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Progression of Coronary Artery Calcium and Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis

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Background—Although the association between coronary artery calcium (CAC) and future heart failure (HF) has been shown previously, the value of CAC progression in the prediction of HF has not been investigated. In this study, we investigated the association of CAC progression with subclinical left ventricular (LV) dysfunction and incident HF in the Multi-Ethnic Study of Atherosclerosis.

Methods and Results—The Multi-Ethnic Study of Atherosclerosis is a population-based study consisting of 6814 men and women aged 45 to 84, free of overt cardiovascular disease at enrollment, who were recruited from 4 ethnicities. We included 5644 Multi-Ethnic Study of Atherosclerosis participants who had baseline and follow-up cardiac computed tomography and were free of HF and coronary heart disease before the second cardiac computed tomography. Mean ($\pm$SD) age was 61.7$\pm$10.2 years and 47.2% were male. The Cox proportional hazard models and multivariable linear regression models were deployed to determine the association of CAC progression with incident HF and subclinical LV dysfunction, respectively. Over a median follow-up of 9.6 (interquartile range: 8.8–10.6) years, 182 participants developed incident HF. CAC progression of 10 units per year was associated with 3% of increased risk of HF independent of overt coronary heart disease (P=0.008). In 2818 participants with available cardiac magnetic resonance images, CAC progression was associated with increased LV end diastolic volume (β=0.16; P=0.03) and LV end systolic volume (β=0.12; P=0.006) after excluding participants with any coronary heart disease.

Conclusions—CAC progression was associated with incident HF and modestly increased LV end diastolic volume and LV end systolic volume at follow-up exam independent of overt coronary heart disease. (*J Am Heart Assoc*. 2017;6:e005253. DOI: 10.1161/JAHA.116.005253.)

Key Words: cardiac computed tomography • cardiac magnetic resonance imaging • coronary artery calcium • coronary artery calcium progression • heart failure

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Heart failure (HF) is a disabling disease with high burden on health care economy.[1] It affects both men and women with a lifetime risk of 20%.[2] Secondary to a combination of population aging and improvement in the managements of acute cardiovascular diseases, incidence and prevalence of HF have been increasing continuously in the past decades.[3] Approximately 5.7 million Americans suffer from HF,[1] and each year more than 550 000 new cases of HF are diagnosed.[4] The most common cause of HF in the United States is coronary artery disease (CAD).[5] CAD plays its role in the pathophysiology of HF through different mechanisms.[6] In addition to clinically overt coronary heart disease (CHD), hypoperfusion and endothelial dysfunction may cause subclinical myocardial damage and dysfunction, which eventually will progress to symptomatic HF.[7] Myocardial dysfunction in the subclinical phase is detectable by cardiac imaging, including echocardiography and cardiac magnetic resonance (CMR). Considering the progressive

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nature of HF and to implement effective risk modification strategies, it is imperative to detect asymptomatic individuals at risk to develop HF.[8] Coronary artery calcium (CAC) measurement by noncontrast cardiac computed tomography is a reliable and accurate tool to detect subclinical atherosclerosis and has a strong correlation with atherosclerotic plaque burden.[9] CAC score has incremental value over traditional risk scoring systems for cardiovascular risk stratification, especially in individuals who are classified as intermediate risk.[10] Serial measurement of CAC score has been introduced as a tool to monitor the progression of subclinical atherosclerosis.[11] CAC progression has a good predictive value for incident CHD and all-cause mortality.[12,13] Although the association between CAC and incident HF has been demonstrated in a few studies independent of CHD,[14–17] the value of CAC progression in prediction of future HF has not been previously evaluated. In this study, we investigate CAC progression as a predictor of incident HF and subclinical left ventricular (LV) dysfunction measured by CMR in a population-based cohort.

Materials and Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective, population-based cohort study including 4 racial/ethnic groups (whites, blacks, Hispanics, and Chinese).The design of MESA has been published in detail previously.[18] Briefly, between July 2000 and August 2002 (Exam 1), 6814 men and women, aged 45 to 84 years and free of clinical cardiovascular disease at enrollment, were recruited from 6 US field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN). All participants gave written informed consents and all study protocols were approved by the institutional review boards of each participating field center. Baseline examination (Exam 1) were followed by 4 more examinations with the following timeline: Exam 2 (September 2002–February 2004); Exam 3 (March 2004–September 2005); Exam 4 (September 2005–May 2007); and Exam 5 (April 2010–December 2011). In this study, we included all MESA participants who had CAC measured by cardiac computed tomography at baseline (Exam 1) and follow-up (Exam 2 or 3). There were 142 participants who developed incident CHD, 58 who developed incident HF, and 35 who developed both incident CHD and HF before their second cardiac computed tomography and were excluded from this analysis.

