Mini-Review

Progression of coronary artery calcification at the crossroads: sign of progression or stabilization of coronary atherosclerosis?

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Abstract: Coronary artery calcification (CAC) has been strongly established as an independent predictor of adverse events, with a significant incremental prognostic value over traditional risk stratification algorithms. CAC progression has been associated with a higher rate of events. In parallel, several randomized studies and meta-analysis have shown the effectiveness of statins to slow progression and even promote plaque regression. However, evidence regarding the effect of routine medical therapy on CAC has yielded conflicting results, with initial studies showing significant CAC regression, and contemporaneous data showing rather the opposite. Accordingly, there is currently a great controversy on whether progression of CAC is a sign of progression or stabilization of coronary artery disease (CAD). The finding of inexorable CAC progression despite the implementation of intensive contemporaneous medical therapy suggests that further understanding of this phenomenon should be undertaken before the implementation of CAC as a surrogate endpoint for longitudinal studies, or for prospective follow-up of patients under routine medical treatment.

Keywords: Prognostic value; statin; longitudinal studies; atherothrombosis; imaging

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Introduction

Coronary artery calcification (CAC) has been strongly established as an independent predictor of adverse events, with a significant incremental prognostic value over traditional risk stratification algorithms (1-3). Asymptomatic and even symptomatic patients with absence of calcifications (CAC zero) assessed by cardiac computed tomography have a very low incidence of events at long-term follow-up (1). Furthermore, CAC progression has been associated with higher rates of events (4).

Routine medical therapy for coronary artery disease (CAD) aims to slow the progression of atherosclerosis. Indeed, a vast number of randomized studies and meta-analysis have shown the effectiveness of statins in secondary prevention, not only by providing a significant reduction in coronary events, but also in their ability to slow progression and even promote plaque regression (5-7). However, evidence regarding the effect of routine medical therapy on CAC has yielded conflicting results, with initial studies showing significant CAC regression, and contemporaneous data showing rather the opposite (8-12). Furthermore, complementary prescription of comprehensive lifestyle modification on top of contemporary secondary prevention strategies in patients with CAD has no impact on CAC progression but significant benefit for blood pressure, heart rate and the need of anti-ischemic medication (13).

Accordingly, there is currently a great controversy on whether progression of CAC is a sign of progression or

stabilization of CAD.

CAC scoring by computed tomography: Etiology and prognostic value

CAC is a hallmark of atherosclerosis, and is highly related to increasing age (14). Since life expectancy has significantly improved in the past decades, it is of utmost importance to refine the role of calcium as a prognostic marker. Both *ex vivo* and intravascular ultrasound (IVUS) studies have shown that CAC is closely related to atherosclerotic plaque burden, although the molecular basis of this process remains uncertain (15-17). Recent molecular imaging studies support the current notion that vascular calcification is not a passive degenerative process, but actually an active process that leads to ectopic mineralization promoted by the expression of multiple pro-osteogenic cytokines, transcription factors, and mineralization-regulating proteins by macrophages and other inflammatory cells (18). In this regard, fluorescence molecular multimodality imaging has shown potential to provide insightful data concerning arterial osteogenesis at much earlier stages of atherosclerosis (19,20).

In one of the first studies addressing the association between CAC and plaque burden in *post mortem* specimens, Sangiorgi *et al*. showed a significant correlation between calcium and plaque areas, being this significant both on a per heart and a per vessel basis (17). Nonetheless, the extent of CAC is not strongly related to the degree of luminal stenosis on a per lesion basis (17,21). Indeed, despite CAC is commonly associated to advanced stages of atherosclerosis and to a more stable and quiescent phenotype, calcifications can be present in early stages of CAD, as discussed above. Besides, most thin-cap fibroatheroma lesions, the main substrate of plaque rupture, show microcalcifications within the necrotic core or at the periphery (14). In addition, studies using advanced imaging including micro-CT and optical coherence tomography (OCT) have related microcalcifications within the thin fibrous cap to vulnerable features, and to an increased risk of plaque disruption (22,23).

Before the widespread installation of multidetector computed tomography (MDCT), early studies using electron beam CT established CAC as an independent predictor of events with an incremental prognostic value over traditional risk stratification algorithms (2,24).

CAC assessment by MDCT is a simple procedure that does not require contrast administration or heart rate lowering medication. CAC has high sensitivity and negative predictive value for the detection of obstructive CAD. Indeed, not only the absence of coronary calcifications (CAC zero) has shown a nearly 100% sensitivity and negative predictive value to rule out obstructive CAD, as discussed above, but also a CAC >400 has shown modest specificity and positive predictive value to identify obstructive CAD (1,25,26). A number of studies have explored the relationship between CAC scoring and myocardial perfusion imaging (MPI). Among them, one study including low risk patients showed that only 2% of patients with CAC <100 have abnormal MPI studies, compared to 31% of patients with CAC >400 (27,28). A CAC score ≥709 has been suggested as the optimal cutoff for detecting CAD missed by SPECT imaging, improving the sensitivity of SPECT from 76% to 86% (29).

