Kidney Medicine

Isolated Diastolic Hypertension and Kidney and Cardiovascular Outcomes in CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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Rationale & Objective: The clinical significance of isolated diastolic hypertension in patients with chronic kidney disease (CKD) is unclear. We assessed the prevalence of isolated diastolic hypertension and its association with adverse kidney and cardiovascular outcomes in participants in the Chronic Renal Insufficiency Cohort (CRIC) study.

Study Design: Prospective cohort study.

Setting & Population: CRIC study participants with complete baseline data on systolic blood pressure (SBP) and diastolic BP (DBP) (N=5,621).

Exposure: Isolated diastolic hypertension defined as SBP ≤ 130 mm Hg and DBP >80 mm Hg.

Reference Group: Normotension, defined as SBP ≤ 130 mm Hg and DBP ≤ 80 mm Hg.

Outcomes: Composite kidney events (50% decline in estimated glomerular filtration rate or onset of kidney failure), composite cardiovascular events (myocardial infarction, heart failure, stroke, or peripheral arterial disease), and all-cause mortality.

Analytical Approach: Cox proportional hazards models adjusted for demographic, health behavior, and clinical covariates.

Results: Of the 5,621 participants, 347 (6.2%) had isolated diastolic hypertension. Among the 347 participants with isolated diastolic hypertension, there was no association between isolated diastolic hypertension and the composite kidney outcome (HR, 1.17; 95% CI, 0.93-1.47; $P = 0.18$), composite cardiovascular events (HR, 0.91; 95% CI, 0.65-1.27; $P = 0.58$), or all-cause mortality (HR, 0.82; 95% CI, 0.57-1.19; $P = 0.30$).

Limitations: Older age of cohort and low number of participants of Asian ethnicity limit generalizability of findings. A relatively small sample size is inadequate to detect modest associations with outcomes.

Conclusions: Isolated diastolic hypertension was not associated with the risk of adverse kidney and cardiovascular events in participants with CKD.

Visual Abstract included

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The 2017 American College of Cardiology or American Heart Association (ACC/AHA) guidelines defined hypertension as blood pressure (BP) equal to or greater than 130/80 mm Hg.[1] This increased the prevalence of isolated diastolic hypertension, defined as diastolic BP greater than or equal to 80 mm Hg with a systolic BP less than 130 mm Hg, from 1.3% to 6.5% in the general population.[2] However, the clinical significance of isolated diastolic hypertension is unclear, and whether treatment is warranted for it remains controversial. For example, though several large studies, particularly in Asian populations, have found an increased incidence of composite cardiovascular events, cardiovascular mortality and strokes in patients with isolated diastolic hypertension,[3-5] and multiple other studies have found no correlation between isolated diastolic hypertension and an increased risk of adverse cardiovascular events.[2,6-9] Age may be an important modifier affecting the relationship of isolated diastolic hypertension to increased cardiovascular risk, with increased cardiovascular risk in populations less than 50 years of age as compared to those older than 50 years of age.[5,10,11] The interpretation of these results is further complicated by the use of varying thresholds of BP in different studies (<160/90, <140/90, and <130/80 mm Hg) and the varied methodologies employed (single clinic BP reading, home BP readings, and ambulatory blood pressure monitoring).[12] The data regarding effect of isolated diastolic hypertension on kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD) are more sparse. The few studies evaluating the association between isolated diastolic hypertension and incident kidney failure, decline in estimated glomerular filtration rate (eGFR), and albuminuria[13-17] have shown conflicting results.

The Chronic Renal Insufficiency Cohort (CRIC) study is a multicenter, prospective cohort study encompassing an ethnically and racially diverse population of patients with eGFR ranging from 20-70 mL/min/1.73 m^2,[18] followed over several years. The CRIC cohort offers a unique opportunity to gain insight into the association between isolated diastolic hypertension and adverse kidney and cardiovascular outcomes in the setting of CKD.

The objective of this paper is to determine the prevalence of isolated diastolic hypertension in patients with CKD and to evaluate the association between isolated diastolic hypertension and adverse kidney and cardiovascular outcomes in this population.

PLAIN LANGUAGE SUMMARY

Clinicians frequently encounter patients with kidney disease who have controlled systolic blood pressure (BP) but high diastolic BP and do not know whether they should intensify BP treatment in an attempt to control the diastolic BP. We examined whether having controlled systolic BP but uncontrolled diastolic BP leads to worse heart and kidney outcomes in patients with chronic kidney disease. We did not find any such association. However, our study was relatively small and had a number of limitations. Till larger studies confirm or refute this finding, we recommend not increasing blood pressure medications to improve the diastolic BP control if the systolic BP is already well controlled in patients with chronic kidney disease.