At Exam 1, standard questionnaires were used to obtain demographic, medical, and family history, medication use, smoking status, household income, and highest education level. Smoking status was defined as never, former, or current smoker. BMI was calculated as weight (kg) divided by the square of height (m^2). Resting blood pressure was measured 3

times using the Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critiko, Tampa, FL) in the upright position and the mean of the last 2 measurements was recorded. Fasting blood glucose as well as total and high-density lipoprotein (HDL) cholesterol were measured in serum. Participants were classified as normal and impaired fasting glucose if fasting blood glucose was <100 mg/dL and 100 to 125 mg/dL respectively. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or the use of insulin or any other hypoglycemic medication. An ElecSys 2010 analyzer (Roche Diagnostics, Indianapolis, IN) was used to measure N-Terminal prohormone of brain natriuretic peptide (NT-proBNP). Electrocardiogram was utilized to measure resting hear rate.

The details of the acquisition method of cardiac computed tomography in MESA has been published previously.[12,19] For each participant 2 consecutive scans were obtained over a standard calcium phantom at both baseline and follow-up exams. All images were transferred to a central computed tomography reading center (Los Angeles Biomedical Research Institute, Torrance, CA) and interpreted by an experienced physician. CAC score was calculated using the method introduced by Agatston et al. The mean of 2 scans at each exam were used for data analysis after being adjusted according to the calcium phantom. The acquisition method of CMR images in MESA has been explained in detail in previous publications.[20,21] CMR was performed using 1.5 Tesla scanners. In Exam 5, the steady-state free precession pulse sequence was used to measure the parameters of cardiac function and structure. All CMR images were analyzed by blinded readers in a central magnetic resonance imaging (MRI) reading center (Johns Hopkins Hospital, Baltimore, MD). CMR images in Exam 5 were quantified using CIM software (version 6.0; UniServices, Auckland, New Zealand). The following CMR variables were used in our study: LV mass (LVM); LV end diastolic volume (LVEDV); LV end systolic volume (LVESV); stroke volume (SV); ejection fraction (EF); and mass-to-volume ratio (MVR; MVR=LV mass/LVEDV). The first 4 variables were indexed to body surface area. In 3 participants, the indexed parameters were not calculated because of missing weight variable. In 1 participant, EF, SV, and LVESV were missing.

Every 9 to 12 months, a telephone interviewer called each participant to find about any interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Inpatient and outpatient medical records and information were received successfully in ≈98% and 95%, respectively. CHD was assessed as any of myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), and CHD death. The end point for our study was a combination of probable and definite HF. Both types required clinical symptoms and signs of HF, such as

shortness of breath or edema. HF was considered probable if a physician made the diagnosis and the patient was receiving medical treatment for HF. Definite HF required to meet at least 1 of the following criteria: (1) pulmonary edema/congestion in chest x-ray; (2) dilated or dysfunctional LV by echocardiography or any ventriculography; or (3) any evidence of LV diastolic dysfunction.

Statistical Analysis

Baseline characteristics are presented using mean±SD or numbers (%). CAC progression (continuous variable) was calculated as follow-up CAC minus baseline CAC divided by interscan period in years (annualized change in CAC). In addition, progressors versus nonprogressores (categorical variable) was defined using the method that was introduced by Berry et al.[22] A participant is considered as a progressor if he or she has:

1. Baseline CAC=0 and follow-up CAC more than zero, or
2. $0 <$ baseline CAC ≤ 100 and annualized change in CAC ≥ 10, or
3. Baseline CAC >100 and annualized relative change in CAC $\geq 10\%$ (annualized change in CAC divided by baseline CAC multiplied by 100).

The Cox proportional hazards (CPH) model was used to evaluate the association of CAC progression, either continuous CAC progression or categorical CAC progression, and time to incident HF in participants free of any CHD or HF before the follow-up CAC measurement. Three separate models were used for the analysis:

Model 1: CPH regression without adjusting covariates other than CAC progression.
Model 2: CPH regression with covariate adjustment for demographics and known risk factors of HF (Exam 1), including age, sex, race, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of antihypertensive medication, total cholesterol, HDL cholesterol, use of lipid-lowering medication, diabetes mellitus, cigarette smoking status, heart rate, creatinine, highest education level, household income, and baseline CAC score. A sensitivity analysis was done by comparing the results with and without adjusting for baseline NT-proBNP. Participants with any CHD and HF before second CAC measurement were excluded.
Model 3: model 2 after excluding the participants with any CHD before and after second CAC measurement. Subgroups analyses were done for participants with baseline CAC=0 and participants with baseline CAC >0.

