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Relation of Diastolic Blood Pressure and Coronary Artery Calcium to Coronary Events and Outcomes (From the Multi-Ethnic Study of Atherosclerosis)

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Abstract

Diastolic blood pressure has a J-curve relationship with coronary heart disease and death. Because this association is thought to reflect reduced coronary perfusion at low diastolic blood pressure, we hypothesized that the J-curve would be most pronounced among persons with coronary artery calcium. Among 6,811 participants from the Multi-Ethnic Study of Atherosclerosis, we used Cox models to examine if diastolic blood pressure category is associated with coronary heart disease events, stroke, and mortality. Analyses were conducted in the sample overall and after stratification by coronary artery calcium score. In multivariable-adjusted analyses, compared with

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Disclosures

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diastolic blood pressure of 80 to 89 mmHg (reference), persons with diastolic blood pressure <60 mmHg had increased risk of coronary heart disease events (hazard ratio 1.69 [95% confidence interval 1.02–2.79]) and all-cause mortality (hazard ratio 1.48 [95% confidence interval 1.10–2.00]), but not stroke. After stratification, associations of diastolic blood pressure <60 mmHg with events were present only among participants with coronary artery calcium >0. Diastolic blood pressure <60 mmHg was not associated with events when coronary artery calcium was zero. However, the association between diastolic blood pressure and events did not demonstrate statistical interaction when stratified by presence or absence of coronary calcium. We also found no interaction in the association between low diastolic blood pressure and events based on race. In conclusion, diastolic blood pressure <60 mmHg was associated with increased risk of coronary heart disease events and all-cause mortality in the sample overall, but this association appeared strongest among individuals with subclinical atherosclerosis.

Keywords

blood pressure; long term adverse effects; risk; coronary disease; mortality

Introduction

Coronary blood flow is unique in that perfusion occurs mainly during diastole.[1] Therefore, very low diastolic blood pressure (DBP) levels are thought to reduce coronary perfusion and may cause ischemia. Observational studies have repeatedly demonstrated that low DBP is associated with an increase in cardiac events, the so-called J-curve.[2–6] Recent data from the CLARIFY (Prospective observational longitudinal registry of patients with stable coronary artery disease) cohort suggest that this association is particularly strong among individuals with known coronary artery disease (CAD).[3] Presumably coronary perfusion distal to vessels with stenosis is impaired further by low DBP. While the association between low DBP and cardiac events is well established among adults with known clinical CAD,[6] little is known about the far larger demographic of persons with subclinical CAD (i.e., atherosclerotic coronary disease without prior clinical diagnosis). Coronary artery calcium (CAC) is a highly specific marker for atherosclerosis and is a reliable method to evaluate cardiac risk.[7–13] The aim of this study was to confirm the association between low DBP and coronary heart disease events (CHD) in a rigorous modern epidemiologic cohort, the Multi-Ethnic Study of Atherosclerosis (MESA), and to test whether this association differs among participants with a CAC score of 0 versus those with CAC > 0.

Methods

MESA is a prospective, diverse, contemporary, community-based cohort.[14,15] Briefly, 6814 participants 45 to 85 years of age without known clinical cardiovascular disease were recruited between 2000 and 2002 from six US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). Participants drew from four different racial groups (White, Chinese-American, African-American, and Hispanic). The MESA cohort was specifically designed to have overlapping racial groups among field centers to minimize confounding of race by site.[16] For the purpose

of this analysis we excluded participants who had missing variables of interest at baseline (n=3). All participants gave informed consent. The Institutional Review Board approved the study at all MESA sites.

Participants' details were obtained at examination 1, including demographics, medical history, medications, and tobacco use. Weight was measured in kilograms and height in meters. The body mass index was calculated as weight in kilograms divided by height in meters squared. Participants were separated into current smokers, former smokers or never smokers based on self-report. Seated systolic blood pressure (SBP) and DBP were recorded at 1 minute intervals after a minimum of 5 minutes rest and calculated as the mean of the last two of three seated measurements using a Dinamap Pro-100 automated oscillometric sphygmomanometer.[15,17] Diabetes was defined by the reported use of insulin or oral hypoglycemic agents, or a fasting glucose concentration of ≥126 mg/dL. Total and high-density lipoprotein cholesterol, and triglycerides were measured after a 12 hour fast. The Friedewald equation was used to calculate the low-density lipoprotein cholesterol.

