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Progression of CAC Score and Risk of Incident CVD

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ABSTRACT

OBJECTIVES The authors sought to determine the relative contributions of baseline coronary artery calcification (CAC), follow-up CAC, and CAC progression on incident cardiovascular disease (CVD).

BACKGROUND Repeat CAC scanning has been proposed as a method to track progression of total atherosclerotic burden. However, whether CAC progression is a useful predictor of future CVD events remains unclear.

METHODS This was a prospective observational study of 5,933 participants free of CVD who underwent 2 examinations, including CAC scores, and subsequent CVD event assessment. CAC progression was calculated using the square root method. The primary outcome was total CVD events (CVD death, nonfatal myocardial infarction, nonfatal atherosclerotic stroke, coronary artery bypass surgery, percutaneous coronary intervention). Secondary outcomes included hard CVD events, total coronary heart disease (CHD) events, and hard CHD events.

RESULTS CAC was detected at baseline in 2,870 individuals (48%). The average time between scans was 3.5 ± 2.0 years. After their second scan, 161 individuals experienced a total CVD event during a mean follow-up of 7.3 years. CAC progression was significantly associated with total CVD events (hazard ratio: 1.14, 95% confidence interval: 1.01 to 1.30 per interquartile range; $p = 0.042$) in the model including baseline CAC, but the contribution of CAC progression was small relative to baseline CAC (chi-square 4.16 vs. 65.92). Furthermore, CAC progression was not associated with total CVD events in the model including follow-up CAC instead of baseline CAC (hazard ratio: 1.05, 95% confidence interval: 0.92 to 1.21; $p = 0.475$). A model that included follow-up CAC alone performed as well as the model that included baseline CAC and CAC progression.

CONCLUSIONS Although CAC progression was independently, but modestly, associated with CVD outcomes, this relationship was no longer significant when including follow-up CAC in the model. These findings imply that if serial CAC scanning is performed, the latest scan should be used for risk assessment, and in this context, CAC progression provides no additional prognostic information. (J Am Coll Cardiol Img 2016;9:1420–9) © 2016 by the American College of Cardiology Foundation.

Coronary artery calcium (CAC) correlates closely with overall atherosclerotic plaque, and predicts incident coronary heart disease (CHD) events, CHD mortality, and total mortality (1–5). However, single measurements of atherosclerosis may not encompass its dynamic nature, and the ability to quantify change in atherosclerosis may enhance prognostic information. Repeat CAC scanning has been proposed as a method to track progression of total atherosclerotic burden (6). Moreover, assessment of CAC progression may serve as a useful clinical tool to further stratify patients into higher

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and lower risk groups for future CHD events and to provide a quantitative assessment of the adequacy of overall CHD risk factor management (7–9). However, only a few studies to date have evaluated the implications of CAC progression, predominantly focusing on CHD outcomes and incremental information of CAC change to the baseline rather than follow-up CAC score.

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Recent guidelines propose the adoption of cardiovascular disease (CVD) risk prediction rather than CHD risk prediction tools for risk stratification (10). The relative contributions of baseline CAC score, follow-up CAC score, CAC progression rates, and overall risk factor status on risk of incident CVD events are not well defined. The primary goal of this study was to determine the risk of CVD events associated with each of these parameters.

METHODS

STUDY POPULATION. The CCLS (Cooper Center Longitudinal Study) is a large, prospective cohort of more than 100,000 patients followed for more than 40 years that was originally developed to assess the relationship between cardiorespiratory fitness (CRF) and health. The CCLS is an updated continuation of the previously described Aerobics Center Longitudinal Study that includes additional clinical variables and mortality surveillance through 2010 (11). The CCLS data come from the Cooper Clinic, a preventive medicine practice initiated in 1970. The majority of patients are U.S. residents, white (90%), and with higher education levels and access to extensive preventive health care. Patients are either self-referred or are referred by their employers for preventive health examinations that include a standardized medical examination by a physician, anthropometric measurements, fasting laboratory studies, and a maximal treadmill exercise test for objectively measured CRF. In 1998, electron beam computed tomography (EBT) scanning for CAC measurements was initiated at Cooper Clinic and continued through 2007, after which the EBT scanner was replaced by a multidetector computed tomography scanner. Only EBT CAC data are included in the current study. Patients signed an informed consent for the use of their data for research. The CCLS database and privacy policies are maintained by the Cooper Institute. The data collection and informed consent are reviewed and approved annually by the Cooper Institute's institutional review board.

Within the CCLS, 8,074 patients had at least 2 clinic visits at which both an EBT scan and a preventive examination were performed. Follow-up information was available on 6,190 of these patients (80%) after the second scan by mail-back survey, review of existing medical records, review of Medicare Administrative Claims data, or death determination. Those individuals with a revascularization event within 90 days of their follow-up EBT were excluded to ensure that the CAC test result did not drive the revascularization procedure (n = 16). Patients were also excluded from these analyses if they had a CVD event before their initial EBT (n = 150), revascularization between EBT scans (n = 66), or CAC regression of 50 Agatston units or greater (n = 25), leaving a final cohort of 5,933 individuals (**Figure 1**).

