Observational Modeling of Strict vs Conventional Blood Pressure Control in Patients With Chronic Kidney Disease

Csaba P. Kovesdy, MD; Jun L. Lu, MD; Miklos Z. Molnar, MD, PhD; Jennie Z. Ma, PhD; Robert B. Canada, MD; Elani Streja, PhD; Kamyar Kalantar-Zadeh, MD, MPH, PhD; Anthony J. Bleyer, MD, MS

Hypertension is a major, reversible cause of morbidity and mortality worldwide, and there have been many retrospective studies and prospective trials that have examined blood pressure. Early retrospective studies initially showed that high blood pressure was associated with heart disease and stroke. Subsequent prospective clinical trials have sought to determine how aggressively to treat elevated blood pressure and have attempted to decrease systolic blood pressure (SBP) to lower and lower levels. Retrospective studies also identified a J-curve of mortality for both SBP and diastolic blood pressure (DBP) in certain groups of patients, raising concerns about the safe limits of blood pressure lowering in these populations.

Prospective randomized clinical trials have the ability to establish a cause-effect relationship between a clinical intervention (eg, the lowering of blood pressure to various predefined targets) and morbidity and mortality. Disadvantages of randomized clinical trials include their immense cost and the fact that study participants may not be representative of the general population (limited external validity). Retrospective cohort studies and clinical trials are complementary in the knowledge that they provide, and observational studies can examine populations that were excluded from clinical trials and treatments that cannot be tested in clinical trials, and hence they can offer valuable practical information. It is also true that

Importance The effect of strict blood pressure control on clinical outcomes in patients with chronic kidney disease (CKD) is unclear.

Objectives To compare the outcomes associated with a treated systolic blood pressure (SBP) of less than 120 mm Hg vs those associated with the currently recommended SBP of less than 140 mm Hg in a national CKD database of US veterans.

Design, Setting, and Participants Historical cohort study using a nationwide cohort of US veterans with prevalent CKD, estimated glomerular filtration rate less than 60 mL/min/1.73 m², and uncontrolled hypertension, who then received 1 or more additional blood pressure medications with evidence of a decrease in SBP. Propensity scores were calculated to reflect each individual’s probability for future SBP less than 120 vs 120 to 139 mm Hg.

Main Outcomes and Measures The effect of SBP on all-cause mortality was evaluated by the log-rank test, and in Cox models adjusted for propensity scores.

Results Using a database of 651,749 patients with CKD, we identified 77,765 individuals meeting the inclusion criteria. A total of 5760 patients experienced follow-up treated SBP of less than 120 mm Hg and 72,005 patients had SBP of 120 to 139 mm Hg. During a median follow-up of 6.0 years, 19,517 patients died, with 2380 deaths in the SBP less than 120 mm Hg group (death rate, 80.9/1000 patient-years [95% CI, 77.7-84.2/1000 patient-years]) and 17,137 deaths in the SBP 120 to 139 mm Hg group (death rate, 41.8/1000 patient-years [95% CI, 41.2-42.4/1000 patient-years]; P < .001). The mortality hazard ratio (95% CI) associated with follow-up SBP less than 120 vs 120 to 139 mm Hg was 1.70 (1.63-1.78) after adjustment for propensity scores.

Conclusions and Relevance Our results suggest that stricter SBP control is associated with higher all-cause mortality in patients with CKD. Confirmation of these findings by ongoing clinical trials would suggest that modeling of therapeutic interventions in observational cohorts may offer useful guidance for the treatment of conditions that lack clinical trial data.

Author Affiliations: Division of Nephrology, Memphis VA Medical Center, Memphis, Tennessee (Kovesdy); Division of Nephrology, University of Tennessee Health Science Center, Memphis (Kovesdy, Lu, Molnar, Canada); Division of Nephrology, University of Virginia, Charlottesville (Ma); Harold Simmons Center for Chronic Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California–Irvine, Orange (Streja, Kalantar-Zadeh); Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, North Carolina (Bleyer).

