Coronary Artery Calcification in Older Adults to Age 99

Prevalence and Risk Factors

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***Background*—**Coronary artery calcification has been proposed as a noninvasive method to assess cardiovascular disease (CVD) risk. However, the prevalence and risk factors for coronary artery calcification in populations >65 years have not been well studied.

***Methods and Results*—**Electron beam tomography was performed to assess coronary artery calcium (CAC) in 614 older adults aged, on average, 80 years (range, 67 to 99 years); 367 (60%) were women, and 143 (23%) were black. Calcium scores ranged from 0 to 5459. Median scores were 622 for men and 205 for women. Scores increased by age and were lower in blacks than in whites. Nine percent of subjects (n=57) had no CAC, and 31% (n=190) had a score lower than 100. A history of CVD was associated with calcium score. Age, male sex, white race, CVD, triglyceride level, pack-years of smoking, and asthma, emphysema, or bronchitis (chronic obstructive pulmonary disease) were independently associated with CAC score in the fourth quartile.

***Conclusions*—**A wide range of CAC scores was observed, suggesting adaptation with aging. CAC may have potential to predict CVD in older adults, but this remains to be determined. **(*Circulation*. 2001;104:2679-2684.)**

Key Words: calcium ■ coronary diseases ■ aging

Electron beam computed tomography (EBT) can rapidly and noninvasively detect and quantify calcified atherosclerotic plaque in the coronary arteries.[1] A higher quantity of coronary artery calcium (CAC) is associated with the likelihood of obstructive lesions by angiography,[1] and it is also associated with an increased risk of future cardiovascular disease (CVD) in middle-aged, referred populations.[2]

The value of screening the elderly is in question because autopsy[3] and clinical[4] studies suggest that coronary artery atherosclerosis and calcification are almost universal in those with advanced old age. No study has yet defined the "typical" levels of CAC found in unreferred populations of older adults, whether a sex difference persists into old age, or whether CAC would predict a higher risk of CVD events or mortality in this age group. Risk factors measured late in life have rather poor discrimination for determining highest risk of CVD events in old age.[5,6] CAC has been proposed as a potential method to improve risk discrimination.[1] In fact, noninvasive measures of disease have been proposed to account for the effect of age in prediction models of CVD risk.[7]

We examined CAC in an elderly cohort. We hypothesized there would be a strong relationship between calcification and age and that CAC would be associated with CVD. This report describes the distribution of CAC in late life and associations with CVD and CVD risk factors.

Methods

Study Population

Participants from the Pittsburgh, Pennsylvania, field center of the Cardiovascular Health Study were recruited for EBT between May 1998 and June 2000.[8] This study was established to determine the risk factors for CVD in older adults.[9,10] Of 727 participants contacted at the last examination in 1998 to 1999, 614 participants (84%) underwent EBT scanning. Of the 113 nonparticipants, 16% died before the scan, 45% were ill, 16% could not travel, and 23% refused. Nonparticipants were of similar age, sex, and race as participants. All participants gave informed consent for examination and follow-up. The protocol was approved by the Institutional Review Board at the University of Pittsburgh.

Coronary Artery Calcification

CAC was assessed using an Imatron C-150 EBT scanner and the Agatston scoring method,[11] as described previously.[8]

Demographic and Cardiovascular Risk Factors

Age was assessed at the time of the EBT scan, and cardiovascular risk factors were assessed between 1992 to 1993 in both the original and added minority cohorts. Hypertension was defined as a participant having an average seated systolic blood pressure >160 mm Hg or an average seated diastolic blood pressure >95 mm Hg or

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A complete list of investigators of the Cardiovascular Heath Study can be found in the Appendix.

