Correlates of Systolic Hypertension in Patients With Chronic Kidney Disease

Rajiv Agarwal, Martin J. Andersen

Abstract—Hypertension in patients with chronic kidney disease (CKD) is predominantly systolic. The contribution of risk factors for hypertension to the overall systolic blood pressure (BP) is unknown. To study the relationship between risk factors for hypertension and systolic BP in patients with CKD, 232 veterans (mean age 67 years; 96% men; 20% black; 39% with diabetes mellitus; estimated glomerular filtration rate [GFR] 48 mL/min per 1.73 m²) had clinic (routine and standardized measurements) and out-of-clinic (home and 24-hour ambulatory) BPs recorded. In multivariate analysis, using 17 risk factors, the log of the urine protein/creatinine ratio was the strongest predictor of systolic BP regardless of the BP measurement technique. The strength of the relationship between proteinuria and systolic BP was in the order ambulatory > home > standardized clinic > routine clinic BP measurement. Other independent predictors were age, race, and number of antihypertensive drugs used, and the model fit was better for out-of-clinic than clinic BP recordings. Estimated GFR was not an independent predictor of systolic BP by any technique. Nocturnal dipping was associated with higher estimated GFR, higher serum albumin, younger age, and less proteinuria. Proteinuria is the most important correlate of systolic BP in older men, the strongest relationship of which was with ambulatory and home systolic BP. Out-of-clinic BP recordings correlate better with target organ damage, as measured by proteinuria, and may be of greater clinical value than clinic BP recordings in predicting hypertension-related outcomes such as end-stage renal disease and death. (Hypertension. 2005;46:514-520.)

Key Words: proteinuria n kidney

Hypertension is very common in patients with chronic kidney disease (CKD); its prevalence increases with falling glomerular filtration rate (GFR) and reaches an estimated 86% in patients with end-stage renal disease (ESRD). In the third National Health and Nutrition Examination Survey, 70% of those with an elevated serum creatinine had hypertension. Sodium and water retention with progressive decrease in GFR is thought to be etiologically related to the high prevalence of hypertension. However, many other factors such as activation of sympathoadrenal system, renin-angiotensin system, and circulating inhibitors of NO are also responsible for the high prevalence of hypertension.

Although blood pressure (BP) control is paramount in preventing the progression of renal disease, factors related to BP control in the CKD population have scarcely been examined. In the Modification of Diet in Renal Disease (MDRD) study, 5 risk factors were found to be independent predictors of the presence of hypertension. In decreasing order of significance, these factors were GFR, body mass index (BMI), black race, increasing age, and male gender. In a survey of 1921 patients with CKD in Europe, the odds of presence of hypertension were increased independently by the following risk factors listed in the order of significance: creatinine clearance, age, presence of diabetes, hypertriglyceridemia, and proteinuria. Although both of these studies evaluated factors associated with the presence or absence of hypertension in patients with CKD, neither evaluated factors associated with BP control.

Using ambulatory BP monitoring, we previously reported poor control of BP, predominantly systolic, in 65% of 232 patients with CKD. However, the relationship between risk factors known to be associated with poor BP control was not examined and remains unknown for patients with CKD. Understanding risk factors may allow for better targeting of BP control. Furthermore, no study has tested the relationship of known risk factors for hypertension with out-of-clinic BP recordings in patients with CKD. If differences exist among risk factors that predict systolic BP in clinic versus out-of-clinic settings, it may point to differences in the predictive value of these BP recordings.

Because hypertension in CKD is predominantly systolic, we explored the relationship between risk factors for hypertension and systolic BP control in a cross-sectional study of veterans with CKD. The independent relationship of several risk factors with systolic BP control obtained in the clinic and out of the clinic by home and ambulatory BP recordings were determined. We also analyzed the correlates of fall in BP with sleep (the dipping phenomenon), which is an independent predictor of poor renal outcomes in the CKD population.
Methods

Subjects

Consecutive patients were recruited from the renal and a general medicine clinic at the Indianapolis Veterans Affairs Hospital if they were ≥18 years of age with a GFR estimated by the 4-component MDRD equation\(^1\) of <60 mL/min per 1.73 m\(^3\). Patients were excluded for BMI >40 kg/m\(^2\), acute renal failure, dialysis or kidney transplantation, changes in their antihypertensive regimens within 2 weeks of study enrollment, or if they had atrial fibrillation.

