Hypertension

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Abstract—The extent to which chronic kidney disease (CKD) affects achievement of blood pressure targets is not comprehensively understood. We evaluated the effects of CKD (estimated glomerular filtration rate: <60 mL/min per 1.73 m^2) on achievement of blood pressure control (nondiabetic: $<140/90$ mm Hg; diabetic: $<130/85$ mm Hg) using data from the Guidelines for Drug Therapy of Hypertension Trial. This 15-month study obtained outpatient blood pressures from 3 Veteran's Affairs institutions. Among 9985 subjects with hypertension, we evaluated the association of CKD with achieved control and antihypertensive medication use. We also explored the association between the number of antihypertensives and systolic, diastolic, and pulse pressure. After 15 months, 41% of participants met blood pressure targets. CKD was not associated with control (adjusted odds ratio: 1.04; 95% CI: 0.93 to 1.15). However, CKD was associated with higher odds of use of ≥3 medications among nondiabetic subjects (odds ratio: 1.46; 95% CI: 1.25 to 1.71) and diabetic subjects (odds ratio: 1.40; 95% CI: 1.17 to 1.66). A significant interaction was observed between CKD and the number of antihypertensives as determinants of diastolic and pulse pressures. Among non-CKD participants, a greater number of antihypertensives (0 compared with 4) was associated with wider pulse pressure ($\Delta5.2$ mm Hg; $P<0.001$), mainly because of higher systolic pressures ($\Delta3.6$ mm Hg; $P=0.001$). Among participants with CKD, although greater numbers of antihypertensives were associated with even wider pulse pressures ($\Delta8.3$ mm Hg; $P<0.001$), this was primarily because of lower diastolic pressures ($\Delta4.8$ mm Hg; $P<0.01$). Among participants with CKD, greater use of antihypertensives was associated with lower diastolic pressures. Given recent evidence suggesting adverse effects of diastolic hypotension, these results suggest potential risks in patients with CKD from aggressive attempts to control systolic blood pressure. (*Hypertension*. 2007;50:474-480.)

Key Words: chronic kidney disease ■ hypertension ■ diastolic blood pressure ■ pulse pressure ■ antihypertensive drugs

Hypertension is a well-known risk factor for cardiovascular disease and the progression of chronic kidney disease (CKD) to end-stage renal disease.[1,2] Despite extensive dissemination of guidelines,[1] achievement of hypertension control targets remains low in the United States.[3–5] The extent to which reduced kidney function affects the achievement of blood pressure targets has not been well studied among subjects with hypertension with and without CKD, despite the known high prevalence of increased serum creatinine levels among subjects with hypertension.[6] Trials of patients with CKD show that achievement of adequate control requires 3 to 4 antihypertensive agents on average.[7,8]

Although up to 70% of persons with CKD have attained adequate blood pressure control in the setting of clinical trials,[7] the impact of CKD on attainment of blood pressure goals and use of antihypertensive therapies has not been thoroughly studied. One study from the National Health and Nutrition Examination Survey III (1988–1994) found higher blood pressure levels and greater use of antihypertensive agents among participants with increased serum creatinine levels.[6] In addition, a study from the National Health and Nutrition Examination Survey IV (1999–2002) found that uncontrolled hypertension in persons with CKD appeared almost entirely attributable to high systolic blood pressure and wide pulse pressure, defined by the difference between systolic and diastolic blood pressures.[9]

We evaluated the effect of CKD on achievement of blood pressure targets and antihypertensive medication use in a

large, multisite, prospective cohort of hypertensive veterans. We specifically explored the associations of CKD with measures of systolic, diastolic, and pulse pressure separately. We hypothesized that CKD would be independently associated with worse systolic blood pressure control despite the greater number of antihypertensive medications. Knowledge of the effects of CKD on the control and treatment of hypertension is important given the high prevalence of CKD in this setting and the poor rates of blood pressure control.[3–5]