Furthermore, CAC scoring is associated to a very low effective radiation dose (~1.0 mSv) and it has been extensively validated as an independent predictor of major adverse cardiac events and total mortality in asymptomatic patients, providing a significant incremental value over traditional risk factors and functional studies (30-33).

Overall, the robust evidence available has led to the inclusion of CAC in a number of guidelines for risk stratification of asymptomatic intermediate risk patients (34,35).

A number of absolute CAC score thresholds have been defined for risk prediction ranging from very low risk to very high risk of events (CAC 0; 1–99; 100–399; 400–999; and ≥1,000), being asymptomatic individuals with CAC >400 at a similar risk of events than patients with established CAD (31-33). Nevertheless, the close relationship between CAC and age mandates an assessment according to age and sex (*Figure 1*). In fact, Becker *et al*. have shown that CAC above the 75th percentile is associated with significantly higher rates of cardiovascular death and myocardial infarction than patients with CAC scores below the 75th percentile (36).

Asymptomatic and even symptomatic patients with absence of calcifications (CAC zero) assessed by MDCT have a very low incidence of events at long-term follow-up (3,17). Of note, a large body of evidence renders the absence of calcification a 5-year safety window, with a 0.10% annual risk of events (2,32,37-41).

Notwithstanding, the absence of calcium does not rule out the presence of plaque. Indeed, CAC zero in symptomatic patients should lead to a cautious interpretation due to a number of factors. Firstly, approximately 30% of acute coronary thromboses, particularly in young women and in smokers, are attributed to plaque erosion, a type of plaque that has no lipid core or calcifications and is therefore so far undetectable to any invasive and non-invasive technique,

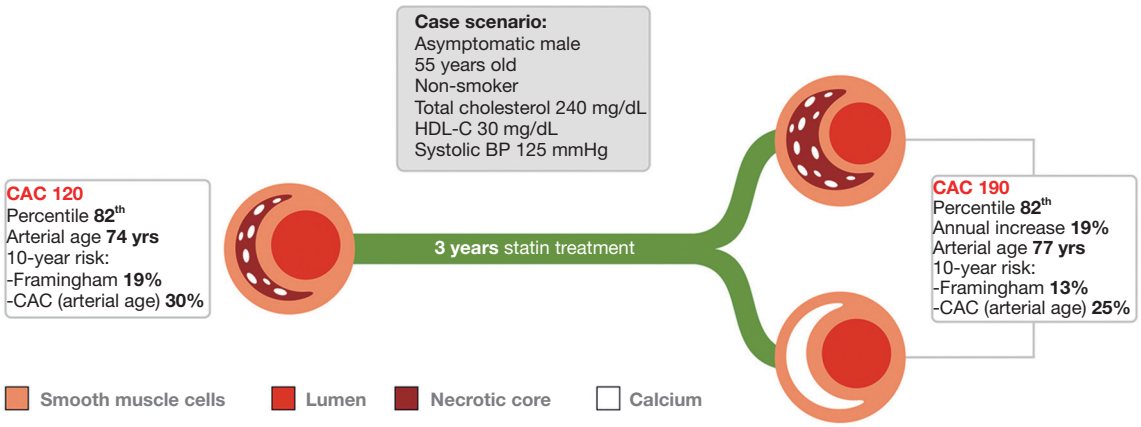

Figure 1 Hypothetical case-scenario of a 55-year-old asymptomatic male with hypercholesterolemia. At baseline, he had a CAC score of 120 (82th percentile). After three years, the patient remained asymptomatic, with normal lipid profile since lipid-lowering therapy with statins was implemented. At follow-up, a significant progression of CAC was observed (CAC 190, annual increase 19%). Paradoxically, the same CAC at follow-up can both be related to a significant plaque progression, or to plaque mineralization as an expression of stabilization. Likewise, although CAC at any time point is a robust independent predictor of events, it can reflect conflicting interpretations (i.e., in two patients with the same CAC and CAC percentile; one can indicate extensive plaque burden with multiple spotty and focal calcifications, and the other can represent stable fibrocalcific plaques). This example represents the limitations of CAC for longitudinal assessments, particularly if plaque stabilization systemic therapies are initiated. CAC, coronary artery calcium.

although recent studies suggested that they might be detected by OCT (42,43). Secondly, spotty calcifications might be occasionally undetected by the 3 mm slices that are routinely used for CAC assessment by MDCT. Spotty calcifications can be more easily identified using either catheter-based techniques (IVUS and OCT) or non-invasive imaging using MDCT coronary angiography. This feature (defined by IVUS as lesions 1 to 4 mm in length containing an arc of calcification of <90°, and <3 mm by MDCT) is commonly observed in culprit lesions of patients with acute coronary syndromes, although it has a low positive predictive value for the prediction of events compared to other high risk findings such as positive remodeling or low attenuation plaques (44,45). Besides, the size of the aforementioned microcalcifications within the thin fibrous cap (<65 μm) precludes non-invasive detection by means of MDCT and even by IVUS.

