Cardiovascular Lifetime Risk Predicts Incidence of Coronary Calcification in Individuals With Low Short-Term Risk: The Dallas Heart Study

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Background—The absence of coronary artery calcium (CAC) in middle age is associated with very low short-term risk for coronary events. However, the long-term implications of a CAC score of 0 are uncertain, particularly among individuals with high cardiovascular lifetime risk. We sought to characterize the association between predicted lifetime risk and incident CAC among individuals with low short-term risk.

Methods and Results—We included 754 Dallas Heart Study participants with serial CAC scans (6.9 years apart) and both low short-term risk and baseline CAC = 0. Lifetime risk for cardiovascular disease was estimated according to risk factor burden. Among this group, 365 individuals (48.4%) were at low lifetime risk and 389 (51.6%) at high lifetime risk. High lifetime risk was associated with higher annualized CAC incidence (4.2% versus 2.7%; \( P < 0.001 \)). Similarly, mean follow-up CAC scores were higher among participants with high lifetime risk (7.8 versus 2.4 Agatston units). After adjustment for age, sex, and race, high lifetime risk remained independently associated with incident CAC (OR 1.60; 95% CI 1.12 to 2.27; \( P = 0.01 \)). When assessing risk factor burden at the follow-up visit, 66.7% of CAC incidence observed in the low lifetime risk group occurred among individuals reclassified to a higher short- or long-term risk category.

Conclusion—Among individuals with low short-term risk and CAC scores of 0, high lifetime risk is associated with a higher incidence of CAC. These findings highlight the importance of lifetime risk even among individuals with very low short-term risk. (J Am Heart Assoc. 2014;3:e001280 doi: 10.1161/JAHA.114.001280)

Key Words: coronary artery calcium • lifetime risk • risk prediction

Coronary artery calcium (CAC) measured by computed tomography is strongly associated with incident coronary heart disease (CHD) and individuals with a CAC score of zero have very low short-term risk for CHD (ie, over 5 to 10 years).\(^1\,^2\) Although the impact of a CAC score of zero on short-term risk is well established, its long-term implications are uncertain, particularly in the setting of high predicted lifetime risk.\(^3\)

Among individuals with low short-term risk (ie, low Framingham risk score), the presence of high predicted lifetime risk is common and translates into marked elevations in long-term CHD event rates.\(^4\) Thus, individuals with zero CAC and high predicted lifetime risk represent a particularly challenging subgroup with apparent discordance between short-term and long-term risk. Since there are no available data on individuals with measured CAC and long-term follow-up (ie, 30+ years), progression of subclinical atherosclerosis is a reasonable surrogate that may identify unfavorable lifetime risk trajectories.

Therefore, we sought to determine the association between predicted lifetime risk and CAC incidence in a large sample of healthy adults with low short-term risk and CAC scores of 0. We hypothesized that high predicted lifetime risk would be associated with greater CAC incidence, identifying a group of individuals with very low short-term risk who might benefit from more intensive risk factor modification.

Methods

Study Sample

The design of the Dallas Heart Study (DHS) and details of variable definitions have been previously described.\(^5\) In brief,
the DHS is a multi-ethnic, population-based, cohort study of Dallas County adults, with deliberate over-sampling of African-Americans. All participants provided written informed consent and the study protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. The first phase of the DHS took place between 2000 and 2002 when the initial cohort underwent a detailed in-home health survey (visit 1), after which participants aged 30 to 65 years returned for blood and urine collection (visit 2). Visit 3 consisted of participants who returned for a detailed clinical examination and imaging studies. DHS phase-2 is a longitudinal follow-up study of DHS phase-1 participants who volunteered to undergo additional assessments between September 2007 and December 2009. These assessments again included an extensive health survey, laboratory testing, and imaging studies. Among DHS phase-1 participants, 2646 had interpretable CAC scans and complete data for all covariates. After excluding 285 participants with prior cardiovascular disease (ie, prior stroke, myocardial infarction, or coronary revascularization) or diabetes, 1560 with CAC>0 and 41 with Framingham risk ≥10%, 762 participants were eligible for inclusion in this study. Of these 762 participants, 8 did not return for CAC scanning in DHS phase-2 resulting in a final sample of 754 individuals with low short-term risk, baseline CAC of zero and a repeat CAC scan (Figure 1).

