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Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events

Implications for Blood Pressure Control

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ABSTRACT

BACKGROUND The optimal systolic blood pressure (SBP) treatment goal is in question, with SPRINT (Systolic Blood Pressure Intervention Trial) suggesting benefit for 120 mm Hg. However, achieving an SBP this low may reduce diastolic blood pressure (DBP) to levels that could compromise myocardial perfusion.

OBJECTIVES This study sought to examine the independent association of DBP with myocardial damage (using high-sensitivity cardiac troponin-T [hs-cTnT]) and with coronary heart disease (CHD), stroke, or death over 21 years.

METHODS The authors studied 11,565 adults from the ARIC (Atherosclerosis Risk In Communities) cohort, analyzing DBP and hs-cTnT associations as well as prospective associations between DBP and events.

RESULTS Mean baseline age was 57 years, 57% of patients were female, and 25% were black. Compared with persons who had DBP between 80 to 89 mm Hg at baseline (ARIC visit 2), the adjusted odds ratio of having hs-cTnT ≥14 ng/l at that visit was 2.2 and 1.5 in those with DBP <60 mm Hg and 60 to 69 mm Hg, respectively. Low DBP at baseline was also independently associated with progressive myocardial damage on the basis of estimated annual change in hs-cTnT over the 6 years between ARIC visits 2 and 4. In addition, compared with a DBP of 80 to 89 mm Hg, a DBP <60 mm Hg was associated with incident CHD and mortality, but not with stroke. The DBP and incident CHD association was strongest with baseline hs-cTnT ≥14 ng/l (p value for interaction <0.001). Associations of low DBP with prevalent hs-cTnT and incident CHD were most pronounced among patients with baseline SBP ≥120 mm Hg.

CONCLUSIONS Particularly among adults with an SBP ≥120 mm Hg, and thus elevated pulse pressure, low DBP was associated with subclinical myocardial damage and CHD events. When titrating treatment to SBP <140 mm Hg, it may be prudent to ensure that DBP levels do not fall below 70 mm Hg, and particularly not below 60 mm Hg. (J Am Coll Cardiol 2016;■:■-■) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CHD = coronary heart disease

DBP = diastolic blood pressure

LVH = left ventricular hypertrophy

SBP = systolic blood pressure

Diastolic blood pressure (DBP) was historically thought to be the main driver of adverse cardiac outcomes in adults with hypertension (1). Although initially overlooked, seminal work from Framingham and other observational cohorts subsequently demonstrated the importance of systolic blood pressure (SBP) (2,3), leading to a paradigm shift whereby SBP became the focus of modern risk assessment and treatment. However, to this day, uncertainty persists about the optimal SBP goal (4-7). For example, SPRINT (Systolic Blood Pressure Intervention Trial) (8) reported reductions in death from cardiovascular disease and heart failure (HF) among high-risk adults without diabetes treated to an SBP target of ≤120 mm Hg. In contrast, blood pressure (BP)-lowering therapy among intermediate-risk adults was not beneficial and showed a trend for harm among those with baseline SBP levels <130 mm Hg in the HOPE-3 (Heart Outcomes Prevention Evaluation) trial (7).

Achieving intensive SBP reductions will inevitably also lower DBP. For example, in a secondary analysis of elderly SPRINT participants, the authors reported that DBP in the intensive-therapy arm fell from a mean of 71.5 mm Hg at baseline to 62 mm Hg during active treatment (9). This is of potential concern due to the known J-curve for DBP and coronary artery disease (CAD) events (10-12). Particularly among persons with obstructive CAD or left ventricular hypertrophy (LVH), a drop in DBP has been shown to reduce coronary perfusion pressure (coronary blood flow occurs primarily in diastole), which can result in ischemia and myocardial damage (13).

High-sensitivity cardiac troponin assays can detect asymptomatic myocardial damage and have been strongly predictive of fatal and nonfatal coronary heart disease (CHD) events in numerous observational studies, including among primary prevention populations (14-17). As such, high-sensitivity cardiac troponin-T (hs-cTnT) may be of value in understanding whether a lower achieved BP, and particularly a low DBP level, is associated with myocardial damage.

Therefore, the aim of this analysis from the ARIC (Atherosclerosis Risk In Communities) cohort study was to determine whether low DBP was associated with either cross-sectional (measured with hs-cTnT at baseline) or progressive (measured with trajectories of temporal hs-cTnT change over follow-up) subclinical myocardial damage. We also evaluated whether low DBP increases the risk for future adverse outcomes, including CHD, stroke, and all-cause death, in the overall study sample as well as after stratification by baseline SBP and baseline hs-cTnT (given that levels ≥14 ng/l are associated with structural heart disease, such as LVH, and subclinical macro/microvascular coronary disease).

