# Comparison of Coronary Artery Calcium Detected by Electron Beam Tomography in Patients With to Those Without Symptomatic Coronary Heart Disease

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**Although the presence of coronary artery calcium (CAC) has been associated with the prevalence and incidence of coronary heart disease (CHD), it is unclear if this association has a threshold or a continuous relation. The aim of this research was to explore the relation between CAC, as detected by electron beam tomography (EBT), and CHD in a cross-sectional study of women and men who presented to a single center for elective screening with EBT from 1995 to 1998. Of 17,967 participants, patients with CHD had higher CAC levels than those without CHD. Using subjects without CAC as the referent group, the odds ratios for prevalent CHD increased significantly across increasing quartiles of CAC in the overall population and in both genders. In a subset of the population, after adjusting for CHD risk factors, CAC scores in the fourth quartile were associated with an odds ratio of 33.8 (p <0.001) for prevalent CHD. Among patients with and without CHD, men were more likely than women to have detectable CAC (58.1% vs 28.3% and 96.1% vs 68.9% respectively, p <0.001 for each); the prevalence of detectable CAC increased with age and was higher in men than in women. There was an increased risk for prevalent CHD at all levels of CAC >0, with the greatest increase in risk occurring in patients with CAC scores >95. These observations support the potential of EBT as a sensitive test for detection of CHD.** 

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The association between coronary artery calcium (CAC) and coronary atherosclerosis has long been recognized,[1] and investigators have searched for a noninvasive method to detect and quantify CAC.[2] Although CAC has been associated with the prevalence of coronary heart disease (CHD),[3] the reported prevalence of CAC detected by electron beam tomography (EBT) varies according to age and gender.[4,5] Generally, men have a higher prevalence of detectable CAC than women, and the prevalence of CAC usually increases with age.[5] The present study examines the age and gender distribution of CAC, as detected by EBT in a large population, to investigate the association between CAC and manifest CHD, and to assess whether a graded association exists between CAC levels and prevalent CHD.

## METHODS

**Study population:** Participants (n = 17,967) were examined in the Cooper Clinic EBT Laboratory between June 1, 1995 and December 31, 1998. Patients were sent by their employers, self-referred, or were referred by their personal physicians for electron beam tomographic examinations. Most were white, college graduates, and employed in executive or professional occupations.[6] They provided written informed consent for use of the examination data in research studies. The institutional review board at The Cooper Institute approved the consent forms and the study annually. In a subset of 5,322 subjects who underwent a complete medical history and physical examination, we adjusted for additional CHD risk factors.

**Electron beam tomographic examinations:** The electron beam tomographic examinations were conducted using a Siemens Evolution scanner (C-150XP, currently running version 12.4 software, Malvern, Pennsylvania). Most of the patients were scanned with a modified Agatston et al[7] protocol. Three-millimeter thick slices with 2-mm table increments were typically used, and 40 slices were obtained during a breath-holding period to complete scanning to the apex of the heart. Scan acquisition time was 100 ms. CAC scores were calculated by the Agatston et al[7] weighted method by multiplying the calcific volume by a range of coefficients that are dependent upon the peak density (coefficient 2, 201 to 300 HU; coefficient 3, 301 to 400 HU; coefficient 4, ≥400 HU). The same assessment software was used and the same chief technician and supervising physician directed the electron beam tomographic laboratory for the duration of this study. Subjects were classified into 5 groups according to

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**TABLE 1** Distribution of Coronary Artery Calcium by Age in 6,314 Women and 11,653 Men Examined at the Cooper Clinic Between June 1995 and December 1998

| | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|
| Age (yrs) | n | Percent With CAC | CAC Scores (mean ± SD) | Median (2.5%–97.5%) | n | Percent With CAC | CAC Scores (mean ± SD) | Median (2.5%–97.5%) |
| 20–29 | 31 | 3.2 | 0.03 ± 0.18 | 0 (0–1) | 55 | 5.5 | 5.6 ± 39.8 | 0 (0–10) |
| 30–39 | 412 | 5.6 | 2.5 ± 35.1 | 0 (0–3) | 1,019 | 20.0 | 9.9 ± 85.3 | 0 (0–83) |
| 40–49 | 1,767 | 12.5 | 9.1 ± 68.7 | 0 (0–75) | 3,497 | 40.7 | 62.0 ± 280.7 | 0 (0–543) |
| 50–59 | 2,450 | 26.9 | 33.8 ± 177.4 | 0 (0–302) | 4,274 | 67.8 | 218.4 ± 542.5 | 21 (0–1,764) |
| 60–69 | 1,247 | 51.2 | 117.0 ± 308.4 | 1 (0–1,130) | 2,124 | 86.4 | 648.7 ± 1,181.1 | 207 (0–3,837) |
| 70–80 | 407 | 76.4 | 409.8 ± 769.7 | 84 (0–2,650) | 684 | 93.9 | 1,107.8 ± 1,527.0 | 555 (0–5,286) |
| Total | 6,314 | 29.4 | 65.3 ± 283.2 | 0 (0–760) | 11,653 | 60.1 | 282.9 ± 781.3 | 8 (0–2,462) |

their CAC status and scores: no CAC, and, in those with detectable CAC, quartiles of CAC scores.

The reproducibility of the measurement of CAC was studied by performing a repeat scan in 20 patients 5 minutes after an initial scan. The technician was blinded to the identity of the patient and clinical data. The median difference of the calcium scores between the 2 scans was 8% (95% confidence interval 3% to 19%) using the method of Wang et al.[8] We randomly chose 25 cases from patients with CHD and another 25 cases from patients without CHD to determine whether the unblinded scoring procedures might affect our results. Spearman's correlation coefficient for the paired readings was $r = 0.99$. No difference was observed in the mean CAC scores between the blinded and unblinded evaluations in subjects with and without CHD.

**Clinical assessments:** Of the study patients, 5,322 had a complete history and physical examination within 30 days of their electron beam tomographic examination that included determination of fasting lipids and blood glucose, which were performed in a certified clinical laboratory. Details of the clinical evaluation procedures have been previously published.[9] Cardiorespiratory fitness level was measured on a treadmill using the modified Balke and Ware protocol.[10] Treadmill time has been shown to correlate highly with directly measured maximal oxygen uptake in women ($r = 0.94$)[11] and men ($r = 0.92$).[12] Maximal METs of patients were calculated from treadmill time using the following formulas: maximal MET level = (treadmill time in minutes $\times$ 1.750) + 10.5/3.5 for women, and maximal MET level = (1.444 $\times$ (time/60) + 14.99)/3.5 for men.[12]

We defined hypertension as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or a history of physician-diagnosed hypertension; high cholesterol as total cholesterol ≥240 mg/dl or a history of physician-diagnosed high cholesterol; obesity as body mass index ≥25; diabetes as fasting plasma glucose ≥126 mg/dl or a history of physician-diagnosed diabetes[13]; and a parental history of cardiovascular disease as either parent having had a history of heart attack or stroke. Smoking habit was categorized into never, quitter, and smoker.

**Definition of coronary heart disease:** CHD was defined as a reported history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary revascularization (coronary angioplasty with and without arterial stent placement and atherectomy) before the electron beam tomographic examination. The data available did not allow us to adequately separate the groups with different coronary artery revascularization procedures.

**Statistical analyses:** We used Statistical Analysis Systems software (SAS Institute, Cary, North Carolina) for all analyses. Univariate and multivariate logistic regression techniques were used to evaluate the association between CAC and prevalent CHD with CAC scores both as continuous and categorical variables.[14] All p values provided are for 2-sided tests and $p$ values $<0.05$ were considered statistically significant.