For the analysis of LV dysfunction, multivariable linear regression models were used to assess the association of CAC progression, either continuous or categorical CAC progression, with each of the MRI parameters of LV function and structure at Exam 5. The same exclusion criteria were applied as in the CPH analysis. Two adjusted models were constructed with the covariates that were used for CPH analysis. Given that the distribution of CAC scores is skewed, the baseline CAC score in the models was transformed by the logarithmic transformation [ln (CAC+1)]. All statistical results were computed using Stata statistical software (version 14.1; StataCorp LP, College Station, TX). *P* value of less than 0.05 was considered significant.

Results

A total of 5644 MESA participants free of HF and CHD before the second CAC measurement were included in this study. The baseline characteristics of the study participants are shown in Table 1. The mean (±SD) interscan period (baseline and follow-up) was 2.4±0.9 years. Baseline CAC was zero in more than half of the cohort population (51.8%), and the majority (84.1%) remained CAC free in the second measurement. Of those with baseline CAC >0 to 100 and >100, 43.3% and 66.9% showed progression based on the above-defined basis for identifying progressors, respectively.

Over a median 9.6 (interquartile range [IQR], 8.8–10.6) years of follow-up from the second CAC measurement (12.2 [IQR, 11.7–12.7] years from Exam 1), 182 participants developed incident HF. Of those with HF, 83 participants developed concomitant CHD. Using CAC progression as a continuous variable, a longitudinal increase in CAC of 10 Agatston Units (AU) per year was associated with 2% (*P*=0.012) of increased risk of HF independent of known risk factors for HF and baseline CAC. This association remained statistically significant after excluding the participants with CHD (Table 2). The association between CAC progression as a categorical variable and HF was not statistically significant in adjusted models. Subgroups analysis were performed for participants with baseline CAC=0 and CAC >0 separately (Table 3). Any change in CAC from zero was associated with a hazard ratio (HR) of 2.52 (*P*=0.003) independent of traditional cardiovascular risk factors. In Figure, Kaplan–Meier curves of cumulative events show higher cumulative incident of HF in progressors compared to nonprogressors (Figure Panel A: full cohort; Figure Panel B: baseline CAC=0; and Figure Panel C: baseline CAC >0). A sensitivity analysis was done on a group of 4664 participants with available baseline NT-proBNP to investigate the effect of adjusting the CPH models for NT-proBNP (Table S1). The magnitude and significance of the associations remained largely unchanged.

Follow-up CMR images (Exam 5) were available for 2818 participants who were free of HF and CHD before the second CAC measurement. Mean±SD of the parameters of LV

Table 1. Baseline Characteristics of Participants

Characteristics	Mean±SD or N (%)	Characteristics	Mean±SD or N (%)
All participants	5644	LDL cholesterol, mg/dL	117.3±31
Males	2662 (47.2)	HDL cholesterol, mg/dL	51±14.7
Age, y	61.7±10.2	Lipid-lowering medication	909 (16.1)
Race		Diabetes mellitus	
White	2232 (39.5)	Normal	4209 (74.8)
Black	1529 (27.1)	Impaired fasting glucose	764 (13.6)
Hispanic	1207 (21.4)	Untreated diabetes mellitus	146 (2.6)
Chinese	676 (12)	Treated diabetes mellitus	508 (9)
Highest education level		Smoking status	
25th percentile	Completed high school/GED	Never smoker	2868 (51)
Median	Some college but no degree	Former smoker	2068 (36.7)
75th percentile	Bachelor's degree	Current smoker	694 (12.3)
Household income		Creatinine, mg/dL	0.95±0.25
25th percentile	$20 000 to $24 999	Heart rate (beats per minute)	63±9.6
Median	$40 000 to $49 999	CAC score=0	2923 (51.8)
75th percentile	$50 000 to $74 999	CAC score >0 to 100	1481 (26.2)
BMI, kg/m^2	28.3±5.4	CAC score >100	1240 (22)
SBP, mm Hg	125.7±21	CAC score (Agatston Unit) in participants with CAC >0	270.6±506
DBP, mm Hg	71.8±10.2		
Blood pressure medication	2023 (35.9%)	Interscan period, yr	2.4±0.9

These figures are numbers (%) and mean±SD. CAC indicates coronary artery calcium; DBP, diastolic blood pressure; GED, general education development; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

function and structure have been summarized in Table S2. Compared to participants with baseline CAC >0, participants with baseline CAC=0 showed higher EF and SV and lower LVM and MVR at the follow-up exam.

