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## Calcification of the heart: mechanisms and therapeutic avenues

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### Abstract

**Introduction:** Coronary artery calcification(CAC) is reflective of atherosclerotic disease and incrementally predictive of future cardiovascular events, independent of traditional risk factors. Extra coronary calcium such as aortic valve calcification, which can be identified and quantified by Computed Tomography(CT) imaging, has shown to predict future cardiovascular events in both asymptomatic and symptomatic (ie - stable angina and acute coronary syndrome) settings. It has hence been a vital tool in studies involving new therapies for cardiovascular disease.

**Areas covered:** In this review, promising therapies on the horizon are reviewed, and the role of cardiac CT and coronary calcification in these studies. A Medline search for peer-reviewed publications using keywords related to coronary calcium score, aortic valve calcium, and therapies targeting the same was carried out.

**Expert commentary:** CT scanning provides a distinct means of detecting and quantifying coronary plaque as well as valvular calcification with excellent reproducibility. Based on voluminous data available, the absence of Coronary calcium serves as a factor to de-risk patients for cardiovascular risk stratification and management algorithms. Newer therapies have shown to lower progression of coronary calcification, hence being beneficial in slowing progression of atherosclerotic disease. As the British Epidemiologist Geoffrey Rose states, the best predictor of a life-threatening disease is the early manifestation of that disease. As CAC represents the early manifestation of atherosclerosis, it is the best-known stratifier of risk today, and its clinical use will continue to rise.

### Keywords

coronary calcium score; aortic valve calcium; statin and calcium score; lipoprotein(a); aged garlic extract; omega 3 fatty acids; calcium score in kidney disease; anticoagulants; coronary calcium

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## 1. Introduction

Coronary artery calcification happens when calcium deposits on the intimal layer of the coronary arteries. It is reflective of atherosclerotic disease and incrementally predictive of

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future cardiovascular events(CVE), independent of traditional cardiovascular risk factors.[1] Calcification of the mitral and aortic valves have similar risk factors and histological characteristics as CAC. Computed Tomography (CT) scanning provides a distinct means of detecting and quantifying coronary plaque as well as valvular calcification.[1] Given the diagnostic accuracy, prognostic utility, non-invasive nature, safety with relatively small radiation hazard, and low cost, cardiac CT imaging has become an exponentially expanding field of cardiology and radiology research. As calcification can not only be detected, but quantified with excellent reproducibility, it has been a vital tool in studies involving new therapies for cardiovascular disease. [2] In this review, we intend to review some of the promising therapies on the horizon, and the role of cardiac CT and cardiac calcification in these studies.

## 2. Calcification of the heart

### 2.1 Risk factors for coronary artery calcification

Higher CAC scores have been noted in men when compared to women, and increasing age has shown a positive correlation with CAC.[3] Ethnic differences in coronary calcification have also been noted. Bild et al. showed that the relative risks for having CAC compared with Caucasians were 0.78 in African-Americans (95% CI 0.74–0.82), 0.85 in Hispanics (95% CI 0.80–0.91), and 0.92 in Chinese (95% CI 0.85–0.995).[4] Ahmed et al. devised a lifestyle score in their study using diet, exercise, body mass index, and smoking status. A positive correlation was seen between the lifestyle score and CAC incidence, rate of calcium progression, all-cause mortality over 7.6 years. [5]

### 2.2 Mechanism of coronary artery calcification

Atherosclerotic plaque in the coronary arteries starts with the accumulation of lipid-laden foamy macrophages and vascular smooth muscle cells leading to intimal thickening. This plaque, in due course of time, is infiltrated by macrophages and T lymphocytes close to the lumen. A lipid-rich necrotic core encapsulated by fibrous tissue, called fibroatheroma then forms. Macrophage infiltration into the lipid pool and focal loss of proteoglycans and collagen matrix is seen in the early phase of atheroma. Late stages of fibroatheroma have acellular debris, increased free cholesterol, and near complete absence of extracellular matrix. Vulnerable plaque or thin cap fibroatheroma consists of a large necrotic core covered by a thin fibrous cap. This cap is infiltrated by macrophages and T-lymphocytes with an absence of smooth muscle cells. When the fibrous cap breaks, plaque rupture occurs. Erosion lesions can happen instead of plaque rupture and would contain proteoglycans and smooth muscle cells but lack endothelium. Healed thrombi include those occurring from healed plaque rupture and erosion.