METHODS

The ARIC study is a prospective observational cohort of 15,792 adults sampled from 4 U.S. communities (Forsyth Country, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland). Study design details have been published (18). Institutional review boards at each site approved the study, and written informed consent was obtained from all participants. Of the 14,348 persons who attended ARIC visit 2 (1990 to 1992), we excluded those with known cardiovascular disease or HF at or prior to visit 2 (n = 1,651) and those missing other variables of interest (n = 1,132). Thus, 11,565 persons were included in our main analytic sample (Online Table 1). For supplemental analyses we generated a secondary subsample of 1,403 visit 2 participants who met SPRINT enrollment criteria (8) (Online Appendix).

MEASUREMENT OF EXPOSURE VARIABLES. Measurement of hs-cTnT occurred at 3 time points over a span of 21 years: visit 2 (1990 to 1992), visit 4 (1996 to 1998), and visit 5 (2011 to 2013). The measurement range of the assay is 3 to 100,000 ng/l. Values ≥14 ng/l represent the 90th percentile in the ARIC sample and the 99th percentile value for a "healthy" reference group ages 20 to 70 years (19). Additional details on hs-cTnT measurements at each visit are available in the Online Appendix.

Demographic and cardiovascular risk factors were assessed at visit 2, with measurements obtained using standardized protocols (18). Participants self-reported race, alcohol use, and smoking status. Body mass index (BMI) was calculated from measured weight and height. After 5 min of seated rest, we recorded BP as the mean of the last 2 of 3 measurements collected over 5-min intervals using a random zero sphygmomanometer. Hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or the use of antihypertensive medications. Antihypertensive drug use was assessed using a medication inventory. Diagnosed diabetes was defined as a self-reported physician diagnosis of diabetes or current use of diabetic medications. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride measurements were obtained after a 12-h fast. Low-density lipoprotein cholesterol was calculated using the Friedewald equation.

FOLLOW-UP FOR CLINICAL OUTCOMES OF INTEREST. Clinical endpoints included CHD, stroke, and

mortality. Of note, stroke was used as a "negative control" because we hypothesized that low DBP would not be adversely associated with this outcome as the physiological relationship between DBP and coronary perfusion should have no bearing on stroke risk. We also conducted a sensitivity analysis for incident HF (Online Appendix). Visit 2 was baseline for analysis of incident events.

The ascertainment of deaths and classification of CHD and stroke in ARIC have been described (20,21). Briefly, hospitalizations and deaths were reported annually by study participants or their proxy and also identified through death certificates from state vital statistics offices and surveillance of hospitals within each ARIC community. CHD events were adjudicated by an ARIC endpoints committee and defined as a definite or probable myocardial infarction, death from CHD, or cardiac procedure (20). Stroke signs, symptoms, neuroimaging (computed tomography or magnetic resonance), and other diagnostic reports were recorded if the list of discharge diagnoses included a cerebrovascular disease code (International Classification of Diseases-9th Revision, codes 430 to 437), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a computed tomography or magnetic resonance imaging report. Each eligible case was classified according to criteria adapted from the National Survey of Stroke (22).

STATISTICAL ANALYSES. Baseline characteristics were compared across 6 categories of DBP (<60, 60 to 69, 70 to 79, 80 to 89, 90 to 99, and ≥100 mm Hg) using analysis of variance for continuous variables and the chi-square test for proportions.

To model the cross-sectional association between DBP categories and baseline hs-cTnT, we defined the outcome of "elevated hs-cTnT" (≥14 ng/l, yes/no) (19). We constructed logistic models with robust SE adjusted for: age (years), race-field center (white persons from Minnesota, white persons from Washington County, white persons from Forsyth County, black persons from Forsyth County, and black persons from Mississippi), sex, BMI in kg/m^2, smoking (current, former, or never), alcohol intake (current, former, or never), SBP (in mm Hg), hypertension medication use (yes/no), diagnosed diabetes (yes/no), low-density lipoprotein cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl), current use of cholesterol-lowering medication (yes/no), and estimated glomerular filtration rate in ml/min/1.73 m^2. We repeated these logistic models after stratification by baseline systolic BP category (<120, 120 to 139, and ≥140 mm Hg), with SBP removed from the adjustment terms. We also modeled DBP as a continuous variable and graphed the adjusted odds ratio (OR) using restricted cubic splines with knots at 57, 68, 75, and 90 mm Hg (the 5th, 35th, 65th, and 95th percentiles, respectively), using 85 mm Hg as the reference value, truncated at the 1st and 99th percentiles (23).

To model the longitudinal association between baseline DBP categories and temporal change in hs-cTnT, we constructed linear models fitted with generalized estimating equations. We used unstructured correlation matrices and robust variance estimation. Persons with hs-cTnT <3 ng/l had values imputed at 1.5 ng/l. Time since baseline was modeled using a linear spline with a knot at 6 years (mean duration between visits 2 and 4). Coefficients of interest were the interactions between DBP categories and time spline terms, which address differences in annual hs-cTnT change according to DBP after adjusting for variables listed previously in the model. We used inverse probability of attrition weighting to account for informative missingness due to differential withdrawal across baseline DBP categories (i.e., different proportions of subjects who died, were lost, or had missing hs-cTnT data during follow-up) (24).