Methods

Design

This study is an analysis from the Guidelines for Drug Therapy of Hypertension Study, a 15-month-long trial of hypertension guideline implementation in primary care outpatient clinics. This trial was conducted between 2002 and 2003 and randomly assigned outpatient primary care clinicians to receive either recommendations from a computer-based decision support system that used pop-up windows to assist in hypertension management or a control pop-up window with a reminder of the patient's blood pressure and current medications.[10] The computer-based decision support system used in the trial was the Assessment and Treatment of Hypertension: Evidence-Based Automation (ATHENA).[11,12] Eligible clinicians were primary care providers (attending physicians, nurse practitioners, or physician's assistants) with a panel size ≥20 hypertensive patients. Study sites included the Veteran's Affairs (VA) Palo Alto Health Care System, the San Francisco VA Medical Center, and the Durham VA Medical Center. The study protocol was approved by the appropriate institutional review boards at each site.

Subjects

Subjects in these analyses were patients treated by participating providers and had a diagnosis of hypertension (International Classification of Diseases, 9th Revision codes 401.1 or 401.9) before the study period (2002–2003). Clinical information for these patients was extracted from the VA computerized records system to include all of the recorded blood pressures at primary care outpatient clinic visits, medications, and comorbidities at study entry and during the study follow-up. Inclusion criteria were a recorded blood pressure at the first clinic visit during the study period and subsequent recorded blood pressures at clinic visits during the follow-up period. Patients were excluded from the trial if they received >4 antihypertensive agents at the start of the study and if they had clinical characteristics suggesting that the standard hypertension guidelines would not apply. Specifically, patients were excluded if they were immunosuppressed; had prescriptions for amiodarone or spironolactone; were pregnant or women of childbearing age; had serum creatinine >2.5 mg/dL; had a diagnosis of malignant hypertension, secondary hypertension, or renal artery stenosis (specifically, malignant hypertension, malignant hypertensive heart disease, malignant hypertensive heart disease without heart failure, malignant hypertensive heart disease with heart failure, secondary hypertension, and renovascular secondary hypertension); or had a diagnosis of narcolepsy, ascites, spinal cord injury, idiopathic subaortic stenosis, or previous organ transplant. A total of 11 473 patients were eligible for analysis. For the present analyses, we excluded those who did not have a baseline creatinine, defined by measurement within 1 year before study entry. This left a cohort of 9985 patients.

Measurements

Major Predictor

Glomerular filtration rate (GFR) was estimated using the standard formula from the Modification of Diet in Renal Disease Study.[13] Serum creatinine was measured at the VA laboratories of each participating medical center. We used the National Kidney Foundation definition of CKD (GFR <60 mL/min per 1.73 m²).[14] To explore the possibility of misclassification by CKD, we measured the

κ statistic for agreement of CKD status using 2 definitions. We compared CKD status agreement by using creatinine measured at visit 1 with CKD status using the average creatinine at visits 1 and 2 (for those who had >1 creatinine).

Secondary Predictors

Age, race/ethnicity, gender, history of smoking, presence of diabetes, and history of congestive heart failure, myocardial infarction, coronary artery disease, or angina were identified from the medical chart. The presence or absence of comorbidities was identified using the International Classification of Disease, Ninth Revision, diagnoses from outpatient encounter forms, inpatient discharge diagnoses, and the computerized problem list. These data sources have high positive and negative predictive values for the presence of common chronic illnesses relevant to drug choices for hypertension.[15] The study arm was recorded to control for potential effects of the intervention.

Outcomes

The outcomes of interest were systolic, diastolic, and pulse pressures and the use of antihypertensive medications. For each patient, blood pressure measurements were extracted for each primary care visit during the 15-month study period. Adequate blood pressure control was defined as achieving a mean blood pressure of <140/90 mm Hg for those without diabetes and <130/85 mm Hg for those with diabetes during the 15-month study period, as per Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines, which were in effect at the time of the study.[16] Medication use was assessed by the presence of active prescriptions in the VA outpatient pharmacy at the beginning and at the end of the study period. The VA context is one of an equal access health care system where the impact of the patient's ability to pay for care is minimized; patients in the VA have very low or no copayments for medication.

