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Racial Differences in Incident Heart Failure among Young Adults

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ABSTRACT

BACKGROUND

The antecedents and epidemiology of heart failure in young adults are poorly understood.

METHODS

We prospectively assessed the incidence of heart failure over a 20-year period among 5115 blacks and whites of both sexes who were 18 to 30 years of age at baseline. Using Cox models, we examined predictors of hospitalization or death from heart failure.

RESULTS

Over the course of 20 years, heart failure developed in 27 participants (mean \pm SD) age at onset, 39 ± 6 years), all but 1 of whom were black. The cumulative incidence of heart failure before the age of 50 years was 1.1% (95% confidence interval [CI], 0.6 to 1.7) in black women, 0.9% (95% CI, 0.5 to 1.4) in black men, 0.08% (95% CI, 0.0 to 0.5) in white women, and 0% (95% CI, 0 to 0.4) in white men ($P=0.001$ for the comparison of black participants and white participants). Among blacks, independent predictors at 18 to 30 years of age of heart failure occurring 15 years, on average, later included higher diastolic blood pressure (hazard ratio per 10.0 mm Hg, 2.1; 95% CI, 1.4 to 3.1), higher body-mass index (the weight in kilograms divided by the square of the height in meters) (hazard ratio per 5.7 units, 1.4; 95% CI, 1.0 to 1.9), lower high-density lipoprotein cholesterol (hazard ratio per 13.3 mg per deciliter [0.34 mmol per liter], 0.6; 95% CI, 0.4 to 1.0), and kidney disease (hazard ratio, 19.8; 95% CI, 4.5 to 87.2). Three quarters of those in whom heart failure subsequently developed had hypertension by the time they were 40 years of age. Depressed systolic function, as assessed on a study echocardiogram when the participants were 23 to 35 years of age, was independently associated with the development of heart failure 10 years, on average, later (hazard ratio for abnormal systolic function, 36.9; 95% CI, 6.9 to 198.3; hazard ratio for borderline systolic function, 3.5; 95% CI, 1.2 to 10.2). Myocardial infarction, drug use, and alcohol use were not associated with the risk of heart failure.

CONCLUSIONS

Incident heart failure before 50 years of age is substantially more common among blacks than among whites. Hypertension, obesity, and systolic dysfunction that are present before a person is 35 years of age are important antecedents that may be targets for the prevention of heart failure. (ClinicalTrials.gov number, NCT00005130.)

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HEART FAILURE IS A MAJOR PUBLIC health problem in the United States, causing substantial morbidity and mortality in the later decades of life. The risk of heart failure rises sharply with increasing age, with rates doubling every 10 years among older adults.^{1,2} Less is known about the incidence of heart failure in persons younger than 50 years of age; one estimate suggests that the 5-year risk of heart failure among 40-year-old white persons is only 0.1 to 0.2%.³

In the United States, blacks have a higher prevalence of heart failure than persons of other races, and they present with symptoms of heart failure at younger ages.^{4,5} The reason for the greater propensity for heart failure among blacks is not fully understood; a higher burden of risk factors such as hypertension, a genetic predisposition to cardiomyopathy, and exposures to toxins, including drugs and alcohol, have all been postulated to play a role.⁴⁻⁶

In this report, we describe the incidence of heart failure and its antecedents among participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study. The CARDIA cohort is a well-characterized cohort of white and black men and women, who were 18 to 30 years of age at the time of enrollment and who have been followed for 20 years, with periodic risk-factor assessments, including echocardiography, and with adjudicated cardiovascular outcomes.

METHODS

STUDY COHORT

The CARDIA study is a multicenter study designed to investigate the development of coronary disease in young adults. The CARDIA study began in 1985–1986 with the enrollment of 5115 blacks and whites of both sexes who were 18 to 30 years of age and were recruited in Birmingham, Alabama; Chicago; Minneapolis; and Oakland, California. The institutional review board at each of the study sites approved the study protocols, and written informed consent was obtained from all participants. The cohort is balanced with respect to race (52% of the participants are black), sex (55% are women), and educational level (40% have ≤12 years of education).⁷ Baseline measurements were repeated, and additional measurements performed, at years 2, 5, 7, 10, 15, and 20. The CARDIA study has had a high retention rate, with 87.5% of

the original cohort completing the annual telephone interview for outcome ascertainment at year 20 and 71.8% completing the in-person examination at year 20.

INCIDENT HEART FAILURE

During their scheduled study examinations and yearly telephone interviews, participants were asked about overnight hospitalizations, and records were requested in cases of suspected cardiovascular events. Deaths were reported to the field centers every 6 months, and records were requested after consent had been obtained from the next of kin. Two members of the end-points committee reviewed each record to determine the primary cause of hospitalization or death; disagreements were resolved by consensus. Hospitalization for heart failure was a prespecified study end point and required both that a final diagnosis of heart failure had been made by a physician and that medical treatment for heart failure had been administered during the hospitalization (administration of a diuretic and of either digitalis or an afterload-reducing agent, such as nitroglycerin, hydralazine, an angiotensin-converting-enzyme [ACE] inhibitor, or an angiotensin-receptor blocker). Heart failure was not a prespecified category for the primary cause of death; a death was considered to be due to heart failure if the adjudicated cause was cardiovascular and if an *International Classification of Diseases, Ninth Revision* (ICD-9) code for heart failure (428) or cardiomyopathy (425) was noted as a contributory cause. We also reviewed hospital and death records for coexisting conditions at the time of the participant's presentation with heart failure; these data were not used in the analyses but are described below.

