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IN DEPTH

Coronary Artery Calcification: Current Concepts and Clinical Implications

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ABSTRACT: Coronary artery calcification (CAC) accompanies the development of advanced atherosclerosis. Its role in atherosclerosis holds great interest because the presence and burden of coronary calcification provide direct evidence of the presence and extent of coronary artery disease; furthermore, CAC predicts future events independently of concomitant conventional cardiovascular risk factors and to a greater extent than any other noninvasive biomarker of this disease. Nevertheless, the relationship between CAC and the susceptibility of a plaque to provoke a thrombotic event remains incompletely understood. This review summarizes the current understanding and literature on CAC. It outlines the pathophysiology of CAC and reviews laboratory, histopathological, and genetic studies, as well as imaging findings, to characterize different types of calcification and to elucidate their implications. Some patterns of calcification such as microcalcification portend increased risk of rupture and cardiovascular events and may improve prognosis assessment noninvasively. However, contemporary computed tomography cannot assess early microcalcification. Limited spatial resolution and blooming artifacts may hinder estimation of degree of coronary artery stenosis. Technical advances such as photon counting detectors and combination with nuclear approaches (eg, NaF imaging) promise to improve the performance of cardiac computed tomography. These innovations may speed achieving the ultimate goal of providing noninvasively specific and clinically actionable information.

Key Words: atherosclerosis ■ calcinosis ■ cardiac imaging techniques ■ coronary angiography ■ coronary vessels ■ plaque, atherosclerotic ■ vascular calcification

Atherosclerosis is a leading and growing cause of morbidity and mortality globally. Cardiovascular disease (CVD) accounted for 17.9 million deaths worldwide in 2019.[1] Atherosclerosis represents the main cause of ischemic heart disease/coronary artery disease (CAD). Coronary artery calcification (CAC) usually accompanies the development of advanced atherosclerosis; the presence and burden of CAC provide direct evidence of the presence and extent of CAD and predict future events independently of concomitant cardiovascular risk factors and to a greater extent than any other noninvasive biomarker of this disease.[2] Hence, several guidelines have incorporated CAC as an additional risk marker to assess an individual's overall cardiovascular risk and to inform management.[3,4] The extent and pattern of calcification have prognostic implications.[5,6] Yet, the relationship between CAC and the susceptibility of a plaque to provoke a thrombotic event remains incompletely understood. Although some studies have highlighted microcalcification and spotty calcification as definable components of vulnerable plaque,[7–9] others have suggested that increasing CAC extent and size represent an advanced stage of atherosclerosis, and sheet calcification may render a plaque less likely to rupture.[10]

The advent of more advanced and precise imaging techniques such as dual-energy computed tomography (DECT) and photon-counting computed tomography (PCCT) permit not only quantitative assessment of coronary calcification but also evaluation of the morphological features of calcification within atherosclerotic plaques. Improvements in technology enable more comprehensive reporting of microscopic changes that

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Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
ALP	alkaline phosphatase
CAC	coronary artery calcification
CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CT	computed tomography
CVD	cardiovascular disease
DECT	dual-energy CT
Lp(a)	lipoprotein(a)
PCCT	photon-counting computed tomography
SCOT-HEART 2	Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction
SMC	smooth muscle cell

heretofore required histopathological study or deduction from macroscopic vascular calcification seen on clinical computed tomography (CT) scans. Assessing calcification patterns together with low-attenuation components could enhance the identification of high-risk plaques and consequently high-risk patients who might merit more intensive therapies.

This review summarizes current understanding of and literature on CAC. It aims to correlate findings from histopathological and imaging studies to understand the clinical implications of CAC.

MECHANISMS OF CALCIFICATION

Mönckeberg Calcification

Arterial calcification results from crystallization of calcium and phosphate in the form of hydroxyapatite, which can deposit in the extracellular matrix of the arterial wall. Multiple mechanisms contribute to this process. Depending on its location and the site of the deposition within the arterial wall, arterial calcification falls into 2 main groups, which have distinct causes and implications: Mönckeberg medial calcification and intimal atherosclerotic calcification.

Mönckeberg sclerosis affects primarily the tunica media of peripheral arteries of the lower extremities in individuals with long-standing diabetes. It derives mainly from the action of osteoblast-like cells. Specifically, intracellular signaling pathways and altered calcium-sensing receptors can lead to differentiation of vascular cells to osteoblast-like cells and osteoid metaplasia.[11,12] In addition to diabetes, this type of medial calcification is associated with factors such as chronic kidney disease, hypercalcemia, high phosphate blood concentration, and elevated parathyroid hormone levels. Mönckeberg sclerosis does not generally involve lipid deposition and inflammatory cell accumulation, at least in its advanced stages.

Intimal Calcification

Atherosclerotic intimal calcification usually associates with atherosclerosis progression. CAC reports primarily on this type of intimal calcification; thus, this review focuses on this intimal process. Intimal calcification is an active process associated with the presence of cardiovascular risk factors such as aging, diabetes, and hyperlipidemia, and the local factors that drive its formation differ from those of medial calcification. Specifically, intimal calcification results from dysmorphic calcium precipitation driven by chondrocyte-like cells, rather than osteoblast-like cells as seen in medial calcification,[8] and by an inflammatory cascade, activated by macrophages and local cytokine release. In particular, death of inflammatory cells within the atheroma and subsequent release of apoptotic bodies nucleate crystal formation[13]; death of smooth muscle cells (SMCs) and macrophages can release matrix vesicles[14]; cholesterol accumulation in the intima can promote inflammation; and phenotypic modulation of SMCs to chondrocyte-like cells leads to bone deposition. These mechanisms promote oxidative stress, inflammation, and consequent calcification within the arterial intima.[15,16]

Recent studies have shown that a variety of biochemical factors modulate SMC phenotype; for example, transforming growth factor-β1 and platelet-derived growth factor can promote the switching from the so-called contractile to secretory phenotype of SMCs, and integrin-α9 can promote its proliferation. Such mediators may serve as therapeutic targets for regulating arterial remodeling.[17] Similarly, matrix vesicles merit consideration as a target for interventions to treat arterial calcification, considering their participation in pathogenesis.[18] Matrix vesicles can initiate calcification by serving as nucleating foci.[19] These membrane-bound microparticles released by cells can contain different material, including protein, DNA, mRNA, microRNA. Their composition dictates different calcification potential.[20] After release, initial mineralization starts within the vesicles until the mineral content grows, causing rupture of the vesicle membrane and release of the content and promoting further local mineralization.[21] Moreover, extracellular vesicles can mediate intercellular communication in the calcifying milieu through microRNA. Certain vesicular microRNAs can induce pro-osteogenic gene expression and activate signaling programs in mesenchymal stem cells, which will then differentiate into osteoblast-like calcifying cells. Overall, extracellular matrix vesicles seem to participate in all stages of the pathogenesis of arterial ossification, from its initiation to its progression.[22]

Endothelial progenitor cells with an osteogenic phenotype (costaining in flow cytometry for the osteoblast marker osteocalcin, ie, osteocalcin-positive endothelial progenitor cell) may play an important role in CAC and may be a potential mechanism of and biomarker for coronary calcification. Patients with early and severe coronary atherosclerosis have high levels of circulating osteocalcin-positive endothelial progenitor cells.[23] This mediator may promote early, accelerated ossification not only in coronary arteries but also in other vascular beds and in aortic valves.[24,25]

In patients with endothelial dysfunction, the osteogenic endothelial progenitor cells are retained within the coronary circulation for the repair of the injured coronary endothelium; however, this may lead to abnormal vascular repair, initiation and progression of CAC, and CAC rather than homeostatic endothelial repair.[24] In the early stage of coronary arterial plaque development, the retention of the osteogenic subset within lesions correlates with a larger extent of necrotic core and calcification.[26,27]

