

NLA Scientific Statement

The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction



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Subclinical coronary atherosclerosis;
Computed tomography;
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Abstract: An Expert Panel of the National Lipid Association reviewed the evidence related to the use of coronary artery calcium (CAC) scoring in clinical practice for adults seen for primary prevention of atherosclerotic cardiovascular disease. Recommendations for optimal use of this test in adults of various races/ethnicities, ages and multiple domains of primary prevention, including those with a 10-year ASCVD risk <20%, those with diabetes or the metabolic syndrome, and those with severe hypercholesterolemia were provided. Recommendations were also made on optimal timing for repeat calcium scoring after an initial test, use of CAC scoring in those taking statins, and its role in informing the clinician patient discussion on the benefit of aspirin and anti-hypertensive drug therapy. Finally, a vision is provided for the future of coronary calcium scoring.

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Abbreviations: CAC, Coronary artery calcium; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; 2018 Cholesterol Guideline, AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol; PCE, Pooled Cohort Equations; LDL-C, LDL cholesterol; hsCRP, High-sensitivity C-reactive protein; Lp(a): lipoprotein a; Apo B, apolipoprotein B; CAC = 0, Coronary calcium score of zero; CAC>0, The presence of coronary calcification; NLA, National Lipid Association; ACC, American College of Cardiology; AHA, American Heart Association; SCCT, Society of Computed, Cardiovascular Tomography; CT, Computed tomography; ECG, electrocardiographic; mSv, millisieverts; MESA, Multi-ethnic Study of Atherosclerosis; MASALA, Mediators of Atherosclerosis in South Asians Living in America; CARDIA, Coronary Artery Risk Development in Young Adults; SPRINT, Systolic Blood Pressure Intervention Trial.

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Introduction

Atherosclerotic cardiovascular disease risk prediction tools, such as the Pooled Cohort Equations, use the presence and quantification of major risk factors in decision-making about statin allocation for primary prevention. The 2018 Cholesterol Guideline suggests the consideration, in individuals at borderline to intermediate risk (5–19.9% 10 year ASCVD risk), of “risk-enhancing factors”, including: a family history of premature ASCVD; persistent elevation of LDL-C of 160 mg/dL or greater; chronic kidney disease; metabolic syndrome; pre-eclampsia; premature menopause; chronic inflammatory diseases; south Asian ethnicity; persistently elevated non-fasting triglycerides of 175 mg/dL or greater; and in selected individuals, if measured, hsCRP 2 mg/L or greater; Lp(a) \geq 50 mg/dL or 125 nmol/L; apo B > 130 mg/dL; or an ankle-brachial index <0.9 to better inform the clinician-patient risk discussion as part of shared decision-making about statin initiation.¹ However, the degree to which such factors quantitatively change the 10-year risk estimate for a given individual is small.^{2,3}

The process of coronary arterial calcification, contributed to by smooth muscle and/or macrophage apoptosis and calcifying matrix vesicles, is a hallmark of ASCVD.⁴ A direct proportional relationship between CAC scores and major adverse clinical ASCVD events has been demonstrated.⁵ For this reason, lipid treatment guidelines have linked treatment intensity to CAC scores. A strategy using lifestyle counseling alone for most low-risk individuals and the addition of pharmacologic therapy for those at high risk is recommended by the 2018 Cholesterol Guideline. However, lipid therapy decision-making for individual patients at borderline and intermediate (5–19.9%) 10-year risk is considerably more nuanced. For that reason, the Guideline states that the use of CAC scoring is reasonable in borderline- or intermediate-risk individuals 40–75 years of age, without ASCVD or diabetes, and with an LDL-C 70–189 mg/dL, when the decision about statin allocation, after use of the PCE and risk-enhancing factors, is uncertain.

Despite these recommendations the practicing clinician is still confronted with multiple questions about how to best use CAC scoring in clinical practice. What are the proper indications for CAC scoring? Do age, sex and race/ethnicity alter its interpretation? How should one interpret the absolute score versus percentiles? Is CAC scoring of value for individuals with diabetes, the metabolic syndrome or severe hypercholesterolemia? What are the implications of CAC=0 or very high CAC scores, and in whom should repeat CAC scoring or additional testing be considered? How should clinicians use CAC scoring information to inform clinical decision making regarding the use of statins and non-statin add-on therapy? Are the results of CAC scoring of value in patients taking statins? Are CAC scores valuable in decision-making about aspirin therapy or hypertension treatment? How should clinicians deal with incidental findings, or with reports of coronary calcification on other imaging studies?

This article provides updates on the evidence-based appropriate use of CAC scoring and makes practical recommendations to aid clinicians in primary prevention treatment decision-making in contemporary clinical practice.

Methodology

A writing committee was assembled with the objective to update the organization’s position on the clinical use of CAC scoring. All members of the writing committee materially contributed to the content of this manuscript. All recommendations were made based on a consensus of the committee’s authors. The completed article was submitted to the NLA Board of Directors, which approved its content. The grading system used for these recommendations employed the 2016 ACC/AHA clinical practice guideline recommendation classification system.⁶ The content of each section is focused on addressing one or more clinically relevant questions. The key points are summarized following the discussion in each section and collated by topic in a separate [Table 1](#). Evidence-based, actionable recommendations are provided when appropriate and are then collated in a separate [Table 1](#). In this document, all recommendations are made for adults in primary prevention in the context of shared decision making. In addition, all comments on 10-year ASCVD risk are based on the use of the PCE, as originally described in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol⁷ and affirmed in the 2018 Cholesterol Guideline.¹ All CAC scores are reported in Agatston units.

Manuscript content

The content of this manuscript is divided into the following sections:

1. Performance, reporting standards, reproducibility, and significance of absolute scores versus percentiles
2. Guideline recommendations for the use of CAC scoring
3. Race/ethnicity, age and gender considerations in CAC scoring
4. Approach to the patient with CAC=0
5. Definition, prognostic significance and treatment of those with a high CAC score, multivessel involvement or left main coronary calcification
6. Evaluation of pulmonary nodules found on CAC scoring exams and incidental coronary calcium found on chest CT exams
7. CAC scoring in patients with severe primary hypercholesterolemia
8. CAC scoring in patients with diabetes or the metabolic syndrome
9. Repeat CAC scoring
10. Use of CAC scoring in patients taking lipid-lowering therapy

Table 1 2015 ACC/AHA clinical practice guideline recommendation classification system.

CLASS (STRENGTH) OF RECOMMENDATION
CLASS I (STRONG) Benefit >>> Risk Suggested phrases for writing recommendations: <ul style="list-style-type: none"> • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administrated/other • Comparative-Effectiveness Phrases: <ul style="list-style-type: none"> ○ Treatment / strategy A is recommended / indicated in preference to treatment B ○ Treatment A should be chosen over treatment B
CLASS IIa (MODERATE) Benefit >> Risk Suggested phrases for writing recommendations: <ul style="list-style-type: none"> • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases: <ul style="list-style-type: none"> ○ Treatment/strategy A is probably recommended/indicted in preference to treatment B ○ It is reasonable to choose treatment A over treatment B
CLASS IIb (WEAK) Benefit ≥ Risk Suggested phrases for writing recommendations: <ul style="list-style-type: none"> • May/might be reasonable • May/might be considered Usefulness/effectiveness is unknown/unclear/uncertain or not well established
CLASS III: No Benefit (MODERATE) Benefit = Risk Suggested phrases for writing recommendations: <ul style="list-style-type: none"> • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other
CLASS III: Harm (STRONG) Risk > Benefit Suggested phrases for writing recommendations: <ul style="list-style-type: none"> • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other

*Modified from the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System

LEVEL (QUALITY) OF EVIDENCE
LEVEL A <ul style="list-style-type: none"> • High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
LEVEL B-R (Randomized) <ul style="list-style-type: none"> • Moderate-quality evidence from 1 or more RCTs • Meta-analysis of moderate-quality RCTs
LEVEL B-NR (Nonrandomized) <ul style="list-style-type: none"> • Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
LEVEL C-LD (Limited Data) <ul style="list-style-type: none"> • Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
LEVEL C-EO (Expert Opinion) <ul style="list-style-type: none"> • Consensus of expert opinion based on clinical experience

*Modified from the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System

11. Use of CAC scoring in allocation of anti-hypertensive and aspirin therapy
12. The future of CAC scoring

Performance, reporting standards, reproducibility, and significance of absolute scores versus percentiles

How is CAC testing performed and reported?

CAC testing is a rapid and highly reproducible CT scan of the heart which does not require the use of contrast or intravenous access. This test can be performed on any CT scanner which has the capability to perform ECG gating – a technique by which data acquisition is performed during a pre-defined portion of the cardiac cycle. A CAC test does not require any special preparation on the part of the patient, and there is no need to fast or to withhold any medications. Prior to the scan, the patient is attached to multiple ECG leads in order to allow for ECG gating. The scan parameters include tube voltage of 120kV with variable tube current (e.g. mA) depending on patient size, to achieve a sufficient balance between radiation dose and image noise.⁸ The scans should be acquired using an axial mode with prospective ECG triggering during diastole. Images should be reconstructed using 3 mm slices for the purpose of calculating the Agatston score, although additional thin slice reconstruction (e.g. 1 mm slice thickness) may be helpful in some cases when there is a small amount of calcium and it is uncertain if it represents noise versus calcified plaque. Quantification is performed using commercially available software, most commonly using the Agatston technique where the total calcium score is a summed score based on the amount and density of calcified plaque.⁹ Per SCCT guidelines, CAC scores should be reported both as total score for the patient, and as scores for each individual coronary artery.¹⁰ The effective radiation exposure from CAC testing averages 1 mSv (range 0.5–2),^{11,12} an amount which is similar to a mammogram, and which represents approximately one third to one half of the annual background radiation exposure in the United States.

How reproducible are CAC scores?

CAC scores have good intra-scan and interscan reproducibility. There is a high agreement (96%) for the presence of CAC > 0.¹³ Among individuals with detectable CAC, interscan variability of the numeric total CAC score has been reported to be as high as 17–19% but appears lower (12%) with more contemporary scanners.¹⁴ Importantly, the small amount of interscan and intra-scan variability is

unlikely to result in a clinically meaningful reclassification of risk and is similar to the variability observed with lipid testing (i.e. 10–15% for LDL-C).

How useful are total CAC scores versus age, gender and ethnicity percentiles in predicting CHD risk?

Both total CAC score and age, sex, and race/ethnicity-based score percentiles should be provided on all score reports because these two aspects of CAC score interpretation provide different risk prediction information to the clinician. CAC score percentiles should be calculated using the MESA CAC Reference tool which is available at <https://www.mesa-nhlbi.org/cacreference.aspx>.¹⁵ Based on data from the Mediators of Atherosclerosis in South Asians Living in America (MA-SALA) study, South Asians should be calculated as Caucasians because of their similar age-adjusted CAC scores.¹⁶ Currently, CAC score percentiles cannot be calculated for patients younger than age 45, as the reference populations from MESA did not include individuals younger than this age. Percentiles for such patients can be assumed to be substantially higher than that estimated if age 45 is substituted for the patient's age in the MESA percentile calculator.

The absolute CAC score is the best predictor of near-term absolute risk (i.e. risk of events over a 5–10 year time horizon).¹⁷ Therefore, the absolute CAC score is the usually best for guiding pharmacologic treatment decisions, such as lipid-lowering therapy, as these are usually based on 5 to 10-year risk models and accordingly, 5 to 10-year number needed to treat (NNT). Most guidelines use absolute CAC score thresholds for prescribing medications such as aspirin and statins.^{1,18}

While the absolute CAC score is best for communicating near-term absolute risk, CAC score percentiles give the best estimation of *lifetime risk trajectory*. This is particularly important in young patients and older patients. For example, in patients younger than 50 years of age, any CAC will classify the patient at a high percentile and, therefore, high lifetime risk.¹⁹ In this way, CAC score percentiles are best for *comparing patients to the age, sex, and race/ethnicity matched peers*. A patient who is 40 years of age with a score of 10 has a relatively low near-term absolute risk (unlikely to have an event in the next 5 years), but very high relative risk compared to age, sex, and race/ethnicity-matched peers, and importantly, very high lifetime cardiovascular risk.¹⁹ In contrast, a patient who is 75 years of age with a score of 10 may have similar near-term absolute risk as the younger example, but a lower risk compared to age, sex, and race/ethnicity-matched peers, and therefore, low lifetime risk, especially in view

	Risk Communication	In Whom to Use
Absolute CAC Score	Best predictor of absolute cardiovascular risk	All patients
CAC Score Percentile	Predicts relative risk vs. age, sex, and race/ethnicity-matched peers Predicts lifetime risk trajectory	Young patients (i.e. age <50) Older patients (i.e. age >70)

Table 2 Recommendations for CAC scoring^a from the 2018 AHA/ACC/Multi-Society Guideline on the Management of Blood Cholesterol^d, the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias^e, and the SCCT Expert Consensus Statement.^f

	AHA/ACC/Multisociety Guideline	ESC/EAS Guidelines	SCCT Expert Consensus Statement
When to consider measuring CAC	In adults 40–75 years of age without diabetes mellitus and with LDL-C 70–189 mg/dL at a 10-year ASCVD risk of 7.5%–19.9%, if a decision about statin therapy is uncertain (COR IIa; LOE B-NR)	As a risk modifier in the cardiovascular risk assessment of asymptomatic individuals at low or moderate risk (COR IIa; LOE B)	In asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5–20% 10-year ASCVD risk group and selectively in the <5% ASCVD group, such as those with a family history of premature coronary artery disease In patients for whom the development or progression of CAC would support intensification or alteration in preventive management, repeat CAC scanning at an interval of 5 years for patients with 0 CAC and a 3–5 year interval for patients with >0 CAC
Treatment recommendations	CAC = 0: it is reasonable to withhold statin therapy and reassess in 5–10 years, as long as higher risk conditions are absent (e.g., diabetes mellitus, strong family history of premature CHD, cigarette smoking) CAC 1–99 and < 75th percentile ^{b,c} : it is reasonable to initiate statin therapy for patients ≥55 years of age CAC ≥100 and/or ≥75th percentile ^c : it is reasonable to initiate statin therapy (unless otherwise deferred by the outcome of clinician-patient risk discussion) (COR IIa; LOE B-NR)	Risk reclassification is of value in people identified as being at moderate risk with CAC score >100 Agatston units	In the 5–20% ASCVD risk group CAC = 0: statin not recommended CAC 1–99: moderate intensity statin if < 75th percentile; moderate to high intensity statin if ≥ 75th percentile CAC 100–299: moderate to high intensity statin + ASA 81 mg CAC ≥300: high-intensity statin + ASA 81 mg

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASA, acetylsalicylic acid (aspirin); ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; COR, class of rating; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; NR, non-randomized.