CORONARY ARTERY CALCIFICATION. CAC was assessed by EBT scan utilizing the Imatron C-150XP or C-300 models (Siemens, Malvern, Pennsylvania). Slices of 3-mm thickness were obtained with 2-mm table increments during a breath-holding protocol. CAC scores were calculated using the Agatston method (12), and CAC quantification in this cohort has been reported previously to be both highly reproducible and free of bias (13).

CLINICAL STATUS. At the baseline visit, study participants answered an extensive history questionnaire, including self-reported medical, family, social, and physical activity history confirmed by the clinic physician. Information about prescription medications was recorded for each participant from the medical record at each clinic visit. Statin use at visits 1 and 2 was assessed through the medical record or through response to a mail-back survey. Height and weight were measured using a standard clinical scale and stadiometer. Body mass index was calculated as weight in kilograms divided by height in meters squared. Seated resting blood pressure was obtained with a mercury sphygmomanometer using the American Heart Association protocol.

BLOOD ANALYSIS. Venous blood samples were collected following a 12-h fast and were assayed for serum cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and glucose using automated techniques at the Cooper Clinic Laboratory following standard procedures.

CRF MEASUREMENT. An objective measure of CRF was obtained according to maximal time on a treadmill

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CAC = coronary artery calcium

CHD = coronary heart disease

CI = confidence interval

CRF = cardiorespiratory fitness

CVD = cardiovascular disease

EBT = electron beam computed tomography

HR = hazard ratio

ICD = International Classification of Diseases

LDL-C = low-density lipoprotein cholesterol

MET = metabolic equivalent of task

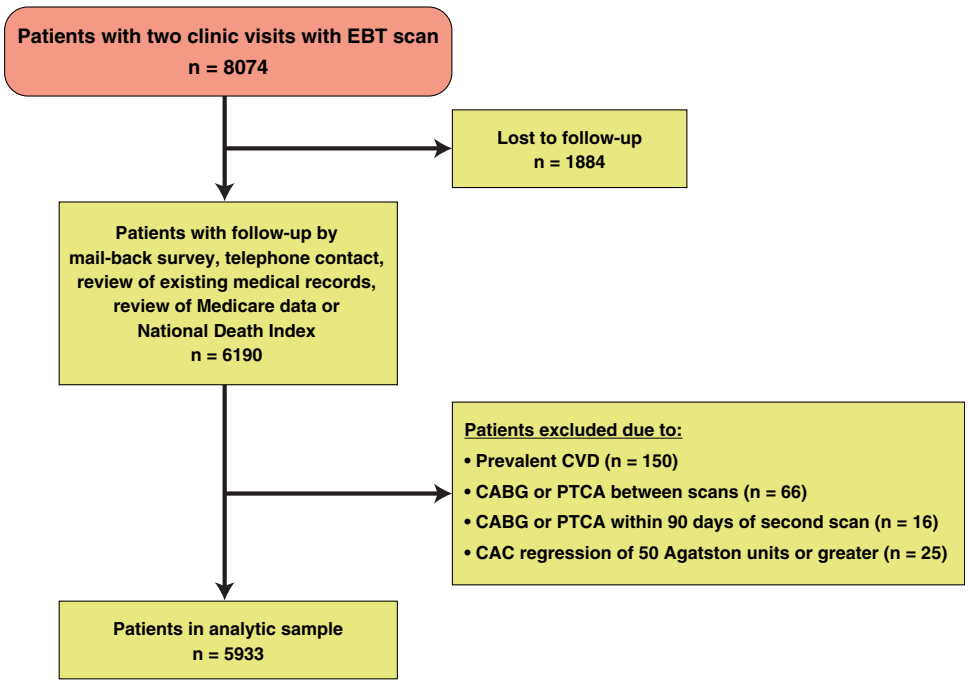
MI = myocardial infarction

PTCA = percutaneous transluminal coronary angioplasty

PY = person-years

Q = quartile

FIGURE 1 Diagram of Patient Selection Process



Of the 8,074 patients with 2 scans, follow-up information was available on 6,190 (80%) after the second scan by mail-back survey, review of existing medical records, Medicare Administrative Claims data, or National Death Index. Individuals with a revascularization event within 90 days of their second scan were excluded to ensure that the CAC result did not drive the revascularization procedure (n = 16). Patients were also excluded if they had a CVD event before their initial scan (n = 150), revascularization between scans (n = 66), or CAC regression of 50 Agatston units or greater (n = 25), leaving a final cohort of 5,933 individuals. CABG = coronary artery bypass graft; CAC = coronary artery calcium; CVD = cardiovascular disease; EBT = electron beam computed tomography; PTCA = percutaneous transluminal coronary angioplasty.

test using the modified-Balke protocol as described elsewhere (11). Maximal metabolic equivalent of task (MET) levels (1 MET = 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$) were estimated by regression from the final treadmill speed and grade (14).