METHODS

Study Design

The CRIC study is a prospective, multicenter observational cohort study of participants with CKD. Details of the design and baseline characteristics of CRIC participants are published elsewhere.[18] Briefly, the CRIC study enrolled racially diverse adult individuals aged 21-74 years with an eGFR between 20 and 70 mL/min/1.73 m^2 from June 2003 to December 2008 (Phase I) and adults aged 45-79 years with an eGFR of 45-70 mL/min/1.73 m^2 between 2013 and 2015 (Phase III). Institutional review boards at each participating center approved the study in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Data Collection

Primary Exposure

Three blood pressure measurements were obtained in the sitting position after at least 5 minutes of quiet rest by a trained staff according to a standard protocol. An aneroid sphygmomanometer was used with 1 of 4 cuff sizes (pediatric, regular adult, large adult, or thigh) based on the participant's arm circumference by specially trained observers.[19] A total of 5,621 CRIC participants with data on both systolic and diastolic BP at study baseline were included in the analysis. An average of 3 blood pressure readings was used for analysis.

Isolated diastolic hypertension was defined as diastolic BP of >80 mm Hg and systolic BP of ≤130 mm Hg; isolated systolic hypertension was defined as systolic BP of >130 mm Hg and diastolic BP of ≤80 mm Hg; systolic diastolic hypertension was defined as systolic BP of >130 mm Hg and diastolic BP of >80 mm Hg. The reference group was normotension, defined as systolic BP of ≤130 mm Hg and diastolic BP of ≤80 mm Hg.

Covariates

Covariates used in the study included demographic characteristics (age, sex, race, and ethnicity), comorbid conditions, laboratory data, and medication use. Race and ethnicity were self-reported as non-Hispanic White, non-Hispanic Black, Hispanic, and other. Current cigarette smoking was determined by self-report. Weight and height were measured using standard protocols, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. History of cardiovascular disease (eg, chronic heart failure, myocardial infarction, or coronary revascularization) was self-reported. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL, a non-fasting glucose level of ≥200 mg/dL, or the use of antidiabetic medications. Serum creatinine was measured on a Roche Modular P chemistry analyzer using a creatinase enzymatic method (Roche Diagnostics). The glomerular filtration rate was estimated at baseline and at every follow-up visit. Additional measures included 24-hour urine total protein value, urine albumin creatinine ratio, and total cholesterol with high density lipoprotein and low density lipoprotein cholesterol values. Documentation of current medication use included ascertainment of angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB), diuretic, β-blocker, calcium channel blocker, and aldosterone antagonist use.

Outcomes

The outcomes of interest were composite kidney events (defined as a 50% decline in eGFR or onset of kidney failure defined as kidney transplantation or initiation of long-term dialysis), composite cardiovascular events (incident, definite or probable myocardial infarction, heart failure, stroke, or peripheral arterial disease), and all-cause mortality. The estimated GFR was calculated from serum creatinine and cystatin C using a CRIC study equation.[20] Time to eGFR halving was imputed assuming a linear decline in kidney function consistent with previous CRIC publications. For participants who developed kidney failure or died during the study period, eGFR before the onset of kidney failure or death was used. Kidney failure was defined as the initiation of dialysis therapy or kidney transplantation.

Cardiovascular events (myocardial infarction [MI], stroke, congestive heart failure [CHF], and peripheral arterial disease [PAD]) were ascertained during the course of the study by asking participants about hospitalizations during the clinic or phone visit. Hospital records were subsequently obtained, and events were adjudicated using predefined event-specific guidelines by blind reviewers. Mortality was ascertained through a report from the next of kin, retrieval of death certificates or obituaries, review of hospital records, and linkage with the social security mortality master file. Participants' follow-up was censored when the dataset was locked for analysis, they were lost to follow-up, when they

achieved the event of interest or died, whichever occurred first. The median follow-up was 16.9 years.

Statistical Analysis

Standard descriptive statistics were used to characterize the study cohort at the CRIC study baseline, stratified by blood pressure categorization. Continuous variables were reported using mean and standard deviation or median and interquartile range and compared using independent t-tests or Wilcoxon rank sum tests when comparing patients with versus without isolated diastolic hypertension and one-way analysis of variances with Bonferroni corrections when comparing all 4 categories of blood pressure. Categorical variables were reported using frequencies and proportions, and differences between groups were compared using χ^2 tests. Cox proportional hazards regression models were used to analyze time to composite kidney and cardiovascular events, death, MI, and CHF for all hypertension groups using normotension as the reference group. Covariates used for adjustment in the models included age, sex, race, clinical center, diabetes status, eGFR, albumin/creatinine ratio, baseline cardiovascular and antihypertensive medications, and low density lipoprotein cholesterol levels. Subset analyses were performed to assess if the association between isolated diastolic hypertension and clinical outcomes of interest is modified by age (below and above 60 years), proteinuria, and the presence of diabetes at study baseline, using separate models based on data subset for each potential modifier. Given the small number of missing covariate data and the large data set, imputation was not performed; participants with missing data were excluded from the multivariable analyses.

For all analyses, a 2-sided P-value of 0.05 was considered statistically significant. All analyses were performed using the R Statistical Computing Environment (R Foundation for Statistical Computing) version 4.1.2. Before running models, variables were tested for normality of distribution using density plots, scale-location plots, Q-Q plots, Cook's Distances, residuals versus leverage, and residuals versus fitted values.