Table 4 shows the association between CAC progression and LV function and structure measured by CMR at Exam 5. Longitudinal increase in CAC was associated with higher LVESV (β=0.09; P<0.05) independent of traditional cardiovascular risk factors. This association remained statistically significant after excluding the participants with any CHD. The

association between CAC progression and LVEDV became statistically significant only after excluding participants with any CHD (β=0.16; P=0.03). Progressors showed statistically significant associations with increased LVESV (β=0.79; P=0.034) and LVEDV (β=1.21; P<0.05). These associations had reduced statistical significance level after excluding the participants with any CHD. Subgroup analyses were done for participants with baseline CAC=0 and CAC >0 (Tables S3 and S4). In participants with baseline CAC=0, CAC progression was associated with increased LVEDV, LVESV, and LVM in

Table 2. Hazard Ratios (95% CIs) Showing the Association Between Changes in CAC and Incident Heart Failure in the Full Cohort

Models (No. of Events/Analyzed)	Model 1* (182/5644)	Model 2[†] (168/5384)	Model 3[‡] (90/5049)
Absolute changes in CAC per year[§]	1.05 (1.04–1.06)[‖]	1.02 (1.004–1.04)[‖]	1.03 (1.01–1.05)[‖]
Progressors vs nonprogressors	2.74 (2.05–3.68)[‖]	1.29 (0.93–1.81)	1.25 (0.79–1.97)

*Model 1: unadjusted.

[†]Model 2: adjusted for age, sex, race, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of antihypertensive medication, total cholesterol, high-density lipoprotein (HDL) cholesterol, use of lipid-lowering medication, diabetes mellitus, cigarette smoking status, heart rate, creatinine, highest education level, household income, and baseline coronary artery calcium (CAC) score (Exam 1).

[‡]Model 3: Model 2 after excluding participants with any coronary heart diseases.

[§]Hazard ratio (HR) per 10 Agatston Unit annual increase in CAC.

[‖]Statistically significant HRs (95% CIs).

Table 3. Hazard Ratios (95% CIs) Showing the Association Between Changes in CAC and Incident Heart Failure in Participants With Baseline CAC=0 and Baseline CAC >0 Separately

Models (No. of Events/Analyzed)	Baseline CAC=0			Baseline CAC >0		
	Model 1* (49/2923)	Model 2† (46/2791)	Model 3‡ (33/2741)	Model 1* (133/2721)	Model 2† (122/2593)	Model 3‡ (57/2308)
Absolute changes in CAC per year§	2.02 (1.47–2.78)‖	1.8 (1.21–2.69)‖	1.79 (1.08–2.95)‖	1.04 (1.03–1.05)‖	1.02 (0.999–1.03)	1.02 (1.001–1.05)‖
Progressors vs nonprogressors	3.74 (2.12–6.62)‖	2.52 (1.36–4.67)‖	2.39 (1.15–4.95)‖	1.54 (1.08–2.19)‖	1.09 (0.74–1.59)	0.98 (0.56–1.68)

*Model 1: unadjusted.

†Model 2: adjusted for age, sex, race, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of antihypertensive medication, total cholesterol, high-density lipoprotein (HDL) cholesterol, use of lipid-lowering medication, diabetes mellitus, cigarette smoking status, heart rate, creatinine, highest education level, household income, and baseline coronary artery calcium (CAC) score (Exam 1).

‡Model 3: Model 2 after excluding participants with any coronary heart diseases.

§Hazard ratio (HR) per 10 Agatston Unit annual increase in CAC.

‖Statistically significant HRs (95% CIs).

multivariate analysis. By excluding participants with any CHD, these associations were no longer significant.

Discussion

Serial CAC measurement has been suggested as a noninvasive method to monitor the progression of CAD.[11] It has been proven, in previous studies, that CAC progression is associated with future CHD and all-cause mortalities.[12,13] In this study, we found CAC progression as a predictor of incident HF independent of traditional risk factors for HF and baseline CAC. We also observed that longitudinal increase in CAC is associated with greater LVESV and LVEDV as measured by CMR independent of known risk factors for HF and overt CHD.

