Pathophysiology and clinical implications of coronary artery calcifications

Luca Saba[a], *Francesco Costa*[b] *and Riccardo Cau*[a]

Purpose of review
To provide a summary of current understanding of coronary artery calcifications (CACs), outlining the role of calcium in atherosclerosis to comprehend the clinical implications of CAC.

Recent findings
CAC serves as a reliable indicator of coronary artery disease (CAD) and it is associated with cardiovascular events. In recognition of its significance, recent global guidelines have integrated CAC assessment into risk evaluation protocols, highlighting its role as a noninvasive tool for evaluating and stratifying patients' risk for cardiovascular events. Beyond the amount of CAC values, also, calcium morphology had been linked to cardiovascular events.
By leveraging CAC assessment, healthcare providers can effectively up or down reclassify patients' risk and tailor preventive strategies accordingly. This comprehensive approach may involve lifestyle modifications, meticulous management of risk factors, and judicious use of preventive medications to mitigate the likelihood of future cardiovascular events, or withhold treatments in those without signs of CAC, to optimize resource use.

Summary
The identification of CAC burden and morphology through noninvasive imaging modalities can reclassify the prediction of future cardiovascular risk and serve as a risk modifier for atherosclerosis. These data underscore the utility of selectively using CAC assessment in both primary and secondary prevention strategies for atherosclerotic cardiovascular disease.

Keywords
atherosclerosis, computed tomography, coronary arteries, vascular calcifications

INTRODUCTION

Cardiovascular disease (CVD) is a pervasive global health concern, responsible for up to 30% of annual fatalities; it stands as the foremost contributor to the global burden of disease [1▪]. Atherosclerosis is a complex and multistep process, and represents a leading cause of CVD. Reducing mortality and morbidity due to coronary artery disease (CAD) is a primary aim in cardiovascular healthcare [2]. Coronary artery calcification (CAC) is a marker of plaque development and vulnerability, providing direct evidence of the extent of CAD burden, and predicting future cardiovascular events. Noninvasive imaging modalities, such as computed tomography (CT), can readily evaluate both the extent of calcifications as well as their patterns, with optimal correlation with prognostic outcome data [3▪▪,4▪].

Coronary calcifications progress and change during the atherosclerosis process and its patterns, its extent, as well as its volume and density have demonstrated a different impact in plaque vulnerability [5,6▪].

In the present review, we summarize the current understanding of the role of atherosclerosis disease as well as the utility of CAC burden and pattern for patients' management and risk stratification. Finally, we highlight the current limitations of noninvasive CAC score as well as potential future directions regarding CAC.

[a]Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), Monserrato (Cagliari) and [b]Department of Cardiology, Messina University Hospital, Messina, Italy

Correspondence to Luca Saba, MD, Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari – Polo di Monserrato s.s. 554 Monserrato (Cagliari) 09045, Italy. Tel: +393280861848; fax +39070485980; e-mail: lucasaba@tiscali.it

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KEY POINTS

- Coronary calcium progression initiates in the early stages of atherosclerosis.
- CAC serves as an effective tool for risk stratification and patient management.
- In addition to CAC burden, coronary calcification patterns are associated with future cardiovascular events.
- Technological advancements in noninvasive imaging modalities may facilitate early detection of significant calcification and calcification activities.

PATHOPHYSIOLOGY OF CALCIUM IN ATHEROSCLEROSIS

The natural history of atherosclerosis involves various stages that are closely linked to the progression of calcifications [5,7–10]. The initial histological evidence of coronary calcifications manifests as microscopic foci (ranging from 0.5 to 15 μm) in regions of severe inflammation, typically observed in the deeper areas of the necrotic core near the internal elastic lamina. Microcalcifications are believed to arise from smooth muscle cell apoptosis, while macrophage-derived matrix vesicles also contribute to the process of microcalcification [5,11–14]. These microcalcifications often merge into larger masses, forming speckles and fragments of calcifications that involve both the necrotic core and the surrounding collagen-rich extracellular matrix. Further progression of calcification leads to the formation of calcified plaques, characterized by calcified sheets. These calcified sheets may fracture, resulting in the development of nodular calcifications associated with fibrin deposition, potentially causing discontinuity of the endothelial lining, and leading to acute thrombosis [15].

