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Progression of Coronary Calcium and Incident Coronary Heart Disease Events

MESA (Multi-Ethnic Study of Atherosclerosis)

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Objectives The study examined whether progression of coronary artery calcium (CAC) is a predictor of future coronary heart disease (CHD) events.

Background CAC predicts CHD events and serial measurement of CAC has been proposed to evaluate atherosclerosis progression.

Methods We studied 6,778 persons (52.8% female) aged 45 to 84 years from the MESA (Multi-Ethnic Study of Atherosclerosis) study. A total of 5,682 persons had baseline and follow-up CAC scans approximately 2.5 ± 0.8 years apart; multiple imputation was used to account for the remainder (n = 1,096) missing follow-up scans. Median follow-up duration from the baseline was 7.6 (max = 9.0) years. CAC change was assessed by absolute change between baseline and follow-up CAC. Cox proportional hazards regression providing hazard ratios (HRs) examined the relation of change in CAC with CHD events, adjusting for age, gender, ethnicity, baseline calcium score, and other risk factors.

Results A total of 343 and 206 hard CHD events occurred. The annual change in CAC averaged 24.9 ± 65.3 Agatston units. Among persons without CAC at baseline (n = 3,396), a 5-unit annual change in CAC was associated with an adjusted HR (95% Confidence Interval) of 1.4 (1.0 to 1.9) for total and 1.5 (1.1 to 2.1) for hard CHD. Among those with CAC >0 at baseline, HRs (per 100 unit annual change) were 1.2 (1.1 to 1.4) and 1.3 (1.1 to 1.5), respectively. Among participants with baseline CAC, those with annual progression of ≥300 units had adjusted HRs of 3.8 (1.5 to 9.6) for total and 6.3 (1.9 to 21.5) for hard CHD compared to those without progression.

Conclusions Progression of CAC is associated with an increased risk for future hard and total CHD events. (J Am Coll Cardiol 2013;61:1231–9) © 2013 by the American College of Cardiology Foundation

Coronary artery calcium (CAC) is strongly associated with atherosclerotic burden and predicts coronary heart disease (CHD) events and mortality (1–4). CAC scanning has been proposed as a measure to track CHD progression and the effects of risk factor modification on atherosclerosis (5,6). Multiple retrospective and 1 prospective study suggest that CAC progression is associated with CHD events (7,8). Recently, follow-up on the basis of a large registry of subjects receiving serial computed tomography (CT) scans showed progression of CAC to be strongly associated with

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Abbreviations and Acronyms

CAC = coronary artery calcium

CHD = coronary heart disease

CT = computed tomography

HR = hazard ratio

total mortality (9). We examined the relation of CAC progression to CHD incidence in a large multiethnic sample of U.S. adults in a population-based prospective study.

Methods

Study population and definitions. The MESA (Multi-Ethnic Study of Atherosclerosis) study is a prospective study of cardiovascular disease (11). A total of 6,814 participants ages 45 to 84 years free of clinical cardiovascular disease and identified as White, Black, Hispanic, or Chinese, were recruited from 6 U.S. communities (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; Los Angeles County, California) in 2000 to 2002. Recruitment was conducted on the basis of lists of residents, dwellings, telephone exchanges, lists of Medicare beneficiaries, and referrals by participants. All participants gave informed consent, and the study protocol was approved by the Institutional Review Board at each site. This report includes 6,778 participants with follow-up for events, of which 5,682 subjects had both baseline (Exam 1) and follow-up (Exam 2 or 3) CT scans and with no interim CHD events. Multiple imputation (12,13) (described subsequently) was used for the 1,096 participants who did not have a follow-up CAC measure, including 141 individuals who experienced a CHD event prior to their second scan.

Measurement of CAC. CAC was measured by electron-beam (3 sites) or multidetector (3 sites) CT. Participants were scanned twice consecutively (at each baseline and follow-up) and scans were read by a trained physician-reader at a centralized reading center (Los Angeles Biomedical Research Institute, Torrance, California). The methodology for acquisition and interpretation of the scans has been published (14–16). Calcium volume scores and Agatston scores were determined on the basis of averaging results from each of the 2 scans done at the examination, and adjusted using a standard calcium phantom. Detectable calcium was defined as a CAC score >0. A repeat pair of scans was performed on one-half of the cohort (randomly selected) at a second MESA study clinical exam (September 2002 to January 2004) and on the other one-half at a third exam (March 2004 to July 2005), averaging 2.5 years after the baseline scans. Mean ± SD absolute and % interscan variability and correlation (r) were 19.8 ± 59.6, 20.82%, and 0.99 between the paired scans at baseline and 23.6 ± 61.7, 22.40%, and 0.99 between the paired scans at follow-up, respectively. The distribution of CAC in the MESA study at baseline by age, gender, and race has been published (17).

