

# Impact of Achieved Blood Pressures on Mortality Risk and End-Stage Renal Disease Among a Large, Diverse Hypertension Population



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## ABSTRACT

**BACKGROUND** Medical data or clinical guidelines have not adequately addressed the ideal blood pressure (BP) treatment targets for survival and renal outcome.

**OBJECTIVES** This study sought to evaluate ranges of treated BP in a large hypertension population and compare risk of mortality and end-stage renal disease (ESRD).

**METHODS** A retrospective cohort study within the Kaiser Permanente Southern California health system was performed from January 1, 2006, to December 31, 2010. Treated hypertensive subjects  $\geq 18$  years of age were studied. Cox proportional hazards regression models were used to evaluate the risks (hazard ratios) for mortality and/or ESRD among different BP categories with and without stratification for diabetes mellitus and older age.

**RESULTS** Among 398,419 treated hypertensive subjects (30% with diabetes mellitus), mortality occurred in 25,182 (6.3%) and ESRD in 4,957 (1.2%). Adjusted hazard ratios (95% confidence intervals [CI]) for composite mortality/ESRD in systolic BP  $< 110$ , 110 to 119, 120 to 129, 140 to 149, 150 to 159, 160 to 169, and  $\geq 170$  compared with 130 to 139 mm Hg were 4.1 (95% CI: 3.8 to 4.3), 1.8 (95% CI: 1.7 to 1.9), 1.1 (95% CI: 1.1 to 1.1), 1.4 (95% CI: 1.4 to 1.5), 2.3 (95% CI: 2.2 to 2.5), 3.3 (95% CI: 3.0 to 3.6), and 4.9 (95% CI: 4.4 to 5.5) respectively. Diastolic BP 60 to 79 mm Hg were associated with the lowest risk. The nadir systolic and diastolic BP for the lowest risk was 137 and 71 mm Hg, respectively. Stratified analyses revealed that the diabetes mellitus population had a similar hazard ratio curve but a lower nadir at 131 and 69 mm Hg but age  $\geq 70$  had a higher nadir (140 and 70 mm Hg).

**CONCLUSIONS** Both higher and lower treated BP compared with 130 to 139 mm Hg systolic and 60 to 79 mm Hg diastolic ranges had worsened outcomes. Our study adds to the growing uncertainty about BP treatment targets. (J Am Coll Cardiol 2014;64:588-97) © 2014 by the American College of Cardiology Foundation.

As treatment and control rates of hypertension (HTN) continue to improve (1,2), discussions have centered on the most appropriate target blood pressures (BP) in treated hypertensive patients, specifically related to how aggressively their HTN should be treated. Current treatment goals have been drafted with the assumption that there is a linear relationship between BP and risk for vascular

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and mortality outcomes. Lower observed BP across all age groups have been associated with the greatest morbidity and survival benefits (3). These observations have led to conclusions that lowering BP along that linear axis will correspond with a proportionate decrease in risk (4). The perception has been the same for the risk of renal failure (5). Indeed, significant risk reductions have been demonstrated in prospective interventional studies that have lowered BP in those with severe HTN (5-13). However, aggressive BP lowering has not convincingly shown benefit (14-19) and may actually predispose individuals to harm (20-24).

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In high-risk populations, such as those with diabetes mellitus (DM) and chronic kidney disease (CKD), interventions to lower BP below current target levels have not demonstrated outcome improvements (14,19,25). In fact, aggressive BP lowering has been associated with worsened outcomes (20-22), which is suggestive of a J-shaped curve. This nonlinear curve is similar to what has already been observed in other cardiovascular disease risk factors (24,26). Thus, for the treated general HTN population, the relationship between treated BP and outcomes is not well-defined. We used a large ethnically diverse population of subjects who were medically treated for HTN to evaluate discrete ranges of achieved BP and subsequent risk for mortality and end-stage renal disease (ESRD).

**METHODS**

A retrospective cohort study was performed among members of Kaiser Permanente Southern California (KPSC) during the period January 1, 2006, through December 31, 2010. KPSC is an integrated health system composed of 14 medical centers and >200 satellite medical offices, with a membership exceeding 3.5 million people. The membership population is ethnically and socioeconomically diverse, reflecting the population of the state of California (27). KPSC complete healthcare encounters are tracked using a common electronic health record and are collected as part of routine clinical care encounters. The KPSC Institutional Review Board approved the study protocol, which was exempt from informed consent.

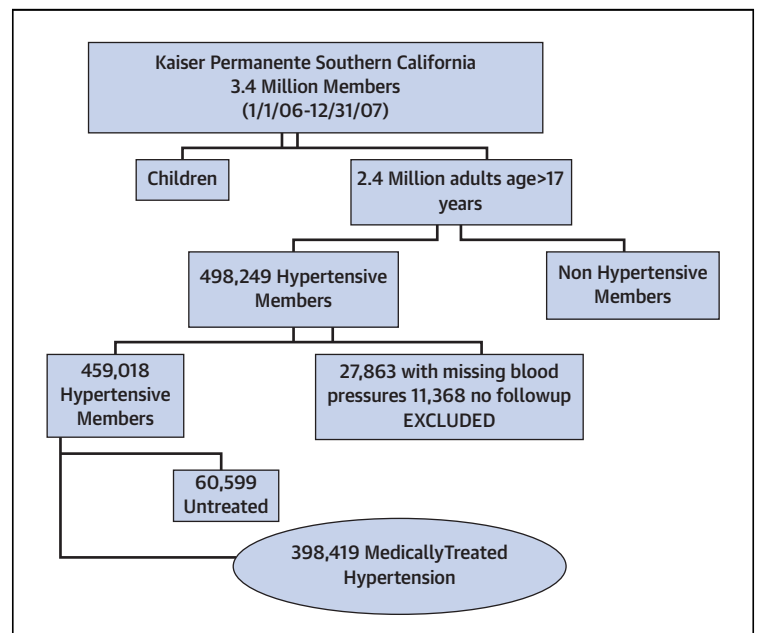
The study population consisted of subjects ≥18 years of age who had a minimum of 6 months of continuous membership in the health plan. The HTN study cohort was identified in a 2-year window (January 1, 2006, to December 31, 2007) and followed up to December 31, 2010. HTN was identified as any member with 2 International Classifications of

Diseases-Ninth Revision (ICD-9) codes, specific to HTN (401.xx, 402.xx, 403.xx, 404.xx, 405.xx). The accuracy of ICD-9 coding for the diagnosis of HTN has been previously validated (28). Recorded BP values at baseline when the cohort was initially identified and all subsequent BP were retrieved. Inclusion criteria were hypertensive patients who had a minimum of 1 outpatient BP measurement and documented prescription(s) for antihypertensive medications. Patients were determined to be on an antihypertensive medication if it was prescribed and filled for ≥7 days within the observation period. Exclusion criteria were subjects <18 years of age, who were on dialysis, or who had received a renal transplant, with no documented diagnosis of HTN, no documented BP, or no documented prescription for antihypertensive medications. Patients with congestive heart failure also were excluded as their BP may not necessarily reflect treated BP values.

