ORIGINAL RESEARCH

Can Antihypertensive Treatment Restore the Risk of Cardiovascular Disease to Ideal Levels?

The Coronary Artery Risk Development in Young Adults (CARDIA) Study and the Multi-Ethnic Study of Atherosclerosis (MESA)

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***Background*—**It is unclear whether antihypertensive treatment can restore cardiovascular disease risk to the risk level of persons with ideal blood pressure (BP) levels.

***Methods and Results*—**Data from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Coronary Artery Risk Development in Young Adults (CARDIA) study were analyzed. Outcomes were compared among participants without or with antihypertensive treatment at 3 BP levels: <120/<80 mm Hg, systolic BP 120 to 139 mm Hg or diastolic BP 80 to 89 mm Hg (120 to 129/≤80 mm Hg for participants with diabetes), and systolic BP ≥140 or diastolic BP ≥90 mm Hg (systolic BP ≥130 or diastolic BP ≥80 mm Hg for participants with diabetes). Among MESA participants aged ≥50 years at baseline, those with BP <120/<80 mm Hg on treatment had higher left ventricular mass index, prevalence of estimated glomerular filtration rate <60 mL/min per 1.73 m^2, prevalence of coronary calcium score >100, and twice the incident cardiovascular disease rate over 9.5 years of follow-up than those with BP <120/<80 mm Hg without treatment. In CARDIA at year 25, persons with BP <120/<80 mm Hg with treatment had much longer exposure to higher BP and higher risk of end-organ damage and subclinical atherosclerosis than those with BP <120/<80 mm Hg without treatment. An exploratory analysis suggested that when cumulative systolic BP was high (eg, >3000 mm Hg–years in 25 years), the increase in left ventricular mass index accelerated.

***Conclusions*—**The data suggest that based on the current approach, antihypertensive treatment cannot restore cardiovascular disease risk to ideal levels. Emphasis should be placed on primordial prevention of BP increases to further reduce cardiovascular disease morbidity and mortality. **(*J Am Heart Assoc*. 2015;4:e002275 doi: 10.1161/JAHA.115.002275)**

Key Words: antihypertensive treatment • cardiovascular disease risk • cumulative blood pressure • end-organ damage

Prospective studies of cardiovascular disease (CVD) have shown that baseline blood pressure (BP) levels measured during young adulthood have a strong and direct association with risk of long-term CVD events, despite potential changes in BP at older ages.[1–3] The Framingham Heart Study reported that BP levels measured at baseline or in the remote past are more predictive of CVD events than BP levels measured more proximally to the event.[4] Similarly, data from the Coronary Artery Risk Development in Young Adults (CARDIA) study suggest that higher BP levels within nonhypertensive ranges at young ages are also strongly associated with subclinical CVD many years later.[5–7]

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Despite the known association of BP levels with CVD events extending well into optimal ranges,[8] BP treatment guidelines have focused on initiation of antihypertensive therapy only after BP exceeds certain thresholds (eg, systolic BP [SBP] ≥140 mm Hg or diastolic BP [DBP] ≥90 mm Hg).[9] It is firmly established that use of antihypertensive medications to lower BP for persons within this hypertensive range is associated with substantially lower risks for cardiovascular outcomes, including stroke, heart failure, and coronary heart disease (CHD).[10–13] Observational studies, however, have shown that after adjustment for CVD risk factors, patients receiving antihypertensive medication still appear to have higher risk of CVD than those not on antihypertensive medication at the same achieved BP levels.[14–17] It is widely assumed that antihypertensive treatment to BP levels <120/<80 mm Hg cannot restore risk levels to those of someone who always maintains such optimal BP levels, but no direct empirical evidence has addressed this point. Furthermore, no data have been shown to explain why lowering BP to the ideal level with medication cannot restore low risk. Existing randomized clinical trial data cannot answer this question because studies have focused only on patients with clinically elevated BP and on short-term outcomes.

Although it remains unclear why recent BP measures are less predictive of CVD events than remote measures, an explanation is that because BP tracks over time, higher BP levels at young ages may be a surrogate for long-term exposure to elevated BP levels. Similarly, BP levels obtained later and closer to CVD events may have been altered by recent changes or interventions and thus may not adequately reflect cumulative damage to the myocardium and vasculature. To date, this issue has not been clearly addressed. We sought to determine whether effective treatment of hypertension can lower the risk of CVD to that seen in those who have always had ideal BP levels and to explore potential mechanisms that may preclude the restoration of low-risk status despite effective antihypertensive therapy.

Methods

Study Participants

The CARDIA study, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), is a multicenter longitudinal study consisting of 5115 black and white women and men aged 18 to 30 years at the baseline examination (Y0) in 1985–1986 who were free of CVD. Seven follow-up examinations took place at years 2, 5, 7, 10, 15, 20 (Y20), and 25 (Y25). Participants in the CARDIA cohort were excluded from the analysis if they did not attend the Y25 examination (n=1617), were missing data on all Y25 outcome measures (n=3), were missing Y25 BP measurements (n=6), were missing data on Y25 covariates (n=231), or developed CVD prior to Y25 (n=94). This left 3164 participants in the primary analytic cohort. An additional person was excluded from analyses involving left ventricular (LV) mass due to an unlikely, large LV mass (502 g). Participants were permitted to be missing data on some but not all Y25 outcomes, thus the sample sizes for different outcomes may be slightly <3164 participants. For participants who attended the baseline and Y25 examinations and at least 4 of 6 intermediate examinations, 25-year cumulative SBP was computed. In the analyses relating 25-year cumulative SBP to LV mass index (LVMI) in untreated CARDIA participants (n=2362), 368 were excluded due to missing LVMI (n=214) or missing 25-year cumulative SBP (n=154) or had cumulative SBP outside of the range 2200 to 3600 mm Hg–years (n=4), leaving 1990 participants for that analysis (Figure 2). In the exploratory analysis in Table 4, 236 participants (137 missing LVMI and 99 missing cumulative SBP) were excluded from the 1669 participants with BP <120/<80 at Y25, leaving 1433 participants. Because the cohort is relatively young and only 2 years of CVD event follow-up data were available after the Y25 examination, there were too few CVD events for statistical analysis.

