ORIGINAL RESEARCH

Does Lowering Low-Density Lipoprotein Cholesterol With Statin Restore Low Risk in Middle-Aged Adults? Analysis of the Observational MESA Study

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BACKGROUND: It is unclear if statin therapy in midlife can restore low cardiovascular risk in hypercholesterolemic individuals.

METHODS AND RESULTS: At baseline, we grouped 5687 MESA (Multi-Ethnic Study of Atherosclerosis) participants aged ≥50 years without clinical cardiovascular disease (CVD) by Adult Treatment Panel III statin treatment recommendation and statin treatment status. We used Cox regression to compare the risks for coronary heart disease and CVD between the untreated group with low-density lipoprotein cholesterol (LDL-C) <100 mg/dL (reference) and other groups, adjusting for CVD risk factors. We also grouped participants by LDL-C level (< or ≥100 mg/dL), coronary artery calcium score (0 or >0 Agatston units), and statin status (untreated or treated) with the untreated LDL-C <100 mg/dL and coronary artery calcium=0 Agatston units as the reference. There were 567 coronary heart disease and 848 CVD events over 15 years of follow-up. The hazard ratios (HRs) for coronary heart disease and CVD in the group with statin-treated LDL-C <100 mg/dL were 1.16 (95% CI, 0.85–1.58) and 1.02 (95% CI, 0.78–1.32), respectively. However, participants with coronary artery calcium >0 Agatston units, treated to LDL-C <100 mg/dL had HRs of 2.6 (95% CI, 1.7–4.2) for coronary heart disease and 1.8 (95% CI, 1.2–2.6) for CVD.

CONCLUSIONS: Individuals treated with statins to LDL-C <100 mg/dL had similar levels of risk for atherosclerotic CVD as individuals with untreated LDL-C <100 mg/dL. However, individuals with coronary artery calcium >0 Agatston units have substantially higher risks despite lipid-lowering therapy, suggesting that statin treatment in midlife may not restore a low-risk state in primary prevention patients with established coronary atherosclerosis.

Key Words: cardiovascular disease ■ cholesterol ■ coronary artery calcium ■ restore low risk ■ statin

Preventive pharmacotherapy instituted after the development of an adverse risk factor, such as use of blood pressure–lowering drugs to treat hypertension, lowers the risk for incident cardiovascular events.[1] However, despite significant risk reduction, patients with hypertension treated back to optimal blood pressure levels (<120/<80 mm Hg) still remain at twice the cardiovascular disease (CVD) risk of those who have untreated optimal blood pressure levels.[2] This is likely attributable to the cumulative end-organ damage (higher left ventricular mass, greater coronary artery calcification, and worsened renal function) that occurs over time before the initiation of blood-pressure–lowering therapy.[2,3] Hypertensive end-organ damage does not appear to be fully reversible; thus, low risk cannot be restored despite treatment down to optimal blood pressure levels.

It is unclear at present whether low risk can be restored with statin treatment in midlife in patients with nonoptimal cholesterol levels. Statins are clearly

CLINICAL PERSPECTIVE

What Is New?

- This study asked whether statin therapy in midlife can restore low cardiovascular risk in people with and without subclinical atherosclerosis.

What Are the Clinical Implications?

- The results suggest that the low-risk state can be restored in patients who do not have advanced coronary atherosclerosis as indicated by a coronary calcium score of 0 Agatston units.
- However, a low-risk state may not necessarily be restored by statin therapy in primary prevention patients with a coronary calcium score of >0 Agatston units.
- Initiation of low-density lipoprotein cholesterol–lowering therapies earlier in the life course may be the optimal atherosclerotic cardiovascular disease prevention approach in some patients.

Nonstandard Abbreviations and Acronyms

AU	Agatston units
MESA	Multi-Ethnic Study of Atherosclerosis
SBP	systolic blood pressure

effective at reducing risk for atherothrombotic events, CVD mortality, and total mortality.[4–6] However, because of the biology of atherosclerosis and the mechanism of action of statins, there is reason to believe that statins may be able to more fully restore the low-risk state of those who maintain low low-density lipoprotein cholesterol (LDL-C) levels naturally. For example, statins lower LDL-C and inflammation, with the result that arterial plaques appear to become less likely to cause clinical events[5]; the associated reduction in clinical events is far out of proportion to the reduction in plaque volume or vessel stenosis.[7–9] In addition, statin therapy does not appear to affect risk estimates in prospective risk models (such as the pooled cohort equations). Risk estimates are similar for the same cholesterol levels regardless of whether an individual is on statin therapy, suggesting that the achieved cholesterol level is a more important predictor than the prior exposure, unlike with blood pressure.[10]

On the other hand, substantial residual risk is observed in several high-risk primary prevention statin trials and all secondary prevention statin trials,[11] suggesting that some lipid-associated risk may be irreversible once significant coronary artery atherosclerosis (end-organ damage) is present. Thus, statins may not restore low risk in all primary prevention patients.

Therefore, we sought to determine whether effective treatment of LDL-C (to <100 mg/dL) with statin therapy is associated with a CVD risk level similar to that observed in people with untreated low LDL-C levels (<100 mg/dL) in a contemporary community-based sample. We explored these associations in the overall cohort and in participants with and without underlying advanced coronary atherosclerosis. We hypothesized that in the overall group, treatment to LDL-C <100 mg/dL would be associated with the same level of risk seen in individuals who entered the cohort with untreated LDL-C <100 mg/dL. However, we also hypothesized that the subgroup of participants who were treated to LDL-C <100 mg/dL and had coronary artery calcium (CAC) scores >0 Agatston units (AU) would have higher risk (residual risk) than those who entered the cohort with CAC=0 AU and untreated low LDL-C levels (<100 mg/dL).

