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Long-Term Prognosis After Coronary Artery Calcium Scoring Among Low-Intermediate Risk Women and Men

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Background—Cardiovascular screening of women using traditional risk factors has been challenging, with results often classifying a majority of women as lower risk than men. The aim of this report was to determine the long-term prognosis of asymptomatic women and men classified at low-intermediate risk undergoing screening with coronary artery calcium (CAC) scoring.

Methods and Results—A total of 2363 asymptomatic women and men with traditional risk factors aggregating into a low-intermediate Framingham risk score (6%–9.9%; 10-year predicted risk) underwent CAC scanning. Individuals were followed up for a median of 14.6 years. We estimated all-cause mortality using Cox proportional hazards models; hazard ratios with 95% confidence intervals were calculated. The area under the curve from a receiver operating characteristics curve analysis was calculated. There were 1072 women who were older (55.6 years) when compared with the 1291 men (46.7 years; $P<0.0001$), resulting in a greater prevalence and extent of CAC; 18.8% of women and 15.1% of men had a CAC score ≥ 100 ($P=0.029$). This older group of women had a 1.44-fold higher 15-year adjusted mortality hazard when compared with men ($P=0.022$). For women, the 15-year mortality ranged from 5.0% for those with a CAC score of 0 to 23.5% for those with a CAC score ≥ 400 ($P<0.001$). For men, the 15-year mortality ranged from 3.5% for those with a CAC score of 0 to 18.0% for those with a CAC score ≥ 400 ($P<0.001$). Women with CAC scores >10 had a higher mortality risk when compared with men.

Conclusions—Our findings extend previous work that CAC effectively identifies high-risk women with a low-intermediate risk factor burden. These data require validation in external cohorts but lend credence to the use of CAC in women to improve risk detection algorithms that are currently based on traditional risk factors. (*Circ Cardiovasc Imaging*. 2016;9:e003742. DOI: 10.1161/CIRCIMAGING.115.003742.)

Key Words: diagnosis ■ prognosis ■ proportional hazards models ■ risk factors ■ ROC curve

A wealth of evidence documents significant sex differences in the prevalence and prognostic use of traditional risk factors.¹ Studies have shown that global risk scores often categorize women as lower risk than men and even updated risk calculators overestimate clinical outcome burden in women when compared with men.^{2–6} Coupled with the persistently higher case fatality rate for women, these data continue to support markers of subclinical atherosclerosis as offering promise for the improved detection of at-risk women. Coronary artery calcium (CAC) is a subcomponent of atherosclerotic plaque, and its extent, as measured using the Agatston score, provides imaging evidence of the disease burden within the epicardial coronary arteries.

See Article by Gulati See Clinical Perspective

In women, CAC scoring has repeatedly been reported to effectively risk stratify women and men, largely including those with an intermediate Framingham risk score (FRS).^{7–9} Given the limitations in the use of global risk scores among women, some have proposed expanding the inclusion criteria for women to those lower risk with an estimated 10-year risk of 6% to 9.9%.¹⁰ Thus, the goal of the current analysis was to determine long-term prognostic use of CAC in a cohort of 2363 asymptomatic women and men with a low-intermediate FRS (10-year predicted risk of coronary heart disease between 6% and 9.9%).

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Methods

Study Population

From 1996 to 1999, a total of 9715 patients were referred to CAC scanning. All patients did not have a previous coronary artery disease (CAD) diagnosis or symptoms suggestive of CAD. Of this group, a subset analysis of 2363 had a calculated low-intermediate FRS (10-year risk of coronary heart disease, 6%–9.9%). All individuals were clinically referred by their physicians for CAD screening evaluation using CAC scoring. Previous reports from this registry have been published.^{11,12} All individuals provided informed consent for participation in this registry. Deidentified data were sent to Emory University School of Medicine, Weill Cornell Medical College, and Cedars-Sinai Medical Center for analysis; institutional review board approval was garnered for data analysis at each of these institutions. Details of this registry have previously been published.^{13,14}

Our subset analysis included asymptomatic women and men with an FRS with expected 10-year risk from 6% to 9.9%. We identified this subset because of the abundant evidence on the effectiveness of risk stratification in those individuals with an intermediate FRS and the data reporting poor discrimination of risk among women.^{6,10}