Corresponding Author: Csaba P. Kovesdy, MD, Division of Nephrology, Memphis VA Medical Center, 1030 Jefferson Ave, Memphis, TN 38104 (csaba.kovesdy@va.gov).
retrospective studies often are in agreement with the results of prospective clinical trials. Patients with chronic kidney disease (CKD) represent a large population with a high prevalence of cardiovascular morbidity and mortality, but they have been excluded from most clinical trials of blood pressure lowering. The few trials that have examined different blood pressure treatment goals in patients with CKD were unable to unequivocally establish the benefit vs risk of stricter blood pressure control, as a result of limitations in which end points they were powered to examine (primarily progression of kidney disease, with mortality or cardiovascular events either not examined or examined as part of composite secondary outcomes) and as a result of discrepancies between results from primary and secondary or post hoc analyses.

The implication is that strict blood pressure control may not be advantageous in patients with CKD, and it could even be deleterious. The Systolic Blood Pressure Interventional Trial (SPRINT) (clinicaltrials.gov Identifier: NCT01206062) is the first major clinical trial of blood pressure lowering with a primary aim to prevent cardiovascular events and mortality that specifically enrolled patients with CKD, but its results will not be available for several years and its strict inclusion and exclusion criteria may limit the generalizability of its findings to a narrow spectrum of the CKD population. Using a large database of US veterans with a wide spectrum of patients with CKD, we examined outcomes associated with stricter (SBP, <120 mm Hg) and conventional (SBP, 120-139 mm Hg) treated blood pressure in patients with baseline uncontrolled hypertension.

Methods

Study Design and Participants

The present study is a historical cohort study that is designed to examine outcomes associated with strict vs conventional SBP control in patients with CKD. A nationwide cohort of US veterans with prevalent CKD was used to identify patients with estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² and uncontrolled systolic hypertension (using the definition applied in the ongoing SPRINT: baseline SBP 130-180 mm Hg with use of 0 or 1 antihypertensives, or SBP 130-170 mm Hg with use of up to 2 antihypertensives, or SBP 130-160 mm Hg with use of up to 3 antihypertensives, or SBP 130-150 mm Hg with use of up to 4 antihypertensives). The generation of our CKD cohort was described previously. Briefly, prevalent CKD was defined on the basis of the presence of a persistent estimated GFR of less than 60 mL/min/1.73 m² on at least 2 occasions separated by no less than 3 months or the presence of a spot urine microalbumin-creatinine ratio of at least 30 mg/g on at least 1 occasion (for those with estimated GFR, ≥60 mL/min/1.73 m²) between October 1, 2004, and September 30, 2006. The GFR was estimated from serum creatinine measurements and demographic characteristics by means of the Chronic Kidney Disease Epidemiology Collaboration equation.

Information about blood pressure, laboratory results, and other follow-up data was collected from the date of cohort entry until the end of follow-up (death or April 30, 2012). All blood pressures measured during clinical practice from October 1, 2004, until April 30, 2012, were recorded and grouped by calendar quarters, and their quarterly mean values were used for analyses to reduce random variability. Exposure to antihypertensive medications was assessed from Veterans Affairs (VA) Pharmacy dispensation records. Antihypertensive medications were classified according to their mechanism of action (α-blockers, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, loop-type and thiazide-type diuretics). Medication classes used in fewer than 5% of participants (vasodilators, potassium-sparing diuretics, combination antihypertensives, and others) were not recorded. Individual exposure to each antihypertensive class and to the total number of antihypertensive classes was assessed during each calendar quarter between October 1, 2004, and April 30, 2012.

Information about prevalent comorbidities was collected from the VA Inpatient and Outpatient Medical SAS Datasets using International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic and procedure codes and Current Procedural Terminology codes recorded from October 1, 2004, until September 30, 2006. Coronary artery disease was defined as the presence of diagnostic codes for coronary artery disease, angina, or myocardial infarction, or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. We calculated the Charlson comorbidity index using the Deyo et al modification for administrative data sets, without including kidney disease.

