ORIGINAL RESEARCH

Increased Proximal Aortic Diameter is Associated With Risk of Cardiovascular Events and All-Cause Mortality in Blacks The Jackson Heart Study

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***Background*—**Enlargement of the proximal aorta is associated with aortic wall tissue remodeling, including fragmentation of the elastin fibers, increased synthesis of collagen, and calcification, all of which are associated with aortic wall stiffening. We hypothesized that the proximal aortic diameter (AoD) is associated with cardiovascular events in a community-based cohort of blacks.

***Methods and Results*—**We investigated the associations between AoD and cardiovascular events among 3018 black participants (mean age, 55.9 years; 69% women) without past history of cardiovascular disease in the Jackson Heart Study. AoD was measured using echocardiography at the level of the sinuses of Valsalva at end diastole. Cardiovascular event was defined as incident myocardial infarction, fatal coronary artery disease, stroke, or heart failure hospitalization. Cox proportional hazards regression models were used to evaluate the association between baseline AoD and cardiovascular events. Over a median follow-up of 8.3 years, there were 258 cardiovascular events (incident rate, 10.5 per 1000 person-years). After adjustment for traditional risk factors, increased AoD was significantly associated with cardiovascular events (hazard ratio per 1-cm increase, 1.72; 95% CI, 1.10–2.69; $P<0.05$). Participants in the top AoD quintile had a higher incidence of cardiovascular events compared to those not in the top quintile (hazard ratio, 1.47; 95% CI, 1.11–1.94; $P<0.005$) after adjustment for risk factors.

***Conclusions*—**Greater AoD was associated with an increased risk of cardiovascular events in a community-based cohort of blacks. AoD may be useful as a predictor of incident cardiovascular events and further investigation is warranted. **(*J Am Heart Assoc*. 2017;6:e005005. DOI: 10.1161/JAHA.116.005005.)**

Key Words: Blacks • aorta • cardiovascular events • echocardiogram • Jackson Heart Study

The proximal aorta plays an important role in aortic hemodynamics and left ventricular (LV) afterload changes.[1–4] The proximal aorta directly receives the blood ejected from the left ventricle and efficiently transports it to peripheral organs. Structural and qualitative changes of the proximal aorta directly affect aortic hemodynamics and LV afterload.[5,6] The diameter of the proximal aorta (AoD) is known to increase as people age.[1] The increase in AoD is associated with tissue remodeling of the aortic wall that involves fragmentation of the elastin fibers, increased synthesis of collagen, and calcification, all of which are associated with aortic wall stiffness.[2,7]

The association between the proximal aorta and cardiovascular events has been examined in several epidemiological studies with conflicting findings.[8–10] An increase in AoD was associated with a higher incidence of cardiovascular events in the CHS (Cardiovascular Health Study)[9] and in an Italian general cohort.[11] Conversely, a smaller AoD was associated with all-cause and cardiovascular mortality in Japanese patients with heart failure (HF).[10] Current literature relating AoD to cardiovascular events in blacks is sparse. Blacks have higher cardiovascular mortality compared with whites or Hispanics,[12,13] probably attributed to a higher incidence of hypertension in the group.[12] Given that aortic stiffness is reported to be higher in blacks than other races, aortic structure and its remodeling may be associated with incident cardiovascular events.[14] Accordingly, the purpose of this

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Accompanying Tables S1 through S5 are available at http://jaha.ahajournals.org/content/6/6/e005005/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What is New?

- The proximal aortic diameter is routinely measured in echocardiographic examinations. However, its clinical importance has not been fully understood.
- In a prospective community-based black cohort, the Jackson Heart Study, increased aortic root diameter was associated with higher risk of cardiovascular events, including incident stroke, coronary heart disease, and heart failure, and also was associated with all-cause mortality.
- This study has added to existing literature on the relation between aortic root size and cardiovascular events by including prospectively collected information on a community-based cohort of blacks.

What are the Clinical Implications?

- Greater aortic diameter (absolute aortic diameter, aortic diameter indexed by height, and aortic diameter indexed by body surface area, and top quintile aortic diameter) was associated with higher cardiovascular event rates.
- Aortic root diameter might serve as a marker of future cardiovascular events among blacks.

study was to investigate the relation between AoD and risk of cardiovascular events in a community-based cohort of blacks, the JHS (Jackson Heart Study).

Methods

Study Participants

The JHS is a prospective, community-based, observational study designed to investigate risk factors for cardiovascular diseases in blacks.[15] Details of the JHS have been described elsewhere.[16] Briefly, 5301 black participants residing in the Jackson, Mississippi, tri-county area (Hinds, Rankin, and Madison) were recruited for the baseline exam between 2000 and 2004 and completed a subsequent 3 study follow-up visits. The JHS was approved by the institutional review boards of Jackson State University, Tugaloo College, and the University of Mississippi Medical Center, Jackson, Mississippi. All study participants gave written informed consent. From the 5301 participants, we excluded those with a past history of cardiovascular disease at baseline (n=488), including HF, stroke, and coronary heart disease (CHD), and those with missing information on the following (in hierarchical order): echocardiographic variables (n=631); blood pressure variables (n=833); and other covariates (n=331; Figure 1). We did not have information about whether participants had bicuspid valves. There were no participants with severe aortic valve regurgitation in our sample. The remaining 3018 participants were included in the final analysis of the current study. The differences of the baseline characteristics between included and excluded participants are provided in Table S1. Included participants were older, more likely to be women, had a higher body mass index (BMI), lower prevalence of current smoking, lower total/high-density lipoprotein (HDL) cholesterol ratio, and higher systolic blood pressure and pulse pressure than excluded participants.

Outcomes

The primary outcome was cardiovascular events defined as CHD, including myocardial infarction and fatal CHD, stroke, or HF hospitalization from enrollment through December 31, 2011. Cardiovascular events were ascertained through directed patient queries during annual telephone follow-up and ongoing surveillance of hospitalizations and subsequently confirmed through the review of hospital records and death certificates.[17] In the JHS cohort, HF hospitalization surveillance began January 1, 2005. HF hospitalizations in the JHS cohort were identified and adjudicated as previously described.[18] Study participants who did not develop cardiovascular events were censored by December 21, 2011. For the analysis of CHD, stroke, and HF hospitalization events, we excluded those with prevalent CHD for the analysis of CHD, those with prevalent stroke for the analysis of stroke, and those with prevalent HF for the analysis of HF hospitalization (Figure 1). The secondary outcome was all-cause mortality. For the analysis of all-cause mortality, participants with cardiovascular disease at baseline were included (Figure 1). Methods for identification of all-cause mortality in the JHS cohort have been described previously.[17] All-cause mortality was ascertained by the annual follow-up unit, vital records, and the National Death Index.[17]

