

CLINICAL RESEARCH

Coronary Artery Disease

Coronary Artery Calcium to Predict All-Cause Mortality in Elderly Men and Women

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- Objectives** We sought to study the prognostic utility of coronary artery calcium (CAC) in the elderly.
- Background** The prognostic significance of CAC in the elderly is not well known.
- Methods** All-cause mortality was assessed in 35,388 patients (3,570 were ≥ 70 years old at screening, and 50% were women) after a mean follow-up of 5.8 ± 3 years.
- Results** In older patients, risk factors and CAC were more prevalent. Overall survival was 97.9% at the end of follow-up. Mortality increased with each age decile with a relative hazard of 1.09 (95% confidence interval: 1.08 to 1.10, $p < 0.0001$), and rates were greater for men than women (hazard ratio: 1.53; 95% confidence interval: 1.32 to 1.77, $p < 0.0001$). Increasing CAC scores were associated with decreasing survival across all age deciles ($p < 0.0001$). Survival for a < 40 -year and ≥ 80 -year-old man with a CAC score ≥ 400 was 88% and 19% (95% and 44% for a woman, $p < 0.0001$), respectively. Among the 20,562 patients with no CAC, annual mortality rates ranged from 0.3% to 2.2% for patients age 40 to 49 years or ≥ 70 years ($p < 0.0001$). The use of CAC allowed us to reclassify more than 40% of the patients ≥ 70 years old more often by excluding risk (i.e., CAC < 400) in those with > 3 risk factors.
- Conclusions** Despite their limited life expectancy, the use of CAC discriminates mortality risk in the elderly. Furthermore, the use of CAC allows physicians to reclassify risk in the elderly. (J Am Coll Cardiol 2008;52:17–23) © 2008 by the American College of Cardiology Foundation

Coronary artery calcium (CAC) is currently recognized as an independent and incremental predictor of events in patients at intermediate risk of coronary artery disease, and several guidelines support selective screening in these patients (1–3). Preliminary evidence has also been found in high-risk subjects such as diabetic patients (4) and smokers (5), where CAC seems to add prognostic significance to risk factors. Whether CAC screening has prognostic value when assessing risk in older patients has not been extensively researched.

The currently used risk estimation tools are heavily influenced by age as a surrogate marker of atherosclerosis burden. Although atherosclerosis progresses with advancing age, there is a substantial heterogeneity among adult indi-

viduals of the same age. If plaque burden were an accurate estimate of risk in older subjects, it could be substituted for age in risk calculations as suggested by Grundy (6). In this prospective observational study, we estimated rates of all-cause death in 35,383 patients referred by primary care physicians for CAC screening. Among these, 3,570 were older than 70 years at the time of screening. We estimated the risk of death in 6 age deciles (< 40 to ≥ 80 years) and in various CAC score categories (from < 10 to $> 1,000$) for both men and women.

Methods

Study cohort and data collection. We included 35,388 asymptomatic patients referred by primary care physicians for CAC screening with electron beam tomography (EBT) in 2 U.S. cities (Nashville, Tennessee, and Torrance, California). Patients with known or suspected coronary artery disease were excluded. At CAC screening, all subjects provided informed consent to the use of their blinded data for research purposes, and further authorization was obtained from the institutional internal review boards. A detailed questionnaire was collected at the time of EBT scanning with the help of a nurse or a research coordinator.

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**Abbreviations
and Acronyms**

CAC = coronary artery calcium
CI = confidence interval
EBT = electron beam tomography
FRS = Framingham risk score
HR = hazard ratio

Risk factors were recorded as categorical variables in all patients. Diabetes was defined as treatment with hypoglycemic agents or insulin, fasting glucose >126 mg/dl or known but untreated hyperglycemia. Hypertension was defined as blood pressure >140/90 mm Hg or treatment with antihypertensive agents. A history of smoking was considered present if patients currently smoked or smoked until 6

months before the study. Hypercholesterolemia was defined as treatment with lipid-lowering drugs, known dyslipidemia not treated with medications, or fasting total cholesterol >200 mg/dl. A positive family history included a first-degree relative who had a major cardiovascular event before age 55 years in men or 65 years in women.

EBT imaging. We performed EBT scans with a C-150 scanner (Imatron, San Francisco, California). About 40 contiguous, 3-mm thick tomographic slices were obtained between the carina and the diaphragm. Exposure time was 100 ms/slice, and the total radiation dose was 0.6 mSv. The CAC score was calculated according to the Agatston method (7).

