OPTICAL COHERENCE TOMOGRAPHY BASED CHARACTERISATION OF CULPRIT LESIONS IN ACUTE CORONARY SYNDROME

Thesis submitted for the degree of
DM Cardiology

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CERTIFICATE

I, **Dr. Avinash Mani,** hereby declare that the project in this book, titled **"OPTICAL COHERENCE TOMOGRAPHY BASED CHARACTERISATION OF CULPRIT LESIONS IN ACUTE CORONARY SYNDROME"** was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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DECLARATION BY CANDIDATE

I, **Dr Avinash Mani,** hereby declare that I have done my thesis entitled **"Optical Coherence Tomography Based Characterisation Of Culprit Lesions In Acute Coronary Syndrome"** under my allotted guides in the department of Cardiology , SCTIMST.

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CERTIFICATE

We hereby certify that the work in this project titled **"Optical Coherence Tomography Based Characterisation Of Culprit Lesions In Acute Coronary Syndrome"** is a certified record of original research work undertaken by Dr Avinash Mani in partial fulfilment of requirement for the purpose of award of DM Cardiology under our guidance and supervision.

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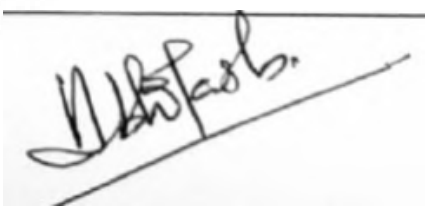

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Optical Coherence Tomography Based Characterisation Of Culprit Lesions In Acute Coronary Syndrome

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SYNOPSIS

Background:

Optical coherence tomography (OCT) can be used to determine culprit lesion morphology in acute coronary syndrome patients which can help guide management.

Aim:

Study of culprit lesion morphology using OCT in ACS patients and evaluation of long-term outcomes.

Methods:

This was a retrospective and prospective study which included patients with acute coronary syndrome, who underwent OCT evaluation, over a period of 4 years. Baseline demographics and clinical characteristics were recorded using structured questionnaire. Angiographic and OCT characteristics of culprit lesion was evaluated. Patients were followed up for one year via hospital visits or telephonic consultations. The primary endpoint of follow up was death, myocardial infarction, all cause hospitalisation and revascularisation. Individual outcomes were also noted separately.

Results:

A total of 32 patients were included in the study. Mean age of study population was 54.4 years and females comprised about 13% of the study population. Majority of patients had NSTEMI on presentation while about 35% patients had received fibrinolysis or PCI before presentation. Majority of participants had multivessel disease on angiography with LAD being the most common culprit

vessel. 45% of patients had complex lesion morphology (ACC/AHA Type B/C) on angiography. Majority of study participants (75%) underwent PCI.

Plaque erosion was the predominant phenotype (62%) on OCT whereas plaque rupture was noted in 32% of the patients. Plaque rupture patients had higher prevalence of thin-cap fibroatheroma and lipid rich plaque($p<0.05$). Lipid content was significantly higher in plaque rupture whereas plaque cap thickness was significantly higher in plaque erosion ($p<0.05$). Area stenosis on OCT was similar in both group of patients. A plaque cap thickness of 82.5μm and higher could predict plaque cap integrity with a sensitivity of 83% and specificity of 91%. A lipid arc greater than 110 degrees could predict plaque cap rupture with a sensitivity of 73% and specificity of 91%.

At the end of one year, 81% patients were on regular follow up. Primary endpoint was noted in 50% of patients. No death was noted during the follow up period. Clinical outcomes were similar between patients with plaque rupture and plaque erosion. Patients who were managed medically, did not have any adverse events on follow up.

Conclusion:

Patients with plaque rupture have higher atherosclerotic burden. Plaque cap thickness and lipid arc can predict plaque stability. Clinical outcomes in patients with plaque rupture and erosion are similar after one-year follow up.

INTRODUCTION

Optical coherence tomography (OCT) has revolutionized the world of interventional cardiology since its inception. It gives superior sensitivity and resolution amongst all available intravascular imaging modalities. It helps to determine tissue characteristics which can determine the modality of treatment needed[1]. OCT has also helped in optimizing the results post percutaneous coronary angioplasty (PCI). Owing to the high resolution of OCT, it can easily detect stent under-expansion, malapposition and edge dissection[1]. All these complications can lead to procedural failure and need to be recognized and corrected immediately. OCT also helps in pre-procedural planning as it detects optimal landing zones for stent and ideal stent length/diameter necessary for the particular vessel and lesion. OCT also plays an important role in evaluation of patients with in-stent restenosis.

Rupture of vulnerable culprit lesion along with subsequent thrombus formation has been termed as the most common cause of acute coronary syndrome(ACS)[2]. It has been long thought that the morphology of culprit plaque rupture is the same across the entire spectrum of acute coronary syndrome. Previously, it was difficult to understand lesion morphology due to lack of sensitive imaging modalities. With the use of OCT, this problem has been tackled as OCT provides high resolution images which can help to understand the lesion characteristics. OCT has helped to determine that the culprit lesion morphology differs in patients across the subsets of acute coronary syndrome[3]. This varied morphology is responsible for the different clinical presentation and course of disease. Using OCT as an imaging tool, quick lesion analysis can be performed in patients which can help to guide management and future course of therapy. In this study, we aim to determine the culprit lesion morphology in patients with acute coronary syndrome.

REVIEW OF LITERATURE

Optical coherence tomography (OCT) is a new type of imaging modality which helps to obtain cross sectional tomographic images of internal microstructure of any object utilizing the coherence of light. OCT images are two dimensional datasets which show the backscattering of light in a particular cross-sectional plane within a tissue mass[4]. OCT tries to achieve balance between imaging resolution and tissue penetration thus lying in between the deep and superficial imaging techniques. OCT imaging was independently developed by two independent researchers around 1990 – Naohiro Tanno of Yamagata university,Japan and James G. Fujimoto of Massachussets Institute of Technology (MIT), United States. Invitro imaging of human retinal tissue and coronary artery was first performed in 1991. It was done to demonstrate the use of this new technique in transparent and turbid media[5]. OCT imaging was first utilized in ophthalmology and has had a very large clinical impact. The first in vivo studies of human macula and optic disc were done in 1993[6]. Later advances in technology enabled OCT to be used for a wide variety of applications. OCT has been applied in vitro to image vessel wall and can determine various plaque morphologies[7]. Currently, OCT is being routinely used in coronary imaging to determine plaque morphology and guide interventional procedures.

Comparison of OCT with ultrasound: -

OCT imaging is similar to ultrasound in its basic principle with the difference being usage of light instead of sound waves. In order to perform cross sectional imaging, it is necessary to measure the internal dimensions of a tissue structure along a single longitudinal plane. The first step in OCT imaging is usually measuring the axial distance or range information within the tissue. OCT

performs imaging by measuring echo time delay and determining the intensity of backscattered light from internal microstructure of tissues. The images formed hence are a two-dimensional or three-dimensional representation of the differences in the backscattering in a particular tissue plane. When a beam of light is directed onto a tissue surface, it is backscattered from structures which have different optical properties as well as from the boundaries between those structures. The dimensions of these structures are determined by measuring the echo time delay from various structures. The basic difference between OCT and ultrasound-based imaging is that velocity of propagation of light is million times faster than velocity of sound. Thus, the distance measurement using light requires ultrafast time resolution.

The most important parameters for imaging are image resolution and imaging depth. The resolution of ultrasound imaging depends directly on the frequency or wavelength of sound waves used. Lower frequency sound waves (10 MHz) can produce spatial resolutions of 150μm with the advantage of greater depth penetration. On the other hand, high frequency sound waves (100MHz) can provide a spatial resolution as high as 15-20 μm but with reduced depth penetration of only a few millimeters. Transverse resolution of ultrasound depends on the ability to focus sound waves but sound waves are difficult to focus at a particular point as compared to light. Thus, the transverse resolution of ultrasound is lower than OCT. Current OCT technologies can give resolution ranging from 5 to 15 μm. The high resolution of OCT permits imaging of specific tissue characteristics. The mechanism of contrast in images is different in various imaging modalities. In ultrasound imaging, there is difference in intensity of backscattering of sound waves due to variable acoustic impedance of tissues, which produces the image contrast.

Fundamentals of OCT imaging: -

OCT is an optical imaging modality which is used to perform high resolution, cross sectional imaging of internal microstructures using the measured echo time delay and magnitude of backscattered light. The functional principle behind OCT imaging is light interference. A light interference setup is the core of any OCT system. Various types of interference configurations are used in OCT systems. The basic components in an OCT system are the light source, coupler, interferometer and detector. In an OCT system, the light emitted from a low coherence source passes through a coupler where it is split into two paths. These separate light paths are directed to different arms of the interferometer – sample arm and reference arm. When light exits either arms, it is modified by various optical components to determine specific beam parameters like shape, depth of focus and intensity of distribution of light. In the reference arm, the light is back-reflected by a reference mirror and it returns to the interference system following the same path but in the opposite direction. In the sample arm, similar phenomenon takes place as the light beam is backscattered by the tissue being imaged. A particular tissue will be made of different materials with difference in indices of refraction and light will be backscattered when it encounters an interface between materials of different refractive index. The light which returns back to the interferometer is again combined by the coupler to generate an interference pattern which is recorded by the detector. For a particular position of the reference mirror, the light propagating in the reference arm travels a certain optical distance. It forms a corresponding interference pattern only with light that traveled the same optical distance along the sample arm, including the portion of the distance traveled inside the sample. Thus, depending on the position of the reference mirror, the returning reference generates interference patterns with light backscattered from corresponding depths within the sample. This helps to determine the dependence on depth of the intensity of light backscattered (Figure 1).

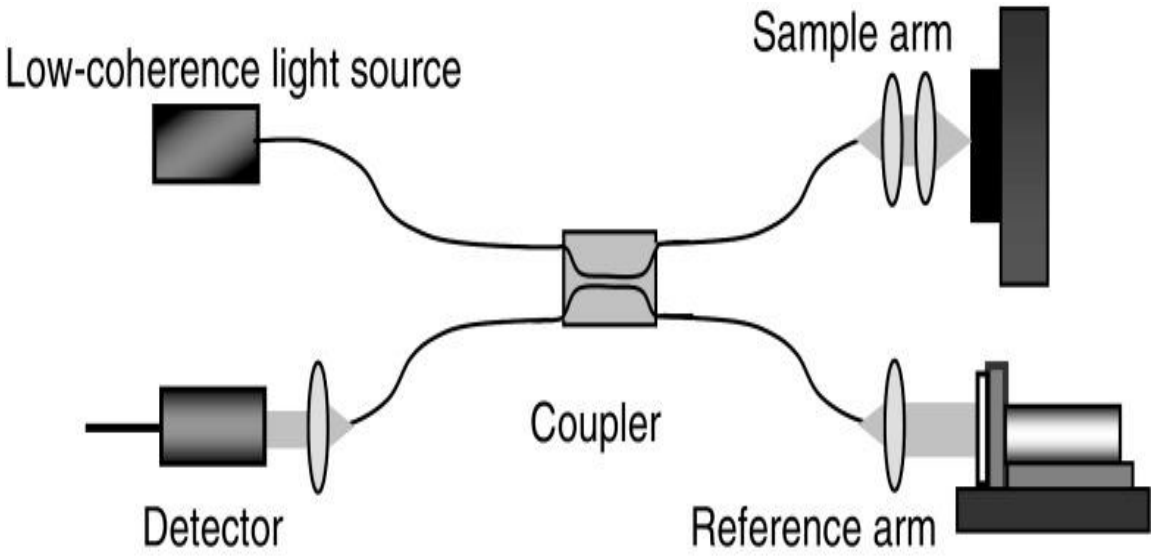

Figure 1. Fiber based OCT system in a Michelson configuration.

The OCT signal recorded by light interference is called a depth scan or an A-scan. To form a complete OCT image, the sample beam has to move across the entire surface of the tissue with an A-scan being recorded at each position of the beam. Thus, a complete set of A-scans are obtained forming the B-scan or the OCT image. The maximum possible depth which can be attained using the OCT system usually depends on the tissue itself.

The light source in an OCT system is a low coherence semiconductor super-luminescent diode (SLD). The characteristics of the SLD are important as the axial resolution of the OCT imaging depends on it. The axial resolution of imaging is given by the formula –

$$\Delta z = \left(2\ln\frac{2}{\pi}\right)\left(\frac{\lambda^2}{\Delta\lambda}\right)$$

where λ and Δλ are the SLD central wavelength and its bandwidth. Therefore, high bandwidth sources are required to achieve high axial resolution[8]. Axial resolutions in the micron and sub-micron range are achieved by using sources with very large spectral bandwidth. The axial and transverse resolutions in OCT

are independent of each other. The transverse resolution is determined by the formula –

$$\Delta x = \frac{4\lambda}{\pi}\left(\frac{f}{d}\right) = 1.27\frac{\lambda}{NA}$$

where NA is the numerical aperture. The transverse resolution is inversely proportional to the numerical aperture of the lens[9]. In OCT systems, there is a trade-off between transverse resolution and depth of field. A high numerical aperture produces a very good transverse resolution but at the cost of short depth of field. On the other hand, a low numerical aperture offers a larger depth of field but with a lower transverse resolution. Most OCT imaging are performed with a low NA lens in order to ensure a depth of field of the order of millimetres.

Optical coherence tomography systems : –

There are two main types of OCT systems in use – time domain OCT (TD-OCT) and Fourier domain OCT (FD-OCT). Fourier-domain OCT imaging can also be done in two ways: by spectral-domain OCT (SD-OCT) and by swept-source OCT (SS-OCT). Full field OCT (FF-OCT) is another method which can help in direct acquisition of 2D OCT images.

TD-OCT is based on a detection technique that uses a low coherent light source and a scanning reference delay. The light source, a low coherence SLD, is split into two halves using an optical splitter. The light from the reference path is reflected back from a reference mirror that is under controlled translation motion, allowing the reference light to travel a known path length and to undergo a measurable variable time delay. The light from the second path is directed onto the sample and is backscattered by its internal structure which produces interference patterns with the reference light that has travelled an equal optical distance. This provides the depth information and the locations of

various structures from within the sample[10]. TD-OCT was the first OCT technology developed in the 1990s.