Measurements

Height, weight, blood pressure, plasma lipids, and glucose were measured, and the body mass index was calculated using standard methods. In DHS phase-1, electron-beam computed tomography (EBCT) measurements of CAC were performed in duplicate 1 to 2 minutes apart on an Imatron 150 XP scanner. In DHS phase-2, CAC was measured by multi-detector computed tomography (MDCT) and was performed on a Toshiba Aquilion 64-Slice MDCT scanner with each participant scanned in duplicate within 1 to 2 minutes. The duplicate CAC scores were determined using the Agatston method and then averaged. DHS phase-1 and DHS phase-2 CAC scores were adjusted using a standard calcium phantom that was scanned with the participant. This adjusted attenuation process has been previously described and allows comparison of scores obtained across different platforms (eg, EBCT in DHS phase-1 and MDCT in DHS phase-2).

Definitions

The Framingham risk score was determined in accordance with the Third Adult Treatment Panel risk assessment tool using age, sex, total and high-density lipoprotein cholesterol levels, smoking, systolic blood pressure, and anti-hypertensive medication use. Low short-term risk was defined as 10-year risk <10%. Participants with diabetes or prevalent cardiovascular disease were excluded from this study. In secondary analysis, low short-term risk was defined as <7.5% 10-year risk using the Pooled Cohort Equations as proposed by the most recent American guidelines. Predicted lifetime risk was determined based on our previously published algorithm (Table 1). For the primary analysis, CAC incidence was defined as a follow-up CAC score >0. As sensitivity analysis, we defined CAC incidence as a follow-up CAC score >10 Agatston units (AU) to minimize false-positive results related to technical artifacts.

Statistical Analysis

Baseline demographic and clinical variables were compared between subjects with low versus high predicted lifetime risk using the chi-square test for categorical variables and Wilcoxon-rank sum for continuous variables. A logistic regression model was used to assess the association between low versus high predicted lifetime risk and incident CAC in univariable and multivariable models. Since blood pressure, total cholesterol, and smoking are included in the predicted lifetime risk variable, only age, sex, and race were added as additional covariates in the multivariable models. Participants were further classified based on their risk factor profile at the follow up visit (ie, DHS phase-2). Individuals were then classified as low-risk if both Framingham and lifetime risk remained low and as high-risk if Framingham risk was ≥10%, lifetime risk was high, or in the presence of diabetes or cardiovascular disease. CAC
incidence was compared across 4 mutually exclusive groups constructed based on baseline and follow-up risk classification (ie, low baseline/low follow-up, low baseline/high follow-up, high baseline/low follow-up, and high baseline/high follow-up).

**Results**

Among 754 DHS participants with low short-term risk and CAC=0 at baseline, lifetime risk stratification resulted in 2 groups of approximately equal size: low short-term/lifetime risk (N=365, 48.4%) and low short-term/high lifetime risk (N=389, 51.6%). Participants in the high predicted lifetime risk group were older (mean age 43.1 years versus 40.5 years; \( P < 0.001 \)) and had a higher burden of traditional risk factors (ie, higher blood pressure, total cholesterol, low density lipoprotein cholesterol, triglycerides and fasting glucose with a higher prevalence of smoking and lower high-density lipoprotein cholesterol levels) (Table 2). They also had higher body-mass indexes and were more likely to report a family history of myocardial infarction and use of statins.

After 6.9 years of follow-up, we observed 182 cases of incident CAC, representing 24.1% of the study sample. High predicted lifetime risk was associated with a higher CAC incidence (29.1% versus 18.9%; \( P=0.001 \)), higher annualized CAC incidence (4.2% versus 2.7%, \( P=0.001 \)), and higher mean follow-up CAC scores (7.8 versus 2.4 AU; \( P < 0.001 \)) (Figure 2). Follow-up CAC scores \( \geq 100 \) AU were only observed in the high lifetime risk group (N=5, 1.3%). After adjusting for age, sex, and race, high lifetime risk remained associated with higher incidence of CAC (OR 1.60, 95% CI 1.12 to 2.27; \( P=0.01 \)) (Table 3).

When CAC incidence was defined as follow-up CAC>10 AU, we observed a similar pattern of results (CAC incidence 10.5% versus 6.3%; OR 1.75, 95% CI 1.03 to 2.98; \( P=0.039 \)). Applying the Pooled Cohort Equations to define low short-term risk as 10-year risk \(<7.5\%\), high lifetime risk remained associated with higher incidence of CAC (OR 1.55, 95% CI 1.02 to 2.37; \( P=0.04 \)).

