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Authors

Kovesdy, Csaba P
Bleyer, Anthony J
Molnar, Miklos Z
et al.

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Blood Pressure and Mortality in US Veterans with Chronic Kidney Disease

Csaba P Kovesdy, MD^{*,†}, Anthony J Bleyer, MD[‡], Miklos Z Molnar, MD PhD^{§,||}, Jennie Z Ma, PhD[¶], John J Sim, MD^{**}, William C Cushman, MD^{*,†}, L Darryl Quarles, MD[†], and Kamyar Kalantar-Zadeh, MD, PhD^{††}

*Memphis VA Medical Center, Memphis, TN, United States

†University of Tennessee Health Science Center, Memphis, TN, United States

‡Wake Forest School of Medicine, Winston Salem, NC, United States

§University Health Network, University of Toronto, Toronto, ON, Canada

||Semmelweis University, Budapest, Hungary

¶University of Virginia, Charlottesville, VA, United States

** Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

†† University of California-Irvine, Orange, CA, United States

Abstract

Background—The ideal blood pressure to lower mortality in non-dialysis dependent chronic kidney disease (CKD) patients is unclear.

Correspondence and reprints: Csaba P Kovesdy, MD FASN, Division of Nephrology, Memphis VA Medical Center, 1030 Jefferson Ave., Memphis, TN 38104, Phone: 901-523 8990 Fax: 901-577-7539, csaba.kovesdy@va.gov.

Postal addresses for all authors

Csaba P Kovesdy, MD, Chief, Division of Nephrology (111B), Memphis VA Medical Center, 1030 Jefferson Ave., Memphis, TN 38104

Anthony J Bleyer, MD, Section on Nephrology, Wake Forest School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157

Miklos Z Molnar, MD PhD, Semmelweis University, Institute of Pathophysiology, Nagyvarad ter 4, H-1089, Budapest, Hungary

Jennie Z. Ma, PhD, Professor, Division of Biostatistics, Department of Public Health Sciences, University of Virginia, P. O. Box 800717, Charlottesville, VA 22908-0717

John J Sim, MD, 4700 Sunset Blvd., Los Angeles, CA 90027

William C Cushman, MD, Chief, Preventive Medicine (111Q), Memphis VA Medical Center, 1030 Jefferson Ave., Memphis, TN 38104

L Darryl Quarles, MD, Director, Division of Nephrology, Department of Medicine, Associate Dean for Research, College of Medicine, 956 Court Ave, Suite B226, Memphis, TN 38163

Kamyar Kalantar-Zadeh, MD PhD, Division of Nephrology & Hypertension, University of California Irvine, School of Medicine, 101 The City Drive South, City Tower, Suite 400 - ZOT: 4088 Orange, California 92868-3217

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Relevant Potential Conflict of Interest:

None of the authors have relevant conflicts of interest.

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none

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Data: not available

Objective—To assess the association of blood pressure (defined as the combination of SBP and DBP at the individual level) with mortality in CKD patients.

Design—Historical cohort during 2005–2012.

Setting—All US Department of Veterans Affairs healthcare facilities.

Patients—651,749 US veterans with CKD.

Measurements—SBP and DBP were examined as all possible combinations of each other in 96 categories (from lowest of <80/<40 mmHg to highest of >210/>120 mmHg, in increments of 10 mmHg). Associations with all-cause mortality were examined in time-dependent Cox models with adjustment for relevant confounders.

Results—Patients with blood pressure of 130–159/70–89 mmHg had the lowest adjusted mortality, and those in whom both SBP and DBP were concomitantly very high or very low had the highest mortality. Patients with moderately elevated SBP combined with DBP levels no lower than 70 mmHg experienced consistently lower mortality rates compared to patients with ideal SBP levels combined with DBP <70 mmHg. Results were consistent in subgroups of patients with normal and elevated levels of urine microalbumin-creatinine ratio.

Limitations—Mostly male patients, inability to establish causality and large number of patients missing proteinuria measurement.

Conclusion—The optimal blood pressure in patients with CKD appears to be 130–149/70–89 mmHg. It may not be advantageous to achieve ideal SBP levels at the expense of lower-than-ideal DBP levels in adults with CKD.

Keywords

chronic kidney disease; blood pressure; mortality

Introduction

Blood pressure is associated with a linearly incremental risk of cardiovascular disease and death in the general population (1–5). Hypertension treatment guidelines recommend treating the elevated systolic component of blood pressure without consideration of the diastolic blood pressure (DBP) (unless it too is elevated) (6). These recommendations could be problematic in individuals with a low DBP, as excessively low DBP has been correlated with mortality (7–9). These issues are especially important in chronic kidney disease (CKD) because these individuals are more likely to have increased vascular stiffness and atherosclerosis, resulting in higher pulse pressures. In addition, the blood pressure treatment targets in patients with non-dialysis dependent CKD have been stricter than in the general population (6;10).

