ORIGINAL RESEARCH

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Time-Updated Systolic Blood Pressure and the Progression of Chronic Kidney Disease

A Cohort Study

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Background: Previous reports of the longitudinal association between achieved blood pressure (BP) and end-stage renal disease (ESRD) among patients with chronic kidney disease (CKD) have not incorporated time-updated BP with appropriate covariate adjustment.

Objective: To assess the association between baseline and time-updated systolic blood pressure (SBP) with CKD progression.

Design: Observational, prospective cohort study. (ClinicalTrials.gov: NCT00304148)

Setting: 7 U.S. clinical centers.

Patients: Patients in the Chronic Renal Insufficiency Cohort Study (n = 3708) followed for a median of 5.7 years (25th to 75th percentile, 4.6 to 6.7 years).

Measurements: The mean of 3 seated SBP measurements made up the visit-specific SBP. Time-updated SBP was the mean of that and all previous visits. Outcomes were ESRD and the composite end point of ESRD or halving of the estimated glomerular filtration rate. Analyses investigating baseline and time-updated SBP used Cox proportional hazards models and marginal structural models, respectively.

Results: Systolic blood pressure was 130 mm Hg or greater at all visits in 19.2% of patients. The hazard ratio for ESRD among patients with SBP of 130 to 139 mm Hg, compared with SBP less than 120 mm Hg, was 1.46 (95% CI, 1.13 to 1.88) using only baseline data and 2.37 (CI, 1.48 to 3.80) using time-updated data. Among patients with SBP of 140 mm Hg or greater, corresponding hazard ratios were 1.46 (CI, 1.18 to 1.88) and 3.37 (CI, 2.26 to 5.03) for models using only baseline data and those using time-updated data, respectively.

Limitation: Blood pressure was measured once annually, and the cohort was not a random sample.

Conclusion: Time-updated SBP greater than 130 mm Hg was more strongly associated with CKD progression than analyses based on baseline SBP.

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* For a list of the Chronic Renal Insufficiency Cohort Study Investigators, see **Appendix 1** (available at www.annals.org).

Hypertension is common in patients with chronic kidney disease (CKD) (1). Observational studies (2, 3) and clinical trials (4–7) provide compelling evidence of the association between elevated blood pressure (BP) and CKD progression, although clinical trial data are inconsistent and may suggest a plateau of effect once BP is decreased to less than 140/90 mm Hg.

In 2003, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure specified a BP target of less than 130/80 mm Hg for persons with CKD or diabetes compared with a BP target of less than 140/90 mm Hg in other hypertensive populations (8). However, the paucity of high-quality evidence to support this lower BP target for patients with CKD, especially those without proteinuria and those with diabetes, has led the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; Kidney Disease: Improving Global Outcomes; and American Diabetes Association to increase BP targets for patients with CKD to less than 140/90 mm Hg (9–11).

Clinical trials and observational studies continue to inform our understanding of the association between BP level and CKD progression—each from an important vantage point. Intention-to-treat analyses from clinical trials provide evidence of the efficacy of antihypertensive therapies, including BP targets, but only in selected study populations eligible for and willing to participate in experimental research. In contrast, analyses of achieved BP from observational studies provide the unique opportunity to study associations of BP with clinical outcomes among a broader, more representative population. Further, when these latter studies take advantage of BP measured over time, they can characterize the longitudinal pattern of hypertension. These longitudinal, observational studies also provide a more robust assessment of associations with outcomes than analyses examining relationships to a single measure of BP that may attenuate with extended follow-up.

The goal of our study was to compare the association between BP and CKD progression using baseline and time-updated BP measurements in CRIC (Chronic Renal Insufficiency Cohort) Study patients, independent of other important time-updated factors. We hypothesized that elevated BP would be associated with more rapid CKD progression and that the association between baseline levels of BP and kidney disease pro-

gression would understate this relationship compared with updated BP levels.

METHODS

Study Design and Population

The CRIC Study enrolled 3939 men and women with mild to moderate CKD between June 2003 and August 2008 at 7 clinical centers in the United States (Ann Arbor and Detroit, Michigan; Baltimore, Maryland; Chicago, Illinois; Cleveland, Ohio; New Orleans, Louisiana; Philadelphia, Pennsylvania; and Oakland, California). Study patients (45% were women, 42% were black, 13% were Hispanic, and 48% had diabetes mellitus) were followed at annual clinic visits, where data were obtained, blood pressure was measured, and blood and urine specimens were collected. Details on study design and baseline patient characteristics were previously published (12–14). Study patients provided written informed consent, and the study protocol was approved by institutional review boards at each of the clinical centers.