Comorbidities, including DM, ischemic heart disease, congestive heart failure, and cerebrovascular disease, were determined on the basis of inpatient and outpatient ICD-9 diagnoses codes. CKD

**ABBREVIATIONS AND ACRONYMS**

- BMI** = body mass index
- BP** = blood pressure
- CCI** = Charlson comorbidity index
- CI** = confidence interval
- CKD** = chronic kidney disease
- DBP** = diastolic blood pressure
- DM** = diabetes mellitus
- eGFR** = estimated glomerular filtration rate
- ESRD** = end-stage renal disease
- HR** = hazards ratio
- HTN** = hypertension
- ICD-9** = International Classifications of Diseases-Ninth Revision
- KPSC** = Kaiser Permanente Southern California
- SBP** = systolic blood pressure



**FIGURE 1 KPSC Treated Hypertension Study Cohort**

A total of 398,419 hypertensive patients met inclusion criteria, meaning that they were treated with hypertensive medicines and had documented blood pressures during the period of follow-up to December 31, 2010. KPSC = Kaiser Permanente Southern California.

**TABLE 1** Characteristics of Treated Hypertension Cohort

	All (N = 398,419)	<110 mm Hg (n = 6,531)	110-119 mm Hg (n = 43,865)	120-129 mm Hg (n = 138,958)	130-139 mm Hg (n = 141,582)	140-149 mm Hg (n = 49,463)	150-159 mm Hg (n = 12,682)	160-169 mm Hg (n = 3,641)	≥170 mm Hg (n = 1,697)	p Value
Age, yrs	64	66 ± 11	64 ± 11	64 ± 10	65 ± 11	65 ± 11	66 ± 12	65 ± 12	66 ± 11	<0.001
Median age, yrs	63	64	62	63	64	64	64	63	64	
Female	55	43	49	54	58	60	61	61	61	<0.001
Race										<0.001
White	41	51	46	43	41	37	33	27	28	
Black	12	7	8	11	13	16	20	22	22	
Hispanic	21	19	20	20	21	23	23	23	24	
Asian/Pacific	8	10	10	9	7	6	5	5	5	
Other	17	13	15	17	17	18	19	22	21	
Blood pressure, mean										
SBP, mm Hg	131	106	116	126	134	144	154	164	179	
DBP, mm Hg	73	63	68	72	75	77	80	84	89	
BMI ≥30 kg/m <sup>2</sup>	43	26	36	43	45	46	45	44	38	<0.001
Creatinine, mg/dl	1.0 ± 0.4	1.1 ± 0.5	1.0 ± 0.4	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.4	1.0 ± 0.5	1.1 ± 0.7	1.2 ± 0.8	<0.001
eGFR, ml/min/1.73 m <sup>2</sup>	74 ± 20	72 ± 21	74 ± 20	75 ± 19	74 ± 19	73 ± 20	72 ± 22	71 ± 22	68 ± 23	<0.001
Chronic kidney disease*	24	28	24	23	23	26	28	29	33	<0.001
Diabetes mellitus	30	40	36	32	27	29	33	34	33	<0.001
Ischemic heart disease	19	43	39	27	16	10	8	9	19	<0.001
Cerebrovascular disease	8	25	19	12	7	4	4	5	8	<0.001

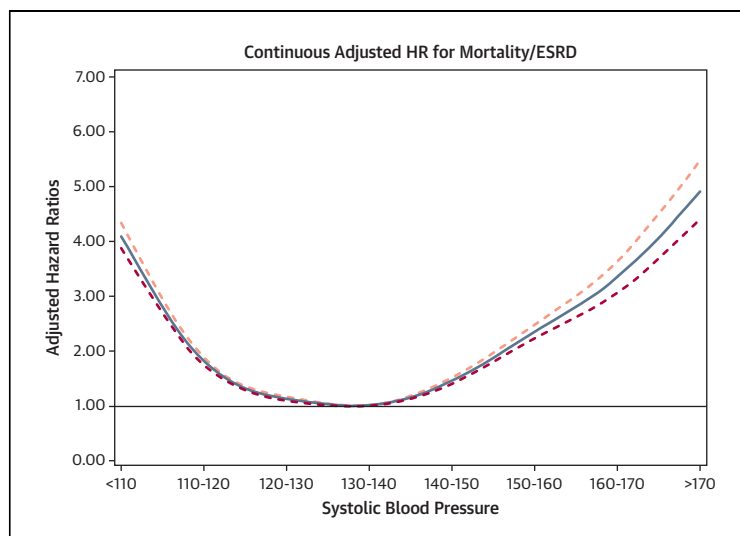
Values are % or mean ± SD. \*Defined as eGFR <60 ml/min/1.73 m<sup>2</sup>.  
BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure.

was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup>, calculated from serum creatinine levels and the CKD Epidemiology Collaboration equation (29). Obesity was defined as

a body mass index (BMI) ≥30. Charlson comorbidity index (CCI) scores also were calculated for each subject.

**KAISER PERMANENTE HTN MANAGEMENT.** Since 2005, KPSC has internally advocated and made available a simplified HTN treatment algorithm to guide therapy for all practitioners treating and managing HTN (30). We have previously described that a majority of the practitioners within KPSC follow the algorithm as demonstrated by medication prescription information (30-32). During the study period, HTN control rates in the KPSC population ranged from 65% to 80% (30-32).

