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

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Abstract

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

Objective—To examine the association of a treated systolic blood pressure (SBP) of <120 mmHg with the currently recommended SBP of <140 mmHg in a national CKD database of United States veterans.

Design—Historical cohort.

Setting—All US Department of Veterans Affairs healthcare facilities.

Participants—Using a database of 651,749 CKD patients, we identified 77,765 individuals with estimated GFR<60 ml/min/1.73m² and uncontrolled hypertension, who then had administration of one or more additional blood pressure medications with evidence of a decrease in systolic blood

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Relevant Potential Conflict of Interest:

None of the authors have relevant conflicts of interest.

CPK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: CPK, AJB, MZM, JZM, RBC, ES and KKZ.

Acquisition of data: CPK, JLL.

Analysis and interpretation of data: CPK, JLL, AJB, MZM, ES and KKZ.

Drafting of the manuscript and approval of the final version: CPK and AJB.

Critical revision of the manuscript for important intellectual content and approval of the final version: JLL, MZM, JZM, RBC, ES and KKZ.

pressure. 5,760 patients experienced follow-up treated blood pressure of <120 mmHg and 72,005 patients had SBP 120–139 mmHg. Propensity scores were calculated to reflect each individual's probability for future SBP<120 vs. 120–139 mmHg.

Main outcome 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—A total of 19,517 patients died during a median follow-up of 6.0 years, with 2,380 deaths in the SBP <120 mmHg group (death rate, 95%CI: 80.9/1000 patient-years, 77.7–84.2) and 17,137 deaths in the SBP 120–<140 mmHg group (41.8/1000 patient-years, 41.2–42.4), $p < 0.001$. The mortality hazard ratio (95%CI) associated with follow-up SBP<120 vs. 120–139 mmHg was 1.70 (95%CI: 1.63–1.78) after adjustment for propensity scores.

Conclusion and Relevance—Our results suggest that stricter SBP control is associated with higher all-cause mortality in CKD patients. 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 which lack clinical trial data.

Keywords

Blood Pressure; Chronic Kidney Disease; Mortality

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 pressure¹. Early retrospective studies initially showed that high blood pressure was associated with heart disease and stroke². Subsequent prospective clinical trials have sought to determine how aggressively to treat elevated blood pressure³, and have attempted to lower systolic blood pressure to lower and lower levels⁴. Retrospective studies also identified a J-curve of mortality for both systolic and diastolic blood pressure in certain groups of patients⁵, raising concerns about the safety of excessive blood pressure lowering in these populations.

Prospective randomized clinical trials have the ability to establish a cause-effect relationship between a clinical intervention (e.g. the lowering of blood pressure to various predefined targets). 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)⁶. Retrospective cohort studies and clinical trials are complementary in the knowledge they provide, and observational studies can examine populations that were excluded from clinical trials and treatments which cannot be tested in clinical trials, and hence they can offer valuable practical information. It is also true that retrospective studies often are in agreement with the results of prospective clinical trials⁷.

Patients with chronic kidney disease (CKD) represent a large population with a high prevalence of cardiovascular morbidity and mortality⁸, which has 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^{9–11} were unable to unequivocally establish the benefit vs. risk of stricter blood pressure control, due to 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 due to discrepancies between results from primary and secondary or post-hoc analyses^{12–15}. Therefore, current guidelines about the ideal target blood pressure in patients with CKD are based on extrapolations from trials done in healthier populations and on expert opinion. A growing body of observational studies suggests that the association of blood pressure with clinical events in patients with CKD is fundamentally different from the general population¹⁶. The implication is that strict BP control may not be advantageous in patients with CKD, and it could even be deleterious⁸. The Systolic Blood Pressure Interventional Trial (SPRINT) trial¹⁷ 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/exclusion criteria may limit the generalizability of its findings to a narrow spectrum of the CKD population. Using a large database of United States Veterans with a wide spectrum of patients with CKD, we examined outcomes associated with stricter (systolic blood pressure (SBP) <120 mmHg) and conventional (SBP 120–139 mmHg) treated blood pressure in patients with baseline uncontrolled hypertension.

