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Association between Coronary Artery Calcium Score and Clinical Events at 1 Year among Asymptomatic Patients

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Abstract: ***Objective: Coronary artery calcium score (CACS) is a well-established test for risk stratifying asymptomatic patients. The study was aimed at estimating the coronary artery calcium score (CACS) and its association with incidence of MACE among atypical chest pain and asymptomatic Intermediate probability CAD patients. Methods: It is a prospective, cross-sectional, observational study. All CT scans were performed on a 256-slice scanner with a 270 millisecond per rotation (Philips Brilliance iCT 256-slice system, Philips Essence Technology). Results: The study was done on 108 patients. Males and females constituted 62% and 38 % respectively of the study population. The mean age of the study population is 54.55 + 7.778 years. In the CACS group-zero were 47 subjects, group 1-99 were 31 subjects, 100-399 were 19 subjects, 400-999 were 10 subjects and more than 1000 were in one. Mean age of male gender in respective CACS group in the study population: CAC group zero – 51.04 years, 1-99 was 52.05 years, 100-399 was 60.14 years and 400-999 was 61.22 years. With increasing age, there is a linear relationship with incremental coronary calcium score. There were 16 (14.81%) subjects who developed MACE at the end of 1-year follow-up. No MACE occurred in the group with a calcium score of zero. CACS group 1-99 AU had 9.68% events, group 100-399 AU had 26.31%, group 400-999 AU had 70% and group >1000 AU had 100% events. It was shown that as the calcium score increases, the risk of events increases. Conclusion: We recommend that in patients asymptomatic and who belong to the intermediate-risk group, suggestive of CAD in whom coronary anatomy is not known, the CACS measurement may be considered the first-line investigation to stratify the risk and assess the risk of MACE. It has the ability to re-classify many into either lower risk, with potential cost-savings in minimizing therapy, or into a higher risk group where appropriate therapies may improve outcomes.***

Keywords: coronary artery disease, coronary artery calcium score, major adverse cardiovascular events, computed tomography, chest pain, coronary angiography

1. Introduction

"Atherosclerosis, is a degenerative-inflammatory process leads to the development of plaques gradually infiltrated with calcium, is the cause of most cases of coronary artery disease. Calcification of the coronary arteries is synonymous with atherosclerosis". Coronary calcification well reflects the extent of the atherosclerotic process.1-4 Calcium deposit may be a component of both critically stenosed and non-obstructive plaques. Large numerical values of the coronary artery calcium score (CACS) are usually present in subjects with high-grade coronary lesions, but may also be found in individuals with extensive atherosclerosis but no critical coronary stenosis. However, noncalcified plaques may be present, especially in younger subjects, and may be prone to rupture.4-7

It can easily be detected with computed tomography without contrast, and the amount can be quantified with a scoring system like the volumetric score or the Agatston score. Agatson score is more commonly used, is based on the product of the area of the calcium deposits and the x-ray attenuation in Hounsfield units. Scores are roughly categorized (with some overlap owing to data from different studies) as: Low risk: 0 Agatston units (AU), Average risk: 1–112 AU, Moderate risk: 100–400 AU, High risk: 400–999 AU, Very high risk: 1, 000 AU.8

Cohort studies with long-term follow-up show that calcification scoring has robust prognostic ability. A pooled analysis of several of these studies[2] showed that a higher score strongly correlated with a higher risk of cardiac events in 3 to 5 years.compared with the risk in people with a score of 0, the risk was twice as high in those with a score of 1 to 112, four times with a score of 100 to 400, seven times with a score of 400 to 499, and 10 times with a score greater than 1, 000.8

The predictive role of CACS for cardiovascular events in asymptomatic subjects has been well studied.9-13 The absence of coronary calcium identifies the subjects with very low risk of subsequent coronary events, [4, 14, 15] and a CACS of more than 400 Agatston units is considered a CAD equivalent, with a 10-year MACE rate of over 20%.9 The Screening for Heart Attack Prevention and Education (SHAPE) guidelines proposed use of CACS value as the basis for risk screening in apparently healthy population of men older than 45 years and women older than 55 years.16

Polonsky and colleagues [12] studied a cohort of 5, 878 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) and estimated the event risk using a model based on Framingham risk characteristics. When the calcification score was added to the prediction model, 26% of the sample was reclassified to a new risk category. In intermediate-risk patients, 292 (16%) were reclassified as high risk, and 712 (39%) were reclassified as low risk, reaching an NRI of 0.55 (95% confidence interval 0.41 to 0.69; *P* <.001). The C statistic for the prediction of cardiovascular events was 0.76 for the model based on Framingham risk characteristics and increased to 0.81 (*P* <.001) by adding calcification scoring.

Erbeland colleagues [13] reported data from the Heinz Nixdorf Recall study, which used calcification scoring to estimate the NRI in 4, 129 patients followed for 5 years. During this time there were 93 coronary deaths and nonfatal myocardial infarctions. The addition of the calcification score to the Framingham risk model resulted in an NRI of 0.21 (*P*

=.0002) for patients with a risk of 6% to 20% and 0.31 (*P* <.0001) for those with a risk of 10% to 20%. They estimated the C statistic (area under the receiver operating characteristic curve; the maximum value is 1.0 and the higher the value the better) for the addition of the calcification score to the Framingham risk model and to the Adult Treatment Panel (ATP) III algorithm. They had reported a significant increase of 0.681 to 0.749 with the Framingham model and 0.653 to 0.755 with the ATP III algorithm.

In symptomatic subjects, the role of calcium scoring is controversial.1, [17-21] Patients with symptoms suggestive of CAD represent a non-uniform group, for whom confirmation or exclusion of CAD diagnosis and assessment of the risk of cardiac events are importance for the choice of a management strategy. Classic risk factors, including age, sex, arterial hypertension, smoking, and dyslipidemia, serve as the basis for the most popular risk calculators, like the Framingham scale[22] and SCORE.2[3]They are useful for cardiovascular risk assessment but have important limitations.

A substantial proportion of patients at risk of cardiovascular events cannot be identified using the classic risk factors. In addition, in young and middle-aged subjects, the risk of cardiovascular events is low even in the presence of several risk factors, while in the elderly population, a small change in the risk profile can have major prognostic implications.2[3]

Villines group[16] described a cohort of 10, 037 patients with coronary symptoms who underwent calcification scoring and computed tomographic coronary angiography and found that stenosis of greater than 50% was present in 3.5% of those who had a score of 0 and in 29% of those with a score higher than 0. So, a score of 0 does not rule out obstructive coronary heart disease if the patient has symptoms. However, these patients may still have coronary artery calcification even if perfusion stress imaging is normal, [24, 25] and coronary calcium scoring may have a role in the evaluation of equivocal stress tests.2[6]

The MESA STUDY-The Multi Ethnic Study of Atherosclerosis (6800 subjects) has stated that all modern Multi Detector Row CT systems are at least as reliable as EBCT for performing and reproducing coronary calcium measurements [24].

Some studies suggest that CACS can provide more valuable diagnostic and prognostic information than that obtained from routine exercise testing and single photon emission computed tomography (CT).1[9] However, other data indicate that up to 20% of symptomatic patients with a negative CACS value can have obstructive coronary lesions.1[7]

Multiple logistic regression analysis determined male sex, presence of diabetes and left anterior descending (LAD) and circumflex (LCX) coronary calcium scores, independent from more distal calcium localization, as sovereign predictors for identification of three-vessel and/or left main CAD[25].

On the basis of a simple algorithm ("noninvasive index"), EBCT calcium scanning in conjunction with risk factor analysis can rule in or rule out angiographically severe disease, i. e., three-vessel and or left main CAD, in symptomatic patients[25]. On average, significant coronary disease (greater than 50% or greater than 70% stenosis by coronary angiography) was reported in 57.2% of the patients. Presence of CAC was reported on average in 65.8% of patients (defined as a score greater than 0 in all but one report).

A cohort study of more than 25, 000 patients had similar conclusions about the magnitude of risk associated with coronary calcification.2[7] They found that the 10-year risk of death was 0.6% in patients with a score of 0, 3.4% with a score of 101 to 399, 5.3% with a score of 400 to 699, 6.1% with a score of 700 to 999, and 12.2% with a score greater than 1, 000.

If a patient's 10-year coronary risk is intermediate (10% to 20%), calcification scoring can reclassify the risk as low or high in about 50% of cases and can improve the accuracy of risk prediction.2[8-30]

Elias-Smaleand others[28] evaluated the effect of calcification scoring in 2, 028 asymptomatic patients, with median followup of 9.2 years and 135 coronary events observed. Addition of the calcification score to the Framingham model significantly improved risk classification, with a net reclassification improvement (NRI) of 0.14 (*P* <.01). Reclassification was most robust in those at intermediate risk, 52% of whom were reclassified, with 30% reclassified to low risk and 22% reclassified to high risk.

There is scarcity of data on Role of coronary artery calcium score (CACS) among asymptomatic Intermediate probability CAD population in India. Documenting the association between coronary artery calcium score (CACS) and the incidence major adverse coronary events (MACEs) may prove to be highly useful in resource poor settings. Further studies can be conducted to establish the utility of Coronary artery calcium score (CACS) as the first-line non-invasive test in risk stratification these patients. Hence we have undertaken this study to assess the coronary artery calcium score (CACS) and to assess the possible association between the CACS and the occurrence of MACE among intermediate probability CAD patients.

2. Review of Literature

Coronary artery calcification (CAC) is pathognomonic for coronary artery atherosclerosis, as this is the vascular disease that causes calcification of coronary arteries [31, 32]. Histopathological and intravascular ultrasound studies have documented the close correlation between plaque burden and CAC [33].

Rumberger and colleagues showed that the total area of CAC correlates in a linear fashion with total area of coronary artery plaque on a segmental, individual, and whole coronary artery system basis. They also demonstrated that coronary calcium generally comprises about 20% of total plaque size [34].

Whether CAC is a result of the ongoing inflammation associated with plaque formation or an attempt to repair damage to the vascular wall is not clearly understood. It is also unknown whether CAC is a dynamic phenomenon, like the ongoing formation and degradation of bone tissue.

Although calcification is ubiquitous in complex coronary atherosclerotic plaques, it is unknown if calcium is more than just an innocent bystander. It has been shown that it predicts an increased risk of plaque rupture and thrombosis[35]. It has been demonstrated that soft plaques with points of weakness adjacent to an area of calcification predispose the plaque to rupture[36, 37]. However, as the calcific and fibrotic plaque lesions are much stiffer than the softer cellular lesions, calcification may actually be an attempt by the arterial walls to stabilize them and thereby reduce the risk of plaque rupture. Early or moderate arcs of calcification render a plaque more prone to rupture, whereas extensive concentric calcification (seen particularly in the very elderly) may render a plaque less likely to rupture. Regardless of the ongoing debate as to the exact composition of the "vulnerable plaque, " CAC is almost always ubiquitous in patients who suffer cardiac events.

Pathophysiology of atherosclerosis

"The main cause of coronary insufficiency is atherosclerotic disease, defined as an inflammatory disorder. " Atherogenesis initiates with lipid accumulation, cell proliferation, and extracellular matrix synthesis. These atherosclerotic plaques are associated with circulating proteins normally associated with bone remodeling, and these proteins regulate the accumulation of the hydroxyapatite form of calcium phosphate in these lesions.

Plaque formation initiates with early accumulation of low density lipoprotein particles (LDL) in the arterial intima. Oxidation of lipid material is responsible for the attack on the endothelium, alter the permeability and increase the expression of adhesion molecules, integrins and selectins, which participate in the migration of monocytes as an innate inflammatory response. Macrophages initiate Low density lipoprotein phagocytosis, resulting in the formation of foam cells that produce cytokines and metalloproteinases, increases inflammatory response and recruits platelets and T lymphocytes. Platelets adhere to the lesion and release prostaglandins and leukotrienes, and growth factors that induce monocytes and smooth muscle cell multiplication. T lymphocytes are presented to lesion antigens by dendritic cells, begin producing cytokines, and modulate adaptive immune response.[38]

Deposition of extracellular matrix produced by the differentiated smooth muscle, cell proliferation, necrosis, and angiogenesis promote expansion of the plaque.[39] The progression of atherosclerotic disease, however, does not obstruct vascular light in the same proportion due to positive remodeling of vessel size which does not compromise the luminal diameter.[39, 40] When maximum capacity is reached, we see negative remodeling and plaque progression to the interior of the artery which, by gradually compromising the flow, may cause myocardial ischemia.[39]

Migration and proliferation of poorly differentiated smooth muscle cells in the intima promotes atherosclerotic plaque mineralization.[40] These cells differentiate into osteoblasts, produce mineralized extracellular matrix, and deposit hydroxyapatite crystals by calcium accumulation in the interior of the lesion[40, 41] in an osteogenesis-like process. Microcalcifications and calcified deposits may lead to plaque cavitation, erosion and rupture, increasing the risk of coronary thrombosis.[41]

In the first few decades of life atherosclerosis begins with a fatty streak in which lipoproteins are deposited in the intimal and medial layers of blood vessels (**Figure 1**). Inflammatory cells such as macrophages and foam cells are recruited to the areas of deposition where they cause apoptosis, creating a necrotic core with calcium deposits.[42, 43]

As the calcium deposits grow, they can be detected by imaging tests such as computed tomography (CT), and quantified to assess the extent of disease[44]

