



Published in final edited form as:

*Am J Cardiol.* 2008 November 1; 102(9): 1136–1141.e1. doi:10.1016/j.amjcard.2008.06.038.

## Defining Normal Distributions of Coronary Artery Calcium in Women and Men from the Framingham Heart Study

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### Abstract

Coronary artery calcium (CAC) may improve risk stratification for coronary heart disease (CHD) beyond traditional risk factors. Participants from the Framingham Heart Study Offspring and Third Generation cohorts (48% women, mean age 53 years), underwent non-contrast electrocardiographically triggered cardiac multidetector computed tomography (MDCT). We determined the prevalence of absolute CAC (Agatston Score >0, >100, >400) and relative age and sex specific strata (25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup>, 95<sup>th</sup> percentile) in a healthy subset free of clinically apparent cardiovascular disease (CLINCVD) or CHD risk factors (n=1586), the overall sample at risk (n=3238), and participants at intermediate Framingham risk score (FRS, 6-20% 10 year CHD event risk) (n=1177). Absolute Agatston Score and relative cutpoints of CAC increased with age and FRS, was higher in men as compared to women in each of the three cohorts, and increased from the healthy subset to the overall cohort to subjects at intermediate risk. However, among subjects with CAC, there was substantial disagreement between absolute and relative cutpoints for labeling subjects as having elevated CAC. In general, more subjects were considered having elevated CAC using relative cutpoints, especially in women and younger participants. Fewer subjects at intermediate FRS have elevated CAC using comparable absolute vs. relative cutpoints (men: 32% Agatston Score >100 vs. 36% >75<sup>th</sup> percentile; women: 24% Agatston Score >100 vs. 34% >75<sup>th</sup> percentile). In conclusion, we provided the distribution of CAC in a healthy subset, the overall cohort, and subjects at intermediate risk from the Framingham Heart Study for both absolute and relative cutpoints of CAC. Absolute cutpoints underestimate the proportion of subjects with elevated CAC, specifically in women, younger persons, and persons at intermediate CHD risk.

### Introduction

We have recently completed a study of multidetector computed tomography (MDCT) in over 3,500 Offspring and Third Generation subjects in Framingham Heart Study. Thus, we had the opportunity to explore the following in this community-based MDCT cohort: 1) to establish normal age- and sex- stratified relative cutpoints for coronary artery calcium (CAC) in a healthy reference cohort free of coronary heart disease (CHD) risk factors; 2) to

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use these cutpoints to identify participants with elevated CAC in the overall population; 3) to formally assess the agreement between absolute and relative cutpoints; and 4) to examine the impact of these cutpoints in the subset of participants at intermediate CHD event risk.

## Methods

Participants for this study were drawn from the Offspring and the Third generation cohorts of the community-based Framingham Heart Study. Selection criteria and study design have been described<sup>1</sup>. Participants in the analysis attended the Offspring seventh examination cycle (1998-2001) or Third Generation first exam cycle (2002–2005) and have complete risk factor information (to allow determination of hypertension, lipids, smoking status, body mass index, and diabetes). Inclusion in the MDCT study was weighted towards participants from larger Framingham Heart Study families and those who resided in the Greater New England area. Men were at least 35 years of age and women at least 40 years of age. In addition, women were non-pregnant, and all participants weighed less than 350 pounds due to MDCT scanner specifications. The Institutional Review Boards of the Boston University Medical Center and Massachusetts General Hospital approved the study. All subjects provided written consent.

Of the 3529 participants scanned, 3505 attended Offspring Exam 7 or Gen 3 Exam 1. Of these, 3496 had a complete risk factor profile. Thus, 3496 participants were available for analysis. Of the 3496 participants, 108 (5%) had incomplete (e.g., missing or skipped slices) or uninterpretable (e.g. pacemaker leads) CT exams. In addition, 150 (7%) had clinically apparent cardiovascular disease (CLINCVD) defined as prior coronary artery bypass graft, valve replacement, percutaneous coronary stent placement, pacemaker, stroke, congestive heart failure, myocardial infarction or coronary insufficiency using previously published Framingham Heart Study criteria<sup>1,2</sup>. Thus, analysis of CAC was performed in 3238 participants of the overall study cohort.

