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Imaging (Q Truong, Section Editor)

Role of Coronary Calcium for Risk Stratification and Prognostication

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Opinion statement

A multitude of studies now support the understanding that an increased coronary artery calcium (CAC) score represents advanced atherosclerosis and high risk for cardiovascular disease (CVD) and, as such, should be treated with conventional therapies for those considered high risk. Data is now available to guide treatment with aspirin, statins, and lifestyle management. The new ACC/AHA 2013 guidelines support intensifying statin therapy when the CAC is ≥75th percentile for age, sex, and ethnicity/race or when the calcium score is ≥300 Agatston units. This allows for aggressive management of those at the highest risk, matching intensity of therapy with intensity of risk. Most importantly, the asymptomatic person rarely needs to undergo evaluation for obstructive disease, even when CAC scores are high, as revascularization with percutaneous coronary interventions does not improve outcomes in asymptomatic persons with preserved left ventricular function. Treatment should be relegated to improvement in lifestyle, diet, exercise, aspirin, statins, and blood pressure control.

Introduction

Coronary artery disease (CAD) is one of the most important causes of death worldwide, and coronary artery calcification (CAC) is one of the best indicators of this disease. Deposition of calcium in the vasculature is mediated by several mechanisms that produce two types of intimal and medial arterial calcifications [1]. In the process of atherosclerosis, inflammatory factors induce osteogenic differentiation in the intima of the coronary arteries [1]. Furthermore, coronary arteries are affected by other mechanisms such as arterial medial calcification which is a highly characteristic feature in patients with diabetes [2]. Also, several other factors alongside

traditional cardiovascular risk factors have shown to develop coronary calcification. Coronary artery calcification can be detected by ECG-gated non-contrast coronary computed tomography (CT) scan with very limited radiation dose [3].

Agatston score is the most practical coronary calcium scoring system which is determined by the product of calcified plaque area and maximum calcium lesion density from 1 to 4 based upon Hounsfield unit [4]. Original Agatston scoring used electron beam CT and measured the calcium based on non-contrast studies. With the revolution of CT scanners, the measurement of CAC using new machines has been validated in several studies [5, 6]. Coronary calcium can also be quantified more accurately with calcium mass score [7] and the calcium volume score [8]. Since the density of calcium is used to calculate Agatston score, Criqui et al. recommended the consideration of the role of calcium density specifically to enhance prediction of incident CVD. Using the Multi-Ethnic Study of Atherosclerosis, they demonstrated that density of calcium is inversely correlated with the cardiovascular events [9]. This strengthened the predictive power of the CAC score fourfold, improving risk prediction, while identifying that lower density lesions are more vulnerable, and high-density lesions represent more stable plaque. Given how extensively studied the Agatston score is and presence of closed correlation between all types of other scores (volume, mass), understanding when to apply the density score is still being considered [8, 10, 11]. For the evaluation of calcium progression, calcium volume is the most accurate scoring method. Other calcium scoring methods similarly have been introduced [11–13], and some studies have derived an accurate calcium score from contrast CT angiography studies [14–16]. Current algorithms, due to the vast data available, still recommend the use of Agatston scoring as the reported measurement when assessing CAC.

Risk factors for coronary artery calcification

The causal factors for coronary artery calcification have been evaluated in several population-based studies. The calcium score increases with age [17], and according to published data, other traditional risk factors including male gender, hyperlipidemia, hypertension, higher body mass index, diabetes mellitus, smoking, and family history of heart attack are all associated with the presence of CAC [18–20]. In the population-based Multi Ethnic Study of Atherosclerosis (MESA), the white race/ethnicity, higher C-reactive protein, lipid-lowering medications, and kidney disease were associated with elevated CAC and they are the factors involving the development and CAC progression [20]. The role of kidney disease in the presence and progression of coronary calcification is well explained in several studies [1, 3]. The role and correlation of inflammation in rheumatologic disease [21], autoimmune disorder [22], and the effect of human immunodeficiency virus [23] with coronary artery disease has been considered in several studies. Table 1 summarizes the risk factors of intimal and medial vascular calcifications [24].

