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Determinants of Incident Atherosclerotic Cardiovascular Disease Events Among Those With Absent Coronary Artery Calcium: Multi-Ethnic Study of Atherosclerosis

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Abstract

Background: The 2018 American Heart Association/ American College of Cardiology Multisociety (AHA/ACC/MS) cholesterol guideline states that statin therapy may be withheld or delayed among intermediate risk individuals in the absence of coronary artery calcium (CAC=0). We evaluated whether traditional cardiovascular risk factors are associated with incident atherosclerotic cardiovascular disease (ASCVD) events among individuals with CAC=0 over long-term follow-up.

Methods: We included participants with CAC=0 at baseline from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study of individuals free of clinical ASCVD at baseline. We used multivariable-adjusted Cox proportional hazards models to study the association between cardiovascular risk factors [cigarette smoking, diabetes mellitus, hypertension, preventive

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medication use (aspirin and statin), family history of premature ASCVD, chronic kidney disease, waist circumference, lipid and inflammatory markers] and adjudicated incident ASCVD outcomes.

Results: We studied 3,416 individuals (mean (SD) age 58 (9) years; 63% were female, 33% White, 31% Black, 12% Chinese-American, and 24% Hispanic. Over a median follow-up of 16 years, there were 189 ASCVD events (composite of CHD and stroke) of which 91 were CHD, 88 were stroke, and 10 were both CHD and stroke events. The unadjusted event rates of ASCVD were ≤5 per 1000-person-years among individuals with CAC=0 for most risk factors with the exception of current cigarette smoking (7.3), diabetes mellitus (8.9), hypertension (5.4), and chronic kidney disease (6.8). After multivariable-adjustment, risk factors that were significantly associated with ASCVD: hazard ratio (HR) 95% confidence interval (CI) included current cigarette smoking: 2.12 (1.32,3.42), diabetes mellitus: 1.68 (1.01,2.80), and hypertension: 1.57 (1.06,2.33).

Conclusions: Current cigarette smoking, diabetes mellitus, and hypertension are independently associated with incident ASCVD over 16-year follow-up among those with CAC=0. Family history of premature ASCVD may be associated with ASCVD risk among women only.

Keywords

Coronary artery calcium; cardiovascular risk factors; atherosclerotic cardiovascular disease

INTRODUCTION

Clinical prevention of atherosclerotic cardiovascular disease (ASCVD) hinges on the appropriate selection of individuals who may benefit from pharmacotherapy.[1] The pooled cohort equations (PCE) are considered the first step for estimation of absolute ASCVD risk and are endorsed by recent guidelines.[2,3] If the decision to treat with statin therapy remains unclear, the 2018 American Heart Association/American College of Cardiology/ Multisociety (AHA/ACC/MS) cholesterol guideline recommends screening for ASCVD risk-enhancing factors among intermediate- or borderline-risk individuals.[3] If uncertainty still exists, measurement of the coronary artery calcium (CAC) score is reasonable to guide treatment allocation in selected individuals (IIa recommendation).

The absence of CAC (CAC=0) is associated with low risk of ASCVD[4] and may therefore be used to justify withholding or postponing statin therapy if there is clinical uncertainty about potential benefit or concerns about statin disutility.[5] While a CAC score of 0 generally portends a favorable prognosis, a small proportion of individuals will experience ASCVD events, particularly during long-term follow-up. Indeed, the 2018 AHA/ACC/MS guideline[6] continues to endorse statin therapy among those with diabetes mellitus, current cigarette smoking, or a strong family history of premature ASCVD presumably because these individuals remain at higher risk of ASCVD events despite CAC=0.[7–10] However, follow up in these prior studies was up to 10 years. Since primary ASCVD prevention generally focuses on a long-term time horizon, it is important to understand which traditional or novel risk factors may be associated with long-term ASCVD events despite CAC=0.

In the present analysis, we evaluate whether traditional cardiovascular risk factors and advanced lipid and inflammatory markers are independently associated with incident ASCVD events among those with baseline CAC=0 over long-term follow-up.

