Article published online: 2021-07-31

Coronary calcium score: An Indian scenario and experience

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Introduction

The World Health Organization (WHO) has predicted that by A.D. 2020, up to three quarters of deaths in developing countries will result from noncommunicable diseases and that coronary heart disease (CHD) will top the list of killers.[1] The incidence, prevalence, hospitalization and mortality from CAD in Asian Indians are three to four times higher than in their European and American counterparts and even higher in comparison with other Asians. Atherosclerosis in young Asian Indians and their high morbidity and mortality from CAD can be attributed to a unique pattern of dyslipidemia, a 'deadly lipid tetrad'. This lipid tetrad consists of elevated lipoprotein A in combination with the lipid triad.[2]

Patients are usually diagnosed with CAD when they develop symptoms, display an abnormal response to stress testing or undergo coronary angiographies. Unfortunately, by that time, the atherosclerotic process is relatively advanced and many patients already have had myocardial infarction or have activity-limiting angina. In many ways, the opportunity for prevention may have been missed or, in retrospect, delayed, in these patients.

Therefore, early detection of CAD could impact this scenario significantly by accelerating prevention efforts and positively impacting patient lifestyle choices, before the development of clinical manifestations of heart disease.

Pathophysiology

Atherosclerotic calcification begins as early as the second decade of life.[3] Calcific deposits are found more frequently and in greater amounts in elderly individuals and more advanced lesions.[4] It is known that calcific plaques are also more in diabetics then nondiabetic. Calcium phosphate (hydroxyapatite, Ca_3 [-PO_4]$_2$ ×Ca [OH] $_2$), which contains 40% calcium by weight, precipitates in diseased coronary arteries.[5]

Technical Issues

Tanenbaum *et al* were the first to report the use of electron-beam CT (EBCT) for detecting calcific deposits in the coronary arteries.[6] In 1992, Agatston *et al*[7] reported the first large clinical series in which EBCT was used to detect calcification in the coronary arteries.

There are currently two CT calcium-scoring systems widely used: the original Agatston method and the "volume" score method.

The Agatston scoring[7] scale is rule-based: Calculate an area for all pixels above a threshold of 130 HU, do so every 3 mm (the slice thickness and spacing used by Agatston *et al*) and multiply it by a density factor. Partial volume effects lead to higher peak values for small lesions (but not for large ones). If the change in peak value happens to be such that it changes the density factor, then it can, theoretically, change the score by a factor of 4.

The "volume" method of Callister *et al*[8] somewhat resolves the issue of slice thickness and spacing by computing a volume above threshold. The volume score is much less dependent on minor changes in slice thickness.

The calcium mass score has recently been reported. Data published by Rumberger *et al*[9] showed that the Agatston, volume and mass scores, when applied properly, can provide similar characterization.

Two basic pieces of information are provided by the CS evaluation:

1. Qualitative evaluation of the presence or absence of coronary calcium.
2. Quantitative evaluation of the degree/extent of calcification

No patient preparation is required. No contrast is required. The presence of a radiologist is also not essential. It is a single

breath-hold study. It may be performed on any multi-slice scanner of 4-slice configuration or higher. On a 64-slice CT scanner, it is a retrospective ECG-gated study with a slice collimation of 30 x 0.6 mm, rotation of 330ms, slice width 3.0, pitch 0.2, kV 120, mAs 300 and a Kernel of 35f.

I highly recommend retrospective reconstructions in at least two phases to get the right CS [Figure 1]. In patients with stents or in those who are post-bypass, a CS study need not be performed.

The axial data is fed into the software, which utilizes only those areas measuring greater than 130 HU and computes the number of lesions, equivalent mass of calcium hydroxyapatate and the score [Figure 2]. It is called the Agatston Equivalent Score as it is done on MSCT and a calibration factor needs to be used. Based on the score, the risk of CAD can be judged [Table 1].

Given this basic information, here is a list of frequently-asked questions (FAQ).

What does coronary calcification exactly mean?
It means that there is atherosclerosis in this vessel. Coronary calcification is nearly ubiquitous in patients with documented CAD[10-12] and is strongly related to age, increasing dramatically after age 50 in men and after age 60 in women. Calcium volume represents one-fifth of the total plaque burden[13-14] (calcified plaques are a tip of the iceberg of atherosclerotic plaques).

What are the sensitivity and specificity of the CS study?
A positive study is nearly 100% specific for atheromatous coronary plaque,[15-19] but is not highly specific for obstructive disease, as both obstructive and nonobstructive lesions have calcification present in the intima.