CALCIFICATION: HISTOPATHOLOGY

Histopathologically, the classification of types of calcifications in atheromata depends on their diameter: microcalcification (0.5–15 μm), punctate calcification (15 μm–1 mm), fragment calcification (>1 mm), sheet calcification (>3 mm), and nodular calcification. Nodular calcium deposits within the atherosclerotic lesions may extend to the media without disruption of the fibrous cap and can arise from fracture of calcified sheets by mechanical stress.[28] The difference among these types of calcification and the progression from one type to the other have undergone study for decades, especially by histological approaches.[29–31] Calcification, by light microscopic examination, appears to begin with microcalcification; foci may then coalesce and form punctate calcification that can aggregate and produce larger areas of fragmented calcification. The growing calcified structures can localize within the necrotic core and reach into the surrounding collagen- and elastin-rich extracellular matrix and form calcified sheets. Sheets of calcification that can encompass at least a quarter of the circumference of the coronary artery by histology are the hallmarks of fibrocalcific plaques. Calcified sheets may generate calcified nodules that can colocalize with fibrin deposition.[32]

Plaque Morphology

Hence, various types of calcifications can complicate different types of atherosclerotic lesions, which, based on morphology, fall into several categories[33]:

- Pathological intimal thickening is characterized by SMC and lipid accumulation near the intima-media border, with hyaluronan and proteoglycan matrix, extracellular lipid pool, and foci of microcalcification or mixed microcalcification/punctate calcification (Figure 1A and 1B).
- Fibroatheroma (FA) is designated as early or late depending on the presence or absence, respectively, of macrophage accumulation in the lipid pool and on the relative extent of matrix proteoglycans in the necrotic core. Early fibroatheroma may contain punctate calcification (Figure 1C); late fibroatheroma contains an acellular or paucicelluar necrotic core, deficient in extracellular matrix, with or without calcification, especially in the form of fragmented calcification (Figure 1D). The temporal characterization of these plaque types is inferential because of limitations in serial histological observations on human atheroma.
- Thin-cap fibroatheroma is characterized by fibrous caps <65 μm thick, with macrophages, lymphocytes, rare SMCs, and large necrotic core (>10% of plaque area) containing calcification (Figure 1E) with or without intraplaque hemorrhage.
- Plaque rupture is attributable to degradation of fibrous cap by matrix metalloproteases and other proteolytic enzymes, including certain cysteinyl proteinases and mast cell–derived proteases,[34] high circumferential stress,[35] microcalcification (Figure 1F), and iron accumulation within the cap,[36] and ultimately is complicated by thrombosis.
- Plaque erosion, which occurs on pathological intimal thickening or fibroatheroma, is characterized by endothelial cell loss but with intact fibrous caps; luminal thrombi contact the denuded intimal layer directly.
- Calcified nodule (range, 2.5 mm[237]), fibrous plaque comprising nodular calcification (Figure 1G), protrudes through the fibrous cap into the lumen and is an uncommon cause of luminal thrombosis.[38]
- Healed plaque is composed of SMCs, proteoglycans, and collagen-rich matrix, with or without disrupted fibrous cap or a "buried cap" that presumably forms as a result of healing of a plaque fissure. The resulting plaques can contain large area of calcification, usually fragmented or sheet (Figure 1H), with few inflammatory cells and a smaller necrotic core (fibrocalcific plaque).[39]

Plaque Visualization

In recent years, histopathological analysis and visualization of coronary calcification have seen great advances in technology. Among these, micro-CT, although not yet available for clinical use, allows much greater detailed imaging and offers a better understanding of calcification progression, especially when correlated with histological and radiograph images (Figure 2.) Micro-CT is an imaging method that allows greater spatial resolution, up to 1

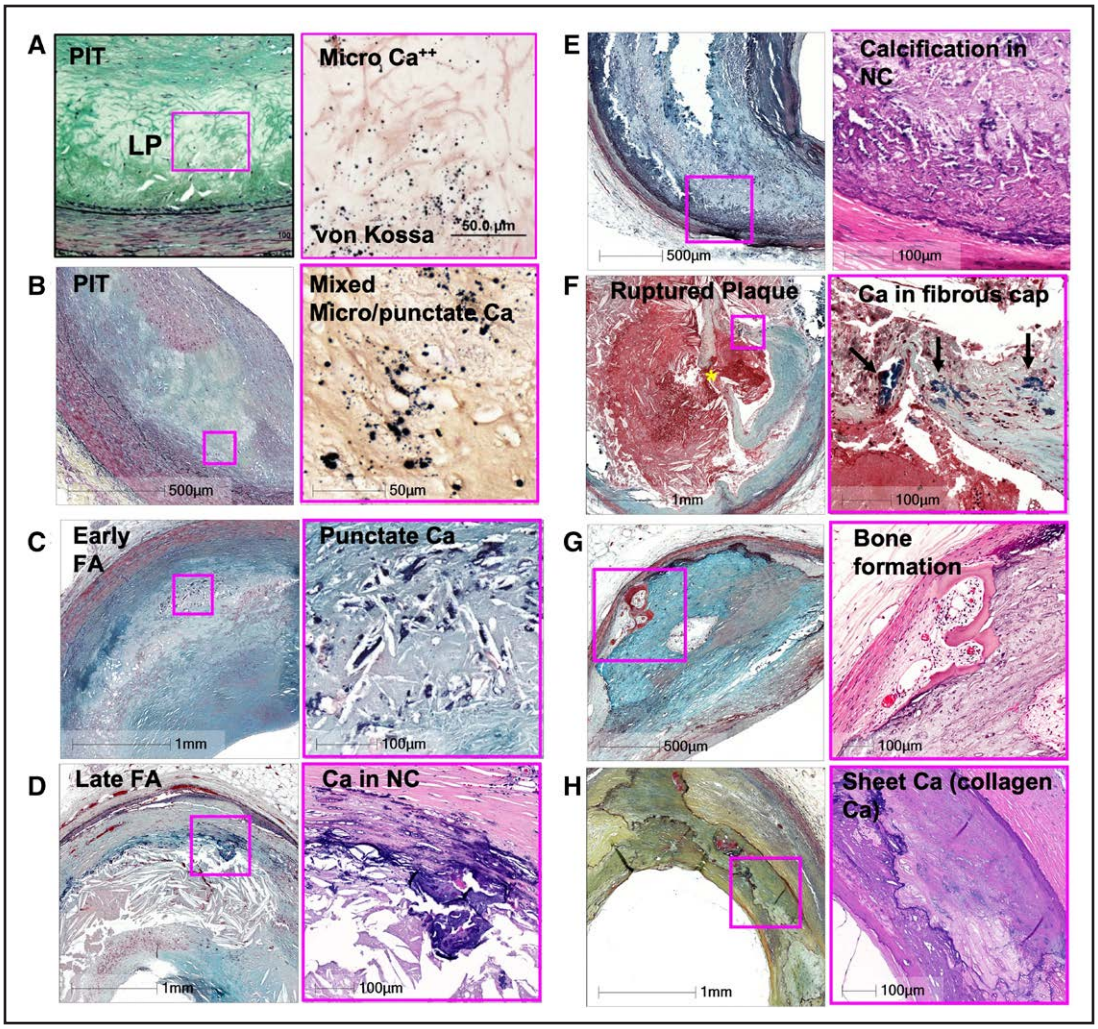

Figure 1. Calcification in various types of plaque.
A, Microcalcification (varies from 0.5 to15 µm) in pathological intimal thickening (PIT). **B**, Mixed punctate and microcalcification may be observed in PIT. **C**, Punctate calcification in early fibroatheroma (FA). **D**, Calcification in late FA occurs as fragmented calcification and is seen near the media involving collagen and necrotic core (NC). **E**, NC calcification. **F**, Plaque rupture showing calcification in the fibrous cap. Asterisk indicates the site of ruptured fibrous cap. **G**, Bone formation near the border of medial layer. **H**, Sheet collagen calcification (collagen Ca). All low-power images are shown with Movat pentachrome stain. High-power images are shown with Von Kossa stain in **A** and **B**, Movat pentachrome stain in **C** and **E**, and hematoxylin-eosin in **D** and **F** through **H**. Modified from Otsuka et al.[32]

