Electron-Beam Tomography Coronary Artery Calcium and Cardiac Events

A 37-Month Follow-Up of 5635 Initially Asymptomatic Low- to Intermediate-Risk Adults

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Background**—**Conventional coronary artery disease (CAD) risk factors fail to explain nearly 50% of CAD events. This study examines the association between electron-beam tomography (EBT) coronary artery calcium (CAC) and cardiac events in initially asymptomatic low- to intermediate-risk individuals, with adjustment for the presence of hypercholesterolemia, hypertension, diabetes, and a history of cigarette smoking.

Methods and Results**—**The study was performed in 8855 initially asymptomatic adults 30 to 76 years old (26% women) who self-referred for EBT CAC screening. Conventional CAD risk factors were elicited by use of a questionnaire. After 37±12 months, information on the occurrence of cardiac events was collected and confirmed by use of medical records and death certificates. In men, events (n=192) were associated with the presence of CAC (RR=10.5, $P<0.001$), diabetes (RR=1.98, $P=0.008$), and smoking (RR=1.4, $P=0.025$), whereas in women, events (n=32) were linked to the presence of CAC (RR=2.6, $P=0.037$) and not risk factors. The presence of CAC provided incremental prognostic information in addition to age and other risk factors.

Conclusions**—**The association between EBT CAC and cardiac events observed in this study of initially asymptomatic, middle-aged, low to intermediate-risk individuals presenting for screening suggests that in this group, knowledge of the presence of EBT CAC provides incremental information in addition to that defined by conventional CAD risk assessment. **(*Circulation*. 2003;107:2571-2576.)**

Key Words: coronary disease ■ calcium ■ follow-up studies ■ risk factors ■ sex

Coronary artery disease (CAD) is the primary cause of death in the United States and will most likely remain the leading cause of death well into the 21st century.[1,2] Prospective epidemiological studies have established the association between major risk factors and the development of clinical CAD.[3–5] However, it has been estimated that these risk factors fail to explain up to 50% of CAD morbidity and mortality.[2,3,6]

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Effective means are available for treating and delaying the progression of symptomatic CAD.[6,7] However, according to Framingham data, nearly 50% of all coronary deaths occur in individuals with no previous history of symptomatic CAD.[8] Thus, defining the magnitude of future risk for the development of clinical CAD is a major focus of effective primary prevention. One proposed screening strategy for subclinical CAD uses electron-beam tomography (EBT).[9,10] EBT noninvasively detects and quantifies coronary artery calcium (CAC), a marker for atherosclerosis.[11]

The purpose of this study was to examine the association between the EBT CAC score and cardiac events (death, myocardial infarction, or coronary revascularization) in a cohort of initially asymptomatic, low- to intermediate-risk individuals, with adjustment for age and the presence of other CAD risk factors.

Methods

Study Protocol

Between January 1993 and December 1995, 10 132 individuals 30 to 76 years old self-referred for EBT CAC screening. Immediately before the EBT scan, all individuals completed a questionnaire that elicited personal demographics, CAD risk factors (past/current cigarette smoking, hypercholesterolemia, diabetes, and hypertension),

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and past medical history. Hypercholesterolemia was defined as a total cholesterol level of >200 mg/dL or the use of cholesterol-lowering medications. Individuals were considered to be diabetic if they reported using oral hypoglycemic agents or insulin and hypertensive if they reported a history of high blood pressure or the use of antihypertensive medications. The validity of self-reported histories of hypercholesterolemia, diabetes, and hypertension was examined in a peripheral study.[12] The κ statistics for hypercholesterolemia, diabetes, and hypertension were 0.796 ($P<0.001$), 0.783 ($P<0.001$), and 0.36 ($P<0.01$), respectively. The incongruity observed for hypertension may have been a result of an abundance of individuals who controlled their high blood pressure with lifestyle modification and presented with normal blood pressure at the time of examination. To validate the cardiovascular health status of the study sample, the prevalence rates of risk factors were compared with the estimated prevalence rates reported for the US population.[13,14]

After individuals who reported a past medical history of chest pain, diagnostic coronary arteriography, coronary revascularization, or myocardial infarction had been excluded, 8855 eligible individuals were contacted via a structured telephone interview or a mailed questionnaire to determine their health status. The Institutional Review Board approved the study protocol and the questionnaires used to obtain data for this study.