A large multicenter study on EBCT for diagnosis of obstructive CAD in symptomatic persons (n=1851) found that the sensitivity and specificity of coronary artery calcified plaques were 96% and 40%, respectively.[20]

Can we use this test to predict luminal narrowing?
There is no one-to-one correlation, but a high CS is a predictor of possible underlying stenosis [Table 2].[21]

Some individuals and institutes do not proceed with CT angiography (CTA) when the CS is high. Though no large study is available to prove or disprove these methods, in my set-up, I proceed with CTA, irrespective of the high calcium score [Figure 3].

How is CS useful in an asymptomatic patient?
Asymptomatic individuals can be categorized into three levels of risk i.e. high risk (>20% risk in 10 years),

Table 1: Interpretation of calcium scores

Calcium score	Plaque burden	Probability of significant CAD	Implications for CV risk
0	No identifiable plaque	Very low, generally < 5%	Very low
1-10	Minimal identifiable plaque burden	Very unlikely, < 10%	Low
11-100	Definite, at least mild atherosclerotic plaque burden	Mild or minimal coronary stenoses likely	Moderate
101-400	Definite, at least moderate atherosclerotic plaque burden	Non obstructive CAD highly likely, although obstructive disease possible	Moderately high
>400	Extensive atherosclerotic plaque burden	High likelihood (>90%) of at least one significant coronary stenosis	High

CAD - Coronary artery disease

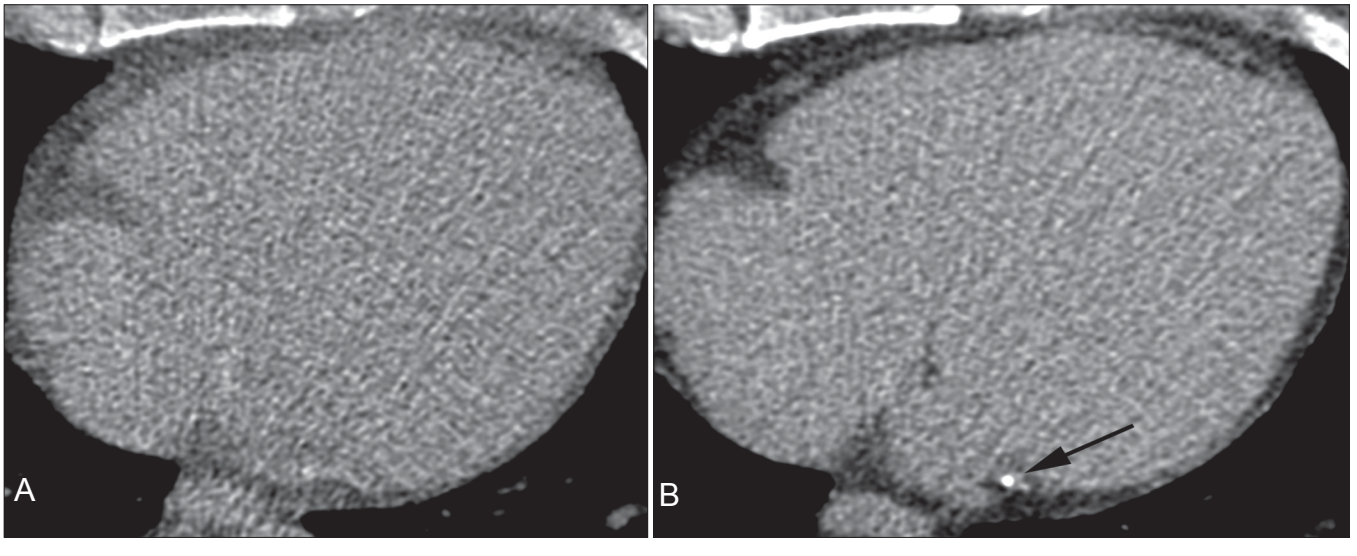

Figure 1 (A-B): The CS raw data image (A) shows no obvious calcification at 55% R-R reconstruction, whereas the calcified plaque (arrow) is well seen in the circumflex artery at 65% reconstruction (B).