The Multi-Ethnic Study of Atherosclerosis (MESA) is also an NHLBI-sponsored multicenter longitudinal study consisting of 6814 white (38%), black (28%), Hispanic (23%), and Chinese (12%) women and men aged 45 to 84 years who were free of CVD at baseline (2000–2002). Participants were excluded from analysis if they had fasting time <8 hours (n=6); missing SBP, low-density lipoprotein cholesterol, diabetes status, or smoking status (n=121); missing antihypertensive medication information (n=2); or prebaseline events (n=4). In addition, because most younger people were in the normotensive group, we excluded 883 participants aged <50 years at baseline to enhance the age comparability between the BP treatment groups. The total sample size for this analysis was 5798.

All participants in both studies signed informed consent, and the studies were approved by the institutional review board of each field center. Details regarding these 2 studies have been published previously.[18,19]

CARDIA Data Collection

All measurements were obtained by centrally trained and certified technicians. Participants were asked to fast for 12 hours and to refrain from smoking and from heavy physical activity for 2 hours before each examination. Seated BP was measured using a random zero sphygmomanometer for the examinations from Y0 to year 15 and an Omron model HEM907XL at Y20 and Y25 examinations. After a 5-minute rest in a quiet room, BP was measured on the right arm at three 1-minute intervals; the average of the second and third measurements was used. A calibration study was conducted (n=800) to convert Y20 and Y25 values to their Y0 equivalents. Total cholesterol was measured enzymatically by the Northwest Lipid

Laboratory, and low-density lipoprotein cholesterol was calculated using the Friedewald equation.[20] Glucose was assayed using hexokinase coupled to glucose-6 phosphate dehydrogenase. Diabetes was defined by fasting glucose ≥126 mg/dL, 2-hour glucose ≥200 mg/dL, HbA1c ≥6.5%, or medication use. Creatinine was measured in serum by the Roche enzymatic method. The estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.[21] For height and weight measurements, the participants wore light clothing without shoes. Sex, race, and smoking data were collected using self-administrated questionnaires. Participants were asked to bring their medications with them to the clinic visits. At Y25, participants underwent 2-dimensionally guided M-mode echocardiography; all studies were read centrally at the Johns Hopkins University Echocardiography Reading Center. LVMI was calculated by dividing the LV mass (in grams) by height (in $m^{2.7}$). Coronary calcium (CAC) levels were measured at Y25 using multidetector computed tomography of the chest.[22] Images were read centrally by the Computed Tomography Reading Center at Wake Forest University. Agatston score was calculated.[23]

MESA Data Collection

All data were collected by centrally trained and certified technicians. Three BP measurements, 1 minute apart, were collected using a Dinamap Pro100 model BP monitor, and the average value of the second and third measurements was used. Sex, race, and smoking data were collected using self-administrated questionnaires. Weight and height were measured using a standard protocol. Again, participants were asked to bring in their medications.

Details regarding lipid measurements have been published.[24] Serum glucose was measured by the glucose-oxidase method. The eGFR was based on cystatin C.[25] Chest computed tomography was performed using either cardiac gated electron-beam or multidetector computed tomography scanners.[22] Images were read centrally for CAC by the Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center. The average Agatston score was used in the analysis.[23] LV mass was obtained by cardiac magnetic resonance imaging. Images were acquired by 1.5T magnetic resonance imaging scanners using a protocol described by Natori et al.[26] The readings were performed centrally by the MESA Magnetic Resonance Imaging Reading Center at Johns Hopkins Hospital. LVMI was calculated using the Dubois formula for body surface area.[27]

CARDIA and MESA Event Follow-up and Adjudication

In CARDIA, participants were contacted every year to inquire about interim hospitalizations. For each self-reported event, medical records were obtained and adjudicated by 2 members of the morbidity and mortality committee. CVD events comprised nonfatal myocardial infarction or stroke; hospitalization for angina pectoris, congestive heart failure (CHF), or transient ischemic attack; revascularization for or angiographically or ultrasound-demonstrated obstruction of carotid artery disease or peripheral arterial disease; fatal atherosclerotic coronary heart disease, fatal stroke, fatal atherosclerotic disease other than coronary or stroke, and fatal nonatherosclerotic cardiac disease. In MESA, incident CVD events were recorded over a mean follow-up of 9.5 years (SD 2.4 years). Every 9 to 12 months, participants were contacted to inquire about interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. Again, for each self-reported event, the medical and hospital records were obtained and adjudicated by 2 members of the morbidity and mortality committee. For this report, all CHD events were classified as myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), and CHD death. All CVD events included all CHD events plus stroke, stroke death, other atherosclerotic death, and other CVD death. CHF was classified as definite, probable, or absent. Definite or probable CHF required heart failure symptoms such as shortness of breath or edema. In addition to symptoms, probable CHF required CHF diagnosed by a physician and medical treatment for CHF. Definite CHF required 1 criterion or more, such as pulmonary edema or congestion by chest x-ray, ventricular dilation or poor LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction.