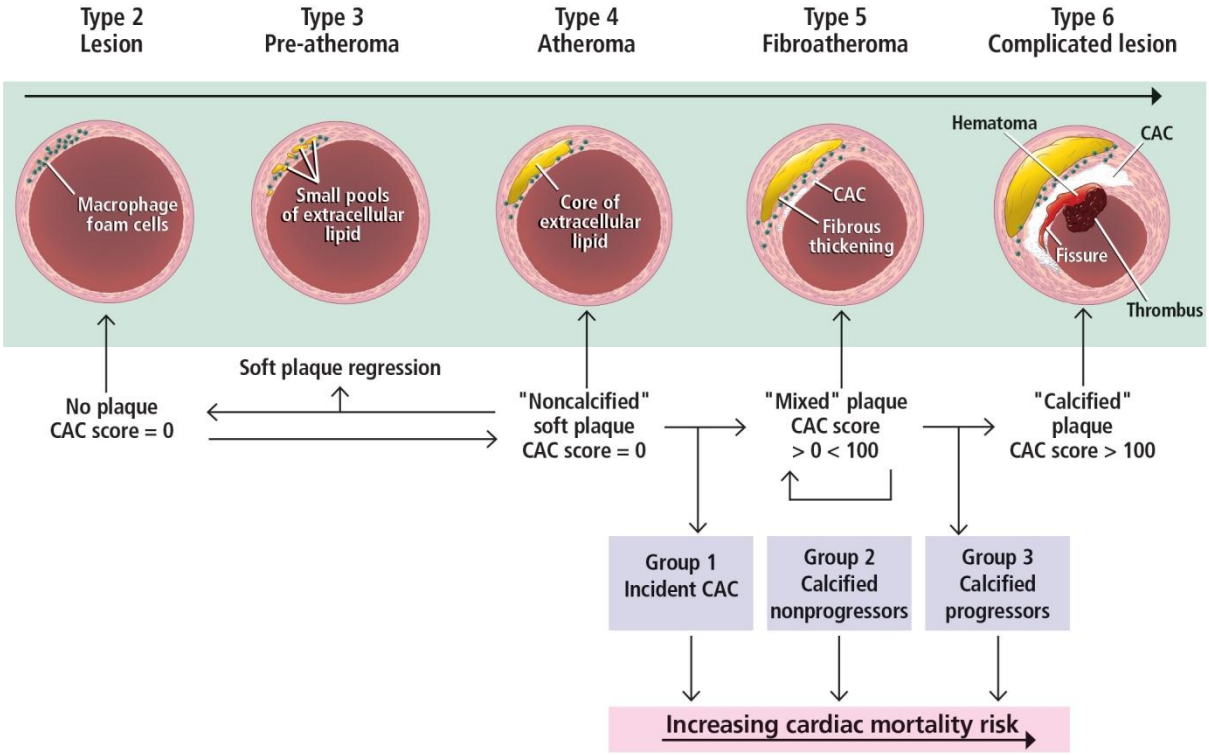

Figure 1: Pathogenic mechanism of atherosclerotic lesions and its relationship to the coronary artery calcium (CAC) score. A type 1 lesion (not depicted) contains lipoproteins that initiate an inflammatory response. A type 2 lesion contains an accumulation of foam cells. The type 3 lesion contains collections of extracellular lipid droplets. Eventually, these extracellular lipid pools form a lipid core, and a type 4 lesion is created. With time, this core develops a fibrous connective-tissue thickening that can calcify and give rise to a type 5 lesion detectable by imaging. Type 6 is a complicated lesion that can include thrombus from plaque rupture

Several diagnostic methods to estimate cardiovascular risk and diagnose subclinical atherosclerosis in asymptomatic patients have been studied. Among them, coronary calcium score has shown better accuracy in the prediction of future risk events and detection of early disease that may be isolated or associated to clinical scores.4[5]

Calcium score capacity for cardiovascular risk stratification has also been compared to the so-called new risk factor, capable of estimating subclinical atherosclerosis, such as carotid intimal-medial layer thickening measurement, ankle-brachial index, and C-reactive protein. However, coronary calcification was more effective in the process of re-stratification of patient groups' risk by clinical score, even when used alone.4[6-48]

CAC has consistently been associated with a greater area under the receiver operating characteristic curve than combinations of risk factors (e. g., Framingham Risk Score [FRS]), as well as the individual risk factors. Figure-2

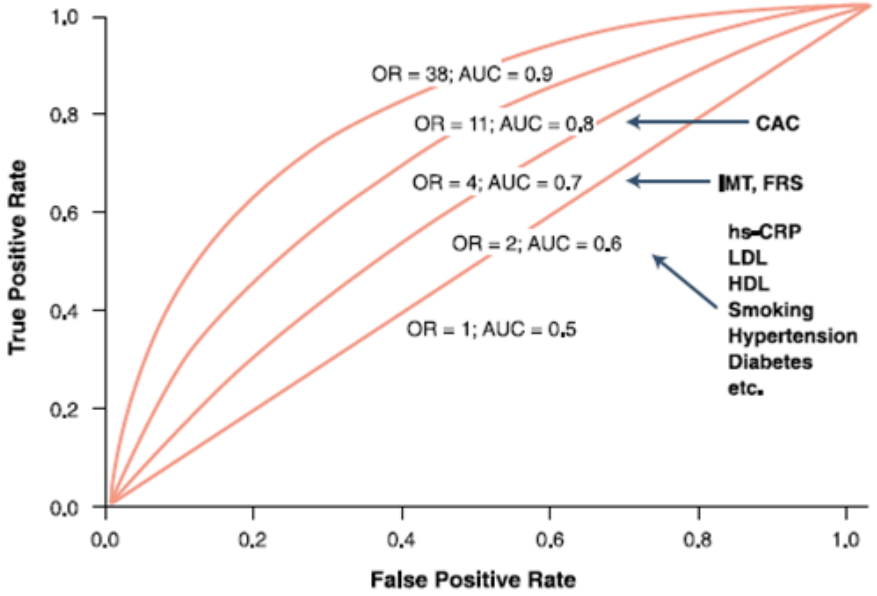

Figure 2: ROC Curve, Its AUC, and Corresponding Odds Ratios

Increased odds ratios associated with novel risk factors are often assumed to have high predictive value for the development of cardiac events. It is only when the odds ratios are in the >4 range that the AUC increases to a minimally acceptable level for clinical utility. Coronary artery calcium, with an odds ratio of ~11, is associated with the greatest AUC.

The net reclassification index (NRI) has been increasingly used to measure the prediction improvement in the risk reclassification increment of new biomarkers compared with more traditional risk factors on the basis of outcomes. The NRI contributed by CAC in the asymptomatic population by 3 major prospective, population-based studies is shown in **Table 1**[12, 15, 28]. The percentage of patients with an FRS risk estimate correctly reclassified by CAC score on the basis of outcomes ranged from 52.0% to 65.6% in the intermediate-risk group, 34.0% to 35.8% in the high-risk group, and 11.6% to 15.0% in the low-risk group, with NRIs for the entire study population ranging from 19% to 25%.

Table 1: Reclassification of FRS Risk by CAC Primary Prevention Outcome Studies

Study	% Reclassified	N	Age, yrs	Follow-up, yrs
MESA [12]				
FRS 0%-6%	11.6			
FRS 6%-20%	54.4	5878	62.2	5.8
FRS >20%	35.8			
NRI	25			
Heinz Nixdorf [13]				
FRS <10%	15.0			
FRS 10%-20%	65.6	4487	45-75	5.0
FRS >20%	34.2			
NRI	22.4			
Rotterdam [28]				
FRS <10%	12			
FRS 10%-20%	52	2028	69.6	9.2
FRS >20%	34			
NRI	19			

NRI = Net Reclassification Index.
FRS = Framingham Risk Score

Comparisons of the NRI for CAC versus the FRS (66%) in the intermediate-risk population with risk markers other than those included in the FRS reveal its overwhelming superiority to ankle-brachial index (3.6%), brachial flow–mediated dilation (2.4%), carotid intima media thickness (10.2%), family history (FH) of premature CHD (16.0%), and hs-CRP (7.9%) [46]. In addition, a combination of multiple blood biomarkers, including hs-CRP, interleukin 8, myeloperoxidase, B-type natriuretic peptide, and plasminogen activator type 1, did not add to the C statistic for CAD outcomes of the FRS (0.75 vs.0.73; p = 0.32), whereas CAC score increased the FRS C statistic to 0.84 (p = 0.003). Moreover, the biomarker combination added nothing to the FRS + CAC score (0.84 vs.0.84) [29].

CAC scores show an uneven distribution in the general population. Previous and recent outcome studies led to the classification scheme proposed in the clinical expert consensus document of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) in 2007 [49]

0 = no calcification
> 0–100 = mild calcification
> 100–400 = moderate calcification
> 400–1000 = severe calcification
> 1000 = extensive calcification

The CAC score plays a role in the stratification of cardiovascular risk. Several studies have shown that the CAC score is strongly associated with the occurrence of major cardiovascular events (all-cause mortality, cardiac mortality, and nonfatal myocardial infarction) in the medium-and long-term follow-up.

In an American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) consensus [8], data from six 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:

- 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).

The CAC score was studied in association with other well-established traditional risk score systems, especially the Framingham risk score, showing the following advantages: independently added value in the prediction of all-cause mortality and mortality due to coronary disease in asymptomatic individuals[8] and reclassification in the category of coronary artery disease risk-60% of atherosclerotic coronary events occur in patients categorized as being at low or intermediate risk according to the Framingham risk score. As an example, among patients at intermediate risk according to the Framingham risk score and with a CAC score > 300, the annual frequency of myocardial infarction or coronary death would be 2.8%, which would place them in a high risk category, the 10-year event frequency therefore being approximately 28%.

Imaging

The ability to image calcification within coronary arteries was recognised even from the earliest days of x-ray technology in the 1920s. Coronary calcification was linked to atherosclerosis in 1950s and calcium seen on fluoroscopy carried prognostic significance.5[0, 51] In the late 1980s it was shown that early CT scanners were more sensitive than fluoroscopy for detecting calcium (62% versus 35%) but the images were affected by motion artefact.5[2]

But in 1990s with the development of ultrafast computed tomography, later known as electron beam computed tomography (EBCT), could generate 3mm thick slices with a scan time (temporal resolution) of 100 milliseconds, gated to the diastolic phase of the cardiac cycle. This allowed the heart to be examined in a single breath hold with minimal movement artefact.

Arthur Agatston (cardiologist), Warren Janowitz (radiologist) and David King (Engineer-Imatron, manufacturer of EBCT), invented a scoring system which later became known as the Agatston score.5[3] Calcium appears bright on a CT image, that means it has a high CT number, or Hounsfield unit (HU). It was resoluted that the cut-off should be 130HU for lesions to be considered calcified. The area of all coronary lesions with HU above this number would be calculated and summed. Lesions with dense calcification would be brighter and a weighting factor between 1 and 4 was applied based upon the peak density (as assessed in HU) of the lesion.5[4] The Agatston score was the product of the calcified area by the weighting factor.

Other methods for both imaging and quantifying coronary calcium have been proposed, comprising thicker slices and scores based upon the number, mass or volume of the lesions.5[5-57] However it is still the original Agatston score that is most commonly used both in trials and clinical practice.

Developments in multi-detector CT (MDCT) technology (predominantly temporal resolution and z-axis coverage) have made it possible to perform CAC reliably in the previous decade. In the beginning MDCT scanners showed significant variability in the calcium score depending upon the image reconstruction and scoring algorithm and were not equivalent to EBCT.5[8] However harmony between calcium scores obtained on MDCT and EBCT has since been established.5[9, 60]

After obtaining the CT images, calcium scores are calculated using commercially available software packages. It usually highlights areas with HU>130 and the reader manually identifies coronary lesions. Then calculates HU and area which provides the Agatston score. Calcification of the mitral annulus, aortic root, pericardium and streak or beam hardening artefact near the inferior wall of the heart can make interpretation of the images more challenging. So, care must be taken by the reader to identify coronary calcification correctly.

EBCT routinely deliveres very low doses during calcium scoring between 0.7 and 1.3 milliSieverts (mSv). Radiation from MDCT was initially higher with some previous studies reporting doses between 3 and 4 mSv.6[1, 62] Guidelines for minimizing radiation exposure during calcium scoring with MDCT have been published and in the recent dose should average between 0.5 and 1.5 mSv on most modern scanners using prospective ECG-gated technique.6[3] This is approximate to 2 breast mammograms.

The HU of any tissue will differ depending upon the energy of the X-Ray used to obtain the image i. e. kiloVolt (kV) setting. A study comparing 100kV to 120kV for CAC found the threshold in defining calcified lesions had to be set higher at 147 HU for 100kV rather than traditional 130 HU.6[4]Although CT coronary angiogram studies are now routinely performed at low radiation doses using 100kV or even 80kV protocols, calcium scoring should be performed at 120kV and reconstructed at 3mm slice thickness in order to derive a conventional Agatston score. Radiation can be minimized by adjusting other scanner settings, particularly scan length and tube current.

Until recently, electron beam tomography (EBT) was the principle method for acquiring the images used for calcium scoring. In fact, most of the data substantiating the importance of calcium scoring was acquired through EBT. Multidetector computed tomography (MDCT) is a newer, widely used imaging technology that will likely completely replace EBT for calcium scoring in the near future.

Electron Beam Tomography

EBT cardiac imaging involves obtaining thin slices (each 3 mm) of the heart and coronary arteries to evaluate for CAC. Usually 30 to 40 axial images are obtained to include the full length of the myocardium. The entire coronary artery tree is imaged during a single 20-to 30-second breathhold. Rapid image acquisition (100 msec) prevents image blurring and allows accurate visualization of very small calcium deposits in the coronary arteries. The calcific deposits in the arterial walls demonstrate a high attenuation compared to the surrounding soft tissue, and this permits the easy identification of CAC without injection of contrast medium.

Multidetector Computed Tomography

MDCT uses a rotating gantry with a special x-ray tube and a variable number of detectors to acquire images while a patient advances through on a moving table. MDCT is able to acquire 165–375-ms images in 0.5–3.0-mm intervals using prospective triggering if the heart rate is steady and < 60 bpm. To avoid coronary motion artifacts, image acquisition below 50 ms is needed, as the right coronary artery (RCA) exhibits translational motion of up to 60 mm/sec. The left anterior descending artery (LAD) and left circumflex artery (LCx) exhibit 20 to 40 mm/sec of translational motion. MDCT, therefore, is plagued by more motion artifacts than is EBCT.