CAD is the most common underlying cause of HF especially in the elderly population.[23] LV remodeling after myocardial infarction is a well-described etiology of HF.[24] The necrotic area will be replaced by fibrotic tissue, which is nonfunctional and less elastic than myocytes.[5] Additionally, ischemia induces activation of neurohormonal cascade, which, in fact, has a negative impact on the remaining normal myocardium.[6] In addition to this pathway, CAD and ischemia may play a crucial rule in the pathophysiology of HF without presenting as a clinically overt CHD.[7] In other words, in many patients, HF is the first presentation of CAD.[15] In our study, we showed that the association of CAC progression and HF remained statistically significant, even after excluding all participants with CHD. Our result is in agreement with a few previous studies that evaluated the association between baseline CAC and HF.[14,15,17]

Kalsch et al in the Heinz Nixdorf Recall Study has shown a significant association between CAC and history of HF in a univariate cross-sectional analysis.[14] This association became statistically insignificant after adjusting for traditional cardiovascular risk factors. The investigators explained this diminished association by the fact that cardiovascular risk factors

like hypertension can lead to both CAC formation and HF. Sakuragi et al recently reported the result of a study on 487 Japanese participants free of CAD and HF at enrollment.[17] During the mean follow-up of 497±315 days, 9 participants developed incident HF without any overt CHD. Higher CAC was associated with higher incidence of HF and higher NT-pro BNP level. The number of incident HFs in this study was limited and the investigators proposed a multicenter study to confirm the association of CAC and HF. In another study, Leening et al investigated the association between baseline CAC and HF in the Rotterdam study.[15] In this population-based study, 1897 participants free of any history of CHD and HF were followed for a median of 6.8 years for incident HF and CHD events. Baseline CAC was strongly associated with higher incidence of HF independent of traditional cardiovascular risk factors. This association remained statistically significant after excluding the participants with incident myocardial infarction or revascularization procedures. This study was done on a Dutch elderly population, and the result cannot be extrapolated to the middle-age population and other ethnic groups.

There are some possible explanations for the association between CAD and HF in patients without overt CHD. Coronary artery endothelial dysfunction is an integral part of the cascade that eventually results in atherosclerotic plaque formation.[25] Dysfunctional endothelium produces more vasoconstrictors like endothelin instead of vasodilator substances.[26] These vasoconstrictor substances have a direct detrimental effect on the myocardium, which eventually lead to myocardial fibrosis and HF.[27] In addition, in patients without clinically overt CHD, chronic ischemia/hypoperfusion may result in a hibernating myocardium.[6] Consequently, in the affected area, apoptosis may occur, which, in turn, will result in myocardial dysfunction.[28]

In the second part of the study, we observed a direct association between CAC progression and follow-up LVESV
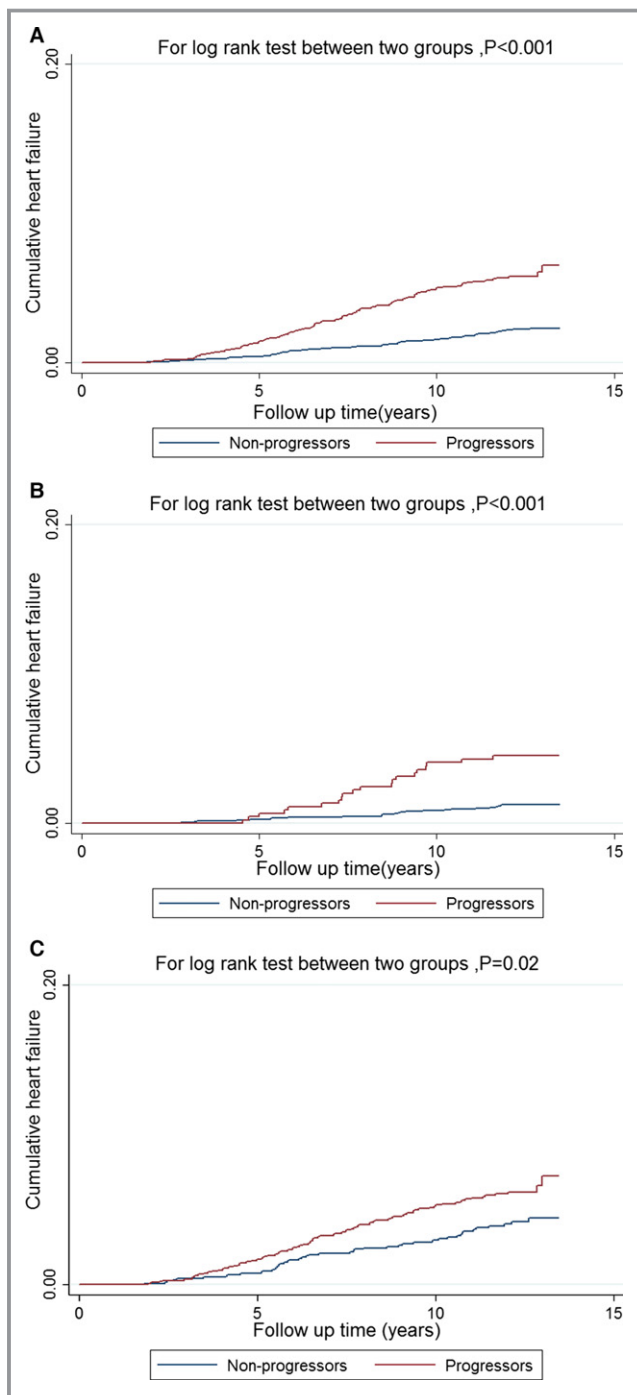
Figure. Kaplan–Meier curves of cumulative events show higher rate of incident heart failure in progressors versus nonprogressors in full cohort (A), in participants free of coronary artery calcium (CAC) at baseline (B), and in participants with baseline CAC >0 (C). The Kaplan–Meier curves for progressors and nonprogressors overlap for the first 3 years of follow-up because we only included the heart failure events that occurred after second CAC measurement.