Statistical Analysis

We compared baseline characteristics of patients with and without CKD using Student's t test for continuous variables or χ^2 tests for categorical variables. To account for the repeated measures of blood pressure, we used generalized estimating equations with the exchangeable correlation matrix to study the association between CKD and systolic blood pressure control during the study period. We used systolic blood pressure control, because only ≈1% of the study sample had isolated diastolic hypertension. We built separate models for diabetic and nondiabetic subjects. We adjusted for the sociodemographic characteristics and comorbidities listed above, as well as the study arm and the number of antihypertensive medications.

We also evaluated the association of CKD with the odds of requiring ≥3 medications at the end of the study period using multivariable logistic regression. We chose to study this association at the end of the study period to capture the extent of treatment after the clinicians had 15 months to optimize blood pressure management. We determined the association of the number of antihypertensive agents with each blood pressure component using the final recorded blood pressure. We also determined the mean systolic, diastolic, and pulse pressures among patients taking 0, 1, 2, 3, 4, or more antihypertensives, stratified by the presence or absence of CKD. We then used linear regression analyses to estimate the independent associations of the number of antihypertensive agents with systolic, diastolic, and pulse pressures separately, after adjustment for variables discussed above. We stratified these models by the presence of CKD and tested for interactions. To explore the potential effect of each medication class, we stratified our CKD cohort based on the use of β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or calcium channel blockers separately. All of the analyses were conducted using SAS statistical software version 9.2. A 2-sided $P \leq 0.05$ was considered significant.

Results

Baseline Characteristics

Among the 9985 patients in this study, the mean number of visits per person during the 15-month period was 3.12 ± 1.32.

TABLE 1.   Comparison of Characteristics of 9985 Veterans With Hypertension by Presence or Absence of CKD

Characteristic (Baseline)	Estimated GFR Categories, mL/min per 1.73 m²		
	CKD n=2075	No CKD n=7910	P
Age, y	74.2±9.4	65.9±11.5	<0.0001
Men	1997 (96.2)	7701 (97.4)	0.007
Race/ethnicity			
White	1046 (50.4)	3598 (45.5)	<0.0001
Black or black/Hispanic	117 (5.6)	1040 (13.2)	
Asian	69 (3.3)	203 (2.6)	
Hispanic/white	54 (2.6)	302 (3.8)	
Unknown	789 (38.0)	2767 (35.0)	
History of smoking	372 (17.9)	2063 (26.1)	<0.0001
History of myocardial infarction	254 (12.2)	713 (9.0)	<0.0001
History of angina	236 (11.4)	696 (8.8)	0.0003
History of coronary artery disease	918 (44.2)	2495 (31.5)	<0.0001
History of congestive heart failure	353 (17.0)	621 (7.9)	<0.0001
History of stroke	280 (13.5)	653 (8.3)	<0.0001
History of diabetes	834 (40.2)	2813 (35.6)	<0.0001
No. of hypertension medications			
0	185 (8.9)	1344 (17.0)	<0.0001
1	531 (25.6)	2761 (34.9)	
2	772 (37.2)	2476 (31.3)	
3	473 (22.8)	1058 (13.4)	
4	114 (5.5)	271 (3.4)	
β-Blockers	870 (41.9)	2768 (35.0)	<0.0001
α-Blockers	542 (26.1)	1419 (17.9)	<0.0001
Calcium channel blockers	640 (30.8)	1979 (25.0)	<0.0001
Diuretics	1041 (50.2)	2605 (32.9)	<0.0001
ACE inhibitors	1055 (50.8)	3429 (43.5)	<0.0001
Angiotensin receptor blockers	150 (7.2)	340 (4.3)	<0.0001
Other HTN medications	7 (0.34)	12 (0.15)	0.08
Creatinine, mg/dL	1.50±0.24	1.02±0.16	<0.0001

Data are n (%) or mean±SD unless otherwise defined.