METHODS

Data Availability Statement

Data from the MESA (Multi-Ethnic Study of Atherosclerosis) study can be requested through the National Institutes of Health's Biologic Specimen and Data Repository Information Coordinating Center Open Program at https://biolincc.nhlbi.nih.gov/studies/mesa/.

Study Participants

The MESA study is a National Heart, Lung, and Blood Institute–sponsored multicenter longitudinal study to examine factors associated with subclinical CVD and the progression from subclinical to clinical CVD.[12] The cohort consists of 6814 White (38%), Black (28%), Hispanic (23%), and Chinese (12%) men and women aged 45 to 84 years free of CVD at baseline (2000–2002) recruited from 6 US communities (Forsyth County, NC; Baltimore City and Baltimore County, MD; Chicago, IL; St. Paul, MN; New York, NY). We excluded participants who were aged <50 years (n=883) at baseline to enhance the age comparability between the cholesterol-treated and -untreated groups. In addition, we excluded participants if they were fasting <8 hours before blood draw (n=6), missing LDL-C (n=94), missing covariates (n=27), or missing antihypertensive medication or lipid-lowering medication data (n=12). We excluded 4 participants who had prebaseline events (n=4) and 20 participants who were missing an event status indicator on all events of interest. Eighty-one participants who were on nonstatin lipid-lowering medication were

also excluded. The sample size for this analysis was 5687 participants. All participants in the study signed the consent form, and the study was approved by the institutional review board of each field center and the data coordinating center. Details regarding the MESA study have been published previously.[12]

Demographic and Risk Factor Measures

All data were collected by centrally trained and certified technicians. Three blood pressure measurements, 1 minute apart, were collected using a Dinamap Pro 100 model monitor, and the average value of the second and third measurements was used. Sex, race/ethnicity, and smoking data were collected using self-administered questionnaires. Weight and height were measured using a standard protocol. Participants were asked to bring in their medications. Total plasma cholesterol, high-density lipoprotein cholesterol, and triglyceride measurements were performed at the Collaborative Studies Clinical Laboratory at Fairview University Medical Center (Minneapolis, MN) in blood samples obtained after a 12-hour fast. Methods regarding lipid measurements have been published.[13] LDL-C was calculated using the Friedewald equation.[14] Serum glucose was measured by the glucose-oxidase method. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or on antihypertensive medications. Diabetes mellitus was defined as fasting serum glucose ≥126 mg/dL or receiving diabetes mellitus medications.

CAC Measurement

Chest computed tomography was performed using either electron-beam (New York, Los Angeles, and Chicago centers) or multidetector (Baltimore, St. Paul, and Forsyth County centers) cardiac gated computed tomography scanners. Images were read centrally for CAC by the Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center. AU score was used in the analysis.[15]

Event Ascertainment and Adjudication

Incident CVD events were recorded over 15 years, with a mean follow-up of 12.4 years (SD, 3.8 years). Participants were contacted every 9 to 12 months to ascertain interim hospitalizations, cardiovascular outpatient diagnoses and procedures, and deaths. Medical and hospital records were obtained and adjudicated by 2 members of the Morbidity and Mortality Committee. In this article, coronary heart disease (CHD) events were defined as myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina followed by revascularization, and CHD death.

CVD events included all CHD events plus stroke, stroke death, other atherosclerotic death, and other CVD death.

Statistical Analysis

In the first set of analyses, designed to compare the risks of individuals at selected LDL-C levels naturally or because of statin treatment, participants were classified into 6 groups, as follows: (1) untreated with LDL-C <100 mg/dL (reference group); (2) optional treatment: untreated and either CHD equivalent (diabetes mellitus or peripheral artery disease) with LDL-C 100 to 129 mg/dL, or ≥2 risk factors (other than diabetes mellitus) with LDL-C 130 to 159 mg/dL, or 0 to 1 risk factor with LDL-C 160 to 189 mg/dL; (3) treatment recommended: untreated and CHD equivalent with LDL-C ≥130 mg/dL or ≥2 risk factors with LDL-C ≥160 mg/dL, or 0 to 1 risk factor with LDL-C ≥190 mg/dL; (4) treated to LDL-C <100 mg/dL; (5) treated and controlled: ≥2 risk factors with treated LDL-C 100 to 129 mg/dL or 0 to 1 risk factor with treated LDL-C 100 to 159 mg/dL; or (6) treated and uncontrolled: CHD equivalent with treated LDL-C ≥100 mg/dL, or ≥2 risk factors with treated LDL-C ≥130 mg/dL, or 0 to 1 risk factor with treated LDL-C ≥160 mg/dL. This classification was based on the Adult Treatment Panel III guidelines[16,17] because these guidelines are contemporaneous with MESA inception dates and represent the practice patterns over the majority of follow-up.