Inclusion and Exclusion Criteria

Patients were eligible for the CRIC Study if they were aged 21 to 74 years and met the following age-specific estimated glomerular filtration rate (eGFR) criteria: 20 to 70 mL/min/1.73 m^2 for persons aged 21 to 44 years, 20 to 60 mL/min/1.73 m^2 for persons aged 45 to 64 years, and 20 to 50 mL/min/1.73 m^2 for persons aged 65 to 74 years. Persons with previous dialysis (for >1 month), NYHA (New York Heart Association) class III or IV heart failure, polycystic kidney disease, or other primary kidney diseases requiring active immunosuppression were excluded. A total of 3708 patients were included in the analysis after excluding patients with missing baseline BP (n = 1), urinary protein (n = 197), and other covariate data (n = 33).

Data Collection

Main Predictor

At each annual clinic visit, 3 seated BP measurements were obtained using a Tycos Classic Hand Aneroid cuff and sphygmomanometer (Welch Allyn) following a standardized protocol. The mean of all BP measurements was used as the BP value for that visit. The time-updated mean BP measurement averaged the mean seated BP at any given visit and those from all previous visits. The analysis examined baseline and time-updated mean SBP continuously per 10–mm Hg increase and by 4 SBP categories (<120 [reference category], 120 to 129, 130 to 139, and ≥140 mm Hg) to evaluate the association of BP with CKD progression.

Outcomes and Censoring Events

Two measures of CKD progression were studied: development of end-stage renal disease (ESRD) and a composite end point of ESRD or halving of eGFR from baseline. End-stage renal disease was defined as receipt of maintenance dialysis or a kidney transplant and was ascertained primarily through self-report. Information collected on ESRD by study investigators was supplemented by the United States Renal Data System. The eGFR was calculated from serum creatinine and cystatin C levels using a CRIC Study equation (15). Time to eGFR halving was imputed assuming a linear decline in kidney function between in-person annual visit measures (16). Patients' follow-up was censored at the time of death (389 participants for ESRD analyses), withdrawal (n = 146), loss to follow-up (n = 171), or the end of the follow-up period, whichever occurred first. Deaths were ascertained from next of kin, death certificates, obituaries, reviews of hospital records, and the Social Security Death Master File. Outcomes were ascertained from study entry through March 2011.

Covariates

Patients self-reported information on sociodemographic characteristics (age, sex, race or ethnicity, and education level) and history of cardiovascular disease at baseline and medication use at baseline and follow-up study visits. Race or ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other. Self-reported history of any cardiovascular disease at baseline included previous myocardial infarction, coronary revascularization, heart failure, stroke, or peripheral arterial disease. Cardiovascular events throughout follow-up were adjudicated by 2 physician reviewers. At each study visit, patients were queried about any medication use in the previous 30 days. All antihypertensive medications were categorized into drug classes, and the total number of antihypertensive drug classes was calculated. Hypertension awareness was determined by a positive response to the question, "Has a [physician] or other health professional ever told you/told you since your last CRIC visit that you have hypertension or high blood pressure?" Anthropometric measures were assessed using standardized protocols. Serum creatinine was measured by an enzymatic method from Ortho Clinical Diagnostics through Octo-

EDITORS' NOTES

Context

Data to inform appropriate blood pressure (BP) targets for patients with chronic kidney disease (CKD) are incomplete. Further, it is not known whether several time-updated BP measures are more strongly associated with the progression of CKD than single baseline measures.

Contribution

In this cohort of patients with CKD, elevated BP on repeated time-updated measures had a stronger association with progression to end-stage renal disease than elevated BP on single baseline measures.

Implication

Future studies of CKD and patient monitoring should incorporate time-updated measures of BP.

ber 2008 and by the Jaffe method from Beckman Coulter thereafter and standardized to isotope dilution mass spectrometry-traceable values (17, 18). Serum cystatin C was measured using a particle-enhanced immunonephelometric assay on the BN II System (Siemens). Urinary total protein and creatinine and plasma glucose were also measured using standard assays. Protein–creatinine ratios (PCRs) from 24-hour and spot urine specimens were highly correlated ($P = 0.96$) and, as such, were used interchangeably. Diabetes mellitus was defined as a fasting glucose level greater than 6.99 mmol/L (126.00 mg/dL), a nonfasting glucose level greater than 11.10 mmol/L (200.00 mg/dL), or use of insulin or other medications for glycemic control.

Statistical Analysis

Summary statistics and distributions of all BP variables were generated. Maximum differences in follow-up SBP from baseline were summarized using 4 categories of absolute differences (<10, 10 to <20, 20 to <30, and ≥30 mm Hg). Study variables were described overall and across baseline SBP categories (<120 mm Hg, 120 to 139 mm Hg, and ≥140 mm Hg) using means and SDs for continuous variables and frequencies and proportions for categorical variables. Differences in characteristics across SBP categories were compared using analysis of variance and chi-square tests, as appropriate. Elevated SBP for each study patient was characterized in 3 ways: as the percentage of study visits with an SBP of 120 mm Hg or greater, 130 mm Hg or greater, and 140 mm Hg or greater. Crude rates and 95% CIs of ESRD and the composite renal end point were calculated overall and within levels of baseline SBP.