Cardiac Risk Factor Collection

Baseline traditional risk factors were obtained in the study participants. Categorical risk factor data were collected and include the following: (1) dyslipidemia was considered present for individuals reporting a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, or current use of lipid-lowering therapy; (2) hypertension was considered present if one self-reported a history of high blood pressure or the use of antihypertensive medication; (3) cigarette smoking was considered present if the subject was an active smoker at the time of scanning; (4) diabetes mellitus was considered present for those individuals with a baseline use of antidiabetic medication or a history of elevated blood glucose measurement of >126 mg/dL; and (5) family history of premature CAD was present if individuals stated that they had an immediate family member with a history of CAD in a male relative <55 years or a female relative <65 years. An estimated FRS was calculated at the Cedars-Sinai Medical Center by 1 coinvestigator (H.G.) using the coefficients in the report by Wilson et al¹ and as previously reported.^{11,14}

CAC Screening Protocol

Individuals underwent electron beam or multislice computed tomography using standardized procedures as previously detailed.^{13,14} A CAC score was calculated using the methods described by Agatston et al.¹⁵ CAC scores were categorized as 0, 1 to 10, 11 to 99, 100 to 399, and ≥400.

Study Outcome

The primary end point of this study was time to all-cause mortality. Mortality status was conducted by querying the National Death Index. Follow-up status was ascertained through May 2014, and average follow-up for surviving patients was 14.6 (range, 12.9–16.8) years.

Statistical Analysis

We compared women and men by categorical risk factors using a χ^2 statistic. A Mantel–Haenszel test of trend χ^2 statistic was used to compare sex by age decile subsets. Age was compared in women and men using ANOVA techniques. From this analysis, the mean and 95% confidence intervals of age were calculated for women and men. The primary aim of this analysis was time to death from all causes. We estimated time to all-cause mortality using univariable and multivariable Cox proportional hazards models. The Harrell *C* statistic was calculated for each model. A total of 159 deaths were reported in our cohort, including 86 deaths in women and 73 deaths in men. A stratified Cox survival analysis was used to plot time to all-cause mortality by sex across CAC score strata. Diabetes mellitus was not excluded from this patient subset as it was not a significant predictor of mortality ($P=0.07$). From the univariable and multivariable models, we calculated the hazard ratios and 95% confidence intervals. A first-order interaction of sex by CAC scores was calculated. Separate Cox models were also used for women and men, and a separate Cox model was used for patients aged <55 and ≥55 years. Among those aged <55 years, a further stratified analysis was performed among smokers and nonsmokers. Model overfitting procedures were considered, which allowed us to include ≤16 degrees of freedom in the multivariable models. The proportional hazards assumption was met for all Cox models. For each of the models, goodness of fit statistics were not statistically significant. Moreover, we calculated the net reclassification improvement of a model, including cardiac risk factors and the added contribution of CAC to a second model using the methods described by Pencina et al¹⁶ for time to death.

Results

Prevalence of Traditional Risk Factors and CAC in Asymptomatic Women and Men With Low-Intermediate FRS

In our patient subset, low-intermediate risk women were nearly a decade older than their male counterparts (55.6 versus 46.7 years; $P<0.0001$). In this subset, 14% of women as compared to no men were ≥70 years old. In general, traditional cardiac risk factors were more prevalent in women, including more hypertension, smoking, and a family history of CAD. With