^aUnits for all CAC scores are Agatston units.

^bCAC scores in the range of 1–99 Agatston units demonstrate evidence of subclinical atherosclerosis, but 10-year event rates largely remain in the intermediate-risk range. Thus clinical judgment and patient preferences should guide decision-making and the potential net benefit of drug therapy should be discussed (Lloyd-Jones 2019).

^cPercentile refers to the distribution for a particular age, sex, and race.

^dGrundy SM, Stone NJ, Bailey AL et al., 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2019 Jun 25; 73 (24):3237–41]. *J Am Coll Cardiol*. 2019; 73 (24):e285–e350. doi:10.1016/j.jacc.2018.11.003.¹

^eMach F, Baigent C, Catapano AL et al., 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020; 41:111–88.²²

^fHecht H, Blaha MJ, Berman DS et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: expert consensus statement from the Society for Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr*. 2017; 11:157–68.²⁰

of competing risks present in older individuals. Several guidelines consider age, sex, and race/ethnicity-based percentile ≥75th to be an indication for statin therapy.^{1,18,20}

Key points

- The absolute CAC score is the best predictor of absolute 5- to 10-year ASCVD event risk and should be used to estimate number needed to treat and guide pharmacologic treatment decisions.

- The CAC score percentile from MESA is the best predictor of relative risk and of lifetime risk trajectory and should be used to estimate lifetime treatment benefit.

Recommendation

- Physicians reporting CAC scores should report both the absolute Agatston CAC score and the age, sex, and race/ethnicity-based CAC percentiles (Class I, LOE B-NR).

Guideline recommendations for the use of CAC scoring

What do guidelines and recommendations advise regarding patient selection and most appropriate clinical use of CAC scoring for ASCVD risk assessment?

The 2018 Cholesterol Guideline provided recommendations regarding the use of CAC that were also endorsed in the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.^{1,18} This Guideline stated that CAC scoring is reasonable to guide the clinician-patient risk discussion in asymptomatic adults, for primary prevention who are 40–75 years of age, with low-density lipoprotein cholesterol (LDL-C) 70–189 mg/dL and at intermediate risk ($\geq 7.5\%$ to $< 20\%$ 10-year ASCVD risk) or in selected patients at borderline risk (5.0–7.4% 10-year risk) if risk-based decisions for statin therapy remain uncertain (COR IIa; LOE B-NR). CAC scoring might also be considered to refine risk assessment for selected low-risk adults ($< 5\%$ estimated 10-year risk), such as those with a strong family history of premature coronary heart disease (CHD), based on clinical judgment. Examples of groups who might benefit from knowing their CAC score include: those reluctant to initiate statin, or who wish to better understand the risk-benefit ratio for statin use; those concerned about restarting statin after discontinuation for statin-associated symptoms such as statin-associated muscle symptoms; older patients (men 55–80 years of age, or women 60–80 years of age) with a low risk factor burden who question need for statin therapy; and middle-aged adults (40–55 years of age) with borderline calculated 10-year risk.^{1,2}

In 2017 the SCCT released an Expert Consensus Statement regarding the value of CAC testing in asymptomatic individuals without ASCVD.²⁰ This document stated that it is appropriate to perform CAC testing in the context of shared decision-making for asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5%–20% 10-year ASCVD risk group, and selectively in the $< 5\%$ ASCVD risk group, such as in patients with a family history of premature coronary artery disease.²¹ These recommendations suggested repeat CAC scanning in patients for whom the development or progression of CAC would support intensification of preventive therapies at an interval of 5 years with a CAC score = 0, and at a 3 to 5-year interval with CAC score > 0 .

The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias stated that CAC scoring should be considered as a risk modifier in patients at low or moderate risk for ASCVD, defined as $< 5\%$ 10-year risk of fatal cardiovascular events using the Systematic Coronary Risk Estimation (SCORE) system, with calculated risk

modified in accordance with prevalence of cardiovascular disease in low- or high-risk European countries.²² The Guidelines recognized the low 10-year risk associated with CAC=0 and higher risk in those with scores of ≥ 100 .

In contrast, the 2018 U.S. Preventive Services Task Force concluded that the current evidence was insufficient to evaluate the balance of benefits and harms of adding certain nontraditional risk factors, including CAC score, to traditional ASCVD risk assessment.²³ Guideline recommendations for the use of CAC scoring are summarized in Table 2.

In whom is CAC assessment not recommended for ASCVD risk assessment?

CAC testing for ASCVD risk assessment is generally not recommended for the broad general population with $< 5\%$ 10-year risk of ASCVD. It is also of less established value in most individuals with a 10-year estimated ASCVD risk $\geq 20\%$, except in older patients with a paucity of major risk factors, in whom the estimated 10-year risk using the Pooled Cohort Equations is largely driven by age, and in whom CAC = 0 or a low CAC score may result in decision to withhold statin therapy. CAC scoring is not recommended for those with clinical ASCVD. In the 2018 ACC/AHA/Multi-society Guideline, clinical ASCVD was defined as: acute coronary syndrome, history of acute myocardial infarction, stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease, including aortic aneurysm, all of atherosclerotic origin.¹

Recommendations

- For adults 40–75 years of age, with LDL-C 70–189 mg/dL and a 10-year ASCVD of 5–19.9%, CAC scoring can be useful to decide on the need for and intensity of preventive therapies. (COR IIa, LOE B-NR)
- For adults 40 years of age or older, with LDL-C 70–189 mg/dL and a 10-year ASCVD risk of $< 5\%$, CAC scoring is reasonable in those with a family history of premature ASCVD, to decide on the need for and intensity of preventive therapies (COR IIa, B-NR)
- For adults with clinical ASCVD, CAC scoring is not recommended. (COR III, no benefit)

Race/ethnicity, sex and age considerations in CAC scoring

What are racial/ethnic differences in coronary artery calcification?

Racial and ethnic differences have been demonstrated in the prevalence of CAC, in 3 large studies, including the Multi-Ethnic Study of Atherosclerosis (MESA); the

Table 3 Prevalence of CAC by Race/Ethnicity in 3 large CAC studies.

	MESA ^a n = 6813		CAC Consortium ^b n = 42,224		MASALA ^c n = 803	
Study Description	Prospective, multicenter community-based study, examining prevalence, correlates and progression of CAC and relation to subsequent CVD events in adults of 4 ethnic categories, 45–84 years of age		Observational cohort of adults referred from 4 centers for CAC scoring, 40–75 years of age, with long-term follow-up for CVD and all-cause mortality		Prospective community-based cohort study to determine risk factors associated with coronary heart disease and CAC incidence and progression in South Asians adults 40–84 years of age	
Ethnicity representation	White (38%), Black (28%), Hispanic (22%), and Asian (12%, primarily Chinese)		White (87%), Asian (4.3%), Hispanic (3.8%), Black (2.3%), and other (1.9%)		Exclusively South Asians	
Sex	Men	Women	Men	Women	Men	Women
Total # studied	3213	3600	27,436	14,788	424	379
% Whites CAC>0	70.4	44.6	64.0	40.3	–	–
% Blacks CAC>0	52.1	36.5	59.7	50.6	–	–
% Hispanics CAC>0	56.5	34.9	63.3	39.2	–	–
% Chinese CAC>0	59.2	41.9	–	–	–	–
% Asians CAC>0	–	–	59.9	35.5	–	–
% South Asians CAC>0	–	–	–	–	62.5	25.9

^aBild DE et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*, 2005.111(10): p. 1313–20.²⁵

^bOrimoloye, OA. et al. Race/Ethnicity and the Prognostic Implications of Coronary Artery Calcium for All-Cause and Cardiovascular Disease Mortality: The Coronary Artery Calcium Consortium. *J Am Heart Assoc*, 2018.7(20): p. e010471.²⁴

^cKanaya AM et al. Comparing coronary artery calcium among U.S. South Asians with four racial/ethnic groups: the MASALA and MESA studies. *Atherosclerosis*, 2014.234(1): p. 102–7.¹⁶

Coronary Artery Calcium (CAC) Consortium²⁴; and MASALA Study.¹⁶ The patient populations, sex and ethnicity representation and percentage found to have detectable coronary calcification (CAC>0) are described in Table 3. In all groups studied CAC>0 was more prevalent in men than women and in Whites than in other Ethnicities.^{16,24,25}

What is the association between coronary artery calcification, race/ethnicity and future CVD risk?

Current CVD risk estimation tools, including the Pooled Cohort Equations, have restricted applicability in racial and ethnic minorities. The use of CAC scoring can overcome these limitations and improve CVD risk discrimination in racial and ethnic minorities. The MESA risk score (<https://www.mesa-nhlbi.org/cacreference.aspx1>), which utilizes traditional risk factors and CAC score, has been developed to provide an accurate estimate of 10-year risk of CHD in Whites, Blacks, Hispanics and Chinese.²⁶ MESA prospectively followed 6814 adults with a median follow up of 11.1 years and CVD events were the outcomes measurement,²⁷ whereas the CAC Consortium retrospectively analyzed data from 42,224 patients referred for CAC scoring for clinical indications, with a median follow up

of 11.7 years. CVD and all-cause mortality were the outcomes assessed.²⁴

In MESA, individuals were assigned to four CAC categories: 0, 1–100, 101–300, >300. Regardless of race and ethnicity, CAC was independently associated with ASCVD events in MESA. Ten-year ASCVD risk was low (<5%) in those with CAC = 0 and was higher (>7.5%) in those with CAC > 100. Despite Blacks and Hispanics having a lower prevalence of CAC and lower CAC scores compared to Whites, their event rates were similar to whites³ (Table 4).

In the CAC Consortium there was a disproportionately high representation of White individuals (87.2%) and a very small representation of Blacks (2.3%) and Hispanics (3.8%). Cumulative incidence and incidence rates of all-cause and CVD mortality were disproportionately higher in Blacks compared to other ethnic/racial groups in all four categories of CAC scoring (0, 1–99, 100–399, ≥400). These racial differences were persistent even when the CAC = 0 (Table 5). Furthermore, in all categories of CAC, the hazard ratios for CVD and all-cause mortality were higher in Blacks and Hispanics than in Whites or Asians.⁴ Regardless of race/ethnicity in both MESA and the CAC Consortium study, the

Table 4 Hazard ratio examining the likelihood of hard atherosclerotic cardiovascular disease events in MESA.

	Model without CAC		Model with CAC	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Race or ethnicity				
White	1.0		1.0	
Black	0.73 (0.58–0.92)	0.008	0.89(0.71–1.13)	0.333
Chinese	0.44 (0.30–0.64)	<0.001	0.48 (0.33–0.71)	<0.001
Hispanic	0.82 (0.63–1.06)	0.132	0.94 (0.73–1.22)	0.666
Age				
45–54	1.0		1.0	
55–64	1.65 (1.21–2.26)	0.002	1.37(1.00–1.88)	0.054
65–74	2.27(1.66–3.10)	<0.001	1.53(1.10–2.11)	0.011
75–85	4.34 (3.12–6.06)	<0.001	2.47 (1.73–352)	<0.001
Sex				
Female	1.0		1.0	
Male	1.63 (1.32–2.00)	<0.001	1.31 (1.06–1.62)	0.012
Lipid-lowering medication at baseline				
No	1.0		1.0	
Yes	1.02 (0.81–1.28)	0.896	0.92 (1.02–151)	0.033
CAC (log₂[CAC+1])				
			1.14(1.11–1.17)	<0.001

Proportional hazard Cox regression models adjusted for variables shown, and, education, income, cigarette smoking status (never, former, current), low-density lipoprotein cholesterol (LDL-C). High-density lipoprotein cholesterol (HDL-C). Diabetes status (yes/no), systolic blood pressure (SBP). Antihypertensive medication use. Nontertorial physical exercise minutes per day, and body mass index.

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CI, confidence interval.

Budoff MJ, Young R, Burke G et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J* 2018; 39, 2401–2408.²⁷

Table 5 Cumulative incidence and incidence rates per 1000 person-years of all-cause and CVD- specific mortality by CAC group for each race/ethnicity group in the CAC consortium.