to 10 µm, which enables the detection of and differentiation between microscopic and macroscopic calcification. Micro-CT acquisition from biological specimens can be further implemented with the use of a radiopaque contrast agent to better delineate adjacent tissues for histopathological analysis. Therefore, iodine enhancement, paired with micro-CT scanning, can further characterize atherosclerotic plaques with specific emphasis on the vascularization in a manner comparable to routine histology while providing whole-volume data.[40] An additional method for plaque visualization and histopathological analysis is electron microscopy. Together with classic histological imaging, it permits investigation of the detailed structure of atherosclerotic plaques and understanding the pathology of atherogenesis (Figure 3). Both scanning and transmission electron microscopy have been used to illustrate the timeline of atherosclerosis. The combined use of all these ex vivo histological imaging techniques provides deeper insights into atherogenesis and calcification development and progression. Hutcheson et al,[41] using high-resolution micro-CT, electron microscopy, and spectroscopic analyses for mineral content evaluation, provided insight into calcific mineral formation and maturation. In their in vitro study, which involved using both human calcified plaque specimens and collagen hydrogels to mimic the plaque environment and structural features, they observed that microcalcification and ultimately large calcification zones result from progressive aggregation of calcifying extracellular matrix vesicles. More important, they suggested that the aggregation kinetics of vesicles may affect the stability of the fibrous cap and that calcification morphology and the collagen content of plaque are interlinked. Indeed, they showed that microcalcification promotes high plaque-destabilizing stress within

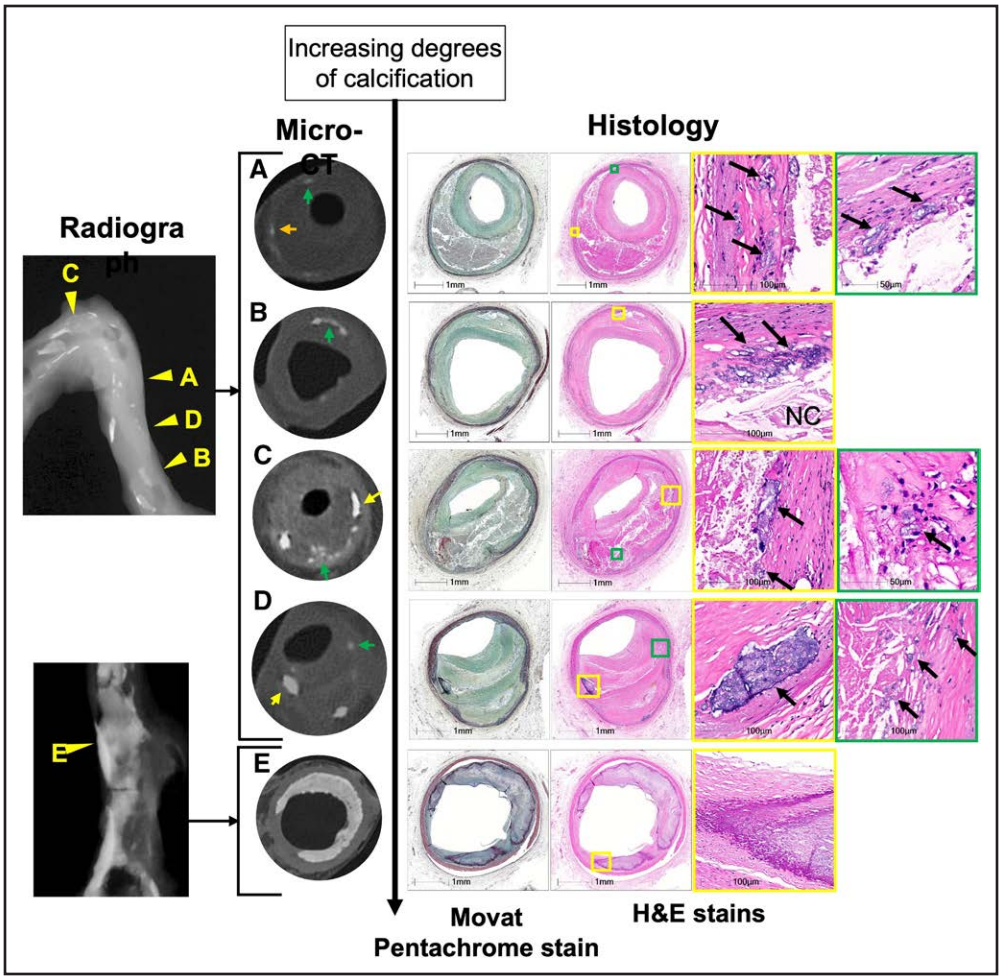

Figure 2. Detection of calcification by various modalities (radiograph, micro-CT, and histology).
A to **E**, Severity of calcification from punctate calcification to sheet calcification by microcomputed tomography (micro-CT). **Right**, Corresponding histological images; **left**, radiograph of the artery. Yellow arrows show the area of calcification in micro-CT; arrowheads in the radiograph show the matching areas. **A**, Micro-CT image can detect punctate calcification (speckled on radiograph) in the border area of a large necrotic core (NC) with adjoining fibrous tissue in late fibroatheroma (FA). **B**, Micro-CT image shows speckled calcification composed of an aggregate of punctate calcification in the early FA. **C** and **D**, Micro-CT show varying sizes of fragmented calcification (yellow arrows) and speckled calcification (green arrows) in the late FA (**C**) and healed plaque rupture (**D**). **E**, Micro-CT showing sheet calcification. H&E indicates hematoxylin-eosin.

the cap extracellular matrix, compromising its structural integrity and leading to its rupture. In addition, they observed an inverse relationship between collagen content within the fibrous cap and microcalcification size, linked to plaque vulnerability; when surrounding collagen is degraded, vesicles can aggregate, nucleate, and form microcalcified foci. These punctate collections of calcium of ≈5 μm in a collagen-poor fibrous cap can increase mechanical stress in the surrounding hyperelastic tissue, favoring rupture.

Moreover, Kelly-Arnold et al[42] examined microcalcification in nonruptured fibrous caps using high-resolution micro-CT. They suggested that potentially dangerous microcalcified structures localize in regions of elevated background stress, usually where the cap is thin. They argue that clusters of such structures in close proximity, parallel to the circumferential (tensile) axis of the fibrous cap, can contribute to high local mechanical stress. High-resolution micro-CT study of human coronary arteries obtained at autopsy has also shown excellent correlation with histology and can distinguish nodular from sheet calcification, allowing plaque to be observed in greater detail compared with radiography alone.[10]

GENETIC DETERMINANTS OF ATHEROMA CALCIFICATION

Understanding the molecular mechanisms of vascular health underlying the genetic risk factors of atherosclerosis may promote new management strategies of patients with or without known CAD.[43] Genetics have a strong influence on calcified atherosclerotic plaques, especially CAC score and calcified plaque volume, as Drobni et al[44] demonstrated in a twin study. The high prevalence of family history of coronary heart disease among young

