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Prevalence and Prognostic Implications of Coronary Artery Calcification in Low-Risk Women
A Meta-analysis

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IMPORTANCE The role of coronary artery calcium (CAC) testing for guiding preventive strategies among women at low cardiovascular disease (CVD) risk based on the American College of Cardiology and American Heart Association CVD prevention guidelines is unclear.

OBJECTIVE To assess the potential utility of CAC testing for CVD risk estimation and stratification among low-risk women.

DESIGN, SETTING, AND PARTICIPANTS Women with 10-year atherosclerotic CVD (ASCVD) risk lower than 7.5% from 5 large population-based cohorts: the Dallas Heart Study (United States), the Framingham Heart Study (United States), the Heinz Nixdorf Recall study (Germany), the Multi-Ethnic Study of Atherosclerosis (United States), and the Rotterdam Study (the Netherlands). The 5 cohorts were selected based on the availability of CAC data in a sizable group of low-risk women from the general population together with the long detailed follow-up data. Across the cohorts, events were assessed from the date of CAC scan (performed from 1998 through 2006) until January 1, 2012; January 1, 2014; or March 6, 2015. Fixed-effects meta-analysis was conducted to combine the results of the 5 studies.

EXPOSURES CAC score by computed tomography.

MAIN OUTCOMES AND MEASURES Main outcome was incident ASCVD, including nonfatal myocardial infarction, coronary heart disease (CHD) death, and stroke. Association of CAC with ASCVD was examined using Cox proportional hazards models. To assess whether CAC was associated with improved ASCVD risk predictions beyond the traditional risk factors, the C statistic and the continuous net reclassification improvement (cNRI) index were calculated.

RESULTS Among 6739 women with low ASCVD risk from the 5 studies, mean age ranged from 44 to 63 years and CAC was present in 36.1%. Across the cohorts, median follow-up ranged from 7.0 to 11.6 years. A total of 165 ASCVD events occurred (64 nonfatal myocardial infarctions, 29 CHD deaths, and 72 strokes), with the ASCVD incidence rates ranging from 1.5 to 6.0 per 1000 person-years. Compared with the absence of CAC (CAC = 0), presence of CAC (CAC >0) was associated with an increased risk of ASCVD (incidence rates per 1000 person-years, 1.41 for CAC absence vs 4.33 for CAC presence; difference, 2.92 [95% CI, 2.02-3.83]; multivariable-adjusted hazard ratio, 2.04 [95% CI, 1.44-2.90]). The addition of CAC to traditional risk factors improved the C statistic from 0.73 (95% CI, 0.69-0.77) to 0.77 (95% CI, 0.74-0.81) and provided a cNRI of 0.20 (95% CI, 0.09-0.31) for ASCVD prediction.

CONCLUSIONS AND RELEVANCE Among women at low ASCVD risk, CAC was present in approximately one-third and was associated with an increased risk of ASCVD and modest improvement in prognostic accuracy compared with traditional risk factors. Further research is needed to assess the clinical utility and cost-effectiveness of this additional accuracy.

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Supplemental content

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Cardiovascular disease (CVD) is a major health problem for women worldwide,[1-3] and adverse trends in CVD risk factors among women are an ongoing concern.[1,4] Considering their longer life expectancy, women constitute a larger proportion of the elderly population with greatest CVD burden.[1,4] Therefore, primary prevention efforts are crucial in this population.

In clinical practice, cardiovascular risk prediction algorithms have an important role in identifying persons at high CVD risk as these individuals have the greatest potential benefit from prevention interventions. However, high-risk individuals comprise a relatively small proportion of the population distribution, and the greatest absolute number of CVD occurs among individuals at low or intermediate risk.[5]

ASCVD *atherosclerotic cardiovascular disease*

CAC *coronary artery calcium*

CHD *coronary heart disease*

cNRI *continuous net reclassification improvement*

The 2013 American College of Cardiology and American Heart Association (ACC/AHA) CVD prevention guidelines recommend statins for a larger proportion of populations.[6] Particularly among low-risk or intermediate-risk individuals, the guidelines leave open the possibility of further testing modalities that may more reliably predict CVD risk. Notably, a large group of women are categorized as having low or intermediate CVD risk and would therefore not typically qualify for pharmacologic management of standard risk factors.[6]

Coronary artery calcium (CAC) scanning allows for the detection of subclinical coronary atherosclerosis, and the presence of CAC in asymptomatic individuals is associated with higher risk for coronary heart disease (CHD) and all-cause mortality.[7,8] In a previous analysis from the Multi-Ethnic Study of Atherosclerosis (MESA), CAC was present in 32% of women with low CHD risk and was associated with 6.5-fold higher CHD risk.[9] As guidelines are updated to broaden the outcome from CHD to CVD and to lower the risk threshold for statin treatment,[6,10] it is important to address the utility of CAC as a potential tool for refining CVD risk assessment in asymptomatic women at low to intermediate CVD risk based on the new guidelines.

