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Age and Outcomes Associated with BP in Patients with Incident CKD

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Abstract

Background and objectives Hypertension is the most important treatable risk factor for cardiovascular outcomes. Many patients with CKD are elderly, but the ideal BP in these individuals is unknown.

Design, setting, participants, & measurements From among 339,887 patients with incident eGFR<60 ml/min per 1.73 m^2, we examined associations of systolic BP (SBP) and diastolic BP (DBP) with all-cause mortality, incident coronary heart disease (CHD), ischemic strokes, and ESRD from the time of developing CKD until the end of follow-up (July 26, 2013, for mortality, CHD, and stroke, and December 31, 2011, for ESRD) in multivariable-adjusted survival models categorized by patients' age.

Results Of the total cohort, 300,424 (88%) had complete data for multivariable analysis. Both SBP and DBP showed a U-shaped association with mortality. SBP displayed a linear association with CHD, stroke, and ESRD, whereas DBP showed no consistent association with either. SBP>140 mmHg was associated with higher incidence of all examined outcomes, but with an incremental attenuation of the observed risk in older compared with younger patients ($P<0.05$ for interaction) The adjusted hazard ratios and 95% confidence intervals associated with SBP≥170 mmHg (compared with 130–139 mmHg) in patients <50, 50–59, 60–69, 70–79, and ≥80 years were 1.95 (1.34 to 2.84), 2.01 (1.75 to 2.30), 1.68 (1.49 to 1.89), 1.39 (1.25 to 1.54), and 1.30 (1.17 to 1.44), respectively. The risk of incident CHD, stroke, and ESRD was incrementally higher with higher SBP in patients aged <80 years but showed no consistent association in those aged ≥80 years ($P<0.05$ for interaction for all outcomes).

Conclusions In veterans with incident CKD, SBP showed different associations in older versus younger patients. The association of higher SBP with adverse outcomes was present but markedly reduced in older individuals, especially in those aged ≥80 years. Elevated DBP showed no consistent association with vascular outcomes in patients with incident CKD.

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Introduction

Hypertension is the number one cardiovascular risk factor (1), yet its control rates remain suboptimal (2). Hypertension is especially common in the elderly (3).

Observational studies examining the effects of BP in elderly offer conflicting evidence. Some indicate linearly worse outcomes with higher BP (4), whereas others suggest that BP has a J-shaped association with outcomes (5–8) and that high BP has a diminished or reversed association with adverse outcomes in elderly patients. Clinical trials offer some indication that treating elevated BP to moderately low levels may decrease cardiovascular events in very old individuals (9,10), but it remains unclear whether using even stricter targets is beneficial (11,12). The 2014 report from the panel members appointed to the Eighth Joint National Committee recommended less stringent BP treatment in patients >60 years of age and without diabetes or CKD (13). More recently, the Systolic Blood Pressure Intervention Trial (SPRINT) showed lower mortality in patients at high cardiovascular risk, including those with mild-to-moderate CKD (14). Although these results offer much-needed evidence for lowering elevated BP toward more stringent targets, the limited external validity of clinical trials will make it difficult to apply SPRINT results to patients with characteristics different from those of SPRINT participants, such as the very old or those with advanced CKD. Furthermore, the safety of SBP even lower than that used in SPRINT remains unclear.

Patients with CKD are at high risk for the adverse effects of high BP, but most patients with CKD are older and may also be more sensitive to the adverse effects of low BP than individuals with normal kidney function (15–19). Therefore, it would be important to consider age as a factor influencing decisions about BP therapy in patients with CKD. However, despite compelling theoretical consideration, there is no clear evidence to inform about the ideal BP in elderly patients with CKD.

We examined the association of systolic BP (SBP) and diastolic BP (DBP) with all-cause mortality and incidence of CHD, ischemic stroke, and ESRD in 339,887 United States veterans with incident CKD, and we hypothesized that the patients' age would significantly modify the association of BP with these outcomes.

Materials and Methods

Study Design and Participants

Analyses were conducted in a historic cohort study examining risk factors in patients with incident CKD (Racial and Cardiovascular Risk Anomalies in CKD study). Details on cohort definition were previously published (20–22). Briefly, the parent cohort consisted of 3,582,478 patients with eGFR≥60 ml/min per 1.73 m^2, based on serum creatinine measurements performed from October 1, 2004, to September 30, 2006. Our analytic sample for this study consisted of 339,887 patients who, during a median follow-up of 7.6 years after the first eGFR measurement from October 1, 2004, to September 30, 2006, developed incident CKD stages 3A–5 (Supplemental Figure 1), defined as two eGFR values of <60 ml/min per 1.73 m^2 and a decrease of ≥25% from baseline eGFR (23). The Research and Development Committees at the Memphis and Long Beach Veterans Affairs (VA) Medical Centers approved the study protocol.

Sociodemographic Characteristics and Comorbidities

Baseline variables were determined at the date of cohort entry (defined as the date of the eGFR value used to diagnose incident CKD). Information about baseline characteristics was obtained from various national VA research data files, as previously described (24–26). We grouped patients into five mutually exclusive categories based on their baseline age (<50, 50–59, 60–69, 70–79, and ≥80 years). Race was determined by combining information from VA and Medicare sources (27,28). Comorbidities and clinical events were assessed using International Classification of Diseases, Ninth Revision (ICD-9) and Common Procedural Terminology codes (Supplemental Material). We calculated the Charlson comorbidity index (CCI) using the Deyo modification for administrative datasets, without including kidney disease (29), and categorized patients according to the presence or absence of comorbidities besides CKD and hypertension (CCI <1 versus ≥1). In an attempt to examine frailty, we identified patients who lost weight, defined as the presence of weight loss >5% during the 12 months leading up to cohort entry or a baseline body mass index (BMI) <18.5 kg/m^2 (30).

BP and Medication Use

Baseline BP was defined as the average of all outpatient BP measurements during the first 90 days following cohort entry. SBP and DBP were categorized into nine and six groups, respectively (SBP, <100 to ≥170 mmHg in 10-mmHg increments; DBP, <50 to ≥90 mmHg in 10-mmHg increments). Exposure to the number of antihypertensive classes used at baseline was assessed from VA pharmacy records and categorized as none versus one to two versus three or more drugs.

