use of antihypertensive medication, elevated BP continues to be a major contributor to chronic kidney disease and the leading cause of ESRD in African-Americans.

It has long been accepted that advanced kidney failure results in hypertension? and that untreated severe and malignant hypertension almost always leads to kidney damage. In the general population, however, severe or malignant hypertension is infrequent and appears to account for only a small proportion of all cases of kidney failure. Likewise, ESRD seems to occur in only a small proportion of all cases of hypertension. Thus, at the population level, it remains unclear whether elevated BP is the cause or consequence of impaired kidney function.

Several prospective studies have identified elevated BP as a strong, independent risk factor for ESRD in the general population. Additional studies have examined the effect of BP on the development of chronic kidney disease in a population of hypertensive patients. However, few epi-
demiology studies have examined the effect of BP on the progression of kidney disease with repeated measures of kidney function. The objectives of the present study were to examine the longitudinal relations between change in treated BP and estimated glomerular filtration rate (GFR) and the incidence of early kidney function decline in treated hypertensive patients.

Methods

Study Participants
This nonconcurrent cohort study was conducted among 890 hypertensive patients who attended the Hypertension Clinic at the Veterans Administration Medical Center of New Orleans (VAMCNO) between 1976 and 1999. Data collection was based on a comprehensive hospital chart review by using standardized data abstraction and face-to-face patient interviews. Study information collected within the calendar year of the first clinic visit was treated as baseline data, and study information collected during subsequent years was treated as follow-up data. Of the eligible study participants, 10 patients’ charts could not be retrieved because of patient transfer or lost medical records, and 34 patients did not have either baseline or follow-up data. In addition, 1 female patient, 13 patients of race other than black or white, and 110 patients with a baseline estimated GFR <60 mL·min⁻¹·m⁻² were excluded, leaving 722 patients in the present analysis.

Exposure Assessment
BPs at baseline and during follow-up were measured by clinic nurses using a standard mercury sphygmomanometer. Systolic and diastolic BP measurements during each calendar year (up to 10 measurements) were averaged to obtain mean values of BP per year. The use of antihypertensive medication was assessed by examining patient medical records and conducting in-person interviews.

Outcome Assessment
Serum creatinine was measured with the modified kinetic Jaffe method at the clinical laboratory of the VAMCNO. Measurements taken during the first year (baseline) and subsequent years (follow-up) were averaged with up to 10 measurements to obtain a mean value per year for analysis. Two outcomes were used in the present analysis: change in estimated GFR and early kidney function decline. GFR, estimated in milliliters per minute per 1.73 m², was calculated by using an abbreviated formula developed for the Modification of Diet in Renal Disease Study: GFR = 186.3 × (serum creatinine level)⁻¹.15 × age⁻⁰.²⁰ × (0.742 if female) × (1.212 if black). The annual change in estimated GFR was calculated by subtracting the previous year’s mean estimated GFR value from the mean of follow-up years for each individual.

We defined incident early kidney function decline as a rise in serum creatinine ≥0.6 mg/dL (3 times the minimum detectable difference established in the Atherosclerosis Risk in Communities study¹⁶,¹⁷) during a median of 7 years of follow-up. Sensitivity analyses with different cutoffs (0.4 mg/dL to 0.8 mg/dL) were conducted with markedly similar results.

Covariable Assessment
Information on age, sex, race, and history of diabetes and dyslipidemia was collected from each study participant’s hospital chart and in-person interview. Education level, annual income, smoking, and alcohol consumption were assessed during the in-person interview. (Race-specific means were assigned to missing data on these variables.) Body weight and height were abstracted from hospital records and used to calculate body mass index (BMI).

Statistical Analysis
The mean or proportion of baseline characteristics of study participants was calculated by race. Treated BP was analyzed as a continuous variable and was also categorized into 3 levels of BP control: (1) systolic BP <140 mm Hg and diastolic BP <90 mm Hg, (2) systolic BP between 140 and 159 mm Hg or diastolic BP between 90 and 94 mm Hg, and (3) systolic BP ≥160 mm Hg or diastolic BP ≥95 mm Hg. Univariate and multivariate mixed-effects models were used to examine the longitudinal effects of time-dependent treated BP (modeled as a continuous and categorical variable) on annual change in estimated GFR. Continuous and categorical BPs recorded for a given year were used to predict change in kidney function in the subsequent year for all statistical models. The cumulative incidence of early kidney function decline over the study period was calculated by race using the Kaplan-Meier product-limit method.²⁰ Extended Cox proportional-hazards models with time-dependent covariables were used to explore the univariate and multivariate relations between time-dependent treated BP and incidence of early kidney function decline.²¹ Multivariate models included the following covariables: baseline GFR, race, age, high school education, income, use of angiotensin-converting enzyme (ACE) inhibitors, history of diabetes, history of dyslipidemia, BMI, and baseline year. Interactions between age and systolic and diastolic BPs were tested in all models. All statistical analyses were performed with the SAS statistical package.²²²³