EBT Imaging Procedure

EBT CAC scans were obtained with a C-100 scanner (GE Imatron). Using ECG triggering at 80% of the RR interval, 2 sets of 100-ms/3-mm images (40 and 20 slices) were acquired.[12] Images were reconstructed to a 512-pixel matrix using sharp kernel and a 26-cm display field of view. At least 4 adjacent pixels (total area of 1 mm^2) with a computed tomography number of ≥130 Hounsfield units were necessary to define a calcified plaque. The CAC score was calculated by use of the Agatston method[15] and expressed further as age/sex percentile.[12]

Determination of Cardiac Events

Events in this study were defined as the occurrence of one of the following: (1) death, (2) myocardial infarction, or (3) revascularization procedure (catheter-based intervention or CABG). Only confirmed events were included in this analysis, and only 1 event per person was counted in the order of its occurrence. Revascularization procedures were considered soft cardiac events, whereas deaths and myocardial infarctions were classified as hard cardiac events. Extensive efforts were made to determine the cause of death: review of hospital records and death certificates as well as conversations with family members. Deaths from heart disease or an unknown cause were considered a hard event. Deaths unrelated to heart disease were excluded from this analysis. Chest pain history, ECG changes, and cardiac enzyme criteria were used in the determination of a myocardial infarction.[16] Reported events were verified with medical records by 2 board-certified cardiologists who were blinded to the EBT CAC screening results.

Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics, CAD risk factor information, and CAC scores. The associations between risk factors, CAC, and cardiac events were examined by use of the Pearson's χ^2 test, multivariable logistic regression, and Cox proportional-hazards regression. Hierarchical Cox proportional-hazards regression was used to compare 2 nested models, including (1) age and other risk factors (smoking history, the presence of diabetes, hypercholesterolemia, and hypertension) and (2) age, other risk factors, and the presence of CAC. The likelihood ratio χ^2 statistics were obtained to determine whether the addition of CAC contributed significantly to the models predicting hard and soft cardiac events. To determine whether the relative risk for cardiac events associated with CAC was graded, the positive CAC score was categorized by use of quartile cutpoints, and negative CAC results (CAC score=0) served as the reference group.

The power to observe significant associations between cardiac events and the presence of CAC in men and women was calculated. These calculations used the known sample size for each sex, the observed relative risks for hard and soft events by sex, and the estimated hard and soft cardiac event rates for the US population of 3% per year[17] and 5% per year,[8] respectively. The significance level was set at 0.05. For men, power was >0.99 for both hard and soft events. In women, calculations yielded a power of 0.21 for hard events and 0.99 for soft events.

Results

The response rate was 64% (5635/8855), and the mean±SD follow-up period was 37±13 months. Responding men were older (mean age, 51±9 versus 50±9 years, $P=0.001$) and reported a history of hypertension more often than nonresponding men (20% versus 18%, $P=0.03$). Among women, there were no differences in the prevalence of risk factors and CAC characteristics between responders and nonresponders. Despite the minimal differences between male responders and nonresponders, it can reasonably be concluded that the responders were a good representation of the screened population.

At the time of EBT CAC screening, the responding participants ranged in age from 30 to 76 years, and the mean age was 50±9 years for 4151 men and 54±9 years for 1484 women. Ninety-five percent of the individuals were white. Cigarette smoking was reported by 48%, diabetes by 3.4%, hypercholesterolemia by 39%, and hypertension by 20% of the study sample.