METHODS

Study design and participants

The study is an historical cohort study that is designed to examine outcomes associated with strict vs. conventional SBP control in patients with CKD. A nation-wide cohort of US veterans with prevalent CKD was used to identify patients with eGFR <60 ml/min and uncontrolled systolic hypertension (using the definition applied in the ongoing SPRINT trial: baseline SBP 130–180 mmHg on 0 or 1 antihypertensives, or SBP 130–170 mmHg on up to 2 antihypertensives, or SBP 130–160 mmHg on up to 3 antihypertensives, or SBP 130–150 mmHg on up to 4 antihypertensives).¹⁷ The generation of our CKD cohort was described previously^{18–20}. Briefly, prevalent CKD was defined based on the presence of a persistent estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m² on at least two occasions separated by no less than 3 months and/or the presence of a spot urine microalbumin-creatinine ratio ≥30 mg/g on at least one occasion (for those with eGFR ≥60)²¹ between October 1, 2004 and September 30, 2006. GFR was estimated from serum creatinine measurements and demographic characteristics by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation²².

Information about blood pressure, laboratory, and other follow up data were 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-averaged values were used for analyses to reduce random variability. Exposure to antihypertensive medications was assessed from VA Pharmacy dispensation records²³. Antihypertensive medications were classified according to their mechanism of action (alpha-, beta- and calcium channel blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB), and loop- and thiazide-type diuretics). Medication classes used in <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– April 30, 2012.

Information about prevalent comorbidities was collected from the VA Inpatient and Outpatient Medical SAS Datasets²⁴ using *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic and procedure codes and *Current Procedural Terminology* codes recorded from October 1, 2004 until September 30, 2006. Coronary artery disease (CAD) 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-modification for administrative datasets, without including kidney disease²⁵.

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 eGFR<60 ml/min/1.73m² and uncontrolled hypertension. In order to model therapeutic interventions resulting in improved blood pressure control we categorized patients based on SBP levels recorded during their follow-up visits. There were 18,243 patients with SBP <120 mmHg on at least 50% of subsequent visits, and 176,034 patients with SBP 120–139 mmHg 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 anyhypertensive medications during follow-up (5,760 patients in the SBP <120 mmHg group and 72,005 patients in the 120–139 mmHg 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 <120 vs. 120–139 mmHg during follow-up from logistic regression. Older age, white race, lower baseline SBP, prevalent coronary artery disease, chronic heart failure, non-diabetic status and higher Charlson index were more likely to be associated with SBP <120 mmHg during follow-up than with 120–139 mmHg. 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 means (standard deviations), medians (interquartile ranges) and proportions. Baseline characteristics of patients with follow-up SBP <120 and 120–139 mmHg were compared using t-tests, non-parametric tests and chi-square tests, as appropriate. The start of the follow-up period was the date of the baseline SBP measurement. Patients were followed 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 (VSF; a registry containing dates of death or last medical/administrative encounter from all available sources in the VA system). The sensitivity and specificity of the VSF using the US National Death index as gold standard were found to be 98.3% and 99.8% respectively²⁶. The association of follow-up SBP of <120 vs. 120–139 mmHg 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 <120 vs. 120–139 mmHg in the overall cohort was examined before and after adjustment for individual propensity scores, and for baseline characteristics (age, gender, race, estimated GFR, systolic and diastolic BP, Charlson comorbidity index, DM, coronary artery disease, chronic heart failure, serum albumin and cholesterol, and use of alpha-, beta- and calcium channel blockers, ACEI/ARB, and loop- and thiazide-type diuretics). Associations were examined separately in subgroups of patients of the overall cohort, after categorization by age, gender, 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 5,000 propensity score-matched patients (2,500 in both SBP groups) defined using the inclusion and exclusion criteria of the CKD portion of the SPRINT trial (eTable 1 and eFigure 1), 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 mmHg, respectively). Statistical analyses were performed using STATA MP versions 11 and 12 (STATA Corporation, College Station, TX). The study protocol was approved by the Research and Development Committee at the Memphis VAMC.

