



CORONARY ARTERY CALCIFICATION;

A PREDICTOR OF SEVERITY OF CORONARY ARTERY DISEASE, BASED ON 64-SLICE CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

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ABSTRACT... Background: Due to increased risk of CAD and cardiovascular events, prediction of severity and/ or complexity of coronary artery disease (CAD) are valuable. Previously association between severity of CAD and total coronary artery calcium (CAC) score was not demonstrated but now there are lot of studies which have proven this association but still association between total CAC score and complexity of CAD is not well established.

Objective: This study was conducted: (1) To investigate the association between coronary artery calcium (CAC) score and CAD assessed by CCTA. (2) To find which one of the two, CAD severity or complexity, is better associated with total CAC score in symptomatic patients having significant CAD. **Study Design:** Observational cross sectional study. **Place and Duration:** The study was conducted at Shifa International Hospital Faisalabad from March 2013 to June 2016.

Materials and Methods: Total 195 consecutive patients of both gender age ≥ 20 years who was referred for CT angiography to our hospital and who fulfill the inclusion and exclusion criteria was included in the study. Before enrollment in the study all patients gave informed consent. Before CT angiography total CAC score was obtained by non- enhanced CT scans. Demographic characteristics of all patients were obtained. Regarding risk factors for CAD, history of hypertension, diabetes mellitus, family H/O ischemic heart disease and hyperlipidemia was noted. In all patients before CT angiography, Lab. investigations including complete blood count, fasting blood sugar, fasting lipid profile, blood urea and serum creatinine levels were obtained. Calcium scores were quantified by the scoring algorithm proposed by Agatston et al. All lesions were added to calculate the total CAC score by the Agatston method. Calcium scores were divided into the following categories: 0, 1–100, 101–400, and ≥ 400 . The degree of stenosis was classified into four categories: (1) no stenosis, (2) minimal or mild stenosis ($\leq 50\%$), (3) moderate stenosis (50%–70%), and (4) severe stenosis ($> 70\%$). CAD was defined when lumen diameter reduction was greater than 50% (moderate or severe stenosis). **Results:** Total 195 patients were studied. 136 (69.7%) were male and 59 (30.3%) were female. Mean age of study population was 52.8 ± 10.38 years. 81 (41.54%) patients had H/O chest pain, 11 (5.64%) had H/O shortness of breath and 96 (49.23%) presented with chest tightness. 104 (53.33%) patients were hypertensive, 71 (36.41%) were diabetic, 67 (34.35%) had increased cholesterol level. In 57 (29.2%) there was no coronary artery disease, 58 (29.7%) had mild CAD, 32 (16.4%) had moderate and 48 (24.6%) had severe coronary artery disease on CT angiography. Single vessel was involved in 38 (19.5%) patients, 20 (10.3%) had two vessel disease and triple vessel disease was present in 22 (11.3%) patients. 104 (53.3%) patients had zero calcium score. 44 (22.6%) had CAC score between 1-100, 37 (19%) had CAC score between 101-400 and more than 400 CAC score was documented in 10 (5.1%) patients. **Conclusions:** This study in addition to patient based analysis also confirms the significant relationship between vessels based CAD and CAC score. The prevalence of multivessel CAD increased in patients with CACS > 100 and there is 100% incidence of CAD in patients with CACS > 1000 . Zero calcium cannot exclude the presence of significant CAD. Our data supports that in symptomatic patients calcium scoring is an additional filter before coronary angiography.

Key words: Coronary artery calcium; coronary artery disease; calcium score; cardiovascular risk

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INTRODUCTION

In the world about one third of all the deaths are caused by atherosclerotic cardiovascular disease and it is number one cause of death in the world. The main dilemma is that 50% acute coronary syndrome occurs in previously asymptomatic patients, and non flow limiting lesions in coronary vessels were present in nearly 70% of acute coronary event victims.¹ In patients who do not have already history of CAD, there are different scoring systems to predict the risk of coronary events in these patients.