CLINICAL ANTECEDENTS MEASURED AT EACH EXAMINATION

Race was reported by the study participants. We used the average of the second and third of three blood-pressure measurements (performed at 1-minute intervals after the participant had been sitting quietly for 5 minutes) and considered hypertension to be present when the systolic blood pressure was 140 mm Hg or higher, the diastolic blood pressure was 90 mm Hg or higher, or the person was taking antihypertensive medications. Weight, in kilograms, was measured with the use of a standard balance-beam scale, with the participant wearing light clothing, and the body-mass index

was calculated as the weight in kilograms divided by the square of the height in meters. Diabetes was considered to be present if the person had a fasting blood glucose level of 126 mg per deciliter (7 mmol per liter) or more or was taking medication for diabetes. Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured, and low-density lipoprotein cholesterol was calculated with the use of the Friedewald equation.⁸ The creatinine level was measured at years 0, 10, 15, and 20; the glomerular filtration rate (GFR) was estimated with the use of the Modification of Diet in Renal Disease equation,⁹ and chronic kidney disease was considered to be present when the GFR was less than 60 ml per minute. Educational level, family history of premature coronary disease, and the use of tobacco, alcohol, and illicit drugs were determined by self-report at each examination. Consumption of more than 14 drinks per week in the case of men or more than 7 in the case of women was considered to be alcohol use above a safe level¹⁰; illicit-drug use was defined as the use of cocaine, amphetamines, or heroin at any time in the participant's life.

ECHOCARDIOGRAPHIC ANTECEDENTS

As part of the examination in year 5, CARDIA participants underwent two-dimensional, guided M-mode echocardiography and Doppler study of transmitral flow velocities performed on an Acuson cardiac ultrasound machine (Siemens).¹¹ All studies were recorded and read at a reading center at the University of California, Irvine. Systolic function was assessed as a continuous measure of ejection fraction (expressed as a percentage) in 1893 participants and as a qualitative ejection-fraction rating in the rest of the participants; we categorized systolic function as abnormal (ejection fraction of <40%, or qualitative rating of abnormal), borderline (ejection fraction of 40 to 60%, or qualitative rating of borderline), or normal. Left ventricular mass (in grams) was derived from the formula of Devereux et al.,¹² and the left-ventricular-mass index was calculated as grams per meter^{2.7}.¹³ Left ventricular hypertrophy was considered to be present if the left-ventricular-mass index was 51 g per meter^{2.7} or more, a cutoff point that has previously been validated for both blacks and whites.¹⁴ Among the 4351 participants who were available for the echocardiographic examination, variables for either ejection fraction or left ventricular hypertrophy were miss-

ing for 121, leaving data from 4230 participants for this analysis.

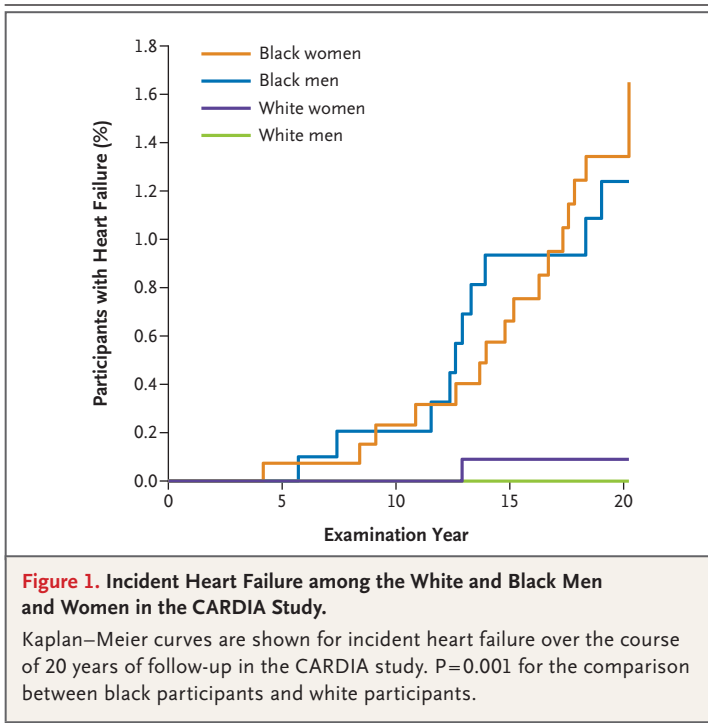
STATISTICAL ANALYSIS

Using t-tests, chi-square tests, and Fisher's exact tests, as appropriate, we compared baseline risk factors in participants in whom heart failure developed with those in participants in whom heart failure did not develop. We used Cox proportional-hazards models to analyze associations between candidate risk factors and heart failure among blacks in unadjusted analyses. We developed two multivariate models, the first including baseline predictors only and the second including time-varying covariates, with predictor values updated at the time of each study visit. Because of the small number of outcomes, we used the forward-selection method to choose predictors for the adjusted analyses, retaining potential risk factors if they remained associated with heart failure at a P value of less than 0.05, and we reported hazard ratios per 1 SD for continuous variables. Finally, we explored the association of systolic dysfunction and left ventricular hypertrophy, as assessed on the echocardiogram obtained in year 5, with the risk of subsequent heart failure in bivariate and multivariate analyses.

