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Predictors of Coronary Heart Disease Events Among Asymptomatic Persons With Low Low-Density Lipoprotein Cholesterol

MESA (Multi-Ethnic Study of Atherosclerosis)

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Objectives Our aim was to identify risk factors for coronary heart disease (CHD) events among asymptomatic persons with low (≤130 mg/dl) low-density lipoprotein cholesterol (LDL-C).

Background Even among persons with low LDL-C, some will still experience CHD events and may benefit from more aggressive pharmacologic and lifestyle therapies.

Methods The MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective cohort of 6,814 participants free of clinical cardiovascular disease. Of 5,627 participants who were not receiving any baseline lipid-lowering therapies, 3,714 (66%) had LDL-C ≤130 mg/dl and were included in the present study. Unadjusted and adjusted hazard ratios were calculated to assess the association of traditional risk factors and biomarkers with CHD events. To determine if subclinical atherosclerosis markers provided additional information beyond traditional risk factors, coronary artery calcium (CAC) and carotid intima media thickness were each separately added to the multivariable model.

Results During a median follow-up of 5.4 years, 120 (3.2%) CHD events were observed. In unadjusted analysis, age, male sex, hypertension, diabetes mellitus, low high-density lipoprotein cholesterol (HDL-C), high triglycerides, and subclinical atherosclerosis markers (CAC >0; carotid intima media thickness ≥1 mm) predicted CHD events. Independent predictors of CHD events included age, male sex, hypertension, diabetes, and low HDL-C. After accounting for all traditional risk factors, the predictive value of CAC was attenuated but remained highly significant. The relationship of all independent clinical predictors remained robust even after accounting for elevated CAC.

Conclusions Among persons with low LDL-C, older age, male sex, hypertension, diabetes, and low HDL-C are associated with adverse CHD events. Even after accounting for all such variables, the presence of CAC provided incremental prognostic value. These results may serve as a basis for deciding which patients with low LDL-C may be considered for more aggressive therapies. (J Am Coll Cardiol 2011;58:364–74) © 2011 by the American College of Cardiology Foundation

Low values of low-density lipoprotein cholesterol (LDL-C) are known to be associated with fewer adverse cardiovascular events in both primary and secondary prevention studies than are normal or elevated LDL-C values. Given this established relationship, the treatment guidelines of the National Cholesterol Education Program (NCEP) have

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identified lowering LDL-C as the primary target of cholesterol-lowering therapy (1). In light of multiple trials that have confirmed the benefit of aggressive cholesterol-lowering therapy, the NCEP amended its guidelines in 2004 and suggested that for high-risk persons, the LDL-C goal is <100 mg/dl, but when risk is very high, an LDL-C goal of <70 mg/dl is a reasonable therapeutic strategy (2). The results of these guidelines have helped to shape a new paradigm shift in which some have argued that when it comes to LDL-C, the lower the better.

To date, there is no known threshold LDL-C level below which no further reduction in risk occurs. A study by Lepper et al. (3) demonstrated that even among patients with very low LDL-C (<60 mg/dl), statin use was safe and was associated with improved survival. The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study found that among apparently healthy persons with LDL <130 mg/dl and high-sensitivity C-reactive protein (hsCRP) ≥2 mg/l, treatment with 20 mg of rosuvastatin significantly reduced the incidence of major cardiovascular events. It is estimated that if these so-called JUPITER criteria are applied to the U.S. population, >11 million new persons may be candidates for statin therapy (4). Given the overall low event rate of most primary prevention trials, many patients need to be treated to prevent 1 cardiovascular event. Thus, identifying further risk markers for cardiovascular events may allow a more precise identification of persons who will benefit from statin therapy.

Given that even among patients with low LDL-C some will still experience cardiovascular events, we sought to identify risk factors for coronary heart disease (CHD) among patients with no known coronary artery disease (CAD) and low LDL-C. We hypothesized that both traditional risk factors (i.e., clinical risk factors, inflammatory biomarkers, lipids) and imaging biomarkers of pre-clinical atherosclerosis will predict CHD events. Our secondary aim was, thus, to identify the incremental value of these imaging markers to the more traditional, widely available clinical risk factors.

Methods

Study participants. Details of the design and organization of the MESA trial have been reported previously (5–7). Between July 2000 and September 2002, 6,814 persons were selected to be members of the MESA cohort at 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). The participants were required to be between 45 and 84 years of age and to have no clinical cardiovascular disease at the time of enrollment in the study. The participants were recruited at each site from lists of residents, dwellings, and telephone company customers. In the last few months of the recruitment period, participants were also recruited from lists of Medicare beneficiaries obtained from the Centers for Medicare and Medicaid Services and by referrals from other participants, to ensure the enrollment of adequate numbers of elderly participants and participants from all 4 ethnic groups. Participants identified themselves as white, black, Hispanic, or Chinese at the time of enrollment. The study was approved by the institutional review boards of each site, and all participants gave written informed consent.

For the purposes of the present study, 2,201 participants (32%) with LDL-C >130 mg/dl were excluded. Of the remaining 4,613 participants, 899 (19%) who were on lipid-lowering therapies at baseline were excluded. The resulting population thus consisted of 3,714 subjects with low LDL-C who were free of cardiovascular disease and were not receiving any lipid-lowering therapies (Fig. 1). Among this group, 1,511 (41%) participants had LDL-C ≤100 mg/dl and the remaining 2,203 (59%) had LDL-C between 101 and 130 mg/dl.