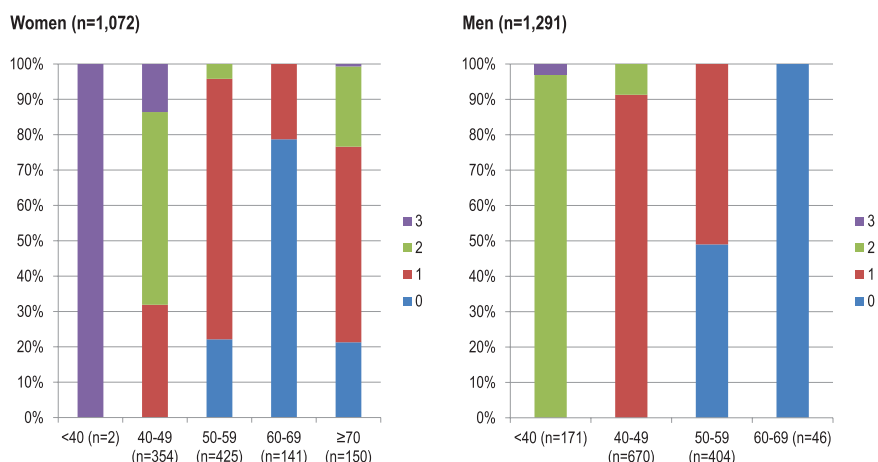


Figure 1. Proportion of asymptomatic women and men classified with a Framingham risk score from 6% to 9.9% based on their age and number of modifiable risk factors (including hypertension, diabetes mellitus, smoking, and dyslipidemia).

Table 1. Prevalence of Traditional Risk Factors and CAC Score Strata Among Women and Men With a Low-Intermediate Estimated Framingham Risk Score

	Women (n=1072)	Men (n=1291)	P Value
Age, mean (95% CI)	55.6 (55.0–56.2)	46.7 (46.4–47.1)	<0.001
Age (by deciles), %			
<40 (n=173)	0.2	13.2	<0.001
40–49 (n=1024)	33.0	51.9	
50–59 (n=829)	39.6	31.3	
60–69 (n=187)	13.2	3.6	
≥70 (n=150)	14.0	0.0	
Hypertension (n=648), %	34.0	21.9	<0.001
Dyslipidemia (n=1082)	42.6	48.4	0.005
Diabetes mellitus (n=73)	3.6	2.5	0.141
Current smoker (n=660)	31.1	25.3	0.002
Family history of CAD (n=1586)	68.3	66.2	0.272
CAC scores, %			
0 (n=1333)	54.7	57.9	0.029
1–10 (n=209)	8.6	9.1	
11–99 (n=425)	18.0	18.0	
100–399 (n=264)	12.5	10.1	
≥400 (n=132)	6.3	5.0	

CAC indicates coronary artery calcium; CAD, coronary artery disease; and CI, confidence interval.

exception, men were more likely to be dyslipidemic when compared with women ($P=0.005$). Younger women and men were more likely to be referred with multiple modifying risk factors (Figure 1; Table 1).

Likely the result of an advanced age in women, more extensive CAC was observed in women when compared with men ($P=0.029$). CAC scores ≥ 100 occurred in 18.8% of women and 15.1% of men.

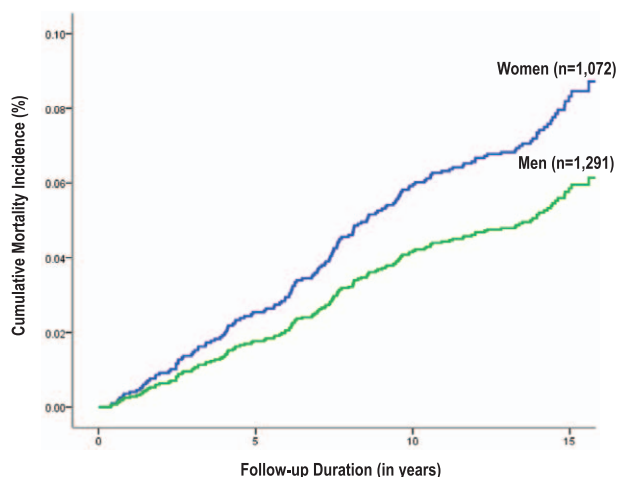


Figure 2. Cumulative all-cause mortality in women and men with low-intermediate Framingham risk scores.

Estimating Long-Term 15-Year Mortality in Women Versus Men

Figure 2 plots overall 15-year mortality in women versus men. Cumulative mortality was 8.8% for women and 6.0% for men ($P<0.0001$). Even in adjusted Cox models, women had a 1.44 higher relative hazard for death when compared with men ($P=0.022$).