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self-reported hypertension and use of antihypertensive medication. Blood was collected and analyzed at the 1992 to 1993 examination,[12] with exception of C-reactive protein, which was run on stored baseline samples in 1997.[13] Diabetes was defined as use of insulin or oral hypoglycemics or if glucose level exceeded 126 mg/dL (7.0 mmol/L). Body mass index was expressed as kilograms per meters squared (kg/m^2). Cigarette smoking was reported as ever versus never, because there were few current smokers, and smoking exposure was also assessed using pack-years. Blood pressures were measured according to a standard protocol. Chronic obstructive pulmonary disease was defined by self-report of asthma, bronchitis, or emphysema diagnosed by a physician.

Other CVD

Prevalent clinical CVD was ascertained at the time of the scan using baseline and adjudicated events data. Baseline self-report data were validated by medical records.[14] Events occurring after baseline were ascertained by phone contact or at the clinic examination every 6 months, validated by medical record review, and adjudicated by committee.[15] CVD included history of myocardial infarction or angina, coronary artery bypass surgery or percutaneous transluminal angioplasty, congestive heart failure, stroke or transient ischemic attack, carotid surgery, peripheral vascular bypass surgery, angioplasty, or reported intermittent claudication. Subclinical CVD was assessed at the 1992 to 1993 examination and defined as an ankle-arm index <0.90, internal carotid wall thickness or common carotid wall thickness >80 percentile of subjects in the Cardiovascular Health Study population, carotid stenosis >25%, major ECG abnormalities, or a positive Rose questionnaire for angina or intermittent claudication.[16]

Statistical Analysis

The calcium score was highly skewed and not transformed to normality by common transformations. Therefore, median calcium scores were compared across demographic groups, and the distribution of characteristics across the quartiled calcium score was examined. For categorical variables, the χ^2 test for trend was used. For continuous variables, means and SD or medians were reported, and either ANOVA or a median test was used as appropriate to establish significance. Multiple logistic regression was used to determine which factors were independently associated with the highest quartile of calcium versus the lower 3 quartiles. Stepwise linear regression was also used to determine factors independently associated with higher calcium score (log transformed).

TABLE 1. Characteristics of the Study Population

	Overall (n=614)	Women (n=367)	Men (n=247)
Age, y	80.4±4.2	80.1±4.0	80.8±4.5
Age group, n (%)			
67–74 y	45 (7.3)	28 (7.6)	17 (6.8)
75–79 y	271 (44.1)	166 (45.2)	105 (42.5)
80–84 y	205 (33.4)	124 (33.8)	81 (32.8)
85–100 y	93 (15.2)	49 (13.4)	44 (17.8)
Race, n (%)			
White	471 (76.7)	282 (76.8)	189 (76.5)
Black	143 (23.3)	85 (23.2)	58 (23.5)
Atherosclerosis group, n (%)			
None (undetected)	205 (33.4)	131 (35.7)	74 (30.0)
Subclinical CVD only	205 (33.4)	130 (35.4)	75 (30.3)
Clinical CVD	204 (33.2)	106 (28.8)	98 (39.7)

Values are mean±SD or n (%).

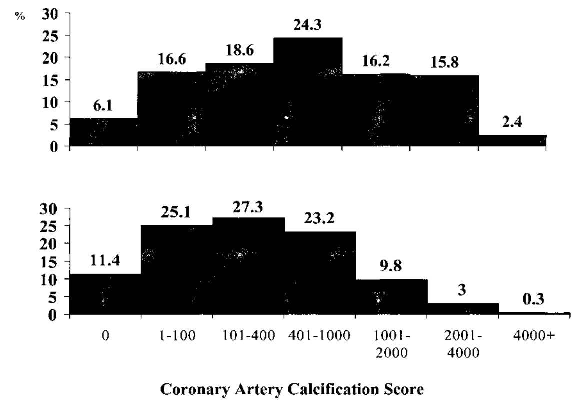

Figure 1. Distribution of CAC scores in men (top) and women (bottom).