Among the 365 participants classified as low lifetime risk in DHS phase-1, 160 (43.8%) remained in the low predicted risk category in DHS phase-2 and 205 (56.2%) were newly classified as high-risk based on the development of cardiovascular disease or diabetes, Framingham risk \( \geq 10\% \) or high lifetime risk (3 reported an interval myocardial infarction or stroke, 12 developed diabetes, 10 had Framingham risk \( \geq 10\% \), and 185 had high lifetime risk). In the high baseline lifetime risk group (n=389), 328 (84.3%) remained in the same short- and long-term risk category and 61 (15.7%) were reclassified into a different group (27 had low lifetime risk, 30 had Framingham risk \( \geq 10\% \), 28 developed diabetes, and 6 developed CVD). Among participants with low lifetime risk in DHS phase-1 and low risk in DHS phase-2, 14.4% developed coronary calcification while, among those with high lifetime risk in DHS-1 and high risk in DHS-2, 30.1% had follow up CAC scores >0. In the group with low lifetime risk at baseline, participants with high short- or long-term risk at follow-up account for 66.7% of incident CAC.

Because high predicted lifetime risk is associated with the presence of at least 1 of 3 major risk factors (ie, smoking, total cholesterol, and hypertension), we performed additional secondary analyses to determine the extent to which our findings were dependent upon any one risk factor. For example, after excluding smokers from the analysis, high predicted lifetime risk was associated with a higher likelihood of CAC incidence when compared to individuals with low predicted lifetime risk (adjusted OR 1.70, 95% CI 1.14 to 2.53; \( P=0.009 \)). Similar findings were observed after excluding individuals with blood pressure \( \geq 160/100 \) mm Hg or on treatment with anti-hypertensive medications and individuals with total cholesterol \( \geq 6.3 \text{mmol/L (240 mg/dL) or on treatment with a statin medication (Table 4).} \)

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**Table 1. Risk Factor Stratification and Predicted Lifetime Risk for Cardiovascular Disease**

| Low Predicted Lifetime Risk | High Predicted Lifetime Risk |
|----------------------------|-----------------------------|
| Low predicted lifetime risk | High predicted lifetime risk |
| All Optimal RF              | ≥1 Not Optimal RF            |
| Systolic/diastolic, mm Hg   | 120 to 139/80 to 89          |
| <120/80                     | 140 to 159/90 to 99          |
| Total cholesterol, mmol/L   | ≥160 (or treated)            |
| <4.7 (180 mg/dL)            | ≥6.3 or treated (240 mg/dL)  |
| Diabetes*                   |                             |
| Smoking                     |                             |
| Predicted lifetime risk (men)|                             |
| Predicted lifetime risk (women)|                             |

Risk factor stratification derived from Lloyd-Jones, et al<sup>10</sup>. RF indicates risk factor. Diabetes was included in the original published stratification. Because all diabetics were considered to have “high short-term risk”, this risk factor was not included in the present paper.

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In a large multi-ethnic population-based cohort, we observed that, among individuals with low short-term risk, the presence of high predicted lifetime risk is associated with a 60% increased risk of CAC incidence over 6.9 years of follow-up. The association between high lifetime risk and CAC incidence was robust and persisted after adopting a more strict definition of incident CAC and after excluding individuals with marked elevations of each risk factor group. This suggests that even among individuals with low Framingham risk scores and zero CAC, predicted lifetime risk identifies a subgroup that is more likely to develop subclinical atherosclerosis and in whom long-term risk likely remains elevated.

**Clinical Implications**

Although the addition of CAC to traditional risk factors has been shown to provide clinically significant improvement in short-term cardiovascular risk prediction, both methods share similar limitations. In particular, both short-term risk and CAC are highly age dependent such that the majority of adults <50 years old have both low short-term risk and zero CAC. Nevertheless, the burden of traditional risk factors in middle age is strongly associated with CHD risk across the remaining lifespan. However, the contribution of CAC to