Examination data and covariates. Information on demographics, smoking, medical conditions, and family history was obtained by questionnaire. Height, weight, fasting total and high-density lipoprotein cholesterol, triglycerides, and glucose levels were determined. Resting blood pressure was measured 3 times, with the average of the last 2 measurements used in analysis. Cholesterol, blood pressure, and diabetes medications were determined by questionnaire and from medication containers. Diabetes was defined as a fasting glucose ≥7.0 mmol/l (126 mg/dl), or use of insulin or oral hypoglycemic medications.

Follow-up. The cohort was followed for incident CHD events for a median of 7.6 (max = 9.0) years following the performance of the baseline CT scan (4.8 years following the second scan for the complete case analysis, see subsequent sections). At intervals of 9 to 12 months, a telephone interviewer inquired about interim hospital admissions, cardiovascular diagnoses, and deaths. An adjudication committee received copies of all death certificates and medical records for hospitalizations and outpatient cardiovascular diagnoses. Total CHD endpoints included myocardial infarction, probable angina if followed by revascularization, resuscitated cardiac arrest, and CHD death. Hard CHD included myocardial infarction and fatal CHD. Two physicians from the MESA study events committee independently reviewed all medical records and death certificates for endpoint classification and assignment of incidence dates. The reviewers were blinded to CT results and used prespecified criteria.

Statistical analysis. Separate analyses were done for those with baseline CAC = 0 (n = 3,396) and those with CAC >0 (n = 3,382). Absolute progression rates were annualized. Analyses were conducted on the basis of Agatston scores with secondary analyses repeated using volume scores. For all missing information, multiple imputation (12,13) using a chained equation approach (18) was used to replace each missing value with a set of 100 plausible substitutes that were consistent with the observed values. For persons without follow-up CAC scans (n = 1,096), follow-up CAC at Exam 2 or 3 was predicted using regression equations on the basis of the observed data, using baseline risk factors, baseline CAC (for those with CAC >0), CHD events, time to CHD event, or last follow-up. Prior literature has described the rationale and necessity of including these variables in multiple imputation prediction equations (19–21) and imputation with repeated measures (13).

Follow-up CAC measures were imputed separately for participants with baseline CAC = 0 and CAC >0 at the time when they would have been given a second scan (estimated or actual date of follow-up exam), and assumed a linear rate of change in CAC. In those with intervening initial CHD events, the degree of progression (and follow-up time) was determined on the basis of the date of occurrence of the event, imputing what the follow-up scan score would have been at that time. A conditional (2-part) imputation was done for subjects with CAC = 0. The first step predicted the likelihood of any CAC progression using logistic regression; the second part was conditioned on the first and only those who were predicted to have had

progression were imputed to have a follow-up CAC score >0. The conditional imputation allowed adequate modeling of the relatively large proportion of participants with baseline CAC = 0 who experienced no progression. Parameter estimates were averaged across the multiple datasets and using Rubin's rules (12) to combine the standard errors when applicable.

CHD event rates were annualized and reported per 1,000 person-years, overall and according to absolute change categories (no change, and >0 in those without CAC at baseline and no/negative change, 0.01 to 99, 100 to 199, 200 to 299, and ≥300 in those with CAC at baseline). In those with CAC at baseline (excluding those with scores <10 due to spuriously high relative changes from small score increases), CHD event rates are also reported in terms of annualized percentage change in CAC (<5%, 5% to <15%, 15% to <30%, and ≥30%).

For those with baseline CAC = 0, Cox proportional hazards regression modeled the change in CAC both as a dichotomous variable comparing those with any progression to those who remained at zero, and as a continuously per 5-U change in progression. For those with CAC >0, we chose intervals of 100 units of change per year compared to those who had ≤0 change, and as a continuous variable in units of 100 change per year. Results are also presented in terms of the annualized percentage of change categories as described previously. In the imputed analyses, follow-up time was calculated from the time of the baseline scan since progression was imputed in cases of intervening CHD events or where second scans were unavailable; for the complete case analysis, it was calculated from the time of the second scan. Models both unadjusted and adjusted for age, gender, ethnicity, and baseline total and high-density lipoprotein cholesterol, lipid-lowering medication, systolic and diastolic blood pressure, hypertension medication, smoking, diabetes, family history, and baseline CAC score were run. Sensitivity analyses were also done adjusting for baseline and follow-up interscan variability as well as including those with percutaneous interventions or bypass surgery, which were not included in the MESA total CHD endpoint. All analyses were conducted with Stata statistical software (version 12.1, College Station, Texas).