Compared with the prevalence rates reported in the National Health and Nutrition Survey (NHANES) and the Atherosclerosis Risk in Communities (ARIC) study, the prevalence figures for CAD risk factors reported in the present study were lower, with the exception of hypercholesterolemia being more prevalent among University of Illinois at Chicago study participants.[13,14]

CAC was detected (CAC score >0) in 74% of men and 51% of women ($P<0.001$). In men, the mean and median CAC scores were 137±376 and 6.7, whereas in women, these figures were 59±263 and 1.01, respectively. In men, all reported risk factors were significantly associated with the presence of CAC, whereas in women, this association was demonstrated for all risk factors but diabetes.

During the follow-up period, 257 events were reported, of which 244 events were confirmed. After deaths unrelated to heart disease (n=20) had been excluded, 224 confirmed events (21 deaths, 37 myocardial infarctions, 92 CABGs, and 74 catheter-based intervention procedures) were used in the analysis. Compared with those without events, individuals who sustained any event were older (mean age, 56±8 versus 51±9 years, $P<0.001$) and had a higher prevalence of smoking (59% versus 47%, $P=0.001$), diabetes (9.4% versus 3.2%, $P<0.001$), and hypertension (34% versus 19%, $P<0.001$). However, individuals with and without events did not differ with regard to the history of hypercholesterolemia. Among individuals with all events, 95% had measurable CAC, with a mean CAC score of 483±686, compared with the CAC prevalence of 67% observed in individuals without events, who had a mean CAC score of 101±321 ($P<0.001$). Men and women who suffered any event did not differ with

TABLE 1. Event Rates for Men and Women With Detectable CAC Compared to No Detectable CAC

	CAC Present	No CAC	*P*
Men			
Total No.	3065	1086	
Hard events, %	1.6	0.3	0.001
Soft events, %	4.5	0.1	<0.001
All events, %	6.1	0.4	<0.001
Women			
Total No.	754	730	
Hard events, %	0.5	0.3	0.4
Soft events, %	2.8	0.7	0.002
All events, %	3.3	1	0.002

regard to mean age and the frequencies of reported risk factors. However, compared with women, men with events had a greater prevalence of CAC (98% versus 78%, $P<0.001$) and a greater mean CAC score (540±721 versus 137±212, $P=0.002$).

Reported events consisted of 58 hard events (37 myocardial infarctions and 21 deaths) and 166 soft events (74 catheter-based interventions and 92 CABGs). When individuals with hard events were compared with those with soft events, the only significant difference was in the mean CAC score, which was higher in those with soft events (569±735 versus 236±442, $P=0.001$).

As presented in Table 1, there was an association between the presence of CAC and all event categories in both sexes, with the exception of hard events in women. The age-adjusted univariable and multivariable association between the risk factors, the presence of CAC, and 3 categories of cardiac events (hard, soft, and all events) is shown in Tables 2 (men) and 3 (women). Most multivariable relative risks were smaller than the univariable relative risks, reflecting positive correlations between the predictors. Controlling for age and other risk factors, the presence of any detectable CAC was significantly associated with hard, soft, and all events in men. In women, detectable CAC was significantly associated with soft and all events. However, an association between detectable CAC and hard events in women could not be established because of a lack of power. The results of the hierarchical Cox proportional-hazards regression analysis are presented in Table 4. When added to age and other risk factors, the presence of CAC contributed significantly to models predicting soft and all events in both sexes and to the model predicting hard events in men.