Micro calcification occurs in these areas in the intima, close to the internal elastic lamina, from macrophage releasing matrix vesicles or apoptosis. These coalesce into larger masses and involve both the necrotic core and the surrounding collagen-rich extracellular matrix to form larger fragments of calcification, extending from the necrotic core to the surrounding collagenous matrix. Further progression of the disease results in calcified plaque. These may

break off and result in nodular calcification with fibrin deposition and may protrude into the lumen or media.

Osteogenesis may rarely be seen in areas of arterial calcification. Bone-related proteins and features such as chondrocyte and osteoblast differentiation, mineralization, bone matrix deposition, and bone resorption have been noted in areas of arterial calcification. [6]

Mechanisms of aortic valve calcification and mitral valve calcification are described below.

### 2.3 Calcification imaging and scoring

Coronary artery calcification can be detected by ECG-gated non-contrast coronary computed tomography (CT) scan with very minimal radiation dose. Agatston et al. derived the Agatston score as the product of calcified plaque area and maximum calcium lesion density from 1 to 4 based upon Hounsfield units[7], which serves as the most feasible and applied method for CAC quantification. Although an electron beam CT scanner was used for the original Agatston scoring system, the measurement of CAC using newer and better scanners have been well validated. [8] Other CAC scoring systems including calcium mass score, calcium volume score, calcium density score are being used as well. Given the vast data available and the close correlation of Agatston score with the other scoring systems, current algorithms recommend the use of Agatston scoring as the reported measurement when assessing CAC. [9]

CAC and CT can be of immense value in a chest-pain unit setting and emergency department as well. Howell et al. analyzed 619 low risk-patients without a history of CAD admitted to the chest pain unit to rule out acute coronary syndrome. While 283 patients underwent no cardiac testing, the others had one of the following: exercise treadmill, myocardial perfusion stress scintigraphy, exercise stress echocardiography and coronary angiography. Exclusion of cardiac testing shortened the length of stay and was not associated with an increase in MACE at six months. CT scanning was not a modality that was used in this study. [10] Other studies have shown significantly reduced length of stay in low-risk patients with chest pain compared with traditional care (25 hours v/s 18 hours [11] and 31 hours v/s 23 hours [12])

Several other diagnostic modalities are available for detecting coronary calcification and also stratify plaque stability, including intravascular ultrasound (IVUS), optical coherence tomography (OCT), angiography, magnetic resonance angiography and near-infrared fluorescence. IVUS and OCT being the two most frequently used methods are invasive, but do allow for detailed plaque assessment and quantification of plaque. Current studies indicate that IVUS is more effective at quantifying overall plaque burden than either OCT, while OCT is more effective at assessing individual lesion morphology. [13]

Though progression of CAC is reflective of atherosclerosis progression, it may not always correlate well with progression in lipid-rich plaque associated with acute coronary syndrome. [14] Also, there are other parameters like plaque burden, vulnerable plaque features, plaque activity, stenosis degree, and ischemia, all of which are known to precede

cardiovascular events. [15] These can be differentiated and quantified by CT Angiography (CTA), with good relationship to Intra Vascular Ultrasound (IVUS). [16]