The group who was untreated with LDL-C <100 mg/dL was used as the reference group. Incident CHD, CVD, and stroke were compared between the reference group and the other 5 groups using the Cox regression analysis, adjusting for age, sex, race/ethnicity, body mass index, current and former smoking, SBP, and hypertension treatment. The primary purpose of this set of analyses was to examine whether participants with LDL-C <100 mg/dL on statin treatment have the same risk for incident CHD, CVD, and stroke as those who have LDL-C <100 mg/dL without statin treatment.

In the second set of analyses, participants were classified into 8 groups stratified by LDL-C level (<100 mg/dL or ≥100 mg/dL), CAC score (0 or >0 AU), and statin treatment status (untreated or treated). In these analyses, the group with CAC=0 AU, LDL-C <100 mg/dL and not on statin treatment was used as the reference group. Cox regression analysis adjusting for the covariates described above plus diabetes mellitus was performed to compare the hazards of incident CHD, CVD, and stroke between each of the other groups (in particular, the group with CAC >0 AU, LDL-C <100 mg/dL, and on statin treatment) and the reference group. The main purpose for this set of analyses was to examine

whether the risks of incident CHD, CVD, and stroke for those with CAC >0 AU, LDL-C <100 mg/dL, and on statin treatment were similar to those with untreated LDL-C <100 mg/dL and CAC=0 AU. We further examined whether greater (≥100 AU) compared with lesser (1–99 AU) burden of CAC was associated with higher risk among those with treated or untreated low LDL-C levels.

The proportional hazards assumption was examined using the time interaction test. For the 6 groups based on the treatment status and the cholesterol level, the overall time interaction tests were not significant (P=0.56, 0.62, and 0.50 for CHD, CVD and stroke, respectively). For the 8 groups classified by LDL-C, statin treatment, and CAC score, again the overall time interaction tests were not significant (P=0.36, 0.34, and 0.53 for CHD, CVD, and stroke, respectively).

RESULTS

Study Sample

There were 5687 participants who experienced 567 CHD, 848 CVD, and 261 stroke events over 15 years of follow-up (with the average follow-up time of 12.4 years). Table 1 presents the baseline characteristics stratified by LDL-C level and treatment eligibility/treatment status. Compared with the untreated with LDL-C <100 mg/dL (reference) group, the treated with LDL-C <100 mg/dL group tended to be slightly older, had more White participants and fewer Black and Hispanic participants, and more people with diabetes mellitus and receiving antihypertensive medication. The untreated/treatment recommended group and the treated but uncontrolled group tended to have more Black participants and fewer White participants, higher body mass index and SBP, and more diabetes mellitus than the reference group. The untreated/optional treatment group had slightly more White participants and fewer Black participants, fewer people on antihypertensive medication, and fewer people with diabetes mellitus. The treated/controlled group had more White participants and fewer Black and Hispanic participants, more people on antihypertensive medication, and fewer people with diabetes mellitus than the reference group.

Risks for CVD Outcomes Based on LDL-C Level and Statin Treatment Status

The incident rates of the reference group with untreated LDL-C <100 mg/dL were 7.9, 12.1, and 3.0 per 1000 person-years for CHD, CVD, and stroke, respectively (Table 2). The corresponding rates of the group with treated LDL-C <100 mg/dL were 11.9, 16.3, and 3.6 per 1000 person-years, for CHD, CVD and stroke, respectively. Compared with the reference group, the

Table 1. Baseline Characteristics by LDL-C and Treatment Status Groups, Age ≥50 years, MESA

		No.	Age, y	Men, %	White, %	Black, %	Hispanic, %	Chinese, %	Never Smoker, %	Former Smoker, %	Current Smoker, %	BMI, kg/m²	SBP, mm Hg	Hypertension Medication, %	Diabetes Mellitus, %
Not on statin therapy at baseline	LDL-C<100 mg/dL	1198	64.0 (9.5)	49	37	30	21	12	49	38	13	27.8 (5.4)	127.0 (21.5)	40	14
	Optional treatment	3043	63.8 (8.9)	47	40	26	22	13	51	39	11	28.1 (5.4)	127.2 (21.2)	33	7
	Treatment recommended	496	64.9 (8.8)	45	29	34	27	10	47	35	18	29.1 (5.5)	135.2 (22.7)	44	35
On statin therapy at baseline	LDL-C<100 mg/dL	465	67.1 (7.9)	48	46	25	17	12	47	43	11	28.8 (5.2)	130.3 (22.7)	68	25
	Controlled	301	66.0 (8.3)	45	51	26	15	8	51	43	6	28.6 (5.0)	128.8 (19.9)	48	0
	Uncontrolled	184	66.6 (8.4)	47	23	44	23	10	52	36	12	29.7 (5.6)	134.0 (22.0)	69	45

Values shown are mean (SD) or percent. Statin Treatment Group Characteristics. Optional treatment: untreated and either CHD equivalent (diabetes mellitus or peripheral artery disease) with LDL-C 100–129 mg/dL, or ≥2 risk factors (other than diabetes mellitus) with LDL-C 130–159 mg/dL, or 0–1 risk factor with LDL-C 160–189 mg/dL. Treatment recommended: untreated and CHD equivalent with LDL-C ≥130 mg/dL or ≥2 risk factors with LDL-C ≥160 mg/dL, or 0–1 risk factor with LDL-C ≥190 mg/dL. Treated and controlled: ≥2 risk factors with treated LDL-C 100–129 mg /dL or 0–1 risk factor with treated LDL-C 100–159 mg/dL. Treated and uncontrolled: CHD equivalent with treated LDL-C ≥100 mg/dL, or ≥2 risk factors with treated LDL-C ≥130 mg/dL, or 0–1 risk factor with treated LDL-C ≥160 mg/dL. BMI indicates body mass index; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; and SBP, systolic blood pressure.