The comparability of MDCT-and EBCT-derived CAC scores has been well proven by a number of studies involving more than 400 patients[65-68]. The most recent study between EBCT and 64-slice MDCT demonstrated that the inter-scan agreement for the presence of CAC was 99%[67]. There was a significant linear relationship between the scores from the 2 scanners and the inter-scanner variability was not significantly different. Multiple studies have further confirmed that 64-slice MDCT and EBCT were comparable for both Agatston and volumetric CAC scanning [68].

The use of the CAC score in asymptomatic subjects at intermediate risk, as determined by traditional clinical stratification methods, such as the Framingham risk score, is considered appropriate/recommended with a good level of evidence by the II Guidelines of the Brazilian Society of Cardiology/Brazilian College of Radiology and Diagnostic Imaging and other international consensus statements[22, 29, 30, 49, 81, 83].

The use of the CAC score is not indicated in high-risk patients, because aggressive preventive measures would already be indicated in such patients[108].

Within the group of patients classified as being at low risk, we have attempted to identify a subgroup with a significant long-term risk of a cardiovascular event, for which preventive measures should be adopted. Recent evidence has shown that a family history of premature CAD (in a male first-degree relative < 55 years of age or female first-degree relative < 65 years of age) is an independent risk factor and is associated with increased atherosclerotic burden[108]

The recommendations for the use of the CAC score in asymptomatic patients, according to the main guidelines published were illustrated in the following table 2.

Table 2

Low risk low risk + family					
Authority guidelines	Low risk	Diabetes mellitus	Family h/o early CAD	Intermediate risk	High risk
2010 ACCF/SCCT/ACR[29]	Inappropriate	-	Appropriate	Appropriate	Uncertain
2014 ACR[30]	Typically inappropriate	-	Can be appropriate	Appropriate	Typically inappropriate
2010 ACCF/AHA[81]	IIb	-	-	IIa	-
2012 ESC[22]	-	-	-	IIa	-
2014 II Diretriz da SBC/CBR[49]	III	IIa	IIa	I	III
2013 ACC/AHA[83]	IIb: If, after risk assessment, the treatment based on the decision is uncertain, evaluation with the CAC score can be considered in order to define the most appropriate therapeutic strategy[†]				

Classes of recommendation: Class I-Conditions for which there is conclusive evidence or, in the absence thereof, general agreement that the procedure is safe and useful/effective; Class II-Conditions for which there is conflicting evidence and/or divergence of opinion on safety, and utility/effectiveness of the procedure; Class IIa-Weight of divergences in favor of the use/effectiveness of the method. Most approve; Class IIb-Safety and utility/effectiveness less well established, with no predominance of opinions in favor. Class III-Conditions in which there is evidence, general agreement or both, that the procedure is not useful and effective, and in some conditions may even be harmful.

Yeboah and workers showed that addition of CAC increased area under the receiver operating characteristic curve of the Framingham risk score from 0.623 to 0.784 in intermediate-risk patients, with CAC showing superior recognition and risk reclassification compared with ankle-brachial index and high-sensitivity C-reactive protein.6[9] In other recent studies by Yeboah et al., CAC demonstrated the strongest ability of all ACC/AHA guideline-endorsed tests to improve to the PCE, [70] showing the lowest number needed to screen for identifying an individual with <7.5% risk to be reclassified as statin eligible with an abnormal test result.7[1]

Outcome studies on the absence of CAC (CAC = 0) extended the knowledge about risk prediction of CAC. Blaha and workers showed that CAC = 0 was the strongest negative risk factor among 13 supposed reassuring factors in MESA (Multi-Ethnic Study of Atherosclerosis).4[8] Pursnani et al. showed that CAC = 0 was accompanied with a low CVD rate (1.6%) in statin-eligible participants.7[3] Mortensen et al.-A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population found that the CAC = 0 could down-classify risk of elderly participants who are statin eligible to statin ineligible, perhaps sparing a significant proportion of the elderly population from taking statin.7[4]

Nasir and colleagues categorized MESA participants according to their ASCVD risk score and presence of CAC. They found that 57% and 45% of the 5 to <7.5% and 7.5 and <20% ASCVD risk groups, respectively, would be expected to have CAC = 0 (and therefore be lower risk). Absence of CAC down-classified both of these groups, which were initially categorized by their ASCVD risk as "statins to be considered" and "statins recommended" to "statins not recommended" (Figure 3).7[5] Nasir et al. found that CAC was not as helpful when ASCVD risk was >20%.

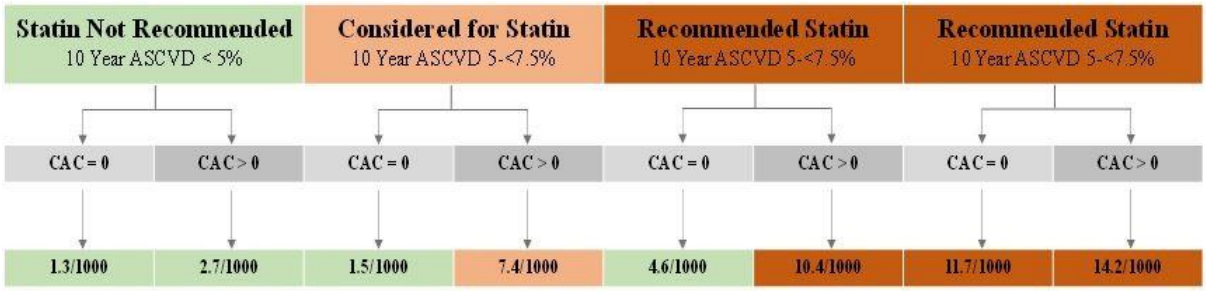

Figure 3: Implication of CAC on Statin Therapy

Society of Cardiovascular Computed Tomography (SCCT) recommended performing CAC scoring in select patients with an ASCVD risk between 5 and 20% in the context of shared decision-making. It also suggested using CAC score in selected patients with ASCVD risk <5%, especially in those with family history of premature coronary heart disease.7[6]

McClelland and team published the MESA coronary heart disease risk score.7[7] It is the first score to incorporate the CAC score into its calculator. It is useful for determining

coronary heart disease risk both before and after consideration of the CAC score. The C-statistic of the MESA coronary heart disease risk score improves from 0.75 to 0.8 when the CAC score is considered in the study.

Miedema and colleagues estimated the number needed to treat (NNT) for distinct CAC strata by applying an expected 18% relative reduction in coronary heart disease to baseline risk estimates. The authors set the number needed to harm of major bleeding to be 442 according to a meta-analysis. They found that participants with CAC ≥ 100 would probably benefit from aspirin therapy regardless of their traditional 10-year risk score. Contrary, participants with CAC zero would likely not benefit from aspirin (NNT = 2, 036, and 808 if Framingham Risk Score were <10% and ≥10, respectively).7[8]

Sangiorgi et al[79] performed a histologic analysis of 723 coronary artery segments. They identified that the amount of calcium correlated well with the area of plaque.

A blend of the data from 5 large prospective, randomized studies, 3 with events defined as CHD death, myocardial infarction, and revascularization[92, 99, 138]and 2 with CHD death and myocardial infarction[13, 95] yields annual event rates that can be translated into 10-year FRS equivalents (Table 3). A CAC score >400 is a CHD equivalent, with 10-year event rates exceeding 20% in asymptomatic patients.

Table 3: Summary of CAC Absolute Event Rates from 14, 856 Patients in 5 Prospective Studies[13, 92, 95, 99, 138]

CAC Score	FRS Equivalent	10-year Event Rate, %
0	Very low	1.1- 1.7
1-100	Low	2.3-5.9
101-400	Intermediate	12.8-16.4
>400	High	22.5-28.6
>1, 000	Very high	37.0

CAC= coronary artery calcium;
FRS= Framinghan Risk Score

In SILICAS study[80], they assessed the predictive value of coronary calcium on the major adverse coronary events (MACEs) including cardiac death, nonfatal myocardial infarction (MI), and coronary revascularization, in order to establish its usefulness as the first-line noninvasive test in subjects with an intermediate probability of CAD. Secondary objectives included the incidence of cardiac death, MI, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG), as well as the number of coronary angiographies and hospitalizations for stable and unstable angina in relation to the CACS.588 Patients were followed up for a mean period of 638+261 days. The primary endpoint, a composite of death, nonfatal MI, PCI, and CABG, occurred in 108 patients (18.4%). There were no primary endpoint events in patients with a CACS of 0 AU, while in those with a positive CACS, 108 patients (30.9%) experienced MACEs (*P* <0.001). For the 4 subgroups of patients with positive CACS (1–99 AU, 100–399 AU, 400–999 AU, and ≥1000 AU), an event occurred in 8%, 39%, 68%, and 91% of the patients, respectively. In patients with a CACS of less than 100 AU, both PCI and CABG were rarely necessary (7% and <1%, respectively). The need for PCI significantly increased with a CACS of 100 AU or higher (33%, 47%, and 44%, for the CACS cut-off values of 100 AU, 400 AU, and 1000 AU), and for CABG, only for CACS of 1000 AU or higher (6%, 12%, and 50%, respectively).

The association between calcium score and major adverse cardiovascular events including all-cause mortality, cardiovascular events and non-fatal myocardial infarction, has been established in a number of studies. A large prospective study involving 25, 253 patients in United States of America with a mean follow-up of 6.8 years showed the calcium score was associated with survival.2[7]

A study of 9715 patients in Tennessee, with the longest follow-up period of 15 years has recently been published.8[2] The all-cause mortality rate at 15 years according to CAC results are as follows: CAC 0: 3%, CAC 1-100: 6-9%, CAC 101-399: 14%, CAC 400-999: 21%, CAC ≥ 1000: 28%.

The 2007 ACC/AHA consensus statement on CAC provided a pooled analysis of studies and found a proportionate rise in annual myocardial infarction or cardiac death rate.4[9] This approximates the event rate of traditional FRS 10-year risk groups of low, intermediate and high.

Every prognostic registry, whether prospective or retrospective, population based or patient-referred, has demonstrated the power of CAC, with relative risks far exceeding all risk factors, whether individually or collectively. Table 4

Table 4: Prognostic Power of Coronary Artery Calcium in Asymptomatic Patients

First author (ref.)	N	Mean age, yrs	Follow-up, yrs	Cac score cut off	Comparator group for RR calculation	RR ratio
Arad et al.9[9]	1173	53	3.6	>160	<160	20.2
Park et al.1[34]	967	67	6.4	>142.1	<3.7	4.9
Raggi et al.1[34]	632	52	2.7	Top quartile	Lowest quartile	13
Wong et al.1[51]	926	54	3.3	>270	First quartile	8.8
Kondos et al.1[34]	5635	51	3.1	>0	No cac	10.5
Greenland et al.8	1312	66	7.0	>300	No cac	3.9
Shaw et al.1[34]	10377	53	5	>400	<10	8.4
Arad et al.1[50]	5585	59	4.3	>100	<100	10.7
Taylor et al.1[34]	2000	40-50	3.0	>44	0	11.8
Vliegenthart et al.1[52]	1795	71	3.3	>1000 400-1000	<100 <100	8.3 4.6
Budoff et al.1[34]	25503	56	6.8	>400	0	9.2
Lagoski et al.9[0]	3601	45-84	3.75	>0	0	6.5
Becker et al.9[5]	1726	57.7	3.4	>400	0	6.8 men

						7.9 women
Detrano et al.9[2]	6814	62.2	3.8	>300	0	14.1
Erbel et al.1[3]	4487	45-75	5	>75th percentile	<25th percentile	11.1 men 3.2 women
Taylor et al.1[34]	1634	42	5.6	>0	0	9.3

Various studies have demonstrated the utility of CAC scores in guiding the clinical management of CAD in asymptomatic patients. The (U. S.) National Cholesterol Education Program guidelines recommend intensification of low-density lipoprotein cholesterol reduction in patients with multiple risk factors and a CAC score above the 75th percentile[104] Other studies have correlated CAC scores with the use of statins and aspirin in primary prevention[48, 78]. **Table 5** summarizes some of those studies.

Table 5: Correlation of CAC scores with the use of statins and aspirin in primary prevention

		CAC score = 0	CAC score 1-100	CAC score >100
Population (% patients) [78]		56%	26%	18%
Annual frequency of events[48]		0.1%	0.5%	1.9%
Annual frequency of cardiovascular events[48]		0.4%	0.8%	2.4%
Number needed to treat (to prevent one cardiovascular event over a five year period)				
Treatment with aspirin-Number needed to treat[28]	FRS <10	2036 808	571* 146*	173 92
Treatment with statins-Number needed to treat[15]	FRS > 10	549	94	24
Treatment recommendations				
Recommended		None	Tailored use of statins + aspirin	Statins + aspirin
Recommendation for all patients	Life style change + monitoring of cardiovascular risk factors			

*The estimated number needed to produce damage from aspirin use (one episode of major bleeding over the five year period) is 442 patients (28). Therefore, when the anticipated benefit exceeds the risk (e. g., when the FRS is ≥ 10% in patients with a calcium score of 1-100), the use of aspirin should be considered. CAC score (Agatston method). FRS, Framingham risk score.

Large number of studies have reported the improvement in AUC for predicting CVD events when CAC is added to traditional risk factors from approximately 0.6 to > 0.7.6[9] Yeboah team, in a MESA study of 6814 patients, compared the ability of different risk markers (CAC, high-sensitivity CRP, ankle-brachial index, brachial FMD, carotid IMT, family history) in improving the ability to predict CVD events when added to FRS.8[6] They found CAC resulted in the highest improvement of AUC from 0.62 to 0.78. Family history was the next best marker at AUC 0.67 with the other markers resulting in only modest improvements over FRS or not at all.

Raggi and workers[87] found patients with diabetes have a higher mortality compared to non-diabetics across all categories of CAC with the exception of CAC of zero. Addition of CAC to FRS improved the accuracy of predicting CVD events from AUC of 0.72 to 0.79. Patients with diabetes had more risk for CVD which develops earlier compared with nondiabetic patients.8[8] CAC could be considered in diabetic patients without known CVD aged 40 to 60 years. Diabetics over 60 years are considered to be high risk and should receive optimal medical therapy.