	CAC=0	CAC 1–99	CAC 100–399	CAC ≥400
White				
Death (n, %)	325, 1.9%	442, 3.8%	365, 6.8%	586, 13.9%
Per 1000	1.7 (1.6, 1.9)	3.3 (3.0, 3.6)	6.1 (5.5, 6.8)	13.1 (12.1, 14.2)
CVD death (n, %)	58, 0.34%	114, 0.97%	118, 2.2%	222, 5.3%
Per 1000	0.31 (0.24, 0.40)	0.85 (0.71, 1.03)	2.0 (1.7, 2.4)	5.0 (4.4, 5.7)
Asian				
Death (n, %)	9, 1.1%	15, 3.2%	10, 5.0%	22, 13.4%
Per 1000	0.93 (0.48, 1.8)	2.7 (1.6, 4.5)	4.4 (2.4, 8.2)	12.6 (8.3, 19.2)
CVD death (n, %)	0, 0%	1, 0.22%	4, 2.0%	11, 6.7%
Per 1000	0	0.18 (0.03, 1.3)	1.8 (0.66, 4.7)	6.3 (3.5, 11.4)
Black				
Death (n, %)	16, 3.7%	26, 8.1%	23, 18.4%	32, 31.4%
Per 1000	3.7 (2.2, 6.0)	7.9 (5.4, 11.6)	19.9 (13.2, 29.9)	41.4 (29.3, 58.6)
CVD death (n, %)	10, 2.33%	7, 2.2%	11, 8.8%	18, 17.7%
Per 1000	2.3 (1.2, 4.2)	2.1 (1.0, 4.4)	9.5 (5.3, 17.2)	23.3 (14.7, 37.0)
Hispanic				
Death (n, %)	13, 2.1%	23, 5.4%	17, 11.0%	29, 20.0%
Per 1000	1.8 (1.1, 3.2)	4.7 (3.1, 7.0)	10.6 (6.6, 17.1)	21.3 (14.8, 30.6)
CVD death (n, %)	6, 0.97%	8, 1.9%	5, 3.3%	15, 10.3%
Per 1000	0.85 (0.38, 1.9)	1.6 (0.81, 3.3)	3.1 (1.3, 7.5)	11.0 (6.6, 18.2)

CAC indicates coronary artery calcium; CVD, cardiovascular disease.

Orimoloye, OA, Budoff MJ, Dardari ZA et al. Race/Ethnicity and the Prognostic Implications of Coronary Artery Calcium for All-Cause and Cardiovascular Disease Mortality: The Coronary Artery Calcium Consortium. *J Am Heart Assoc.* 2018; 7:e010471. DOI: 10.1161/JAHA.118.010471.²⁴

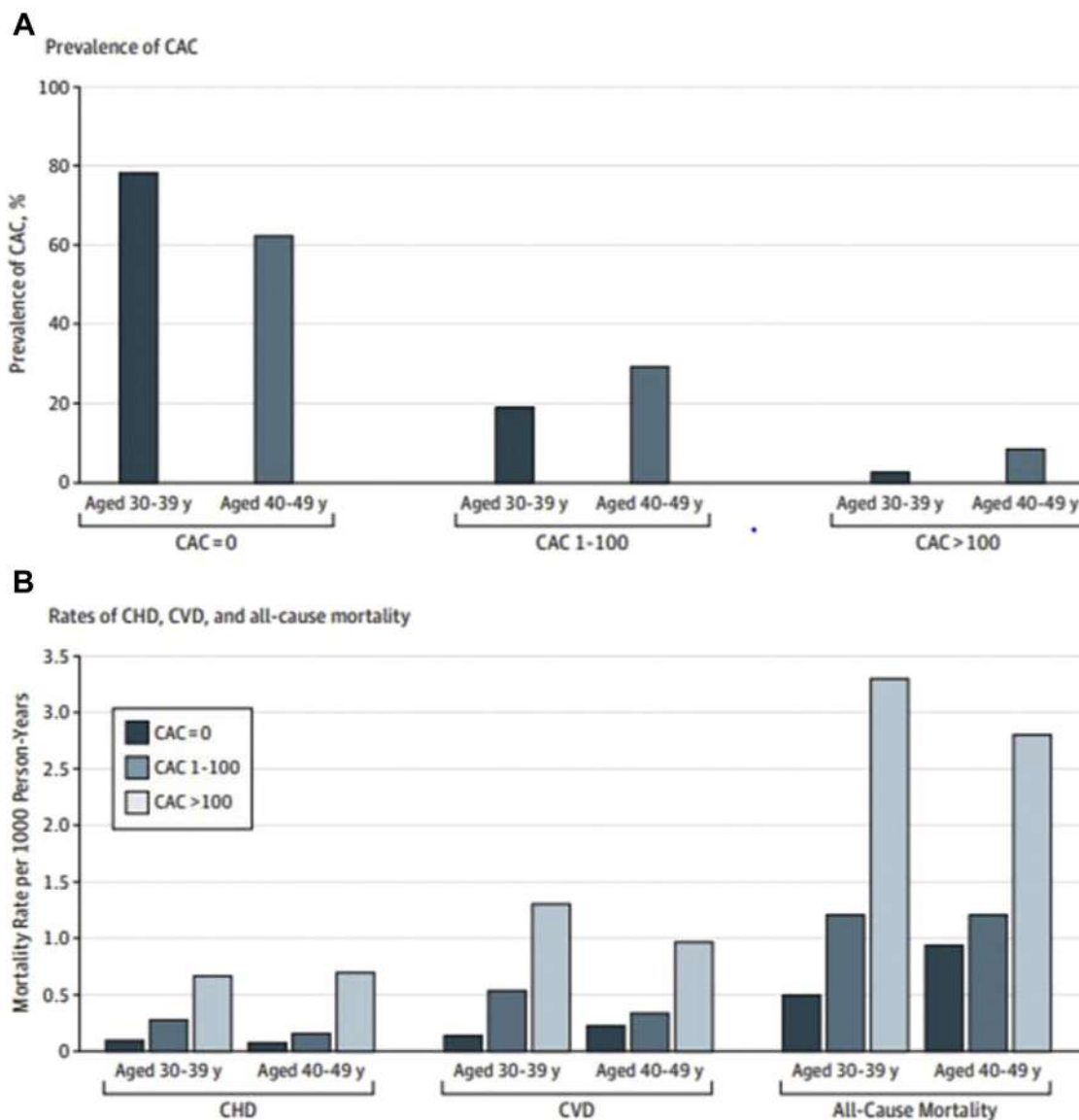


Fig. 1 Interplay of CAC and Race/Ethnicity on Risk of All-Cause and CVD-Specific Mortality in Young Adults the CAC Consortium. A. Prevalence of CAC in 4544 asymptomatic individuals aged 30–39 years and 17,802 individuals aged 40–49 years enrolled in the CAC Consortium stratified by baseline CAC. B. Subsequent rates of CHD, CVD, and all-cause mortality. The CAC prevalence was categorized according to Agatston scores. Miedema MD, Dardari ZA, Nasir K et al. Association of Coronary Artery Calcium With Long-term, Cause-Specific Mortality Among Young Adults. *JAMA Network Open*; 2019; 2(7): e197440.¹⁹

hazard ratio for CVD and all-cause mortality increased proportionally to the calcium score.

In which patients younger than 40 years of age should coronary calcium scoring be considered and what are the treatment implications?

Current CVD risk equations that guide decisions regarding preventive medications are largely driven by age. Despite the presence of cardiovascular risk factors and elevated lifetime risks of CVD, the 10-year estimates of CVD risk are low in younger adults. CAC can stratify risk in younger adults who may benefit from aggressive CVD preventive therapies, such as those with a family history of premature ASCVD or those with multiple major ASCVD risk factors.

The CARDIA Study is a prospective, community-based cohort of 5115 asymptomatic Black and White adults aged 18–30 years who have been followed for ~30 years. At year 15 of the study, 3043 participants (mean age 40.3 years) underwent CAC testing and were followed up for 12.5 years. The prevalence of CAC was 10.2%. There was a 5-fold increase in fatal and nonfatal CHD and a 3-fold increase in any CVD event in those participants with CAC >0 compared to those with CAC = 0. Additionally, CAC scores as low as 1–19 increased the risk of CHD events by 2.6-fold and CAC ≥100 increased the risk of CHD event by 9.8-fold compared to those with CAC = 0.²⁸ The CARDIA Study was limited by a relatively small sample size and overall few CHD and CVD related events.

The CAC Consortium studied 22,346 participants aged 30–49 years who were followed for a mean of 12.7 years. The overall prevalence of any CAC was 34.4%, and 7.2% had significantly elevated CAC >100. The prevalence of traditional cardiac risk factors (hypertension, hyperlipidemia, current smoking, diabetes, family history of CHD) was statistically significantly higher among individuals with CAC >100 compared to those with a CAC score of 0. Among individuals with a CAC of >100 there was a statistically significantly elevated risk of mortality compared to those with a CAC score of 0 (>5-fold increased risk of CHD mortality and 3-fold increased risk of CVD mortality). When stratified by age groups, the prevalence of CAC 1–100 and >100 were higher in individuals who were 40–49 years of age compared to those 30–39 years of age. In both age categories, there was a graded increase in CHD, CVD and all-cause mortality events across the increasing CAC categories (Fig. 1). Despite lower CAC prevalence in the younger cohort, the mortality rates were similar between the groups 30–39 and 40–49 years of age who had CAC >100. The substantial prevalence of CAC in these individuals reinforces the value of healthy lifestyle beginning at a young age.¹⁹

In which patients 76 years of age and older should coronary calcium scoring be considered and what are the treatment implications?

CAC scoring is of value in selected older individuals for CVD risk reclassification. The largest prospective CAC scoring investigation exclusively in older adults, The Rotterdam Coronary Calcium Study, prospectively studied 2028 asymptomatic individuals, age 69.6 ± 6.2 years for the development of CHD events over a median follow-up of 9.2 years. During that period 135 hard coronary events were observed. The subjects were divided into low (<10%), intermediate (10–20%) and high (>20% 10-year risk groups). The study showed that CAC scoring, as compared to Framingham risk scoring alone, reclassified risk in 52% of those in the intermediate risk category. The CAC score cutoffs that this study derived for reclassification to either high or low risk were 615 and 50 respectively.²⁹ CAC = 0 may also be used as a “de-risking” strategy in older adults.³⁰ More accurate risk reclassification aids the clinician in making more appropriate preventive therapy decisions, either to initiate or withhold statin therapy.¹

Key points

- Racial/ethnic differences have been demonstrated in the prevalence of CAC. However, the CAC score is independently associated with ASCVD events, regardless of race and ethnicity.
- Relative ASCVD risk increases proportionally with CAC scores similarly with all races and ethnicities. For a given CAC score incidence rates of CVD and all-cause mortality are higher in Blacks and Hispanics compared to Whites and Asians.

- CAC scoring may be used selectively to risk stratify adults <40 years of age to more intensive CVD preventive therapies when CAC is identified.
- In adults 76–80 years of age, CAC scoring may be selectively used to re-classify ASCVD risk and aid in statin treatment decisions.

Recommendations

- Clinicians should use CAC scoring, when indicated, for ASCVD risk assessment, regardless of the patient’s race/ethnicity or gender. (COR I, B-NR)
- In selected individuals <40 years of age with multiple major ASCVD risk factors or a family history of premature ASCVD, it is reasonable to use CAC >0 as a factor favoring intensification of lifestyle therapy and, if necessary, initiation of statin therapy. (COR IIa, B-NR)
- In adults 76–80 years of age with an LDL-C of 70–189 mg/dL in whom the decision to employ statin therapy is uncertain, CAC scoring is useful in ASCVD risk reclassification^{31–33} (COR IIa, B-NR)

Approach to the patient with CAC = 0

What is the long term cardiovascular and non-cardiovascular prognosis of patients with CAC = 0?

CAC = 0 is associated with highly favorable prognosis and is one of the strongest “negative risk factors” for the future cardiovascular events and total mortality.³⁴ Several early studies demonstrated that patients with CAC = 0 suffer a very low mortality rate of approximately 1–2% over the following 10 years.^{35,36} Subsequently, studies showed that CAC = 0 is associated with favorable cardiovascular prognosis, including in older patients,³⁷ those with metabolic syndrome,³⁸ dyslipidemia,³⁹ and multiple traditional risk factors.^{40,41} Patients with CAC = 0 also experience low rates of important non-cardiovascular diseases, including chronic kidney disease, dementia, and cancer.⁴² Taken together, CAC = 0 can be seen as a sign of resilience to traditional and non-traditional risk factors and an overall maker of healthy aging.

CAC = 0 is the single strongest negative predictor for developing a cardiovascular event. A 2016 study from MESA compared CAC = 0 to 12 other negative risk markers, including absence of family history, healthy lifestyle, hsCRP <2 mg/L, low N-terminal pro-brain natriuretic peptide, and absence of carotid plaque.⁴³ A finding of CAC = 0 was much more reassuring than all other markers for reducing an individual patient’s post-test risk of developing clinical cardiovascular disease.

The value of CAC = 0 to re-classify ASCVD risk in those at borderline and intermediate ASCVD risk, the group for whom its use has been deemed most appropriate in the 2018 Cholesterol Guideline, was defined in a study of the MESA population. In this study of 4203 non-diabetic adults with a mean age of 59 ± 9 years of age,

589 had a 10-year risk of 5–7.4% (borderline risk) and 1381 had a 10-year risk of 7.5–19.9% (intermediate risk). Among those at borderline risk, 57% had CAC = 0, and among those at intermediate-risk 45.0% had CAC = 0. Therefore, CAC = 0 reclassified ASCVD risk in 49% (956 of 1970) of such individuals.³⁷ The knowledge of which adults with 5–19.9% 10-year risk have CAC = 0 has important treatment implications, described in section 2 below.