Outcomes

Outcomes of interest were all-cause mortality, incident coronary heart disease (CHD), incident ischemic strokes, and ESRD. Deaths were identified from the VA Vital Status Files, the sensitivity and specificity of which are 98.3% and 99.8%, respectively (31). CHD and stroke were defined as the composite of a first ICD-9 or Current Procedural Terminology code for acute myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting, and for ischemic stroke, following the date of incident CKD in patients without such diagnoses before this date (Supplemental Figure 1). Information on ESRD was obtained from the US Renal Data System.

Statistical Analyses

Data are expressed as means±SDs, medians (interquartile ranges), and proportions and were examined across SBP categories. Patients were followed from cohort entry until death or were censored at the date of the last encounter, or on July 26, 2013, for mortality (median follow-up, 4.8 years), CHD (median follow-up, 4.9 years), and stroke (median follow-up, 4.8 years), and December 31, 2011, for ESRD (median follow-up, 3.8 years).

The association of SBP and DBP with outcomes was examined in crude and adjusted Cox models. Models were adjusted on the basis of *a priori* considerations for baseline age, sex, race, marital status, per capita income, eGFR, prevalent comorbidities (hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, malignancies, liver disease, rheumatologic diseases, chronic lung disease, dementia, HIV/AIDS, depression, weight loss or low BMI, and CCI), number of antihypertensive medications, and DBP or SBP. A total of 300,424 patients (88% of the total sample) had complete data for analysis. Because of the relatively low proportion of missingness, these values were not imputed. Sensitivity analyses were performed in subgroups divided by CCI of <1 versus ≥1 and the presence or absence of weight loss or low BMI. Interactions were examined by inclusion of multiplicative interaction terms for SBP/DBP and age, accounting for nonlinear associations (32). Statistical analyses were performed using Stata MP software, version 12 (StataCorp., College Station, TX).

Results

The mean±SD age of the cohort at baseline was 69.2±10.4 years, 96.8% of patients were men, and the mean baseline eGFR was 48±9 ml/min per 1.73 m^2. Baseline characteristics of the overall cohort, and of patients categorized by their baseline SBP, are shown in Table 1. Patients with higher SBP were more likely to be black and to have diabetes mellitus and hypertension and less likely to have CHD, congestive heart failure, and chronic lung disease. Comorbidities were common in all SBP groups, but the proportion of patients with CCI≥1 and with weight loss or low BMI was highest in those with the lowest SBP. Most patients received at least one antihypertensive medication, including 91% of patients with SBP<100 mmHg.

Table 1. Baseline characteristics

Variable	Overall (*N*=339,887)	Systolic BP								
		<100 mmHg (*n*=8712)	100–109 mmHg (*n*=22,474)	110–119 mmHg (*n*=53,318)	120–129 mmHg (*n*=80,073)	130–139 mmHg (*n*=90,361)	140–149 mmHg (*n*=48,010)	150–159 mmHg (*n*=22,370)	160–169 mmHg (*n*=9070)	≥170 mmHg (*n*=5499)
Age, yr	69±10	70±11	68±11	69±11	69±10	70±10	69±10	69±10	69±11	68±11
Men	328,918 (97)	8490 (97)	21,743 (97)	51,504 (97)	77,400 (97)	87,513 (97)	46,491 (97)	21,673 (97)	8813 (97)	5291 (96)
Race										
White	254,068 (79)	6826 (83)	17,623 (82)	41,164 (81)	60,879 (80)	67,693 (79)	34,634 (76)	15,707 (74)	6094 (71)	3448 (66)
Black	54,852 (17)	1084 (13)	3042 (14)	7506 (15)	12,003 (16)	13,956 (16)	8,986 (20)	4649 (22)	2127 (25)	1499 (29)
Hispanic	7834 (2)	159 (2)	436 (2)	1156 (2)	1808 (2)	2156 (3)	1190 (3)	546 (3)	234 (3)	149 (3)
Other	5843 (2)	159 (2)	390 (2)	919 (2)	1376 (2)	1534 (2)	829 (2)	382 (2)	150 (2)	104 (2)
Marital status										
Married	181,870 (55)	4714 (56)	11,696 (54)	27,919 (54)	42,896 (55)	49,949 (57)	25,526 (55)	11,782 (54)	4730 (54)	2658 (50)
Single	24,186 (7)	649 (8)	1785 (8)	4016 (8)	5711 (7)	5,878 (7)	3457 (7)	1602 (7)	659 (8)	429 (8)
Divorced	83,163 (25)	2088 (25)	5735 (26)	13,662 (26)	19,685 (25)	20,783 (24)	11,749 (25)	5586 (26)	2312 (26)	1563 (29)
Widower	39,806 (12)	991 (12)	2496 (12)	6010 (12)	9076 (12)	10,943 (13)	5803 (12)	2724 (13)	1089 (12)	674 (13)
eGFR, ml/min per 1.73 m^2	48±9	47±9	48±9	48±9	48±9	48±9	48±9	48±9	48±8	48±8
BMI, kg/m^2	30±6	28±6	29±6	30±6	30±6	30±6	30±6	30±6	30±6	30±7
Weight loss or low BMI	53,980 (17)	2083 (26)	5048 (24)	10,366 (21)	13,453 (18)	12,307 (15)	6229 (14)	2772 (13)	1079 (13)	643 (13)
Per capita income, US$	22,097 (12,103–33,029)	22,616 (12,305–33,757)	21,939 (11,851–32,477)	21,917 (12,007–32,592)	22,209 (12,118–33,004)	22,841 (12,369–33,953)	21,889 (12,124–32,837)	21,143 (11,876–32,665)	20,271 (11,722–32,363)	19,339 (11,276–31,455)
Systolic BP, mmHg	131±16	95±5	106±3	115±3	125±3	135±3	145±3	155±3	164±3	180±10
Diastolic BP, mmHg	71±10	57±7	62±7	66±8	70±8	73±9	76±9	80±10	83±11	89±13
Hypertension	296,490 (87)	6683 (77)	17,810 (79)	43,926 (82)	68,798 (86)	80,463 (89)	44,061 (92)	20,913 (93)	8573 (95)	5263 (96)
Diabetes mellitus	167,568 (49)	3800 (44)	10,323 (46)	25,231 (47)	38,989 (49)	44,554 (49)	24,600 (51)	11,980 (54)	5029 (55)	3062 (56)
Coronary heart disease	135,091 (40)	4785 (55)	11,381 (51)	23,890 (45)	32,236 (40)	33,566 (37)	16,754 (35)	7790 (35)	3039 (34)	1650 (30)
Congestive heart failure	52,738 (16)	2904 (33)	6431 (29)	11,075 (21)	12,164 (15)	10,684 (12)	5486 (11)	2486 (11)	944 (10)	564 (10)
Stroke	38,318 (11)	974 (11)	2527 (11)	6053 (11)	9002 (11)	9864 (11)	5449 (11)	2719 (12)	1101 (12)	629 (11)
Peripheral artery disease	16,309 (5)	398 (5)	1087 (5)	2649 (5)	3807 (5)	4114 (5)	2371 (5)	1158 (5)	479 (5)	246 (4)
Chronic lung disease	95,745 (28)	2844 (33)	7591 (34)	17,116 (32)	23,819 (30)	23,938 (26)	12,158 (25)	5245 (23)	1973 (22)	1061 (19)
Dementia	5054 (1)	141 (2)	324 (1)	841 (2)	1316 (2)	1311 (1)	674 (1)	284 (1)	115 (1)	48 (1)
Rheumatologic disease	7980 (2)	221 (3)	582 (3)	1375 (3)	2022 (3)	2052 (2)	1020 (2)	476 (2)	155 (2)	77 (1)
Liver disease	8475 (2)	362 (4)	1217 (5)	1896 (4)	2055 (3)	1607 (2)	823 (2)	323 (1)	117 (1)	75 (1)
Malignancies	62,843 (18)	1425 (16)	4138 (18)	10,220 (19)	15,483 (19)	16,787 (19)	8780 (18)	3860 (17)	1381 (15)	769 (14)
AIDS/HIV	3010 (0.9)	85 (1)	272 (1)	673 (1)	750 (0.9)	639 (0.7)	349 (0.7)	148 (0.7)	63 (0.7)	31 (0.6)
Depression	38,279 (11)	956 (11)	2951 (13)	7114 (13)	9673 (12)	9533 (11)	4873 (10)	2019 (9)	713 (8)	447 (8)
CCI≥1	203,090 (60)	5961 (69)	15,256 (68)	33,899 (64)	48,320 (60)	51,420 (57)	27,363 (57)	12,781 (57)	5122 (57)	2968 (54)
Number of antihypertensive medications										
0	28,150 (8)	770 (9)	2019 (9)	5079 (10)	7263 (9)	7513 (8)	3384 (7)	1369 (6)	459 (5)	294 (5)
1–2	129,981 (38)	2745 (32)	7854 (35)	20,534 (39)	32,142 (40)	36,324 (40)	18,141 (38)	7790 (35)	2939 (32)	1512 (28)
≥3	181,756 (53)	5197 (59)	12,601 (56)	27,705 (52)	40,668 (51)	46,524 (51)	26,485 (55)	13,211 (59)	5672 (63)	3693 (67)