## 2.4 Coronary artery calcification and statin eligibility

Statins have been shown to reduce cardiovascular events [17] and used for both primary and secondary prevention of Atherosclerotic Cardiovascular Disease (ASCVD). This group of drugs has been studied extensively in secondary prevention trials. Arad et al. with the St. Francis Heart Study conducted a double-blinded, placebo-controlled randomized clinical trial of atorvastatin 20 mg, vitamin C, and E daily versus matching placebos, for a mean duration for 4.3 years. The study included 1,005 asymptomatic, apparently healthy 50–70 year old individuals, with Coronary Artery Calcium score (CAC) at or above the 80th percentile for age and gender. A significant reduction was noted in low-density lipoprotein-cholesterol (LDL-C), triglycerides and total cholesterol. Also noted was a 42% reduction in ASCVD events in the study population with baseline CAC >400 (5-year NNT 18.5). [18] For primary prevention, however, there has been considerable debate regarding the target population for statins. When Nasir et al. studied the Multi-Ethnic Study of Atherosclerosis (MESA) participants between the ages of 45 to 75 years, without known Cardiovascular disease (CVD), nearly two-thirds were eligible for statins per ACC/AHA guidelines, and almost half of them did not have coronary calcium. The group hence had a lower 10-year observed ASCVD risk than the threshold recommended for treatment. The same risk, however, was above the threshold for statin recommendation in the presence of a higher CAC burden. [19] Sarwar et al. reviewed 49 articles with over 85,000 patients, examining the diagnostic and prognostic utility of CAC. Even in groups considered as high risk per traditional risk stratification, favorable prognosis was noted in individuals with CAC=0. Event rate in asymptomatic participants was as low as 0.5%, and symptomatic patients were 1.8%. They hence concluded that the future risk of cardiovascular events was very low in the absence of CAC. [20]

Similar results have been seen in studies involving different patient populations, like patients with diabetes mellitus (DM). In a study conducted by Kiramijyan et al., subjects with no CAC progression had comparable outcomes with or without diabetes, indicating that the main marker of mortality was the CAC progression itself. [21] Statin therapy has shown a decreased rate of CAC progression even in patients with DM. [22]

Rijlaarsdam-Hermsen et al. studied 137 patients with stable chest symptoms, and no coronary calcium for 44.6 months and no major adverse cardiac event (MACE) occurred. Hence, they concluded that the negative predictive value for CAC by CT scanning as the first-line test was 100%, in comparison to 66.4% for exercise stress testing. [23] This was consistent with prior studies emphasizing the good prognostic value of the absence of CAC. [24, 25] Based on the voluminous data available, the absence of CAC could serve as a factor in the reclassification of risk groups and management algorithms.

Although statins have time and again shown to reduce lipid levels, studies have not demonstrated a positive effect on CAC progression. [26] Studies have shown that statin therapy can significantly lower progression of low attenuation plaque and non calcified plaque compared to non-statin users, but similar results were not noted for calcified plaque.

[27] Taking the pathophysiology of plaque formation into consideration, it is possible to intervene to regress non calcified plaque. However, it is unclear if the same can be done for calcified plaque. It has also been proposed that when decrease the soft lipid core of a calcified plaque, the density of the plaque and its Agatston calcium score might increase, whereas its volume might decrease. It is also likely that statins would need more time to have their positive effect reach the downstream step of calcification in the atherosclerotic process.[26]

## 2.5 Aortic valve calcification

Aortic valve calcification (AVC), which can be identified and quantified by CT imaging, is a subclinical form of Calcified Aortic Valve stenosis (CAVS), which affects over 2.5 million individuals in North America. [28] Aortic stenosis and coronary artery calcification share common risk factors and have similar pathophysiological mechanisms. The endothelial damage that triggers the subsequent deposition of lipid and an intense inflammatory response is seen in both conditions. However, inflammation appears to have a lesser role in aortic stenosis which could explain statins not causing a decrease in aortic calcification in major RCTs.[29] Current treatment options consist solely of valve replacement. In a ten center survey conducted by Bach et al., approximately 50% of patients with severe aortic stenosis(AS) were referred for cardiothoracic surgery, and ≈40% of them underwent aortic valve replacement until 2011.[30] After the FDA approval of Transcatheter Aortic Valve Replacement (TAVR), between 2012 and 2015, there have been 54,782 TAVR procedures performed between the 418 TAVR sites. [31]

The mechanism behind calcification in the valve and the possibility of targeted medical therapy have spiked the curiosity of investigators. A meta-analysis of randomized lipid trials (n=2344) on patients with AS looked into the effects of lipid-lowering therapy on clinical outcomes and stenosis progression, using echographic indicators to measure AS severity. No statistical difference was found between the study and control group.[32] Other randomized controlled trials have not shown a decrease in the progression of aortic valve disease with lipid-lowering therapy. [33, 34] However, all these trials were conducted with the target population already having well-established valve disease and in some cases, older population. With the same hypothesis, Dimitrow et al. investigated the effect of atorvastatin therapy on biomarkers of calcification in patients with early stages of aortic valve disease, i.e. aortic sclerosis. A decrease was noted in the levels of all three biomarkers: osteoprotegerin ( $p < 0.05$ ), soluble receptor activator of nuclear factor (NF)-kappaB ligand ( $p < 0.05$ ), and osteopontin ( $p = NS$ ). [35]