Key Points

Question What is the value of coronary artery calcium (CAC) for cardiovascular risk assessment among women with 10-year atherosclerotic cardiovascular disease (ASCVD) risk less than 7.5% (low risk of CVD)?

Findings Among 6739 low-risk women from 5 large population-based cohorts, compared with CAC absence, CAC presence was associated with an increased risk of ASCVD (incidence rates per 1000 person-years, 1.41 for CAC absence vs 4.33 for CAC presence). Addition of CAC to traditional risk factors led to modest improvement in prognostic accuracy.

Meaning Among women at low risk of ASCVD, CAC was present in approximately one-third and was associated with an increased risk of ASCVD and modest improvement in prognostic accuracy compared with traditional risk factors.

Methods

Cohorts

Women were included from 5 population-based cohorts: the Dallas Heart Study (DHS; United States),[11] the Framingham Heart Study (FHS; United States),[12,13] the Multi-Ethnic Study of Atherosclerosis (MESA; United States),[14] the Heinz Nixdorf Recall (HNR; Germany) study,[15] and the Rotterdam Study (RS; the Netherlands).[16] The 5 cohorts were selected based on the availability of CAC data in a sizable group of low-risk women from the general population together with the long detailed follow-up data. The DHS was approved by the institutional review board of the University of Texas Southwestern Medical Center. The institutional review boards of the Boston University Medical Center and Massachusetts General Hospital approved the FHS. The HNR study was approved at each step by the local ethics committee. MESA was a multicenter study; all clinical sites and the coordinating center had approval from their individual institutional review boards to perform the study, including the follow-up. The RS was approved by the medical ethics committee according to the Population Study Act Rotterdam Study executed by the Ministry of Health, Welfare, and Sports of the Netherlands. In all 5 cohort studies, written informed consent was obtained from all participants. Description of the included cohorts is provided in the Supplement.

For all cohorts, the exclusion criteria were as follows: previous history of coronary artery disease, stroke, chronic kidney disease with glomerular filtration rate less than 30 mL/min/1.73 m^2, treatment with statin, low-density lipoprotein (LDL) cholesterol levels at 190 mg/dL or higher (to convert LDL to mmol/L, multiply by 0.0259), and being older than 79 years. In a secondary analysis with CHD as the outcome, individuals with diabetes were additionally excluded. All other women from each cohort who underwent CAC scanning and had sufficient data to calculate their risk scores were eligible for this analysis.

CAC Scan

Data from the CAC scan at year 0 for each cohort were used to allow for the maximum follow-up period. Total CAC score, based on the sum of the individual coronary arteries (left main, left anterior descending, circumflex, and right coronary arteries), was quantified by the Agatston method.[17] CAC was measured by a C-150XP electron beam computed tomography scanner (Imatron) in DHS, an 8-slice multidetector computed tomography scanner (Lightspeed Ultra, General Electric) in FHS, a nonenhanced C-100 or C-150 electron beam computed tomography scanner (General Electric Imatron) in HNR, a cardiac-gated electron beam computed tomography scanner (used in Chicago, Illinois; Los Angeles, California; and New York, New York) or a multidetector computed tomography scanner (used in Baltimore, Maryland; Forsyth County, North Carolina; and Minneapolis, Minnesota) in MESA, and a C-150 electron beam computed tomography

scanner (General Electric Imatron) or 16-slice or 64-slice multidetector computed tomography scanners (SOMATOM Sensation 16 or 64, Siemens) in RS, using the protocols described previously. More details regarding CAC assessment are provided in the Supplement.

Clinical Outcomes

The primary outcome was incident atherosclerotic CVD (ASCVD), a composite of nonfatal myocardial infarction, death due to CHD, and stroke. Moreover, total CHD—a composite of nonfatal myocardial infarction and death due to CHD—was examined as the secondary outcome. Details regarding the clinical outcomes for each cohort are provided in the Supplement.