**OUTCOMES.** The primary outcome evaluated was a composite of mortality or ESRD. Because mortality is a strong competing risk for subjects who progress to ESRD (33), the composite outcome was studied to minimize confounding of mortality on ESRD. ESRD, defined as treatment with dialysis or renal transplantation, is captured within an internal KPSC database that includes all dialysis and renal transplant patients along with comprehensive clinical care information. Mortality information was obtained from hospitalization records, outside billing records, state vital statistics, and Social Security Administration death files. For the latter 2 sources, a probabilistic match was made on the basis of name, address, birth date, Social Security Number (when available), and

**FIGURE 2** Continuous HR for Mortality/ESRD Across SBP

Hazard ratios (HR) for mortality/end-stage renal disease (ESRD) with 95% confidence intervals. The nadir systolic blood pressure (SBP) associated with the lowest risk was estimated at 137 mm Hg. A test on the relationship between the HR and quadratic term of the ordered BP levels gave a significant result for nonlinearity ( $p < 0.001$ ).

**TABLE 2 Crude Event Rates per SBP and Length of Follow-Up**

	All	<110	110-119	120-129	130-139	140-149	150-159	160-169	≥170
<b>Event</b>									
Mortality	25,182	1,396	4,101	7,659	6,837	3,286	1,244	405	254
	6.3	21.5	9.3	5.5	4.8	6.7	9.9	11.4	15.8
ESRD	4,957	159	486	1,166	1,381	1,010	435	203	117
	1.2	2.4	1.1	0.8	1.0	2.0	3.4	5.6	6.9
Mortality/ESRD	28,919	1,494	4,402	8,486	7,908	4,107	1,595	571	356
	7.3	22.9	10.0	6.1	5.6	8.3	12.6	15.7	21.0
<b>Length of follow-up, yrs</b>									
Median	4.5	4.1	4.5	4.5	4.5	4.4	4.1	3.8	3.0
Mean	4.0	3.5	4.0	4.1	4.1	3.9	3.5	3.2	2.8

Values are n or %.  
ESRD = end-stage renal disease; SBP = systolic blood pressure.

other demographic information. Because data from these latter sources may be delayed, December 31, 2010, was used to censor follow-up.

Secondary outcomes included ESRD and mortality separately as competing risks and in stratified analyses of those with or without DM, age <70 or ≥70 years, and CCI scores.

The arithmetic means of all outpatient BP values were used in the analyses. The values were then categorized into systolic blood pressure (SBP) increments of 10 mm Hg in the following manner: <110, 110 to 119, 120 to 129, 130 to 139, 140 to 149, 150 to 159, 160 to 169, ≥170. Similar analyses were performed using diastolic BP (DBP) increments of 10 mm Hg in the following manner: <50, 50 to 59, 60 to 69, 70 to 79, 80 to 89, 90 to 99, and ≥100. Differences in the distributions of continuous and ordinal variables were tested using the Kruskal-Wallis test and for categorical variables, the chi-square test. Given the large size of the population and data, no imputations were performed for any missing values (e.g., eGFR).

Cox proportional hazards regression models were used to calculate hazard ratios (HR) among different SBP categories for mortality, ESRD, and the composite of mortality/ESRD. The 130 to 139 and 80 to 89 mm Hg categories were used as the reference category for SBP and DBP, respectively. Adjusted HR were estimated adjusting for age, sex, race, BMI ≥30, CKD, DM, and comorbidities of ischemic heart disease and cerebrovascular disease. Proportionality assumptions were tested by both graphic approaches and the addition of interaction terms with time. A cubic spline smoothing technique was used to interpolate the overall trend of risks through the range of BP. To determine the nadir where the risk is lowest, a secondary analysis was performed by treating SBP/DBP as continuous variables and included a quadratic term. These analyses were repeated in subgroups on

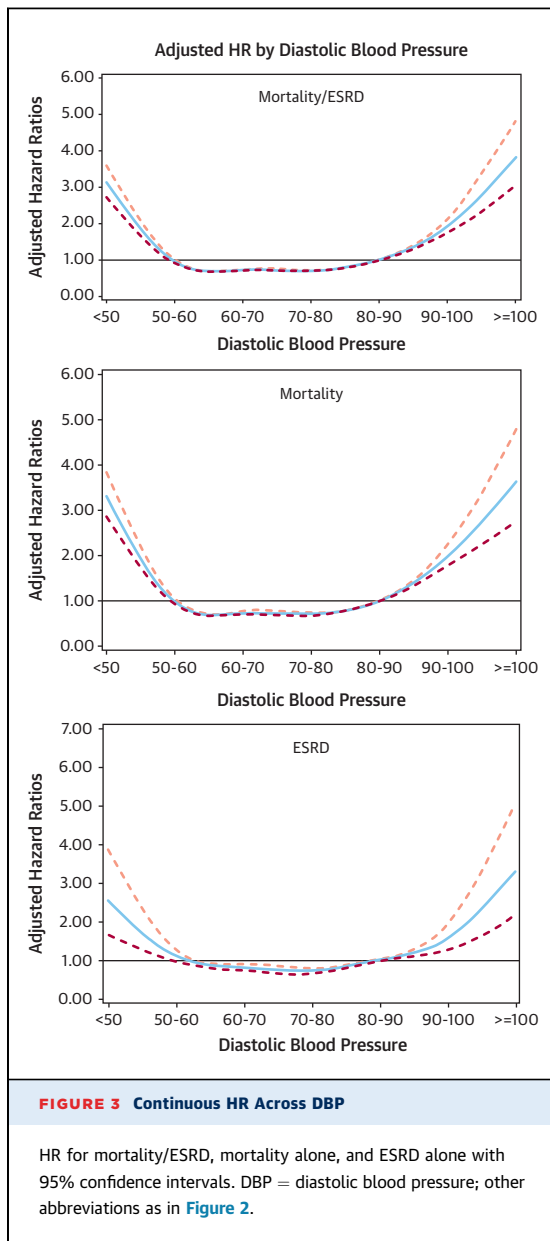
the basis of DM status, age, and CCI scores. All statistical analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, North Carolina) statistical software. Results with p values <0.05 were considered statistically significant.

**SENSITIVITY ANALYSIS.** We performed sensitivity analyses using single baseline BP defined as the values closest in date to the second ICD-9-coded HTN date. Subgroup analyses also were performed in those who died. BP values within 60 days of death were excluded to control for any residual confounding on BP from end of life. The mean BP before and within 60 days of death were also compared.