RESULTS

Baseline Characteristics

A total of 5,621 CRIC participants with data on both systolic and diastolic BP at study baseline were included in the analysis. The mean age of all participants was 59.6 ± 10.7 years; 44% were females, 43 % were non-Hispanic Blacks, and 13% were Hispanic. There were several differences in baseline characteristics between participants stratified by the defined BP phenotypes.(Table 1). Notably, participants with isolated diastolic hypertension were younger, less likely to have diabetes and prevalent cardiovascular disease, had a higher GFR and lower proteinuria. Other baseline characteristics of the study participants by blood pressure categories are summarized in Table 1.

Prevalence of Isolated diastolic hypertension across CKD Stages

Prevalence of isolated diastolic hypertension in the entire cohort was 6.2 % (347 of the 5,621); 6% of participants with CKD stage 3a, 5% of participants with CKD stage 3b, and 4% of participants with CKD stage 4 had isolated diastolic hypertension as shown in Table 2.

Association between Isolated Diastolic Hypertension and Composite Kidney Outcome

There was no statistically significant difference in the risk of developing composite kidney outcome in participants with isolated diastolic hypertension as compared with the normotensive group (HR, 1.17; 95% CI, 0.93-1.47; P = 0.17) (Table 3). This was consistent when stratified by age, and proteinuria (Table S1). Subgroup analyses (Fig 1) by age ≤ 60 years and >60 years showed similar results when comparing participants with isolated diastolic hypertension with those with normotension (HR, 1.14; 95% CI, 0.88-1.48 P = 0.31 and HR, 1.55; 95% CI, 0.84-2.83; P = 0.16, respectively, Table S1). In exploratory analyses, participants with isolated diastolic hypertension with diabetes mellitus at study baseline had an increased risk of composite kidney outcome (HR, 1.69; 95% CI, 1.06-2.69; P = 0.03) compared with participants with normotension; in participants without diabetes, there was no association between isolated diastolic hypertension and the composite kidney outcome (HR, 0.95; 95% CI, 0.72-1.25; P = 0.70) (Fig 1).

Secondary analysis including only the participants treated with antihypertensive medications showed an increased risk of composite kidney outcomes in participants with isolated diastolic hypertension as compared with those with normotension (HR, 1.28; 95% CI, 1.01-1.62; P = 0.04) (Table S2)

Association between Isolated Diastolic Hypertension and Composite Cardiovascular Outcome and All-Cause Mortality

There was no significant difference in the risk of composite of cardiovascular outcome in participants with isolated diastolic hypertension as compared with normotensive participants (HR, 0.91; 95% CI, 0.65-1.27; P = 0.58, Table 4). By contrast, isolated systolic hypertension conferred an increased risk of composite cardiovascular events as compared with normotension (HR, 1.20; 95% CI, 1.03-1.39; P = 0.02). Systolic diastolic hypertension conferred an increased risk for both composite cardiovascular outcome and all-cause mortality compared with normotension (adjusted HR, 1.41; 95% CI, 1.17-1.71; P < 0.001 and adjusted HR, 1.42; 95% CI, 1.16-1.74; P < 0.001, respectively). Isolated diastolic hypertension was not associated with increased risk of individual components of composite cardiovascular outcomes, namely CHF, stroke, MI, and PAD (Table S3).

There was no significant difference in the risk of all-cause mortality in participants with isolated diastolic

Table 1. Characteristics of CRIC participants by Blood Pressure phenotypes at Baseline Visit