METHODS

Study Design and Population

Details of the Multi-Ethnic Study of Atherosclerosis (MESA) design have been reported elsewhere.[11] Briefly, MESA is a prospective cohort study of 6,814 U.S adults aged 45 to 84 years of White, Black, Hispanic, or Chinese American race/ethnicity. Participants were enrolled from 6 U.S. field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota) between 2000 and 2002. Five subsequent visits occurred between 2002-2004 (visit 2), 2004-2005 (visit 3), 2005-2007 (visit 4), 2010-2011 (visit 5), and 2016-2018 (visit 6). All participants were required to be free of clinical ASCVD at the time of enrollment. Institutional review boards at each site approved the study, and all participants provided written informed consent. MESA data are publicly available either from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center repository https://biolincc.nhlbi.nih.gov/studies/mesa/ or from the MESA coordinating center https://www.mesa-nhlbi.org/ with an approved study proposal.

Ascertainment of Incident Outcome

The primary outcome for this analysis was a combination of hard ASCVD events, which included myocardial infarction, resuscitated cardiac arrest, coronary heart disease (CHD) death, stroke, or stroke death. Secondary outcomes included 1) coronary heart disease (CHD) events which were comprised of myocardial infarction, resuscitated cardiac arrest, and fatal CHD; 2) stroke including fatal and non-fatal events; 3) and all-cause mortality.[11]

Assessment of Coronary Artery Calcium

CAC was assessed at baseline using either an electron-beam CT scanner (Chicago, Los Angeles, and New York centers) or a multidetector CT system (Baltimore, Forsyth County, and St. Paul centers). Each participant was scanned twice and all images were interpreted at the central reading center (the Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance).[12] A CAC score was calculated for each scan, and the mean score of the two scans was used in all analyses. Intraobserver and interobserver agreement were excellent (kappa statistics, 0.93 and 0.90, respectively).[13]

Assessment of Covariates

Information pertaining to demographics, medical history, medication use, and cigarette smoking was collected using validated questionnaires. Anthropometric measurements were performed according to predefined protocols. Increased waist circumference was defined as ≥90 cm for men or ≥80 cm for women. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured three times and the average of the last two measurements

was used in these analyses. Hypertension was defined according to the 2017 ACC/AHA Guideline for High Blood Pressure in Adults as SBP ≥130 or DBP 80 mm/Hg, as a history of physician-diagnosed hypertension, or taking a medication for hypertension.[14] MESA participants at visit 2 were asked about family history of premature ASCVD, which was defined as any first-degree relative (mother, father, sibling, or child) with CHD or heart attack or stroke occurring before the age of 55 years in men and 65 years in women, respectively. With the exception of family history of premature ASCVD, all other risk factors were assessed at MESA visit 1.

A central laboratory (University of Vermont, Burlington, VT, USA) measured concentrations of fasting lipids (total and high-density lipoprotein cholesterol (HDL-C), triglycerides), and glucose from visit 1 samples. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. Lipoprotein [a] Lp(a) mass concentration was evaluated using a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) that controls for the size heterogeneity of apolipoprotein(a).[15] Diabetes mellitus was defined as a fasting glucose of ≥126 mg/dL or use of hypoglycemic medication (oral agents and/or insulin). Chronic kidney disease (CKD) was defined according to the KDIGO guideline as glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 or the presence of microalbuminuria (albumin-to-creatinine ratio >30 mg/g). High-sensitivity C-reactive protein (hsCRP) was measured using the BNII nephelometer. Intra-assay and inter-assay coefficients of variation (CV) ranged from 2.3 to 4.4% and 2.1 to 5.7%, respectively.[16] ASCVD risk was estimated using the pooled cohort equations (PCE) at the baseline study visit.[17]

Statistical Analysis

Baseline characteristics were tabulated for those with CAC=0 at baseline and stratified by development of incident ASCVD events at follow up. Continuous variables were reported using mean (standard deviation) or median (interquartile range), while categorical variables were summarized as count (percentage).