Results

Overall 3,382 (49.9%) of participants had CAC at baseline; 12% of our sample were Black, 28% were Chinese, 38% were White, and 22% were Hispanic. Participants with CAC at baseline were more likely to be older and male, and have diabetes, have previously smoked, have a family history of MI or stroke, and be on lipid-lowering or antihypertensive medication. Of those with baseline CAC = 0, 84.2% were still 0 at the follow-up scan and 15.8% showed progression (median progression 2.2 U/year). For those with CAC >0, 15.2% did not progress, whereas 84.8% showed progression (median progression 28.9 U/year) (Table 1). Among those with baseline CAC scores of 0, 0.001 to 99, 100 to 199, 200 to 299, and ≥300, median annual progression was 2.2, 8.3, 28.4, 44.0, and 103.3 units/year, respectively, for the imputed analysis and 0, 7.9, 27.7, 43.2, and 95.5 U/year, respectively, for the nonimputed analysis. There were 343 total incident CHD events, of which 206 were hard CHD events (of which 148 and 88 occurred before a second scan so were thus included in imputed analyses).

Figure 1 shows the Kaplan-Meier failure estimates with incident CHD being significantly greater comparing any to no CAC change among those with baseline CAC = 0 ($p < 0.001$ for the log-rank test). Figure 2 shows successively greater cumulative proportions of incident CHD events according to annual CAC change groupings among those with baseline CAC >0 ($p < 0.001$ comparing CAC change groups). Kaplan-Meier estimates were also determined for the nonimputed samples (see Online Appendix).

Among those with CAC = 0 at baseline, compared to persons with no increase in CAC, any increases were associated with 1.4- to 1.5-fold greater risks for CHD events in adjusted analyses (Table 2). There was a 50% greater risk for both total and hard CHD events per annual increase of 5 U. The imputed models tended to have more statistical power, although results were similar regardless of which analytic strategy was used.

In Table 3, future CHD risk by progression of CAC in those with CAC >0 at baseline is compared to those with no progression of CAC. Annual CAC increases of ≥100 U conferred significant 2- to 3-fold greater risks for total and hard CHD events in adjusted analyses, with annual total CHD event rates of 3% to 6%/year. Moreover, in secondary analyses (not shown) comparing the impact of using volume scores versus Agatston scores, virtually identical results were obtained, with the adjusted risk (hazard ratio [95% confidence interval]) of total CHD per SD unit absolute change in CAC per year of 1.2 (1.1 to 1.3) for both Agatston score and for volume score. Baseline CAC was expectedly the greatest contributor to risk ($t = 4.76$, $p < 0.001$), followed by gender ($t = 3.78$, $p < 0.001$), systolic blood pressure ($t = 3.55$, $p < 0.001$), and total cholesterol ($t = 3.28$, $p = 0.001$); annualized calcium change was the next most important predictor ($t = 2.92$, $p < 0.001$) of total CHD events.

Table 4 shows the risk of total CHD events according to percentage change categories in CAC and by annualized percentage change as a continuous variable. Those with 15% to 29% annual increases in CAC had an increased risk (hazard ratio [HR]: 1.6) for total CHD events relative to those with progression <5% annually.

In separate analyses (not shown), we examined the threshold for which annualized absolute and relative (percent change) progression were best associated with total CHD event risk (comparing those at or above vs. below different cutpoints using Cox proportional hazards regression in fully adjusted analyses); cutpoints at or above 25

Table 1 Descriptive Statistics: MESA

	Baseline CAC = 0	Baseline CAC >0
Overall	3,396	3,382
Men	1,243 (36.6%)	1,953 (42.2%)
Women	2,153 (63.4%)	1,429 (57.8%)
Caucasian	1,125 (33.1%)	1,489 (44.0%)
Black	398 (11.7%)	402 (11.9%)
Chinese	1,061 (31.2%)	819 (24.2%)
Hispanic	812 (23.9%)	672 (19.9%)
Taking lipid-lowering medication	10.6%	21.8%
Taking antihypertensive medication		
Smoker	28.8%	45.8%
Never	56.0%	44.6%
Former	30.8%	42.5%
Current	13.2%	12.9%
Diabetes	9.3%	15.9%
Family history of MI or stroke	37.1%	48.3%
Age, yrs	58.0 ± 9.1	66.4 ± 9.5
Total cholesterol, mmol/l (mg/dl)	5.0 (193.7) ± 0.9 (35.0)	5.1 (194.6) ± 0.9 (36.4)
HDL-C, mmol/l (mg/dl)	1.4 (52.5) ± 0.4 (15.0)	1.3 (49.5) ± 0.4 (14.5)
SBP, mm Hg	122.4 ± 20.5	130.8 ± 21.7
DBP, mm Hg	71.2 ± 10.3	72.6 ± 10.2
CAC at baseline	0	290.8 ± 545.9
Median follow-up duration, yrs	7.6 (max = 9.0)	7.6 (max = 8.9)
Years between exams	2.5 ± 0.8	2.4 ± 0.9
Incidence of CAC in those with CAC = 0	535 (15.8%)	
Median (25–75%tiles) CAC change/yr in those with incident CAC	2.2 (0.7–5.9)	
Progression of CAC in those with CAC >0		2,869 (84.8%)
Median CAC change/yr in those with progression of CAC		28.9 (60.9–529.1)