The relative risk for hard events at increasing quartiles of the positive CAC score in men was graded as shown in Table

TABLE 2. Univariable and Multivariable Association Between Risk Factors, CAC, and Cardiac Events in Men

	Univariable		6-Predictor Model	
	Relative Risk	95% CI	Relative Risk	95% CI
Hard events				
Age (y)	1.07‡	1.04–1.1	1.06‡	1.03–1.09
Cigarette use (yes/no)	1.22	0.71–2.09	1.06	0.61–1.84
Hypercholesterolemia (yes/no)	0.68	0.38–1.23	0.66	0.36–1.19
Diabetes (yes/no)	1.2	0.29–4.95	0.89	0.21–3.68
Hypertension (yes/no)	1.73	0.95–3.15	1.23	0.67–2.28
Presence of CAC	5.8†	1.81–18.6	3.86*	1.17–12.70
Soft events				
Age (y)	1.07‡	1.05–1.09	1.05‡	1.03–1.07
Cigarette use (yes/no)	1.9‡	1.35–2.68	1.56*	1.1–2.2
Hypercholesterolemia (yes/no)	1.02	0.73–1.43	0.96	0.68–1.35
Diabetes (yes/no)	3.51‡	2.06–6.00	2.38†	1.38–4.09
Hypertension (yes/no)	2.12‡	1.49–3.10	1.37	0.96–1.96
Presence of CAC	49.4‡	6.91–353.17	26.8‡	3.72–193.11
All events				
Age (y)	1.07‡	1.06–1.09	1.05‡	1.04–1.07
Cigarette use (yes/no)	1.68‡	1.26–2.24	1.39*	1.04–1.87
Hypercholesterolemia (yes/no)	0.92	0.68–1.23	0.87	0.65–1.17
Diabetes (yes/no)	2.87‡	1.74–4.72	1.98†	1.19–3.28
Hypertension (yes/no)	2.01‡	1.49–2.72	1.33	0.98–1.81
Presence of CAC	16.71‡	6.21–44.99	10.46‡	3.85–28.40

The 6-predictor Cox proportional hazards regression models included simultaneously all variables listed in the table.

*$0.01<P<0.05$, †$0.001<P<0.01$, ‡$P<0.001$.

TABLE 3. Univariable and Multivariable Association Between Risk Factors, CAC, and Cardiac Events in Women

	Univariable		6-Predictor Model	
	Relative Risk	95% CI	Relative Risk	95% CI
Hard events				
Age (y)	1.01	0.93–1.10	1.01	0.92–1.10
Cigarette use (yes/no)	0.64	0.12–3.51	0.59	0.10–3.48
Hypercholesterolemia (yes/no)	0.61	0.11–3.32	0.55	0.10–3.13
Diabetes (yes/no)	12.17†	2.22–66.64	6.61	0.99–44.04
Hypertension (yes/no)	7.4*	1.36–40.43	4.65	0.73–29.48
Presence of CAC	1.78	0.33–9.75	1.53	0.23–10.09
Soft events				
Age (y)	1.04	1.00–1.08	1.02	0.97–1.07
Cigarette use (yes/no)	1.5	0.69–3.25	1.42	0.65–3.12
Hypercholesterolemia (yes/no)	1.48	0.69–3.21	1.28	0.59–2.77
Diabetes (yes/no)	2.22	0.53–9.42	1.64	0.36–7.41
Hypertension (yes/no)	2.02	0.90–4.54	1.5	0.64–3.52
Presence of CAC	3.95†	1.49–10.49	3.08*	1.11–8.58
All events				
Age (y)	1.03	1.00–1.07	1.02	0.98–1.06
Cigarette use (yes/no)	1.23	0.64–2.58	1.19	0.59–2.43
Hypercholesterolemia (yes/no)	1.26	0.63–2.52	1.09	0.54–2.19
Diabetes (yes/no)	3.75*	1.31–10.70	2.64	0.86–8.06
Hypertension (yes/no)	2.6†	1.28–5.27	1.85	0.87–3.94
Presence of CAC	3.33†	1.44–7.70	2.57*	1.06–6.23

The 6-predictor Cox proportional hazards regression models included simultaneously all variables listed in the table.

*$0.01<P<0.05$, †$0.001<P<0.01$.

5. Table 6 demonstrates that in both sexes, increasing CAC score posed graded relative risk for the occurrence of revascularization procedures. Generally, the risk observed in men was orders of magnitude greater than in women.