Recent guidelines from the Kidney Disease Improving Global Outcomes (K-DIGO) initiative advocate a BP treatment target of <140/90 mmHg in patients with CKD who have no proteinuria, and a stricter target of <130/80 mmHg in patients with microalbuminuria and macroalbuminuria (11). These targets emphasize the lowering of systolic blood pressure (SBP), without considering the potential clinical effects of low diastolic pressures. Lower

systolic guidelines in albuminuric patients will likely result in even lower diastolic pressures with treatment.

The presence of a J-curve for DBP in this case could negate the benefits of lowering SBP (12), yet very little is known about the level of DBP in CKD patients that could be regarded as safe in this context, especially since observational studies examining SBP or DBP separately may be unable to provide sufficient information about the combined effect of the two components on clinical outcomes. Previous studies that have examined the association of SBP and DBP in CKD patients did not include sufficiently large number of patients to allow for a granular examination of systolic-diastolic combinations in order to inform if elevated SBP combined with ideal DBP, or ideal SBP combined with low DBP is more advantageous for survival.

We examined the association of both systolic and diastolic components of blood pressure with all-cause mortality in a large national cohort of US veterans with non-dialysis dependent CKD. We assessed the effect of SBP and DBP on mortality separately, and we also examined the effects of actual blood pressures (i.e. the combination of SBP and DBP levels at the individual level) in order to determine what levels are associated with the most optimal outcome.

Methods

Cohort definition

The generation of our CKD cohort was described previously (13;14). We used all serum creatinine measurements obtained in clinical settings in all US Department of Veterans Affairs (VA) health care facilities between October 1, 2004 and September 30, 2006 from the VA Decision Support System (DSS) National Data Extracts Laboratory Results file (a VA-wide database containing select laboratory results obtained in the clinical setting) (15). GFR was estimated from serum creatinine measurements and demographic characteristics by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (16). We identified patients with CKD based on a stable estimated GFR (eGFR) based on a predefined algorithm and the presence of an elevated spot urine microalbumin/creatinine ratio (for those with eGFR ≥ 60) (17). The algorithm for cohort definition is shown in Appendix Figure 1. Of a total of 4,381,049 patients with any available eGFR we identified 651,749 patients with non-dialysis dependent CKD, available blood pressure measurements and sufficient follow-up for survival analysis.

Socio-demographic characteristics, blood pressure, medication use, comorbidities and laboratory measurements

Data on patients' age, gender, race and blood pressure was obtained through the VA Corporate Data Warehouse (CDW). Information on race was complemented with data obtained from Medicare through the VA-Medicare data merge project (18).

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 in the course of clinical practice in all VA facilities 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. We identified exposure to antihypertensive medications and lipid lowering agents based on VA Pharmacy dispensation records (19). 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. Exposure to each medication category was assessed longitudinally between October 1, 2004- April 30, 2012, by recording the presence or absence of outpatient dispensations during each calendar quarter.

Data on comorbidities was collected from the VA Inpatient and Outpatient Medical SAS Datasets (20;21) 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. Prevalent 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 disease (22). Data on laboratory variables was collected between October 1, 2004- April 30, 2012 by using the DSS National Data Extracts Laboratory Results file (15). To minimize random variability all available laboratory values were grouped by calendar quarters, and their quarterly-averaged values were used in analyses.

Statistical analyses

Descriptive analyses were performed and skewed variables were log-transformed. Data points were missing for race (1.5%), serum cholesterol (4.4%) and urine microalbumin-creatinine ratio (UACR, 80%). Due to the high degree of missingness for the latter variable, UACR was not included in the main multivariable models, and models including UACR were treated as exploratory analyses. There were a total of 624,746 patients (95.9% of the total study population) with complete data available for the fully adjusted main multivariable models. Missing values in this model were not imputed due to their relatively small proportion.

The start of the follow-up period was the date of the first available blood pressure measurement after October 1, 2004. 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% respectively (23).

Blood pressure was examined separately as SBP and DBP; due to previous studies suggesting a non-linear association with mortality for these variables (24;25) they were treated as continuous variables and analyzed using restricted cubic splines with two knots at

the 33rd and 66th percentile values for SBP (126 and 139 mmHg) and DBP (66 and 76 mmHg), using the “uvsr” command in Stata (26). In order to better characterize the role of actual blood pressure levels (i.e., the combination of SBP and DBP levels in any individual) we first categorized blood pressure levels according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): normal (SBP <120 and DBP <80), pre-hypertension (SBP 120–139 or DBP 80–89, whichever is higher), stage 1 hypertension (SBP 140–159 or DBP 90–99, whichever is higher) and stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg, whichever is higher). The JNC 7 categorization is defined by the presence of a high SBP or DBP, hence these categories may not accurately represent the effects of low levels of SBP or DBP that may be combined with high levels of their counterparts. In order to assess associations of actual BP levels that equally account for the effects of various combinations of high, normal or low SBP and DBP levels we categorized patients by mutually exclusive combinations of 15 SBP categories (<80 through ≥210 mmHg in 10 mmHg increments) and 10 DBP categories (<40 through ≥120 mmHg in 10 mmHg increments); of these 150 possible categories we examined in our analyses 96 categories that included at least 500 patients each.