CVD EVENT ASCERTAINMENT. Death events in this subcohort of the CCLS including the specific cause of death were ascertained through 2010 using the National Death Index Plus service. Cardiovascular death was classified with either International Classification of Diseases-9th edition (ICD-9) (deaths through 1999) codes 390–449 or ICD-10 (deaths after 1999) codes I00–I99. After assessing for death events, 3 sequential measures were undertaken to further define the cardiovascular status of the living patients.

Information on nonfatal CVD events was sought via mail-back survey. The mail-back survey contained questions related to demographics, cardiovascular risk factors (including hypertension, diabetes, cigarette use), cardiovascular disease history including, but not limited to, myocardial infarction (MI), stroke, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), or stent and medication history focusing on the use of aspirin, statins, hypertension medication, and diabetes medication. Current contact information was obtained through web-based people finder databases, U.S. Postal Service change of address searches, or other public records. Patients were mailed and/or e-mailed up to 3 surveys if they were nonresponders. Finally, 2 attempts were made to contact nonresponders by telephone to obtain follow-up information verbally.

In those survey nonresponders who had clinic follow-up after the second EBT scan during the years of 2009 through 2011, 1 of 2 physicians (N.B.R.) reviewed the Cooper Clinic medical record to complete the follow-up surveys. All surveys were manually reviewed and entered into the study database.

Finally, in those survey nonresponders without clinic follow-up and who were ≥65 years of age by 2009 and eligible for Medicare for a time period

between 1999 through 2009, Medicare data were obtained from the Centers for Medicare & Medicaid Services. Chronic Conditions Data Warehouse, ICD-9, and Healthcare Common Procedure Coding System codes Online Appendix A were used to identify nonfatal CVD events from the Medicare claims data. The Chronic Conditions Data Warehouse identifies chronic conditions within the Medicare population via well-established algorithms (15).

For authentication purposes, primary hospital records were then obtained for the identified incident CVD events. These events were adjudicated independently by 2 board certified cardiologists (N.B.R., S.G.L., or A.K.) with adjudication by a third cardiologist (B.D.L.) in the event of a disagreement. The primary outcome of interest was a composite of total CVD events (CVD death, nonfatal MI, nonfatal atherosclerotic stroke, CABG, PTCA, or stent). Secondary outcomes were hard CVD (CVD death, nonfatal MI, nonfatal atherosclerotic stroke), total CHD (nonfatal MI, CABG, PTCA, or stent or CHD death), and hard CHD (nonfatal MI or CHD death).

STATISTICAL METHODS. Means and SDs were used to summarize continuous demographic and clinical characteristics of the sample, and counts and percentages to summarize categorical characteristics. Coronary calcium, which has a mixed discrete and continuous distribution, was summarized using the median and interquartile range (25th to 75th percentile). For patients with detectable CAC at both visits, CAC progression was calculated as the annualized difference between the square root of baseline and square root of follow-up CAC score. Sensitivity analyses were also performed using absolute difference in scores and percent change in scores (16). Tests for trends in age, follow-up time, and levels of CAC across ordered quartiles of CAC progression rates were made using the Jonckheere-Terpstra nonparametric method; corresponding trends in cardiovascular event rates, calculated as the total number of events divided by the total follow-up time, were made using the Wald method in the context of an exponential survival model. Unadjusted comparisons of event rates were based on log-rank tests. Proportional hazards regression was used to model cardiovascular events and to estimate hazard ratios (HR) per interquartile range of each CAC variable. Models were adjusted for sex, baseline age, smoking, glucose, cholesterol, systolic blood pressure, statin use, CRF, and the interscan interval. Harrell's c-index (17) was used to compare models using baseline CAC or follow-up CAC and CAC progression. The proportional hazards assumption in all models was tested using cumulative sums of Martingale residuals (18).

RESULTS

Coronary calcium was detected (>0 Agatston units) on the baseline EBT scan in 2,870 individuals (48%) and was not detected in the remaining 3,063 individuals (Table 1). The average time between the baseline and follow-up scan was 3.5 ± 2.0 years. Individuals with detectable CAC were older (57.3 ± 9.0 years vs. 49.2 ± 8.3 years), more likely to be on statin therapy at baseline (22.0% vs. 7.7%), had higher systolic blood pressure (126.5 ± 15.0 mm Hg vs. 120.2 ± 14.1 mm Hg), and lower CRF (10.8 ± 2.3 METs vs. 11.2 ± 2.3 METs).

