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Eligibility of Individuals with Subclinical Coronary Artery Calcium and Intermediate Coronary Heart Disease Risk for Reclassification (from the Framingham Heart Study)

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Abstract

Coronary artery calcium (CAC) predicts risk for coronary heart disease (CHD) events and it is possible that CAC testing may further stratify risk in individuals at intermediate CHD risk. We sought to determine the percentage of individuals at intermediate CHD risk who could potentially be reclassified as high CHD risk based on the presence of a high CAC score as well as the prevalence, treatment, and control of CHD risk factors in this group. Framingham Heart Study Offspring and Third Generation cohort participants underwent multidetector CT (n=3,529; mean age=51 years; 48% women). High CAC was defined as either $\geq 90^{\text{th}}$ age- and sex-specific percentiles based on a healthy reference group or by an absolute modified Agatston score of 100 Hounsfield units (HU). The prevalence of CHD risk factors (hypertension, hypercholesterolemia, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, smoking, and obesity), and their treatment, and control was compared between non-diabetic subjects with and without high CAC. Of the 595 participants at intermediate CHD risk, 22% had CAC $\geq 90^{\text{th}}$ percentile and 39% had CAC ≥ 100 and could be eligible for reclassification as high CHD risk based on the presence of a high CAC score. There were no statistically significant differences in

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Christopher J. O'Donnell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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prevalence, treatment, and control of risk factors between those with and without high CAC. In conclusion, the prevalence of CHD risk factors did not differ between intermediate risk individuals with and without high CAC. Approximately 25% of intermediate risk persons have high CAC scores and may be eligible for reclassification into a higher risk category.

Keywords

coronary artery calcium; coronary heart disease; Framingham risk score; reclassification

Introduction

The presence of a high CAC score may identify high risk persons, who are currently classified as intermediate risk using traditional criteria, in whom aggressive preventive therapies may be warranted. Thus, the objective of our study was to determine the proportion of individuals at intermediate CHD risk who are eligible for being reclassified to the high CHD risk group based on the presence of a high CAC score using available thresholds of CAC. Randomized control trials may be required to justify aggressive treatment of risk factors in individuals with high CAC scores. Therefore, in order to estimate the potential impact in the community of risk factor modification in this higher risk subgroup, we sought to examine the prevalence, treatment, and control of CVD risk factors in participants with an elevated CAC score among those at intermediate CHD risk.

Methods

The original Framingham Heart Study (FHS) cohort, Offspring cohort, and Third Generation cohort have been described previously.^{1–3} Briefly, the original FHS cohort began in 1948 when 5,209 participants were enrolled to undergo biennial clinic examinations. The Offspring cohort began in 1971 when 5,124 children and spouses of the children of the original cohort participants were enrolled. The Third Generation cohort began in 2002 when 4,095 children of the Offspring cohort participants were enrolled. Participants in the Offspring and Third Generation cohorts were invited to enroll in the MDCT substudy. Inclusion in the substudy was weighted toward those individuals from larger FHS families and who were residing in the greater New England area. A total of 3,529 participants (1,422 from Offspring, 2,093 from Third Generation) underwent MDCT scanning to measure their coronary artery calcium. To be eligible for the study, participants were required to weigh less than 160 kilograms, to be at least 35 years of age if male or 40 years of age if female, and non-pregnant. Additional exclusion criteria for the present analysis included missing data on CAC measurements or a history of CHD (myocardial infarction, angina, coronary insufficiency, coronary artery bypass graft, or angioplasty) prior to the CT scan. Of the 3,250 eligible participants, the present analysis focused on the 595 participants with intermediate CHD risk. A secondary analysis included the 2,410 participants with low CHD risk.