Clinical Covariates

At visit 1, systolic and diastolic blood pressures were measured in the right arm of participants twice using the random-0 blood pressure sphygmomanometer (Hawksley and Sons Limited, Sussex, United Kingdom). The first blood pressure was obtained after allowing the participant to rest for 5 minutes in a seated position and a second blood pressure was obtained after waiting 1 additional minute. The average of the 2 measurements was used. Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure. BMI was calculated as body weight (kg)/(height (m))^2. Current smoking status was defined as yes or no based on self-report at the time of the baseline exam. Information on hypertensive medications was obtained from participants at the time of the baseline exam. Venous blood samples were drawn from each participant after more than 8 hours of fasting at visit 1. Fasting plasma glucose, hemoglobin A1c,

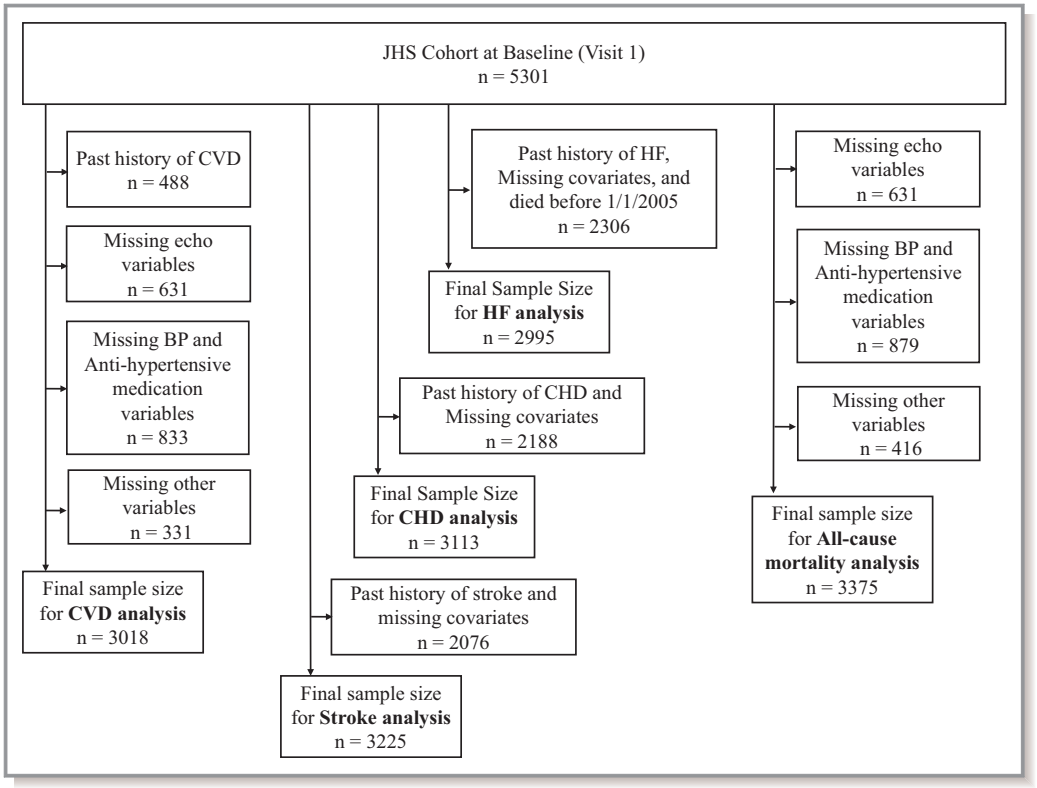

Figure 1. Inclusion and exclusion of study participants in each analysis. BP indicates blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; JHS, Jackson Heart Study.

total cholesterol concentration, and high-density lipoprotein (HDL) cholesterol concentration were assessed using standard laboratory techniques. Diabetes mellitus was defined as the use of diabetes mellitus medications, a hemoglobin A1c ≥6.5%, or a fasting blood glucose ≥126 mg/dL at baseline. The ratio of total cholesterol/HDL cholesterol was used as a covariate of lipid metabolism status.

Echocardiographic Parameters

Echocardiograms were performed by appropriately trained sonographers and interpreted by experienced cardiologists in the Echocardiography Reading Center at the University of Mississippi Medical Center. Standard echocardiographic views were obtained by trained sonographers and measurements were performed by 1 interpreting cardiologist (T.E.S.) who was blinded to participants' clinical data.[19] The following echocardiographic variables were used for the study: AoD (measured on 2-dimensional [2D] images at the sinuses of Valsalva at end diastole), LV diastolic dimension (LVDd; measured on 2D images at end diastole), LV systolic dimension (LVDs; measured on 2D images at end systole), LV posterior wall thickness at end diastole (PWd; measured on 2D images at end diastole), LV interventricular septum wall thickness at end diastole (IVSd; measured on 2D images at end diastole), LV end-diastolic volume (LVEDV; calculated as $7\times(\text{LVDd})^3/(100\times(\text{LVDd}+2.4))$, LV end-systolic volume (LVESV; calculated as $7\times(\text{LVDs})^3/(100\times(\text{LVDs}+2.4))$, stroke volume (SV; calculated as LVEDV−LVESV), LV mass index (LVMI; calculated as $0.8\{1.04[(\text{LVDd}+\text{IVSd}+\text{PWd})^3-(\text{LVDd})^3]+0.6\}$ and indexed to body surface area), relative wall thickness ($2\times\text{PWd}/\text{LVDd}$), and LV ejection fraction (LVEF; calculated as $100\times\text{SV}/\text{LVEDV}$).

Statistical Analysis

Data are presented as mean±SD for continuous variables and percentages for categorical variables. Clinical and demographic characteristics were examined by sex-specific quintiles of AoD as performed in a previous study[9]: The bottom 4 quintiles were grouped into 1 category and served as a reference for comparison with the top quintile. Differences between the 2 groups were assessed using the Student *t* test for continuous variable and chi-square tests for categorical variables. We used 1-way ANOVA for comparisons of continuous variables among quintiles and chi-square tests for comparisons of categorical variables among quintiles.