Table 2: CS v/s obstructive coronary artery disease

Study	Total No. of Pts.	Sensitivity (%)	Pts with obstructive disease	Specificity (%)	Pts without obstructive disease
Rumberger et al	139	98	65	39	74
Budoff et al	710	95	427	44	235
Kajinami et al	251	91	133	50	118
Total weighted average	1100	95	625	46	475

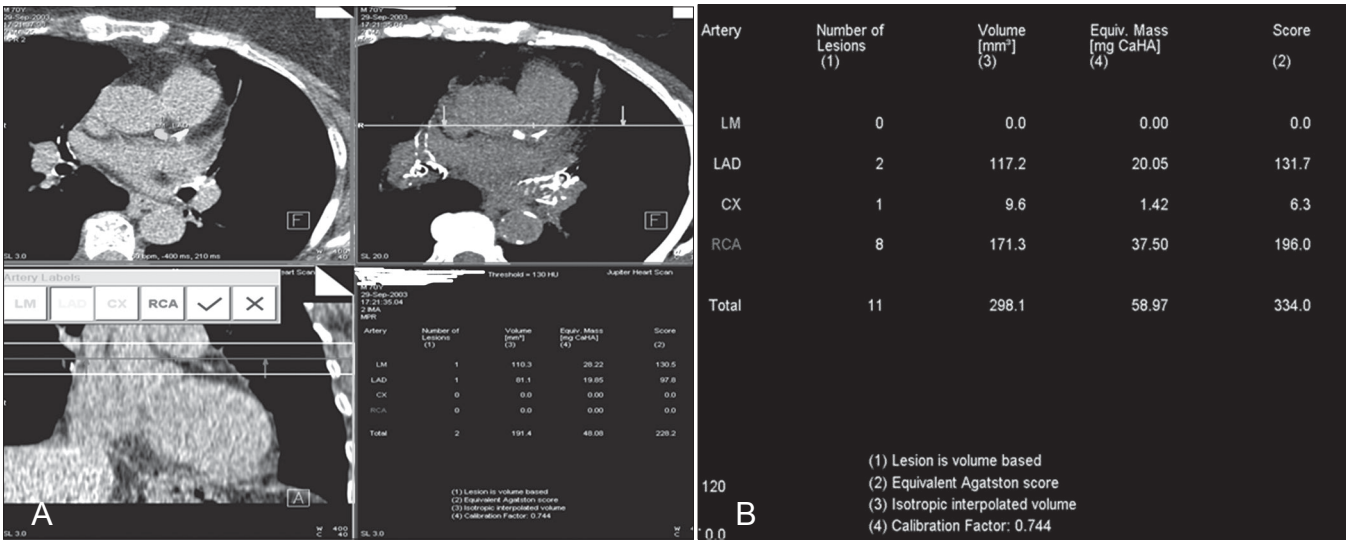

Figure 2 (A-B): Method of calcium score measurement. The LAD calcium (A) is identified by the computer (arrow) and the score is then obtained (B).

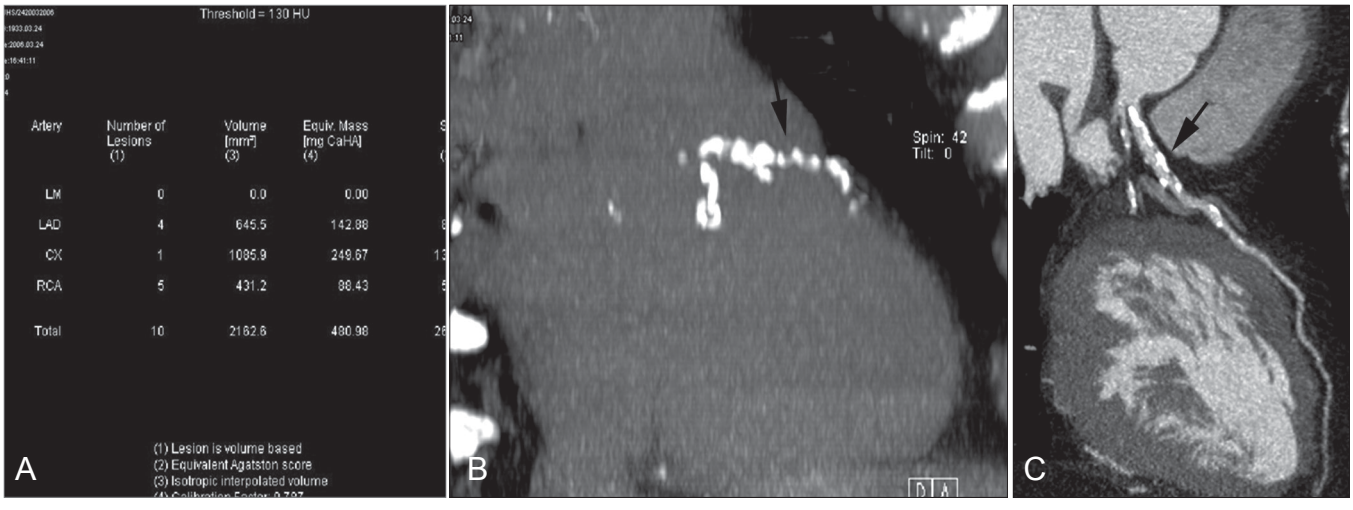

Figure 3 (A-C): The CS is 2685 (A), with dense calcium seen along the LAD (B). The lumen is still however well seen (C).