Data exists to show that elevated LDL-C levels have been associated with AVC.[36] Based on this information, Smith et al. investigated the causal relationship using Mendelian randomization approach. They used weighted genetic risk scores(GRS), a measure of genetic predisposition to elevation in plasma lipids in 3 Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), where data from CT imaging was available (n=6942). They showed that the genetic predisposition to elevated LDL-C was associated with early AVC and incident disease. The explanation to this being, although LDL-C plays a role in calcification and mineralization phase of the early disease process, it

may not play a major role in the progression of the disease. Other factors like hemodynamic forces and remodeling may play a vital role in the later stages of the disease process.[37] This is supported by the evidence that in MESA, the association between LDL-C and aortic valve calcium was more among younger participants.[38]

Small dense LDL particles remain in circulation longer, and are able to infiltrate tissue better and get oxidized rapidly. Mohty et al found oxidized LDL(OxLDL) in a high proportion (91%) of the valvular tissue of patients with severe AS. They also found that the valves with higher OxLDL values had significantly higher densities of macrophages, leucocytes and T cells. Valves with the highest OxLDL scores had increased expression TNF $\alpha$ . After adjusting for confounding variables, the percentage of small LDL was significantly associated with the progression rate of peak gradient in the stenotic aortic valves (p=0.03). These findings supports the hypothesis that the accumulation of oxLDL within the valvular tissue may contribute to the inflammatory and calcifying processes leading to Aortic Stenosis (AS). If the atherogenic dyslipidemia characterized by a high proportion of small dense LDL particles in the plasma enhances the accumulation of oxLDL in the valve, aortic valve calcification progresses.[39]

Lipoprotein (A) (Lp(a)) is also a well-known risk factor for ischemic cardiovascular disease. [40] The inheritance and atherosclerotic potential of Lp(a) was first described by Berg in 1963. [41] Over the years, this has been confirmed by multiple observational and genetic studies.[42]The European guidelines on vascular disease prevention in clinical practice [43] and the consensus paper of the European Atherosclerosis Society [40] suggest using Lp(a) levels for risk stratification, as well as for screening in groups at risk. Apart from coronary calcification, it has been shown that genetic variation in the LPA locus, mediated by Lp(a) levels, is associated with aortic valve calcification. [44] Aortic valve leaflets are subjected to more cellular damage than coronary arteries due to repetitive mechanical stress. Lp(a), which is involved in tissue repair then binds to the denuded leaflets, in turn leading to an increase in foam cell formation, inflammation and atheroma formation.

Hemodynamics and molecular mechanisms also play a role in cardiac calcification. The gain of function and loss of function mutations of the Lrp5 receptor and the activation of the canonical Wnt pathway is important in osteoblastogenesis. It has been suggested that in the presence of hyperlipidemia and oxidative stress, the pressure in the heart acts as a mechanism to signal the Lrp5 receptor via the identified mechanostat effect on the protein to signal the Wnt pathway in different locations of the heart. The magnitude of this signal and it's effect is based on the pressure in that region of the heart. Calcification hence develops on the aortic and mitral valves where the pressures are high, whereas there is no calcification on the right-sided valves.[45]

These data support the notion that medical therapy should be targeted towards elevated LDL-C and Lp(a) levels, to decrease the aortic calcification in at-risk individuals, rather than patients with already developed disease. This would also reduce the cost and complications that come with advanced disease and valve replacement procedures. Calcifications of the aortic valve [ 46], as have other extracoronary sites (i.e. – mitral annulus, thoracic aorta), all have been shown to be robust predictors of future events. [40, 47, 48] Similarly,

extracoronary and CAC has been shown to predict future CVD events in stable angina [49] and acute coronary settings,[50] all available with <1 millisievert of radiation with CT scanning.[51]