**TABLE 3 Crude and Adjusted Hazards Ratios for Mortality/ESRD by SBP**

	Multivariate Cox Regression Analysis (95% CI) for Mortality/ESRD by SBP		p Value
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
<b>Systolic blood pressure, mm Hg</b>			
<110	5.00 (4.73-5.28)	4.10 (3.87-4.33)*	<0.001
110-119	1.86 (1.79-1.93)	1.81 (1.74-1.88)	<0.001
120-129	1.08 (1.05-1.11)	1.12 (1.08-1.15)	<0.001
130-139	—	—	—
140-149	1.61 (1.55-1.67)	1.44 (1.39-1.50)	<0.001
150-159	2.80 (2.65-2.95)	2.34 (2.22-2.47)	<0.001
160-169	3.97 (3.64-4.32)	3.33 (3.05-3.63)	<0.001
≥170	6.41 (5.75-7.13)	4.91 (4.41-5.47)	<0.001
<b>Age (every 5-yr increase)</b>			
Male vs. female	1.49 (1.48-1.50)	1.40 (1.39-1.41)	<0.001
Black vs. white	1.28 (1.25-1.31)	1.33 (1.30-1.37)	<0.001
DM	1.50 (1.46-1.54)	1.57 (1.37-1.61)	<0.001
CKD	3.13 (3.06-3.20)	1.40 (1.53-1.43)	<0.001
Cerebrovascular disease	2.75 (2.67-2.83)	1.46 (1.41-1.50)	<0.001
Ischemic heart disease	2.16 (2.11-2.22)	1.25 (1.22-1.28)	<0.001

\*Adjusted hazards ratios were estimated with adjustment for age, sex, race, BMI ≥30 kg/m<sup>2</sup>, CKD, DM and comorbidities of ischemic heart disease, and cerebrovascular disease.  
CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; ESRD = end-stage renal disease; HR = hazard ratio.



Different subpopulations were considered in additional sensitivity analyses. We performed separate analyses after removing those with  $eGFR < 60$  ml/min/1.73 m<sup>2</sup>, thereby removing the confounding of CKD itself on ESRD/mortality risk. We also tested whether there was an interaction between pre-existing cardiovascular disease and BP on the outcomes studied. If there were significant interactions, BP variables were evaluated in those with and without cardiovascular disease. We also performed separate analyses, excluding all patients with cancer or dementia diagnoses as deteriorating health status may confound the BP relationship.

## RESULTS

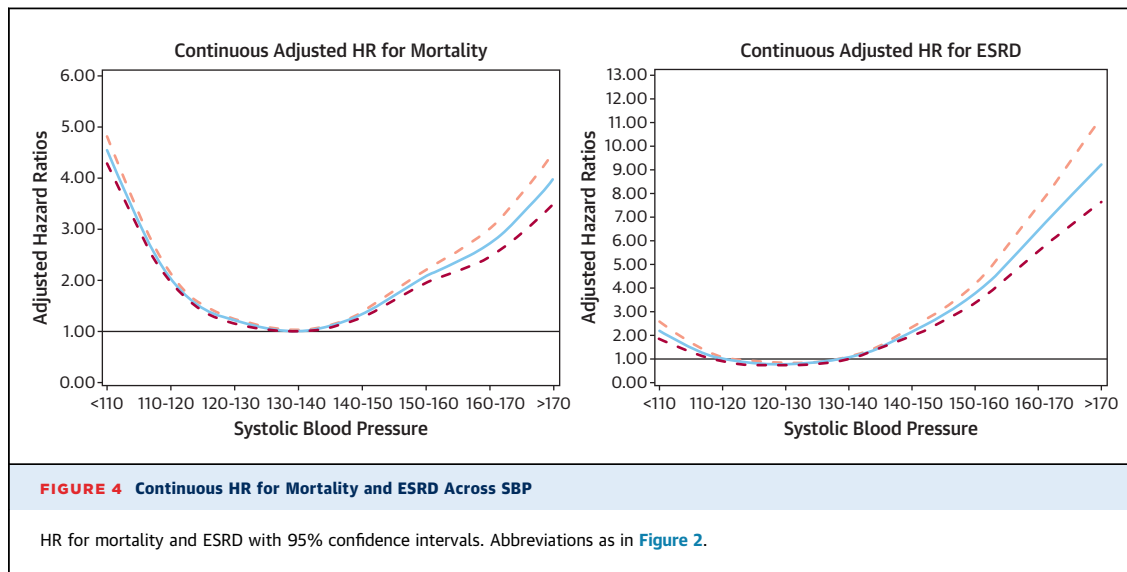
A total of 398,419 treated hypertensive patients were identified for the study cohort and analyses (Fig. 1). At baseline, the mean age of the population was 64 years. The cohort was composed of 55% women, 41% whites, 12% blacks, and 21% Hispanics (Table 1). The mean BP for the cohort was 131/73 mm Hg with standard deviations for SBP (11 mm Hg) and DBP (8 mm Hg), respectively. In those who died, the mean SBP decreased 7 mm Hg during the 60 days before death (124 vs. 131 mm Hg [ $p < 0.01$ ]). DBP differences were not as pronounced with a decrease of 3 mm Hg (70 mm Hg before and 67 mm Hg within 60 days of mortality [ $p < 0.01$ ]).

Overall, 83% of the HTN population was considered controlled ( $< 140$  mm Hg) during the observation period. BMI information was available in 99% of the study cohort (4,397 with missing BMI) and 43% were considered obese. The prevalence of comorbidities were as follows: DM 30%; ischemic heart disease 19%; and cerebrovascular disease 8%. The mean serum creatinine and eGFR of the cohort were 1.0 mg/dl and 74 ml/min/1.73 m<sup>2</sup>, respectively. Overall, 24% of the population had an eGFR below 60 ml/min/1.73 m<sup>2</sup>.

Medications administered to the patient cohort were generally reflective of the KPSC HTN treatment guidelines (Online Table 1, Online Figure 1). Diuretic agents (80%), angiotensin-converting enzyme inhibitors (70%), beta-blockers (44%), and calcium channel blockers (37%) were the most frequently used antihypertensive medications.