At study entry, those with CKD were older; had more coronary artery disease, heart failure, and diabetes; had higher serum creatinine values; and used a greater number of antihypertensive medications at baseline. Diuretics, ACE inhibitors, and angiotensin receptor blockers were used more frequently in CKD patients than in non-CKD patients (Table 1). Overall, 41% of the cohort met blood pressure targets at baseline.

CKD and Blood Pressure Control
Rates of blood pressure control were similar among those with and without CKD in unadjusted analyses. In those with estimated GFR <45 mL/min per 1.73 m², 43.5% attained blood pressure targets compared with 41% in those with GFR 45 to 60 mL/min per 1.73 m² and 40% in those with GFR >60 mL/min per 1.73 m² (P=0.32). In a multivariable linear model using repeated measures to account for longitudinal measure of blood pressure over 15 months, CKD was not independently associated with systolic blood pressure control. Among nondiabetic subjects, odds ratios (ORs) for systolic blood pressure control were 1.05 (95% CI: 0.94 to 1.17; P=0.36) for those with estimated GFR 45 to 60 mL/min per 1.73 m² and 1.10 (95% CI: 0.92 to 1.31; P=0.28) for those with estimated GFR <45 mL/min per 1.73 m². Among diabetic subjects, results were similar, with OR at 1.07 (95% CI: 0.92 to 1.23; P=0.39) and 0.97 (95% CI: 0.77 to 1.22; P=0.78), respectively, for estimated GFR 45 to 60 and <45 mL/min per 1.73 m².

CKD and Antihypertensive Medication Use
CKD was significantly associated with a greater likelihood of requiring ≥3 medications among nondiabetic and diabetic subjects at the end of the study period. After adjustment for sociodemographic characteristics, comorbidities, and study arm, CKD remained associated with a 40% greater odds of requiring ≥3 medications in both diabetics and nondiabetic subjects (Table 2). Among patients with CKD who were prescribed 4 antihypertensive drugs (n=132), only 34% achieved blood pressure control. Among those without CKD who received 4 antihypertensive drugs (n=379), 38% achieved blood pressure control.

To explore possible misclassification, we conducted a sensitivity analysis comparing 2 definitions of CKD (1 using creatinine at visit 1 and 1 using the average creatinine of visit 1 and 2 including only those who had >1 creatinine). The agreement was very high, with a κ statistic of 0.88 (95% CI: 0.86 to 0.89). We replicated the results of our Table 2, including only those participants who had >1 creatinine during the study period and whose CKD status was the same at >1 visit. The results were essentially unchanged; the association of CKD with a requirement of ≥3 antihypertensive medications among nondiabetic subjects (adjusted OR: 1.57; 95% CI: 1.32 to 1.87) and among diabetic subjects (adjusted OR: 1.50; 95% CI: 1.24 to 1.83) was essentially the same.

Effect of CKD and Use of Antihypertensives on Each Blood Pressure Component
In unadjusted repeated-measures analyses, the presence of CKD was associated with slightly higher systolic blood pressure over the 15-month period (0.9 mm Hg; P=0.02) but with a significantly lower diastolic blood pressure (−4.3 mm Hg; P<0.001) and a significantly wider pulse pressure (5.2 mm Hg; P<0.001) compared with participants without CKD. After multivariable analysis, CKD remained associated with lower diastolic blood pressure (−0.7 mm Hg; P=0.002) but was not significantly associated with mean systolic or pulse pressures (P>0.20 for both).