intermediate risk and low risk (<10% risk in 10 years) for CHD. Data from Greenland *et al*[22] demonstrated that intermediate-risk patients with an elevated CS score (intermediate Framingham Risk Score (FRS) and CS > 300) had an annual hard event rate of 2.8% or a 10-year rate of 28% and thus would be considered high risk. This would mean that the estimated risk in the intermediate patient with a CS score of 0 might be reduced by at least two-fold, while the risk of a person with a CS score of > 300 would be increased by about two-fold. Thus, the person with high CS and intermediate FRS is now reclassified as high risk. If the calcium score were 0 or very low, the patient's post-test risk assessment would be reduced. Low-risk (<10% 10-year risk) and high-risk (>20% 10-year risk) patients do not benefit from CS measurement (Class III, Level of Evidence: B).[23]

Therefore a positive or negative scan in the intermediate group can help reclassify individuals into higher or lower risk groups respectively and therefore further support instituting or withholding long-term preventive measures.

What does positive scan mean and how does it help in treatment decisions?

This is the first time that the AHA evidence-based scoring

system[24] has been incorporated into the AHA's evaluation of cardiac CT. The purpose of the scoring system is to assist the clinician in interpreting these recommendations and formulating treatment decisions. A positive scan[24] means:

1. It confirms the presence of coronary atherosclerotic plaque.
2. The greater the amount of calcification, the greater the likelihood of obstructive disease, but there is no one-to-one relationship and findings may not be site specific.
3. The total amount of calcification correlates best with the total amount of atherosclerotic plaque, although the true "plaque burden" is underestimated.
4. A high calcium score may be consistent with moderate-to-high risk of a cardiovascular \ event within the next two to five years.

EBCT has also been used to monitor the change in calcium score with statin therapy. In a retrospective study of 149 men and women with no history of CHD, 105 were treated with a statin and of those, only patients whose LDL-C was reduced to <120 mg/dl had a mean relative decrease in calcium score (p=0.01).[25]

One study claims statins reduce risk by only 30% and a direct measurement of change in atherosclerosis burden may provide a clue to the persistent risk measured in subjects at risk.[26] However another study failed to show a significant effect of statins on outcomes when calcium scores were high (*P*=0.08).[27]

Several large observational studies, such as MESA (utilizing both EBCT and MDCT)[28] and RECALL (using EBCT),[29] are currently under way to also assess the prognostic value of increasing CS burden in population-based samples.

What is the indication for doing a CS study independently?

The European Cardiovascular Guidelines state, "The calcium score is an important parameter to detect asymptomatic individuals at high risk for future CVD events, independent of the traditional risk factors."[30]

The Screening for Heart Attack Prevention and Education (SHAPE) task-force report, appearing as a Pfizer-funded supplement to the *American Journal of Cardiology*[31] recommends screening of all at-risk men between the ages of 45 and 75 and all women aged 55 to 75 years, unless they have none of the following: cholesterol >200 mg/dL, blood pressure >120/80 mm Hg, diabetes, smoking, family history or metabolic syndrome.

What does a negative CS mean to an asymptomatic individual?

It means[32] that the presence of significant luminal obstructive disease is highly unlikely. A zero score is associated with a low risk for a cardiovascular event in the next two to five years.

How good is the reliability and reproducibility of results on follow-up?