Prognostic role of CAC and risk stratification

Despite etiology, coronary calcium is considered the leading risk predictor for coronary events [25–35]. Long-term prognosis prediction using CAC has been studied in several populations. In a large population study with 25,253 asymptomatic individuals with long follow-up, CAC was shown to be a strong independent predictor for all-cause mortality [34]. They demonstrated that C-index defined from the ROC curve was significantly higher for CAC (C-index 0.813 (0.585–0.637)) in comparison to other risk factors (C-index 0.611

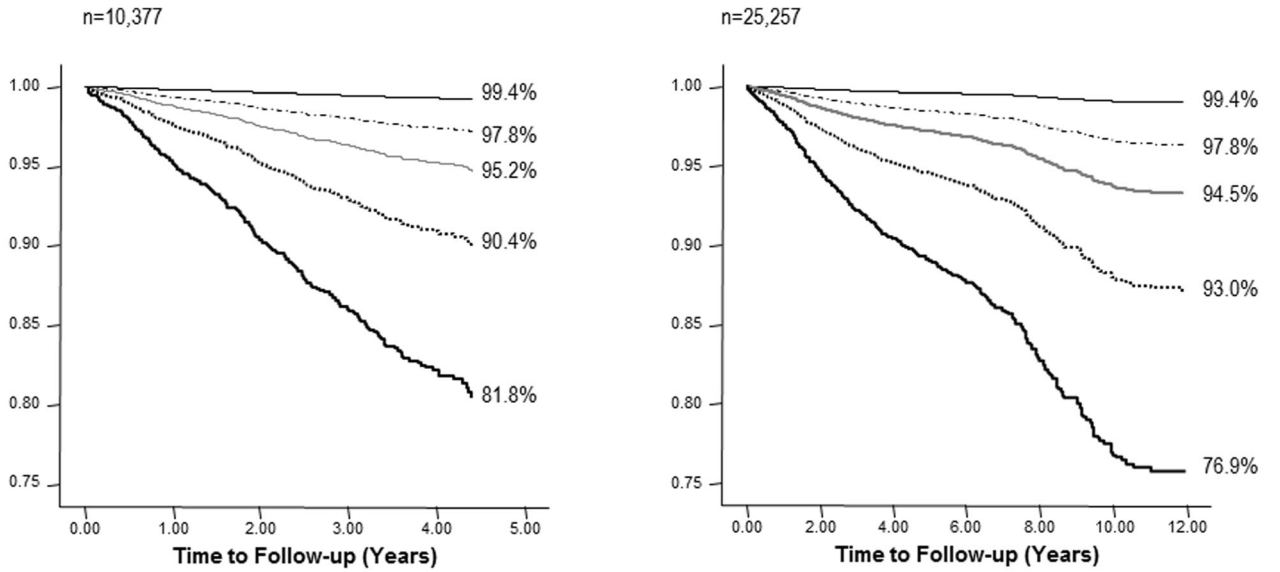
Table 1. Risk factors for coronary calcification [24]

Risk factor	Intimal calcification	Medial calcification
Advanced age	Yes	Yes
Diabetes mellitus	Yes	Yes
Dyslipidemia	Yes	No
Hypertension	Yes	No
Male	Yes	No
Cigarette smoking	Yes	No
Renal etiology dysfunction		
Decreased GFR	No	Yes
Hypercalcemia	No	Yes
Hyperphosphatemia	Yes	Yes
PTH abnormalities	No	No
Duration of dialysis	No	Yes