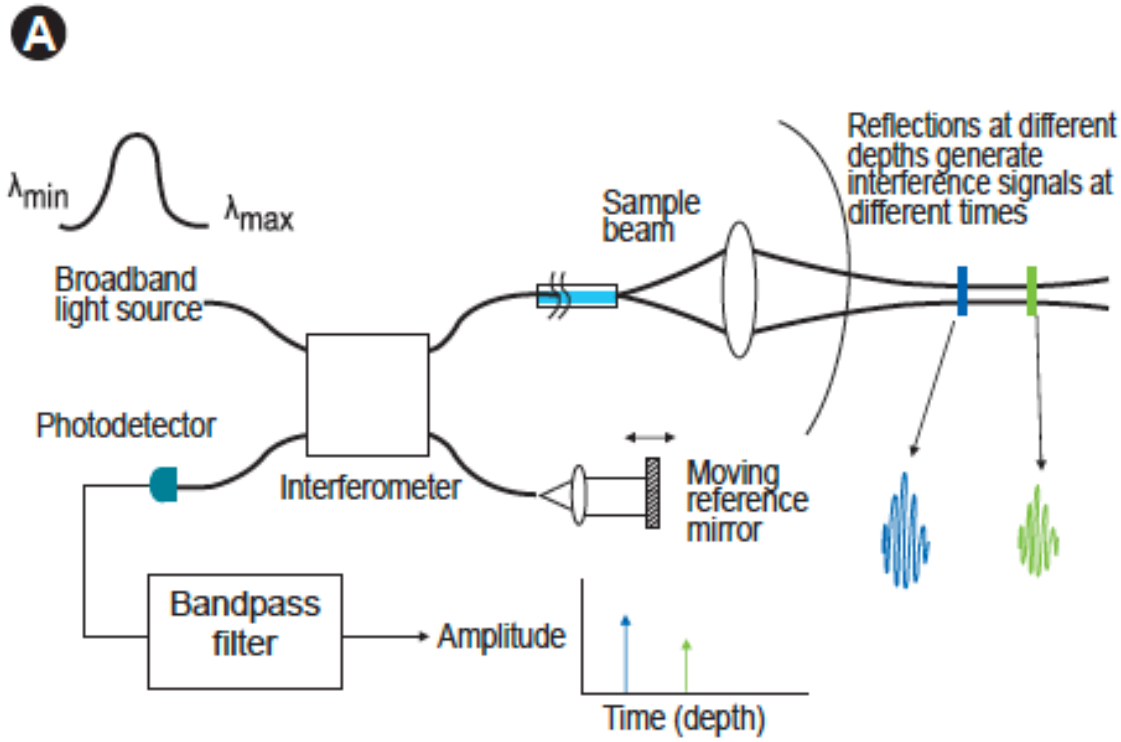

Figure 2. Time domain optical coherence tomography system

In FD-OCT, the light echoes come back at the same time from all axial depths and are detected as modulations in the source spectrum, with all the spectral components being captured simultaneously. The main difference between the two technologies is that the reference arm in an FD-OCT system has a static mirror instead of a moving one as seen in TD-OCT. This removes the limitations imposed by the inertia of the mechanical device thus allowing higher data acquisition speeds in a FD-OCT system. The current generated in an FD-OCT detection system by incoming light, at a particular instant, is a function dependent on the source wavelength sampled at that instant. The acquired data is sampled into an axial scan information by performing an

inverse Fourier transform. FD-OCT can also image by 2 methods – SD-OCT and SS-OCT.

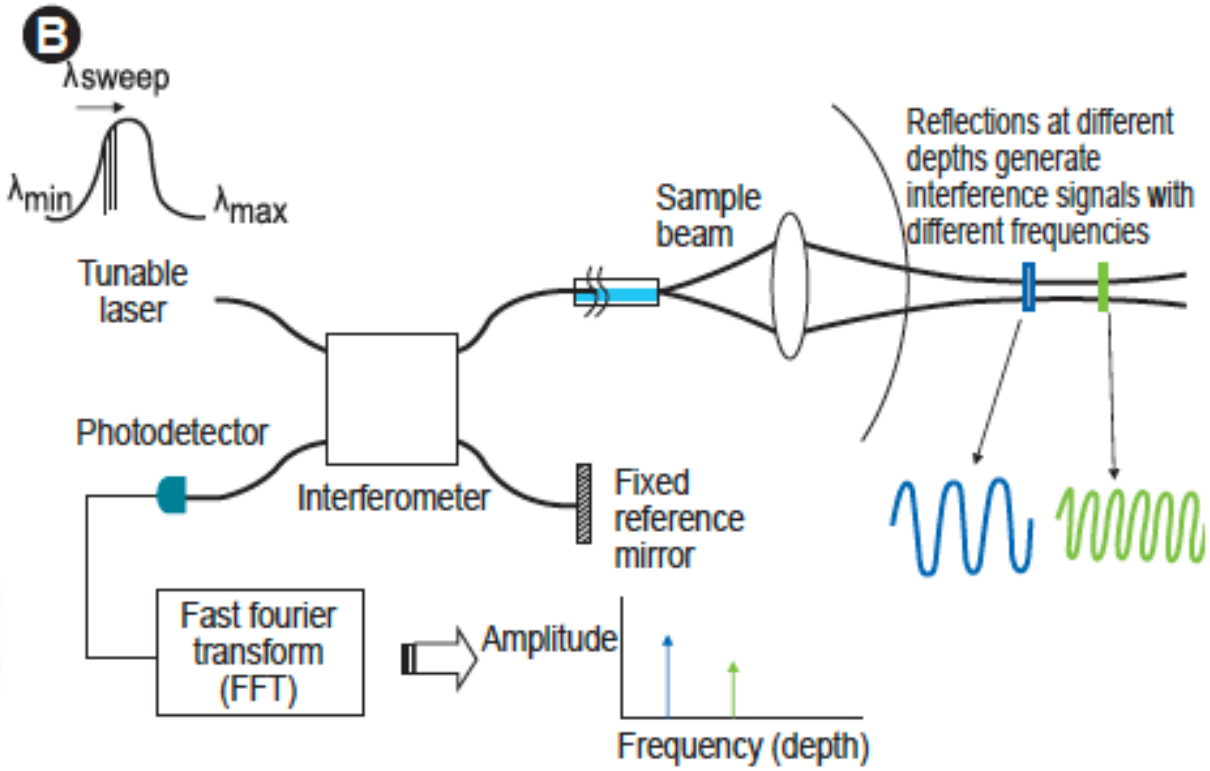

Figure 3. Fourier domain optical coherence tomography system

The core of an SD-OCT is a Michelson-type interferometer with a stationary reference mirror. After the returning beams have been coupled at the level of the beam splitter, their spectrum is spread out with a diffraction grating and detected by a high-speed CCD line camera. A Fourier transform is performed on the spectrally-resolved interference pattern detected by the camera array thus obtaining the reflectivity as a function of depth which gives the A-scan[11]. The acquisition rates in such systems are limited by the rate of the line sensor.

The SS-OCT uses a broadband source that scans in a controlled way a laser with a narrow spectral line across the available bandwidth of the source.

The reference beam is reflected from a fixed mirror and forms an interference pattern with the light backscattered by the sample that is subsequently detected by a point detector. The advantage of point detection lies in the higher signal : noise ratio detection available as compared to line or area detectors. The output in SS-OCT is a wavenumber-dependent photo-current that is recorded by the point detector simultaneously[12]. The A-scan is obtained by performing Fourier-transform of the detected signal over one sweep of the laser across the available broadband. In the system, the coherence length of the scanned laser determines the maximum imaging depth of the system while the wavelength range over which the laser is swept determines the axial resolution of the system. Thus, a scanning laser with a narrow linewidth enables a deeper imaging depth while a wider sweep range produces OCT images with higher axial resolution.

The data acquisition speed for a typical Fourier domain device is usually 45–100 times faster than for TD-OCT. Faster acquisition of larger number of scans allows 3D reconstruction of tissue imaged which gives better understanding of the pathology. High acquisition speeds are associated with lesser movement artefacts. The signal to noise ratio of FD-OCT Is much better as compared to TD-OCT. Due to all these properties, FD-OCT has been determined to have a sensitivity advantage over TD-OCT[8].

Another OCT imaging technique, full field OCT, creates tomographic images in an en face orientation. These images are perpendicular to the optical axis of the sample arm and are acquired in one shot. In FF-OCT, the entire field is illuminated with a low coherence light source. The properties of the light source produce a high axial resolution of about 1 μm and a similar transverse resolution. The tomographic images are generated by combining en face interference patterns corresponding to different depths within the sample. In FF-OCT, it is necessary to record two or more phase-displaced en face interference patterns, so that a tomographic image corresponding to a sample slice located at a specific distance underneath the surface can be obtained. The phase shift is

achieved by displacing the reference mirror with a high resolution piezoelectric translation stage.

Various properties of OCT make it a valuable tool for use in biomedical imaging. OCT can image with axial resolutions of 1 to 15 μm, much higher resolution that the conventional ultrasound. This resolution approaches that of histopathology, allowing architectural morphology and some cellular features to be detailed with precision. OCT imaging can be performed directly through air without requiring direct contact with the tissue or a transducing medium. Imaging can be performed in situ thus obviating the need for biopsy of tissue. Real time imaging is performed without the need for specimen processing as in histopathology. Pathology can be monitored on screen and recorded for offline analysis. OCT is based on fibre optics and it can be combined with a range of instruments like catheters, endoscopes and laparoscopes which will enable imaging inside the body. It is compact and portable, thus making its use easy and simple.

Intravascular OCT : -

Intravascular imaging has revolutionised the field of interventional cardiology as it gives an insight into the plaque characteristics and the vessel wall, things which were beyond the scope of conventional angiography. OCT imaging provides a high axial resolution of 10-15 μm which is about 10 times higher than the axial resolution provided by intravascular ultrasound (IVUS). This high resolution enables accurate identification of different layers of vessel wall and separate components of the atherosclerotic plaque like collagen, calcium and lipid. OCT provides virtual histology of the tissue under investigation and autopsy studies have shown that OCT has high sensitivity and specificity (90%) for detection of various components of atherosclerotic plaque, especially lipid[13]. Another study by Kume et al. showed that OCT had sensitivity and specificity[14].

Intravascular OCT is used extensively in the field of cardiology. It is used in both diagnosis and aiding intervention.

OCT in study of plaque morphology:

Due to the high axial resolution of OCT in comparison to other intravascular imaging modalities, it helps in characterising the plaque morphology. On the basis of OCT imaging, plaques can be classified as fibrous plaque, calcified plaque and lipid rich plaque[1]. Fibrous plaque are show homogenous rich signal with low attenuation. Calcific plaque is defined as low backscatter with low attenuation and well defined borders. Lipid plaque are characterised by low backscatter and high attenuation with undefined borders. OCT can also detect other plaque characteristics like plaque cap thickness , lipid arc, presence of macrophages in the plaque cap and associated thrombus. Due to the high resolution of OCT, plaque cap thickness can be measured and can be used as an objective parameter in identifying high risk unstable plaques. OCT imaging helps in identification of thin plaque cap which are prone to rupture[15]. Studies have shown that plaque cap thickness < 65 μm is usually seen in patients with acute coronary syndrome and is considered as a vulnerable plaque[16]. Thin cap fibroatheroma were defined as lipid rich plaque with thin plaque cap (plaque cap thickness < 65 μm) on OCT[17]. OCT can accurately identify presence of plaque rupture which is commonly seen in patients with acute coronary syndrome. OCT was found to be the most sensitive modality in comparison with IVUS and angioscopy in detection of plaque erosion and plaque rupture in patients with myocardial infarction[18]. OCT imaging can also reliably identify and distinguish red thrombus and white thrombus[19].

OCT can also be used to identify presence of macrophages within the plaque cap, which is a marker of high inflammatory activity within the plaque. Higher density of macrophages are noted in patients with ACS as compared with stable CAD patients[20]. OCT can also identify plaque erosion which is

defined as irregular endothelial surface with intact plaque cap and luminal thrombus. Previous studies have shown the prevalence of thrombus in 27-31% patients with ACS[21].

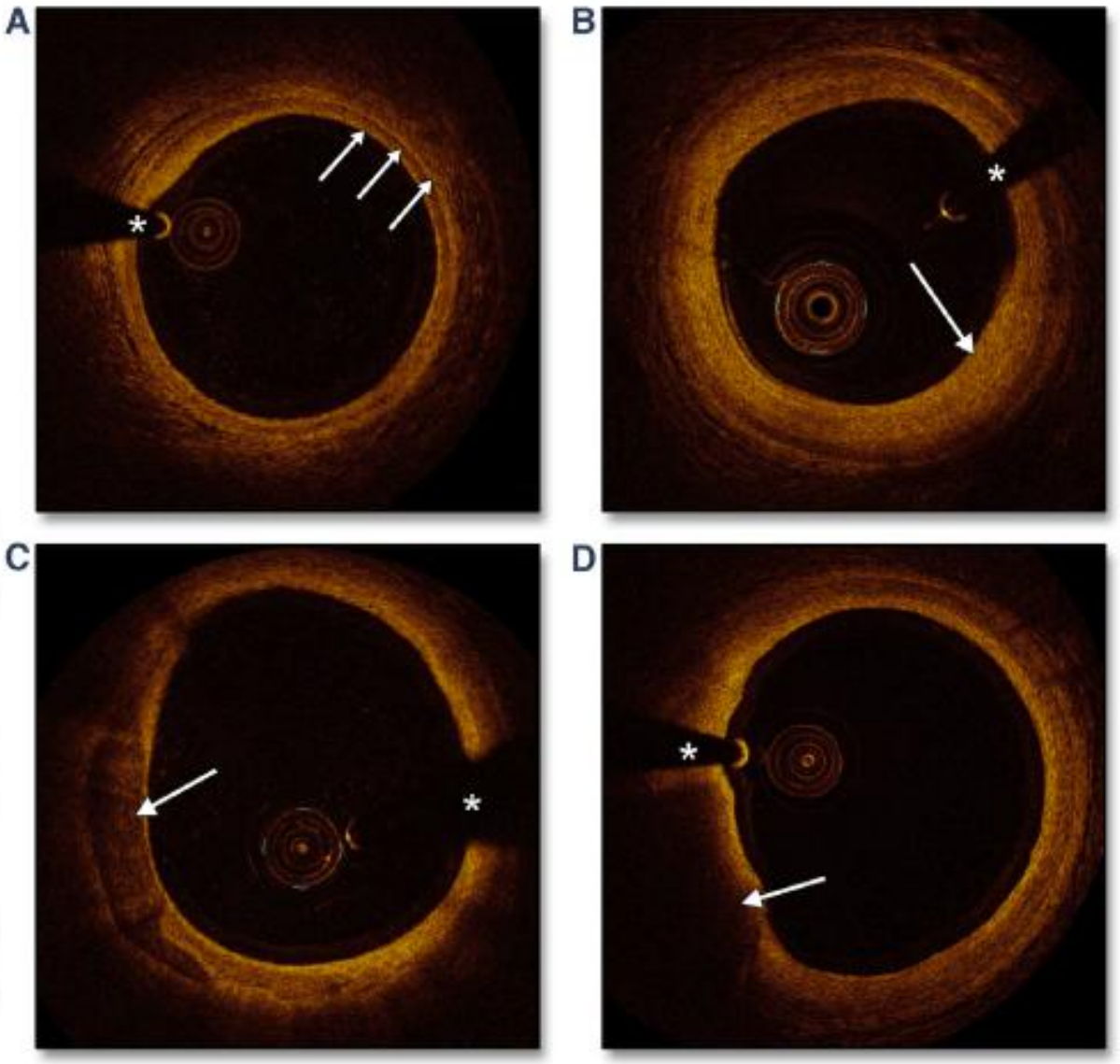

Figure 4. A. Layers of normal vessel wall with arrows showing internal elastic lamina, media and external elastic lamina. B. Concentric fibrous plaque. C. Calcified plaque. D. necrotic core.