Table 2. Adjusted HR* for CHD, CVD, and Stroke by LDL-C and Treatment Groups, Age ≥50 years, MESA 15-Year Follow-Up

		CHD[†]			CVD[‡]			Stroke		
		No.	Rate[§]	HR (95% CI)	No.	Rate[§]	HR (95% CI)	No.	Rate[§]	HR (95% CI)
Untreated	LDL-C<100 mg/dL	112	7.9	1	170	12.1	1	44	3.0	1
	Optional treatment	246	6.7	0.89 (0.71–1.11)	401	11.1	0.97 (0.81–1.16)	142	3.8	1.28 (0.91–1.80)
	Treatment recommended	73	13.3	1.57[¶] (1.17–2.11)	97	18.0	1.33[‖] (1.04–1.71)	29	5.1	1.38 (0.86–2.22)
Treated	LDL-C<100 mg/dL	64	11.9	1.16 (0.85–1.58)	87	16.3	1.02 (0.78–1.32)	20	3.6	0.88 (0.52–1.50)
	Controlled	37	9.9	1.13 (0.78–1.65)	49	13.3	0.99 (0.72–1.36)	14	3.6	1.06 (0.58–1.94)
	Uncontrolled	35	17.9	1.93[#] (1.31–2.82)	44	22.7	1.55[‖] (1.11–2.17)	12	5.6	1.43 (0.76–2.72)

BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and SBP, systolic blood pressure.

*Adjusted for age, sex, race/ethnicity, BMI, current and former smoking, SBP, and hypertension treatment.

[†]CHD: MI, resuscitated cardiac arrest, definite angina, probable angina followed by revascularization, CHD death.

[‡]CVD: CHD, stroke, stroke death, other atherosclerotic death, and other CVD death.

[§]Rate per 1000 person-years.

[‖]$P<0.05$.

[¶]$P<0.01$.

[#]$P<0.001$.

hazard ratios (HRs) and corresponding 95% CIs for the group with treated LDL-C <100 mg/dL were 1.16 (0.85–1.58), 1.02 (0.78–1.32), and 0.88 (0.52–1.50), for CHD, CVD, and stroke, respectively, after adjustment for age, sex, race/ethnicity, body mass index, current and former smoking, SBP, and antihypertensive medication; thus, overall among individuals treated with statin to LDL-C<100 mg/dL, adjusted hazards were similar to those with untreated LDL-C <100 mg/dL.

For participants who were untreated but eligible for optional treatment, there were no significant differences in adjusted hazards for CHD, CVD, or stroke compared with the reference group. Among those who were untreated but who would be recommended for statin therapy because of elevated LDL-C and concomitant risk factors, adjusted hazards for CHD and CVD were significantly higher, whereas adjusted hazards for stroke were higher but were not significantly higher. Among participants treated with statins, those who were treated and controlled to recommended levels had nonsignificantly higher adjusted hazards for CHD, and stroke, whereas those who were treated and uncontrolled to recommended levels had significantly higher adjusted hazards for CHD (HR, 1.93; 95% CI, 1.31–2.82) and CVD (HR, 1.55; 95% CI, 1.11–2.17). For stroke, the HR was higher but not significantly higher.

Risks for CVD Outcomes Based on LDL-C Level and Statin Treatment Status, Stratified by Presence of CAC

Table 3 provides the baseline characteristics of the sample when stratified by LDL-C, statin treatment status, and CAC score at baseline. Among those with LDL-C <100 mg/dL at baseline (N=1663), 38.4% were untreated and had CAC=0 AU, 8.5% were treated and had CAC=0 AU, 33.6% were untreated and had CAC >0 AU, and 19.5% were treated with CAC >0 AU. Overall, the group with untreated LDL-C <100 mg/dL and with CAC=0 AU (the reference group) at baseline tended to be younger, have fewer male and White participants, lower body mass index, fewer people on antihypertensive medications, lower SBP, and fewer people with diabetes mellitus than most of the other groups.

Table 4 presents the number of events, incident rates, and adjusted HRs for CHD, CVD, and stroke. Compared with the reference group, the group with treated LDL-C <100 mg/dL and CAC=0 AU had adjusted HRs (95% CI) of 0.84 (0.37–1.93), 0.74 (0.39–1.39), and 0.76 (0.28–2.01), for CHD, CVD, and stroke, respectively (Table 4). Conversely, those with LDL-C <100 mg/dL and CAC >0 AU, whether treated or untreated, had 2.6-fold higher hazards for CHD and 1.8-fold higher hazards for CVD compared with the reference group. We also observed a dose response among those with CAC, with higher hazards for CHD and CVD among those with CAC ≥100 AU compared with those with CAC of 1 to 99 AU (Table 4). Thus, the presence of subclinical coronary atherosclerosis modified the association of statin treatment and LDL-C level with CHD and CVD outcomes. As expected, adjusted hazards were also higher for participants with LDL-C ≥100 mg/dL and CAC >0 AU, regardless of treatment status.