The association of blood pressure levels with all-cause mortality was examined in time-dependent Cox models, with adjustment for potential confounders. Variables were included in multivariable models if they could be considered confounders (27) based on theoretical considerations. Associations were examined sequentially in models with incremental multivariable adjustments: unadjusted (Model 1), age, gender and race (Model 2), model 2 plus comorbid conditions (diabetes, CAD, heart failure (HF), cerebrovascular disease and Charlson comorbidity index) (Model 3), model 3 plus medications (ACEI/ARB, alpha-, beta- and calcium channel blockers, loop and thiazide diuretics, and cholesterol lowering agents) (Model 4) and model 4 plus eGFR and blood cholesterol (Model 5). Longitudinal data such as blood pressures, medications and laboratory variables were evaluated as time-dependent variables in Cox models.

We also examined the association of blood pressure with mortality in subgroups of patients categorized by sociodemographic characteristics, presence or absence of key comorbid conditions, their level of baseline kidney function and the presence or absence of microalbuminuria and the use of any antihypertensive medication throughout the follow-up period. Sensitivity analyses were performed using only baseline values for blood pressure, laboratory variables and medication use. Statistical analyses were performed using STATA MP version 11 (STATA Corporation, College Station, TX). The study protocol was approved by the Research and Development Committee at the Memphis VAMC.

Role of the Funding Source

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Results

Baseline characteristics overall and in patients categorized by their JNC 7 hypertension categories are shown in Table 1. The mean±SD age of the cohort at baseline was 73.8±9.7 years, 88% and 10% of patients were white and black, respectively, 43% were diabetic, and the mean estimated GFR (eGFR) was 50.4±14.4 ml/min/1.73m². There were a total of total 18,545,929 blood pressure measurements (median 15/patient, IQR 7–32). The mean±SD baseline SBP and DBP were 135±18 and 72±11, respectively, and 62% of patients had a blood pressure <140/90 mmHg. Patients with higher blood pressure were more likely to be black and diabetic and less likely to have HF and cardiovascular disease, were more likely to use antihypertensive medications except for loop diuretics, and had higher blood cholesterol and UACR levels. A total of 211,635 patients (32.5% of the entire cohort) had an SBP>140 accompanied by DBP<70 at least once during follow-up. Patients with this BP pattern were older (76.0±8.2 vs. 72.8±10.2 years) and were more likely to be diabetic (52 vs. 39%).

Mortality

A total of 238,640 patients died (mortality rate: 73.5/1000 patient-years, 95% confidence interval [CI]: 73.2–73.8) during a median follow-up of 5.8 years. When analyzed separately the association of both SBP and DBP with mortality was U-shaped, with both lower and higher levels showing a significant association with higher mortality even after multivariable adjustment in time dependent analyses (Figure 1 panels A and B) and in analyses using only baseline values of all variables (Appendix Figure 2). The best outcomes were associated with SBP levels of ~140–160 mmHg and DBP levels of ~80–90 mmHg.

Among patients categorized according to JNC 7 blood pressure categories those with stage 1 hypertension (SBP 140–159 or DBP 90–99 mmHg) had the lowest mortality and those with SBP <120 and DBP <80 had the highest mortality independent of confounders (Table 2). Associations remained essentially the same after additional adjustment for UACR (hazard ratios, 95%CI associated with categories of SBP<120&DBP<80, and stage 1 and stage 2 hypertension, compared to prehypertension: 1.49 (1.46–1.53), 0.92 (0.89–0.94) and 0.98 (0.94–1.03)). When examining the same associations in pre-defined subgroups of patients a similar pattern was present for all subgroups (including patient with and without diabetes mellitus, and patients with various levels of estimated GFR and UACR), except for younger patients (in whom prehypertension was associated with the lowest mortality), in patients with HF (in whom stage 2 hypertension was associated with the lowest mortality) and in patients who were never treated with antihypertensive medications (in whom prehypertension was associated with the lowest, and stage 2 hypertension with the highest mortality) (Figure 2).

Table 3 shows the unadjusted and multivariable adjusted hazard ratios associated with 96 mutually exclusive combinations of SBP and DBP categories. In crude and adjusted analyses blood pressures of 130–139/90–99 and 130–159/70–89 mmHg, respectively were associated with the lowest mortality. Combinations of lower SBP and lower DBP (i.e. comparing cells diagonally in Table 3) were associated with relatively lower mortality only if the lower DBP component was above approximately 70 mmHg. Below this DBP level lower BP levels were associated with higher mortality and SBP levels <120 mmHg were

associated with higher mortality irrespective of the level of the accompanying DBP component.

Discussion

In this investigation of the association of SBP/DBP combinations with all-cause mortality in a national cohort of US veterans with CKD, we found that categories of lower SBP/DBP combinations are associated with lower mortality only as long as the DBP component remains above a threshold of approximately 70 mmHg, and that patients with BP values in the range of 130–159/70–89 mmHg had the lowest mortality. Patients who might be considered to have “ideal” blood pressure (<130/80) actually had increased mortality due to the inclusion of individuals with low systolic and diastolic blood pressures. Patients with stage 1 hypertension actually experienced the lowest mortality. These associations were consistent in diabetic and non-diabetic patients and in patients with or without microalbuminuria.