In atherosclerotic plaque formation CAC has a pivot role² and this calcium in atherosclerotic plaque is quantified by total CAC Score known as Agatston score. For accurate quantification of total CAC score, currently a non-invasive method multi detector computed tomography (MDCT) is used.³

In patients with intermediate risk of CAD, conventional scoring system as clinical examination, Stress tests and Framingham Risk Score (FRS) have limited ability to predict the cardiovascular events in future.⁴ To predict these cardiac events and to improve risk stratification in low to intermediate risk patients, now Coronary artery Calcium Score (CACS) has been regarded a potential tool. This tool has the advantages to directly visualize and locate the plaques precisely by using computed tomography (CT) because CAC is a surrogate marker for atherosclerotic plaque burden.⁵ Conventional risk factors as mentioned above only provide statistical probability of developing CAD in these patients but CAC by using Agatston Calcium Scoring system can allow direct individual assessment of each patient by quantification of calcium.⁶ For risk stratification and cardiac event assessment, Biomed Research International have supported the vital use of CACS.⁵ The gold standard investigation to diagnose and to know the severity of coronary artery stenosis is conventional coronary angiography (CCA), however this diagnostic modality is inconvenient, expensive and invasive for the patients. Non invasive technique most commonly used in routine clinical

practice is CACS. Most of the studies describing diagnostic and prognostic value of CACS were conducted in Western countries⁷ and very few studies are reported from Asian countries^{8,9}. From Western countries, our disease pattern, population and health care system is different.¹⁰ Prevalence of coronary calcification is different in African (52.1%), Chinese (59.6%), Caucasian (70.4%) and Hispanic (56.5%) populations. Compared with Caucasian the relative risk of death was 0.85 in China, 1.58 in Hispanic and 2.97 in Africa.⁴ By using 64- multislice computed tomography (64-MSCT) in this study, we aim to validate the relationship between CACS and CAD.

This imaging modality was used in low to moderate risk patients for risk assessment. When comparing with other traditional risk factors scoring systems as FRS, it has a superior role to predict future cardiac events because FRS does not incorporate family history and many components of metabolic syndrome. CACS further reclassifies moderate risk patients into lower or high risk patients. According to NICE guidelines, in UK, in patients presenting with chest pain in emergency department, zero calcium is used as gatekeeper for any further investigation. Many international studies have shown that angiographically proven significant CAD is related to total CAC score.¹¹ In our study we will review the controversial issues and limitations regarding the CAC scoring along with technical facts and clinical application of CAC scoring so in future the use of this imaging modality may be better clarified.

CALCIUM SCORING, IMAGING MODALITIES AND SCORING TECHNIQUES

More recently multidetector computed tomography (MDCT) has been used for calcium scoring but formerly, electron beam computed tomography (EBCT) was used. The advantage of MDCT is that, it has good image quality and higher spatial resolution but to limit motion artifacts we need heart rate control. In Electron beam computed tomography we can get faster imaging with higher temporal resolution.

CAC is defined as a hyper-attenuating lesion >130

Hounsfield units with an area of ≥ 3 pixels and this CAC can be quantified by several methods. With ECG-triggered mode CAC is typically scanned with 2.5-3 mm thick axial images. The Agatston score is calculated by multiplying the lesion area (mm^2) by a density factor (between 1 and 4).¹² The radiation dose in CAC calculation is low with effective dose of < 1.5 mSv.¹³ Severity of CAD can be assessed by specific pattern of calcification; nodular pattern is associated with less severe CAD whereas shell like and diffuse pattern is associated with severe stenosis.¹⁴

MATERIALS AND METHODS

In the prediction of Coronary artery disease (CAD), Coronary artery calcification (CAC) measured on 64- slice computed tomography has been well studied and we sought to evaluate the role of the CAC score in the diagnosis of CAD in a large tertiary care referral centre. Few studies have given information regarding role of CTA to predict future cardiac events and compare CACS with coronary computed tomography angiography (CCTA). This study was conducted at Shifa International Hospital Faisalabad from March 2013 to June 2016.

INCLUSION CRITERIA

Any patient (Male or Female) of age ≥ 20 years who was referred for CT angiography to our hospital was included in the study who had:

1. Low to intermediate probability of CAD on history.
2. Intermediate diagnostic test results on ETT or Stress Thallium.
3. Inability to perform non-invasive tests like ETT.

EXCLUSION CRITERIA

1. Patients with previous H/O CABG
2. Past history of PCI
3. Patients with H/O MI
4. End stage renal failure
5. Atrial fibrillation
6. Any Malignancy
7. Previous H/O Valvular heart disease or/ and Valvular replacement
8. Patients having H/O contrast allergy