We observed a highly significant interaction between CKD and the number of antihypertensives as a predictor of diastolic blood pressure (interaction P=0.001) and pulse

TABLE 2. Odds of Using ≥3 Antihypertensive Agents at End of Study Among 9985 Veterans With Hypertension, Stratified by Diabetes Status

Diabetes Status	No. on ≥3 Medications (%)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)*	P
Nondiabetic (n=6338)					
No CKD†	901 (18)	1.0 (Referent)	...	1.0 (Referent)	...
CKD	330 (27)	1.69 (1.46 to 1.95)	<0.0001	1.46 (1.25 to 1.71)	<0.0001
Diabetic (n=3647)					
No CKD	783 (28)	1.0 (Referent)	...	1.0 (Referent)	...
CKD	302 (36)	1.47 (1.25 to 1.73)	<0.0001	1.40 (1.17 to 1.66)	0.0002

*Logistic models adjusted for race, gender, age, heart disease (angina, myocardial infarction, or coronary artery disease), smoking, heart failure, and study arm.

†CKD=GFR <60 mL/min per 1.73 m^2.

pressure (interaction $P=0.09$) but not systolic blood pressure (interaction $P=0.52$). In unadjusted analyses, use of a greater number of antihypertensives was associated with a progressive widening of pulse pressure and lowering of diastolic blood pressure, particularly among persons with CKD (Table 3).

Among non-CKD patients, a greater number of antihypertensives was associated with higher systolic blood pressures, modestly lower diastolic blood pressures, and wider pulse pressures after multivariable adjustment. Mean systolic pressure among those taking 0 antihypertensives was 136 mm Hg (95% CI: 135 to 137 mm Hg) compared with 140 mm Hg (95% CI: 138 to 141 mm Hg) among those taking 4 medications (P for linear trend=0.05). Mean diastolic pressure was 76 mm Hg (95% CI: 75 to 77 mm Hg) versus 74 mm Hg (95% CI: 73 to 75 mm Hg) for 0 compared with 4 medications ($P<0.001$). Pulse pressure was wider among those taking 4 medications compared with 0 (66 mm Hg; 95% CI: 64 to 67 mm Hg; versus 60 mm Hg; 95% CI: 59 to 61 mm Hg; $P<0.001$).

In contrast, in the setting of CKD, a higher number of antihypertensives was associated with substantially wider pulse pressures and lower diastolic blood pressure levels but not with systolic blood pressure. Among those taking no antihypertensives, mean diastolic pressure was 74 mm Hg (95% CI: 72 to 76 mm Hg) compared with 69 mm Hg (95% CI: 67 to 71 mm Hg) for those taking 4 medications (P for

linear trend: <0.001), An even greater widening of pulse pressure was observed among those with CKD, with mean pulse pressure 63 mm Hg (95% CI: 60 to 66 mm Hg) versus 72 mm Hg (95% CI: 69 to 74 mm Hg) for 0 compared with 4 medications (P for linear trend: <0.001). The greater number of antihypertensive medication use was not associated with systolic blood pressure in the setting of CKD ($P=0.27$).