and LVEDV, independent of baseline CAC, traditional cardiovascular risk factors, and overt CHD. The result of our study is in line with a few previous studies that investigated the

relationship between subclinical atherosclerosis and LV dysfunction.[29,30] Edvardsen et al studied the relation between regional CAC and regional LV systolic dysfunction in 509 MESA participants.[29] High regional CAC were associated with regional myocardial dysfunction defined by LV circumferential strain and strain rate in the same perfusion territory. However, this study did not show any association between increased CAC and decrease in SV and EF. In another study, Colletti et al investigated the association between CAC and LV dysfunction measured by CMR.[30] At enrollment, the participants of the South Bay Heart Watch (SBHW) were older than 45 years with various cardiovascular risk factors, but without any evidence of CHD. CAC was measured in a group of 1312 SBHW participants. After a mean of ≈11 years, 386 participants underwent CMR to measure LV function parameter, including EF, peak filling rate, and regional wall motion abnormalities (RWMAs). The association between baseline CAC and follow-up RWMA remained statistically significant even after adjusting for cardiovascular risk factors.

The clinical importance of subclinical LV dilatation has been shown in previous studies.[31–33] In a study on participants of the Framingham Heart Study and Framingham Offspring Study, 4744 individuals free of myocardial infarction and HF who underwent echocardiography at baseline were followed for incident HF.[32] It was shown that increased LVED and LVES dimensions were associated with higher incidence of future HF. In another study, Yeboah et al demonstrated the association between LV dilatation measured by CMR at baseline with incident HF in 4974 MESA participants during over 9.4 years follow-up.[33]

In our study, progressors failed to show any statistically significant increase in incidence of HF or subclinical decrease in EF and SV in adjusted models. There are some explanations for this finding. CAC and HF share many common risk factors like SBP, which behave as confounders in their relation. The association between CAC and HF is not as strong as the association between CAC and CHD, and by categorizing the participants, there is not enough power to detect this association. Finally, there are many different definitions in the literature for progressors. Utilizing different methods to define progressors will cause at least minor discrepancy in the results.

Strength and Limitations

MESA is a well-designed, multiethnic, population-based study with long-term follow-up. In addition to the general strength of MESA, our study is the first to investigate the association of CAC progression with HF and subclinical LV dysfunction. There are some limitations that need to be mentioned. MESA participants were free of any cardiovascular disease at study entry, and the number of events can be different from general

Table 4. Estimated Regression Coefficients and Their 95% Confidence Intervals Showing the Association Between CAC Progression and the Left Ventricular Function and Structure Measures by Cardiac Magnetic Resonance in Full Cohort

	Models (n)	Absolute Changes in CAC Per Year*	Progressors vs Nonprogressors
EF	Model 1[†] (2721)	−0.04 (−0.11 to 0.03)	−0.24 (−0.88 to 0.41)
	Model 2[‡] (2598)	−0.07 (−0.15 to 0.01)	−0.01 (−0.67 to 0.64)
SV	Model 1 (2719)	0.05 (−0.04 to 0.14)	0.42 (−0.33 to 1.17)
	Model 2 (2596)	0.04 (−0.06 to 0.13)	0.53 (−0.24 to 1.3)
LVEDV	Model 1 (2720)	0.14 (−0.01 to 0.28)	1.21 (0.02–2.39)[§]
	Model 2 (2597)	0.16 (0.01–0.31)[§]	0.98 (−0.21–2.18)
LVESV	Model 1 (2719)	0.09 (0.002–0.18)[§]	0.79 (0.06–1.51)[§]
	Model 2 (2596)	0.12 (0.03–0.21)[§]	0.44 (−0.26 to 1.15)
LVM	Model 1 (2720)	0.08 (−0.03 to 0.20)	0.70 (−0.31 to 1.70)
	Model 2 (2597)	0.1 (−0.03 to 0.23)	0.61 (−0.42 to 1.64)
MVR	Model 1 (2722)	−0.001 (−0.003 to 0.001)	−0.01 (−0.02 to 0.01)
	Model 2 (2599)	−0.001 (−0.003 to 0.001)	−0.01 (−0.02 to 0.01)

CAC indicates coronary artery calcium; EF, ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVM, left ventricular mass; MVR, mass to volume ratio; SV, stroke volume.