Fifteen-Year All-Cause Mortality Rates by CAC Scores in Women and Men

For women, CAC scores had 15-year mortality ranging from 5.0% for CAC score of 0 to 23.5% for a CAC score ≥ 400 (Figure 3; $P<0.001$). For men, CAC scores had 15-year mortality ranging from 3.5% for CAC score of 0 to 18.0% for a CAC score ≥ 400 ($P<0.001$).

Multivariable Risk Models in Women and Men

In separate models, CAC was a significant correlate of long-term mortality in women and men. In risk factor-adjusted models, the relative hazard for death ranged from 1.9 to 6.5 for women with CAC scores from 1 to 10 to ≥ 400 ($P<0.0001$). Among women, based on a stepwise Cox model, CAC scores were the single greatest correlate of long-term mortality followed by age, hypertension, and smoking. By comparison, for men, the hazard ratios were 1.7, 2.9, 4.1, and 2.7, respectively, for CAC scores of 1 to 10, 11 to 99, 100 to 399, and ≥ 400 ($P<0.0001$). Among men, based on a stepwise Cox model, CAC scores were the single greatest correlate of long-term mortality followed by smoking (Table 2). The Harrell *C* statistic for the individual models for risk factors alone and for models, including risk factors with the CAC scores, is reported in Table 3 for women and men. The models containing risk factors plus CAC scores have a higher Harrell *C* statistic for women and men.

Net Reclassification Improvement Statistics

The net reclassification improvement for women was 0.155 ($P=0.002$) and 0.094 for men ($P=0.03$). Of the female survivors, 93 and 33 women were correctly and incorrectly reclassified to a lower risk patient subset based on CAC findings, with a total of 6.2% correct reclassification of low-risk women. This may be compared with only 3.9% of men correctly reclassified as low risk based on CAC findings. There was a similar pattern of a higher percent correct reclassification of high-risk women when compared with men although the numbers (in general) were small (Figure 4A and 4B).

Discussion

Considerable focus has been placed on the evaluation of sex-specific differences in case fatality rates and in the overall burden of cardiovascular disease among women and men.^{17,18} Data have been conflicting as to whether women are at an elevated risk or whether they are at lower risk when compared with their male counterparts. In many cases, age and other comorbidities accentuate sex-specific risk differences.^{17,18} Yet, for most of the global risk scores, the ability to precisely and reliably categorize risk in women has often been suboptimal when compared with men.⁵ Even for the updated risk calculators, the ability to