Data are presented as mean±SD, medians (interquartile ranges), or number (% of total). Weight loss or low body mass index (BMI) defined as a decrease in weight of >5% in the last 12 months before baseline or a BMI<18.5 kg/m^2 at baseline. CCI, Charlson comorbidity index.

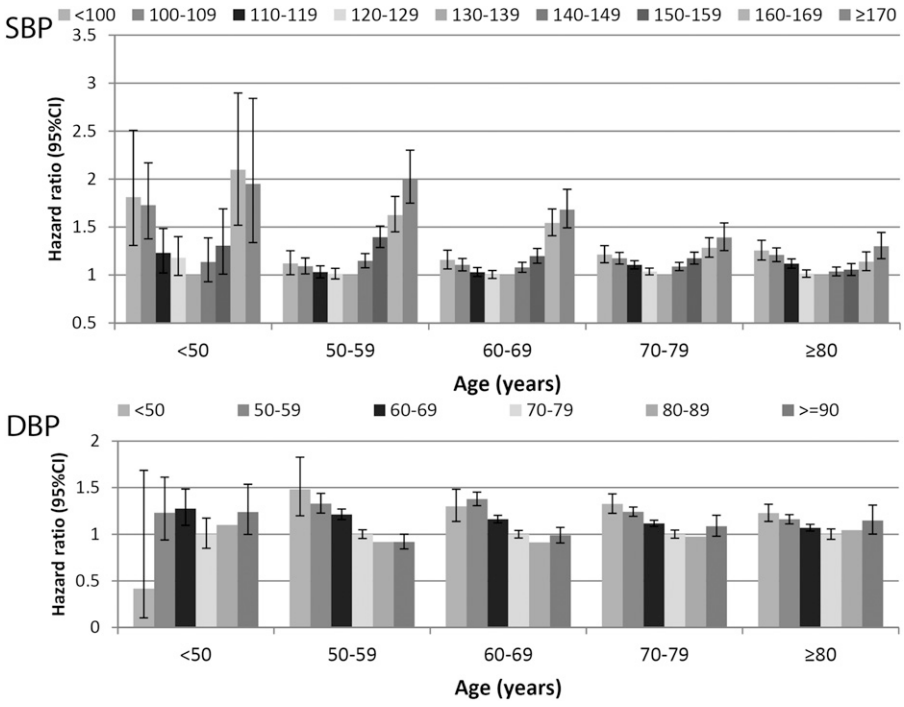

Figure 1. | Association of systolic BP (SBP) and diastolic BP (DBP) with all-cause mortality, among 300,424 patients with incident CKD of different ages, in multivariable-adjusted Cox models. Models were adjusted for age, sex, race, marital status, per capita income, eGFR, prevalent comorbid conditions (hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, peripheral artery disease, malignancies, liver disease, rheumatologic diseases, chronic lung disease, dementia, HIV/AIDS, depression, weight loss, and Charlson comorbidity index), number of antihypertensive medications prescribed at baseline, and baseline DBP (for SBP analyses) and baseline SBP (for DBP analyses). 95% CI, 95% confidence interval.