The association of baseline SBP with renal end points was examined using Cox proportional hazards models with adjustment for baseline age, sex, race or ethnicity, education level, history of cardiovascular disease, number of antihypertensive medication drug classes received, use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker, hypertension awareness, body mass index, diabetes, eGFR, and urinary PCR. Adjustment for eGFR and urinary PCR included quadratic spline terms. To examine the potential effect of death as a competing risk rather than a censoring event, competing risk sensitivity analyses of baseline SBP on renal end points were conducted using the stcrreg command in Stata/MP, version 13.1 (StataCorp). To assess the relationship between time-updated SBP and outcomes, analytic approaches, such as marginal structural models (MSMs), are needed that control for the challenges created by the fact that changing level of kidney function is potentially both a consequence and a cause of elevated BP (that is, time-updated kidney function is a time-dependent confounder) (19–21). Marginal structural models were used with time-updated SBP data and adjustment for the same covariates as the baseline SBP models (**Appendix 2**, available at www.annals.org). All covariates with the exception of sex, race or ethnicity, education level, and hypertension awareness were time-updated. Hazard ratios and 95% CIs were reported for all models. Systolic blood pressure was modeled in terms of hazard ratios per 10–mm Hg increase and across discrete categories (<120, 120 to 129, 130 to 139, and ≥140 mm Hg). Hazard ratio estimates using MSM and categorical SBP should be interpreted as the risk for the renal end point for someone whose mean SBP across study visits was always in that BP category. Additional examples of hazard ratios associated with an SBP history that included some proportion of the study period with mean SBP across different SBP categories were also calculated. This was done by weighting the regression coefficients for each SBP category according to the percentage of the study period SBP fell within each of the categories. We calculated the cumulative incidence of ESRD over follow-up in 4 hypothetical scenarios. These scenarios used the MSMs in which we assumed that all patients followed the same SBP history (that is, SBP was always <120, 120 to 129, 130 to 139, or ≥140 mm Hg) (**Appendix 2**) (22, 23).

We explored effect modification by an a priori–selected set of baseline characteristics, including age (<55 and ≥55 years), sex, race or ethnicity, diabetes status, level of kidney function (eGFR <45 and ≥45 mL/min/1.73m^2), urinary PCR (<22.6 and ≥22.6 mg/mmol), and use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and calcium-channel blockers. Stratified analyses of the hazard ratio of the composite renal end point per 10–mm Hg increase in time-updated SBP using MSM across these variables were reported. All analyses, with the exception of competing risk models, were performed using SAS, version 9.3 (SAS Institute), using the phreg and genmod procedures for baseline and time-updated analyses, respectively.

Role of the Funding Source

The CRIC Study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. The National Institute of Diabetes and Digestive and Kidney Diseases partnered with the CRIC Steering Committee in the design, conduct, and analysis of the study and approved the submission of the manuscript for publication.

RESULTS

At study entry, patients had a mean SBP of 128.1 mm Hg, a mean age of 58.4 years, a mean body mass index of 32.1 kg/m^2, a mean eGFR of 45.0 mL/min/1.73 m^2, and a mean urinary PCR of 112.3 mg/mmol (**Table**). In addition, most (91.8%) patients reported use of at least 1 antihypertensive medication, approximately two thirds (68.7%) reported use of either an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and all were prescribed an average of 2 to 3 antihypertensive medication classes.

The median duration of follow-up was 5.7 years (25th to 75th percentile, 4.6 to 6.7 years). The within-patient mean SBP over time ranged from 74 to 218 mm Hg (mean SBP, 128.6 mm Hg [SD, 19.1 mm Hg]). Vari-