## 2.6 Mitral valve calcification

Mitral Annular Calcification (MAC) affects the posterior annulus more than the anterior annulus. Its prevalence is reported to be 8–15% in general population and increases with age and in patients with Chronic Kidney Disease (CKD) and multiple cardiovascular risk factors. Though it has been described as a chronic, age-related, degenerative, noninflammatory process in the fibrous support structure of the mitral valve, recent studies have shown a strong association between cardiovascular risk factors and MAC, strongly suggesting that MAC could be another form of atherosclerosis. [52] In a study by Kanjanauthai et al. in the MESA cohort, the characteristics associated with MAC included age ( $p < 0.01$ ), female gender ( $p < 0.01$ ), increased BMI ( $p = 0.03$ ), and former smoking status ( $p < 0.08$ ). They concluded that the risk factors of MAC were largely similar to CVD risk factors in multi-ethnic groups.[53]

In conditions that increase mitral valve stress such as hypertension, aortic stenosis and hypertrophic cardiomyopathy, LV peak systolic pressure and hence mitral valve closing pressure is increased, in turn causing excess annular tension and subsequent annular degenerative calcification. Similarly, the excess annular tension exerted by redundant hypermobile leaflets in mitral valve prolapse also contribute to MAC. [52] In CKD patients, when the calcium-phosphorus product exceeds its solubility in serum, tissue deposition of calcium takes place, producing the characteristic lesion of MAC. MAC has also been commonly noted in congenital conditions such as Marfan's syndrome[54] and Hurler's syndrome[55]. However, the reason for increased incidence remains unclear. Caseous calcification of the mitral annulus (CCMA) is a rare variant of MAC. The inner core of the lesion is filled with material of toothpaste-like consistency, the byproduct of liquefaction necrosis. Histologic examination reveals sterile, amorphous acellular eosinophilic material with macrophage and lymphocyte infiltration. Hemodynamically significant MR, MS can occur with CCMA due to mass effect. [56]

As discussed above, MAC affects the Posterior Mitral Leaflet (PML) more often and as PML motion does not appear to contribute as significantly to gradient creation as anterior leaflet motion. Hence, hemodynamically significant mitral stenosis due to MAC is not very common. Mitral annular calcification can also cause mild to moderate mitral regurgitation (MR) due to loss of annular sphincter function secondary to calcium deposition in the left ventricle base. The calcium extending beneath and elevating the PML renders less surface area is available for coaptation, and MR results. Traction exerted on the chords by the elevated leaflet can also cause chordal elongation and rupture.[56] There are inconsistent results regarding the association between MAC and stroke. [57, 58] MAC is strongly associated with Atrial Fibrillation (AF), and this appears to be partially mediated through left atrial enlargement. The interatrial and intra-atrial conduction processes can also be interrupted by MAC, leading to conduction system and atrial conduction defects, thus resulting in AF. Higher incidence of atrioventricular block, bundle branch block, and

intra-ventricular conduction delay has also been noted in patients with MAC, suggesting that diffuse degenerative conduction system disease is frequently associated with MAC. Severe MAC can cause surgical challenges as well by predisposing to cardiac rupture at the atrioventricular junction, rupture of the LV free wall and injury to the circumflex artery when debridement of MAC is performed. Severe MAC has frequently been considered a contraindication for percutaneous mitral repair in the past and is an independent predictor of permanent pacemaker implantation and reduction in MR improvement following TAVR.

As newer surgical and percutaneous techniques and instruments to overcome the problem of MAC are being developed to reduce the peri-procedural risk of complications, pre-operative use of chest CT could be of vital value. Multiple studies using CT for the detection of MAC have shown high accuracy and reproducibility.[53, 59, 60]. Not only does CT allow for vital anatomical information, but also good measurement reproducibility between different types of scanners allows for following the progression of calcification over time.

