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LETTERS TO THE EDITOR

The 10-Year Prognostic Value of Zero and Minimal CAC



Prospective studies consistently show the strong additive value of coronary artery calcium (CAC) to traditional risk factors in predicting atherosclerotic cardiovascular disease (ASCVD) (1). Apart from identifying persons at high risk, the group with the majority of events, CAC has a unique screening role in its power of zero, identifying those at low risk of intermediate-term events despite their risk factor burden (2).

Although recent long-term retrospective studies examined all-cause mortality, 10-year prospective data on absent CAC (CAC = 0) and minimal CAC (1 to 10) to predict ASCVD events are lacking (3). Furthermore, the hazard of ASCVD risk factors in this low-risk group has not been described. We leveraged 10-year follow-up in MESA (Multi-Ethnic Study of Atherosclerosis) to address these questions.

The MESA methods have been described (4). An ethnically diverse sample of 6,814 participants 45 to 84 years of age and free of ASCVD were enrolled and followed for all-cause strokes, myocardial infarctions (MIs), and cardiovascular deaths. Each participant underwent 2 CAC scans. The average Agatston score was taken as the CAC score; 2 scores of 0 were considered CAC = 0. Event rates were stratified by 10-year risk categories from the 2013 American College of Cardiology/American Heart Association ASCVD risk estimator. Cox proportional hazards models were developed to estimate hazard ratios (HRs) for age, sex, ethnicity, family history, smoking, diabetes, hypertension, high-sensitivity C-reactive protein >2 mg/l, non-high-density lipoprotein (non-HDL), HDL, and carotid intima-media thickness >75th percentile (0.989 mm).

Among the 3,923 MESA participants with a baseline CAC of 0 to 10 (58.4 ± 9.3 years of age; 62% female), there were 3,415 with CAC = 0 score and 508 with CAC 1 to 10. Participants with CAC 1 to 10 had a higher risk profile than those without CAC. Participants without CAC were more likely to be female (63% vs. 51%), were younger (58 years old vs. 62 years old), had less prevalence of family history of CHD (37% vs. 43%), and had a lower prevalence of hypertension (38% vs.

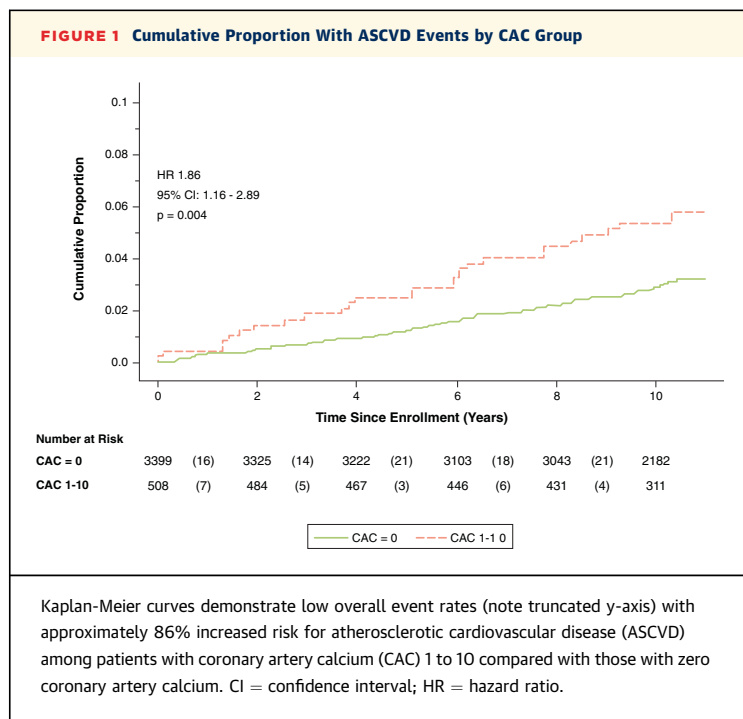
49%) (all $p < 0.01$). The average non-HDL and proportion with carotid intima-media thickness >75th percentile were lower, whereas the average HDL was higher, in participants without CAC.