Mortality

A total of 100,763 patients died (63.0 deaths/1000 patient-years [PY]; 95% confidence interval [95% CI], 62.6 to 63.4) during a median follow-up of 4.8 years (range, 0.2–8.8 years), and mortality rates were higher in older patients in all SBP categories. Age modified the association of SBP with mortality (P for interaction <0.001). Compared with an SBP of 130–139 mmHg, SBP≥140 mmHg was associated with higher crude mortality rates in all age groups, but with attenuation of these differences in older patients (Supplemental Figure 2, Supplemental Table 1). The same pattern was evident in multivariable Cox models: The adjusted hazard ratio (aHRs) associated with SBP≥170 mmHg (compared with 130–139 mmHg) in patients aged <50, 50–59, 60–69, 70–79, and ≥80 years were 1.95 (95% CI, 1.34 to 2.84), 2.01 (95% CI, 1.75 to 2.30), 1.68 (95% CI, 1.49 to 1.89), 1.39 (95% CI, 1.25 to 1.54), and 1.30 (95% CI, 1.17 to 1.44), respectively (Figure 1, Table 2). SBP<120 mmHg was associated with higher mortality in all age groups. The lowest mortality was associated with SBP of 120–139 mmHg in patients <80 years and with SBP of 120–159 mmHg in patients ≥80 years. Lower DBP was also associated with higher mortality in all age groups, with the lowest mortality seen in patients with DBP of 70–79 mmHg in patients <50 years and 80–89 mmHg in patients ≥50 years (Figure 1, Table 3, Supplemental Figure 3, Supplemental Table 2). Results were similar when we examined association in patients without weight loss or low BMI or comorbidities (Supplemental Figures 4 and 5). There was no consistent trend in the associations between SBP or DBP and mortality in any age group among patients who had weight loss or low BMI.

Incident CHD

A total of 9450 patients experienced an incident CHD event (9.8 events/1000 PY; 95% CI, 9.6 to 10.0). Incident CHD rates were similar or lower in older versus younger individuals (Supplemental Tables 1 and 2). Age modified the association of SBP with CHD (P for interaction <0.001). Higher SBP was associated with higher crude CHD rates in patients aged <80 years, with a significant attenuation in the older age groups (Supplemental Figure 2, Supplemental Table 1). Results were similar in multivariable-adjusted Cox models: The aHRs associated with SBP≥170 mmHg (compared with 130–139 mmHg) in patients <50, 50–59, 60–69, 70–79, and ≥80 years were 2.42 (95% CI, 1.26 to 4.66), 1.91 (95% CI, 1.45 to 2.50), 1.39 (95% CI, 1.04 to 1.86), 1.71 (95% CI, 1.27 to 2.29), and 1.36 (95% CI, 0.87 to 2.13), respectively (Figure 2, Table 2). The lowest CHD incidence was associated with SBP<110 mmHg in patients <70 years, and with SBP<140 mmHg in patients ≥70 years. DBP showed no association with CHD. Associations showed a similar pattern when we examined incident CHD in patients without weight loss or low BMI and in those with or without comorbidities (Supplemental Figures 6 and 7). There was no consistent association

Table 2. Multivariable-adjusted hazard ratios and 95% confidence intervals of different outcomes, associated with different systolic BP values in patients of different ages