The standard clinic examination at the Offspring seventh cycle or Third Generation first exam cycle included a physician interview, a physical examination, and laboratory tests. Body mass index was defined as weight (kilograms) divided by the square of height (meters), and was measured at each index examination. Diabetes was defined as a fasting glucose  $\geq 126$  mg/dL at a Framingham examination or treatment with either insulin or a hypoglycemic agent. Participants were considered to be current smokers if they smoked at least one cigarette per day for the last year. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of anti-hypertensive drug treatment. Hyperlipidemia was defined as total cholesterol of at least 240 mg/dL or use of lipid-lowering drug treatment. These data points were used to create a healthy reference sample by excluding individuals with any of the following conditions from the overall study sample: hypertension, hyperlipidemia, adult onset diabetes, cigarette smoking, and obesity (body mass index  $>30\text{kg/m}^2$ ).

Subjects were imaged on an eight-slice MDCT scanner (LightSpeed Ultra, General Electric, Milwaukee, WI) with prospective electrocardiographic triggering during a single breath hold in mid-inspiration (typically 18 seconds) using sequential data acquisition. Before the scan a test breath hold was performed to ensure compliance. Scans were prospectively initiated at 50% of the RR interval, which has been widely used for MDCT based measurements of CAC and has been shown to provide the best average image quality for MDCT based data acquisition<sup>3</sup>. Forty-eight contiguous 2.5-mm thick slices (120 kVp, 320/400 mA (for  $<$  and  $>$  220 pounds of body weight, respectively), gantry rotation time and temporal resolution 500 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 a second time after briefly being repositioned on the table.

All CT scans were read independently by an experienced reader for the presence and amount of CAC, using a dedicated offline workstation (Aquarius, Terarecon, San Mateo, CA). A calcified lesion was defined as an area of at least 3 connected pixels with an attenuation  $>130$  Hounsfield Units applying 3-dimensional connectivity criteria (six points). The Agatston Score was calculated by multiplying the area of each lesion with a weighted attenuation score dependent on the maximal attenuation within the lesion as described elsewhere<sup>4</sup>. The area was calculated for each calcified lesion by multiplying the number of pixels  $P_N$  above 130 Hounsfield Units with the pixel area  $P_A$  in  $\text{mm}^2$  using isotropic interpolation. If an individual lesion appeared in more than one cross-section, the Agatston Score derived for each individual cross-section were added to provide the Agatston Score of the entire lesion. This approach has been shown to be highly reproducible in our laboratory<sup>5</sup>. While the method for calculation of the Agatston Score has been designated for Electron Beam Tomography<sup>4</sup>, studies have shown excellent correlation between the two CT scanners<sup>6,7</sup>. Thus, we used the expression “Agatston Score” in this study.

To determine potential selection bias, differences in background characteristics between subjects who were scanned and subjects who were not scanned were performed using the two-sample t-test for continuous outcomes and Fisher’s Exact test for dichotomous outcomes. To assess the absolute and relative distributions of CAC in the overall cohort and the healthy reference sample we determined the following: 1) Prevalence – the number of subjects with the presence of any CAC; 2) extent of CAC according to absolute cutpoints (defined as strata of 1-100, 101-400, and  $>400$  Agatston Score) and relative cutpoints (defined as the 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, and 90<sup>th</sup> percentiles within age- and sex-specific strata). The distributions were also analyzed following an approach similar to McClelland et al. (shown in the appendix)<sup>8</sup>.

We defined moderately or severely elevated CAC as an Agatston Score  $>100$  and  $400$  or  $>75^{\text{th}}$  and  $>90^{\text{th}}$  percentile, respectively. We then compared the agreement between absolute and relative cut-points to identify subjects with moderately and severely elevated CAC in the overall cohort and among participants with CAC.