Blood Pressure Phenotypes (N=5,621)						
Characteristics	**All (N=5,621)**	**Normotensive (n=2,919)**	**Isolated Diastolic Hypertension (n=347)**	**Isolated Systolic Hypertension (n=1,447)**	**Systolic Diastolic Hypertension (n=908)**	***P***
Age, y (mean ± SD)	59.6 ± 10.7	59.5 ± 10.9	51.6 ± 11.2	63.8 ± 8.2	56 ± 10.4	< 0.001*
Women, n (%)	2,455 (44)	1,298 (44)	130 (37)	708 (49)	319 (35)	< 0.001*
Race/Ethnicity, n (%)						< 0.001*
Non-Hispanic White	2,273 (40)	1,473 (50)	134 (39)	460 (32)	206 (23)	—
Non-Hispanic Black	2,422 (43)	1,067 (37)	154 (44)	691 (48)	510 (56)	—
Hispanic	728 (13)	285 (10)	37 (11)	242 (17)	164 (18)	—
Others	198 (4)	94 (3)	22 (6)	54 (4)	28 (3)	—
Any cardiovascular disease, n (%)	1,884 (34)	966 (33)	62 (18)	563 (39)	293 (32)	< 0.001*
Diabetes mellitus, n (%)	2,890 (51)	1,340 (46)	81 (23)	1,006 (70)	463 (51)	<0.001*
BMI, kg/m^2 (mean ± SD)	32.3 ± 7.6	32.1 ± 7.6	32.1 ± 7.8	32.7 ± 7.5	32.5 ± 7.8	0.05
Waist Circumference, cm (mean ± SD)	106.8 ± 17.5	106.5 ± 17.7	105.2 ± 16.5	107.9 ± 17.5	106.2 ± 42.7	0.02*
Smoking status, n (%)	707 (13)	339 (12)	45 (13)	178 (12)	145 (16)	0.007*
eGFR, mL/min/1.73 m^2 (mean ± SD)	48 ± 16.7	49.4 ± 17.0	52.8 ±17.6	44.5 ± 15.2	47.2 ± 16.7	<0.001*
eGFR category, mL/min/1.73m^2, n (%)						<0.001*
<30	842 (15)	375 (13)	32 (9)	275 (19)	160 (18)	—
30-60	1,289 (23)	758 (26)	115 (33)	219 (15)	197 (22)	—
>60	3,486 (62)	1,784 (61)	200 (58)	951 (66)	551 (61)	—
24 h urine protein, g/24 h, median (q1 and q3)	0.2 (0.1-0.9)	0.1 (0.1-0.5)	0.2 (0.1-0.8)	0.40 (0.10-1.50)	0.7 (0.15-2.33)	<0.001*
LDL, mg/dL (mean ± SD)	102.7 ± 35.6	99.6 ± 34	108.4 ± 35.0	100.7 ± 35.6	112.7 ± 38.3	<0.001*
Systolic BP, mm Hg (mean ± SD)	128.6 ± 21.4	113.3 ± 10.7	121.7 ± 6.3	145.3 ± 13.1	153.6 ± 18.7	<0.001*
Diastolic BP, mm Hg (mean ± SD)	71.1 ± 12.6	65.1 ± 8.8	84.6 ± 3.8	68.3 ± 8.4	89.7 ± 8.2	<0.001*
Number of antihypertensive medications (mean ± SD)	2.6 ± 1.5	2.4 ± 1.5	1.9 ± 1.3	3 ± 1.4	2.8 ± 1.5	<0.001*
Diuretics, n (%)	3,095 (55)	1,527 (53)	145 (42)	898 (62)	525 (58)	<0.001*
Renin angiotensin aldosterone system inhibitors, n (%)	3,844 (69)	1,987 (68)	214 (62)	1,029 (72)	614 (68)	0.01*
β-blockers, n (%)	2,755 (49)	1,325 (46)	115 (34)	825 (57)	490 (54)	<0.001*
Calcium channel blockers, n (%)	2,314 (41)	987 (34)	110 (32)	798 (56)	419 (47)	<0.001*

Note: Isolated diastolic: diastolic blood pressure (BP) > 80 mm Hg with systolic BP ≤ 130 mm Hg, normotension: systolic BP ≤ 130mm Hg and diastolic BP ≤ 80 mm Hg, isolated systolic hypertension: systolic BP >130 mm Hg and diastolic BP ≤ 80 mm Hg, and systolic diastolic hypertension: systolic BP >130 mm Hg and diastolic BP >80 mm Hg.

Renin angiotensin aldosterone system inhibitors include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor blockers.

Diuretics include loop, thiazide, and potassium sparing diuretics (excludes mineralocorticoid receptor blockers).

*P<0.05. LDL, low density lipoprotein.

Table 2. Prevalence of Blood Pressure phenotypes by stage of CKD based on eGFR

	All (N=5,621)	Normotension (n=2,919)	Isolated Diastolic Hypertension (n=347)	Isolated Systolic Hypertension (n=1,447)	Systolic Diastolic Hypertension (n=908)
Stage of CKD n (%)					
1	73 (100)	54 (74)	7 (10)	7 (10)	5 (7)
2	1,216 (100)	704 (58)	108 (9)	212 (17)	192 (16)
3a	1,761 (100)	912 (52)	111 (6)	463 (26)	275 (16)
3b	1,725 (100)	872 (51)	89 (5)	488 (28)	276 (16)
4	834 (100)	373 (45)	31 (4)	271 (32)	159 (19)
5	8 (100)	2 (25)	1 (13)	4 (50)	1 (13)

Note: Isolated diastolic: diastolic blood pressure (BP) > 80 mm Hg with systolic BP ≤ 130 mm Hg, Normotension: systolic BP ≤ 130mm Hg and diastolic BP ≤ 80 mm Hg, isolated systolic hypertension: systolic BP >130 mm Hg and diastolic BP ≤ 80 mm Hg, and systolic diastolic hypertension: systolic BP >130 mm Hg and diastolic BP >80 mm Hg.
CKD stages: Stage 1: eGFR ≥ 90 mL/min/1.73 m^2; Stage 2: eGFR 60-89 mL/min/1.73 m^2; Stage 3a: eGFR 45-59 mL/min/1.73 m^2; Stage 3b: eGFR 30-44 mL/min/1.73 m^2; Stage 4: eGFR 15-29 mL/min/1.73 m^2; and Stage 5: eGFR <15 mL/min/1.73m^2.
CKD, chronic kidney disease.

hypertension as compared with normotensive participants (HR, 0.82; 95% CI, 0.57-1.19; P = 0.30) (Table 4).