We also estimated the adjusted differences (in millimeters of mercury) in each blood pressure component among those taking 0, 1, 2, 3, and 4 medications at the end of the study period, stratified by CKD. Among those without CKD, we found that pulse pressure widening with a greater number of antihypertensives was mostly attributable to increases in systolic blood pressure. In contrast, among those with CKD, pulse pressure widening was almost entirely attributable to lower diastolic blood pressures (Figure, panels a and b). When we limited these analyses to persons with uncontrolled hypertension, we observed a similar pattern of associations of even greater magnitude.
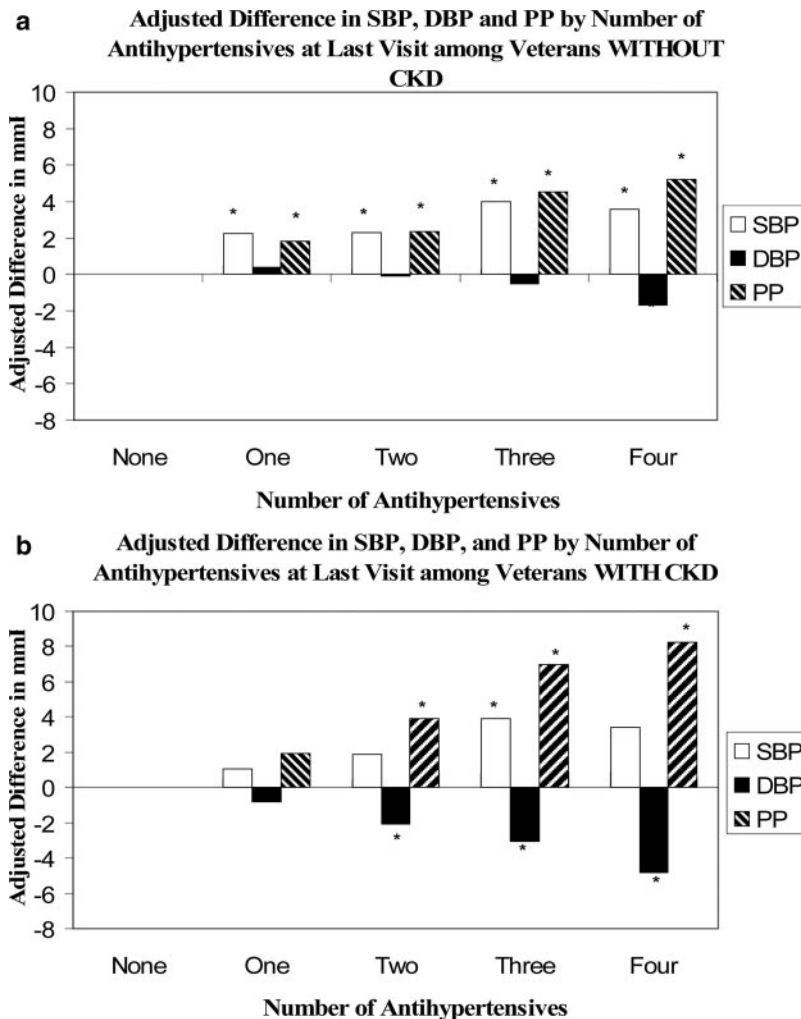
In addition, we stratified our results by age (<65 and >65 years) and found similar patterns of wider pulse pressure associated with a higher number of medications for both groups in unadjusted analyses. Surprisingly, the increase in pulse pressure associated with a higher number of medications was somewhat larger in magnitude among younger participants (54 to 68 mm Hg; $P<0.01$) compared with older

TABLE 3. Unadjusted Mean Systolic, Diastolic, and Pulse Pressures at End of Study by Number of Antihypertensive Medications

Mean, mm Hg	No HTN Medications (n=1184)	1 Medication (n=3112)	2 Medications (n=3373)	3 Medications (n=1805)	4 Medications (n=511)	P for Trend
CKD*						
Mean SBP	137±21	139±20	139±19	141±20	140±19	0.27
Mean DBP	74±13	73±12	72±12	71±13	68±13	<0.001
Mean PP	63±20	65±18	67±17	70±17	72±18	<0.001
No CKD						
Mean SBP	136±16	139±17	138±18	140±19	140±18	0.13
Mean DBP	77±11	77±11	76±12	74±13	73±13	<0.001
Mean PP	59±15	62±15	63±16	66±16	66±16	<0.001

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

*CKD=GFR <60 mL/min per 1.73 m^2.

a

Adjusted Difference in SBP, DBP and PP by Number of Antihypertensives at Last Visit among Veterans WITHOUT CKD

b

Adjusted Difference in SBP, DBP, and PP by Number of Antihypertensives at Last Visit among Veterans WITH CKD

*$P<0.05$ for multivariate linear estimate (reference group=0 antihypertensives) adjusted for age, gender, race/ethnicity, smoking, history of diabetes, angina, myocardial infarction, heart failure, coronary artery disease, and study arm. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and PP, pulse pressure.

participants (65 to 72 mm Hg; $P<0.01$). However, the increase in pulse pressure among the younger participants was mainly because of increasing systolic blood pressure with higher number of medications (132 to 144 mm Hg; $P=0.02$). Among older participants, the change in pulse pressure was primarily because of lower diastolic blood pressure (73 to 67 mm Hg; $P<0.01$).

