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Review Article

Coronary Artery Calcification: A 'Rock Solid' Cardiac Test?

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2. Keywords

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1. Absract

Coronary Artery Calcification (CAC) is very well studied and documented marker of coronary atherosclerotic burden. This has been confirmed by various techniques. It has been shown to have a strong incremental value to Framingham cardiac risk score assessment. It significantly helps reassess the cardiac risks in genders, asymptomatic people, diabetics, patients with kidney disease and hypertensive.

1.1. Case report 1: A young man of Indian origin living in North Carolina was visiting India where he was noted to have chest pains. During work up there, he was asked to have his coronary artery calcium score which came back very high at 1305. He was placed on some medications and came back to the US and had coronary angiography with 3-vessel Coronary Artery Disease (CAD) requiring stents of multiple arteries.

1.2. Case report 2: A professional colleague of mine, a 61-year-old MD with dyslipidemia, diabetes, hypertension and GERD underwent a stress echo for frequent palpitations. His stress test was unremarkable. Because of continued palpitations, CAC was requested for further evaluation. It came back as 535 which is quite high. Based on this very high score in the setting of multiple cardiac risk factors and recurrent palpitations, he underwent coronary angiography which was completely normal! Something did not make sense here: was the CAC reporting was incorrect or there were artifacts being seen as CAC? Does one need to review the coronary angiography report?

1.3. Case report 3: Our current US president, Mr Trump has CAC reports in the news:

He is 70-yr old with CAC score of 34 in 2009, 98 in 2013 and 133 in 2017 which is obviously more than 100 and thus high risk for CAD events. A score more than 100 indicates a 10-fold higher risk of future myocardial infarctions. Obviously we do not know the complete cardiac history of our current President, however based on this latest CAC score, he will be well advised to pursue aggressive lifestyle modifications: regular exercise, weight loss, BP control, watching his HbA1C and statin therapy.

Based on the fact that the Presidents get their CAC score frequently, I would imagine that this cardiovascular marker must have a solid validity and therefore it should be considered for public at large and I will review the data to see if the evidence supports this conviction.

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3. Intuduction

CAC is sine qua non with atherosclerosis. It is one surrogate marker that is almost always consistent with atherosclerosis/CAD. In addition, it can reduce vascular compliance and impair myocardial perfusion [1]. Physicians in general love the numbers: Blood pressure, blood sugar, HbA1C, weight, Body Mass Index (BMI), lipid profile, Prostate Specific Antigen (PSA), cancer markers and so on. Therefore, it is imperative that we would embrace the CAC right away. However this issue is somewhat more complicated and therefore we will review the CAC literature.

4. Pathogenesis

Atherosclerosis is known to be a chronic inflammatory process where various components of the immune system may be involved. High plasma lipid concentration may initiate the process of atherosclerosis. Endothelial cells, leukocytes and intimal smooth muscle cells as well as other traditional/conventional risk factors such as smoking, hypertension and diabetes all play an important part in the process of atherosclerosis. Alkaline phosphatase enzyme which is the main enzyme mechanism for bone formation is equally as important for CAC and is considered a molecular marker of vascular calcification [2]. Mineralization in the vascular intima and media and calcific deposits are regulated by mostly by vascular smooth muscle cells and also by other cells including micro vascular pericytes, adventitial my fibroblasts etc [3]. Coronary calcification is mostly considered an actively regulated process and not passive calcium deposition. Certain chemicals/ matrix proteins are produced by vascular pericytes-like cells, smooth muscle cells or foam cells. These could be osteopontin, osteonectin, Osteoprotegerin (OPG) and a few others. OPG has been shown to be markedly elevated and correlates well with higher CAC in asymptomatic diabetics and patients with chronic renal disease. Calcification might start as early as the second decade of life into fatty streaks and grows progressively into various stages of plaque lesions (Stage IV to VII).

5. Clinical Perspective of CAC?

A number of studies have demonstrated the following findings:The amount of coronary calcium correlates well with the atherosclerotic burden where it represents about 1/5th of the total burden.