Secondary analysis including only the participants treated with antihypertensive medications did not show an association between isolated diastolic hypertension and composite cardiovascular outcome or all-cause mortality (Tables S4 and S5).

Sensitivity Analyses

We performed sensitivity analyses using the following definitions of the BP categories: Normotension: SBP of <130 mm Hg and DBP of <80 mm Hg, isolated diastolic hypertension: SBP of <130 mm Hg and DBP of ≥80 mm Hg, isolated systolic hypertension: SBP of ≥130 mm Hg and diastolic BP of <80 mm Hg and systolic diastolic hypertension: SBP of ≥130 mm Hg and diastolic of ≥80 mm Hg.

Using the revised definitions, there was an increased risk of composite kidney outcome (HR, 1.27; 95% CI, 1.01-1.59; P = 0.038) in the group with isolated diastolic hypertension as compared with normotensive group (Table S6). There was no association between presence of isolated diastolic hypertension and composite cardiovascular outcome and all-cause mortality (Tables S7 and S8) using the revised definitions.

DISCUSSION

In this analysis of participants with CKD in the CRIC study, isolated diastolic hypertension was not associated with an increased risk of developing adverse kidney or cardiovascular outcomes or all-cause mortality compared with participants with normotension (Fig 2). This relationship was consistent in patients younger and older than 60 years of age and was not modified by the degree of proteinuria.

Isolated diastolic hypertension is a phenotype of hypertension defined by normal systolic and elevated diastolic BP. The prevalence rate of 6.2% in the CRIC cohort is in keeping with the reported prevalence of isolated diastolic hypertension of 7% in participants with CKD in NHANES IV.[21] Similar to previous epidemiologic observations,[22] isolated diastolic hypertension was more common in males than in females and in younger rather than

Table 3. Association Between Isolated Diastolic Hypertension and Composite Kidney outcome

BP Phenotype	No. of Patients at Baseline in Each Category	No. of Events	Event Rate Per 1,000 Person-Y	Unadjusted	Model A	Model B	Model C
				HR (95% CI)			
Normotension (reference group)	2,919	701	35	—	—	—	—
Isolated diastolic hypertension	347	107	41	1.16 (0.94-1.42); *P* = 0.16	0.93 (0.76-1.14); *P* = 0.5	1.20 (0.97-1.49); *P* = 0.1	1.17 (0.93-1.47); *P* = 0.17
Isolated systolic hypertension	1,447	568	82	2.41 (2.15-2.69); *P* < 0.001*	2.44 (2.18-2.75); *P* < 0.001*	1.97 (1.73-2.23); *P* < 0.001*	1.44 (1.26-1.65); *P* < 0.001*
Systolic diastolic hypertension	908	424	96	2.80 (2.48-3.16); *P* < 0.001*	2.40 (2.12-2.71); *P* < 0.001*	2.18 (1.91-2.50); *P* < 0.001*	1.67 (1.45-1.93); *P* < 0.001*

Note: Model A: adjusted for age (years), sex (men or women), race (non-Hispanic White, non-Hispanic Black, Hispanic, and others), and center (7 categories). Model B: adjusted for model A plus diabetes mellitus (yes or no), smoking status (never or past or current), cardiovascular disease (yes or no), BMI (kg/m^2), antihypertensive medications, and low density lipoprotein cholesterol (mg/dL). Model C: adjusted for model B plus eGFR (mL/min/1.73 m^2) and 24-hour urine protein.
Composite kidney outcome defined as 50% decrease in eGFR or end-stage kidney disease defined as kidney transplantation or start of long-term dialysis.
*$P < 0.05$