Mortality ascertainment. Patients were followed for a mean of 5.8 ± 3 years (median 5.0 years, interquartile range: 3.8 to 6.8 years) after CAC screening. The occurrence of all-cause death was verified via the National Death Index. Follow-up was completed in 100% of patients. In total 838 deaths were recorded, 320 in women and 518 in men.

Statistical methods. Categorical variables were compared with the chi-square test. The mean (standard deviation) number of risk factors was compared across age deciles with the analysis of variance techniques. Univariable and multivariable Cox proportional hazards survival models were calculated,

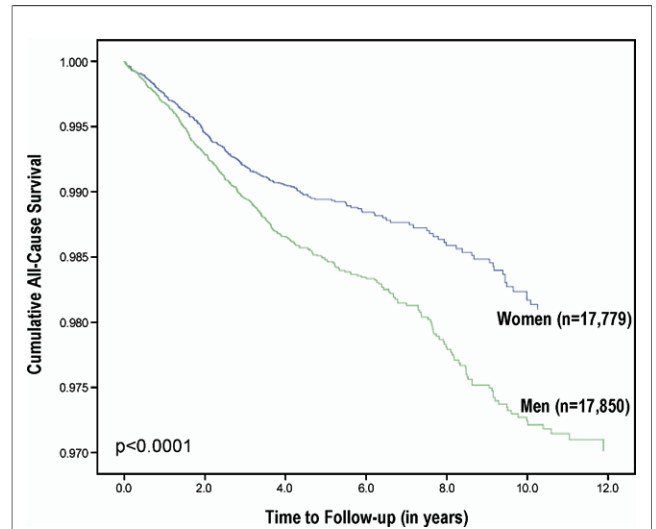


Figure 1 Unadjusted Survival by Gender

including hazard ratios (HRs) and 95% confidence intervals (CIs) for time to all-cause mortality. From the multivariable models, risk-adjusted survival rates were calculated. We calculated annual mortality rates by dividing the predicted mortality by total follow-up time (in years). Separate Cox models for CAC scores were devised for each age decile. Within each age decile multivariable model, a gender by CAC first-order test for interaction was calculated. Finally, a comparison of risk reclassification was performed with a categorical comparison of the Framingham risk score (FRS) groups by CAC scores <math>< 400</math> and

Table 1 Clinical Characteristics of the Study Cohort (N = 35,383)

	Age (yrs)						p Value
	<40	40-49	50-59	60-69	70-79	≥ 80	
n	2,571	9,319	12,478	7,449	3,122	448	
Women	50%	52%	51%	47%	46%	47%	<0.0001
Family history of coronary artery disease	42%	41%	41%	38%	38%	34%	<0.0001
Smoking	15%	16%	16%	14%	12%	5%	<0.0001
Diabetes mellitus	2%	3%	5%	7%	10%	10%	<0.0001
Hypertension	24%	30%	36%	42%	46%	46%	<0.0001
Hyperlipidemia	22%	28%	32%	34%	35%	31%	<0.0001
Number of risk factors	0.9 ± 1	1.0 ± 1	1.1 ± 1	1.3 ± 1	1.6 ± 1	1.6 ± 1	<0.0001
Percent with ≥ 3 risk factors	11%	15%	17%	21%	31%	29%	<0.0001
Prevalence of calcium score							<0.0001
<10	90%	76%	58%	40%	25%	16%	
11-100	8%	16%	22%	24%	21%	16%	
101-400	1.4%	6%	13%	20%	25%	24%	
01-1,000	0.4%	2%	5%	10%	16%	18%	
>1,000	0.2%	0.4%	2%	6%	13%	27%	