There were a total of 651,749 patients with non–dialysis-dependent CKD and available blood pressure measurements in our cohort (Figure 1), of whom 301,097 patients had estimated GFR less than 60 mL/min/1.73 m² and uncontrolled hypertension. To model therapeutic interventions resulting in improved blood pressure control, we categorized patients on the basis of SBP levels recorded during their follow-up visits. There were 18,243 patients with SBP less than 120 mm Hg on at least 50% of subsequent visits and 176,034 patients with SBP 120 to 139 mm Hg on at least 50% of subsequent visits. To minimize chances that lower SBP levels during follow-up occurred as a result of clinical events and not antihypertensive interventions, we only included patients who experienced an increase in the total number of antihypertensive medications used during follow-up (5,760 patients in the SBP < 120 mm Hg group and 72,005 patients in the 120-139 mm Hg group). To alleviate the bias caused by differences in baseline clinical characteristics in reference to subsequent SBP levels, we estimated propensity scores for the likelihood of SBP less than 120 vs 120 to 139 mm Hg during follow-up from logistic regression. Older age, white race, lower baseline SBP, prevalent coronary artery disease, chronic heart failure, nondiabetic status, and higher Charlson comorbidity index were more likely to be associated with SBP less than 120 mm Hg during follow-up than with 120 to 139 mm Hg. As secondary analysis, a propensity
score–matched cohort was generated by a 1-to-1 nearest neighbor matching without replacement using the “psmatch2” command suite in Stata. The propensity-matched cohort consisted of 11,520 patients, 5,760 in each group (Figure 1).

**Statistical Analyses**

Data were expressed as mean (SD), median (interquartile range), and proportion. Baseline characteristics of patients with follow-up SBP less than 120 and 120 to 139 mm Hg were compared using t tests, nonparametric tests, and χ² tests, as appropriate. The start of the follow-up period was the date of the baseline SBP measurement. Patients were observed until death or were censored at the date of the last health care or administrative VA encounter, as documented in the VA Vital Status Files (a registry containing dates of death or last medical and/or administrative encounter from all available sources in the VA system). The sensitivity and specificity of the Vital Status Files using the US National Death Index as gold standard, were found to be 98.3% and 99.8%, respectively.\(^{25}\) The association of follow-up SBP of less than 120 vs 120 to 139 mm Hg with all-cause mortality was examined by the Kaplan-Meier method and the log-rank test, according to the intention-to-treat principle. Associations were examined first in the overall cohort of 77,765 patients and then in the propensity-matched cohort of 11,520 patients using Cox models. The association of follow-up SBP less than 120 vs 120 to 139 mm Hg in the overall cohort was examined before and after adjustment for individual propensity scores and for baseline characteristics (age, sex, race, estimated GFR, SBP and DBP, Charlson comorbidity index, diabetes mellitus, coronary artery disease, chronic heart failure, serum albumin and cholesterol levels, and use of α-blockers, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and loop-type or thiazide-type diuretics). Associations were

**Figure 1. Algorithm Used to Define the Study Cohort**

- **651,749** Patients with non-dialysis-dependent CKD and available BP measurement
- **540,499** Patients with eGFR ≥60 mL/min/1.73 m²
- **296,603** Patients with no or controlled hypertension
- **301,097** Patients with baseline eGFR <60 mL/min/1.73 m² and uncontrolled hypertension
- **106,820** Patients had unchanged or increased SBP during follow-up
- **18,243** Patients had SBP <120 mm Hg at >50% of follow-up visits
- **176,034** Patients had SBP 120-139 mm Hg at >50% of follow-up visits
- **116,512** Patients had unchanged or decreased No. of BP medications during follow-up
- **5760** Patients had SBP <120 mm Hg and increased No. of BP medications during follow-up
- **72,005** Patients had SBP 120-139 mm Hg and increased No. of BP medications during follow-up
- **116,512** Patients with baseline eGFR ≥60 mL/min/1.73 m² and controlled hypertension
- **54,049** Patients with eGFR ≥60 mL/min/1.73 m² and controlled hypertension
- **29,660** Patients with no or controlled hypertension
- **29,660** Patients with baseline eGFR <60 mL/min/1.73 m² and uncontrolled hypertension
- **1,068,200** Patients had unchanged or increased SBP during follow-up
- **18,243** Patients had SBP <120 mm Hg at >50% of follow-up visits
- **176,034** Patients had SBP 120-139 mm Hg at >50% of follow-up visits
- **116,512** Patients had unchanged or decreased No. of BP medications during follow-up
- **5760** Patients with SBP <120 mm Hg and increased No. of BP medications during follow-up
- **72,005** Patients with SBP 120-139 mm Hg and increased No. of BP medications during follow-up
- **5760** Patients with SBP <120 mm Hg and increased No. of BP medications during follow-up
- **5760** Patients with SBP 120-139 mm Hg and increased No. of BP medications during follow-up

