

Why Is There So Much Calcium, and Can We Prevent It?

Reviewing primary, secondary, and tertiary approaches to preventing the incidence, progression, and recurrence of atherosclerotic cardiovascular disease and related events.

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Coronary artery calcification (CAC) may represent varying degrees of atherosclerotic cardiovascular disease (ASCVD) and is a significant contributor to ischemic heart disease. The presence and extent of CAC have been directly correlated to the presence and extent of future coronary events.¹ This relationship has been shown to be independently associated with ASCVD, with the association often stronger than other traditional risk factors and noninvasive biomarkers.² Therefore, it is important to understand why there is CAC and to discuss preventive strategies.

WHY IS THERE INCREASING CAC?

CAC continues to increase primarily due to increased prevalence of associated risk factors, particularly diabetes, chronic kidney disease (CKD), uncontrolled hypertension, obesity, and dyslipidemia.³ Prevalence estimates for diabetes among adults aged ≥ 18 years were 10.3% in 2001 to 2004 and increased to 13.2% in 2017 to 2020. Among children and adolescents from 2002 to 2018, the overall incidence of both type 1 and type 2 diabetes significantly increased across all racial and ethnic groups.⁴ Similarly, the prevalence of CKD continues to rise and is estimated to affect > 840 million (approximately 1 in 10 people) worldwide, with an exponentially increasing death rate.⁵ Hypertension control rates have worsened, especially among young adults aged 18 to 44 years, and observational studies have shown a graded increase in CAC, with higher systolic blood pressure beginning as low as 90 mm Hg.⁶ Obesity remains an epidemic, with rates

of obesity and severe obesity increasing from 30.5% and 4.7% in 2000 to 42.4% and 9.2% in 2018, respectively.⁷

Dyslipidemia remains a strong independent risk factor for CAC. The rate of dyslipidemia remains high, despite aggressive low-density lipoprotein cholesterol (LDL-C) control, due to the evolving phenotypic spectrum of dyslipidemia. Familial hypercholesterolemia remains underdiagnosed and undertreated, often due to the population being young, asymptomatic adults and the absence of clear, universal diagnostic criteria. Individuals with discordant high apolipoprotein B (ApoB) and low LDL-C have a 1.5- to 2.3-fold higher risk of developing CAC 25 years later.⁶ However, ApoB dyslipidemia remains underdiagnosed because it does not appear on a standard lipid panel and does not have universal diagnostic criteria. Guidelines do indicate that a higher level of lipoprotein(a) is a long-term risk factor; however, guidelines still differ on who should get tested and how to stratify risk. Randomized controlled trials are ongoing to show therapeutic benefit in reducing high lipoprotein(a), which may help in improved diagnostic and therapeutic rates.⁶

A discussion of preventive strategies should come from the understanding that CAC exists on a continuum. In this article, we address primary, secondary, and tertiary approaches to disease prevention.

PRIMARY PREVENTION

Primary prevention targets action to prevent disease or injury from occurring. Risk scores are used to identify the individuals who are more vulnerable. The pooled

cohort equations predict risk of ASCVD. The CAC score is an additional tool used to further stratify intermediate-risk individuals, especially those at risk of progressive coronary calcification. Agatston et al first described the technique for CAC scoring in 1990.⁸ Over time, the CAC score has become one of the best predictors of absolute risk of cardiovascular events over a 10-year time period, especially in intermediate-risk individuals.⁹ CAC testing is a rapid and highly reproducible CT scan of the heart that does not require contrast or intravenous access. This test can be performed on any CT scanner with ECG gating capability. There is no requirement to fast or give medications prior to or during the scan. CAC scores are shown to have good intra- and interscan reproducibility.¹⁰

The 2018 cholesterol guidelines provided recommendations that were further endorsed by the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on prevention of cardiovascular disease.^{11,12} These guidelines stated that CAC scoring is reasonable to guide the clinician-patient risk discussion in asymptomatic adults aged 40 to 75 years with an LDL-C of 70 to 189 mg/dL and at intermediate risk (10-year ASCVD risk, 7.5%-20%) or in selected "borderline-risk" patients (10-year ASCVD risk, 5%-7.4%) if risk-based decisions for statin therapy remain uncertain (class of recommendation [COR], IIa; level of evidence [LOE], B-NR). Groups that may benefit from knowing their CAC score include those hesitant to initiate or restart statin therapy, older patients (men aged 55-80 years, women aged 60-80 years) with a low risk factor burden, and middle-aged adults (aged 40-55 years) with borderline 10-year ASCVD risk. The emphasis on intermediate-risk individuals is because there is less established value of CAC scoring in populations with a 10-year ASCVD risk of either < 5% or > 20% risk. Additionally, CAC scoring should not be used in individuals who already have clinical ASCVD, defined as prior acute coronary syndrome, stroke, revascularization, or peripheral disease.¹⁰ The integration of CAC scoring with traditional scores allows for a more complete risk profile and a tailored preventive strategy for CAC.