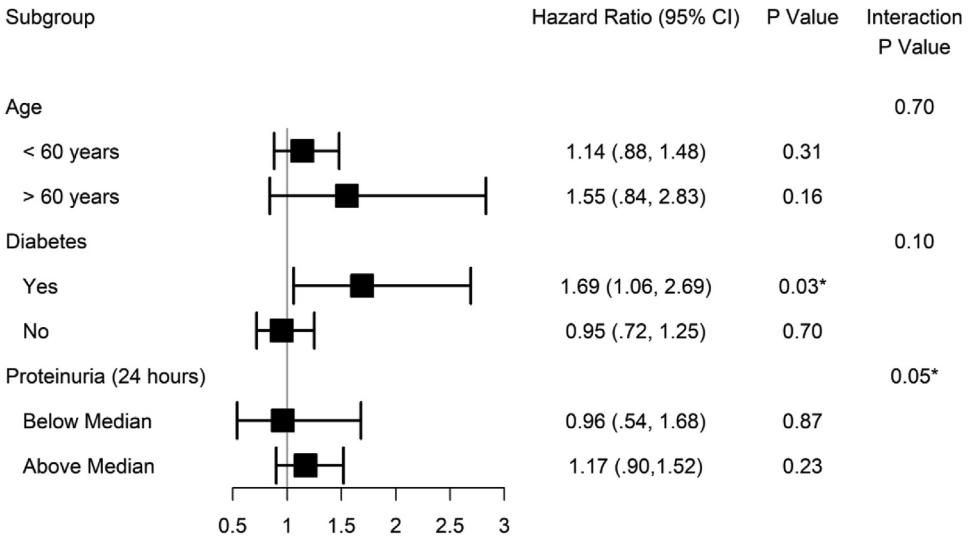

Figure 1. Association between isolated diastolic hypertension and composite kidney outcomes by age, presence or absence of diabetes mellitus, and severity of proteinuria. Forest Plot showing hazard ratios for the association between isolated diastolic hypertension and composite kidney outcomes, based on separate models within patients' subset by age group (≤ 60 years and > 60 years), comorbid diabetes (yes or no), and severity of proteinuria (below or above median [0.1296 g/24 h]). Reference group is participants with normotension. *$P < 0.05$.

Table 4. Associated Between Isolated Diastolic Hypertension and Composite Cardiovascular Outcome and All-Cause Mortality

Composite of MI, stroke, PAD, and CHF

	No. of Patients at Baseline in Each Category	No. of Events	Event Rate Per 1,000 Person-Y	Unadjusted	Model A	Model B	Model C
				HR (95% CI)			
Normotension (reference group)	2,919	694	32	—	—	—	—
Isolated diastolic hypertension	347	51	17	0.55 (0.41-0.73); $P < 0.001$*	0.65 (0.49-0.87); $P = 0.004$*	0.90 (0.64-1.26); $P = 0.53$	0.91 (0.65-1.27); $P = 0.58$
Isolated systolic hypertension	1,447	450	58	1.71 (1.52-1.93); $P < 0.001$*	1.51 (1.33-1.70); $P < 0.001$*	1.33 (1.15-1.54); $P < 0.001$*	1.20 (1.03-1.39); $P = 0.02$*
Systolic diastolic hypertension	908	245	49	1.46 (1.26-1.69); $P < 0.001$*	1.51 (1.30-1.75); $P < 0.001$*	1.55 (1.30-1.85); $P < 0.001$*	1.41 (1.17-1.71); $P < 0.001$*

All-cause mortality

	N (no. of Patients at Baseline in Each Category)	No. of Events	Event Rate Per 1,000 Person-Y	Unadjusted	Model A	Model B	Model C
				HR (95% CI)			
Normotension (reference group)	2,919	624	24	—	—	—	—
Isolated diastolic hypertension	347	36	10	0.42 (0.30-0.58); $P < 0.001$*	0.59 (0.41-0.81); $P = 0.002$*	0.75 (0.52-1.09); $P = 0.13$	0.82 (0.57-1.19); $P = 0.30$
Isolated systolic hypertension	1,447	350	36	1.58 (1.38-1.80); $P < 0.001$*	1.24 (1.09-1.42); $P = 0.002$*	1.12 (96-1.31); $P = 0.14$	1.11 (0.94-1.30); $P = 0.22$
Systolic diastolic hypertension	908	176	29	1.23 (1.04-1.45); $P = 0.02$*	1.26 (1.07-1.50); $P = 0.007$*	1.41 (1.16-1.70); $P < 0.001$*	1.42 (1.16-1.74); $P < 0.001$*

Note: Model A: adjusted for age (years), sex (men or women), race (non-Hispanic White, non-Hispanic Black, Hispanic, and others), and center (7 categories). Model B: adjusted for model A plus diabetes mellitus (yes or no), smoking status (never or past or current), cardiovascular disease (yes or no), BMI (kg/m^2), antihypertensive medications, and low density lipoprotein cholesterol (mg/dL). Model C: adjusted for model B plus eGFR (mL/min/1.73 m^2) and 24-hour urine protein (gm).
*$P < 0.05$.