Lastly, we determined the distribution of CAC within the Framingham Risk Score (FRS) categories (low:  $<6\%$ , intermediate:  $6\text{-}20\%$ , and high:  $>20\%$  10 year event risk)<sup>9</sup> and determined the fraction of subjects at intermediate risk, who have elevated CAC according to absolute and relative cutpoints. A two-sided p-value  $<0.05$  was considered to indicate statistical significance for all tests.

## Results

The mean AS and the AS defining each percentile increased with age in both men and women and was consistently higher in men versus women within each age stratum (Table 1a). Similar percentiles were noted in women who were about 10 years older than men. The prevalence of CAC was  $30.3\%$  ( $n=500/1652$ ) in the overall healthy reference sample,  $40.5\%$  ( $n=325/803$ ) in men, and  $20.6\%$  ( $n=175/849$ ) in women. While  $20.6\%$  of men  $<45$  years of age had CAC, women  $<55$  years of age rarely had CAC (Table 1b). The prevalence of CAC as well as the fraction of subjects having moderately elevated CAC (Agatston Score  $>100$ ) or severely elevated CAC (Agatston Score  $>400$ ) increased with age and was higher in men than in women. The proportion of participants with moderately elevated CAC (AS  $>100$ ) was very low ( $<3\%$ ) among women  $<55$  and men  $<45$ . Similarly, the proportion of

participants with severely elevated CAC (Agatston Score >400) was very low (<3%) among men < age 55 and women < age 75.

The prevalence of having any CAC was 43% (n=1382/3240) for the entire sample, 52.9% (n=874/1652) in men, and 32.0% (n=508/1588) in women. The prevalence of CAC was especially low among women < 45 years (7.6%). The proportion of participants with moderately elevated CAC (AS >100) was very low (<3%) among women < age 45. Similarly, the proportion of participants with severely elevated CAC (AS >400) was very low (<3%) among women < age 55 and men < age 45.

Thus, the prevalence of any CAC in the overall study population was 12.4% higher than in the healthy reference sample. The magnitude of increase in prevalence was similar in men (12.4%) and women (11.4%). The CAC distributions by age and sex were similar to the healthy subset (Tables 2a and b). However, an additional 5.2% of men, 3.7% of women, and 4.4% of the total subjects were identified as having severely elevated CAC when the 90<sup>th</sup> percentile of the healthy reference sample was applied to differentiate normal from elevated CAC. Within age groups this fraction varied with age from 1.1% (> age 75) to 9.6% (age 55-64) in men and from 0.1% (> age 75) to 8.8% (age 45-54) in women. This effect was smaller and only an additional 1.7% of the overall cohort was identified as having moderately elevated CAC when the 75<sup>th</sup> percentile of the healthy referent sample.

The overall prevalence of CAC in subjects at intermediate risk was remarkably high with 64% (n=817/1277). Among men 67% (n=325/798) and among women 58% (n=175/379) had CAC. Thus, the prevalence of any CAC in subjects at intermediate CHD risk using the FRS was 33.3% higher than in the healthy reference sample. The magnitude of increase in prevalence compared to the healthy reference sample was 27% in men and 38% in women. The CAC distributions by age and sex were similar to the healthy subset. In addition, the presence of CAC, the median Agatston Score, the percentiles, and the fraction of subjects with an Agatston Score >100 or >400 increased with FRS category in both men and women was observed (Table 3). When the 90<sup>th</sup> percentile of the healthy reference sample was applied to differentiate normal from elevated CAC, relatively few subjects were additionally identified in the low risk group (1.3% of men and 3.2% of women) but more in the intermediate risk group (7.7% of men and 10% of women).

Significantly fewer subjects were labeled as having moderately or severely elevated CAC using the absolute cutpoints (17.0% and 6.8% with Agatston Score >100 or > 400, respectively) compared with relative cutpoints (26.7% and 14.4% >75<sup>th</sup> or 90<sup>th</sup> percentile, respectively). This discrepancy appeared to be larger in women than men. Among women, only 10.6% had an Agatston Score >100 while 22.0% were above the 75<sup>th</sup> percentile, and only 2.9% had an Agatston Score >400 while 13.7% were above the 90<sup>th</sup> percentile. Among men, 23.1% had an Agatston Score >100 while 31.2% were above the 75<sup>th</sup> percentile, and 10.6% had an Agatston Score >400 while 15.2% were above the 90<sup>th</sup> percentile.