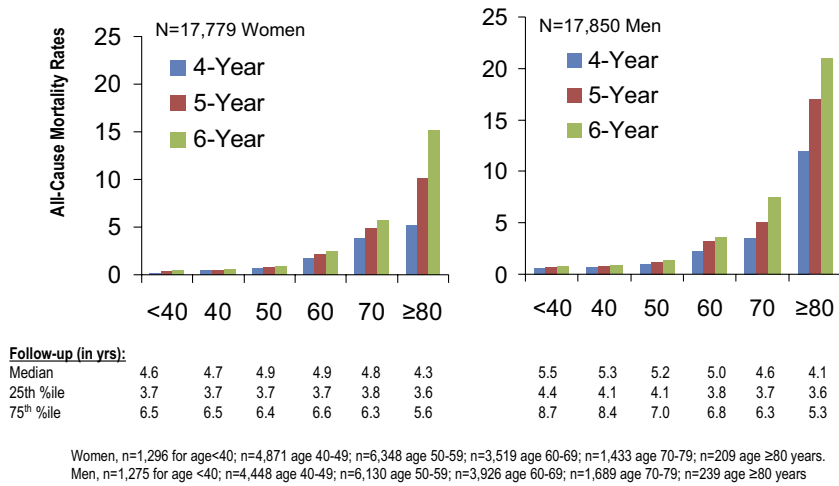


Figure 2 Gender-Specific Mortality Rates

Unadjusted all-cause mortality rates by gender and age deciles at 4 to 6 years of follow-up.

Results

Clinical characteristics of study patients. The patients' characteristics are shown in Table 1; at screening, 3,570 patients were ≥70 years old. Older patients had a greater risk factor burden, except for smoking. The average number of risk factors was 1.6 for patients age ≥70 years and 0.9 for those age <40 years (p < 0.0001).

Cumulative survival and survival according to calcium score. Overall survival was 97.9% but varied by gender (98.2% for women; 97.1% for men, p < 0.0001) (Fig. 1). The relative hazard was increased for older patients and men. Overall mortality increased with each age decile (HR: 1.09, 95% CI: 1.08 to 1.10, p < 0.0001) (Fig. 2).

Mortality rates were greater for men than women (HR: 1.53, 95% CI: 1.32 to 1.77, p < 0.0001).

Cumulative survival for CAC subsets varied by age (Fig. 3). In men, CAC scores from 0 to 10 were associated with risk-adjusted survival rates from 99.7% to 96.8% for those age <40 to ≥80 years (p < 0.0001). For women, the corresponding rates were 99.8% and 98.1%, respectively (p < 0.0001). Cumulative unadjusted survival of <40- and ≥80-year-old men with a calcium score ≥400 was 88% and 19%, respectively. By comparison, the survival of <40- and ≥80-year-old women with a calcium score ≥400 was 95% and 44%, respectively (p < 0.0001).

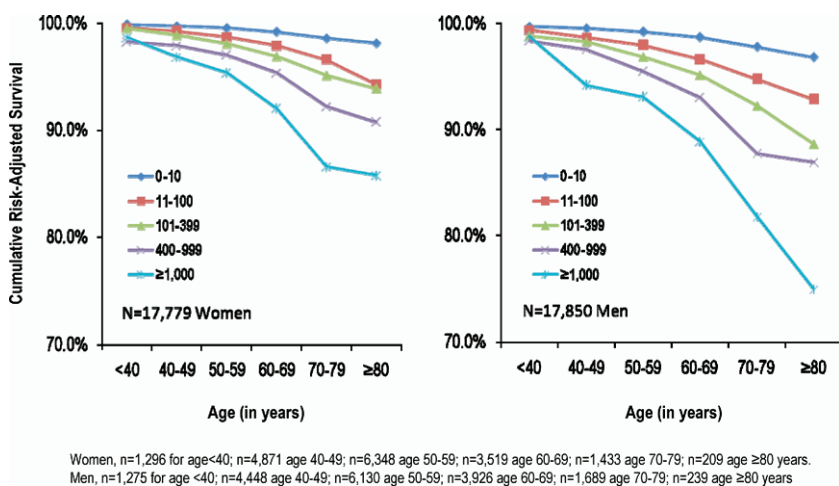


Figure 3 Gender-Specific Survival According to Calcium Score

Risk-adjusted survival by coronary artery calcium across age deciles in women and men.

Table 2	Risk-Adjusted Hazard Ratios (95% Confidence Intervals) for Death According to CAC Scores Within Separate Models by Age Decile		
	CAC 11 to 100	CAC 101 to 400	CAC >400
Age <40 yrs	0.71 (0.09-5.47) p = 0.75	11.20 (3.16-36.66) p < 0.0001	13.11 (2.68-64.22) p = 0.002
Age 40-49 yrs	2.81 (1.40-5.67) p = 0.004	5.91 (2.74-12.72) p < 0.0001	14.73 (6.75-32.17) p < 0.0001
Age 50-59 yrs	2.60 (1.68-4.02) p < 0.0001	2.67 (1.64-4.35) p < 0.0001	7.81 (5.02-12.15) p < 0.0001
Age 60-69 yrs	2.58 (1.65-4.04) p < 0.0001	3.95 (2.57-6.07) p < 0.0001	7.86 (5.21-11.87) p < 0.0001
Age 70-79 yrs	2.94 (1.64-5.27) p < 0.0001	3.92 (2.26-6.80) p < 0.0001	6.19 (3.64-10.51) p < 0.0001
Age ≥80 yrs	6.26 (1.39-28.30) p = 0.017	5.32 (1.20-23.49) p = 0.028	11.71 (2.83-48.46) p = 0.001