Values are n (%), %, mean ± SD, and median (25%–75%). Subjects include both imputed and nonimputed cases.
CAC = coronary artery calcium; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; SBP = systolic blood pressure.

units absolute change per year (e.g., HR: 2.9, $p < 0.001$ for 25 U), or 15% annual increases (HR: 1.4, $p < 0.05$) in CAC were identified.

We also conducted a sensitivity analysis and compared results from the total (imputed) and not imputed (complete case) samples. In adjusted analyses, among those with CAC = 0 at baseline, HRs per 5 U increase in CAC were identical (1.4, $p < 0.05$) for the total and not imputed samples (Table 5). Among those with CAC> 0 at baseline, a 100 unit annual progression of CAC associated with HRs (95% Confidence interval) of 1.2 (1.1 to 1.4) and 1.3 (1.2 to 1.5), respectively (Table 6).

The MESA total CHD endpoint does not include incident percutaneous interventions or bypass surgery because of concern that referral bias arising from the calcium score could influence these events; including 29 such events in our nonimputed analyses for total CHD showed adjusted HRs for those with annual CAC increases of 100 to 199, 200 to 299, and 300+ versus no or negative change that were greater than when these events were not included (3.8 vs. 3.1, 4.7 vs. 3.2, and 5.8 vs. 3.8, respectively, all $p < 0.001$).

Finally, we examined the impact of adjusting for baseline and follow-up interscan variability on total CHD by adding these terms to the Cox proportional hazards regression and found no relation with event risk (for baseline: HR: 0.8, 0.6 to 1.2; follow-up interscan variability: HR: 0.8, 0.5 to 1.3). Results were largely unaffected with adjusted HRs for those with score increases of 100 to 199, 200 to 299, and 300+ versus no or negative change of 1.8 (1.0 to 3.2), 2.0 (1.0 to 4.0), and 2.4 (1.1 to 5.4), respectively, and 1.2 (1.1 to 1.4) per 100 U annual change (compare to Table 3 not adjusted for interscan variability).

Discussion

Serial evaluation of CAC has been proposed for measuring progression of atherosclerosis, and thus to predict CHD in asymptomatic individuals. We observed graded relationships of CAC progression with CHD event risk, strongly suggesting that the functions are linear, with greater progression associated with greater risk. We demonstrated that progression of CAC is associated with total and hard CHD risk; these relationships remained significant after adjusting for risk factors and baseline calcium. We demonstrated that those with annual progression of ≥300 U were 3 times more likely to suffer CHD events in adjusted analyses. Compared with those without progression of CAC, any progression of

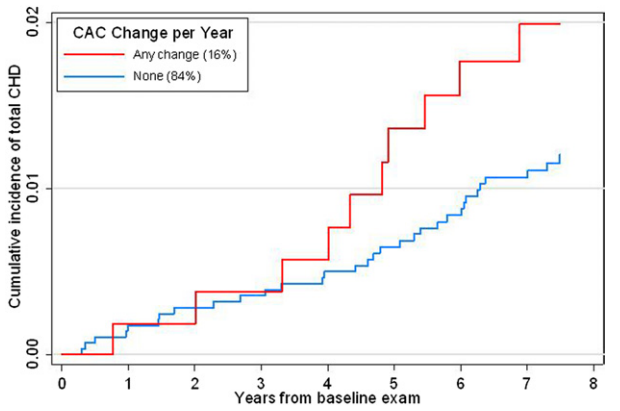

Figure 1 **Kaplan-Meier Plot of Cumulative Incidence of Total CHD Among Persons With CAC = 0 at Baseline**

Numbers in parenthesis indicate proportion of subjects in each group. Imputed and nonimputed subjects are included. For log-rank test comparing any versus no change in coronary artery calcium (CAC), $p < 0.001$. CHD = coronary heart disease.

CAC in those with CAC = 0 at baseline and progression of at least 100 units in those with CAC >0 at baseline were associated with increased CHD risk, with event rates of 3% to 6%/year.

Our results are consistent with earlier smaller studies showing that persons who experienced CHD events had also greater progression of CAC (7,8), as well as a recent prospective study demonstrating a strong relation with total mortality (9). The 3.3-fold increased mortality risk seen with CAC progression is similar to our 2- to 4-fold adjusted HRs for CHD events. In a retrospective follow-up study of 817 persons, CAC progression was the strongest predictor of myocardial infarction (26). Another study showed a 17-fold relative risk for acute myocardial infarction for patients exhibiting ≥15% CAC progression when compared to that of patients without CAC progression (7).