Results
Table 1 shows the baseline characteristics of the 722 male, hypertensive study participants by race. Study participants were predominantly African-Americans (70%). Compared with the white patients, African-Americans were younger and more likely to have an annual income <$10,000 per year. Also, African-Americans were less likely to have a history of dyslipidemia at baseline compared with their white counterparts. The proportions of study participants taking antihypertensive medication and mean systolic BPs were similar among both groups; however, African-Americans had a higher mean diastolic BP, a lower mean BMI, and a higher estimated GFR.

Over a median follow-up of 7 years, the mean annual change in treated systolic and diastolic BPs, respectively, was −1.52 and −2.11 mm Hg in whites and −0.73 and −1.59 mm Hg in African-Americans. The mean annual change in estimated GFR was −1.34 mL·min⁻¹·m⁻² in both whites and African-Americans. The cumulative incidence of early kidney function decline at year 15 was 20.7% and 25.2% for whites and African-Americans, respectively (log-rank probability value, 0.251). Furthermore, the cumulative incidence of early kidney function decline by baseline BP level is shown in the Figure. For participants with a treated baseline systolic/diastolic BP of <140 and <90 mm Hg, 140 to 159 or 90 to 94 mm Hg, and ≥160 or ≥95 mm Hg, the cumulative incidences were 7.3%, 25.3%, and 38.5%, respectively (log-rank probability value, 0.003).

Higher systolic and diastolic BPs were significantly associated with a greater decrease in estimated GFR in univariate and multivariate models (Table 2). A 1-SD increase in systolic (18 mm Hg) and diastolic (10 mm Hg) BP was associated with an annual decline in estimated GFR of −0.92 (P = 0.001) and −0.83 (P = 0.003) mL·min⁻¹·m⁻², respectively, after adjusting for baseline GFR, age, race, high school education, income, use of ACE inhibitors, history of diabetes, history of dyslipidemia, and BMI. When both systolic and diastolic BPs were included in the same model simultaneously, only systolic BP remained a statistically significant predictor of risk. For example, a 1-SD increase in
systolic and diastolic BP was associated with an annual decline in estimated GFR of \(-0.67\) \((P=0.04)\) and \(-0.51\) \((P=0.11)\) mL·min\(^{-1} \cdot \text{1.73 m}^2\), respectively, after multivariate adjustment.

The mean annual change in estimated GFR associated with different levels of BP control over follow-up is presented in Table 3. Compared with patients with a treated SBP/DBP of \(\leq 140\) and \(\leq 90\) mm Hg, those with a treated SBP/DBP of 140 to 159 or 90 to 94 mm Hg had a nonsignificantly greater reduction in estimated GFR, whereas those with a treated SBP/DBP \(\geq 160\) or \(\geq 95\) mm Hg had a significantly greater reduction in estimated GFR, after adjustment for important covariates.

The multivariate adjusted relative risk of early kidney function decline associated with a 1-SD change in systolic and diastolic BP was 1.81 (95% confidence interval [CI], 1.29 to 2.55) and 1.55 (95% CI, 1.08 to 2.22), respectively, after adjusting for baseline GFR, age, race, high school education, income, use of ACE inhibitors, history of diabetes, history of dyslipidemia, and BMI (Table 4). In the multivariate models that included both systolic and diastolic BP simultaneously, a 1-SD increase in systolic and diastolic BP was associated with early kidney function decline, with relative risks of 1.70 (95% CI, 1.13 to 2.57) and 1.12 (95% CI, 0.74 to 1.71), respectively.

The relative risk of early kidney function decline associated with a treated SBP/DBP \(\geq 160\) or \(\geq 95\) mm Hg, compared with \(< 140\) and \(< 90\) mm Hg was 5.21 (95% CI, 2.06 to 13.21), after similar adjustment (Table 5). The multivariate adjusted relative risk associated with a treated SBP/DBP of 140 to 159 or 90 to 94 mm Hg, compared with \(\leq 140\) and \(< 90\) mm Hg was 1.82 (95% CI, 0.68 to 4.90). No significant interactions between age and systolic or diastolic BP on the progression of kidney disease were found in any of the models (not shown).