Statistical Analysis

For each cohort, the 10-year risk for ASCVD for eligible participants was calculated using the variables from the ACC/AHA pooled cohort equations; namely, age, total and high-density lipoprotein (HDL) cholesterol levels, current smoking status, systolic blood pressure, use of antihypertensive medication, and diabetes.[18]

Baseline characteristics were presented for the total population of each cohort and according to CAC presence. Participants were classified both by status of CAC (CAC presence [CAC >0] or CAC absence [CAC = 0]) and by severity of CAC burden (strata: CAC = 0, >0-100, >100). Absence of CAC in the coronary arteries indicates a very low likelihood of presence of atherosclerotic plaque and subsequently a significant luminal obstructive disease.[19] Presence of any CAC, even minimal or mild CAC, carries an important clinical relevance.[19] CAC categories of 1 to 99, 100 to 299, 300 to 999, and 1000 or more have repeatedly shown an incremental relationship with future cardiovascular events in different populations.[7,20]

Considering the low risk of the population included in the current analysis and the distribution of CAC in this population, the most clinically relevant cut points of 0 and 100 were selected for the analyses. The incidence rate of the event per 1000 person-years of follow-up for the total population of low-risk women and for each category of CAC (status and strata) was calculated. The difference in the incidence rates of events between the strata compared with CAC absence (as the referent) was calculated.

Cox proportional hazard regression models were used to examine the association of CAC with event outcomes. Details regarding evaluating the proportional hazards assumption are provided in the Supplement. In short, all models met the proportional hazards assumption. In particular, hazard ratios (HR) for the association between continuous CAC (ie, for each unit increase in the natural log-transformed [CAC score + 1]), between CAC presence vs CAC absence, and between each CAC stratum (using CAC absence as the referent) with the event outcome were computed. The HRs were adjusted for traditional cardiovascular risk factors including age, race/ethnicity (if applicable), scanner type (if applicable) total and HDL cholesterol levels, current smoking status, systolic blood pressure, use of antihypertensive medication, and diabetes.

For the primary analyses, 2 survival models were fit. The original base survival Cox model included the variables from the ACC/AHA pooled cohort equations and was fitted as age, total and HDL cholesterol levels, current smoking status, systolic blood pressure, use of antihypertensive medication, and diabetes.[18] The second extended survival model additionally included CAC score in its continuous form (ie, natural log-transformed [CAC score + 1]). The performance of the base model and the extended model in prediction of the event outcome were then compared. Ten-year ASCVD predicted risks from the base model and from the extended model were used to evaluate the predictive ability of CAC score for events beyond the conventional cardiovascular risk factors used in the pooled cohort equation.

The discrimination of the base and the extended risk prediction models was assessed using the C statistic. Discrimination refers to the ability of the model to assign a higher risk to individuals who develop the outcome of interest compared with those who remain free of disease. To examine the ability of the CAC score to reclassify women categorized as low-risk or intermediate-risk based on the pooled cohort equation, the continuous net reclassification improvement (cNRI) index was calculated.[21]

Individual-level data were not made available outside each study center. Each of the 5 cohorts performed the analyses at its own research center based on a common analysis plan and delivered the results as aggregate summaries. A fixed-effects meta-analysis was then conducted to combine the summary results from the 5 studies. Two-sided *P* values were reported. I^2 statistics for the assessment of statistical heterogeneity between cohort studies were computed. Values less than 50% were assumed to entail little heterogeneity, and values greater than 75% were assumed to show substantial heterogeneity.[22] As no significant heterogeneity was identified and findings from both fixed-effects and random-effects approaches were similar, fixed-effects estimates were reported.

In a secondary set of analyses, the added predictive ability of CAC in prediction of CHD beyond the traditional risk factors was evaluated. The 10-year risk for CHD for eligible participants was calculated using the variables from the Framingham risk score, including age, total and HDL cholesterol levels, current smoking status, systolic blood pressure, and use of antihypertensive medication.[23] Based on the Third Report of the Adult Treatment Panel (ATP-III) of the National Cholesterol Education Program, the threshold of 10% was used to define women at low CHD risk.[10]

Information regarding missing values in different cohorts is provided in the Supplement. Briefly, in FHS, HNR, and MESA, only participants without any missing data were included in the analyses. Information on several covariates was missing in up to 3.8% of participants in DHS and to 5.5% of participants in the RS. Multiple imputation was carried out in these 2 cohorts. All analyses were performed using SAS (SAS Institute), version 9.3, and R (R Foundation for Statistical Computing), version 3.2.3. A 2-sided *P* value of .05 or less denoted statistical significance.