When doing a repeat study, the following needs to be taken into consideration:

- The same generation scanner should be used
- Heart-rate (HR) should be acceptable
- Mass equivalent should be used for subsequent follow-up
- Exclude pericardial and/or mitral valve calcification [Figure 4]

The AHA Writing Group proposes that the following minimum requirements be met in scanning for CS:[33]

1. Use of an electron beam scanner or a 4-level (or greater) MDCT scanner

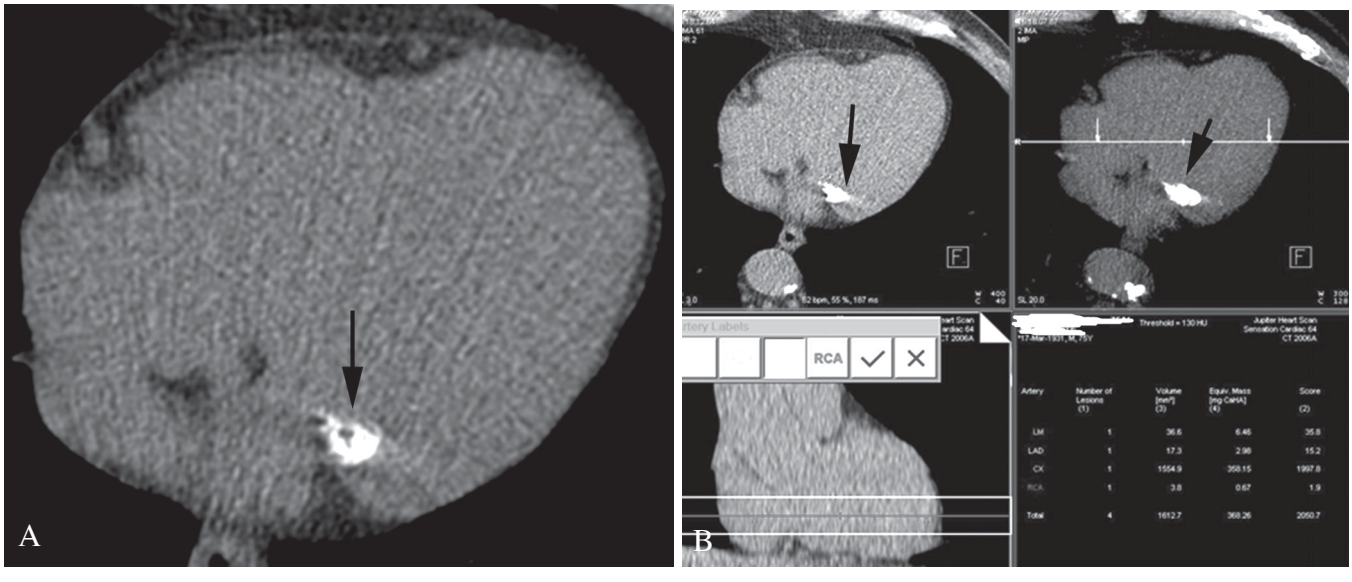

Figure 4 (A-B): The axial raw data image (A) show coarse calcification near the AV groove (arrow), which may be mistakenly included in the CS calculations (arrowhead).

2. Cardiac gating
3. Prospective triggering for reducing radiation exposure
4. A gantry rotation of at least 500 ms
5. Reconstructed slice thickness of 2.5 to 3 mm to minimize radiation in asymptomatic persons (and to provide consistency with established results)
6. Early to mid-diastolic gating.

The International Consortium for the Standardization of Cardiac CT revealed that MSCT is an equal and potentially superior cardiac imaging modality compared to EBCT.[33] Increased temporal resolution and reduction in slice thickness improve CS results. In a two-year prospective study[34] of 1173 asymptomatic patients without documented CAD, CS was measured by EBCT and found to be predictive of CAD events. Patients with CS score > 100 had a positive predictive value (PPV) of 5.5%, whereas patients with CS scores > 680 had a PPV of 14.0%. The negative predictive value (NPV) was >99% for all CS thresholds.

What are the results of comparison studies between EBCT and MDCT for performing CS examinations?

Several studies comparing these modalities have been published. Becker *et al*[35] studied 100 patients comparing MDCT with EBCT and reported a variability of 32% between the two modalities. Knez *et al*[36] studied the diagnostic accuracy of MDCT compared with EBCT in 99 symptomatic male patients (60±10 years). The mean variability between the MDCT- and EBCT-derived scores was 17%.

In epidemiologic studies of CS in broad population groups, measures by MDCT and EBCT may well provide important insight into the atherosclerotic process, a hypothesis currently under investigation in large, population-based studies (Multi-Ethnic Study of Atherosclerosis [MESA][28] and the Heinz Nixdorf RECALL study.[29]

What are the limitations of CS?