In an exploratory analysis, findings were similar to those in Table 4 when we considered low LDL-C

Table 3. Baseline Characteristics of 8 Groups Stratified by CAC, LDL-C, and Statin Treatment, Age ≥50 Years, MESA

LDL-C Level	Statin Treatment	CAC (AU)	No.	Age	Men, %	Race/ Ethnicity, %	BMI	Current Smoker, %	Hypertension Medication, %	SBP	Diabetes Mellitus, %
				Mean (SD)		White/Black/ Hispanic/ Chinese	Mean (SD)			Mean (SD)	
LDL-C<100 mg/dL	No	0	639	60.7 (8.6)	37	33/33/23/11	27.7 (5.5)	13	35	124 (21)	12
	Yes	0	141	64.5 (7.2)	37	33/35/20/13	28.7 (5.7)	13	64	127 (24)	22
	No	>0	559	67.8 (9.0)	63	41/27/19/13	27.9 (5.3)	13	46	131 (21)	16
	Yes	>0	324	68.3 (7.9)	53	52/21/16/11	28.8 (5.0)	9	70	132 (22)	27
	Yes	1–99*	152	66.6 (7.8)	42	49/24/14/12	28.9 (4.8)	9	66	129 (18)	21
	Yes	≥100†	172	69.8 (7.6)	62	53/19/17/11	28.7 (5.3)	9	73	134 (25)	31
LDL-C≥100 mg/dL	No	0	1660	60.5 (7.8)	35	33/31/24/12	28.4 (5.6)	12	28	125 (21)	8
	Yes	0	158	62.4 (7.2)	29	30/41/19/10	29.4 (5.2)	6	49	128 (19)	13
	No	>0	1879	67.1 (8.7)	57	43/24/21/12	28.1 (5.2)	12	41	131 (22)	13
	Yes	>0	327	68.1 (8.2)	52	46/29/18/8	28.9 (5.2)	9	60	132 (21)	19

Values shown are mean (SD) or percent. AU indicates Agatston Unit; BMI, body mass index; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; and SBP, systolic blood pressure.

*Restricted to 0<CAC<100 subgroup.

†Restricted to CAC≥100 subgroup.

levels to be <100 mg/dL for those with CAC=0 AU and <70 mg/dL for those with CAC >0 AU, regardless of statin treatment (Table 5). Thus, among those individuals with CAC, treatment even to LDL-C <70 mg/dL was still associated with residual risk compared with those who were untreated with LDL-C <100 mg/dL.

Sensitivity Analysis

Since the average ages between the reference group and the group with CAC >0 AU and treated LDL-C <100 mg/dL differ by 7.6 years, residual confounding could exist despite the statistical adjustment for age. Thus, we conducted a sensitivity analysis by matching the people in the reference group and the people in the group with CAC > 0 AU and treated LDL-C <100 mg/dL for age (within 5 years). Table S1 presents the age and baseline characteristics of the 299 matched pairs in the 2 groups. The mean ages are similar (67.3 and 67.5 years). Except for the group with CAC=0 AU and untreated LDL-C <100 mg/dL, of which there are more people with diabetes mellitus and more people on antihypertension treatments (probably attributable to older age), all other data are very similar to those in Table 3. The adjusted HRs for the CAC >0 AU and treated LDL-C <100 mg/dL group (compared with the reference group) are 3.10 (1.67–5.74) and 1.73

(1.10–2.72), for CHD and CVD, respectively. These results are very similar to the results in Table 4, providing reassurance regarding the main findings as presented in Table 4.

DISCUSSION

In this analysis of data from the MESA cohort study, middle-aged individuals treated with statins to LDL-C <100 mg/dL had overall similar levels of risk for atherosclerotic cardiovascular disease (ASCVD) as individuals who entered the cohort with untreated LDL-C values <100 mg/dL. Untreated individuals who were recommended for treatment by contemporary guidelines but were not treated, and individuals who were treated, but not to recommended LDL-C goals, also had higher ASCVD risks than participants who entered the cohort with untreated LDL-C values <100 mg/dL.

Among those with untreated or treated LDL-C <100 mg/dL at baseline, the majority had some CAC. Whereas the overall hazards were similar between treated and untreated participants with LDL-C <100 mg/dL, when we stratified by the presence of CAC, those with CAC >0 AU had 2.6 times the risk for CHD and 1.8 times the risk for CVD events as those

Table 4. Risk Factor–Adjusted* HRs for Incident CHD, CVD, and Stroke Stratified by CAC, LDL-C and Statin Treatment, Age ≥50 Years, MESA 15-Year Follow-Up