The 2010 ACC/AHA Risk Assessment Guideline awarded a Class IIa recommendation for all adults older than 40 years of age with diabetes. Patients with diabetes and a CAC score >0 have higher risks than those without diabetes and similar CAC score, but the absence of CAC conveys a similar low risk in both groups (**Table 6)** [134]. Therefore, the more appropriate rationale is for a straightforward risk classification as with any other risk factor, allowing for the possibility of downgrading risk.

Table 6: Relationship of CAC to Events in Asymptomatic Diabetic Patients

First Author (Ref.)	N	Prevalence	HR	AUC	Event rate/yr
Wong et al.1[34]	1823	Any CAC No DM, 53% DM, 75.3%			
Becker et al.1[34]	DM 716	0 CAC, 15% CAC >400, 42%		CAC, 0.77 FRS, 0.68 UKPDS, 0.71 (p < 0.01)	0 CAC, 0.2% >400, 5.6%
Eikeles et al[134]	DM 589		Compared with CAC 0–10: CAC >1, 000, 13.8 CAC 401–1, 000, 8.4 CAC 101–400, 7.1 CAC 11–100, 4.0 CAC 0–10, 1	CAC, 0.73 UKPDS, 0.63 (p < 0.03)	<10, 0%
Anand et al.1[34]	DM 510	CAC <10, 53.7%	Compared with CAC <100: CAC >1, 000, 58 CAC 401–1, 000, 41 CAC 101–400, 10 CAC 0–100, 1	CAC, 0.92 UKPDS, 0.74 FRS, 0.60 (p < 0.001)	

Malik et al.1[34]	DM 881 NO DM 4036		Inc CAC 2.9–6.5 Inc CAC 2.6–9.5	CAC + RF: 0.78–0.80 RF: 0.72–0.73 (p < 0.001)	1.5% 0.5%

Women have traditionally lower risk than men when same age and risk factors are considered.8[6]But, in a study of 2447 women undergoing CAC, FRS frequently disparage their risk even in presence of CAC > 100 or CAC > 75th percentile.8[9] A MESA sub-study of FRS 'low risk' women found 6% had CAC >100 and 4% had CAC > 300.9[0]High CAC was predictive of CVD events even in this 'low risk' group of women with an adjusted hazard ratio of 8.3. As most women under 60 years would be classified as 'low risk' by FRS, perhaps CAC is appropriate for those with 6-10% 10-year risk.

Report from the Multi-Ethnic Study of Atherosclerosis (MESA) [92], a cut-point of 300 CAC was used to define high risk. For noncalcified plaques detected by CT angiography, a highly reproducible method for quantification is not yet available and currently more qualitative instead of quantitative analyses are provided[93].

MESA, a National Heart, Lung, and Blood Institute–sponsored prospective population cohort registry evaluation of 6, 814 individuals followed for 3.8 years[92]in the initial report and as long as 14.5 years in subgroups.

Compared with patients with a CAC score of 0, the hazard ratios (HRs) for a coronary event were 7.73 for those with a CAC score of 101 to 300, and 9.67 for aCAC score > 300 (p <0.001).9[2]

A study by Detrano et al[92], who followed 6722 patients for a mean of 3.9 years and compared clinical risk factors (age, gender, blood pressure, serum cholesterol, smoking, diabetes, family history of CAD, serum triglycerides, serum creatinine, body mass index, waist circumference, and hip circumference), alone and in combination with the CAC score, found area under the curve values of 0.79 and 0.83, respectively. Other studies [8, 87, 95, 97] are quoted in Table

Table 7: Comparison of the CAC score and Framingham risk score, alone and in combination, as predictors of major cardiovascular events, based on the area under the curve

	Sample	Follow-up	Area under the (ROC) curve*		
Study	Number of patients/age	Years (mean)	CACS	FRS	CACS + FRS
Raggi et al.8[7]	10377	5	-	0.68 (M) / 0.67 (F)	0.72 (M) / 0.75 (F)
Greenland et al.8	1312 / > 45 years	7	-	0.63	0.68
Arad et al.9[9]	4613 / 50-70 years	4.3	0.79	0.69	-
Becker et al.9[5]	1726 / 57.7 ± 13.3 years	3.3	0.81	0.63	-

Area under the (ROC) curve > 0.7: satisfactory performance. CACS, coronary artery calcium score; FRS, Framingham risk score; M, males; F, females.

The prognostic value of CAC scoring has been shown to be excellent in multiple large studies[94, 95]. In a study by Raggi et al [87], they elegantly demonstrated a graded annualized event rate in a cohort of 632 asymptomatic patients followed for 32 months. Patients with 0 scores had an annualized event rate of 0.1%. Patients with scores of 1 to 99 had an event rate of 2.1%; scores of 100 to 400, an event rate of 4.1%; and scores > 400, an event rate of 4.8%. Positive CAC scores are associated with an annualized event rate of > 2.0%, which signifies a high-risk state (20% 10-year risk by Framingham) [49].

Shaw and colleagues [97] showed that primary end point increases proportionally with CAC score, even after adjustment for Framingham risk factors. In this retrospective study of 10, 377 patients, they found that CAC scoring had superior outcome classification ability compared with Framingham risk assessment (area under the ROC curve 0.73 vs.0.67; *P* < 0.001). Even more impressive, after patients were stratified according to their Framingham risk, CAC scores were able to further risk stratify these patients. This additional risk stratification was particularly strong in the group of patients with intermediate Framingham risk scores. Finally, they also showed that the relative risk of death for a CAC score of 10 is comparable to the relative mortality risk of diabetes, smoking, and hypertension [97].

In a cohort of 5635 asymptomatic patients, Kondos and colleagues [98] showed the relative risk for cardiac events with a positive CAC score is 10.5, compared with only 1.98 for diabetes and 1.4 for smoking.

The St. Francis Heart Study, a prospective study of 5585 predominantly moderate-to moderately high-risk asymptomatic patients, confirmed earlier study results by showing an increasing event rate with increasing CAC scores[99]. CAC scores > 100 were associated with relative risks from 12-to 32-fold, which represented an absolute event rate of > 2% per year.

There are conflicting results regarding the site, extent of coronary artery calcification and the angiographic grades based on various available data. Atherosclerotic plaque proceeds through progressive stages where instability and rupture can be followed by calcification, perhaps to provide stability to an unstable lesion. As the occurrence of calcification reflects an advanced stage of plaque development, some researchers have proposed that the correlation between coronary calcification and acute coronary events may be suboptimal based largely on angiographic series.

There is no known association between vulnerable plaque and coronary artery calcification. The relation of arterial calcification, like that of angiographic coronary artery stenosis, to the probability of plaque rupture is unknown[100].

Albeit radiographically detected coronary artery calcium can provide an estimate of total coronary plaque burden, due to arterial remodeling, calcium does not concentrate exclusively at sites with severe coronary artery stenosis [101].

It is the co-incidence of calcified and non-calcified plaque that provides the means for estimating acute coronary events. Moreover, albeit CAC detection cannot localize a stenotic lesion or one that is prone to rupture, CAC scoring may be able to globally define a patient's CHD event risk by virtue of its strong association with total coronary atherosclerotic disease burden, as shown by correlation with pathologic lesions.

The Committee judged that it may be reasonable to consider use of CAC measurement in such patients based on available evidence that demonstrates incremental risk prediction information in this selected (intermediate risk) patient group. This conclusion is based on the possibility that such patients might be reclassified to a higher risk status based on high CAC score, and additional patient management may be modified[102].

In order to understand this apparent conflict between the stability of a calcified lesion and CHD event rates, one must recognize the relation between atherosclerotic plaque extent and more prevalent calcified and noncalcified plaque. That is, patients who have calcified plaque are also more likely to have non-calcified or "soft" plaque that is prone to rupture and acute coronary thrombosis.

An analysis of the predictive accuracy of CAC in patients with an intermediate FRS disclose that for a score greater than or equal to 400, the patient's 10-year CHD risk would achieve risk equivalent status similar to that recognized with diabetes or peripheral arterial disease. Thus, clinical decision-making could potentially be transformed by CAC measurement in patients initially judged to be at intermediate risk (10% to 20% in 10 years).1[03]

Most unanticipated cardiovascular events occur in persons at intermediate risk of coronary artery disease (10%–20% 10-year risk). The absence of CAC by cardiac CT is affiliated with a low adverse event risk and hence could be used as a tool to counsel patients about their risk of such events[104].

We included 588 patients (mean age, 61.1 ±9.7 years; women, 64%). The median follow-up period was 707 days. There were 239 patients (49.3%) with no coronary calcium. In these patients, no MACEs were observed, while in those with positive CACS values, they occurred in 108 patients (30.9%) (P<0.001). The incidence of MACEs was dependent on the CACS values, reaching 91% in those with a CACS of 1000 or higher Agatston units.8[0]

RECALL STUDY-The Heinz-Nixdorf Risk factors Evaluation of Coronary Calcium, and Lifestyle study (4200 subjects) provides unbiased information on the extent of coronary calcium in the general German population from a suburban community[26].

O'Rourke, and collegues study is a meta-analysis of various studies which asses the diagnostic or prognostic accuracy of coronary artery calcium. Patients with nonobstructive coronary disease are defined by a stenosis of 50% or 20%. The weighted-average (by sample size) sensitivity and specificity were 80.4% and 39.9%, respectively, whereas specificity values ranged from 21% to 100%. Predictive accuracy ranged from 41% to 95%. Significant coronary calcium scores had a higher accuracy in detecting disease with stenosis >50%. Because this study was conducted in a symptomatic population with an angiographic end point, its application is limited to such patients[105].

Several recent trials in both symptomatic and asymptomatic[104] patients have studied whether the extent of CAC as assessed by EBCT can predict subsequent patient outcome. In 422 symptomatic patients followed for 30 ± 12 months[106] cardiac events were 10-fold higher in patients with a CACS above the 75th percentile for age (9.5 percent) versus those below the 25th percentile (0.9 percent). The CACS remained the best single predictor of risk after adjustment. Wong and colleagues also showed that the CACS severity predicted subsequent events independent of age, gender, and patient risk-factor profile[107].

Calcium score, moreover adding supplementary information to scintigraphy, it is a powerful tool in the assessment of coronary disease. Yet, some situations stand out, as calcium score zero.1[08, 110-112]Absence of calcium in the coronary arteries does not mean absence of atherosclerosis, as there may be non-calcified plaques. But, this situation correlates to a disease of lower extension.1[11, 112]

Albeit the use of Calcium Score in asymptomatic patients is included in more recent guidelines, that is not the case for symptomatic patients.1[13-115]Still, in exams like scintigraphy, [116]literature indicates that, in low or intermediate symptoms and risk of coronary disease, a score of zero is able to deviate the presence of perfusion alterations.

The absence of coronary calcium has been shown to ward off ischemia caused by CAD in patients with low or intermediate symptoms and probability of significant diseases, and CS, when used in conjunction with scintigraphy, shows increase in specificity and positive predictive value of the diagnostic strategy (Figure 4).1[16-118]

However, in the acute presentation of symptoms in the emergency room or in high-risk patients for CAD, the use of Calcium Score is limited, since atherothrombotic phenomena of acute coronary syndromes may be present without calcification. Absence of calcium in symptomatic patients with coronary angiography indication does not exclude the presence of significant lesions.1[19] In such cases, CS does not add diagnostic and prognostic information, and has lower event prediction power than scintigraphy.1[20-122]

Budoff and colleagues, [123] study results, concluded that the value of calcium scoring is its high negative predictive value (about 98%); a negative score (no calcification) is strongly associated with the absence of obstructive coronary disease.

Kavousi and colleagues, [124] in a subsequent meta-analysis of 6, 739 women at low risk of atherosclerotic cardiovascular disease based on the American College of

Cardiology/American Heart Association (ACC/AHA) pooled cohort equation (10-year risk < 7.5%), found that 36.1% had calcium scores greater than 0.compared with those whose score was 0, those with higher scores had a higher risk of adverve events. The incidence rates per 1, 000 person-years were 1.41 vs 4.33 (relative risk 2.92, 95% CI 2.02–3.83; multivariable-adjusted hazard ratio 2.04, 95% CI 1.44–2.90). This study was limited because the population was mostly of European descent, making it less generalizable to non-European populations. Calcium scoring has also been shown to be a strong predictor of incident cardiovascular events across different races beyond traditional risk factors such as hypertension, hyperlipidemia, and tobacco use.

Blaha and workers[48] concluded that a score of 0 would indicate that the patient had a low risk of cardiovascular disease. A test with these characteristics is helpful in excluding cardiovascular disease or at least in determining that it is less likely to be present in a patient deemed to be at intermediate risk.

Carr and colleagues[126] found an association between calcium and coronary heart disease in a younger population (ages 32–46). In 12.5 years of follow-up, the hazard ratio for cardiovascular events increased exponentially with the calcium score: 2.6 (95% CI 1.0–5.7, *P* =.03) with calcium scores of 1 through 19 and 9.8 (95% CI 4.5–20.5, *P* <.001) with scores greater than 100.

Detrano and team[127] in a study of 6, 722 patients with diverse ethnic backgrounds, found that the adjusted risk of a coronary event was increased by a factor of 7.73 for calcium scores between 101 and 300 and by a factor of 9.67 for scores above 300 (*P* <.001). The limitation of this study was that the patients and physicians were informed of the scores, which could have led to bias.