1. The amount of calcium does not correlate with the severity of angiographic coronary stenosis and this is most likely due to the remodeling process whereby there is an increase in size of the arteries compensating for the atherosclerotic plaque.

2. Furthermore, presence and extent of calcification do not predict the future risk of plaque rupture. As a matter of fact, there are various theories regarding the effect of calcium on plaque stability:

3. There are experts believing that calcification may stabilize the plaques directly while others think it could be the result of plaque rupture, a kind of protective phenomenon and thus helping heal the plaque and reduce the future likelihood of plaque rupture.

4. Abedin et al. suggest that the vessel is rendered less vulnerable to rupture only when extensive calcification has occurred whereas the early stages of calcification may actually increase plaque vulnerability. It has been shown that calcified atherosclerotic plaque is 5 times stiffer than cellular plaque. In the initial stages of calcification, plaques are most prone to rupture at areas of interface between high- and low-density tissues [4-10].

5.1. There are two kinds of CAC recognized

1. Atherosclerotic CAC: Calcium deposits are typically found in the intima. Inflammatory mediators and dyslipidemic elements induce osteogenic differentiation of vascular smooth muscle cells within the atherosclerotic lesions in the intima causing CAC.

2. Medial artery calcification (Monckeberg's sclerosis): mostly associated with advanced age, diabetes and chronic renal disease and is known to cause adverse cardiovascular events [4].

Higher is the CAC score, more is the atherosclerotic plaque burden. At least one study has reported that recurrent plaque rupture and hemorrhage with subsequent healing might result in the development of obstructive fibro calcific lesions and these kinds of findings are seen in patients with stable angina and sudden coronary death [5].

6. Prevalence of CAC

CAC is age and gender dependent and occur in 90% of men and 67% of women older than 70 years of age. CAC is most frequent in Caucasians and much less common in Hispanics and African-Americans. Greater the CAC score, worse the degree of atherosclerosis and more future cardiac events [11-3].

7. Association with Diabetes

There are reports of advanced glycation end-products promoting mineralization of micro vascular pericytes and tight glycemic control might slow CAC in type 1 diabetes [6]. Patients with diabetes have higher prevalence of CAC and higher score of CAC and that is consistent with higher grade of vulnerable plaques in the coronaries [7]. However it has been reported that it could be the obesity than glycaemia in diabetic patients responsible for pathogenesis of CAC as noted in the Framingham Heart Study

that once BMI was adjusted, CAC had no strong relationship to fasting blood sugar in these patients [8].

8. Association with Chronic Kidney Disease (CKD)

It is well documented that the patients with CKD have greater cardiovascular morbidity and mortality most likely due to the presence of CAC and accelerated atherosclerosis. Hypercalcemia and hyperphosphatemia are known to stimulate CAC as well. CAC can be quite high in younger patients undergoing renal dialysis. However there are other reports not showing any strong relationship between CKD and CAC.

9. Diet, Calcium Intake and CAC

High calcium diets have not been to shown to cause/increase CAC score. There has been no documented relationship between the dietary intake of calcium and CAD [9].