Of great interest has been whether risk-reducing therapies such as statins may retard progression of atherosclerosis assessed by serial CAC scanning. In our study, mean progression rates were 46.2 for those not on statins compared to 60.0 for statin users ($p < 0.001$) and among those who suffered a CHD event, those on statins actually had more progression than those who were not on statins (119.3 U/year vs. 55.7 U/year, respectively, among those with CAC >0); this is not surprising from an observational study such as MESA where people receiving statins are generally of higher risk than those not receiving statins. This important observation argues against the concept that increased CAC on statins is benign or reflects only conversion of noncalcified to calcified plaque rather than progression of the underlying atherosclerotic process, although both processes may be present. Two important clinical trials did not show differences in CAC progression between those treated versus not treated with statins (5,6).

Important to understanding factors related to the progression of CAC is the baseline calcium score, a strong predictor of CAC progression (27,28). While baseline CAC can be considered a confounder, it can also be considered part of the causal pathway between CHD risk factors and CAC progression. Persons with higher baseline CAC have a higher risk factor burden and, perhaps, more uncalcified atherosclerotic plaques destined for calcification and, thus, may exhibit greater future CAC progression. Thus, including baseline CAC in the model could account for effects that variables of interest may have had before the initial scan (22). We show that CAC progression predicts CHD events even after adjustment for baseline risk factors and baseline calcium score. Other reports also document the low progression and event rate in those with CAC = 0 at baseline (6), which indicates a low risk of future CHD events for at least 5 years (29).

We observed greater relative (%) increases in CAC (15% or greater) to be associated with only modest increases in CHD risk that were less consistent than that seen with absolute increases. One explanation is that persons with lower baseline scores but greater relative increases (e.g., increases from 15 to 30) are likely to be associated with less risk than smaller relative, but greater absolute increases in someone with greater CAC burden (e.g., an increase from 400 to 500) who is at higher risk from the outset. These examples indicate why our findings regarding absolute CAC increases are likely to be more applicable to most individual patients, except in those with very high CAC scores (e.g., a 25% increase in CAC score in someone with a baseline score of 1,000 is likely to be more important than an increase in score of 100 U).

In our study, those with missing follow-up CAC scores had this information imputed on the basis of predicted

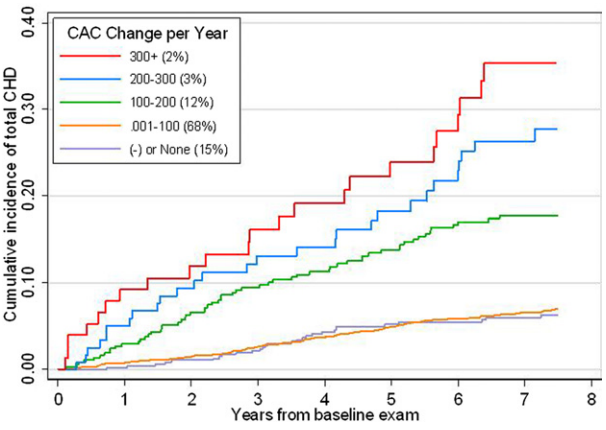

Figure 2 **Kaplan-Meier Plot of Cumulative Incidence of Total CHD Among Persons with CAC >0 at Baseline**

Numbers in parenthesis indicate proportion of subjects in each group. Imputed and nonimputed subjects are included. For log-rank test across CAC change groups, $p < 0.001$. Abbreviations as in Figure 1.

Table 2 Hazard Ratio Examining the Likelihood of Total CHD and Hard CHD by Progression of CAC Among Those With CAC = 0 at Baseline (Multi-Ethnic Study of Atherosclerosis MESA)

	Total CHD	Hard CHD
Event rate per 1,000 person-years, annualized rate (%) [events/subjects]		
Absolute Δ in CAC/yr		
No change	1.6 (0.16) [34/2,861]	1.1 (0.11) [24/2,861]
Any progression	2.6 (0.26) [10/535]	1.8 (0.18) [7/535]
Total	1.8 (0.18) [44/3,396]	1.3 (0.13) [31/3,396]
Hazard ratio (95% confidence interval)		
Unadjusted absolute Δ in CAC/yr	[44/3,396]	[31/3,396]
No change	Reference	Reference
Any progression	1.5 (0.7–3.5)	1.5 (0.6–3.9)
Adjusted absolute Δ in CAC/yr*	[44/3,396]	[31/3,396]
No change	Reference	Reference
Any progression	1.0 (0.4–2.3)	1.1 (0.4–2.8)
Unadjusted absolute Δ in CAC/yr (per 5 U)	[44/3,396] 1.3† (1.1–1.8)	[31/3,396] 1.4† (1.1–1.9)
Adjusted absolute Δ in CAC/yr* (per 5 U)	[44/3,396] 1.4† (1.0–1.9)	[31/3,396] 1.5† (1.1–2.1)