## 2.7 Calcification and anticoagulants

Vitamin K antagonists (VKA) have long been the mainstay of oral anticoagulation therapy. Several studies have however revealed that VKA are associated with higher calcification in the heart, both in the coronary arteries and the aortic valve. [61, 62] Koos et al. used CT imaging to quantify coronary and aortic valve calcification in patients on long-term oral anticoagulation with VKA and compared it to those not on anticoagulation. The patients on VKA had higher coronary calcium (p=0.024) as well as aortic valve calcium (p=0.002). [63] The mechanism behind this is that VKA cause decreased activation of matrix Gla protein, which is a potent inhibitor of tissue calcification. On the contrary, patients who are taking oral vitamin K have been noted to have lesser calcification in the heart. [64]

Novel anticoagulants which do not act via the vitamin K pathway might help overcome this problem. Apixaban, an oral direct factor Xa inhibitor was shown to be superior to warfarin in preventing stroke and systemic embolism. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, the rate of myocardial infarction (MI) in the apixaban group was 12% lower than the warfarin group. [65] In another study, rivaroxaban, another anticoagulant which acts via direct inhibition of factor Xa as well, promoted atherosclerotic plaque stability in apo-E deficient mice,[66]by inhibiting inflammatory activation of macrophages[67].

Win et al. conducted a study by comparing coronary plaque volume and composition as assessed by CT imaging in patients receiving VKA versus apixaban. When compared to the apixaban group, the patients receiving VKA had higher calcified plaque ( $\beta_2 = 18.28$ ; p = 0.04), but also had significant progression in total plaque volume ( $\beta_2 = 28.54$ ; p = 0.03), low attenuation plaque ( $\beta_2 = 3.58$ ; p = 0.02) and calcified plaque ( $\beta_2 = 14.10$ ; p = 0.005) after being adjusted for confounding factors. [68, 69] Similar trials are being conducted comparing rivaroxaban to warfarin. (<https://clinicaltrials.gov/ct2/show/NCT02376010>). As CAC progression has a strong association with coronary artery disease(CAD) and mortality, [70] these studies might provide more information for a better selection of oral anticoagulation therapy in atrial fibrillation patients.



## 2.8 Calcification in end stage renal disease patients

Cardiovascular disease is the number one cause of death in End Stage Renal Disease (ESRD) patients. [71] About half of incident dialysis patients have evidence of coronary artery calcification.[72]As kidney function deteriorates, patients are more at risk for coronary calcification. In the Chronic Renal Insufficiency Cohort (CRIC) Study, a strong and graded relationship between CAC and Chronic Kidney Disease (CKD) was observed in 1908 participants with CKD. [73] Other studies that have been conducted have provided varied and conflicting results about the relationship of CAC with CKD. As decreased kidney function is an important predictor of cardiovascular death, [74] and CAC is a predictor of cardiovascular death as well, the association between CAC and CKD needs further clearer understanding.

Abnormal phosphate metabolism in CKD patients could explain the increase in CAC and MAC in this group. As regulation of phosphate metabolism is mainly by the kidney, ESRD patients have a positive phosphate balance due to an imbalance in the phosphate metabolism. This excess phosphate when taken up by vascular smooth muscle cells, stimulates proteins involved in bone formation, thus initiating and promoting calcification.[75] This has led to the hypothesis that calcium-free phosphate binder sevelamer is associated with lesser coronary calcification when compared to calcium-based phosphate binders (CBPB). This was shown in a cross-sectional study by Shantouf et al. in 117 maintenance hemodialysis patients, where the patients on sevelamer had lesser CAC. [76] In Calcium Acetate/ Sevelamer Evaluation Study 2(CARE-2), hemodialysis patients in both groups received intensive statin therapy to lower LDL-C levels. It was then noted that both sevelamer and CPBP groups had similar progression of CAC at the end of one year.[77] Wan et al. in a meta-analysis of 31 studies and 4,395 participants, concluded that sevelamer benefits dialysis patients regarding both coronary calcium and aortic valve calcium.[78] Over time, CT imaging has become an indispensable tool to measure calcification in these studies.