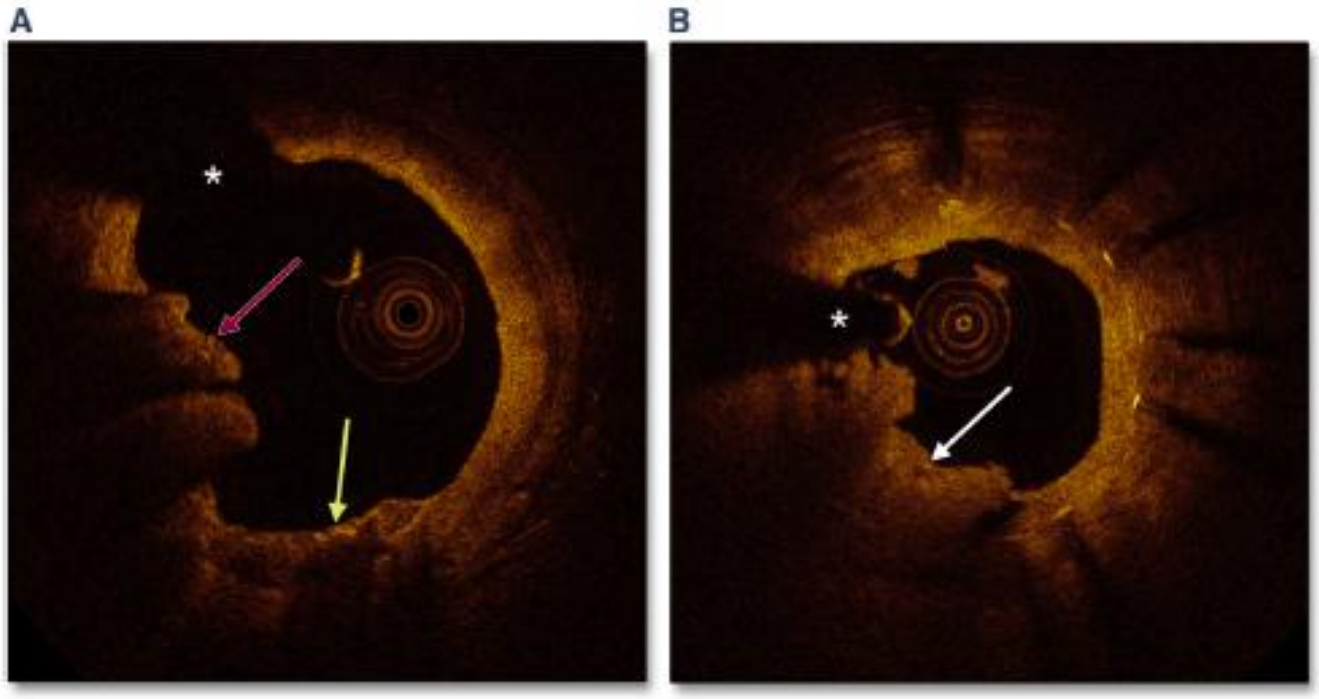

Figure 5. A. Red thrombus (red arrow) in a case of calcified plaque (yellow arrow). B. White thrombus (white arrow) in a case of stent thrombosis.

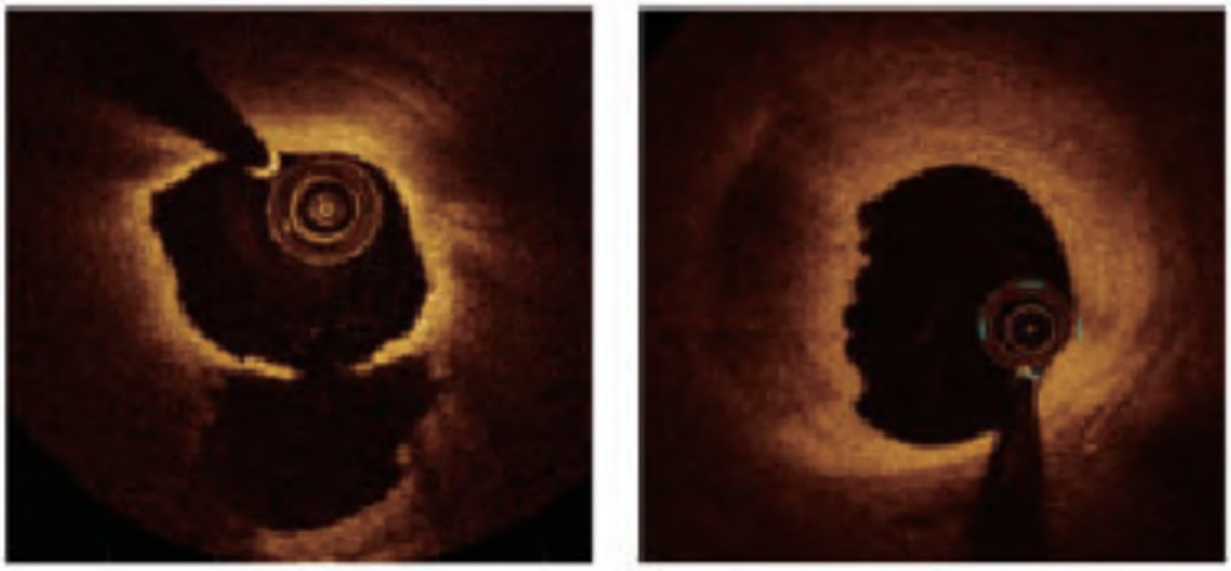

Figure 6. Plaque rupture and plaque erosion on OCT imaging.

OCT use in PCI:

Intravascular imaging has been used to optimise results post PCI. IVUS has been traditionally used for improvement of outcomes during PCI. IVUS-XPL[22] and CTO-IVUS[23] trials have shown reduction in major adverse events post PCI with adjunctive use of IVUS. Owing to the high resolution of OCT, it has also been used in PCI for optimisation of results. DOCTORS trial showed a significant improvement in post PCI FFR in ACS patients in whom OCT was used for optimisation of PCI[24]. Better stent coverage was noted with OCT used in stable CAD patients who underwent PCI in the DETECT-OCT study[25]. ILLUMIEN III[26] and OPINION[27] trials showed that OCT is non inferior to IVUS in terms of optimisation results post PCI. The high resolution provided by OCT helps in early detection of post stent complications which can be corrected during the procedure.

OCT can be used before PCI for studying lesion characteristics and planning of the intervention. It can be used to detect calcified plaque. Measurement of calcium arc and thickness will provide necessary information regarding need of lesion preparation. Calcium arc of >180 degrees and calcium plaque thickness >500μm are predictors of stent underexpansion and poor results after PCI[28]. Evidence of calcium fractures post lesion preparation predicts good stent expansion. Stent underexpansion is an important cause of in-stent restenosis. OCT can be used to measure the actual vessel size and determine the appropriate stent size. OCT based approach includes measuring the mean luminal diameter and upsizing by 0.25mm for the stent size as shown in the OPINION study. The ideal stent length can be obtained by investigating the proposed landing zones using OCT. Avoiding landing zones with plaque burden >50% prevents stent malapposition and reduces MACE events[29]. Co-registration of OCT with coronary angiography is an important tool which will facilitate selection of appropriate size stent as well as its implantation[30].

OCT also helps in optimising PCI results after stent implantation. Optimal stent expansion is very important for long term success. Stent under-

expansion can cause stent failure. Post procedure minimum stent area > 5.5 mm^2 on IVUS has been demonstrated to be adequate in non-left main lesions[31]. OCT derived stent area of 4.5 mm^2 was found to predict adverse cardiac events in post PCI patients in the CLI-OPCI study[32]. Stent malapposition is another frequent finding noted in patients with stent failure. At the end of PCI, OCT can better identify stent malapposition as compared with IVUS[26]. OCT studies in acute stent thrombosis have shown high rates of malapposition – 27% in PRESTIGE[33] study and 60% in PESTO[34] study, respectively. Immediate detection of malapposition during PCI can be rectified and adverse events can be prevented. OCT can also help identify stent edge dissections which can cause stent failure in future. Large dissections >200μm located at the distal stent edge was shown to be an independent predictor of MACE in the CLI-OPCI study[32].

OCT can also be used to study the mechanisms of stent failure. The different causes of stent failure like stent underexpansion, malapposition and Neoatherosclerosis can be detected by OCT. Neoatherosclerosis can be detected only by OCT owing to its high resolution which helps in tissue characterisation. Detection of morphology of in-stent restenosis and stent thrombus is possible only with OCT. OCT helps to characterise the neo-intimal hyperplasia as homogenous, heterogenous and layered morphology. Identification of different morphology of tissue in cases of stent failure helps in management decisions.

STUDY HYPOTHESIS

The hypothesis formulated at the onset of the study was -

1. Morphology of culprit lesions varies amongst patients with acute coronary syndrome.

2. Culprit lesion morphology determines long term outcomes.

STUDY OBJECTIVES

Primary objectives –

1. Study of morphology of culprit lesions in patients presenting with acute coronary syndrome.

2. Correlation of lesion characteristics with culprit lesion morphology.

Secondary objectives –

1. Clinical outcomes in different plaque morphology patients after a follow up period of 12 months.

MATERIALS AND METHODS

Study population -

This was a single center retrospective and prospective study which included patients with acute coronary syndrome (ACS) who underwent optical coherence tomography evaluation over a period of 4 years. All patients presenting with acute coronary syndrome were screened for inclusion in the study. Acute coronary syndrome patients included patients presenting with unstable angina (UA), Non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). UA was defined as (i) crescendo angina either at rest/exertion, not fully relieved with nitrates (ii) ST segment depression or T wave inversion on electrocardiogram (ECG) (iii) No troponin elevation (troponin T < 0.1 ng/ml), associated with angiographic evidence of coronary stenosis > 50%. NSTEMI was defined as (i) symptoms associated with myocardial infarction – angina, dyspnea, chest tightness, sense of impending doom. (ii) new findings of > 1mm ST- depression and/or T wave inversion in 2 contiguous leads on ECG. (iii) Troponin elevation (>0.1ng/ml). STEMI was defined as (i) symptoms associated with myocardial infarction – ongoing chest pain (ii) ST elevation > 1mm in 2 contiguous leads in 12 lead ECG (iii) elevated biomarker (troponin/creatine kinase).

All patients, above 18 years of age, who present with acute coronary syndrome to our hospital and have an OCT analysis done were included in our study. Patients who present within 6 weeks of index event and undergo OCT analysis at our center were also included in this study. Patients with renal dysfunction and serum creatinine >2 mg/dl, cardiogenic shock, left main coronary artery stenosis and ectatic coronaries were excluded from the study. The hospital records were also screened for patients with acute coronary syndrome who had underwent OCT analysis, from the year 2015. All cases

fulfilling the inclusion criteria were included in the study. Cases who fulfilled the inclusion criteria but had sub-optimal OCT images were excluded from the study. Informed and valid consent was obtained from all patients before the procedure. This protocol was approved by the institutional ethics committee at Sreechitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Thiruvananthapuram (SCT/IEC/1297/OCTOBER-2018).

Study protocol –

All patients, included in the study, had a thorough physical examination risk factor assessment. Specific cardiovascular risk factors like diabetes, hypertension, hyperlipidemia, smoking and family history of coronary artery disease were elicited. 12 lead ECG was obtained to determine the culprit vessel territory. All patients underwent 2-D Transthoracic echocardiography (TTE) for determination of left ventricular (LV) function, regional wall motion abnormality and any valvular abnormality like mitral regurgitation or aortic regurgitation. Hemogram, renal function test and lipid profile were performed in all patients to assess baseline characteristics. Biomarker estimation [troponins and N terminal brain natriuretic peptide (NT-ProBNP)] were done. Patients who had an ACS event within the past 6 weeks and were referred to our hospital, had a detailed analysis done in terms of risk factors, treatment received during the acute event – thrombolysis or medical management, ongoing medications and current symptoms. Patients with ACS planned for primary percutaneous coronary intervention (PCI) were given loading doses of anti-platelets – aspirin 300mg and clopidogrel 600mg. Some patients also received ticagrelor 180mg in place of clopidogrel – the choice between clopidogrel and ticagrelor was based on operator preference.

After transfer to catheterization lab, patients were given intravenous unfractionated heparin bolus (70U/kg) after securing arterial access. Coronary angiogram (CAG) was performed in the standard views for left and right

coronary system and the lesions were analyzed. In case of total occlusion with TIMI 0 flow distally, low pressure balloon dilatation with a small size balloon was performed. In case of large angiographically visible thrombus (grade 3/4), thrombus aspiration was done using 6 F aspiration catheter (STEMI Cath) in order to achieve TIMI III flow distally. After establishment of flow distally, OCT analysis of culprit lesion was performed. A 2.7F OCT catheter (Dragon Fly, St Jude system) was introduced over a 0.014" guidewire and passed distal to lesion. Frame rates were 100fps and pullback speed were 25mm/s allowing 75mm pullback in less than 3 seconds. Contrast flush using low osmolar iodinated contrast (Omnipaque) was used to flush the vessel in order to obtain optimal clearance. Pull back was done after contrast flush and the region of the interest in the vessel was imaged. The images and data were stored offline for detailed analysis.

Patients who were enrolled in the study after screening of hospital records, had all baseline data analyzed including risk factors, echocardiography analysis and biomarker values. CAG and OCT data was retrieved and analyzed for quality of images and pertinent information.

After enrollment, the patients were followed up at every three-monthly interval. Follow up was done using out-patient visits or telephonic calls. Any adverse event in the follow up period like mortality, all-cause hospitalization, myocardial infarction and revascularization was recorded using a pre-specified questionnaire.

Angiographic analysis –

All CAG performed were analyzed by using Quantitative coronary angiography (QCA) tool using the diagnostic catheter(6F) for purpose of calibration. Analysis was performed by 2 independent observers who were blinded to the clinical history and OCT findings. The culprit lesion morphology on angiogram was decided on the basis of ACC/AHA lesion classification. Type A lesions

were defined as concentric, discrete lesions (length of <10mm) which are easily accessible, having a smooth contour, devoid of any calcification and thrombus, present in non-ostial location without involving any side branch and having a non-angulated segment of < 45°. Type B lesions were defined as tubular (length 10-20mm), eccentric, having an irregular contour with moderate- severe calcification/thrombus, having moderate tortuosity of proximal segment, either in ostial or bifurcation location. Total occlusions of < 3 months duration were classified as Type B lesion. Type C were defined as diffuse lesions (>20mm length), having extreme tortuosity and angulation >90° of proximal segment. Total occlusions > 3months duration and degenerated friable vein grafts were classified as Type C lesions. In-stent restenosis was defined as >50% stenosis in previously implanted stent segment.