Severe coronary calcification has proven to be an independent risk predictor and it is complementary to virtually all other forms of coronary artery disease evaluation, be it clinical-through risk scores-or complementary-via other non-invasive methods and functional tests-as exercise stress test and scintigraphy.1[28-133, 135]

High calcium score is an indicator of increased risk for cardiovascular events such as heart attack and cardiac death, with higher accuracy, alone or in joint assessments, than clinical risk scores (Figure 5 and 6). Its presence indicates a poor prognosis in these patients, reclassifying them to high-risk groups, regardless of population characteristics.1[08-112]

The presence of a severely high calcium score is also related to a higher frequency of significant lesions, even in patients with normal scintigraphy.1[28] In persistently symptomatic patients with no perfusion alterations, extensive coronary calcification is correlated to the presence of significant lesions and may indicate the need for coronary angiography and percutaneous or surgical intervention.1[29]

Extensive coronary calcification is related to a higher incidence of significant obstructive disease and revascularization, even when the result of the provocative test is normal.1[30-132]

Increased coronary calcification is therefore able to correlate to the presence of obstructive lesion, even when the provocative test is normal, minimizing false-negative results with the combined use of both methods.1[33] This joint strategy is also able to refer patients who would benefit from additional investigation or invasive approaches (Figure 7 and 8).1[36]

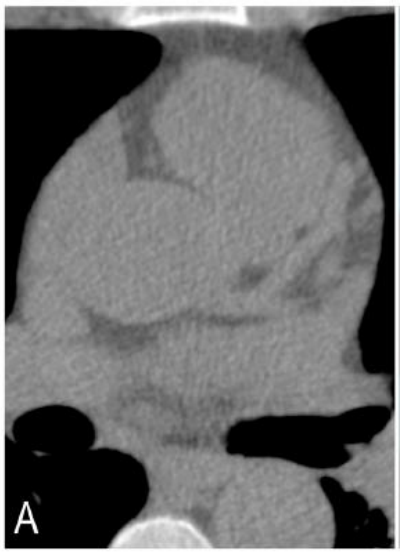

Figure 4: Patient with calcium score zero. (A) Absence of calcified plaques. Risk of coronary disease below 5% and low risk of cardiovascular events (0, 1% per year)

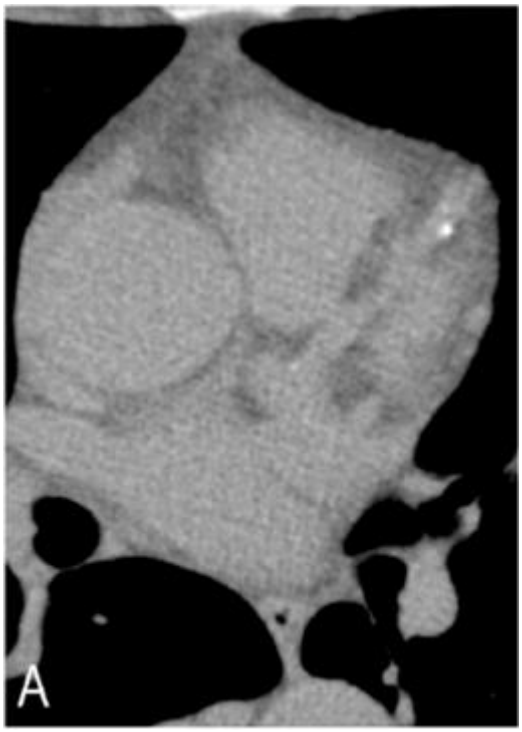

Figure 5: Patient with calcium score 1-10. (A) Minimal quantity of calcified plaques in the territory of the anterior descending artery. Probable risk (obstructive coronary disease below 10%)

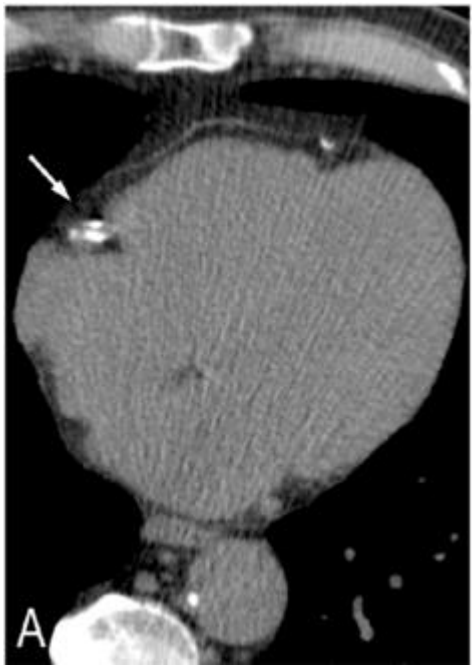

Figure 6: Patient with calcium score 11-100. (A) Discreet quantity of calcified plaques in the territory of the right coronary. Definite coronary artery disease, though discreet

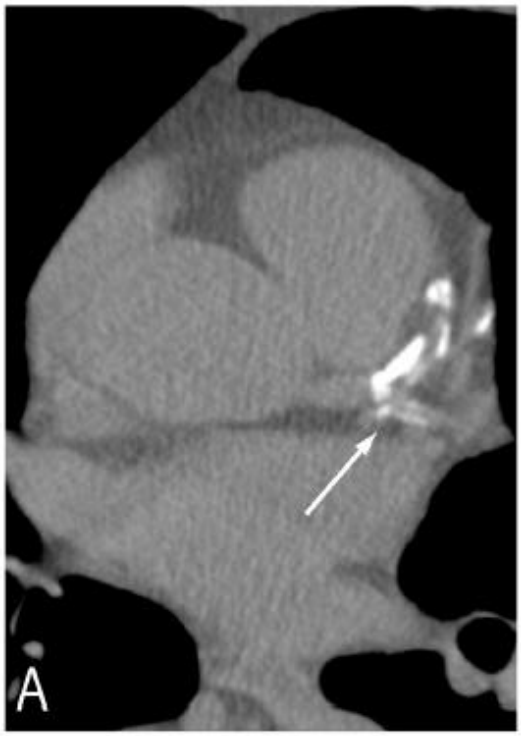

Figure 7: Patient with calcium score 101-400. (A) Moderate quantity of calcified plaque in the territories of the anterior descending and circumflex arteries. Moderate coronary arterial disease

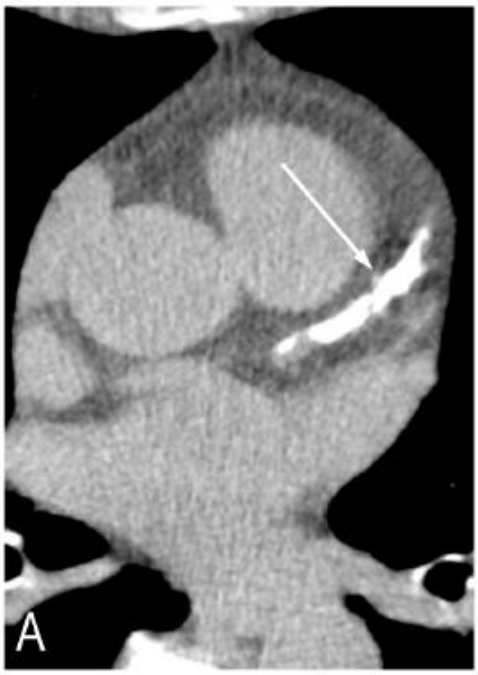

Figure 8: Patient with calcium score above 400. (A) Large quantity of calcified plaques in the territory of the anterior descending artery. Significant coronary artery disease

Both the absolute CACS and the relative CACS percentiles adjusted for age and gender predicted subsequent death and nonfatal MI. Hard cardiac events occurred in only 0.3 percent of subjects with a normal EBCT, but this increased to 13 percent in those with a CACS >400. A very high CACS 1000 may portend a particularly high risk of death or MI (i. e., 25 percent per year) [137]

The ROTTERDAM HEART STUDY[138] investigated 1795 asymptomatic participants (mean age 71 years) who had CAC and measured risk factors. During a mean follow up of 3.3 years, the multivariate-adjusted relative risk of coronary events was 3.1 (95 percent CI, 1.2–7.9) for calcium scores of 101 to 400, 4.6 (95 percent CI, 1.8–11.8) for calcium scores of 401 to 1000, and 8.3 (95 percent CI, 3.3–21.1) for calcium scores >1000 compared with calcium scores of 0 to 100.

The COOPER CLINIC STUDY[139] conducted in 10, 746 adults who were 22 to 96 years of age and free of known CHD. During a mean follow up of 3.5 years, 81 hard events (CHD death, nonfatal MI) occurred. Age-adjusted rates (per 1000 person years) of hard events were computed according to four CAC categories: no detectable CAC and incremental sex-specific thirds of detectable CAC; these rates were, respectively, 0.4, 1.5, 4.8, and 8.7 (trend $p < 0.0001$) for men and 0.7, 2.3, 3.1, and 6.3 (trend $p < 0.02$) for women.

Raggi and colleagues[154]demonstrated an annual event rate of 0.11% in asymptomatic subjects with a CAC score of 0 (10-year risk of only 1.1%), and in the St. Francis Heart Study scores of 0 were associated with a 0.12% annual event rate over 4.3 years[99]. In the MESA[92], a CAC score of 0 was associated with a 0.11% annual event rate. In a meta-analysis of 64, 873 patients followed for 4.2 years[153], the coronary event rate was 0.13% per year in the 25, 903 patients with a CAC score of 0 compared with 1% per year

for the 42, 283 with a CAC score >0. In an analysis of all-cause mortality in 44, 052 asymptomatic patients followed for 5.6 years[155,] the number of deaths per 1, 000 patient-years for the 19, 898 patients with a CAC score of 0 was 0.87 compared with 1.92 for those with a CAC score of 1 to 10 and 7.48 for those with a CAC score >10.

Aims and Objectives

The study was aimed at estimating the coronary artery calcium score (CACS) and its association with incidence of MACE among atypical chest pain and asymptomatic Intermediate probability CAD patients.

Primary objective

To assesses the coronary artery calcium score (CACS) of the atypical chest pain and asymptomatic Intermediate probability CAD patients (absolute 10 year cardiovascular risk score 10 to 20) presenting to a tertiary cardiac care centre.

Secondary objectives

1) To assess the incidence of Major adverse cardiovascular events (MACE: including cardiac death, nonfatal myocardial infarction (MI), and coronary revascularization) at 1 year follow up.

2) To assess the association between the coronary artery calcium score (CACS) and stable and unstable angina patients at 1 year follow up.

3. Material and Methods

a) **Study Site**: The study was conducted in the department of cardiology, Ramesh Cardiac and Multispeciality hospital Pvt. Ltd, Vijayawada.
b) **Study Population:** Patients attending Cardiology department of Ramesh Cardiac and Multispeciality hospital Pvt. Ltd, Vijayawada.
c) **Study Design:** A prospective, cross-sectional, observational study.
d) **Sample size**: Sample size was calculated assuming the proportion of CACS positivity as 50.7% as per the study by Parma Z **e**t al. The other parameters considered for sample size calculation were 10% absolute precision and 95% confidence level. The following formula was used for sample size calculation.

$$N = \frac{Z^2 P(1-P)}{d^2}$$

Where *n* = Sample size
Z= Z statistic for a level of confidence level= 1.960
P = Expected prevalence/proportion of outcome= 0.507
d = Precision= 0.1

The required sample size as per the above-mentioned calculation was 96. To account for a non-participation rate/ loss to follow up rate of a about 5%, another 5, subjects will be added to the sample size. Hence the final required sample size would be 101.

e) **Duration of Study:** Recruitment of the study participants was done for a one year period between 1st April, 2017 to 31st March, 2018.
f) **Sampling method:** All the eligible subjects were selected sequentially until the sample size was reached.
g) **Inclusion criteria:**
- Intermediate risk patients (absolute 10 year cardiovascular risk score 10 to 20) who are asymptomatic.
- Atypical chest pain patients.
- Family history of pre-mature cardiovascular disease.

h) **Exclusion criteria:**
- Patients with-Chronic kidney disease
- Uncontrolled tachycardia
- Technically inadequate CT

i) **Methodology: Clinical evaluation:** After obtaining informed consent all individuals are subjected to detailed history and clinical examination. Each patient had a standard questionnaire regarding diabetes mellitus type 2, systemic arterial hypertension, dyslipidemia, smoking, family history of premature coronary artery disease.

Systemic arterial hypertension was defined according to ACC/AHA guidelines 2017.

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions); DBP, diastolic blood pressure; and SBP, systolic blood pressure

Diabetes mellitus was defined according to ADA standards of medical care in diabetes 2015.
Criteria for the diagnosis of diabetes-
HbA1C >6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. * OR
FPG >26 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h. * OR 2-h PG >200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. * OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Dyslipidemia was defined according to ESC/EAS guidelines 2016. A positive history of smoking was defined as smoking or smoking cessation within 3 months of the examination. Family history of pre-mature coronary artery disease was defined as the presence of CAD in first-degree relatives younger than 55 (men) or 65 (women) years of age. The family history of coronary heart disease was obtained by

asking participants whether any member in their immediate family (first-degree relatives) experienced a fatal or nonfatal myocardial infarction and/or coronary angioplasty/coronary artery bypass surgery. The event was considered premature if it occurred before the age of 55 years in male relatives and before 65 year of age in female relatives, whereas events reported after these age cutoffs were considered late onset in nature.

Diagnostic evaluation: After the clinical assessment, patients underwent diagnostic evaluation on the same day of clinical evaluation who are having atypical chest pain and had calculated intermediate risk using Global risk scores (such as the Framingham Risk Score [FRS] – age, gender, LDL or total cholesterol, HDL cholesterol, systolic blood pressure, currently being treated for hypertension, diabetes, smoker) that use multiple traditional cardiovascular risk factors obtained for risk assessment in all asymptomatic adults. All patients had underwent ECG, 2d Echocardiography, routine blood investigations, and coronary artery calcium score.

Cardiac CT imaging protocol
All CT scans were performed on a 256-slice scanner with a 270milli second per rotation (Philips Brilliance iCT 256-slice system, Philips Essence Technology). Non-enhanced CT scan for calcium scoring was performed from the level of tracheal bifurcation to the diaphragm using the following parameters: 120 KVp, 300 mA, 0.270 s, slice thickness of 3 mm, and intervals of 3 mm, 80 mm coverage per gantry rotation. The calcium scores of each area at each vessel were calculated at an offline commercially available workstation with dedicated software and the scores were quantified by the scoring algorithm proposed by Agatston et al.1[27], and calcium scores were classified into the following categories: 1 = 0 CACS; 2 = 1–99 CACS; 3 = 100–399 CACS; 4 = 400-999 CACS and 5 ≥ 1000 CACS.