**EVENT RATES.** A total of 28,919 subjects (7.3%) in the cohort reached the composite outcome of mortality or ESRD (Table 2). The mean and median lengths of follow-up were 4.0 and 4.5 years, respectively. The lowest and highest SBP groups had the greatest rates of mortality/ESRD (22.9% and 15.7%). Accounting for events separately, mortality occurred in 25,182 (6.3%), whereas ESRD occurred in 4,957 (1.2%). Mortality rates were higher in the lowest and highest SBP as well. ESRD rates, however, appeared to increase across higher SBP categories (6.9% of subjects  $\geq 170$  mm Hg). By contrast, there did not appear to be a disproportionate increase in ESRD with the lowest SBP groups (3.4% of subjects  $< 110$  mm Hg).

**MULTIVARIABLE REGRESSION ANALYSES.** Adjusted HR for composite mortality/ESRD outcomes using SBP 130 to 139 mm Hg as the reference demonstrated greater risk with higher and also lower SBP (Fig. 2, Table 3). With SBP modeled as a continuous variable and using a quadratic term, the calculated nadir for



mortality/ESRD was 137 mm Hg. DBP revealed a wider range of optimal outcomes. Compared with DBP 80 to 89, the adjusted HR were lower for the range of 60 to 79. DBP both lower and higher than the 60 to 79 range demonstrated worse outcomes (Table 4, Fig. 3). The nadir DBP was estimated to be 71 mm Hg. After removing those with cancer and dementia and then further adjusting for CCI scores (0, 1, and ≥2), eGFR, and BMI as continuous variables, the mortality/ESRD HR were 3.80 (95% confidence interval [CI]: 3.52 to 4.11), 1.72 (95% CI: 1.63 to 1.80), 1.10 (95% CI: 1.06 to 1.15), 1.50 (95% CI: 1.43 to 1.58), 2.44 (95% CI: 2.27 to 2.62), 3.22 (95% CI: 2.88 to 3.61), and 5.02 (95% CI: 4.34, to 5.80) for SBP <110, 110 to 119, 120 to 129, 140 to 149, 150 to 159, 160 to 169, and >169 mm Hg, respectively compared with mortality/ESRD HR associated with SBP 130 to 139 mm Hg.

The mortality-only analyses revealed a similar U-shaped trend (Fig. 4, Online Table 2). The ESRD-only analyses suggested a more linear relationship (Fig. 4, Online Table 3). After removing those with cancer and dementia and then further adjusting for CCI scores (0, 1, and ≥2), eGFR, and BMI as continuous variables, the mortality HR were 4.26 (95% CI: 3.92 to 4.63), 1.95 (95% CI: 1.84 to 2.05), 1.19 (95% CI: 1.14 to 1.25), 1.34 (95% CI: 1.27 to 1.42), 2.12 (95% CI: 1.95 to 2.30), 2.43 (95% CI: 2.12 to 2.80), 3.72 (95% CI: 3.10 to 4.48) for SBP <110, 110 to 119, 120 to 129, 140 to 149, 150 to 159, 160 to 169, and >169 mm Hg, respectively compared with the mortality HR associated with SBP 130 to 139 mm Hg.

**STRATIFIED ANALYSES.** HR for mortality/ESRD in patients with DM, compared with nondiabetic

patients, were shifted to lower BP experiencing better outcomes. The nadir BP in patients with DM were 131 and 69 mm Hg for SBP and DBP, respectively, as compared with 142 and 73 mm Hg in nondiabetic patients (Table 5).

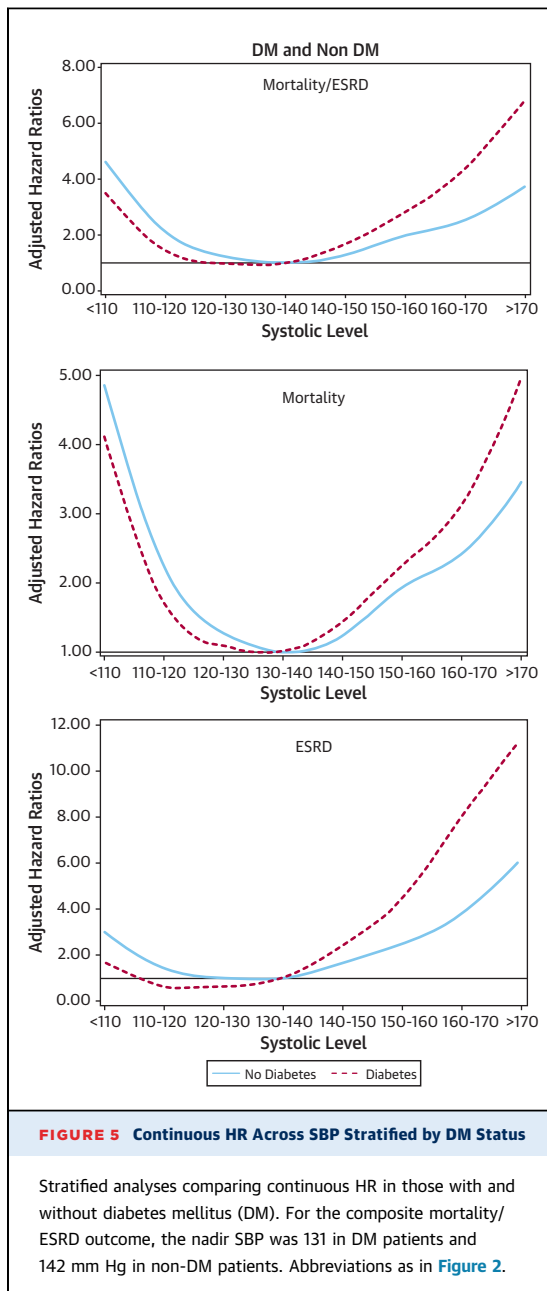
When mortality alone was evaluated, nondiabetic patients appeared to have better survival in the higher ranges of BP than did the diabetic subpopulation (Fig. 5, Online Table 4). For the ESRD-only analyses, persons with DM, compared with nondiabetic patients, experienced better outcomes in the lower ranges of BP. However, persons with DM did worse with higher BP than did those without DM (Online Table 5).