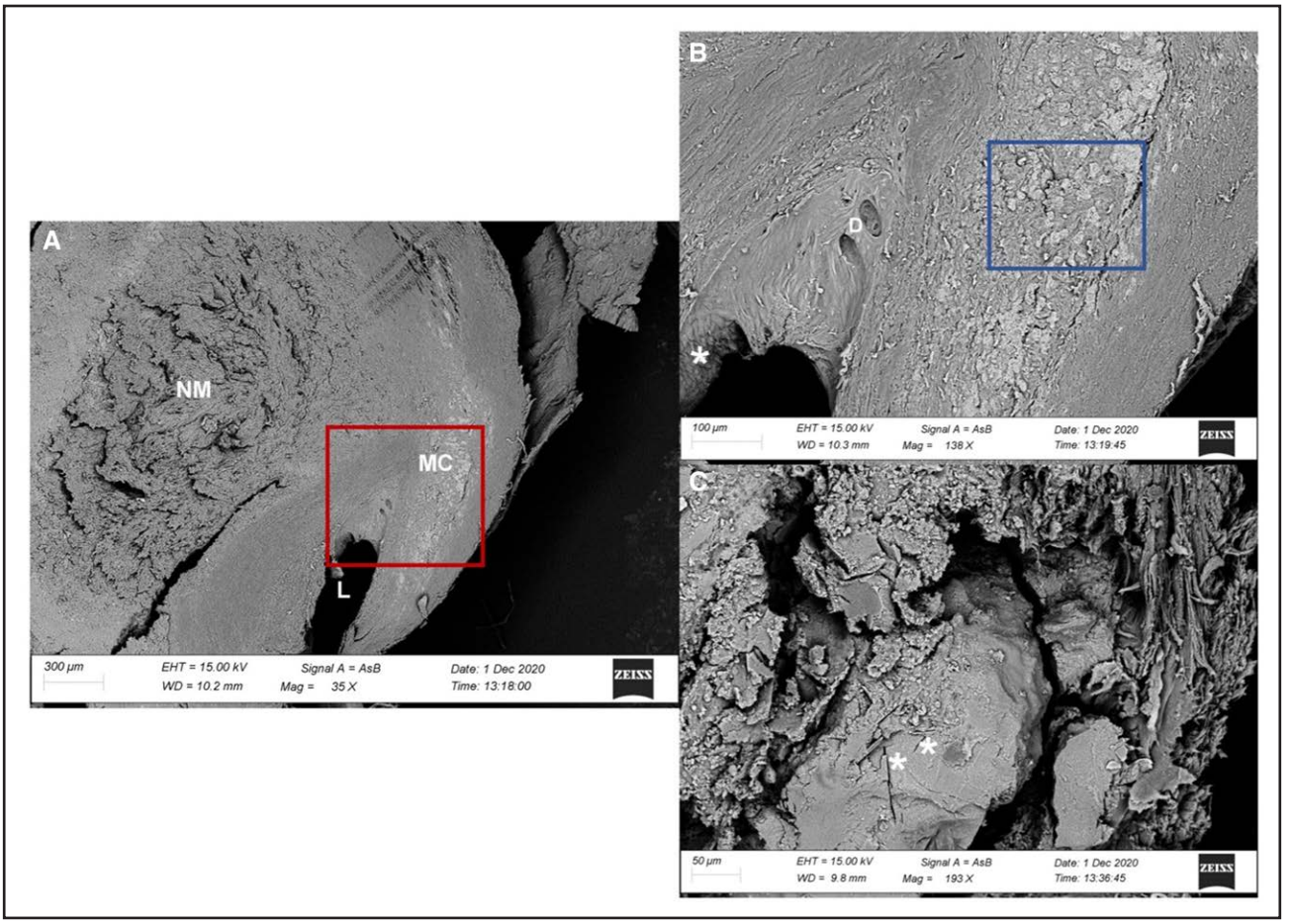

Figure 3. Electron microscopy images.
Low- (**A**), medium- (**B** [red boxed area in **A**]), and high- (**C** [blue boxed area in (**B**)]) magnification scans from a transversal section of carotid artery observed by backscattered electron probe (BSE). **A**, The lumen (L) of the vessel is remarkably reduced and eccentrically constricted by the large necrotic mass (NM) in the thickness of the tunica media. The tunica intima appears strongly altered even at low magnification. The BSE mode, used to analyze differences in tissue density, highlights an area with numerous microcalcifications (MCs) within the tunica media with a light gray-white tone. **B**, Greater enlargement of the vessel lumen shows the presence of small diverticula (D) and important differences in the shape of the endothelial cells; some of them in fact appear taller and less distended (asterisk) according to the blood flow. In the thickness of the tunica media, the microcalcifications of the plaque are distinguished by definition and size. **C**, Partially sectioned microcalcification useful for showing the internal structure. The calcified mass in calcium phosphate appears fairly homogeneous centrally, with some traces of the presence of cholesterol crystals (asterisk). In the periphery, small centers of crystalline aggregation are visible, which suggest a progressive growth of the calcified mass.

adults (mean±SD age, 43±5 years[4,5]) with CAC further supports genetic influences on CAC.[45] In addition, genetic factors influence CAC progression, as shown by Cassidy-Bushrow et al,[46] who found that heritability of CAC progression was 40%, with 14% of the variation explained by genetic factors. Genome-wide association studies showed that 3 single nucleotide polymorphisms attained genome-wide significance for association with CAC,[47] and two of them are also positively associated with CAC progression.[48]

In addition, Klenke et al[49] observed that genetic variations in the G-protein signal pathways influence CAC progression. In particular, they studied 3 single nucleotide polymorphisms and risk alleles in the signaling pathway, ADRB2, GNAS, and GNB3 specifically, and found that the presence of risk alleles was associated with increased 5-year CAC progression and accelerated increase in CAC over 5 years compared with what was expected with respect to baseline CAC. Thus, they suggested the importance of this pathway for genetic heritability of CAC.

Last, detection of cardiovascular calcification in children and adolescents can relate to underlying hereditary disorders linked to increased arterial calcification; thus, disorders caused by altered purine or phosphate metabolism, interferonopathies, and Gaucher disease merit further evaluation in this specific population.[50]

LABORATORY TESTS

Recent studies have also investigated the potential role of specific serum biomarkers as predictors of coronary calcification, its pattern, and its progression (Table 1.) Ren et al[51] studied the association between serum

Table 1. Literature on Laboratory Findings and Their Correlation With Calcification

Laboratory marker	Correlation	Reference
↑ALP	↑Spotty calcification	51
↑ALP	↑Calcified nodule	52
↑Phosphate	↑CAC	53
↓Irisin	↑CAC progression	54
↑MMPs	↑CAC	55
↓1,5-AG	↑Calcium index in patients with diabetes	56
↑Lp(a)	↑CAC volume and rapid progression	57, 58
↑Lp(a) in middle age	↑CAC (>100) in older age	59

1,5-AG indicates 1,5-anhydro-D-glucitol; ALP, alkaline phosphatase; CAC, coronary artery calcification; Lp(a), lipoprotein(a); MMP, metalloproteinases.

alkaline phosphatase (ALP) and calcification patterns and plaque morphology. ALP is a membrane-bound metalloenzyme that catalyzes hydrolysis of pyrophosphate, an inhibitor of vascular calcification. They found that patients with higher ALP serum levels had higher risks of having coronary calcification, especially spotty calcification, and minimum lumen area <4.0 mm^2, features that are associated with plaque instability and increased risk of major adverse cardiovascular events. Hence, they proposed ALP as an independent predictor of and biochemical marker for calcification and plaque vulnerability. Similarly, Li et al[52] found an association between calcified nodules, a characteristic of some plaques that have ruptured, and high serum ALP level.

In addition, Campos-Obando et al[53] found that high serum phosphate levels correlate with CAC in the general population and that this association is also evident for individuals with normal phosphate levels and in the absence of chronic kidney disease, challenging the concept that only marked hyperphosphatemia in the setting of chronic kidney disease promotes calcification.