Abbreviations and Acronyms

CAC = coronary artery calcium
CAD = coronary artery disease
CHD = coronary heart disease
CI = confidence interval
CIMT = carotid intima media thickness
CT = computed tomography
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
hsCRP = high-sensitivity C-reactive protein
IMT = intima media thickness
LDL-C = low-density lipoprotein cholesterol
NCEP = National Cholesterol Education Program
ROC = receiver-operating characteristic

Computed tomography scanning. Carr et al. (8) have reported details of the methods used by the MESA trial for computed tomography (CT) scanning and for interpretation of the scans. Each of the 6 MESA centers assessed the amount of coronary artery calcium (CAC) with the use of either an electron-beam CT scanner (at the Chicago, Los Angeles, and New York centers) or a multidetector CT system (at the Baltimore,

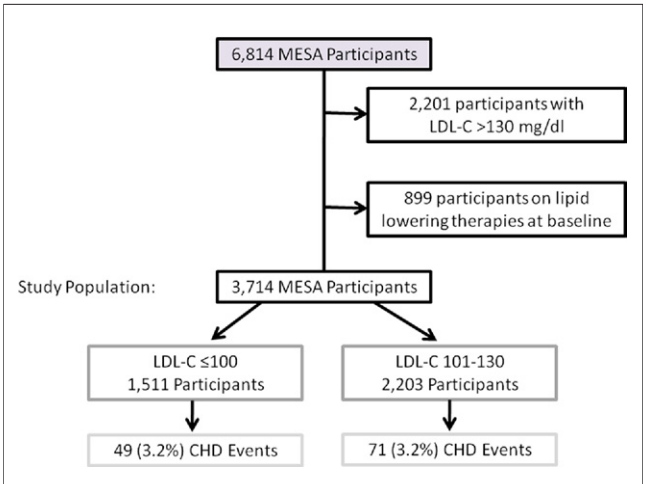

Figure 1 Flowchart Illustrating Study Population

CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis.

Forsyth County, and St. Paul centers). Certified technologists placed radiographic phantoms containing identical and known concentrations of calcium beneath the thorax of each participant and then scanned the participant 2 times.

A radiologist or cardiologist read all CT scans at a single center (the Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance, California) and used an interactive scoring system similar to that of Yaghoubi et al. (9). The reader–work station interface calibrated each tomographic image according to the estimated attenuation of the calcium phantom and then identified and quantified the CAC in each image. The coronary calcium score (Agatston score) (10) was calculated for each scan, and the mean of the 2 scans was used in all analyses. Intraobserver and interobserver agreement was excellent (kappa statistics 0.93 and 0.90, respectively).

Carotid intima media thickness. Trained technicians in each center performed B-mode ultrasonography of the right and left near and far walls of the internal carotid and common carotid arteries (11). Images were recorded using the Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, Wisconsin). An ultrasound reading center (Department of Radiology, Tufts Medical Center, Boston, Massachusetts) measured maximal carotid intima media thickness (CIMT) of the internal and common carotid sites as the mean of the maximum intima media thickness (IMT) of the near and far walls of the right and left sides.

Risk factors. As part of the baseline examination, clinical teams at each of the 6 centers collected information on cardiovascular risk factors, including family history, history of smoking, hypertension, and diabetes mellitus. Using a Dinamap Pro 1000 automated oscillometric sphygmomanometer (Critikon), resting blood pressure was measured 3 times with the participant in the seated position. A central laboratory (University of Vermont, Burlington, Vermont) measured levels of total and high-density lipoprotein cholesterol (HDL-C), triglycerides, plasma glucose, and hsCRP in blood samples obtained after a 12-h fast.

Diabetes was defined as a fasting plasma glucose level >125 mg/dl or a history of medical treatment for diabetes. The body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Family history of CHD was obtained by asking the participants whether any member of their immediate family (parents, siblings, and children) had had a fatal or nonfatal myocardial infarction, coronary angioplasty, or coronary artery bypass graft surgery. The participants were classified as current cigarette smokers, former smokers, or persons who had never smoked.

Follow-up. New cardiovascular events were recorded for a median of 5.4 years. At intervals of 9 to 12 months, an interviewer contacted each participant or a family member by telephone to inquire about interim hospital admissions, outpatient diagnoses of cardiovascular disease, and deaths. To verify self-reported diagnoses, medical records were reviewed for participants who had been hospitalized or received an outpatient diagnosis of cardiovascular disease. Records were obtained for 98% of reported cardiovascular events associated with hospitalization. For participants who had died of cardiovascular causes outside the hospital, interviews were conducted with the next of kin and copies of death certificates were requested.

Trained personnel abstracted data from medical records that reported possible cardiovascular events. Two physicians who were members of the MESA trial mortality and morbidity review committee independently classified events and assigned incidence dates. If they disagreed, the full committee made the final classification.

Coronary heart disease events consisted of myocardial infarction, angina, resuscitated cardiac arrest, or CHD death. The diagnosis of myocardial infarction was based on a combination of symptoms, electrocardiographic findings, and levels of cardiac biomarkers. Hospital records and family interviews were used to determine whether deaths were related to CHD. A death was considered related to CHD if it occurred within 28 days after a myocardial infarction, if the participant had chest pain within the 72 h before death, or if the patient had a history of CHD and there was no known nonatherosclerotic, noncardiac cause of death.

The adjudicators graded angina as definite, probable, or absent on the basis of their clinical judgment. A classification of definite or probable angina required clear and definite documentation of symptoms distinct from the diagnosis of myocardial infarction. A classification of definite angina also required objective evidence of reversible myocardial ischemia or obstructive CAD. A more detailed description of the MESA trial follow-up methods is available online (12).

Statistical analysis. We used chi-square tests for categorical variables and 1-way analysis of variance tests for continuous variables to assess for differences among participants with and without CHD events. Medians of C-reactive protein were compared using the Kruskal-Wallis equality of populations rank test.