While vascular calcification serves as a marker of coronary atherosclerosis, its association with a higher rate of acute events is still not fully understood. Indeed, several histological and imaging studies have suggested that higher calcium burden provides stability to plaques rather than inducing stability [16–19]. Conversely, other studies have highlighted that microcalcifications (<50 μm) or spotty calcifications (<1 mm) may be associated with plaque vulnerability, attributable to localized tissue stress and the accelerated progression of plaque volume [20–22].

These findings underscore the complexity of interpreting CAC scores. Instead of directly pinpointing future culprit lesions, CAC scores predominantly reflect the overall burden of coronary atherosclerosis. Therefore, contemporary perspectives emphasize the significance of analyzing calcium patterns in assessing plaque vulnerability.

NONINVASIVE CORONARY ARTERY CALCIFICATION EVALUATIONS

CT stands out as the primary noninvasive method for identifying CAC using the Agatston score. This scoring system combines all calcified lesions, considering both the extent of calcification and its highest density (measured at over 130 Hounsfield units). One significant drawback of this scoring system lies in its vulnerability to minor fluctuations in image noise when determining maximal plaque attenuation, thereby impacting the resultant score [23]. Despite technological advancements that have introduced alternative CAC scoring methods such as volume score and mass score, the Agatston score remains the most widely adopted in clinical practice, and most international guidelines use a threshold of more than 100 for clinical decisions [24▪▪]. This is mainly due to its extensive validation and robust evidence base [25,26▪▪,27,28]. Additionally, the use of vendor-provided software simplifies the postprocessing required for calculating the Agatston score, making it more accessible and practical for routine clinical use [23] (Fig. 1).

Additionally, current CT scans are limited in assessing the earlier stage of calcifications in atherosclerosis due to its spatial resolution. Indeed, to ensure accurate detection on CT imaging, the calcification should have a diameter greater than 0.4 mm [29].

Although not yet applicable in clinical settings, Micro-CT enables superior spatial resolution, reaching up to 2 μm. This heightened resolution facilitates highly detailed imaging, providing deeper insights into the progression of calcification. It enables the distinction between microscopic and macroscopic calcifications, thereby enhancing the ability to detect and differentiate between them [5,11].

Additionally, promising results are emerging with the newly introduced photon counting detectors, which enables better spatial resolution, soft tissue contrast, and lower imaging noise. Ex-vivo and in-vivo studies have demonstrated improved morphological detection of calcium in atherosclerosis [30▪–32▪].

An alternative modality capable to identify imaging calcification activity is the 18F-sodium fluoride (18F-NaF) PET imaging. 18F-NaF stands out as a valuable tool for tracking calcification activity, surpassing the resolution limits of CT scans. Specifically, it excels in detecting newly formed calcium deposits, particularly in areas of microcalcification