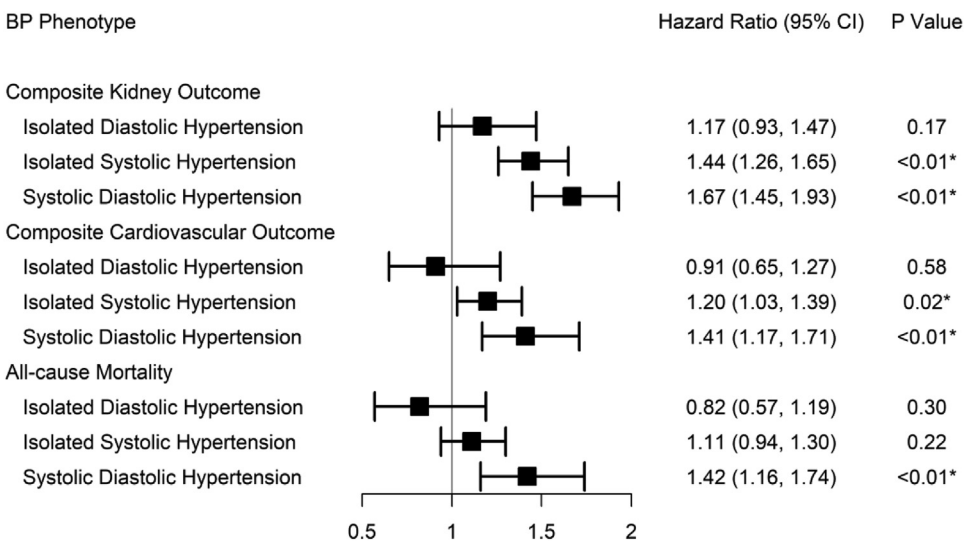

Figure 2. Association between BP phenotypes and clinical outcomes. Association between blood pressure (BP) phenotypes, and clinical outcomes, such as composite kidney outcome, composite cardiovascular outcome, and all-cause mortality. Reference group is participants with normotension. *$P < 0.05$.

older participants. Of importance, in our cohort, there was no association between presence of isolated diastolic hypertension and obesity, in contrast to some previous population-based studies.[23] Patients with isolated diastolic hypertension were less likely to have diabetes mellitus and prevalent atherosclerotic cardiovascular disease as compared with other BP phenotypes, in distinction to other epidemiologic observations.[23] The reasons for these discordant findings are unclear.

There is a lack of clarity on the clinical implication of isolated diastolic hypertension, particularly in the context of CKD; the 2021 KDIGO guidelines on management of BP in CKD only recommend a target SBP of <120 mm Hg, with no recommendation for a target DBP.[24] A previous retrospective study examining the optimal BP in more than 600,000 US veterans with CKD concluded that the optimal BP in patients with CKD is between 130-159/70-89 mm Hg.[25] A more recent cross-sectional study examining the association between isolated diastolic hypertension and target organ damage in 2,459 Chinese patients with CKD using ambulatory BP monitoring concluded that among patients younger than 60 years of age, isolated diastolic hypertension was associated with lower eGFR and higher albumin creatinine ratio, whereas in patients older than 60 years, isolated diastolic hypertension was not associated with any adverse kidney or cardiovascular parameters.[16] Our data shows that irrespective of age, having diastolic BP of >80 mm Hg with controlled systolic BP does not pose a greater risk of adverse kidney and cardiovascular outcomes in patients with CKD.

There could be several reasons behind these differing conclusions. First, as has been previously noted, isolated diastolic hypertension constitutes a risk factor for adverse cardiovascular outcomes in Asian but not in American and European populations.[5] Only 4% participants in the CRIC cohort were of non-White, non-Black, non-Hispanic ethnicity whereas 100% of the participants in the study by Hao et al[16] were of Chinese ethnicity. The mechanisms behind variable association between isolated diastolic hypertension and adverse outcomes in different ethnicities remain to be elucidated. Second, in the CRIC cohort, BP is measured in the office using sphygmomanometer by trained observers while in the study by Hao et al, mean 24-hour ambulatory BP monitoring performed with automated measurements was used. It has been shown previously that automated BP measurements may underestimate diastolic BP by as much as 3 mm Hg,[26] leading to misclassification of some patients with isolated diastolic hypertension as normotensives. There is also known to be a steeper relationship between adverse cardiovascular events and 24-hour mean BP than between adverse cardiovascular events and clinic BP,[27] which could have underestimated any possible effect in our study.

A recent large insurer database consisting of general outpatient population found an independent influence of diastolic hypertension on the risk of adverse cardiovascular events irrespective of the definition of hypertension as ≥ 140/90 or ≥ 130/80 mm Hg,[12] However, in this analysis, BP was obtained retrospectively from a clinical database in a general population and extrapolation of these findings to a CKD population is limited by the differing clinical characteristics of the 2 populations and by the differing methodologies and clinical rigor employed in measuring BP. Our findings were consistent with those from the NHANES and ARIC cohorts, which found no association between isolated diastolic hypertension as defined by 2017 ACC/AHA guidelines and cardiovascular risk in more than 17,000 US adults. This analysis also

employed a mean of 3 or 2 BP readings obtained after 5 minutes of rest in a sitting position using standardized protocols[2] similar to our analysis.