Results

Participants' ages ranged from 67 to 99 years, with mean age of 80.4 years (Table 1). Men were similar in age and race distribution to the women, but a higher proportion had clinical CVD (P=0.021). CAC scores ranged from 0 to 5459, with a mean of 671 and median of 330 (622 for men and 205 for women; P<0.0001), and this broad distribution of scores was seen in both men and women (Figure 1). Fifty-seven participants (9.3%) had a score of 0 (6% of men compared with 11.4% of women; P=0.024). An additional 133 (21.7%) had a score <100, and 336 (54.7%) had a score <400. Fewer women than men had a score >1000 (13% of women compared with 34% of men; P<0.0001). The median score increased with age in both men and women but, in women, the score lagged about 10 years behind the men (Figure 2). For example, the score was 542 for women aged 85 to 99 years compared with 539 in men aged 75 to 79 years.

Those in the highest quartile of CAC score were older, more likely to be men, and less likely to be black (all P<0.0001; Table 2). In the lowest quartile of calcium, 9.7% were >85 years compared with 26.3% in the highest quartile. In the lowest quartile, 71.0% were women compared with only 40.1% in the highest quartile. Those in the higher quartiles were less likely to be black. All differences were significant with adjustment for age and sex.

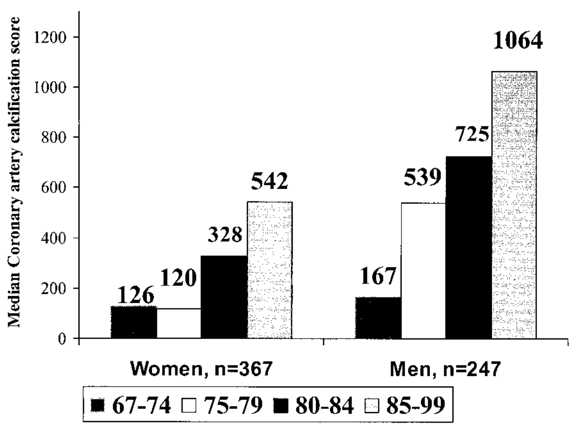

Figure 2. Median CAC scores in men and women by age group.

TABLE 2. Demographics by Quartiles of CAC Score (n=614)

Characteristic	CAC Score ≤56 (n=155)	57–332 (n=154)	333–917 (n=153)	≥918–5459 (n=152)	Trend, ANOVA, or Median Test *P*	Adjusted *P*
Age at scan, y	79.2±4.0	79.7±3.9	80.5±4.1	82.1±4.3	<0.0001	
Age category, n (%)						
67–74 y	20 (12.9)	11 (7.1)	11 (7.2)	3 (2.0)		
75–79 y	79 (51.0)	81 (52.6)	63 (41.2)	48 (31.6)		
80–84 y	41 (26.4)	46 (29.9)	57 (37.3)	61 (40.1)		
85–100 y	15 (9.7)	16 (10.4)	22 (14.4)	40 (26.3)	<0.0001	
Sex, n (%)						
Female	110 (71.0)	111 (72.1)	85 (55.6)	61 (40.1)		
Male	45 (29.0)	43 (27.9)	68 (44.4)	91 (59.9)	<0.0001	<0.0001*
Race, n (%)						
White	95 (61.3)	120 (77.9)	121 (79.1)	135 (88.8)		
Black	60 (38.7)	34 (22.1)	32 (20.9)	17 (11.2)	<0.0001	<0.0001†

Values are mean±SD or n (%).
*Adjusted for age.
†Adjusted for age and sex.

Higher calcium scores were associated with the prevalence of clinical CVD (for those with clinical CVD: median 683, range 0 to 5459; for those with subclinical CVD by other measures: median 374, range 0 to 4151; for those without atherosclerosis by other study measures: median 122, range 0 to 3736; $P<0.0001$). Forty percent of those with clinical CVD were in the highest calcium score quartile compared with 18.6% in the lowest quartile (Table 3). Conversely, of those without CVD by other measures, 13.2% were in the highest quartile and 37.1% were in the lowest quartile. This pattern was seen for both men and women, and associations remained significant after adjusting for age.