BP indicates blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
examined separately in subgroups of patients of the overall cohort, after categorization by age, sex, race, the level of the Charlson comorbidity index and estimated GFR, and the presence or absence of key comorbid conditions.

Analyses were repeated in a cohort of 5000 propensity score–matched patients (2500 in both SBP groups) defined using the inclusion and exclusion criteria of the CKD portion of the SPRINT (eBox and eFigure 1 in the Supplement), with the exception of the proteinuria criterion. Sensitivity analyses were performed by comparing all patients with decreased SBP during follow-up irrespective of the number of antihypertensive medications used and by considering a stricter definition of follow-up SBP of at least 75% of measurements falling in the desired target categories (<120 and 120-139 mm Hg, respectively). Statistical analyses were performed using Stata MP, versions 11 and 12 (StataCorp). The study protocol was approved by the Research and Development Committee at the Memphis VA Medical Center.

Results

Baseline characteristics of the patients with follow-up SBP less than 120 and 120 to 139 mm Hg in the overall and the propensity-matched cohorts are shown in the Table. Patients with follow-up SBP less than 120 mm Hg in the overall cohort were older and in general had a higher prevalence of comorbid conditions except for diabetes mellitus. These differences were not present in the propensity score–matched cohort. The SBP less than 120 mm Hg group had...
lower baseline SBP and similar (albeit statistically different) baseline DBP levels.

Subsequent SBP and DBP levels throughout the follow-up period were significantly lower in the less than 120 compared with the 120 to 139 mm Hg group, in both the overall and the propensity score–matched cohorts (Figure 2). Patients increasingly used more antihypertensive medications over time. Specifically, the median (interquartile range) number of antihypertensive medications increased from 2 (1-2) at baseline to 3 (2-4) during follow-up in both SBP groups and in both cohorts.

A total of 19,517 patients died (death rate, 44.4/1000 patient-years [95% CI, 43.8-45.0/1000 patient-years]) during a median follow-up of 6.0 years. In the SBP less than 120 mm Hg group, 2,380 deaths occurred (death rate, 41.8/1000 patient-years [95% CI, 41.2-42.4/1000 patient-years]). Mortality was significantly higher in the SBP less than 120 mm Hg group compared with the SBP 120 to 139 mm Hg group, in both the overall and the propensity score–matched cohorts (P < .001 for both) (Figure 3). The unadjusted hazard ratio (HR) (95% CI) of mortality associated with follow-up SBP less than 120 vs 120 to 139 mm Hg in the overall cohort was 2.08 (1.99-2.17), which was attenuated but remained significant after adjustment for propensity scores (1.70 [1.63-1.78]), after adjustment for differences in baseline characteristics (1.74 [1.65-1.83]), and in the propensity score–matched cohort (1.61 [1.51-1.71]). The risk associated with SBP less than 120 mm Hg was significantly higher in all examined subgroups (Figure 4). The results remained consistent in the cohort defined according to SPRINT inclusion and exclusion criteria (eFigure 2 in the Supplement) and in sensitivity analyses including all patients irrespective of antihypertensive medication use, and
when target SBP levels for both groups were required to be present on more than 75% of follow-up measurements (results not shown).