Value are n(%) [events/subjects] or hazard ratios (95% Confidence interval). *Adjusted for baseline age, gender, ethnicity, total cholesterol, HDL-C, lipid lowering medication, SBP and DBP, antihypertensive medication, smoking, diabetes, and family history; change (Δ) analysis includes imputed and nonimputed subjects; follow-up time is calculated from the time of the baseline scan. †$p < 0.05$ (2-tailed).

CHD = coronary heart disease; other abbreviations as in Table 1.

CAC values from baseline CAC and risk factor relationships. We present both nonimputed (only cases with follow-up) and imputed cases in this study. Multiple imputation is optimal for treating subjects likely to have been missing at random, whereas complete case analysis requires the stringent and unlikely assumption that the values are missing completely at random (13,23,24). Our follow-up CAC scores were clearly not missing completely at random because the probability of missing a second scan was related to other factors such as a greater likelihood of experiencing

Table 3 Hazard Ratio Examining the Likelihood of Total CHD and Hard CHD by Progression of CAC Among Those With CAC > 0 at Baseline (Multi-Ethnic Study of Atherosclerosis)

	Total CHD	Hard CHD
Event rate per 1,000 person-years, annualized rate (%) [events/subjects]		
Absolute Δ in CAC/yr		
No or negative change	9.7 (0.97) [33/513]	5.8 (0.58) [21/513]
0.001–100	9.8 (0.98) [157/2,309]	5.8 (0.58) [94/2,309]
100–200	28.4 (2.84) [62/372]	15.0 (1.50) [35/372]
200–300	39.6 (3.96) [25/113]	19.4 (1.94) [13/113]
300+	56.3 (5.63) [22/75]	28.3 (2.83) [12/75]
Total	13.1 (1.31) [299/3,382]	7.5 (0.75) [175/3,382]
Hazard ratio (95% confidence interval)		
Unadjusted absolute Δ in CAC/yr	[Model: 299/3,382]	[Model: 175/3,382]
No or negative change	Reference	Reference
0.001–100	1.0 (0.6–1.7)	1.0 (0.5–1.9)
100–200	3.0§ (1.7–5.4)	2.6† (1.2–5.8)
200–300	4.3§ (2.4–8.4)	3.3‡ (1.9–8.6)
300+	5.9§ (3.0–11.6)	5.0§ (2.2–11.6)
Adjusted absolute Δ in CAC/yr*	[Model: 299/3,382]	[Model: 175/3,382]
No or negative change	Reference	Reference
0.001–100	1.0 (0.6–1.7)	1.0 (0.5–1.9)
100–200	2.1† (1.1–3.8)	1.9 (0.8–4.5)
200–300	2.4† (1.1–5.1)	2.1 (0.7–6.3)
300+	2.8† (1.2–5.4)	3.0† (1.0–8.9)
Unadjusted absolute Δ in CAC/yr (per 100 U)	[Model: 299/3,382] 1.5§ (1.4–1.7)	[Model: 175/3,382] 1.5§ (1.3–1.6)
Adjusted absolute Δ in CAC/yr* (per 100 U)	[Model: 299/3382] 1.2§ (1.1–1.4)	[Model: 175/3,382] 1.3† (1.1–1.5)

Values are n (%) [events/subjects] or hazard ratio (95% Confidence interval). *Adjusted for baseline age, gender, ethnicity, total cholesterol, HDL-C, lipid lowering medication, SBP and DBP, antihypertensive medication, smoking, diabetes, family history, and baseline CAC; change (Δ) analysis includes imputed and nonimputed subjects; follow-up is calculated from the time of the baseline scan. †$p < 0.05$ (2-tailed). ‡$p < 0.01$ (2-tailed). §$p < 0.001$ (2-tailed).

Abbreviations as in Tables 1 and 2.