RESULTS

During 20 years of follow-up of the 5115 study participants, incident heart failure occurred in 27 men and women and was more common than myocardial infarction (which occurred in 16 participants). With the exception of one white woman, all of the participants in whom heart failure developed were black (P=0.001) (Fig. 1). The cumulative incidence of heart failure in black women was 1.1% (95% confidence interval [CI], 0.6 to 1.7) and the cumulative incidence in black men was 0.9% (95% CI, 0.5 to 1.4), with a mean (\pm SD) age at onset of 39 \pm 6 years. The cumulative incidence of heart failure among white women was 0.08% (95% CI, 0 to 0.5), and the cumulative incidence among white men was 0% (95% CI, 0 to 0.4). Heart failure resulted in death in the case of three black men (accounting for 4.5% of all deaths among black men) and two black women (7.7% of all deaths among black women).

The baseline characteristics (assessed when participants were 18 to 30 years of age) differed between blacks in whom heart failure subsequently



developed and white and black participants in whom heart failure did not develop (Table 1). As compared with all those in whom heart failure did not develop, blacks in whom heart failure subsequently developed had higher baseline systolic and diastolic blood pressures and were more likely to have hypertension. They were also more likely to be obese, to have diabetes, or to have chronic kidney disease. Alcohol and drug use did not differ significantly between blacks in whom heart failure subsequently developed and participants in whom it did not. Blacks in whom heart failure subsequently developed were more likely to have borderline or abnormal systolic function or left ventricular hypertrophy.

Because heart failure occurred almost exclusively in blacks, we restricted the Cox regression analyses to data from black participants. In bivariate models of baseline predictors (Table 2), higher blood pressure, higher body-mass index, fewer years of education, lower HDL cholesterol, the presence of chronic kidney disease, and the presence of diabetes were all associated with the subsequent development of heart failure. In multivariate models, higher diastolic blood pressure, higher body-mass index, lower HDL cholesterol, and the presence of chronic kidney disease were each independently associated with the risk of

heart failure. Each standard-deviation increase (10.0 mm Hg) in diastolic blood pressure among blacks at 18 to 30 years of age doubled the risk that heart failure would occur, on average, 15 years later.

During the first 10 years of the CARDIA study, clinical hypertension was more common among black participants in whom heart failure subsequently developed than among blacks in whom it did not (Fig. 2). By year 10, when participants were 28 to 40 years of age, 75% of those in whom heart failure subsequently developed had hypertension, as compared with 12% of those in whom heart failure did not develop ($P<0.001$). Most participants with hypertension were not being treated for the condition or were being treated but had poorly controlled blood pressure. At baseline, 75% of all black participants with hypertension (66 of 88) were not taking medication, and another 9% (8 of 88) had poorly controlled blood pressure even though they reported taking antihypertensive medications; all of the black participants with hypertension in whom heart failure subsequently developed had untreated or poorly controlled hypertension. By year 10, 57% of black participants with hypertension (137 of 239) were not taking antihypertensive medications, and 19% (45 of 239) had poorly controlled blood pressure; among those in whom heart failure subsequently developed, 87% had untreated or poorly controlled hypertension.

To examine antecedents more proximal to the onset of heart failure, we used data from each examination and time-varying covariates. Over the entire course of 20 years, the following variables were associated with heart failure in bivariate models: higher diastolic blood pressure (hazard ratio per 10.0 mm Hg, 1.8; 95% CI, 1.5 to 2.2; $P<0.001$), higher systolic blood pressure (hazard ratio per 10.9 mm Hg, 1.7; 95% CI, 1.4 to 2.0; $P<0.001$), higher body-mass index (hazard ratio per 5.7 units, 1.7; 95% CI, 1.3 to 2.1; $P<0.001$), presence of diabetes (hazard ratio, 5.5; 95% CI, 2.4 to 13; $P<0.001$), and presence of chronic kidney disease (hazard ratio, 7.7; 95% CI, 1.8 to 31.0; $P=0.006$). Neither alcohol use nor drug use was associated with the development of heart failure (hazard ratio for alcohol use, 1.0; 95% CI, 0.4 to 2.5; $P=0.97$; hazard ratio for drug use, 1.1; 95% CI, 0.5 to 2.4; $P=0.82$). In multivariate models, higher systolic blood pressure and the presence of diabetes each remained independently associated with

Table 1. Characteristics of Study Participants, According to Subsequent Development of Heart Failure.*