RESULTS

Baseline characteristics of the patients with follow-up SBP <120 and 120–139 mmHg in the overall and the propensity-matched cohort are shown in Table 1. Patients with follow-up SBP <120 mmHg 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 <120 mmHg 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 <120 compared to the 120–139 mmHg group, in both the overall and the propensity score-matched cohorts (Figure 2). Patients increasingly used more antihypertensive medications over time. Specifically, the median number of antihypertensive medications increased from 2 (interquartile range 1 to 2) at baseline to 3 (2 to 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% confidence interval [CI]: 43.8–45.0) during a median follow-up of 6.0 years. 2,380 deaths occurred in the SBP <120 mmHg group (death rate, 95%CI: 80.9/1000 patient-years, 77.7–84.2) and 17,137 deaths occurred in the SBP 120–139 mmHg group (death rate, 95%CI: 41.8/1000 patient-years, 41.2–42.4). Mortality was significantly higher in the SBP <120 mmHg compared to the SBP 120–139 mmHg group, in both the overall and the propensity score-matched cohort (Figure 3, $p < 0.001$ for both). The unadjusted hazard ratio (95%CI) of mortality associated with follow-up SBP <120 vs. 120–139 mmHg in the overall cohort was 2.08 (1.99–2.17),

wich was attenuated but remained significant after djustment for propensity scores (HR: 1.70, 95%CI: 1.63–1.78), after adjustment for differences in baseline characteristics (HR: 1.74, 95%CI: 1.65–1.83), and in the propensity score-matched cohort (HR: 1.61, 95%CI: 1.51–1.71). The risk associated with SBP<120 was significantly higher in all examined subgroups (Figure 4). The results remained consistent in the cohort defined according to SPRINT inclusion/excluision criteria (eFigure 2), and in sensitivity analyses including all patients irrespective of antihypertensive medication use, and when requiring that target SBP levels for both groups be present on >75% of follow-up measurements (results not shown).

COMMENT

In our database containing over 650,000 patients with chronic kidney disease, 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 mmHg) SBP arm had significantly lower systolic and diastolic pressures and experienced significantly higher mortality compared to patients in the SBP 120–139 mmHg arm. These results were consistent in various subgroups of patients, and also in a sub-cohort modelled based on the inclusion/exclusion criteria of the currently ongoing SPRINT trial¹⁷. 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 Committee (JNC 8) for the management of high blood pressure in adults has advocated less stringent treatment targets in patients with CKD compared to previous guidelines²⁷, 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 were either not examined or were only included as part of composite secondary end points. These end points will be primarily examined in the ongoing SPRINT study, 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 trial 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, and because of different reasons underlying observed events in the two 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 which need to be considered when interpreting our results. We examined almost exclusively male (97.45%) and predominantly white (91.3%) patients. Fortunately, most prospective trials have not shown a significant difference in intervention effects between male and female patients^{3;4;28}. 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 carefully 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 (e.g. 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 proven to be successful, this could corroborate the role that observational studies could have 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 where 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 suffer from a significant number of various metabolic and other abnormalities. It is very 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 towards effective treatments. Hopefully, 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 <120 mmHg was associated with higher all-cause mortality compared to an SBP of 120–139 mmHg. Such an observational approach to estimate treatment targets for BP lowering in patients with CKD could be a useful complement to clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CPK is an employee of the US Department of Veterans Affairs. Opinions expressed in this Article are those of the authors' and do not represent the official opinion of the US Department of Veterans Affairs.