The associations between CVD risk factors and the calcium score quartiles were then analyzed separately for men and women (Tables 4 and 5). In both men and women, age was associated with higher calcium levels. Although fewer blacks were among those with the highest levels of coronary calcium, the association between race and coronary calcium quartile was significant for men only. The prevalence of hypertension or diabetes was not significantly different across quartiles of calcium score. There was also no difference in the level of total, LDL, or HDL cholesterol across quartiles of CAC in either men or women. The median triglyceride level increased across the calcium quartiles for both men and women, although the relationship was borderline significant only in women ($P=0.05$). Smoking exposure, as measured by pack-years, was significantly different across CAC quartiles for both women ($P=0.02$) and men ($P=0.01$). Median C-reactive protein level was associated with a higher level of CAC in women ($P=0.003$). In men, C-reactive protein levels tended to be lower overall and seemed to be unrelated to the calcium score. Overall, those at the extremes of the distribu-

TABLE 3. Association Between Prevalence of CVD and Quartiles of CAC Score

Atherosclerosis Group	Overall (n=614)	CAC Score ≤56 (n=155)	57–332 (n=154)	333–917 (n=153)	≥918–5459 (n=152)	Age-Adjusted *P*
Overall						
No CVD	205	76 (37.1)	59 (28.8)	43 (21.0)	27 (13.2)	
Subclinical CVD	205	41 (20.0)	57 (27.8)	64 (31.2)	43 (21.0)	
Clinical CVD	204	38 (18.6)	38 (18.6)	46 (22.6)	82 (40.2)	<0.0001
Women						
No CVD	131	55 (42.0)	43 (32.8)	18 (13.7)	15 (11.5)	
Subclinical CVD	130	28 (21.5)	39 (30.0)	42 (32.3)	21 (16.2)	
Clinical CVD	106	27 (25.5)	29 (27.4)	25 (23.6)	25 (23.6)	0.0006
Men						
No CVD	74	21 (28.4)	16 (21.6)	25 (33.8)	12 (16.2)	
Subclinical CVD	75	13 (17.3)	18 (24.0)	22 (29.3)	22 (29.3)	
Clinical CVD	98	11 (11.2)	9 (9.2)	21 (21.4)	57 (58.2)	<0.0001

Values are n (%).

TABLE 4. Prevalence and Means/Medians of Baseline Risk Factors by Level of CAC in Men

Characteristics	CAC Score ≤56 (n=45)	57–332 (n=43)	333–917 (n=68)	≥918 (n=91)	Trend, ANOVA, or Median Test *P*
Age at scan, y	79.9±5.0	79.2±3.7	80.5±4.5	82.1±4.2	0.001
Race, n (%)					
White	19 (42)	34 (79)	53 (78)	83 (91)	
Black	26 (58)	9 (21)	15 (22)	8 (9)	<0.0001
Hypertension, n (%)	13 (28.9)	11 (26.2)	20 (29.4)	31 (34.4)	0.77
Diabetes, n (%)	8 (17.8)	7 (16.7)	9 (13.2)	14 (16.1)	0.76
Total cholesterol, mg/dL	193.4±39.6	194.3±26.1	202.9±32.5	203.9±33.7	0.20
HDL, mg/dL	58.3±10.8	47.2±9.1	45.3±9.1	46.3±10.4	0.44
LDL, mg/dL	109.9±28.6	114.2±29.0	117.5±27.1	117.9±33.4	0.49
Triglycerides, mg/dL	96	109	108	116	0.36
Ever smoked, n (%)	24 (54.6)	22 (52.4)	49 (73.1)	65 (72.2)	0.028
Pack-years smoked, y	11.0	36.3	19.8	30.5	0.01
COPD, n (%)	5 (11)	2 (5)	13 (19)	19 (21)	0.07
Body mass index, kg/m^2	27.2±4.0	26.9±4.4	26.0±3.3	26.6±3.4	0.37
Fibrinogen, mg/dL	304.0	300.0	311.5	305.0	0.89
Creatinine, mg/dL	1.20	1.10	1.20	1.20	0.44
C-reactive protein, mg/dL	1.47	1.69	1.58	1.52	0.89