Use of the age/sex CAC score percentile allows the ranking of an individual's test result against a matched population.[12] Table 7 displays hard and soft event rates by age/sex CAC score quartiles. The event rates among the first 3 quartiles did not differ significantly in men or women. However, the event rate among individuals with CAC scores in the highest age/sex quartile was greater than the combined event rate observed in the first 3 quartiles. This difference was significant for both hard and soft events in men and for soft events in women. Individuals with CAC scores in the highest age/sex quartile accounted for 46% of the hard and 74% of the soft events in men and 50% of the hard and 58% of the soft events in women.

Discussion

The purpose of this study was to examine the association between the EBT CAC score and the occurrence of death, myocardial infarction, or the need for coronary revascular-

TABLE 4. Changes in Goodness-of-Fit Measures With Addition of CAC to Risk Factors in Models Predicting Cardiac Events

	Likelihood Ratio χ^2 Change	
	Men	Women
Hard events	7.12†	0.2
Soft events	42.87‡	5.49*
All events	46.47‡	4.89*

The hierarchical Cox proportional-hazards regression analysis was performed separately for men and women. Initial model included predictors age, cigarette smoking, hypercholesterolemia, diabetes, and hypertension. The presence of any detectable CAC was subsequently added to the model.

*$0.01<P<0.05$, †$0.001<P<0.01$, ‡$P<0.001$.

TABLE 5. Association Between CAC Score Categories and Hard Events in Men

	CAC Score Range	Relative Risk	95% CI
	0.0	1.0†	Referent
Quartile 1	1.0–3.8	1.76	0.39–7.88
Quartile 2	4.0–30.5	2.84	0.73–11.11
Quartile 3	31–169	5.61†	1.57–20.06
Quartile 4	170–7,000	7.24†	2.01–26.15

The multivariable Cox proportional-hazards regression analysis was performed with adjustment for age and other CAD risk factors.

†$0.001<P<0.01$.

TABLE 6. Association Between CAC Score Categories and Soft Events in Men and Women

	Men			Women		
	CAC Score Range	Relative Risk	95% CI	CAC Score Range	Relative Risk	95% CI
	0.0	1.00‡	Referent	0.0	1.00‡	Referent
Quartile 1	1.0–3.8	4.05	0.42–38.91	1.0–2.7	1.38	0.26–7.18
Quartile 2	4.0–30.5	15.71†	2.04–121.14	2.8–20.4	1.44	0.27–7.59
Quartile 3	31–169	26.18†	3.49–196.43	20.5–107	2.19	0.49–9.77
Quartile 4	170–7,000	124.05‡	16.98–906.07	107–6,860	10.39‡	3.22–33.56

Quartile cutpoints for the positive CAC score were obtained separately for men and women.

The multivariable Cox proportional-hazards regression analysis was performed separately in men and women, with adjustment for age and other CAD risk factors.

†$0.001<P<0.01$, ‡$P<0.001$.

ization in a cohort of initially asymptomatic, low– to intermediate–cardiac risk men and women while controlling for age and other CAD risk factors. The present study demonstrated an association between cardiac events and self-reported cigarette smoking, hypertension, and diabetes. Multivariable risk calculations also demonstrated that measurable CAC was independently associated with cardiac events. Generally, relative risks associated with the presence of CAC were greater than those associated with the risk factors. The presence of any detectable CAC provided incremental prognostic information when added to models that included age and the presence of hypercholesterolemia, hypertension, diabetes, and cigarette smoking.

In the present study, the hard event rate among individuals with CAC scores in the highest age/sex quartile (CAC score ≥75% of the control population) was at least twice as high as in individuals with CAC scores in the first 3 quartiles combined. These findings are consistent with observations from another study, which demonstrated that high age/sex CAC score percentiles were prevalent in initially asymptomatic individuals who experienced a hard event.[18,19] Because the significance of a given absolute CAC score is influenced by age and sex, using the age/sex CAC score percentile may allow for a more accurate assessment of an individual's risk.