Statistical Analysis

CARDIA participants were classified into 6 BP treatment groups defined by whether they were treated or untreated with antihypertensive medication at Y25 and the severity level of BP at Y25 as categorized by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, or JNC 7: normal (untreated BP <120/<80 mm Hg), treated and well controlled (BP <120/<80 mm Hg), untreated prehypertension (SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg, or SBP 120 to 129 with DBP <80 mm Hg for participants with diabetes), treated and controlled (BP in prehypertension ranges), untreated hypertension (BP ≥140/≥90 mm Hg or BP ≥130/≥80 mm Hg for participants with diabetes), and treated and uncontrolled (BP in untreated hypertension ranges).[9] Similar categories were used to define BP strata for MESA participants at baseline. For CARDIA participants who attended the baseline and Y25 examinations and at least 4 of 6 intermediate examinations at years 2, 5, 7, 10, 15, and Y20, the cumulative SBP (in mm Hg–years) was calculated by summing

the product of the average SBP and the time interval (in years) between 2 consecutive examinations over the 25 years.

Analyses were conducted using SAS statistical software (version 9.4; SAS Institute) and R software (R Foundation for Statistical Computing). Cox regression was used to obtain hazard ratios (HRs) for the 6 baseline BP groups for incident CHD, CVD, heart failure, and stroke in MESA participants, adjusting for the baseline covariates age, sex, race, body mass index, smoking status, low-density lipoprotein cholesterol, and cholesterol medication. In addition, we reran the Cox regression models using the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) criteria[28] due to changes in the treatment criteria. Under the JNC 8 criteria, the initiation of antihypertensive medication for those aged >60 years is delayed until they have SBP >150 or DBP >90 mm Hg. The proportional hazards assumption was examined using the time interaction test and the supremum test. All tests were insignificant except for the comparison of incident CVD between the groups of people with BP <120/<80 mm Hg without medication and prehypertension patients without medication; this comparison was borderline significant (P=0.07 and P=0.04 for the time interaction and supremum tests, respectively). This comparison is not the focus of the paper, and the HR was not statistically significant.

For CARDIA, a generalized estimating equation model was used to obtain estimates of age-, sex-, and race-adjusted SBP and DBP at the 8 examination visits (Figure 1). ANCOVA was used to estimate the CARDIA Y25 covariate-adjusted prevalence and MESA baseline covariate-adjusted prevalence of CAC score >100 and eGFR <60 mL/min per 1.73 m^2 for the 6 groups, and multiple logistic regression was used to test significance. ANCOVA was used to compare the Y25 covariate-adjusted LVMI among 6 BP groups.

In addition, in CARDIA, a large number of participants were excluded from the analytic sample due to missing Y25 examinations, cumulative SBP, or LVMI. We compared baseline age, sex, race, body mass index, smoking status, BP, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting glucose, education, serum creatinine, alcohol intake, and total physical activity between those who were included in the sample and those who were excluded from the sample. The variables that were significantly different between the 2 groups were used to develop a propensity equation for inclusion based on the logistic regression model for each end-organ-damage variable (ie, LVMI, CAC, and eGFR). The inverse propensity probability of inclusion was used to perform the weighted regression analysis as sensitivity analyses for findings in Table 3.

A generalized additive model was used to model the nonlinear relation of LVMI with cumulative SBP, adjusting for the Y25 covariates. In the analysis, the adjusted mean of LVMI is a smooth function of the cumulative SBP with additive structure. The function is estimated by a nonparametric spline method. An exploratory analysis was also performed to estimate the potential break point. Specifically, we fit a special piecewise linear model, which assumes that LVMI is linearly related to cumulative SBP, with the slope of the regression line changing at an unknown cumulative SBP level. In addition, the Davies test[29] was performed to test the existence of the changing point. The main statistical analysis was conducted using the packages *segmented* and *mgcv* in R.3.1.3 (R Foundation for Statistical Computing) (Figure 2).

Results

Study Sample

Baseline characteristics of MESA participants and baseline and Y25 characteristics of CARDIA participants are presented in Tables 1 and 2, respectively, stratified by BP and treatment groups (at baseline for MESA and at Y25 for CARDIA). In MESA, the group with untreated BP <120/<80 mm Hg tended to be younger and leaner than the other groups (Table 1). In CARDIA, the group with untreated BP <120/<80 mm Hg at Y25 had a higher proportion of women and white participants, a lower prevalence of current smoking, and lower average body mass index at baseline and at Y25 than the other groups (Table 2).

Incident CVD Events in MESA

Risk factor–adjusted HRs for 9.5-year incident CVD, CHD, heart failure, and stroke are presented in Table 3 for the 6 BP groups, using the original JNC 7 criteria and the JNC 8 criteria. Under the JNC 7 criteria, MESA participants with treated and well-controlled BP had HRs of 2.19 (P<0.01), 2.02 (P<0.01), 1.70 (P=0.09), and 2.56 (P=0.01) for CVD, CHD, heart failure, and stroke, respectively, compared with those with untreated BP <120/<80 mm Hg. For the other 4 groups, except for CHD and stroke in the untreated prehypertensive group, the HRs for incident CVD, CHD, and stroke were all significantly higher than for the group with untreated BP <120/<80 mm Hg.

Similarly, participants with treated and controlled hypertension had significantly higher hazards for incident CVD, CHD, and heart failure compared with untreated prehypertensive participants. Moreover, HRs for incident CVD, CHD, heart failure, and stroke were similar between participants with treated but uncontrolled hypertension and untreated hypertension.