Cross-Sectional Analysis

First, to investigate the relationships among AoD, age, and anthropometric measures, we examined simple correlations separately in each sex. Second, we performed multiple linear

regression analyses also separately in each sex to determine the best measure of AoD by comparing Akaike information criteria and R^2 of the model that included combinations of variables of age, height, weight, and squares of these variables to the base model, including only age, height, and weight (model 1). When squares of these variables were added to the base model, only age squared in men and weight squared in women were statistically significant, but their contributions to the model were weak (decrement in Akaike information criteria and increment in R^2 were 2, 0.003 for age squared in men, and 1, 0.001 for weight squared in women, respectively). Therefore, for the following analyses to examine the relationships between AoD and blood pressure variables, we adjusted for age, height, and weight. We examined the relationships between AoD and blood pressure variables (systolic blood pressure: model 2, diastolic blood pressure: model 3, and pulse pressure: model 4) because blood pressure variables have been also associated with AoD in several previous studies.[1,6]

We additionally examined the relationship between AoD and a simple arterial stiffness indicator: pulse pressure/SV. Pulse pressure/SV is the inverse of total arterial compliance (model 5).[20]

Longitudinal Analysis

To illustrate the effect of AoD on outcomes, Kaplan–Meier curves for cumulative survival free from cardiovascular events were constructed for 2 groups of participants and compared using log-rank tests. Cox proportional hazards models after testing for proportionality assumption were used to estimate the hazard ratios (HRs) of cardiovascular events or all-cause mortality using AoD as a continuous variable as well as categorical variable (top quintile versus the rest). We used absolute AoD, AoD indexed to height (in cm), and AoD indexed to body surface area (BSA; in m^2) as suggested by previous literature and guidelines.[11] Two models, minimally and fully adjusted models, were constructed to evaluate associations of AoD with outcomes, and we did not include squared measures for any of the variables in these analyses. Model 1 included adjustment for age and sex, whereas model 2 additionally included BMI, history of hypertension, ratio of total cholesterol/HDL cholesterol, history of diabetes mellitus, and smoking status. When we used AoD indexed to height or BSA in model 2, we removed BMI from the model to avoid multicollinearity. Stratified analyses were then performed to estimate the HRs based on age <70 or ≥ 70 years, sex, systolic blood pressure <140 or ≥ 140 mm Hg, hypertension medication use, BMI <30 or ≥ 30 kg/m^2, ratio of total cholesterol/HDL cholesterol <3.5 or ≥ 3.5, diabetes mellitus, and smoking status. Interactions of these variables (age, sex, blood pressure, smoking status, total to HDL ratio, and diabetes mellitus status) with AoD were examined using interaction terms in the models. All analyses were performed using SAS software (version 9.4 for Windows; SAS Institute Inc, Cary, NC). A 2-sided $P<0.05$ was considered significant.

Results

Baseline Characteristics

Table 1 shows clinical, demographic, and echocardiographic characteristics of the study cohort classified into the sex-specific top quintile of AoD (35.2 ± 2.8 mm) and the other quintiles (30.8 ± 2.8 mm). The participants in the top AoD quintile were older, had higher BMI, systolic blood pressure, diastolic blood pressure, pulse pressure, and had larger LV dimensions or volumes both in systole and diastole. LVEF was not significantly different between groups. We also provided baseline characteristics based on absolute AoD quintiles, AoD/height quintiles, and AoD/BSA quintiles (Tables S2 through S4). Age and blood pressure variables were similarly and consistently associated with absolute AoD, AoD/height, and AoD/BSA. However, the relationships between AoD variables and BMI, hemoglobin A1C, rate of diabetes mellitus history, and total/HDL cholesterol ratio were different (opposite direction) between when AoD/height and AoD/BSA were used.

Relationships Among AoD, Age, Anthropometric Measures, and Blood Pressure Variables

Correlations among AoD, age, and anthropometric measures are shown in Table 2. AoD was positively correlated with age, height, weight, and BSA in both sexes ($P<0.001$ for all). Using multiple linear regression analysis, age, height, and weight were still significantly associated with AoD in both sexes ($P<0.01$ for all; Table 3, model 1). After adjusting for age, height, and weight, diastolic blood pressure and pulse pressure, but not systolic pressure, were significantly associated with AoD in men, whereas systolic pressure and diastolic pressure, but not pulse pressure, were significantly associated with AoD in women (Table 3, models 2–4). AoD was negatively associated with a simple arterial stiffness indicator in both sexes (Table 3, model 5).

AoD and Cardiovascular Events

Over a median follow-up of 8.3 years, there were 258 cardiovascular events (incident rate, 10.5 per 1000 person-years). There were 129 CHD, 97 stroke, and 139 HF hospitalization events in each. Figure 2 shows the Kaplan–Meier survival curves for incident cardiovascular events for the top AoD quintile and the bottom 4 quintiles. The top AoD

Table 1. Baseline Patient Characteristics

Variables	Bottom 4 AoD Quintiles (30.8±2.8 mm) (n=2422)	Top AoD Quintile (35.2±2.8 mm) (n=596)	*P* Value
Age, y	55±12	60±12	<0.001
BMI, kg/m^2	31.7±6.9	33.7±7.8	<0.001
Diabetes mellitus, n (%)	475 (20)	128 (21)	0.30
Current smokers, n (%)	253 (10)	51 (9)	0.20
Hemoglobin A1c, %	5.9±1.2	5.9±1.1	0.90
Total/HDL cholesterol ratio	4.1±1.3	4.0±1.2	0.53
SBP, mm Hg	126±17	131±18	<0.001
DBP, mm Hg	79±10	80±10	0.003
Pulse pressure, mm Hg	47±15	51±17	<0.001
Heart rate, bpm	65±10	65±11	0.83
LVDd, mm	48.2±4.5	51.3±17.1	<0.001
LVDs, mm	29.6±4.8	30.0±5.3	<0.001
LVEDV, mL	156±29	161±32	<0.001
LVESV, mL	57±19	60±23	0.019
SV, mL	98±20	102±20	<0.001
LVMI, g/m^2	72±25	79±24	<0.001
Relative wall thickness	0.36±0.07	0.36±0.09	0.007
LVEF, %	63.3±9.0	63.5±8.5	0.53

Data are presented as mean±SD for continuous variables and percentages for categorical variables. Student *t* test for continuous variables and chi-square tests for categorical variables were used for comparison of 2 groups. AoD indicates diameter of proximal aorta; BMI, body mass index; DBP, diastolic blood pressure; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mas index; SBP, systolic blood pressure; SV, stroke volume.

quintile had a higher risk of cardiovascular events than the bottom 4 quintiles (unadjusted HR, 2.05; 95% CI, 1.58–2.67; *P*<0.0001). The Kaplan–Meier survival curve for each component of the cardiovascular events is also shown. Table 4 shows HRs and 95% CIs of cardiovascular events based on AoD. AoD, AoD indexed to height, and top AoD quintile were associated with incident cardiovascular events (model 1; *P*<0.01). On the other hand, AoD indexed by BSA was not associated with cardiovascular events. After adjusting for conventional cardiovascular disease risk factors, AoD, AoD indexed by height, AoD indexed by BSA, and top AoD quintile were significant (HR, 1.72 per 1-cm increase; 95% CI, 1.10–2.69; *P*<0.05; HR, 2.87 per 1-cm/m increase; 95% CI, 1.42–5.79; *P*<0.005; HR, 2.69 per 1-cm/m^2 increase; 95% CI, 1.32–5.48; *P*<0.01; HR [versus the rest], 1.47; 95% CI, 1.11–1.94; *P*<0.005, respectively). There were not any AoD indices that were consistently associated with CHD, stroke, and HF hospitalization events. Figure 3 shows the results of stratified analyses for cardiovascular events. The association of AoD with cardiovascular events was qualitatively consistent across all subgroups.