In those with baseline CAC, a total of 161 individuals experienced a CVD event and 55 a hard CVD event over a mean follow-up of 7.3 years after their second scan. Compared with those without detectable CAC, individuals with detectable CAC at baseline had higher total CVD event rates (7.70 vs. 1.44 events per 1,000 person-years [PY] of follow-up; $p < 0.001$), as well as hard CVD event rates (2.68 events vs. 1.14 events per 1,000 PY; $p = 0.001$). Among individuals without detectable baseline CAC, those who developed CAC in follow-up had event rates that were not statistically different than those who remained with a CAC score of 0 (total CVD rate 1.39 vs. 1.70 per 1,000 PY, $p = 0.617$; hard CVD rate 1.10 vs. 1.36 per 1,000 PY, $p = 0.655$; total CHD rate 0.52 vs. 1.02 per 1,000 PY, $p = 0.249$; hard CHD rate 0.23 vs. 0.68 per 1,000 PY, $p = 0.161$) (Table 1). The median CAC score of the follow-up scan in those who developed CAC was 8.0 Agatston units (25th, 75th percentile: 3.0, 20.0). The range of time between the second CAC and events are as follows: MI (mean 4.8 years, range 4 months to 8.2 years), CABG (mean 4.6 years, range 4 months to 9.6 years), PCI (mean 4.3 years, range 4 months to 10.5 years), and CVD-related death (mean 5.3 years, range 1.1 years to 9.4 years).

In our generally healthy cohort, we have fewer hard CVD events ($n = 55$) and hard CHD events ($n = 24$) for our analyses, which limits our statistical power, and have more robust estimates for total cardiovascular events ($n = 161$). Table 2 shows the rates of total CVD events, hard CVD events, total CHD events, and hard CHD events across quartiles of CAC progression rates in those individuals with baseline CAC. Initial and second CAC scores, as well as age, increased across these quartiles. Rates of total CVD events increased across quartiles of CAC progression rates (range 4.36 [quartile (Q) 1] to 12.98 [Q4] per 1,000 PY; p for trend <0.001). Rates of hard CVD events also trended higher across quartiles of progression rates (range 2.27 per 1,000 PY [Q1] to 3.84 per 1,000 PY [Q4]; p for trend = 0.122), but these analyses were limited by

TABLE 1 Characteristics of 5,933 Cooper Center Longitudinal Study Patients With 2 or More CAC Scores by EBT Scanning According to Baseline CAC Category

	Baseline CAC = 0 (n = 3,063)	Baseline CAC >0 (n = 2,870)
Men	64.1	85.6
Age, yrs	49.2 ± 8.3	57.3 ± 9.0
Smoker	8.7	9.8
Statin use at baseline CAC	7.7	22.0
Statin use at follow-up CAC	14.9	43.0
Statin use ever	39.0	75.7
Body mass index, kg/m^2	25.9 ± 4.0	26.8 ± 3.7
Resting systolic blood pressure, mm Hg	120.2 ± 14.1	126.5 ± 15.0
Resting diastolic blood pressure, mm Hg	81.2 ± 9.6	83.2 ± 9.6
Fasting blood glucose, mg/dl	96.2 ± 13.7	100.5 ± 20.1
Total cholesterol, mg/dl	199.8 ± 34.9	201.6 ± 36.5
Low density lipoprotein cholesterol, mg/dl	119.4 ± 30.9	122.7 ± 31.7
High density lipoprotein cholesterol, mg/dl	56.9 ± 17.3	53.3 ± 15.4
Triglycerides, mg/dl	117.6 ± 76.4	131.0 ± 110.4
Cardiorespiratory fitness, MET	11.2 ± 2.3	10.8 ± 2.3
Coronary artery calcium at baseline CAC, Agatston units	0 (0–0)	99 (24–326)
Coronary artery calcium at follow-up CAC, Agatston units	0 (0–0)	154 (52–464)
Event rates per 1,000 person-yrs (events) according to baseline CAC		
Person-years of follow-up	20,193.7	20,921.4
Total cardiovascular disease	1.44 (29)	7.70 (161)
Hard cardiovascular disease	1.14 (23)	2.68 (55)
Total coronary heart disease	0.59 (12)	6.21 (130)
Hard coronary heart disease	0.30 (6)	1.15 (24)

Events Rates per 1,000 Person-Yrs (Events) According to Baseline CAC and Follow-Up CAC Categories	Baseline CAC = 0 Follow-Up CAC = 0 (n = 2,600)	Baseline CAC = 0 Follow-Up CAC >0 (n = 463)	Baseline CAC >0 Follow-Up CAC >0 (n = 2,870)
Person-yrs of follow-up	17,252.2	2,941.5	20,921.4
Total cardiovascular disease	1.39 (24)	1.70 (5)	7.70 (161)
Hard cardiovascular disease	1.10 (19)	1.36 (4)	2.68 (55)
Total coronary heart disease	0.52 (9)	1.02 (3)	6.21 (130)
Hard coronary heart disease	0.23 (94)	0.68 (2)	1.15 (24)

Values are %, mean ± SD, median (interquartile range), or event rate (# events). Total CVD events = nonfatal myocardial infarction, nonfatal atherosclerotic stroke, CABG, PTCA, stent, or CVD death. Hard CVD events = nonfatal myocardial infarction, nonfatal atherosclerotic stroke, or CVD death. Total CHD events = nonfatal myocardial infarction, CABG, PTCA, stent, or CHD death. Hard CHD events = nonfatal myocardial infarction or CHD death. Values of p for comparison between events rates for individuals without detectable baseline CAC and those who developed CAC in follow-up (total CVD rate p = 0.617; hard CVD rate p = 0.655; total CHD rate p = 0.249; hard CHD rate p = 0.161).