A medical history was obtained and physical examination performed on each participant. Specifically, the etiology of CKD and the presence of cardiovascular disease (coronary artery disease [CAD], peripheral vascular disease [PVD], cerebrovascular disease [CVD]) and histories of gout and smoking were obtained for all enrolled patients. CAD was defined as a previous history of myocardial infarction, coronary artery bypass surgery, or angiplasty. PVD was defined as a previous history of nontraumatic amputation, lower extremity bypass surgery, or abdominal aortic aneurysm. CVD was defined as a previous history of stroke. Actual medications being taken by the subjects were recorded.

Urine creatinine assay was performed with a modification of Jaffe reaction (Boehringer Mannheim catalog No. 450019), and urine protein assay was performed with a turbidimetric method using benzethonium chloride read at 550 nm using a Hitachi 911 analyzer (Boehringer Mannheim; Roche Diagnostics Corp). A single random urine specimen was used from each participant.

The institutional review board of Indiana University and the research and development committee of the Richard L. Roudebush Veterans Affairs Medical Center approved this study, and all patients gave their written, informed consent.

BP Measurement

Clinic BPs

Standardized clinic BPs were obtained by one nurse trained in BP measurement according to national guidelines.\(^1\) Using an appropriate cuff size 3, measurements via the Omron 412C semiautomatic BP monitor were obtained in both arms. The higher of the 2 averages from each arm was defined as the patient’s clinic BP. The same arm was used to determine the home and ambulatory BPs.

Routine clinic BPs (R-CBPs) were those obtained by the clinic nurses using an automated device (DINAMAP 1846SX; Critikon).

No protocol was defined to measure R-CBP. All R-CBPs were made in the afternoon. Standardized clinic BPs were averaged over 2 visits; one was an afternoon visit as the R-CBPs and a second that typically was in the morning.

Home BPs

After instruction in use by one research nurse, the patients recorded their home BP via the same Omron 412C BP monitor that was used to collect their standardized clinic BP. The patients took their home BP in the morning, afternoon, and evening for 1 week and recorded their home BP into diaries. At the end of the week, both the monitors and diaries were returned to the investigators. Because the recordings from the first day be inaccurate,\(^1\) they were discarded in calculating the patients’ average home BP. Patients with <9 home BP were excluded from final analysis.

Ambulatory BPs

The patients underwent 24-hour ambulatory BP monitoring with the Spacelabs 90207 monitor (Spacelabs, Inc.), a monitor that has been validated by the British Hypertension Society and the Association for the Advancement of Medical Instrumentation protocols. The monitor recorded BPs every 20 minutes during the day (6:00 AM to 10:00 PM) and every 30 minutes at night (10:00 PM to 6:00 AM). These periods were also used to define night and day BP averages. The patients recorded their sleep and wake times during the ambulatory BP monitoring. Ambulatory BP monitoring was considered adequate if 14 systolic and diastolic measurements were obtained during the day and 7 during the night based on the guidelines of the European Society of Hypertension.\(^1\) Several definitions of dipping were tested using systolic BP. These included night BP minus day BP, asleep minus awake BP, night-to-day ratio, and asleep-to-awake ratio. Dipping was defined as a ≥10 mm Hg reduction in asleep ambulatory BP compared with awake ambulatory BP. It was also defined as a ≥10% reduction in asleep ambulatory BP compared with awake ambulatory BP.\(^1\)

Statistical Analysis

Seventeen risk factors were tested for association with systolic BP measured by 4 methods (see Tables 3 and 4). Ambulatory BP was further analyzed by circadian BP (see Table 5) as well as dipping index definitions (see Table 6). One-way ANOVA was used to compare continuous risk factors, and the χ\(^2\) test was used for dichotomous risk factors. Only significant risk factors are reported in each table. Then, multivariate step-wise regression analysis was used to find the most important risk factors among the significant risk factors in each of the 4 measurement methods (see Table 4) and in each of the dipping definitions (see Table 7).