Table 2. Correlations Among AoD, Age, and Anthropometric Measures, by Sex

	Men		Women	
Variables	Coefficient*	*P* Value	Coefficient*	*P* Value
Age	0.142	<0.001	0.143	<0.001
Height	0.126	<0.001	0.193	<0.001
Weight	0.150	<0.001	0.227	<0.001
BSA	0.115	<0.001	0.169	<0.001

AoD indicates diameter of proximal aorta, BSA, body surface area.
*Represents Pearson's correlation coefficient.

AoD and All-Cause Mortality

Baseline characteristics for this analysis, including participants with cardiovascular events at baseline, are shown in Table S5. The relationships between the top AoD quintile and bottom 4 AoD quintiles were quite similar to those for the main analysis. Over a median follow-up of 8.3 years, there were 337 deaths from all causes (mortality rate, 12.0 per 1000 person-years). Table 5 shows HRs and 95% CIs of all-cause mortality based on AoD. After adjustment for age and sex, only AoD indexed to height was associated with risk of mortality from all causes (*P*<0.05), whereas absolute AoD, AoD indexed to BSA, and top AoD quintile were not. After adjustment for known cardiovascular disease risk factors, AoD indexed to height and AoD indexed to BSA were associated with risk of all-cause mortality (HR, 1.94 per 1-cm/m increase; 95% CI, 1.08–3.48; *P*<0.05, and HR, 1.86 per 1 cm/m^2; 95% CI, 1.08–3.18; *P*<0.05, respectively).

Discussion

In this community-based black cohort, all forms of AoD (AoD, AoD/height, and AoD/BSA, top AoD quintile versus bottom 4 quintiles) were associated with risk of cardiovascular events after adjustment for relevant risk factors. In secondary analyses, AoD indexed to height or BSA was associated with all-cause mortality after adjustment for these risk factors. In cross sectional analyses, AoD was associated with age, height, and weight in both sexes. AoD was also positively correlated with diastolic blood pressure and negatively with pulse pressure in men and positively correlated with both systolic and diastolic blood pressure in women.

Several previous reports described the relationship between AoD and cardiovascular disease. In the Cardiovascular Health Study, a greater AoD was associated with a

Table 3. Associations Among AoD, Age, Anthropometric Measures, and Blood Pressure Variables Assessed in Multiple Regression Models

Variables	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	Model 4 β (95% CI)	Model 5 β (95% CI)
Men					
Age, y	0.005 (0.003, 0.006)*	0.005 (0.003, 0.006)*	0.005 (0.004, 0.007)*	0.005 (0.003, 0.006)*	0.005 (0.004, 0.006)*
Height, cm	0.005 (0.002, 0.008)*	0.005 (0.002, 0.008)*	0.005 (0.002, 0.008)*	0.005 (0.002, 0.008)*	0.006 (0.004, 0.008)†
Weight, kg	0.002 (0.001, 0.003)*	0.002 (0.001, 0.003)*	0.002 (0.001, 0.003)*	0.002 (0.001, 0.003)*	0.003 (0.002, 0.003)*
SBP, mm Hg		0.000 (-81×10^{-5}, 0.002)			
DBP, mm Hg			0.004 (0.002, 0.006)*		
PP, mm Hg				−0.002 (−0.003, -21×10^{-5})‡	
PP/SV, mm Hg/mL					−0.117 (−0.170, −0.064)*
Women					
Age, y	0.004 (0.003, 0.005)*	0.004 (0.003, 0.005)*	0.005 (0.004, 0.006)*	0.005 (0.004, 0.006)*	0.005 (0.004, 0.007)*
Height, cm	0.007 (0.005, 0.008)*	0.007 (0.005, 0.009)*	0.006 (0.004, 0.008)*	0.007 (0.005, 0.008)*	0.004 (0.001, 0.007)*
Weight, kg	0.003 (0.002, 0.003)*	0.003 (0.002, 0.003)*	0.003 (0.002, 0.003)*	0.003 (0.002, 0.003)*	0.002 (0.001, 0.003)*
SBP, mm Hg		0.001 (0.001, 0.002)*			
DBP, mm Hg			0.004 (0.003, 0.006)*		
PP, mm Hg				-48×10^{-5} (−0.001, 0.000)	
PP/SV, mm Hg/mL					−0.129 (−0.216, −0.041)*

Model 1 included age, height, and weight. Model 2 included model 1+SBP. Model 3 included model 1+DBP. Model 4 included model 1+PP. Model 5 included model 1+PP/SV. AoD indicates diameter of proximal aorta; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; SV, stroke volume.
*$P<0.05$.
†$P<0.01$.
‡$P<0.005$.

higher incidence of several cardiovascular events, including incident HF, stroke, cardiovascular mortality, and all-cause mortality.[9] In the Pamela study, a larger AoD indexed to height, but not absolute AoD or AoD indexed to BSA, was associated with cardiovascular events.[11] In the Framingham Heart Study, a larger AoD was associated with incident HF.[8] Our study results are in line with these previous studies and extend the finding to a community based cohort of blacks. On the other hand, a smaller AoD was associated both with higher all-cause mortality and cardiovascular mortality among Japanese HF patients with mainly reduced LVEF.[10] The inconsistent finding in the Japanese study could be attributed to a difference in race, age range, or underlying conditions (ie, general population versus HF patients) among the cohorts.

There are several mechanisms linking AoD to cardiovascular events. In the current study, AoD was positively correlated with age. Age-associated enlargement of AoD is thought to be associated with tissue remodeling of the aortic wall that includes a reduction in elastin fiber, increased collagen deposition, and increased calcification.[2,7] These structural alterations are associated with increased aortic stiffness.[2,7,21] Thus, we speculate that the resultant functional changes of the aorta might contribute to the relationship between AoD and cardiovascular events observed in this study. However, in men, AoD was negatively associated with pulse pressure, and in women AoD was not associated with pulse pressure. AoD was negatively associated with an arterial stiffness indicator in both sexes. These results suggest that although the enlargement of AoD could reflect aortic wall remodeling, the increased diameter itself does not contribute to increased aortic stiffness. Of note, in this study, pulse pressure was positively associated with both cardiovascular events and all-cause mortality, whereas diastolic blood pressure, which was positively correlated with AoD in both sexes, was not associated with cardiovascular events or all-cause mortality after adjustment (data not shown). Several previous studies have reported negative correlations between AoD and central or peripheral pulse pressure, and some of them showed a negative correlation between AoD and characteristic impedance of the proximal aorta.[6,10,22] Several reports suggested that enlargement of the arterial lumen diameter might compensate for age-related increases in arterial stiffness and limit deterioration of the buffering capacity of the central artery, and it could be a maladaptive