Table. Baseline Characteristics of Participants, by Baseline SBP*

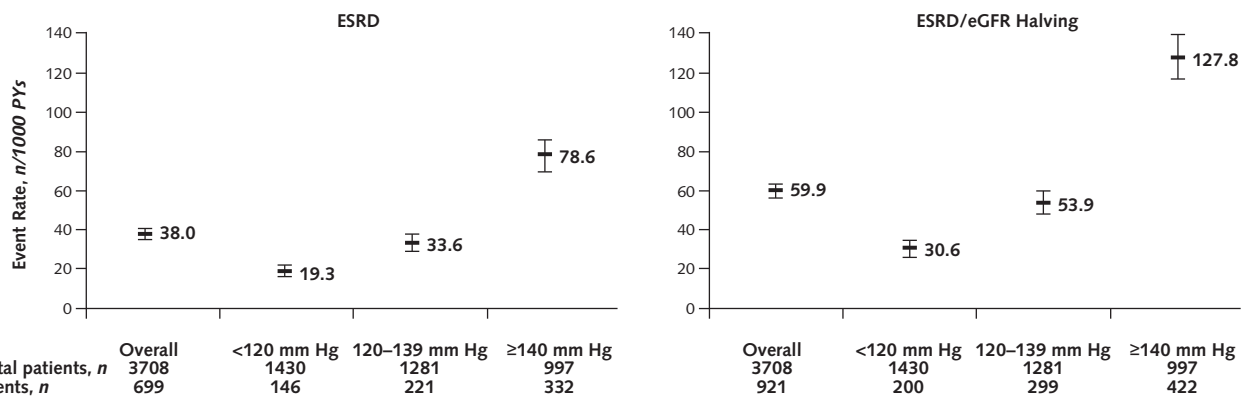
Characteristic	Overall (*n* = 3708)	Mean Baseline SBP			*P* Value†
		<120 mm Hg (*n* = 1430)	120–139 mm Hg (*n* = 1281)	≥140 mm Hg (*n* = 997)	
Demographic					
Mean age (SD), *y*	58.4 (10.9)	56.3 (11.7)	59.2 (10.5)	60.3 (9.7)	<0.001
Women, *n (%)*	1682 (45.4)	657 (45.9)	560 (43.7)	465 (46.6)	0.32
Race/ethnicity, *n (%)*					<0.001
Hispanic	430 (11.6)	124 (8.7)	127 (9.9)	179 (18.0)	
Non-Hispanic black	1548 (41.8)	476 (33.3)	538 (42.0)	534 (53.6)	
Non-Hispanic white	1585 (42.8)	772 (54.0)	565 (44.1)	248 (24.9)	
Other	145 (3.9)	58 (4.1)	51 (4.0)	36 (3.6)	
Medical history/lifestyle					
Diabetes mellitus, *n (%)*	1782 (48.4)	525 (36.7)	622 (48.6)	635 (63.7)	<0.001
Current smoker, *n (%)*	481 (13.0)	178 (12.5)	156 (12.2)	147 (14.7)	0.147
Family history of kidney disease, *n (%)*	578 (15.6)	189 (13.2)	218 (17.0)	171 (17.2)	0.007
High school education, *n (%)*	2963 (79.9)	1242 (86.9)	1025 (80.0)	696 (69.8)	<0.001
Cardiovascular disease, *n (%)*	1239 (33.4)	406 (28.4)	434 (33.9)	399 (40.0)	<0.001
Mean BMI (SD), kg/m^2	32.1 (7.9)	31.5 (7.7)	32.5 (7.7)	32.5 (8.2)	0.002
BP					
Mean SBP (SD), *mm Hg*	128.1 (21.8)	107.7 (8.7)	128.9 (5.7)	156.3 (15.3)	<0.001
Mean DBP (SD), *mm Hg*	71.3 (12.7)	65.2 (9.7)	72.3 (11.2)	78.9 (13.9)	<0.001
Antihypertensive medication use					
Any antihypertensive drug, *n (%)*	3405 (91.8)	1237 (86.5)	1203 (93.9)	965 (96.8)	<0.001
Mean antihypertensive drug classes (SD), *n*	2.6 (1.5)	2.2 (1.5)	2.7 (1.5)	3.1 (1.5)	<0.001
ACE inhibitor or ARB, *n (%)*	2549 (68.7)	970 (67.8)	884 (69.0)	695 (69.7)	0.65
Calcium-channel blocker, *n (%)*	1505 (40.6)	399 (27.9)	575 (44.9)	531 (53.3)	<0.001
Biochemical markers					
Mean eGFR (SD), $mL/min/1.73\ m^2$	45.0 (16.8)	47.9 (18.1)	45.4 (16.1)	40.3 (14.7)	<0.001
Mean urinary protein–creatinine ratio (SD), *mg/mmol*	112.3 (264.9)	44.9 (109.4)	96.8 (226.9)	229.1 (396.6)	<0.001

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure.
* Percentages may not sum to 100 due to rounding.
† *P* values were calculated using analysis of variance and the chi-square test, as appropriate.

ability of time-updated SBP from baseline was within 10, 10 to less than 20, 20 to less than 30, and 30 mm Hg or greater for 24.8%, 25.8%, 22.7%, and 26.7% of patients, respectively. A total of 33.1%, 19.2%, and 10.6% of the patients had SBP at or greater than 120, 130, and 140 mm Hg, respectively, at all study visits.

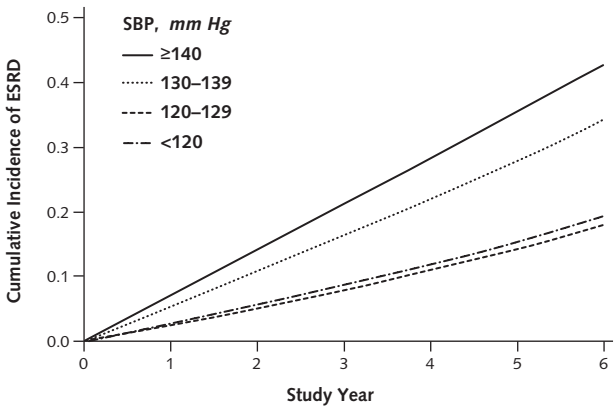
During follow-up, 699 patients developed ESRD and 921 reached the composite renal end point (event rates, 38.0 and 59.9 per 1000 person-years, respectively) (Figure 1). Event rates were substantially greater at higher levels of baseline SBP. Figure 2 depicts the estimated cumulative incidence of ESRD across time-

Figure 1. Crude event rates (95% CIs) of ESRD and the renal composite end point of ESRD or halving of eGFR from baseline, overall and by level of SBP at baseline in the Chronic Renal Insufficiency Cohort Study.



eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; PY = person-year; SBP = systolic blood pressure.