CABG = coronary artery bypass graft; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; EBT = electron beam computed tomography; MET = metabolic equivalents; PTCA = percutaneous transluminal coronary angioplasty.

smaller sample size. Similarly, rates of total CHD events increased across quartiles of CAC progression rates (range 3.03 [Q1] to 10.97 [Q4] per 1,000 PY; p for trend <0.001). Rates of hard CHD events also trended higher across quartiles of progression rates (range 0.95 per 1,000 PY [Q1] to 1.83 per 1,000 PY [Q4]; p for trend = 0.224), but these analyses were limited by smaller sample size. Survival curves for CAC ascertainment and CVD events (where time zero represents the time of the second scan) demonstrate that the failure probability by levels of baseline CAC or by second CAC is essentially superimposable for both total CVD events and hard CVD events (Figure 2).

The multivariable adjusted risk of total and hard CVD events as well as total and hard CHD events associated with the presence and progression of CAC is presented in Table 3. The rate of CAC progression by square root method was significantly associated with total CVD events (HR: 1.14, 95% confidence interval [CI]: 1.01 to 1.30 per interquartile range; p = 0.042) in the model including the baseline CAC measurement, but the overall contribution of CAC progression was small relative to baseline CAC (chi square 4.16 vs. 65.92) Furthermore, the rate of CAC progression was not associated with total CVD events in the model including the follow-up CAC measurement in place of baseline CAC (HR: 1.05, 95% CI: 0.92 to 1.21 per interquartile range; p = 0.475). Finally, a model that included follow-up CAC alone performed as well as the model that included baseline CAC and CAC progression rate in discriminating between total CVD events and non-events (Harrell's c-index 0.751 vs. 0.750, respectively). For hard CVD, total CHD, and hard CHD events, the effect estimates were qualitatively similar to the results with total CVD, but with fewer events and lower statistical power. In these analyses, the rate of CAC progression by the square root method was not significantly associated with events.

In analyses modeling CAC progression (using absolute score changes and percent changes), there was still no independent association between CAC progression and CVD outcomes when including the follow-up CAC score (as shown in Online Appendix B). We did not include the log and quadratic methods of quantifying progression because there is no precedent in the published reports. With respect to incident hard CVD outcomes, the rate of CAC progression was not associated with these events in the fully adjusted model; however, both baseline CAC and follow-up CAC were significantly associated with hard CVD outcomes (HR: 1.36, 95% CI: 1.08 to 1.71 and HR: 1.42, 95% CI: 1.11 to 1.81), respectively.

After adjustment for sex, baseline age, smoking, cholesterol, systolic blood pressure, statin use, CRF, CAC variables, substituting diabetes for glucose did not change the results in that CAC progression remained modestly associated with atherosclerotic CVD in analyses adjusted for baseline CAC, but not after adjusting for follow-up CAC. In sensitivity analyses including only subjects with baseline CAC >10, our findings were unchanged. No evidence was found for violation of the proportional hazards

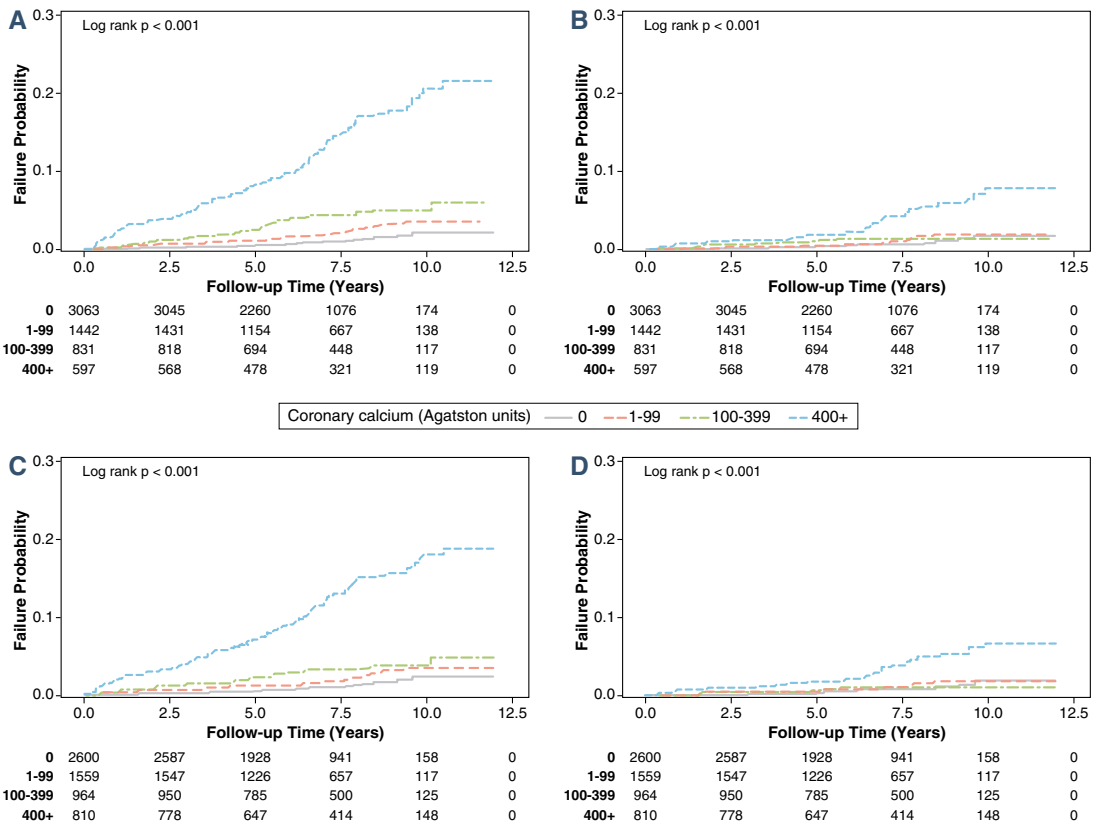
TABLE 2 Cardiovascular Events by Quartile of CAC Progression Rate*