Some studies have implicated other serum markers of arterial calcification. Hisamatsu et al[54] examined serum irisin levels and their association with prevalence and progression of coronary atherosclerosis. Irisin is an exercise-induced hormone, secreted by skeletal muscle, and its levels are inversely associated with CAC progression and could serve as a biomarker of coronary atherosclerotic burden in asymptomatic patients without obesity. Furthermore, other blood biomarkers, including matrix metalloproteinases, especially matrix metalloproteinase-2 and -9, associate positively with CAC, perhaps related to their role in extracellular matrix degradation and initiation and development of calcification[55]; 1,5-anhydro-D-glucitol (1,5-AG), a marker of glycemic status in patients with diabetes, correlated inversely with calcium index, presence of fibrocalcific lesions, and overall increased risk of CAC and may predict future major adverse cardiovascular events in patients with diabetes.[56] Moreover, serum uric acid may be increased in patients who showed a higher prevalence of thin-cap fibroatheroma and macrophage accumulation and in those with plaques characterized by longer calcification length and thinner fibrous cap.[60] Another marker that may correlate with early atherosclerosis is the presence of osteogenic monocytes, cells involved in plaque development, within the coronary circulation. As Collin et al[61] showed in their study, retention of such cells was associated with a larger extent of calcification and necrotic core. Subsequent maturation of monocytes into macrophages in the early phases of atherosclerosis is associated with an unbalanced turnover of cells, which contributes to inflammation and plaque expansion.

Last, some studies have focused on lipoprotein(a) [Lp(a)], a cholesterol-rich low-density lipoprotein bound with apolipoprotein B_{100}, which has proatherogenic, proinflammatory and prothrombotic activity. Elevated levels of Lp(a) are a highly prevalent genetic risk factor for CVD that correlates positively with CAC. Indeed, Garg et al[57] and Ong et al[58] have shown that elevated Lp(a) is associated with a rapid CAC progression and an increase in CAC volume, especially in patients with higher levels of inflammation and coagulation markers, thus suggesting Lp(a) as a marker of CAC progression. Similarly, Obisesan et al[59] suggested that high levels of Lp(a) in middle age (59.2±4.3 years of age) are associated with elevated CAC (>100) in older age. They also found that increased Lp(a) is associated with increased aortic valve calcification and more rapid progression of aortic stenosis, underlying the importance of cardiac CT in the evaluation of cardiac calcifications among patients with high Lp(a) levels.

IMAGING

Direct noninvasive detection of CAC through CT scanning started in the 1980s with the use of electron-beam CT scanning,[62–64] followed in the late 1990s by multidetector CT scanning, which allowed higher spatial resolution compared with electron-beam CT with inferior temporal resolution compensated for by retrospective ECG-gated spiral acquisition technique. In the following decades, CT technologies evolved very rapidly, enhancing conditions for noninvasive coronary imaging. Although evolving imaging techniques have offered constant improvements in CAC scanning, the methods for the assessment and quantifications of CAC underwent standardization in the early days of electron-beam CT by the Agatston method[65]; newer and more reliable/reproducible scores such as calcium mass and calcium volume were developed, but clinical adoption lagged because the mainstream epidemiological literature used the Agatston method, which continues today. This lack of

interest initially limited efforts to improve calcium detection with alternative scores not based on electron-beam CT. In the meantime, plaque imaging with coronary CT angiography (CCTA) developed rapidly and is providing more insight into qualitative and quantitative assessment of different plaque components.

Differentiating calcification subtypes with noninvasive imaging remains a challenge for contemporary cardiovascular imaging. On one hand, certain plaque features, including some patterns of calcification, which portend a higher risk of rupture and cardiovascular events, may improve the assessment of prognosis. On the other hand, CT scanning struggles to assess early microcalcification and grade of stenosis because of limited spatial resolution and the influence of blooming artifacts. Hence, there is a need for high-spatial-resolution noninvasive imaging modalities with fewer artifacts and more accuracy. These innovations may help reach the ultimate goal of noninvasively providing specific and clinically actionable information on features delineated by direct histopathological studies (Table 2).

CORONARY CT ANGIOGRAPHY

Plaque characterization with CCTA has already yielded exceptional and detailed results. Well-known high-risk plaque features delineated by CCTA include positive remodeling, low attenuation, the napkin-ring sign, and spotty calcification.[72] In fact, CT analyses among patients with acute coronary syndrome (ACS) showed that culprit lesions tend to have spotty calcification (focal calcification <3 mm in diameter), whereas nonculprit lesions tend to have contiguous calcium deposits (>3 mm[66,73]; Figure 4). Although data are consistent in that the presence of a spotty pattern of calcium deposits characterizes high-risk plaques, discrepancies arise when highly dense calcified plaques (>1000 Hounsfield units on CCTA) are considered. Some studies suggest that this type of calcification is associated with stable disease and lower risk of future ACS, as seen in a case-control study from the ICONIC study (Incident Coronary Syndromes Identified by Computed Tomography), in which patients who experienced ACS exhibited less dense plaque on a per-patient and per-lesion basis.[67] This finding also derives support from data that suggest that statin treatment was associated with increased calcification burden but reduced necrotic core volume on follow-up[74] (Figure 5). However, other authors[68,69,75] have recently suggested that CAC >1000 indicates higher all-cause and CVD mortality. In their study, which included 2869 adults from the cohort CAC Consortium study, Peng et al[68] suggested that highly dense plaque denotes high risk. The discrepancy could reflect that CAC score combines CAC volume and density, and although isolated higher CAC density may be a marker of stable plaque, higher CAC volume signifies more plaque burden and higher CVD risk. These considerations highlight the need for guidelines that adopt a more fluid stratification algorithm for primary versus secondary prevention.[69] To reduce blooming artifacts caused by calcification-induced beam hardening, the development of deblooming algorithms has shown promise and should lead to improvement of CCTA diagnostic accuracy.[76]

High-spatial-resolution CCTA scanners have been developed to reduce partial volume and beam-hardening artifacts. This type of scanner is designed to have higher in-plane spatial resolution (0.2–0.23 mm) compared with traditional 64-section multidetector CT with standard definition of 0.5 to 0.75 mm. Pontone et al[77] compared image quality, evaluability, diagnostic accuracy, and radiation exposure of high-spatial-resolution CCTA (0.23 mm) and standard spatial resolution CCTA (0.625 mm) among patients at high risk of CAD using invasive coronary angiography as the reference method. They found that high-resolution compared with standard-resolution CCTA improved evaluability and accuracy of calcified lesions in this clinical setting. CCTA discloses not only calcification but also low-attenuation regions of atheroma and positive

Table 2. Literature on Imaging Findings and Their Clinical Correlation

	Definition	Clinical correlation	Reference
CT			
Spotty calcification	<3 mm in diameter	Culprit lesion; risk of CAD death or nonfatal MI	66
Highly dense calcified plaques	>1000 HU	Stable disease; reduced event risk	67
Highly dense calcified plaques	>1000 HU	Higher risk of CVD, CHD, cancer, and all-cause mortality compared with CAC score 0 and 400–999	68, 69
PET-CT			
^{18}F-NaF uptake	Positive (focal uptake with TBR >25% than a proximal reference lesion)	Culprit lesion of patients with MI and high-risk lesion on IVUS among patients with stable angina	70
^{18}F-NaF uptake	Positive (focal uptake with TBRmax >1.25)	Rapid 1-y progression of coronary calcification in patients with stable CAD	71

CAD indicates coronary artery disease; CHD, coronary heart disease; CT, computed tomography; CVD, cardiovascular disease; HU, Hounsfield units; IVUS, intravascular ultrasound; MI, myocardial infarction; PET, positron emission tomography; and TBR, tissue-to-background ratio.