Table 1. Characteristics of Study Cohorts for Total Population of Women With 10-Year ASCVD Risk Less Than 7.5% at Year 0

Parameter	DHS (n = 1141)	FHS (n = 1335)	HNR (n = 1497)	MESA (n = 2279)	RS (n = 487)
Age, mean (SD), y	44.0 (9.1)	49.5 (8.0)	56.7 (6.6)	58.2 (8.8)	63.3 (2.8)
Race/ethnicity, No.(%)					
White	381 (33.4)	NA	NA	859 (37.7)	NA
Black	550 (48.2)	NA	NA	621 (27.3)	NA
Hispanic	198 (17.4)	NA	NA	491 (21.5)	NA
Chinese	12 (1.1)	NA	NA	308 (13.5)	NA
Blood pressure, mean (SD), mm Hg					
Systolic	122.0 (15.8)	117.8 (117.8)	122.9 (18.1)	120.1 (19.3)	132.6 (15.8)
Diastolic	77.0 (9.0)	73.5 (9.0)	77.8 (10.1)	68.3 (9.8)	75.8 (9.3)
BMI, mean (SD)	30.7 (7.2)	26.7 (7.1)	26.8 (5.0)	28.5 (6.4)	27.0 (4.3)
Cholesterol, mean (SD), mg/dL					
Total	177.5 (34.8)	196.0 (33.6)	225.8 (33.4)	197.7 (32.5)	229.4 (30.4)
High-density lipoprotein	54.1 (15.2)	63.2 (17.0)	67.4 (16.7)	57.6 (15.8)	65.7 (16.1)
Triglycerides	103.2 (71.5)	101.9 (57.7)	119.1 (72.9)	118.3 (68.5)	111.0 ± 48.0)
Fasting blood glucose, mean (SD), mg/dL	95.4 (26.4)	93.3 (14.4)	103.6 (18.4)	90.6 (22.9)	98.5 (17.4)
Diabetes mellitus, No. (%)	60 (5.3)	31 (2.3)	70 (4.7)	130 (5.7)	32 (6.6)
C-reactive protein, mean (SD), mg/L	5.6 (5.6)	3.2 (4.7)	3.0 (12.8)	4.5 (6.2)	2.0 (2.7)
Current smoker, No. (%)	231 (20.3)	168 (12.6)	334 (22.3)	176 (7.7)	17 (3.5)
Antihypertensive medication, No. (%)	144 (13.2)	158 (11.8)	326 (21.8)	493 (21.6)	40 (8.2)
Family history of premature CHD, No. (%)	233 (20.4)	248 (23.3)[a]	154 (14.0)[b]	916 (42.4)	88 (18.1)
CAC >0, No. (%)	476 (41.7)	337 (25.2)	678 (45.3)	620 (27.2)	324 (66.5)
CAC (Agatston score), median (25th-75th percentiles)	0 (0-1.4)	0 (0-0.6)	0 (0-14.2)	0 (0-3.5)	3.3 (0-35.1)
Follow-up time, median (25th-75th percentiles), y[c]	10.2 (9.7-10.7)	9.5 (8.3-10.0)	11.6 (10.6-12.4)	11.4 (10.8-11.8)	7.0 (5.2-10.9)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease (composed of nonfatal myocardial infarction, coronary heart disease death, stroke); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAC, coronary artery calcium.; DHS, Dallas Heart Study; FHS, Framingham Heart Study; HNR, Heinz Nixdorf Recall; MESA, Multi-Ethnic Study of Atherosclerosis; NA, not applicable; RS, Rotterdam Study.

SI Conversion Factors: To convert C-reactive protein to nmol/L, multiply by 9.524; glucose to mmol/L, multiply by 0.0555; high-density lipoprotein and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

[a] Data for family history of premature coronary heart disease was not available for everyone, therefore the denominator for this frequency is 1065 (ie, 23.3% = 248 of 1065 individuals).

[b] Excluding individuals with no information on biological parents (eg, deceased during World War II).

[c] Follow-up time was from the date of coronary calcium computed tomography until the end of follow-up.

Results

CAC for Prediction of ASCVD Among Women at Low Risk for ASCVD (10-Year ASCVD Risk <7.5%)

The analysis of the utility of CAC in prediction of ASCVD among low-risk women with 10-year ASCVD risk less than 7.5% included 6739 women from 5 population-based cohort studies. Baseline characteristics of women at low ASCVD risk in 5 population-based cohort studies are presented in **Table 1.** The mean age ranged from 44 to 63 years among the included studies. Among women at low ASCVD risk in 5 different cohorts, 2.3% to 6.6% had diabetes at baseline. Family history of premature CHD was reported by 14.0% to 42.4% of women in different studies. The CAC presence (CAC >0) varied from 25.2% to 66.5% in the different cohorts. In total, CAC was present in 36.1% of all low-ASCVD risk women included in this meta-analysis (2435 of 6739 women).

The characteristics of women at low ASCVD risk stratified by CAC presence are shown in eTable 1 in Supplement. Overall, women at low ASCVD risk with CAC (CAC presence group) were older and had a more unfavorable cardiovascular risk profile compared with those with no evidence of CAC (CAC absence group). Prevalence of diabetes and family history of premature CHD were also higher among the CAC presence group compared with the CAC absence group.