Unadjusted incidence rates of events were reported as the number of events per 1000-person-years among those with presence versus absence of cardiovascular risk factors. We also calculated event rates by estimated ASCVD risk based on the PCE (<7.5%, 7.5%–<15%, 15%–<20%)[6]. Given that age is weighted heavily in the PCE, we also stratified event rates by age categories (45–54, 55–64, 65–74, and ≥75 years).

After confirming the proportionality assumption using Schoenfeld residuals, we used multivariable Cox proportional hazards models to examine the association between cardiovascular risk factors and incident outcomes. Models were adjusted for age, sex, race/ethnicity, education, presence of healthcare insurance, and all risk factors included in this analysis. Results were further stratified by sex and multiplicative interaction testing was performed in the multivariable-adjusted model.

In sensitivity analyses, we excluded participants on lipid lowering therapy at the baseline MESA study visit. We further adjusted for pack-years of cigarette smoking given the cumulative effect of smoking burden on ASCVD risk.[18] We used two higher cut-offs to classify hypertension (≥140/90 mm Hg and ≥150/90 mm Hg). We also assessed incidence

rates of the individual components of ASCVD (CHD and stroke) among those diagnosed with hypertension at baseline. We evaluated the association between family history of premature ASCVD and incident ASCVD stratifying by baseline and incident statin use and performed analyses separately for men versus women. We also evaluated development of incident risk factors between visits 2 and 6 among those with absent risk factors at baseline (visit 1). We modeled the development of incident risk factors as binary (development of a cardiovascular risk factor at any MESA visit after baseline versus absence of risk factors during all visits) or as time-varying. Similar multivariable-adjusted Cox proportional hazards models as above were used to study the association between incident risk factors and ASCVD outcomes.

A p-value < 0.05 was considered statistically significant. All analyses were conducted using Stata version 16.1 (StataCorp, College Station, TX).

RESULTS

The study population consisted of 3,416 individuals with CAC=0 with a mean (SD) age 58 (9) years; 63% were female, 33% White, 31% Black, 12% Chinese-American, 24% Hispanic, and 27% at intermediate risk of ASCVD (PCE 7.5%–<20%). The prevalence of risk factors was as follows: 13% current smoking, 9% diabetes mellitus, 49% hypertension, 18% family history of premature ASCVD and 8% CKD. Compared to participants who did not develop ASCVD, those who did were older (61 vs. 58 years), had higher SBP (131 vs. 122 mm Hg), higher estimated mean 10-year ASCVD risk (10.7% vs. 4.8%), were more likely to currently smoke (23% vs. 13%), have diabetes mellitus (19% vs. 9%), hypertension (66% vs. 48%), CKD (23% vs. 14%), and estimated ASCVD risk ≥7.5% (66% vs. 37%); all p<0.05 (Table 1).

Over a median follow up time of 16 years, a total of 189 ASCVD events (composite of CHD and stroke) occurred among those with CAC=0, of which 91 were CHD, 88 were stroke, 10 were both CHD and stroke events, and 443 were all-cause deaths. The unadjusted incidence rates of ASCVD were ≤5 per 1000-person-years for most risk factors with the exception of current cigarette smoking (7.3), diabetes mellitus (8.9), hypertension (5.4), and CKD (6.8). ASCVD event rates were 6.2 per 1000 person-years among those with estimated baseline ASCVD risk 7.5%–<15% and 5.87 per 1000 person-years among those with estimated ASCVD risk 15%–<20% (Table 2).