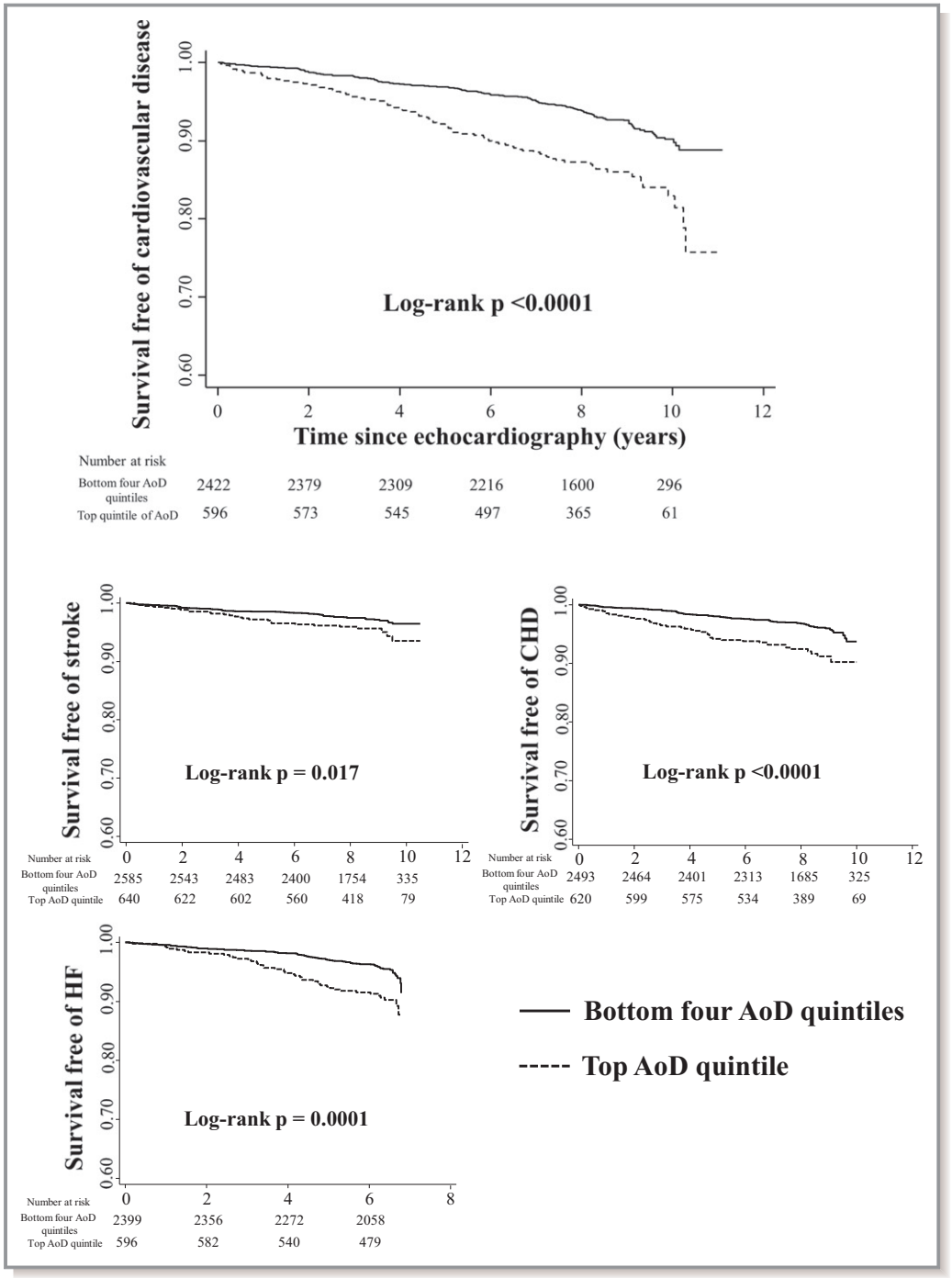

Figure 2. Kaplan–Meier survival curves. AoD indicates proximal aortic diameter; CHD, coronary heart disease. Heart failure (HF) hospitalization surveillance began January 1, 2005 in the Jackson Heart Study, and its follow-up period is less than those of the other events.

process, leading to a poor prognosis.[23–25] This concept may explain the discrepancy of the study results between the negative correlation of AoD with an arterial stiffness indicator in both sexes and the positive association of AoD with cardiovascular events. However, as we noted above, the tissue remodeling of the aorta at the time of enlargement of aorta has been associated with increased stiffness of the aortic wall. Therefore, we believe that further investigation of the relationships between these components (aortic wall stiffness, whole aortic stiffness, and hemodynamic indicator) and aortic remodeling is warranted.

We observed sex differences in the relationships between AoD and aortic characteristics. In our cross-sectional study, AoD was negatively associated with pulse pressure and

Table 4. HRs for Cardiovascular Events in Relation to Increases in AoD

Variables		All Cardiovascular Events HR (95% CI)*	Stroke HR (95% CI)*	CHD HR (95% CI)*	HF HR (95% CI)*
AoD	Model 1	1.85 (1.22–2.80)†	1.30 (0.68–2.50)	1.57 (0.88–2.80)	1.84 (1.05–3.21)‡
	Model 2	1.72 (1.10–2.69)‡	1.36 (0.71–2.60)	1.51 (0.85–2.67)	1.47 (0.82–2.61)
AoD/height	Model 1	3.21 (1.59–6.45)†	2.04 (0.67–6.17)	2.81 (1.05–7.49)‡	3.03 (1.17–7.82)‡
	Model 2	2.87 (1.42–5.79)†	1.92 (0.63–5.83)	2.42 (0.92–6.41)	2.77 (1.06–7.24)‡
AoD/BSA	Model 1	1.45 (0.77–2.74)	2.42 (0.91–6.42)	2.10 (0.88–5.04)	0.72 (0.30–1.74)
	Model 2	2.69 (1.32–5.48)§	3.35 (1.24–9.07)‡	2.80 (1.15–6.83)‡	0.95 (0.38–2.36)
AoD top quintile	Model 1	1.55 (1.19–2.02)†	1.30 (0.83–2.02)	1.75 (1.21–2.54)†	1.44 (1.00–2.06)‡
	Model 2	1.47 (1.11–1.94)†	1.36 (0.87–2.13)	1.76 (1.21–2.56)†	1.23 (0.85–1.78)

Model 1 included adjustment by age, sex. Model 2 included model 1 plus body mass index, history of hypertension, ratio of total cholesterol/high-density lipoprotein cholesterol, past history of diabetes mellitus, and current smoking status. AoD indicates diameter of proximal aorta; BSA, body surface area; CHD, coronary heart disease; HF, heart failure; HR, hazard ratio.
*Represents per 1-cm increase for AoD, per 1-cm/m increase for AoD/height, per 1-cm/m^2 increase for AoD/BSA, and against the other quintiles for AoD top quintile.
†P<0.05.
‡P<0.01.
§P<0.005.

positively associated with diastolic blood pressure in men. On the other hand, AoD was positively associated with systolic and diastolic blood pressure in women. Age-related changes in arterial characteristics, including stiffness, may be different between men and women, and other factors, including discontinuation of antihypertensive medication, lipid-lowering medication, and education, might influence the changes.[26,27] Of note, no sex differences were observed in the longitudinal analysis. Therefore, AoD may be used as a predictor of incident cardiovascular events in both sexes in blacks.