To model the prospective association between baseline DBP categories and clinical outcomes, we constructed Cox models, adjusted for the variables in the model. We verified the proportionality of the hazards visually and with Schoenfeld residuals. We also modeled DBP as a continuous variable and graphed the adjusted hazard ratio (HR) using restricted cubic splines (23). We repeated each of the models described earlier in the SPRINT-eligible subsample. We also conducted a sensitivity analysis in the primary study sample with DBP as a time-varying exposure using updated DBP values at visits 2, 3, and 4. This time-varying outcomes analysis also included adjustment for SBP, hypertension medication use, and estimated glomerular filtration rate as time-varying covariables. Furthermore, in a supplemental analysis, we repeated the categorical Cox models in the primary sample after stratification by the following variables of interest: 1) baseline antihypertensive treatment status (with hypertension medication use [yes/no] removed from the adjustment terms); 2) baseline hs-cTnT category (<14 or ≥14 ng/l); 3) baseline presence of LVH by electrocardiogram (ECG); and 4) baseline SBP category (<120, 120 to 139, and ≥140 mm Hg, with SBP removed from the adjustment terms). In these stratified analyses, we compressed the DBP categories to preserve power (<60, 60 to 79, 80 to 89, and >90 mm Hg).

Finally, we conducted a number of further sensitivity analyses exploring the continuous relationships

of: 1) DBP with elevated hs-cTnT and incident CHD with and without additional adjustment for SBP; 2) SBP with elevated hs-cTnT and incident CHD with and without additional adjustment for DBP; and 3) pulse pressure (SBP − DBP) with elevated hs-cTnT and incident CHD after adjustment for confounders. All models were tested for interaction by age, sex, and race. The level of significance was defined as $p < 0.05$ (2-sided).

RESULTS

Per characteristics of the sample by baseline DBP, individuals with lower DBP tended to be older, female, white, have lower BMI, and have healthier lipid profiles (**Table 1**). As expected, persons with higher DBP tended to have higher SBP and more frequent use of antihypertensive medications. With the exception of sex and BMI, similar differences according to DBP category were noted in the SPRINT-eligible subsample (Online Table 2). Interaction terms for age, sex, and race were nonsignificant in all models.

Compared with persons with baseline DBP between 80 to 89 mm Hg, the adjusted OR of having hs-cTnT ≥14 ng/l at baseline was 2.2 (95% confidence interval [CI]: 1.2 to 4.1) and 1.5 (95% CI: 1.0 to 2.3) in those with DBP <60 and 60 to 69 mm Hg, respectively (**Table 2**). When DBP was modeled continuously using linear splines, there was a linear inverse relationship between DBP and hs-cTnT when DBP was <65 mm Hg (**Figure 1**). There appeared to be similar associations among the SPRINT-eligible subsample (e.g., OR: 1.7 for DBP <60 mm Hg; OR: 1.2 for DBP 60 to 69 mm Hg, relative to 80 to 89 mm Hg); however, these findings were not statistically significant (Online Table 3).

Low DBP at baseline also was independently associated with progressive myocardial damage, as assessed by estimated annual change in hs-cTnT over the 6 years between visits 2 and 4. Compared with having a DBP of 80 to 89 mm Hg, the estimated annual change in hs-cTnT was +1.5 ng/l (95% CI: 0.5 to 2.4 ng/l) per year higher in the DBP <60 mm Hg group and +1.0 ng/l (95% CI: 0.3 to 1.6 ng/l) per year higher in the DBP 60 to 69 mm Hg group.