The unadjusted incidence rates of ASCVD and all-cause mortality (per 1000 person-years) for each risk factor stratified by categories of estimated 10-year ASCVD risk and age are shown in Supplementary Tables1 and 2, **respectively**. There was a graded higher risk of ASCVD and mortality for most cardiovascular risk factors with higher estimated ASCVD risk categories (Supplementary Table 1). Among intermediate risk participants (estimated ASCVD risk 7.5%–<15%), the incidence rate of ASCVD was highest among current smokers (11.4). Among those with estimated ASCVD risk 15%–<20%, the incidence rate of ASCVD was highest among those with diabetes (16.6) followed by current smokers (14.6). Similarly, there was a graded higher risk of ASCVD and mortality for most cardiovascular risk factors with higher age categories (Supplementary Table 2). Among those aged 45-54

years the highest ASCVD event rates were noted among those with diabetes mellitus (7.3) and current smokers (5.2).

After multivariable-adjustment, risk factors that remained significantly associated with ASCVD: hazard ratio (HR) 95% confidence interval (CI) included current cigarette smoking: 2.12 (1.32,3.42), diabetes mellitus: 1.68 (1.01,2.80), and hypertension: 1.57 (1.06,2.33) (Table 3). Analyses excluding statin users and additional adjustment for pack-years of smoking yielded similar results (not shown).

In sex-stratified analyses, current smoking remained significantly associated with ASCVD among men only. Among men, the incidence rate of ASCVD was 10.1 per 1000 person-years for current smokers, while the event rate among women was 5.2. Family history of premature ASCVD was significantly associated with incident ASCVD among women only. The corresponding incidence rate among those with premature ASCVD was 4.6 for women and 4.4 for men. There was no significant interaction between sex and any cardiovascular risk factors in the multivariable-adjusted Cox regression model (p-for interaction >0.05) (Supplementary Table 3.

Risk factors that were significantly associated with all-cause mortality among those with CAC=0 included current cigarette smoking: 2.66 (1.89,3.74) and a 10 cm higher waist circumference: 1.10 (1.00,1.21) (Table 3). In sex-stratified analyses, current cigarette smoking was a significant risk factor for all-cause mortality in both men and women, while waist circumference was significant among women only (Supplementary Table 3). There was no significant interaction between sex and any cardiovascular risk factors in the association with all-cause mortality (p-for interaction >0.05).

In analyses of incident CHD, only current cigarette smoking was a significant risk factor: 2.19 (1.14,4.17), while hypertension: 1.91 (1.09,3.35) was significantly associated with stroke (Supplementary Table 4).

Sensitivity Analyses

Among those who developed an ASCVD event over follow up, 59% developed incident hypertension, 10% incident diabetes mellitus, and 3% of never smokers at baseline were current smokers over subsequent MESA follow up visits. Among those not on statin or aspirin use at baseline, 43% initiated statin therapy visits and 49% were on aspirin therapy. There was no significant association between incident cardiovascular risk factors and incident ASCVD (results not shown). For example, there was no statistically significant association between incident hypertension (modeled as a time-varying covariate) and risk of ASCVD: 1.44 (0.93,2.24).

The incidence rate of composite ASCVD was 5.4 per 1000 person-years among those with hypertension defined as blood pressure ≥130/80 mm Hg. Examining the individual components of ASCVD we found that the incidence rate (per 1000 person-years) of CHD was 2.7 and of stroke was 3.1. We further evaluated incidence rates of ASCVD using different blood pressure thresholds to classify hypertension. Using a cutoff ≥140/90 mm Hg

the incidence rate of ASCVD (per 1000 person-years) was 5.9 and using ≥150/90 mm Hg it was 5.7.

Among those with family history of premature ASCVD, 39.5% received statin over follow-up (40.7% among women and 36.9% among men). Among those without family history of premature ASCVD, 33.9% received statin over follow-up. Among those with family history of premature ASCVD, the incidence rate of ASCVD (per 1000 person-years) was 4.8 among those not on statin at baseline and 2.9 among those who were on a statin. ASCVD incidence rate (per 1000 person-years) among those never started on a statin (neither at baseline nor follow-up) was 3.2 and among those with incident statin use it was 6.9.