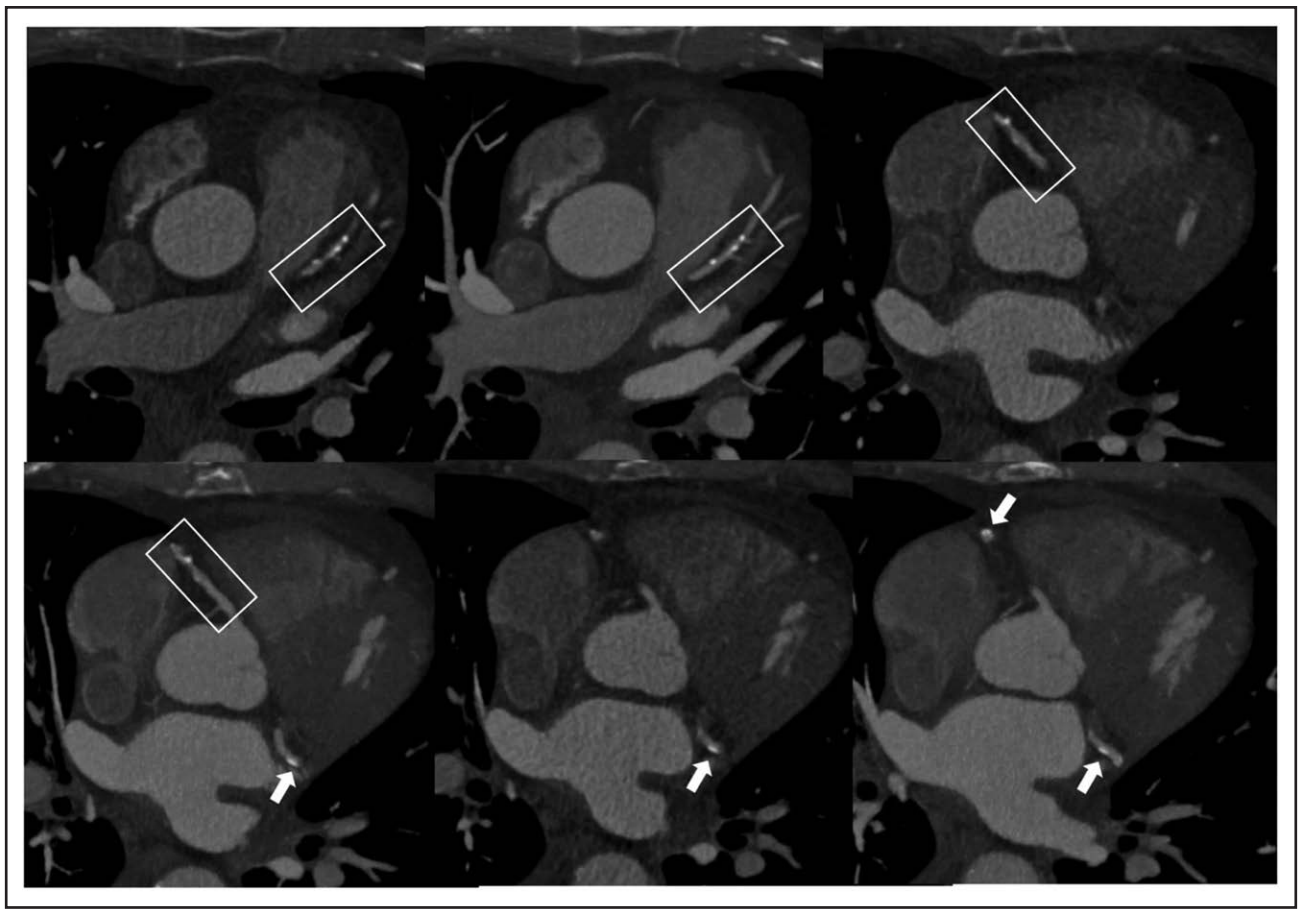

Figure 4. Atherosclerotic plaque as seen in CCTA.
Male patient, 67 years of age with history of diabetes. Coronary computed tomography angiography (CCTA) images show diffuse mixed atherosclerotic plaques with a 3-vessel distribution (box and arrows).

arterial remodeling that also correlate with plaques that provoke ACS, features not apparent on invasive contrast luminograms.

POSITRON EMISSION TOMOGRAPHY

The use of positron emission tomography fluorine imaging to identify high-risk plaques has shown promising results in terms of spatial resolution and accuracy in the detection of calcium deposits that are below the resolution of CT (200–500 µm). ^{18}F-NaF positron emission tomography–CT localized recently ruptured plaques and identified high-risk coronary lesions among patients with stable CAD.[70] Similarly, Doris et al[71] investigated the relationship between ^{18}F-NaF uptake and coronary calcification progression in stable CAD and identified ^{18}F-NaF as a marker of future progression, able to identify patients and coronary segments with rapid progression. This modality also visualized areas interpreted as showing initial and ongoing calcification activity, providing complementary information to CT.[78] The prognostic value of ^{18}F-NaF positron emission tomography–CT as a marker of coronary plaque vulnerability is being evaluated by ongoing prospective PREFFIR study (Prediction of Recurrent Events With ^{18}F-Fluoride).[79]

PCCT AND DECT

Better spatial resolution, soft-tissue contrast, and radiation dose efficiency are the main capabilities of PCCT, a recent advance in imaging technology. PCCT allows significantly better image quality and diagnostic confidence of CCTA compared with conventional CT. Sandstedt et al[80] compared the accuracy of coronary calcium quantification in an ex vivo study and obtained better accuracy in PCCT images, which offered reduced partial volume averaging, better morphological depiction of CAC, and lower image noise. Similarly, VanMeter et al[81] showed that PCCT images had fewer blooming artifacts, less volume overestimation compared with micro-CT, and greater volume quantification accuracy compared with energy-integrating detector CT. Furthermore, in an in vivo study, Si-Mohamed et al[82] compared PCCT with energy-integrating detector dual-layer CT in 3 independent blinded analyses. They found that CCTA obtained with PCCT demonstrated

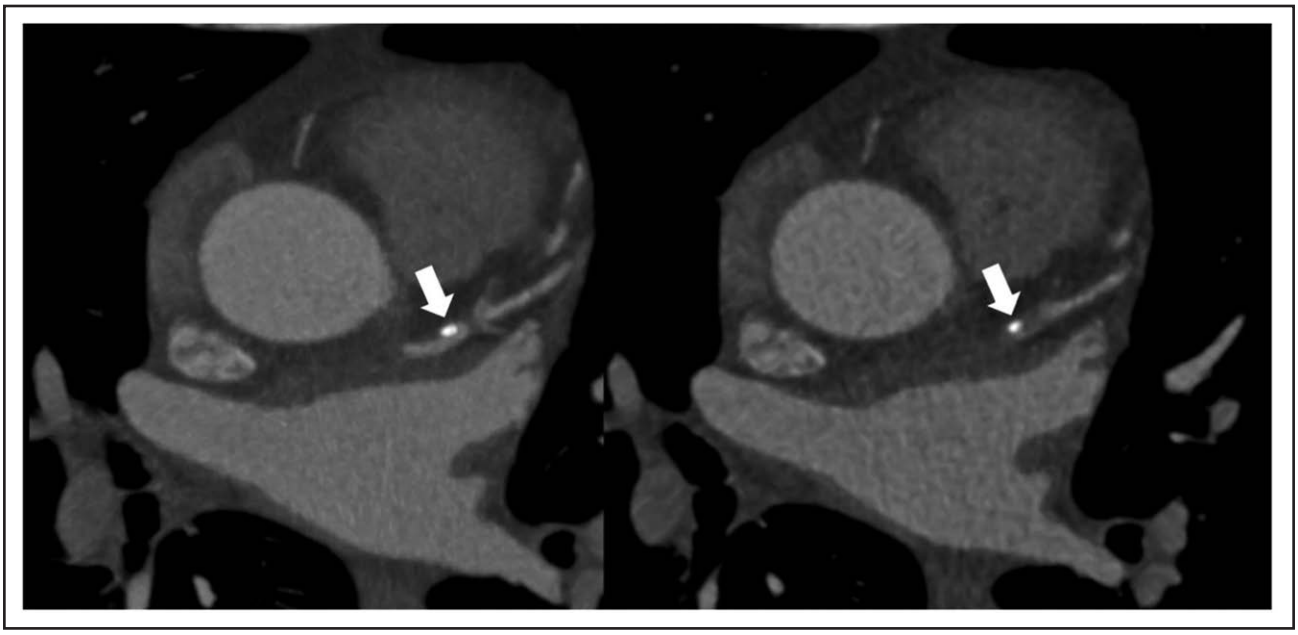

Figure 5. Atherosclerotic plaque as seen in CCTA.
Intermediate-risk 71-year-old patient presenting with acute chest pain and no known history of coronary artery disease. Coronary computed tomography angiography (CCTA) image shows highly dense calcified plaque (arrows).

improved results in humans and better diagnostic quality of coronary calcification.