*Coefficient (95% CI) per 10 Agatston Unit annual increase in CAC.

[†]Model 1: adjusted for age, sex, race, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of antihypertensive medication, total cholesterol, high-density lipoprotein (HDL) cholesterol, use of lipid-lowering medication, diabetes mellitus, cigarette smoking status, heart rate, creatinine, highest education level, household income, and baseline CAC score (Exam 1).

[‡]Model 2: Model 1 after excluding participants with any coronary heart diseases.

[§]Statistically significant coefficients (95% CIs).

population. The HF event ascertainment in MESA is based on the data collected from medical records at the time of diagnosis and therefore is subject to misclassification from accuracy and performance of the diagnostic tools, such as echocardiography and clinical data. Nevertheless, this is the standard method in most of the large-scale, prospective cohort studies, where the event ascertainment and data collection on events are often performed after the events have already occurred.[34–36] Additionally, given the unavailability of EF at the time of diagnosis of HF for all participants, we did not differentiate cases into HF with preserved EF and HF with reduced EF. For the subclinical assessment of LV, CMR was available for less than half of the participants. Although we found a statistically significant association between longitudinal increase in CAC and LVESV and LVEDV, the strength of the association is not strong enough to be meaningfully translated into clinical practice.

Conclusion

In a multiethnic, population-based study, we have shown that CAC progression predicts incident HF and increased LVEDV and LVESV measured by CMR at follow-up exam independent of traditional cardiovascular risk factor, baseline CAC, and overt CHD. Despite the presence of the statistically significant association between CAC progression and subclinical LV dilatation in participants free of any CHD, these weak associations may not be of any clinical significance. We recommend further research to identify the subgroup of individuals who will benefit from serial CAC measurement for cardiovascular risk stratification.

Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Hazard ratio's (95% CIs) showing the association between CAC progression and incident heart failure in participants with available measurements of baseline NT-proBNP.

Models (Number of events/analyzed)	Model 1* (142/4664)	Model 2† (135/4497)	Model 3‡ (75/4214)
Absolute changes in CAC per year§	**1.06**	**1.02**	**1.03**
	(1.05-1.07)	**(1.003-1.04)**	**(1.001-1.05)**
Progressors vs. non-progressors	**2.68**	1.21	1.22
	(1.92-3.73)	(0.83-1.75)	(0.74-2.03)

Statistically significant HRs (95% CIs) are showed in bold. *Model1: unadjusted. †Model 2: adjusted for age, gender, race, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of antihypertensive medication, total cholesterol, high density lipoprotein (HDL) cholesterol, use of lipid lowering medication, diabetes, cigarette smoking status, heart rate, creatinine, highest education level, household income , baseline CAC score and N-terminal prohormone of brain natriuretic peptide (NT-proBNP , all covariates from Exam 1) .‡ Model3: Model 3 after excluding participants with any coronary heart diseases. §Hazard ration per 10 U annual increase in CAC.

Table S2. Comparing the parameter of LV function and structure measured by cardiac magnetic resonance in

participants with baseline CAC=0 and participants with baseline CAC>0

MRI parameter at Exam 5 (unit)	Baseline CAC=0	Baseline CAC>0	P value
EF (%)	62.2 ± 7.1	61.6 ± 7.4	**0.01**
SV (ml/m²)	40.2 ± 8.2	39.1 ± 8.8	**0.001**
LVEDV (ml/m²)	64.9 ± 13.1	64.1 ± 14.8	0.1
LVESV (ml/m²)	24.7 ± 8	24.9 ± 9.1	0.52
LM (gram/m²)	64.5 ± 13.3	68.1 ± 13.7	**<0.001**
MVR (gram/ml)	1 ± 0.2	1.1 ± 0.2	**<0.001**

Statistically significant p-values are showed in bold. CAC: coronary artery calcium, EF: ejection fraction; SV: stroke

volume; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVM: left

ventricular mass; MVR: mass to volume ration.