Figure 2. Estimated cumulative incidence of ESRD across categories of time-updated SBP among patients of the Chronic Renal Insufficiency Cohort Study.



ESRD = end-stage renal disease; SBP = systolic blood pressure.

updated SBP categories. After 5 years of follow-up, the estimated cumulative incidence of ESRD among those with time-updated SBP between 130 and 139 and 140 mm Hg or greater was 28.3% and 35.4%, respectively, compared with 15.0% and 14.0% among those with SBP less than 120 and 120 to 129 mm Hg.

After multivariable adjustment, each 10–mm Hg increase in baseline and time-updated SBP was significantly associated with a 9% and 26% higher rate of ESRD, respectively, as well as an 11% and 25% higher rate of the composite renal end point (**Appendix Table**, available at www.annals.org). Analyses of baseline and time-updated mean BP using diastolic BP, mean arterial pressure, and pulse pressure yielded similar results (data not shown). Patients with baseline SBP greater than 130 mm Hg had significantly higher risk for renal end points than those whose baseline SBP was less than 120 mm Hg. Hazard ratios from sensitivity analyses of baseline SBP treating death as a competing risk rather than a censoring event were only slightly attenuated and demonstrated similar patterns to the primary analyses (data not shown). Patients who always had a mean time-updated SBP of 130 to 139 or 140 mm Hg or greater had a 2.4- to nearly 4-fold higher rate of the renal end points than those with mean SBP less than 120 mm Hg (reference group) (**Table 2**). Patients with mean time-updated SBP between 130 and 139 mm Hg for one half of the study period and 140 mm Hg or greater for the remaining half of the study period had a 2.8-fold higher rate of ESRD than those whose mean SBP was always less than 120 mm Hg (data not shown). In addition, those with mean SBP of 120 to 129, 130 to 139, and 140 mm Hg or greater, each for one third of the study period, had 1.9-fold higher rates of ESRD than the reference group.

The strength of the association between SBP and the composite renal end point using time-updated SBP did not differ significantly across subgroups stratified by age, sex, race or ethnicity, diabetes, baseline eGFR, proteinuria, or antihypertensive medication use (**Figure 3**).

DISCUSSION

We investigated and compared the association between elevated BP and CKD progression using baseline and time-updated SBP with appropriate adjustment for time-updated covariates in a well-characterized cohort with mild to moderate CKD. Our analyses of the association between baseline BP and renal end points were similar in magnitude to previous reports (2, 3). As we had hypothesized, we demonstrated a stronger association between achieved BP and renal end points using time-updated SBP and marginal structural analysis with appropriate handling of time-dependent confounding. In particular, we saw a 2.6-fold increased risk for the composite renal end point for those whose mean SBP across study visits was always 130 to 139 mm Hg compared with less than 120 mm Hg. Our findings underscore that prolonged exposure to SBP of 130 mm Hg or greater among persons with and without proteinuria and with and without diabetes is associated with important increases in the risk for CKD progression.

Achieved BP analyses to date are highly consistent in demonstrating a graded increase in renal events associated with higher BP (2, 3, 24, 25). Indeed, an achieved BP analysis of data from the African American Study of Kidney Disease and Hypertension (but not its original intention-to-treat analysis) recapitulated previous achieved BP findings (26). However, these achieved BP analyses typically report associations substantially lower in magnitude than our MSM findings with time-updated SBP. We postulate that the disparate findings may reflect methodological shortcomings of previous work. First, most earlier studies relied on BP measurements from a single time point. This is an important limitation given the variability of BP over time, especially in the setting of CKD. These analyses investigated risk based on snapshots of BP exposure and cannot relate prolonged BP history to outcomes. Second, reports using time-updated BP used traditional statistical modeling techniques (that is, time-updated Cox regression) that inadequately adjusted for eGFR over time given its role in this setting as a time-dependent confounder (24–26). Last, several key confounders, including proteinuria, were often not adjusted for or were inadequately characterized, thus potentially introducing meaningful residual confounding. To our knowledge, our study is the first to report the impact of a history of elevated, achieved BP on CKD progression in an unbiased fashion.