Another topic to be given consideration is that ESRD patients frequently have vitamin K deficiency. This has been studied in patients on dialysis, as well as in individuals with earlier stages of CKD. These patients generally have a lower caloric intake as compared to the general population. Also, their diet is restricted in protein and potassium, which are good sources of Vitamin K. Markers of vitamin K status: undercarboxylated osteocalcin(ucOC), the primary vitamin K-dependent protein in bone and undercarboxylated prothrombin (PIVKA-II), which reflect hepatic vitamin K status and is not affected by kidney function have been studied in CKD patients. [79, 80] However, no study has studied the association of these biomarkers with coronary calcification. As we know, vitamin K antagonist warfarin is associated with increased calcification of the heart. In one study involving dialysis patients, warfarin use was associated with more aortic valve calcium.[81]

## 2.9 Calcification and supplemental preventive therapy

Despite all the above mentioned therapeutic discoveries and more, the battle against cardiovascular disease is long from being won. This emphasizes preventive medicine. Several studies and publications have reinforced this approach to medicine.[82] Apart from diet, lifestyle modifications and risk factor management, supplemental therapies have been

shown to be a vital part of primary prevention. One such therapy is Garlic (*Allium sativum* L.). The beneficial effects of garlic have been long known and described[83], even appearing in ancient Indian texts.[84] The first scientific study regarding this was published in the 1950s.[85] The efficacy, benefits, standardization, and safety of this supplement continues to be documented. [86, 87, 88]

The effect of Kyolic brand aged garlic extract(KB AGE) on coronary calcification has been studied in three studies thus far.[89, 90, 91] In 23 patients with known CAD or high-risk for CAD, Budoff et al. showed that KB AGE reduced the progression of CAC measured by CT imaging when compared with placebo ( $7.5 \pm 9.4\%$  v/s  $22.2 \pm 18.5\%$  respectively,  $p=0.046$ ) over one year.[89] The other two studies used additional treatments along with KB AGE and showed positive results for reducing CAC progression. [90, 91] Apart from CAC, it has also shown a decrease in the progression of low attenuated plaque in patients with metabolic syndrome. [92] Hence, it can be hypothesized that garlic may decrease rates of cardiovascular events, hence warranting further larger trials regarding the cardioprotective effects of garlic.

Another such dietary therapy that is worth a mention as preventive therapy are long chain omega 3 fatty acids/fish oil. The AHA Guidelines have also recommended that patients with CAD should be advised to take omega-3 fatty acids daily. [93] The recent 2017AHA guidelines also recommend treatment with omega-3 fatty acids for patients with clinical CVD. [94]Their effect on coronary calcium is yet to be established. Among 5, 488 participants from the MESA study with no clinical cardiovascular disease, fish oil did not show a beneficial effect on coronary calcification, as measured by CT imaging.[95] However, two Japanese studies found that higher level of serum long-chain  $\omega$ 3 fatty acids correlated with and a lower incidence of CAC in Japanese men, [96]when compared to Caucasian men, [97]though clear association could not be shown. Trials to determine the effect of different types of fish oil on coronary calcification and the variable results it may have on different patient populations are being done. [98]

### 3. Conclusion

CT imaging and CAC continues to be a globally expanding tool in the field of cardiology research. Valvular calcification share risk factors and some similarities with atherosclerosis. With the vast data available, CAC can potentially be used as a CAD risk stratification tool. An understanding of the pathophysiology of cardiac calcification will aid in the development of newer therapeutic avenues and thus help tailor management to specific target populations. Along with CAC, utilizing CTA would give a more comprehensive data set inclusive of other parameters like total plaque burden, vulnerable plaque features, the degree of stenosis and ischemia which could be imperative in clinical scenarios as well as research studies.

### 4. Expert commentary

More than 2,500 peer-reviewed papers have investigated into coronary artery calcium for risk assessment in the asymptomatic population. CT scanning provides a distinct means of detecting and quantifying coronary calcification as well as valvular calcification with