OCT analysis –

All OCT images were analyzed offline by 2 independent investigators who were blinded to the clinical presentation and angiography findings. In case of a dispute, a consensus finding was agreed upon. The images were assessed for culprit lesion morphology.

Plaque rupture was defined as discontinuity in the fibrous cap of plaque along with a cavity formation.

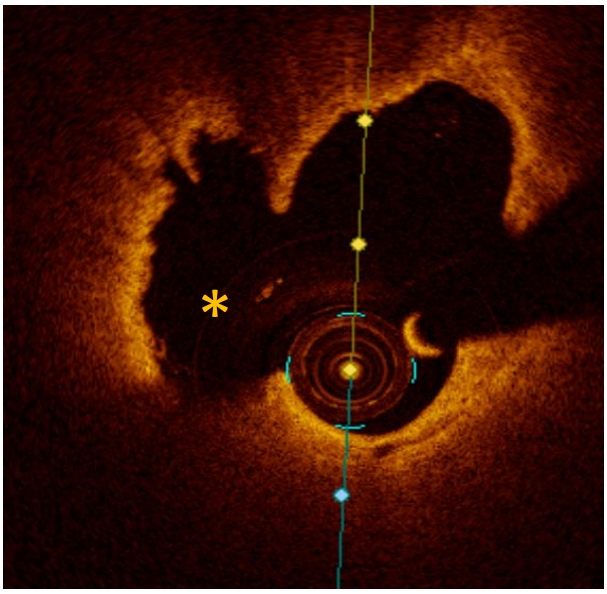

Figure 7. Plaque rupture with ruptured cavity (asterisk)

Plaque erosion was defined as irregular luminal surface with overall intact fibrous cap and presence of intracoronary thrombus.

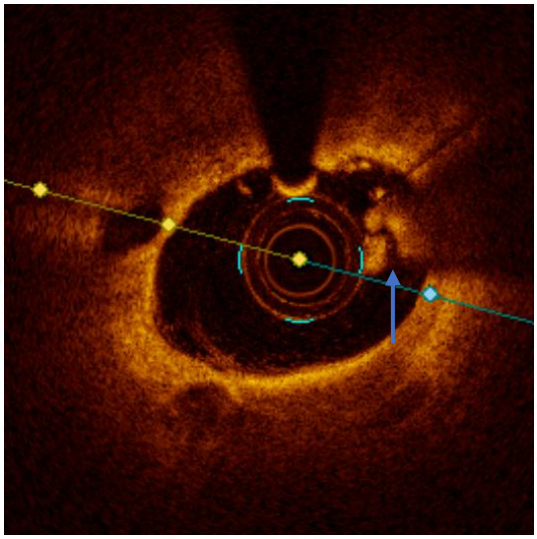

Figure 8. Plaque erosion with presence of red thrombus (arrow).

Intracoronary thrombus was defined as protruding mass into the lumen from the surface of vessel wall. Red thrombus was defined as protruding mass with high attenuation – no structure was seen beneath the thrombus.

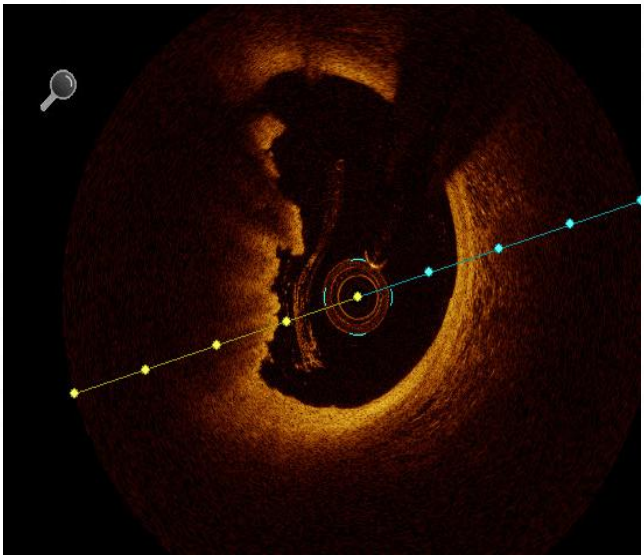

Figure 9. Red thrombus on OCT

White thrombus was defined as protruding mass with low attenuation.

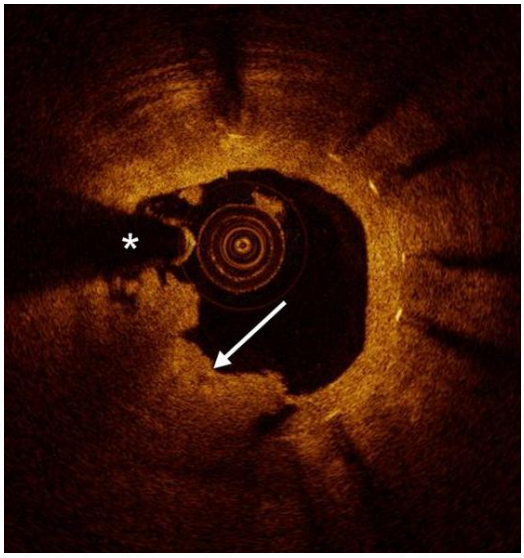

Figure 10. White thrombus in a case of in-stent restenosis

Calcific nodule was defined as a calcium plaque protruding into the vessel lumen.

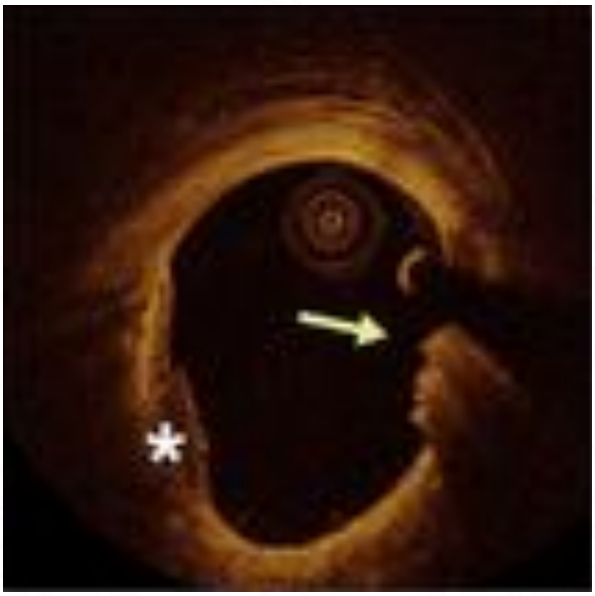

Figure 11. Calcified nodule protruding into vessel lumen (asterisk) with a red thrombus (arrow).

Fibrous plaque was defined as predominant thickening of intima with high backscatter.

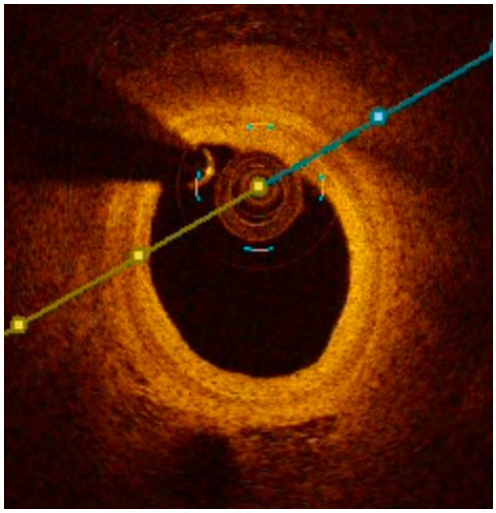

Figure 12. Fibrous plaque.

Lipid plaque was defined as plaque containing significant lipid pool (low backscatter with ill-defined borders). Lipid arc was measured as the angle subtended by the largest lipid pool in the circumference of the vessel.

Plaques with lipid arc > 90˚ were considered to be lipid rich plaque whereas plaques with lipid arc < 90° were considered to be fibrofatty plaques.

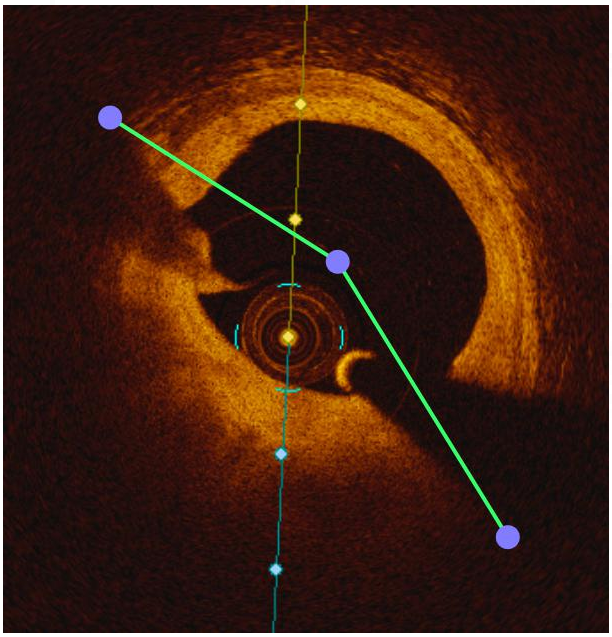

Figure 13. Lipid plaque with a large lipid pool – defined by a lipid arc of 150˚

Macrophages were defined as bright spots in the arterial wall associated with mild shadowing. They are usually located at the junction of the intimal cap and the lipid pool.

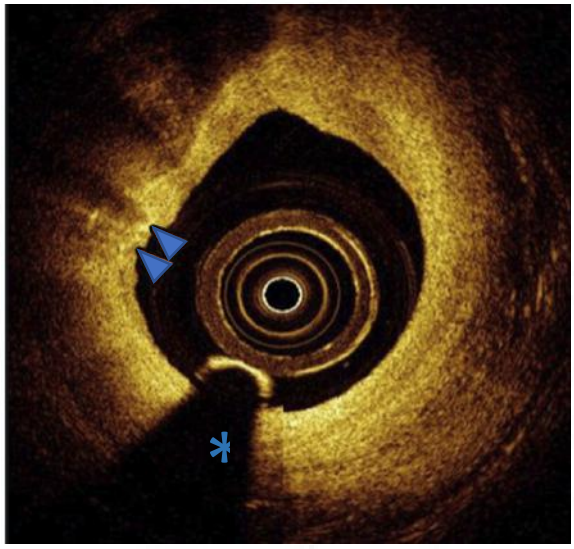

Figure 14. Macrophages in the intimal layer (triangles) as bright spots.

Plaque cap thickness was defined as the minimum distance from vessel lumen to inner border of the lipid pool.

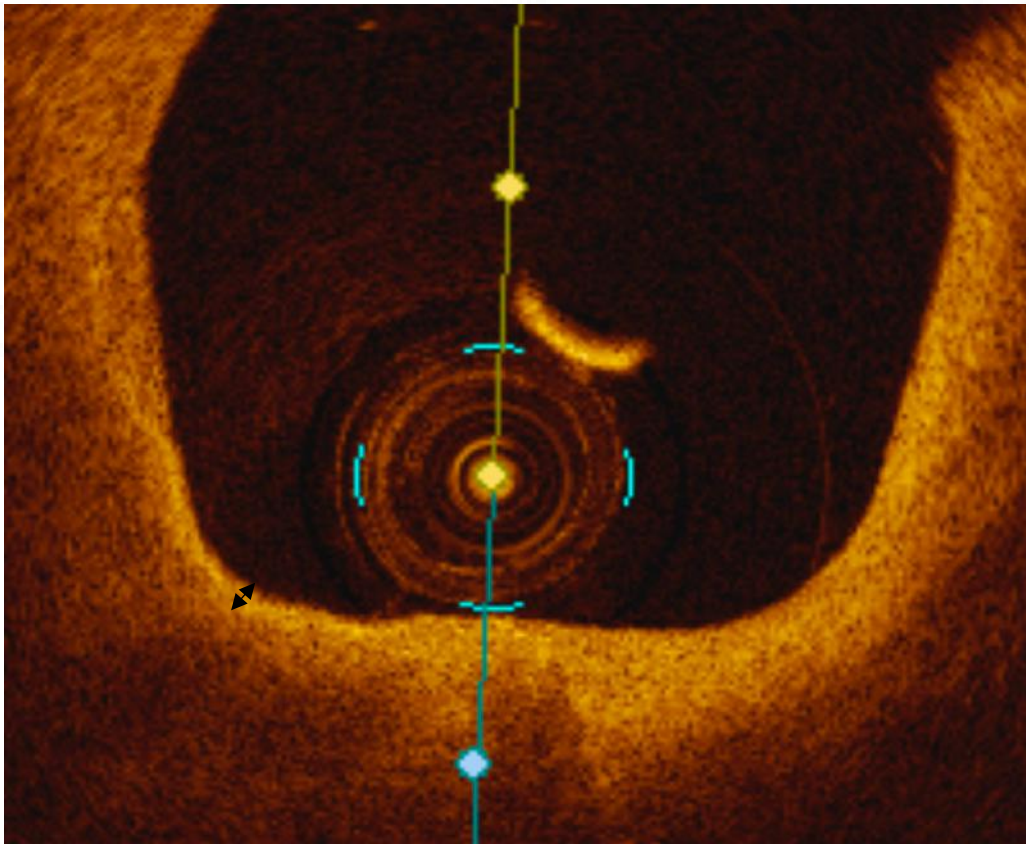

Figure 15. Plaque cap thickness denoted by double headed arrow.

In ruptured plaque, cap thickness was measured at the flap of tissue between the vessel lumen and plaque cavity – minimum thickness was taken.
Thin cap fibroatheroma was defined as a plaque cap thickness of < 65μm.

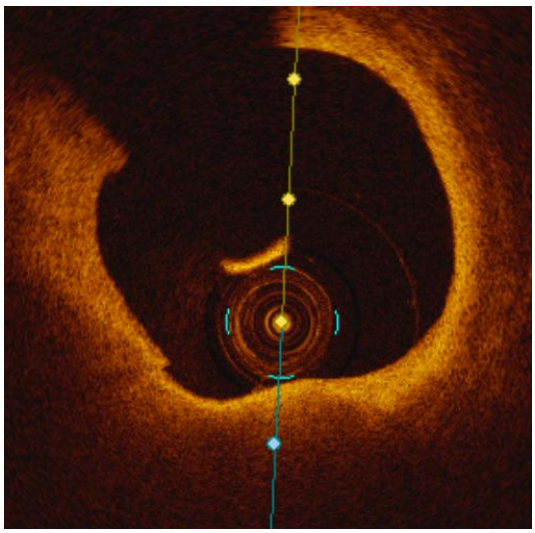

Figure 16 . Thin cap fibroatheroma (arrow) with a plaque cap thickness of <65μm.