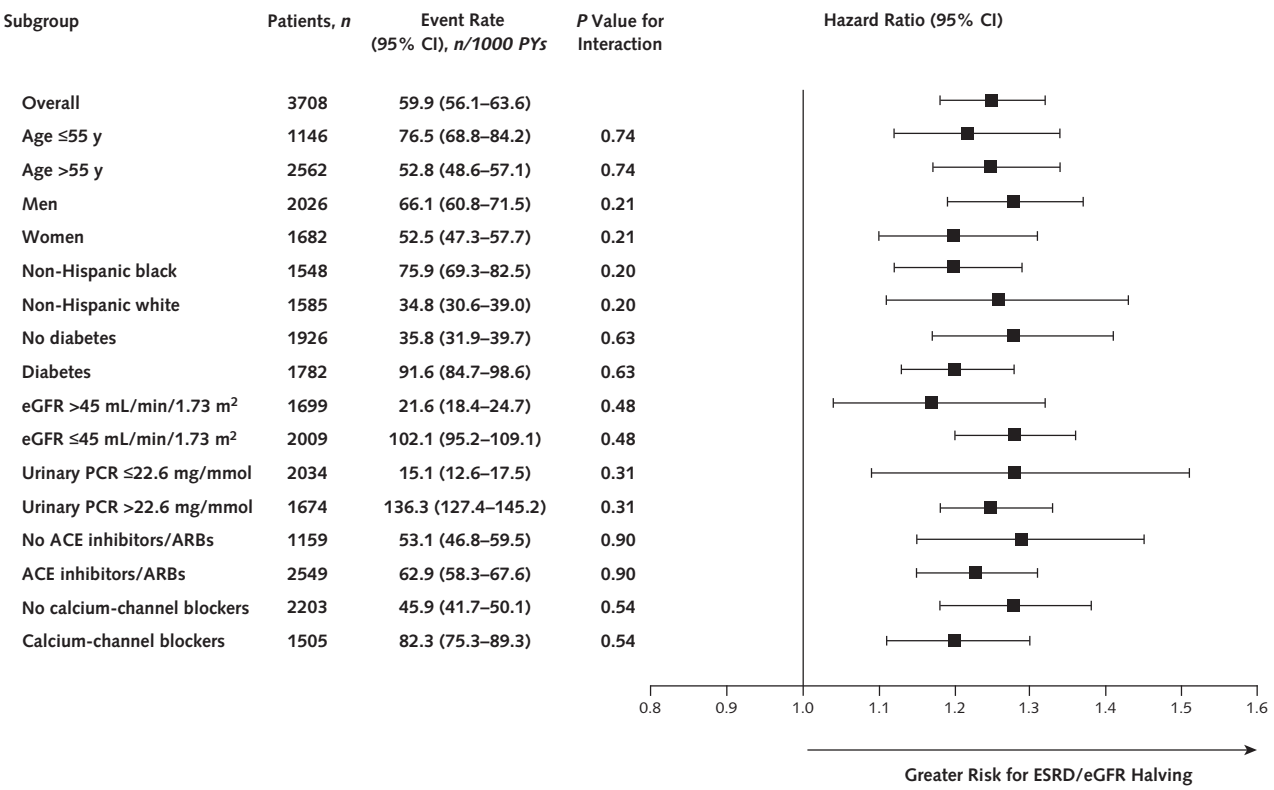
Within clinical trials, varying targets for optimal BP control have been used and inconsistent findings have been reported (4–7, 27–33). In addition, these studies have reported differential effects of BP lowering across subgroups with and without diabetes, and with and without proteinuria. In an attempt to address the variability in findings from clinical trials, recent meta-analyses of pharmacologic clinical trials of intensive BP

lowering have been performed. The first meta-analysis, primarily in persons with nondiabetic CKD, concluded that intensive BP lowering significantly reduced risk for CKD progression but only among those with proteinuria (34). The second meta-analysis among persons with diabetes demonstrated reductions in the level of proteinuria but not in the rate of CKD progression (35). These analyses of intention-to-treat data from clinical trials conflict with many findings from the current achieved BP analysis—namely that "lower" levels of SBP beginning at 130 mm Hg are associated with increased risk for CKD progression among all subgroups. These differences likely arise from several factors, including the fundamental differences in questions addressed by intention-to-treat versus achieved BP analyses, differing study populations, varying success across subgroups in reaching lower BP goals in clinical trials, and potentially residual confounding in our achieved BP analyses. Additional large clinical trials, such as the Systolic Blood Pressure Intervention Trial, should further elucidate the effect of BP lowering on important outcomes, including kidney outcomes, especially if analyses include both intention-to-treat and achieved BP analyses using MSMs or similar methods.

Our study had many positive features. It was a large, multicenter, prospective study of mild to moderate CKD, including similar proportions of patients with and without diabetes. The study population included a diverse population of men and women, non-Hispanic whites, non-Hispanic blacks, and Hispanics with a wide age range and broad set of underlying causes of CKD. Patient retention in the CRIC Study was excellent (90% retained and actively under study as of the year 5 visit), and linkage with the United States Renal Data System and national death databases maximized capture of primary study end points. Extensive annual data collection included standardized measurement of BP, kidney function, proteinuria, and several other relevant factors. Blood pressure was measured by highly trained research personnel in triplicate. As such, CRIC BP data are likely more accurate than regularly acquired office measurements.