| Table 2. Baseline Characteristics Stratified by Predicted Lifetime Risk |
|-------------------------------------------------|-------------------------------------------------|---|
| | Low Short-Term/Low Lifetime Risk | Low Short-Term/High Lifetime Risk | P Value |
| N | 365 | 389 | NA |
| Age, y* | 40.5 (±7.7) | 43.1 (±8.3) | <0.001 |
| Women | 68.0% | 67.4% | 0.862 |
| Race | | | 0.061 |
| Black | 37.8% | 44.2% | |
| White | 39.7% | 40.6% | |
| Hispanic | 19.5% | 13.4% | |
| Other | 3.0% | 1.8% | |
| Smoking | 0% | 39.1% | <0.001 |
| SBP, mm Hg† | 116 (108 to 124) | 124 (113 to 136) | <0.001 |
| TC, mg/dL† | 163 (145 to 179) | 193 (161 to 214) | <0.001 |
| LDL, mg/dL† | 92 (75 to 109) | 113 (87 to 136) | <0.001 |
| HDL, mg/dL† | 50 (42 to 61) | 51 (43 to 61) | 0.260 |
| Triglycerides, mg/dL† | 76 (57 to 107) | 96 (66 to 146) | <0.001 |
| Fasting glucose, mg/dL† | 89 (82 to 95) | 90 (83 to 97) | 0.036 |
| Statin therapy | 0% | 5.7% | <0.001 |
| Antihypertensive therapy | 0% | 16.2% | <0.001 |
| BMI, kg/m²† | 26.4 (23.4 to 29.4) | 27.6 (24.1 to 31.3) | <0.001 |
| FHMI | 23.6% | 31.1% | 0.020 |
| Framingham risk‡ | <1% (<1% to 1%) | 1% (<1% to 2%) | <0.001 |

BMI indicates body mass index; FHMI, family history of myocardial infarction; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

*Mean (±standard deviation).
†Median (interquartile range).
‡Predicted 10 year risk of coronary heart disease events according to the Adult Treatment Panel III/Framingham risk score, median (interquartile range).
Table 3. Coronary Artery Calcium Incidence According to Predicted Lifetime Risk Group Strata

|                          | Low Short-Term/ Low Lifetime Risk | Low Short-Term/ High Lifetime Risk | P Value |
|--------------------------|-----------------------------------|-----------------------------------|---------|
| CAC incidence            | 18.9%                             | 29.1%                             | 0.001   |
| Annualized CAC incidence | 2.7%                              | 4.2%                              | 0.001   |
| CAC incidence OR (95% CI)| Reference                         | 1.76 (1.25 to 2.47)               | 0.001   |
| CAC incidence OR adjusted (95% CI)<sup>†</sup> | Reference | 1.60 (1.12 to 2.27) | 0.010   |
| Follow up CAC score*     | 2.4 AU (±9.49)                    | 7.8 AU (±41.67)                   | <0.001  |

AU indicates Agatston units; CAC, coronary artery calcium.
*Mean (±standard deviation).
†Adjusted for age, sex and race.

Table 4. Odds Ratio of CAC Incidence Based on the Presence of Predicted High Lifetime Risk in Selected Subgroups

|                          | OR      | 95% CI           | P Value |
|--------------------------|---------|------------------|---------|
| Excluding smokers (n=602; events=145) |         |                  |         |
| Model 1                  | 1.76    | 1.25 to 2.47     | <0.001  |
| Model 2                  | 1.70    | 1.14 to 2.53     | 0.009   |
| Excluding TC ≥6.3 mmol/L (240 mg/dL) or on treatment with statins (n=700; events=161) |         |                  |         |
| Model 1                  | 1.62    | 1.14 to 2.32     | 0.008   |
| Model 2                  | 1.51    | 1.04 to 2.18     | 0.029   |
| Excluding stage 2 hypertension (n=693; events=155) |         |                  |         |
| Model 1                  | 1.52    | 1.06 to 2.18     | 0.022   |
| Model 2                  | 1.36    | 0.93 to 1.97     | 0.110   |

Stage 2 hypertension was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg or on treatment for hypertension. Model 1: Unadjusted analysis. Model 2: Adjusted for age, sex and race. TC, total cholesterol.