An eight-slice MDCT scanner (LightSpeed Ultra, General Electric, Milwaukee, WI) with prospective ECG triggering during a single breath hold in mid-inspiration (typically 18 seconds) using sequential data acquisition was used to image each participant. Scans were prospectively initiated at 50% of the RR interval, which has been commonly used for MDCT based measurements of CAC and has been shown to provide the best average image quality.⁴ Forty-eight contiguous 2.5-mm thick slices (120 kVp, 320 mA for <220 pounds and 400 mA >220 pounds of body weight), gantry rotation time 500 ms, temporal resolution 330 ms) were acquired. The effective radiation exposure was 1.0–1.25 mSv for 320 mA and

400 mA, respectively. Images were reconstructed using a field of view of 35 cm. Each participant was scanned twice.

CT scans were downloaded onto a dedicated offline workstation (Aquarius, Terarecon, San Mateo, CA) and were assessed for the presence of CAC by an experienced technician. A calcified lesion was identified as an area of 3 or more connected pixels with a CT attenuation >130 Hounsfield units (HU) applying 3-dimensional connectivity criteria (six points). The Agatston score (AS) was calculated as previously described⁵; the area of each calcified lesion was multiplied by a weighted CT attenuation score dependent on the maximal CT attenuation (HU) within the lesion. The number of pixels (P_N) above 130 HU was multiplied by the pixel area (P_A) in mm^2 using isotropic interpolation in order to determine the area of each calcified lesion.⁶ If a particular lesion was observed in multiple CT cross-sections, the AS was defined as the sum of the AS from each individual cross-section.

We defined CAC thresholds in two ways. First, the presence of CAC was defined by $\geq 90^{\text{th}}$ percentile age-, sex-, and cohort-specific cutpoints based on a healthy referent sample (free of hyperlipidemia, diabetes, hypertension, smoking, and prevalent CVD).⁷ Percentile cutpoints, which are generalizable to healthy persons in the community, have been proposed by several groups, given the marked distribution of CAC by age and sex.^{8, 9} Second, we used an absolute CAC cutpoint of ≥ 100 versus <100 , a commonly used threshold in past analyses, prior to the availability of community-based samples, that is extensively cited in recent CAC consensus statements.^{10, 11} Risk factor measurements were obtained prior to the conduct of CAC measurements.

At each examination, FHS participants underwent a routine physical examination, medical history interview, and laboratory tests. Risk factors were assessed at the seventh Offspring examination (1998–2001), occurring approximately four years prior to the MDCT substudy, and at the first examination of the Third Generation cohort (2002–2005), occurring contemporaneously with the MDCT substudy. Hypertension was defined as a systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg or treatment with an anti-hypertensive medication. Hypertension control was defined as a blood pressure of $<140/90$ mm Hg. Hypercholesterolemia was defined as a total cholesterol ≥ 240 mg/dL or lipid treatment. Hypercholesterolemia control was defined as a total cholesterol <200 mg/dL. Low HDL levels were defined by established criteria: a value of <40 mg/dL for men or <50 mg/dL for women. High LDL and LDL control were defined based on the ATPIII guidelines.¹² Impaired fasting glucose was defined as a fasting blood glucose of 100–125 mg/dL. Current smoking was defined by having smoked at least one cigarette per day for the previous year. Diabetes mellitus was defined as a fasting plasma glucose level of ≥ 126 mg/dL or treatment with insulin or a hypoglycemic agent. Obesity was defined by a body mass index (BMI) of ≥ 30 kg/m^2 .

Framingham risk score (accounting for age) was calculated for each participant, as previously described.¹³ Participants were divided into three risk groups based on their 10-year Framingham risk score: low ($<10\%$), intermediate ($10\text{--}20\%$), and high ($>20\%$).¹² In secondary analyses, we used a lower threshold for the low ($<6\%$) and intermediate ($6\text{--}20\%$) risk groups, which have been described in a previous consensus statement.¹⁴ Any participant with diabetes was assigned to the high risk group.