We used unadjusted and adjusted Cox proportional hazards regression analyses to estimate hazard ratio (HR) for CHD events. The CAC score was examined as a binary score (presence or absence of any CAC) and as a categorical variable (0, 1 to 100, 101 to 400, and >400). CIMT was examined across a binary cutpoint (with ≥1 mm considered elevated) as well as across increasing quartiles of CIMT thickness. Low HDL-C was defined as <40 mg/dl for men and <50 mg/dl for women. Elevated triglycerides were considered ≥150 mg/dl.

All risk factors that have an established association with CHD events were included in the multivariable model. To isolate the effect of adding imaging markers (CAC and CIMT) to clinical and biomarker data, which are more readily available to clinicians, the multivariable model was

Table 1 Baseline Characteristics of Study Participants

Variable	Total Population
n	3,714
Age, yrs	61.6 ± 10.5
Sex, % male	47.9
Race, %	
Caucasian	36.9
Chinese	13.0
African American	28.5
Hispanic	21.7
Cigarette smoking, %	
Never	49.5
Former	36.6
Current	13.9
Hypertension, %	42.5
Diabetes mellitus, %	12.8
Total cholesterol, mg/dl	178.5.8 ± 24.6
HDL, mg/dl	51.9 ± 16.1
LDL, mg/dl	102.4 ± 19.8
TG, mg/dl	103 (72–154)
Non-HDL, mg/dl	126.6 ± 23.8
CRP, mg/l	1.87 (0.79–4.31)
IMT >1 mm, %	31.1
CAC score >0, %	44.4
Framingham risk score	7.45

Values are n, mean ± SD, %, or median (interquartile range).
CAC = coronary artery calcium; CRP = C-reactive protein; HDL = high-density lipoprotein; IMT = intima media thickness; IQR = interquartile range; LDL = low-density lipoprotein; TG = triglycerides.

initially computed without any imaging markers. We then separately added CAC (both as binary and categorical variable) and CIMT to the multivariable model to determine the incremental predictive value of these markers. In addition, CAC and CIMT were also added to a multivariable model that included the Framingham risk score (as a continuous variable). We compared the area under the receiver-operating characteristic (ROC) curve to identify the incremental value of adding CAC to a multivariable model that includes nonimaging clinical characteristics as well as to the Framingham risk score.

To describe the frequency of coronary events according to time, we constructed Nelson-Aalen cumulative hazard ratios curves for CHD events among participants with LDL-C ≤130 mg/dl. The data were stratified according to the presence or absence of CAC score. All analyses were performed with Stata software version 11.0 (StataCorp, College Station, Texas). Two-tailed p values <0.05 were considered significant.

Results

Baseline characteristics. The final study population consisted of 3,714 participants (age 62 ± 11 years, 48% males). Table 1 shows the baseline characteristics of the entire study population.

CHD events. During the mean follow-up of 5.4 years (range 0 to 7 years), 120 (3.2%) subjects experienced CHD events, corresponding to 5.9 CHD events per 1,000 person-years of follow-up. Table 2 shows the baseline characteristics of the study population stratified by participants who had and did not have CHD events. Participants experiencing CHD events were more likely to be older males with diabetes and hypertension and to have higher levels of triglycerides but lower HDL-C. Correspondingly, they were found to have a significantly higher Framingham risk score (13.9% vs. 7.2% risk of a hard CHD event over the next decade, $p < 0.001$). Participants experiencing CHD events during the follow-up period had a higher baseline prevalence of CAC as well a higher baseline CIMT. There was no difference in the CHD event rate for participants with LDL-C ≤100 mg/dl versus those with LDL-C between 101 and 130 mg/dl (Fig. 2). Figure 3 illustrates the relationship of CAC and CIMT with CHD events. There was a stepwise increase in events rates across increasing categories of CAC. Conversely, there was a less pronounced relationship between CHD events across increasing quartiles of CIMT.

Unadjusted predictors of CHD events. Among the 3,714 participants with LDL-C ≤130 mg/dl, significant predictors of CHD events included older age, male sex, diabetes, hypertension, low HDL-C, and elevated triglycerides (Table 3). However, family history of myocardial infarction, tobacco use, and elevated hsCRP were not associated with an increased risk.

Of the imaging markers evaluated, the presence of any CAC was the most powerful predictor of events (HR: 13.5)

Table 2 Baseline Characteristics Stratified by Occurrence of CHD Events During Follow-Up

Variable	No CHD	CHD	p Value
Age, yrs	61.3	69.1	<0.001
Sex, % male	46.9	75.0	<0.001
Total cholesterol, mg/dl	178.6	176.1	0.27
Non-HDL cholesterol, mg/dl	126.4	131.0	0.04
HDL cholesterol, mg/dl	52.2	45.1	<0.001
LDL cholesterol, mg/dl	102.3	103.0	0.70
Triglycerides, mg/dl, median	102.0	125.5	0.002
Race, %			0.39
Caucasian	36.6	43.3	
Chinese	13.1	9.2	
African American	28.6	27.5	
Hispanic	21.7	20.0	
Hypertension, %	41.5	70.8	<0.001
Diabetes mellitus, %	12.3	29.2	<0.001
Cigarette smoking, %			0.15
Never	49.8	42.5	
Former	36.3	45.0	
Current	14.0	12.5	
CRP, mg/l, median	1.89	1.66	0.85*
CAC >0, %	42.9	89.2	<0.001
Carotid IMT >1 mm, %	30.4	53.1	<0.001
Framingham risk score	7.2	13.9	<0.001

*By Kruskal-Wallis.
CHD = coronary heart disease; other abbreviations as in Table 1.