When this analysis was rerun using JNC 8 criteria, the results were similar, except that in the prehypertension group, the HRs for CHD and stroke were also significantly higher

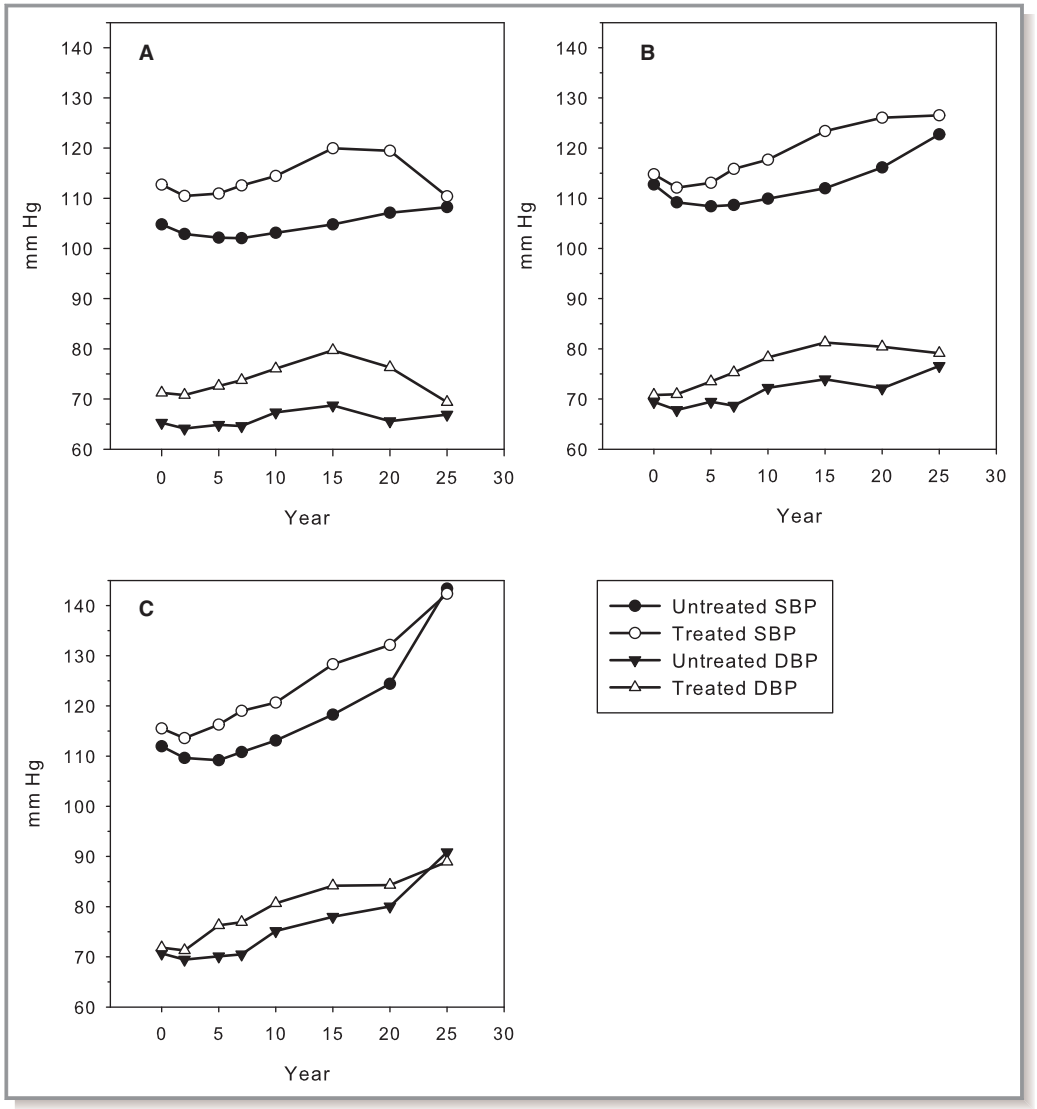

Figure 1. Age-, race-, and sex-adjusted BP over time by Y25 BP level and antihypertensive treatment status. Mean BP for CARDIA participants at Y25: (A) BP <120/<80 mm Hg. (B) SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg (or SBP 120 to 129 with DBP <80 mm Hg for people with diabetes), (C) BP ≥140/≥90 mm Hg (or BP ≥130/≥80 mm Hg for people with diabetes). The number of participants in each group is given in Table 2. BP indicates blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; SBP, systolic blood pressure; Y25, year 25.

than for the group with untreated BP <120/<80 mm Hg. In addition, for the prehypertension group, based on the JNC 8 criteria, the HRs for CVD, CHD, heart failure, and stroke were 1.65, 1.45, 1.45, and 2.22, respectively; these HRs are all higher than the corresponding HRs—1.42, 1.29, 1.41, and 1.76 for CVD, CHD, heart failure, and stroke, respectively—for the prehypertension group based on the JNC 7 criteria (Table 3).

Long-Term BP Levels in CARDIA

Figure 1A shows the average BP at Y0 and at years 2, 5, 7, 10, 15, Y20, and Y25 for normotensive participants in CARDIA at Y25 (closed circles) and hypertensive participants with treated and well-controlled BP at Y25 (open circles). At Y0, the average BPs in all 6 groups were much lower than 120/80 mm Hg. The average SBPs and DBPs of participants who became hypertensive but had well-controlled BP with treatment at Y25 were already much higher at Y0 than the average SBPs and DBPs of normotensive participants. Participants who became hypertensive over time had greater elevations in BP, as expected, and then returned to ideal BP levels with treatment by Y25. Similar BP patterns were also observed between the Y25 prehypertension group and the treated and controlled group (Figure 1B) and between the treated but uncontrolled group and the untreated hypertension group