Follow-up for the current analyses started from the date of CAC scan. Across the cohorts, the CAC scans were performed from 1998 through 2006 and ASCVD events were assessed until January 1, 2012; January 1, 2014; or March 6, 2015. Details regarding dates of study enrollment, CAC scan, and end of follow-up for different cohorts are provided in eTable 2 in the Supplement. Median follow-up for the ASCVD analyses ranged from 7.0 to 11.6 years and a total of 165 ASCVD events (including 64 nonfatal myocardial infarctions, 29 CHD deaths, and 72 strokes) occurred. The total ASCVD incidence rate in the 5 cohorts ranged from 1.5 to 6.0 per 1000 person-years.

Presence of CAC and severity of CAC burden were accompanied by higher ASCVD incidence rates across all cohorts. The incidence rate per 1000 person-years for the ASCVD event ranged from 0.45 to 3.15 in the CAC absence group and from 3.08 to 7.50 in the CAC presence group. Overall, CAC presence was associated with an ASCVD incidence rate of 4.33 per 1000 person-years, whereas the CAC absence was associated with an ASCVD incidence rate of 1.41 per 1000 person-years (difference, 2.92 [95% CI, 2.02-3.83] per 1000 person-years) (**Table 2**). When classified by severity of CAC

Table 2. Incident Event Rates for ASCVD Among Low-Risk Women (10-Year ASCVD Risk <7.5%) by CAC Status

	CAC Absence Group (CAC = 0)			CAC Presence Group (CAC >0)			
Cohort	No. of Events (Total Individuals)	PY of Follow-up	No. of Events per 1000 PY[a]	No. of Events (Total Individuals)	PY of Follow-up	No. of Events per 1000 PY[a]	IRD (95% CI)[b]
DHS	3 (665)	6647	0.45	14 (476)	4548	3.08	2.63 (0.94 to 4.32)
FHS	10 (998)	8932	1.12	10 (337)	2921	3.42	2.30 (0.07 to 4.54)
HNR	12 (819)	9312	1.29	30 (678)	7356	4.08	2.79 (1.16 to 4.42)
MESA	33 (1659)	17884	1.85	30 (620)	6428	4.67	2.82 (1.04 to 4.61)
RS	4 (163)	1268	3.15	19 (324)	2532	7.50	4.35 (−0.23 to 8.93)
All cohorts	62 (4304)	44043	1.41	103 (2435)	23785	4.33	2.92 (2.02 to 3.83)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease (composed of nonfatal myocardial infarction, coronary heart disease death, stroke); CAC, coronary artery calcium; DHS, Dallas Heart Study; FHS, Framingham Heart Study; HNR, Heinz Nixdorf Recall; IRD, incidence rate difference; MESA, Multi-Ethnic Study of Atherosclerosis; PY, person-years of follow-up; RS, Rotterdam Study.

[a] No. of events per 1000 PY indicates number of ASCVD events in each category per 1000 person-years of follow-up in that category (incidence rate).

[b] ASCVD incidence rate difference (95% CI) for CAC presence (CAC >0) vs CAC absence (CAC = 0).

Table 3. Incident Event Rates for ASCVD Among Low-Risk Women (10-Year ASCVD Risk <7.5%) by CAC Strata

	CAC Absence (CAC = 0)		CAC >0-100				CAC >100			
Cohort	No. of Events (Total Individuals)	No. of Events per 1000 PY[a]	No. of Events (Total Individuals)	PY of Follow-up	No. of Events per 1000 PY	IRD (95% CI)[b]	No. of Events (Total Individuals)	PY of Follow-up	No. of Events per 1000 PY[a]	IRD (95% CI)[c]
DHS	3 (665)	0.45	11 (438)	4218	2.61	2.16 (0.53 to 3.78)	3 (38)	331	9.06	8.61 (−1.66 to 18.88)
FHS	10 (998)	1.12	4 (263)	2326	1.72	0.60 (−1.22 to 2.42)	6 (74)	595	10.08	8.96 (0.87 to 17.06)
HNR	12 (819)	1.29	18 (559)	6110	2.95	1.66 (0.11 to 3.20)	12 (119)	1245	9.64	8.35 (2.85 to 13.85)
MESA	33 (1659)	1.85	13 (438)	4614	2.82	0.97 (−0.68 to 2.63)	17 (182)	1813	9.38	7.53 (3.03 to 12.03)
RS	4 (163)	3.15	13 (253)	1970	6.60	3.45 (−1.29 to 8.18)	6 (71)	562	10.68	7.53 (−1.56 to 16.61)
All cohorts	62 (4304)	1.41	59 (1951)	19238	3.07	1.66 (0.80 to 2.52)	44 (484)	4546	9.68	8.27 (5.39 to 11.15)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease (composed of nonfatal myocardial infarction, coronary heart disease death, stroke); CAC, coronary artery calcium; DHS, Dallas Heart Study; FHS, Framingham Heart Study; HNR, Heinz Nixdorf Recall; IRD, incidence rate difference; PY, person-years of follow-up; MESA, Multi-Ethnic Study of Atherosclerosis; RS, Rotterdam Study.