The following 17 risk factors were tested for associations: age, race (black or white, coded as 0 and 1), BMI, use of alcohol, current smoking, gout (active disease or past history versus absence of gout), CAD, stroke, PVD, etiology of kidney disease (coded 1 for diabetes, and 0 for nondiabetic kidney disease), use of antihypertensive drugs, number of antihypertensive drugs, total cholesterol, serum albumin, hemoglobin, log of urine protein/creatinine ratio and estimated GFR. Urine protein/creatinine ratio was log transformed to approximate the data to a normal distribution.

The standardized β-coefficient reflects the change in the dependent variable (in this case, systolic BP) for 1 SD change in the independent variable. By examining the standardized β-coefficients, the strength of the associations between predictor variables can be assessed; the largest β-coefficient would indicate the strongest association. The adjusted r\(^2\) is provided to compare multivariate regressions with a varying number of risk factors. All analyses were performed using SPSS software (version 13.0; SPSS Inc).

Results

The clinical characteristics of the study population are shown in Table 1 and are reflective of the Veteran population.

The nature and amount of drug use is shown in Table 2. Nearly 90% of the CKD patients received treatment for hypertension, and the mean number of drugs used was 2.66 in the overall population. Among patients who were treated, the mean number of drugs used was 2.97. The commonest agents were renin-angiotensin system inhibitors, followed by β-blockers.

Bivariate Relationship Between BP and Risk Factors

The bivariate relationship between the risk factor and systolic BP are shown in Table 3. The strength of the relationship can be ascertained by the examination of r\(^2\), where r\(^2\) is a measure of the proportion of the variance accounted for by the risk factor.

Listed in order of strength of correlation, routine clinic systolic BP was higher with log urine protein/creatinine ratio, absence of CAD, higher total cholesterol, number of antihypertensive drugs, use of antihypertensive drugs, nonuse of alcohol, and older age. No association was seen with estimated GFR, diabetic renal disease, race, albumin, or hemoglobin.

Standardized clinic systolic BP was higher with log urine protein/creatinine ratio, lower estimated GFR, greater number of antihypertensive drugs, lower hemoglobin, older age, use of antihypertensives, diabetic kidney disease, black race, and lack of alcohol use.
Home systolic BP was associated with log urine protein/creatinine ratio, number of antihypertensive drugs, estimated GFR, diabetic kidney disease, antihypertensive drug use, age, hemoglobin, and black race.

Ambulatory systolic BP was associated with log urine protein/creatinine ratio, number of antihypertensive drugs, estimated GFR, diabetic kidney disease, antihypertensive drug use, hemoglobin, serum albumin, and black race.

Also notable is that the strength of the relationship with log protein to creatinine ratio as the independent predictor of systolic BP increased from routine ($r^2=0.099; P<0.0001$) to standardized clinic systolic BP ($r^2=0.184; P<0.0001$). Whereas the strength of the relationship increased from standardized to home BP ($r^2=0.260; P<0.0001$), there was not as dramatic an improvement in model fit with 24-hour ambulatory BP monitoring ($r^2=0.272; P<0.0001$).

**Multivariate Relationship Between BP and Risk Factors**

In multivariate analysis, the log of the protein/creatinine ratio was the strongest predictor of systolic BP regardless of the BP measurement technique (Table 4). The strength of the relationship between proteinuria and systolic BP was in the following order: 24-hour ambulatory > home > standardized > R-CBP.

BP medication number was also a significant predictor regardless of the BP measurement method and followed the order: home > ambulatory > standardized > routine systolic BP.

There were differences in predictor variables by BP measurement technique. CAD and total cholesterol were significant independent predictors only for routine systolic BP but not for any other BP measurement method. Age was a significant predictor for all except ambulatory BP. Blacks had a higher BP by standardized and ambulatory BP recording but not for other methods.