Total 195 consecutive patients of age ≥ 20 years, of any gender with symptoms suggestive of CAD who fulfill the inclusion and exclusion criteria were enrolled in the study. Before enrollment in the study all patients gave informed consent and the study protocol was approved by the local Hospital Ethical Committee. All the patients underwent 64 - slice computed tomography coronary angiography (CTA) for assessment of CAD. Before CT angiography total CAC score was obtained by non-enhanced CT scans. Demographic characteristics of all patients were obtained. Detailed medical history including past history was taken. A detailed physical examination with special emphasis on CVS was performed. History of any drug allergy especially to contrast was obtained. ECG of all patients was done for rate and rhythm. A base line echocardiography was performed to identify any valvular or structural heart disease. Regarding risk factors for CAD, history of hypertension, diabetes mellitus, family H/O ischemic heart disease and hyperlipidemia was noted. Patient was labeled hypertensive on the basis of hospital record or if patient was taking antihypertensive medications or his/her BP was $\geq 140/90$ mmHg. Diabetes was identified on the basis of hospital record or if patient was taking anti diabetic medications (Insulin/ OHGA) or fasting blood sugar was ≥ 126 mg/ dl. Dyslipidemia was defined if total serum cholesterol was ≥ 180 mg/ dl in fasting state or patient was on statin therapy for it. In all patients before CT angiography, Lab. investigations including complete blood count, fasting blood sugar, fasting lipid profile, blood urea and serum creatinine levels were obtained. Patients were considered smokers if still they were smoking (Huqa and/ or Cigarettes). Body mass index (BMI) was calculated by weight in kilogram divided by body surface area in m^2 (kg/m^2). All patients underwent CCA and MSCT for CACS.

CARDIAC CT IMAGING PROTOCOL

Coronary artery calcification measurement

CT angiography was performed by using a 64 - slice CT scanner (Aquilion 64, Toshiba Medical Systems, Tochigi, Japan). For calcium scoring

non enhanced CT scan from tracheal bifurcation to diaphragm was performed using the following parameters: 120KVp, 300 mA, 0.25 s. Slice thickness was 3 mm with interval of 3 mm. and gantry rotation time 0.4 s.¹⁵

Commercially available an offline workstation with dedicated software (Software Vitrea 2 V3.9.0.1, MN, USA) was used to calculate the calcium scores of each area at each vessel and the scores were quantified by using Agatston scoring algorithm proposed by Agatston et al⁶ and it was defined as the presence of a lesion with an area greater than 1 mm², and peak intensity greater than 130 Hounsfield Units. All lesions were added to calculate the total CAC score by the Agatston method. Calcium scores were divided into the following categories: 0, 1–100, 101–400 and ≥ 400 .

Those CT angiographic projections which showed most severe narrowing were used to measure minimal lumen diameter. The severity of stenosis was classified into four categories: (1) no stenosis, (2) $\leq 50\%$ (mild stenosis) (3) 50%–70%, (moderate stenosis) and (4) $> 70\%$ (severe stenosis). If any patient had lumen diameter less than 50% (moderate or severe stenosis) he/ she was labeled to have CAD.

STATISTICAL ANALYSIS

All the data was analyzed by SPSS (Statistical Package for Social Sciences) Version 20.0 for Windows. Categorical variables were expressed as frequencies and percentages and continue variables were presented as means \pm SD (Standard Deviation). Qualitative variables were compared using chi sq test. 5% level of significance was used. All tests applied were two tailed.

RESULTS

Total 195 patients were studied. 136(69.7%) were male and 59 (30.3%) were female. Mean age of study population was 52.8 ± 10.38 years and range was 24–76 years. 81(41.54%) patients presented with chest pain, 11(5.64%) with shortness of breath and 96(49.23%) with chest tightness. 27(13.81%) have associated sweating. In 56(28.71%) patients

pain was radiating to left arm. 104(53.33%) patients were hypertensive, 71(36.41%) were diabetic, 67(34.35%) had increased cholesterol level. 34(17.44%) were obese with body mass index greater than 30. 87(44.61%) patients had H/O smoking and 37(18.97%) had family history of IHD. Table I

In 57 (29.2%) there was no coronary artery disease, 58(29.7%) had mild CAD, 32 (16.4%) had moderate and 48 (24.6%) had severe coronary artery disease on CT angiography. Single vessel was involved in 38(19.5%) patients, 20(10.3%) had two vessel disease and Triple vessel disease was presented in 22(11.3%) patients. Left main stem disease was noted overall in 13(6.7%) patients. Table II

104(53.3%) patients had zero calcium score. 44(22.6%) had CAC score between 1-100, 37(19%) had CAC score between 101-400 and more than 400 CAC score was documented in 10 (5.1%) patients. Table II, Fig 1.