TABLE 1 Patient Characteristics*

	Overall	DBP <60 mm Hg	DBP 60-69 mm Hg	DBP 70-79 mm Hg	DBP 80-89 mm Hg	DBP 90-99 mm Hg	DBP ≥100 mm Hg	p Value
n	11,565 (100)	1,087 (9.4)	3,728 (32.2)	4,249 (36.7)	1,902 (16.4)	487 (4.2)	112 (1.0)	
Age, yrs	56.7 ± 5.7	57.7 ± 6.0	56.9 ± 5.8	56.5 ± 5.6	56.5 ± 5.6	56.3 ± 5.7	55.1 ± 5.4	<0.001
Female	57.3	72.5	63.7	54.5	47.8	41.1	39.3	<0.001
Black	24.5	13.2	20	24.5	32.9	41.3	64.3	<0.001
SBP, mm Hg	121.0 ± 18.5	103.4 ± 14.5	112.1 ± 13.2	122.4 ± 13.6	135.4 ± 15.0	149.5 ± 17.2	167.7 ± 22.7	<0.001
Antihypertensive medication use	28	18.2	22.4	28.2	37.9	47.6	53.6	<0.001
Left ventricular hypertrophy by ECG	2.2	1.1	1.2	2.0	3.2	7.0	17.0	<0.001
Smoking status								<0.001
Never smoking	41.2	34	41.3	42	44.3	38.2	42.9	
Current smoker	21.8	32.4	24.1	18.9	17.8	20.7	29.5	
Former smoker	36.9	33.6	34.6	39.2	37.9	41.1	27.7	
Drinking status								0.51
Never drinking	22.7	24.7	23	23.1	21	20.5	21.4	
Current drinker	57.6	55.7	57.2	57.7	59.1	57.5	58.9	
Former drinker	19.6	19.6	19.7	19.2	19.9	22	19.6	
Diagnosed diabetes	7.8	8.8	8.3	7.3	7.7	5.7	5.4	0.163
BMI, kg/m^2	27.8 ± 5.3	25.7 ± 4.8	27.1 ± 5.0	28.2 ± 5.2	28.9 ± 5.4	29.7 ± 6.2	30.6 ± 7.4	<0.001
LDL-C, mg/dl	133.1 ± 36.6	131.3 ± 37.0	131.4 ± 36.0	133.5 ± 36.6	135.3 ± 37.2	136.7 ± 38.3	141.7 ± 36.2	<0.001
HDL-C, mg/dl	50.6 ± 16.8	52.3 ± 16.8	51.6 ± 16.9	49.7 ± 16.4	50.0 ± 17.5	49.0 ± 15.8	49.2 ± 14.4	<0.001
Triglycerides, mg/dl	127.2 ± 64.5	120.1 ± 60.9	123.2 ± 61.9	129.6 ± 65.5	132.2 ± 67.2	133.8 ± 69.6	126.6 ± 67.0	<0.001
Lipid medication	5.2	4.8	5.4	5.8	4.5	2.3	0.9	0.002
eGFR, ml/min/1.73 m^2	96.8 ± 15.2	97.2 ± 13.5	96.7 ± 14.8	96.7 ± 15.2	97.2 ± 16.0	96.0 ± 17.5	95.2 ± 20.4	0.469

Values are n (%), mean ± SD, or %. *Categories of diastolic blood pressure (DBP) at baseline (ARIC visit 2, 1990–1992).

BMI = body mass index; ECG = electrocardiograph; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

TABLE 2 Elevated hs-cTnT and Expected Annual Change in hs-cTnT

	Cross-Sectional Analysis Elevated hs-cTNT (≥14 ng/l)			Longitudinal Analysis Adjusted* Beta-Coefficients† Estimated Additional Annual Change in hs-cTNT, ng/l (95% CI)			
Visit 2 DBP	n/N	Adjusted* Odds Ratio‡ (95% CI)	p Value	Annual Change Between Visits 2 and 4	p Value	Annual Change Between Visits 4 and 5	p Value
<60 mm Hg	39/1,087	**2.24 (1.22 to 4.10)**	**0.01**	**1.46 (0.51 to 2.40)**	**0.002**	−0.09 (−0.69 to 0.51)	0.77
60–69 mm Hg	120/3,728	**1.52 (1.00 to 2.32)**	**0.05**	**0.95 (0.28 to 1.61)**	**0.005**	0.32 (−0.69 to 1.34)	0.54
70–79 mm Hg	144/4,249	1.02 (0.71 to 1.47)	0.90	**0.85 (0.27 to 1.44)**	**0.004**	0.02 (−0.26 to 0.31)	0.86
80–89 mm Hg	102/1,902	1.00 (reference)	–	0 (reference)	–	0 (reference)	–
90–99 mm Hg	36/487	1.06 (0.61 to 1.83)	0.84	−0.73 (−1.47 to 0.01)	0.06	0.26 (−0.07 to 0.60)	0.13
≥100 mm Hg	14/112	1.54 (0.63 to 3.78)	0.34	−0.99 (−2.58 to 0.58)	0.21	0.43 (−0.32 to 1.18)	0.26

Significant values are indicated in **bold**. *Adjusted for age, race-center, sex, body mass index, smoking, alcohol intake, SBP, hypertension medication use, diagnosed diabetes, LDL-C, HDL-C, triglycerides, current use of cholesterol-lowering medication, and eGFR. †Linear model with generalized estimating equations and inverse probability of attrition weighting. ‡Logistic model for cross-sectional association between DBP and baseline elevated high-sensitivity cardiac troponin T (hs-cTnT).

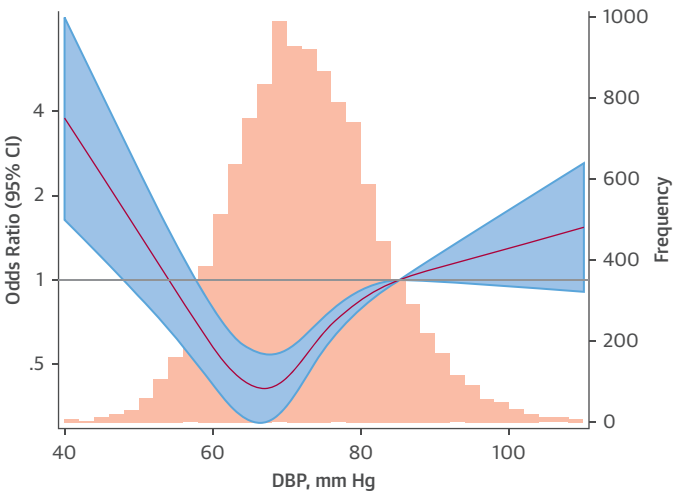
CI = confidence interval; other abbreviations as in Table 1.