10. Cardiac Risk Factors: Correlation with CAC

Conventional risk factors are able to predict only about two-thirds of those patients who will eventually develop CAD. About one third of patients dying of CAD in the US are classified as being low risk with the Framingham Risk index score. Also about 50% of patients with newly diagnosed CAD, the first presentation is either MI or sudden cardiac death. In addition, the conventional risk factors are associated with increase/higher CAC score: Advanced age, diabetes, dyslipidemia, hypertension, male gender, hyperphosphatemia in renal failure and tobacco smoking. Commonly used traditional risk algorithms include the Framingham Risk Score (FRS), PROCAM score (Prospective Cardiovascular Munster), the European risk prediction system called SCORE (Systemic Cardiovascular Risk Evaluation) predict the 10-year absolute risk of cardiovascular events. Novel risk factors have been proposed to be added to enhance the disease detection, more so in asymptomatic patients including homocysteine, fibrinogen, lipoprotein A, C-reactive protein and CAC score. Amongst all of these, CAC score provides the best incremental risk stratification. 2/3 of men with heart attacks are considered low risk by Framingham Risk Score and do not qualify for lipid lowering agents until after their initial heart attack. CAC identifies them and gives us a chance to make a difference before the first MI. CAC score can detect and accurately quantify subclinical CAD in coronaries to refine the current risk stratification strategies. The prevalence of coronary calcification is significantly higher in subjects with traditional cardiovascular risk factors such as hypertension, diabetes, obesity, infrequent exercise, previous smoking, and hypercholesterolemia. There is a significant, continuous graded relationship between prevalence of coronary calcium, mean CAC scores, and the number of risk factors. The prevalence of CAC deposits is 40% in asymptomatic men aged younger than 60 years with no risk factors as opposed to 74% in those with three or more risk factors. However, in older men (>60 years of age), the prevalence of CAC deposits is more than 80% regardless of the number of risk factors present. In a recent study, CAC measurements in the second- and third-generation descendants of original Framingham cohorts were performed and showed that parental premature cardiovascular disease was associated with a significantly high likelihood of coronary calcification in the offspring.

11. Methods of CAC Detection

Conventional fluoroscopy gave the very 1st impression of CAC in 1950s, however recent revolution in CT scanning technology made the EBCT (Electron-Beam Computerized Tomography), the method of choice for CAC detection. Further improvements in CT technology included: helical/spiral CT, 16- and 6-slice scanners, and finally 320-detector machines that can scan it in a heartbeat or two. The radiation dose can be in the range of 0.8-1.3 mSV (average of 1 mSv). MSCT (Multi slice CT) scanners have a great resolution as well with similar radiation dose range and similar accuracy and reproducibility. CT-scan–based CAC scores are known to add prognostic value for predicting MI and cardiac death, more so in patients at intermediate risk for cardiac events. The most recent American College of Cardiology/American Heart Association guidelines recommend that noninvasive measurement of CAC score is reasonable for cardiac risk assessment in asymptomatic patients at intermediate risk (those with a 10- 20% rate of coronary events over 10 years; class IIa, Level of Evidence: B) [14,15].

There are at least two more methods of CAC scoring which are invasive: Coronary angiography and IVUS (Intra Vascular Ultra Sound). Angiographic CAC can be divided into 3 groups: none/mild, moderate, and severe. Severe calcification is most commonly defined as radiopacities seen without cardiac motion before contrast injection, usually affecting both sides of the arterial lumen, and moderate calcification as radiopacities noted only during the cardiac cycle before contrast injection [16]. IVUS is much more accurate than coronary angiography for CAC detection with sensitivity of 90-100% and specificity of 99-100% [17]. The calcified plaque on grayscale IVUS is a bright echo with acoustic shadowing and the extent of calcification can be well graded.

12. CAC Score: Agatston Score

12.1. Methods of calculation

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

12.2. Density factor

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

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

12.3. Guidelines for coronary calcium scoring by 2010 ACCF task force

- 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)

12.4. 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

12.5. Coronary Calcium Score Interpretation

Based on a number of studies, the following definitions are used to relate the coronary artery calcium score to the extent of atherosclerotic coronary artery disease:

- Coronary calcium score 0: No identifiable plaque. Risk of coronary artery disease very low (<5%).
- Coronary calcium score 1-10: Minimal identifiable plaque. Risk of coronary artery disease low (<10%).
- Coronary calcium score 11-100: Definite, at least mild atherosclerotic plaque. Mild or minimal coronary narrowings likely.
- Coronary calcium score 101-400: Definite, at least moderate atherosclerotic plaque. Mild coronary artery disease highly likely. Significant narrowings possible.
- Coronary calcium score > 400: Extensive atherosclerotic plaque. High likelihood of at least one significant coronary narrowing.