The association of lower blood pressure with increased mortality has been previously described repeatedly in dialysis patients (7;28–32). In non-dialysis dependent CKD patients a post-hoc analysis of the Irbesartan Diabetic Nephropathy Trial (33) and two smaller single center studies (24;25) have described J-shaped associations of blood pressure with mortality. Similar J-curve phenomena have been described in the elderly (34), and in patients with pre-existing coronary artery disease (35;36). Interestingly, low DBP has recently also been shown to be a risk factor for ESRD (37). While these studies showed the relationship between low diastolic blood pressures and survival, they did not examine the large group of patients with both a high systolic blood pressure and a low DBP. The critical role of low DBP in limiting the benefits of treating elevated SBP was shown in a post-hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP), in which an achieved DBP below 60 mmHg was associated with increased stroke risk (12). A consistent J-curve for cardiac events and DBP was also apparent in a meta-analysis of antihypertensive trials (38). To the best of our knowledge (including after a structured Medline search) our study is the first to examine the mortality risk associated with discrete combinations of granular SBP/DBP categories.

Current treatment paradigms primarily emphasize the higher of the two components of blood pressure (SBP and DBP), based on the assumption that only elevated blood pressure levels are deleterious. Under circumstances when this assumption may not hold (like in the case of our study population) such categorization ignores the potential negative effects of low levels of either SBP or DBP that are linked with their normal or elevated counterparts.

An especially problematic blood pressure pattern is the one where an elevated SBP combines with a low DBP, which is common in patients with CKD (39;40). Aside from the recognition that the high pulse pressure seen with this blood pressure pattern is associated with elevated mortality (7–9), a particularly vexing practical issue is to determine if lowering the blood pressure in such individuals is beneficial through achieving an SBP associated with a lower mortality, or detrimental through concomitantly inducing an even lower DBP that is associated with higher mortality (12). Nearly one-third (32.5%) of the

patients in this cohort had a SBP >140 and diastolic <70 mm Hg at some point during the observation period. Our granular analyses of blood pressure categories indicated that categories of lower SBP/DBP combinations are associated with lower mortality only as long as the DBP component remains above a threshold of approximately 70 mmHg.

These data may indicate that lowering SBP towards the strict limits recommended by current guidelines (SBP <130 mmHg or even lower in patients with CKD (6;10;11)) at the expense of lowering DBP below approximately 70 mmHg may be deleterious, but the observational nature of these results limits their interpretability. Therefore, randomized trials are needed to clarify the optimal BP treatment goals in patient with CKD. In the general hypertensive population, trials have demonstrated reduction in cardiovascular events with BP goals of <150 mmHg systolic or <90 mm Hg diastolic. Conversely, a recent large clinical trial of strict blood pressure control in high-risk diabetics has failed to show a reduction in cardiovascular outcomes (41;42), and three trials in CKD have failed to prove that substantially lower BP goals (consistent with <130/80 mmHg) significantly reduce major renal outcomes (43–45). The NIH-sponsored Systolic Blood Pressure Intervention Trial (SPRINT) has been initiated to examine whether a SBP goal <120 mmHg will reduce cardiovascular and renal events compared with a SBP goal of <140 mmHg in high-risk persons with SBP $\geq$ 130 mmHg, including many with eGFR 20–59 ml/min (ClinicalTrials.gov number NCT01206062, www.sprinttrial.org).

The J-shaped association of blood pressure with outcomes could be caused by compromised blood flow to vital organs (especially low diastolic blood pressure compromising coronary perfusion), or it could be a result of confounding by the presence of stiff arteries, or the high comorbidity-burden (e.g., HF (46)) characteristic of populations with this association pattern. It is possible that all three mechanisms could play a role in the associations observed in our study. Our results would suggest that further analyses should be carried out in past and future blood pressure treatment trials to determine if active intervention improves survival in individuals with low diastolic blood pressures.

Our study is notable for its large size and its representativeness of the entire US veteran population. Our study also needs to be interpreted with the recognition of its shortcomings. Since this was an observational study, only associations, but no cause-effect relationships can be established from it. Specifically, we cannot conclude that the mortality risk associated with various blood pressure levels in our study is equivalent to the risk imparted by the same blood pressure levels when they occur as a result of antihypertensive interventions in clinical practice. Our cohort consisted of US veterans who were almost exclusively men; hence our findings may not apply to women or to the general population. We tried to account for several potential confounding risk factors, but residual confounders could remain present. We have explored the role of microalbuminuria in the associations between BP and mortality, but due to the relatively low proportion of patients with available UACR measurements in our cohort we regard these results as exploratory, and they would need to be confirmed in other studies. We used time-dependent analyses to account for temporal changes in blood pressure and in various confounders such as medication use and kidney function. Longitudinal changes in blood pressure and kidney function could be both causes and consequences of each other, which are difficult to discern using standard

analytical techniques. Nevertheless, kidney function did not appear to modify the association of blood pressure with mortality in any of the models, including those using exclusively baseline data. Since the BP levels reported in usual clinical settings, including Department of Veterans Affairs clinics (47), often overestimate BP by 5–10 mmHg compared with research-quality BP measurements, it is possible that the BP ranges we report would be lower if BP determinations were taken more accurately.