Over a median of 10.3 years, there were 123 ASCVD events (98 among participants with a CAC = 0 score) including 64 strokes, 41 MIs, and 18 CHD deaths. There were 12 hemorrhagic, 4 cardioembolic, 9 small-vessel, and 13 large-vessel strokes, as well as 26 strokes of unknown origin. The proportions of incident strokes (53% vs. 48%), MIs (33% vs. 36%), and CHD deaths (14% vs. 16%) were not significantly different in the CAC = 0 and CAC 1 to 10 groups, respectively.

The overall event rate was 3.2 in 1,000 person-years including 2.9 in 1,000 person-years if CAC was absent and 5.4 in 1,000 person-years if CAC was 1 to 10. The unadjusted hazard for ASCVD with CAC 1 to 10 was nearly twice that of a CAC = 0 score (HR: 1.86; 95% confidence interval [CI]: 1.16 to 2.89) (Figure 1). Across subgroups of risk (e.g., age >65 years, diabetes, smoking) when CAC was absent, none of the event rates exceeded the 7.5% 10-year risk threshold established by the 2013 American College of Cardiology/American Heart Association cholesterol treatment guidelines (5). In participants with a CAC = 0 score and an ASCVD risk between 1% and 15%, the event rate did not exceed 4.4 in 1,000 person-years. In those with a CAC = 0 score and a >15% ASCVD risk, the event rate was 7.3 in 1,000 person-years.

In multivariable models among participants with absent CAC, only age (HR: 1.5; 95% CI: 1.2 to 1.9), smoking (HR: 3.0; 95% CI: 1.8 to 5.1), and hypertension (HR: 2.0; 95% CI: 1.3 to 3.3) significantly predicted ASCVD. Similarly, among participants with CAC 1 to 10, age and smoking remained significant predictors, but hypertension was a much stronger predictor (HR: 9.9; 95% CI: 2.7 to 36.2) than for absent CAC (p for interaction = 0.02). Findings were similar when statin users were excluded.

Our analysis provides 10-year ASCVD event rates among individuals with absent or minimal CAC. Importantly, one-half of the events are strokes, and hypertension and smoking are strong modifiable risk factors. With ASCVD rates much lower than 7.5% when CAC is absent, lifestyle modifications, smoking cessation, and hypertension control should be top priorities. Among persons with absent CAC, statin therapy may be considered for longer-term risk

FIGURE 1 Cumulative Proportion With ASCVD Events by CAC Group

reduction beyond 10 years, although balanced with the risk of side effects (i.e., myalgia, hyperglycemia).

The absence of CAC identifies those persons at low absolute 10-year ASCVD risk. This aspect of CAC scanning should be factored into the clinician-patient discussion.

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Family History of CHD Is Associated With Severe CAC in South Asians



Comparing the MASALA and MESA Studies

South Asians (SA) have higher rates of atherosclerotic cardiovascular disease (ASCVD) than most ethnic groups (1). Modifiable risk factors only partially explain this disparity, suggesting a familial or genetic influence on ASCVD pathogenesis. The association of a family history of coronary heart disease (FH) with coronary artery calcium (CAC) in SA is unknown and may inform preventive approaches in this high-risk population. We analyzed the association between FH and CAC in SA compared with other racial or ethnic groups in the United States.

We included participants 45 to 84 years of age from 2 community-based studies: MASALA (Mediators of Atherosclerosis in South Asians Living in America) and MESA (Multi-Ethnic Study of Atherosclerosis). MASALA was designed with methods similar to those used in MESA to allow for cross-ethnic comparisons. Methods of both studies have been described (2,3). After excluding MASALA participants younger than 44 years of age and those missing FH information, the study population included 7,197 participants with mean age of 61 ± 10 years and 47% men (802 SA, 2,470 Non-Hispanic whites [NHW], 1,782 African Americans [AA], 1,405 Hispanics [HP], and 738 Chinese Americans [CA]).

CAC was measured at baseline as previously described (2,3). FH consisted of a self-reported