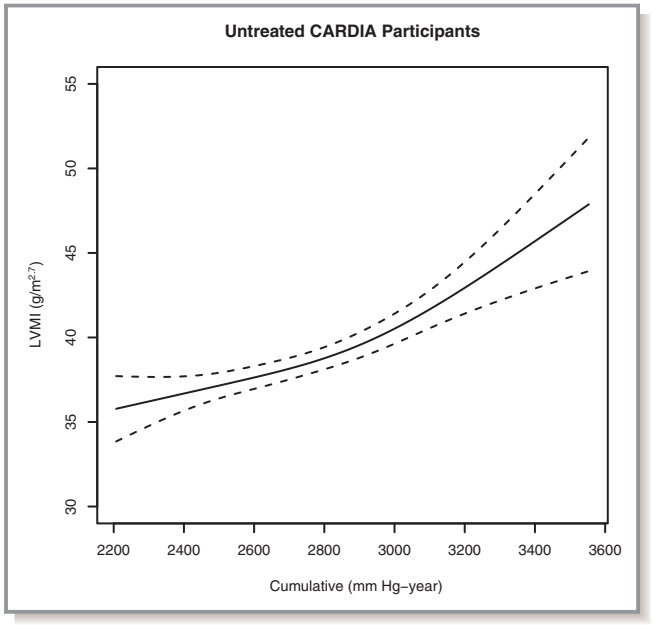

Figure 2. Adjusted relationship by spline regression between LVMI and 25-year cumulative systolic blood pressure in untreated CARDIA participants (n=1990). Spline (solid line) with 95% pointwise confidence band (dotted lines) is adjusted for year 25 age, sex, race, body mass index, smoking status, diabetes, low-density lipoprotein cholesterol, and cholesterol medication. The slopes at the break point of 2885 cumulative mm Hg–years were estimated to be 0.5 g/m$^{2.7}$ per 100 mm Hg–years (95% CI 0.2 to 0.8) before 2885 mm Hg–years and after 2885 mm Hg–years is 1.4 g/m$^{2.7}$ per 100 mm Hg–years (95% CI 0.7 to 2.1). CARDIA indicates Coronary Artery Risk Development in Young Adults; LVMI, left ventricular mass index.

(Figure 1C), although differences between the latter 2 groups were not as large. These data suggest that even participants on antihypertensive medication with well-controlled BP (<120/<80 mm Hg at Y25) have generally experienced a longer period (in our study, ≥25 years) of BP at much higher levels than those of the normotensive group.

BP Levels and End-Organ Damage or Subclinical Atherosclerosis

In both CARDIA participants at Y25 and MESA participants at baseline with BP (treated or untreated) either <120/<80 mm Hg or from 120/80 to 139/89 mm Hg, those on antihypertensive treatment had significantly higher LVMI, a significantly higher prevalence of eGFR <60 mL/min per 1.73 m^2, and a significantly higher prevalence of CAC score >100 than the corresponding group without treatment (Table 4).

In CARDIA, those who were excluded from the analyses tended to be younger, men, black, and current smokers, with higher SBP, DBP, low-density lipoprotein cholesterol, fasting glucose, alcohol intake, and creatinine and lower education at baseline. These baseline characteristics were used to develop a propensity equation for inclusion for each variable described for end-organ damage. A sensitivity analysis was performed using the inverse propensity probability as the weights in the regression analyses. The results were similar to those in Table 4, with no material change (data not shown).

Figure 2 demonstrates the relationship between cumulative SBP over 25 years and LVMI in CARDIA. In general, LVMI was higher with greater exposure to cumulative SBP, and when cumulative SBP exposure was high, the increase in LVMI accelerated. In the changing point analysis, the Davies test was significant for the existence of a change point, confirming that the association between cumulative SBP exposure and LVMI is not constant (P=0.04). The estimator of the change point in the piecewise linear regression was 2885 mm Hg–years. The slopes estimated before and after the break point of 2885 mm Hg–years were 0.5 and 1.4 g/m$^{2.7}$ per 100 mm Hg–years, respectively. Because stroke and transient ischemic attack are strongly associated with high BP and are unlikely to affect LV mass directly, the results may be overly conservative with the exclusion of these diseases. In a sensitivity analysis, we reran the change point analysis excluding CVD, except for stroke and transient ischemic attack, prior to Y25. The change point in this case was estimated at 2982 mm Hg–years with slopes before and after this point of 0.5 and 2.1 g/m$^{2.7}$ per 100 mm Hg–years, respectively. The Davies test showed P=0.002.

The CARDIA data also allowed an exploratory examination of whether early detection of hypertension and controlling BP to <120/<80 mm Hg could prevent increasing end-organ damage. The group of CARDIA participants with treated BP <120/<80 mm Hg at Y25 was further classified into 2 subgroups. Group 2 included those who initiated treatment by year 15, Y20, or Y25 with cumulative SBP <3000 mm Hg–years and BP <120/<80 mm Hg in subsequent years through Y25; group 3 included those who initiated treatment by year 15 or Y20 but were not always well controlled until Y25 or those who had a cumulative SBP ≥3000 mm Hg–years. Group 1 consisted of normotensive participants at Y25. The adjusted average LVMIs, prevalence of CAC score >100, and prevalence of eGFR <60 mL/min per 1.73 m^2 of group 2 were all lower (significantly or borderline significantly) than those of group 3 even though they were higher (not statistically significant) than those of group 1 (Table 5).

Discussion

The results of this study demonstrate that in MESA participants aged ≥50 years at baseline, those with well-controlled hypertension (<120/<80 mm Hg) on antihypertensive med-

Table 1. Baseline (2000–2002) Characteristics of MESA Participants Aged ≥50 Years Stratified by Baseline BP Level and Antihypertensive Treatment Status