We examined several indices of AoD (ie, absolute AoD, AoD indexed to height, and AoD indexed to BSA). AoD indexed to BSA has been recommended in the current American Society of Echocardiography and European Association of Echocardiography guidelines.[28] However, in several previous cross-sectional and longitudinal studies, height was the most

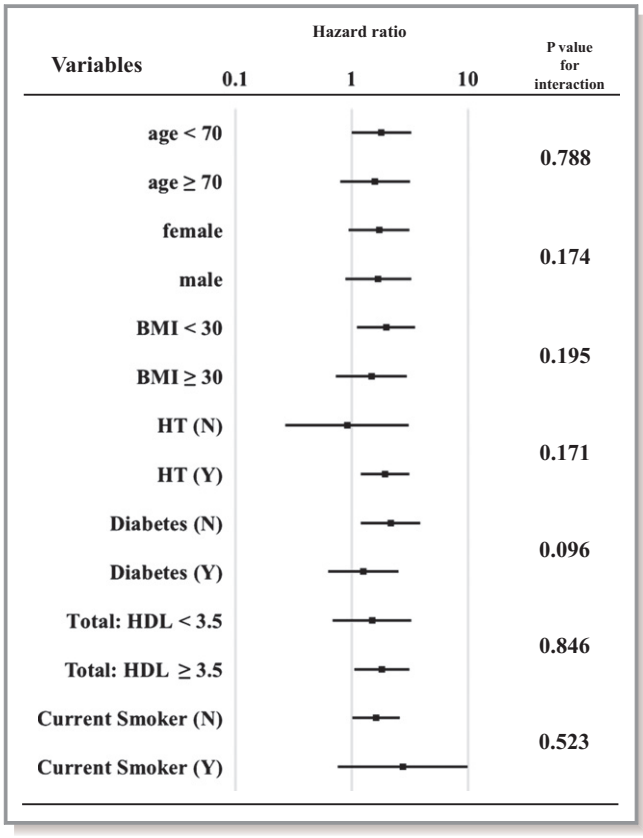

Figure 3. Stratified analysis of hazard ratios for aortic diameter and cardiovascular events. BMI indicates body mass index; BP Meds, antihypertensive medication; HDL, high-density lipoprotein cholesterol; HT, hypertension; SBP, systolic blood pressure; Total, total cholesterol.

Table 5. HRs for All-Cause Mortality in Relation to Increases in AoD

Variables		All-Cause Mortality HR (95% CI)*
AoD (per 1-cm increase)	Model 1	1.26 (0.89–1.78)
	Model 2	1.25 (0.88–1.76)
AoD/height (per 1-cm/m increase)	Model 1	1.99 (1.11–3.58)†
	Model 2	1.94 (1.08–3.48)†
AoD/BSA (per 1-cm/m^2 increase)	Model 1	1.59 (0.94–2.71)
	Model 2	1.86 (1.08–3.18)†
AoD top quintile (vs the rest)	Model 1	1.25 (0.98–1.59)
	Model 2	1.22 (0.96–1.56)

Model 1 included adjustment by age, sex. Model 2 included model 1 plus body mass index, history of hypertension, ratio of total cholesterol/high-denisty lipoprotein cholesterol, past history of diabetes mellitus, and current smoking status. AoD indicates diameter of proximal aorta; BSA, body surface area; HR, hazard ratio.
*Represents per 1-cm increase for AoD, per 1-cm/m increase for AoD/height, per 1-cm/m^2 increase for AoD/BSA, and against the other quintiles for AoD Top quintile.
†P<0.05.

important determinant of AoD and therefore was regarded as more appropriate to normalize AoD.[1,10,11] In the cross-sectional analysis of the current study, height and BSA were significantly correlated with AoD, but both correlations were modest. These results are similar to the study results performed in whites.[1] With regard to baseline characteristics, age and blood pressure variables were similarly and consistently associated with all the AoD indices. However, there were significant differences in some baseline characteristics between when AoD/height was used and when AoD/BSA was used. When participants were divided into AoD/BSA quintiles, Q1 participants had quite larger BMIs than Q5 participants (38.5±8.3 versus 27.1±4.3). Accordingly, the Q1 participants had higher hemoglobin A1c, total/HDL cholesterol ratio, and higher rate of diabetes mellitus than Q5 participants. On the other hand, when participants were divided into AoD/height quintiles, Q1 participants had lower BMI than Q5 participants. In obese participants, the BSA is very large, and AoD/BSA becomes much smaller. Therefore, we think the AoD/BSA was relatively small in obese participants. On the other hand, AoD/height is not influenced by obesity. These differences might contribute to the differences in baseline characteristics when different AoD indices are used. These differences in baseline characteristics should be recognized if different AoD indices are utilized. In our longitudinal analysis, all AoD indices, including absolute AoD, AoD indexed to height, and AoD indexed to BSA, were associated with increased risk of cardiovascular events after adjustment for possible confounders. However, only AoD indexed to height or BSA was associated with all-cause mortality. These results suggest that AoD indexed to height or BSA can be incorporated into risk prediction models for future cardiovascular events or all-cause mortality. Absolute AoD, although not associated with all-cause mortality in our study, can be easily measured and was associated with cardiovascular events in the current study. Thus, we think that absolute AoD can be useful in clinical settings as a qualitative predictor of incident cardiovascular events.

Our study has a few limitations. First, around 37% of all the JHS participants were excluded from this study mainly because of missing antihypertensive medication variable and missing echo parameters. Antihypertensive medication use is a significant risk factor for cardiovascular events in this population.[29] Therefore, we excluded those participants. The majority of these participants were overweight or obese; the quality of echocardiography was suboptimal for use in the current investigation. Therefore, exclusion of these individuals may have introduced some degree of bias in our results. Second, there are some differences in the characteristics between included and excluded study participants. Third, a single measurement of AoD was used for the current study. It is not clear whether or how changes in AoD with time may have affected outcomes in the study cohort. However, our focus was not on serial change of AoD, but its association with risk of cardiovascular events. Fourth, augmentation index, pulse wave velocity, or central aortic pressure was not available at the time of echocardiography. These measurements might have provided us information to better understand the inter-relationship among AoD, central blood pressure, and cardiovascular events. Last, we did not have detailed information about aortic valve anatomy in the study participants, and we could not evaluate the potential influence of bicuspid valve aortopathy.