In MESA, adults 75–84 years of age with CAC = 0 zero had an approximate 98% survival rate at 8.5 years, which was higher than the 45–54 years old individuals with CAC>100 (82.9%). However, in this older group, there was an 11-fold and 20-fold increased risk of hard CHD events in those with CAC of 1–100 and CAC greater than 100, respectively, compared to those with CAC = 0.³¹

A retrospective study of 44,052 asymptomatic individuals who were referred for cardiovascular risk stratification

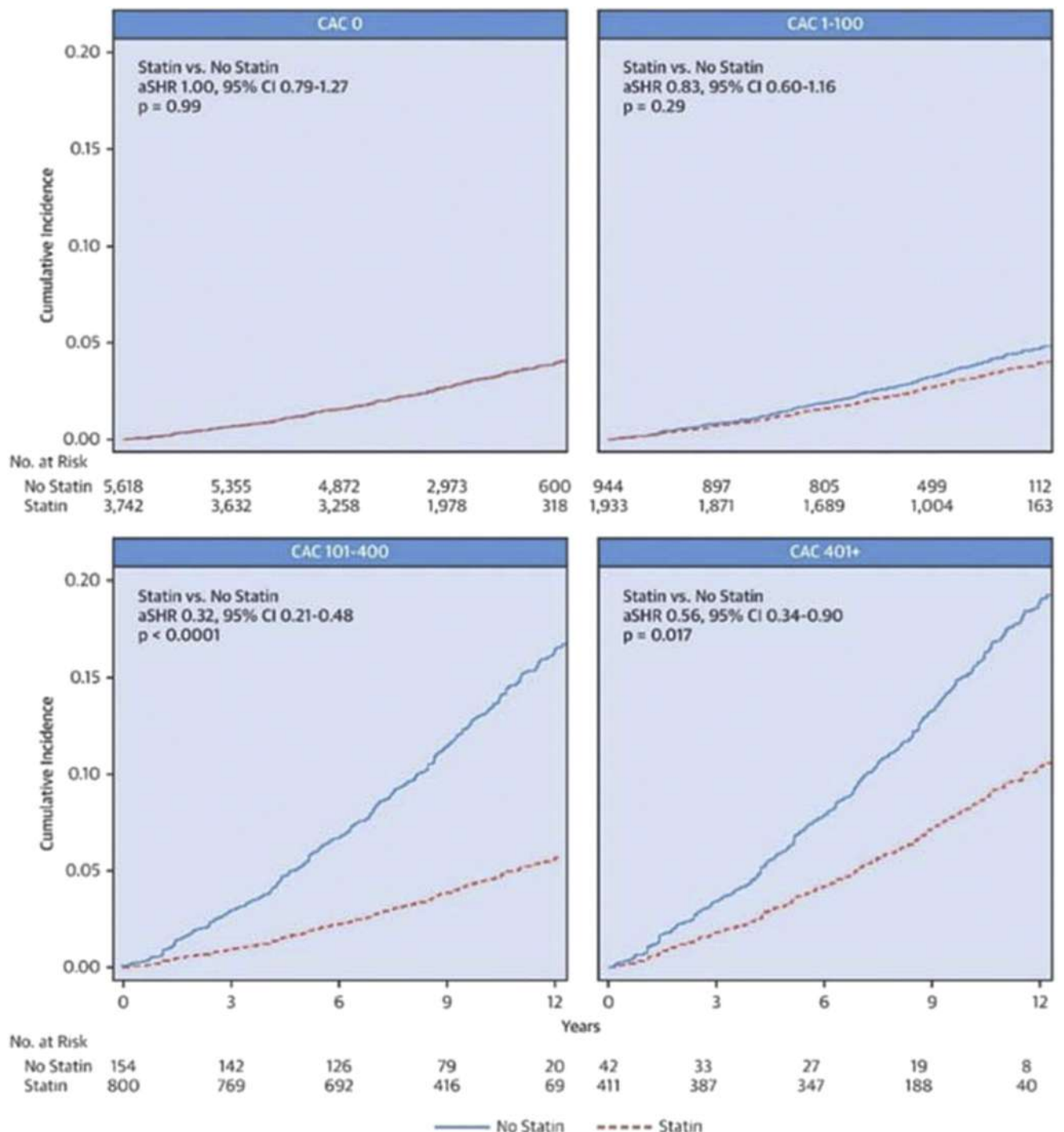


Fig. 2 Cumulative incidence of MACE stratified by statin treatment and CAC severity. Mitchell JD, Fergestrom N, Gage BF et al. Impact of Statins on Cardiovascular Outcomes Following Coronary Artery Calcium Scoring. *J Am Coll Cardiol.* 2018; 72(25):3233–42.⁴⁸

using CAC showed that 16% of the 1663 patients aged ≥ 75 years of age had a calcium score of zero. These individuals had a survival rate of 98% at a mean follow up of 5.6 years.³²

In the BioImage study, 86% of the study participants (aged 55–80 years) qualified for statin therapy for primary prevention due to a 10-year ASCVD risk of $\geq 7.5\%$. In this population, CAC = 0 as well as CAC < 10 were the strongest negative risk factors for development of cardiovascular disease over a median follow-up of 2.7 years.³³

How should the clinician use CAC = 0 for clinical decision-making regarding statin therapy

The 2018 Cholesterol Guideline states that it is reasonable to use CAC = 0 to defer initiation of statin therapy in borderline or intermediate risk individuals 40–75 years of age with LDL-C 70–189 mg/dL and without diabetes, current cigarette smoking or a strong family history of premature ASCVD.¹ Consideration to defer statin therapy for CAC = 0 is also advised in the 2017 recommendations of the SCCT.⁴⁴ These recommendations are supported by studies that apply knowledge of CAC scores to the results of several clinical trials.

A landmark study estimated that the 5-year number need to treat (NNT) to prevent a first coronary event in individuals with LDL-C < 130 mg/dL and hsCRP ≥ 2 mg/dL treated with rosuvastatin 20 mg daily. The NNT for those receiving placebo was 549 for those with CAC = 0 versus 24 for those with a score $\gg 100$.⁴⁵ Further support for the use of CAC scoring for risk-appropriate statin allocation was provided in a study that applied the prevalence data of CAC = 0 from MESA³⁷ to the placebo group of the Third Heart Outcomes Prevention Evaluation (HOPE-3).⁴⁶ This analysis showed that for those with CAC = 0, the projected number needed to treat to prevent one event with rosuvastatin 10 mg daily for 5.6 years was 206, compared to 50 for individuals with a CAC score of ≥ 100 .⁴⁷

A study of patients in a large registry demonstrated that patients with CAC = 0 receive minimal to no near-term benefit from statin therapy, while patients with detectable CAC accrue a clear benefit from statins (Fig. 2).⁴⁸ In addition, the 2018 Cholesterol Guideline supports the use CAC = 0 to re-classify risk of adults 76–80 years of age, with LDL-C 70–189 mg/dL, to potentially avoid statin initiation.¹

Key points

- CAC = 0 is associated with highly favorable cardiovascular and non-cardiovascular prognosis. CAC = 0 is the strongest “negative risk marker” for ASCVD
- In the absence of diabetes mellitus, active cigarette smoking or a family history of premature ASCVD, statin therapy in those with CAC = 0 is associated with limited short to intermediate-term ASCVD risk reduction benefit.

- The absolute ASCVD risk reduction with statin therapy is proportional to the CAC score.

Recommendations

- In adults 40–75 years of age with LDL-C 70–189 mg/dL and without diabetes, active cigarette smoking or a family history of premature ASCVD, it is reasonable to defer statin initiation in those with CAC = 0 (COR IIa, B-NR)
- In adults age 76–80 years of age in whom the decision about initiation of statin therapy is uncertain, it is reasonable to use CAC = 0 as a factor favoring avoidance of statin therapy (COR IIa IIaB-NR)

Definition, prognostic significance and treatment of those with a high CAC score, multivessel involvement or left main coronary calcification

What constitutes a high CAC score and what is the prognostic significance of a high CAC score?

Cholesterol Guideline documents issued by the AHA and ACC have used CAC scoring to improve discrimination and reclassification of risk for clinical ASCVD and to inform risk-appropriate statin treatment decision-making. Three studies below address the definition and clinical significance of “high CAC scores.”

A study of the MESA cohort examined the relationship between CAC and ASCVD outcomes in 6814 adults, 45–84 years of age, prospectively followed over a median of 11.1 years. Five hundred incident ASCVD events were observed and 10-year event rates were categorized into those with scores of 0, 1–99, 100–299 and ≥ 300 . Those with a CAC score > 100 , regardless of their demographic subset, had a Kaplan Meier cumulative 10-year incidence of hard ASCVD events of $> 7.5\%$, a finding supportive of initiation of statin therapy in the 2018 Cholesterol Guideline. Those with a score of 300 or greater had a 10-year incidence consistently $> 15\%$, and in the 75 to 84 year-old group, $\geq 25\%$.²⁷

A 2018 study of the prospective Heinz Nixdorf Recall cohort from Germany, examined the predictive value of coronary calcium scoring and progression versus traditional risk factors on the risk of subsequent cardiovascular events. A group of 3281 individuals, 45–74 years of age and free of clinical cardiovascular disease, underwent baseline CAC scoring and repeat CAC scoring after a mean of 5.1 years. The incidence of hard coronary and cardiovascular events, as well as total cardiovascular events (including revascularization) were recorded with a follow-up of 7.8 ± 2.2 years after the second CAC scoring exam. The study showed that those with a CAC score > 400 had a projected 10-year hard ASCVD event rate of 13.5% .⁴⁹

A study from the CAC Consortium retrospectively evaluated 66,366 asymptomatic adults with a mean patient

follow-up of 12.3 ± 3.9 years for the development of cardiovascular disease, coronary heart disease, cancer and all-cause mortality. Those with scores ≥ 1000 had multivariable hazard ratios adjusted for conventional risk factors of 5.04- (95% CI: 3.92 to 6.48), 6.79- (95% CI: 4.74 to 9.73), 1.55- (95% CI: 1.23 to 1.95), and 2.89-fold (95% CI: 2.53 to 3.31) risk of CVD, CHD, cancer, and all-cause mortality, respectively compared to those with CAC = 0. This study, which reported data on 2869 patients (86.3% men) with CAC scores ≥ 1000 , mean age 66.3 ± 9.7 years, and compared their CVD and CHD mortality to those with scores of 400–999 showed that both CVD and CHD mortality of those with a CAC score ≥ 1000 was more than double that of those with scores of 400–999.⁵⁰ The authors pointed out that the annualized CVD death rate of 0.8% per year for those with a CAC score ≥ 1000 was similar to that observed in the placebo group of Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER),⁵¹ in which the annualized death rate was 0.77% per year.

An additional consideration in deciding the prognostic significance of a high CAC score is an individual's exercise habits and functional capacity. A study of 21,578 generally healthy men seen at the Cooper Clinic was performed to assess the cross-sectional association of prevalent CAC with high levels of physical activity and to determine whether high-level physical activity was associated with increased all-cause and CVD mortality. The studied population had a baseline mean (SD) age of 51.7 (8.4) years, and represented those seen at this Clinic over a 15 year period from January 1998 to December 2013. The subjects' self-reported aerobic physical activity was estimated using minutes of aerobic activity per week multiplied by the estimated metabolic equivalent (MET) value for the type of activity in which they engaged. The activity level was reported as MET-minutes per week and was categorized into the following 3 groups: at least 3000 or more, 1500 to 2999, and less than 1500 MET-min/week. A level of 3000 MET-minutes per week is equivalent to more than 5 h per week of vigorous exercise. Baseline CAC scores were obtained and mortal events, including the specific cause of death, were evaluated through 2014 using National Death Index Plus. Over a mean follow-up (standard deviation) of 10.4 (4.3) years, 759 subjects died, including 180 CVD deaths. Among those with physical activity of at least 3000 MET-min/week, 40 all-cause and 10 CVD deaths occurred. Men with at least 3000 MET-min/week were more likely to have prevalent a CAC score of at least 100 (relative risk, 1.11; 95% CI, 1.03–1.20) compared with those who performed less physical activity. Among those at the >3000 MET-min/week level and a CAC score ≥ 100 , the mean CAC score was 807, as compared to those at the <1500 MET-min/week, who had a mean CAC score 736. Despite these differences, those in the higher-level activity group were no more likely to die from all-cause or CVD, a finding suggesting that habitual high-level physical activity may have protective effects, even in those with high CAC scores.⁵² This perspective was further supported by a study of 2653 patients aged 65–84 years who

were referred for CAC scanning on a clinical basis, had more than 1 year of follow-up for all-cause mortality, and had a median follow-up of 11.4 years (interquartile range 6–15 years).⁵³

Which patients with a high CAC score, left main coronary calcification or diffuse coronary calcification should have additional cardiac testing?

There is evidence that the distribution of CAC within the coronary tree predicts risk.⁵⁴ For a given CAC score, a more diffuse CAC distribution (more coronaries involved, i.e. 3 coronary involvement vs. 1 coronary involvement) is associated with higher risk.⁵⁵ The only individual coronary artery where vessel-specific CAC appears to add to the total CAC score is the left main coronary artery. There is evidence that greater left main CAC predicts risk beyond the total CAC score, particularly when $>25\%$ of the total CAC score is present within the left main.⁵⁶

More diffuse regional distribution of CAC or high left main CAC involvement should generally be viewed as an additional factor favoring more aggressive preventive pharmacotherapy. It should not routinely trigger downstream stress testing in those asymptomatic individuals who report a normal functional capacity. The presence of advanced left main coronary calcification should only prompt further workup (stress testing, cardiac catheterization) in the presence of concomitant clinically relevant cardiovascular symptoms.

There are no data to support the benefit of coronary angiography in asymptomatic individuals with high CAC scores, including those demonstrated to have an ischemic response to exercise testing. Even in patients with stable CAD and moderate to severe ischemia on stress testing, an RCT of 5179 subjects showed no benefit on cardiovascular outcomes of an initial invasive strategy (coronary angiography and percutaneous revascularization when feasible) and medical therapy versus an initial conservative strategy of medical therapy alone and coronary angiography if medical therapy failed.⁵⁷

How should clinicians use high CAC scores to allocate statin therapy or the potential addition of non-statin add-on therapies to statins?