The association between EBT CAC and the development of clinical CAD has been explored previously by several groups of researchers.[18–21] Differences in the EBT imaging protocol, CAC score cutpoints, and statistical analyses used in these studies do not allow the direct comparison of the reported estimates of risk. In general, however, these studies demonstrated a strong association between EBT CAC and the occurrence of CAD events in initially asymptomatic, low- to intermediate-risk individuals. In agreement with our findings, the relative risk for cardiac events was graded and independent of age and other risk factors. In a study of high-risk individuals, an association between CAC and cardiac events was reported, but CAC was not as powerful a predictor in this older group as in lower-risk groups.[22]

It is necessary to comment on the event categories used in the present study. Because deaths from unknown causes were considered hard cardiac events, the relative risks for hard events might be diluted if some of these deaths were in fact noncoronary in nature. However, among 21 recorded deaths, only 3 occurred before the age of 45 years, when CAD is not the primary cause of death. In this study, the number of soft events was greater than that of hard events. Higher CAC scores observed, on average, in individuals with soft events suggest that revascularization procedures might be triggered by positive EBT CAC screening results. Although hard and soft events were analyzed separately in this study, the results of the analyses that included soft events should be interpreted with caution.

The follow-up response rate of 64% may be a limitation, yet data indicate that survey research response rates are typically <70% when no incentive is offered for survey completion.[23] In this study, when individuals were asked to provide information regarding their health for survey research purposes, no incentive was provided in return. Although the

TABLE 7. Event Rates by Age/Sex Quartiles of CAC Score

	Age/Sex Quartiles of CAC Score					
	1 (1% to 24%)	2 (25% to 49%)	3 (50% to 74%)	4 (≥75%)	Combined 1 to 3 (1% to 74%)	*P**
Men, n	509	1344	1264	1034	3117	
Hard events, %	1.4	1.0	0.6	2.3	0.9	<0.001
Soft events, %	0.4	1.1	1.5	10.1	1.2	<0.001
Women, n	24	289	781	390	1094	
Hard events, %	...	0.7	0.1	0.8	0.3	0.2
Soft events, %	...	0.7	1.2	3.8	1.0	0.001

**P* values are shown for the comparison of event rates between the fourth quartile and the first 3 quartiles combined.

true health status of the nonresponders is unknown, it can be assumed to be very similar to that of the responders, because the risk-factor profiles (aside from the minimal differences in the mean age and the prevalence of hypertension in men) and CAC characteristics were comparable between the 2 groups. The reliance on data obtained from self-referred individuals can be considered a limitation of the study, because volunteers for clinical research are believed to represent the extremes of the population, the healthiest and those that self-refer for personal reasons.[10] In this affluent, health-conscious population, the prevalence rates of CAD risk factors, with the exception of hypercholesterolemia, were lower than those reported for the general population. It is possible that in a less healthy population, the relative risk for cardiac events associated with risk factors might be higher. In addition, use of cholesterol-lowering therapy as a criterion for hypercholesterolemia could potentially attenuate the expected association between elevated serum cholesterol and cardiac events. Similarly, possible beneficial lifestyle behaviors motivated by a positive CAC score could potentially attenuate the association between risk factors and cardiac events.[24]

In summary, although office-based risk assessment remains the current recommendation for risk stratification in the general population, the association between EBT CAC and cardiac events observed in this study of initially asymptomatic, middle-aged, low– to intermediate–cardiac risk individuals presenting for screening (the "worried well") suggests that in this group, knowledge of the presence and the extent of EBT CAC provides incremental information beyond that defined by single or combined conventional CAD risk factor assessment. Population-based studies examining the usefulness of EBT CAC screening as an adjunct to office-based CAD risk assessment are needed.

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