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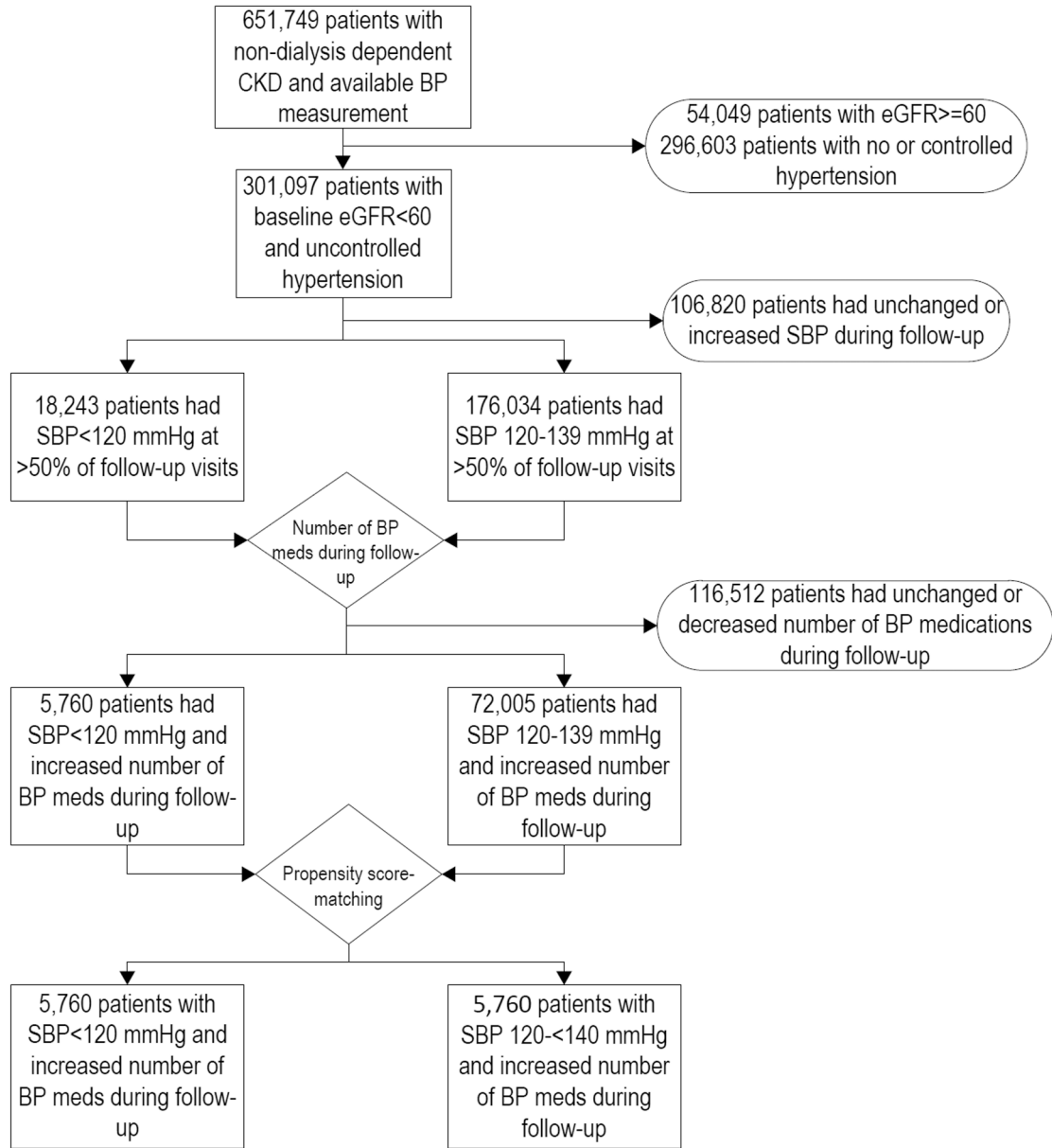


Figure 1.
Algorithm used to define the study cohort.