	BP <120/<80 mm Hg at Baseline		SBP 120 to 139 or DBP 80 to 89 mm Hg (or 120 to 129/<80 mm Hg for Participants With Diabetes) at Baseline		SBP ≥140 or DBP ≥90 mm Hg (or ≥130 or ≥80 for Participants With Diabetes) at Baseline	
	Untreated	Treated to This Level	Untreated	Treated to This Level	Untreated	Treated to This level
n	1621	588	1069	740	757	1023
Age, y	60.6 (8.2)	65.1 (8.9)	63.7 (8.9)	65.9 (8.6)	66.8 (8.9)	68.2 (8.3)
Men, n (%)	736 (45.4)	287 (48.8)	569 (53.2)	358 (48.4)	359 (47.4)	424 (41.5)
Race, n (%)						
White	742 (45.8)	265 (45.1)	441 (41.3)	270 (36.5)	273 (36.1)	266 (26.0)
Black	288 (17.8)	183 (31.1)	252 (23.6)	278 (37.6)	206 (27.2)	419 (41.0)
Hispanic	354 (21.8)	98 (16.7)	246 (23.0)	120 (16.2)	178 (23.5)	233 (22.8)
Chinese	237 (14.6)	42 (7.1)	130 (12.2)	72 (9.7)	100 (13.2)	105 (10.3)
BMI, kg/m^2	26.6 (4.9)	29.5 (5.8)	28.1 (4.9)	29.4 (5.1)	28.2 (5.3)	29.7 (5.8)
Current smoker, n (%)	226 (13.9)	64 (10.9)	147 (13.8)	69 (9.3)	81 (10.7)	96 (9.4)

Values shown are mean (SD) or n (%). BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; MESA, Multi-Ethnic Study of Atherosclerosis; SBP, systolic blood pressure.

ication still had twice the risk of incident CVD events in the next 9.5 years than participants with ideal BP levels without treatment. The CARDIA results indicate that middle-aged adults with well-controlled BP on medication had longer exposure to higher BP levels than adults with ideal BP without medication and had significantly higher risk of end-organ damage, as measured by LVMI, renal function, and subclinical atherosclerosis. We observed these findings even in CARDIA participants who had mean BP levels below the typical threshold for diagnosing hypertension. In addition, our exploratory analysis suggested empirically that when cumulative SBP was high, the increase in LVMI accelerated.

Previous studies have shown that higher BP levels, even those not considered clinically high, at younger ages are strongly associated with clinical and subclinical CVD.[1–3,6,7] Results from the Framingham Heart Study showed BP levels in the remote past as more predictive of incident CVD than more recent BP levels.[4] Loria et al reported that BP levels in young adulthood (ages 18 to 30 years) were significantly associated with coronary calcium 15 years later and that this association

Table 2. Baseline (1985–1986) and Y25 Characteristics of CARDIA Participants Stratified by Y25 BP Level and Antihypertensive Treatment Status

	BP <120/<80 mm Hg at Y25		SBP 120 to 139 or DBP 80 to 89 mm Hg (or 120 to 129/<80 mm Hg for Participants With Diabetes) at Y25		SBP ≥140 or DBP ≥90 mm Hg (or ≥130 or ≥80 for Participants With Diabetes) at Y25	
	Untreated	Treated to This Level	Untreated	Treated to This Level	Untreated	Treated to This Level
n	1334	335	802	264	227	202
Baseline age, y	24.8 (3.7)	25.6 (3.6)	24.9 (3.5)	25.6 (3.4)	24.9 (3.5)	25.9 (3.5)
Y25 age (y)	49.9 (3.7)	50.6 (3.6)	50.1 (3.5)	50.6 (3.5)	50.1 (3.5)	50.9 (3.6)
Men, n (%)	455 (34.1)	124 (37.0)	467 (58.2)	118 (44.7)	102 (44.9)	87 (43.1)
Black, n (%)	411 (30.8)	189 (56.4)	368 (45.9)	177 (67.1)	145 (63.9)	164 (81.2)
Baseline BMI, kg/m^2	23.1 (3.9)	26.0 (6.0)	24.1 (4.1)	25.9 (5.5)	25.4 (5.0)	28.0 (6.1)
Y25 BMI, kg/m^2	27.7 (6.0)	33.1 (8.2)	29.4 (5.9)	33.1 (7.7)	32.6 (7.3)	36.1 (8.7)
Baseline current smoker, n (%)	309 (23.3)	108 (32.4)	198 (24.8)	64 (24.5)	62 (27.4)	65 (32.2)
Y25 current smoker, n (%)	171 (12.8)	64 (19.1)	137 (17.1)	44 (16.7)	52 (22.9)	39 (19.3)

Values shown are mean (SD) or n (%). BMI indicates body mass index; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; SBP, systolic blood pressure; Y25, year 25.

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Table 3. Multivariable-Adjusted* Hazard Ratios for CVD†, CHD‡, Heart Failure, and Stroke Stratified by Baseline BP Stratum and Antihypertensive Treatment Status, MESA Participants Aged ≥50 Years