Discussion

In our database containing more than 650,000 patients with CKD, we were able to identify 77,765 individuals with CKD and baseline uncontrolled hypertension and who experienced blood pressure changes similar to what would be expected in a clinical trial or in clinical practice. During follow-up, patients in the lower (<120 mm Hg) SBP arm had significantly lower SBP and DBP and experienced significantly higher mortality compared with patients in the SBP 120 to 139 mm Hg arm. These results were consistent in various subgroups of patients and also in a subcohort modeled on the basis of the inclusion and exclusion criteria of the currently ongoing SPRINT. Our results suggest that SBP levels that are lower than currently recommended treatment targets may not be beneficial and may even be harmful. These findings are in concordance with other recent observational studies that showed a J-shaped association between SBP and major clinical outcomes.1,8

Ideal blood pressure targets in patients with CKD remain a matter of lively debate. The recently released guidelines by the Eighth Joint National Committee26 for the management of high blood pressure in adults has advocated less stringent treatment targets in patients with CKD compared with previous guidelines, largely because of the lack of conclusive data from clinical trials to support stricter blood pressure targets. Previous trials in patients with CKD have primarily examined the renoprotective effects of various blood pressure treatment targets on progression of CKD,9–11 but outcomes such as mortality or cardiovascular events either were not
examined or were only included as part of composite secondary end points. These end points will be primarily examined in the ongoing SPRINT, but it is possible that its results may not be applicable to all segments of a heterogeneous group such as the population with CKD. Our study examined a much wider population with CKD than that typically included in a clinical trial and hence could provide more generalizable findings. This could be important if (once completed) the SPRINT confirms our findings, in that it may allow for wider-ranging recommendations about ideal blood pressure treatment targets in all patients with CKD.

The results of observational studies can be biased, often because of markedly different patient characteristics in the groups compared, and because of different reasons underlying observed events in the 2 types of studies. We tried to minimize these biases by selecting patients according to specific criteria, by only considering patients whose decrease in blood pressure levels occurred in parallel with an enhanced antihypertensive regimen, and by using propensity scores to identify and to adjust for clinical characteristics that could bias different blood pressure responses. There were limitations to our cohort that need to be considered when our results are interpreted. We examined almost exclusively male (97.4%) and predominantly white (91.3%) patients. Fortunately, most prospective blood pressure trials have not shown a significant difference in intervention effects between male and female patients. Comorbid conditions in our cohort were not determined by a group of researchers using strict criteria but were based on medical records generated in the course of clinical practice. Unmeasured comorbidities could have affected our outcomes in spite of careful accounting for relevant measured comorbidities. The fact that the number of antihypertensives needed to achieve the strict and conventional SBP outcomes in our study was similar suggests that determinants of individual responsiveness to antihypertensives (eg, relative hypovolemia or decreased ejection fraction) could be important unmeasured confounders.

To the best of our knowledge prior to our study, a clinical trial modeling approach has not been attempted for blood pressure lowering in patients with CKD. If our approach is shown to be successful, this could corroborate the role that observational studies could play in the planning of clinical trials by determining the likelihood of the best treatment targets, by estimating event rates, and by identifying subgroups most or least likely to respond to certain interventions. In cases in which clinical trials are not feasible or not ethically possible, observational studies could provide much-needed information about the treatments most likely to be effective. This could be especially important in patients with CKD, who experience a substantial number of metabolic and other abnormalities. It is likely that clinical trials will not be available for all the abnormalities found in patients with CKD, in which case the modeling of clinical trials from large observational data sets may offer the best evidence toward effective treatments. It is hoped that these prospective modeling techniques will improve over time, such that they will be helpful in the selection and design of future clinical trials.

Conclusions

In summary, we have found that in a cohort of patients with CKD and uncontrolled hypertension, lowering of the SBP to less than 120 mm Hg was associated with higher all-cause mortality compared with an SBP of 120 to 139 mm Hg. Such an observational approach to estimate treatment targets for blood pressure lowering in patients with CKD could be a useful complement to clinical trials.