## RESULTS

The population consisted of 17,967 women and men (20 to 80 years of age, mean ± SD 54.4 ± 10.4). A total of 781 patients had CHD before EBT. Of these, 452 (57.9%) had a history of myocardial infarction only. The prevalence of CAC and the mean and median CAC scores by age for women and men (n = 17,186) are listed in Table 1. CAC was not normally distributed and the amount of calcium varied greatly among subjects of similar ages. Only 3.2% of the women and 5.5% of the men 20 to 29 years old had any detectable CAC. The prevalence of CAC and average CAC scores increased with increasing age. Overall, women were less likely than men to have detectable CAC (29.4% vs 60.1%, $p <0.001$) and had lower mean CAC scores (65.3 vs 283.2, $p <0.001$) than men at all ages. Compared with subjects with no manifest CHD, those with known CHD had a higher prevalence of detectable CAC and higher average CAC scores (Table 2). These associations did not change after adjustment for age. The prevalence of detectable CAC in patients with known CHD was 68.9% and 96.1% in women and men, respectively. Almost 1/3 of the women with prevalent CHD had no CAC.

Because of concern that the various coronary artery revascularization procedures may themselves lead to an increased deposition of CAC, we compared CAC levels in patients with CHD with or without a history of percutaneous coronary artery intervention and by-

**TABLE 2** Coronary Artery Calcium Distribution by Coronary Heart Disease Status in 6,314 Women and 11,653 Men Examined at the Cooper Clinic Between June 1995 and December 1998

| | Women (n = 6,314) CHD | | Men (n = 11,653) CHD | |
|---|---|---|---|---|
| Status | 0 | + | 0 | + |
| No. of patients | 6,153 | 161 | 11,033 | 620 |
| Age (yrs) | | | | |
| Mean ± SD | 53.3 ± 9.8 | 61.8 ± 10.5 | 52.1 ± 9.9 | 61.6 ± 9.2 |
| Median (2.5%–97.5%) | 53 (35–74) | 63 (40–79) | 52 (34–73) | 62 (43–78) |
| Prevalence with detectable CAC | 28.3%† | 68.9%*† | 58.1%† | 96.1%*† |
| CAC scores | | | | |
| Mean ± SD | 55.3 ± 257.4† | 448.1 ± 683.4* | 208.8 ± 586.7† | 1,600.3 ± 1,876.4* |
| Median (2.5%–97.5%) | 0 (0–547) | 130 (0–2,170) | 5 (0–1,858) | 1,064 (0–7,014) |
| Age-adjusted CAC scores | | | | |
| Mean ± SD | 48.9 ± 582.4 | 294.01 ± 590.0* | 223.2 ± 576.1 | 1,449.61 ± 582.6* |

*p <0.001 when patients without CHD are compared with patients with CHD within gender.
†p <0.001 when women and men without CHD are compared with women and men with CHD within disease status groups.

**TABLE 3** Odds Ratios (OR) of Myocardial Infarction Only (n = 452) by CAC Scores in 17,638 Women and Men Aged 20 to 80 Years Examined at the Cooper Clinic Between June 1995 and December 1998

| | CAC Score* | Age-Adjusted | | | | | | Age- and Gender-adjusted | |
|---|---|---|---|---|---|---|---|---|---|
| | No CAC (n = 9,105) | Women (n = 6,314) | | | Men (n = 11,653) | | | | |
| CAC Score Quartile* | With CAC (n = 8,862) | n | Prevalence (%) | OR (95% CI) | n | Prevalence (%) | OR (95% CI) | n | OR (95% CI) |
| | No CAC | 4,443 | 0.8 | 1.0 (Referent) | 4,635 | 0.3 | 1.0 (Referent) | 9,078 | 1.0 (Referent) |
| Quartile 1 | 1–15 | 589 | 1.2 | 1.2 (0.5–2.8) | 1,592 | 0.8 | 2.3 (1.1–5.1) | 2,181 | 1.5 (0.9–2.6) |
| Quartile 2 | 16–94 | 561 | 3.0 | 2.8 (1.5–5.2) | 1,665 | 1.2 | 3.3 (1.6–6.7) | 2,226 | 2.6 (1.7–4.1) |
| Quartile 3 | 95–396 | 417 | 4.1 | 3.4 (1.8–6.4) | 1,751 | 2.6 | 6.4 (3.4–12.1) | 2,168 | 4.1 (2.7–6.2) |
| Quartile 4 | ≥397 | 250 | 12.8 | 9.8 (5.4–17.9) | 1,735 | 14.7 | 35.2 (19.5–63.7) | 1,985 | 20.5 (14.2–29.7) |
| p Value for trend test | | <0.001 | | | <0.001 | | | <0.001 | |