Interestingly, even among individuals with low risk factor burden (ie, low lifetime risk), 18.9% developed CAC and 6.3% had CAC scores >10 AU over a follow-up period of 6.9 years. In the low lifetime risk group, two-thirds of CAC incidence occurred among individuals who were reclassified as high risk at follow-up suggesting the importance of future risk factor levels on the development of atherosclerosis. Although risk factor burden at middle age has a strong association with long-term cardiovascular risk, maintaining a favorable risk factor profile may be equally important and the current recommended strategy of serial assessment of risk factor burden should be applied to individuals with low predicted risk.<sup>9</sup>

Current Study in Context

Previous studies have shown that among participants with low short-term risk, high predicted lifetime risk is associated with a higher prevalence and progression of atherosclerosis as measured by CAC and carotid intima media thickness. However, the association between high predicted lifetime risk and CAC incidence among low risk adults has not been reported. The present study extends these prior observations to show that even among those without CAC at middle age, high predicted lifetime risk is associated with the development of subclinical atherosclerosis and identifies an unfavorable trajectory that is likely to result in higher long-term event rates.

A warranty period of 4 years has been proposed for CAC scores of zero.<sup>16</sup> This warranty period is based on a study by Min et al where 422 individuals with no baseline coronary calcification underwent annual CAC scans up to 5 years. They showed that the cumulative incidence of CAC was 15% by year 4 and 25% by year 5 and that the mean time to conversion was 4.1 years. Though several risk factors were associated with CAC incidence, they saw no correlation between cardiovascular risk profiles and accelerated time to conversion. In an analysis of the Multi-Ethnic Study of Atherosclerosis (MESA), Kronmal et al also found that several
traditional risk factors such as high blood pressure, high low-density lipoprotein cholesterol levels, diabetes, and family history of myocardial infarction were associated with CAC incidence. In line with those findings, our study suggests that CAC scores of zero should to be considered in the context of risk factor burden and lifetime risk. In the present study of relatively young adults, almost 30% of individuals with low short-term and high lifetime risk developed measurable coronary calcification by the end of the follow-up period (ie, 6.9 years).

Although CAC progression (ie, increasing CAC among those with CAC=0 at baseline) has been consistently associated with CHD events, the short-term impact of CAC incidence on clinical outcomes remains uncertain. In a study by Budoff et al, CAC progression but not incidence predicted all-cause mortality in 4609 patients scanned 3.1±2 years apart and followed for 5.4±3.4 years after the second CAC scan. A larger study from the MESA cohort included 6778 individuals scanned 2.5±0.8 years apart and followed for 7.6 years after the first scan. Although CAC progression was a strong predictor of CHD, the impact of CAC incidence was more modest. The discordance between short-term and long-term risk is well established, and therefore, the more modest impact of CAC incidence on short-term event rates is not inconsistent with a high lifetime risk for CHD. In other words, individuals with incident CAC usually have low overall CAC scores, which translate into low short-term event rates but are likely to result in high long-term risk.

In contrast to short-term risk estimation strategies that provide objective data on short-term event rates, long-term risk estimation strategies provide insight into risk trajectories across the lifespan. Importantly, these risk estimation strategies are often in conflict. We have previously shown in multiple cohorts that about half of all adults with a low Framingham risk score have high predicted lifetime risk. Our data are consistent with this distinction and suggest that, even among middle age individuals with zero CAC, high predicted lifetime risk does identify a subgroup of low short-term risk individuals who are on a different risk trajectory as demonstrated by a higher CAC incidence in the short-term.

Limitations
Coronary calcium scores are subject to noise and measurement variations, which could result in imprecise estimates of CAC incidence. By using duplicate scans in each visit and demonstrating the consistency of our findings with more strict CAC incidence definitions, we believe that our results reflect true biological effects. Ideally the impact of predicted lifetime risk in the subgroup of individuals with low Framingham risk and CAC scores of 0 would be assessed in cohorts with long-term follow-up where the measured outcome would be clinical CHD events. Unfortunately, since CAC is a relatively new marker, these data will not be available for the foreseeable future. The Dallas Heart Study is a relatively young cohort with a high proportion of African-Americans, which may limit the generalizability of our findings to other populations.

Conclusion
In the present study we demonstrate that, among individuals with low Framingham risk scores and no coronary calcification, high predicted lifetime risk identifies a group with higher incidence of CAC. Even in this group with very low short-term event rates, risk factor burden is associated with higher incidence of subclinical atherosclerosis. Our findings suggest that among middle-aged individuals with a CAC score of 0, high predicted lifetime risk can identify a group who may benefit from more aggressive preventive interventions.

Future studies assessing long-term cardiovascular event rates among individuals with high risk factor burden and no CAC are needed to confirm the unfavorable risk trajectory suggested by this study.

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Disclosures
None.

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