The model fit indicated progressive improvement in fit in the order ambulatory = home > standardized > routine systolic BP (Table 4). The risk factors accounted for 32.4% of the variance in the case of ambulatory systolic BP and 32.7% of the variance for the home BP model, but only 26.8% of variance for standardized clinic BP and 19.1% of variance for R-CBP.

At higher estimated GFRs, the MDRD formula may be inaccurate. Therefore, we reanalyzed the data after excluding participants with serum creatinine of $>1.5$ mg/dL. Log urine protein-to-creatinine ratio remained the most robust predictor of systolic BP regardless of the BP measurement method. In analyses limited to black participants, log urine protein-to-creatinine ratio remained the best predictor for ambulatory systolic BP.

**Dipping Phenomenon and Its Correlates**

Night systolic BP was lower than day by $4.98\pm10.7$ mm Hg, whereas asleep systolic BP was lower than awake systolic by...
TABLE 3. Bivariate Relationships Between Predictors and Respective Systolic BP

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Routine Clinic</th>
<th>Standardized Clinic</th>
<th>Home</th>
<th>24-Hour Ambulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Std β</td>
<td>r²</td>
<td>P</td>
<td>Std β</td>
</tr>
<tr>
<td><strong>Continuous variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.135</td>
<td>0.018</td>
<td>0.041</td>
<td>0.24</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.16</td>
<td>0.026</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Log urine protein/creatinine</td>
<td>0.315</td>
<td>0.099</td>
<td>&lt;0.0001</td>
<td>0.43</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.254</td>
<td>0.064</td>
<td>&lt;0.0001</td>
<td>-0.147</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.301</td>
<td>0.091</td>
<td>&lt;0.0001</td>
<td>-0.286</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomous variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (white vs nonwhite)</td>
<td>-0.156</td>
<td>0.024</td>
<td>0.017</td>
<td>-0.138</td>
</tr>
<tr>
<td>Etiology of renal disease (diabetes vs nondiabetes)</td>
<td>0.17</td>
<td>0.028</td>
<td>0.011</td>
<td>0.242</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>-0.139</td>
<td>0.139</td>
<td>0.035</td>
<td>-0.133</td>
</tr>
<tr>
<td>CAD</td>
<td>-0.167</td>
<td>0.028</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>BP medication use</td>
<td>0.148</td>
<td>0.022</td>
<td>0.024</td>
<td>0.19</td>
</tr>
<tr>
<td>No. of BP medications</td>
<td>0.153</td>
<td>0.023</td>
<td>0.020</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Standardized β (Std β) reflects the change in the dependent variable for 1 SD change in the independent variable. A larger standardized β reflects greater strength of the association.

### Discussion

The major finding of the study was the strong association of proteinuria, over and above other risk factors, especially estimated GFR with systolic BP. This association was not affected by the way BP was measured, although the strength of the association increased in the order: ambulatory → home → standardized clinic → routine clinic. Estimated GFR was not a significant correlate of systolic hypertension after accounting for proteinuria regardless of the BP measurement technique. The strong association of proteinuria with poor BP control may be attributable to the tight relationship of proteinuria with vascular disease. Although low GFR is recognized as a cardiovascular risk factor, proteinuria in patients with CKD may be a better marker of the presence of vascular disease. The shared mechanisms that underlie poor vascular compliance, proteinuria, and systolic hypertension may account for the strong association between proteinuria and systolic hypertension in CKD.
We also observed different associations of risk factors with systolic BP, depending on the setting in which they were taken. Routine clinic systolic BP was associated with total cholesterol but not with estimated GFR, hemoglobin, race, or etiology of renal disease. This was in direct contradistinction to all other techniques of BP monitoring. This lack of association is likely attributable to poor technique of routine BP measurement methods and misclassification of hypertension.6 The poorer model fit for routine systolic BP compared with other methods also suggests that routine methods for BP measurement in the CKD clinic may not be optimal for detection of target organ damage.