Previous studies indicate that age may be an important modifier of the relationship between the presence of isolated diastolic hypertension and adverse kidney and cardiovascular outcomes. Isolated diastolic hypertension was found to be a risk factor for development of CKD in a young Korean cohort comprising of 3,030,884 participants aged 20-39 years who were not on antihypertensives at baseline. The risk of developing CKD was found to be similar in isolated diastolic hypertension and isolated systolic hypertension groups.[14] Our cohort was significantly older than the Korean cohort (the mean age of Korean participants who developed CKD was 35 ± 3.82 years and of those who did not develop CKD was 31.8 ± 4.8 years), which may explain the discordant results. The IDACO study employing 24-hour ambulatory BP monitoring found that isolated diastolic hypertension defined by 2017 ACC/AHA criteria is not a risk factor for cardiovascular disease in adults aged 50 years or older but is a risk factor among younger adults,[10] consistent with our findings. The physiologic reasons for the influence of age on the relationship between isolated diastolic hypertension and adverse CV outcomes are unclear; however, possible reasons may include the fact that the prevalence of isolated diastolic hypertension decreases with advancing age because of decreasing compliance of large blood vessels possibly leading to false positive isolated diastolic hypertension ascertainments in older populations.[10]

This study has several strengths. First, it is a large cohort of well characterized participants with CKD that has been closely followed up over a long period of time. Blood pressure measurement is standardized and performed by trained observers, and all outcomes are rigorously ascertained, increasing confidence in the findings. However, several limitations of the study are to be noted: the study included a low number of participants of Asian ethnicity, limiting its generalizability. Also, the mean age of participants was close to 60 years and the findings may not apply to a younger population. Analyses are based on BP measurements at baseline visits only, and it is possible that changes in blood pressure over the follow-up period may lead to cross-over of participants between the different blood pressure categories. It is also impossible to rule out confounding effect of subsequent changes in antihypertensive medications or BP control on the target outcomes. Though this is the largest study examining the effect of isolated diastolic hypertension on adverse kidney and cardiovascular outcomes in CKD, the small sample size of the isolated diastolic hypertension cohort may be inadequate to detect modest associations with the target outcomes. Because this is an observational study, the possibility of unknown residual confounders cannot be discounted.

In summary, in this analysis of CRIC study participants with CKD, isolated diastolic hypertension was present in 6.2% of participants. The presence of isolated diastolic hypertension at baseline was not associated with a higher risk of major adverse kidney and cardiovascular events or all-cause mortality in this population. However, randomized clinical trials are needed to define target diastolic BP in the population with CKD.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Association Between Isolated Diastolic Hypertension and Composite Kidney Outcome by Age, Presence or Absence of Diabetes Mellitus and Severity of Proteinuria

Table S2. Association Between Isolated Diastolic Hypertension and Composite Kidney Outcome in Patients on Antihypertensive Medications

Table S3. Association Between Isolated Diastolic Hypertension and Heart Failure, Stroke, Myocardial Infarction, and Peripheral Arterial Disease

Table S4. Association Between Isolated Diastolic Hypertension and Composite Cardiovascular Outcome in Patients on Antihypertensive Medication

Table S5. Association Between Isolated Diastolic Hypertension and All-Cause Mortality in Patients on Antihypertensive Medication

Table S6. Association Between Isolated Diastolic Hypertension and Composite Kidney Outcome Using Revised Definitions for Blood Pressure (BP) Phenotypes

Table S7. Association Between Isolated Diastolic Hypertension and Composite Cardiovascular Outcome Using Revised Definitions for Blood Pressure (BP) Phenotypes

Table S8. Association Between Isolated Diastolic Hypertension and All-Cause Mortality Using Revised Definitions for Blood Pressure (BP) Phenotypes

ARTICLE INFORMATION

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Is isolated diastolic hypertension associated with an increased risk of adverse kidney and cardiovascular events in patients with CKD?

Kidney Medicine

Prospective observational cohort
Chronic Renal Insufficiency Cohort (CRIC) Study

N = 5,621 adults with CKD
eGFR 20 to 70 ml/min/1.73 m^2

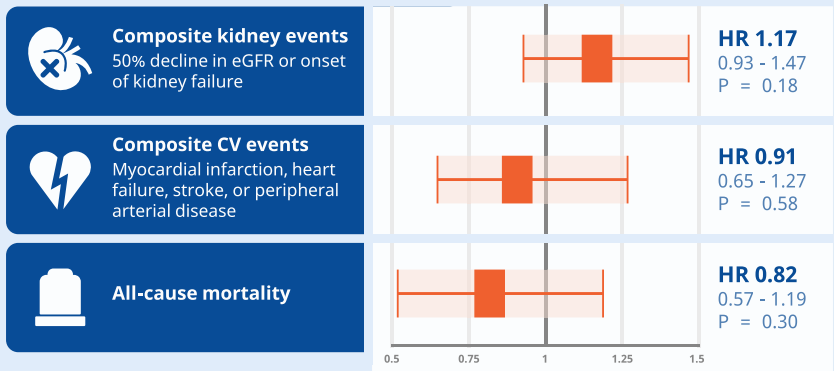
Mean age
59.6 ± 10.7 years

347 (6.2%) with isolated diastolic hypertension
DBP > 80 mmHg

Normotensive reference group

Associations between isolated diastolic hypertension and outcomes

Model adjusted for demographic, health behavior, and clinical covariates
Hazard ratio, 95% CI



Conclusion: Isolated diastolic hypertension is not associated with an increased risk of adverse kidney and cardiovascular events in individuals with CKD.

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