Hazard ratios compared with coronary artery calcium (CAC) scores from 0 to 10.

For men with CAC scores $\geq 1,000$, risk-adjusted survival ranged from 98.8% to 74.9% for those <40 to ≥ 80 years ($p < 0.0001$). Corresponding survival rates for women ranged from 98.6% to 85.8% ($p < 0.0001$).

Table 2 details the risk-adjusted HRs by CAC score subsets compared with CAC scores from 0 to 10, in separate multivariable models within each age decile. For patients <40 years old with CAC scores >400, the relative hazards were 13-fold greater than with scores from 0 to 10 ($p < 0.0001$). The HRs for CAC scores >400 were also in-

creased in older patients compared with CAC scores of 0 to 10, although merely 2-fold.

Table 3 shows the risk factor-adjusted HRs from an interaction of age by gender. For patients age <40 years, HRs were elevated from 2- to 44-fold for men versus women ($p < 0.0001$) in low to high calcium scores. Hazard ratios difference between men and women were attenuated with increasing age.

For the 20,562 patients without CAC, annual mortality rates ranged from 0.3% for those ages 40 to 49 years to 2.2% for those ≥ 70 years ($p < 0.0001$) (Fig. 4). The resulting HRs were elevated 4.13-fold (95% CI: 1.71 to 9.97, $p < 0.0001$) for those age ≥ 70 years ($p < 0.0001$).

Reclassification of risk. Figure 5 shows the proportion of patients that could be reclassified based on a CAC score ≥ 400 . The proportion ranged from 14.1% to 43.1% among women and 9.0% to 45.2% among men ($p < 0.0001$). The majority of patients reclassified had CAC <400 with a high FRS. Among women and men with >3 risk factors, 66.6% and 75% had CAC scores <400, respectively. Among women with 0 to 2 risk factors, 2.7% age <40 years were reclassified as opposed to 61.5% and 30.5% of those age 70 to 79 and >80 years. For men, the respective proportions were 4.3%, 43.9%, and 28.8% ($p < 0.0001$ for both

Table 3	Risk-Adjusted Hazard Ratios (95% Confidence Intervals) From an Interaction of Gender by CAC Score in Age Decile Subsets		
	Hazard Ratio	95% Confidence Interval	p Value
Age <40 yrs			<0.0001
CAC score			
11-100	1.94	0.26-14.78	0.52
101-399	11.60	2.61-51.47	0.001
≥ 400	44.00	5.22-370.92	0.001
Age 40-49 yrs			<0.0001
CAC score			
11-100	2.56	1.13-5.81	0.025
101-399	8.86	3.89-20.22	<0.0001
≥ 400	22.19	9.55-51.54	<0.0001
Age 50-59 yrs			<0.0001
CAC score			
11-100	2.10	1.31-3.35	0.002
101-399	2.04	1.19-3.49	0.01
≥ 400	6.58	4.24-10.21	<0.0001
Age 60-69 yrs			<0.0001
CAC score			
11-100	1.93	1.30-2.86	0.001
101-399	3.00	2.11-4.25	<0.0001
≥ 400	5.10	3.68-7.06	<0.0001
Age 70-79 yrs			<0.0001
CAC score			
11-100	1.52	0.96-2.40	0.075
101-399	1.69	1.12-2.54	0.012
≥ 400	3.04	2.20-4.21	<0.0001
Age ≥ 80 yrs			<0.0001
CAC score			
11-100	1.71	0.70-4.16	0.24
101-399	1.03	0.45-2.38	0.94
≥ 400	3.21	1.94-5.32	<0.0001

CAC = coronary artery calcium.

