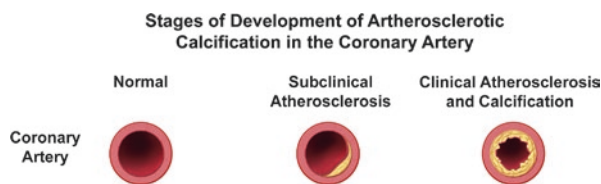

Introduction

Coronary artery calcification (CAC) is a measure of the burden of atherosclerosis in the heart arteries and is measured by CT. The imaging technique measures the amount of calcification in the artery—the amount of bone, which develops in cholesterol-mediated atherosclerosis. Other components of the atherosclerotic plaque, including fatty (eg. cholesterol-rich components), often accompany CAC and can be present even in the absence of CAC—pre-clinical atherosclerosis—non-calcified.

Subclinical Atherosclerosis

Atherosclerosis is a chronic, progressive, inflammatory disease with a long asymptomatic phase, as shown in Fig. 2.1. This long asymptomatic phase of the disease mechanism, is the critical time point for identifying risk factors, initial stages of disease and any sign of early calcification to treat, modify and try to halt, slow or reverse progression. Disease progression can lead eventually to the occurrence of acute cardiovascular events such as myocardial infarction, unstable angina pectoris and sudden cardiac death. While the disease is still in a subclinical stage, however, the presence of atherosclerosis can be identified by several methods, including coronary angiography, intravascular ultrasonography, B-mode ultrasonography, computed tomography and magnetic resonance imaging. Based on the results of imaging studies, statin therapy can slow, halt or even reverse the progression of atherosclerotic disease, depending on the intensity of treatment. Whether to screen and treat patients for subclinical atherosclerosis remains controversial. Although atheroma plaque burden reduction has not yet been definitively correlated with significant decreases in risk for acute coronary events in asymptomatic patients, statin therapy contributes significantly to the risk reduction observed in clinical trials in patients with and

Fig. 2.1 The progression of coronary artery atherosclerosis from subclinical to clinical disease



without overt coronary disease [1]. High dose statin therapy is not only associated with decreased cardiovascular events and mortality, in intravascular ultrasound studies high-dose statins are associated with mild decrease of atheroma volume, particularly in women [2].

Some guidelines have recommended that screening for subclinical atherosclerosis, especially by CAC, might be appropriate in people at intermediate risk for heart disease (eg, 10-year estimate risk of 10–20%) but not for lower-risk general population screening or for people with preexisting heart disease or most other high-risk conditions. However, recent guidelines notes that those with diabetes mellitus who are ≥ 40 years of age may be suitable for screening or risk by coronary calcium [3]. According to the latest ACC/AHA cholesterol management guidelines [4], when treatment decisions are uncertain after 10-year risk is estimated, then the patient and clinician should take into consideration additional factors that modify the risk estimate, including an elevated CAC score or an ABI of >0.9 . There are still limited data demonstrating whether screening with these and other imaging modalities can improve patient outcomes or whether it only increased downstream medical care costs. In part due to the complexity in defining the timing of therapy for the entire spectrum of the biologic effect of atherosclerosis—from subclinical to clinical manifestation of the disease, as shown in Fig. 2.1.

The Agatston Score

The Agatston score is a semi-automated tool to calculate a score based on the extent of coronary artery calcification detected by an unenhanced low-dose CT scan, which is routinely performed in patients undergoing cardiac CT. Due to an extensive body of research, it allows for an early risk stratification as patients with a high Agatston score (>160) have an increased risk for a major adverse cardiac event (MACE) [5].

The Agatston Score is the calculation of the amount of calcification, which is present in the anatomic location of the heart. The measurement of calcification in the heart with the use of CT imaging has helped to define the extent of calcification, and also to define prognosis in this patient population. The presence of any CAC, which indicates that at least some atherosclerotic plaque is present, is defined by an Agatston Score ≥ 100 or a score ≥ 75 th percentile for one's age and sex; however, although they predict short-to intermediate-term risk, absolute CAC cutoffs offer

more prognostic information across all age groups in both males and females. An Agatston score ≥ 400 has been noted to be an indication for further diagnostic evaluation (eg. exercise testing or myocardial perfusion imaging) for coronary artery disease (CAD). Further understanding of coronary calcification will help to understanding, the biology, risk to patients and future long-term clinical trials in this field to slow progression of disease [6].