The proportion of participants with CVD risk factors (hypertension, hypercholesterolemia, diabetes, low HDL, impaired fasting glucose, current smoking, $\text{BMI} \geq 30$ kg/m^2) was related to presence of a high CAC score among those in the low and intermediate risk groups. Among those with a given risk factor (e.g., hypertension), proportions of participants who

were treated and controlled were also calculated. The p-value for the comparison between those with and without high CAC was calculated using a generalized estimating equations (GEE) model that adjusted for age, sex, and relatedness between the study participants. All statistical analyses were done using SAS (v.8.1, SAS Institute, Cary, NC). A p-value of <0.05 was considered statistically significant.

Results

Characteristics of the study sample are presented in Table 1. Of the 3,250 eligible participants with CT scan data, 595 were classified as having intermediate CHD risk. Of these 595 individuals, 22% had a CAC score $\geq 90^{\text{th}}$ percentile based on a healthy referent sample and 39% had a CAC score ≥ 100 HU. Risk factor levels were similar between those with and without high CAC. However, those with CAC ≥ 100 HU were older than those with CAC <100 HU.

Tables 2a and 2b show a cross-classification of risk group determined by Framingham risk score alone versus risk group determined by both Framingham risk score and CAC. Overall, approximately 22% of participants in the intermediate risk group are eligible for reclassification to a higher risk group using a high CAC score (90th percentile cutpoint) (Table 2a). Approximately 25% of intermediate risk individuals were staged down to the low risk group based on their having a CAC score of zero. Using the absolute Agatston score cutpoint of 100, 39% of intermediate risk subjects would be re-classified to a higher risk group based upon a high CAC score and 25% would be staged down (Table 2b).

Table 3 presents the distribution of CVD risk factors between those with and without high CAC. Participants with high CAC tended to have a higher prevalence of hypercholesterolemia than those without high CAC, although the difference was not statistically significant when using the 90th percentile cutpoint. Proportions of individuals with hypertension, low HDL cholesterol, impaired fasting glucose, and high BMI did not appear to differ between those with and without high CAC based on the 90th percentile cutpoint. Additionally, participants in the intermediate CHD risk group with high CAC were equally likely to receive hypertension and hypercholesterolemia treatment, and there were no statistically significant differences in hypertension control or hypercholesterolemia control. Similar relations of risk factor prevalence, treatment, and control were noted when an absolute Agatston score threshold of 100 was used instead of a 90th percentile cutpoint.

In a secondary analysis, we repeated our main analysis using the cutpoint of 6–20% to define intermediate risk. Of the 1102 individuals at intermediate risk (defined as 6–20%), 19% (n=208) had a CAC score $\geq 90^{\text{th}}$ percentile and 30% (n=327) had a CAC ≥ 100 HU and could be considered for reclassification to the high risk group.

We also repeated our main analysis among the 2,410 participants at low CHD risk. Within the low CHD risk group, approximately 11% of participants had a CAC score $\geq 90^{\text{th}}$ percentile and 8% had a CAC ≥ 100 HU and thus could be eligible for reclassification to the intermediate risk group. Participants with CAC $\geq 90^{\text{th}}$ percentile were more likely than those without a high CAC score to have hypertension (23% vs. 13%; p-value <0.0001), hypercholesterolemia (22% vs. 13%; p-value=0.0003), high LDL (24% vs. 15%; p-value=0.0003), current smoking (19% vs. 11%; p-value = 0.0001), and obesity (29% vs. 21%; p-value=0.004). There were no differences in the prevalence of low HDL cholesterol or impaired fasting glucose between those with high and low CAC. There were no significant differences in the prevalence of treatment or control for hypertension or hypercholesterolemia. Similar results were observed when the 100 HU absolute cutpoint was used. However, the difference in prevalence of hypertension between those with and

without high CAC was no longer statistically significant (p -value=0.31) and those with CAC ≥ 100 HU were more likely to have their high LDL controlled than those with CAC < 100 HU (51% vs. 32%; p -value=0.03).