Follow-up: All individuals were followed up periodically at 1 month, 3 months, 6 months and 1year after enrolment into study and events were recorded and analysed. All deaths and hospitalisations were recorded. Cause of death was ascertained from admission medical records if death happened in the hospital or through telephonic interview with the family. Deaths were categorised as cardiac and non-cardiac. Reasons for admissions were ascertained from medical records.

Clinical events recorded were:
Stable angina,
Unstable angina,
Myocardial infarction and
Death form cardiovascular cause.
Stable angina was defined according to ACC/AHA guidelines 2014. Unstable angina was defined according to ACC/AHA guidelines 2014. Myocardial infarction was defined according to Third Universal Definition of Myocardial Infarction.

Major Adverse Cardiovascular events (MACE) was defined as the occurrence of cardiac death or myocardial infarction orneed of revascularization.

Statistical Methods
Continuous data will be summarized as Mean ± SD (standard deviation) while discrete (categorical) in number and percentage.

Quantitative data will be analyzed by-mean, SD, T TEST
Qualitative data will be analyzed by –

- Percentage,
- Chi square test,
- Fisher exact test.

Descriptive analysis was carried out by mean and standard deviation for normally distributed quantitative variables, the median and interquartile range for non-normally distributed quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram and pie diagram.

The association between categorical variables and non-normally distributed quantitative variables was assessed by comparison of median values across the groups using Mann Whitney U test/ Kruskal Wallis test. The association between two quantitative variables was assessed by person/ Spearman rank correlation coefficient.

Association between two categorical variables was assessed by cross tabulation. Statistical significance of the difference between the proportions was assessed by chi square test/ Fisher's exact test.

Statistical significance
P>0.05 is not significant
P<0.05 is significant
P<0.01 is highly significant

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

Ethical considerations:
The study was approved by the institutional human ethics committee. Informed written consent was obtained from all the participants after providing detailed information on objectives of the study, risks and benefits involved and voluntary nature of participation. The confidentiality of the study participants was maintained throughout the study.

4. Results & Observations

The final analysis included 108 subjects as per inclusion criteria.

Table 8: Distribution of study subjects based on their age category (N=108)

Age group (years)	Frequency	Percent
40-50 Years	34	31.5%
51-60 Years	52	48.1%
>61 Years	22	20.4%
Total	108	100.0%
Mean Age	54.55 + 7.778	

Majority (48.1 %) of the patients were observed in age groups of 51 to 60 years. The proportion of patients who

were aged between 40-50 years was 31.5%, aged 61 and above years was 20.4 %.

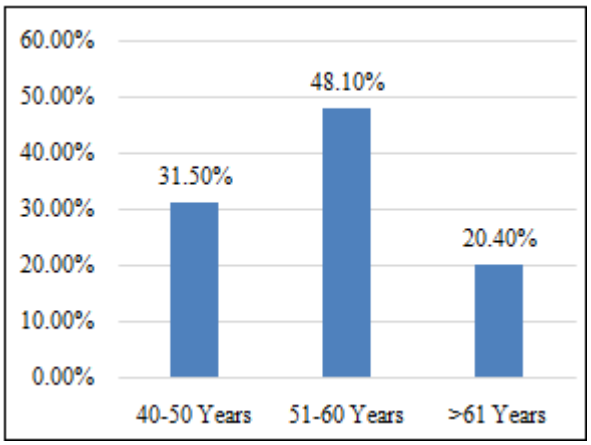

Figure 9: Distribution of study subjects based on their age category

Table 9: Distribution of study subjects based on their Gender (N=108)

Gender	Frequency	Percent
Males	67	62.0%
Females	41	38.0%
Total	108	100.0%

Males constituted 62% of the study population and females constituted remaining 38% of the study population.

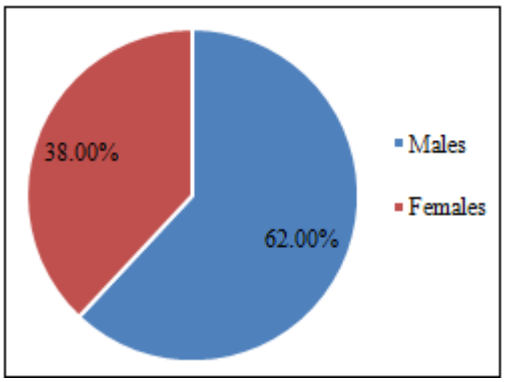

Figure 10: Distribution of study subjects based on their Gender

Table 10: Distribution of study subjects based on the risk factor –systemic hypertension in the study population (N=108)

Risk Factor	Frequency	Percent
Hypertensive	59	54.6%
Non-hypertensive	49	45.4%
Total	108	100.0%

Risk factor systemic hypertension constituted 54.6% of the study population and non-hypertensives constituted remaining 45.4% of the study population.

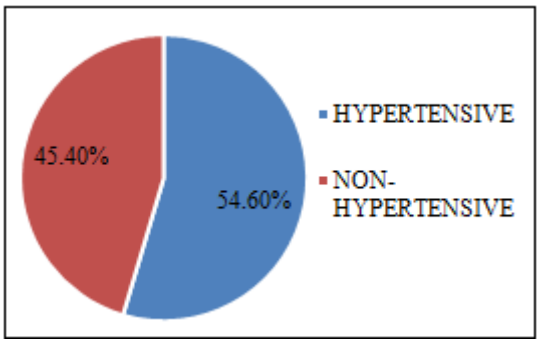

Figure 11: Distribution of study subjects based on the risk factor –systemic hypertension

Table 11: Distribution of study subjects based on the risk factor –diabetes mellitus in the study population (N=108)

Risk Factor	Frequency	Percent
Diabetic	40	37.0%
Non-diabetic	68	63.0%
Total	108	100.0%

Diabetes mellitus type-2 constituted 37% of the study population and non-diabetics constituted remaining 63% of the study population.

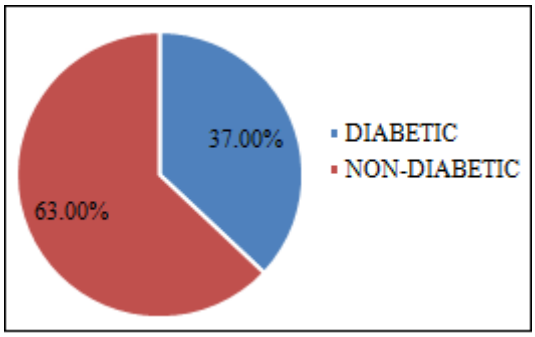

Figure 12: Pie chart of risk factor-diabetes mellitus type-2 in the study population (N=108)

Table 12: Descriptive analysis of risk factor – Family history of pre-mature CAD in the study population (N=108)

Family H/O Pre-Mature CAD	Frequency	Percent
Positive	65	60.2%
Negative	43	39.8%
Total	108	100.0%

Risk factor of family history of pre-mature of CAD constituted 60.2% of the study population and negative subjects constituted remaining 39.8% of the study population.

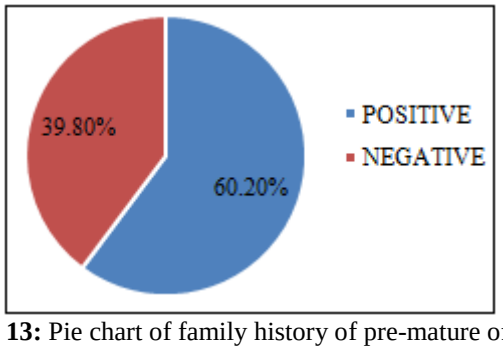

Figure 13: Pie chart of family history of pre-mature of CAD in the study population (N=108)

Table 13: Descriptive analysis of smoking habit in the study population (N=108)

	Frequency	Percent
Smokers	21	19.4%
Non-Smokers	87	80.6%
Total	108	100.0%

Risk factor-smoking constituted 19.4% of the study population and non-smokers constituted remaining 80.6% of the study population.

Table 14: Descriptive analysis of CACS groups and respective frequency in the study population (N=108)

CACS Groups	Frequency	Percent
0	47	43.5%
1-99	31	28.7%
100-399	19	17.6%
400-999	10	9.3%
>1000	1	0.9%
Total	108	100.0%

CACS groups and respective frequency in the study population. In CACS group zero 47 subjects, group 1-99 were 31 subjects, 100-399 were 19 subjects, 400-999 were 10 subjects and more than 1000 in one. The overall number of subjects with CACS positive status was 61 (66.5%) among the study population.

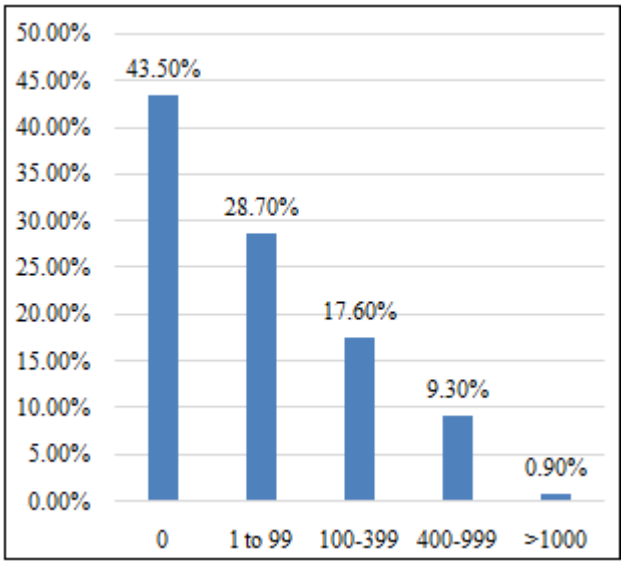

Figure 14: Bar chart of CACS groups and respective frequency in the study population (N=108)

Table 15: Descriptive analysis of diabetic subjects with positive calcium score in the study population (N=108)

			CAC category		Total
			Positive CACS	Negative CACS	
Diabetes Mellitus	Yes	N	31	9	40
		%	50.8%	19.1%	37.0%
	No	N	30	38	68
		%	49.2%	80.9%	63.0%
Total		N	61	47	108
		%	100.0%	100.0%	100.0%

Chi-Square: 11.418, P Value: 0.001, Statistically significant

Positive CAC score is present in 50.8% patients with diabetes and negative CAC score is present in 19.1% diabetic patients. The association between the groups was found to be statistically significant.

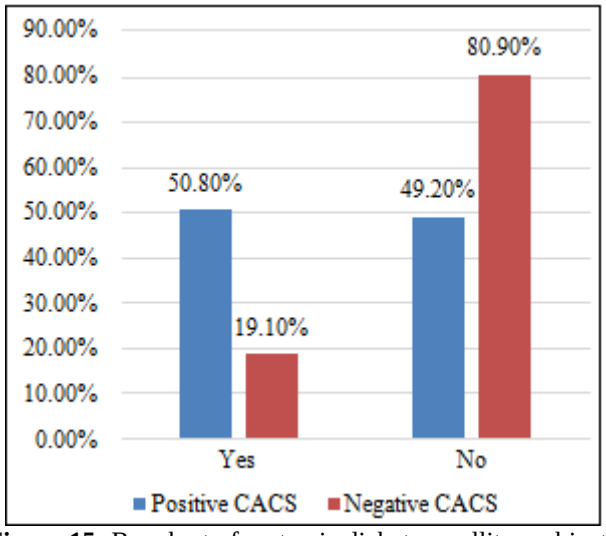

Figure 15: Bar chart of systemic diabetes mellitus subjects with positive calcium in the study population (N=108)

Table 16: Descriptive analysis of systemic hypertension subjects with positive calcium score in the study population (N=108)

			CAC category		Total
			Positive CACS	Negative CACS	
Hypertension	Yes	N	19	40	59
		%	31.1%	85.1%	54.6%
	No	N	42	7	49
		%	68.9%	14.9%	45.4%
Total		N	61	47	108
		%	100.0%	100.0%	100.0%

Chi-Square: 31.184, P Value: 0.001, Statistically significant

Positive CAC score is present in 31.1% patients with hypertension and negative CAC score is present in 85.1% hypertensive patients. The association between the groups was found to be statistically significant.

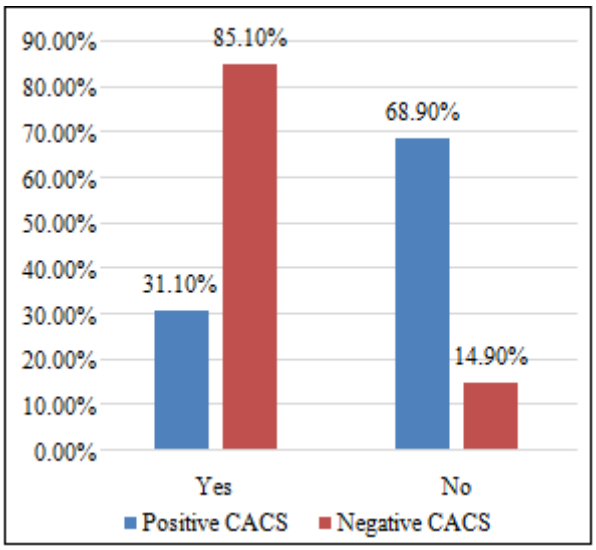

Figure 16: Bar chart of hypertension with positive calcium in the study population (N=108)

Table 17: Descriptive analysis of smokers with positive calcium in the study population (N=108)

			CAC category		Total
			Positive CACS	Negative CACS	
Smoking	Yes	N	14	7	21
		%	23.0%	14.9%	19.4%
	No	N	47	40	87
		%	77.0%	85.1%	80.6%
Total		N	61	47	108
		%	100.0%	100.0%	100.0%

Chi-Square: 1.100, P Value: 0.212, Statistically not significant

Positive CAC score is present in 23% smokers and negative CAC score is present in 14.9% smokers. The association between the groups was found to be statistically not significant. But clinically found to have significant association between smokers and coronary calcium.