A limitation of coronary calcium scanning is that although calcium deposition occurs relatively early in the atherosclerotic process, plaque material very initially is not calcified. Fallavollita et al[37] compared EBCT detection of calcium with coronary angiography in 106 patients under the age of 50 and found 85% sensitivity and 45% specificity in patients with significant stenosis, defined as greater than 50% diameter narrowing on angiography. For multi-vessel disease, sensitivity was 94%, while in single-vessel disease it was 75%. Positive predictive value was 66%. Because negative predictive value was only 70%, the authors emphasized that the absence of EBCT calcium may not exclude significant coronary disease in this younger patient group.

In a more recent multi-center study[38] of 710 enrolled patients, 427 had significant angiographic disease and coronary calcification was detected in 404, yielding a sensitivity of 95%. Of the 23 patients without calcification, 83% had single-vessel disease on angiography. Of the 283 patients without angiographically significant disease, 124 had negative EBCT studies. This is a reminder to us, of the possibility of missing patients with coronary artery disease when the CS is low.

What is the radiation dose in CS examinations?

Hunold *et al*[39] performed a study of radiation doses during cardiac examinations. CS scanning was performed with EBCT and 4-level MDCT using prospective triggering to assess each patient's effective radiation exposure, which was then compared with measurements made during cardiac catheterization. EBCT yielded effective doses of 1.0 and 1.3 mSv for men and women, whereas MDCT using 100 mAs, 140 kV and 500-ms rotation yielded 1.5 mSv for men and 1.8 mSv for women. Invasive coronary angiography yielded effective doses of 2.1 and 2.5 mSv for men and women, respectively.

Because retrospective gating exposes the patient to significantly higher radiation, several techniques have been implemented to reduce those exposures i.e. dose modulation and Mahnken *et al*[40] have studied this in detail.

The AHA Writing Group, reviewing the available literature, endorses the use of a prospective ECG trigger for measurement of CS with a slice collimation of 1.5 to 3 mm for clinical practice. EBCT systems have an effective dose of 0.7 to 1 mSv (for men) and 0.9 to 1.3 mSv (for women) and MDCT systems have an effective dose of 1 to 1.5 mSv (for men) and 1 to 1.8 mSv (for women).[41,42]

How does CS fit in with other cardiac tests? [Table 3]

The principal tests for detecting asymptomatic CAD include resting and exercise ECGs, which can provide evidence of previous silent myocardial infarction and silent or inducible myocardial ischemia. Several resting ECG findings (ST depression, T-wave inversion, Q waves and left axis deviation) increase the likelihood of coronary atherosclerosis and of future coronary events. One third to one half of patients with angiographically normal coronary arteries have Q waves, T-wave inversion or ST-T changes on their resting ECG.[43-45] Conversely, a normal ECG does not rule out CAD.[46]

Table 3: Comparison chart of sensitivity and specificity for non invasive testing and angiography JACC 1999:33:453-62

Testing pathway	Sensitivity (%)	Specificity (%)
TMET	68	77
THALLIUM	90	77
ECHO	84	87
CT (score > 0)	95	46
CT (score > 37)	90	77
CT (score > 80)	84	84
CT (score > 168	71	90
ANGIO	100	100

Furthermore, most coronary events occur in persons without resting ECG abnormalities.[47-48] thus, routine ECG testing in asymptomatic persons, in whom the pretest probability of having CAD is relatively low, is not an efficient process for detecting CAD or for predicting future coronary events. The exercise ECG is more accurate than the resting ECG for detecting clinically important CAD.

Most patients with asymptomatic CAD do not have a positive exercise ECG, however[49-52] ECG changes often do not become apparent until an atherosclerotic plaque has progressed to the point that it significantly impedes coronary blood flow.[50,53] In addition, most asymptomatic persons with an abnormal exercise ECG result (usually defined by a specific magnitude of ST-segment depression) do not have underlying CAD.[53,54] A 1989 meta-analysis found considerable variability in the accuracy of exercise-induced ST depression for predicting CAD (sensitivity 23-100%, specificity 17-100%).[55]

Thus it is noted that CS is a better sensitive assessment tool for diagnosing the presence of early CAD and extent of plaque burden then routine screening tests, except for the fact that there is radiation exposure during this procedure, which is the result why there is still no recommendation for mass screening of the general population by the AHA.

Conclusion

To summarize, CS scanning is a relatively accurate and non-invasive way of determining whether or not underlying atherosclerotic coronary artery disease is present. It also provides an estimate of the extent and severity of coronary disease. This information can then be utilized to optimize patient care, helping to appropriately tailor prevention goals and to determine further evaluation and follow up, if needed.

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Source of Support: Nil, **Conflict of Interest:** None declared.