The interpretation of CAC scores in statin users is more nuanced. This is due to the density paradox, a phenomenon in which statins increase plaque density, theoretically stabilizing plaque composition while paradoxically raising the CAC score, as density is upweighted.¹³ This was well described by the PARADIGM study, a prospective multinational study of 1,255 statin-naïve and statin-taking patients without history of coronary artery disease who underwent serial coronary CTA. Statins were associated with a slower rate of overall atheroma progression and a reduction

of high-risk features, but an increase in plaque calcification. However, this increased calcification did not affect the progression of stenosis severity and may represent stabilization of atherosclerotic lesions.¹³ Given the evolving understanding, international societies have taken a cautionary approach to CAC scores in statin users with the 2018 AHA/ACC cholesterol management guidelines stating there is no clinical utility for CAC scoring among statin users and the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines suggesting CAC scores in statin users should be interpreted with caution.^{11,14} Recent studies suggest that increases in CAC scores by statins are modest and therefore very elevated CAC scores, such as > 400, should still be interpreted as extensive atherosclerosis and warrant aggressive management.¹⁵ Further studies are still needed to evaluate the nuanced approach of statins to CAC scores, perhaps using scoring methods that focus on calcium volume or characterization of density to best understand the protective nature of modified plaque.

SECONDARY PREVENTION

Secondary prevention targets action to reduce the impact of subclinical disease. Regarding CAC specifically, recent studies have sought to determine at what level individuals with elevated CAC scores who have not had an ASCVD event should be treated as aggressively as individuals who have already survived an ASCVD event.¹⁶ In the 2023 multinational CONFIRM registry, authors compared ASCVD event rates in individuals with and without established ASCVD, grouped by CAC score 0, 1 to 100, 101 to 300, and > 300. Only CAC > 300 was not statistically different compared to those with previous ASCVD (adjusted hazard ratio, 0.944; 95% CI, 0.717-1.244; *P* = .683).¹⁶

Many trials have studied the cardiovascular effectiveness of supplements, including vitamin D, calcium, and vitamin K2, among others. The majority of evidence supports a neutral impact of supplements on cardiovascular and mortality endpoints. The current endocrinology and cardiovascular guidelines continue to suggest calcium and vitamin D supplementation to maintain bone homeostasis and in patients unable to achieve adequate oral intake. Current evidence does not support the use of supplements for cardiovascular health.¹⁷ There are ongoing trials to evaluate the effects of supplements, particularly vitamins K2 and D3, in patients with severe CAC.¹⁸

TERTIARY PREVENTION

Tertiary prevention targets action to modify and reduce the adverse consequences of already established

clinical disease. For CAC, strategies include understanding the role of intravascular imaging to evaluate criteria for calcium modification and understanding techniques to specifically treat calcified lesions, including specialty balloons, atherectomy, and intravascular lithotripsy (IVL).

Evaluation for Calcium Modification

Although CAC can be identified fluoroscopically, the overall sensitivity and specificity for detecting the presence of target lesion calcium are 50% and 95%, respectively, when compared to intravascular imaging. Intravascular imaging has many additional advantages. Both intravascular ultrasound (IVUS) and optical coherence tomography (OCT) can identify the presence and absence of calcified nodules; measure calcium extent, including arc, thickness, and length; and are associated with improved outcomes in patients undergoing complex percutaneous coronary intervention (PCI). OCT can additionally measure the thickness of calcium. The 2021 ACC/AHA/Society for Cardiovascular Angiography & Interventions (SCAI) coronary artery revascularization guidelines gave a COR IIa, LOE B-R recommendation for IVUS as “procedural guidance, particularly in left main or complex coronary artery stenting, to reduce ischemic events” and for OCT as “a reasonable alternative to IVUS for procedural guidance, except in ostial left main disease.”¹⁹

The SCAI Publications and Executive Committees officially endorsed the criteria for coronary calcium modification in an expert consensus statement.²⁰ These criteria recommend calcium modification for lesions with 360° arc of calcification or > 270° arc and > 5 mm length of calcium. Additional characteristics of calcified lesions that may require calcium modification include presence of calcified nodule, lesion external elastic lamina (EEL) < 3.5 mm or negative remodeling (defined as lesion EEL diameter < distal EEL diameter), or minimum thickness of calcium > 0.5 mm by OCT.²¹

Evaluating the need for calcium modification is crucial because calcified lesions increase procedural complexity and risk. When CAC is present during PCI, there are increased risks for major adverse cardiovascular events (MACE) due to stent underexpansion, target vessel failure, in-stent restenosis (ISR), and stent thrombosis. For this reason, several tools have been developed to specifically modify and treat calcified lesions.