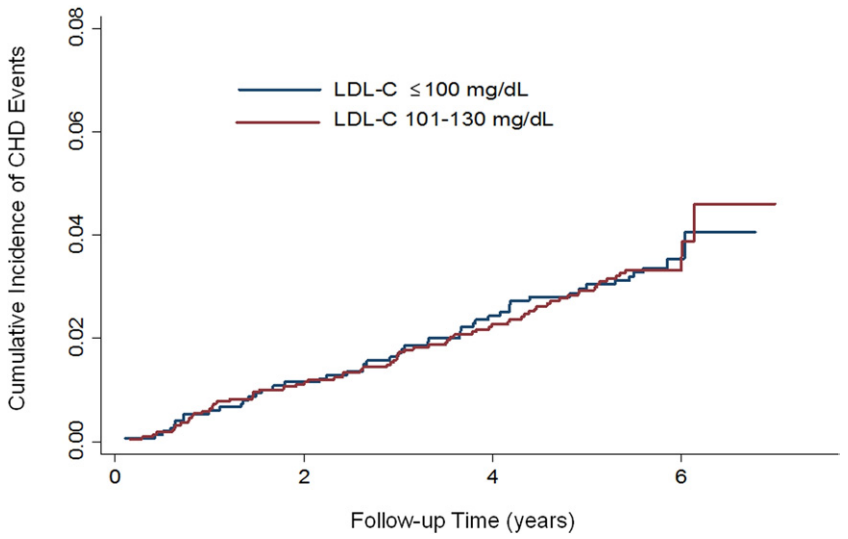

Figure 2 **Cumulative Incidence of CHD Events According to Baseline LDL-C Levels**

The incidence of CHD is compared over time by baseline LDL-C. There was no difference in event rate for participants with LDL-C ≤100 mg/dl **(blue line)** versus those with LDL-C between 101 and 130 mg/dl **(red line)**. Abbreviations as in Figure 1.

and demonstrated a step-wise increased level of risk across categories of increasing CAC scores. Increased CIMT was also found to have a significant unadjusted association with CHD events.

Multivariable-adjusted predictors. In the initial multivariable model (Table 3) consisting of traditional risk factors only, advanced age, male sex, hypertension, diabetes, and low HDL-C levels emerged as independent predictors of CHD events among participants with LDL-C ≤130 mg/dl. When CAC was added to the multivariable model, all other independent clinical predictors remained robust; however, the presence of CAC provided significant incremental value for predicting CHD events (HR: 4.23; 95% confidence interval [CI]: 2.28 to 7.86). Furthermore, there was a stepwise increase in risk across escalating categories of higher CAC scores, with HRs of 2.67 (95% CI: 1.32 to 5.39), 5.84 (95% CI: 2.88 to 11.85), and 9.29 (95% CI: 4.49 to 19.2) for CAC 1 to 100, 101 to 400, and >400,

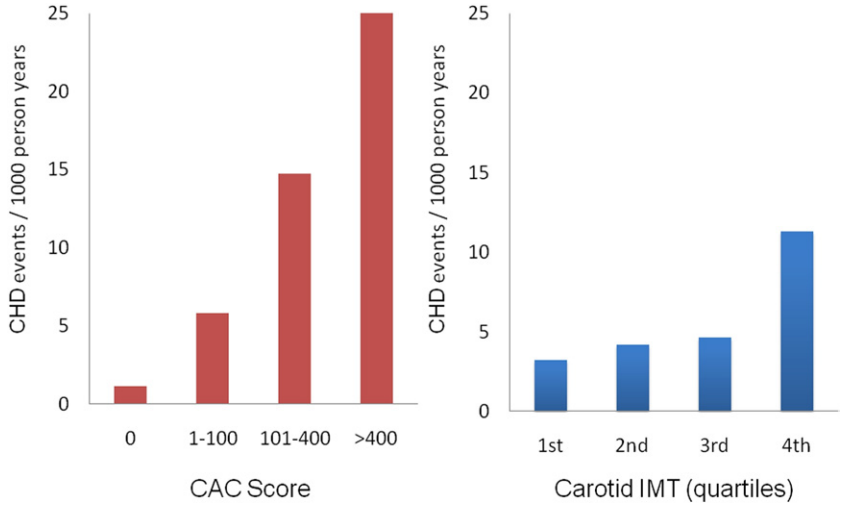

Figure 3 **CHD Outcomes Across CAC and Carotid IMT**

The rates of incident coronary heart disease (CHD) per 1,000 person-years at risk are displayed by increasing categories of coronary artery calcium (CAC) and carotid intima media thickness (IMT). There was a substantial stepwise increase in event rates across increasing categories of CAC, but a less pronounced relationship between CHD events across increasing quartiles of carotid IMT.