We did not find an association between BMI and systolic BP, even in bivariate analysis, regardless of BP technique. In the MDRD study, the prevalence of hypertension increased from 70% with a BMI at the 10th percentile to 94% with a BMI at the 97th percentile.4 This relationship was independent of GFR. The average BMI of our population was 30.4 compared with 27.5 kg/m² in the hypertensive MDRD cohort. One possible reason for the lack of association between obesity and hypertension may be because of the much higher BMI in our population, which may have a ceiling effect on BP. Another reason could be the different comparisons made in the MDRD and our study. Whereas the MDRD study analyzed the relationship between mean arterial pressure and BMI, we analyzed the systolic BP with BMI.

Nocturnal dipping, when assessed by patient diaries, showed greater difference in sleeping and awake systolic BP than when using the “fixed-clock” method that yields the night–day differences. Therefore, it appears that the asleep–awake difference is likely attributable to poor technique of routine BP measurement in the CKD clinic may not be optimal for detection of target organ damage.

### TABLE 6. Bivariate Relationships Between Predictors and Dipping Index by Ambulatory Systolic BP

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Night/Day Ratio</th>
<th>Asleep/Awake Ratio</th>
<th>Night–Day Difference</th>
<th>Asleep–Awake Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Std β</td>
<td>r²</td>
<td>P</td>
<td>Std β</td>
</tr>
<tr>
<td>Continuous variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.176</td>
<td>0.031</td>
<td>0.007</td>
<td>0.243</td>
</tr>
<tr>
<td>Log urine protein/creatinine</td>
<td>0.224</td>
<td>0.05</td>
<td>0.001</td>
<td>0.248</td>
</tr>
<tr>
<td>Albumin</td>
<td>−0.221</td>
<td>0.049</td>
<td>0.001</td>
<td>−0.201</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>−0.163</td>
<td>0.026</td>
<td>0.015</td>
<td>−0.163</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td>−0.238</td>
<td>0.057</td>
<td>&lt;0.0001</td>
<td>−0.282</td>
</tr>
<tr>
<td>Dichotomous variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology of renal disease (diabetes vs nondiabetes)</td>
<td>0.143</td>
<td>0.02</td>
<td>0.030</td>
<td>0.141</td>
</tr>
<tr>
<td>No. of BP medications</td>
<td>0.204</td>
<td>0.042</td>
<td>0.002</td>
<td>0.203</td>
</tr>
</tbody>
</table>

Standardized β (Std β) reflects the change in the dependent variable for 1 SD change in the independent variable. A larger standardized β reflects greater strength of the association.
common pathogenesis of nondipping with atherosclerotic process. 27

Some limitations of our data should be recognized. The effect of gender could not be tested, given a predominantly male population. Thus, the results of the study may not be applicable to women. No information on cardiac function was available in these patients, thus the prediction of systolic BP was devoid of cardiac output. No direct measurements of vascular stiffness were made, so we can only speculate that the association between proteinuria and higher systolic BP was attributable to increased vascular stiffness.

In perspective, the differences between predictors of systolic BP by routine clinic measurements and other methods as well as substantially weaker fit of the overall model suggests that R-CBP measurements may be associated with poor long-term prediction of clinical end points such as ESRD or death. Standardized BP measurements are a better option for clinical decision making, but home BP monitoring may be a superior tool because the model fit is nearly equivalent between home and ambulatory BP recordings. Log urine protein/creatinine ratio, number of antihypertensive drugs, older age, and black race are the best correlates of poor BP control in veterans with CKD.

In patients who are normotensive before dialysis, uncontrolled hypertension is seen only in 4% after onset of dialysis, whereas in those patients with uncontrolled hypertension before dialysis, 30% remain uncontrolled after institution of dialysis therapy. 28 If uncontrolled hypertension in patients with CKD before ESRD is an important predictor for hypertension during ESRD, it would appear that better control of hypertension in hemodialysis patients should start with better control of hypertension before ESRD to reduce the dismal cardiovascular outcomes in the ESRD population.

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References
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