In an American College of Cardiology Foundation/American Heart Association (ACCF/AHA) consensus, data from 6 large studies that collectively included 27,622 asymptomatic patients were aggregated and the relative risk of major cardiovascular events was calculated for patients with a positive CAC score and for those with a CAC score of zero. The following results were obtained (28):

- - CAC score of 100-400: relative risk of 4.3 (95% CI:3.1-6.1);
- - CAC score of 401-999: relative risk of 7.2 (95% CI:5.2-9.9);
- - CAC score > 1000: relative risk of 10.8 (95% CI:4.2-27.7).

13. CAC Scoring: PROS and CONS

13.1. PROS of CAC Scoring

13.1.1. Reclassifying Intermediate Risk Patients: A novel risk factor eg C - reactive protein (CRP) can reclassify 1-6% people, while the CAC score can reclassify as much as 50% people. In MESA (Multi-Ethnic Study of Atherosclerosis), 65.9% people were properly reclassified using the CAC score [18]. Similarly in the St Francis Heart Study, 55% the study participants were reclassified (16% to high risk and 39% to low risk) [19]. In addition, by doing so, it has been proven that CAC scoring is then definitely cost-effective and promotes more compliance to medical therapies [20].

13.1.2. Health Care Costs: 50% intermediate risk patients have CAC score of zero which means the risk of heart attacks and cardiac death is very low (<5%) over the next 10 years. Knowing so may avoid expensive tests and unnecessary medications as demonstrated by one study, EISNER where patients were randomly assigned to CAC scoring or no testing and those with zero score were found to have lower healthcare costs for the next 4 years [21].

13.1.3. Improving Current Cardiac Risk Models: Most cardiac risk score models are imprecise and may overestimate the risk. For example Framingham Risk Score method overestimates the risk category. CAC score does help to reclassify proper risk group in about 50% people. The 2013 ACC/AHA cholesterol treatment guidelines and the 2016 US Preventive Services Task Force guidelines use this calculator to determine statin eligibility and numerous studies have shown that it overestimates risk. Overestimating

risk based on this model raises the possibility of more than a billion people worldwide taking statins [22].

13.1.4. Lifestyle Change Motivation: People who know that that their coronary arteries are full of calcium will definitely be motivated to make healthy lifestyle changes. A meta-analysis of 6 studies with more than 11,000 patients found a 2-3 fold increase in the initiation of aspirin, lipid-lowering drugs, BP–lowering drugs and lifestyle changes in those with calcium versus those with a zero CAC score [23]. CAC is a strong motivator for behavioral change and by measuring serial CAC, we can determine the subjects with residual risk after the initial trial at therapy.

13.1.5. Improved Cardiac Care: Better risk prediction of cardiac events may improve decision-making. For example, statins reduce the risk for a cardiac event by, say, 25%. By having more precise cardiac risk prediction with CAC score, a 25% reduction in someone with a 15% 10-year risk for an event is much bigger in absolute terms of risk reduction than a 25% reduction in someone with only a <5% 10-year risk (no or very low calcium). A study of 4778 participants from three US cohorts, with a mean age of 70.1 years found that CAC score was superior to age in discriminating between lower and higher coronary heart disease risk in older adults. CAC score was more likely than age to provide higher category-free net reclassification improvement among participants who experienced an atherosclerotic cardiovascular disease [24].

13.1.6. Personal Experience of MDs:

A. Growth or stability of coronary calcium correlates very strongly with event risk. I have found that when a patient has a repeat calcium score and it is increasing by more than 15% annually, it is the strongest motivator for behavioral changes that I have ever seen.

B. The study MESA has demonstrated that while carotid US is twice as powerful as traditional risk factors to determine heart attack risk, coronary calcium is ten times more powerful than all traditional risk factors. The radiation of <1 msv (the same as a mammogram) should not be considered a reason to not screen for the disease that kills one out of four Americans. People living in Colorado get >2 msv more cosmic radiation annually than someone at sea level.

C. Those who are determined to qualify for a statin based on traditional risk factors, in the best circumstances, demonstrate <50% compliance after 1 year. One study demonstrated a 91% compliance with statin therapy after 3 years based on calcium scores in the top quartile.