Neo-intimal hyperplasia was defined as presence of fibrotic tissue growth inside the stent struts. Neo-intimal hyperplasia was further classified into homogenous and heterogenous types depending on OCT characteristics. Neoatherosclerosis was defined as presence of lipid pool along with fibrous tissue within the stent struts.

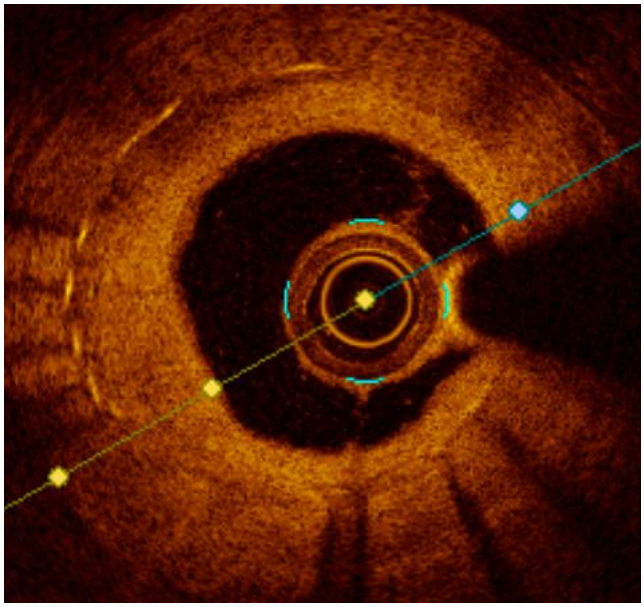

Figure 17. Neointimal hyperplasia (homogenous type)

Data analysis –

All the data was collected using a pre-specified structured questionnaire. Data was presented as summary statistics. The patients were followed up for a period of 1 year. The primary endpoint was a composite of death, myocardial infarction, all-cause hospitalization events or revascularization. Secondary endpoints were all-cause hospitalization events, myocardial infarction, target lesion revascularization, target vessel revascularization and revascularization of other vessels.

Categorical variables were presented as proportions and continuous variables were presented as mean with standard deviation. Chi-square test was used for determining association between categorical variables. Independent sample t-test was used to compare mean values of continuous variables. We conducted multivariate logistic regression analysis for predicting various factors associated with primary and secondary outcomes. We also conducted multivariate regression analysis for predicting various factors associated with specific lesion morphology. We report the odds ratio (OR), their 95% C.I. and p-value for all the variables in the multivariate model. ROC curve was drawn to

predict the sensitivity and specificity of plaque cap thickness as a predictor for plaque rupture. A p-value of <0.05 was considered statistically significant. All analysis was done using SPSS v25 (IBM, Armonk, NY).

RESULTS

A total of 32 patients with acute coronary syndrome, who underwent OCT, were included in the study. These patients included those who presented as unstable angina, NSTEMI and STEMI.

Baseline demographics:

The mean age of the study population was 54.4 ± 11.7 years (range 23-75 years).

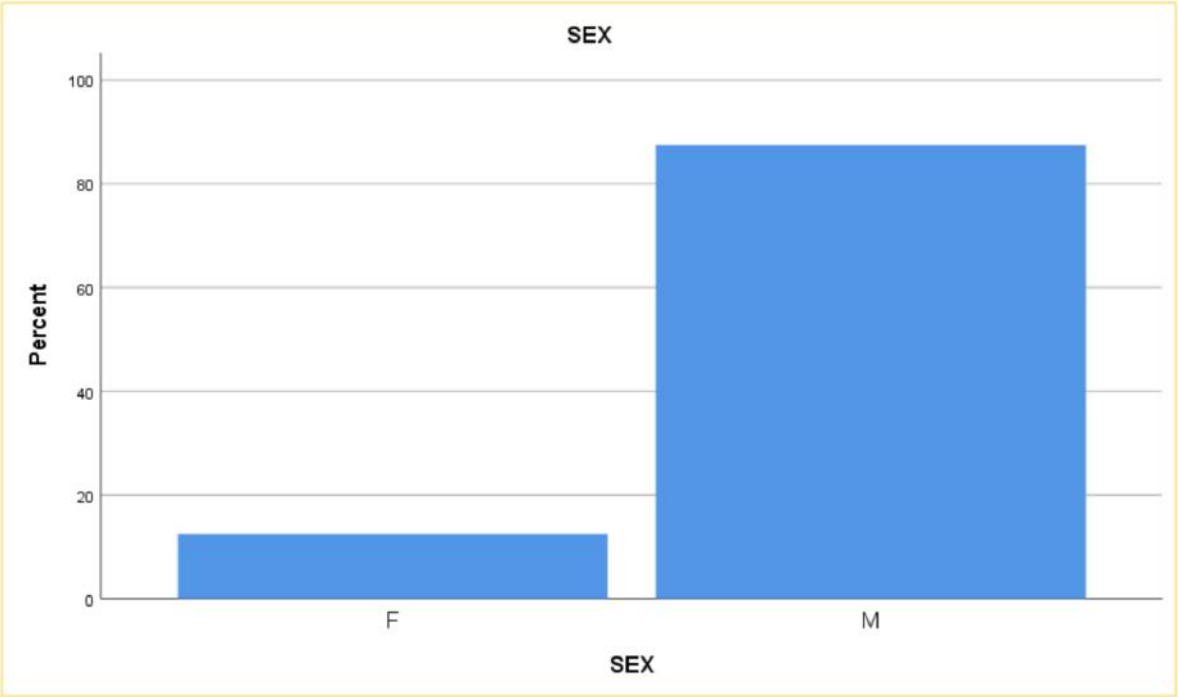

Figure 18. Sex distribution in the study population.

Females comprised 12.5% (n=4) of the study population. Mean age of female population was 58.7 years.

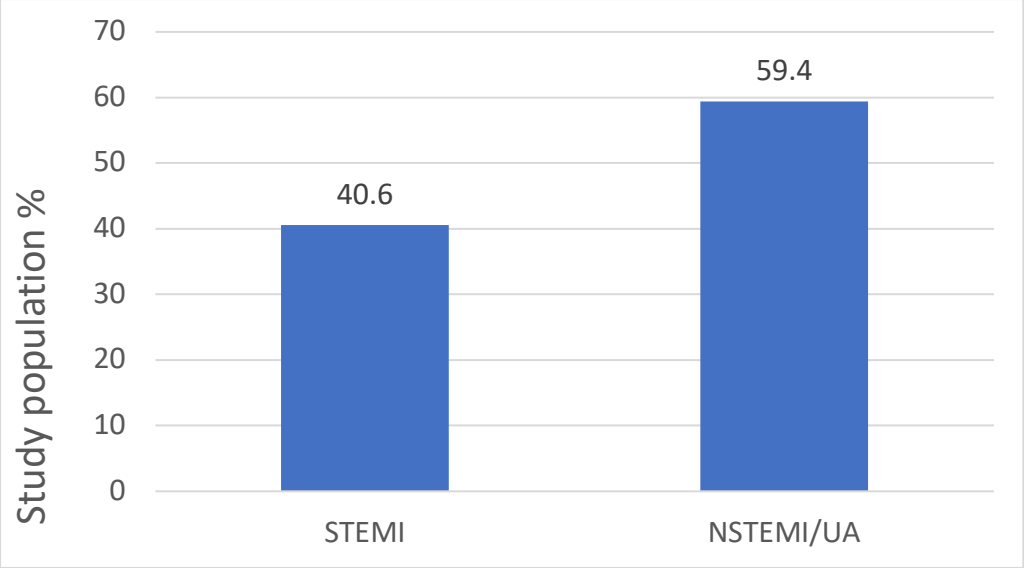

Figure 19. Clinical presentation of the study participants

About 40% of the study population had STEMI on presentation whereas the rest of the patients had unstable angina/NSTEMI.

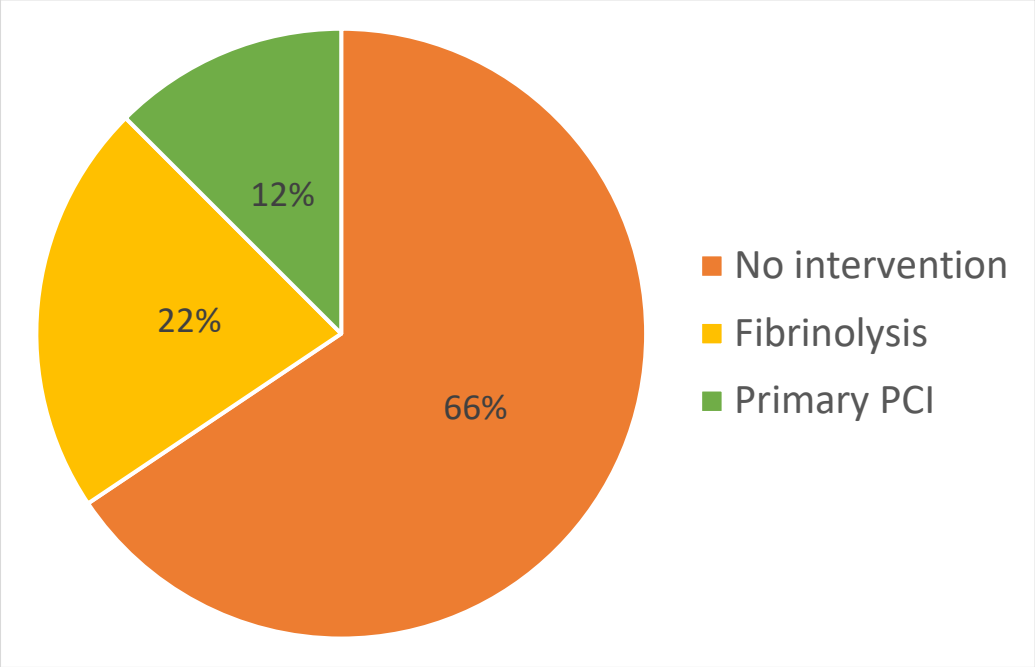

Figure 20. Mode of therapy received by study participants before presenting to our hospital.

Prior to presentation, 22% of patients had received fibrinolysis whereas 12% had undergone primary PCI at the referring hospital.

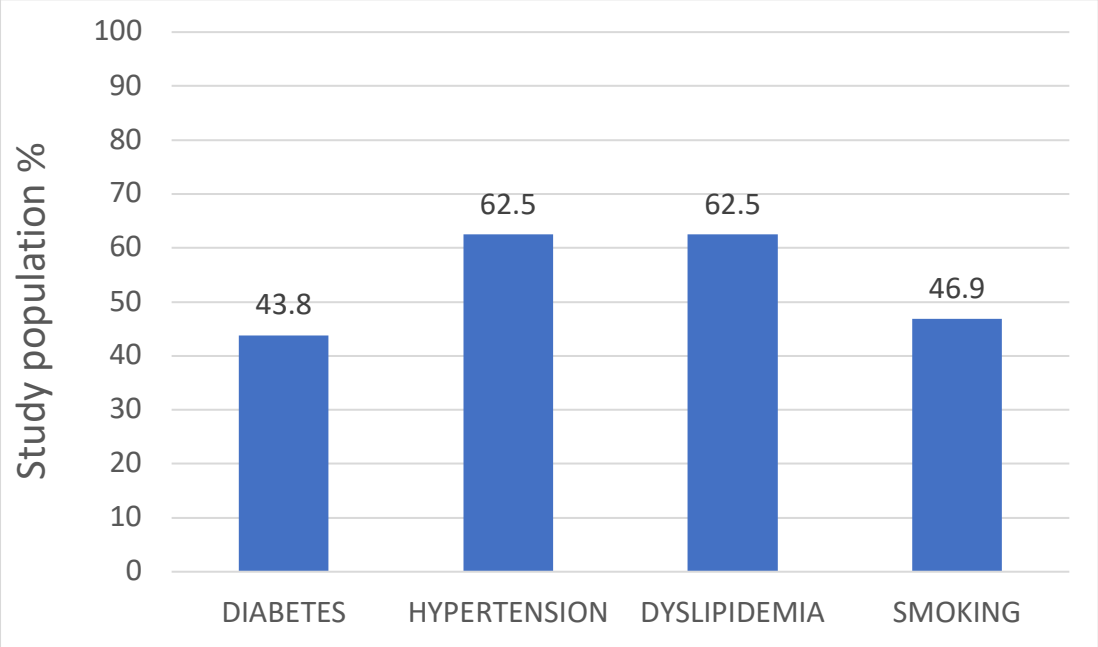

Figure 21. Risk factor distribution in the study population.

In the study population, 44% had diabetes, 47% were current or ex-smokers and 62.5% patients had hypertension and dyslipidemia.

43.8% patients (n=14) had past history of acute coronary syndrome whereas 37.5% (n=12) had past history of revascularisation (PCI/CABG).

On clinical examination, heart failure on presentation was noted in 6.3 % patients (n=2). Mean cardiothoracic ratio on chest x-ray was 0.52 ± 0.04. 2-D transthoracic echo showed a LV end diastolic dimension of 48.06 ± 6.4 mm whereas LV end systolic dimension was noted to be 31.16 ± 5.7 mm. The LV ejection fraction was 57.8 ± 13.2 %, indicating a normal LV function in the study population.

The baseline laboratory investigations showed a hemoglobin of 13.6 ± 2.04 gm/dl and ESR 17.9 ± 17.4 mm/hour. Baseline lipid profile levels showed total cholesterol of 161.35 ± 63.1 mg/dl, LDL – cholesterol of 97.9 ± 52.6

mg/dl, HDL – cholesterol of 38.7 ± 9.7 mg/dl and serum triglycerides of 119.69 ± 57.1 mg/dl. Baseline serum creatinine was 1.05 ± 0.25 mg/dl.

Angiographic results:

Baseline angiography was performed in all the study participants and the characteristics were analysed.