excellent reproducibility. The event rate in patients with a CAC score of 0 is meager and represents a population who is largely going to remain free of ASCVD for at least a decade. CAC has been shown to positively affect initiation of and adherence to medication and lifestyle changes. Multiple therapies (ie sevelamer, garlic, ACE inhibitors) have shown to lower progression of coronary calcification, hence being beneficial in slowing progression of atherosclerotic disease. CAC efficiently uncovers higher-risk patients who most need to be treated and identifies those who will most benefit from therapy, irrespective of risk factors. CAC screening has also proved beneficial in different patient populations including diabetics. As CAC represents the early manifestation of atherosclerosis, it is the best-known stratifier of ASCVD risk. The presence of atherosclerosis visible on CAC scan is a better indicator of CAD than risk factors of heart disease, and this has been validated in multiple large epidemiologic and cohort studies. Serial CAC scanning deserves consideration when there is a clinical dilemma during assessing treatment response or residual disease, as those with CAC progression are at increased risk of future CVD, independent of risk factors and baseline CAC score. CAC progression, in multiple studies, has been associated with a 5–8 fold increased risk of events and may identify those persons who have active atherosclerotic activity, and those without CAC may have quiescent disease. Further studies are also warranted. The low radiation dose and non-invasive nature of the test make repeat scanning less of a problem. Another advantage to CAC screening is that it can also be incorporated with other imaging studies. Although low dose CT chest scanning is not ideal for CAC measurement, ECG gating can be done during the scan without any increase in radiation. This makes CAC screening possible in patients undergoing lung CT if needed. Recent validated techniques for measuring bone mineral density on the CAC scan images has made screening for osteoporosis cost effective and more convenient for the patient as well. Research involving newer modalities of treatment for cardiovascular disease are increasingly using CT scanning for CAC assessment as well as CTA for non-calcified plaque assessment. It's accuracy and excellent reproducibility adds to its value in research studies. Over the past couple of decades, CAC screening has come a long way and is now being incorporated into guidelines in many countries, notably the NICE guidelines in the United Kingdom. The Net Reclassification Index (NRI) data showed the ability of CAC score to personalize treatment to the individual, rather than extrapolate treatment from risk-factor based strategies derived from large global population studies.[99] As discussed above, treatment strategies that are being developed for valvular calcification also are using CT scanning for measurement of calcification. Though coronary calcium is a strong predictor of cardiovascular events, coronary CT angiography provides more data on parameters that are known to influence cardiovascular event risk. Hence, utilizing CTA would give a more comprehensive data set which could be imperative in research studies.

## 5. Five-year view

Coronary calcium scanning will continue to increase in utility, with guidelines supporting its use in asymptomatic cohorts for ASCVD risk stratification. Studies continue to be published demonstrating the superiority of coronary artery calcium as compared to other risk stratification tools (i.e., Pooled Risk Cohort, c-reactive protein, carotid intima-media thickness). As studies continue to emerge demonstrating superior survival and ability to

improve delivery of medications (matching intensity of therapy with the intensity of risk), the utility will climb. The ancillary measures available on these tests (i.e., valve calcification, bone density, assessment of non-alcoholic liver disease, epicardial/visceral fat) will increase the cost-effectiveness of these tests allowing for evaluation of multiple conditions with one scan.

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\* of interest

\*\* of considerable interest

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### Key issues

- Coronary calcification and extra-coronary calcification like aortic valve calcification have been shown to be robust predictors of future cardiovascular events. This can be identified and quantified by Cardiac Computed Tomography(CT) imaging and has hence been a critical tool in studies involving new therapies for cardiovascular disease.
- Even in groups considered as high risk per traditional risk stratification, a favorable prognosis has been noted in individuals with CAC=0. Statin therapy has shown decreased rates of CAC progression. Hence, the absence of CAC could serve as a factor in the reclassification of risk groups and management algorithms.
- Elevated LDL-C, small LDL particles, oxidized LDL and Lp(A) levels have been associated with Aortic valve calcification.
- Vitamin K Antagonists like warfarin have been associated with higher rates of calcification in the heart. Novel anticoagulants, which do not act via vitamin K pathway have been shown to bypass this problem.
- As kidney function deteriorates, patients are more at risk for coronary calcification, which could be attributed to abnormal phosphate metabolism. Some studies have shown that sevelamer hence has a lower rate of coronary calcium progression than calcium-based phosphate binders.
- Supplemental therapy with aged garlic extract is being studied and has shown to reduce coronary calcium as well as low attenuated plaque progression.
- Though coronary calcium is a strong predictor of cardiovascular events, coronary CT angiography provides more data on parameters that are known to influence cardiovascular event risk. Hence, utilizing CTA would give a more comprehensive data set which could be imperative in research studies.