We describe a J-shaped association between SBP and DBP and all-cause mortality in patients with non-dialysis dependent CKD. The combination of low SBP and low DBP is associated with the highest mortality in this population. In addition, DBP levels below approximately 70 mmHg appear to confer increased mortality even in patients with moderately high SBP. Clinical trials are needed to inform us about the ideal blood pressure levels to be targeted by antihypertensive therapy in patients with CKD. Until such trials become available it is prudent to regard low blood pressures as potentially deleterious in this patient population, and we suggest caution in lowering BP to levels below what has been demonstrated to be beneficial in randomized controlled trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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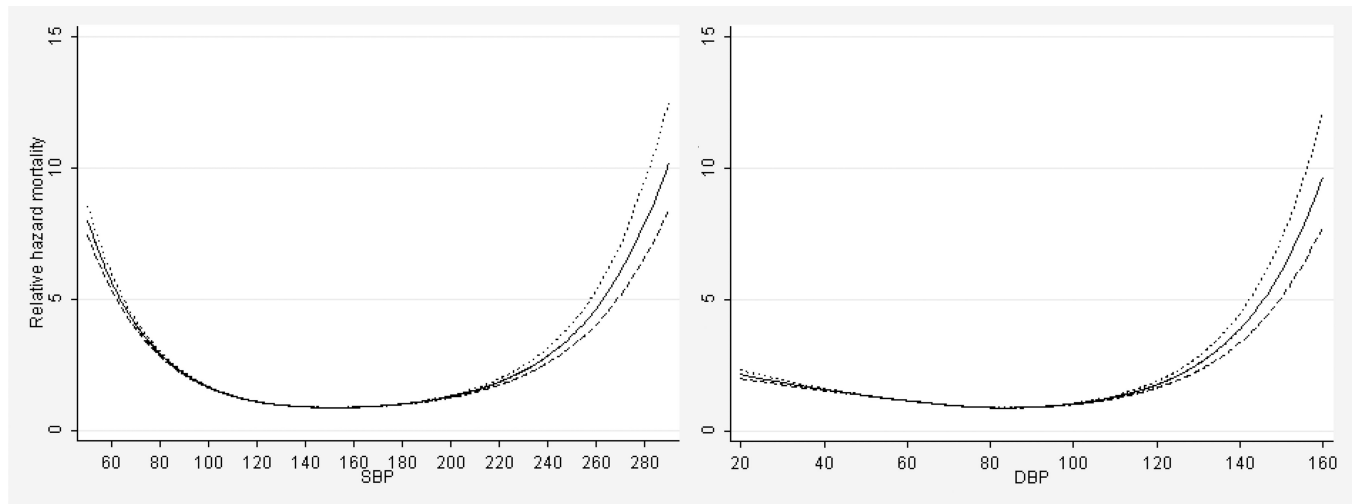
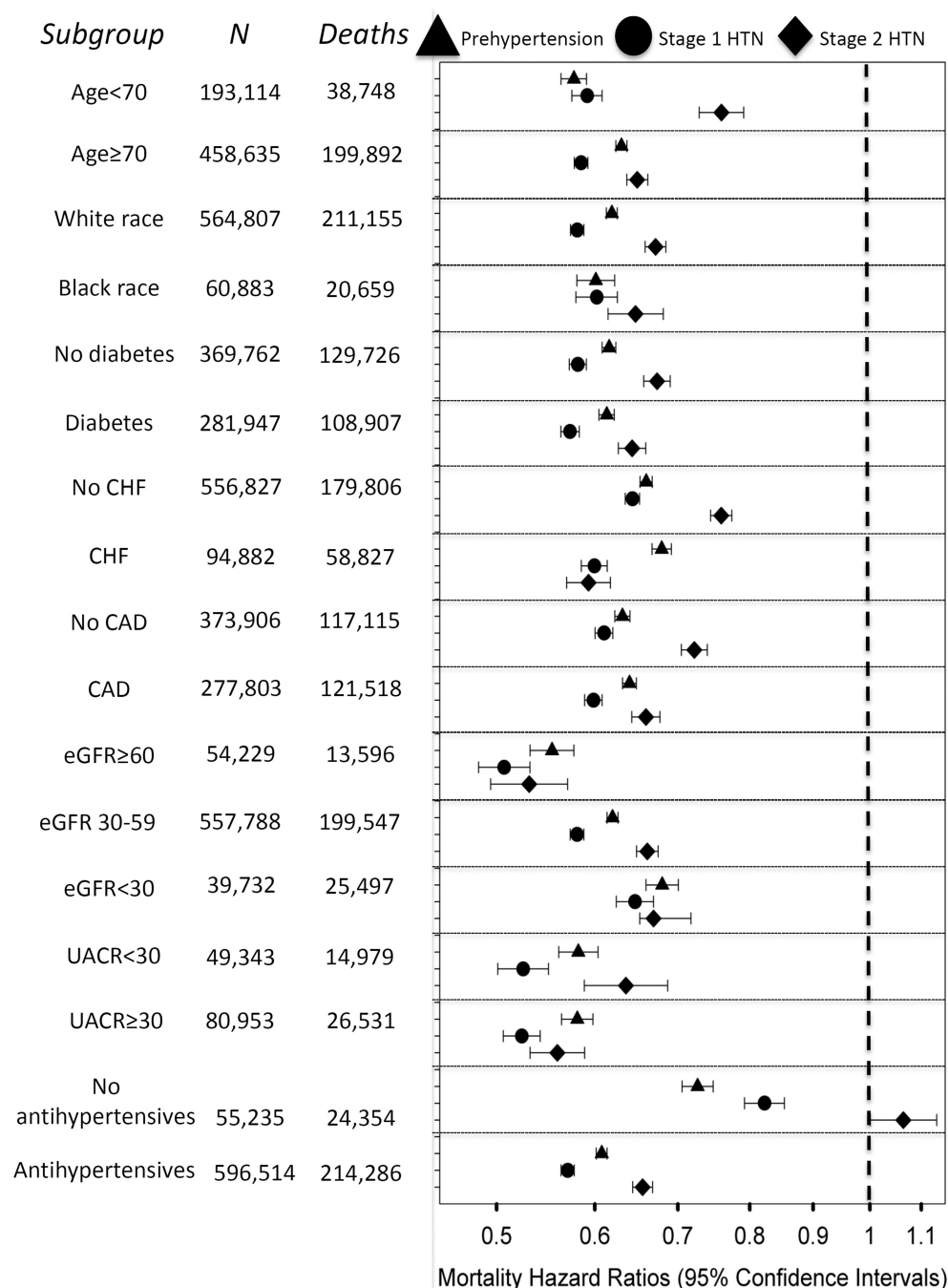