**AGE.** The estimated nadirs of BP for mortality/ESRD in age ≥70 years were 140 and 70 mm Hg for SBP and DBP, compared with younger subjects whose

**TABLE 4** Adjusted HR on the Basis of DBP

	Multivariate Cox Regression Analysis (95% CI) by DBP		
	Mortality/ESRD	Mortality	ESRD
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Diastolic blood pressure, mm Hg			
<50	3.14 (2.73-3.61)	3.32 (2.88-3.83)	2.54 (1.65-3.90)
50-59	0.96 (0.91-1.02)	0.98 (0.92-1.04)	1.12 (0.98-1.27)
60-69	0.72 (0.69-0.76)	0.73 (0.69-0.76)	0.82 (0.74-0.90)
70-79	0.70 (0.67-0.73)	0.71 (0.68-0.74)	0.72 (0.66-0.79)
80-89	—	—	—
90-99	1.92 (1.73-2.13)	1.99 (1.77-2.24)	1.56 (1.26-1.92)
≥100	3.83 (3.04-4.83)	3.65 (2.77-4.80)	3.30 (2.18-5.00)

Adjusted HR were estimated with adjustment for age, sex, race, BMI ≥30 kg/m<sup>2</sup>, CKD, DM and comorbidities of ischemic heart disease, and cerebrovascular disease.  
Abbreviations as in Tables 1 and 2.



nadir were 133 and 76 mm Hg. For ESRD risk alone, the age <70 years group fared better with lower BP ranges compared with those age  $\geq$ 70 years but were more susceptible with higher BP (Online Table 5).

**CHARLSON COMORBIDITY INDEX.** Compared with a CCI score of 1, the adjusted mortality/ESRD HR were 0.43 (95% CI: 0.28 to 0.65) for CCI score of 0 and 1.49 (95% CI: 1.16 to 1.92) for CCI scores of 2 or higher. Adjusted mortality/ESRD HR within subjects with CCI scores of 0, 1, and 2 or higher continued to

demonstrate a similar BP curve. Mortality/ESRD HR for those with CCI 0 were 1.15, 0.49, 1.58, 2.54, 1.52, and 2.29 for SBP 110 to 119, 120 to 129, 140 to 149, 150 to 159, 160 to 169, and >169 mm Hg, respectively. For CCI 1, the mortality/ESRD HR were 22.32, 1.64, 0.80, 1.24, 2.40, 7.31, and 9.16 compared with those with CCI 2 or higher, where the mortality/ESRD HR were 3.78, 1.72, 1.10, 1.50, 2.44, 3.21, and 5.01 for SBP <110, 110 to 119, 120 to 129, 140 to 149, 150 to 159, 160 to 169, and >169 mmHg, respectively compared to 130 to 139 mm Hg, respectively (Online Table 6).

#### SENSITIVITY ANALYSES. Baseline Versus Averaged BP.

Using single baseline BP, the multivariable adjusted HR for ESRD/mortality compared with SBP 130 to 139 mm Hg were 1.47 (95% CI: 1.39 to 1.55), 1.15 (95% CI: 1.09 to 1.21), 1.02 (95% CI: 0.97 to 1.07), 1.08 (95% CI: 1.02 to 1.14), 1.20 (95% CI: 1.13 to 1.28), 1.21 (95% CI: 1.12 to 1.31), and 1.52 (95% CI: 1.41 to 1.63) for SBP <110, 110 to 119, 120 to 129, 140 to 149, 150 to 159, 160 to 169, and >169 mm Hg, respectively. Mortality-alone HR were 1.74 (95% CI: 1.63 to 1.85), 1.27 (95% CI: 1.19 to 1.35), 1.06 (95% CI: 1.00 to 1.12), 1.04 (95% CI: 0.97 to 1.11), 1.12 (95% CI: 1.04 to 1.21), 1.10 (95% CI: 1.00 to 1.21), and 1.28 (95% CI: 1.16 to 1.40). ESRD-alone HR were 1.07 (95% CI: 0.98 to 1.18), 0.95 (95% CI: 0.87 to 1.04), 0.96 (95% CI: 0.88 to 1.04), 1.11 (95% CI: 1.02 to 1.21), 1.27 (95% CI: 1.15 to 1.40), 1.39 (95% CI: 1.23 to 1.56), and 1.8 (95% CI: 1.64 to 2.02) for the same BP ranges. After removing BP within 60 days of those who experienced mortality or ESRD event, the adjusted HR revealed a similar trend with mortality/ESRD HR of 3.84 (95% CI: 3.62 to 4.07), 1.77 (95% CI: 1.71 to 1.84), 1.10 (95% CI: 1.07 to 1.14), 1.46 (95% CI: 1.40, to 1.52), 2.36 (95% CI: 2.23 to 2.49), 3.24 (95% CI: 2.96 to 3.54), and 4.72 (95% CI: 4.20 to 5.31) for SBP <110, 110 to 119, 120 to 129, 140 to 149, 150 to 159, 160 to 169, and >169 mm Hg, respectively.

**Pre-existing cardiovascular disease.** When tested, the interactions between ischemic heart disease and BP were significant for mortality ( $p < 0.001$ ) and combined mortality/ESRD ( $p < 0.001$ ). The interaction between cerebrovascular disease and BP were significant for mortality/ESRD only ( $p = 0.02$ ). HR for mortality/ESRD outcomes were performed in those with and without pre-existing ischemic heart disease and also in those with and without cerebrovascular disease. Compared with those without cardiovascular disease and SBP 130 to 139 mm Hg, the mortality/ESRD HR in those with pre-existing ischemic heart disease were 4.19, 2.21, 1.43, 1.36, 2.03, 3.73, 4.38, and 7.69; and in those with pre-existing cerebrovascular disease, the mortality/ESRD

HR were 6.18, 2.33, 1.63, 1.44, 2.06, 2.74, 4.05, and 4.77 for SBP <110, 110 to 119, 120 to 129, 130 to 139, 140 to 149, 150 to 159, 160 to 169, and >169 mm Hg, respectively (Online Table 7).

**CKD.** Every 10 ml/min/1.73 m<sup>2</sup> decline in eGFR was associated with a mortality/ESRD HR of 1.08 (95% CI: 1.07 to 1.09). Sensitivity analyses were performed after removing subjects with eGFR<60 ml/min/1.73 m<sup>2</sup> to examine the impact of pre-existing CKD. Essentially similar associations were observed when the CKD population was removed from the analyses (data not shown). Less than 1% (2,922) of the population had missing eGFR values. Urine protein quantitation was not performed or it was unavailable for the majority of the population (>80%).