Specialty Balloons

Semicompliant and noncompliant balloons are single layer, have no surface microsurgical blades, and are relatively fixed diameter with high pressure. Although useful for lesions with minimal or thin calcium, they have

several limitations with more calcified lesions, including increased risk of vessel perforation, balloon perforation, inconsistent plaque dilation, and uncontrolled dissection. To that end, there are several specialty balloons that can modify severe calcification, including cutting, scoring, and very-high-pressure balloons (OPN NC, SIS Medical AG).

The currently available Wolverine cutting balloon (Boston Scientific Corporation) is a semicompliant balloon with three or four microsurgical blades bonded longitudinally along its surface. When the balloon is inflated, the blades make small incisions that create predictable dissection planes along the calcium. This allows for improved vessel compliance, greater stent expansion, and reduced recoil. Cutting balloons should be used primarily to create fractures in calcium rather than optimally dilate the lesion due to risk of vessel perforation. To reduce the risk of perforation, the SCAI expert consensus statement recommends the following: (1) decrease the size of the cutting balloon by 0.5 mm compared with the reference artery diameter and follow cutting balloon inflation with a 1:1 sized noncompliant balloon; and (2) if multiple inflations with a cutting balloon are performed, move the cutting balloon slightly proximally or distally to cut in different areas.²⁰

Scoring balloons are built on a semicompliant balloon with a helical nitinol scoring element along the surface. This design also allows for circumferential dilation force against the lesion. Both cutting and scoring balloons have the technical advantage of less slippage than conventional balloons, which is particularly useful in ostial lesions.²⁰

The OPN balloon is a double-layer balloon that can be inflated to very high pressures with increased protection against protruding calcium. However, these must be used carefully due to higher risk of vessel perforation. In de novo lesions, the SCAI expert consensus statement recommends undersizing the OPN balloon by 0.5 mm; in ISR, the recommendation is to size 1:1.²⁰

Atherectomy

There are three main mechanisms of atherectomy used in calcified lesions: rotational, orbital, and laser atherectomy. Rotational atherectomy (RA) uses a high-speed rotational device with a diamond-tipped burr to break larger calcification into smaller particles < 10 µm that are theoretically tolerated by the distal circulation. Based on positive randomized studies, the 2021 ACC/AHA/SCAI coronary artery revascularization guidelines gave RA a COR IIa, LOE B-R recommendation to prepare heavily calcified lesions and improve procedural success.¹⁹ Similarly, orbital atherectomy (OA) operates on the

principle of ablating large calcium into smaller particles, although OA additionally exerts a centrifugal force on the vessel wall. The larger orbit of rotation allows for increased ablation field.²¹ The 2021 guidelines gave OA a COR IIb, LOE B-NR recommendation for use of OA in heavily calcified lesions. Laser atherectomy uses a xenon chloride system to generate ultraviolet light to modify calcium without thermal injury. Unfortunately, evidence is lacking, and it overall has limited impact on severe calcification.²⁰

IVL

The Shockwave IVL system (Shockwave Medical) features a balloon that emits pulsatile sonic pressure waves to create macro- and microfractures. Shockwave IVL received FDA premarket approval in 2021 after the Disrupt CAD III trial showed successful device delivery, low procedural complications, and low rates of primary outcomes, including MACE, stent thrombosis, and target vessel failure. The SCAI expert consensus statement recommends IVL for modifying circumferential calcium in balloon-crossable lesions. IVL can be used in combination with atherectomy, especially in longer or more complex lesions requiring multiple modification strategies. The main limitation is deliverability, although this can be optimized by increasing guide support.²⁰

SUMMARY

CAC remains a major cause of ischemic heart disease, with significant expected rates of growth in the coming years. Recent studies have suggested an estimated time period for CAC conversion (CAC = 0 to CAC > 0) for low-, intermediate-, and high-risk men at 7, 4, and 3 years and for women at 8, 5, and 3 years, respectively.²² These rates are certainly faster in populations with significant disease already and will continue to grow as the prevalence of risk factors continues to increase. It is important to aggressively approach preventive strategies at the primary, secondary, and tertiary levels to prevent the incidence, progression, and recurrence of cardiovascular events. ■

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Disclosures: Consultant to and research grant from Abbott.

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