There are several strengths of our study. First, to our knowledge, this is the first report examining the relationship between AoD and cardiovascular events in a large, community-based cohort of blacks. The JHS is the largest US-based cohort with contemporary data on cardiovascular risk factors among blacks, a population with a greater burden of cardiovascular morbidity and mortality.[12,30] Second, data were prospectively collected using standardized methods for AoD measurement, assessment of blood pressure, and covariates at baseline. Finally, all cardiovascular events in the JHS were adjudicated by clinical reviewers reducing the potential for event misclassification.

In conclusion, a larger AoD was associated with increased risk of cardiovascular events in a community-based black cohort. Dilation of the proximal aorta, which is easily measured by echocardiography in clinical settings, may be useful as a qualitative predictor of incident cardiovascular events and all-cause mortality.

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Disclosures

None.

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Supplemental Material

Table S1. Differences of Baseline Characteristics Between Included and Excluded Participants

Variables	Included Participants (n = 3018)	Excluded Participants (n = 1795)	p value
Age (years)	56 ± 12	52 ± 14	<0.001
Female, n (%)	2077 (69)	1024 (58)	<0.001
Body mass index (kg/m^2)	32.1 ± 7.1	31.1 ± 7.4	<0.001
Diabetes mellitus, n (%)	603 (20)	365 (21)	0.42
Current smokers, n (%)	304 (10)	298 (17)	<0.001
Hemoglobin A1c (%)	5.9 ± 1.2	6.0 ± 1.4	0.26
Total / HDL cholesterol ratio	4.1 ± 1.3	4.2 ± 1.4	<0.001
SBP (mmHg)	127 ± 18	126 ± 19	0.004
DBP (mmHg)	79 ± 10	79 ± 11	0.47
Pulse Pressure (mmHg)	48 ± 16	47 ± 16	0.005
Heart Rate (bpm)	65 ±10	65 ± 11	0.83

Data are presented as mean ± standard deviation for continuous variables and percentages for categorical variables. Student t-test for continuous variables and chi-square tests for categorical variables were used for comparison of two groups.

SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high density lipoprotein

Table S2. Baseline characteristics according to AoD quintiles

Variables	Q1	Q2	Q3	Q4	Q5	p value
Age (years)	53 ± 12	54 ± 12	57 ± 12	57 ± 11	60 ± 12	**<0.001**
Body mass index (kg/m^2)	30.3 ± 6.6	31.6 ± 6.7	32.3 ± 6.7	32.6 ± 7.1	33.7 ± 7.8	**<0.001**
Diabetes mellitus, n (%)	93 (15)	115 (19)	134 (22)	133 (22)	128 (22)	**0.004**
Current smokers, n (%)	60 (10)	80 (13)	64 (11)	49 (8)	51 (9)	**0.040**
Hemoglobin A1c (%)	5.8 ± 1.1	5.9 ± 1.1	6.0 ± 1.2	6.0 ± 1.2	5.9 ± 1.1	**0.029**
Total / HDL cholesterol ratio	3.9 ± 1.2	4.1 ± 1.4	4.1 ± 1.2	4.2 ± 1.3	4.0 ± 1.2	**0.099**
SBP (mmHg)	124 ± 16	125 ± 17	127 ± 18	128 ± 18	131 ± 18	**<0.001**
DBP (mmHg)	78 ± 10	78 ± 10	79 ± 10	80 ± 10	80 ± 10	**<0.001**
Pulse Pressure (mmHg)	47 ± 14	47 ± 15	48 ± 16	48 ± 15	51 ± 17	**<0.001**
LVDd (mm)	48 ± 4	48 ± 4	48 ± 4	48 ± 5	49 ± 5	**<0.001**

LVDs (mm)	30 ± 5	29 ± 4	30 ± 5	29 ± 5	30 ± 5	0.121
LVEDV (ml)	108 ± 23	107 ± 20	111 ± 24	111 ± 25	114 ± 26	**<0.001**
LVESV (ml)	35 ± 15	34 ± 12	35 ± 15	35 ±14	36 ± 17	0.086
Stroke volume (ml)	73 ± 16	73 ± 15	76 ± 17	77 ± 18	78 ± 17	**<0.001**
LVMI (g/m^2)	71 ± 19	71 ± 37	73 ± 19	74 ± 17	79 ± 24	**<0.001**
Relative wall thickness	0.36 ± 0.07	0.35 ± 0.06	0.36 ± 0.07	0.36 ± 0.07	0.36 ± 0.09	**0.044**
LVEF (%)	68 ± 10	69 ± 8	69 ± 8	69 ± 11	69 ± 9	0.075

Data are presented as mean ± standard deviation for continuous variables and percentages for categorical variables. One-way analysis of variance was used for comparisons of continuous variables and chi-square tests were used for comparisons of categorical variables. AoD: diameter of proximal aorta, SBP: systolic blood pressure, DBP: diastolic blood pressure, Ea: effective arterial elastance, Ees: end-systolic elastance, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mas index, LVEF: left ventricular ejection fraction, E: peak early mitral inflow velocity, A: late mitral inflow velocity

Table S3. Baseline characteristics according to AoD / Height quintiles

Variables	Q1	Q2	Q3	Q4	Q5	p value
Age (years)	52 ± 12	54 ± 12	57 ± 12	57 ± 11	60 ± 12	**<0.001**
Body mass index (kg/m^2)	30.3 ± 6.6	31.6 ± 6.7	32.3 ± 6.7	32.5 ± 7.1	33.7 ± 7.8	**<0.001**
Diabetes mellitus, n (%)	93 (15)	115 (19)	134 (22)	133 (22)	128 (22)	**0.017**
Current smokers, n (%)	60 (10)	80 (13)	64 (11)	49 (8)	51 (9)	**0.025**
Hemoglobin A1c (%)	5.8 ± 1.1	5.8 ± 1.1	6.0 ± 1.2	6.0 ± 1.2	5.9 ± 1.1	**0.004**
Total / HDL cholesterol ratio	3.9 ± 1.2	4.1 ± 1.4	4.1 ± 1.2	4.2 ± 1.3	4.0 ± 1.2	**0.045**
SBP (mmHg)	124 ± 16	125 ± 17	127 ± 18	128 ± 18	131 ± 18	**<0.001**
DBP (mmHg)	78 ± 10	78 ± 10	79 ± 10	80 ± 10	80 ± 10	**<0.001**
Pulse Pressure (mmHg)	47 ± 14	47 ± 15	48 ± 16	48 ± 15	51 ± 17	**<0.001**
LVDd (mm)	48 ± 4	48 ± 4	48 ± 4	48 ± 5	49 ± 4	**<0.001**