DECT, also called spectral CT, is another emerging type of CT that potentially provides great anatomic information on arterial calcification. DECT enhances plaque visualization and enables an accurate assessment of high-risk plaque features by combining information on vulnerable features on CT and effective atomic number.[83,84] This approach also permits subtraction of calcified plaques from the image, improving intracavity visualization of patients with severely calcified coronary arteries, a limitation of conventional CCTA.[85] Moreover, the use of multiple virtual monoenergetic images can reduce blooming artifacts caused by highly dense calcification.[86]

From this perspective, PCCT holds great promise because the intrinsic capability of counting and classifying photon energies allows spectral imaging associated with much higher spatial and contrast resolution altogether. Moreover, current clinical PCCT technologies are embedded into cardiac-designed CT scanners, which means dual-source CT scanners with much higher temporal resolution (ie, 66-millisecond effective temporal resolution in hardware) compared with single-source CT scanners (ie, 120–125 milliseconds at best in hardware). The significant reduction of residual motion artifacts is another factor that improves spatial and contrast resolution.

CLINICAL IMPLICATIONS

The identification of high-risk coronary plaque features through noninvasive imaging techniques has important clinical implications for accurate identification of patients at elevated risk of acute cardiovascular events. CCTA and CAC scoring play a crucial role in the identification and quantification of atherosclerotic disease, thus directing the intensification of preventive interventions through lifestyle changes and risk factor management. As Budoff et al[87] recently showed, a fine line separates primary and secondary prevention among patients with high CAC score. They demonstrated that patients without known CAD with CAC score >300 have a risk of major adverse cardiac events similar to that of stable high-risk patients with known CVD (after myocardial infarction). This finding has particular importance because high-risk patients with known CVD are treated with more intensive therapies (eg, addition of nonstatin therapy such as ezetimibe), which hitherto have not been recommended for primary prevention. Thus, further studies are needed to clarify the role of CAC in treatment stratification, but high CAC score may serve as a secondary prevention risk equivalent, which would prompt reconsideration of the current standard of care. However, when the role of CAC score in the management and prevention of CVD is considered, sex differences have to be taken into consideration to avoid bias and undertreatment of female population. It has been shown that the application of CAC score alone significantly underestimates the cardiovascular risk of women[88] and that CAC develops later in the female population compared with men, with a comparable CAC score between the 2 groups with a 10-year difference.[89] Hence, risk stratification methods that apply sex-specific CAC cutoffs have been suggested to account for sex-based discrepancies in coronary calcium distribution.[90,91] Many studies have focused on sex differences in atherosclerosis and in calcification specifically, but the overall

key takeaway when considering CAC score in a clinical setting is that CAC exhibits significant differences between women and men that cannot be denied or taken nonchalantly.[92,93]

CCTA can assess and define the presence of features associated with greater propensity to provoke an ACS. Among these characteristics, calcification features mark an increased incidence of CVD and cardiovascular mortality. CAC predicts future risk of ACS much better than any blood biomarker thus, guidelines incorporate it as a risk-enhancing feature. Advances in CT techniques allow better and more in-depth visualization of CAC, a welcome evolution because not all types of calcifications have the same implications for clinical outcome.[94] Several ongoing trials are examining whether the use of CAC improves clinical outcome. The results of such studies should clarify the role of CAC in the stratification of preventive treatment in future guidelines. The SCOT-HEART 2 trial (Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction; NCT03920176) is investigating CCTA-guided management compared with current standard of care. The ROBINSCA trial (Risk or Benefit in Screening for Cardiovascular Disease) is examining whether CAC screening–guided preventive therapy is effective in reducing morbidity and mortality among asymptomatic adults. The CAC PREVENTABLE trial (Pragmatic Evaluation of Events and Benefits of Lipid Lowering in the Elderly) is part of the Pragmatic Evaluation of Events and Benefits of Lipid Lowering in the Elderly Study (NCT04262206), which will evaluate the benefit of statin therapy among elderly without known CVD and its correlation with CAC score. The CorCal trial (Effectiveness of a Proactive Cardiovascular Primary Prevention Strategy, With or Without the Use of Coronary Calcium Screening, in Preventing Future Major Adverse Cardiac Events; NCT03439267) is testing the effectiveness of a proactive cardiovascular primary prevention strategy, with or without CAC screening, in preventing future major adverse cardiac events compared with current standard of care.

DISCUSSION AND CONCLUSIONS

Broadly, CAC progresses with plaque type and degree of luminal stenosis and advances with atherosclerosis. It reliably predicts future major adverse atherosclerotic

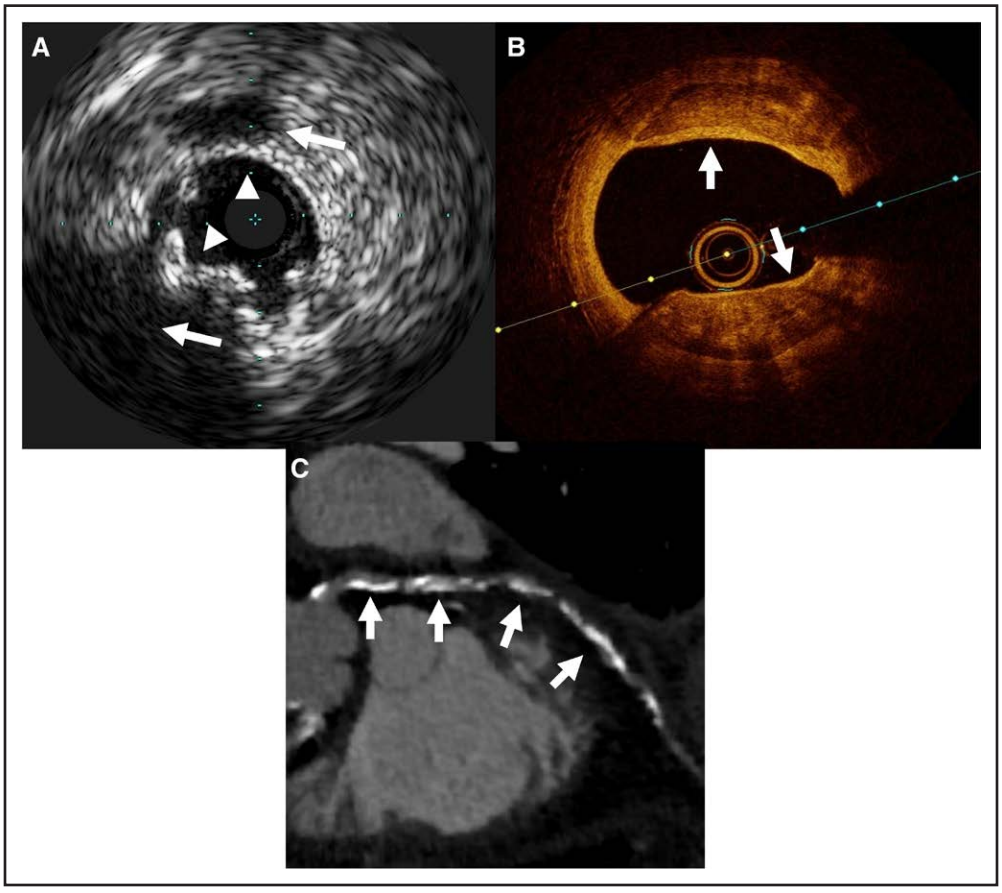

Figure 6. Invasive and noninvasive imaging of atherosclerotic plaque.
A 72-year-old male patient with a coronary artery calcium score of 357. **A**, Intravascular ultrasound shows multiple calcifications (white arrowheads) with shadowing (white arrows). **B**, Optical coherence tomography shows multiple superficial calcifications, seen as signal-poor heterogeneous regions with well-delineated borders (white arrows). **C**, Coronary computed tomography angiography shows diffuse mixed plaque, predominantly calcified (white arrows).