**DISCUSSION**

This observational study of a large diverse cohort of persons with medically treated HTN demonstrates that achieved BP in both relatively higher and lower ranges are associated with worsened risk of mortality and ESRD. We observed a U-shaped curve for the composite outcome of mortality/ESRD at SBP >139 and <130 mm Hg (Central Illustration). There were incremental risk increases in both directions. DBP <60 and >79 mm Hg similarly had greater risk. The nadir BP associated with the best outcome were 137 mm Hg for systolic and 71 mm Hg for diastolic. SBP and ESRD risk alone demonstrated a somewhat J-shaped curve with a lower risk in the SBP 110 to 139 mm Hg range. However, this did not account for the competing risk of mortality and thus, may be misleading when ESRD alone is evaluated.

Our study population included large numbers of diabetic patients and patients ≥70 years of age. The stratified analyses in both DM and age ≥70 populations demonstrated a similar U-shaped risk curve. Clinical trials evaluating aggressive BP reduction have focused more on DM populations, and it has not been clear if those study results would apply to hypertensive nondiabetic patients. In our study, patients with DM overall had better outcomes at lower BP than did nondiabetic patients, but their optimal BP were still within the 130 to 139 mm Hg systolic range.

Historically, lower observed BP has been associated with better survival from vascular disease and mortality outcomes (3,5). Interventional studies that reduced BP in extreme HTN populations have demonstrated significant improvement in morbidity and mortality in both DM and nondiabetic patients (5-13,34). This has led to large population-based initiatives to raise awareness about HTN and to implement strategies for HTN control. The emphasis

**TABLE 5 Stratified Analysis: HR for Mortality/ESRD**

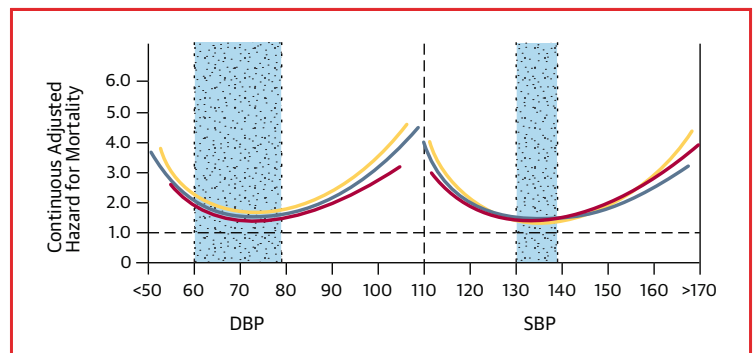
Multivariate Cox Regression Analysis (95% CI) for Mortality/ESRD by SBP (Adjusted for Age, Race, Sex, DM, HTN)

	DM	Nondiabetes	Age <70 yrs	Age ≥70 yrs
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Systolic blood pressure				
<110	3.50 (3.20-3.82)	4.62 (4.30-4.98)	3.92 (3.55-4.32)	4.13 (3.86-4.42)
110-19	1.43 (1.35-1.52)	2.12 (2.02-2.22)	1.64 (1.54-1.75)	1.90 (1.81-1.99)
120-129	0.97 (0.92-1.02)	1.23 (1.18-1.28)	1.02 (0.96-1.07)	1.19 (1.14-1.24)
130-139	—	—	—	—
140-149	1.68 (1.58-1.78)	1.29 (1.22-1.35)	1.62 (1.52-1.73)	1.33 (1.27-1.39)
150-159	2.82 (2.59-3.04)	1.98 (1.84-2.13)	2.94 (2.69-3.22)	1.99 (1.86-2.13)
160-169	4.38 (3.89-4.93)	2.53 (2.23-2.86)	4.72 (4.13-5.39)	2.56 (2.28-2.86)
≥170	6.85 (5.88-7.98)	3.73 (3.20-4.35)	8.24 (6.99-9.72)	3.46 (3.00-3.98)

HTN = hypertension; other abbreviations as in Tables 1 and 2.

has been to treat on the assumption of “the lower the better.” Even as lower has been observed as better (3), it may not necessarily apply to the “treated” HTN population.

The setting of the ideal BP targets in the HTN population has not been satisfactorily addressed. Whereas high BP is detrimental, the benefits of treatment have been demonstrated mostly at achieved SBP >130 mm Hg (5-13,34-36). Aggressive HTN treatment to very low BP may have untoward consequences and may be at the expense of greater costs on the patients and the health delivery environment. In fact, several studies have suggested worsened outcomes with relatively lower treated BP (8,23), whereas others have suggested that there may be no proven benefit of treating those with mild HTN unless there is evidence of end-organ damage



**CENTRAL ILLUSTRATION Where Is the Ideal BP in Those Treated for Hypertension?**

Cubic spline smoothing on the basis of multivariable Cox regression analyses demonstrating mortality/end-stage renal disease hazard ratios across ranges of blood pressure (BP). Achieved systolic blood pressure (SBP) range 130 to 139 and diastolic blood pressure (DBP) range 60 to 79 mm Hg were associated with the best outcomes.



(37,38). The recent 2014 evidence-based guidelines for management of high blood pressure now suggest higher BP goals and threshold for treatment in those with DM, CKD, and age  $\geq 60$  years (39). However, we are unaware of any recommendations cautioning on thresholds for low treatment BP.

**STUDY LIMITATIONS.** The achieved BP may not necessarily reflect the treated goal BP but may instead represent a biomarker for a sicker population. One example of this limitation is the disproportionate prevalence of ischemic heart disease across the BP ranges. The tested interactions between ischemic heart disease and BP demonstrated significance implying that pre-existing cardiovascular disease may affect the HR. Nevertheless, in separate analyses of the populations with and without cardiovascular disease, the HR across BP continued to demonstrate a U-shaped curve.

Obesity was also highly prevalent in our population with 43% having a BMI  $\geq 30$  kg/m<sup>2</sup>. Our cohort also demonstrated an obesity paradox similar to that described in the past in other high-risk populations (40). Obesity had a protective effect where those who were obese (BMI  $\geq 30$  kg/m<sup>2</sup>) had a mortality/ESRD HR of 0.85 (95% CI: 0.83 to 0.88). Furthermore, every BMI increase of 5 kg/m<sup>2</sup> was associated with mortality/ESRD HR of 0.87 (95% CI: 0.86 to 0.89).