[a] No. of events per 1000 PY indicates number of ASCVD events in each stratum per 1000 person-years of follow-up in that stratum (incidence rate).

[b] ASCVD incidence rate difference (95% CI) for the category of CAC greater than 0 to 100 vs CAC absence.

[c] ASCVD incidence rate difference (95% CI) for the category of CAC greater than 100 vs CAC absence.

burden, the ASCVD incidence rate per 1000 person-years ranged from 1.72 to 6.60 for the stratum of CAC greater than 0 to 100 and from 9.06 to 10.68 for the stratum of CAC greater than 100 (**Table 3**). Compared with CAC absence, the strata of CAC greater than 0 to 100 and CAC greater than 100 were associated with an increase in the ASCVD incidence rate per 1000 person-years of 1.66 (95% CI, 0.80-2.52) and 8.27 (95% CI, 5.39-11.15), respectively (Table 3).

Among women at low ASCVD risk, presence and severity of CAC burden were also associated with statistically significant multivariable adjusted HRs. Compared with the CAC absence group, the HR from the fixed-effects meta-analysis was 2.04 (95% CI, 1.44-2.90) for the CAC presence group, and 1.53 (95% CI, 1.02-2.29) for the CAC greater than 0 to 100 and 4.02 (95% CI, 2.61-6.19) for the CAC greater than 100 strata. When CAC was analyzed continuously (natural log-transformed [CAC score + 1]), the HR from the fixed-effects meta-analysis was 1.29 (95% CI, 1.20-1.39) (**Table 4**).

The added predictive ability of CAC in terms of discrimination and reclassification above the conventional cardiovascular risk factors that form the pooled cohort equation is shown in **Table 5**. The C statistic of the base model (containing the risk factors from the pooled cohort equation) in prediction of ASCVD events ranged from 0.66 to 0.78 in different cohorts. The addition of CAC to the base model resulted in an increase in the C statistic in all 5 cohorts. The overall C statistic increased from 0.73 (95% CI, 0.69-0.77) for the base

Table 4. Hazard Ratios for ASCVD Among Low-Risk Women (10-Year ASCVD Risk <7.5%) for Continuous CAC, by CAC Status, and by CAC Strata

	Hazard Ratio (95% CI) for ASCVD[a]			
Cohort	Continuous CAC[b]	CAC Presence (CAC >0) vs CAC Absence (CAC = 0)	CAC >0-100 vs CAC Absence	CAC >100 vs CAC Absence
DHS	1.70 (1.27-2.28)	4.92 (1.28-18.92)	4.35 (1.10-17.25)	14.08 (2.23-89.03)
FHS	1.24 (1.00-1.54)	1.44 (0.55-3.82)	0.84 (0.25-2.84)	3.75 (1.16-12.17)
HNR	1.28 (1.11-1.47)	2.23 (1.12-4.45)	1.79 (0.85-3.76)	4.24 (1.79-10.04)
MESA	1.29 (1.15-1.44)	1.93 (1.14-3.26)	1.25 (0.64-2.41)	3.78 (1.98-7.18)
RS	1.20 (0.98-1.47)	1.82 (0.60-5.47)	1.59 (0.51-4.99)	2.67 (0.73-9.79)
Fixed effects	1.29 (1.20-1.39)	2.04 (1.44-2.90)	1.53 (1.02-2.29)	4.02 (2.61-6.19)
I^2, %[c]	1.2	0.0	0.0	0.0
P value for I^2	.40	.68	.45	.69

Abbreviations: ASCVD, atherosclerotic cardiovascular disease (composed of nonfatal myocardial infarction, coronary heart disease death, stroke); CAC, coronary artery calcium; DHS, Dallas Heart Study; FHS, Framingham Heart Study; HNR, Heinz Nixdorf Recall; MESA, Multi-Ethnic Study of Atherosclerosis; RS, Rotterdam Study.

[a] Hazard ratios (95% CIs) are adjusted for age, race/ethnicity (if applicable), total cholesterol, high-density lipoprotein cholesterol, current smoking, systolic blood pressure, antihypertensive medication, and diabetes.