There are also important limitations. First, we measured BP only once each year, which may not accurately reflect BP levels over the entire year and may have resulted in misclassification of our key exposure. Second, we lacked data on some potentially important unmeasured confounders, such as duration of hypertension or BP levels before enrollment into the study and adherence to antihypertensive therapies. Third, data on antihypertensive medication use were self-reported and reflected only the 30 days preceding any

Figure 3. Forest plot of crude event rates (95% CIs) and multivariable-adjusted hazard ratios per 10–mm Hg increase in mean SBP over time on development of ESRD or halving of eGFR overall and by subgroups using marginal structural models.



Models were stratified by clinical center and adjusted for age, sex, race/ethnicity, education level, history of cardiovascular disease, number of antihypertensive medication drug classes received, use of an ACE inhibitor/ARB, hypertension awareness, body mass index, diabetes, eGFR, urinary PCR, and study time. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; PCR = protein–creatinine ratio; PY = person-year.

study visit, which could have led to misclassification of this important time-varying exposure. Fourth, we may have lacked the power to detect significant effect modification by level of proteinuria because of the relatively low levels of protein excretion among most patients. Finally, the observational (nonrandomized) design of our study precludes definitive determination of optimal target level of BP for patients with CKD.

Our study confirmed previous reports from observational studies of the relationship between a single (baseline) elevated measure of BP and a higher rate of renal end points. However, use of time-updated BP with appropriate adjustment for updated covariates revealed a considerably larger magnitude of association between elevated SBP and CKD progression (a previously unreported finding). This study also suggests that prolonged exposure to SBP greater than 130 mm Hg may portend increased risk for progressive loss of kidney function among persons with CKD regardless of diabetes or proteinuria status. The relevance of these findings for clinical practice guidelines must be assessed within the context of existing and emerging evidence from other observational and interventional studies.

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Reproducible Research Statement: *Study protocol:* Available at www.niddkrepository.org/studies/cric/cric%20protocols. *Statistical code:* Available from Dr. Anderson (e-mail, andersah@mail.med.upenn.edu). *Data set:* Not available.

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Current author addresses and author contributions are available at www.annals.org.

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Appendix 1: CRIC Study Investigators

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Appendix 2: Analyses of Time-Updated SBP

Our analyses of time-updated SBP used MSMs, which apply inverse probability weighting in a discrete time failure model (19). A substantial body of work has emerged demonstrating the usefulness of statistical tools, such as MSMs, in the areas of HIV and CKD (20, 35). In brief, MSM is a 2-step approach wherein models were first fit to predict mean SBP during follow-up (that is, the exposure of interest), followed by inverse-probability weighted structural models that were fit for the outcomes. In both models, the data structure was set up so each person could contribute several records, each 1 year in length, depending on the number of annual study visits. For example, a person with 5 study visits contributed 5 records in the data set.

In the first step (that is, calculating the exposure weights), the SBP measure at each study visit was divided into 4 categories based on the quartiles of the distribution. A multinomial logistic regression model was fit on the categorical SBP measures with adjustment for concurrent age; sex; race or ethnicity; education level; history of cardiovascular disease; diabetes mellitus status, body mass index; number of antihypertensive medication classes received; use of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; hypertension awareness; and urinary PCR, eGFR, and measured SBP from the previous 3 study visits, if available. Quadratic spline terms for urinary PCR and eGFR were incorporated to account for nonlinear relationships. We calculated the weights that were used in the second step based on the predicted probability of seeing a history of SBP categories during all study visits that were the same as what were seen.

The weight for a particular study visit was calculated as one over the cumulative probabilities of the observed SBP history up to that visit, calculated as the product of the probabilities of the observed SBP categories up to that visit.

To improve model stability and statistical efficiency, we stabilized the weights by multiplying the estimated probability of observed SBP history conditional on baseline-only predictors (that is, baseline age, sex, race or ethnicity, education level, history of cardiovascular disease, diabetes mellitus status, body mass index, number of antihypertensive medication classes received, use of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, hypertension awareness, PCR [quadratic spline], eGFR [quadratic spline], and SBP) (19, 20). This was done by fitting a second model for categorical SBP using the baseline-only predictors.