*CAC score distribution based on combined scores of women and men.
CI = confidence interval.

pass surgery and performed separate risk analyses in patients with myocardial infarction alone and in those with all CHD. The age-adjusted means of CAC for patients with CHD with or without a history of percutaneous coronary artery intervention and bypass surgery were 1,403.5 and 1,333.2 ($p = 0.573$). In patients with myocardial infarction alone, the odds for CHD in those with CAC in quartile 4 were almost 10-fold greater in women and 35-fold greater in men (odds ratio 40.8, 95% confidence interval 26.3 to 63.4) compared with those without CAC (Table 3). Results were similar in patients with all CHD (Table 4). In both analyses overall, and among the subsets of women and men, the test for trend was highly significant across CAC quartiles, with CHD risk increasing with increasing CAC score. There appeared to be a clear threshold between quartiles 2 and 3, at a CAC score of >95, after which the trend markedly increased. It should also be noted that at similar levels of CAC, particularly in quartiles 1 to 3, the risks for prevalent CHD are remarkably similar for women and men.

In the subset of 5,322 subjects who underwent a complete medical history and physical examination, of whom 165 had CHD, a multivariable model that included age, gender, fitness (METs), history of high cholesterol, hypertension, or diabetes, cigarette smoking, obesity, and a parental history of cardiovascular disease was used to generate adjusted odds ratios for CHD (Table 5). After adjustment for age, gender, and the presence of CHD risk factors, the quartile-specific odds ratios were slightly attenuated, but there remained a strong and significant increasing association between CAC scores and prevalent CHD (Table 6). The age- and gender-adjusted odds ratios for myocardial infarction only were similar to odds ratios for all CHD.

## DISCUSSION

The presence of calcium in the coronary arteries is an indicator of atherosclerosis.[15–17] More than 40 years ago, Blankenhorn[1] found that the extent of coronary artery calcification was associated with the severity of coronary atherosclerosis in pathologic specimens. With the advent of EBT, it has become possible to evaluate CAC accurately in vivo. Several investigators have reported a positive relation between the presence of CAC and CHD in studies with small samples, studies that included mostly men, and in studies where CAC was associated with CHD-related events in symptomatic patients who underwent coronary angiography.[18] In our study, which included

**TABLE 4** Odds Ratios of CHD (n = 781) by CAC Scores in 17,967 Women and Men Aged 20 to 80 Years Examined at the Cooper Clinic Between June 1995 and December 1998

| CAC Score Quartile* | CAC Score* No CAC (n = 9,105) / With CAC (N = 8,862) | Age-adjusted: Women (n = 6,314) n | Women Prevalence (%) | Women OR (95% CI) | Age-adjusted: Men (n = 11,653) n | Men Prevalence (%) | Men OR (95% CI) | Age- and Gender-adjusted n | Age- and Gender-adjusted OR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | No CAC | 4,459 | 1.1 | 1.0 (Referent) | 4,646 | 0.5 | 1.0 (Referent) | 9,105 | 1.0 (Referent) |
| Quartile 1 | 1–15 | 591 | 1.5 | 1.1 (0.6–2.3) | 1,601 | 1.3 | 2.3 (1.3–4.2) | 2,192 | 1.6 (1.0–2.4) |
| Quartile 2 | 16–94 | 561 | 3.0 | 2.0 (1.1–3.6) | 1,676 | 1.9 | 3.0 (1.8–5.2) | 2,237 | 2.3 (1.6–3.3) |
| Quartile 3 | 95–396 | 431 | 7.2 | 4.6 (2.8–7.6) | 1,785 | 4.4 | 6.8 (4.2–10.9) | 2,216 | 5.0 (3.6–6.9) |
| Quartile 4 | ≥397 | 272 | 19.9 | 12.8 (7.8–21.0) | 1,945 | 23.9 | 40.8 (26.3–63.4) | 2,217 | 26.2 (19.6–35.1) |
| p Value for trend test | | <0.001 | | | <0.001 | | | <0.001 | |

CHD was defined as a reported history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary revascularization (coronary angioplasty with and without arterial stent placement and atherectomy).