If this analysis was restricted to subjects with CAC, among women only 9.1% had an Agatston Score > 400 while 42.7% were above the 90<sup>th</sup> percentile. Among men, 20.0% men had Agatston Score > 400 while 28.7% were above the 90<sup>th</sup> percentile.

For the overall sample, there was a modest degree of disagreement between absolute and relative cutpoints in 12.6% and 17.6% of participants for Agatston Score >400 vs. 90<sup>th</sup> percentile and Agatston Score >100 vs. 75<sup>th</sup> percentile, respectively.

However, when we examined the proportion of subjects with discordance between absolute and relative cutpoints, we noted that, if subjects without CAC (57%) were excluded, the disagreement became substantial and occurred in 29.3% of participants for an Agatston

Score >400 vs. >90<sup>th</sup> percentile and in 40.9% for an Agatston Score >100 vs. >75<sup>th</sup> percentile, respectively.

In subjects at intermediate CHD risk by the FRS, in whom an elevated Agatston Score may guide restratification of cardiovascular event risk more subjects had CAC above the 90<sup>th</sup> percentile (relative cutpoints) compared to an Agatston Score >400. However, the fraction of subjects eligible for restratification of risk was almost similar if an Agatston Score >100 was used as the absolute threshold (Table 3). There were no significant differences in any of the distributions using one or two scans.

## Discussion

In this study, we establish normal values and distributions of CAC in a community-based sample of healthy white men and women free of CLINCVD and any CHD risk factors. We further establish the absolute and relative distribution of CAC in a larger cohort of subjects free of CLINCVD and in subjects at intermediate risk for cardiovascular events.

We found similar age and sex associations of CAC that in all three cohorts. There was a remarkable consistency in the data in that the prevalence of CAC, the mean Agatston Score, the fraction of subjects with an Agatston Score >100 or >400, and the nominal percentiles were always lowest in the healthy reference group and highest in subjects at intermediate FRS.

We further demonstrate that using the 90<sup>th</sup> percentile of the healthy reference sample as a relative cutpoint, we determined that 15.2% of men, 13.7% of women, and 14.4% of total subjects within a community-based white sample free of CLINCVD have substantially elevated CAC. Thus, by applying the relative cutpoints from the healthy reference sample, we identified almost 50% more an additional 52%, 37%, and 44% of subjects with elevated CAC as compared to using cutpoints from the overall cohort at risk.

In addition, we formally compared the agreement between absolute and relative cutpoints for participants having moderately (Agatston Score >100 vs. 75<sup>th</sup> percentile) or severely (Agatston Score >400 vs. 90<sup>th</sup> percentile) elevated CAC. We determined that the disagreement is modest for the overall cohort, 12.6% and 17.6% of participants for Agatston Score >400 vs. 90<sup>th</sup> percentile and Agatston Score >100 vs. 75<sup>th</sup> percentile; respectively, but is driven by the fact that 57% of subjects have no CAC. However, in the 43% of subjects with evidence of any CAC, the population of greatest interest, the disagreement among subjects with any CAC was substantial and occurred in 29.3% and 40.9% of participants for Agatston Score >400 vs. 90<sup>th</sup> percentile and Agatston Score >100 vs. 75<sup>th</sup> percentile, respectively.

Similar findings were observed in the subset of subjects at intermediate CHD risk, a subset in which CAC has been recommended to improve risk stratification<sup>9</sup>. The discrepancy between relative and absolute cutpoints was attenuated in women at intermediate CHD risk by the FRS (13.2 vs. 2%; respectively). It appears that among participants at intermediate CHD risk, fewer individuals are further identified at risk when using absolute CAC values rather than percentiles. Thus, the assessment of the distribution of CAC using percentiles may yield additional information compared with absolute values, with the potential to further improve prediction of CHD events in individuals at intermediate FHS risk.