Table 3 Unadjusted and Adjusted Hazard Ratios for CHD Events

Variable	Unadjusted	Adjusted for Traditional Risk Factors	Adjusted for All Risk Factors (CAC + CIMT Included)*
Age, 10 yrs	2.12 (1.76–2.55)	1.88 (1.51–2.34)	1.26 (1.00–1.62)
Male	3.37 (2.23–5.10)	2.88 (1.82–4.56)	1.77 (1.09–2.87)
Race			
Caucasian	(Reference)	(Reference)	(Reference)
Chinese	0.61 (0.32–1.17)	0.72 (0.36–1.43)	0.88 (0.44–1.77)
African American	0.86 (0.56–1.33)	0.70 (0.42–1.17)	0.97 (0.57–1.66)
Hispanic	0.83 (0.51–1.35)	0.70 (0.41–1.19)	0.91 (0.52–1.57)
Hypertension	3.46 (2.32–5.09)	2.30 (1.47–3.59)	2.13 (1.34–3.38)
Diabetes mellitus	3.01 (2.03–4.46)	1.64 (1.05–2.58)	1.37 (0.86–2.20)
Family history of MI	1.39 (0.95–2.04)	1.30 (0.87–1.93)	1.10 (0.73–1.66)
Low HDL-C	2.47 (1.72–3.55)	2.44 (1.59–3.74)	2.29 (1.47–3.56)
High TG	1.93 (1.34–2.78)	1.31 (0.85–2.02)	1.17 (0.75–1.85)
hsCRP >2 mg/l	0.91 (0.64–1.31)	0.94 (0.63–1.41)	0.86 (0.57–1.31)
Cigarette smoking			
Never	(Reference)	(Reference)	(Reference)
Former	1.44 (0.98–2.11)	1.15 (0.75–1.76)	1.13 (0.73–1.76)
Current	1.06 (0.60–1.88)	1.40 (0.75–2.63)	1.22 (0.65–2.32)
Framingham risk score, 1% increase	1.10 (1.08–1.12)	—	1.04 (1.02–1.07)†
CIMT ≥1 mm	2.63 (1.82–3.81)	—	1.05 (0.68–1.62)
CIMT quartiles		—	
1	(Reference)	—	(Reference)‡
2	1.27 (0.66–2.43)	—	0.79 (0.38–1.63)
3	1.39 (0.73–2.63)	—	0.96 (0.49–1.86)
4	3.44 (1.97–6.02)	—	0.94 (0.51–1.72)
CAC score >0	10.92 (6.14–19.42)	—	4.12 (2.20–7.71)§
0	(Reference)	—	(Reference)
1–100	5.13 (2.66–9.91)	—	2.75 (1.36–5.56)
101–400	13.08 (6.92–24.72)	—	5.82 (2.84–11.93)
>400	26.66 (14.35–49.53)	—	9.05 (4.27–19.20)

Values are hazard ratios (95% confidence interval). *Multivariable model using carotid intima media thickness (CIMT) ≥1 mm and 4 calcium groups. †Multivariable model including Framingham risk score, CIMT ≥1 mm, and 4 calcium groups. ‡Multivariable model using 4 quartiles of CIMT and 4 calcium groups. §Multivariable model using CIMT ≥1 mm and CAC >0.
hsCRP = high-sensitivity C-reactive protein; other abbreviations as in Tables 1 and 2.

respectively. Similar HRs were obtained when CAC was added to a multivariable model that included the Framingham risk score (HR: 4.13, 95% CI: 2.05 to 8.35; HR: 9.66, 95% CI: 4.81 to 19.40; and HR: 16.98, 95% CI: 8.36 to 34.49) for CAC 1 to 100, 101 to 400, and >400, respectively.

When adding CAC to the multivariable model that included all traditional risk factors, the area under the ROC curve increased from 0.815 to 0.857 ($p < 0.001$). When CAC was added to the Framingham risk score, the area under the ROC curve increased from 0.756 to 0.829 ($p < 0.001$) (Online Fig. 1).

Conversely, when increased CIMT (≥1 mm) was introduced to the multivariable model that consisted of all traditional risk factors, its association was no longer significant (HR: 1.42, 95% CI: 0.93 to 2.18). Similar lack of statistical significance of CIMT in our multivariable model was observed across increasing quartiles of CIMT (HR: 0.79, 95% CI: 0.38 to 1.62; HR: 0.97, 95% CI: 0.50 to 1.88; and HR: 1.30, 95% CI: 0.71 to 2.36 for the second, third, and fourth quartiles, respectively, when the lowest quartile was used as the reference group) or if continuous IMT (per standard deviation increase) was used to represent this risk factor in the model (HR: 1.10, 95% CI: 0.94 to 1.30).

In the final multivariable model consisting of all traditional risk factors as well as CAC and CIMT, the presence of any CAC was associated with a fourfold increased risk of CHD events; the respective risk was 9-fold higher among subjects with CAC >400. In this same model, hypertension and low HDL-C were the strongest nonimaging clinical risk predictors and were each associated with an approximately 2-fold higher risk of CHD events (Table 3).

CHD outcomes combining multiple risk factors. Among participants with LDL-C <130 mg/dl, aside from age and sex, the 3 independent clinical predictors that emerged as significant risk factors were hypertension, diabetes, and low HDL-C. Figure 4 demonstrates the unadjusted cumulative event curves for CHD events according to increasing number of these 3 risk factors. The differences among these curves were statistically significant ($p < 0.001$). In age- and sex-adjusted analysis, as compared with subjects having no underlying diabetes mellitus, hypertension, or low HDL-C (36%), the HRs for CHD events for subjects with 1 risk factor (42%), 2 risk factors (18%), and all 3 risk factors (4%)

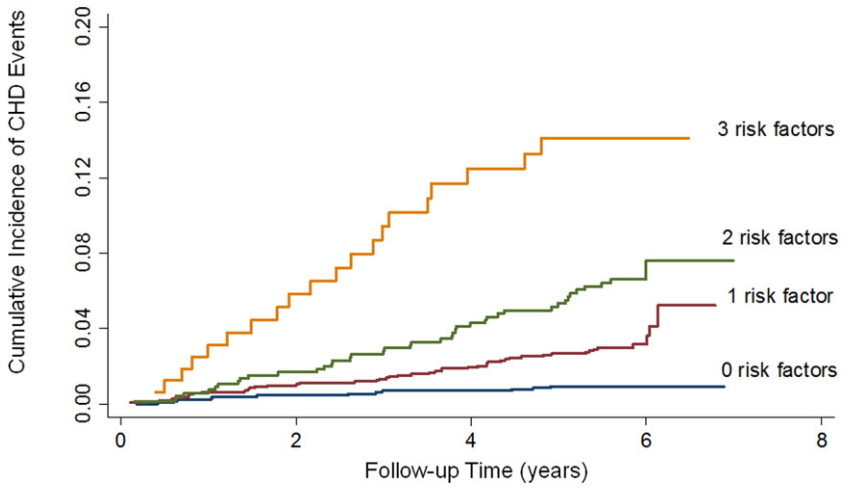

Figure 4 **Cumulative Incidence of CHD Events Across Increased Number of Risk Factors Among Persons With Low LDL-C**

The incidence of CHD over time is compared by number of baseline risk factors among persons with low (≤130 mg/dl) LDL-C. Risk factors include hypertension, diabetes mellitus, and low high-density lipoprotein cholesterol. Abbreviations as in Figure 1.

were 2.79 (95% CI: 1.47 to 5.36), 5.15 (95% CI: 2.70 to 9.84) and 9.97 (95% CI: 4.84 to 20.54), respectively. This relationship persisted even after adjusting for increased categories of CAC (HRs: 2.39, 4.14, and 6.80, respectively, for subjects with 1, 2, or 3 risk factors).