Characteristic	White Participants†		Black Participants		P Value‡	
	No Subsequent Heart Failure (N=2477)	No Subsequent Heart Failure (N=2611)	Subsequent Heart Failure (N=26)	Blacks with Subsequent Heart Failure vs. All Participants without Subsequent Heart Failure	Blacks with Subsequent Heart Failure vs. Blacks without Subsequent Heart Failure	
Demographic						
Age (yr)	25±3	24±4	26±3	0.12	0.06	
Male sex (%)	47	44	38	0.56	0.69	
Educational level (%)				0.03	0.31	
<12 yr	6	13	23			
12 yr	21	38	38.5			
>12 yr	73	49	38.5			
Clinical						
Blood pressure (mm Hg)						
Diastolic	68.4±9.2	68.7±9.6	78.7±11.5	<0.001	<0.001	
Systolic	109.3±10.9	111.4±10.9	120.6±10.8	<0.001	<0.001	
Hypertension (%)	2	3	19	<0.001	<0.001	
Body-mass index§	23.6±4.0	25.2±5.6	32.0±9.7	<0.001	0.001	
Obesity (%)¶	6	16	34	0.002	0.03	
Diabetes (%)	1	2	12	0.008	0.01	
Cholesterol (mg/dl)¶¶						
HDL	51.8±13.0	54.6±13.3	45.6±11.2	0.004	<0.001	
LDL	108.5±30.0	109.5±32.2	113.5±46.7	0.62	0.65	
Chronic kidney disease (%)	6	1	8	0.19	0.01	
Family history of premature coronary disease (%)	14	10	15	0.54	0.31	
Current tobacco use (%)	27	34	38	0.40	0.67	
Alcohol use above a safe level (%)**	16	9	8	0.76	1.0	
Illicit-drug use (%)	52	29	35	0.69	0.52	
Previous pregnancy (% of women)	40	63	69	0.21	0.80	
Echocardiographic						
Ejection fraction	0.63±0.06	0.63±0.15	0.54±0.09	0.02	0.07	
Systolic dysfunction (%)††						
Borderline	9	10	19	<0.001	<0.001	
Abnormal	0.2	0.3	8			
Left-ventricular-mass index (g/m ^{2.7})	33.5±8.5	36.5±9.6	47.4±19.6	<0.001	<0.001	
Left ventricular hypertrophy (%)	4	7	26	0.003	0.01	

* Plus-minus values are means ±SD. Baseline data are shown for all characteristics except illicit-drug use, which was determined by self-report at year 2, and echocardiographic findings, which are based on study echocardiograms obtained from 4230 participants at year 5. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† The one white woman with heart failure was excluded from this analysis.

‡ The P values were calculated with use of Fisher's exact test of proportions (for categorical variables) or Student's t-test of means (for continuous variables).

§ The body-mass index is the weight in kilograms divided by the square of the height in meters. Obesity was defined as a body-mass index of 30 or higher.

¶ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

|| The higher prevalence of chronic kidney disease in whites as compared with blacks in this age group is a consequence of the use of Modification of Diet in Renal Disease (MDRD) equation (including its race coefficient) to estimate the glomerular filtration rate. The MDRD equation has not been validated extensively in young adults, most of whom have normal kidney function.

** Consumption of more than 14 drinks per week in the case of men or more than 7 in the case of women was considered to be alcohol use above a safe level.¹⁰

†† Borderline was defined as an ejection fraction of 40 to 60% or a qualitative assessment indicating borderline systolic function; abnormal was defined as an ejection fraction of less than 40% or a qualitative assessment indicating abnormal systolic function.

Table 2. Hazard Ratios for Subsequent Heart Failure According to Baseline Antecedents among 2637 Black Participants in the CARDIA Study.*

Risk Factor	Bivariate Models		Multivariate Model†‡	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age (per 3.8 yr)	1.5 (1.0–2.3)	0.05		
Male sex	0.9 (0.4–2.0)	0.81		
Educational level				
<12 yr	2.6 (1.0–7.2)	0.06		
12 yr	1.4 (0.6–3.4)	0.42		
>12 yr	—	—		
Blood pressure‡				
Diastolic (per 10.0 mm Hg)	2.5 (1.8–3.5)	<0.001	2.1 (1.4–3.1)	<0.001
Systolic (per 10.9 mm Hg)	1.9 (1.4–2.6)	<0.001		
Body-mass index (per 5.7 units)§	2.0 (1.6–2.5)	<0.001	1.4 (1.0–1.9)	0.02
Diabetes	6.7 (2.0–22.3)	0.002		
Cholesterol¶				
HDL (per 13.3 mg/dl)	0.4 (0.2–0.7)	<0.001	0.6 (0.4–1.0)	0.05
LDL (per 32.4 mg/dl)	1.1 (0.7–1.6)	0.70		
Chronic kidney disease	13.8 (3.2–58.7)	<0.001	19.8 (4.5–87.2)	<0.001
Family history of premature coronary disease	1.6 (0.5–4.6)	0.40		
Current tobacco use	1.4 (0.6–3.1)	0.41		
Alcohol use above a safe level	0.9 (0.2–3.8)	0.88		
Previous pregnancy	1.3 (0.4–3.7)	0.63		

* Participants were 18 to 30 years of age at baseline. Hazard ratios for continuous variables are reported per 1 SD. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† Variables were selected with the use of a forward selection method and were retained if they were associated with heart failure at a significance level of less than 0.05.

‡ Systolic blood pressure and diastolic blood pressure were collinear. Each was significant in the multivariate models without the other present. When both were presented for forward selection (as they were in the multivariate models above), diastolic blood pressure was retained in the final model. Replacing diastolic blood pressure with systolic blood pressure would have left the hazard ratios for the other covariates unchanged; the adjusted hazard ratio for systolic blood pressure per 10.9 mm Hg was 1.5 (95% CI, 1.1 to 2.1; $P=0.01$).