In contrast to previous publications, we defined “normal CAC” by assessing the distribution of CAC in a cohort free of CLINCVD and risk factors. The distributions of CAC using both relative and absolute cutpoints as they relate to age- and sex-based differences in our community-based sample of white men and women free of CLINCVD were very similar to

those described for the white subset of the Multiethnic Study of Atherosclerosis<sup>8</sup> and similar to data from a self-referred cohort published earlier by Hoff<sup>10</sup>. However, the Agatston Score for age- and sex-specific percentiles is often different, i.e. the 90<sup>th</sup> percentile for men age 45-54 in these three studies varies, with the Agatston Score cutpoint being 166, 110, and 154, respectively. These cutpoint differences may be related in part to differences in sample size and CT technology used (Electron Beam Tomography by Hoff vs. both Electron Beam Tomography and MDCT in the Multiethnic Study of Atherosclerosis vs. MDCT in the FHS, respectively).

Age and sex are the dominant predictors for the prevalence and extent of CAC. However, the totality of evidence from prior studies has assumed that normality is based upon pre-specified absolute thresholds (i.e. 0, >100, >400 Agatston Score). Indeed, because data are extremely limited regarding relative thresholds, these absolute thresholds are assumed in the most recent American Heart Association guidelines.<sup>9,11</sup> The concept of relative cutpoints derived from a healthy reference sample, defined similarly to our criteria, was introduced in a recent report from Multiethnic Study of Atherosclerosis 8. We have extended this concept and applied these cutpoints to our overall community-based cohort free of CLINCV. Initial data suggest that while percentile ranks may enable improved risk stratification, absolute CAC scores are superior in predicting the probability of obstructive coronary artery disease<sup>12</sup>.

Our findings regarding substantial differences between absolute and relative cutpoints and findings from Multiethnic Study of Atherosclerosis suggest that normal values of CAC should be more appropriately defined using age- and sex-specific strata and should be derived from a subset free of any CHD risk factors. Using such values as the reference for normal cutpoints may maximize the diagnostic yield from CAC beyond and above traditional risk factors. While our data suggest that relative CAC cutpoints may be more appropriately describe risk in women and younger individuals, confirmation through prospective outcome studies is needed.

The derivation of normal values for CAC based upon hard cardiovascular endpoints requires prospective trials of tens of thousands of men and women, so we are currently limited to use of cross-sectional community-based data to define normal values for CAC. Such definitions are prerequisites for defining any preventive or therapeutic measures to improve primary prevention of CHD related mortality based on CAC.

While some have advocated use of MDCT testing for CAC screening in *all* middle-aged men and women<sup>13</sup>, the most recent consensus statements recommend that CAC screening be considered in men and women with intermediate FRS<sup>9</sup>. However, because relatively few individuals, particularly women, are in this group, further research is warranted to define the intermediate risk populations to be considered for screening. Overall, a definitive answer as to which method should be applied in clinical practice cannot be provided based upon the available data.

Our study was conducted in men and women who were white and the distributions may not be extrapolated to other racial or ethnic groups. In addition, the healthy reference subset was relatively small and especially the data in elderly women and women at high FRS may be variable. Also, longitudinal follow-up data on the incidence of cardiovascular events in subjects with MDCT scans are not available at this time. The CT scanning was performed on an eight-slice MDCT scanner and thus, the exact percentiles may vary with those obtained using other CT scanners.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

Supported by the NHLBI's Framingham Heart Study (NIH/NHLBI Contract N01-HC-25195)

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**Table 1a**

Definition of relative and absolute distributions of coronary artery calcium in the healthy referent sample consisting of women and men free of clinically apparent cardiovascular disease or traditional risk factors. Mean and percentiles of Agatston Score by age in women and men.