Other worth mentioning lesions are calcified nodules. These protrusive superficial lesions, although very infrequent, have been related to plaque rupture and acute coronary thrombosis, and MDCT might be able to identify them (43,46).

Meaning of CAC progression

Progression of CAD is undoubtedly related to adverse clinical outcomes. Based on the robust evidence confirming the role of CAC as an independent predictor of death and myocardial infarction, and the fact that CAC is closely associated to the extent of CAD; it might be assumed that CAC progression would also portent a worse prognosis (32,47,48).

This might potentially be related to the fact that spotty calcifications are associated with a larger atherosclerotic burden and to accelerated plaque progression despite use of secondary prevention strategies (49).

Nonetheless, evidence in this regard is inconclusive and the clinical significance of CAC progression remains to be established. In a consecutive series of 4,609 asymptomatic individuals who underwent serial scanning, Budoff *et al.* found that CAC progression (defined as difference between square root of baseline and square root of follow-up CAC score >2.5; or >15% yearly increase) added a significant incremental value over baseline CAC, time between scans, and demographical characteristics in predicting all-cause mortality (4).

More recently, a subanalysis of the Multi-Ethnic Study of Atherosclerosis (MESA) study showed a linear relationship between CAC progression and risk of cardiovascular events, and identified a three- to six-fold increased rate of events in those with an annual progression ≥300 units (50).

CAC progression has been related to several traditional modifiable and non-modifiable cardiovascular risk factors, as well as to novel risk factors such as C-reactive protein, cystatin-C, and to low adiponectin levels (51-54). However, there are no conclusive findings regarding their specific predictive value.

Routine medical therapy for CAD aims to slow the progression of atherosclerosis. Conventional and novel, predominantly lipid lowering, pharmacological strategies have attempted to achieve plaque stabilization and even shown to promote plaque regression (7,55,56). More in particular, aggressive lipid-lowering with high-dose statins has overall accomplished this goal, as assessed by several IVUS studies (6,7,57).

Nonetheless, the significance of CAC alterations with regard to the underlying shift in plaque volume remains unknown. CAC progression might be attributed to plaque progression into a more unstable phenotype with accumulation of microcalcifications, and this would be justified by the aforementioned evidence supporting the deleterious role of CAC progression. However, CAC progression in the context of lifestyle modification and lipid lowering therapies might also be related to a shift towards a more stable phenotype. This paradox is portrayed in *Figure 1*. In other words: (I) does CAC progression mean plaque progression or plaque stabilization?

Effect of statins on CAC

Lipid lowering therapies showed a strikingly improved clinical outcome of patients with CAD, both in the primary and secondary prevention realms (58,59). Reversal of coronary atherosclerosis with intensive statin therapy has been reported in both the peripheral and coronary circulation using diverse invasive and non-invasive imaging tools (6,7,60-64). Indeed, a recent study using IVUS radiofrequency data (RF) analysis demonstrated that in patients with ST-elevation acute myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention, high-dose rosuvastatin therapy over 13 months leads to regression of coronary atherosclerosis in non culprit vessels. In this study, 74% of patients showed regression in at least one non-culprit vessel. Of note, plaque regression could not be attributed to changes in the necrotic core extent or in the number of IVUS-derived thin cap fibroatheromas (65).

Similarly, the long term results of the Study of coronary Atheroma by inTravascular Ultrasound: the effect of Rosuvastatin *vs.* atorvastatiN (SATURN) demonstrated that high-dose statin therapy promoted a significant regression in percent atheroma volume, despite both the necrotic core volume and the frequency of fibroatheromas remained stable. Of note, a significant increase in dense calcium volume was reported in this study (57).

Accordingly, the mechanisms involved in plaque stabilization and regression are still not fully understood, being so far ascribed to changes in LDL-C and HDL-C (60,64,66).

The observed plaque stabilization effect induced by statins might potentially be attributed to pleomorphic effect including a decrease in the lipid content of plaques, a reduction in the inflammatory burden and an improvement in endothelial function; all promoting a more stable phenotype (67-71). Notwithstanding, most evidence in this regard remains inconclusive or speculative.