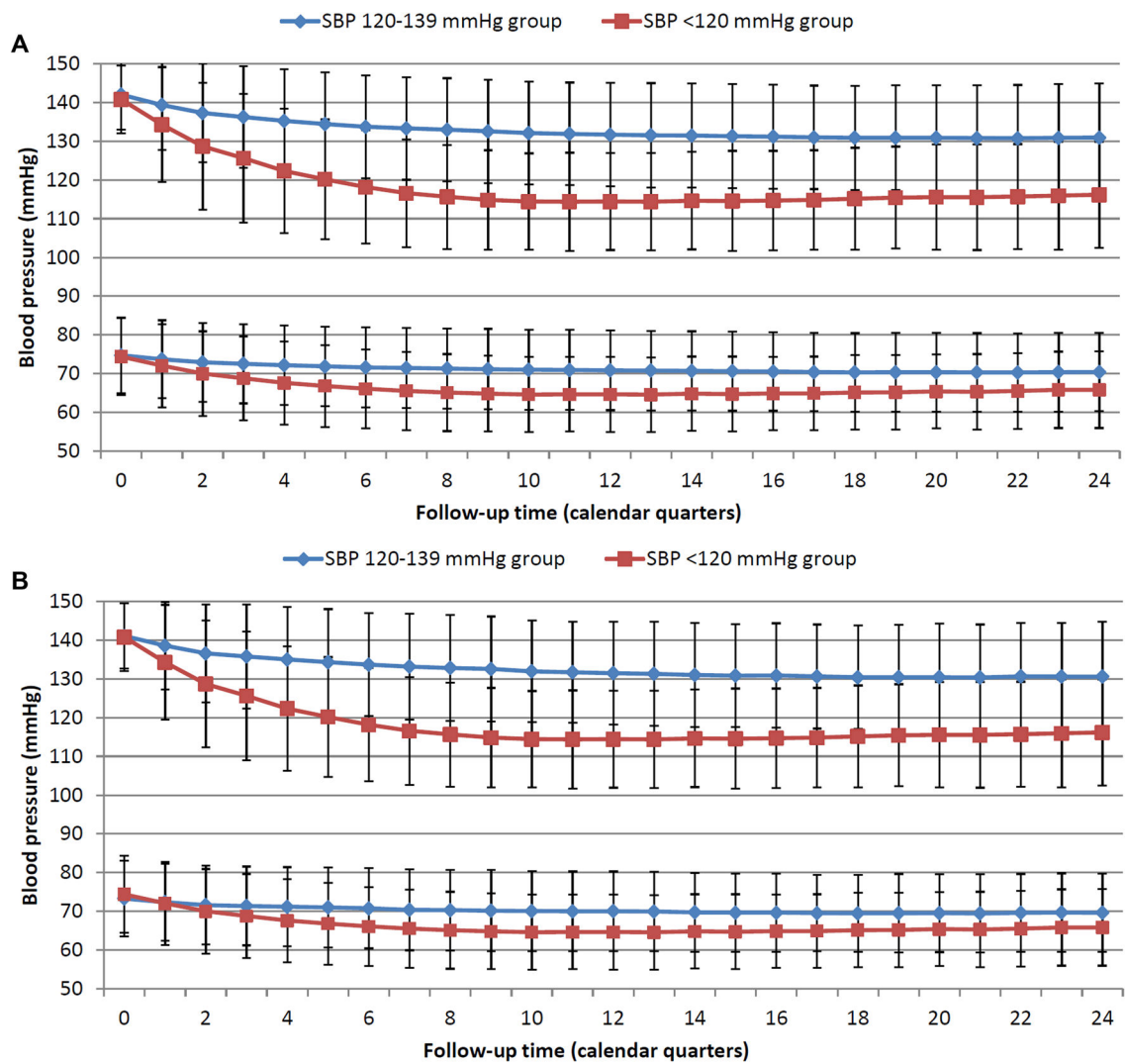


Figure 2. Mean follow-up systolic and diastolic blood pressures in patients with SBP <120 vs. 120–139 mmHg in the overall cohort (Panel A) and in the propensity score-matched cohort (Panel B).