To explore the effects of different types of medications, we stratified our CKD cohort based on use of β-blockers, diuretics, ACE inhibitors, and calcium channel blockers and evaluated the effects of the use of 4 versus 0 antihypertensives in each pair of subgroups. We found a very interesting pattern of attenuated increases in pulse pressures by a higher number of medications among users of β-blockers ($\Delta 8$ mm Hg for users versus $\Delta 13$ mm Hg for nonusers), diuretics ($\Delta 5$ versus $\Delta 10$ mm Hg), and ACE inhibitors ($\Delta 5$ versus $\Delta 12$ mm Hg). In contrast, among users of calcium channel blockers, the widening in pulse pressure was of larger magnitude ($\Delta 15$ mm Hg) compared with nonusers ($\Delta 6$ mm Hg). These patterns were observed in adjusted analyses as well.

Discussion

We found that CKD was not significantly associated with achievement of blood pressure targets among a large prospec-

tive cohort of hypertensive veterans, but rather CKD was associated with the use of a greater number of antihypertensive medications. Moreover, we observed an intriguing interaction between CKD and the number of antihypertensive medications as determinants of systolic and diastolic blood pressure levels. Among those without CKD, persons prescribed a greater number of antihypertensives were characterized by higher systolic blood pressure and wider pulse pressure. In contrast, among those with CKD, a higher number of medications was associated with only modest increases in systolic blood pressure but large decreases in diastolic blood pressure and even wider pulse pressures. These findings suggest that greater use of antihypertensive medications in patients with CKD may lower diastolic blood pressure with less effect on systolic blood pressure. Alternatively, a wide pulse pressure in a patient with CKD may be a marker of refractory systolic hypertension resulting from poor vascular compliance.

This pattern of systolic blood pressure resistance and diastolic blood pressure susceptibility to antihypertensive treatment among those with CKD may be related to arterial stiffness. In persons with normal vascular hemodynamics, ejection of blood from the heart generates a pressure wave that propagates and is then reflected back by distal arteries

during diastole. In the presence of aortic stiffness, this reflected wave occurs earlier, leading to augmentation of aortic pressures during systole (higher systolic blood pressure) and reductions during diastole (lower diastolic blood pressure). Age and hypertension may change the properties of central arteries, and constriction and remodeling of distal arteries may also play a role in this altered wave reflection pattern.[17] Reduced kidney function is associated with large artery stiffness.[18] In addition, kidney microvasculature may be particularly susceptible to the effects of stiffness in larger, upstream arteries and to pulse pressure changes.[19] It has been postulated that direct renal factors (ie, calcium-phosphate abnormalities, fluid redistribution, and oxidative stress) may also affect pulse wave reflections independent of well-established risk factors.[20] Therefore, in persons with kidney dysfunction, we can hypothesize that large arterial stiffness may explain the intractability of the systolic component to antihypertensive therapy, whereas poor vascular compliance and alterations in the renal microvasculature may exacerbate a susceptibility to diastolic hypotension. Our results persisted even after adjustment for comorbidities, such as heart failure and coronary artery disease, which may alter vascular architecture.

Studies have shown a J-shaped association between diastolic blood pressure levels and risk of adverse outcomes among patients with and without CKD. Excessive lowering of diastolic pressure (to levels <84 to 85 mm Hg) was associated with a higher risk of death and adverse cardiovascular outcomes in these studies.[21–23] In addition, wide pulse pressure (a marker of vascular stiffness) has been associated with adverse cardiovascular outcomes.[24,25] Wide pulse pressure is prevalent among those with CKD,[9] even among those with mild renal dysfunction before the onset of CKD.[26] The apparent association between increased use of antihypertensives with decreased diastolic blood pressure among CKD patients in our study raises the concern that the pursuit of systolic blood pressure control may have adverse cardiovascular consequences.