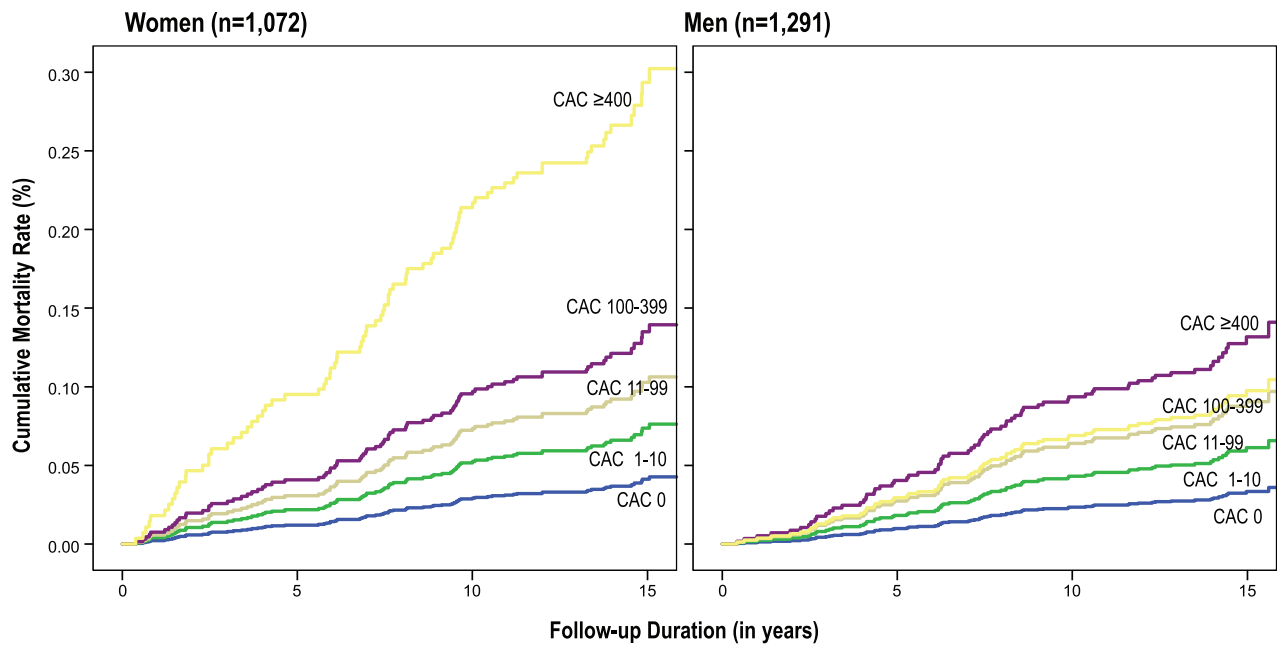


Figure 3. Cumulative 15-year mortality rate among women and men with low-intermediate Framingham risk scores based on coronary artery calcium (CAC) scores.

estimate risk in women is far from optimal. In 1 recent report from the Women’s Health Study, the predicted event rates from the risk calculator overestimated event rates by 1.4- to 1.9-fold when compared with the observed event data.⁶ It seems that integration of global risk based on risk factors is consistently subpar for women when compared with men.¹⁰

This finding that risk calculators perform poorly in women is problematic as they form the basis for guideline-directed preventive treatment. Moreover, although medical treatment is recommended for higher risk patients, there remains a sizeable

proportion of the population with borderline risk scores at an elevated but not intermediate risk who may benefit from guided lifestyle changes to improve their long-term outlook. The lack of precision of risk calculators in women and the importance of lifestyle alterations in improving risk factor control remain an important goal for at-risk patients with an FRS or other global score insufficient to warrant medical management. Accordingly, our evaluation of the effectiveness of risk stratification in women with a low-intermediate FRS has relevance to guide the selection of those likely to benefit

Table 2. Cox Proportional Hazards Models Estimating 15-Year Mortality By CAC Scores in Women and Men With a Low-Intermediate Framingham Risk Score

	Women (n=1072)		Men (n=1291)	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Univariable model				
CAC score		<0.001		<0.001
1–10	1.82 (0.78–4.23)	0.16	1.86 (0.80–4.31)	0.15
11–99	2.58 (1.41–4.71)	0.002	2.79 (1.54–5.05)	0.001
100–399	3.44 (1.85–6.43)	<0.001	4.15 (2.20–7.82)	<0.001
≥400	8.26 (4.51–15.13)	<0.001	3.02 (1.23–7.32)	0.016
Multivariable model*				
CAC score		<0.001		<0.001
1–10	1.92 (0.82–4.47)	0.13	1.73 (0.74–4.02)	0.21
11–99	2.37 (1.29–4.35)	0.005	2.88 (1.59–5.23)	<0.001
100–399	2.99 (1.60–5.60)	0.001	4.10 (2.17–7.74)	<0.001
≥400	6.53 (3.50–12.21)	<0.001	2.71 (1.10–6.69)	0.031

CAC indicates coronary artery calcium; and CI, confidence interval.

*Covariates in the multivariable model include age, family history of coronary artery disease and modifying risk factors, including hypertension, dyslipidemia, smoking, and diabetes mellitus.

Table 3. Harrell C Statistic for Prognostic Models, Including Risk Factors Alone, and for Risk Factors Plus CAC Scores, As Reported for Women and Men

	Risk Factors Alone	Plus CAC Scores
Women	0.68	0.73
	Model $X^2=47$	Model $X^2=79$
	$P<0.0001$	$P<0.0001$
Men	0.63	0.70
	Model $X^2=20$	Model $X^2=38$
	$P=0.01$	$P<0.0001$

CAC indicates coronary artery calcium.