		Multivariable-Adjusted* Hazard Ratio (95% CI)									
				JNC 7 Criteria				JNC 8 Criteria			
		BP <120/<80 mm Hg at Baseline		SBP 120 to 139 or DBP 80 to 89 mm Hg (or 120 to 129/<80 mm Hg for Participants With Diabetes) at Baseline		SBP ≥140 or DBP ≥90 mm Hg (or ≥130 or ≥80 for Participants With Diabetes) at Baseline		SBP 120 to 149 or DBP 80 to 89 mm Hg for ParticipantsAged ≥60 Years (or 120 to 139/80 to 89 mm Hg for Those Aged <60 Years, CKD, or Diabetes)		SBP ≥150 or DBP ≥90 mm Hg for ParticipantsAged ≥60 Years (or ≥140 or ≥90 for Those Aged <60 Years, CKD, or Diabetes)	
	Number of Events	Untreated	Treated and Well Controlled	Untreated	Treated and Controlled	Untreated	Treated But Uncontrolled	Untreated	Treated	Untreated	Treated
n		1621	588	1069	740	757	1023	1301	1009	525	754
CVD† (n=5798)	603	1 (ref)	2.19 (1.56, 3.07) <0.0001	1.42 (1.03, 1.95) 0.03	2.21§ (1.60, 3.05) <0.0001	2.76 (2.04, 3.72) <0.0001	2.96 (2.20, 3.97) <0.0001	1.65 (1.23, 2.21) 0.0009	2.31§ (1.71, 3.11) <0.0001	2.83 (2.05, 3.92) <0.0001	2.99 (2.20, 4.06) <0.0001
CHD‡ (n=5798)	423	1 (ref)	2.02 (1.37, 2.97) 0.0004	1.29 (0.89, 1.86) 0.18	2.09§ (1.45, 3.03) <0.0001	2.28 (1.60, 3.25) <0.0001	2.52 (1.79, 3.55) <0.0001	1.45 (1.03, 2.04) 0.03	2.13§ (1.51, 3.01) <0.0001	2.35 (1.60, 3.47) <0.0001	2.55 (1.78, 3.65) <0.0001
Heart failure (n=5798)	226	1 (ref)	1.70 (0.92, 3.12) 0.09	1.41 (0.80, 2.51) 0.24	2.42§ (1.40, 4.19) 0.002	2.43 (1.42, 4.15) 0.001	3.04 (1.83, 5.04) <0.0001	1.45 (0.85, 2.49) 0.17	2.34§ (1.40, 3.93) 0.001	2.89 (1.65, 5.07) 0.0002	3.37 (2.01, 5.65) <0.0001
Stroke (n=5798)	171	1 (ref)	2.56 (1.25, 5.28) 0.01	1.76 (0.90, 3.45) 0.10	3.13 (1.62, 6.09) 0.0007	4.20 (2.27, 7.76) <0.0001	4.67 (2.55, 8.56) <0.0001	2.22 (1.19, 4.13) 0.01	3.37 (1.81, 6.27) 0.0001	4.17 (2.17, 8.01) <0.0001	4.69 (2.52, 8.72) <0.0001

BP indicates blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC 8, Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; MESA, Multi-Ethnic Study of Atherosclerosis; ref, reference; SBP, systolic blood pressure.

*Adjusted for age, sex, race, body mass index, current smoking, former smoking, diabetes, low-density lipoprotein cholesterol, and cholesterol medication measured at baseline.

†CVD: CHD plus stroke, stroke death, other atherosclerotic death, and other CVD death.

‡CHD: myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), CHD death.

§$P<0.05$ for pairwise comparison within BP stratum.

Table 4. Adjusted* Measures of End-Organ Damage Stratified by Y25 BP Level (CARDIA) or Baseline BP Level (MESA) and Antihypertensive Treatment Status

	BP <120/<80 mm Hg at Y25		SBP 120 to 139 or DBP 80 to 89 mm Hg (or 120 to 129/<80 mm Hg for Participants With Diabetes) at Y25		SBP ≥140 or DBP ≥90 mm Hg (or ≥130 or ≥80 for Participants With Diabetes) at Y25	
CARDIA Y25 (n=3164)	Untreated	Treated to This Level	Untreated	Treated to This Level	Untreated	Treated to This Level
Echo LVMI*, g/m$^{2.7}$, mean (SEM) (n=2836)	37.9 (0.3)	39.9 (0.6)†	39.2 (0.4)†	42.2 (0.6)†‡	43.0 (0.7)†	43.9 (0.8)†
CAC >100*§, prevalence, % (n=2890)	5.3	10.7†	7.9†	14.8†‡	9.9†	12.7†
eGFR <60*§ (creatinine), prevalence, % (n=3160)	0.8	3.9†	0.6	2.1‡	1.4	6.3†‡
	BP <120/<80 mm Hg at Baseline		SBP 120 to 139 or Diastolic BP 80 to 89 mm Hg (or 120 to 129/<80 mm Hg for Participants With Diabetes) at Baseline		SBP ≥140 or Diastolic BP ≥90 mm Hg (or ≥130 or ≥80 for Participants With Diabetes) at Baseline	
MESA Age ≥50 at Baseline (n=5802)	Untreated	Treated to This Level	Untreated	Treated to This Level	Untreated	Treated to This Level
MRI LVMI*, g/m^2, mean (SEM) (n=4220)	34.4 (0.2)	36.1 (0.3)†	35.8 (0.2)†	36.9 (0.3)†‡	38.5 (0.3)†	39.8 (0.3)†‡
CAC >100*§, prevalence, % (n=5798)	21.9	28.5†	23.3	28.2†‡	28.1†	32.4†‡
eGFR <60*§ (cystatin C), prevalence, % (n=5764)	4.7	10.0†	3.3	6.9†‡	3.6	10.2†‡

BP indicates blood pressure; CAC, coronary calcium; CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; MESA, Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging; SBP, systolic blood pressure; Y25, year 25.
*Adjusted for age, sex, race, body mass index, smoking status, diabetes, low-density lipoprotein cholesterol, and cholesterol medication.
†P<0.01 for comparison with the untreated BP <120/<80 mm Hg group.
‡P<0.05 for pairwise comparison within BP stratum.
§ANCOVA was used to estimate the prevalence rates in the 6 groups, adjusting for the covariates measured at Y25 for CARDIA and at baseline for MESA; multiple logistic regression was used to test for the significant differences between groups.

was much stronger than the association with concurrent BP levels.[6] Pletcher et al reported that prehypertension during young adulthood was strongly associated with coronary calcium many years later.[7] In addition, the Framingham Heart Study, Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study (CHS) all demonstrated that for

Table 5. BP Treatment Status, Cumulative SBP, and Adjusted* Measures of End-Organ Damage in People With BP <120/80 mm Hg at Y25, CARDIA