We also found that, in contrast to other antihypertensives, the use of calcium channel blockers was associated with a pattern of pulse pressures of wider magnitude compared with those nonusers among veterans with CKD. These data suggest that participants with CKD may be particularly susceptible to diastolic hypotension and increased pulse pressures when using calcium channel blockers as part of their antihypertensive regimen. The interpretation of these results is limited by power because of the low number of participants taking only 1 or 2 antihypertensive drugs in each category. Therefore, it is unclear whether there is an independent effect between individual classes of medications and pulse pressure beyond the number of antihypertensives. Future studies should focus on the effect of calcium channel blockers on arterial compliance in the presence of CKD.

The lack of association between CKD and blood pressure control but its positive association with higher medication use may have important implications for hypertension treatment. Previous clinical trials found that patients with CKD may require 3 to 4 antihypertensive medications on average to achieve control.[7,8] Our results suggest that, in a routine outpatient clinic environment, even the prescription of multiple antihypertensive medications does not lead to consistent blood pressure control. In fact, among those with CKD who were prescribed 4 drugs, only one third achieved their blood pressure targets. More importantly, the use of higher numbers of antihypertensives in CKD patients appeared to disproportionately reduce diastolic blood pressure. These findings suggest that control of systolic blood pressure may be impossible in some patients without excessive diastolic blood pressure lowering, at least using currently available antihypertensive drugs. These problems could be exacerbated with the greater implementation of Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines, which mandate even lower blood pressures in patients with CKD.[1] Ideally, new studies should focus on identifying antihypertensive agents that preferentially lower systolic blood pressure, particularly in those with CKD.

Our study has the advantage of being a large, prospective, multisite, community cohort with repeated measures of blood pressure. In addition, we believe our study is able to adequately capture medication use data, given the low cost of drugs at VA pharmacies. Moreover, the observed effect sizes of the lower diastolic blood pressures (up to −6 mm Hg) are comparable to clinically relevant recommendations currently suggested in hypertension treatment guidelines, such as dietary sodium reduction, moderation in alcohol consumption, and physical activity.[1] However, our findings have certain limitations. Because we used data from the last visit to study the association of antihypertensive use and changes in each blood pressure component, we cannot infer causality in this association. Moreover, we cannot assume that patients were adherent to treatment, but the correlation of lower diastolic pressure with the greater number of medications suggests a therapeutic effect. Our population excluded those with creatine >2.5 at baseline, which limits the power to test associations among those with severe kidney dysfunction, particularly those with stage 4 and 5 CKD. Moreover, a large part of our cohort was using diuretics, which may potentially affect GFR. However, our results were consistent across stages of CKD, making it less likely that the use of diuretics is an important confounder in our results. We did not adjust for left ventricular function, but our results were robust when adjusting for a diagnosis of heart failure. Assessment and Treatment of Hypertension: Evidence-Based Automation was not designed to make recommendations on >4 drugs and, therefore, we cannot study effects beyond 4 medications. In addition, we estimated GFR from creatinine but we did not calibrate creatinine measures to the Cleveland Clinic. Therefore, this may potentially affect the GFR estimates at each site.

Perspectives

In conclusion, CKD was not an independent predictor of blood pressure control in this study, but it was associated with increased use of antihypertensive medications. In addition, prescription of a higher number of antihypertensives was associated with widening pulse pressure, mainly driven by lower diastolic blood pressure levels among those with CKD.

Because excessive lowering of diastolic blood pressure has been associated with adverse cardiovascular outcomes,[23] future studies should evaluate whether diastolic hypotension may explain part of the association between CKD and adverse cardiovascular outcomes. In addition, further studies should focus on finding agents that preferentially reduce systolic blood pressure in patients with CKD.

Disclosures

None.

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