13.2. CONS of CAC Scoring

13.2.1. Radiation exposure and Health care: In 2014, Dr Steven Nissen from the Cleveland Clinic, Ohio had to response in response to being asked about CAC score test and his answer was: "Exposing patients to radiation in order to motivate them…take a deep breath and think about that." Well, he might be right in so many ways. On an individual level, 1-2 mSv exposure to one person at one time may do no damage, however on a societal level, this recommendation to millions over the years may exposure to cancer risks and there are data in this regard. In addition, one can mention here an interesting observation from The EISNER trial studying CAC screening effects on medical management, reported "statistically" positive results. However, this trial is a classic case of statistical significance not equating to clinical significance. Participants who underwent scanning had an incremental 2–mmHg drop in systolic blood pressure (–7 mmHg vs –5 mm Hg) and an incremental 6-mg/dL drop in LDL cholesterol (–17 vs –11 mg/dL) compared with those who did not. Needless to say, these changes will not make any meaningful clinical outcome to the patients' health [25].

13.2.2. Lack of Randomized Trials: There is one meaningful trial worth mentioning: In the single-center St. Francis heart study, approximately 1000 people with a CAC score above the 80th percentile for their age and gender were randomly assigned to atorvastatin 20 mg daily or placebo. The rate of cardiac events was lower in the statin group, however this did not reach statistical significance (6.9% vs 9.9%; P=0.08) [19]. There are no other adequately powered outcomes trials on CAC screening that can be reported here.

13.2.3. Incidental Findings and Higher Health Care Cost:

One problem using CAC score as a screening test is that it can lead to further tests and many a times that is unnecessary and also might hurt the patients in process in addition to adding up health care costs. Moreover, many a times there are incidental findings which might even be benign and might lead to further work-up and higher cost again. Therefore it is not that uncommon to see sometimes patients having nuclear scans and coronary angiography even though the CAC could have been zero!

14. CAC and Statins: Plaque Paradox!

Statins work to stabilize plaques by converting softer, cholesterol-filled plaques that are prone to rupture into more stable calcified plaques that are relatively inert. In one analysis, the most aggressively treated patients—the high-intensity statin patient—if anything developed more calcification! The paradoxical relationship between atheroma regression and increases in coronary calcium also suggests that the relationship between statins and coronary calcification is poorly understood. The CAC score or its progression might not be as predictive once plaque-altering treatment statins are initiated [26-8]. Increase calcification might be a part of plaque stabilization and therefore all calcium are not the same?

It might be the "spotty calcification" found within the coronary tree, the plaques which seem more resistant to statin therapy and more frequently found within culprit lesions of patients presenting with acute coronary syndromes.

15. Summary: CAC is a Presidential Score

President Clinton while in the office was deemed to be in great cardiac health and his statin was discontinued. Soon after leaving the office, he underwent an Emergency room visit and thought to have GI issues. However further work up led to coronary angiography and cardiac bypass surgery. At the time of his surgery, CAC score was reported to be more than 1000! Needless to say, if this score was available to President Clinton's physician's way before his heart condition was diagnosed, the approach of management would have been very different! Even though, President Clinton did not benefit from this score, since then it has become a part of presidential physical examination and thus subsequent Presidents Bush, Obama and Trump have had their CAC score measured. Calcium Score is like the "mammogram of the heart" and is inexpensive, produces similar radiation exposure as a breast mammogram, and will inform your patients for the next 5 years if they are at increased risk for a heart attack or cardiovascular death. President Clinton didn't get a CAC score while in the White House; he ended up with emergency bypass surgery. President Trump has a moderately elevated score and now he has the opportunity to potentially avoid a similar fate. The new guidelines also state: "If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of one or more of the following—family history, hs-CRP, CAC score, or ankle brachial index-may be considered to inform treatment decision making." CAC equals atherosclerosis and there is no stronger predictor of cardiovascular events. The American College of Cardiology/ American Heart Association Guidelines state: "Assessing CAC is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment." [29].

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