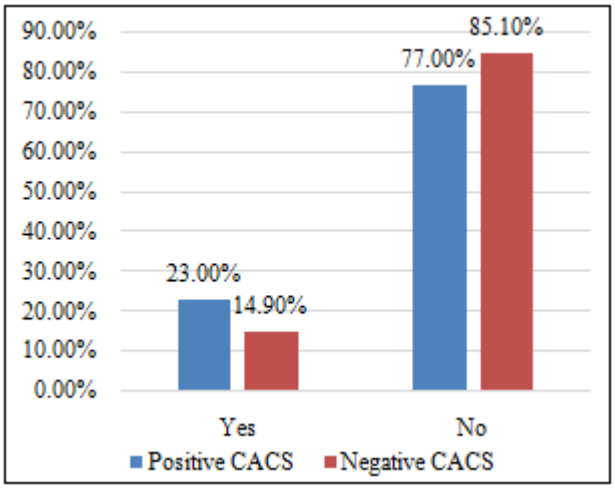

Figure 17: Bar chart subjects of smokers with positive calcium score in the study population (N=108)

Table 18: Descriptive analysis of subjects of family history of pre-mature CAD with positive calcium score in the study population (N=108)

			CAC category		Total
			Positive CACS	Negative CACS	
Family H/O CAD	Yes	N	42	23	65
		%	68.9%	48.9%	60.2%
	No	N	19	24	43
		%	31.1%	51.1%	39.8%
Total		N	61	47	108
		%	100.0%	100.0%	100.0%

(Chi-Square: 4.394, P Value: 0.029, Statistically significant)

Positive CAC score is present in 68.9% patients with family history of CAD and negative CAC score is present in 48.9% patients with family history of CAD. The association between the groups was found to be statistically significant.

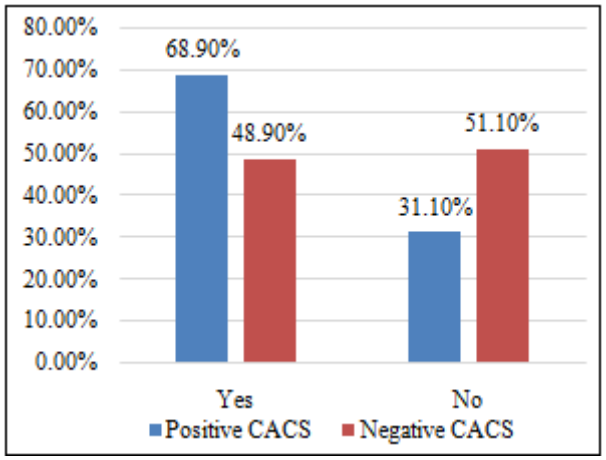

Figure 18: Bar chart of family history of pre-mature CAD with positive calcium score in the study population in the study population (N=108)

Table 19: Descriptive analysis of respective genders with positive calcium score in the study population in the study population (N=108)

			CAC category		Total
			Positive CACS	Negative CACS	
Gender	Males	N	44	23	67
		%	72.1%	48.9%	62.0%
	Females	N	17	24	41
		%	27.9%	51.1%	38.0%
Total		N	61	47	108
		%	100.0%	100.0%	100.0%

(Chi-Square: 6.064, P Value: 0.012, Statistically significant)

Respective genders with positive calcium score in the study population in the study population. Positive CAC score is present in 72.1% male patients and negative CAC score is present in 48.9% male patients. . Positive CAC score is present in 27.9 % female patients and negative CAC score is present in 51.1 % female patients. The association between the groups was found to be statistically significant. Male gender found to have significant association with coronary calcium.

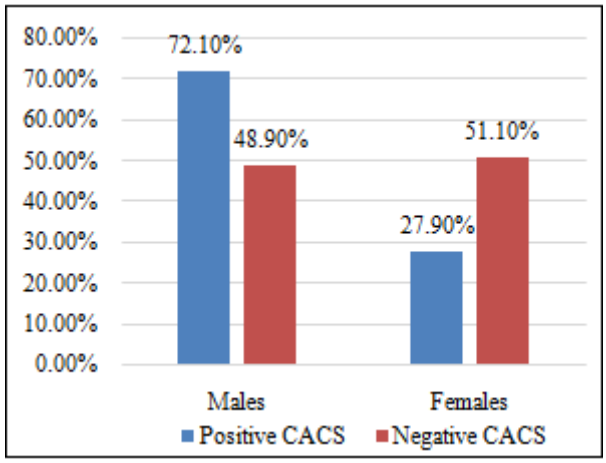

Figure 19: Bar chart of respective genders with positive calcium score in the study population in the study population

Table 20: Descriptive analysis of mean age of positive and negative calcium score in the study population (N=108)

Mean Age						P-value
CAC category	N	Minimum	Maximum	Mean	Std. Deviation	
Positive	61	40	70	56.69	7.352	t = 4.2700 df = 106 P value <0.001
Negative	47	40	62	51.06	5.998	

Mean age of positive and negative calcium score in the study population were calculated respectively. Mean age of positive calcium score group was 56.69 years in the study population and 51.06 years with negative calcium score group in the study population.

Table 21: Occurrence of major cardiovascular events among the study population

MACE	*Number*	*Percentage*
Overall MACE		
Yes	**16**	**14.81**
No	**92**	**85.19**
Timing of development of MACE		
Within 1 month	**0**	**0**
Between 1 to 3 months	**3**	**2.78**
Between 3 to 6 months	**7**	**6.48**
Between 6 months to 1 Year	**6**	**5.55**
No MACE	92	85.19
Type of MACE		
PCI	12	**11.11**
CABG	4	**3.70**
No MACE	92	85.19

Telephonic follow up after enrolment into study	Stable angina	Unstable angina	MI	Death
0 – 1 month	0	0	0	0
1 – 3 months	0	3	0	0
3 – 6 months	0	7	0	0
6 – 12 months	1	4	1	0

All the individuals were followed up periodically over telephone-1 month, 3 months, 6 months and 1year after enrolment into study. Patients were enquired about specific events (stable angina, unstable angina, myocardial infarction and death). Five patients who had events were living far away from our centre, and the event data retrieved through telephonic interview. For the remaining patients who had the events, hospital records of these patients were retrieved and ascertained accordingly and were physically followed up periodically. There were 16 (14.81%) subjects who developed MACE at the end of 1 year follow up. Out of them 3 (2.78%) events happened 1 month to 3 months and 7 (6.48%) happened between 3 month to 6 months follow up period and remaining 6 (5.55%) events happened between 6 months to 1 year. Among 108 subjects 12 (11.11%) subjects underwent PCI and 4 (3.70%) underwent CABG.

Table 22: Descriptive analysis of event occurrence in different CACS groups in the study population

Positive CACS	Frequency	Event Occurrence
1-99	3	9.68%
100-399	5	26.31%
400-999	7	70%
>1000	1	100%

No events occurred in group with calcium score zero. CACS group 1-99 AU had 9.68% events, group 100-399 AU had 26.31%, group 400-999 AU had 70% and group >1000 AU had 100% events. It was shown that as the calcium score increases the risk of events increases.

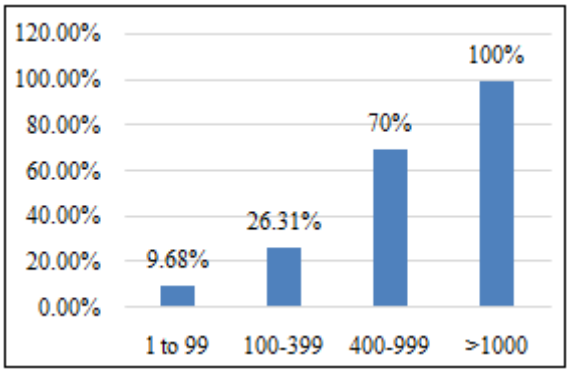

Figure 20: Bar chart of event occurrence in different CACS groups in the study population

5. Discussion

The present study was conducted in the department of cardiology, Dr Ramesh cardiac and multispecialty hospital Pvt. Ltd. Vijayawada from 1st april 2017 to 31st march, 2018.

In a cohort of 108 consecutive patients at predominantly intermediate risk for CAD, and with no prior documented coronary artery disease, we observed that the presence of coronary artery calcium in general, but in particular in the subgroups with incremental CACS values, is an excellent predictor of MACEs at medium term. In our study, CACS was treated as the first non-invasive diagnostic test. Any previous non-invasive tests were not taken into consideration.

The FHS (Framingham Heart Study) included the CAC measurement by MDCT to the examinations of the Framingham Offspring and Third Generation cohorts in 2005. The FHS is limited to white men and women, but distributions of CAC >0 and CAC >100 were similar to those previously reported from MESA. An analysis from the CAC data evaluated whether information on the distribution of CAC and coronary dominance, as detected by MDCT, was incremental to the traditional Agatston score in predicting incident CHD. During a median follow-up of 7 years, the number of coronary arteries with CAC and the presence of CAC in the proximal dominant coronary artery were significantly associated with major CHD events after multivariate adjustment for Framingham risk score and categories of Agatston score. This analysis suggested that additional information from MDCT can augment the traditional Agatston score for risk prediction.1[47]

In our study majority (48.10%) of the patients were observed in age groups of 51 to 60 years. The proportion of patients who were aged between 40-50 years was 31.50 %, aged 61 and above years was 20.40 %. Majority of the patients were within the age group of 51 to 60 years (n = 52), which is in line with that observed by Pereira et al[125] in their studies. This further reinforces the observation made by McClelland et al[111] that CAC increases with age.
Males constituted 62% of the study population and females constituted remaining 38% of the study population. Several

studies done in calcium score recorded a similar ratio, suggestive of a likely higher prevalence in males compared to females.1[09, 111, 112.]

Mean age is54.55 + 7.778 years in our study. The mean age in the HNR study[146] was 59 + 8 years, and 53% of participants were women. Among 1, 918 men, CAC prevalence was 82%, and in 2, 148 women, CAC prevalence was 55%. CAC > 400 was found in 16.3% of men and 4.4% of women. The mean age of the population was 53.9 ± 9.2 years, which was slightly higher compared to similar studies done in Brazilians and African Americans.1[25] The MESA study studied 2, 600 asymptomatic women, mean age 61.5 years, the median Agatston score was 0 (interquartile range, 0-26), CHD occurred in 53 (2%) subjects [96]. The area under the curve (AUC) for CHD increased significantly from 0.805 for the base model to 0.835 with the addition of CAC scanning in women. AUC in our study was 0.922. Similar findings were observed in a study by Raggi *et al*. supporting the role of the Agatston score as a risk stratification tool for women.

A meta-analysis in low-risk women[149] found that CAC >0 was present in approximately one-third and was associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD) and modest improvement in prognostic accuracy compared with traditional risk factors. A meta-analysis was conducted in elderly subjects (mean age 70 years) [148] from among 4, 778 participants from 3 U. S. cohorts, including MESA, Framingham, and the Cardiovascular Health Study. Over 11 years of follow-up, 405 coronary heart disease (CHD) and 228 stroke events occurred. CAC score (vs. age) had a greater association with incident CHD and modestly improved prediction of incident stroke. Findings were similar in the Rotterdam and HNR cohorts.

Moreover, the study also included assessment of the traditional risk factors that predisposes patients to CAD. Statistics from the data we collated showed that hypertension was one of the prevalent risk factor among the study population (n =59, 54.6 %). Risk factor diabetes melltus type-2 was, prevalent in 37% (n = 40) of the patients. A similar trend was observed by Schuhbaeck et al[84]in their study on patients with suspected CAD, where hypertension and diabetes accounted for 56% and 10%, respectively.

Risk factor with family history of pre-mature of CAD constituted 60.2 % of the study population. Risk factor-smoking constituted 19.40 % of the study population.

In CACS group with zero AU there were 47 subjects, group with CACS 1-99 AU constituted 31 subjects, 100-399 AU were 19 subjects, 400-999 AU were 10 subjects and more than 1000 AU in one. Mean age of male gender in respective CACS group in the study population was; cacs group zero – 51.04 years, 1-99 AU was 52.05 years, 100-399 AU was 60.14yrs and 400-999 AU was 61.22 years. With increasing age there is an linear relationship with incremental coronary calcium score.
As discussed, majority of the patients in our study had a CS of 0 (n = 47, 43.51%), with the CS between 1 and 400 and >400 accounting for 46.30% (n = 50) and 10.19% (n = 11) of patients, respectively. Similar results have been reported by other studies.8[5, 91] Further analysis of the CS based on gender showed that the nine subjects who had a CS >400 were males, buttressing the fact that coronary artery calcification is more prevalent in men compared to women.1[09, 111, 112] Subsequent analysis based on age revealed that majority of patients in CS = 0 category were within the age groups of 40–50 years and 51–60 years. The eleven patients with CS >400 were found within the age groups of 51–60 years (n = 5) and more-than 60 years (n = 6). This suggests further that a rising CS may be associated with an increase in age as noted by other studies.8[5, 111] In addition, as observed by Rao et al[85] in a similar study that there was a negligible risk of developing CAD in subjects with CS = 0, it presupposes that majority of the patients involved in our study are at a lower risk of developing CAD. The *P*-value observed indicates that the distribution of CAC is significantly affected by the age of our study population.

Diabetic subjects with positive calcium score constituted 50.8 % in our diabetic population. Kramer et al.9[4] reviewed eight studies involving a collective total of 6, 521 patients and found that individuals with diabetes and a CAC score < 10 were 6.8 times less susceptible to all-cause mortality and cardiovascular events, as well as to cardiovascular events alone, than were those with diabetes and a CAC score > 10. A CAC score > 10 was associated with an increased risk of mortality and cardiovascular events in such individuals, with high sensitivity and low specificity.

Raggi et al.8[7] also found that patients with diabetes have a greater increase in risk for mortality associated with a given degree of calcium than the non-diabetic patients. Diabetic patients without any evidence of coronary calcification have a survival rate similar to non-diabetic patients with a zero calcium score during 5 years of follow-up. These results suggest that coronary calcium might be useful to further stratify short-term risk in diabetic patients.