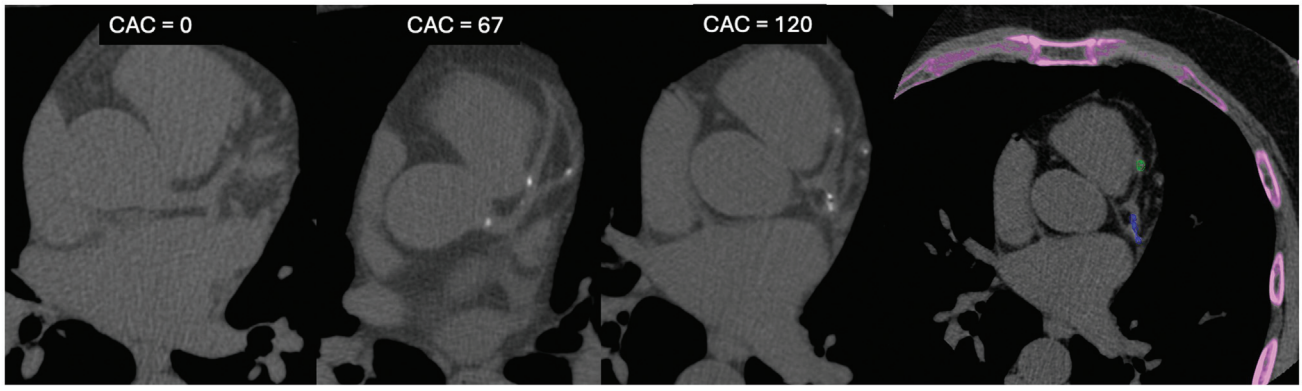

FIGURE 1. Noncontrast gated computed tomography images for coronary artery calcification reveal various grades of coronary calcifications (a–c). (d) displays an automated analysis using commercially available software (Vitrea), which highlights any structure attenuating at least 130 Hounsfield Units (pink in d). Regions of interest were subsequently placed around the calcifications in the coronary arteries, with distinct colors assigned to each segment for clarity, all performed manually.

compared to larger, more visible deposits. This enhanced detection in microcalcification areas is attributed to the significantly greater surface area of hydroxyapatite, the primary component of calcified plaque, present in these finely distributed deposits [33] (Fig. 2).