There were a total of 247 men in the study. Values are mean±SD, median, or n (%). COPD indicates chronic obstructive pulmonary disease.

tion (lowest versus highest quartile) had more pronounced differences in the risk factors in the expected direction. Rank correlations between risk factors and the calcium score quartile were low (<0.20) and not significant except for age, race, sex, and pack-years of smoking. Results were similar when those with clinical CVD were excluded.

Finally, we evaluated risk factors predicting a CAC score in the fourth quartile (Table 6). Men with clinical CVD who

TABLE 5. Prevalence and Means/Medians of Baseline Risk Factors by Level of CAC in Women

Characteristics	CAC Score ≤56 (n=110)	57–332 (n=111)	333–917 (n=85)	≥918 (n=61)	Trend, ANOVA, or Median Test *P*
Age at scan, y	78.9±3.4	79.9±4.0	80.5±3.7	82.2±4.6	<0.0001
Race, n (%)					
White	76 (69)	86 (78)	68 (80)	52 (85)	
Black	34 (31)	25 (22)	17 (20)	9 (15)	0.09
Hypertension, n (%)	35 (32.1)	30 (27.5)	31 (37.4)	19 (31.7)	0.55
Diabetes, n (%)	9 (8.3)	15 (13.8)	8 (9.6)	7 (11.9)	0.64
Total cholesterol, mg/dL	221±39	224.4±36.5	225.9±38.9	232.3±40.1	0.33
HDL, mg/dL	58.7±14.9	56.7±13.3	58.2±15.1	54.1±16.2	0.24
LDL, mg/dL	125.3±32.8	123.2±29.9	126.1±29.4	130.6±34.2	0.55
Triglycerides, mg/dL	111.5	117.0	115.0	152.0	0.050
Ever smoked, n (%)	55 (52.4)	59 (54.6)	48 (60.0)	37 (62.7)	0.53
Pack-years smoked, y	18.0	24.9	25.0	30.0	0.02
COPD, n (%)	24 (22)	31 (28)	18 (21)	24 (39)	0.05
Body mass index, kg/m^2	26.9±4.3	27.3±5.0	27.2±5.0	26.7±4.7	0.87
Fibrinogen, mg/dL	314.0	322.0	324.0	313.0	0.31
Creatinine, mg/dL	0.90	0.90	0.90	0.90	0.86
C-reactive protein, mg/dL	1.40	3.04	2.32	2.05	0.003

There were 367 women in the study. Values are mean±SD, median, or n (%). COPD indicates chronic obstructive pulmonary disease.

TABLE 6. Multiple Logistic Regression: Factors Independently Associated With Highest Quartile of Calcium Score

Variable	Odds Ratio	95% Confidence Interval	*P*
Sex	2.582	1.86, 3.57	$<$0.0001
Clinical CVD	2.052	1.46, 2.88	$<$0.0001
Age at scan (year)	1.107	1.06, 1.15	$<$0.0001
White race	2.131	1.46, 3.10	$<$0.0001
Pack-years smoking	1.012	1.006, 1.02	$<$0.0001
COPD	1.466	1.002, 2.15	0.048
Triglycerides	1.004	1.001, 1.006	0.005

COPD indicates chronic obstructive pulmonary disease.

were older or of white race were more likely to be in the top quartile. In addition, triglycerides, smoking exposure, and history of chronic obstructive pulmonary disease were independently associated with the highest quartile. Results were similar when using the log of the calcium score as the dependent variable.

Discussion

The key findings of this study were that the extent of coronary artery calcification was strongly associated with age through the ninth decade in men and women and was associated with CVD. Second, risk factor levels were only weakly associated with the extent of CAC in these older adults.