Method of Calculation Agatston Score

The calculation is based on the weighted density score given to the highest attenuation value (HU) multiplied by area of the calcification speck. The calculation is based on the weighted density score given to the highest attenuation value (HU) multiplied by area of the calcification speck.

Density Factor

130–199 HU: 1
200–299 HU: 2
300–399 HU: 3
400+ HU: 4

For example, if a calcified spec has a maximum attenuation value of 400 HU and occupies 8 mm² area then its calcium score will be 32. The score of every calcified speck is summed up to give the total calcium score.

Grading of Coronary Artery Disease (Based on Total Calcium Score)

no evidence of CAD: 0 calcium score
minimal: 1–10
mild: 11–100
moderate: 101–400
severe: >400

Guidelines for Coronary Calcium Scoring by 2010 Task Force [3]

intermediate cardiovascular risk and asymptomatic adults (class IIa)
low-to-intermediate risk and asymptomatic adults (class IIb)
low risk and asymptomatic (class III)
asymptomatic adults with diabetes, 40 years of age and older (class IIa)

Prevalence of Coronary Artery Calcification

Coronary artery calcification (CAC) is highly prevalent in patients with coronary heart disease (CHD) and is associated with major adverse cardiovascular events. Further studies showed that the extent of coronary artery calcification (CAC) strongly correlated with the degree of atherosclerosis and the rate of future cardiac events [7]. The NHLBI's MESA [8] measured CAC in 6814 participants 45–84 years of age, including Caucasian ($n = 2619$), African American ($n = 1898$), Hispanic ($n = 1494$), and Chinese ($n = 803$) males and females. The prevalence and 75th percentile levels of CAC were highest in white males and lowest in African American and Hispanic females. Significant ethnic differences persisted after adjustment for risk factors, with the RR of coronary calcium being 225 less in African Americans, 15% less in Hispanics, and 8% less in Chinese than in whites.

In addition, a recent cost-effectiveness analysis based on data from MESA reported that CAC testing and statin treatment for those with $CAC > 0$ was cost effective in intermediate-risk scenarios (CV risk 5–10%) [9]. Furthermore, a recent MESA analysis compared these CAC-based treatment strategies to a “treat all” strategy and to treatment according to the ATPIII guidelines with clinical and economic modeled over both 5- and 10-year time horizons. The results consistently demonstrated that it is both cost-saving and more effective to scan intermediate-risk patients for CAC and to treat those with $CAC \geq 1$ that to use treatment based on established risk assessment guidelines.

Renal failure is a unique subset of patients with more aggressive coronary artery calcification and coronary atherosclerosis. This is impacted by not only increased cardiovascular risk factors of hypertension and diabetes, but abnormalities in calcium and phosphorus metabolism contribute to intense calcific coronary disease seen. Coronary artery calcification even in the renal failure population continues to be a strong risk predictor for cardiovascular events [10]. This calcification in renal patients occurs not only in the intimal tissue as it does in non-renal patients but also occurs in the media, suggesting a unique mechanism of calcification in the renal failure population [11].

To date, effective medical treatment of CAC has not been identified. Several strategies of percutaneous coronary intervention have been applied to CHD patients with CAC, but with unsatisfactory results. Prognosis of CAC is still a major problem of CHD patients. Thus, more details about the mechanisms of CAC need to be elucidated in order to improve the understanding and treatment of CAC.

MESA Defines CAC Profiles

Coronary artery calcium (CAC) has been demonstrated to be associated with the risk of coronary heart disease. The Multi-Ethnic Study of Atherosclerosis (MESA) provides a unique opportunity to examine the distribution of CAC on the basis of age, gender, and race/ethnicity in a cohort free of clinical cardiovascular disease and treated diabetes. MESA is a prospective cohort study designed to investigate