Table S3. Estimated regression coefficients and their 95% confidence intervals showing the association between CAC progression and the left ventricular function and structure measures by cardiac MRI in participants with baseline CAC=0.

	Models(n)	Absolute changes in CAC per year‡	Progressors vs. non- progressors
EF	Model 1* (1545)	-0.48 (-2.04 to 1.08)	-0.22 (-1.21 to 0.77)
	Model 2† (1521)	-0.38 (-1.96 to 1.18)	-0.11 (-1.11 to 0.89)
SV	Model 1 (1544)	1.26 (-0.53 to 3.05)	0.16 (-0.98 to 1.30)
	Model 2 (1520)	0.93 (-0.87 to 2.73)	0.12 (-1.03 to 1.27)
LVEDV	Model 1 (1544)	**2.96 (0.21 to 5.70)**	0.75 (-0.99 to 2.50)
	Model 2 (1520)	2.22(-0.52 to 4.97)	0.50 (-1.26 to 2.25)
LVESV	Model 1 (1544)	**1.7 (0.02 to 3.37)**	0.59 (-0.47 to 1.65)
	Model 2 (1520)	1.29 (-0.38 to 2.95)	0.37 (-0.69 to 1.44)
LVM	Model 1 (1544)	**2.45 (0.11 to 4.78)**	0.77 (-0.71 to 2.25)
	Model 2 (1520)	2.10 (-0.25 to 4.45)	0.75 (-0.74 to 2.25)
MVR	Model 1 (1545)	-0.01 (-0.06 to 0.03)	0.01 (-0.02 to 0.04)
	Model 2 (1521)	-0.01 (-0.05 to 0.04)	0.01 (-0.02 to 0.04)

Statistically significant coefficients (95% CIs) are showed in bold.*Model 1: adjusted for age, sex, race, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of antihypertensive medication, total cholesterol, high density lipoprotein (HDL) cholesterol, use of lipid lowering medication, diabetes , cigarette smoking status, heart rate, creatinine, highest education level, household income and baseline CAC score (Exam 1).† Model2: Model 1 after excluding participants with any coronary heart diseases. ‡Coefficient (95% CI) per 10 Agatston Unit annual increase in CAC. CAC: coronary artery calcium, EF: ejection fraction; SV: stroke volume; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVM: left ventricular mass; MVR: mass to volume ration.

Table S4. Estimated regression coefficients and their 95% confidence intervals showing the association between CAC progression and the left ventricular function and structure measures by cardiac MRI in participants with baseline CAC>0.

	Models(n)	Absolute changes in CAC per year‡	CAC progression vs. no progression
EF	Model 1* (1176)	-0.02 (-0.1 to 0.06)	-0.32 (-1.19 to 0.54)
	Model 2† (1077)	-0.05 (-0.13 to 0.03)	0.01 (-0.87 to 0.89)
SV	Model 1 (1175)	0.05 (-0.05 to 0.15)	0.58 (-0.44 to 1.61)
	Model 2 (1076)	0.04 (-0.06 to 0.15)	0.83 (-0.24 to 1.90)
LVEDV	Model 1 (1176)	0.12 (-0.05 to 0.28)	1.55 (-0.12 to 3.23)
	Model 2 (1077)	0.15 (-0.02 to 0.32)	1.35 (-0.33 to 3.04)
LVESV	Model 1 (1175)	0.07 (-0.03 to 0.17)	0.97 (-0.07 to 2.01)
	Model 2 (1076)	**0.11 (0.01 to 0.20)**	0.52 (-0.45 to 1.49)
LVM	Model 1 (1176)	0.07 (-0.06 to 0.21)	0.68 (-0.72 to 2.09)
	Model 2 (1077)	0.09 (-0.06 to 0.23)	0.56 (-0.91 to 2.04)
MVR	Model 1 (1177)	-0.001 (-0.003 to 0.001)	-0.01 (-0.04 to 0.01)
	Model 2 (1078)	-0.001 (-0.003 to 0.001)	-0.01 (-0.04 to 0.01)

Statistically significant coefficients (95% CIs) are showed in bold. *Model 1: adjusted for age, sex, race, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of antihypertensive medication, total cholesterol, high density lipoprotein (HDL) cholesterol, use of lipid lowering medication, diabetes, cigarette smoking status, heart rate, creatinine, highest education level, household income and baseline CAC score (Exam 1). † Model2: Model 1 after excluding participants with any coronary heart diseases. ‡Coefficient (95% CI) per 10 Agatston Unit annual increase in CAC. CAC: coronary artery calcium, EF: ejection fraction; SV: stroke volume; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVM: left ventricular mass; MVR: mass to volume ration.