Based on data from MESA, and consistent with the recommendations of the 2018 Cholesterol Guideline, a CAC score ≥ 100 , associated with a 10-year ASCVD risk $>7.5\%$, is a clear indication to engage in a clinician patient discussion about initiation of statin therapy.²⁷ In most such patients, a moderate intensity statin is initiated. For those with a CAC score of >300 per MESA or >400 in the Heinz Nixdorf Recall Study, with 10-year hard ASCVD risk in the 13 to $>15\%$ range, moderate or possibly high intensity statin therapy is reasonable. For those with scores >1000 , based on data from the CAC Consortium, the use of high intensity or maximally tolerated statins and concomitant statin add on LDL-C lowering therapy may be warranted in those with an LDL-C threshold ≥ 70 mg/dL. In all

patients, and especially in those with higher ASCVD risk, concomitant attention to effective management of all other ASCVD risk factors is warranted.

Key points

- For a given CAC score, a diffuse distribution of CAC suggests higher risk than more localized CAC.
- The presence of left main coronary calcification, especially when >25% of the total score is in the left main, suggests higher risk
- There is no evidence to support the benefit of performing stress testing, or invasive coronary arteriography in asymptomatic individuals with high coronary calcium scores.
- A CAC score ≥ 100 is associated with >7.5% 10-year ASCVD risk, the guideline-based threshold of statin benefit in primary prevention.
- A CAC score ≥ 300 is associated with proportionately higher ASCVD risk than those with scores >100, a finding suggesting benefit from greater LDL-C lowering.
- A CAC score ≥ 1000 is associated with an annual risk similar to that of the placebo group in the FOURIER trial, a finding consistent with the potential value of very aggressive LDL-C lowering along with other ASCVD risk reduction strategies.

Recommendations

- In adults with predominant left main coronary calcification, multi-vessel coronary involvement, or a high CAC score, stress testing or invasive coronary arteriography, in the absence of clinically relevant symptoms, is not recommended. (COR III-Harm)
- In adults with CAC scores ≥ 100 , initiation of statin therapy is recommended. (COR I, LOE B-NR)
- In adults with CAC scores ≥ 300 , and especially in those with CAC scores ≥ 1000 , it is reasonable to use high intensity statin therapy, and if necessary, guideline-based add-on LDL-C lowering therapies to achieve a $\geq 50\%$ reduction in LDL-C, and optimally an LDL-C <70 mg/dL (COR IIa, LOE C-LD).

Management of pulmonary nodules and incidental coronary calcium found on chest CT studies

How should the clinician evaluate pulmonary nodules noted during CAC testing?

Incidental findings, particularly pulmonary nodules, may be observed in about 10% of asymptomatic patients sent for coronary calcium scoring.⁵⁸ Most are benign, but there are established protocols for follow-up depending upon clinical characteristics of the patient, and the size and characteristics of the nodules: solid or subsolid, single or multiple.^{44,58} In general, isolated nodules that are <6 mm in size, in the

absence of immunosuppressive therapy or a known primary malignancy, are generally benign. When a pulmonary nodule is found, characteristics associated with a higher risk of malignancy include age >40 years (risk increases with age), heavy smoking, larger nodule size, irregular or spiculated margins, and upper lobe location.^{59,60} In such individuals, further evaluation in accordance with the Fleischner Society Guidelines, should be undertaken.⁵⁸

How should the clinician evaluate incidental coronary artery calcium found on chest CT imaging done for indications other than coronary calcium scoring?

The SCCT and the Society of Thoracic Radiology recommend at least qualitative interpretation of CAC on all CT scans of the chest, regardless of indication (Class I recommendation). In patients with incidental findings of CAC on thoracic CT imaging, qualitative indication of severity (mild, moderate, heavy/severe) should be reported. For those with mild calcification, a dedicated coronary calcium scoring study is useful to aid in clinical decision making. The presence of moderate or severe calcification generally correlates with a CAC score of ≥ 100 , a guideline-based indication for statin benefit.^{2,61}

Recommendations

- In adults found on a CAC scoring exam to have one or more pulmonary nodules, follow-up testing should be done in accordance with the Fleischner Society recommendations. (COR I, C-EO)
- In adults found on a chest CT exam not done for coronary calcium scoring to have incidental mild CAC, it may be reasonable to obtain a dedicated CT scan for CAC scoring to guide preventive treatment decision-making (Class IIb, C-LD)
- In adults found on a chest CT exam to have incidental moderate or severe CAC, initiation of statin therapy without dedicated CAC imaging is reasonable. Class (IIa, LOE B-NR)

CAC scoring in patients with severe primary hypercholesterolemia

Is there a role for CAC scoring in patients with severe primary hypercholesterolemia?

Because individuals with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) harbor a hazard ratio for clinical coronary heart disease of up to 5.0 as compared to those with LDL-C <130 mg/dL⁶² and because those with monogenic variants associated with familial hypercholesterolemia have an even greater risk than those without such variants,⁶³ there is guideline consensus that all such individuals merit aggressive LDL-C lowering. However, the remains heterogeneity of risk among such patients.⁶⁴ In addition, many such individuals remain untreated or are treated sub-

optimally.⁶⁵ The question is whether the use of CAC scoring provides additional clinically useful information that might support the use of add-on therapy to maximally tolerated statins in those without additional major ASCVD risk factors or strong family histories of premature ASCVD.⁶⁶

There are limited data on CAC scoring in patients with severe hypercholesterolemia. A study examined ASCVD outcomes in a cohort of 206 patients (63.6% females) with molecularly proven heterozygous FH seen in a university lipid clinic in Brazil, mean age 45 ± 14 years, with baseline LDL-C 269 ± 70 mg/dL. The patients were followed for a median of 3.7 years (interquartile range 2.7–6.8 years). 49% ($n = 101$) had a CAC score of zero and none of these had ASCVD events over the short term follow-up period of this study, as compared to those with scores of 1–100 or >100 , who had annualized rates of events per 1000 patients of 26.4 (95% CI, 12.9–51.8) and 44.1 (95% CI, 26–104.1).⁶⁷ These data support strong risk discrimination with the use of CAC in this population. However, while these data suggested a favorable short-term prognosis for CAC = 0 in such patients, they do not preclude the value of aggressive long-term LDL-C lowering to reduce the hazard ratio for ASCVD in those with heterozygous FH.

A study of the MESA cohort identified 246 individuals, mean age 63 ± 9.4 years, 42% male, with LDL-C ≥ 190 mg/dL. Multivariable-adjusted Cox regression was used to associate CAC = 0 with incident cardiovascular events over a median follow-up of 13.2 years. Those with CAC = 0 had an ASCVD incidence rate of 4.7 per 1000 person-years and a risk of 0.4% per year. In comparison, those with CAC >0 had an incidence rate of 26.4 per 1000 person-years and a rate of 2.0% per year. In this study, other factors associated with low risk included younger age, female sex and the absence of diabetes.⁶⁸

These studies support the perspective that in selected patients with severe primary hypercholesterolemia without additional factors known to be associated with higher risk, such as extreme LDL-C elevation, the presence of additional major risk factors or a family history of premature ASCVD, CAC scoring may be considered to further inform the clinician patient discussion related to the need for add-on therapy to maximally tolerated statins.

Key points

- Limited data on CAC scoring in individuals with LDL-C ≥ 190 mg/dL indicate that CAC scoring may aid in both short- and intermediate-term ASCVD risk prediction. The finding of CAC >0 identifies a group in which particularly aggressive LDL-C lowering strategies should be undertaken.
- In individuals with severe primary hypercholesterolemia, the finding of CAC = 0 does not preclude the need for long term evidence-based LDL-C lowering therapy.

Recommendations

- In selected adults with severe primary hypercholesterolemia, in the absence of extreme LDL-C elevation, additional major ASCVD risk factors or a family history of premature ASCVD, CAC scoring may be reasonable to inform decision-making about the need for add-on therapy to maximally tolerated statins. (COR IIB, C-LD).
- In adults with severe primary hypercholesterolemia and CAC >0 , heightened ASCVD risk status is confirmed, favoring more aggressive, guideline based LDL-C lowering. (COR IIA, C-LD)

CAC scoring in patients with diabetes and/or the metabolic syndrome

Should CAC scoring be used to decide to delay or intensify statin treatment for primary prevention of ASCVD in people aged 40–75 years with diabetes?

Because several intervention trials with moderate statin therapy in cohorts with mainly type 2 diabetes aged 40–75 years have shown benefit in reducing ASCVD events, this treatment is recommended for people with diabetes in this age group,⁶⁹ although there have been no such trials in those with type 1 diabetes. There is, however, substantial heterogeneity of ASCVD risk in this population related to age, ASCVD risk factors and duration and severity of diabetes, with ASCVD risk estimates ranging from $<7.5\%$ to $>20\%$ by quantitative risk factor assessment using the PCE.⁷⁰ Since evidence indicates that benefit in reduction of ASCVD is related to the intensity of statin treatment, high-intensity statin therapy is preferred for primary prevention in higher risk individuals, defined as men 50 years of age and older, women 60 years of age and older, or those with multiple risk factors,¹ even though there is no specific clinical trial evidence to support this recommendation in cohorts with diabetes.

Because CAC has been shown to predict ASCVD events independent of standard risk factors in both type 1 and type 2 diabetes, CAC scoring can be helpful in improving the accuracy of estimating ASCVD risk in this population. In studies of CAC in type 2 diabetes, the majority of individuals had CAC >0 .^{38,71,72} The reverse was true for studies in type 1 diabetes although these reports were in younger individuals.^{73–75} In MESA (average age 62 years) the 10-year risk for ASCVD in those with type 2 diabetes who had CAC = 0 (37% of the cohort) was 8.2%, while for the majority with CAC >0 the ASCVD risk was substantially higher (CAC 1–99 10 year risk = 15%; CAC >100 10 year risk was $>20\%$).³⁸ These data argue against the exclusive use of CAC to support withholding statin therapy. However, it may be reasonable to use CAC to more precisely identify those with higher ASCVD risk ($>15\%$ 10 year risk) for high-intensity statin treatment or additive

treatment with ezetimibe if an LDL-C lowering of $\geq 50\%$ is not achieved with statin therapy.

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications study was an observational study of 1394 subjects with type 1 diabetes, from the original DCCT cohort who agreed to undergo CAC scoring 7–9 years after completion of the DCCT. Their average age was 43 years and they were examined for CVD events and MACE over 10–13 years. The study showed that those with CAC = 0 (70.7% of the cohort), 1–99 (19.1%), 100–300 (5.6%) and >300 (4.6%) had a 5-year absolute risk of MACE of 2.5%, 2.8%, 13.9% and 18.2% respectively.⁷³ Thus, it may be reasonable in selected type 1 diabetic adults in this age group to obtain CAC scoring to refine risk assessment and to inform statin and other preventive treatment decision making.

Does CAC scoring help to identify people with diabetes who are <40 or >75 years for initiation or intensification of statin therapy?

There are no clinical trials of statin treatment informed by CAC scoring in people with diabetes in these age groups, nor have estimates of ASCVD risk using quantitative risk assessment been developed to guide statin treatment decisions. Evidence indicates that ASCVD event rates are low in individuals <20 years of age but increase in the third and fourth decades in relation to duration of diabetes, standard risk factors and development of diabetic microvascular complications.⁷⁰ In a large cohort of adults aged 32–43 years, CARDIA found that CAC>0 was associated with increased ASCVD events over 12.5 years of follow-up (for CAC>20 the ASCVD event rate was >8.0%).⁷⁶ In a small group of adults with type 2 diabetes (n = 181) aged 32–39 years and with diabetes duration of 8–15 years, 24% had CAC 1–100 and 8% had CAC>100. There have been several studies of CAC in type 1 diabetes encompassing this age range demonstrating an association between CAC and ASCVD events independent of standard risk factors.^{73–75} In one study the CAC prevalence in the age range of 30–39 years was approximately 20% in women and 35% in men.⁶

The 2018 Cholesterol Guideline states that it may be reasonable to recommend a statin for those type 1 diabetic adults 20–39 years of age with diabetes-specific risk enhancers (≥ 20 years of type 1 diabetes, albuminuria [≥ 30 mcg of albumin/mg creatinine], estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m², retinopathy, neuropathy, or ankle-brachial index<0.9). As coronary calcification is uncommon in individuals <30 years of age and as the presence of CAC identifies those with diabetes at higher ASCVD risk, CAC scoring may be useful to inform decision-making about initiation of statin treatment in individuals 30–39 years of age with diabetes, especially in those with diabetes-specific risk enhancers in whom the decision to initiate a statin is uncertain.¹

Several studies have investigated the associations between CAC and ASCVD events in individuals >60

years of age although none have been conducted in cohorts with diabetes. Among subjects in the 75 to 84 year-old age group in MESA, 65% of whom had hypertension, 15% with diabetes and 21% on lipid lowering treatment, about 85% had CAC>0.³¹ As in all age groups, the severity of CAC was strongly associated with CHD events over a 8.5 year follow-up period, and those with CAC = 0 had an event rate of 1.8%/10 years as compared to $\geq 21.3\%$ in those with CAC>100. Therefore, given the potential for increased risk associated with statin therapy in some older individuals and the fact that the onset of diabetes may be of unknown or short duration, it is reasonable to employ CAC scoring to decide whether to newly initiate statin therapy in those >75 years of age.

Should CAC scoring be used to identify individuals with the metabolic syndrome, without diabetes and at low or intermediate ASCVD risk based on the Pooled Cohort Equations, who might benefit from initiation of statin therapy for primary prevention?