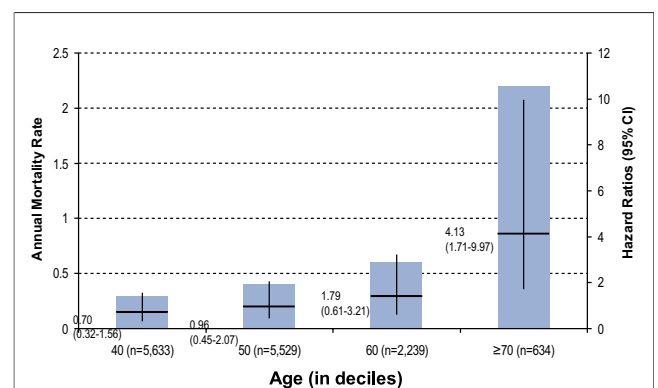
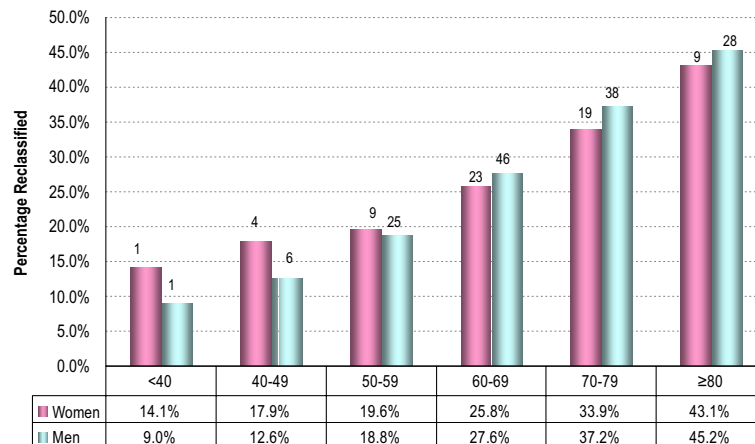


Figure 4 Risk of Death Without CAC

Annual mortality (left y-axis) in patients without CAC by age decile including hazard ratios (95% CIs; right y-axis) compared with patients <40 years. The hazard ratios are shown next to the bar graphs. CAC = coronary artery calcium; CI = confidence interval.



% Reclassified to Lower Risk Group							
Women	97.2%	93.3%	76.0%	58.9%	49.0%	27.8%	
Men	96.7%	89.7%	72.9%	55.1%	56.2%	30.8%	
% Reclassified to Higher Risk Group							
Women	2.8%	6.7%	24.0%	41.1%	51.0%	72.2%	
Men	3.3%	10.3%	27.1%	44.9%	3.8%	69.2%	

Figure 5 Reclassification of Risk With the Use of Coronary Calcium Scoring

Percentage of patients reclassified based on coronary artery calcium (CAC) <400 or ≥400 (p < 0.0001 for women and men) beyond the Framingham risk score (FRS). With a high FRS, patients were reclassified if CAC <400. With a low-intermediate FRS, patients were reclassified if CAC ≥400. The numbers at the top of each column indicate the number of deaths identified beyond those defined by the FRS in each patient subset.

genders). Finally, Table 4 demonstrates the cost to identify one new high-risk case (CAC ≥400) and 1 death among low-intermediate risk patients. The cost decreases for older age groups compared with younger ones.

Discussion

The use of CAC is considered to be an age-dependent phenomenon, and most studies on CAC screening have not included the elderly. Our data show that the use of CAC has prognostic utility even in the elderly, and those patients without CAC have a good outcome compared with high CAC. Several elderly patients had no CAC and 56% with >3 risk factors had CAC <400; hence, they could be

reclassified to a lower risk status. For younger patients, the relative risk ratios revealed a wide gradient between those with and without CAC, likely because of the fact that baseline risk and comorbidities affect risk in different ways in the young and the elderly. Young patients without CAC are at very low risk. However, among these patients, high-risk CAC scores occur in subjects with considerable comorbidity, perhaps as the result of referral bias, with a resultant greater relative risk of death. Conversely, most of our elderly patients had some degree of comorbidity and risk factor burden, thus increasing their mortality risk.