Table 4 Hazard Ratio Examining the Likelihood of Total CHD and Hard CHD by Progression of CAC According to Percentage Annual Change From Baseline (Multi-Ethnic Study of Atherosclerosis MESA)

	Total CHD	Hard CHD
Event rate per 1,000 person-years' annualized rate (%) [events/subjects]		
Percentage Δ in CAC/yr		
<5%	11.2 (1.12) [43/580]	6.8 (0.68) [27/580]
5–14%	15.2 (1.52) [61/585]	8.3 (0.83) [35/585]
15–29%	17.8 (1.78) [84/708]	9.7 (0.97) [47/708]
≥30%	14.4 (1.44) [95/1,001]	8.7 (0.87) [58/1,001]
Total	14.8 (1.48) [283/2,874]	8.5 (0.85) [167/2,874]
Hazard ratio (95% confidence interval)		
Unadjusted percentage Δ in CAC/yr	[Model: 283/2,874]	[Model: 167/2,874]
<5%	Reference	Reference
5–14%	1.4 (0.8–2.3)	1.2 (0.6–2.4)
15–29%	1.6† (1.0–2.6)	1.4 (0.8–2.6)
≥30%	1.3 (0.8–2.1)	1.3 (0.7–2.5)
Adjusted percentage Δ in CAC/yr*	[Model: 283/2,874]	[Model: 167/2,874]
<5%	Reference	Reference
5–14%	1.1 (0.7–1.8)	1.0 (0.5–1.9)
15–29%	1.6 (1.0–2.5)	1.4 (0.8–2.6)
≥30%	1.5 (0.9–2.4)	1.4 (0.7–2.8)

Values are n (%) [events/subjects] or hazard ratios (95% Confidence interval). Persons with baseline CAC <10 excluded due to substantial percentage changes that can result from small absolute changes. *Adjusted for baseline age, gender, ethnicity, total cholesterol, HDL-C, lipid lowering medication, SBP and DBP, antihypertensive medication, smoking, diabetes, family history, and baseline CAC; change = (Δ); analysis includes imputed and nonimputed subjects; follow-up is calculated from the time of the baseline scan. †$p < 0.05$ (2-tailed).

Abbreviations as in Tables 1 and 2.

an event (2.2 vs. 0.8 per 1,000 person-years) as well as greater mean annual progression (73.1 vs. 44.9 U) compared to observed cases in the CAC >0 group; thus, exclusion of such individuals would have potentially biased the results toward the null. It is worth noting that the results from the imputed data showed no unexpected or major differences when compared to the estimates from data that were not imputed. While a complete case approach requires excluding intervening CHD events before a follow-up CAC scan, the imputed models included these events, a major advantage. Multiple imputation by using all available data provides for more accurate estimates of effect sizes, despite little impact on our findings.

Strengths of MESA include standardized risk factor assessment, protocols for CAC scanning and interpretation, and event ascertainment (11,14). Our data involved progres-

Table 5 Hazard Ratio Examining the Likelihood of Total CHD by Progression of CAC Among Those With CAC = 0 at Baseline (Multi-Ethnic Study of Atherosclerosis), With and Without Imputed Values

	Total CHD Imputed	Total CHD Not imputed
Event rate per 1,000 person-years' annualized rate (%) [events/subjects]		
Absolute Δ in CAC/yr		
No change	1.6 (0.16) [34/2,861]	1.2 (0.12) [15/2,470]
Any progression	2.6 (0.26) [10/535]	3.1 (0.31) [7/469]
Total	1.8 (0.18) [44/3,396]	1.5 (0.15) [22/2,939]
Hazard ratio (95% confidence interval)		
Unadjusted absolute Δ in CAC/yr	[Model: 44/3,396]	[Model: 22/2,939]
No change	Reference	Reference
Any progression	1.5 (0.7–3.5)	2.6† (1.1–6.5)
Adjusted absolute Δ in CAC/yr*	[Model: 44/3,396]	[Model: 22/2,939]
No change	Reference	Reference
Any progression	1.0 (0.4–2.3)	2.1 (0.8–5.3)
Unadjusted absolute Δ in CAC/yr (per 5 units)	[Model: 44/3,396] 1.3† (1.1–1.8)	[Model: 22/2,939] 1.4‡ (1.2–1.8)
Adjusted absolute Δ in CAC/yr* (per 5 units)	[Model: 44/3,396] 1.4† (1.0–1.9)	[Model: 22/2,754] 1.4† (1.1–1.8)

Adjusted for baseline age, gender, ethnicity, total cholesterol, HDL, lipid lowering medication, SBP, DBP, HTN medication, smoking, diabetes, and family history; change (Δ); for the nonimputed analyses, survival time is calculated as the time between hard CHD and exam 2 or exam 3 depending on whether the follow-up CAC score is from exam 2/3. †$p < 0.05$ (2-tailed). ‡$p < 0.01$ (2-tailed).

Abbreviations as in Tables 1 and 2.