In addition, we evaluated how the presence of CAC modifies the risk profile offered by each of these predictors. Figure 5 shows the cumulative time to event curves for each of these risk factors stratified by the presence or absence of CAC. For each independent predictor, the presence of CAC was found to be associated with higher events. To analyze the additive effect of multiple risk factors and how the presence or absence of CAC may modify this risk, Figure 6 shows the cumulative time to event curves across escalating number of risk factors. Regardless of the number of risk factors present, the presence of CAC was found to consistently be associated with higher CHD events.

Discussion

Our study shows that, among persons with no known CAD and low LDL-C, clinical and imaging risk markers can be used to identify patients who have increased risk of having CHD events develop. In such populations, male sex, older age, hypertension, low HDL-C, and diabetes can each be used to identify persons who have a higher risk of future events. When considered collectively, the presence of multiple such risk factors can be used to identify the group that is most likely to experience future events. However, our study also shows that even after accounting for all relevant traditional clinical risk factors (and even after considering populations with multiple coexisting risk factors), the presence and burden of CAC can be used to further enhance risk assessment, whereas its absence is associated with a very low event rate.

There are several important reasons to study populations with low LDL-C. First, although many of the risk factors identified in our study (i.e., hypertension, low HDL-C) have been extensively studied, the relevance of these risk factors among persons with baseline low LDL-C is less established. When considering a group of patients with no known CAD and low LDL-C, it is thus important to demonstrate that previously recognized risk factors (which were validated in more heterogeneous populations) remain significant. For instance, deGoma et al. (13) showed that, among persons with low LDL-C, low HDL-C is still associated with increased risk. However, many persons in their study had known ischemic heart disease and more than half of them were receiving lipid-lowering therapies. A recent analysis from the JUPITER study (14) suggests that, among patients treated with potent statin therapy, low HDL-C is not predictive of residual cardiovascular risk. However, when examining the patients who were randomly assigned to the placebo group (i.e., patients not on lipid-lowering therapies, and therefore very similar to the patients included in our study), low HDL-C was associated with a substantially elevated risk. Another important reason to specifically study populations with low LDL-C is to examine whether imaging risk factors have any additional predictive value after considering all traditional risk factors and nonimaging biomarkers that are typically available to clinicians. Conversely, it is also important to examine whether the predictive power of such risk factors persists after accounting for imaging biomarkers such as CIMT and CAC.