GFR ¼ glomerular filtration rate; PTH ¼ parathyroid hormone

(0.794–0.832)) (Fig. 1). Multiple studies from MESA show the power of CAC alone or in addition to other traditional risk factors such as Framingham risk score (FRS) for identification of cardiovascular prognosis [9, 25, 27, 36]. In asymptomatic patients in the MESA study with a moderate Framingham risk score (estimated 10-year CHD risk >5 and <20%), comparison of the area under the receiver operator characteristic curves (AUC) in models with and without risk factors showed that CAC had the strongest association when compared with other novel risk factors (such as carotid intimal media thickness, c-reactive protein, ankle-brachial index, or family history). Coronary calcium itself plays a role as a risk marker of CAD and it has been shown as the most influential for the reclassification of patients with moderate cardiovascular risk (Fig. 2) [27]. McClellan et al. conducted the validation study of a novel risk score using CAC which was developed in MESA study [25, 37, 38] in the database of Heinz Nixdorf Recall Study (HNR) and Dallas Heart Study (DHS), C-index for events was 0.779 and 0.816 in the HNR and DHS, respectively, and the difference between probability of event and nonevent was excellent (7.8 to 9.5%) [37]. In a study on 2028 asymptomatic elder populations (Rotterdam Study), CAC improved CHD risk prediction and reclassified 52% of moderate FRS-based CHD risk men and women [39].

In practice, the CAC score has been used for risk stratification as a better predictor of the events when traditional risk-based decisions are uncertain and while initiation of pharmacological therapy remains unclear in asymptomatic individuals [40, 41]. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults recommends measurement of CAC in asymptomatic adults with diabetes, 40 years of age and older for cardiovascular risk assessment (Class IIa recommendation) [42]. If CAC is greater than 300 Agatston units or more than 75th percentile for age-gender and ethnicity, the preventive management will change and risk shifted upward. Emphasis of the new 2013 guideline [40] for estimated CVD risk is on the risk



CAC Score	(5 Yr Mortality = 1.2%)	(12-Yr Mortality = 2.1%)	Difference
0-10	99.4%	99.4%	0.0%
11-100	97.8%	97.8%	0.0%
101-400	95.2%	94.5%	0.7%
401-1,000	90.4%	93.0%	0.6%
>1,000	81.8%	76.9%	4.9%

χ^2=1503, p<0.0001, interaction p<o.0001

Fig. 1. Comparison of near- and long-term survival in two different large cohorts [34].

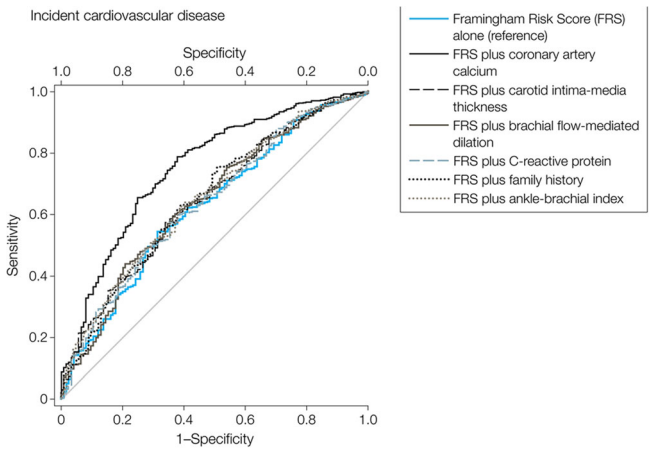


Fig. 2. The area under the curve (AUC) for FRS comparison with adding other risk factors to detect incident cardiovascular disease in MESA intermediate risk population [27].

factors only over the CAC in low to moderate risk group (<7.5%) in comparison with 2010 guideline [42]. This change is the result of lower threshold of primary prevention and statin use present in 2013 lipid guideline (start statin in CVD risk >7.5%) [43]. Studies showed that the new guidelines grossly overestimate cardiovascular events rate, and in the Heinz Nixon study, this overestimation was up to 63.2% more than real events [44, 45]. In a post hoc analysis of St. Francis Study, Waheed et al. stratified 990 asymptomatic individuals by CAC >80th percentile and calculated eligibility of statin based on the 2013 ACC/AHA guideline. More than 35% of those deemed not eligible for statins by the guidelines had high CAC >300 [46]. They concluded that combination of both clinical risk score and CAC score improved risk stratification significantly. In a meta-analysis, risk stratification models for CAC scores are likely to be the most useful approach to improving risk assessment for those at intermediate risk (10–20% 10-year risk of MACE) [41].