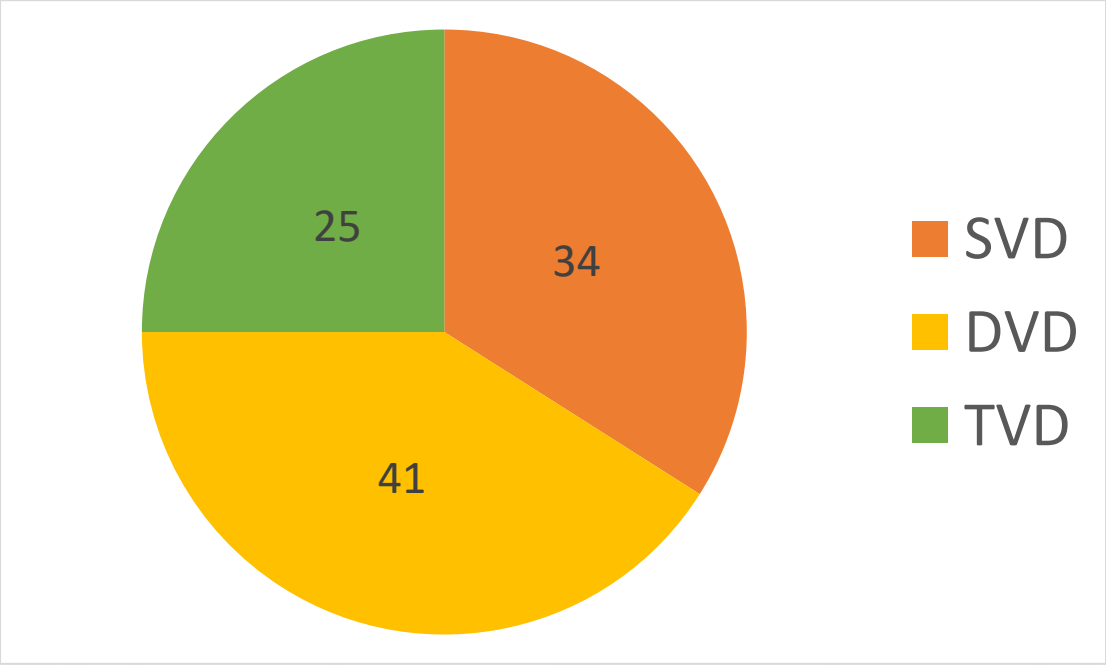

Figure 22. Severity of CAD in the study population.

Angiography revealed that majority of the study population had double vessel disease with single vessel disease seen in 34% and triple vessel disease seen in 25% of the study population, respectively.

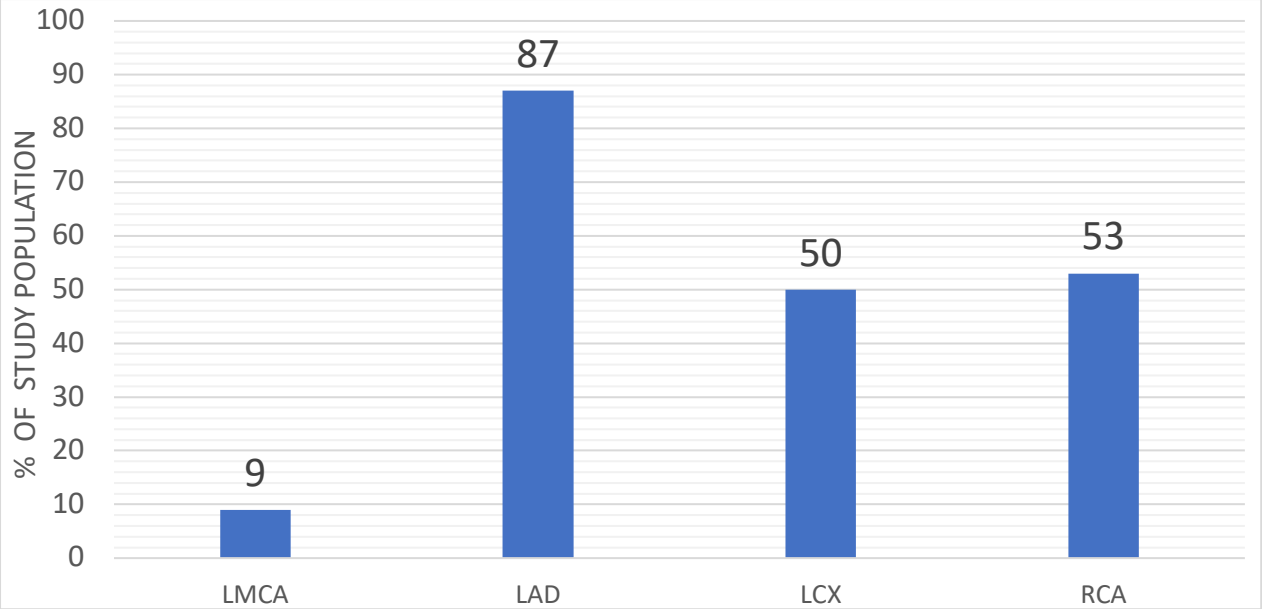

Figure 23. Pattern of vessel involvement in the study group.

Amongst the vessels, LAD was most commonly involved in 87% of study population followed by RCA in 53% of the population. Left main coronary artery involvement was noted in 9% of study population.

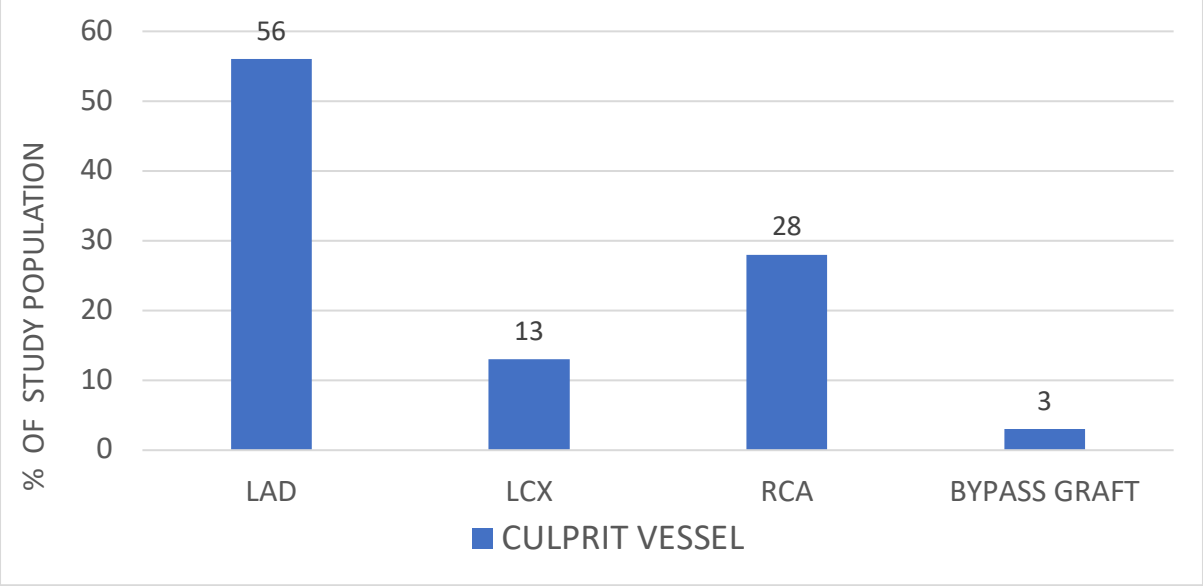

Figure 24. Pattern of culprit vessel involvement in the study group.

LAD was the most common culprit vessel in the study population (56%) followed by RCA (28%). Bypass graft (saphenous venous graft) was the culprit vessel in 3 %(n=1) of study participants.

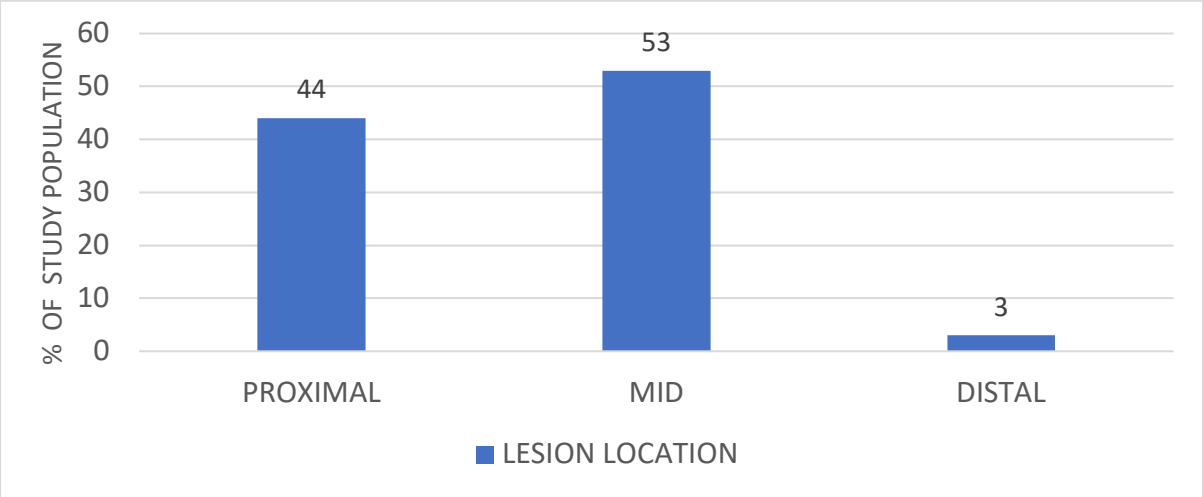

Figure 25. Location of culprit lesion within the vessel.

In the culprit vessel, culprit lesions were most commonly located in the mid segment (53%) followed by proximal segment (44%).

The average lesion length noted on angiography was 22.28 ± 10.3 mm.

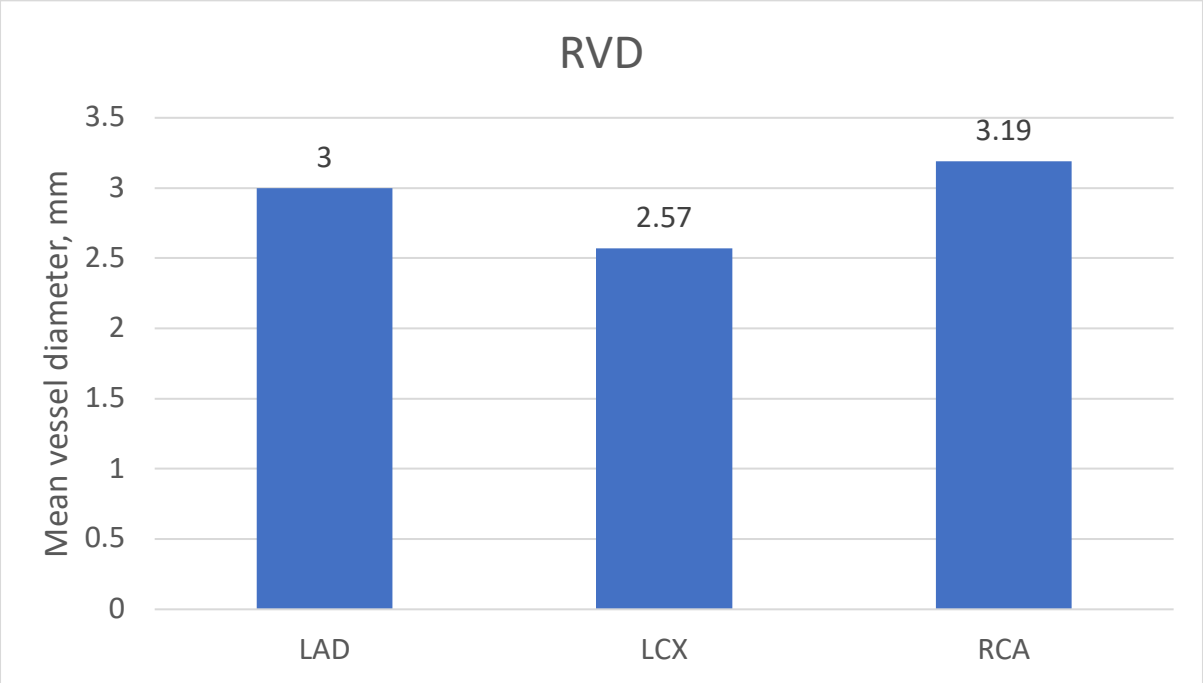

Figure 26. Mean reference vessel diameter noted on CAG.

The average reference vessel diameter for LAD, LCX and RCA was 3 mm, 2.57 mm and 3.19 mm, respectively. The mean percentage diameter stenosis noted on angiography was 76.2 ± 13.9.

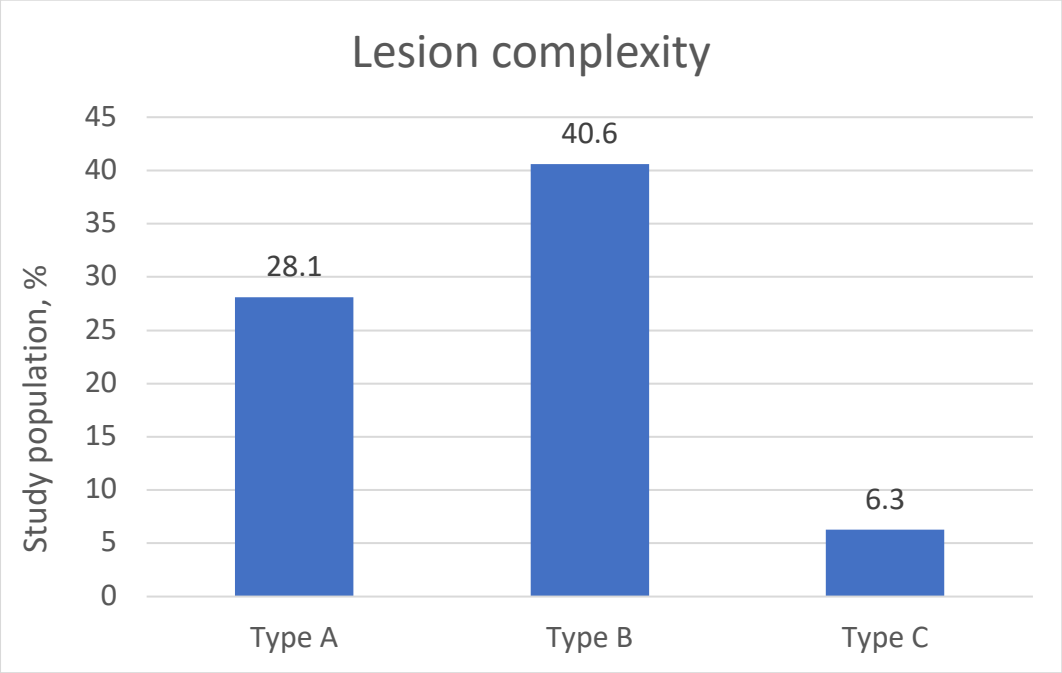

Figure 27. Lesion complexity in study participants.

Based on ACC/AHA lesion complexity, majority of study participants (40.6%) had Type B lesion followed by Type A lesion in 28.1%. Other lesions which are not included in the ACC/AHA lesion classification were also noted in the study participants. Spontaneous coronary artery dissection was noted in 6.3% (n=2) of the study population. In-stent restenosis was noted in 18.7% (n=6) of the study population whereas myocardial bridge was noted in 3.1% (n=1) of the participants.

OCT analysis:

OCT was analysed for the characteristics of the culprit lesion.