Outcome per Age Category, yr	Systolic BP							
	<100 mmHg (*n*=8712)	100–109 mmHg (*n*=22,474)	110–119 mmHg (*n*=53,318)	120–129 mmHg (*n*=80,073)	140–149 mmHg (*n*=48,010)	150–159 mmHg (*n*=22,370)	160–169 mmHg (*n*=9070)	≥170 mmHg (*n*=5499)
Mortality								
<50	1.81 (1.31 to 2.51)	1.73 (1.38 to 2.17)	1.23 (1.02 to 1.48)	1.18 (1 to 1.4)	1.14 (0.93 to 1.39)	1.31 (1.01 to 1.69)	2.10 (1.52 to 2.9)	1.95 (1.34 to 2.84)
50–59	1.12 (1 to 1.25)	1.09 (1.01 to 1.18)	1.03 (0.97 to 1.09)	1.01 (0.96 to 1.07)	1.15 (1.08 to 1.22)	1.39 (1.29 to 1.51)	1.62 (1.45 to 1.82)	2.01 (1.75 to 2.30)
60–69	1.16 (1.06 to 1.26)	1.11 (1.04 to 1.17)	1.03 (0.98 to 1.08)	1.00 (0.96 to 1.05)	1.08 (1.03 to 1.13)	1.20 (1.12 to 1.28)	1.54 (1.41 to 1.69)	1.68 (1.49 to 1.89)
70–79	1.21 (1.13 to 1.31)	1.17 (1.11 to 1.24)	1.11 (1.06 to 1.15)	1.04 (1.00 to 1.07)	1.09 (1.04 to 1.13)	1.17 (1.11 to 1.24)	1.28 (1.19 to 1.39)	1.39 (1.25 to 1.54)
≥80	1.25 (1.16–1.36)	1.21 (1.14 to 1.28)	1.12 (1.07 to 1.17)	1.01 (0.98 to 1.05)	1.04 (0.99 to 1.08)	1.06 (1.00 to 1.12)	1.14 (1.05 to 1.24)	1.30 (1.17 to 1.44)
Coronary heart disease								
<50	0.59 (0.18 to 1.97)	0.43 (0.20 to 0.94)	0.79 (0.51 to 1.21)	0.89 (0.62 to 1.29)	1.48 (1.04 to 2.12)	1.49 (0.92 to 2.42)	1.49 (0.77 to 2.87)	2.49 (1.29 to 4.79)
50–59	0.68 (0.48 to 0.96)	0.64 (0.52 to 0.80)	0.76 (0.66 to 0.88)	0.82 (0.73 to 0.93)	1.22 (1.07 to 1.38)	1.57 (1.34 to 1.82)	1.70 (1.37 to 2.10)	1.92 (1.46 to 2.52)
60–69	0.67 (0.48 to 0.94)	0.91 (0.76 to 1.10)	0.83 (0.73 to 0.94)	0.93 (0.83 to 1.03)	1.18 (1.05 to 1.32)	1.3 (1.12 to 1.51)	1.69 (1.38 to 2.07)	1.38 (1.03 to 1.85)
70–79	0.86 (0.58 to 1.26)	0.91 (0.72 to 1.15)	0.97 (0.83 to 1.13)	0.91 (0.80 to 1.04)	1.08 (0.94 to 1.24)	1.36 (1.14 to 1.61)	1.53 (1.21 to 1.94)	1.70 (1.26 to 2.28)
≥80	0.62 (0.34 to 1.12)	0.87 (0.61 to 1.23)	1.05 (0.84 to 1.30)	0.96 (0.80 to 1.15)	1.30 (1.08 to 1.57)	1.23 (0.96 to 1.58)	1.40 (0.99 to 1.99)	1.37 (0.88 to 2.14)
Stroke								
<50	0.27 (0.06 to 1.15)	1.02 (0.60 to 1.74)	1.05 (0.72 to 1.52)	0.99 (0.72 to 1.38)	1.46 (1.04 to 2.04)	1.24 (0.79 to 1.96)	1.84 (1.04 to 3.24)	1.99 (1.05 to 3.79)
50–59	0.54 (0.40 to 0.72)	0.76 (0.64 to 0.90)	0.78 (0.69 to 0.89)	0.93 (0.84 to 1.04)	1.34 (1.20 to 1.50)	1.52 (1.32 to 1.75)	1.86 (1.54 to 2.25)	2.28 (1.82 to 2.86)
60–69	0.67 (0.52 to 0.85)	0.82 (0.71 to 0.95)	0.83 (0.74 to 0.92)	0.90 (0.82 to 0.98)	1.14 (1.04 to 1.26)	1.38 (1.21 to 1.56)	1.56 (1.31 to 1.87)	1.98 (1.59 to 2.46)
70–79	0.67 (0.52 to 0.88)	0.73 (0.61 to 0.86)	0.92 (0.82 to 1.03)	0.91 (0.83 to 1.00)	1.1 (0.99 to 1.22)	1.24 (1.09 to 1.42)	1.59 (1.32 to 1.91)	1.79 (1.41 to 2.27)
≥80	0.59 (0.39 to 0.90)	0.97 (0.77 to 1.22)	0.92 (0.78 to 1.08)	1.12 (0.98 to 1.28)	1.23 (1.07 to 1.43)	1.27 (1.05 to 1.53)	1.38 (1.06 to 1.80)	1.26 (0.89 to 1.79)
ESRD								
<50	0.51 (0.20 to 1.30)	0.42 (0.22 to 0.79)	0.44 (0.29 to 0.67)	0.57 (0.40 to 0.80)	2.06 (1.54 to 2.76)	3.41 (2.46 to 4.73)	4.85 (3.27 to 7.20)	7.49 (4.82 to 11.64)
50–59	0.52 (0.34 to 0.80)	0.48 (0.36 to 0.64)	0.37 (0.30 to 0.46)	0.59 (0.50 to 0.69)	1.70 (1.48 to 1.96)	2.79 (2.40 to 3.25)	4.37 (3.65 to 5.24)	6.04 (4.92 to 7.42)
60–69	0.28 (0.15 to 0.54)	0.52 (0.37 to 0.72)	0.50 (0.40 to 0.64)	0.57 (0.46 to 0.69)	1.51 (1.26 to 1.80)	2.47 (2.02 to 3.02)	3.97 (3.11 to 5.08)	7.08 (5.43 to 9.23)
70–79	0.63 (0.33 to 1.18)	0.48 (0.30 to 0.77)	0.59 (0.43 to 0.80)	0.84 (0.66 to 1.07)	1.37 (1.07 to 1.74)	1.65 (1.22 to 2.22)	2.92 (2.05 to 4.17)	3.68 (2.37 to 5.72)
≥80	0.55 (0.17 to 1.84)	0.71 (0.33 to 1.54)	0.79 (0.47 to 1.34)	0.78 (0.50 to 1.23)	1.44 (0.93 to 2.24)	0.96 (0.49 to 1.86)	1.86 (0.86 to 4.00)	2.95 (1.28 to 6.79)

Patients with systolic BP of 130–139 mmHg served as referent category.

Table 3. Multivariable-adjusted hazard ratios and 95% confidence intervals of different outcomes, associated with different diastolic BP values in patients of different ages

Outcome per Age Category, yr	Diastolic BP				
	<50 mmHg (*n*=5896)	50–59 mmHg (*n*=34,045)	60–69 mmHg (*n*=110,117)	80–89 mmHg (*n*=57,306)	≥90 mmHg (*n*=13,305)
Mortality					
<50	0.42 (0.10 to 1.69)	1.23 (0.94 to 1.61)	1.28 (1.10 to 1.49)	1.10 (0.95 to 1.27)	1.24 (1.00 to 1.54)
50–59	1.48 (1.20 to 1.83)	1.33 (1.23 to 1.44)	1.21 (1.16 to 1.27)	0.92 (0.87 to 0.97)	0.92 (0.84 to 1.00)
60–69	1.30 (1.14 to 1.48)	1.38 (1.31 to 1.45)	1.16 (1.12 to 1.20)	0.91 (0.87 to 0.95)	0.99 (0.91 to 1.07)
70–79	1.33 (1.22 to 1.43)	1.24 (1.19 to 1.29)	1.12 (1.08 to 1.15)	0.97 (0.93 to 1.02)	1.09 (0.98 to 1.20)
≥80	1.23 (1.14 to 1.32)	1.16 (1.11 to 1.21)	1.07 (1.03 to 1.11)	1.04 (0.99 to 1.10)	1.15 (1.00 to 1.31)
Coronary heart disease					
<50	0.00 (0.00 to 0.00)	0.92 (0.40 to 2.16)	0.68 (0.43 to 1.08)	1.04 (0.78 to 1.40)	1.04 (0.68 to 1.60)
50–59	0.77 (0.34 to 1.73)	1.06 (0.84 to 1.34)	1.04 (0.93 to 1.16)	0.9 (0.81 to 1.00)	0.73 (0.61 to 0.88)
60–69	1.47 (0.97 to 2.24)	1.23 (1.05 to 1.46)	1.14 (1.04 to 1.26)	0.94 (0.85 to 1.05)	0.82 (0.67 to 1.00)
70–79	0.93 (0.62 to 1.39)	1.07 (0.90 to 1.26)	1.14 (1.02 to 1.27)	0.94 (0.81 to 1.09)	0.82 (0.59 to 1.16)
≥80	0.72 (0.44 to 1.18)	1.04 (0.84 to 1.29)	1.15 (0.99 to 1.34)	0.90 (0.71 to 1.14)	0.74 (0.39 to 1.41)
Stroke					
<50	0.00 (0.00 to 0.00)	0.84 (0.42 to 1.69)	0.92 (0.66 to 1.29)	0.81 (0.61 to 1.07)	0.99 (0.68 to 1.45)
50–59	1.01 (0.58 to 1.75)	1.12 (0.93 to 1.34)	1.10 (1.00 to 1.21)	0.95 (0.87 to 1.05)	0.87 (0.75 to 1.01)
60–69	1.13 (0.80 to 1.61)	1.08 (0.95 to 1.24)	1.13 (1.04 to 1.22)	0.94 (0.86 to 1.03)	0.98 (0.84 to 1.15)
70–79	1.13 (0.88 to 1.47)	1.11 (0.99 to 1.25)	1.12 (1.04 to 1.22)	0.84 (0.75 to 0.95)	1.05 (0.83 to 1.34)
≥80	0.73 (0.52 to 1.03)	1.00 (0.86 to 1.17)	0.99 (0.89 to 1.11)	0.86 (0.72 to 1.03)	0.93 (0.61 to 1.41)
ESRD					
<50	0.00 (0.00 to 0.00)	1.24 (0.57 to 2.70)	0.78 (0.52 to 1.18)	1.29 (1.01 to 1.65)	1.24 (0.90 to 1.70)
50–59	1.47 (0.61 to 3.55)	1.22 (0.90 to 1.65)	0.93 (0.80 to 1.08)	1.19 (1.06 to 1.33)	1.02 (0.87 to 1.21)
60–69	1.43 (0.63 to 3.22)	1.63 (1.27 to 2.10)	1.15 (0.99 to 1.34)	1.03 (0.88 to 1.20)	0.87 (0.67 to 1.13)
70–79	1.23 (0.62 to 2.43)	1.31 (0.98 to 1.75)	1.14 (0.93 to 1.39)	1.27 (0.99 to 1.63)	0.90 (0.53 to 1.55)
≥80	1.49 (0.65 to 3.40)	0.80 (0.47 to 1.38)	1.10 (0.77 to 1.58)	0.82 (0.45 to 1.49)	0.68 (0.16 to 2.86)