cardiovascular events in asymptomatic patients and in the PROMISE study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain).[95] CAC can also predict ACS events in apparently stable patients who present with suspected CAD, thanks to its higher sensitivity for future cardiovascular events compared with functional testing. In addition, because most events occurred in patients with positive CAC, thanks to its discriminatory ability, CAC testing or CCTA can aid the initial evaluation of new-onset chest discomfort. Although CAC score correlates with coronary atherosclerotic burden, its evaluation with Agatston score by cardiac CT may permit identification of vulnerable patients who have increased risk of developing ACS, beyond characterizing a single vulnerable plaque.[96] Conversely, CCTA, with its higher discriminatory ability for CAD than CAC score and functional testing, may better identify plaques with propensity to rupture, and its use provides significantly better prognostic information compared with functional testing modalities alone.[97,98]

Nonetheless, a debate persists as to whether the predictive ability of CAC relates to the presence of a specific calcified plaque as source of future events or reflects its excellent ability to assess the overall burden of coronary atherosclerosis, with many events actually arising from noncalcified plaques.[99] To address this question, combined pathological and radiological studies can relate calcification subtypes to different grades of plaque/patient vulnerability, and a combination of imaging techniques can provide better understanding of calcified plaque (Figure 6). Although invasive imaging techniques such as intravascular ultrasound and optical coherence tomography have been used to understand and correlate the changes in atherosclerotic plaque with clinical events, the presence of calcification often affects plaque analysis, and it tends to be an exclusion criterion from progression/regression studies[100] (Figure 7). However, culprit lesions and ruptured plaques seem to have more spotty calcification, indicating that spotty calcium

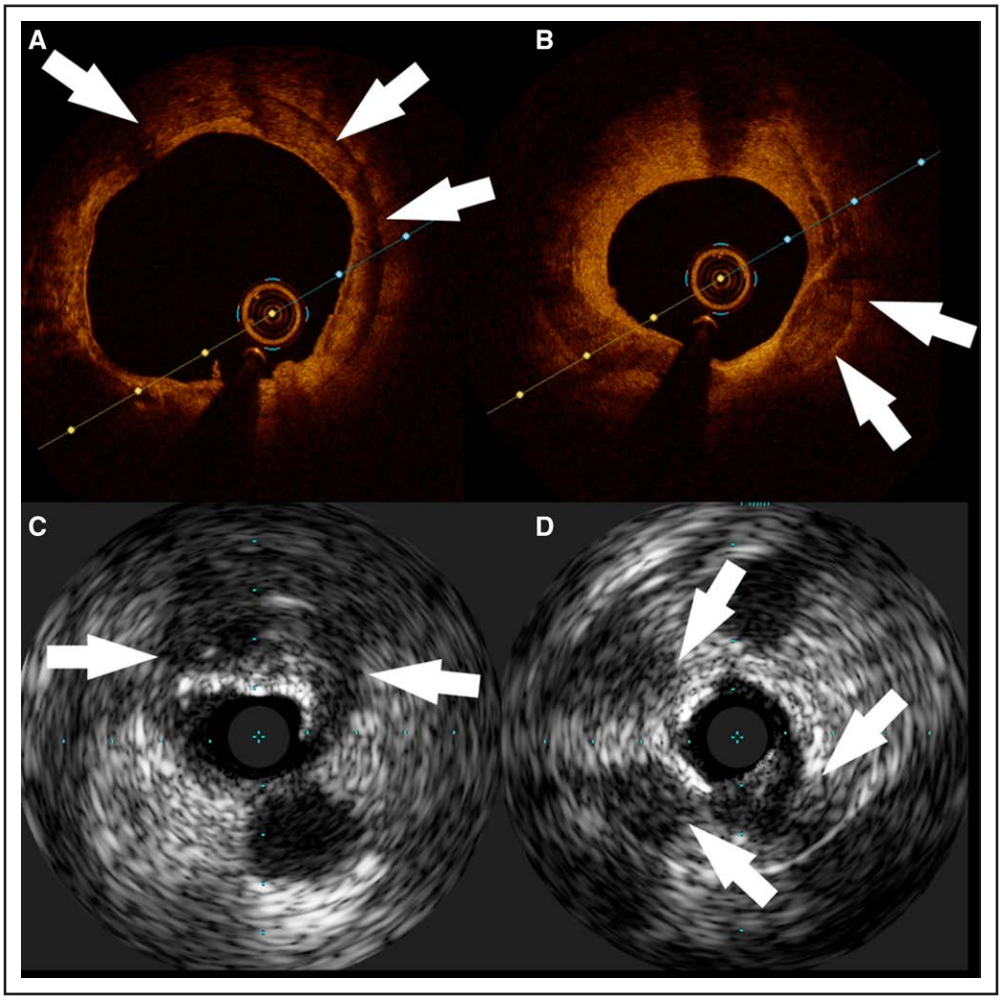

Figure 7. Coronary atherosclerotic plaque images obtained with invasive imaging techniques.
Optical coherence tomography (**A** and **B**) and intravascular ultrasound (**C** and **D**) show different types of calcifications. **A**, Concentric calcification (white arrows) on the right coronary artery (RCA) in a 74-year-old male patient. **B**, Superficial calcification (white arrows) on the left anterior descending artery in a 67-year-old male patient. **C**, Big superficial calcification with a posterior cone of shadow (white arrows) on the left circumflex artery in a 72-year-old male patient. **D**, Multiple clusters of calcifications (white arrows) on the RCA in a 62-year-old male patient.

deposits within unstable lesion may represent a marker of ruptured and subsequently healed plaques.[101,102]

Limitations of CAC scoring include its limited ability to track responses to interventions with serial imaging. For example, guidelines have stated that there is no clinical utility for evaluation of CAC score among statin users because statin treatment may increase CAC, but overall lower risk of ACS.[103] However, recent findings have shown that statin use does not weaken the prognostic utility of CAC and suggest that this limitation can be overcome.[104] Thus, high CAC remains predictive of CVD and coronary heart disease mortality.[105] Debates continue about the decision to withhold therapies in those with low or no detectable CAC, and the debate is extending to imaging as well. In fact, undergoing imaging tests might increase a patient's compliance with preventive treatment and therapy adherence. Despite the promising results concerning the high discriminatory power of CAC for CVD risk prediction compared with polygenic scores or high-sensitivity C-reactive protein, very few studies have compared outcomes on the basis of allocation of therapy by CAC head-to-head with other nonimaging risk markers.[106,107] However, the role of polygenic scores among young adults who have not developed CAC yet requires further research. Last, we need to recognize that no properly powered and rigorous randomized trial has allocated therapy based on CAC and shown a clinical benefit. The SCOT-HEART 2 trial currently underway may close this gap using CCTA, which, however, because of its intrinsic limitations (eg, use of contrast media, higher radiation dose compared with CAC scan), may limit the generalizability of the study.

The promise of more advanced imaging techniques should enable following the progression of morphological characteristics of calcification to contribute to prognostic assessment of high-risk, vulnerable patients and may be helpful in the development of novel therapies.[108] For example, fragmented calcification on histology corresponds to spotty calcification on CCTA, which links to greater risk of rupture compared with sheet calcification on histology, which corresponds to diffuse/dense calcification on radiology.[109] Microcalcification, considered a high-risk plaque feature on histology, still presents a challenge for current noninvasive imaging techniques, but advanced imaging modalities such as PCCT and DECT offer promising results. Further studies with these novel technologies will open the door to more accurate visualization of microcalcified areas within coronary plaques and better risk stratification, identifying those vulnerable patients who will benefit from more aggressive preventive therapy.

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