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RESEARCH LETTER

Coronary Artery Calcium Score–Directed Primary Prevention With Statins on the Basis of the 2018 American College of Cardiology/American Heart Association/ Multisociety Cholesterol Guidelines

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The 2018 multisociety guidelines on cholesterol management[1] state that the coronary artery calcium (CAC) score can help guide statin therapy in people at intermediate risk for atherosclerotic cardiovascular disease (ASCVD) who are uncertain whether they should take a statin. With a CAC score of 0, a "no statin" approach is reasonable when diabetes mellitus, active smoking, or family history of premature coronary heart disease is absent.[1] Thus, we assessed how CAC score would reclassify statin therapy according to the 2018 guidelines, and the association of CAC score with incident ASCVD, in participants with intermediate 10-year ASCVD risk from the FHS (Framingham Heart Study), for whom the 2013 guidelines would recommend statins. We found that CAC score reclassifies one third of intermediate-risk individuals to a "no statin" approach, and that CAC score ≥100th or ≥75th percentile confers a substantially higher risk for ASCVD than CAC score of 0.

Specifically, we applied the 2018 guidelines retrospectively to an asymptomatic FHS primary prevention population,[2] aged 40 to 75 years, with intermediate 10-year ASCVD risk (7.5% to <20%), no prevalent ASCVD, no reported statin use, no diabetes mellitus, no current smoking, low-density lipoprotein cholesterol level of 70 to 189 mg/dL, and computed tomography–based CAC scoring. Participants consented to the original study. Secondary use of data was approved by our institutional review board, and informed consent was waived for this post hoc study using existing data. CAC score–guided reclassification to "no statin" (CAC score, 0) or "initiate statin" (CAC score, ≥100th or ≥75th percentile by age and sex[3]) was assessed according to the multisociety guidelines. Participants were followed up for a median of 14.7 (quartile 1–quartile 3, 11.7–16.8) years for incident ASCVD, as defined in the Table. Of 389 participants with intermediate ASCVD risk (mean, 57.4 years; 34.4% women), 31.4% (122/389) had CAC score of 0, 28.5% (111/389) had CAC score of 1 to 99 and <75th percentile, and 40.1% (156/389) had CAC score ≥100th or ≥75th percentile. Risk factors were similarly distributed across CAC score strata.

To further support the appropriateness of a lower-risk "no statin" reclassification for participants with a CAC score of 0, incident ASCVD occurred in 4.9% (6/122, including 4 coronary heart disease events) for CAC score of 0, 9.0% (10/111) for CAC score of 1 to 99 and <75th percentile, and 21.2% (33/156) for CAC score ≥100th or ≥75th percentile. Cox proportional

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Table. Baseline Characteristics and Incident ASCVD in Nonsmokers Without Diabetes Mellitus and Intermediate 10-Year ASCVD Risk (7.5% to <20%) Subgrouped by CAC Score Strata

Characteristics	Intermediate 10-y ASCVD Risk			
	Total (N=389; 100%)	CAC Score of 0 (N=122; 31.4%)	CAC Score of 1–99 and <75th Percentile (N=111; 28.5%)	CAC Score >100th or ≥75th Percentile (N=156; 40.1%)
Age, y	57.4±5.9	56.5±6.0	58.8±5.6	57.2±5.9
Women	134 (34.4)	52 (42.6)	32 (28.8)	50 (32.1)
BMI, kg/m^2	28.9±4.8	28.3±5	29±4.6	29.3±4.7
Hypertension	175 (45)	54 (44.3)	40 (36)	81 (51.9)
SBP, mm Hg	127 (118–137)	128 (118–137)	125 (116–132)	130 (120–141)
DBP, mm Hg	79 (72–85)	79 (73–84)	77 (70–84)	79 (73–87)
Total cholesterol, mg/dL	209.6±31.9	210.2±33.5	209.6±30.3	209.2±31.9
LDL, mg/dL	130.6±26.5	130.8±27.3	130.5±25.1	130.6±27.1
HDL, mg/dL	48.8±14.1	48.7±13.1	51.5±15.4	47.1±13.7
ASCVD events				
Time to follow-up, y	14.7 (11.7–16.8)	15.3 (11.9–16.9)	15.4 (11.7–16.9)	14.5 (11.6–16.7)
ASCVD events	49 (12.6)	6 (4.9)	10 (9.0)	33 (21.2)
Adjusted HR (95% CI)*		Reference	2.0 (0.7–5.5)	5.0 (2.1–12.1)
P value		…	0.19	<0.001

Data are presented as number (percentage), mean±SD, or median (interquartile range). ASCVD events are defined as atherosclerotic cardiovascular events: acute coronary syndrome, myocardial infarction, angina pectoris, coronary insufficiency, ischemic stroke, transient ischemic attack, cardiovascular death, and claudication. ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; and SBP, systolic blood pressure.

*Adjusted for ASCVD risk.

hazards models were used to predict the risk of ASCVD by CAC score category, adjusting for the ASCVD risk score. Compared with CAC score of 0, participants with CAC score ≥100th or ≥75th percentile had significantly greater risk for ASCVD, with an ASCVD risk score–adjusted hazard ratio of 5.0 (95% CI, 2.1–12.7; *P*<0.001; Table).

The 2018 guidelines define the highest-risk category as CAC score ≥100th or ≥75th percentile. To explore the contribution of the ≥75th percentile criterion, we examined the 41 patients who had a CAC score of 1 to 99 but were also ≥75th percentile. Five (12.2%) had an ASCVD event, which was only marginally higher than the event rate (9.0%; 10/111) for those with a CAC score of 1 to 99 and <75th percentile, and substantially lower than the event rate (24.4%; 28/115) with a CAC score ≥100th percentile.

The prior 2013 guidelines would recommend statins for all participants in of our sample. A previous study including FHS participants across all levels of 10-year ASCVD risk found that one third of those eligible for statin by 2013 guidelines had a CAC score of 0.[4] This is a similar proportion as in our study's cohort at intermediate 10-year ASCVD risk. Similarly, in a multiethnic cohort of the MESA (Multi-Ethnic Study of Atherosclerosis), 44% of those recommended for statin treatment (across all levels of ASCVD risk) had no CAC and a markedly lower ASCVD event rate than those with CAC (4.2 versus 11.2 per 1000 person-years).[5]

Limitations of our study include the relatively small number of participants and modest number of outcome events. We did not account for family history. FHS participants were overwhelmingly White individuals and from the same geographic area; generalizability to other demographics warrants further study. CAC score was evaluated at a single point in time, whereas some recommend reevaluation of risk factors and potentially CAC score at 5 or 10 years in those with CAC score of 0,[1] whereas newer evidence suggests a 3- to 7-year interval.[6] Data are available by application at https://framinghamheartstudy.org/fhs-for-researchers/.

In conclusion, 1 in 3 FHS participants at intermediate ASCVD risk could be reclassified to "no statin" on the basis of a CAC score of 0 and the 2018 guidelines. CAC score ≥100th or ≥75th percentile was associated with substantially higher long-term risk of ASCVD.

ARTICLE INFORMATION

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