Patients with diastolic BP of 70–79 mmHg served as referent category.

between SBP and CHD in any age group among patients with weight loss or low BMI. DBP showed no consistent association with CHD overall or in subgroups (Figure 2, Table 3, Supplemental Figures 3, 6, and 7, Supplemental Table 2).

Incident Stroke

A total of 14,557 patients experienced an incident ischemic stroke (10.4 events/1000 PY; 95% CI, 10.2 to 10.6). Incident stroke rates were similar or lower in older versus younger individuals (Supplemental Tables 1 and 2). Age modified the association of SBP with stroke (*P* for interaction <0.001). Higher SBP was associated with linearly higher crude stroke rates in all age groups, with the lowest risk seen in patients with SBP<100 mmHg (Supplemental Figure 2, Supplemental Table 1). The multivariable-adjusted association of higher SBP with stroke was strongest among the youngest patients and was attenuated among older patients: The aHRs associated with SBP≥170 mmHg (compared with 130–139 mmHg) in patients <50, 50–59, 60–69, 70–79, and ≥80 years were 1.99 (95% CI, 1.05 to 3.79), 2.28 (95% CI, 1.82 to 2.86), 1.98 (95% CI, 1.59 to 2.46), 1.79 (95% CI, 1.41 to 2.27), and 1.26 (95% CI, 0.89 to 1.79), respectively (Figure 3, Table 2). DBP showed no association with stroke (Figure 3, Table 3, Supplemental Figure 3, Supplemental Table 2). Associations showed a similar pattern in all examined subgroups (Supplemental Figures 8 and 9).

Incident ESRD

A total of 5161 patients experienced ESRD (3.3 events/1000 PY; 95% CI, 3.2 to 3.3). ESRD rates were lower in older than younger individuals (Supplemental Tables 1 and 2). Age modified the association of SBP with ESRD (*P* for interaction <0.001). Higher SBP was associated with higher crude ESRD rates in all age groups, but with an attenuation in older patients (Supplemental Figure 2, Supplemental Table 1). Results were similar in multivariable-adjusted Cox models: The aHRs associated with SBP≥170 (compared with 130–139 mmHg) in patients <50, 50–59, 60–69, 70–79, and ≥80 years were 7.59 (95% CI, 4.89 to 11.79), 6.06 (95% CI, 4.93 to 7.47), 7.07 (95% CI, 5.42 to 9.22), 3.68 (95% CI, 2.37 to 5.72), and 2.95 (95% CI, 1.28 to 6.80), respectively (Figure 4, Table 2). The association of SBP with ESRD was linearly incremental in patients <80 years. While SBP≥170 mmHg was associated with significantly higher ESRD risk in patients ≥80 years, SBP<170 mmHg showed no consistent association with ESRD in this age group (Figure 4). DBP showed no association with ESRD (Figure 4, Table 3, Supplemental Figure 3, Supplemental Table 2). Associations showed a similar pattern in all examined subgroups (Supplemental Figures 10 and 11).