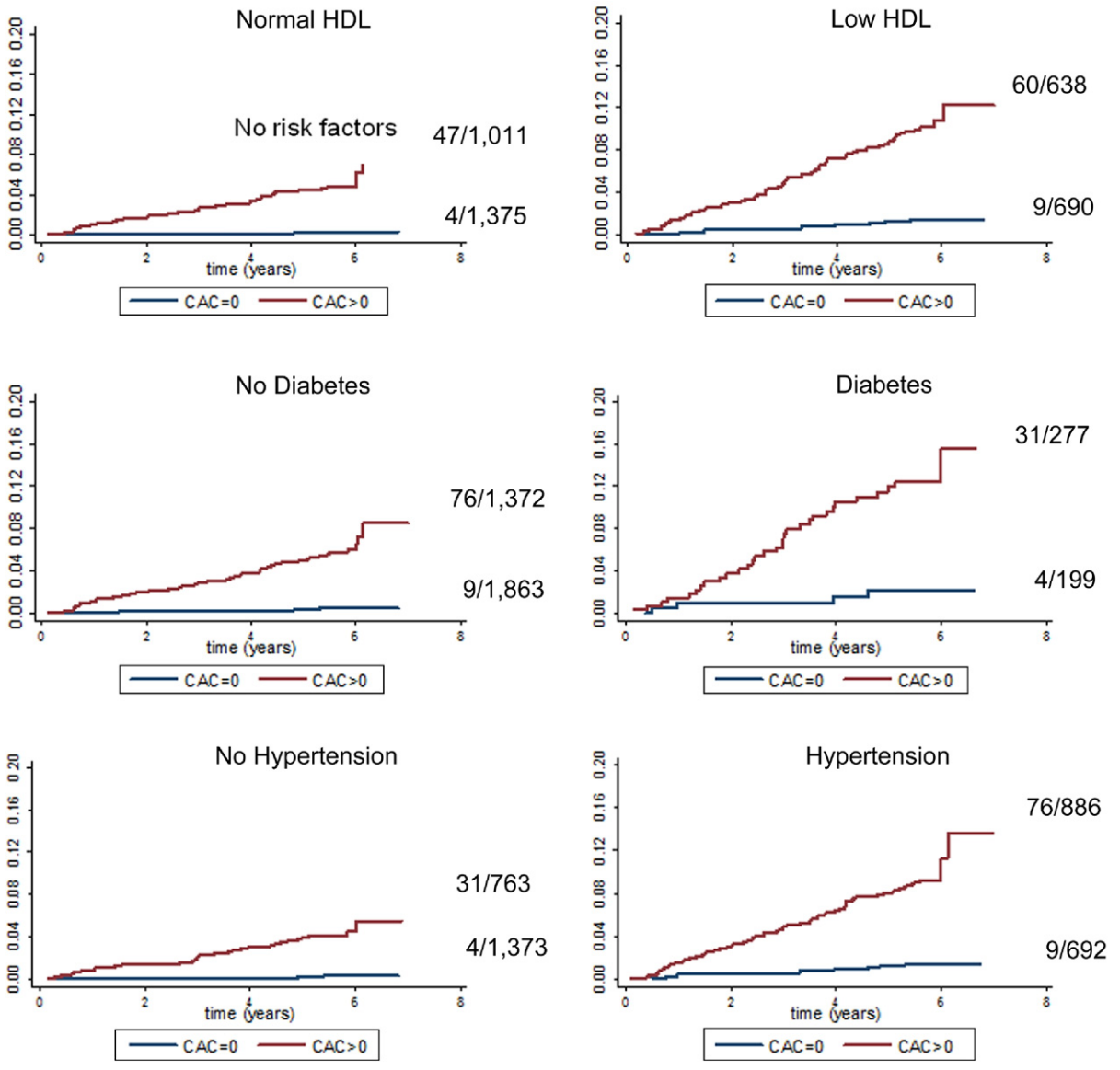

Figure 5 **Cumulative Incidence of CHD Events Among Participants With Low LDL-C (≤130 mg/dl) Across Risk Factors and Stratified by Presence or Absence of CAC**

The incidence of CHD over time is compared among participants with and without low high-density lipoprotein (HDL) cholesterol, diabetes mellitus, and hypertension. For each graph, separate cumulative incidence curves are displayed for participants with coronary artery calcifications (CAC [CAC >0]) **(red lines)** and without CAC (CAC = 0) **(blue lines)**. Next to each curve, the total number of events as well as the number of at-risk persons is displayed. For each individual risk factor—and regardless if present or absent—the presence of CAC provides incremental prognostic value. Abbreviations as in Figure 1.

Although the NCEP recommendation for treating patients to achieve LDL <100 mg/dl is reserved for patients at very high risk, recent trends have shown that clinicians are now using high doses of statins (15) even for patients who may already be at NCEP goal levels. While such practice patterns are based on intuition rather than evidence, we do know that even among patients with very low LDL, there remains a subgroup of patients who experience cardiovascular events. Thus, risk stratification beyond LDL-C may be important in more accurately identifying CHD risk.

Whereas numerous studies have sought to identify and assess different methods of risk stratification that would add value beyond that of LDL-C levels, far less is known about whether it is possible to distinguish high-risk from low-risk patients from among patients who already have very low LDL-C levels. Indeed, the identification of such patients may help to identify a subgroup of patients who would be appropriate candidates for more aggressive therapies.

Our findings support the need for comprehensive risk assessment in patients with low LDL-C. Specifically, low

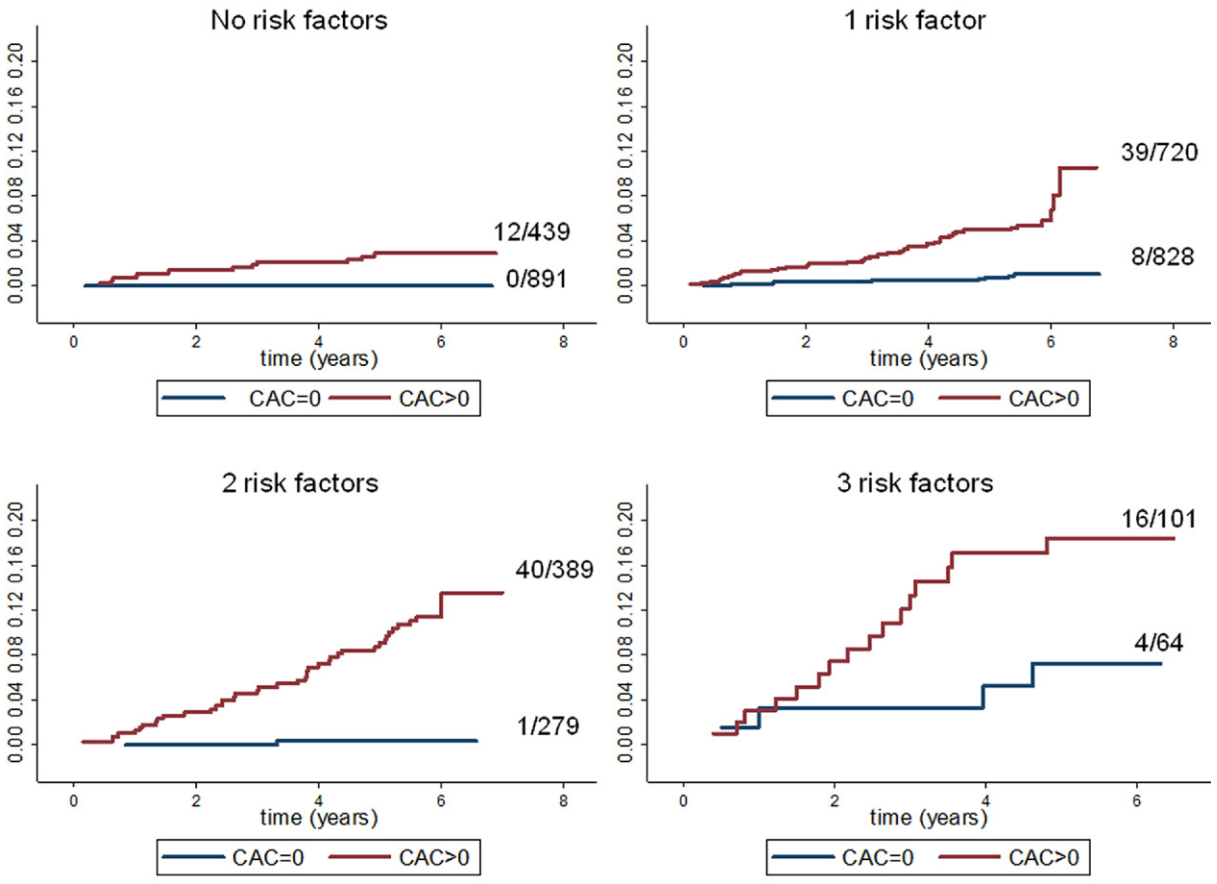

Figure 6 **Cumulative Incidence of CHD Events Among Participants With Low LDL-C (≤130 mg/dl) Across an Increasing Number of Risk Factors and Stratified by Presence or Absence of CAC**