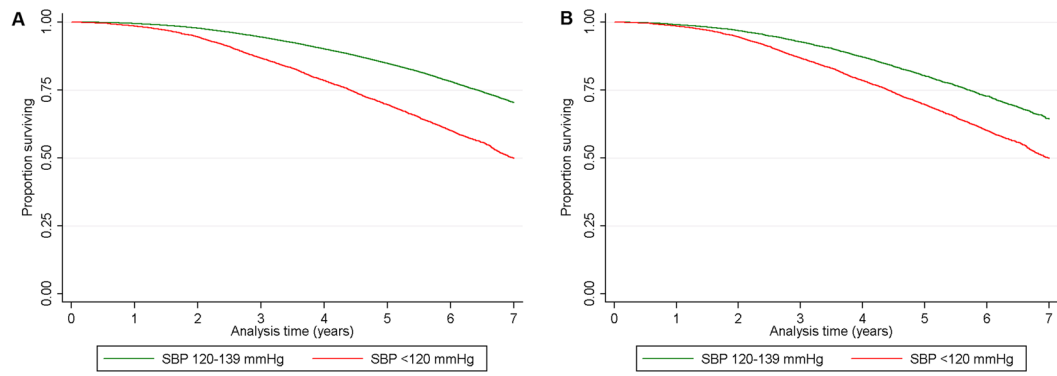


Figure 3.

Kaplan-Meier survival curves of patients with follow-up SBP <120 vs. 120–139 mmHg in the overall cohort (Panel A) and in the propensity score-matched cohort (Panel B).

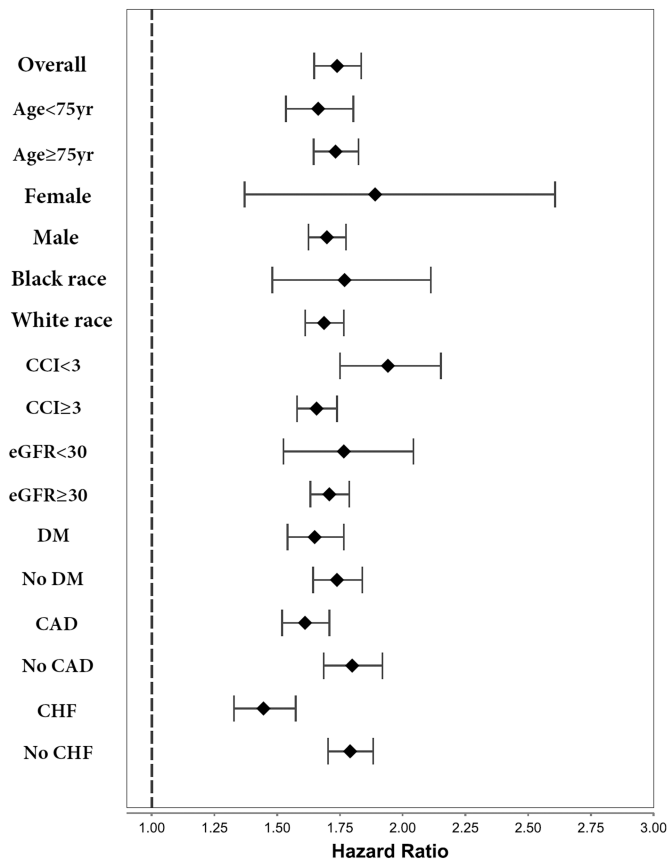


Figure 4.

Propensity score-adjusted hazard ratios (95% confidence intervals) of all-cause mortality associated with SBP <120 vs. 120–139 mmHg in various subgroups of patients in the overall cohort.

CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CAD, coronary artery disease; CHF, chronic heart failure.