CAC was measured in all participants at examination 1.[14] Each of the six MESA centers evaluated the amount of CAC using either a cardiac-gated electron-beam CT scanner (Imatron C-150XL, GE Imatron, San Francisco, CA) or a sixty four-slice multi-detector CT system following standard protocols developed by the MESA CT Committee. Each participant was scanned two times. The average Agatston score was used in analyses. All the CT scans were read by a radiologist or cardiologist at the Harbor-UCLA Research and Education Institute (Torrance, CA) to quantify CAC. Intra-observer ($\kappa = 0.93$) and inter-observer ($\kappa = 0.90$) agreements were excellent.

The major clinical outcomes included *a-priori* in this analysis were CHD, stroke and mortality during a follow-up of 12 years up to December 2013.[16] At 9 to 12 month intervals, participants or a family member were contacted to inquire about outpatient visits, hospital admissions, and deaths. Self-reported diagnoses were verified using medical records of outpatient visits and hospitalizations. For deaths, interviews with the next of kin and death certificates were used to verify potential events. Two physicians from the MESA mortality and morbidity review committee independently adjudicated all events.

CHD events were defined by a definite or probable myocardial infarction, death from CHD, likely angina resulting in coronary artery revascularization, or resuscitated cardiac arrest. A diagnosis of myocardial infarction was based on symptoms, electrocardiogram, and cardiac biomarker levels. A death was considered to be due to CHD if the death occurred within 28 days of a myocardial infarction, the individual had chest pain within 72 hours of death or the participant had known CHD and no other non-cardiac cause of death was found.

A stroke was identified using *International Classification of Diseases* procedure or diagnoses codes for eligible conditions. For fatal events *International Classification of Diseases*, 10th Revision codes of all deaths were reviewed by study staff. A stroke was considered to be present if there was a focal neurologic deficit that lasted 24 hours or until death, or if < 24 hours, there was a brain CT or MRI that confirmed a lesion without a nonvascular cause. We

included stroke as a negative-control outcome, as low DBP should not lower cerebral perfusion (which occurs throughout the entire cardiac cycle).

We divided DBP into 6 categories: < 60, 60 to 69, 70 to 79, 80 to 89 (reference), 90 to 99 and > 100 mmHg.[2] Baseline characteristics were compared between the categories using analysis of variance or Kruskal Wallis test for continuous variables, or chi-squared test for categorical variables. In supplementary cross-sectional analysis we compared DBP categories with baseline CAC. To model the prospective association between DBP categories and clinical outcomes, we constructed Cox proportional hazard models. We also modeled DBP as a continuous variable and graphed the hazard ratio (HR) using restricted cubic splines with knots at 60, 70, 80, and 90 mmHg. Multivariable models were adjusted for age (years), race (white, Chinese-American, African-American, Hispanic), MESA site, body mass index (kg/m^2), cigarette smoking (current, former, or never), SBP (mmHg), anti-hypertensive medication use (yes/no), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), lipid lowering medication use (yes/no), and diabetes mellitus (yes/no). We tested for multiplicative interaction in the association between low DBP categories and events based on race and baseline CAC level (0 vs. >0).

We repeated the analyses after stratifying baseline SBP into three categories: < 120, 120 to 139 and ≥140 mmHg, with removal of SBP as an adjustment term. To evaluate if the associations between DBP and outcomes are related to baseline CAC, we also repeated the analyses after stratification by examination 1 CAC (Agatston score = 0 or > 0) and tested for statistical interaction. In supplementary analysis, we also repeated the analyses after stratification by CAC ≤ 100 or > 100. We considered a 2-sided $p < 0.05$ as statistically significant.