subclinical cardiovascular disease in a multiethnic cohort free of clinical cardiovascular disease. The percentiles of the CAC distribution were estimated with nonparametric techniques. Treated diabetics were excluded from analysis. There were 6110 included in the analysis, with 53% female and an average age of 62 years. Men had greater calcium levels than women, and calcium amount and prevalence were steadily higher with increasing age. There were significant differences in calcium by race, and these associations differed across age and gender. For women, whites had the highest percentiles and Hispanics generally had the lowest; in the oldest age group, however, Chinese women had the lowest values. Overall, Chinese and black women were intermediate, with their order dependent on age. For men, whites consistently had the highest percentiles, and Hispanics had the second highest. Blacks were lowest at the younger ages, and Chinese were lowest at the older ages. At the MESA public website (<http://www.mesa-nhlbi.org>), an interactive form allows one to enter an age, gender, race/ethnicity, and CAC score to obtain a corresponding estimated percentile. The information provided here can be used to examine whether a patient has a high CAC score relative to others with the same age, gender, and race/ethnicity who do not have clinical cardiovascular disease or treated diabetes [12].

MESA has defined the importance of measuring coronary artery calcium (CAC) in addition to traditional risk factors for coronary heart disease (CHD) risk prediction. This database is the first to developing a risk score incorporating CAC levels. In 2015, MESA developed a novel risk score to estimate 10-year CHD risk using CAC and traditional risk factors. Investigators developed algorithms in the MESA (Multi-Ethnic Study of Atherosclerosis), a prospective community-based cohort study of 6814 participants age 45–84 years, who were free of clinical heart disease at baseline and followed for 10 years. Inclusion of CAC in the MESA risk score offered significant improvements in risk prediction. Additionally, the difference in estimated 10-year risk between events and non-events was approximately 8–9%. Investigators determined that an accurate estimate of 10-year CHD risk can be obtained using traditional risk factors and CAC. The MESA risk score, which is available online on the MESA web site for easy use, can be used to aid clinicians when communicating risk to patients and when determining risk-based treatment strategies [13].

Coronary Artery Calcium (CAC) Score Reference Values web tool will provide the estimated probability of non-zero calcium, and the 25th, 50th, 75th, and 90th percentiles of the calcium score distribution for a particular age, gender and race. Additionally, if an observed calcium score is entered the program will provide the estimated percentile for this particular score. These reference values are based on participants in the MESA study who were free of clinical cardiovascular disease and treated diabetes at baseline. These participants were between 45 and 84 years of age, and identified themselves as White, African-American, Hispanic, or Chinese. The current tool is thus applicable only for these four race/ethnicity categories and within this age range. At this time, the risk associated with a particular calcium score is unknown. Thus, the information in this tool cannot necessarily be used to conclude that a patient is “high risk”, but can indicate whether they have a high calcium score relative to others with the same age, gender, and race/ethnicity [13].

MESA in Coronary Artery Calcification Versus Calcific Aortic Valve Disease: The Role of Lp(a)

Of great mechanistic importance, the MESA dataset defined the role of Lp(a) in CAVD, but CAC was not associated with Lp(a). The inclusion of CAC into statistical models did not appreciably influence relations of Lp(a) and AVC in the sub-cohort or among races/ethnicities. The presence of existing coronary artery calcification did not affect these associations of Lp(a) and CAVD. There were no significant findings in Hispanics or Chinese. In contrast, CAC was only associated with CAVD in the sub-cohort using a regression model and adjusting for age, sex, education, diabetes, systolic blood pressure, hypertension meds, smoking, LDL, HDL, and triglycerides ($p < 0.001$). All of the traditional risk factors important in the development of CAVD [14].

MESA Defines Gene Expression Profiles

The MESA database also defined gene expression profiles by measuring RNA expression extracted from peripheral blood leukocytes. Coronary artery calcium (CAC) is a strong indicator of total atherosclerosis burden. Epidemiological data have shown substantial differences in CAC prevalence and severity between African Americans and whites. Microarray gene expression profiling of peripheral blood leukocytes was performed from 119 healthy women aged 50 years or above in the Multi-Ethnic Study of Atherosclerosis cohort; 48 women had CAC score >100 and carotid intima-media thickness (IMT) >1 mm, while 71 had CAC <10 and IMT <0.65 mm. When 17 African Americans were compared with 41 whites in the low-CAC group, 409 differentially expressed genes were identified. In addition, 316 differentially expressed genes were identified between the high- and low-CAC groups. Furthermore, genes expressed lower in African Americans also tend to express lower in individuals with low CAC. The data suggest a connection between immune response and vascular calcification and the result provides a potential mechanistic explanation for the lower prevalence and severity of CAC in African Americans compared with whites [15].