Because BP declines toward the end of life (41), the mean BP over the observation period may have confounding effects, as they may reflect the processes that lead to ESRD or death rather than the actual treated BP. Indeed, the BP within 60 days of death were significantly lower than BP before death. We did perform several sensitivity analyses to control for such residual confounding. We used single baseline BP values instead of mean BP over time, but we continued to find a similar BP curve. We also performed Cox regression analyses, after excluding BP within 60 days of mortality or ESRD. However, these sensitivity analyses cannot account for confounding due to reverse causality where the near end-of-life state may lead to low BP.

The effect of medication treatment and duration on outcomes is a confounder that cannot be accounted for in this study. The different medicine classes and the number of medicines may have had additional pleotropic effects in addition to the BP-lowering effect. There is also confounding by indication for patients who received different medicine classes or numbers of medicines that were not evaluated in our study. Physician bias may have been another limitation as patients that practitioners identified as more ill may have been seen more frequently and treated with more

aggressive BP approaches. In addition, we were unable to fully account for variables, such as smoking, diet, and physical activity.

Despite these potential limitations, the strengths of our study lie in the large, ethnically diverse, and sex-balanced HTN population that included large numbers of diabetic patients and elderly patients. The clinical encounter information including vital signs, medications, comorbidities, and utilization data were reliably captured for the cohort. In addition, the standardized treatment approaches for HTN lessen some of the confounding from heterogeneity among the individual practitioners.

## CONCLUSIONS

We found that treated HTN patients with BP in the range of 130 to 139 mm Hg systolic and 60 to 79 mm Hg diastolic experienced the lowest risk for the composite outcome of mortality and ESRD. Patients with either higher or lower BP departing from these ranges were found to be at greater risk for these outcomes. Whereas current U.S. guidelines emphasize the upper limits of therapeutic goals (39), the potential dangers of overtreatment may need to be considered. In the current HTN management environment, both escalation and withdrawal of medications may be appropriate for optimal outcomes in an HTN population.

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## PERSPECTIVES

### COMPETENCY IN MEDICAL KNOWLEDGE:

Treatment of hypertension reduces morbidity and mortality, but optimal blood pressure targets have not been clearly defined.

**COMPETENCY IN PATIENT CARE:** Compared with blood pressure ranges of 130 to 139 mm Hg systolic and 60 to 79 mm Hg diastolic, both higher and lower pressure ranges are associated with worse outcomes in hypertensive patients on treatment.

**TRANSLATIONAL OUTLOOK:** Additional studies are necessary to determine whether the target blood pressure associated with optimal outcomes varies with the type of antihypertensive therapy utilized.

## REFERENCES

1. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. *Hypertension* 2008;52:818-27.
2. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA* 2010;303:2043-50.
3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
4. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002;288:1882-8.
5. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996;334:13-8.
6. Group VACS. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 1967;202:1028-34.
7. SHEP. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;265:3255-64.
8. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008;336:1121-3.
9. Group UPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-13.
10. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755-62.
11. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022-31.
12. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;350:757-64.
13. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;355:865-72.
14. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85.
15. Appel LJ, Wright JT Jr., Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;363:918-29.
16. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008;31:2115-27.
17. Ogihara T, Saruta T, Rakugi H, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension* 2010;56:196-202.
18. Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;382:507-15.
19. Wright JT Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002;288:2421-31.
20. Iseki K, Miyasato F, Tokuyama K, et al. Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. *Kidney Int* 1997;51:1212-7.
21. Port FK, Hulbert-Shearon TE, Wolfe RA, et al. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. *Am J Kidney Dis* 1999;33:507-17.
22. Kovesdy CP, Bleyer AJ, Molnar MZ, et al. Blood Pressure and Mortality in U.S. Veterans With Chronic Kidney Disease: A Cohort Study. *Annals of Internal Medicine* 2013;159:233-42.
23. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.
24. Bangalore S, Messerli FH, Wun CC, et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J* 2010;31:2897-908.
25. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005;365:939-46.
26. Verma S, Gupta M, Holmes DT, et al. Plasma renin activity predicts cardiovascular mortality in the Heart Outcomes Prevention Evaluation (HOPE) study. *Eur Heart J* 2011;32:2135-42.
27. Koenig C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. *Perm J* 2012;16:37-41.
28. Bhandari SK, Pashayan S, Liu IL, et al. 25-hydroxyvitamin D levels and hypertension rates. *J Clin Hypertens (Greenwich)* 2011;13:170-7.
29. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604-12.
30. Sim JJ, Bhandari SK, Shi J, et al. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clin Proc* 2013;88:1099-107.
31. Sim JJ, Bhandari SK, Shi J, et al. Plasma renin activity (PRA) levels and antihypertensive drug use in a large healthcare system. *Am J Hypertens* 2011;25:379-88.
32. Sim JJ, Handler J, Jacobsen SJ, Kanter MH. Systemic implementation strategies to improve hypertension: the Kaiser Permanente Southern California experience. *Can J Cardiol* 2014;30:544-52.
33. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
34. Zanchetti A. Blood pressure targets of anti-hypertensive treatment: up and down the J-shaped curve. *Eur Heart J* 2010;31:2837-40.
35. Perry HM Jr., Davis BR, Price TR, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 2000;284:465-71.
36. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010;304:61-8.
37. DeFelice A, Willard J, Lawrence J, et al. The risks associated with short-term placebo-controlled antihypertensive clinical trials: a descriptive meta-analysis. *J Hum Hypertens* 2008;22:659-68.
38. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. *Cochrane Database Syst Rev* 2012;8:CD006742.
39. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507-20.
40. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368:666-78.
41. Diehr PH, Thielke SM, Newman AB, Hirsch C, Tracy R. Decline in health for older adults: five-year change in 13 key measures of standardized health. *J Gerontol A Biol Sci Med Sci* 2013;68:1059-67.

**KEY WORDS** blood pressure goals, hypertension treatment, mortality risk, renal failure risk, treatment risk

**APPENDIX** For supplemental tables and a figure, please see the online version of this article.