Results

Participants with lower DBP were more likely to be older, female, White, have lower BMI, better lipid profiles and lower CAC levels (Table 1). They were less likely to be African-American and current smokers. Lower DBP was associated with lower SBP and less frequent use of antihypertensive medications.

During a median follow-up of 12 years, there were 356 CHD events, 236 strokes and 974 deaths among the 6,811 participants included. Compared with participants with baseline DBP 80 to 89 mmHg (Table 2), DBP < 60 mmHg was associated with increased hazard ratio (HR) of CHD events and mortality, but not with stroke. Using linear splines to model DBP continuously, there appeared to be an inverse relationship between DBP and CHD events, particularly when DBP was <60 mmHg (Figure 1A). A similar inverse relationship was observed for mortality but was less evident for stroke (Figure 1B and 1C). There was no interaction by race on the association between low DBP and excess CHD or death in our MESA sample.

When our primary sample was stratified by SBP, there was a statistically non-significant trend towards increased risk of CHD events among participants who had both DBP < 60

mmHg and SBP > 120 mmHg (Table 3). In addition, compared with individuals with DBP 80 to 89 mmHg, mortality was statistically significantly increased when DBP < 60 mmHg, but only among those who also had SBP of 120 to 139 mmHg.

After stratifying the study sample by CAC, relative hazards for both CHD events and all-cause mortality were higher among participants with DBP < 60 mmHg in the CAC > 0 group in multivariable-adjusted analyses (Table 4). In comparison, DBP < 60 mmHg was not associated with a statistically significant increased risk of CHD events or mortality in the CAC = 0 group. As expected, a low DBP was not associated with stroke in either CAC group. However, no statistical interaction was demonstrated between DBP and risk of CHD events or mortality according to CAC level; either in age, sex and race/ethnicity adjusted analyses or in multivariable-adjusted analyses. In supplementary analyses, there was no association between baseline DBP categories and either baseline CAC at exam 1 or incident CAC over follow-up at subsequent MESA exams (Supplementary Table 1). When CAC was stratified as ≤ 100 or > 100, similar trends for low DBP and excess CHD events among persons with calcified atherosclerosis were noted, although these results did not reach statistical significance (Supplementary Table 2).

Discussion

The current study builds on previous analyses reporting the J-curve relationship between low DBP and increased risk of CHD and mortality.[2,4] First, we demonstrate a CHD and mortality J-curve in the ethnically diverse and contemporary MESA cohort, noting in particular that individuals with a DBP < 60 mmHg had increased risk of CHD events. This corroborates the results of previous studies comprising less diverse cohorts enrolled many decades ago.[2–4,6] Second, we demonstrate, to our knowledge for the first time, that the association between low DBP and events appears to be stronger among individuals with evidence of baseline subclinical atherosclerosis (based on the presence of CAC on cardiac CT imaging) compared to those without (CAC=0). Thus, the J-curve between low DBP appears to not only be important for persons with known clinical CAD, but also may be relevant to the much larger cohort of adults without clinical disease who have subclinical atherosclerosis. A number of studies have demonstrated that individuals with higher CAC have a higher burden of hemodynamically significant CAD.[18–20] However, no statistical interaction was found between CAC with DBP and CHD or mortality likely due to the limited number of events reducing statistical power. In addition, although data support the association between CAC and hemodynamically significant CAD, this association is admittedly not perfect. Thus, a lack of interaction may also be due to conservative confounding due to the lack of perfect correlation between the presence of CAC and presence of hemodynamically obstructive CAD. Third, we demonstrated that the J-curve does not appear to be dependent on race, given there was no multiplicative interaction in the association between low DBP and events by race.