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

|| Consumption of more than 14 drinks per week in the case of men or more than 7 in the case of women was considered to be alcohol use above a safe level.¹⁰

the development of heart failure (hazard ratio per 10.9 mm Hg systolic blood pressure, 1.7; 95% CI, 1.4 to 2.0; $P<0.001$; hazard ratio for diabetes, 4.9; 95% CI, 2.1 to 12; $P<0.001$), as did higher diastolic blood pressure in models in which diastolic blood pressure was substituted for systolic blood pressure (hazard ratio per 10 mm Hg, 1.8; 95% CI, 1.5 to 2.2; $P<0.001$).

Systolic dysfunction and left ventricular hypertrophy as assessed on the study echocardiogram in year 5 were independently associated with the development of heart failure an average of 10

years later (Table 3). After additional adjustment for clinical variables, systolic dysfunction remained strongly associated with the subsequent development of heart failure, whereas the association of left ventricular hypertrophy with subsequent heart failure was markedly diminished and was not significant.

Information in clinical records with respect to coexisting conditions that were present at the time the participant presented with heart failure (Table 4) was consistent with study measurements of clinical antecedents (Tables 1, 2, and 3). Hyper-

tension, chronic kidney disease, and diabetes were commonly noted in the records of hospitalizations for heart failure among blacks; of 22 black participants hospitalized for heart failure, 17 were recorded as having hypertension, 9 as having chronic kidney disease, and 5 as having diabetes. Coronary disease was uncommon; none of the hospital or death records noted concurrent or previous myocardial infarction, and most of the cardiac-catheterization reports and autopsy records (eight of nine) noted mild or absent coronary disease. Although alcohol use above a safe level was noted in 3 of 10 cases of heart failure in men and cocaine use in 1 of the 10, none of the 16 records that documented the presence of heart failure in black women commented on these factors. We had information on systolic function from the hospital records of 17 participants; an ejection fraction of less than 50% was recorded for 14 of these participants. Evidence of dilated cardiomyopathy was noted on the autopsy records of 4 of the participants who died (an autopsy was not performed on the fifth participant who died).

DISCUSSION

In this large cohort of white and black young adults, incident heart failure was substantially more common among blacks. Heart failure developed before the age of 50 years in 1 of 100 black men and black women in the CARDIA study, a rate that was 20 times the incidence in whites. Heart failure occurred in blacks when they were 39 years of age, on average, and was predicted by the presence of hypertension, obesity, chronic kidney disease, and depressed systolic function 10 to 15 years earlier. These findings have important implications for efforts aimed at preventing heart failure in this high-risk population.

Previous research on the epidemiology of heart failure has focused on older adults.^{2,3,15} Several recent studies showed that the incidence of heart failure was up to two times as high in blacks as in whites¹⁶⁻¹⁸; the populations in these studies were largely elderly, with a mean age at the start of observation that ranged from 55 to 74 years. The one large cohort that included younger adults and that had low rates of incident heart failure before 50 years of age was predominantly white^{1,3}; the low rate of heart failure that we saw in white participants in the CARDIA study is consistent with the estimates from this cohort. National data

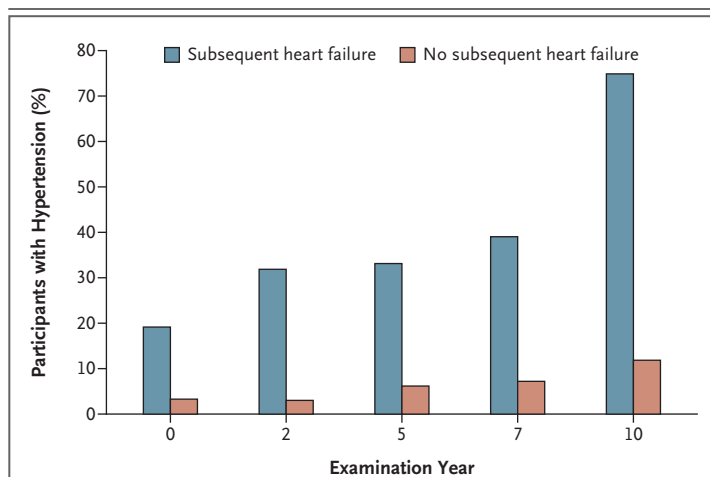


Figure 2. Proportion of Blacks with Hypertension in the First 10 Years of the CARDIA Study, According to Status with Respect to the Subsequent Development of Heart Failure.

By examination year 10, among blacks in whom heart failure subsequently developed, 75% had hypertension, as compared with 12% of blacks in whom heart failure did not develop ($P < 0.001$).

have been used to compare the prevalence of heart failure across various demographic groups over the entire age spectrum,^{2,4} although prevalence estimates may understate the burden of disease, given the high rate of death associated with heart failure (5 of the 26 cases of heart failure among black participants in the CARDIA study resulted in death). Our findings are consistent with those from these previous reports and extend them by making the additional observation of substantial rates of incident heart failure among black men and women early in adulthood.