Risk stratification in specific groups

Patients with low cholesterol

Blankstein et al. evaluated the usefulness of CAC for decision making of statin therapy in patients with low-normal LDL-c. They assessed 3714 asymptomatic people with LDL-c <130 mg/dl who were not receiving statins. After 5.4-year follow-up, the CHD event rate was 3.2%. They indicated that presence of CAC provided significant incremental value for predicting CHD events (HR 4.23; 95% confidence interval [CI] 2.28 to 7.86). They also reported substantial stepwise increase in event rates across increasing categories of CAC [47]. Based on 2013 AHA/ACC Blood Cholesterol Guideline, if decision was unclear to initiate statins in non-diabetes people <40 or >75 years old and LDL-C <190, CAC >300 has a beneficial implementation to make a more accurate decision with statin consumption (class IIb) [43].

CAC in symptomatic patients

Calcium score of zero has a very powerful predictor of event-free survival and among asymptomatic population is associated with very low risk cardiovascular events [48], but usage of CAC in symptomatic patients in the emergency department beyond coronary CTA is not widely used [49], since patients may have a CAC of zero but severe stenosis resulted by a non-calcified plaque by CT angiography. In ROMICAT II trial, 473 low intermediate symptomatic patients were randomized to CT angiography and underwent CAC scanning. Among 58% of population with CAC of zero, two (0.8%) developed acute coronary syndrome (ACS). Authors concluded that calcium score of zero does not completely exclude ACS [49], and CT angiography is recommended in lieu of a CAC scan for those with symptoms.

CAC in diabetes

In the diabetic population, several studies have pointed to the high prevalence of coronary plaque [50, 51]; the role of CAC to identification of actual risk of event has been described in several studies [36]. Although CAC has a major role in evaluating a patient's overall cardiovascular risk [36, 52, 53], the use of CAC

measurements for risk stratification in the diabetic population is warranted and recommended in the guidelines as a class IIa recommendation [42, 54]. Every person with diabetes over 40 years old will receive statin as a part of the primary prevention program (statin dosage is defined by the pooled cohort 10-year CHD risk), and CAC can affect intensification of that therapy or decisions about therapy when patient preference is considered [42, 54]. Furthermore, the use of CAC is quite informative in persons under age 40, where recommendations are less clear, and CAC could help the re-classification of this specific population (class IIb) [43].

Treatment

- Consideration of predisposing factors and underlying causes of coronary calcification should be the first step of treatment. There is no doubt that lifestyle modification has a positive role in controlling the progression of atherosclerosis in individual with coronary atherosclerosis [55–58] (class I).

Lifestyle modification

- At least 30 min, 7 days per week physical activity (minimum 5 days per week) and weight management to keep body mass index (BMI) of 18.5 to 24.9 kg/m2 (waist circumference in women <35 in. (<89 cm) and men <40 in. (<102 cm)) is recommended by guidelines of preventive cardiovascular disease. The initial goal of weight loss therapy should be used to reduce body weight by approximately 5 to 10% from baseline.
- Smoking cessation intervention is highly recommended in patients with any CAC score, and the role of diet such as daily eating of a variety of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats was indicated in several studies and supported by CVD prevention interventions.
- Proper modification of CVD risk factors and coronary calcium, as a result of atherosclerosis process, is an important strategy. Given the extensive evidence demonstrating the ability of blood pressure control to reduce cardiovascular events [59–62], high blood pressure should be treated based on established guidelines [59].

Specific drug treatment

Aspirin

- Aspirin, a famous thromboxane synthesis blocker, is one of the most popular antiplatelet drugs that clinical guidelines have recommended to prevent cardiovascular events [54, 58]. In a meta-analysis on six primary prevention trials, they showed that vascular mortality would not reduce in primary prevention by aspirin [63]. The current guideline in primary prevention recommend aspirin for only high

cardiovascular risk of CHD while the majority of events occur in non-high risk people.

- Calcium scores can be used as an appropriate tool to regulate aspirin consumption in the asymptomatic non-diabetes population. In a study on 4229 participants from the Multi Ethnic Study of Atherosclerosis (MESA), individuals with CAC ≥100 regardless of other traditional CHD risk factors had an estimated net benefit with aspirin [64•]. Furthermore, the study also illustrated that consumption of aspirin in a zero CAC population is not appropriate as it may cause major internal bleeding (5-year number needed to treat (NNT) = 2036 for individuals with a Framingham risk score [FRS] <10% and 808 for FRS ≥10%; 5-year number needed to harm (NNH) = 442) [45, 64•].