*CAC score distribution based on combined scores of women and men.

Abbreviation as in Table 3.

**TABLE 5** Baseline Characteristics of 1,271 Women and 4,051 Men With Measured Coronary Heart Disease (CHD) Risk Factors Examined at the Cooper Clinic Between June 1995 and December 1998

| Characteristics | CHD* + (n = 165) | CHD* 0 (n = 5,157) | p Value |
|---|---|---|---|
| Age (yrs), mean ± SD | 59.9 ± 8.9 | 51.1 ± 9.5 | 0.001 |
| Men | 152 (92.1%) | 3,899 (75.6%) | 0.001 |
| Women | 13 (7.9%) | 1,258 (24.4%) | |
| CAC score quartile | | | 0.001 |
| No CAC | 27 (10.3%) | 2,678 (51.9%) | |
| Quartile 1 | 4 (2.4%) | 680 (13.2%) | |
| Quartile 2 | 9 (5.5%) | 671 (13.0%) | |
| Quartile 3 | 23 (13.9%) | 650 (12.6%) | |
| Quartile 4 | 112 (67.9%) | 478 (9.3%) | |
| Systemic hypertension | 56 (33.9%) | 909 (17.6%) | 0.001 |
| Diabetes | 17 (10.3%) | 231 (4.5%) | 0.002 |
| High cholesterol (≥240 mg/dl) | 65 (39.4%) | 1,744 (33.8%) | 0.137 |
| Body mass index (≥25 kg/m$^2$) | 104 (63.0%) | 3,243 (62.9%) | 0.970 |
| Fitness (METs) (mean ± SD) | 10.4 ± 1.9 | 11.1 ± 2.2 | 0.001 |
| Parental history of cardiovascular disease | 13 (7.9%) | 87 (1.7%) | 0.001 |
| Smoking status | | | |
| Never | 73 (44.2%) | 3,066 (59.5%) | 0.001 |
| Quitter | 76 (46.1%) | 1,486 (28.8%) | |
| Smoker | 16 (9.7%) | 605 (11.7%) | |

*CHD was defined as a reported history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary revascularization (coronary angioplasty with and without arterial stent placement and atherectomy).

large numbers of women and men across a very broad age range, we found that 96% of subjects with prevalent CHD had detectable CAC. This is consistent with results from the earlier, previously mentioned prevalence studies noted.[7,19]

Our finding of an increasing prevalence of CAC with age in women <60 years is not consistent with results of previous studies. Wong et al[5] reported a similar proportion of CAC in women <40 (30%), 40 to 49 (30%), and 50 to 59 years old (27%). In our large sample, CAC prevalence increased across all age groups in women and men. Wong et al[5] also reported a lower prevalence of CAC in men (15%) than in women (30%) <40 years of age. In our study, women had a lower prevalence of detectable CAC than men in all age groups. These differences are most likely due to the small sample size in the study by Wong et al.[5]

Recently, an investigation using the same population as in this study presented age- and gender-based percentiles for CAC in women and men that showed that CAC increased with age and was lower in women than in men at all ages.[20] Our findings are consistent with these results and with the increasing prevalence of coronary atherosclerosis with age in pathologic studies in women and men. Detectable CAC was rare in women and men 20 to 29 years old, which is consistent with the rarity of clinical CHD in this age group.[17] In addition, within each age group, we documented a large variation in CAC scores in women and men, similar to the distribution of CAC scores found in a previous study.[4] Also, our observation that >30% of women with prevalent CHD had no CAC is worthy of future investigations that will be carried out in longitudinal studies being undertaken in this population. The association between CAC and many of the known cardiovascular risk factors has been demonstrated in a number of previous studies.[5] Because the presence and amount of CAC may be steps on the pathway between risk factors (known and unknown) and CHD-related outcomes, the variability of CAC may be an indicator of the heterogenous distribution of underlying cardiovascular risk factors in this population.