DISCUSSION

Several observations can be made from the present study. First, we found that the long-term risk of ASCVD events continues to remain low (5 per 1000 person-years) in most people with baseline CAC=0 (mean age 58, follow up to mean age 74). Second, current cigarette smoking, diabetes mellitus, and hypertension are associated with incident ASCVD events among those with CAC=0 at baseline. Third, 16-year event rates among those with CAC=0 but with diabetes or cigarette smoking are close to the threshold of 7.5% over 10 years generally considered to be appropriate for initiation of statin therapy in primary prevention. Fourth, among those with CAC=0 who develop ASCVD events, CHD and stroke related event rates are numerically comparable.

The present analyses support recommendations made by the 2018 AHA/ACC/MS cholesterol guideline that continues to favor statin therapy among individuals with CAC=0 if diabetes mellitus or current cigarette smoking are present. ASCVD event rates were highest among individuals with CAC=0 and diabetes mellitus in our study. A prior study by Malik et al also showed that ASCVD event rates were especially high with concomitant insulin use or HbA1c ≥7%.[19] We also found that ASCVD event rates were high among current smokers particularly among those who were at intermediate risk of ASCVD.

We found no significant association between family history of premature ASCVD and incident ASCVD in multivariable-adjusted models. Among those with family history of premature ASCVD, the incidence rate of ASCVD was lower among those on a statin at baseline presumably because statin therapy lowers ASCVD risk among those with cardiovascular risk factors. ASCVD event rates were lower among those never started on a statin compared to those with incident statin use over follow up likely because those who were started on statin therapy represented patients with other cardiovascular comorbidities leading to initiation of statin therapy by their treating clinician.

Incidence rates of ASCVD were slightly higher among women than men with family history of premature ASCVD though incident statin use was also higher in women. Similarly, the higher incident statin use among women may reflect a worse cardiovascular risk profile among women at follow up prompting statin use. This could explain why family history of premature ASCVD was associated with incident ASCVD among women only. As incidence rates of ASCVD were less than 5 per 1000-person years in both men and women with

family history of premature ASCVD and CAC=0, it may be reasonable to defer statin therapy in this group. The 2018 AHA/ACC/MS cholesterol guideline listed family history of premature CHD as an exception to statin deferral even in the presence of CAC=0. Close surveillance is still recommended with updated screening of cardiovascular risk factors and possibly repeating CAC measurement given the higher likelihood of developing subclinical atherosclerosis over time in persons with family history of premature CHD.[20]”

We found that the hazard ratio of ASCVD was significantly higher among those with hypertension, which may be driven by the excess risk of stroke among individuals with CAC=0. Incidence rates of ASCVD were not appreciably different using more stringent blood pressure thresholds as compared to the 2017 ACC/AHA guidelines. There was no statistically significant association between incident hypertension and incident ASCVD events. In age-stratified analyses (Supplementary Table 2), we found that ASCVD event rates were relatively high among those less than 65 years old. Therefore, it is important to control blood pressure in in individuals with hypertension and CAC=0 through lifestyle modification and antihypertensive treatment. Statin therapy can be added in this group to further lower ASCVD risk.

Our results confirm that the warranty period of CAC=0 may extend up to 15 years among most individuals.[21] These results are reassuring for most patient groups if clinicians and patients opt to measure CAC when there is clinical uncertainty after risk assessment. A recent study from MESA found that among those with CAC=0, the estimated warranty period of CAC >0 varied from 3 to 7 years.[22] Presence of diabetes was associated with significantly shorter warranty period and therefore a shorter time when retesting CAC would be indicated, while family history of CHD and cigarette smoking had a smaller impact on the warranty period.