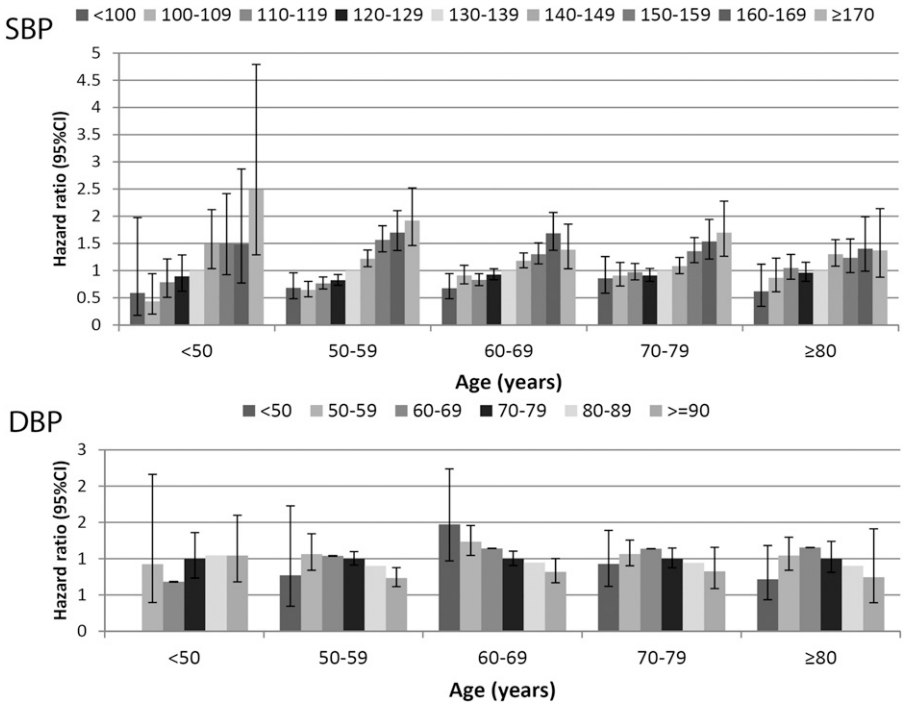

Figure 2. | Association of systolic BP (SBP) and diastolic BP (DBP) with incident coronary heart disease (first occurrence of a myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), among 204,796 patients with incident CKD of different ages, in multivariable-adjusted Cox models. Models were adjusted for age, sex, race, marital status, per capita income, eGFR, prevalent comorbid conditions (hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, peripheral artery disease, malignancies, liver disease, rheumatologic diseases, chronic lung disease, dementia, HIV/AIDS, depression, weight loss or low body mass index, and Charlson comorbidity index), number of antihypertensive medications prescribed at baseline, and baseline DBP (for SBP analyses) and baseline SBP (for DBP analyses). 95% CI, 95% confidence interval.

Discussion

We describe systematic differences across age groups in the relationship of SBP with outcomes in patients with incident CKD. Low DBP was associated with higher mortality, but DBP showed no consistent associations with cardiovascular outcomes. Our results reinforce the significant association of elevated SBP with all the studied outcomes but suggest weaker associations in the elderly, especially in patients aged ≥80 years. The best outcomes were seen with SBP of 120–139 mmHg in patients <80 years and of 120–159 mmHg in those ≥80 years. Our results concerning mortality are similar to the findings from a recent analysis of 21,015 patients with CKD from northern California and extend its findings to a larger population and to several other outcomes (33).

Current hypertension treatment guidelines recommend a target BP of <140/90 mmHg for most patients (13). The elderly are considered a special category (3), in part because of scarce clinical trial evidence in this population, and in part because of empirical and theoretical concerns over their tolerance of excessive BP lowering (34,35). The elderly may be more susceptible to deleterious effects of low BP as a result of age- and comorbidity-related alterations in hemodynamic autoregulatory mechanisms (15–19). This, however, cannot explain the diminished association of elevated SBP with outcomes in the elderly. A possible explanation could be the presence of competing risk from causes of death unrelated to BP (*e.g.*, malignancies or infections), which disproportionately affect the elderly, or adverse effects associated with the treatment of hypertension in the elderly (*e.g.*, falls) (36). Such effects may manifest most markedly in frail patients (37,38), a suggestion indirectly supported by the lack of associations in our subgroup analyses in individuals with weight loss or low BMI.

The attenuation of mortality risk associated with higher SBP in elderly patients described in our study echoes results from earlier studies reporting similarly weaker or absent associations of a multitude of traditional risk factors with mortality in elderly individuals, such as hypercholesterolemia (39), obesity (40), and comorbidity burden in general (41), as well as a more robust association of functional status with mortality (41). Furthermore, the association of cardiovascular diseases with mortality is also diminished in older populations (42,43), and risk factors such as hypertension, hypercholesterolemia, and obesity were less associated with incident CHD in previous studies (44). This supports our findings of relatively lower risk of cardiovascular event rates associated with higher SBP in the oldest age groups with CKD. Our findings of generally lower crude cardiovascular and renal event rates in older versus younger individuals also suggest that pathologic processes responsible for morbidity may be distinctly different in the elderly and could be affected by competing risk from the higher mortality seen in this group.

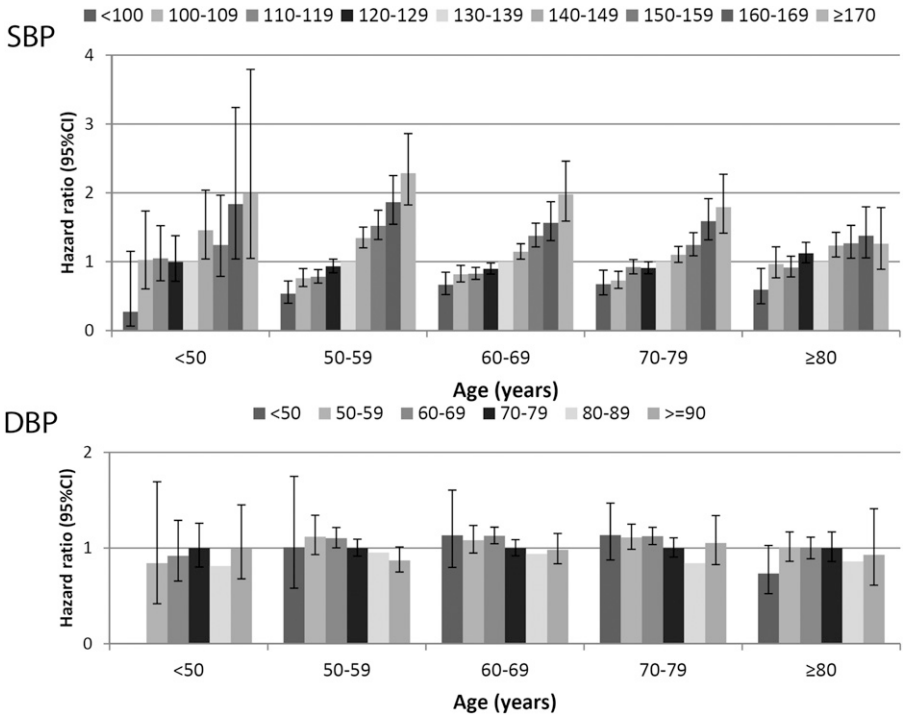

Figure 3. | Association of systolic BP (SBP) and diastolic BP (DBP) with incident ischemic stroke, among 301,569 patients with incident CKD of different ages, in multivariable-adjusted Cox models. Models were adjusted for age, sex, race, marital status, per capita income, eGFR, prevalent comorbid conditions (hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, peripheral artery disease, malignancies, liver disease, rheumatologic diseases, chronic lung disease, dementia, HIV/AIDS, depression, weight loss or low body mass index, and Charlson comorbidity index), number of antihypertensive medications prescribed at baseline, and baseline DBP (for SBP analyses) and baseline SBP (for DBP analyses). 95% CI, 95% confidence interval.