Table 1

Characteristics of patients with follow-up systolic blood pressure <120 and 120–139 mmHg groups, in the overall and in the propensity score-matched cohorts

	Complete cohort		P value	Propensity score-matched cohort		P value
	SBP <120 mmHg (N=5,760)	SBP 120–139 mmHg (N=72,005)		SBP <120 mmHg (N=5,760)	SBP 120–139 mmHg (N=5,760)	
Age	75.0±9.2	73.5±9.2	<0.001	75.0±9.2	75.2±8.6	0.23
Gender (male)	5,636 (97.9)	70,248 (97.6)	0.17	5,636 (97.9)	5,638 (97.9)	0.9
Race			<0.001			0.07
White	5,202 (91.1)	62,234 (88.9)		5,202 (91.1)	5,159 (90.2)	
Black	363 (6.4)	5,876 (8.3)		363 (6.4)	433 (7.6)	
Hispanic	893 (1.3)	57 (1.0)		57 (1.0)	54 (0.9)	
Other	86 (1.5)	1,155 (1.6)		86 (1.5)	77 (1.4)	
Cardiovascular disease	2,917 (50.6)	27,469 (38.2)	<0.001	2,917 (50.6)	2,929 (50.9)	0.8
DM	2,196 (38.1)	28,625 (39.8)	0.015	2,196 (38.1)	2,187 (38.0)	0.9
CHF	1,104 (19.2)	6,520 (9.1)	<0.001	1,104 (19.2)	1,117 (19.4)	0.8
Cerebrovascular disease	899 (15.6)	9,423 (13.1)	<0.001	899 (15.6)	903 (15.7)	0.9
CCI	3.9±1.7	3.6±1.6	<0.001	3.9±1.7	3.9±1.8	0.3
eGFR (ml/min/1.73m ²)	48.1±9.5	48.8±9.1	<0.001	48.1±9.5	48.0±9.5	0.4
Baseline SBP (mmHg)	140.8±8.7	142.1±9.0	<0.001	140.8±8.7	141.1±8.5	0.025
Baseline DBP (mmHg)	74.4±9.9	74.7±9.8	0.007	74.4±9.9	73.3±9.7	<0.001
Mean follow-up SBP (mmHg)	119.1±5.5	133.1±5.6	<0.001	119.1±5.5	132.7±5.6	<0.001
Mean follow-up DBP (mmHg)	66.2±6.6	71.1±7.1	<0.001	66.2±6.6	70.1±7.1	<0.001
Number of BP meds at baseline	2 (1, 2)	2 (1, 2)	0.4	2 (1, 2)	2 (1, 2)	<0.001
Number of BP meds during follow-up	3 (2, 4)	3 (2, 4)	<0.001	3 (2, 4)	3 (2, 4)	<0.001
Baseline ACEI/ARB	2,155 (37.4)	27,843 (38.7)	0.06	2,155 (37.4)	2,292 (39.8)	0.009
Baseline α-blocker	1,068 (18.5)	12,745 (17.7)	0.1	1,068 (18.5)	1,027 (17.7)	0.3
Baseline β-blocker	2,578 (44.8)	28,775 (40.0)	<0.001	2,578 (44.8)	2,616 (45.4)	0.5
Baseline calcium channel blocker	1,175 (20.4)	20,333 (28.2)	<0.001	1,175 (20.4)	1,658 (28.8)	<0.001
Baseline loop diuretics	1,363 (23.7)	10,283 (14.3)	<0.001	1,363 (23.7)	1,174 (20.4)	<0.001
Baseline thiazide diuretics	788 (13.7)	15,129 (21.0)	<0.001	788 (13.7)	1,154 (20.0)	<0.001
Serum albumin (g/dl)	3.99±0.41	4.02±0.4	<0.001	3.99±0.41	4.02±0.4	0.02

	Complete cohort		Propensity score-matched cohort		P value
	SBP <120 mmHg (N=5,760)	SBP 120–139 mmHg (N=72,005)	SBP <120 mmHg (N=5,760)	SBP 120–139 mmHg (N=5,760)	
Blood cholesterol (mg/dl)	168±38	172±38	168±38	169±37	0.09

Data is presented as means ± SD, medians (interquartile ranges) or number (% of total). ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; CHF, chronic heart failure.