	Quartile 1 (n = 717)	Quartile 2 (n = 718)	Quartile 3 (n = 718)	Quartile 4 (n = 717)	p Value for Trend
Age, yrs	56.5	56.8	57.3	58.7	<0.001
Baseline CAC, Agatston units	50 (11–132)	67 (19–207)	106 (29–328)	299 (90–724)	<0.001
Follow-up CAC, Agatston units	52 (13–134)	100 (41–269)	193 (82–488)	523 (215–1130)	<0.001
Event rate per 1,000 person-years (events)					
Person-years of follow-up	5,279.5	4,993.0	5,179.6	5,469.3	0.001
Total cardiovascular disease	4.36 (23)	7.01 (35)	6.18 (32)	12.98 (71)	<0.001
Hard cardiovascular disease	2.27 (12)	3.00 (9)	2.51 (13)	3.84 (21)	0.122
Total coronary heart disease	3.03 (16)	6.01 (30)	4.63 (24)	10.97 (60)	<0.001
Hard coronary heart disease	0.95 (5)	0.80 (4)	0.97 (5)	1.83 (10)	0.224

Values are mean, median (interquartile range), or event rate (# events). Total and hard CVD events and total and hard CHD events are as described in Table 1. *As determined by the square root method = (sqrt [follow-up CAC]-sqrt[baseline CAC]/(t2-t1),sqrt(AU)/year).

Abbreviations as in Table 1.

FIGURE 2 Kaplan-Meier Survival Curves



Survival curves for CAC ascertainment and CVD events (where time zero represents the time of the second scan) demonstrate that the failure probability by levels of baseline CAC or by second CAC is essentially superimposable for both total CVD events and hard CVD events. **(A)** Baseline CAC ascertainment and total CVD events. **(B)** Baseline CAC ascertainment and hard CVD events. **(C)** Second CAC ascertainment and total CVD events. **(D)** Second CAC ascertainment and hard CVD events.

TABLE 3 Association Between CAC and Risk of CVD Events

	HR* (per IQR)	95% Confidence Interval	p Value	Chi-Square
Total cardiovascular disease				
CAC progression	1.14	(1.01–1.30)	0.042	4.16
Baseline CAC	1.69	(1.49–1.91)	<0.001	65.92
CAC progression	1.05	(0.92–1.21)	0.475	0.51
Follow-up CAC	1.77	(1.55–2.03)	<0.001	68.77
Hard cardiovascular disease				
CAC progression	1.14	(0.90–1.45)	0.287	1.13
Baseline CAC	1.36	(1.08–1.70)	0.009	6.78
CAC progression	1.08	(0.84–1.40)	0.549	0.36
Follow-up CAC	1.42	(1.11–1.81)	0.006	7.62
Total coronary heart disease				
CAC progression	1.13	(0.98–1.30)	0.104	2.64
Baseline CAC	1.84	(1.61–2.10)	<0.001	80.89
CAC progression	1.02	(0.87–1.19)	0.795	0.07
Follow-up CAC	1.94	(1.68–2.24)	<0.001	82.71
Hard coronary heart disease				
CAC progression	1.11	(0.73–1.69)	0.615	0.25
Baseline CAC	1.67	(1.23–2.26)	<0.001	10.99
CAC progression	1.01	(0.65–1.57)	0.972	0.001
Follow-up CAC	1.78	(1.28–2.47)	<0.001	11.79

Total and hard CVD events and total and hard CHD events are as described in Table 1. CAC progression was determined by the square root method = (sqrt [follow-up CAC]-sqrt[baseline CAC]/(t2-t1),sqrt(AU)/year). *Adjusted for baseline age, sex, smoking status, glucose, cholesterol, resting systolic blood pressure, statin use, cardiorespiratory fitness and interscan interval.