Furthermore, MESA demonstrated that low ($<10\%$) to intermediate (10–20%) predicted Framingham risk; cases ($N = 48$) had coronary artery calcium (CAC) score > 100 and carotid intima-media thickness (IMT) >1.0 mm, whereas controls ($N = 71$) had CAC < 10 and IMT <0.65 mm. The RNA profiling study identified two major expression profiles significantly associated with significant atherosclerosis, among those with Framingham risk score $<10\%$. Ontology analysis of the gene signature reveals activation of a major innate immune pathway, toll-like receptors and IL-1R signaling, in individuals with significant atherosclerosis. Gene expression profiles of peripheral blood may be a useful tool to identify individuals with significant burden of atherosclerosis, even among those with low predicted risk by clinical factors. Furthermore, the data suggest a critical association between

atherosclerosis and the innate immune system and inflammation via TLR signaling in lower risk individuals [16].

Atherogenesis

Atherogenesis begins at sites of endothelial injury secondary to known risk factors for cardiovascular disease [3]. Early initiating events responsible for atherogenesis may result from a variety of factors, including increased local shear forces from hypertension, elevated plasma concentrations of LDL-C and remnant lipoprotein particles, cigarette smoke, low serum HDL-C and impaired reverse cholesterol transport, insulin resistance, and diabetes mellitus. These factors decrease endothelial cell production of nitric oxide, thereby impairing vasodilatory capacity and the normal barrier and protective functions of the vascular endothelium [17, 18]. As a result, LDL-C infiltrates the subendothelial space, where it can be oxidatively modified to initiate abnormal atherogenesis in the vessel.

Abnormal endothelial function, secondary to oxidative stress initiates a cascade of steps including attachment of circulation monocytes, activation of growth factors and development of an atherosclerotic lesion, composed of lipid-laden foam cells, proliferating and synthetic vascular smooth muscle cells which are differentiating into an osteogenic phenotype for future calcification, or bone formation.

The Molecular Biology of Vascular Calcification

The role of lipids in vascular calcification, have been the focus of intense investigation over the past 100 years. Lipids and other cardiovascular risk factors induce oxidative stress [19–21] in the aortic valve endothelium similar to vascular endothelium [22] which in turn activates the secretion of cytokines and growth factors important in cell signaling as shown in Fig. 2.2. The early atherosclerotic and abnormal oxidative stress environment also plays a role in the activation of the calcification process in the myofibroblast cell. Cardiovascular risk factors, cell proliferation [23] and cyclic stretch [24] play a role in the activation of these cells to transition to a calcifying phenotype. There is also increasing evidence that these cells undergo specific differentiation steps towards the development of this bone phenotype as shown in *in vitro* studies [25–27]. The signaling molecules important in the development of vascular atherosclerosis are also important in the development of valve calcification including: MMP [28, 29], Interleukin 1 [30], transforming growth factor-beta (TGF-beta) [31], purine nucleotides [32, 33], RANK [34], osteoprotegerin (OPG) [34], elastolytic cathepsins S, K, and V and their inhibitor Cystatin C in stenotic aortic valves [35] Toll-like receptors [36], TNF alpha [37], MAP Kinase [23] and the canonical Wnt pathway [38–40]. Similar to vascular atherosclerosis these events are potential cellular targets for pharmacologic agents to slow this disease process. HMG CoA Reductase agents, angiotensin converting enzyme (ACE)