An increase in risk of adverse cardiovascular events with low DBP has been reported extensively in the past.[2–4,6,21–23] In a systematic review of thirteen studies, the J-curve phenomenon was demonstrated with increased CHD events when treated DBP < 85 mmHg.[24] More recently, McEvoy et al. demonstrated that low DBP was associated with

increased odds of elevated high-sensitivity troponin T, and on follow-up increased CHD events and all-cause mortality but not stroke.[2] Our results support these observations in a more recent and diverse cohort, while also demonstrating no association between DBP and stroke (Figure 1). The lack of an association of stroke is of importance, as it suggests that the association between low DBP and CHD is not confounded by vascular stiffness (which would increase stroke risk), but due to reduced coronary perfusion pressure.[25] In our study the risk of CHD and mortality in higher DBP ranges was more flat likely due to adjustment for SBP. High DBP would be expected to correlate with high SBP and, thus, by adjusting for SBP in our analysis, the effect of high DBP on outcomes would be attenuated.

In keeping with the proposed mechanism of reduced coronary perfusion, the risk of low DBP is most pronounced in persons with underlying CAD. Individuals with known CAD and hypertension enrolled in the international verapamil-trandolapril study (INVEST) study and CLARIFY registries had increased risk of cardiovascular events and mortality when DBP < 60 mmHg.[3,22,23] In the current study, CAC > 0 among persons without known clinical CAD identified individuals at higher relative risk of CHD events and all-cause mortality when DBP < 60 mmHg. There was no association between low DBP and events among those without calcified coronary atherosclerosis; however, due to the moderate sample size we cannot rule out that these individuals may also be at risk (albeit of lower magnitude) from low DBP.

Our results have clinical implications. In the modern post-SPRINT (Systolic Blood Pressure Intervention Trial) era,[26] where lower BP targets are increasingly being recommended,[27] our data suggest that clinicians may need to exercise caution when choosing an intensive BP target strategy, particularly among adults who have elevated pulse pressure (with, as a consequence, higher risk of excessive DBP lowering to achieve a given SBP target). Our results do not contradict the presumed benefits of SBP control,[26] as long as DBP is not excessively reduced, particularly among persons with known CAD including elevated CAC.[28] Whether the assessment of CAC specifically for the indication of testing whether a low DBP level may cause harm in a given individual is clinically worthwhile needs future study.

The strengths of our study include a large community-based sample, rigorous ascertainment of covariates, long-term follow-up for adverse events, consistent event adjudication, and a diverse cohort with four major race/ethnicities represented. However, our study also has several limitations. The limited number of events reduces the statistical power of our analyses among certain subgroups. For example, this limited power may explain the lack of a significant association between DBP < 60 mmHg and events when the sample was stratified by SBP and in the CAC = 0 group. In addition, despite our rigorous statistical analyses, we cannot completely rule out the possibility of chance explaining the association seen with DBP < 60 mmHg and CHD events and mortality among individuals with CAC > 0. Although CAC is a sensitive technique to identify calcified plaque, approximately 4% of asymptomatic individuals have entirely non-calcified plaques[13] and would not be identified using CAC. These individuals with non-calcified plaques could still be at increased risk of CHD and death due to excessive lowering of DBP. Further, although individuals with higher CAC are more likely to have a higher burden of obstructive CAD,[18–20] the amount of CAC

present in any one individual cannot be used to accurately quantify their burden of obstructive CAD for clinical purposes.[29,30] Our study supports the concept that low DBP may be associated with coronary events among persons with CAC, but as an observational study, we cannot prove that our association is causal.