Unfortunately, no guidelines address the conundrum of BP targets in elderly patients with CKD, even though most patients with CKD are elderly and their comorbidities make them susceptible to deleterious effects of low BP (15–19). In a previous analysis of veterans with prevalent CKD, we found that both SBP and DBP displayed a J-shaped association with all-cause mortality (45). We now extend these findings by demonstrating that elevated SBP is indeed associated with a multitude of adverse outcomes in all age groups, including the very old, but also that in the latter group these associations are subdued and that the ideal SBP could be extended to a level as high as 150 mmHg. Our findings therefore support current clinical guidelines, although the observational nature of our study does not allow the direct application of these results to clinical practice.

Our results do not provide an unequivocal answer to whether an SBP<130 mmHg is favorable or not. In a previous observational modeling of strict versus conventional BP control, patients with CKD whose SBP decreased to <120 mmHg after increased antihypertensive medication use experienced significantly higher mortality compared with those whose SBP decreased to 120–139 mmHg (46). The SPRINT study showed that treating SBP to a target of <120 mmHg (with an overall achieved SBP of 121.4 mmHg) versus <140 mmHg (with an achieved SBP of 136.2 mmHg) resulted in significantly lower all-cause mortality rate and nominally lower composite cardiovascular event rate in patients with CKD (14). These results support our findings regarding the lower risk of CHD and stroke associated with lower SBP but may be discordant with the J-shaped mortality seen in our and other observational studies, even though we have only detected statistically significantly higher mortality for patients with SBP<110 mmHg. SPRINT enrollees had markedly lower all-cause mortality rates compared with the populations examined in observational studies, which may be experiencing relatively more deaths unrelated to cardiovascular events. It is unclear whether they would derive a mortality benefit from SBP lowering to levels even stricter than those achieved in SPRINT.

Several limitations of our study should be acknowledged. This being an observational study, only associations, but no cause-and-effect relationships, can be established from it. Our cohort consisted mostly of men; hence, the findings may not be generalizable to women. We used multivariable-adjusted analyses, but the presence of residual confounders cannot be excluded. We used weight loss or low BMI in place of frailty because additional criteria for the standard definition of the latter (30) were not available in our database. We captured comorbidities and clinical events using diagnostic codes, not the more accurate adjudication procedures used in clinical trials. The lower cardiovascular and renal event rates seen in patients with low SBP in our cohort could have been affected by competing risk from higher mortality seen in these groups; hence, these associations need to be interpreted with proper caution, and without implying a protective effect from low SBP on such outcomes.

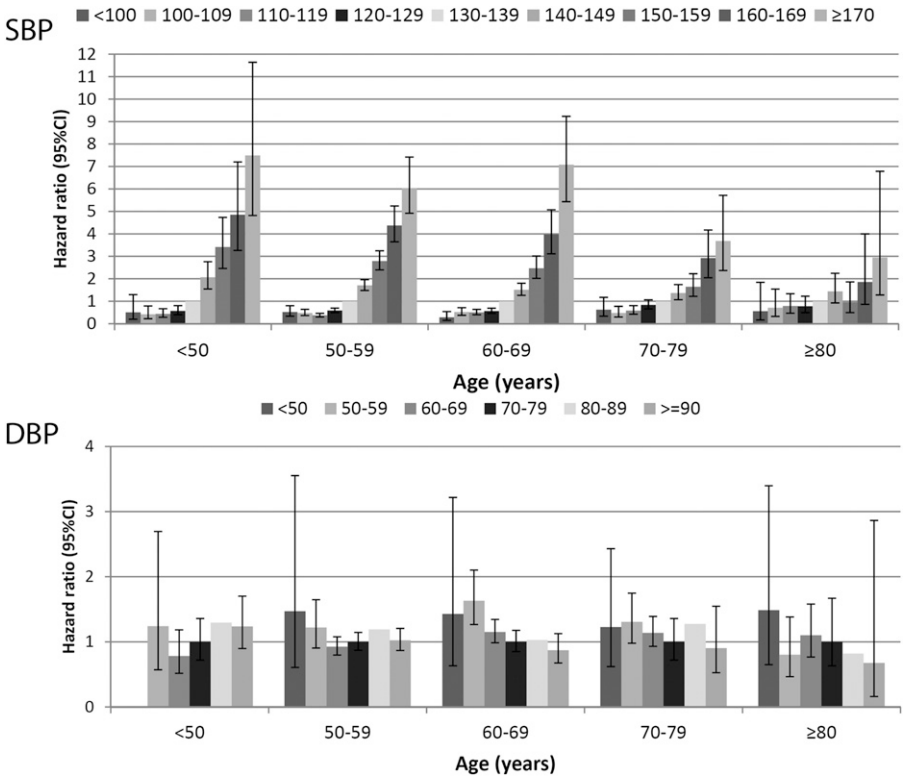

Figure 4. | Association of systolic BP (SBP) and diastolic BP (DBP) with incident ESRD (initiation of RRT or preemptive kidney transplantation), among 300,424 patients with incident CKD of different ages, in multivariable-adjusted Cox models. Models were adjusted for age, sex, race, marital status, per capita income, eGFR, prevalent comorbid conditions (hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, peripheral artery disease, malignancies, liver disease, rheumatologic diseases, chronic lung disease, dementia, HIV/AIDS, depression, weight loss or low body mass index, and Charlson comorbidity index), number of antihypertensive medications prescribed at baseline, and baseline DBP (for SBP analyses) and baseline SBP (for DBP analyses). 95% CI, 95% confidence interval.

In conclusion, SBP>130–139 mmHg is associated with higher mortality and higher incidence of CHD, stroke, and ESRD in patients with CKD of all ages, but the strength of these associations diminishes with advanced age. DBP<70 mmHg is associated with higher mortality, but DBP shows no association with cardiovascular outcomes. Our results reinforce that treatment of hypertension in younger patients with CKD toward targets recommended by current clinical guidelines is paramount to improve outcomes in these patients. In very elderly patients with CKD, a more cautious BP-lowering strategy may be reasonable.

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Disclosures

None.

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