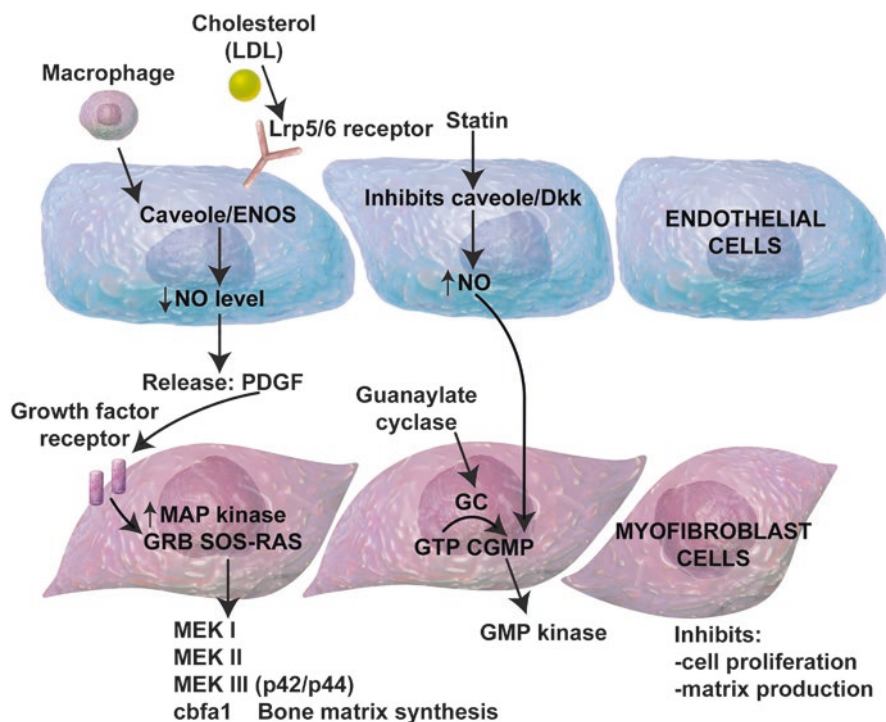


Fig. 2.2 Signaling pathways in the development of vascular atherosclerosis

inhibitors, and angiotensin receptor blockers (ARBs), provide an interesting approach for targeting in this disease.

Interventional Therapy for CAC

CAC increases the likelihood of procedural failure and complications after balloon angioplasty [41]. Besides, the force applied from the balloon to the vessel wall might not be uniform across the length of the lesion, due to varying amounts of calcification, which increases the risk for dissection and acute vessel closure, MI, restenosis, and MACE [42]. Rotational atherectomy abrades hard tissue into smaller particles ($<10\ \mu\text{m}$) while deflecting off softer elastic tissue [43]. Therefore, rotational atherectomy has a selective effect on hard lesions, but not the soft tissues. In the pre-stent era, the use of rotational atherectomy alone was associated with increased neo-intimal hyperplasia, restenosis, and repeat revascularization, which was most likely due to platelet activation and thermal injury [44]. Excimer laser coronary atherectomy (ELCA) can dilate resistant lesions through a photoacoustic mechanism. In-stent restenosis can be treated by ELCA with similar outcomes as rotational atherectomy [45].

Similarly, it can facilitate stent expansion when high-pressure non-compliant balloon inflation fails to adequately expand a stent due to calcific or fibrotic coronary disease.

Orbital atherectomy is a newer form of atherectomy, which utilizes an orbiting eccentric diamond-coated crown which removes plaque by creating increasing debulked areas at the tip by an increasing size of an orbital field as the speed of the device is increased. (Diamondback 360° Orbital Atherectomy System, Cardiovascular Systems, Inc., St. Paul, MN). In ORBIT II this device was shown to facilitate stent delivery and improved outcomes compared with historic controls [46]. While feasible, the specific role of orbital atherectomy in percutaneous coronary revascularization awaits prospective randomized trials to demonstrate benefit.

Coronary artery bypass graft surgery remains a viable option for revascularization and has an increased role in patients with class III to IV CAC based on intravascular ultrasound, as well as anticipated difficulty in performing percutaneous coronary revascularization. However, increased morbidity and mortality occurs from challenges in bypassing the coronary artery and increased embolic complications with cross-clamping a calcified and atherosclerotic aorta [47, 48].

Thus, coronary artery calcification remains not only a marker of early atherosclerosis it is an end-stage manifestation of severe coronary atherosclerosis which challenges our ability for safe and successful revascularization. Determining how to balance the beneficial effects of calcification on plaque stability while gaining insight on how to safely influence this process and potentially reverse it to facilitate revascularization will be needed to advance the treatment of coronary artery disease.

Summary

Results from MESA [49] and the current guidelines of the treatment of cardiovascular heart disease [3], have indicated that CAC screening is most useful for identifying patients with early atherosclerosis, with the most powerful identifier is the patient with no CAC, who do not need therapy. The absence of subclinical atherosclerosis, indicates that patient who are at low risk have a better long-term survival [49].

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Osteocardiology

Cardiac Bone Formation

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