In our prospective community-based cohort, we found that DBP < 60 mmHg was associated with increased risk of CHD events and all-cause mortality. This association appears strongest among individuals with CAC > 0. Thus, clinicians may need to exercise particular caution in treating individuals with low DBP (and wide pulse pressure) to intensive SBP targets, particularly among persons known to have subclinical coronary atherosclerosis by CAC imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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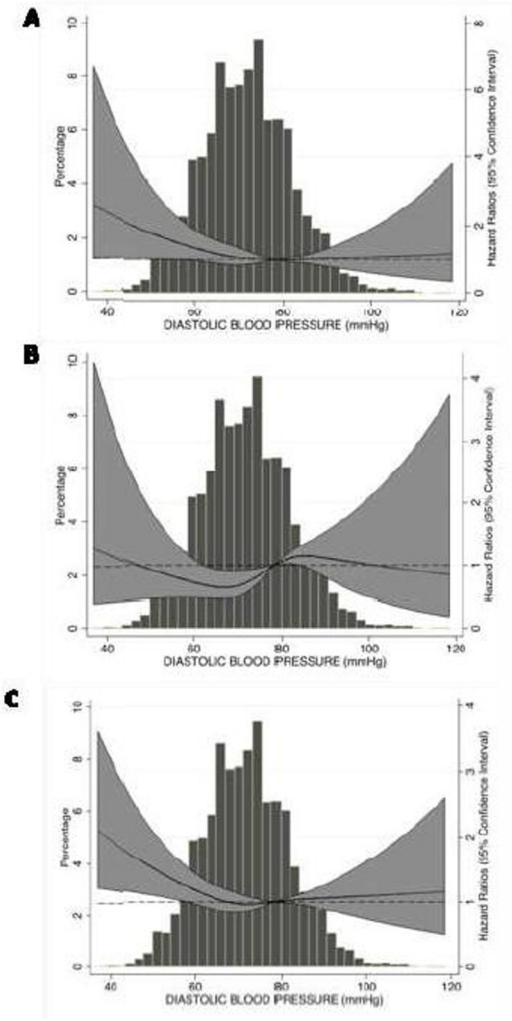

Figure 1.

Multivariable-adjusted hazard ratios for the continuous association of baseline diastolic blood pressure with (A) incident coronary heart disease events, (B) incident stroke events, and (C) all-cause mortality during a median of 12 years follow-up. Percentage are the percent of study participants at each point shown in the background histogram. The shaded area around the regression line represents the 95% confidence interval. Model adjusted for age (years), sex, race/ethnicity, site, body mass index (kg), cigarette smoking, systolic blood pressure (mmHg), anti-hypertensive medication use, low-density lipoprotein cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl), lipid lowering medication use, and diabetes mellitus status.

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Table 1

Baseline characteristics of the study population by diastolic blood pressure categories

Variable	Overall (N=6811)	Diastolic blood pressure (mmHg)					p-value
		<60 (N=780)	60–69 (N=2126)	70–79 (N=2461)	80–89 (N=1132)	≥90 (N=312)	
Age (years)	62 (10)	63 (11)	63 (11)	62 (10)	62 (10)	61 (10)	0.001
Men	3211 (47%)	148 (19%)	780 (37%)	1374 (56%)	704 (62%)	205 (66%)	<0.001
White	2620 (38%)	402 (52%)	856 (40%)	940 (38%)	347 (31%)	75 (24%)	<0.001
Chinese-American	803 (12%)	89 (11%)	258 (12%)	282 (11%)	140 (12%)	34 (11%)	
Black	1892 (28%)	124 (16%)	499 (23%)	734 (30%)	394 (35%)	141 (45%)	
Hispanic	1496 (22%)	165 (21%)	513 (24%)	505 (21%)	251 (22%)	62 (20%)	
Cigarette smoker							0.02
Never	3416 (50%)	407 (52%)	1104 (52%)	1231 (50%)	526 (47%)	148 (48%)	
Former	2486 (37%)	272 (35%)	735 (35%)	914 (37%)	456 (40%)	109 (35%)	
Current	887 (13%)	98 (13%)	281 (13%)	306 (12%)	148 (13%)	54 (17%)	
Systolic blood pressure (mmHg)	127 (21)	107 (16)	118 (17)	129 (18)	142 (18)	160 (20)	<0.001
Body mass index (kg/m2)	28 (5)	28 (6)	28 (6)	28 (5)	29 (5)	29 (5)	<0.001
Antihypertensive medication use	2534 (37%)	239 (31%)	720 (34%)	897 (36%)	510 (45%)	168 (54%)	<0.001
Diabetes mellitus	858 (13%)	97 (12%)	273 (13%)	299 (12%)	151 (13%)	38 (12%)	0.89
Low density lipoprotein cholesterol (mg/dl)	117 (31)	114 (31)	116 (31)	118 (32)	119 (32)	120 (32)	0.002
High density lipoprotein cholesterol (mg/dl)	51 (15)	55 (15)	52 (16)	50 (14)	49 (14)	50 (15)	<0.001
Triglycerides (mg/dl)	132 (89)	125 (95)	128 (72)	131 (84)	141 (109)	141 (119)	0.0001
Lipid medication	1100 (16%)	128 (16%)	370 (17%)	384 (16%)	179 (16%)	39 (13%)	0.18
Coronary artery calcium	0 (0–87)	0 (0–62)	0 (0–78)	2 (0–90)	4 (0–107)	7 (0–124)	0.0001

Continuous variables presented as mean (standard deviation) or median (interquartile range). Categorical variables presented as count (percentage).