HR = hazard ratio; IQR = interquartile range; other abbreviations as in Table 1.

assumption among the CAC variables or other covariates.

In the cohort with CAC >0 at baseline, 22% were taking statins at the time of the baseline CAC scan, and 43% were taking statins at the time of the follow-up scan; corresponding LDL-C values were 104.7 ± 28.0 mg/dl and 91.9 ± 23.8 mg/dl. In the subgroup not taking statins at either scan, our results were qualitatively similar. Although the rate of CAC progression was associated with total CVD events in the model with the baseline scan (p = 0.04), it was no longer significant in the model replacing baseline CAC with follow-up CAC.

DISCUSSION

This study adds to the published reports examining the association between CAC progression and CVD outcomes, because the study demonstrates the independent association of the follow-up CAC score with CVD outcomes in a large, generally healthy population. Our results demonstrate that although CAC progression may carry some prognostic information, this information is largely encompassed by the follow-up CAC score. This finding has important implications in that it simplifies the clinical interpretation of serial CAC scores for subsequent CVD risk by eliminating the need for the clinician to apply 1 or more complicated progression calculation methodologies to follow-up CAC scores and instead allows the clinician to focus on the risk associated with the absolute score alone.

Assessment of coronary atherosclerotic burden by quantifying CAC is a potent tool to improve risk assessment. Not only does prevalent CAC predict incident CHD events, CHD mortality, and total mortality, the majority of published studies have reported that CAC provides information about future CHD events better than standard and emerging risk factors in men and women, as well as in different ethnic groups (19–21). Given the extant published reports, there is uncertainty about the role of CAC in estimating CVD risk. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines recently provided a Class IIb recommendation for CAC assessment when the risk-based treatment decision is uncertain using the new Pooled Cohort Equations to assess 10-year CVD risk (10). Importantly, the authors of these guidelines cite the absence of data on CAC improving CVD risk prediction as the main reason CAC did not receive a higher recommendation.

Because atherosclerosis is a progressive process, repeat CAC scanning has been proposed as a clinical tool to track progression of total atherosclerotic burden and to further risk stratify patients in terms of future CHD events (7–9). A critical requirement is the adoption of a standard definition of CAC progression and the application of a standard method of measuring that progression (6). A number of statistical approaches have been used to define CAC progression: 1) the absolute difference between baseline and follow-up CAC in absolute change increments (9); 2) percent annualized difference between baseline and follow-up CAC >15% (22); 3) difference between the square root of the baseline CAC and the square root of the follow-up CAC >2.5 (SQRT method) (23); and 4) the natural logarithm plus 25 difference (the MESA method) (24).

We have reported that different methods of assessing change in CAC will result in different estimates of CAC progression with only moderate concordance and will be associated with different CHD risk factors (25). Because this method has been most closely associated with mortality, in our primary analysis, CAC progression was calculated as the annualized difference between the square root of baseline and square root of follow-up CAC score (16). We also evaluated other methods of calculating CAC progression and observed similar findings.

A small number of retrospective studies and prospective studies have examined the relationship between CAC progression and incident cardiovascular events (9,16,22). In an observational study by Raggi et al. (22) of patients who underwent serial CAC scanning a mean interval of 1.9 years apart, those with progression >15% per year had a 17-fold increase in MI compared with those with <15% progression per year. In a subsequent paper by Budoff et al. (16), 3 different methods of quantifying CAC progression were all associated with all-cause mortality, but the square root model was deemed to be superior. More recently, in 6,778 participants prospectively followed in the MESA (Multi-Ethnic Study of Atherosclerosis) study, there was an independent association between CAC progression and CHD outcomes. However, the follow-up CAC score was not used in the multivariable models. Additionally, follow-up CAC data were not available in 1,096 individuals (necessitating imputing of these data in the final analysis), and CHD outcomes were evaluated rather than a broader composite including stroke (9). Kiramijyan et al. (26) evaluated the impact of CAC progression and statin therapy on clinical outcomes in subjects with and without diabetes mellitus. CAC progression and all-cause mortality rates were greater in patients with diabetes compared to control subjects (26). Henein et al. (27) pooled data from the St. Francis Heart Study (419 and 432 patients treated with placebo and 20 mg atorvastatin daily, respectively) and the EBEAT (EBCT Assessment of Coronary Calcification in High-Risk Patients with Minimal or Moderate Coronary Atherosclerosis Receiving Intensive Lipid Lowering Atorvastatin) study (164 and 179 patients, respectively, treated with 10 mg and 80 mg atorvastatin daily) and found that baseline and progression of CAC were greater in patients with events. However, only baseline CAC and family history of premature CVD, but not CAC progression, were independent predictors of events.