However, DBP at visit 2 was not associated with higher annual hs-cTNT change in the follow-up period occurring after visit 4 (i.e., from 1996 to 1998 to visit 5 in 2011 to 2013) (**Table 2**).

Consistent with results for hs-cTnT, low DBP was associated with subsequent CHD and mortality over a median follow-up of 21 years. The highest relative hazard for events was among persons with a DBP <60 mm Hg for both CHD (HR: 1.5; 95% CI: 1.2 to 1.9) and for all-cause mortality (HR: 1.3; 95% CI: 1.1 to 1.6) compared with DBP 80 to 89 mm Hg. Unlike mortality, there also was increased CHD risk among persons with a DBP of 60 to 69 mm Hg (HR: 1.23; 95% CI: 1.05 to 1.44) and 70 to 79 mm Hg (HR: 1.20; 95% CI: 1.05 to 1.37) (**Table 3**). When evaluating the subcomponents of CHD outcome, this association appeared stronger for fatal CHD and myocardial infarction, relative to revascularization (Online Table 4). As expected, there was no association between DBP and stroke after accounting for SBP and clinical confounders (**Table 3**). The results of our supplemental analysis for incident HF were similar to those for CHD, with a trend for increased risk at low DBP (Online Table 5). Additionally, we found similar associations between low DBP and CHD events in the SPRINT-eligible subsample (Online Table 6). Furthermore, DBP <60 mm Hg was consistently associated with excess risk for events in our sensitivity analysis evaluating DBP as a time-varying exposure and with adjustment for SBP, antihypertensive medication use, and renal function as time-varying confounders (Online Table 7).

When our primary sample was stratified by baseline antihypertensive treatment status, the association between DBP categories and CHD events was qualitatively similar as in the sample overall (Online Table 8). However, when the sample was stratified by baseline hs-cTnT (<14 or ≥14 ng/l), the risk for subsequent CHD was highest among those with both low DBP and baseline myocardial damage (HR: 2.6; 95% CI: 1.3 to 5.0 for DBP of <60 mm Hg among persons with hs-cTnT ≥14 ng/l; compared with HR: 1.3; 95% CI: 1.1 to 1.7 for those with hs-cTnT <14 ng/l;

FIGURE 1 Relationship Between DBP and Elevated hs-cTnT



When diastolic blood pressure (DBP) was <65 mm Hg, a linear inverse relationship between DBP and high-sensitivity cardiac troponin-T (hs-cTnT) emerged when DBP was modeled continuously using linear splines. The odds ratio was adjusted for age (years), race-center, sex, body mass index, smoking, alcohol intake, systolic BP, hypertension medication use, diagnosed diabetes, low- and high-density lipoprotein cholesterol, triglycerides, current use of cholesterol-lowering medication, and estimated glomerular filtration rate. Restricted cubic spline provided odds of elevated hs-cTnT (≥14 ng/l) with background distributional histogram of baseline DBP. Frequency = number of participants at each point on background histogram. The **shaded area** around the regression line represents the 95% confidence interval (CI).

TABLE 3 CHD, Stroke, or Mortality Events

	CHD			Stroke			Mortality		
Visit 2 DBP	n/N	HR* (95% CI)	p Value	n/N	HR* (95% CI)	p Value	n/N	HR* (95% CI)	p Value
<60 mm Hg	165/1,087	**1.49 (1.20–1.85)**	**<0.001**	56/1,084	1.13 (0.79–1.61)	0.52	345/1,087	**1.32 (1.13–1.55)**	**<0.001**
60–69 mm Hg	547/3,728	**1.23 (1.05–1.44)**	**0.01**	197/3,722	1.03 (0.80–1.32)	0.83	1,017/3,727	1.10 (0.98–1.23)	0.12
70–79 mm Hg	752/4,247	**1.20 (1.05–1.37)**	**0.01**	271/4,234	1.07 (0.86–1.32)	0.55	1,142/4,247	0.99 (0.89–1.10)	0.89
80–89 mm Hg	350/1,902	1.00 (reference)	–	143/1,894	1.00 (reference)	–	597/1,902	1.00 (reference)	–
90–99 mm Hg	104/487	0.93 (0.74–1.16)	0.52	53/484	1.20 (0.87–1.66)	0.27	189/487	1.01 (0.85–1.19)	0.92
≥100 mm Hg	25/112	0.76 (0.50–1.17)	0.21	19/112	1.50 (0.90–2.50)	0.12	49/112	1.03 (0.76–1.40)	0.84

Significant values are indicated in **bold**. *Cox Model adjusted for same variables as in Table 2.
CHD = coronary heart disease; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

p value for interaction <0.001). Similarly, there was a trend toward excess hazard for CHD among persons with low DBP and baseline LVH by ECG (although results were underpowered due to low numbers of participants with LVH) (Online Table 8).