P-value calculated using ANOVA or Kruskal Wallis test for continuous variables; chi-square test for categorical variables

Table 2

Hazard ratios (95% confidence interval) for the association of diastolic blood pressure and incident coronary heart disease, stroke, and mortality events

Visit 1 Diastolic Blood Pressure (mmHg)	n/N	CHD Hazard ratio (95% CI)*	p-value	n/N	Stroke Hazard ratio (95% CI)*	p- value	n/N	Mortality Hazard ratio (95% CI)*	p- value
<60	38/779	**1.69 (1.02, 2.79)**	**0.04**	19/779	0.73 (0.39, 1.39)	0.34	127/779	**1.48 (1.10, 2.00)**	**0.01**
60–69	101/2123	1.23 (0.86, 1.78)	0.26	60/2123	0.71 (0.45, 1.10)	0.12	291/2123	1.11 (0.89, 1.39)	0.37
70–79	123/2460	1.07 (0.78, 1.47)	0.67	84/2460	0.84 (0.58, 1.21)	0.35	345/2460	1.10 (0.90, 1.35)	0.35
80–89	67/1132	1.00 (ref)	-	52/1132	1.00 (ref)	-	157/1132	1.00 (ref)	-
≥90	27/312	1.23 (0.77, 1.97)	0.39	21/312	1.17 (0.68, 2.01)	0.56	54/312	1.15 (0.83, 1.58)	0.41

Significant values are indicated in **bold**

*Adjusted for age (years), sex, race/ethnicity, site, body mass index (kg), cigarette smoking, systolic blood pressure (mmHg), anti-hypertensive medication use, low-density lipoprotein cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl), lipid lowering medication use, diabetes mellitus

CHD = coronary heart disease; CI = confidence interval.

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Table 3

Hazard ratios (95% confidence interval) for the association of diastolic blood pressure with incident coronary heart disease, stroke, and mortality, stratified by baseline systolic blood pressure

Visit 1 DBP (mmHg)	Visit 1 SBP (mmHg)	n/N	CHD Hazard ratios (95% CI)*	p- value	n/N	Stroke Hazard ratios (95% CI)*	p- value	n/N	Mortality Hazard ratios (95% CI)*	p- value
<60	<120	26/651	0.85 (0.24, 3.02)	0.80	12/651	0.31 (0.08, 1.24)	0.10	87/651	2.20 (0.68, 7.15)	0.19
60–69		49/1283	0.95 (0.29, 3.12)	0.93	22/1283	0.38 (0.11, 1.34)	0.13	126/1283	2.09 (0.66, 6.65)	0.21
70–79		17/915	0.52 (0.15, 1.80)	0.31	15/915	0.45 (0.13, 1.59)	0.21	66/915	1.93 (0.60, 6.18)	0.27
80–89		3/88	1.00 (ref)	–	3/88	1.00 (ref)	–	3/88	1.00 (ref)	–
≥90		–	–	–	–	–	–	–	–	–
<60	120–139	8/99	1.71 (0.71, 4.10)	0.23	4/99	0.68 (0.21, 2.23)	0.52	29/99	**1.95 (1.17, 3.24)**	**0.01**
60–69		31/580	0.99 (0.55, 1.79)	0.98	17/580	0.45 (0.21, 0.97)	0.04	101/580	1.16 (0.80. 1.69)	0.43
70–79		49/952	0.93 (0.57, 1.54)	0.79	32/952	0.81 (0.44, 1.50)	0.50	136/952	1.16 (0.83, 1.62)	0.39
80–89		25/486	1.00 (ref)	–	17/486	1.00 (ref)	–	51/486	1.00 (ref)	–
≥90		2/45	1.01 (0.23, 4.34)	0.99	0/45	–	–	3/45	0.84 (0.26, 2.73)	–
<60	≥140	4/29	1.79 (0.61, 5.25)	0.29	3/29	1.36 (0.40, 4.62)	0.63	11/29	1.46 (0.74, 2.87)	0.27
60–69		21/260	1.04 (0.58, 1.86)	0.89	21/260	1.05 (0.59, 1.90)	0.88	64/260	0.95 (0.67, 1.33)	0.75
70–79		57/593	1.35 (0.88, 2.08)	0.17	37/593	0.92 (0.56, 1.50)	0.73	143/593	1.08 (0.83, 1.41)	0.55
80–89		39/558	1.00 (ref)	–	32/558	1.00 (ref)	–	103/558	1.00 (ref)	–
≥90		25/267	1.67 (0.99, 2.80)	0.054	21/267	1.52 (0.86, 2.69)	0.15	51/267	1.19 (0.85, 1.69)	0.32