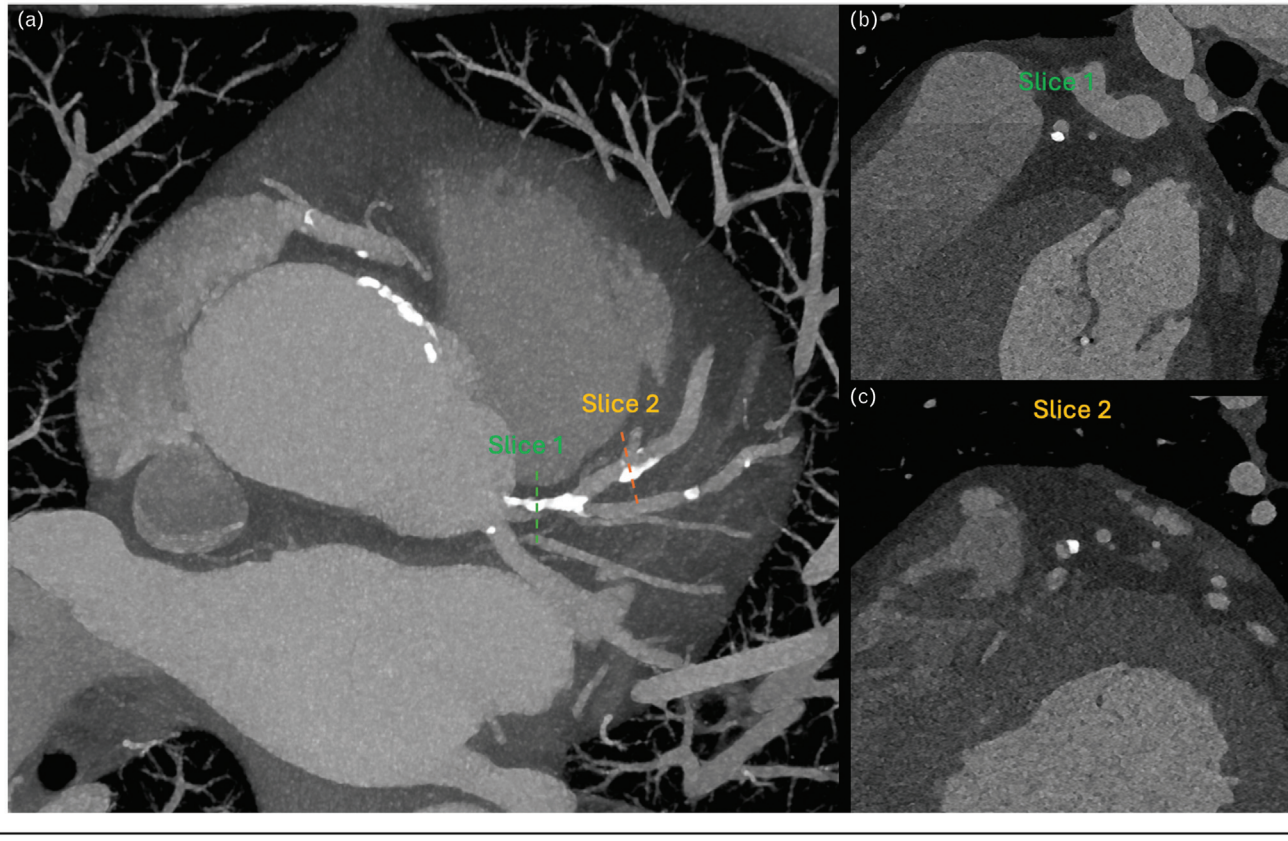

FIGURE 2. Calcium scoring was conducted using photon-counting computed tomography for a patient with coronary calcifications. The axial oblique maximum intensity projection image (a) illustrates coronary artery calcification, predominantly situated within the proximal region (as depicted in the corresponding axial cross-sectional image orthogonal to the longitudinal axis of the vessel in b) and mid-left coronary artery (as shown in the corresponding axial cross-sectional image orthogonal to the longitudinal axis of the vessel in c).

CLINICAL IMPLICATIONS

Over the past three decades, CAC score has emerged as a highly specific marker of CAD and a reflection of overall disease burden. Early identification of CAC holds significant prognostic value for predicting future CVD risk.

Guidelines worldwide underscore the significance of CAC in both reclassifying up or down the risk of atherosclerotic CVD and in guiding decisions regarding the initiation or continuation of preventive pharmacotherapies. For instance, most current guidelines agree that a CAC score of 0 leads to a decision to downgrade risk and withhold statin therapy [24▪▪]. These data are supported by several landmark studies that have underscored the significance of a CAC score of 0 in asymptomatic patients, as well as in individuals experiencing stable chest pain with a low to intermediate pretest probability of CAD [34–36,37▪▪]. The recent published subgroup analysis from the Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) trial indicated that a CAC score of 0 is associated with a very low adverse event rate over a median 3.5-year follow-up period in individuals experiencing stable chest pain and presenting with an intermediate pretest probability of CAD [37▪▪].

Perhaps the most crucial question regarding CAC is whether a calcium score of 0 via the Agatston score truly reflects the absence of 'significant' coronary calcifications, or if the widespread clinical adoption of photon counting CT technology can further refine stratification toward cardiovascular events by identifying smaller 'significant' calcifications.

Further prospective longitudinal studies with this emerging technology are warranted to gain a deeper understanding of the clinical impact of noninvasive assessment of CAC.

In the evaluation of symptomatic patients with suspected CAD, CAC score can be used for enhancing the pretest probability of obstructive CAD to identify low-risk patients for whom testing may be deferred [38]. Winther *et al.* developed a new score by combining a pretest probability model (Diamond-Forrester approach using sex, age, and symptoms) with CAC score demonstrating an increased diagnostic accuracy in predicting the prevalence of obstructive CAD in comparison with pretest probability model (area under the curve of 85 vs. 72) allowing to reclassify 54% of patients as having a low clinical likelihood of CAD, as compared with 11% with the PTP model [39]. McClelland *et al.* [40] determined that the incorporation of CAC into the Multi-Ethnic Study of Atherosclerosis (MESA) risk score led to significant enhancements in risk prediction (C-statistic 0.80 vs. 0.75; $P < 0.0001$). External validation in both the Recall and Dallas Heart studies further demonstrated very good to excellent discrimination and calibration for the model incorporating CAC [40]. Importantly, CAC should be considered a risk marker rather than a diagnostic tool to exclude the presence of CAD (e.g. softer plaques especially in younger patients) [36].

The 2021 American College of Cardiology (ACC)/American Heart Association (AHA) Joint Committee guidelines recommended the utilization of contemporary scoring systems published within the last 10 years (incorporating CAC score) over scores derived from historical patient series. Data regarding the presence and extent of CAC can be obtained either through a dedicated CAC scan or, if accessible, by visually estimating CAC from prior noncardiac chest CT scans [38].

In addition to symptomatic individuals, the MESA, a population-based prospective cohort study, has explored the prevalence, risk factors, and progression of CAD in participants with no signs of CVD at baseline. Budoff *et al.* [28] assessed the association between CAC and atherosclerotic CVD events over a median follow-up period of 11.1 years in 6814 asymptomatic individuals without clinical CVD at baseline from the MESA study. The 10-year atherosclerotic CVD event rates rise consistently with increasing CAC categories. Event rates for individuals with a CAC score of 0 ranged from 1.3 to 5.6%, whereas rates for those with a CAC score exceeding 300 ranged from 13.1 to 25.6% [28].