We identified potentially modifiable antecedents of heart failure in blacks that were present more than a decade before the onset of clinical heart failure. Each increase of 10 mm Hg in diastolic blood pressure among blacks who were in their 20s doubled the likelihood that heart failure would develop when they were in their 40s, and three quarters of those in whom heart failure developed had hypertension early in adulthood. Obesity also contributes to the risk of heart failure, either directly¹⁹ or through the associated rise in blood pressure and the development of type 2 diabetes. This latter observation is consistent with our finding that an increased body-mass index was an early independent risk factor for heart failure, with diabetes confounding or, more likely, mediating this association when findings from the

Table 3. Hazard Ratios for the Subsequent Development of Heart Failure in Blacks According to Echocardiographic Measures at Year 5.*

Echocardiographic Measure	Bivariate Model		Multivariate Model Adjusted for the Other Echocardiographic Measure†		Multivariate Model Additionally Adjusted for Clinical Measures‡	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Systolic function§						
Abnormal	34.2 (7.6–154.2)	<0.001	27.0 (5.7–128.0)	<0.001	36.9 (6.9–198.3)	<0.001
Borderline	3.1 (1.1–9.0)	0.04	3.0 (1.1–8.5)	0.04	3.5 (1.2–10.0)	0.02
Left ventricular hypertrophy	6.0 (2.2–16.6)	<0.001	5.0 (1.7–14.6)	0.003	1.9 (0.4–7.4)	0.33

* At year 5, study participants were 23 to 35 years of age. Hazard ratios for continuous variables are reported per 1 SD.

† Models for systolic function were adjusted for left ventricular hypertrophy; models for left ventricular hypertrophy were adjusted for systolic function.

‡ All models were adjusted for diastolic blood pressure, body-mass index, high-density lipoprotein cholesterol, chronic kidney disease, and the other echocardiographic measure.

§ Abnormal systolic function was defined as an ejection fraction of less than 40% or a qualitative rating of abnormal; borderline systolic function was defined as an ejection fraction of 40 to 60% or a qualitative rating of borderline.

entire 20 years of follow-up were considered. Low HDL cholesterol in young adulthood may play a role in cardiac remodeling, particularly in patients with hypertensive disease.^{20,21} Chronic kidney disease is a strong predictor of heart failure, and black men are disproportionately affected by declining kidney function in young adulthood.²² Our finding that clinical factors increased the risk of heart failure even many years later is consistent with observations in older cohorts²³⁻²⁶ and suggests that these factors may be targets for the prevention of heart failure in young adults.

We found that blacks in whom heart failure subsequently developed were more likely than those in whom it did not develop to have systolic dysfunction and left ventricular hypertrophy in young adulthood, 10 years before the onset of clinical heart failure. These structural and functional cardiac changes may be the consequence of underlying clinical factors such as hypertension and obesity and may mediate the association between these factors and heart failure.^{27,28} Systolic dysfunction remained a strong risk factor for heart failure independently of the other clinical risk factors, including blood pressure. Several studies have identified polymorphisms that appear to be linked to heart failure and systolic dysfunction in blacks, and some studies have shown that the risk associated with these polymorphisms is greatest among blacks with hypertension.^{4,5,29,30} Most of these studies are limited by the small numbers of black participants and the lack of longitudinal data to determine how clinical and genetic factors may

interact in the development of this disease. This is an important area for further study.

Our results with respect to systolic dysfunction have implications for the identification of persons who are at high risk for the development of heart failure and also have implications for the prevention of this disease. Current guidelines recommend initiating treatment for asymptomatic systolic dysfunction with ACE inhibitors and beta-blockers before the onset of symptoms of heart failure.^{4,31-33} Although screening for systolic dysfunction in the general population has several limitations,³⁴ screening high-risk groups (e.g., persons with hypertension) in order to target therapies may be an important tool for the prevention of heart failure.^{35,36} Young adults have not been included in clinical trials of preventive therapies or screening strategies, and the benefits and risks of these approaches in a young at-risk population are not known. However, the high rate of borderline or abnormal systolic function that we observed in both white and black participants (9% among whites and 13% among blacks), and its strong association with the subsequent development of clinical heart failure before the age of 50 years among blacks, underscore the importance of this area of investigation.

Our study also highlights the potential for preventing heart failure through interventions that decrease the prevalence of obesity and high blood pressure. Obesity was common among black participants in the CARDIA study, particularly black women,^{37,38} and it is possible that preventing obe-

Table 4. Characteristics of Study Participants Who Died from or Were Hospitalized for Incident Heart Failure.*