Figure 1.

Multivariable adjusted relative hazards (hazard ratios, 95% confidence intervals) of all-cause mortality associated with systolic blood pressure (**Panel A**) and diastolic blood pressure (**Panel B**) levels relative to a hypothetical patient with the mean level of time-varying SBP (133 mmHg) and DBP (71 mmHg), respectively, in time-dependent Cox models using restricted cubic splines, adjusted for age, gender, race, diabetes mellitus, cardiovascular and cerebrovascular disease, heart failure, the Charlson comorbidity index, medications (angiotensin converting enzyme inhibitors/angiotensin receptor blockers, alpha-, beta- and calcium channel blockers, loop and thiazide diuretics, and cholesterol lowering agents), estimated glomerular filtration rate and blood cholesterol. SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Figure 2.**

Forest plot of the multivariable adjusted mortality hazard ratios (95% confidence intervals) associated with blood pressure categories defined according to cutoffs established by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The group with systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg served as referent. Estimates are from time-dependent Cox models adjusted for age, gender, race, diabetes mellitus, cardiovascular and cerebrovascular disease, heart failure, the Charlson comorbidity index, medications

(angiotensin converting enzyme inhibitors/angiotensin receptor blockers, alpha-, beta- and calcium channel blockers, loop and thiazide diuretics, and cholesterol lowering agents), estimated glomerular filtration rate and blood cholesterol.

CHF, chronic heart failure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; UACR, urine microalbumin creatinine ratio

Table 1
Baseline Patient Characteristics, Overall and by JNC 7 Hypertension Category at Baseline