In contrast to the studies described in the preceding text in which variations in CAC progression rate were associated with differences in outcomes, Erbel et al. (28) examined the progression of CAC in 3,481 participants enrolled in the HNR (Heinz Nixdorf Recall) study to create a mathematical model to predict CAC progression. They found that the individual CAC value increases with age along the given percentile at baseline; thus, for both the total cohort and individual participants, the progression of CAC over time follows an exponential curvature once the calcification process has started. In their analysis, this did not appear to be modified significantly by risk factor modification. Thus, they concluded that CAC progression is heritable, inevitable, and predictable. In these participants, however, risk factor control was far from optimal using current clinical standards. For example, at 5-year follow-up, in those men with CAC score >90th percentile, the average LDL-C was 136 (only 34% were on lipid-lowering medication) and the average systolic blood pressure was 143 mm Hg (only 56% were on antihypertensive medications). Thus, these results suggest CAC progression is inevitable in the setting of inadequately controlled risk factors.

In our study, whereas CAC progression was independently, but modestly, associated with CVD outcomes, this relationship was no longer significant when including the follow-up CAC score in the model. This null finding was consistent when evaluating different methods of calculating CAC progression. The importance of this finding is that it simplifies the debate regarding the optimal method of quantifying CAC progression for clinical purposes. Ultimately, the follow up CAC score alone can be used for risk assessment decisions without specific focus on the progression rate.

Although prior guidelines provided a stronger recommendation for CAC scanning (Class IIa) for cardiovascular risk assessment (19), the most recent ACC/AHA Cholesterol Guidelines have downgraded this recommendation to IIB. Further, repeat CAC scanning is not advocated in the guidelines at this time (10). However, the current study indicates that if repeat CAC scanning data is available, the most recent scan is the more informative on future CVD risk.

Strengths of this study include the large sample size with extensive anthropometric and laboratory phenotyping in addition to the CAC scoring and objective fitness assessment. Notably, using multiple strategies, follow-up information regarding morbid and mortal events was obtained in 80% of this large study cohort. Previous use of questionnaires alone yielded on average a 60% response rate for mail-back surveys in the CCLS cohort. In addition, the outcomes were verified using primary source data with adjudication by board-certified cardiologists. Finally, new CVD guidelines have focused on CVD risk assessment and reduction, including stroke, rather than just CHD; our study is the first to our knowledge to examine this CVD endpoint with CAC progression.

STUDY LIMITATIONS. Limitations of this study include the relative homogeneity of the population. There may be some selection bias inherent in the CCLS database because this is not a randomly selected population. However, the distribution of CAC scores

and available estimates of event rates are comparable to other studies of cardiovascular disease prevention, many of which have their own selection biases. The CCLS population is similar to other large, well-characterized cohorts in regard to exercise habits, fitness, chronic disease, and several clinical variables (29-31). The homogeneity of our sample may, in fact, be a strength because it reduces the likelihood of confounding by unmeasured factors such as occupation, income, and other sociodemographic variables known to influence health separate from fitness or drug treatment. Thus, the internal validity of this sample is very high, similar to other databases investigating cardiovascular health such as the Harvard Alumni Health Study, Nurses' Health Study or the Health Professionals Follow-up Study (32). In addition, we are unable to assess the value of CAC progression with longer scanning intervals (i.e., >3.5 years), but suspect the primacy of the subsequent CAC score to remain consistent with such analyses. Finally, we do not have specific information regarding statin therapy including dose, duration of therapy, and impact of treatment on lipid parameters to assess the impact of statin therapy, if present, on progression of CAC.

CONCLUSIONS

In a large cohort with paired CAC scanning an average of 3.5 years apart, CAC progression was independently, but modestly, associated with CVD events. However, because the prognostic information of CAC progression was largely encompassed by the follow-up CAC score, repeat CAC data, if available, can be interpreted without complicated progression analyses, and risk assessment can be based on the most current CAC score.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Repeat CAC scanning has been proposed as a method to track progression of total atherosclerotic burden. However, whether CAC progression, initial CAC, or follow-up CAC is the best predictor of future CVD events is a matter of debate. This study demonstrated that whereas CAC progression was independently, but modestly, associated with CVD outcomes, this relationship was no longer significant when including follow-up CAC in the model. The importance of this finding is that it simplifies the debate regarding the optimal method of quantifying CAC progression for clinical purposes. Ultimately, the follow-up CAC score alone can be used for risk assessment decisions without specific focus on the progression rate.

TRANSLATIONAL OUTLOOK: Although there are multiple studies evaluating the role of initial CAC and CAC progression in estimating CHD risk, there is insufficient information regarding the role of initial CAC and CAC progression in estimating CVD risk. The recent ACC/AHA Task Force on Practice Guidelines recently provided a Class IIb recommendation for initial CAC assessment when the risk-based treatment decision is uncertain using the new Pooled Cohort Equations to assess 10-year CVD risk. Importantly, the authors of these guidelines cite the absence of data on CAC improving CVD risk prediction as the main reason CAC did not receive a higher recommendation. Further studies are needed to evaluate the relative contributions of initial CAC score, follow-up CAC score, and CAC progression in improving CVD risk prediction.

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KEY WORDS imaging, outcomes, subclinical atherosclerosis

APPENDIX For supplemental tables, please see the online version of this article.