[b] CAC was used as a continuous variable (natural log-transformed [CAC score + 1]) in the model.

[c] I^2 statistic indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity.

Table 5. Model Comparison With Addition of CAC to Baseline Risk Prediction Model for ASCVD

	C Statistic (95% CI)			
Cohort	Baseline Model[a]	With Addition of CAC[b]	Delta of C Statistic (95% CI)	Continuous NRI (95% CI)
DHS	0.73 (0.64 to 0.83)	0.78 (0.66 to 0.86)	0.05 (−0.06 to 0.15)	0.35 (−0.16 to 0.85)
FHS	0.78 (0.68 to 0.88)	0.78 (0.67 to 0.88)	0.00 (−0.03 to 0.04)	0.33 (−0.11 to 0.76)
HNR	0.75 (0.67 to 0.82)	0.80 (0.73 to 0.86)	0.05 (−0.01 to 0.11)	0.21 (0.05 to 0.40)
MESA	0.70 (0.63 to 0.77)	0.74 (0.66 to 0.82)	0.04 (−0.02 to 0.10)	0.23 (0.0 to 0.45)
RS	0.66 (0.48 to 0.83)	0.72 (0.56 to 0.87)	0.06 (−0.06 to 0.18)	−0.05 (−0.31 to 0.33)
Fixed effects	0.73 (0.69 to 0.77)	0.77 (0.74 to 0.81)	0.02 (0.00 to 0.05)	0.20 (0.09 to 0.31)
I^2, %[c]	0.0	0.0	0.0	0.0
P value for I^2	.64	.77	.50	.54

Abbreviations: ASCVD, atherosclerotic cardiovascular disease (composed of nonfatal myocardial infarction, coronary heart disease death, stroke); CAC, coronary artery calcium; DHS, Dallas Heart Study; FHS, Framingham Heart Study; HNR, Heinz Nixdorf Recall; MESA, Multi-Ethnic Study of Atherosclerosis; NRI, net reclassification improvement; RS, Rotterdam Study.

[a] Baseline model includes age, race/ethnicity (if applicable), total cholesterol, high density lipoprotein (HDL) cholesterol, current smoking, systolic blood pressure, antihypertensive medication, and diabetes.

[b] CAC was added as a continuous variable (natural log-transformed [CAC score + 1]) to the baseline model.

[c] I^2 statistic indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity.

model to 0.77 (95% CI, 0.74-0.81) for the model with the addition of CAC. The delta C statistic from the fixed-effects meta-analysis after addition of CAC was 0.02 (95% CI, 0.00-0.05); *P* value = .08. When examining risk stratification, the overall cNRI after addition of CAC to the base model was 0.20 (95% CI, 0.09-0.31).

CAC for Prediction of CHD Among Women at Low Risk for CHD (10-Year CHD Risk <10%)

The secondary analysis on the value of CAC in the prediction of CHD events among low-risk women with 10-year CHD risk less than 10% included 7772 women from 5 population-based cohort studies. Across the cohorts, median follow-up for the CHD analyses ranged from 7.7 to 11.6 years and a total of 150 CHD events occurred, including 93 nonfatal myocardial infarctions and 57 CHD deaths. The total CHD incidence rate in the 5 cohorts ranged from 0.5 to 3.8 per 1000 person-years. The results for this set of analyses are presented in eTables 3 through 8 in the Supplement.

Discussion

This meta-analysis involving data on 6739 women from 5 population-based cohort studies showed that coronary calcification was present in 36% of the women who were categorized as having low risk for cardiovascular disease based on the most recent ACC/AHA guidelines. Among these low-risk women,

presence of CAC was associated with an increase of 2.92 per 1000 person-years in ASCVD incidence rate. Addition of CAC to the most recent algorithm for prediction of cardiovascular events was associated with a small improvement in discrimination and a cNRI index of 0.20 for women categorized as low risk by the new guidelines.

Guidelines for CVD prevention recommend use of a system evaluating the combined effect of risk factors as the basis for clinical decision making. The CVD prevention guidelines tend to focus the pharmacologic therapies on "high-risk" individuals exceeding specific risk thresholds. This approach has been successful in directing treatment to those who may realize the greatest benefit. However, the high-risk strategy precludes treatment from a larger group of individuals—predominantly younger adults and many women—despite their relatively high rates of significantly elevated and modifiable risk factors. Over the past 2 decades, guidelines have changed in terms of extending the scope of the outcome from CHD to CVD as well as lowering the risk threshold for statin treatment. Yet a sizeable number of women from the 5 large population-based cohorts included in the current meta-analysis were categorized as being at low ASCVD risk based on the most recent ACC/AHA guidelines for CVD prevention.[6]

Burden of calcification of the coronary arteries is viewed as an integrated measure reflecting the cumulative exposure to risk factors over the lifetime. Presence of CAC has been suggested to improve cardiovascular risk prediction and stratification above the current risk-scoring algorithms. Recent evidence points toward the value of CAC in improvement of CHD risk predictions in the general population,[24,25] among women,[9] and among younger individuals.[26] However, in the light of the new amendments introduced by the most recent ACC/AHA guidelines for cardiovascular prevention,[6] the potential benefit of CAC testing among women who are classified as low risk remains unclear.