Characteristic	Overall (n = 651 749)	JNC 7 Hypertension Category *			
		Normal (n = 132 249)	Prehypertension (n = 295 937)	Stage 1 Hypertension (n = 169 416)	Stage 2 Hypertension (n = 54 147)
Mean age (SD), y	73.8 (9.7)	74.0 (9.8)	73.8 (9.7)	73.8 (9.7)	73.9 (10.0)
Female, n (%)	17 633 (2.7)	3042 (2.3)	7960 (2.7)	4637 (2.7)	1634 (3.0)
Black, n (%)	60 883 (9.3)	9190 (6.9)	25 093 (8.5)	18 748 (11.1)	7852 (14.5)
Mean BMI (SD), kg/m ²	29.3 (5.8)	28.7 (5.7)	29.4 (5.7)	29.6 (5.8)	29.5 (6.0)
Diabetes mellitus, n (%)	281 947 (43.3)	54 288 (41.0)	126 035 (42.6)	76 171 (45.0)	25 453 (47.0)
Coronary artery disease, n (%)	277 803 (42.6)	66 940 (50.6)	123 970 (41.9)	66 144 (39.0)	20 749 (38.3)
Cerebrovascular disease, n (%)	96 995 (14.9)	19 774 (15.0)	42 019 (14.2)	25 975 (15.3)	9227 (17.0)
CHF, n (%)	94 882 (14.6)	28 409 (21.5)	39 742 (13.4)	20 042 (11.8)	6689 (12.4)
Mean Charlson Comorbidity Index score (SD)	3.7 (1.9)	3.8 (1.9)	3.7 (1.9)	3.7 (1.9)	3.7 (1.9)
Medication use, n (%)					
ACE inhibitor/ARB	349 980 (53.7)	69 013 (52.2)	153 162 (51.8)	94 649 (55.9)	33 156 (61.2)
Calcium-channel blocker	223 095 (34.2)	31 932 (24.1)	95 489 (32.3)	69 332 (40.9)	26 342 (48.6)
β-Blocker	323 979 (49.7)	69 196 (52.3)	139 909 (47.3)	84 336 (49.8)	30 538 (56.4)
α-Blocker	155 760 (23.9)	31 295 (23.7)	69 985 (23.6)	40 961 (24.2)	13 519 (25.0)
Loop diuretic	158 063 (24.3)	40 184 (30.4)	66 794 (22.6)	37 845 (22.3)	13 240 (24.5)
Thiazide diuretic	166 651 (25.6)	24 746 (18.7)	71 574 (24.2)	51 149 (30.2)	19 182 (35.4)
Statin	446 177 (68.5)	92 579 (70.0)	204 006 (68.9)	114 241 (67.4)	35 351 (65.3)
Mean eGFR (SD), mL/min per 1.73 m ²	50.4 (14.4)	49.5 (13.4)	50.8 (14.1)	50.7 (15.1)	49.9 (15.1)
CKD stage, n (%) [†]					
1	16 930 (2.6)	2465 (1.9)	7578 (2.6)	5170 (3.1)	1717 (3.2)
2	31 642 (4.8)	4760 (3.6)	14 132 (4.8)	9504 (5.6)	3246 (6.0)
3A	405 756 (62.3)	83 336 (63.0)	188 620 (63.7)	103 083 (60.8)	30 717 (56.7)
3B	157 380 (24.1)	33 312 (25.2)	69 374 (23.4)	40 779 (24.1)	13 915 (25.7)
4	35 782 (5.5)	7601 (5.7)	14 641 (4.9)	9644 (5.7)	3896 (7.2)
5	4259 (0.7)	775 (0.6)	1592 (0.5)	1236 (0.7)	656 (1.2)

Characteristic	Overall (n = 651 749)	JNC 7 Hypertension Category *			
		Normal (n = 132 249)	Prehypertension (n = 295 937)	Stage 1 Hypertension (n = 169 416)	Stage 2 Hypertension (n = 54 147)
Mean cholesterol level (SD)					
mmol/L	4.40 (1.01)	4.25 (0.98)	4.38 (0.98)	4.48 (1.01)	4.58 (1.09)
mg/dL	170 (39)	164 (38)	169 (38)	173 (39)	177 (42)
Mean hemoglobin level (SD), g/dL	13.8 (1.7)	13.7 (1.7)	13.9 (1.7)	13.9 (1.7)	13.8 (1.7)
Mean albumin level (SD), g/L	40 (4)	39 (4)	40 (4)	40 (4)	40 (4)
Mean potassium level (SD), mmol/L	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)
Median UACR (IQR), mg/g	40 (13–94)	33 (10–72)	38 (12–86)	46 (17–111)	58 (26–157)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blockers; BMI = body mass index; CHF = chronic heart failure; CKD = chronic kidney disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; IQR = interquartile range; SBP = systolic blood pressure; UACR = urinary microalbumin–creatinine ratio.

* Normal = SBP <120 mm Hg and DBP <80 mm Hg; prehypertension = SBP of 120 to 139 mm Hg or DBP of 80 to 89 mm Hg; stage 1 hypertension = SBP of 140 to 159 mm Hg or DBP of 90 to 99 mm Hg; stage 2 hypertension = SBP ≥160 mm Hg or DBP ≥100 mm Hg.

† CKD staging was done according to criteria by the Kidney Disease: Improving Global Outcomes. The CKD stages represent patients with eGFRs ≥90 mL/min per 1.73 m² (stage 1, if accompanied by UACR ≥30 mg/g), 60–89 mL/min per 1.73 m² (stage 2, if accompanied by UACR ≥30 mg/g), 45–59 mL/min per 1.73 m² (stage 3A), 30–44 mL/min per 1.73 m² (stage 3B), 15–29 mL/min per 1.73 m² (stage 4), and <15 mL/min/1.73 m² but not receiving renal replacement therapy (stage 5).