The incidence of CHD over time is compared among participants with increasing numbers of the following risk factors: hypertension, diabetes mellitus, and low high-density lipoprotein cholesterol. For each graph, separate cumulative incidence curves are displayed for participants with coronary artery calcifications (CAC [CAC >0]) **(red lines)** and without CAC (CAC = 0) **(blue lines)**. Next to each curve, the total number of events as well as the number of at-risk persons is displayed. The presence or absence of CAC provides incremental prognostic value across increased numbers of traditional risk factors. Abbreviations as in Figure 1.

HDL-C and the presence of hypertension or diabetes should alert clinicians of patients who might benefit from preventive measures. While systematic screening for CAC cannot be suggested on the basis of our findings (and such a strategy is also unlikely to be a cost-effective strategy), for selected persons, those for whom such information would result in a change in medical therapy, assessing for CAC may be a reasonable approach. In such patients, the presence of CAC would translate into a higher risk profile and could thus be used to initiate or intensify medical management. Conversely, the absence of coronary calcification can be used as a reassurance and may signal that there is no need to intensify current therapies, or the threshold for LDL-C–lowering therapy can be higher than if there was advanced subclinical atherosclerosis. In particular, middle-aged persons who have 2 or fewer risk factors and no coronary calcification (Fig. 6) have an extremely low event rate over a 6-year follow-up.

Recently, the JUPITER study demonstrated that, among persons with LDL <130 mg/dl and hsCRP ≥2 mg/l, treatment with 20 mg of rosuvastatin significantly reduced the incidence of major cardiovascular events, whereas in our study, hsCRP was not found to be a predictor of future events. It is thought that JUPITER participants represent adults who are more likely to benefit from statin therapy; however, since no "control group" of individuals with low hsCRP was included in that study, it is unclear whether patients with low hsCRP who would have otherwise met criteria for inclusion in the JUPITER study would have also benefited from the pharmacological intervention studied. A recent population study from the ARIC (Atherosclerosis Risk in Communities) study has shown that JUPITER eligible patients with a hsCRP >2 mg/l have a higher event rate than those who have a lower CRP (16), but other studies did not identify any relationship between hsCRP and cardiovascular risk (17–19).

Our study attempted to explore the added value of imaging for pre-clinical atherosclerosis. Although we found CAC to be a powerful predictor among persons with low LDL-C, the association of CIMT with events was weaker. Nevertheless, there are convincing data supporting the independent prognostic value of CIMT, and, therefore, the reason for the attenuated relationship observed in our study is not entirely clear.

Although our study identifies CAC as a powerful risk marker, the potential benefits of CAC scanning need to be weighed against the potential harmful effects of radiation. The mean effective radiation dose of a CAC scan when using appropriate protocols is 1 mSv (20). Although causality has not been firmly established, using this dose, the estimated cancer risk of a single CAC scan of a patient at age 55 years may be expected to result in a lifetime excess risk of 3 and 8 cancers per 100,000 persons for men and women, respectively (21).

Study limitations. In our study, patients and their physicians were informed of their CAC score. This process might have caused patients with higher CAC to receive more preventive therapies. However, in such cases, the effect of CAC on subsequent events would be attenuated. Our study also eliminated patients who were treated with lipid-lowering therapies at baseline. That may have introduced a selection bias because patients on lipid-lowering therapies were older and more likely to have other comorbidities such as hypertension and diabetes. Consequently, patients excluded for this reason also had a higher Framingham risk score as well as an increased burden of pre-clinical atherosclerosis.

Our study is limited by a relatively low event rate, and it is therefore possible that increased events over a longer follow-up of the MESA study cohort may identify additional risk factors over time. Finally, although our study can be used to identify important associations with risk of CHD events, future prospective randomized trials will be required to determine whether clinical outcomes can be improved by detecting and treating such higher-risk persons.

Conclusions

Among an ethnically diverse, middle-aged and older cohort with low LDL-C and no known baseline cardiovascular disease, older age, male sex, hypertension, diabetes, and low HDL-C were associated with increased risk of subsequent CHD events. After accounting for all such variables and even among persons with multiple clinical risk factors, the presence of CAC provided incremental prognostic value. While these results may serve as a basis for deciding which patients with low LDL-C may be considered for more aggressive therapies, future studies are needed to identify whether selective treatment of particular subgroups of patients with low LDL-C would translate into improved outcomes.

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Key Words: atherosclerosis ■ cardiovascular events ■ coronary artery calcium ■ prevention ■ risk factors.

APPENDIX

For a supplemental figure and table, please see the online version of this article.

Predictors of Coronary Heart Disease Events Among Asymptomatic Persons With Low Low-Density Lipoprotein Cholesterol: MESA (Multi-Ethnic Study of Atherosclerosis)

Ron Blankstein, Matthew J. Budoff, Leslee J. Shaw, David C. Goff, Jr, Joseph F. Polak, Joao Lima, Roger S. Blumenthal, and Khurram Nasir

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