CAC was conceived as a non-invasive imaging tool aimed at non-invasive assessment of CAD (72). Later on, it has been proposed as a useful tool to monitor the impact of diverse medical therapies on atherosclerosis (8).

Evidence regarding the effect of routine medical therapy on CAC has yielded conflicting results, with initial studies showing significant CAC regression, and contemporaneous data showing rather the opposite (8-10,73).

Indeed, a study published in the *New England of Medicine* in 1998 reported a significant reduction in coronary artery calcium volume assessed using electron-beam CT, proposing a new surrogate endpoint for future prospective clinical studies exploring the effect of drug therapies on CAD (8). The study of Callister *et al*. promoted the idea that CAC regression could be used as an appealing imaging endpoint of both primary and secondary prevention strategies (74-76).

Nonetheless, all the randomized controlled clinical trials performed have consistently reported a persistent CAC progression despite intensive lipid-lowering treatment (*Table 1*) (10,77-80). In fact, a recent meta-analysis that included 8 pooled clinical trials evaluating the effect of high intensity, low intensity or no statin on the percent atheroma volume as assessed by IVUS, showed that aggressive statin therapy induced a significant reduction in percent atheroma volume. Of note, high intensity treatment with statins also promoted a significant increase in calcium index compared to the other two groups (11). Indeed, a recent meta-analysis showed continuing progression of coronary calcification despite treatment with statins (12).

Therefore, in brief: (I) CAC progression is an independent predictor of events; (II) statins promote plaque regression;

Table 1 Randomized controlled trials exploring the effect of statins on CAC

Study or author	Reference	n	Treatment arm	Follow-up	Percent CAC change (%/year)	
					Treatment	Control
SALTIRE	(10)	102	Atorvastatin	24 months	26	18
Terry *et al.*	(77)	80	Simvastatin	12 months	9	5
Schmermund *et al.*	(78)	366	High dose atorvastatin	12 months	27	25
BELLES	(79)	475	High dose atorvastatin	12 months	15	14
St. Francis Heart Study	(80)	1,005	Atorvastatin	52 months	38	36

CAC, coronary artery calcium; SALTIRE, Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression; BELLES, Beyond Endorsed Lipid Lowering with EBT Scanning.

and (III) statins promote CAC progression.

These paradoxical results are puzzling and warrant the conduction of further studies aimed at the pathophysiological and clinical discrimination between plaque volume progression and CAC progression.

One of the potential explanations might be that conventional reading of CAC studies does not make a distinction between spotty calcifications and dense calcium.

Future discrimination between these two completely different sources of coronary calcium might become a major breakthrough in CAC imaging, since spotty calcifications have been recognized as a marker of high risk plaques (81,82).

Regarding future alternative therapeutic approaches, the combined application of molecular imaging agents with anticalcification drugs such as bisphosphonate might potentially enable targeting at different stages of the disease (18).

Future perspectives

Should the Agatston score be revisited? CAC progression seems inevitable and predictable, with limited influence of cardiovascular risk factors (83).

The unquestioned clinical benefit of statins observed in secondary prevention surpasses the expected benefit based on their lipid lowering effect, being this at least in part explained by their supposed ability to decrease the lipid and macrophage content and to increase the fibrous cap thickness in atherosclerotic plaques, promoting a shift into more stable, calcified lesions (69,84,85).

As it was recently postulated by Shaw *et al.*, CAC predicts risk via an intrinsic property or by being a marker of coexisting high-risk plaques in a stabilization process commanded by coronary artery mineralization (86)? Accordingly, based on the available conflicting evidence, it remains unknown whether CAC progression as a single endpoint can discriminate between two opposite outcomes such as plaque stabilization and atherosclerotic plaque progression (*Figure 1*). As discussed above, conventional CAC scoring comprises the quantification of coronary calcifications both on per vessel and per patient basis, leading to robust risk stratification of asymptomatic patients as a once-only study. Future developments of the technique warrant the conception of *second-generation* CAC capable to discriminate between different calcification patterns and spatial distribution, possibly leading to a refinement of the prognostic value and to the application of the technique to longitudinal studies (46).

Until then, the usefulness of CAC once the patient is under statin treatment should be limited. Indeed, a number of medical therapies and even supplementations often used for the management of patients with hypertension or related complications such as atrial fibrillation have shown a significant association to CAC and/or plaque stabilization (55,87,88). The finding of inexorable CAC progression despite the implementation of intensive contemporaneous medical therapy might suggest that further understanding of this phenomenon should be undertaken before the implementation of CAC as a surrogate endpoint for longitudinal studies, or for prospective follow-up of patients under routine medical treatment (9,12,78).

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Footnote

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