from exercise and dietary recommendations toward improved risk factor control. Our results revealed that CAC was highly effective at risk stratifying this subset of women. In particular, among women aged ≥ 55 years, CAC scores >10 were associated with a higher relative hazard for death when compared with men. These data were surprising, but they may reflect

the under appreciation of global risk for these older women. Moreover, it may also be noted that our lengthy follow-up may have unearthed findings that would not have been reported for shorter term (more typical) follow-up of 3 to 5 years.^{13,19}

Long-Term Outcomes and Older-Aged Women

Importantly, our women were nearly a decade older than their male counterparts despite having a similar low-intermediate FRS. This older age certainly would precipitate the greater mortality risk and association with CAC scores in women when compared with men. But it remains important to note that in population cohorts, global risk scores calculate as many as $\geq 90\%$ of women to lower risk categories.²⁰ Thus, if global risk scores are the foundation of preventive care, then caveats of age and the burden of subclinical atherosclerosis should play a prominent role in understanding (particularly) long-term risk among women and men. We think that our longer duration of follow-up of 15 years approximates previous reports that have provided lifetime risk estimates.²¹⁻²³

A Women:

NRI: 0.155 (p=0.0022)
 6.2% Improved Detection of Low Risk
 9.3% Improved Detection of High Risk

Model with Risk Factors + CAC

Model with Risk Factors	<5.0%	5.0%-12.4%	$\geq 12.5\%$	Column (%)
Nonevents (n=986)				
<7.5%	325 (33.0%)	15 (1.5%)	2 (0.2%)	34.7%
5.0% - 12.4%	60 (6.1%)	462 (46.9%)	15 (1.5%)	54.5%
$\geq 12.5\%$	0 (0%)	33 (3.3%)	74 (7.5%)	10.9%
Row total (%)	39.0%	51.7%	9.2%	
Events (n=86)				
<5.0%	11 (12.8%)	1 (1.2%)	1 (1.2%)	31.5%
5.0%-12.4%	2 (2.3%)	34 (39.5%)	11 (12.8%)	20.5%
$\geq 12.5\%$	0 (0.0%)	3 (3.5%)	23 (26.7%)	1.4%
Row (%)	15.1%	44.2%	40.7%	

B Men:

NRI: 0.094 (p=0.033)
 3.9% Improved Detection of Low Risk
 5.5% Improved Detection of High Risk

Model with Risk Factors + CAC

Model with Risk Factors	<5.0%	5.0%-12.4%	$\geq 12.5\%$	Column (%)
Nonevents (n=1,218)				
<7.5%	620 (50.9%)	18 (1.5%)	1 (0.1%)	52.5%
5.0% - 12.4%	81 (6.7%)	463 (38.0%)	14 (1.1%)	45.8%
$\geq 12.5\%$	0 (0.0%)	0 (0.0%)	21 (1.7%)	1.7%
Row total (%)	57.6%	39.5%	3.0%	
Events (n=73)				
<5.0%	21 (28.8%)	1 (1.4%)	1 (1.4%)	32.9%
5.0%-12.4%	3 (4.1%)	41 (56.2%)	5 (6.8%)	67.1%
$\geq 12.5\%$	0 (0.0%)	0 (0.0%)	1 (1.4%)	1.4%
Row (%)	32.9%	57.5%	9.6%	

Figure 4. A, Net reclassification improvement (NRI) of coronary artery calcium (CAC) over and above a model containing traditional cardiac risk factors in women with a low-intermediate Framingham risk score (FRS). The groupings applied for our NRI analysis were based on categories of 15-year mortality. **B,** NRI of CAC over and above a model containing traditional cardiac risk factors in men with a low-intermediate FRS. The groupings applied for our NRI analysis were based on categories of 15-year mortality.