Clinical characteristics	Number	Percentage
Age mean (years) 52.8 ± 10.38		
Gender:		
Men (%)	136	69.7%
Women (%)	59	30.3%
Obesity	34	17.44%
Risk factors:		
Dyslipidemia	67	34.35%
Hypertension	104	53.3%
Smoking history (%)	87	44.61%
Diabetes Mellitus	71	36.41%
F/H of IHD	37	18.97%
Mode of Presentation:		
Chest Pain	81	41.54%
Chest Tightness	96	49.23%
Dyspnoea	11	5.64%

Table-I. Baseline characteristics and risk factors of study population (n= 195)

Calcium scoring	0	1-100	101- 400	.>400	
Number of cases	104(53.3%)	44(22.6%)	37(19%)	10(5.1%)	
Degree of stenosis (n = 195)					
Severity of CAD	CAC 0	1-100	101-400	>400	Total Patients
0=No CAD	56	0	1	0	57(29.2%)
1= Minimal or mild CAD	33	20	5	0	58(29.7%)
2=Moderate CAD	07	15	08	02	32(16.4%)
3=Severe CAD	08	09	23	08	48(24.6%)
No CAD= 0+1(n=115)	89	20	6	0	195 (100%)
CAD= 2+3(n=80)	15	24	31	10	
Coronary artery disease (n=80)					
One vessel Disease n=38(19.5%)	3(7.9%)	12(31.57%)	8(21.05%)		15(39.47%)
Two vessel Disease n=20(10.3%)	2(10%)	3(15%)	6(30%)		9(45%)
Three vessel Disease n=22(11.3%)	0	4(18.18%)	7(31.82%)		11(50%)

Table-II. The correlation between calcium scoring and degree of stenosis, coronary artery disease (CAD) (n= 195)
Statistically significant (P < 0.001).

Degree of stenosis	LAD (n =195)		RCA (n=195)		LCX (n=195)		LMS (n= 195)		RI(n=11)	
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
0	90	102.55± 303.28	89	112.55± 213.49	105	75.37± 174.29	122	56.18± 181.46	5	91.42 ± 143.48
Mild or Minimal disease	53	219 ± 235.01	66	211.04± 265.64	58	129.17 ± 233.59	60	141.40± 133.39	2	179.13 ± 214.79
Moderate Disease	35	267 ± 321.03	25	242.61 ± 254.54	23	149.32± 109.23	10	188.71± 117.82	2	243.57±381.43
Severe Disease	17	344.12±637.02	15	361.06 ± 219.36	9	319.07±395.55	3	215.53± 138.92	2	331.04±251.22

Table-III. Calcium score in vessel-based distribution of coronary artery stenosis or coronary artery disease (CAD).
Statistically significant (P < 0.001).

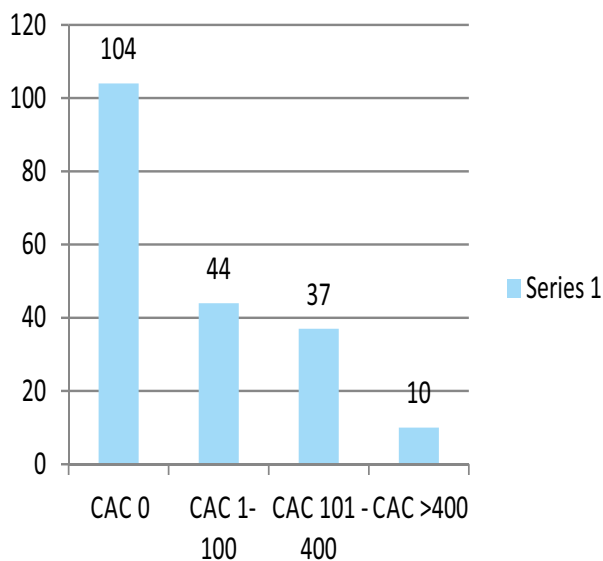


Fig-1. Distribution of patients according to calcium score (N=195)