	Mean plaque cap thickness in µm (SD)
Study population (n=32)	99.87 (42.5)
Thin cap fibroatheroma (n=9)	56.33 (3.3)

Table 1. Mean plaque cap thickness across the study group.

Minimum plaque cap thickness was measured on OCT. Mean plaque cap thickness noted in the study population was 99.87 ± 42.5 µm. Thin cap fibroatheroma (plaque cap thickness < 65 µm) was noted in 28% (n=9) of the study population. Patients with thin cap fibroatheroma had a mean plaque cap thickness of 56.33 ± 3.3 µm.

Lipid content of the plaque was estimated using the lipid arc. The degree of lipid arc was calculated and that was used to characterize the morphology as fibrous, fibrofatty and lipid rich plaque.

	Lipid arc in degrees, mean (SD)
Study population (n=32)	74.87 (75.45)
Lipid plaques (n=12)	143.29 (56.4)

Fibrofatty plaque (n=7)	58 (8.36)

Table 2. Distribution of lipid arc in the study population.

The mean lipid arc noted in the entire study population was 74.87 ± 75.45 degrees. In patients with lipid plaques, the mean lipid arc noted was 143.29 ± 56.4 degrees whereas in fibrofatty plaques, the mean lipid arc was 58 ± 8.36 degrees.

PLAQUE TYPE	**N (%)**
Fibrous plaque	7 (22%)
Fibrofatty plaque	5 (15.6%)
Lipid rich plaque	14 (43.8%)
ISR	
Homogenous	3 (9.4)
Heterogenous	2 (6.3)
Neo-atheroma	1 (3.1)

Table 3. Frequency of different types of coronary plaques.

Depending on the lipid composition of the plaque, they were divided into fibrous, fibrofatty and lipid rich plaque. Majority of patients had lipid rich plaque (43.8%) followed by fibrous plaque (22%) and fibrofatty plaque

(15.6%). In-stent restenosis (ISR) was noted in 18.8% of the study participants. Amongst the ISR patients, homogenous form of ISR was the most common morphology noted in 9.4% of the patients followed by heterogenous form in 6.3%. Neo-atheroma was noted in 1 patient on OCT analysis.

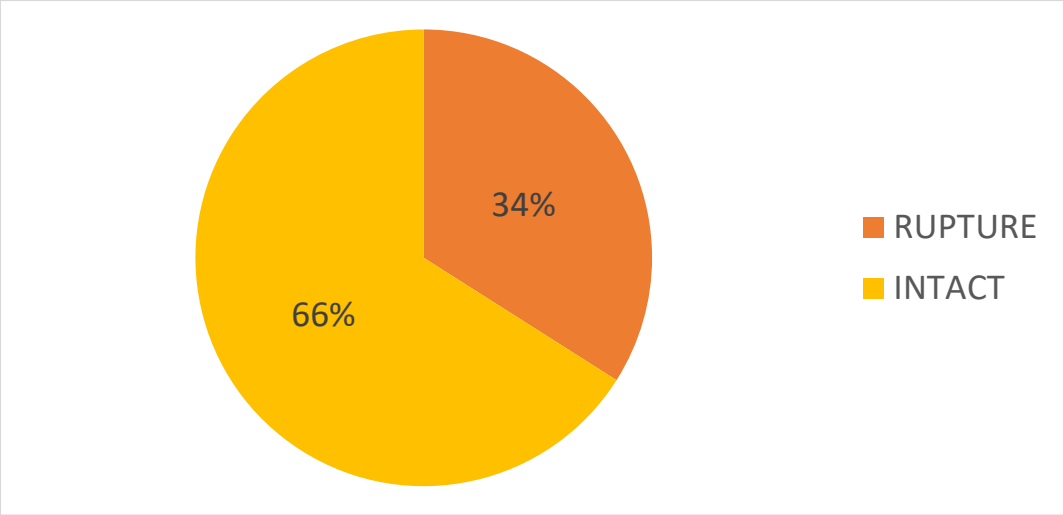

Figure 28. Plaque cap integrity in the study population.

OCT is the most sensitive modality to detect integrity of the plaque cap. In the current study, 34% of the patients had plaque rupture whereas rest patients had an intact plaque cap.

OCT also has high detection rates for intracoronary thrombus owing to its high sensitivity. Presence of red and white thrombus during OCT was noted.

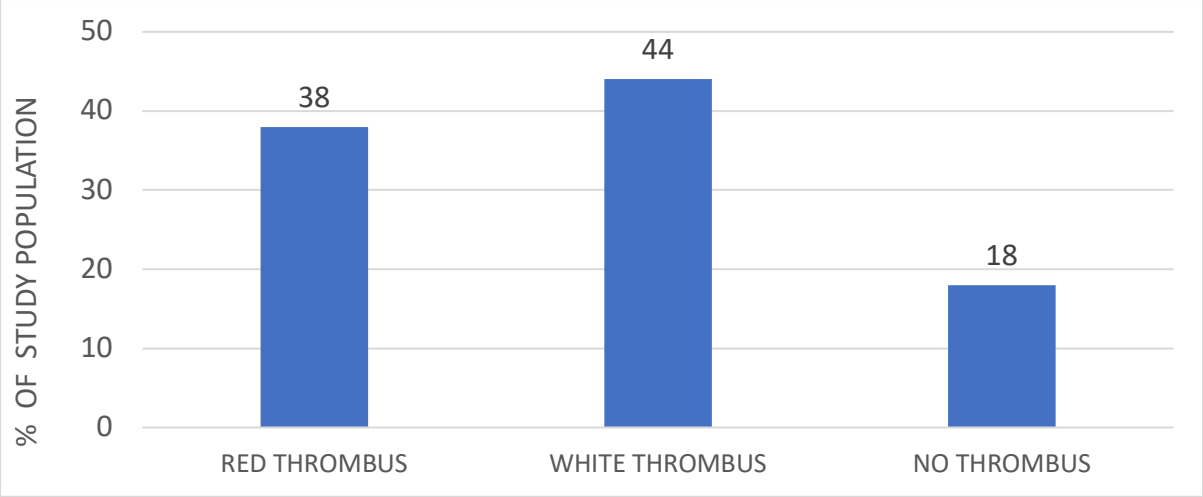

Figure 29. Distribution of thrombus burden in the study population.

82% of the study population were noted to have intracoronary thrombus on OCT. White thrombus was the predominant form noted in 44% of the patients whereas red thrombus was noted in 38% of the patients.

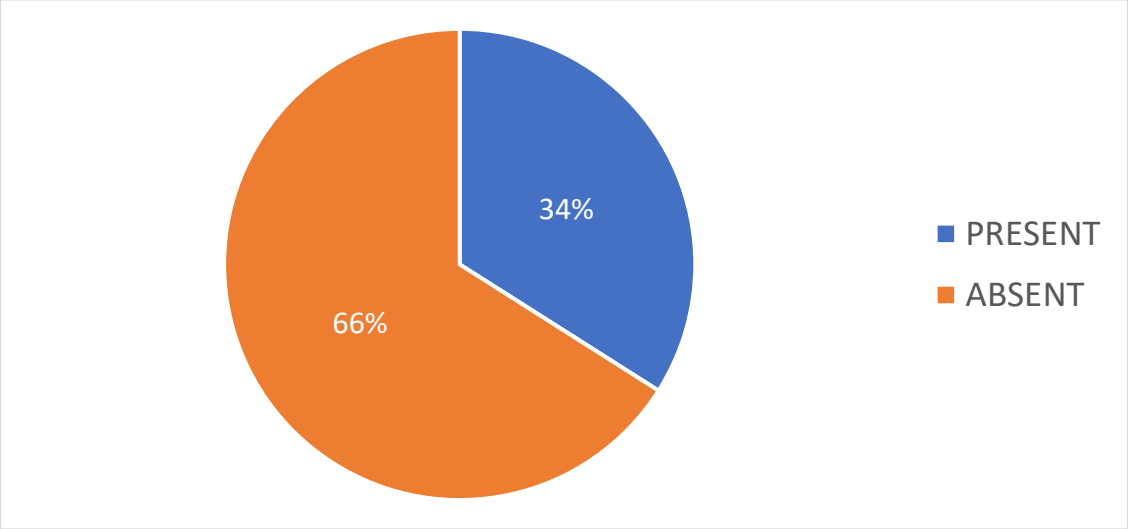

Figure 30. Presence of macrophages in the study population.

Macrophages were detected in 34% of the study population. OCT has high sensitivity in detection of macrophages in plaque cap.

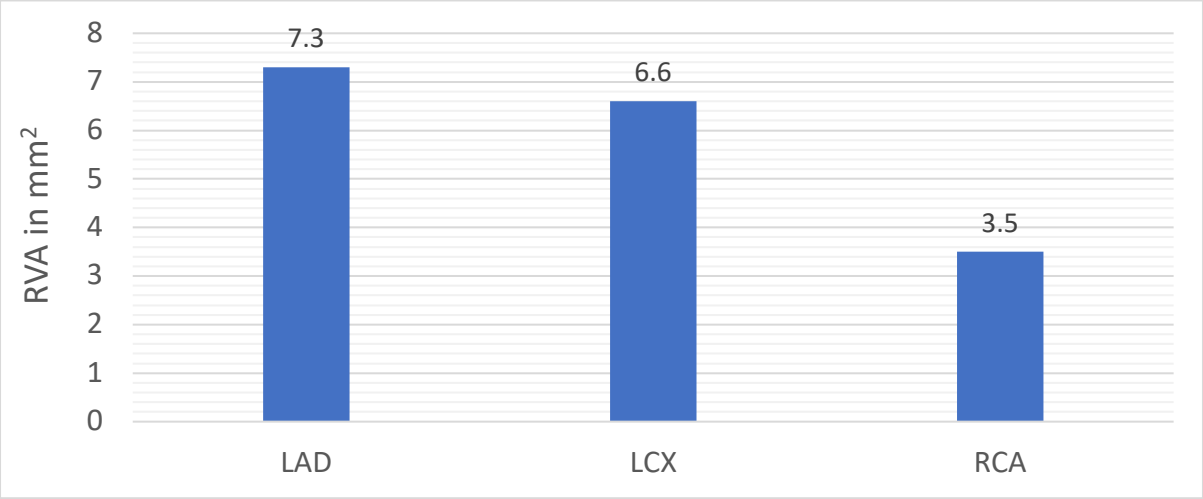

Figure 31. Reference vessel area among the study participants.

Reference vessel area on OCT was noted for the different vessels. The mean reference vessel area of LAD, LCX and RCA were 7.3 mm^2, 6.6 mm^2 and 3.5 mm^2, respectively.

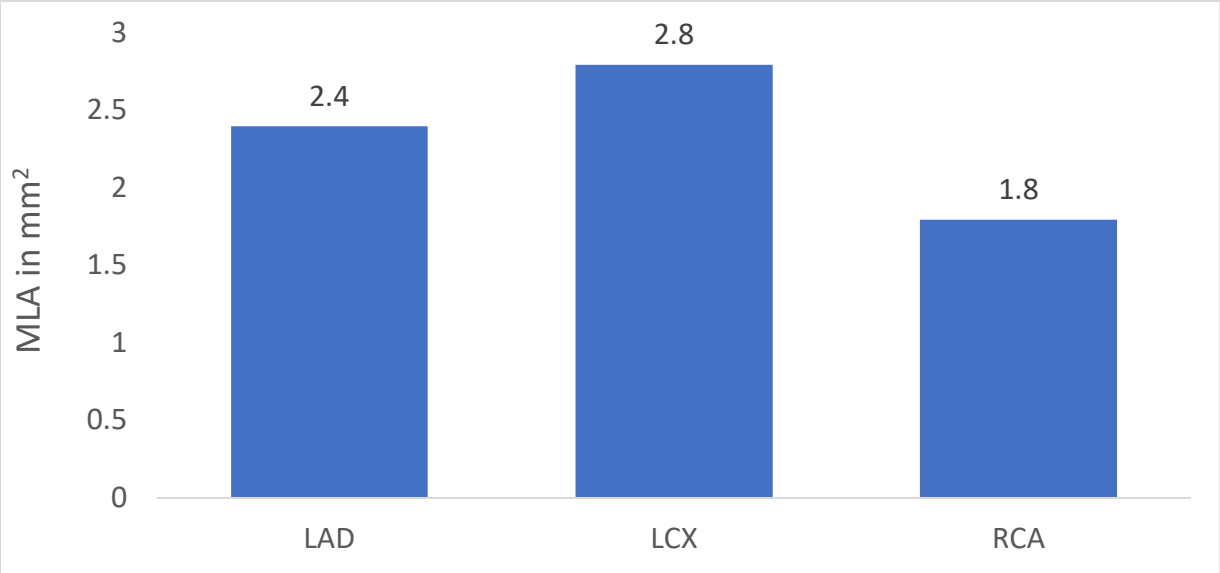

Figure 32. Minimum luminal area amongst the study population.

LCX had the highest minimum luminal area on OCT (2.8mm^2) whereas RCA had the least minimum lumen area (1.8 mm^2). LAD had a minimum luminal area of 2.4 mm^2.

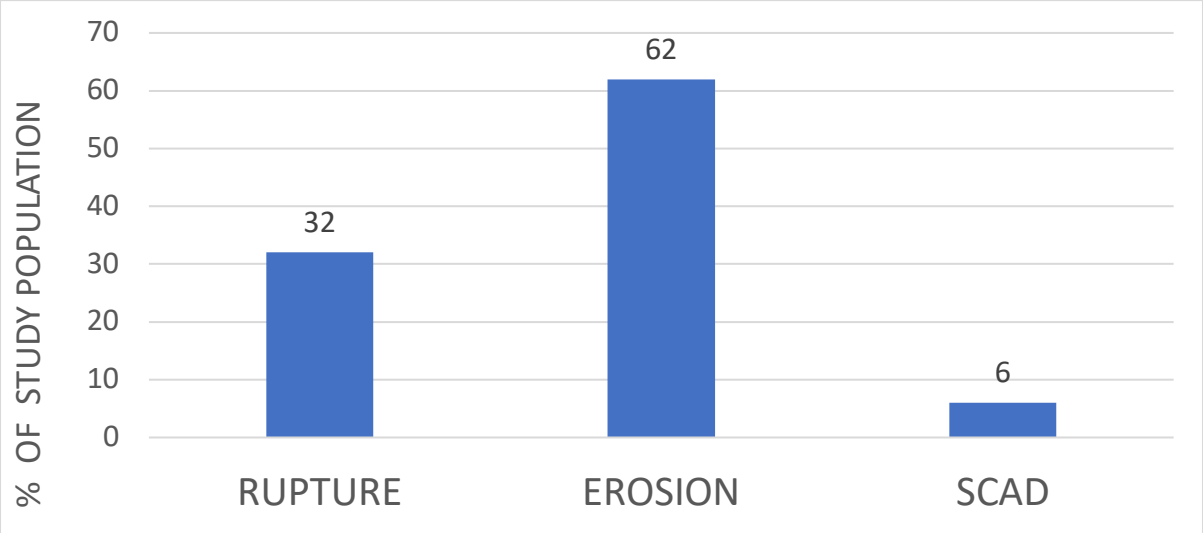

Figure 33. Mechanism of ACS in the study population.