Whether the association between CAC and CHD has a threshold or graded response is also an important issue.[17] It appears from our data that there may be a threshold at a CAC score of >95 for the risk of prevalent CHD. Above this level of CAC, there appears to be a steep increase in risk as CAC scores

**TABLE 6** Odds Ratios (OR) of CHD (n = 165) by CAC Scores Categories in 5,322 Women and Men With Measured Conventional CHD Risk Factors Examined at the Cooper Clinic Between June 1995 and December 1998

| CAC Score* | Age- and Gender-Adjusted OR (95% CI) for CHD | Multivariable-adjusted OR* (95% CI) for CHD |
|---|---|---|
| No CAC | 1.0 (Referent) | 1.0 (Referent) |
| Quartile 1 | 1.5 (0.4–4.7) | 1.2 (0.3–4.35) |
| Quartile 2 | 3.1 (1.2–7.9) | 2.5 (0.9–7.0) |
| Quartile 3 | 5.0 (2.2–11.7) | 4.8 (2.0–11.8) |
| Quartile 4 | 39.6 (18.6–84.3) | 33.8 (14.9–76.6) |
| p Value for trend test | <0.001 | <0.001 |

*Adjusted for age, gender, fitness (METs), history of high cholesterol, hypertension, or diabetes, cigarette smoking, diabetes, obesity, and a parental history of cardiovascular disease.
Abbreviation as in Table 3.

increase, with the odds for myocardial infarction alone in those in the top quartile of CAC scores (≥396) being 12.8 and 35.2 in women and men, respectively (using those without detectable CAC as the referent group). In the lower quartiles of calcium scores, the odds for CHD in women and men were remarkably similar. These results deserve further investigation in larger populations, particularly of women. The strong independent association between CAC and prevalent CHD at levels of CAC >95 remained in the sizeable subgroup with a complete medical examination, which allowed for multivariate adjustment using selected indexes of known CHD risk factors. A similar strong association between CAC and CHD has also been reported in 1 small prospective study.[20]

There are some limitations to this cross-sectional study. The representativeness of our study group deserves comment. Study subjects came from middle and upper socioeconomic strata, were predominately white, and were not randomly selected from the general population. Despite these characteristics, we have demonstrated, in previous studies, that this cohort was similar to other well-characterized population cohorts with regard to blood pressure, cholesterol, weight, and cardiorespiratory fitness.[6,21] Whether our results would apply to lower socioeconomic strata or more ethnically diverse populations remains to be determined.

We used a modified Agatston method protocol with 3-mm-thick scans with a table advancement of 2 mm between scans. Although this procedure may produce slightly higher scores compared with the traditional Agatston method (3-mm scans with a 3-mm table advancement between scans), our quartile cutpoints are very close to those that other centers have reported. Although coronary revascularization procedures could affect the buildup of CAC, we did not find a statistical difference between patients with CHD with and without a history of such interventions. We also found that in a risk analysis comparing patients with myocardial infarction alone with all patients with CHD, there was no difference in the shape of the risk curve, although relative risk estimates were generally higher in the group with any manifestation of CHD. As in many other studies,[22,23] readers of the electron beam tomographic scans in our study were not blinded to the clinical data. However, in using a blinding procedure in reading the electron beam tomographic scans of 50 randomly selected patients with and without CHD, we found that scores were nearly identical to scores evaluated in the unblinded procedure used in the present study.

Misclassification of CHD may exist due to the nature of the self-reports used in this study. In previous studies in our population, we showed that our well-educated patients were able to provide accurate self-reports of medical diagnoses.[24] We did not identify patients with angina pectoris and silent myocardial infarction, and whether CAC is associated with these conditions deserves further study. Instead of using absolute CAC score to categorize the CAC score group as done in this study, other methods such as age- and gender-specific category may be also worthy of further exploration.

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