**Discussion**

This study documented a strong and consistent association between treated BP level and lower GFR and early kidney function decline in male hypertensive patients without chronic kidney disease (ie, estimated GFR \(\leq 60\) mL/min) at baseline. We found that systolic BP was a much stronger predictor of kidney function decline than was diastolic BP. These results have important clinical and public health implications. Hypertension is a commonly assigned underlying cause of incident ESRD cases in the United States, and hypertensive ESRD incidence continues to climb. In 2000, \(~ 96\) 192 persons in the United States either initiated chronic dialysis therapy or received a kidney transplant for ESRD. The total prevalent ESRD population in that same year was 373 217 persons, with a corresponding estimated overall direct cost of \(>\$19.4\) billion. Our findings show the effectiveness of improved BP control on slowing the decline in kidney function among hypertensive patients and underscore the importance of achieving and maintaining intensive BP treatment goal recommendations in the national treatment guidelines.

The uniqueness of our study derives from the use of a longitudinal design whereby multiple measures of exposure and outcome were obtained during follow-up. In addition, means of up to 10 measures each year in serum creatinine and

**TABLE 1. Baseline Characteristics of 722 Male, Hypertensive Patients by Race**

<table>
<thead>
<tr>
<th>Variables</th>
<th>White</th>
<th>African American</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>218</td>
<td>504</td>
<td>...</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>60.0 (9.9)</td>
<td>56.7 (12.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school education, %</td>
<td>64.6</td>
<td>63.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Annual income (&lt;$10 000)/y, %</td>
<td>35.2</td>
<td>46.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Use of antihypertension medication, %</td>
<td>97.7</td>
<td>97.6</td>
<td>0.94</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>6.4</td>
<td>7.3</td>
<td>0.66</td>
</tr>
<tr>
<td>History of dyslipidemia, %</td>
<td>14.2</td>
<td>6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m(^2)</td>
<td>29.9 (5.7)</td>
<td>27.8 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor use, %</td>
<td>56.8</td>
<td>80.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mm Hg</td>
<td>150.3 (18.2)</td>
<td>149.1 (17.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diastolic BP, mean (SD), mm Hg</td>
<td>85.8 (10.1)</td>
<td>88.9 (10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td>1.1 (0.1)</td>
<td>1.2 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR, mL per min per 1.73 m(^2)</td>
<td>77.7 (13.2)</td>
<td>86.4 (17.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cumulative incidence of early kidney function decline among hypertensive men by level of BP. SBP indicates systolic blood pressure, and DBP, diastolic blood pressure.
BP were used in our analyses, thus allowing for substantial precision and validity. In addition to providing increased statistical power, longitudinal studies such as the current investigation are also more robust with respect to biases commonly found in observational studies because they are insensitive to absent covariates that do not change with time.25

Few epidemiologic studies have examined the effect of changes in BP on the progression of kidney disease in treated hypertensive patients. A study by Rostand et al12 examined 94 patients with treated hypertension over an average of 58 months to determine the frequency with which kidney function deteriorated and the factors associated with deterioration. These authors concluded that although kidney function was preserved in 85% of patients, it deteriorated in some patients despite good BP control. No significant association was found between BP and rise in serum creatinine in multivariate models. The small sample size in that study, however, might have impaired their statistical power to detect a significant association. In addition, only 1 BP measurement at baseline and 2 serum creatinine measurements (an initial and 1 final) were used to assess the relation of BP and kidney function deterioration.

Another study assessed the effect of treatment of hypertension on the development of ESRD among 5730 black and 6182 nonblack male veterans from 32 Veterans Administration Hypertension Screening and Treatment Program clinics14 and demonstrated that a high pretreatment systolic BP was independently associated with an increased risk of ESRD. Because our study used change in estimated GFR as the outcome measure, we were able to observe the early decline of kidney function and reduce bias because of elevated BP as a consequence of established kidney disease. It is extremely difficult to distinguish cause-and-effect relationships between BP and kidney disease in observational studies.2,3,7,26 Key advantages to our study are that we examined this relation among hypertensive men who were initially free of chronic kidney disease and we had repeated measures of BP and kidney function over a prolonged period of follow-up. Thus, we can effectively emphasize the importance of interventions aimed at the primary prevention of chronic kidney disease.

A third study, in a subset of the Multiple Risk Factor Intervention Trial (MRFIT)13 population, examined data on 5524 men with mild hypertension and no evident kidney damage at baseline. In this study, BP control was associated with a slow decline in kidney function (measured by reciprocal serum creatinine slope) among participants with untreated mild hypertension.13 In the MRFIT cohort, mild hypertension was defined as the average of 2 diastolic BP measurements ≥90 mm Hg and not taking antihypertensive medications. Our study examined the relation between BP and risk of chronic kidney disease among treated hypertensive patients and showed consistent findings.