Table 6 Hazard Ratio Examining the Likelihood of Total CHD by Progression of CAC Among Those With CAC > 0 at Baseline (Multi-Ethnic Study of Atherosclerosis), With and Without Imputed Values

	Total CHD Imputed	Total CHD Not imputed
Event rate per 1,000 person-years' annualized rate (%) [events/subjects]		
Absolute Δ in CAC/yr		
No or negative change	9.7 (0.97) [33/513]	7.0 (0.70) [13/358]
0.001–100	9.8 (0.98) [157/2,309]	11.5 (1.15) [112/2,027]
100–200	28.4 (2.84) [62/372]	28.1 (2.81) [29/234]
200–300	39.6 (3.96) [25/113]	31.4 (3.14) [10/72]
300+	56.3 (5.63) [22/75]	43.4 (4.34) [9/52]
Total	13.1 (1.31) [299/3,382]	13.1 (1.31) [173/2,743]
Hazard ratio (95% confidence interval)		
Unadjusted absolute Δ in CAC/yr	[Model: 299/3,382]	[Model: 173/2,743]
No or negative change	Reference	Reference
0.001–100	1.0 (0.6–1.7)	1.6 (0.9–2.8)
100–200	3.0§ (1.7–5.4)	3.9§ (2.0–7.5)
200–300	4.3§ (2.4–8.4)	4.3‡ (1.9–9.9)
300+	5.9§ (3.0–11.6)	5.9§ (2.5–13.8)
Adjusted absolute Δ in CAC/yr*	[Model: 299/3,382]	[Model: 160/2,542]
No or negative change	Reference	Reference
0.001–100	1.0 (0.6–1.7)	1.7 (0.9–3.2)
100–200	2.1† (1.1–3.8)	3.1‡ (1.5–6.4)
200–300	2.4† (1.1–5.1)	3.2† (1.3–7.9)
300+	2.8† (1.2–5.4)	3.8‡ (1.5–9.6)
Unadjusted absolute Δ in CAC/yr (per 100 units)	[Model: 299/3,382] 1.5§ (1.4–1.7)	[Model: 160/2,543] 1.5§ (1.3–1.6)
Adjusted absolute Δ in CAC/yr* (per 100 units)	[Model: 299/3,382] 1.2§ (1.1–1.4)	[Model: 160/2,542] 1.3§ (1.2–1.5)

Values are n (%) [events/subjects] or hazard ratios (95% Confidence interval). *Adjusted for baseline age, gender, ethnicity, total cholesterol, HDL-C, lipid lowering medication, SBP and DBP, antihypertensive medication, smoking, diabetes, family history, and baseline CAC; change (Δ); the imputed sample includes both imputed and nonimputed subjects and follow-up time is calculated from the date of the baseline scan; for the nonimputed analyses, survival time is calculated as the time between hard CHD and exam 2 or exam 3 depending on whether the follow-up CAC score is from exam 2/3. †$p < 0.05$ (2-tailed). ‡$p < 0.01$ (2-tailed). §$p < 0.001$ (2-tailed).

Abbreviations as in Tables 1 and 2.

sion of CAC measured over a mean of 2.5 years assuming a linear relation of time with extent of CAC progression, so findings may have differed if longer term progression had been studied, if the relation of time to progression were nonlinear, or if a greater follow-up for events had been conducted. Also, while the variance between our 2 paired scans at baseline and follow-up, greater with higher absolute CAC scores, would be expected to also relate to progression of CAC; however, incorporating interscan variability into our model had a negligible effect and CAC progression still remained significantly associated with CHD event risk. Our analyses are also conducted on the basis of Agatston scores as these are more clinically utilized; however, we also ran our primary analyses using volume score and found indistinguishable results. Also, in MESA a high correlation (≥0.99) is seen between Agatston and volume scores so it is not surprising the results are robust regardless of which score is used.

Current guidelines suggest a CAC scan is reasonable for risk assessment in those of low-intermediate or intermediate risk, or with diabetes (30). The current study adds evidence from a large well-characterized prospective study that CAC progression predicts CHD events, independent of traditional risk factors and baseline CAC scores (31). Our data showing increases in CAC scores predict worse outcomes clearly identifies those at greater risk and could motivate greater adherence to preventive therapies; further study is recommended to determine whether serial CAC measures can be recommended in certain subgroups to optimize CHD risk assessment and patient outcomes (32). Also, radiation exposure has decreased over recent years to below 1 mSv in most cases (10); the CT heart scan is lower in radiation than most other cardiology diagnostic procedures and now comparable to mammography (33).

Conclusions

Progression of CAC is associated with incident hard and total CHD events in a large multiethnic cohort with CAC scans averaging 2.5 years apart. This suggests that serial scans may identify some people at high risk of CHD events who could potentially benefit from a more intense risk factor modification strategy. Further study should examine if such a strategy decreases CHD outcomes and is effective and cost-effective.

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Key Words: atherosclerosis ■ coronary calcification ■ coronary heart disease ■ imaging.

APPENDIX

For supplementary tables and figures, please see the online version of this article.