Patients affected by diabetes mellitus have been shown to have extensive coronary artery calcium deposits on EBT imaging [140-142]. In this large observational study, we showed that the presence of any degree of coronary artery calcium in patients with diabetes mellitus portends a higher risk for all-cause mortality than in non-diabetic patients. Additionally, the absence of coronary artery calcium indicated a low short-term risk of death for diabetic patients as well as subjects without diabetes. Therefore, the absence of measurable atherosclerosis appears to be an important modifier of outcome even in the presence of established severe risk factors for atherosclerosis such as diabetes mellitus. Our clinical experience closely resembles the observations recently made by Kang et al.1[43] and Giri et al.1[44]. In those studies, patients affected by diabetes mellitus who underwent a stress myocardial perfusion single-photon emission computed tomography had a much greater risk of acute coronary events and death than did non-diabetic individuals for any degree of demonstrable perfusion abnormality. Similar data were published by Marwick and colleagues [145] using stress echocardiographic techniques. Taken together, these findings suggest that any extent of

disease burden is more dangerous in diabetic patients than in non-diabetic individuals.

Systemic hypertension subjects with positive calcium score constituted 31.1 % in the hypertensive group. It was observed that calcium score had no significant relationship in the hypertensive group.

Smokers with positive calcium score constituted 23 % of the smoker population, which was Statistically not significant but clinically found to have association with coronary calcium. subjects of family history of pre-mature CAD with positive calcium score constituted 68.9% in the risk group, showing statistically significant association with coronary calcium. Males with positive calcium score constituted 72.1 % of the gender population and females with positive calcium score constituted 27.9%, which was statistically significant. Male sex showed a close association with the coronary calcium.

Mean age of positive calcium score group was 56.69 years and 51.06 years with negative calcium score group in the study population. CACS group zero with mean calcium score of zero had a mean age of 51.06 years, CACS group 1-99 with mean CAC of 27.20 AU had mean age of 53.32 years, CACS group 100-399 with mean CAC of 201.57 AU had mean age of 59.37 years, CACS group 400-999 with mean CAC of 588.16 AU had mean age of 61.30 years, CACS group >1000 with mean CAC of 1321.24 AU had mean age of 64 years. It was shown in our study that with increase in age, there is linear association with increment in mean CAC in each CACS group. So, as age increases the coronary artery calcium score increases.

There were 16 events in the study population during the follow-up. Out of 108 subjects percutaneous intervention was needed in 12 and coronary artery bypass surgery in four subjects. No events occurred in group with calcium score zero. CACS group 1-99 AU had 9.68% (n = 3) events, group 100-399 AU had 26.31% (n = 5), group 400-999 AU had 70% (n = 7) and group >1000 AU had 100% (n = 1) event rate. It was shown that as the calcium score increases the risk of events increases. Only patients with positive cacs required revascularization during follow-up. In Cacs<100 AU, PCI and CABG rarely necessary. Need for PCI significantly increased with cacs>100 AU. CABG needed in cacs>565 AU in our study group. Our findings were similar to the study done by Lamont et al. A large study by Lamont et al[139] reported a follow-up on 11, 000 patients who underwent screening medical examination including CAC score during 1995–2000. In a mean follow-up of 3.5 years in asymptomatic men and women, CHD events (nonfatal MI and CHD-related deaths) were higher with a CAC score >400.

No primary end point noticed in cac – 0 AU. Incidence of primary end point was dependant on cac score values.

Notably, in our group, no MACE occurred in patients with a CACS of 0 AU. This is in contrast to the results of the Coronary CT Angiography Evaluation for Clinical Outcomes (CONFIRM) registry, [8] in which symptomatic patients with a CACS of 0 AU had the same MACE rate as those with positive CACS values. It has to be noted, however, that the CONFIRM findings concerned only a small group of patients (1.8%) in whom obstructive coronary lesions were present. The CORE64 study[17]reported a high (19%) proportion of patients with coronary stenosis in the absence of calcium, but their population was different than ours because it only included patients with clinical indications to invasive coronary angiography.

Our findings are compatible with those of Sarwar et al, [15]who reported a low, 1.8% incidence of MACEs during the 42-month follow-up in a large group of symptomatic patients with no coronary calcium. In this group, the relative risk of cardiac events was very low (RR, 0.09; *P* <0.0001) when compared with patients with positive CACS values. The absence of MACE in our group with a negative CACS can be explained by the age of our population. Noncalcified obstructive or nonobstructive plaques are mostly present in patients younger than 45 years, [6, 26] whose contribution to our group was low.

In our study, a CACS of 1 AU or higher was associated with a risk of MACEs. However, only 9.68% of the patients with a CACS of 1 AU or higher but lower than 100 AU experienced MACEs. We found that in asymptomatic subjects, the optimal cut-off value for the prediction of MACE is 82 AU. This is similar to the findings of Keelan et al, [18] who reported a 3-fold increase in the incidence of hard cardiac events in patients with a CACS of more than 100 AU than in those with a CACS of less than 20 AU. Also Schmermund et al[26] found a significant increase in MACEs in symptomatic subjects with CACS exceeding 100 AU. Traditionally, subjects with a CACS of less than 100 AU, 100–399 AU, and exceeding 400 AU are classified as being at low, intermediate, and high risk, respectively.1[2] These values, however, were established for asymptomatic subjects and were based on the diagnostic rather than prognostic predictors.2[7]

We confirmed that these strata are useful for risk stratification in asymptomatic patients. Our results are in accordance with the data published by Al-Mallah et al, [20] whose study groups had similar characteristics (symptomatic, mean age of 56 years, 50% of men, 56% of patients with a CACS of 0 AU). They found that a CACS exceeding 400 AU improved prediction of hard cardiac events beyond clinical data. In our study, the introduction of an additional stratum with a CACS exceeding 1000 AU enabled the identification of a very high-risk group, with an 100% rate of MACE. CAC score >400 is a CHD equivalent, with 10-year event rates exceeding 20% in asymptomatic patients.

An analysis of all-cause mortality in 44, 052 asymptomatic patients followed for 5.6 years, the number of deaths per 1, 000 patient-years was 7.48 for a CAC score >10 compared with 1.92 for a CAC score of 1 to 10 and 0.87 for CAC score of 0 [153]. Metaanalysis done in 64, 873 patients followed for 4.2 years, the coronary event rate was 1% per year for the 42, 283 with a CAC score >0 compared with 0.13% per year in the 25, 903 patients with a CAC score of 0 [15]. In the Heinz Nixdorf Recall Study [13], 4, 487 subjects without CHD were followed for 5 years. The prevalence of

low (score <100), intermediate (score 100 to 399), and high (score > 400) CAC scores was 72.9%, 16.8%, and 10.3%, respectively ($p < 0.0001$). The relative risk of a CAC score higher than the 75th versus the 25th percentile or lower was 11.1 ($p < 0.0001$) for men and 3.2 (p ¼ 0.006) for women. The relative risk associated with doubling of the CAC score was 1.32 (95% CI: 1.2 to –1.45; $p < 0.001$) in men and 1.25 (95% CI: 1.11 to 1.42; $p < 0.0001$) in women. Adding CAC score to the Adult Treatment Panel III categories improved the receiver-operating characteristic C index from 0.602 to 0.727 in men and from 0.660 to 0.723 in women.

Our results indicate that coronary artery calcium scanning is a useful first-choice noninvasive method for risk stratification of asymptomatic patients of intermediate risk group. The widespread use of this approach is, however, limited by the radiation exposure, availability, and cost. The effective radiation dose with a coronary artery calcium scan should average at about 1.0 to 1.5 mSv, and should not exceed 3.0 mSv, which is less than the amount of radiation received each year from natural sources.2[8] In our study, these standards have been observed. In our study the effective radiation dose was between 1 to 1.2 mSv. With current technical improvements, radiation exposure during coronary calcium scanning may be as low as that in mammography (0.8 mSv).8 Still, it should be stressed that this is not always achievable, and even low radiation doses cannot be neglected.2[9]

Our study as it is a single-centre, small sample size study, selection bias is likely, despite the inclusion of consecutive patients. Most importantly, however, coronary revascularization procedures, which are a component of MACEs, might have been influenced by the CACS findings. However, other authors also used MACE as the primary endpoint, [7, 14] since in the intermediate-risk populations, death and MI rates are low, and the outcome is mostly driven by the need for revascularization. We conclude that in patients with intermediate risk in whom coronary anatomy is not known, the CACS measurement may be considered the first-choice of non-invasive method for risk stratification, early detection of high-risk asymptomatic individuals and to estimate the risk of MACE.

6. Summary and Conclusion

- Final study done in 108 patients. Males constituted 62 % of the study population and females constituted remaining 38 % of the study population.
- Mean age of the study population is 54.55 + 7.778 years.
- Majority (48.1%) of the patients were observed in age groups of 51 to 60 years. The proportion of patients who were aged between 40-50 years was 31.50%, aged 61 and above years was 20.4 %.
- Risk factor systemic hypertension constituted 54.60% and Diabetes mellitus type-2 constituted 37% of the study population.
- Risk factor family history of pre-mature of CAD constituted 60.2% of the study population and smokers constituted 19.4 % of the study population.
- In CACS group-zero were 47 subjects, group 1-99 were 31 subjects, 100-399 were 19 subjects, 400-999 were 10 subjects and more than 1000 in one.
- Mean age of male gender in respective CACS group in the studypopulation. caca group zero – 51.04 years, 1-99 was 52.05 years, 100-399 was 60.14 years and 400-999 was 61.22 years. With increasing age there is an linear relationship with incremental coronary calcium score.
- Diabetic subjects with positive calcium score constituted 50.8 % of the diabetic subjectsand systemic hypertension subjects with positive calcium score constituted 31.1 % of the hypertensive subjects.
- Smokerswith positive calcium score constituted 23 % among smokers group andSubjects with family history of pre-mature CAD with positive calcium score constituted 68.9% of the family risk population.
- Males with positive calcium score constituted 72.1 % and females with positive calcium score constituted 27.9 % of the gender population.
- Mean age of positive calcium score group was 56.69 + 7.352 years in the study population and 51.06+ 5.998 years in negative calcium score group in the study population.
- There were 16 (14.81%) subjects who developed MACE at the end of 1 year follow up. Out of them 3 (2.78%) events happened between 1 month to 3 months and 7 (6.48%) happened between 3 month to 6 months and remaining 6 (5.55%) events happened between 6 months to 1 yearfollow up period. Among 108 subjects 12 (11.11%) subjects underwent PCI and 4 (3.70%) underwent CABG.

- No MACE have occurred in group with calcium score zero. CACS group 1-99 AU had 9.68% events, group 100-399 AU had 26.31%, group 400-999 AU had 70% and group >1000 AU had 100% events. It was shown that as the calcium score increases the risk of events increases.

7. Limitations

- The study was conducted at a tertiary care center with multidisciplinary care. Hence the results may not be applicable to the general population.
- Smaller sample size.
- Short duration of follow-up.
- The effective radiation dose for this procedure varies. The risks associated with CAC screening are a small but measurable excess risk of cancer and the risk of unnecessary downstream tests and procedures.
- CT scanning is, in general, not recommended for pregnant women unless medically necessary because of potential risk to the fetus in the womb.
- A high calcium score may sometimes be followed by other diagnostic tests for heart disease, which may or may not provide results with clinical value and can be associated with side effects.

8. Recommendations

- We recommend that in patients asymptomatic and who belong to the intermediate risk group, suggestive of CAD

in whom coronary anatomy is not known, the CACS measurement may be considered the first-line investigation to stratify the risk and assess the risk of MACE.

- CACS results allow identifying patients requiring invasive coronary angiography. This may strengthen the role of coronary calcium scoring as a complement to classic cardiovascular risk assessment.
- It has the ability to re-classify many into either lower risk, with potential cost-savings in minimizing therapy or into higher risk group where appropriate therapies may improve outcomes.

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Study Performa

Case No.: Hospital IP/ID No:
Name: Age/Sex:
Address: Religion:
Caste/Tribe:
Occupation:
Date of Admission:
Date of CAC:
CAG No:

Diagnosis

Risk Factors							
DM	HTN	Smoking	Family History	DYSLIPIDEMIA			
				HDL	TC	LDL	TGL

AGATSON Score				
LCA	LAD	LCX	RCA	Total

CAG FINDINGS	
LM	
LAD	
LCX	
RCA	

Telephonic follow up after enrolment into study	Stable angina	Unstable angina	MI	Death
0 – 1 month				
1 – 3 months				
3 – 6 months				
6 – 12 months				

Abbreviations

Glossary	Abbreviations
CACS	Coronary artery calcium score
AU	Agatston units
MESA	Multi-Ethnic Study of Atherosclerosis
NRI	Net Reclassification Index
CAD	Coronary Artery Disease
CAG	Coronary Angiography
FRS	Framingham Risk Score
CT	Computed Tomography
EBCT	Electron Beam Computed Tomography
MDCT	Multidetector Computed Tomography
CAC	Coronary Artery Calcium/Calcification.
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein
Hs-CRP	High-sensitivity C-reactive protein
ROC	Receiver Operating Characteristic
AUC	Area Under Curve
IMT	Intima Media Thickness
OR	Odds Ratio
RR	Relative Risk
HR	Hazard Ratio
CHD	Coronary Heart Disease
ACCF/AHA	American College of Cardiology Foundation/American Heart Association
HU	Hounsfield Unit
MSv	Milli-Sieverts
Kv	KiloVolt
mSec	Milli-Seconds

LAD	Left anterior descending artery
LCX	Left circumflex artery
RCA	Right coronary artery
ECG	Electrocardiogram
MACE	Major Adverse Cardiac Events
INC	Increasing
RF	Risk Factors
DM	Diabetes Mellitus
HTN	Hypertension
CVD	Cardiovascular Disease
M	Male
F	Female
N	Number
SCCT	Society of Cardiovascular Computed Tomography
ACR	American College of Radiology
ESC	European Society of Cardiology
SBC	Brazilian Society of Cardiology
CBR	Brazilian College of Radiology and Diagnostic Imaging
UKPDS	United Kingdom Prospective Diabetes Study
NPV	Negative Predictive Value
NNT	Number Needed to Treat
PCI	Percutaneous Coronary Intervention
CABG	Coronary Artery Bypass Grafting
MI	Myocardial Infarction
SVD	Single vessel disease
DVD	Double vessel disease
TVD	Triple vessel disease