	1	2	3
Group	No Treatment, Never Had BP ≥120/≥80 mm Hg	Initiated Treatment at Y15, Y20, or Y25 and Well Controlled at All Treated Visits With Cumulative SBP <3000 mm Hg–Years	Initiated Treatment and Well Controlled at Y25 But With Cumulative SBP ≥3000 mm Hg–Years OR Initiated Treatment Prior To or at Y20 But Not Well Controlled Before Y25
n	1159	152	122
Cumulative SBP, mm Hg–years, unadjusted mean (SD)	2597 (159)	2759 (124)	3018 (190)
Echo LVMI*, g/m$^{2.7}$, mean (SEM)	36.7 (0.2)	37.8 (0.7)	39.7 (0.8)‡‖
CAC >100*†, prevalence, %	4.2	5.4	17.9‡§
eGFR <60*† (creatinine), prevalence, %	0.9	2.1	6.9‡§

BP, blood pressure; CAC, coronary calcium; CARDIA, Coronary Artery Risk Development in Young Adults; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; SBP, systolic blood pressure; Y, year.
*Adjusted for age, race, sex, diabetes, low-density lipoprotein cholesterol, cholesterol medication, body mass index, and smoking status measured at Y25.
†ANCOVA was used to estimate the prevalence rates in the 3 groups, adjusting for the Y25 covariates; multiple logistic regression was used to test for the significant differences between groups.
‡P<0.001 compared with group 1.
§P<0.05 compared with group 2.
‖P=0.06 compared with group 2.

the same BP levels, those on antihypertensive medication had higher risk of incident CVD and mortality.[14–17] The results are echoed in more recent broad-based risk prediction equations that include antihypertensive therapy as a covariate with a positive coefficient.[30,31] In this study, we further demonstrated that even people with well-controlled BP (to <120/<80 mm Hg) on antihypertensive medication—although BP was assessed at 1 point in time—may have a risk of incident CVD double that of people who have never had high BP.

These results do not suggest that antihypertensive therapy is ineffective for CVD risk reduction. Our observational study was not designed to answer this question. An immense array of clinical trial data has established unequivocally that lowering BP with antihypertensive medications lowers the risk of incident CVD in middle-aged and older adults, particularly heart failure and stroke in patients with hypertension.[10–13,32] Results from the Losartan Intervention for Endpoint Reduction trial also suggest the regression of the electrocardiographic evidence of hypertrophy on treatment.[33] Our data, however, indicate that based on the current approach for treating hypertension, the restoration of BP levels ≤120/80 mm Hg with antihypertensive medication may not fully restore the low risk of persons maintaining these ideal BP levels consistently without medication. It is unclear whether earlier treatment to maintain similar cumulative exposure to BP would abolish this excess CVD risk. This study indicates that for participants with similar BP levels, those on antihypertensive treatment have much higher cumulative BP exposure over time than those not treated. Consequently, many have developed end-organ damage that treatment may not completely reverse. Several large-scale epidemiological studies indicate that CVD risk increases as BP increases, even within the normal BP range,[8,32] thus the assumption that long-term exposure to higher BP levels may lead to end-organ damage is reasonable. To our knowledge, this study is the first that provides direct evidence to support this theory and to explain why, in observational studies and at the same BP levels, people on antihypertensive treatment have a higher risk of incident CVD than people not on treatment. In addition, the exploratory analysis of the relationship between cumulative SBP and LVMI suggests that when cumulative SBP is high (eg, >3000 mm Hg–years), despite good control of BP with antihypertensive medication, LVMI remains significantly higher than it does in people with normal BP without treatment. The cumulative SBP of 3000 mm Hg–years is not very high. If, for example, a person's SBP increases evenly from 110 to 140 mm Hg over 25 years, that person's cumulative SBP is 3125 mm Hg. This finding suggests that there may be a "point of no return" for BP, that is, after reaching high levels, damage to an end organ may be difficult to reverse to the levels of those who never had hypertension.

The results of this study also raise a question about recent BP treatment recommendations to delay the initiation of antihypertensive medication for those aged >60 years until they exceed SBP of 150 or DBP of 90 mm Hg.[28] The higher HRs for CVD, CHD, heart failure, and stroke in the prehypertension group based on JNC 8 criteria compared with the corresponding HRs in prehypertension groups based on JNC 7 criteria suggest that postponing treatment from 140 to 150 mm Hg in people aged ≥60 years may increase the risk of incident CVD events. This delay in treatment will also increase cumulative BP exposure and thus may increase end-organ damage and the risk of reaching the point of no return, if it exists.

Results from the Trial of Preventing Hypertension (TROPHY) study suggest that reductions in incident hypertension and lower overall cumulative exposure to BP levels can be achieved with pharmacological therapy in those with prehypertensive BP levels.[34] An even more desirable approach would be effective implementation of social, public health, and medical care policies to promote maintenance of ideal BP levels from youth into older age and to help restore ideal BP in people on antihypertensive medication through healthier diets and lifestyle modifications.

In the CARDIA study, a large number of participants were excluded due to nonparticipation in the Y25 examination and missing LVMI or cumulative SBP. The large missing values may create biases in the results. We compared those who were included in the analysis and those who were excluded from the analysis with respect to the baseline characteristics. We then developed a propensity equation for inclusion based on the characteristics that were significantly different between the 2 groups. For each end-organ-damage variable, we used the inverse propensity probability for inclusion to perform the weighed regression analyses. The results are very similar, thus the CARDIA findings are unlikely to be biased.

These data from the CARDIA and MESA studies provide a unique opportunity to examine whether BP treatment can lower CVD risk to ideal levels; however, the findings are from observational studies, not randomized controlled clinical trials, and take into account neither the potential adverse effects of antihypertensive medications nor their financial costs. In addition, because the BP measurements were taken at a single visit, there may be some misclassification due to day-to-day variability. Consequently, the results should be interpreted with caution. Nonetheless, among all 6 BP strata in both studies, the normotensive group showed the lowest risk of end-organ damage and clinical CVD. These results clearly indicate that, from a public health standpoint, health care providers should place more emphasis on primordial prevention of BP elevation to further reduce CVD morbidity and mortality.

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Disclosures

None.

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