There is reason to believe that older adults might differ from younger adults in the rate of progression of atherosclerosis, the level of compensatory dilation or stiffening, and/or in plaque stability. Intracoronary ultrasound illustrates that there is compensatory dilation of the coronary artery at the site of obstruction.[17] Our study suggests that such compensation may well occur with aging based on the fact that those $>$85 years in our study had median levels of coronary calcium well over the threshold for significant obstructive disease,[1] yet 57% had not had a cardiovascular event. These high levels of calcification are unusual in middle-aged and younger adults. Although CAC represents the extent of atherosclerosis, a given level of calcium may have different a predictive value in the old than in the young. This hypothesis must be tested prospectively.

The utility of CAC assessment in older adults has been questioned because most clinical series show that calcification is nearly universal[4] and not discriminatory. Our data refute this in that the range of calcification was quite broad, spanning the lowest to the highest levels. Furthermore, the extent of calcification was associated with the extent of CVD (clinical or subclinical by other measures) in our study. Therefore, it seems likely that it may also discriminate risk prospectively in this older cohort.

These data extend findings in middle-aged adults in that there is a very strong effect of age on CAC scores. Calcification is first detected in most men at around age 40, whereas women first show calcification around age 50.[18] Raggi et al[19] reported median calcium levels of zero in middle-aged women and median scores of 151 in men and 24 in women aged 65 to 70 years. In our group, the medians for men and women up to age 75 were 167 and 126, with substantially higher scores in each subsequent 5-year age group. Although women had lower levels of calcification than men, levels in the oldest age group were similar to those of men ≈10 years younger.

Blacks were less likely to have extensive coronary artery calcification in this cohort than were whites. The literature on differences in CAC by race is just beginning to emerge, with one study showing similar rates of calcification in blacks and whites[20] and one showing lower rates in blacks.[21] It is possible that the blacks recruited into this study are not representative of those in these other studies or in the community or, because of their age, are a unique survival group. Because they were recruited later, the blacks were somewhat younger than the whites; however, this association persisted with adjustment for age. More detailed analyses of these differences in our cohort are underway.

The finding of weak associations between the extent of coronary calcification and baseline risk factors, including hypertension, diabetes, and cholesterol, was consistent with other studies showing that such risk factors are attenuated in their associations with disease in old age.[22–24] We examined risk factors assessed ≈5 years before the scan. Risk factor levels in older adults decline in those who become ill and in those whose risk factors are treated, so these prior risk factor levels should better reflect risk factor exposure than current levels in older adults.[25,26] Furthermore, all studies of elderly individuals are subject to survivor bias, which results in truncation of the distributions of risk factors and disease. For example, in our study, men had low levels of C-reactive protein at all levels of calcification, supporting a survival bias in the men. Also, these surviving individuals represent less than half of the original 1501 members of the Cardiovascular Health Study cohort in Pittsburgh. However, these individuals would be similar to older adults seen in a community. Nevertheless, such bias is an important limitation to consider.

Because so many older adults are at risk, further study of risk discrimination is needed.[7] On the basis of current recommendations, high scores such as those noted in these older adults could potentially stimulate further evaluation for invasive therapy, despite a lack of evidence for intervening in asymptomatic people. In this study, 59% of men and 36% of women had scores $>$400, which is the current guideline for referral for evaluation for obstructive disease.[13] This approach would be unrealistic given the large number of older adults who would have high scores.

In summary, CAC scanning detected a broad range of disease in these older adults, and many with higher levels of calcification would not have been distinguished by traditional risk factors. The higher levels of CAC in those with clinical disease suggest that it should predict events prospectively. Although higher CAC has been shown to predict events in middle-aged, clinically-referred populations, it remains to be determined whether the risk associated with CAC is attenuated with age.

Appendix

Participating Institutions and Principal Staff of the Cardiovascular Health Study

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