After stratifying the study sample by SBP categories, both myocardial damage and clinical event outcomes varied according to baseline DBP levels (Table 4). The association of low DBP (specifically DBP <60 mm Hg) with both prevalent myocardial damage and incident CHD appeared to be primarily driven by excess risk among those with an SBP ≥120 mm Hg (in other words, pulse pressure >60 mm Hg). These results were consistent in a number of sensitivity analyses, demonstrating that: 1) low DBP, modeled continuously, is a risk factor for elevated hs-cTnT and incident CHD (particularly after adjusting for SBP) (Online Figure 1); 2) despite the adverse associations with low DBP, high SBP is also a risk factor for elevated hs-cTnT and incident CHD (Online Figure 2); 3) as such, pulse pressure >60 mm Hg appears to be an important driver of these results (Online Figure 3); and 4) consistent with this, the association of low DBP with hs-cTnT and incident CHD is most evident among those with an SBP ≥120 mm Hg (Online Figure 4).

DISCUSSION

Our results have a number of potential implications, particularly in the post-SPRINT era where the threshold for diagnosing and treating hypertension could be redefined (25). Despite the undeniable clinical benefits reported in SPRINT, one of many concerns related to aggressive SBP reduction with pharmacotherapy is the possibility of myocardial

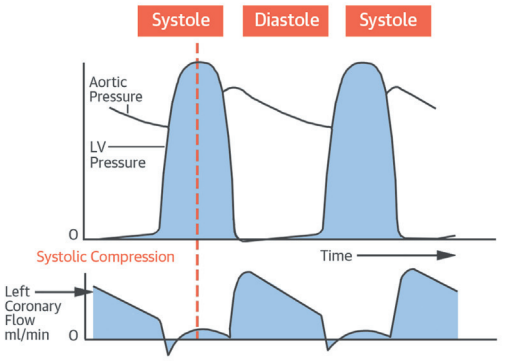
TABLE 4 Elevated hs-cTnT and Events*

		Cross-Sectional Analysis for Elevated hs-cTnT (≥14 ng/l)			Prospective Proportional Hazards Analysis for Incident Outcomes					
Visit 2 SBP	Visit 2 DBP	n/N	Adjusted† Odds Ratio‡ (95% CI)	p Value	n/N	Adjusted† CHD HR§ (95% CI)	p Value	n/N	Adjusted† Mortality HR§ (95% CI)	p Value
<120 mm Hg	<60 mm Hg	26/957	1.16 (0.47–2.86)	0.74	130/957	1.05 (0.71–1.54)	0.81	281/957	1.23 (0.89–1.70)	0.22
	60–79 mm Hg	109/4,891	0.86 (0.40–1.88)	0.71	637/4,891	0.97 (0.69–1.36)	0.85	1,061/4,891	1.07 (0.79–1.45)	0.66
	80–89 mm Hg	9/227	1.00 (reference)	–	37/227	1.00 (reference)	–	45/227	1.00 (reference)	–
	≥90 mm Hg	0/7	–	–	0/7	–	–	1/7	0.91 (0.12–6.60)	0.94
120–139 mm Hg	<60 mm Hg	9/101	**2.49 (1.06–5.84)**	**0.03**	26/101	**1.71 (1.11–2.63)**	**0.01**	49/101	1.25 (0.91–1.71)	0.17
	60–79 mm Hg	98/2,507	0.90 (0.59–1.36)	0.61	497/2,505	1.17 (0.97–1.40)	0.09	800/2,505	0.99 (0.85–1.14)	0.85
	80–89 mm Hg	41/1,033	1.00 (reference)	–	176/1,033	1.00 (reference)	–	275/1,033	1.00 (reference)	–
	≥90 mm Hg	7/144	1.15 (0.50–2.64)	0.75	31/144	1.19 (0.81–1.75)	0.36	37/144	1.00 (0.71–1.41)	0.99
≥140 mm Hg	<60 mm Hg	4/29	1.45 (0.38–5.53)	0.59	9/29	1.46 (0.73–2.92)	0.29	15/29	0.97 (0.57–1.65)	0.90
	60–79 mm Hg	57/579	0.94 (0.60–1.46)	0.77	165/579	**1.31 (1.03–1.66)**	**0.03**	298/579	1.02 (0.86–1.21)	0.78
	80–89 mm Hg	52/642	1.00 (reference)	–	137/642	1.00 (reference)	–	277/642	1.00 (reference)	–
	≥90 mm Hg	43/448	0.87 (0.54–1.41)	0.58	98/448	1.02 (0.78–1.33)	0.89	200/448	1.02 (0.85–1.24)	0.81