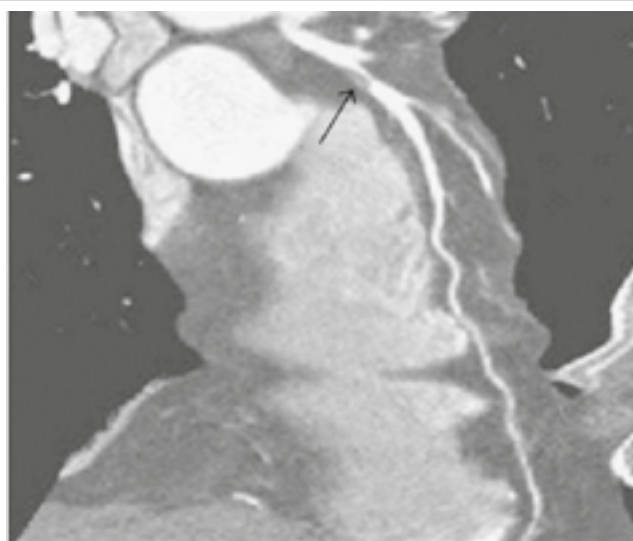


Fig-2. CT angiography of a 50 years old male with zero calcium score but he was symptomatic. CT angio showed a soft plaque in proximal lad as arrow showed



Figure-3. Conventional Coronary Angiogram confirms the severe stenosis in proximal LAD (white arrow).

Regarding the LAD disease 17 (35.4%) patients had severe CAD with CAC score between 101-400 and all the patients 2(4.2%) who had CAC score >400 had severe CAD. Regarding disease in RCA 89(45.64%) patients had severe CAD and most of these patients had CACS >200. Two patients had CACS >400 and all were suffering from severe disease in RCA. Regarding disease in left Circumflex artery, 56(98%) with zero calcium had no disease but there was only 1 patient who had CAC >400 and was suffering from severe disease.

DISCUSSION

In USA Coronary artery disease (CAD) is still the major cause of death and due to survival of acute cardiac events patients it imposes a large economic burden. In the world many risk scoring tools and modalities have adapted to identify and help out high risk patients. Now Coronary artery calcium (CAC) scoring is an area of intense investigation to determine cardiovascular

risks because calcium is almost exclusively detected in plaque of atherosclerotic arteries.¹⁶ Now CAC scoring along with other traditional and conventional scoring systems such as Framingham risk score has become an integral part of preventive cardiology in determining high risk patients of coronary artery disease and for cardiovascular risk assessment now it has been considered as a powerful tool. In UK according to NICE guidelines in patients with low to intermediate risk for CAD and presenting with chest pain in emergency CAC testing has become an integral part of management. Regarding the use of this non-invasive modality many national and international guidelines have been made. The focus of our study is on the use of CAC as a tool for risk stratification in asymptomatic and symptomatic patients.

CAC and Diagnostic Accuracy of Coronary CT Angiography (CCTA)

The specificity of CCTA can decrease in severe calcification and it is due to blooming artifacts of severe calcification. Heavy calcification can limit lumen assessment so can give false positive results. On a patient basis, with CAC scores 0-100, 101-400, and >400, specificity was 91.2, 88.2 and 84.0 % and sensitivity was 95.8, 95.6 and 99.0 % respectively¹⁷ and this suggested that sensitivity and specificity of CCTA for significant coronary artery stenosis is high even in the presence of severe coronary calcification. Probability of artifacts and false positive results of CCTA is more if coronary calcification is limited to a small area as compared to even and diffuse calcification and due to this mechanism, CCTA may be non diagnostic in patients with CAC of 100 and may have good diagnostic quality in patients with CAC of 1500.¹⁸

Role of CAC Scoring in Evaluation of Patients with Chest Pain

In emergency department patients presenting with chest pain, zero CAC score can play a role of "gatekeeper" because in these patients zero calcium can diagnose non-obstructive CAD with a sensitivity of > 95% and negative predictive value of 99% and in these patients to know severity of

coronary artery stenosis CAC was confidently used to decide which patients need further invasive or non-invasive coronary angiogram¹⁹. In asymptomatic patients, retesting of CAC scoring is still a subject of debate but if patient becomes symptomatic who was previously asymptomatic then CAC score should be repeated otherwise there is no need to re-assess CAC score.²⁰

Health care provider can give two take home messages to patients with zero calcium that:

- a) Chances of CAD event in next 10 years is very low <1%.²¹
- b) Patients should know that zero calcium does not mean absence of atherosclerotic plaque, because plaque may be exclusively non calcified that cannot identify by CAC testing.

In emergency department (ED) CAC scoring is cost effective. Raggi et al²² conducted a study in which he used two protocols: CAC scanning as an initial test of choice or exercise treadmill test first and he calculated there was 65% cost reduction when CAC scoring approach was used as first line test. In a study conducted in UK at the Brighton and Sussex University Hospitals, it was concluded that in patients with a pretest probability <30% CAC scoring is cost effective and in patients with probability >30% nuclear scan or invasive angiography was more cost effective than CAC scanning as first line test. In asymptomatic females CAC scoring is good risk stratification as compared to other conventional cardiovascular risk scoring modalities. 2600 women with a median Agatston Score of 0 (Range 0-26) were enrolled in MESA study and they found that 2% of studied population got CAD.²³ When CAC was increased from 0.672 to 0.75 in a study conducted by Raggi et al²² there was significant increase in death estimation (p 0.0001).