It is currently challenging to identify asymptomatic elderly subjects at greater risk. The FRS (8) and European SCORE (Systemic COronary Risk Evaluation) (9) have an

Table 4 Cost Analysis to Identify 1 New High-Risk Case and 1 Death Among Low-Intermediate Risk Patients

Age Decile, yrs	Cost to Identify 1 New High-Risk Patient With CAC ≥400		Cost to Identify 1 Death in a High-Risk Patient With CAC ≥400	
	Women	Men	Women	Men
30-39	\$22,260 (0.4%)	\$23,280 (0.4%)	\$111,300 (0.1%)	\$116,400 (0.1%)
40-49	\$6,354 (1.6%)	\$6,774 (1.5%)	\$133,433 (0.1%)	\$65,483 (0.2%)
50-59	\$1,736 (5.8%)	\$1,667 (6.0%)	\$57,856 (0.2%)	\$20,872 (0.5%)
60-69	\$743 (13.5%)	\$752 (13.3%)	\$12,022 (0.8%)	\$6,702 (1.5%)
70-79	\$405 (24.7%)	\$412 (24.3%)	\$5,332 (1.9%)	\$2,995 (3.3%)
≥80	\$247 (40.5%)	\$248 (40.4%)	\$1,700 (5.9%)	\$593 (16.9%)

For the left 2 columns, the percentage in parentheses indicates the proportion of high-risk patients with a coronary artery calcium (CAC) score ≥400. For the right 2 columns, the percentage in parentheses indicates the death rate for high-risk patients with CAC ≥400.

upper age limit, and the predictive power of traditional risk factors diminishes with advancing age (10,11). Furthermore, the uniform weight attributed to age in risk algorithms does not take into consideration the heterogeneity of adult populations, which may induce risk miscalculation and lead to inaccurate therapeutic elections. The use of atherosclerosis imaging may help improve risk assessment in the elderly.

Grundy (6) suggested that age be corrected for the burden of atherosclerosis found on noninvasive imaging. Similarly, discussants at the Prevention-V Conference suggested the integration of CAC scoring with traditional risk factors to improve global risk prediction (12). However, the current evidence on CAC scoring in the elderly is limited. Vliegenthart et al. (13) recruited 1,795 asymptomatic patients, with a mean age of 71 years, and recorded 88 cardiovascular events during a mean follow-up period of 3.3 years. They reported a graded and statistically significant risk of events with increasing CAC scores in individuals <69 years or >70 years. The risk of cardiovascular events was very low in patients with CAC = 0 to 100 and increased 8.2-fold (95% CI: 3.3 to 20.5) in patients with CAC >1,000.

Abbott et al. (14) reported on 224 very old (ages 84 to 96 years) Japanese men living in Hawaii. A total of 17 deaths occurred during 2.5 years of follow-up but none in patients with a CAC <10. As in the previous study (13), the death rate increased significantly as the CAC score increased ($p < 0.001$). Newman et al. (15) followed 559 patients (336 women) ages 70 to 99 years for 5 years. They reported that both CAC and carotid intima-media thickness are accurate predictors of cardiovascular events and death. The top quartile of each measurement was associated with ~2-fold increased risk of events. Limitations of these previous studies included a small total number of events, enrollment of very elderly men (14), and the lack of a comparison of risk between young and older people (14,15).

On the contrary, we followed a large number of patients of all ages ($n = 3,560$ >70 years, 50% women), and recorded numerous deaths. Because risk factors lose prediction power with advancing age, and the absence of CAC matches a low risk, it may be appropriate to mitigate prevention efforts in elderly patients with no evidence of subclinical atherosclerosis. In Western nations, the elderly are the most rapidly growing segment of the population, imposing increasing cost of care; hence, the need to focus resources on truly necessary interventions exists.

Study limitations. There were a few limitations to this study: we collected only categorical risk factors, and obtained information on vital status alone; the latter may have reduced the predictive ability of CAC for cardiovascular events. Nonetheless, all-cause death is not affected by verification bias as other end points are (16), and most deaths in adults are primarily linked to cardiovascular diseases.

Conclusions

We conclude that the use of CAC scoring is an effective risk stratification tool in the elderly as well as young patients, rendering CAC of potential utility even in high-risk patients such as those with diabetes (17), those with renal failure (18), those who smoke (5) and, now, the elderly. The use CAC screening in the elderly may allow the implementation of new risk scoring methods as proposed by Grundy (6), where the burden of atherosclerosis is substituted for age (19). It may not be ethical to design studies to assess whether the absence of CAC allows withholding preventive therapies in elderly patients with risk factors. However, the low risk associated with the absence of CAC, and the relative cost utility of the method, could encourage some physicians to mitigate the intensity of primary prevention in the elderly even in the absence of strong prospective evidence.

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- Key Words:** coronary calcium ■ prognosis ■ elderly ■ gender ■ mortality.