The presence of diabetes mellitus, cigarette smoking, or family history of premature ASCVD is associated with a higher likelihood of presence of CAC and conversion from CAC 0 to >0.[7–9] Follow-up ranged from 2.5 to 10 years in these previous studies. A study by Joshi et al found that over a median of 10.4 years, hypertension and cigarette smoking significantly predicted ASCVD events among those with CAC=0 at baseline.[10]

Identifying risk factors that are associated with incident ASCVD outcomes among those with CAC=0 can inform treatment decisions with statins. Our results are reassuring that for most risk factors, absolute event rates remain low in the presence of CAC=0. Indeed, a prior study from the SCAPIS cohort showed that among participants with CAC=0, 5% had CCTA-detected atherosclerosis and 0.4% had significant stenosis.[23] Therefore, withholding statin therapy for long-term or postponing it is reasonable if there is any disutility regarding the potential benefit of statins on the patient’s part. A previous study demonstrated that CAC testing was cost-effective if there was patient disutility which was defined as the willingness to trade 2 weeks of perfect health to avoid 10 years of taking statins.[5] On the other hand, although a CAC score of 0 does indicate relatively low risk in those with smoking or diabetes, the absolute ASCVD event rates are close to or exceed the threshold for consideration of statin therapy. Therefore, clinicians should consider statin therapy using a shared decision making approach that includes informing patients on options

for risk reduction, perceived benefits of treatment, and allowing patients to engage in informed decision making based on their preferences and values.[24,25] Should statin therapy be deferred due to disutility on the part of the patient, it may be reasonable to repeat a CAC scan and reinitiate a preventive pharmacotherapy discussion within 5 years given the shorter warranty period in these individuals.[22] In all cases, clinicians should stress the importance of tight control of risk factors including smoking cessation, hemoglobin A1c and blood pressure control using medications and lifestyle modification.

Our results also highlight the importance of 10-year ASCVD risk assessment in primary ASCVD prevention. We noted that the observed ASCVD event rates in people with calculated 10-year ASCVD risk of ≥7.5% remain very close to the statin net benefit threshold[26,27] when these people are followed for long-term 16-year follow-up (Table 2). Similarly, the presence of risk factors in those with calculated 10-year ASCVD risk ≥7.5% portends a worse prognosis over long-term (Supplementary Table 1). A higher 10-year ASCVD risk in such cases is likely a marker of a longer duration for the presence of a risk factor (by capturing age in calculation of the 10-year ASCVD risk) as well as the interaction between various risk factors. These results reaffirm that an initial treatment strategy with statin therapy is reasonable in those with intermediate ASCVD risk as long as patient and the clinician are comfortable with a strategy of long-term statin use. On the other hand, if there is any disutility associated with long-term statin use, CAC remains an excellent tool available to the clinicians and patients to further guide the risk discussion surrounding long-term statin use.[5]

Our study has limitations. We presented rates per person-years, which are equivalent to yearly averages, though we acknowledge that event rates are likely not homogenously distributed throughout the entire follow-up period. The projected benefit of preventive therapies may differ by duration of follow-up and aging of the cohort, though this was not considered in the present study. However, as ASCVD prevention involves risk reduction strategies over a long-term horizon, we believe that average event rates are still helpful information for both the patient and clinician to gauge risk of ASCVD. Furthermore, AHA/ACC prevention and cholesterol guidelines also utilize average ASCVD event rates as percentages for risk stratification and guiding statin therapy. Although we performed sex-stratified analyses, we were underpowered to perform analyses by racial/ethnic groups. The association between LDL-C and incident events can be difficult to interpret due to confounding by indication for statin use especially given the high proportion of incident statin therapy over follow up. Similarly, the effect of intervening antihypertensive therapy may not be adequately assessed. Some risk factors for common mortality causes, such as breast cancer, are missing. Lastly, CHD deaths may have been underestimated as a result of difficulties in adjudication, although we believe this measurement error would be likely random and similar to what may be found in any epidemiological study.

In summary, the overall risk for ASCVD among a majority of individuals with CAC 0 continues to remain low at long-term follow-up. Current cigarette smoking, diabetes mellitus, or hypertension are associated with incident ASCVD events and mortality at long-term follow-up among those with CAC 0. Family history of premature ASCVD may be associated with ASCVD risk among women only. In such individuals, initiation and the

long-term use of statin therapy along with a heart-healthy life style and risk factor control may be warranted as part of the clinician patient risk discussion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST DISCLOSURES

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*Significant where noted (>$10,000); remainder modest (<$10,000).