	Statin Treatment	CAC (AU)	No.	CHD[†]			CVD[‡]			Stroke		
				No.	Rate[§]	HR (95% CI)	No.	Rate[§]	HR (95% CI)	No.	Rate[§]	HR (95% CI)
LDL-C<100 mg/dL	No	0	639	28	3.5	1	52	6.5	1	21	2.6	1
	Yes	0	141	7	4.0	0.84 (0.37–1.93)	12	6.8	0.74 (0.39–1.39)	5	2.8	0.76 (0.28–2.01)
	No	>0	559	84	13.8	2.55[ǁ] (1.65–3.94)	118	19.5	1.85[ǁ] (1.33–2.58)	23	3.6	0.90 (0.49–1.65)
	Yes	>0	324	57	15.8	2.64[ǁ] (1.66–4.21)	75	20.9	1.78[ǁ] (1.24–2.56)	15	3.9	0.85 (0.43–1.67)
		1–99[¶]	152	20	11.0	2.15[#] (1.20–3.83)	27	14.9	1.47 (0.92–2.36)	6	3.1	0.78 (0.31–1.96)
		≥100**	172	37	20.8	3.05[ǁ] (1.84–5.06)	48	27.0	2.02[ǁ] (1.35–3.03)	9	4.7	0.89 (0.40–1.99)
LDL-C≥100 mg/dL	No	0	1660	45	2.1	0.63 (0.39–1.01)	99	4.7	0.75 (0.53–1.05)	48	2.2	0.89 (0.53–1.49)
	Yes	0	158	10	4.9	1.32 (0.64–2.71)	12	5.9	0.83 (0.44–1.55)	4	1.9	0.65 (0.22–1.90)
	No	>0	1879	274	13.1	2.63[ǁ] (1.77–3.90)	399	19.6	2.01[ǁ] (1.49–2.70)	123	5.7	1.46 (0.91–2.35)
	Yes	>0	327	62	17.1	3.20[ǁ] (2.03–5.04)	81	22.7	2.14[ǁ] (1.50–3.05)	22	5.7	1.33 (0.72–2.44)

AU indicates Agatston units; BMI, body mass index; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; and SBP, systolic blood pressure.

*Adjusted for age, sex, race/ethnicity, BMI, current and former smoking, SBP, hypertension treatment, and diabetes mellitus.

[†]CHD: MI, resuscitated cardiac arrest, definite angina, probable angina followed by revascularization, CHD death.

[‡]CVD: CHD, stroke, stroke death, other atherosclerotic death, and other CVD death.

[§]Rate per 1000 person-years.

[ǁ]P<0.001.

[¶]Restricted to 0<CAC<100 AU subgroup.

[#]P<0.05.

**Restricted to CAC≥100 AU subgroup.

with CAC=0 AU and an untreated LDL <100 mg/dL. Of note, the HRs for CHD and CVD are lower in the CAC >0 AU group treated to LDL-C <70 mg/dL when compared to the group treated to LDL-C <100 mg/dL, suggesting added benefit of treating to lower LDL-C levels. However, those with CAC >0 AU who were treated to LDL-C <70 mg/dL still had significantly higher HRs for CHD events when compared with the lowest-risk reference group. These data strongly suggest that the presence of calcified coronary atherosclerosis represents a stage of atherosclerosis beyond which LDL-C reduction with statin therapy alone may not fully reduce CHD and CVD risk to the level of those without calcified atherosclerosis.

Our results do not contradict the well-established effectiveness of statins for ASCVD risk reduction in patients with subclinical atherosclerosis.[18–20] The focus of our analysis was to see if statins can restore risk to the *lowest levels* observed in our sample when CAC is present; thus, we used the *lowest risk group as the referent*, whereas previous studies of statin effectiveness use the *untreated group at a similar level of risk or CAC status* as the referent. Of note, in studies of statin effectiveness, the absolute rates observed in the statin treated arms are often higher than are observed in the groups without CAC, which also support the findings we report.[20] Our results suggest that true low risk (the risks observed in the low LDL-C group without CAC) can be restored in those with elevated LDL-C but no CAC. However, in the presence of CAC, statin benefit is present but insufficient to restore a participant to the lowest category of risk. In total, these results continue to support the use of statins in patients with CAC; however, they also suggest that there may be benefit to the prevention of CAC. These results are similar to previous observations of CVD risk in treated individuals with hypertension, where low risk status is not restored through the treatment of hypertension to optimal levels.[2] Thus, treating coronary artery atherosclerosis determinants, like atherogenic lipoprotein levels, earlier in the life course in some patients may be a more effective preventive strategy than waiting until advanced atherosclerosis is present to initiate treatment.

Atherosclerosis is the underlying disease that causes most forms of heart attack and stroke. As such, it is not surprising that CAC, a radiographic manifestation

Table 5. Risk Factor Adjusted* HRs for Incident CHD, CVD, and Stroke Stratified by Coronary Calcium, LDL-C (mg/dL), and Statin Treatment, Age ≥50 Years, MESA 15-Year Follow-Up

CAC & LDL-C status	Statin Use	CHD[†]			CVD[‡]			Stroke		
		No.	Rate[§]	HR (95% CI)	No.	Rate[§]	HR (95% CI)	No.	Rate[§]	HR (95% CI)
CAC=0 AU & LDL-C (mg/dL) <100	No	28/639	3.5	1	52	6.5	1	21	2.6	1
CAC=0 AU & LDL-C (mg/dL) <100	Yes	7/141	4.0	0.84 (0.37–1.93)	12	6.8	0.74 (0.40–1.39)	5	2.8	0.76 (0.29–2.02)
CAC=0 AU & LDL-C (mg/dL) ≥100	No	45/1660	2.1	0.63 (0.39–1.01)	99	4.7	0.75 (0.53–1.04)	48	2.2	0.89 (0.53–1.48)
CAC=0 AU & LDL-C (mg/dL) ≥100	Yes	10/158	4.9	1.31 (0.64–2.71)	12	5.9	0.82 (0.44–1.55)	4	1.9	0.65 (0.22–1.90)
CAC >0 AU & LDL-C (mg/dL) <70	No	15/93	16.3	2.81[¶] (1.49–5.31)	20	21.8	1.90[¶] (1.13–3.20)	2	2.1	0.47 (0.11–2.04)
CAC >0 AU & LDL-C (mg/dL) <70	Yes	9/60	12.8	2.16[¶] (1.01–4.60)	13	18.2	1.57 (0.85–2.90)	2	2.7	0.62 (0.15–2.68)
CAC >0 AU & LDL-C (mg/dL) ≥70	No	343/2345	13.2	2.61[#] (1.76–3.86)	497	19.5	1.98[#] (1.48–2.65)	144	5.3	1.37 (0.86–2.20)
CAC >0 AU & LDL-C (mg/dL) ≥70	Yes	110/591	16.9	3.01[#] (1.96–4.60)	143	22.2	2.00[#] (1.44–2.77)	35	5.0	1.14 (0.65–1.98)