Our results coincide with the results of study conducted by Budoff et al²⁴ in which he investigated the distribution of calcification and its correlation with the severity and extent of CAD. Schmermund et al²⁵ in his study used CAC scoring to distinguish patients with or without 3 vessel and/or left main stem (LMS) coronary

artery disease. Our study showed on vessel based analysis there is moderate correlation between CAC score and atherosclerotic disease and these results coincides with many recently conducted studies results.⁸ In our study there was a statistically significant correlation between CAC score in RCA, LAD and LCX and degree of stenosis (p < 0.001) and in patients with significant CAD in these vessels high CAC score was present than those without CAD (p <0.001). Regarding LMS disease the correlation between CACS and presence of CAD was not significant and this result may be due to bifurcation of LMS into LAD and LCX and CAC near this bifurcation can be assigned to different vessels. To predict future cardiac event, the ability of CAC is not absolute, though it is associated with high risk of cardiovascular events. CAC score does not have linear correlation with severity of CAD. As shown in Fig 2 & 3 in a study conducted by Budoff et al²⁴ a 53 years old male has zero calcium score but CT angiography and conventional Angiography confirm tight stenosis in proximal LAD having soft plaque so zero calcium does not exclude the presence of CAD.

Absence or zero calcium only rule out atheroma without calcified plaque ≥ 1 mm in diameter but non-calcified, soft, vulnerable lipid laden plaque cannot be rule out²⁶ and it only reflects 20% of plaque burden of total atherosclerotic plaque burden and can over look soft plaque that can cause acute coronary event.²⁷ It was demonstrated in many international studies that only 7% patients with zero calcium had obstructive CAD while obstructive CAD was present in 17% patients when CAC was (1-100).²⁸ In our study single vessel CAD was present in 38(19.5%) of patients having zero calcium and these results coincide with other studies but angiography revealed that these patients have soft plaque that cause severe stenosis in proximal LAD and this percentage is quite high as compared with previous reports and that may be due to small number of sample size with a great pretest probability.

CONCLUSION AND FUTURE DIRECTIONS

This study in addition to patient based analysis

also confirms the significant relationship between vessels based CAD and CAC score. The prevalence of multivessel CAD increased in patients with CACS >100 and when CACS > 100 there is 100% incidence of CAD. In symptomatic patients, CAC scoring is an additional filter before invasive conventional angiogram even though zero calcium does not exclude the presence of significant CAD. CAC scoring is a mature technology and in future it will become a modality of choice for risk stratification in patients with intermediate risk for CAD and in some selective cases with low and high risk factors it can be used. In current era in patients with chest pain but stable, CAC scoring and CT angio is the best modality to rule out obstructive CAD and it can be used in asymptomatic patients for risk stratification and as a scoring tool. With the development of newer technology, plaque characterization will be clearer beyond merely calcification and chances of radiation will decrease. CAC scoring cannot detect non-calcified atheromatous plaque. CT angio is the best tool to detect non-calcified plaque in a noninvasive way and in future it will be a great help for cardiologist to differentiate between stable plaque and vulnerable plaque. We must educate and trained the cardiologist and educate the public for the proper use of this powerful imaging modality. Some more studies in future are needed to establish the correlation among CACS, CAD, and clinical or Framingham's risks factors in each patient.

LIMITATIONS OF THE STUDY

There are several limitations in our study.

1. The sample size in our study of 195 is relatively small so it cannot give the true picture.
2. Our study included symptomatic patients who underwent 64-MSCT and subsequent CCA.
3. Our study also does not assess the high-risk patients.
4. CACS cannot be used to assess calcified plaques having density <130HU.
5. It cannot assess non calcified soft plaques

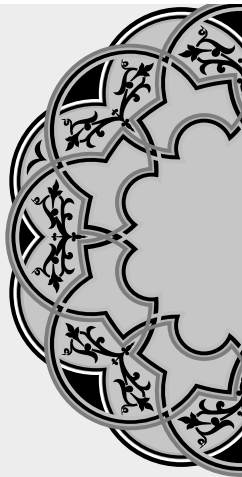
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*“Every day may not be good but
there is something good in every day.”*

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

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