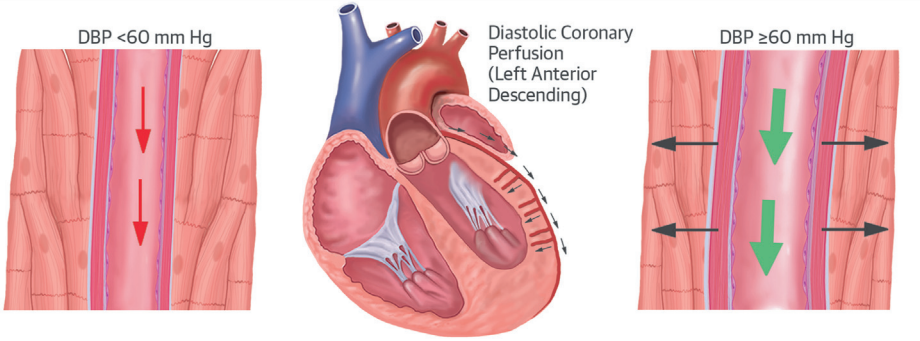
Significant values are indicated in **bold.** *According to DBP level, after stratification by SBP. †Adjusted for same variables as in Table 2, except for SBP. ‡Logistic model for cross-sectional association between DBP and baseline elevated hs-cTnT. §Cox model for prospective association between DBP and incident events.
Abbreviations as in Tables 1 to 3.

CENTRAL ILLUSTRATION Low DBP and Cardiac Events

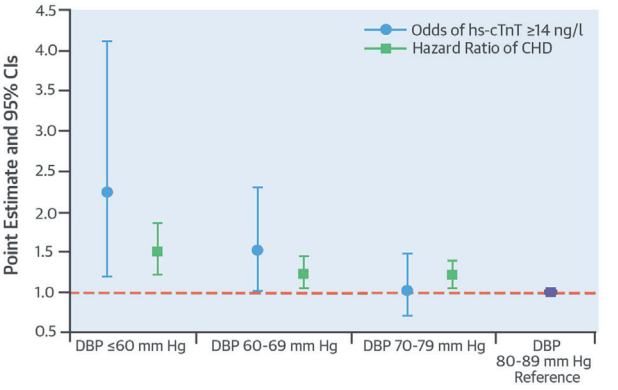
A. Coronary Blood Flow Occurs in Diastole



B. Diastolic BP Drives Coronary Perfusion Gradient



C. Low Diastolic BP Associated with Elevated hs-cTnT and CHD



McEvoy, J.W. et al. J Am Coll Cardiol. 2016;■(■):■-■.

This analysis examined associations between diastolic blood pressure (DBP), high-sensitivity cardiac troponin-T (hs-cTnT), and coronary heart disease (CHD). Several potential mechanisms of myocardial damage emerged. **(A)** Coronary blood flow occurs primarily during diastole. During systole, left ventricular (LV) pressure equals aortic pressure and, hence, coronary perfusion is diminished. **(B)** Coronary blood flow may be reduced when DBP is lowered (e.g., <60 mm Hg) due to a lower perfusion gradient between aortic diastolic pressure and LV diastolic pressure, particularly among individuals with known coronary artery disease or LV hypertrophy. The **green arrows** indicate adequate coronary blood flow in the setting of diastolic BP ≥60 mm Hg; the **black arrows** indicate the increased intraluminal pressure and coronary perfusion gradient associated with diastolic BP ≥60 mm Hg; and the **red arrows** indicate inadequate coronary blood flow in the setting of diastolic BP <60 mm Hg. **(C)** Low DBP levels were independently associated with increased levels of hs-cTnT; this translated into increased risk for CHD, heart failure, and mortality among those with low DBP in our sample. CI = confidence interval.

ischemia by lowering DBP. This is a concern on the basis of strong physiological rationale and a wealth of prior observational data. Indeed, there was a trend toward harm with intensive BP treatment among participants enrolled in the HOPE-3 (Heart Outcomes Prevention Evaluation-3) study who had a baseline SBP <131.5 mm Hg (7). We extended these findings by demonstrating that, at any given SBP: 1) low DBP was cross-sectionally associated with prevalent myocardial damage; 2) low DBP was prospectively associated with near-term progression of myocardial damage; 3) low DBP was prospectively associated with incident CHD events (and mortality), but, as expected, not with incident stroke; and 4) the association between low DBP and incident CHD appeared to be strongest among those with evidence of preceding myocardial damage at baseline. Considered in isolation, each of these 4 findings holds clinical importance; however, taken together, they form a compelling argument that excessively low DBP may directly harm the myocardium.

A J-curve has been repeatedly demonstrated for DBP and coronary events (13). For example, in a study of 902 patients with hypertension, Cruickshank et al. (10) found a J-shaped relationship between death from CHD and treated DBP in patients with CAD. The nadir of the J-curve in DBP was at 85 to 90 mm Hg, with an increase of CHD mortality on either side of this range. Farnett et al. (11) confirmed this J-shaped relationship in their meta-analysis. The INVEST (International Verapamil-Trandolapril) study enrolled 22,576 patients with CAD and hypertension and found that the primary outcome doubled when DBP was <70 mm Hg and quadrupled when it was <60 mm Hg (12,26). Our findings supported these data, particularly by demonstrating increased risk for CHD events at DBP levels <80 mm Hg in the main sample and at DBP levels <60 mm Hg in the smaller SPRINT-eligible subsample (the latter sensitivity analysis lacked power to demonstrate increased risk for CHD at DBP levels between 60 to 80 mm Hg). This finding was independent of baseline antihypertensive treatment, suggesting that both "native" and "on-treatment" DBP lowering might have the same effect on the myocardium (hence, the presence of low DBP may be more important than the cause, whether that cause be native vascular stiffness or drug treatment, for example).