Previous Reports on Prognosis by CAC Among Women

Among our cohort of low-intermediate FRS women, CAC scores had 15-year mortality rates ranging from 5.0% for CAC score of 0 to 23.5% for a CAC score ≥ 400 ($P < 0.001$). By comparison, for men, 15-year mortality rates ranged from 3.5% to 18.0% for CAC scores from 0 to ≥ 400 ($P < 0.001$). Interestingly, various CAC scores had a higher mortality risk in women when compared with men. The relative hazards for deaths ranged from 2- to 6-fold higher for women when compared with men with CAC scores > 10 to ≥ 400 . Previous reports from our investigative group have examined the prognostic use of CAC among women over shorter durations of follow-up (≈ 5 years).^{24,25} In general, some exploratory findings report an elevated mortality risk among women with higher risk CAC scores.²⁶ However, from a meta-analysis of 3 studies, including 6,481 women and 13,697 men, a comparative analysis revealed no statistical differences by sex across mild- to high-risk CAC scores ($P = 0.66$).²⁶ Our findings reveal that women who are of less than intermediate risk (and not candidates for CAC screening based on current clinical practice guidelines) have a higher long-term mortality risk. Importantly, CAC findings significantly elevated the relative hazard for 15-year mortality in women when compared with men. These findings from our single-center registry support that women at risk who may benefit from CAC screening include women with a low-intermediate FRS. No randomized trial evidence is available to precisely define treatment options for this lower risk group of women. But we think that the benefit of CAC screening in this lower risk cohort is not for discerning guideline-directed statin therapy but in focusing clinical care toward lifestyle modification and improved adherence to risk factor modifying therapy.

Registry Limitations

We have provided details of registry limitations in previous reports.^{11,12} This report includes data collection and follow-up from a single center with generalizability limited to outpatient centers with similar referral patterns. Our report details a significantly longer duration of follow-up than previous CAC prognostic studies; yet, death from all causes was the lone, primary end point for this registry.¹⁰ Data from other cardiovascular events may have altered our presented findings. Death misclassification is common when cardiovascular causality is determined and is not of concern when evaluating death from all causes.²⁷ Also, the categorical risk factor data set did not include information on blood pressure and glucose, which may have resulted in an overestimation in the value of CAC scoring. The FRS was calculated based on β coefficients in the report by Wilson et al.¹ A new risk calculator has been published to improve detection of minority population subsets, notably black individuals, although validation cohorts have not elicited marked improvement in outcome discrimination for women when compared with previous series applying the FRS.^{6,28}

Conclusions

The primary findings in this report are that CAC may effectively risk stratify women who are slightly lower risk than those conventionally targeted to undergo imaging for screening,

including those with an intermediate FRS. Our cohort represents an at-risk group below the current threshold targeted for statin therapy but whose risk assessment findings represent an opportunity to guide the intensity of lifestyle recommendations. Moreover, given the reduced capacity of global risk scores to accurately and reliably classify risk in women, our findings provide information on an at-risk but with largely an insufficient risk factor burden to warrant statin therapy based on current guidelines.^{29,30} However, our findings are important as they focus on an at-risk cohort, particularly women, whose risk may be under appreciated and further guided by screening with CAC. The long-term follow-up of our cohort provides a unique perspective on the use of CAC in women and men with a low-intermediate FRS. Women have a greater prevalence of CAC, an elevated mortality, and an increased relative hazard for 15-year death when compared with their male counterparts. These findings of an elevated mortality for women when compared with men with a CAC score > 10 were noteworthy and add to the evidence that CAC is a valuable adjunct for selected screening of patient cohorts where global risk scores may fall short of optimal detection of risk among women.

Disclosures

None.

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CLINICAL PERSPECTIVE

The use of coronary artery calcium screening has repeatedly been reported to effectively risk stratify women and men, including those with an intermediate Framingham risk score (FRS). Given the limitations of the use of global risk scores among women, some have proposed expanding the inclusion criteria for women to those at lower risk with an estimated 10-year risk of 6% to 9.9%. The goal of the current analysis was to determine the long-term prognostic use of coronary artery calcium in a cohort of 2363 asymptomatic women and men with a low-intermediate FRS (10-year predicted risk of coronary heart disease between 6% and 9.9%). Our findings extend previous work that coronary artery calcium effectively identifies high-risk women with a low-intermediate risk factor burden. These data require validation in external cohorts but lend credence to the use of coronary artery calcium in women to improve risk detection algorithms that are currently based on traditional risk factors.

Long-Term Prognosis After Coronary Artery Calcium Scoring Among Low-Intermediate Risk Women and Men

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