The CAC score is regarded as a determinant for pharmacological therapy initiation, with varying thresholds according to different guidelines. A CAC score exceeding 100 is typically aligned with various guidelines as a threshold for initiating statin therapy, whereas initiation low-dose aspirin or antihypertensive drug is controversial [24▪▪].

The CAC score is limited to evaluating the calcified components of atherosclerotic disease and does not provide insight into other qualitative and quantitative plaque components (e.g. low attenuation plaques). In this scenario, coronary CT angiography (CCTA), acquired with technical differences in scan acquisition in comparison with CAC (3 mm compared to 0.5 mm slice thickness) and after contrast media administration, provides more in-depth details about coronary plaque components, including low-density and small calcifications as well as low attenuation plaques [35].

Despite the increased radiation effective dose with CCTA (around 5–20 mSv compared to 1–5 mSv), assessing additional plaque characteristics through CCTA can enhance risk stratification in both asymptomatic and symptomatic individuals. This has

been demonstrated in the Coronary CT Angiography Evaluation For Clinical Outcomes International Multicenter (CONFIRM) Study and in a posthoc analysis of the SCOT-HEART Study [35,41,42].

In line with this evidence, beyond assessing CAC burden, the CAD-RADS score [43] and its update [44] emphasize the significance of high-risk plaque features, which include spotty calcifications, (referred to as tiny punctate lesions within the plaque), low attenuation plaque (less than 30 Hounsfield Units), positive remodeling, and the "napkin ring sign.'.

Although CCTA is a frontline noninvasive diagnostic test for obstructive CAD in symptomatic patients and provides valuable prognostic information in both symptomatic and asymptomatic individuals, its role in primary prevention remains uncertain [45]. The incremental value of CCTA in this context is still debated, with no strong evidence supporting its routine use for primary prevention. Ongoing trials, such as SCOT-HEART 2 (NCT03920176), are expected to clarify the potential clinical impact of a CCTA-based strategy in guiding primary prevention therapies.

From a pathological standpoint, solely assessing the CAC score is insufficient to fully comprehend the complexities of CAD, as an elevated calcium burden might be linked to stable plaque. Consequently, some individuals with a high CAC burden could potentially avoid pharmacological therapy and its inherent side effects. Functional imaging techniques such as NaF-PET may offer improved stratification of patients with high CAC scores, distinguishing between those with stable and unstable plaque, compared to CT measurements. The ongoing prospective PREFFIR study (Prediction of Recurrent Events With 18F-Fluoride) is assessing the prognostic significance of 18F-NaF PET-CT as an indicator of coronary plaque vulnerability.

Nevertheless, it is crucial to account for sex differences when assessing the role of CAC score in managing and preventing CVD. Studies have demonstrated that relying solely on the CAC score substantially underestimates cardiovascular risk in women. Despite CAC tends to develop later in women compared to men, with women exhibiting a similar CAC score to men but with a delay of approximately 10 years, women have a two-fold increased risk of cardiovascular death as compared with men with the same CAC burden [46]. As a result, there is a growing recognition of the need for risk stratification methods that incorporate sex-specific CAC cutoffs to address the disparities in coronary calcium distribution based on sex [47].

To enhance predictive accuracy of calcium score, there is a need for a new CAC scoring system that utilizes higher-resolution CT imaging and functional imaging modalities. Furthermore, this scoring system should consider not only the absolute amount of CAC but also the localization and pattern of coronary calcifications.

CONCLUSION

CAC progression is associated with the advancement of atherosclerosis. It serves as a reliable predictor of future cardiovascular events in both asymptomatic patients and those with suspected CAD. However, ongoing debates question whether CAC's predictive ability stems from specific calcified plaques or reflects its overall assessment of coronary atherosclerosis burden, with some events originating from noncalcified plaques. Advanced imaging techniques, such as photon-counting CT and 18F-NaF imaging, show promise in visualizing microcalcified areas within coronary plaques, aiding in risk stratification and guiding preventive therapy development.

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Conflicts of interest

The authors report no financial relationships or other potential conflicts of interest relevant to this submission.

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