LVDs (mm)	29 ± 4	29 ± 4	30 ± 4	29 ± 5	30 ± 4	0.468
LVEDV (ml)	107 ± 23	107 ± 20	111 ± 24	111 ± 25	113 ± 23	**<0.001**
LVESV (ml)	35 ± 14	34 ± 12	35 ± 15	35 ±14	36 ± 14	0.468
Stroke volume (ml)	73 ± 16	73 ± 15	76 ± 17	76 ± 18	78 ± 16	**<0.001**
LVMI (g/m^2)	80 ± 26	80 ± 44	79 ± 24	81 ± 28	83 ± 48	0.417
Relative wall thickness	0.35 ± 0.06	0.35 ± 0.06	0.35 ± 0.07	0.36 ± 0.07	0.36 ± 0.09	0.326
LVEF (%)	68 ± 10	69 ± 8	69 ± 8	69 ± 11	69 ± 8	0.422

Data are presented as mean ± standard deviation for continuous variables and percentages for categorical variables. One-way analysis of variance was used for comparisons of continuous variables and chi-square tests were used for comparisons of categorical variables. AoD: diameter of proximal aorta, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mas index, LVEF: left ventricular ejection fraction, E: peak early mitral inflow velocity, A: late mitral inflow velocity

Table S4. Baseline characteristics according to AoD / BSA quintiles

Variables	Q1	Q2	Q3	Q4	Q5	p value
Age (years)	52 ± 11	54 ± 12	56 ± 12	58 ± 12	60 ± 13	**<0.001**
Body mass index (kg/m^2)	38.5 ± 8.3	33.4 ± 6.2	31.7 ± 5.4	29.7 ± 4.8	27.1 ± 4.3	**<0.001**
Diabetes mellitus, n (%)	141 (23)	144 (24)	134 (22)	100 (17)	84 (14)	**<0.001**
Current smokers, n (%)	61 (10)	56 (9)	64 (11)	58 (10)	65 (11)	0.896
Hemoglobin A1c (%)	6.0 ± 1.3	6.0 ± 1.3	6.0 ± 1.2	5.8 ± 0.9	5.7 ± 1.0	**<0.001**
Total / HDL cholesterol ratio	4.2 ± 1.4	4.1 ± 1.3	4.2 ± 1.3	4.0 ± 1.2	3.9 ± 1.2	**<0.001**
SBP (mmHg)	126 ± 16	126 ± 16	126 ± 17	128 ± 18	130 ± 20	**<0.001**
DBP (mmHg)	79 ± 10	79 ± 10	79 ± 10	79 ± 10	79 ± 11	0.370
Pulse Pressure (mmHg)	47 ± 14	47 ± 14	47 ± 15	49 ± 16	51 ± 18	**0.003**
LVDd (mm)	49.0 ± 4.5	48.3 ± 4.3	48.1 ± 4.1	48.1 ± 4.3	47.6 ± 4.5	**<0.001**

LVDs (mm)	8.8 ± 1.5	8.5 ± 1.5	8.5 ± 1.4	8.5 ± 1.9	8.4 ± 1.5	**<0.001**
LVEDV (ml)	114 ± 25	110 ± 23	109 ± 21	109 ± 23	107 ± 23	**<0.001**
LVESV (ml)	37 ± 17	35 ± 14	34 ± 12	34 ± 12	33 ± 14	**<0.001**
Stroke volume (ml)	77 ± 18	75 ± 16	75 ± 16	75 ± 16	73 ± 16	**<0.001**
LVMI (g/m^2)	71 ± 24	75 ± 23	78 ± 24	87 ± 58	90 ± 29	**<0.001**
Relative wall thickness	0.36 ± 0.07	0.36 ± 0.07	0.35 ± 0.06	0.35 ± 0.09	0.36 ± 0.07	**0.014**
LVEF (%)	68 ± 11	68 ± 8	69 ± 7	69 ± 8	69 ± 11	0.090

Data are presented as mean ± standard deviation for continuous variables and percentages for categorical variables. One-way analysis of variance was used for comparisons of continuous variables and chi-square tests were used for comparisons of categorical variables. AoD: diameter of proximal aorta, SBP: systolic blood pressure, DBP: diastolic blood pressure, Ea: effective arterial elastance, Ees: end-systolic elastance, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mas index, LVEF: left ventricular ejection fraction, E: peak early mitral inflow velocity, A: late mitral inflow velocity

Table S5. Baseline Patient Characteristics for All-cause Mortality Analysis

Variables	Bottom Four Quintiles AoD (30.7 ± 2.7 mm) (n = 2706)	Top Quintile AoD (35.6 ± 2.5 mm) (n = 669)	p value
Age (years)	56 ± 11	59 ± 11	<0.001
Body mass index (kg/m^2)	31.7 ± 6.9	33.2 ± 7.8	<0.001
Diabetes mellitus, n (%)	565 (21)	157 (24)	0.15
Current smokers, n (%)	297 (11)	69 (10)	0.62
Hemoglobin A1c (%)	5.9 ± 1.2	6.0 ± 1.4	0.061
Total / HDL cholesterol ratio	4.1 ± 1.3	4.0 ± 1.3	0.96
SBP (mmHg)	127 ± 18	130 ± 18	<0.001
DBP (mmHg)	79 ± 10	80 ± 11	<0.001
Pulse Pressure (mmHg)	49 ± 16	50 ± 16	0.035
Heart Rate (bpm)	66 ±11	65 ± 11	0.010
LVDd (mm)	48.1 ± 4.6	49.6 ± 4.6	<0.001
LVDs (mm)	29.5 ± 4.8	30.4 ± 5.1	<0.001
LVEDV (ml)	156 ± 31	166 ± 32	<0.001
LVESV (ml)	58 ± 22	62 ± 23	<0.001
Stroke volume (ml)	98 ± 20	104 ± 21	<0.001

LVMI (g/m^2)	74 ± 25	80 ± 24	<0.001
Relative wall thickness	0.36 ± 0.07	0.36 ± 0.09	0.028
LVEF (%)	63.0 ± 9.3	63.2 ± 8.6	0.71

Data are presented as mean ± standard deviation for continuous variables and percentages for categorical variables. Student t-test for continuous variables and chi-square tests for categorical variables were used for comparison of two groups.

AoD: diameter of proximal aorta, SBP: systolic blood pressure, DBP: diastolic blood pressure, Ea: effective arterial elastance, Ees: end-systolic elastance, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mas index, LVEF: left ventricular ejection fraction, E: peak early mitral inflow velocity, A: late mitral inflow velocity