AU indicates Agatston unit; BMI, body mass index; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; and SBP, systolic blood pressure.

*Adjusted for age, sex, race/ethnicity, BMI, current and former smoking, SBP, hypertension treatment, and diabetes mellitus.

[†]CHD: MI, resuscitated cardiac arrest, definite angina, probable angina followed by revascularization, CHD death.

[‡]CVD: CHD, stroke, stroke death, other atherosclerotic death, and other CVD death.

[§]Rate per 1000 person-years.

[ǁ]$P<0.01$.

[¶]$P<0.05$.

[#]$P<0.001$.

of advanced atherosclerosis and high atherosclerotic burden, performs very well as a risk stratification tool in intermediate-risk patients.[21–23] Likewise, the ability of a CAC score of 0 AU to reclassify risk to substantially lower levels in intermediate-risk patients has been demonstrated and is emphasized in current guidelines as a reasonable justification to delay or forgo the initiation of statin therapy.[22–24] If viewed exclusively through the lens of ASCVD risk, this approach is reasonable—the overall (nonstratified) results we report above support this approach. However, such an approach may allow for the development of advanced coronary artery atherosclerosis in the interim. Whereas earlier initiation of statin treatment may prevent or delay the onset of advanced atherosclerosis, our CAC-stratified analysis suggests that some of the ASCVD risk attributable to coronary atherosclerosis may not be reversible once CAC is present. Thus, an opportunity to maintain low risk may have been lost by delaying therapy in some patients. Thus, our findings could help inform the "risk discussion" around statin initiation for patients with intermediate 10-year risk and a CAC score of 0 AU.

The findings we present are consistent with decades of secondary prevention trial data, as individuals treated with maximum tolerated medical therapy, including high-intensity statins, have substantial residual risk for recurrent ASCVD events.[11] Residual risk in secondary prevention patients is likely driven by significant plaque burden, inflammation, and plaque instability. We posit that, like secondary prevention patients, individuals with asymptomatic CAC have significant plaque burden and, thus, residual risk even when well treated with statins to lower LDL-C levels.

These findings are also consistent with what is understood about the underlying pathobiology of ASCVD events as well. Plaques initiate and mature over decades in most individuals.[25] The deposition of calcium within and around plaques is a marker of a high burden of advanced atherosclerosis. Although treatment with LDL-C–lowering therapies can lead to some degree of plaque regression and stabilization, the plaques themselves become permanent fixtures in the arterial wall. Thus, some of the risk that results from these plaques may be permanent as well.

MESA is a high-quality CVD cohort study, with in-person assessment of CVD risk factors and close follow-up for CVD events. Of note, much of what is known about the role of CAC scoring in CVD risk assessment has been derived from analyses conducted within the MESA study.[21,24,26] Thus, we have a high degree of confidence in the quality of exposure and outcome data used in this analysis. However, several limitations should be noted as well. First, to be included in this analysis, individuals must have been enrolled in MESA at the baseline exam. Thus, individuals who died or developed CVD before the age of 50 years

were not included in the sample. Consequently, survival bias could be present, but this would likely bias our results toward the null, meaning that the effects reported above may in fact be an underestimate of the true effects of prevalent CAC on residual ASCVD risk. Second, CAC scoring does not detect noncalcified, "soft" plaque. Although a similar amount of residual risk could be present in participants with noncalcified plaque, these data do not directly address this question; thus, such an inference should be made with caution. Third, statin therapy assignment was not randomized in MESA; thus, unmeasured confounders could explain the residual risks seen in patients with CAC who were treated with statins. For example, MESA participants treated with statins may have been perceived to be at higher risk by clinicians; thus, the initiation of statin therapy, not CAC, may be a marker of increased risk. However, similar patterns of higher risk were seen in MESA participants with CAC who were not on statin therapy, suggesting that CAC, not statins, is the marker of risk. Furthermore, although confounding by indication may weaken the statin treatment effect observed in this analysis, individuals with CAC treated to LDL-C <70 mg/dL had lower risk point estimates than were observed in participants with CAC who were treated to an LDL-C >70 mg/dL. Further, statin treatment to LDL-C <100 mg/dL was not associated with higher risk than was observed in the reference group when CAC was not considered in the analysis despite higher predicted risks in these groups, again suggesting that the expected effects of statin therapy were present.

It is important to note that an observational study such as this is the only way to answer our primary research question: "Does treatment with statins restore low risk in middle-aged adults with and without coronary atherosclerosis?" It is not possible to design a randomized controlled clinical trial to answer this question, as the low-risk reference group would never be included in such a study.