The remaining coauthors report no relevant conflicts of interest.

ABBREVIATIONS

ACC/AHA/MS	American Heart Association/ American College of Cardiology/Multisociety

ASCVD	Atherosclerotic Cardiovascular Disease
CAC	Coronary Artery Calcium
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
PCE	Pooled Cohort Equations

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Clinical Perspective

What is new?

- Among individuals without coronary artery calcium (CAC=0), cigarette smoking, diabetes mellitus, and hypertension are independently associated with incident atherosclerotic cardiovascular disease events over long-term follow-up.

What are the clinical implications?

- Among individuals with CAC=0 who are current smokers, have diabetes mellitus, or hypertension, initiation and the long-term use of statin therapy along with a heart-healthy life style and risk factor modification may be warranted as part of the clinician patient risk discussion.

Table 1.

Baseline characteristics of the study population among those with baseline coronary artery calcium 0, stratified by development of incident atherosclerotic cardiovascular disease

	Incident ASCVD		
	No (N= 3,212)	**Yes (N= 189)**	**p-value**
Age	58 (9)	61 (9)	<0.001
Sex			
Women	2,047 (64%)	109 (58%)	0.09
Men	1,165 (36%)	80 (42%)	
Race/Ethnicity			0.06
White	1,068 (33%)	56 (30%)	
Chinese-American	386 (12%)	13 (7%)	
Black	992 (31%)	70 (37%)	
Hispanic American	766 (24%)	50 (26%)	
Graduate or professional school	587 (18%)	28 (15%)	0.15
Presence of health insurance	2,847 (89%)	165 (88%)	0.61
Cigarette smoking status			<0.001
Never	1,811 (57%)	84 (45%)	
Former	983 (31%)	60 (32%)	
Current	406 (13%)	44 (23%)	
Diabetes mellitus	279 (9%)	35 (19%)	<0.001
Hypertension	1,545 (48%)	124 (66%)	<0.001
Systolic BP, mm Hg	122 (20)	131 (23)	<0.001
Aspirin use	428 (14%)	33 (18%)	0.13
Statin use	306 (10%)	21 (11%)	0.47
Waist circumference, cm	96.5 (14.8)	99.1 (14.6)	0.02
Family history of premature ASCVD	468 (18%)	34 (23%)	0.13
Chronic kidney disease	440 (14%)	43 (23%)	0.001
HDL-C, mg/dL	53 (15)	50 (14)	0.01
Triglycerides, mg/dL	116 (31)	115 (31)	0.54
LDL-C, mg/dL	126 (81)	138 (133)	0.07
*Lp(a), mg/dL	18.2 (7.6–40.8)	18.4 (8.4–47.0)	0.70
*hsCRP, mg/L	1.92 (0.82–4.26)	2.55 (0.86–4.99)	0.06
10-year ASCVD risk, %	4.84 (2.05–10.68)	10.68 (4.61–18.77)	<0.001
<7.5%	2,022 (63%)	65 (34%)	
7.5%–<15%	646 (20%)	60 (32%)	
15%–<20%	199 (6%)	17 (9%)	

Continuous variables are summarized as mean (standard deviation) or median (interquartile range)* as appropriate. Categorical variables are summarized as count (percentage)

Abbreviations: BP (blood pressure); CHD (coronary heart disease); HDL-C (high-density lipoprotein cholesterol); LDL-C (low-density lipoprotein cholesterol); Lp(a) (lipoprotein (a)); hsCRP (high-sensitivity C-reactive protein); ASCVD (atherosclerotic cardiovascular disease)

Table 2.