	Men				Women					
	<45	45-54	55-64	65-74	75	<45	45-54	55-64	65-74	75
<b>Age (years)</b>										
<b>N</b>	371	250	108	57	17	290	318	154	69	18
<b>Mean</b>	12	49	191	400	660	2	3	39	55	224
<b>SE</b>	4	14	55	68	217	1	1	13	14	62
<b>25<sup>th</sup></b>	0	0	0	40	73	0	0	0	0	1
<b>50<sup>th</sup></b>	0	0	30	173	188	0	0	0	4	95
<b>75<sup>th</sup></b>	0	21	162	585	736	0	0	17	43	355
<b>90<sup>th</sup></b>	8	108	315	1230	2119	0	1	91	212	690
<b>95<sup>th</sup></b>	31.	199	656	1609	3079	1	10	154	308	870

**Table 1b**

Definition of relative and absolute distributions of coronary artery calcium in the healthy referent sample consisting of women and men free of clinically apparent cardiovascular disease or traditional risk factors. Prevalence and absolute cutpoints of coronary artery calcium by age in men and women.

Age (years)	Men					Women				
	<45	45-54	55-64	65-74	75+	<45	45-54	55-64	65-74	75+
N	371	250	108	57	17	290	318	154	69	19
>0	20.8%	42.4%	68.5%	89.5%	100.0%	6.2%	10.4%	44.2%	60.9%	77.8%
>100	1.9%	10.4%	31.5%	59.6%	58.8%	0.7%	0.9%	9.1%	18.8%	50.0%
>400	0.5%	2.4%	8.3%	33.3%	47.1%	0.0%	0.0%	1.9%	2.9%	22.2%

**Table 2a**

Definition of relative and absolute distributions of coronary artery calcium in women and men free of clinically apparent CVD in the overall Framingham Heart Study Sample, Offspring and Third Generation participants combined. Mean and percentiles of Agatston Score by age in women and men.

Age (years)	Men				Women					
	<45	45-54	55-64	65-74	75	<45	45-54	55-64	65-74	75
N	631	536	265	157	63	406	549	353	201	79
Mean	15	75	267	586	890	2	10	60	111	300
SE	3	11	38	60	141	1	2	10	16	60
25 <sup>th</sup>	0	0	2	68	84	0	0	0	0	33
50 <sup>th</sup>	0	1	70	254	427	0	0	0	18	150
75 <sup>th</sup>	1	41	256	770	1434	0	0	33	142	338
90 <sup>th</sup>	23	166	570	1732	2119	0	11	137	289	690
95 <sup>th</sup>	70	395	936	2181	3204	2	38	331	456	1696

**Table 2b**

Definition of relative and absolute distributions of coronary artery calcium in women and men free of clinically apparent CVD in the overall Framingham Heart Study Sample, Offspring and Third Generation participants combined. Prevalence and absolute cutpoints of coronary artery calcium by age in men and women.

Age (years)	Men				Women					
	<45	45-54	55-64	65-74	75+	<45	45-54	55-64	65-74	75+
<b>Overall Study Cohort Free of Cardiovascular Disease</b>										
N	631	536	265	157	63	406	549	353	201	79
>0	26.5%	53.7%	79.6%	93.0%	98.4%	7.9%	18.8%	46.5%	69.7%	87.3%
>100	4.0%	16.2%	43.0%	70.1%	73.0%	0.7%	3.1%	11.9%	29.9%	59.5%
>400	0.3%	4.5%	17.0%	43.9%	55.6%	0.0%	0.5%	4.0%	6.5%	20.3%

**Table 3**

Absolute and relative (90<sup>th</sup> Percentile) cutpoints for men and women stratified by the 10 -year coronary heart disease event risk defined by the Framingham Risk Score as low (<6%), intermediate (6-20%), or high (>20%) in the overall study population of subjects free of cardiovascular disease.

FRS	Men			Women	
	Low <6%	Intermediate 6-20%	High >20%	Low <6%	Intermediate* 6-20%
N	741	798	113	1197	379
Median	0	18	294	0	5
>90 <sup>th</sup> #	11.3%	17.7%	23.0%	13.2%	20.0%
>0	32%	67%	90%	23%	58%
>100	7%	32%	68%	6%	24%
>400	2%	14%	47%	2%	7%

FRS: Framingham Risk Score;

# indicates the percentage of individuals above the 90<sup>th</sup> percentile of the healthy reference cohort;

\* no results shown for women with high FRS because the sample size was too small