We also found weaker associations with mortality at the lowest DBP levels. Given the results for CHD, the association between low DBP and incident HF that we demonstrated in our sensitivity analysis may represent ischemic heart failure events. In contrast, there were no associations found for stroke, our "negative control," which lacks biological plausibility for increased risk according to DBP. Furthermore, a novel feature of this analysis was that our results suggested that the association between DBP and CHD events might relate to subclinical myocardial injury at lower perfusion pressures, as implicated by our findings of higher hs-cTnT levels at baseline and during follow-up among participants with low DBP (**Central Illustration**). We note that the association between DBP at visit 2 and temporal change in hs-cTnT was most pronounced over the period when hs-cTnT was next measured (6 years later at visit 4) and had little effect on hs-cTnT change between visits 4 and 5. That the association between DBP and temporal change in hs-cTnT was strong for proximate hs-cTnT measurements and weaker for distal measurements was not surprising given that BP levels are highly labile over time.

Longstanding hypertension and LVH have been shown to narrow the range of coronary perfusion autoregulation, especially in the subendocardium (27). Thus, in patients with hypertension and LVH, ischemia can occur with a low DBP even in the absence of coronary stenosis. For example, Lindblad et al. (28) reported that lowering DBP in 1,121 men with hypertension and with LVH by ECG increased the risk for CHD events. This result was compatible with our finding that persons with subclinical myocardial damage at baseline (as indicated by hs-cTnT ≥14 ng/l) appear to have the highest risk of future CHD when DBP is low.

It is important to note that all of the previously mentioned findings represent the results of statistical models that consider DBP in isolation. However, DBP is inextricably related to SBP. Therefore, we also evaluated the association between DBP and outcomes within subcategories of SBP.

This analysis demonstrated that the association of low DBP with both subclinical myocardial damage and incident CHD was strongest among persons with an SBP range of 120 to 139 mm Hg. There was also a trend toward higher risk of progression of subclinical myocardial damage and incident CHD among those with DBP <60 and SBP ≥140 mm Hg; however, due to low numbers of events in this group, our estimates were imprecise. In contrast, no trend toward myocardial damage or CHD was noted among those with DBP <60 mm Hg and SBP <120 mm Hg.

These results suggest that discordance between SBP and DBP (i.e., elevated pulse pressure) might be an important factor linking low DBP to myocardial outcomes (29). Indeed, because systolic pressure is the main determinant of cardiac afterload and, thus, a primary driver of myocardial energy requirements (30), it is not surprising that our results appear to

demonstrate that adverse myocardial outcomes seem most likely when both DBP is low (when myocardial energy supply is reduced due to lower coronary perfusion pressure) and SBP is ≥120 mm Hg (when myocardial energy demand is higher).

STUDY LIMITATIONS. This was an observational study, and our inferences might not reflect direct causal effects. For example, we cannot know for sure whether the association between low DBP and outcomes in our analysis was due to low DBP from drug treatment, from arterial stiffness, or from a combination of both. The sensitivity analysis evaluating a SPRINT-eligible subsample was underpowered due to small sample size. Additionally, SPRINT investigators used automated oscillometric meters (8), which tend to report similar or slightly lower SBP readings than manual random zero sphygmomanometers and higher DBP readings (the latter being usually around 2.5 mm Hg higher) (31,32). The longitudinal analysis of DBP and temporal change in hs-cTnT might have been influenced by significant drop-out between visits 4 and 5, despite our use of inverse-probability of attrition weighting to account for this.

CONCLUSIONS

Our results suggested that low DBP levels, particularly <60 mm Hg, might harm the myocardium and are associated with subsequent CHD. However, this phenomenon appears to be most likely in clinical settings where SBP is ≥120 mm Hg and pulse pressure is higher. Thus, among patients being treated to SBP goals of 140 mm Hg or lower, attention may need to be paid not only to SBP, but also, importantly, to achieved DBP. Diastolic and systolic BP are inextricably linked, and our results highlighted the importance of not ignoring the former and focusing only on the latter, instead emphasizing the need to consider both in the optimal treatment of adults with hypertension.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Both systolic and diastolic BP should be considered in managing adults with hypertension. Lowering of DBP to <70 mm Hg, and particularly <60 mm Hg, is independently associated with higher blood levels of hs-cTnT, more frequent coronary disease events, HF, and mortality, particularly when SBP exceeds 120 mm Hg, resulting in higher pulse pressure.

TRANSLATIONAL OUTLOOK: The SPRINT and HOPE-3 trial datasets should be evaluated to determine whether there is an association between achieved DBP and adverse outcomes.

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KEY WORDS coronary heart disease, coronary perfusion, high-sensitivity troponin, hypertension, J-curve

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this article.