Significant values are indicated in **bold**

*Adjusted for age (years), sex, race/ethnicity, site, body mass index (kg), cigarette smoking, systolic blood pressure (mmHg), anti-hypertensive medication use, low-density lipoprotein cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl), lipid lowering medication use, diabetes mellitus

DBP = diastolic blood pressure; SBP = systolic blood pressure; CHD = coronary heart disease; CI = confidence interval.

Table 4

Hazard ratios (95% confidence interval) for the association of diastolic blood pressure and all coronary heart disease events stratified by baseline coronary artery calcium (0 versus >0)

Outcomes	Visit 1 DBP (mmHg)	n/N	CAC = 0 (95% CI)*	n/N	CAC > 0 (95% CI)*	Interaction p-value†
Coronary heart disease	< 60	6/441	1.37 (0.41, 4.60)	32/338	**1.77 (1.02, 3.07)**	0.91
	60–69	21/1114	1.42 (0.61, 3.30)	80/1009	1.19 (0.79, 1.78)	
	70–79	21/1195	0.98 (0.46, 2.08)	102/1265	1.07 (0.75, 1.51)	
	80–89	12/531	1.00 (ref)	55/601	1.00 (ref)	
	≥90	5/133	0.98 (0.32, 2.99)	22/179	1.31 (0.78, 2.20)	
Stroke	< 60	7/441	1.06 (0.36, 3.14)	12/338	0.63 (0.28, 1.40)	0.45
	60–69	14/1114	0.59 (0.26, 1.34)	46/1009	0.75 (0.44, 1.28)	
	70–79	24/1195	0.76 (0.40, 1.45)	60/1265	0.87 (0.55, 1.36)	
	80–89	19/531	1.00 (ref)	33/601	1.00 (ref)	
	≥90	8/133	0.91 (0.36, 2.25)	13/179	1.27 (0.64, 2.52)	
Mortality	< 60	33/441	1.36 (0.77, 2.40)	94/338	**1.55 (1.09, 2.21)**	0.32
	60–69	78/1114	1.02 (0.66, 1.56)	213/1009	1.17 (0.89, 1.53)	
	70–79	85/1195	0.89 (0.61, 1.29)	260/1265	1.19 (0.93, 1.51)	
	80–89	50/531	1.00 (ref)	107/601	1.00 (ref)	
	≥90	12/133	0.63 (0.33, 1.23)	42/179	1.42 (0.98, 2.07)	

Significant values are indicated in **bold**

*Adjusted for age (years), sex, race/ethnicity, site, body mass index (kg), cigarette smoking, systolic blood pressure (mmHg), anti-hypertensive medication use, low-density lipoprotein cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl), lipid lowering medication use, diabetes mellitus

†p-value represents interaction between DBP categories and CAC > 0

DBP = diastolic blood pressure; CAC = coronary artery calcium; CI = confidence interval.