Participant No.	Type of Event	Age of Participant	Ejection Fraction	Coexisting Conditions at Presentation†
		yr	%	
1	Death	21–25		Dilated cardiomyopathy, left ventricular hypertrophy (weight, 630 g), no coronary heart disease
2	Death	21–25		Dilated cardiomyopathy, left ventricular hypertrophy (530 g), no coronary heart disease
3	Death	36–40		End-stage renal disease
4	Death	36–40		Mild coronary heart disease, dilated cardiomyopathy, left ventricular hypertrophy (430 g)
5	Hospitalization and death	31–35	16	Hypertension, chronic kidney disease, alcohol use, dilated cardiomyopathy, moderate coronary heart disease, left ventricular hypertrophy (825 g)
6	Hospitalization	31–35	15	Hypertension, anemia, family history of premature coronary disease
7	Hospitalization	36–40	15	Hypertension, chronic kidney disease, diabetes
8	Hospitalization	41–45	15	Hypertension
9	Hospitalization	31–35	24	Chronic kidney disease, obstructive sleep apnea, no coronary heart disease (as assessed by cardiac catheterization)
10	Hospitalization	36–40	25	Atrial fibrillation
11	Hospitalization	41–45	25	Diabetes, no coronary heart disease (as assessed by cardiac catheterization)
12	Hospitalization	46–50	25	Hypertension, end-stage renal disease, diabetes, mild coronary heart disease (as assessed by cardiac catheterization)
13	Hospitalization	41–45	30	Hypertension, chronic kidney disease, atrial fibrillation, alcohol use
14	Hospitalization	46–50	30	Hypertension, obstructive sleep apnea, anemia
15	Hospitalization	31–35	30	Recent pregnancy, family history of premature coronary disease
16	Hospitalization	46–50	39	Hypertension, chronic kidney disease, alcoholism
17	Hospitalization	41–45	40	Hypertension
18	Hospitalization	46–50	40	Hypertension, family history of premature coronary disease, newly diagnosed diabetes, no coronary heart disease (as assessed by cardiac catheterization)
19	Hospitalization	41–45	48	Hypertension, atrial fibrillation
20	Hospitalization	36–40	>50	Hypertension
21	Hospitalization	41–45	>50	Hypertension, chronic kidney disease, cocaine use
22	Hospitalization	41–45	>50	Mitral stenosis (as assessed by echocardiography), no coronary heart disease (as assessed by cardiac catheterization)
23	Hospitalization	46–50	>50	Hypertension, diabetes
24	Hospitalization	36–40	NR	Hypertension, end-stage renal disease, diabetes
25	Hospitalization	36–40	NR	End-stage renal disease, sickle cell disease
26	Hospitalization	41–45	NR	Hypertension, peripartum
27	Hospitalization	41–45	NR	Hypertension, obstructive sleep apnea

* Data were obtained from death records for patients who died and from hospital records for those who were hospitalized. To protect the privacy of study participants and their families, age is presented in 5-year ranges, and race and sex have been omitted. NR denotes not recorded.

† All cardiac conditions in participants who died were identified at autopsy.

sity in this population may reduce the subsequent incidence of heart failure. Recent national data suggest that young adults with hypertension are much less likely than their middle-aged counterparts to be aware of this diagnosis or to be receiving treatment.^{39,40} The reasons for low rates of treatment for hypertension among young adults may include barriers in access to medical care.^{41,42} It has been suggested that blood-pressure control may be more difficult to achieve among black patients, although a consensus statement on treating hypertension in blacks concluded that the failure of health professionals to initiate therapy early in accordance with established guidelines was the major obstacle to achieving effective blood-pressure control.^{43,44} When they receive treatment according to the guidelines, blacks and whites appear to have similar rates of control.⁴⁵

Physicians may be reluctant to treat younger patients with hypertension because of the perceived large number needed to treat to prevent cardiovascular outcomes that are still rare and often far in the future. In the course of 20 years of follow-up in the CARDIA study, the cumulative incidence of heart failure among blacks who had hypertension at baseline (when their average age was 24 years) was 5.6%, as compared with 0.8% among those who did not have hypertension at baseline. Most of the persons with hypertension at baseline were not receiving antihypertensive treatment. A trial of antihypertensive therapy in older participants, including blacks, showed that diuretic therapy, in particular, was associated with considerable reductions in the risk of heart failure.⁴⁶ Thus, although treatment for hypertension and reduction of the risk of heart failure have not been studied in this age group, our data suggest that the number of young, black patients with hypertension that would need to be treated to prevent one case of heart failure before 50 years of age could be as low as 21.

Because we observed only a single heart-failure event among white participants, we are limited in our ability to assess whether racial differences in risk factors account for the racial differences in the incidence of heart failure. The fact that blacks and whites in the CARDIA study actually had similar mean levels of blood pressure and ejection fraction in young adulthood (Table 1) is worthy of comment. More black participants were obese at

baseline, and hypertension developed more often in blacks than in whites when the participants were in their 20s and 30s,³⁷ but whether these observations explain the substantially higher rates of heart failure in blacks than in whites warrants further investigation. The small number of outcomes in our study limits the precision of our descriptive observations, as well as our ability to explore a broader range of clinical antecedents and mediators. Because we defined incident heart failure on the basis of hospitalization for or death from heart failure, heart failure that was identified in the outpatient setting was missed in these analyses. Another limitation of the study was that the retention rate for outcome ascertainment was 87.5% by year 20; since black men are the demographic group most likely to be lost to follow-up, we may have underestimated the incidence of heart failure, particularly in this group.

Despite these limitations, the clear strength of this study is the large, well-characterized cohort of white and black young adults for whom we had rich longitudinal clinical and echocardiographic data and adjudicated heart-failure outcomes. Heart failure occurs at a disproportionately high rate among young and middle-aged blacks as compared with whites, and it is not a rare condition. Elevated blood pressure, obesity, chronic kidney disease, and systolic dysfunction early in adulthood are important antecedents that could become targets for screening and interventions aimed at the prevention of heart failure. Studies are needed to examine the benefits and risks of these early approaches to preventing this serious disease in black young adults.