The 2018 Cholesterol Guideline identifies the metabolic syndrome as an ASCVD risk enhancer, the presence of which favors statin initiation or intensification in those at 5–19.9% 10-year ASCVD risk. About one third of adults have the metabolic syndrome and the prevalence increases with age.⁷⁷ Although the presence of the metabolic syndrome increases overall risk for ASCVD as compared to those without the metabolic syndrome, there is considerable heterogeneity of ASCVD risk in these individuals. In MESA 44.8% of those with metabolic syndrome but no diabetes had CAC = 0 and their 10-year ASCVD risk was <5% whereas those with CAC>0 had a 10-year ASCVD risk averaging at least 10% or higher.³⁸ Thus, CAC may be of use in risk stratification in those with the metabolic syndrome.

Recommendations

- In adults 40–75 years of age with type 2 diabetes and an LDL-C 70–189, a moderate- or high-intensity statin is indicated, regardless of CAC score. (COR I, LOE A)
- In adults 40–75 years of age with type 2 diabetes age in whom the decision has been made to initiate statin therapy, it is reasonable, for those with a CAC score >100, to choose a high-intensity statin. (COR IIa, LOE C-LD)
- In adults 30–39 years of age with long-standing diabetes (type 1 diabetes of ≥ 20 years duration or type 2 diabetes of ≥ 10 years duration) and risk factors or microangiopathy, CAC scoring may be reasonable to aid in ASCVD risk stratification and statin treatment shared decision making. (COR IIb, LOE C-LD)
- In adults older than 75 years of age with type 2 diabetes, in whom the decision to employ a statin for primary prevention is uncertain, CAC scoring is reasonable to aid in statin treatment shared decision making (COR IIa, LOE C-LD).

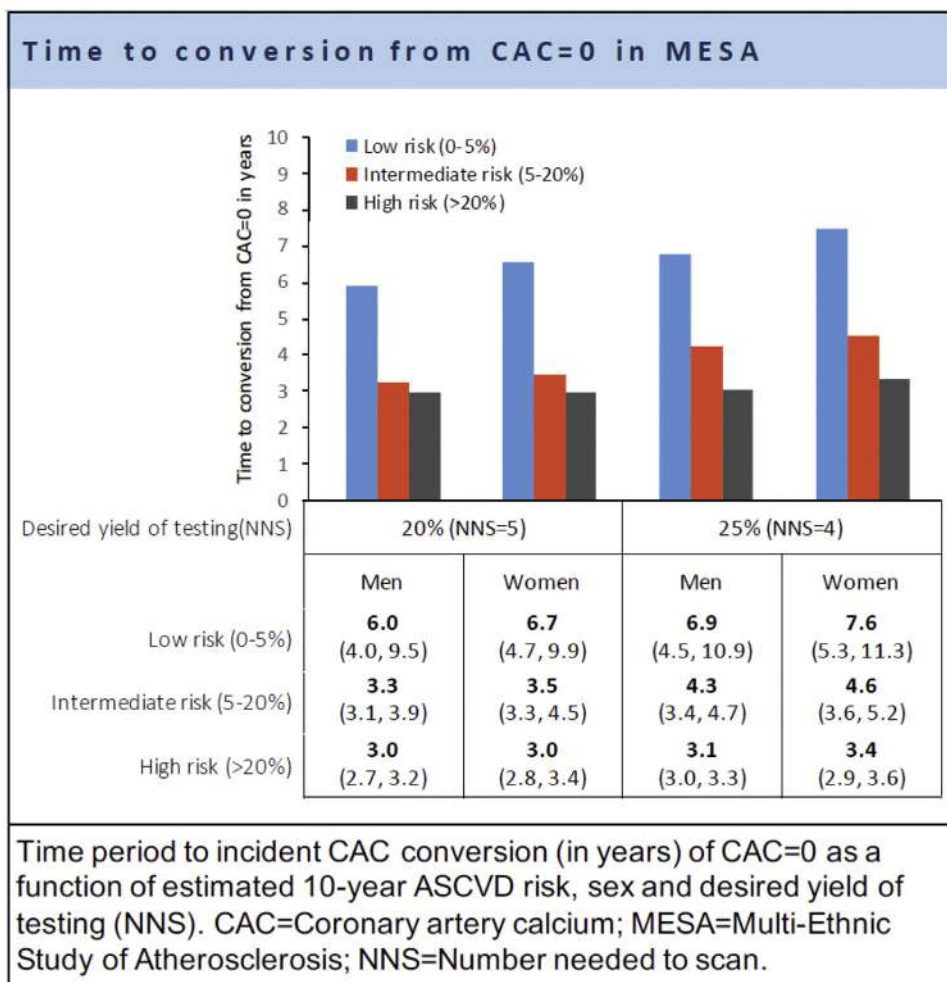


Fig. 3 Time to Conversion from CAC = 0 to CAC>0 in MESA. The warranty period (recommended re-scan interval) of CAC = 0 varies as a function of age, sex, cardiovascular risk and desired yield of testing. Dzaye O, Dardari ZA, Cainzos-Achirica M et al. Incidence of New Coronary Calcification: Time to Conversion From CAC = 0. *J Am Coll Cardiol.* 2020; 75(13):1610–13.⁷⁸

Repeat CAC scoring

At what intervals should CAC scoring be repeated?

A key question when considering repeat CAC scoring relates to the predictive value of CAC progression for subsequent clinical ASCVD. In the previously cited Heinz Nixdorf Recall cohort, in which CAC progression and ASCVD events were assessed a mean of 7.2 years after two serial CAC scans done 5.1 years apart, absolute CAC progression was greater in those with versus without documented coronary events. The results of the second CT scan were more predictive than the actual change in CAC scores between the two time points. Those with CAC = 0 on both examinations had an excellent prognosis, with a 10-year risk of hard cardiovascular events of 2.0%. Individuals with a baseline CAC score 1–399 and follow-up score <400 had a 10-year risk of hard CVD events of 5.2% and of total CVD events of 9.1%. Those with a baseline score of 1–399 and follow-up score ≥400 had a 10-year risk of 19.1%. Finally, those with a baseline CAC score ≥400 had a 10-year CVD risk of 13.5% and total

CVD events of 30.9%.⁴⁹ They further demonstrated that strongly accelerated CAC progression was associated with higher overall mortality and CV events.

A study of the MESA cohort examined the incidence of newly detected CAC after an initial CAC = 0.⁷⁸ It showed that the warranty period of CAC = 0 varies by age, sex, baseline cardiovascular risk, and the desired yield of testing (i.e. the number needed to screen, defined by the prevalence of new CAC>0 that is considered reasonable for clinical detection. In low risk patients (<5% 10-year risk), about 20–25% will develop newly detected CAC in 5–7 years. In borderline to intermediate risk patients (5–19.9% 10-year risk), in whom CAC scoring is most often performed, 20–25% develop new CAC>0 in approximately 3–5 years. In high risk patients (>20% 10-year risk), 20–25% develop CAC in 3 years (Fig. 3). In a follow-up study from MESA, it was shown that the diabetes sub-group develops new CAC at a faster rate compared to those without diabetes, with rates similar to the general high-risk population with 10-year ASCVD risk >20%. For example, approximately 20–25% of those with diabetes develop new CAC>0 in

approximately 3–5 years, similar to 20–25% of high-risk individuals who develop CAC over approximately 3–4 years.⁷⁹

Clinicians should be reassured that CAC generally progresses very slowly, and on an exponential scale, and thus, it is extremely unlikely that retesting over the recommended intervals will miss progression to a high CAC score. The vast majority of patients in whom new CAC is detected will have a score <25 (in MESA, mean score of 7 in those progressing to CAC>0 over 6 years⁸⁰), and in MESA <10% of all individuals with CAC = 0 developed CAC >100 over 10-year follow-up. These data match prior data on this topic.⁸¹

A repeat CAC score in 3–5 years may be useful for patients with low positive CAC scores (1–99) to assess for faster than median progression (i.e. >20–25%/year), a clinical scenario in which more aggressive preventive pharmacotherapy may be considered.⁸² While repeat CAC testing should not commonly be done in most patients whose baseline CAC scores are ≥100, a repeat scan at a 3 year interval in an individual with LDL-C persistently ≥70 mg/dL could be useful to identify those with an increase in CAC score to ≥400, in whom more aggressive LDL-C lowering therapy might be considered. However, repeat CAC testing cannot be used to test the efficacy of statin therapy, as statins do not diminish or slow the near-term progression of mineralized calcium within the atherosclerotic plaque.

Key points

- Recommended timing for repeat CAC scoring depends upon the baseline ASCVD risk of the individual, varying from 3 to 7 years.

- CAC scores increase by approximately 20–25% per year. Hence, the Agatston score generally increases exponentially, with scores in the range of 0–100 providing the greatest risk discrimination compared to higher scores.
- CAC should be measured only if such measurement will change treatment decisions.
- CAC does not regress.
- CAC progression cannot be used to measure the efficacy of statin therapy (statins modestly *increase* the CAC score). Statins delipidate plaque, decreasing volume of calcified plaque.
- In individuals who undergo repeat CAC scoring, progression of >20–25% per year or an increase to a score of ≥400 in an individual with a previous CAC score >0 is consistent with accelerated ASCVD progression.

Recommendations

- In adults with CAC = 0, it is reasonable to repeat CAC scoring at the following intervals:
 - Low risk (<5% 10-year risk): 5–7 years
 - Borderline to intermediate risk (5–19.9% 10-year risk): 3–5 years
 - High risk or diabetes: 3 years

(Class IIa, B-NR).

- In adults with CAC scores 1–99, it may be reasonable to repeat CAC scoring in 3–5 years if the results might change treatment decisions (Class IIb LOE B-NR).
- In adults with CAC scores ≥100 and an LDL-C ≥70 mg/dL, repeat CAC scoring at 3 years may be reasonable to assess for accelerated progression (>20–25% per year) and/or an increase to a CAC score >300, findings that

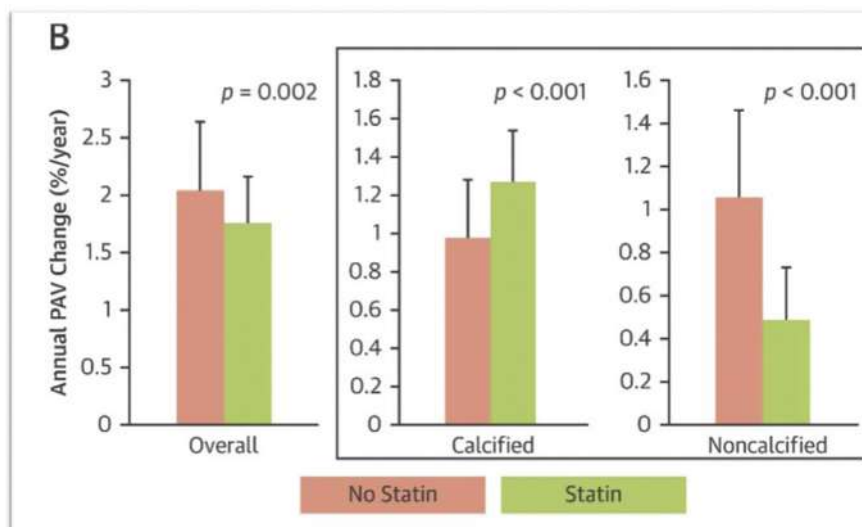


Fig. 4 Effect of statin therapy on plaque type. Statins decrease total plaque, decrease non-calcified plaque, yet increase calcified plaque. This has implications for the CAC score in the setting of statin use. Statins can modestly increase the CAC score due to plaque delipidation and associated increased density of calcium mineralization. Lee S-E, Chang H-J, Sung JM et al. Effects of Statins on Coronary Atherosclerotic Plaques: The PARADIGM Study. *JACC Cardiovasc Img* 2018; 11 (10):1475–84.⁸⁶

may favor more aggressive LDL-C lowering. (Class IIb, LOE C-LD).

Use of CAC scoring in those taking statins

What are the implications of CAC scores obtained in patients taking statins?

There are two principal issues in considering CAC testing in patients taking statins: 1) What is the effect of statins on calcified plaque? and 2) Does CAC remain a risk predictor in patients with a history of statin therapy?

It is now well established that statins delipidate atherosclerotic plaque, converting lipid-rich plaque into lipid-depleted plaque.⁸³ In this process, plaque calcification, or its density can modestly increase. This is well established in CT angiography literature, where statins are known to decrease overall and non-calcified plaque, yet modestly increase calcified plaque (Fig. 4). CAC scores do not decrease with statin therapy. While the only randomized trial of statins versus placebo in those with CAC>0, the St. Francis Heart Study,⁸⁴ showed no difference in CAC progression in those randomized to atorvastatin 20 mg vs placebo, other evidence from both intravascular ultrasound (IVUS) and coronary CT angiography suggests that statins can increase calcification (perhaps as a part of plaque stabilization).^{85,86} Since the Agatston CAC score is upweighted with increasingly dense plaque, general consensus is that CAC scores may increase slightly in patients taking chronic statin therapy, as compared to untreated patients.⁵ However, while statins may increase calcification of existing plaque, statins do not cause new plaque initiation. Statins appear to only modify existing plaques.

A study from the CAC consortium of 28,025 adults 40–75 years of age, mean age 53.9 ± 10.9 years, 6151 of whom were statin users, assessed, using an age- and sex-adjusted Cox regression model adjusted for traditional ASCVD risk factors, the association of CAC and CAC components including CAC area, volume, and density with coronary heart disease and cardiovascular disease (CVD) mortality. Over a median of 11.2 years of follow-up, a total of 395 total CVD and 182 CHD deaths were recorded. Among statin users each unit increase in log CAC score was associated with an increase in CVD mortality (1.2; 95% CI = 1.1–1.3) and CHD mortality (HR, 1.2; 95% CI = 1.1–1.4). The volume score and CAC area were similarly associated with outcomes in statin users and non-users. The volume score and CAC area were associated with CVD and CHD mortality in both statin users and non-users. CAC density predicted risk in non-users, but did not predict risk in those taking statins.⁸⁷

In summary, the CAC score remains a predictor of risk in patients with a history of statin exposure. Evidence from both MESA and the CAC Consortium suggests that CAC scores increase similarly in patients taking statins vs. statin naïve.⁸⁸ Therefore, in selected patients, including those with statin intolerance, CAC scoring can be used to further

risk stratify individuals taking statins or with a history of statin exposure, and may guide intensity of lipid-lowering therapy, aspirin recommendations, and other preventive decision-making.