Discussion

In this study we estimated that 22% of intermediate CHD risk (10–20%) individuals would be eligible for reclassification to the high CHD risk group based on the presence of a CAC score $\geq 90^{\text{th}}$ percentile. When using an absolute CAC cutpoint of 100 HU, approximately 40% of intermediate risk individuals could be reclassified as high risk. It is important to note that the 100 HU cutpoint does not account for age, which would explain the larger proportion of individuals reclassified with the absolute cutpoint relative to the percentile cutpoint. Additionally, we found that the prevalence of CVD risk factors, treatment, and control did not differ substantially between intermediate CHD risk participants with and without high CAC. In a secondary analysis of low CHD risk participants, approximately 10% had a high CAC score. Low CHD risk individuals with high CAC had a higher prevalence of hypertension, hypercholesterolemia, high LDL cholesterol, obesity, and current smoking compared to those without high CAC.

Persons at intermediate CHD risk are an important subset of the population at elevated risk, in whom CAC predicts increased risk for CHD independent of traditional risk factors in diverse populations.^{10, 15} Our study is the first, to our knowledge, to examine the risk factor burden, treatment, and control among individuals with intermediate Framingham risk scores and high CAC. In intermediate risk subjects, risk factor prevalence was high but was not significantly different in those with versus without high CAC. This underscores the point that CAC screening should not be used to simply identify those with modifiable risk factors; risk factor screening itself accomplishes this goal. Knowledge of a high CAC may alter the clinician threshold for initiation of treatments indicated by existing guidelines for cholesterol lowering or hypertension treatment.¹⁶

Cross-classification analysis of intermediate Framingham risk score persons with high CAC provides an estimate of the proportion of subjects for whom more aggressive guidelines for treatment or control of risk factors might be considered in the future. A prior study of CAC in ~10,000 asymptomatic individuals showed that 55% of low-risk individuals were shifted to the intermediate risk group and 45% of intermediate risk individuals were shifted to the high risk group when the Framingham risk score was recalculated using a CAC-adjusted age.¹⁷ These percentages are greater than what we found in our study perhaps due to their use of a calcium-adjusted age variable rather than the simple calcium cutpoints used in our study.

At present, the available evidence is insufficient for making guideline recommendations that CAC screening be used in decisions to intensify the treatment and control of risk factors or even lower the threshold for initiation of lipid lowering or blood pressure lowering drug therapies.^{12, 18} However, because high CAC indicates a high burden of subclinical coronary atherosclerosis and an increased risk for CHD events,^{15, 19–25} it is worthwhile to identify whether any subset of asymptomatic subjects with high CAC should be considered a “CHD risk equivalent”. In our study sample, if high CAC were used to reassign patients into a CHD risk equivalent category, 22% of intermediate risk individuals would be re-classified to a higher risk category using age- and sex- specific percentiles and 39 percent using an absolute Agatston score cutpoint of 100 HU, respectively. By current guidelines, individuals with a high burden of atherosclerosis in other arterial beds, such as those with peripheral artery disease or abdominal aortic aneurysm, are classified as a CHD risk equivalent, regardless of the presence of symptoms.¹² If some persons at intermediate risk with high

CAC were reclassified as a “CHD risk equivalent”, this might result in lowering the current guideline threshold for initiation of lipid lowering therapy.