Unadjusted incidence rates of atherosclerotic cardiovascular disease and all-cause mortality among those with CAC=0 at baseline (median follow up time 15.9 years)

	ASCVD (per 1000-person years)	All-Cause Mortality (per 1000-person years)
Cigarette smoking status		
Never	3.07	7.15
Former	4.05	9.11
Current	7.30	13.86
Diabetes mellitus		
No	3.46	7.79
Yes	8.92	13.49
Hypertension		
No	2.55	5.11
Yes	5.44	12.42
Aspirin use		
No	3.78	8.11
Yes	5.16	11.14
Statin use		
No	3.83	8.54
Yes	4.56	9.47
Increased waist circumference		
No	2.97	6.61
Yes	4.14	9.09
Family history of premature ASCVD		
No	3.49	7.72
Yes	4.54	5.98
CKD		
No	3.48	7.29
Yes	6.75	17.06
HDL-C ≤50 mg/dL		
No	3.50	8.35
Yes	4.31	8.85
Triglycerides ≥150 mg/dL		
No	3.65	8.42
Yes	4.62	9.11
LDL-C ≥130 mg/dL		
No	4.02	8.96
Yes	3.68	7.87
Lp(a) ≥50 mg/dL		
No	3.71	8.68

	ASCVD (per 1000-person years)	All-Cause Mortality (per 1000-person years)
Yes	4.64	8.35
hsCRP ≥2 mg/L		
No	3.33	7.58
Yes	4.53	9.69
Calculated ASCVD risk		
<7.5%	2.09	3.67
7.5%–<15%	6.19	11.51
15%–<20%	5.87	16.83

Abbreviations: CHD (coronary heart disease); HDL-C (high-density lipoprotein cholesterol); LDL-C (low-density lipoprotein cholesterol); Lp(a) (lipoprotein (a)); hsCRP (high-sensitivity C-reactive protein); ASCVD (atherosclerotic cardiovascular disease)

Increased waist circumference is defined as ≥90 cm for men or ≥80 cm for women

Table 3.

Multivariable-adjusted hazard ratios (95% confidence interval) for the association of cardiovascular risk factors and incident atherosclerotic cardiovascular disease and all-cause mortality among those with coronary artery calcium 0 at baseline

	ASCVD	All-Cause Mortality
Cigarette smoking status		
Never	1.00 (ref)	1.00 (ref)
Former	1.07 (0.71,1.61)	1.04 (0.79,1.38)
Current	**2.12 (1.32,3.42)**	**2.66 (1.89,3.74)**
Diabetes mellitus	**1.68 (1.01,2.80)**	1.13 (0.78,1.63)
Hypertension	**1.57 (1.06,2.33)**	**1.37 (1.03,1.81)**
Aspirin use	1.06 (0.66,1.69)	0.79 (0.57,1.10)
Time varying statin use	0.81 (0.53,1.24)	0.79 (0.59,1.05)
Waist circumference, per 10 cm	1.05 (0.91,1.20)	**1.10 (1.00,1.21)**
Family history of premature ASCVD	1.30 (0.86,1.96)	0.83 (0.59,1.17)
Chronic kidney disease	1.23 (0.77,1.95)	1.14 (0.84,1.53)
HDL-C, per 10 mg/dL	0.92 (0.79,1.06)	0.96 (0.87,1.07)
Triglycerides, per 10 mg/dL	1.00 (0.97,1.03)	0.99 (0.97,1.02)
LDL-C, per 10 mg/dL	0.99 (0.94,1.05)	0.97 (0.92,1.01)
*Lp(a), per 5 mg/dL	1.07 (0.46,2.49)	1.21 (0.66,2.22)
*hsCRP, per mg/L	1.00 (0.84,1.19)	1.12 (0.99,1.26)

Abbreviations: SBP (systolic blood pressure); CHD (coronary heart disease); HDL-C (high-density lipoprotein cholesterol); LDL-C (low-density lipoprotein cholesterol); Lp(a) (lipoprotein (a)); hsCRP (high-sensitivity C-reactive protein).

*Lp(a) and hsCRP are log-transformed

Model is adjusted for age, sex, race/ethnicity, education, presence of healthcare insurance and all listed risk factors

BOLDED items are significant statistically significant (P < 0.05)