Key points

- Statins delipidate plaque, decreasing volume of non-calcified plaque and increasing volume of calcified plaque.
- CAC scoring remains a risk predictor in statin-treated patients, similar to risk discrimination observed in statin naïve patients.

Use of CAC scoring in allocation of aspirin and anti-hypertensive therapy

What is the evidence that CAC scoring should trigger consideration of aspirin therapy?

In the current era of preventive cardiology, the margin of net benefit of low-dose aspirin therapy in primary prevention is small. This conclusion is based on data from three large recent clinical trials, where small benefits of aspirin on cardiovascular event reduction were counterbalanced by risk of bleeding.⁸⁹ New guidelines from the ACC/AHA have now assigned low-dose aspirin a less favorable IIb recommendation in high risk primary prevention patients who are not at high risk of bleeding.¹⁸

Data using observed cardiovascular event rates and observed major bleeding rates suggest that the CAC score can be useful in determining which patients might receive a net benefit from aspirin. In a study of 6470 MESA participants over a median follow-up of more than 14 years, investigators showed that the Pooled Cohort Equations could identify no group that would reliably receive net ASCVD risk benefit from aspirin therapy. This finding is explained by the observation that the risk of bleeding increases as calculated risk from the Pooled Cohort Equations increases. In contrast, while CAC scoring strongly predicted ASCVD events, no consistent association was found between CAC burden and bleeding risk (Fig. 5). Their models show that individuals with CAC = 0 are more likely to be harmed by aspirin than be helped (number needed to harm (NNH) > NNT).⁹⁰ In contrast, and consistent with prior models,^{91,92} individuals with CAC>100 are expected to derive a net benefit from aspirin therapy (NNT > NNH).

More recently a cohort study of 2191 participants in the Dallas Heart Study with no clinical ASCVD and not taking aspirin at baseline, were followed for a median of 12.2 years. During that time there were 116 major bleeding events and 123 ASCVD events. Applying meta analysis estimates, irrespective of the CAC score, aspirin therapy was associated with net harm in those with <20% 10 year ASCVD risk and net benefit in those with $\geq 20\%$ risk.

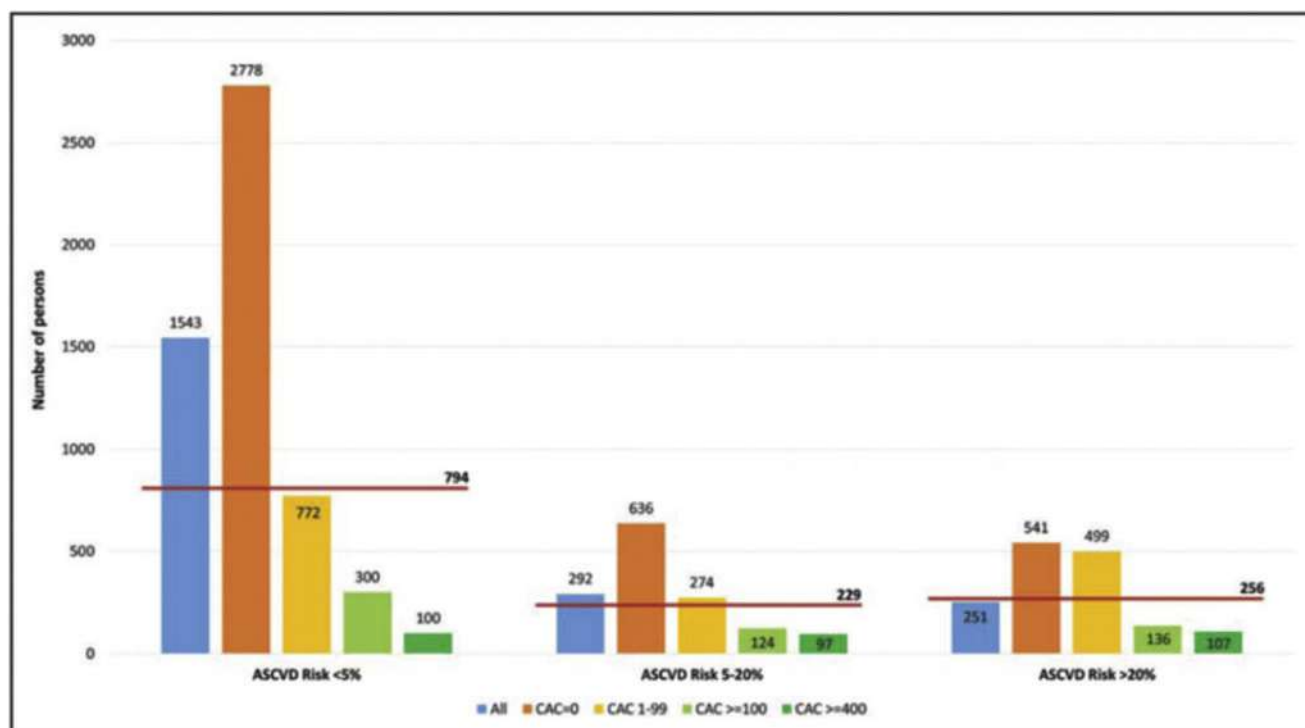


Fig. 5 Interaction of ASCVD risk and CAC score in predicting the net benefit of aspirin therapy in primary prevention. Using the ASCVD risk score, there is no group in which the benefit of aspirin therapy outweighs risk. In contrast, CAC>100 consistently identifies a population anticipated to receive greater benefit than harm from statins. Cainzos-Achirica M, Miedema MD, McEvoy JW et al. Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2020; 141(19):1541–1553.⁹⁰

Among those at low risk of bleeding, aspirin therapy was associated with net benefit in those $\geq 5\%$ 10-year ASCVD risk with CAC scores ≥ 100 . In those at high bleeding risk, there was net harm from aspirin regardless of the CAC score or estimated ASCVD risk.⁹³

Key points

- The ASCVD risk score as determined by the Pooled Cohort Equations does not appear to identify any group of patients predicted to receive clear net benefit from aspirin therapy, since bleeding risk rises with increasing calculated risk.
- CAC ≥ 100 appears to identify a subgroup of patients, in the setting of low bleeding risk, in whom the benefit of aspirin therapy exceeds bleeding risk.

Recommendations

- In patients with CAC ≥ 100 , therapy with aspirin 81 mg daily is reasonable for those who do not have bleeding-related contraindications to such therapy (Class IIA, LOE B-NR).

Is knowledge of a patient's CAC score useful in allocation of anti-hypertensive therapy?

The 2017 ACC/AHA/MS high blood pressure guidelines introduced risk prediction into the treatment algorithm for

hypertension.⁹⁴ Specifically, in patients with Stage 1 hypertension (systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg), pharmacologic therapy was recommended only in the presence of established ASCVD or calculated 10-year ASCVD risk $\geq 10\%$ using the Pooled Cohort Equations. Given the ability of CAC to reclassify patients after traditional PCE-based risk scoring, it was logical to study CAC as a tool to drive decision-making in patients with hypertension.

A 2017 study of 3733 individuals showed that CAC is particularly useful for reclassifying risk in individuals with stage 1 hypertension with 10-year ASCVD risk of 5–15%. The authors argued that in the presence of CAC = 0, an initial non-pharmacologic approach would be appropriate, while anti-hypertensives might be considered when CAC > 100.⁹⁵

Other investigators have studied the potential role of CAC in selecting blood pressure targets among patients with established or treated hypertension. The goal was to define a CAC threshold that identified patients at commensurate risk as those enrolled in the National Heart Lung and Blood Institute-funded SPRINT, which established a benefit of aggressive vs. standard blood pressure goals in high-risk patients. A study of 16,167 hypertensive patients demonstrated that CAC remains a strong risk predictor in this population, and that a CAC score of approximately 220 (range 165–270) identified patients with SPRINT-equivalent risk. In patients with CAC scores above this

threshold, the authors suggested that more aggressive blood pressure goals could be considered.⁹⁶

Key points

- CAC appears to reclassify risk in patients with Stage 1 hypertension, and may be useful for guiding decisions about pharmacotherapy.
- A CAC score 220 appears to identify patients with annual ASCVD risk similar to those enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT). CAC may be useful in guiding blood pressure targets

The future of CAC scoring

While the use of CAC scoring continues to increase throughout the world, there are remaining barriers to more widespread use. These include perceptions of cost-effectiveness, lack of specific CAC-based clinical trials, and limited insurance coverage. Fortunately, all of these issues are actively being addressed, as described below.

Many new innovations regarding CAC scoring are also under development. These include consideration of a new comprehensive CAC score, use of polygenic risk scores to determine age of first CAC testing, and development of new CAC-based risk communication tools.

Is CAC scoring cost-effective?

Multiple cost-effectiveness studies have now been conducted pointing to robust cost-effectiveness of CAC scoring to inform risk-based treatment decisions about the use of statins in borderline- to intermediate- risk patients.^{97–100} However, these conclusions are sensitive to several assumptions. First, cost-effectiveness of CAC scoring is predicated on the assumption that statins have minimal (not zero) side effects and that low risk patients have a general preference for avoiding lifelong preventive pharmacotherapy. Without these assumptions, treating all, regardless of risk, in the setting of low-cost, generic statins, becomes the preferred option. However, studies affirming cost-effectiveness of CAC scoring fit well into the current guideline-based framework of shared decision making. In addition, CAC scoring appears most cost effective when cost of the test is <\$300, and optimally <\$150. In 2020, many medical centers charge between \$50–\$150 out of pocket for a CAC scoring test.

Are there clinical outcomes trials with CAC as entry criteria supporting the use of CAC scoring?

To date, clinical trials directly testing a CAC scoring-based strategy are sparse. The St. Francis Heart Study was a double-blind, placebo-controlled randomized clinical trial of atorvastatin 20 mg daily and anti-oxidant vitamins versus matching placebo in 1005 asymptomatic, apparently healthy men and women age 50–70 years with coronary calcium scores at or above the 80th percentile for age and

gender to determine whether this treatment would significantly reduce the primary end point, a composite of all ASCVD events. Although the study was underpowered to assess the incidence of ASCVD events, the primary endpoint was not achieved. A post hoc analysis suggested ASCVD risk reduction in those with CAC scores >400.^{84,101} The EISNER trial showed that patients randomized to CAC scoring experience modest improvements in downstream risk factor control without an overall increase in downstream testing.¹⁰²

In 2020, the NHLBI convened a workshop on future CAC-based trial designs. Several innovative approaches were endorsed by the panel.¹⁰³ Fortunately, there are several large-scale trials already underway in Europe^{104,105} and at least one in the United States ([ClinicalTrials.gov Identifier: NCT03439267](https://clinicaltrials.gov/ct2/show/study/NCT03439267)) that will significantly improve our knowledge about the CAC score.

Is CAC typically covered by insurance?

In 2020, CAC scoring is not widely covered by insurance, although coverage is rapidly increasing in the private insurance sector. This is driven by advocacy and endorsement in guidelines such as the 2018 ACC/AHA/MS Cholesterol Guideline. One of the complicated issues is that CAC scoring is already a relatively inexpensive test, with market forces in many areas producing highly competitive pricing.

What is the future of CAC score reporting?

It is notable that the basis for the Agatston CAC score was created in 1989 using now outdated CT scanner technology, and has not been updated since. The Agatston score uses several assumptions that do not hold up to modern scrutiny. For example, it is plaque with lower calcified density that is associated with higher risk, rather than with higher density as included in the Agatston score.⁸⁰ While the Agatston score does not account for the distribution of plaque in the coronary tree, it is now known that more diffuse calcified plaque distribution is associated with higher risk.¹⁰⁶ Further, consideration of calcification in the aortic valve and aorta – all visible on a routine CAC scan – substantially improves overall risk prediction, but is not routinely considered. A routine CAC scan can also quantify epicardial, pericardial, and liver fat. It is likely that a new comprehensive CAC score will be developed in the future taking into account the above-mentioned issues and others.⁵⁴

What is relationship of polygenic risk scores and CAC?

Polygenic risk scores demonstrate the importance of genetic variants as etiologic factors in ASCVD, but are poor predictors of ASCVD risk, as estimates of relative risk such as hazard ratios or odds ratios inadequately assess the discriminatory value of these scores as screening tests.¹⁰⁷ As these scores can be measured early in life, polygenic risk scores might be used in the future to determine when patients might most benefit from their first CAC score. There is active research in this area.

What new tools facilitating CAC-based risk communication are being developed?

A MESA 10-year ASCVD Risk Score is anticipated in 2021. Additional MESA tools in development include a coronary/cardiovascular age calculator that translates the MESA Risk Score to an equivalent age (the age at which an otherwise healthy patient would have the same risk as another patient after considering risk factors and CAC). An extension of CAC percentiles to the younger age group (age 30–45) is under development by combining prospective cohort data with large registries of real-world data.