Our data show that approximately 50% of individuals in the intermediate risk group with high CAC have a total cholesterol ≥ 200 mg/dL (or LDL ≥ 100 mg/dL) with overall low rates of treatment and control. Thus, many persons at intermediate risk with high CAC would be candidates for lipid lowering therapy if the current guideline threshold were lowered. In the recently completed JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, there were substantial reductions in CHD outcomes in subjects with elevated CHD risk (as determined by high sensitivity C-reactive protein ≥ 2 mg/dL) and normal level of LDL (< 130 mg/dL) who were randomized to rosuvastatin.²⁶ The majority of subjects in the trial were classified as at least intermediate CHD risk based upon the presence of at least one risk factor in addition to an elevated level of C-reactive protein or the presence of a Framingham risk score $> 10\%$.²⁶ Given the substantial proportion of subjects at intermediate CHD risk that might benefit from more intensive lipid lowering therapy, further clinical trials may be warranted to test the hypothesis that benefit would be conferred by lipid lowering treatment in persons with high CAC and normal or high-normal levels of LDL. Our findings suggest that subclinical disease testing in intermediate risk persons would identify a substantially large subgroup of higher risk persons to test such lipid-lowering hypotheses. Similarly, given clear evidence of benefit from ramipril in CARE and HOPE, trial designs could include randomization of intermediate risk persons with high CAC to ramipril versus usual therapy.^{27, 28} Further research is warranted to determine whether CAC testing should be considered as a CHD risk equivalent and if so, what exact thresholds of CAC might be considered a CHD risk equivalent.

One of the major limitations of this study was the small number of participants with high CAC, which may have limited our power. Additionally, the study sample is predominantly white and of European descent; thus our findings may not be applicable to other ethnic or racial groups. However, findings from the Multi-Ethnic Study of Atherosclerosis (MESA) suggest similar associations between CAC and CHD outcomes across different racial and ethnic groups.¹⁵ Finally, at the time of the study an 8-slice MDCT scanner was used and not the current standard of 32- or 64-slice scanners. However, previous studies have suggested that differences between CT scanners are minimal on the population level.⁹

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Table 1

Baseline characteristics of intermediate coronary heart disease risk (10–20%) study participants by coronary artery calcium score.

Variable	Coronary Artery Calcium Score			
	<90 th percentile (n=463)	≥90 th percentile (n=132)	<100 HU (n=361)	≥100 HU (n=234)
Women	129 (28%)	43 (33%)	116 (32%)	56 (24%)
Age (years)	57 (9)	56 (9)	54 (8)	61 (9)
Systolic blood pressure (mm Hg)	130 (16)	134 (17)	131 (16)	132 (16)
Diastolic blood pressure (mm Hg)	80 (9)	79 (10)	81 (9)	77 (9)
Total cholesterol (mg/dL)	210 (38)	207 (41)	212 (40)	204 (35)
LDL cholesterol (mg/dL)	132 (33)	130 (34)	134 (34)	127 (31)
HDL cholesterol (mg/dL)	44 (11)	44 (11)	43 (9)	45 (13)
Fasting blood glucose (mg/dL)	99 (9)	101 (8)	99 (9)	101 (9)
Body mass index (kg/m ²)	29.4 (4.5)	29.7 (5.3)	29.4 (4.5)	29.4 (5.0)

Note: All values are mean (standard deviation) unless otherwise indicated

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein

Table 2a

Cross-classification of risk group based on Framingham risk score by risk group based on Framingham risk score plus coronary artery calcium (CAC) score $\geq 90^{\text{th}}$ percentile.

Framingham Risk Score	Framingham Risk Score + CAC*		
	Low	Intermediate	High
Low (<10%)	2150 (89%)	260 (11%)	2410
Intermediate (10–20%)	150 (25%)	313 (53%)	132 (22%)
High (>20%)		245 (100%)	245

* Presence of CAC $\geq 90^{\text{th}}$ percentile moves an individual up one risk category

Presence of CAC = 0 HU moves an individual down one risk category

Table 2b

Cross-classification of risk group based on Framingham risk score by risk group based on Framingham risk score plus coronary artery calcium (CAC) score ≥ 100 HU.

Framingham Risk Score	Framingham Risk Score + CAC*		
	Low	Intermediate	High
Low (<10%)	2224 (92%)	186 (8%)	2410
Intermediate (10-20%)	150 (25%)	211 (36%)	234 (39%)
High (>20%)		245 (100%)	245

* Presence of CAC ≥ 100 HU moves an individual up one risk category
Presence of CAC = 0 HU moves an individual down one risk category

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