In the past 8 years, several nonstatin therapies have been shown to reduce ASCVD risk when added to background statin therapy. In this context, the persistent risks observed in participants with CAC who were treated with statins and the relatively lower, but *persistent*, risk seen in those treated to LDL-C <70 mg/dL suggest that there is benefit to treating subclinical atherosclerosis even more intensively. However, equipoise exists about the best treatment strategy in this population (eg, anti-inflammatory drugs or further lipid-lowering therapies). Given the rapid uptake in imaging modalities for subclinical atherosclerosis, the aging population, poor cardiovascular health in the US population, and multiple ASCVD risk-lowering therapies that are now available, a randomized controlled clinical trial testing the efficacy of aggressive LDL-C lowering and the addition of additive therapies

(eg, proprotein convertase subtilisin/kexin type 9, ezetimibe, iscosapent ethyl, canakinumab, and aspirin) in patients with subclinical atherosclerosis may be warranted.

In summary, these data demonstrate that individuals without advanced coronary atherosclerosis who are treated to recommended low LDL-C thresholds have similar risk levels as those who naturally have low LDL-C levels. However, statin-treated individuals with CAC do benefit from statin therapy but have substantial observed residual risk. This observation suggests that some degree of ASCVD risk may not be completely reversible through statin therapy alone once advanced coronary atherosclerosis develops. The clinical implication is that delaying statin therapy in individuals without CAC may result in a missed opportunity, or critical window, after which low ASCVD risk cannot be restored to optimal levels. Thus, initiation of LDL-C–lowering therapies earlier in the life course may be the optimal ASCVD prevention approach in some patients.

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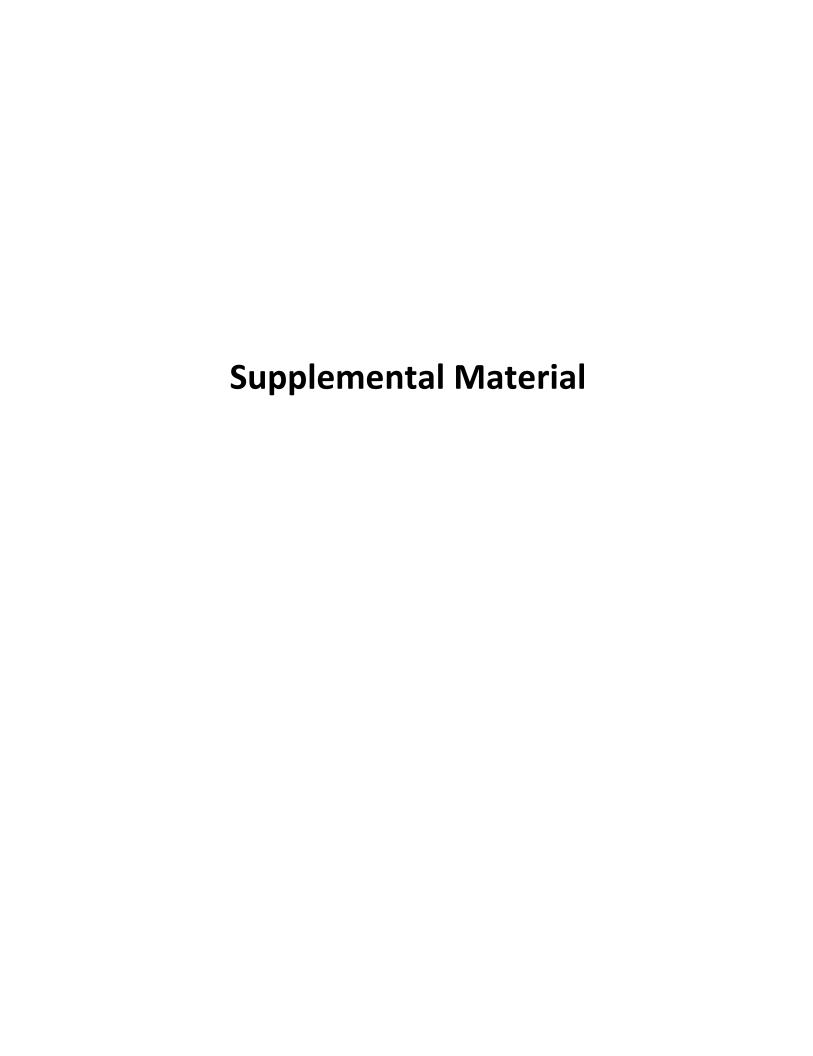
Supplemental Material

Table S1. Baseline characteristics of 299 participants with CAC=0 age-matched to 299 participants with CAC>0, Age ≥ 50 Years, MESA 15-Year Follow-Up.

	CAC = 0 and untreated LDL-C < 100 mg/dL	CAC > 0 and statin treated LDL-C < 100 mg/dL
	N=299	N=299
Age, years	67.3 (7.5)	67.5 (7.7)
Female	61.9%	46.5%
BMI, kg/m^2	27.4 (5.1)	28.9 (5.0)
Hypertension medication	42.5%	68.9%
Current smoker	10.7%	10.0%
Former smoker	33.8%	48.8%
Systolic blood pressure, mmHg	129 (22)	132 (22)
Diabetes	15.7%	26.4%

CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; BMI, body mass index; SD, standard deviation.
Values shown are mean (SD) or percent.