Also, Young et al27 examined the relation between baseline BP and incident decline in kidney function among 2181 elderly men and women participating in the Systolic Hypertension in the Elderly Program. They found adjusted relative risks (95% CIs) of 2.4 (1.67 to 3.56) and 1.3 (0.87 to 1.91) for decline in kidney function associated with the highest versus lowest quartile of systolic and diastolic BP, respectively. Young et al further determined that systolic rather than diastolic BP was a stronger predictor of decline in kidney function. Our study found similar results, showing that systolic BP was a strong, independent predictor of reduced kidney function and incident early kidney function decline by using multiple measures of BP and GFR over time.

### TABLE 2. Mean Annual Change and 95% CI in Estimated GFR

<table>
<thead>
<tr>
<th>Model</th>
<th>Systolic BP (18 mm Hg)</th>
<th>Diastolic BP (10 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>−0.85 (−1.31, −0.38)‡</td>
<td>−0.33 (−0.77, 0.10)</td>
</tr>
<tr>
<td>Age- and race-adjusted</td>
<td>−0.81 (−1.29, −0.34)‡</td>
<td>−0.44 (−0.89, 0.02)</td>
</tr>
<tr>
<td>Multivariate-adjusted*</td>
<td>−0.92 (−1.49, −0.36)†</td>
<td>−0.83 (−1.38, −0.28)†</td>
</tr>
</tbody>
</table>

Estimated GFR is in ml per min per 1.73 m² and is associated with time-dependent systolic and diastolic BP.

*Adjusted for baseline GFR, race, age, high school education, income, use of ACE inhibitors, history of diabetes, history of dyslipidemia, BMI, and baseline year.

†P<0.01, ‡P<0.001.

### TABLE 3. Mean Annual Change and 95% CI in Estimated GFR

<table>
<thead>
<tr>
<th>Model</th>
<th>Systolic/Diastolic BP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;140 and &lt;90</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>. .</td>
</tr>
<tr>
<td>Age- and race-adjusted</td>
<td>. .</td>
</tr>
<tr>
<td>Multivariate-adjusted*</td>
<td>. .</td>
</tr>
</tbody>
</table>

Estimated GFR is in milliliters per minute per 1.73 m² and is associated with time-dependent levels of BP control.

*Adjusted for baseline GFR, race, age, high school education, income, use of ACE inhibitors, history of diabetes, history of dyslipidemia, BMI, and baseline year.

†P<0.001.
Several BP-lowering trials have demonstrated that reduction in BP might slow the progression of kidney disease among hypertensive subjects; however, all of these studies were conducted among persons who already had kidney disease and thus, are consistent with the concept that BP is a promoter of kidney disease. Our findings suggested that BP might play a role in the initiation of kidney damage, in addition to being an important risk factor for the progression of kidney disease. In a meta-analysis of 10 randomized trial including 26,521 hypertensive patients without kidney disease, Hsu et al. examined the hypothesis that nonmalignant hypertension might be an initiator of renal insufficiency. Overall, treated patients had lower BP and fewer cardiovascular events. However, patients randomized to antihypertensive therapy (or more intensive therapy) did not have a significant reduction in their risk of developing renal dysfunction (relative risk, 0.97; 95% CI, 0.78 to 1.21; \( P = 0.77 \)). In this meta-analysis, the outcome (renal dysfunction) was not consistent among all studies, and the average follow-up time was only 3.8 years. Compared with clinical trials, our findings might be more generalizable to the hypertensive patient population.

There are several limitations to our study. First, the study participants were identified through hospital records. If potential study participants were missing from the investigation because of death, survival bias might have occurred. Higher BP and higher serum creatinine are both strong risk factors for total mortality. Therefore, the effect caused by fewer study participants would likely have biased the regression coefficients toward zero and the estimates of relative risks toward 1. Second, kidney function was estimated by using a prediction equation based on serum creatinine, age, race, and sex rather than on inulin or iothalamate clearance methods. Furthermore, no data were available on urine proteins; therefore, excluding patients on the basis of direct evidence of impaired glomerular permeability was not possible. However, serum creatinine has been widely used in clinical and public health practice as an indicator of kidney function. As such, our findings have direct clinical and public health implications. In addition, our study used an average of multiple measurements of serum creatinine taken during a given year of follow-up, and it might provide a more reliable estimate of a participant’s usual kidney function than a single clearance measure. Finally, our study was conducted in male veterans, and our findings might only be applied to this population. Caution should be used when making inferences for women based on these results. However, our investigation included a large number of patients who are often underrepresented in studies, such as African-Americans and persons of low socioeconomic status.

### Perspectives

Our study supports the hypothesis that BP, especially systolic BP, is an important determinant in the decline of kidney function in treated hypertensive patients. Furthermore, our findings, from a longitudinal study design, show the effectiveness of greater control of BP among hypertensive patients in slowing the initiation and progression of kidney disease and that might subsequently prevent or prolong the onset of hypertensive ESRD.

### Acknowledgment

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### References

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