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REFERENCES

- Kannel WB. Incidence and epidemiology of heart failure. *Heart Fail Rev* 2000; 5:167-73.
- Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics — 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117(4):e25-e146.
- Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;106:3068-72.
- Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112(12):e154-e235.
- Yancy CW. Heart failure in African Americans. *Am J Cardiol* 2005;96:3i-12i.
- Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation* 2008;117: 2544-65.
- Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988; 41:1105-16.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
- Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247-54.
- National Institute on Alcohol Abuse and Alcoholism. What is a safe level of drinking? (Accessed February 20, 2009, at <http://www.niaaa.nih.gov/FAQs/General-English/default.htm#safelevel>.)
- Gardin JM, Wagenknecht LE, Anton-Culver H, et al. Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women: the CARDIA study. *Circulation* 1995;92: 380-7.
- Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57:450-8.
- de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992;20:1251-60.
- Nunez E, Arnett DK, Benjamin EJ, et al. Optimal threshold value for left ventricular hypertrophy in blacks: the Atherosclerosis Risk in Communities study. *Hypertension* 2005;45:58-63.
- Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292:344-50.
- Bahrani H, Kronmal R, Bluemke DA, et al. Differences in the incidence of congestive heart failure by ethnicity: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med* 2008;168:2138-45.
- Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol* 2008;101:1016-22.
- Kalogeropoulos A, Georgiopoulou V, Kritchevsky SB, et al. Epidemiology of incident heart failure in a contemporary elderly population: the Health, Aging, and Body Composition Study. *Arch Intern Med* (in press).
- Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305-13.
- Horio T, Miyazato J, Kamide K, Tak-iushi S, Kawano Y. Influence of low-high density lipoprotein cholesterol on left ventricular hypertrophy and diastolic function in essential hypertension. *Am J Hypertens* 2003;16:938-44.
- Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;22:Suppl:6A-13A.
- Stehman-Breen CO, Gillen D, Steffes M, et al. Racial differences in early-onset renal disease among young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *J Am Soc Nephrol* 2003;14:2352-7.
- Bibbins-Domingo K, Chertow GM, Fried LF, et al. Renal function and heart failure risk in older black and white individuals: the Health, Aging, and Body Composition Study. *Arch Intern Med* 2006;166: 1396-402.
- Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2003;138:10-6.
- Lee DS, Massaro JM, Wang TJ, et al. Antecedent blood pressure, body mass index, and the risk of incident heart failure in later life. *Hypertension* 2007;50: 869-76.
- Sarnak MJ, Katz R, Stehman-Breen CO, et al. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med* 2005;142:497-505.
- Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry: the Framingham Heart Study. *JAMA* 1991;266:231-6.
- Lauer MS, Brozena S. Heart failure. Influence of contemporary versus 30-year blood pressure levels on left ventricular mass and geometry: the Framingham Heart Study. *J Am Coll Cardiol* 1991;18: 1287-94.
- Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure: the Rotterdam Study. *Eur Heart J* 2004;25:1614-9.
- Konstam MA. Comment — Val-HeFT and angiotensin-receptor blockers in perspective: a tale of the blind man and the elephant. *J Card Fail* 2002;8:56-8.
- Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003;348:2007-18.
- Konstam MA, Kronenberg MW, Rousseau ME, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. *Circulation* 1993;88:2277-83.
- Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. *N Engl J Med* 1992;327: 669-77.
- Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of “asymptomatic” left ventricular systolic dysfunction: implications for screening. *Ann Intern Med* 2003;138:907-16.
- Struthers AD, Morris AD. Screening for and treating left-ventricular abnormalities in diabetes mellitus: a new way of reducing cardiac deaths. *Lancet* 2002; 359:1430-2.
- Goldberg LR, Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction. *Circulation* 2006;113:2851-60.
- Liu K, Ruth KJ, Flack JM, et al. Blood pressure in young blacks and whites: relevance of obesity and lifestyle factors in determining differences. *Circulation* 1996; 93:60-6.

38. Lewis CE, Jacobs DR Jr, McCreath H, et al. Weight gain continues in the 1990s: 10-year trends in weight and overweight from the CARDIA Study. *Am J Epidemiol* 2000;151:1172-81.
39. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007;49:69-75.
40. Gu Q, Paulose-Ram R, Dillon C, Burt V. Antihypertensive medication use among US adults with hypertension. *Circulation* 2006;113:213-21.
41. Ostchega Y, Hughes JP, Wright JD, McDowell MA, Louis T. Are demographic characteristics, health care access and utilization, and comorbid conditions associated with hypertension among US adults? *Am J Hypertens* 2008;21:159-65.
42. Victor RG, Leonard D, Hess P, et al. Factors associated with hypertension awareness, treatment, and control in Dallas County, Texas. *Arch Intern Med* 2008;168:1285-93.
43. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med* 2003;163:1555-65.
44. Douglas JG, Bakris GL, Epstein M, et al. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med* 2003;163:525-41.
45. Racial/ethnic disparities in prevalence, treatment, and control of hypertension — United States, 1999–2002. *MMWR Morb Mortal Wkly Rep* 2005;54:7-9.
46. Wright JT Jr, Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and non-black patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA* 2005;293:1595-608.

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