Statins

- There are several studies showing the benefit of statins on cardiovascular outcome [59, 65, 66]. Similarly, in patients with non-zero CAC score, one of the most important ways to prevent cardiovascular events is to control patient's plasma cholesterol levels [61, 67–71].
- Statins are reversible inhibitors of microsomal HMG-CoA reductase, which decreases intracellular cholesterol production [49, 72]. Studies using CT angiography and intravascular ultrasound (IVUS) showed reduction in coronary plaque volume and stabilization of plaque by statins [71, 73–75]. Atorvastatin 20 mg daily was examined in a double-blind, placebo-controlled randomized clinical trial for evaluating MACE in St. Francis Heart randomized study. This study showed that atorvastatin reduced cardiovascular events by 42% in those with CAC >400 (20 of 229 [8.7%] vs. 36 of 240 [15.0%], p 0.046). The number needed to treat (NNT) with statins was only 16 in this population. Given that they used Agatston method for calculating CAC, there was no effect on calcium progression [76••]. In 5534 of the MESA population, the NNT with statin therapy to prevent CV events was 30 in those with no lipid abnormalities and CAC >100 [77]. In a small randomized double-blind controlled trial in patients with systemic lupus erythematosus, Plazak et al. found that the progression of atherosclerosis was restricted 1 year after consumption of atorvastatin 40 mg daily [78].
- Based on the 2013 cholesterol guidelines, CAC scores >75th percentile for age and gender or ≥300 (Agatston units) are deemed as high risk. High-dose statin therapy is recommended for this high-risk population while CAC scores <75th percentile and <300 should be treated with low- to moderate-dose statins [43].

Other drugs

Several small randomized trials showed significant reduction in CAC progression with consumption of calcium channel blockers [79], estrogen therapy [80], aged garlic extract [81, 82], and sevelamer [83, 84]. Larger prospective trials

regarding these medications need to performed before any clinical recommendation.

Interventional procedures

- Although coronary artery calcification is a part of the atherosclerotic process, interventional procedures such as percutaneous coronary intervention and CABG should not be performed solely based on the amount of CAC. However, interventional procedures should be taken when there is convincing evidence for revascularization such as severe stenosis in result of CAC. Although drug-eluting stents and devices for plaque modification have improved interventional outcomes in calcified vessels compared with bare-metal stents, the likelihood of later complications increases incrementally with the presence of CAC for angioplasty [85].

Emerging therapies

PCSK9 inhibitors

- Proprotein convertase subtilisin/kexin 9 is an enzyme expressed in the liver and intestines as it binds to the LDL receptors (LDL-R) in the cell surface and promotes degradation of LDL-R. PCSK9 inhibitors prevent degradation of LDL-R by binding with PSCK9. This increases the amount of LDL-R resulting in more washing of the LDL cholesterol (LDL-c).
- PSCK9 inhibitors are monoclonal antibodies administered subcutaneously once a month or every 2 weeks and have shown to reduce LDL-c by over 50% [86–88]. There is no clinical trial yet to support, but this novel drug may open a new window for better control of blood cholesterol and, therefore, prevent the progression of atherosclerotic plaque in future.

Conclusion

CAC is a powerful tool in predicting future cardiovascular events in accordance with current guidelines. Calcium scores should be used as a necessary guide to regulate the proper use of anti-atherosclerosis medications like aspirin and statins. CAC has been shown in multiple studies to improve statin adherence; increase initiation of aspirin, blood pressure, and cholesterol therapies in those at risk; and enhance weight loss among those with positive scores. Currently, statins are the most effective and important form of medication as it has shown to have positive effects on patients with coronary calcification outcome. Novel anti-hyperlipidemia drugs, such as PCSK9 inhibitors, should also be further investigated to evaluate its effectiveness on the prevention of CAC progression.

Compliance with Ethical Standards

Conflict of Interest
Negin Nezarat and Michael Kim each declare no potential conflicts of interest.
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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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