This study demonstrated, for the first time to our knowledge, that CAC was present in a large proportion (36%) of women with a 10-year ASCVD risk of less than 7.5%. The hazard of developing an ASCVD event was higher when CAC was detectable (fixed-effect HR, 2.04). These results further strengthen the current evidence by showing that CAC has the potential to modestly improve risk discrimination and to further risk stratify asymptomatic individuals categorized as having low ASCVD risk by the recent guidelines. Although results regarding direct comparison of the added predictive accuracy of CAC with other subclinical measures of atherosclerosis, including carotid intima-media thickness or ankle brachial index, in the same population of women are not available, comparison of the results from the current study with earlier studies on CVD prediction indicates relatively larger improvements in both discrimination and reclassification measures for CAC compared with carotid intima-media thickness or ankle brachial index.[24,27,28]

Absence of CAC was associated with an overall low ASCVD incidence rate of 1.41 per 1000 person-years. Although CAC presence in the coronary arteries (CAC>0) was associated with an increase of 2.92 per 1000 person-years in the ASCVD event rate, the overall incidence rate across the cohorts was 4.33 per 1000 person-years for CAC presence. This is still below the typical treatment threshold (7.5% ASCVD risk) recommended by the new guidelines. Only larger burden of coronary atherosclerosis (ie, CAC >100) was associated with greater ASCVD incidence rates exceeding the new treatment threshold of 7.5%. However, when drug costs and treatment-related disutility are low, recent cost-effectiveness analyses suggest statin therapy to be cost-effective among men and women with ASCVD risk as low as 3% to 4%.[29,30]

The decision regarding the use of CAC among low-risk women needs to consider the broader context and whether any additional testing is justifiable vs simply treating all such women with statins based on risk factor scores alone. Emerging evidence indicates that CAC screening and identification of CAC abnormalities may lead to favorable improvements in cardiovascular risk factors.[31] Additionally, CAC testing has been shown to improve therapeutic compliance not only in terms of adherence to medication but also with lifestyle changes including diet and exercise.[32,33]

However, a formal analysis taking into consideration the economic costs of coronary calcium scan, cost of preventive medications, benefits and risk of adverse effects of medications, as well as cancer-related risk associated with radiation is needed to determine if the additional predictive information provided by CAC testing is cost-effective in this specific subset of women. Although the amount of radiation for computed tomography scanning is small, radiation exposure could lead to an excess risk for cancer, especially among younger patients and women. Because the association between radiation and incidence of cancers seems to be cumulative, risks increase for each scan performed, suggesting that in the setting of primary screening of asymptomatic individuals repetitive scans might be inappropriate.

Another important consideration includes the balance of risks and benefits of additional diagnostic testing that may be recommended to follow up incidental findings such as lung nodules. Findings from the current study support the need for further studies to better define which group of low-risk women have the highest yield from CAC testing. Besides considering the cost-effectiveness, the ultimate decision regarding the application of CAC testing among women at low cardiovascular risk remains to be verified in randomized clinical trials testing the value of CAC in improving the outcomes.

Major strengths of this study include the large sample size comprising the major population-based studies with available data on CAC, the geographically diverse nature of the cohorts, and the analysis based on individual-level data through the availability of standardized risk factor data together with detailed follow-up information in different cohorts.

This study also has several limitations. First, this study included only 5 cohorts that were selected based on the availability of CAC data in a sizable group of low-risk women from the general population together with the long detailed

follow-up data. Second, most of the included participants were of European descent. Although 2 of the included cohorts (DHS and MESA) also included black, Hispanic, and Chinese individuals, race/ethnicity was included in the models as a covariate, and we did not have enough power to perform separate analysis in different racial groups. Results of the current study, therefore, might not be generalizable to non-European populations. Third, the numbers of ASCVD events for several CAC categories were relatively small.

Conclusions

Among women at low risk of ASCVD, CAC was present in approximately one-third and was associated with increased risk of ASCVD and modest improvement in prognostic accuracy compared with traditional risk factors. Further research is needed to assess the clinical utility and cost-effectiveness of this additional accuracy.

ARTICLE INFORMATION

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