Patients with missing SBP who returned for a later study visit during the analysis time period (84 of 3708 patients [2%]) were considered to have stable SBP from the visit at the beginning of the interval until SBP was next measured. The median number of actual BP measurements was 5 (25th to 75th percentile, 3 to 9 measurements). Patients with missing SBP who never returned for a study visit during the remainder of the period under study were censored in the analyses. A total of 171 were censored due to missing visits with no return visit before the administrative cutoff date of the current analysis. Another 146 formally withdrew during this study period. Patients lost to follow-up may be systematically different from those who were adherent to the study schedule. Characteristics of patients who withdrew from the study or died and those who were still in the study differed. To correct the possible bias due to informative censoring, we applied the same modeling strategy described above for SBP. We fit 2 logistic regression models for the binary indicator of censoring using time-updated predictors and the baseline-only predictors. We calculated the censoring weight as the cumulative product of the predicted probability of censoring using baseline-only predictors divided by the cumulative product of the predicted probability of censoring using the additional time-updated predictors. The final weight for each observation in the second step is the product of the exposure weight multiplied by the censoring weight. Truncation of weights in MSM is a standard approach to reduce some of the imprecision (that is, inflation of SEs of the effect estimates) introduced by large weights (36). We truncated final weights at 10 (only 8 observations were truncated) to improve precision while not biasing the point estimates themselves. Truncated and nontruncated analyses gave similar results (data not shown).

One key assumption for MSM is the so-called positivity assumption. Specific to this study, it requires that the probability of being in any of the 4 SBP categories conditional on any combination of the predictors has to be strictly positive (that is, for any stratum corresponding to a particular combination of the predictors, there are persons in all 4 SBP categories). Assuming that no person was seen in 1 of the 4 SBP categories for a particular combination of the predictors, we would be unable to make any inference on this particular stratum (that is, no causal contrast could be made with respect to the other 3 SBP categories). Given our large sample size and our definition of SBP categories based on the quartiles of the distribution, we believed this assumption was satisfied, confirmed by the distribution of the final weights used in the second step. The largest final weight we saw for a particular observation in the second step was 41. The weight for a particular observation will go to infinity if the positivity assumption is violated.

In the second step, we fit a discrete time failure model for the outcome (that is, ESRD) by applying the final weight derived in the first step to the study visit level data using the genmod procedure in SAS, version 9.3. In the model, we included the mean SBP up to the current study visit and the time since enrollment to allow the baseline hazard to change linearly over time. In addition, to allow for valid inference, we included the baseline-only predictors from the stabilizing weights deriving the numerator weight in the first step (20, 21). We also refit the model by summarizing the SBP history as the percentage of time being spent in each SBP category.

Sensitivity analyses were performed to assess the effect of our handling of intermittent missing SBP data in the MSMs. Rather than assuming that SBP remained unchanged across the time interval until the next BP measurement, we censored follow-up for patients who missed an annual visit. These sensitivity analyses yielded effect estimates that were nearly identical to the primary analyses.

Cumulative incidence estimates were derived for all 4 time-updated SBP categories. We first estimated the cumulative incidence of ESRD during follow-up as if all persons had SBP less than 120 mm Hg throughout the follow-up period. To do so, we estimated the hazard rate of ESRD at each follow-up year based on the weighted discrete time failure model for the outcome by setting the SBP to less than 120 mm Hg for all persons while leaving the other baseline covariates unchanged. We then estimated the cumulative incidence of ESRD at each follow-up year based on the estimated hazard rate of ESRD (22, 37). We repeated this procedure 3 additional times for each of the remaining SBP categories to derive cumulative incidence estimates for all 4 time-updated SBP categories.

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Appendix Table. Multivariable Associations of Baseline and Time-Updated SBP With Renal End Points*

Renal End Point	Hazard Ratio (95% CI)	
	Models of Baseline SBP	Models of Time-Updated SBP†
ESRD		
Continuous SBP per 10–mm Hg increase	1.09 (1.05–1.13)	1.26 (1.18–1.34)
Categorical SBP‡		
120–129 mm Hg	1.07 (0.82–1.39)	0.92 (0.54–1.56)
130–139 mm Hg	1.46 (1.13–1.88)	2.37 (1.48–3.80)
≥140 mm Hg	1.46 (1.18–1.88)	3.37 (2.26–5.03)
ESRD/eGFR halving		
Continuous SBP per 10–mm Hg increase	1.11 (1.07–1.15)	1.25 (1.18–1.32)
Categorical SBP‡		
120–129 mm Hg	1.04 (0.83–1.30)	1.13 (0.72–1.76)
130–139 mm Hg	1.49 (1.20–1.85)	2.63 (1.79–3.86)
≥140 mm Hg	1.71 (1.41–2.08)	3.66 (2.58–5.19)

eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; SBP = systolic blood pressure.

* All models were stratified by clinical center and adjusted for age, sex, race/ethnicity, education, hypertension awareness, history of cardiovascular disease, body mass index, number of antihypertensive medication classes received, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use, diabetes status, eGFR, and urinary protein–creatinine ratio.

† Using marginal structural models with adjustment for all covariates listed above and study time (all time-updated except for sex, race/ethnicity, education level, and hypertension awareness); hazard ratio estimates depicted using marginal structural models and categorical SBP reflect the risk for the renal end point for selected scenarios in which SBP at all study visits consistently fell into that BP category.

‡ Reference was <120 mm Hg.