Conclusions

CAC scoring is a widely available, safe, cost-effective, rapidly performed test that improves discrimination of those at risk for ASCVD and serves to better reclassify risk, when used in conjunction with global risk scoring systems, than other clinically available tools. Its predictive value has been consistently demonstrated in men and women of all studied races and ethnicities. While there have been no large, prospective randomized controlled ASCVD outcomes trials that utilized CAC scores as entry criteria, the evidence base supporting the clinical use of CAC scoring in primary prevention continues to grow and points to its valuable role to aid in the allocation of preventive therapies to those most likely to benefit. With the advent of future refinements in this technique and increased access based on lower cost and greater insurance coverage, more clinicians will be able to utilize this powerful tool to provide higher quality preventive care for their patients.

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NLA Scientific Statement on Coronary Calcium Scoring: Key Points

For all clinicians ordering CAC scoring

CAC scoring should be done only if the results will alter treatment decisions.

Absolute scores vs. percentiles

The absolute CAC score is the best predictor of absolute 5- to 10-year ASCVD event risk and should be used to estimate number needed to treat and guide pharmacologic treatment decisions.

The CAC score percentile derived from MESA is the best predictor of relative risk and of lifetime risk trajectory, and should be used to estimate lifetime treatment benefit.

Race/ethnicity

Racial/ethnic differences have been demonstrated in the prevalence of CAC. However, the CAC score is independently associated with ASCVD event risk, regardless of race and ethnicity.

Relative ASCVD risk increases proportionally with CAC scores similarly with all races and ethnicities.

For a given CAC score incidence rates of CVD and all-cause mortality are higher in Blacks and Hispanics compared to Whites and Asians.

Younger adults

CAC scoring may be used selectively to risk stratify adults <40 years of age to more intensive CVD preventive therapies when CAC is identified.

Older adults

In adults 76–80 years of age, CAC scoring may be selectively used to re-classify ASCVD risk and aid in statin treatment decisions.

CAC = 0

CAC = 0 is associated with highly favorable cardiovascular and non-cardiovascular prognosis. CAC = 0 is the strongest “negative risk marker” for ASCVD.

In the absence of diabetes mellitus, active cigarette smoking or a family history of premature ASCVD, statin therapy in those with CAC = 0 is associated with limited expected benefit from statin therapy.

The absolute ASCVD risk reduction with statin therapy is proportional to the CAC score.

High CAC scores and ASCVD risk

For a given CAC score, a diffuse distribution of CAC suggests higher risk than more localized CAC.

The presence of left main coronary calcification, especially when >25% of the total score is in the left main, suggests higher risk.

High CAC scores and cardiac testing

There is no evidence to support the benefit of performing stress testing, or invasive coronary arteriography in asymptomatic individuals with high coronary calcium scores.

CAC-Guided LDL-C lowering therapy

A CAC score ≥ 100 is associated with >7.5% 10-year ASCVD risk, the guideline-based threshold of statin benefit in primary prevention.

A CAC score ≥ 300 is associated with proportionately higher ASCVD risk than those with scores >100, a finding suggesting benefit from greater LDL-C lowering.

A CAC score ≥ 1000 is associated with an annual risk similar to that of the placebo group in the FOURIER trial, a finding consistent with the potential value of very aggressive LDL-C lowering along with other ASCVD risk reduction strategies.

CAC and severe primary hypercholesterolemia

Limited data on CAC scoring in individuals with LDL-C ≥ 190 mg/dL indicate that CAC scoring may aid in both short- and intermediate-term ASCVD risk prediction. The finding of CAC >0 identifies a group in which particularly aggressive LDL-C lowering strategies should be undertaken.

In individuals with severe primary hypercholesterolemia, the finding of CAC = 0 does not preclude the need for long term evidence-based LDL-C lowering therapy.

Repeat CAC scoring

Recommended timing for repeat CAC scoring depends upon the baseline estimated ASCVD risk of the individual, varying from 3 to 7 years.

CAC progression

CAC scores generally increase by approximately 20–25% per year. Hence, the Agatston score generally increases exponentially, with scores in the range of 0–100 providing the greatest risk discrimination compared to higher scores.

CAC does not regress.

CAC progression cannot be used to measure the efficacy of statin therapy (statins modestly increase the CAC score). Statins delipidate plaque, decreasing volume of calcified plaque.

CAC scoring in statin-treated patients

CAC scoring remains an ASCVD risk predictor in statin-treated patients, with similar risk discrimination to that observed in statin naïve patients.

CAC scoring and aspirin therapy

The ASCVD risk score, as determined by the PCE, does not appear to identify any group of patients predicted to receive clear net benefit from aspirin therapy, since bleeding risk rises with increasing calculated risk.

A CAC score >100 appears to identify a subgroup of patients in whom benefit of aspirin therapy exceeds bleeding risk.

CAC scoring and hypertension treatment

CAC scoring appears to reclassify risk in patients with Stage 1 hypertension, and may be useful to guide decisions about pharmacotherapy.

A CAC score of approximately 220 appears to identify patients with annual ASCVD risk similar to those enrolled in SPRINT. Thus, CAC scoring may be considered in guiding blood pressure targets.

Cost of CAC scoring

CAC scoring appears to be cost-effective, particularly when the cost per test is <\$150, as it helps to identify those many who would otherwise be prescribed lifelong preventive treatment with low likelihood of benefit.

Insurance coverage for CAC testing has increased, but more widespread coverage is needed.

NLA Scientific Statement on Coronary Calcium Scoring: Recommendations

Absolute scores versus percentiles

Physicians reporting CAC scores should report both the absolute Agatston CAC score and the age, sex, and race/ethnicity-based CAC percentiles (Class I, LOE B-NR).

Borderline to intermediate risk adults

For adults 40–75 years of age, with LDL-C 70–189 mg/dL and a 10-year ASCVD of 5–19.9%, CAC scoring, can be useful to aid clinicians in determining the need for and intensity of preventive therapies. (COR IIa, LOE B-NR).

Low risk adults

For adults 40 years of age or older, with LDL-C 70–189 mg/dL and a 10-year ASCVD risk of <5%, CAC scoring is reasonable, in those with a strong family history of premature ASCVD, to decide on the need for and intensity of preventive therapies (COR IIa, B-NR).

Individuals with clinical ASCVD

For adults with clinical ASCVD, CAC scoring is not recommended. (COR III, no benefit).

Race/ethnicity

Clinicians should use CAC scoring, when indicated, for ASCVD risk assessment, regardless of the patient's race/ethnicity or gender. (COR I, B-NR).

Adults less than 40 years of age

In selected adults <40 years of age with multiple major ASCVD risk factors or a family history of premature ASCVD, it is reasonable to use CAC>0 as a factor favoring intensification of lifestyle therapy and, if necessary, initiation of statin therapy. (COR IIa, B-NR).

CAC = 0

In adults 40–75 years of age with LDL-C 70–189 mg/dL and without diabetes, active cigarette smoking or a family history of premature ASCVD, it is reasonable to defer statin initiation in those with CAC = 0 (COR IIa, B-NR).

In adults age 76–80 years of age in whom the decision about initiation of statin therapy is uncertain, it is reasonable to use CAC = 0 as a factor favoring avoidance of statin therapy (COR IIb, B-NR).

High CAC scores

In adults with predominant left main coronary calcification, multi-vessel coronary involvement, or a high CAC score, stress testing or invasive coronary arteriography, in the absence of clinically relevant symptoms, is not recommended. (COR III-Harm).

In adults with CAC scores ≥ 100 , initiation of statin therapy is recommended (COR I, LOE B-NR).

In adults with CAC scores ≥ 300 , and especially in those with CAC scores ≥ 1000 , it is reasonable to use high intensity statin therapy, and if necessary, guideline-based add-on LDL-C lowering therapies to achieve a $\geq 50\%$ reduction in LDL-C, and optimally and LDL-C <70 mg/dL (COR IIa, LOE C-LD).

Incidental findings

In adults found on a CAC scoring exam to have one or more pulmonary nodules, follow-up testing should be done in accordance with the Fleischner Society recommendations (COR I, C-EO).

In adults found on a chest CT to have incidental mild CAC, it may be reasonable to obtain a dedicated CT scan for coronary calcium scoring to guide preventive treatment decision-making (COR IIb, C-LD).

In adults found on a chest CT to have incidental moderate or severe CAC, initiation of statin therapy without dedicated CAC imaging is reasonable. (COR IIa, LOE B-NR).

Severe primary hypercholesterolemia

In selected adults with severe primary hypercholesterolemia, in the absence of extreme LDL-C elevation, additional major ASCVD risk factors or a family history of premature ASCVD, CAC scoring may be reasonable to inform decision-making about the need for add-on therapy to maximally tolerated statins. (COR IIb, C-LD).

In adults with severe primary hypercholesterolemia and CAC>0, heightened ASCVD risk status is confirmed, favoring more aggressive, guideline based LDL-C lowering. (COR IIa, C-LD).

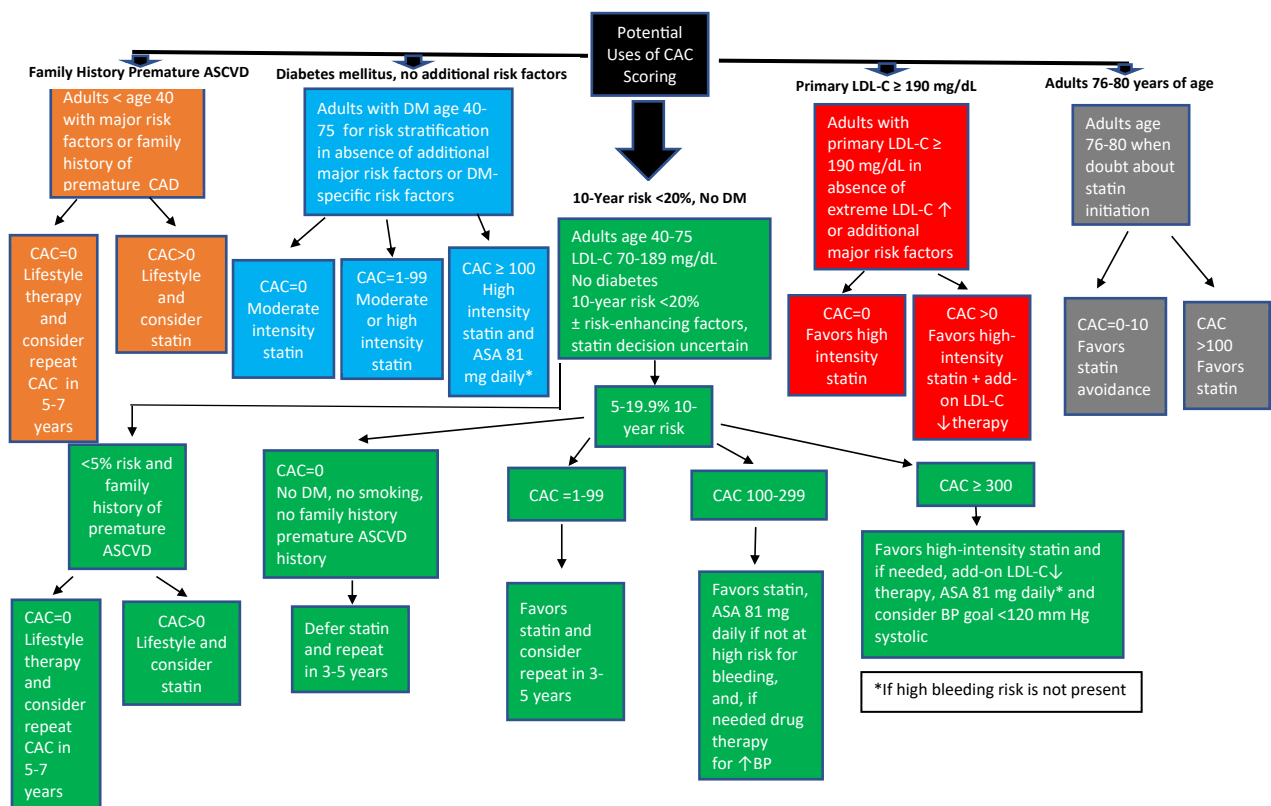
Diabetes mellitus

In adults 40–75 years of age with diabetes mellitus and an LDL-C 70–189, a moderate or high intensity statin is indicated, regardless of CAC score. (COR I, LOE A).

In adults 40–75 years of age with diabetes mellitus in whom the decision has been made to initiate statin therapy, it is reasonable, for those with a CAC score >100, to choose a high intensity statin. (COR IIa, LOE C-LD).

In adults 30–39 years of age with long-standing diabetes mellitus (type 1 diabetes of >20 years duration or type 2 diabetes of >10 years duration) and risk factors or microangiopathy, CAC scoring may be reasonable to aid in ASCVD risk stratification and statin treatment shared decision making (COR IIb, LOE C-LD).

In adults older than 75 years of age with type 2 diabetes, in whom the decision to employ a statin for primary prevention is uncertain, CAC scoring is



reasonable to aid in statin treatment shared decision making (COR IIa, LOE C-LD).

Repeat CAC scoring

In adults with CAC = 0, it is reasonable to repeat CAC scoring at the following intervals:

- Low risk (<5% 10 year risk): 5–7 years
- Borderline to intermediate risk (5–19.9% 10 year risk): 3–5 years
- High risk or diabetes: 3 years

(C (CORIIa, B-NR)

In adults with CAC scores 1–99, it may be reasonable to repeat CAC scoring in 3–5 years if the results might change treatment decisions (COR IIb LOE B-NR).

In adults with CAC scores ≥100 and an LDL-C ≥70 mg/dL, repeat CAC scoring at 3 years may be reasonable to assess for accelerated progression (>20–25% per year) and/or an increase to a CAC score >300, findings that may favor more aggressive LDL-C lowering (Class IIb, LOE C-LD).

Aspirin therapy

In patients with CAC >100, therapy with aspirin 81 mg daily is reasonable for who do not have bleeding-related contraindications to such therapy (Class IIa, LOE B-NR).

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