Table 2

HRs of All-Cause Mortality Associated With Hypertension Categories*

Model [†]	HR (95% CI)			
	Patients With SBP <120 mm Hg and DBP <80 mm Hg	Patients With SBP of 120–139 mm Hg or DBP of 80–89 mm Hg	Patients With SBP of 140–159 mm Hg or DBP of 90–99 mm Hg	Patients With SBP ≥160 mm Hg or DBP ≥100 mm Hg
1	1.62 (1.61–1.64)	1.00 (reference)	0.94 (0.93–0.95)	1.08 (1.06–1.10)
2	1.59 (1.58–1.61)	1.00 (reference)	0.93 (0.92–0.95)	1.04 (1.02–1.06)
3	1.48 (1.46–1.49)	1.00 (reference)	0.94 (0.93–0.95)	1.06 (1.04–1.07)
4	1.44 (1.42–1.45)	1.00 (reference)	0.95 (0.94–0.96)	1.05 (1.03–1.07)
5	1.42 (1.41–1.43)	1.00 (reference)	0.95 (0.94–0.96)	1.05 (1.03–1.07)

DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.

* Categories were defined according to mutually exclusive cutoffs established by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure associations, based on the concomitant presence of SBP and DBP in each person. Associations were examined in time-dependent Cox models. All comparisons were significant at $P < 0.001$.

[†] Models represent unadjusted association (model 1) and associations after adjustment for age, sex, and race (model 2); model 2 variables plus diabetes mellitus, cardiovascular and cerebrovascular disease, chronic heart failure, Charlson Comorbidity Index scores (model 3); model 3 variables plus medication use (angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; α -blockers, β -blockers, and calcium-channel blockers; loop and thiazide diuretics; and cholesterol-lowering agents) (model 4); and model 4 variables plus estimated glomerular filtration rates and blood cholesterol levels (model 5).

Table 3
Mortality HRs Associated With Mutually Exclusive Categories of SBP and DBP Combinations*

Variable		HR													
		SBP <80 mm Hg	SBP of 80-89 mm Hg	SBP of 90-99 mm Hg	SBP of 100-109 mm Hg	SBP of 110-119 mm Hg	SBP of 120-129 mm Hg	SBP of 130-139 mm Hg	SBP of 140-149 mm Hg	SBP of 150-159 mm Hg	SBP of 160-169 mm Hg	SBP of 170-179 mm Hg	SBP of 180-189 mm Hg	SBP of 190-199 mm Hg	SBP of 200-209 mm Hg
DBP															
Crude model															
<40 mm Hg	5.88	5.56	5.20	4.19	3.32	3.07	3.07								
40-49 mm Hg	6.03	5.32	4.64	3.45	2.87	2.50	2.44	2.36	2.77	3.25					
50-59	5.84	4.91	3.84	3.01	2.52	2.10	1.82	1.94	2.16	2.26	3.04	2.29			
60-69 mm Hg		4.72	3.28	2.49	2.07	1.75	1.55	1.62	1.74	1.81	2.12	2.37	1.76		
70-79 mm Hg			2.67	1.81	1.41	1.25	1.17	1.25	1.39	1.51	1.67	1.89	1.84	1.89	2.09
80-89 mm Hg				2.01	1.12	0.94	0.90	Reference	1.12	1.26	1.49	1.68	1.99	1.94	1.96
90-99 mm Hg					1.75	0.93	0.78	0.85	0.98	1.13	1.34	1.40	1.42	1.89	1.59
100-109 mm Hg							1.19	0.79	0.89	1.05	1.21	1.39	1.76	1.60	1.69
110-119 mm Hg									0.95	1.03	1.27	1.06	1.42	1.81	1.88
≥120 mm Hg											1.38			2.14	1.74
Adjusted model†															
<40 mm Hg	2.56	2.42	2.55	2.15	1.73	1.69	1.91								
40-49 mm Hg	2.99	2.69	2.31	1.77	1.58	1.39	1.37	1.30	1.50	1.83					
50-59 mm Hg	3.25	2.88	2.24	1.77	1.51	1.27	1.14	1.17	1.27	1.32	1.63	1.20			
60-69 mm Hg		3.11	2.32	1.82	1.48	1.23	1.09	1.09	1.12	1.13	1.28	1.36	1.00		
70-79 mm Hg			2.05	1.70	1.34	1.14	1.01	1.01	1.04	1.07	1.12	1.19	1.11	1.17	1.26
80-89 mm Hg				1.82	1.27	1.08	0.98	Reference	1.01	1.07	1.13	1.22	1.43	1.25	1.35
90-99 mm Hg					1.57	1.26	1.08	1.10	1.15	1.18	1.25	1.23	1.16	1.38	1.04
100-109 mm Hg							1.53	1.16	1.31	1.33	1.37	1.30	1.62	1.40	1.42
110-119 mm Hg									1.11	1.28	1.81	1.35	1.89	1.85	1.71
≥120 mm Hg											1.62			2.44	2.06

DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.

* Blood pressure of 140–149/80–89 mm Hg served as reference. Cells in which the HR were significantly different ($P < 0.050$) from the reference category are bold.

† Adjusted for age, sex, race, diabetes mellitus, cardiovascular and cerebrovascular disease, chronic heart failure, Charlson Comorbidity Index score, medication use (angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; α -blockers, β -blockers, and calcium-channel blockers; loop and thiazide diuretics; and cholesterol-lowering agents), estimated glomerular filtration rates, and blood cholesterol levels.