The cause of acute coronary syndrome in the study population was plaque erosion in 62%, plaque rupture in 32% and SCAD in 6%, respectively.

Management:

	PLAQUE RUPTURE (N=10)	**PLAQUE EROSION (N=20)**	**SCAD (N=2)**
Medical management, n (%)	1 (10%)	5 (25%)	0
PCI, n (%)	9 (90%)	13 (65%)	2 (100%)

CABG, n (%)	0	2 (10%)	0

Table 4. Distribution of therapy received by the study participants.

In our study group, majority of the participants underwent revascularisation with PCI (75%) whereas 2 patients underwent CABG. Around 19% patients were kept on medical management. Majority of these patients had plaque erosion. 90% of patients with plaque rupture and 65% of patients with plaque erosion underwent PCI. Both patients with SCAD underwent PCI.

Demographics & Clinical characteristics	**N = 6**
Age in years, mean (SD)	56.3 (18.8)
Clinical presentation, n (%)	
STEMI	2 (33)
NSTEMI	4 (67)
Diameter stenosis % (QCA), mean (SD)	61.7 (9.8)
Lesion complexity on angiography, n	
Simple (type A)	3 (50)
Complex (type B)	3 (50)
Plaque cap thickness in μm, mean (SD)	104 (26.8)
Lipid arc in degrees, mean (SD)	36.6 (62.1)
Lipid plaque, n (%)	1 (17)
Plaque morphology, n (%)	

Rupture	1 (17)
Erosion	5 (83)
Thrombus, n (%)	
Red	3 (50)
White	1 (17)
Presence of macrophages, n (%)	1 (17)
MLA on OCT in mm^2, mean (SD)	3.82 (1.2)
Area stenosis (%), mean (SD)	49.5 (11.7)

Table 5. Baseline characteristics and imaging findings in patients who underwent medical management.

The baseline characteristics of the patients who underwent medical management are outlined in Table 5. Mean age of the patients was 56.3 years. Majority of the patients had NSTEMI on presentation. Average diameter stenosis on angiography was 61.7%. There was equal prevalence of type A and type B/C lesions on angiography in this subset of patients. Average plaque cap thickness was 104 μm. The average lipid arc was 36.6 degrees. Only one out of six patients had a lipid rich plaque. Plaque erosion was noted in 83% (n=5) of patients whereas plaque rupture was noted in one patient. 50% patients had red thrombus on OCT. One patient had macrophage in plaque cap. Average minimum lumen area and area stenosis in this subset was 3.82 mm^2 and 49.5%, respectively.

Analysis of baseline variables:

	Patients with plaque rupture	Patients with plaque erosion	P value
Age in years, mean (SD)	54.9 (13.6)	53.5 (11.5)	0.778
Females, n(%)	1 (10)	3 (15)	0.704
Clinical presentation, n(%) STEMI UA/NSTEMI	 4 (40) 6 (60)	 9 (45) 11 (55)	0.794
Fibrinolysis, n(%)	3 (30)	4 (20)	0.542
Primary PCI, n (%)	1 (10)	3 (15)	0.704
Diabetes Mellitus, n(%)	3 (30)	10 (50)	0.297
Hypertension, n(%)	7 (70)	12 (60)	0.592
Dyslipidemia, n(%)	8 (80)	12 (60)	0.273
Smoker, n(%)	3 (30)	11 (55)	0.196
Past h/o ACS, n(%)	3 (30)	10 (50)	0.297
Past h/o revascularisation (PCI/CABG), n (%)	3 (30)	9 (45)	0.429
Clinical heart failure, n(%)	0 (0)	1 (5)	0.472
Cardiothoracic ratio on CXR, mean (SD)	0.52 (0.01)	0.51 (0.04)	0.468
2-D echocardiography findings, mean (SD) LVID (diastole), mm LVID (systole), mm LVEF, %	 47.3 (3.7) 31.4 (4.8) 58.4 (9.2)	 46.9 (5.6) 29.9 (3.9) 59.5 (14.1)	 0.861 0.368 0.816
Lab investigations, mean(SD) Hemoglobin , g/dl ESR, mm Serum creatinine, mg/dl Total cholesterol, mg/dl LDL-cholesterol, mg/dl HDL-cholesterol, mg/dl Triglycerides, mg/dl	 13.7 (1.8) 25.1 (21.2) 1.1 (0.25) 174.2 (76) 109.0 (66.7) 35.5 (6.5) 119.8 (57.4)	 13.8 (2.1) 13.4 (13.8) 1.0 (0.24) 158.9 (51.4) 96.1 (41.5) 40.8 (10.2) 119.2 (57.3)	 0.863 0.079 0.314 0.526 0.528 0.151 0.980

Table 6. Comparison of baseline characteristics between patients with plaque rupture and plaque erosion.

The baseline variables of all the study participants were analysed. Association and correlation were sought between clinical characteristics and OCT findings.

There was no difference in the baseline characteristics of the patients with plaque rupture and plaque erosion. Mean age and mode of presentation was similar between the groups. There was no difference in patients who had received fibrinolysis/primary PCI before presentation. Risk factor profile was similar between the two groups. Echo showed normal LV dimensions and normal LV ejection fraction in both groups. No difference was noted in the lipid profile values between the two groups (Chi-square test showed p values >0.05).

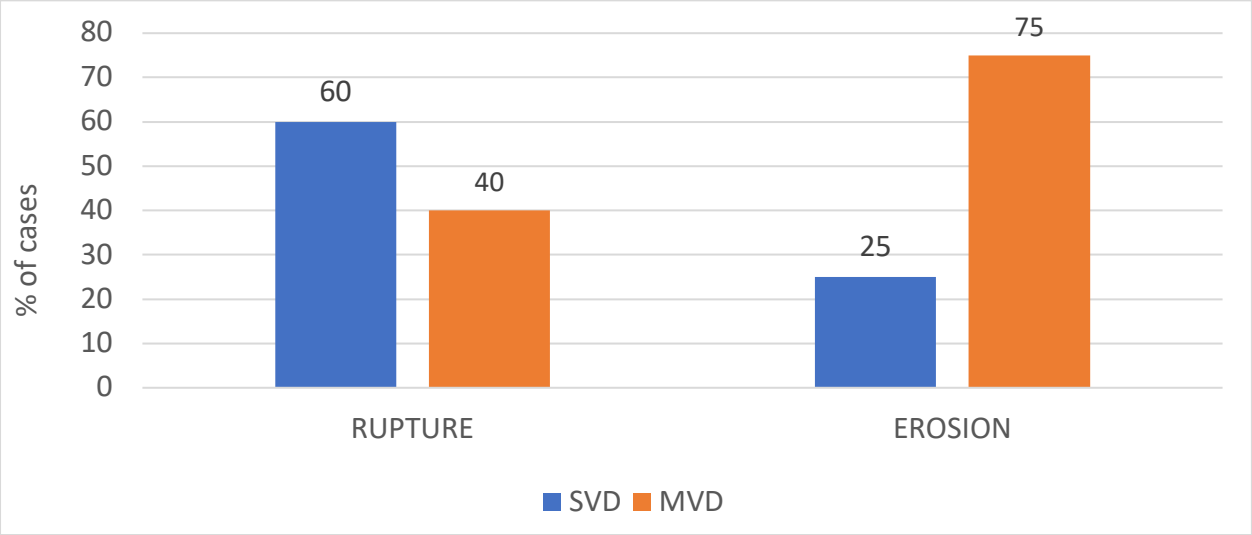

Figure 34. Distribution of CAD severity according to mechanism of ACS

No difference was noted between the incidence of single vessel disease and multivessel disease amongst patients with plaque rupture and erosion. (Chi-square test, p =0.061)

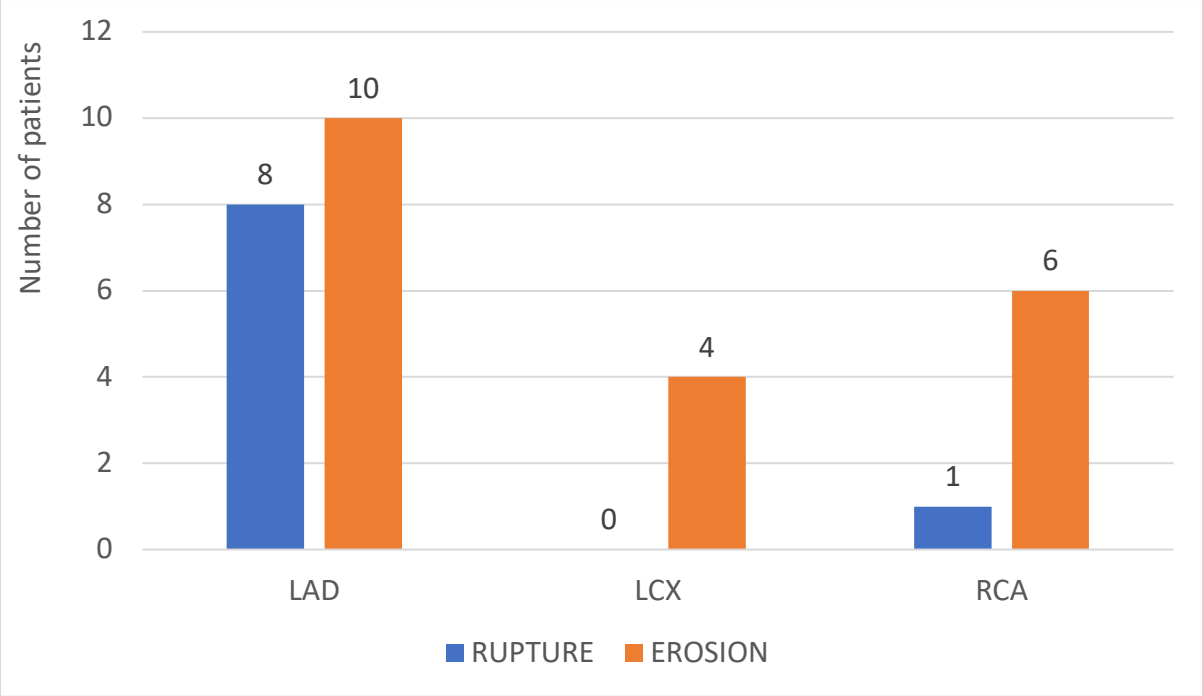

Figure 35. Vessel distribution according to mechanism of ACS.

Any difference in the culprit vessel location between plaque rupture and plaque morphology patients were sought for. Chi-square test revealed that there was no significant difference between the 2 groups in terms of culprit vessel location (p=0.091).

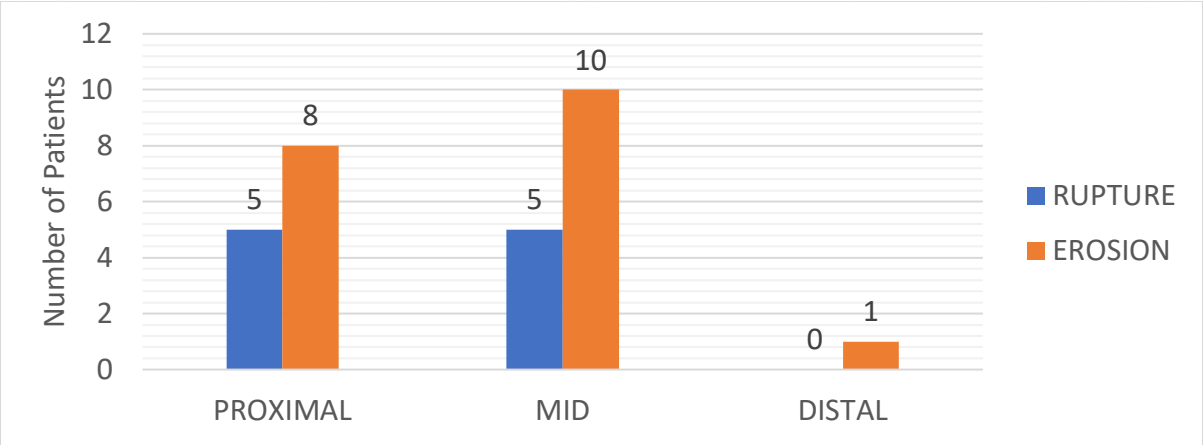

Figure 36. Distribution of lesion location according to mechanism of ACS.

Culprit lesion location within the culprit vessel was analysed. Majority of lesions were located in mid segment. Chi-square test revealed that there was no significant difference in culprit lesion location amongst patients with plaque rupture and plaque erosion (p=0.731).

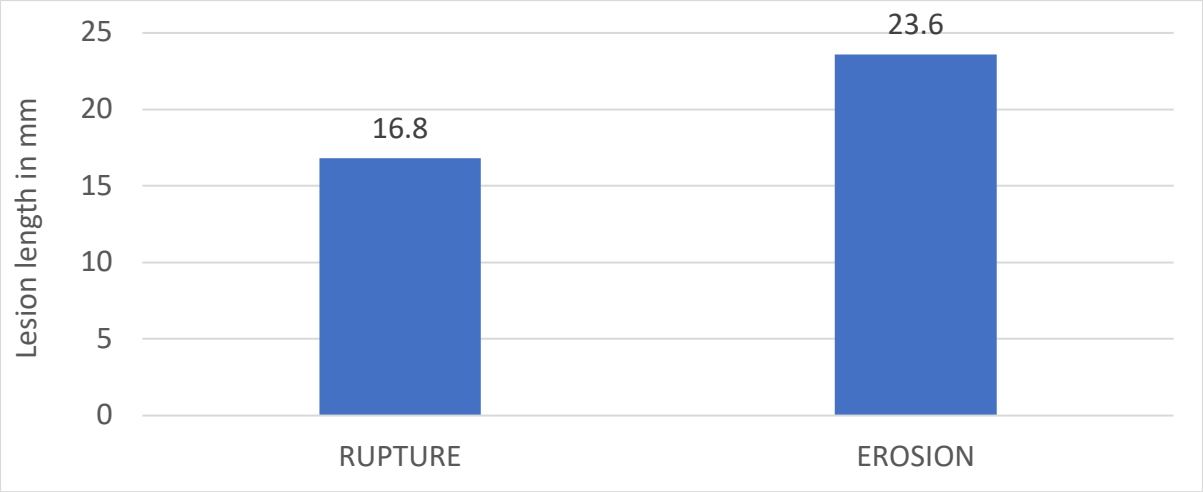

Figure 37. Distribution of lesion length according to mechanism of ACS.

The average lesion length was analysed in both the groups. Mean lesion lengths noted in plaque rupture and plaque erosion groups were 16.8mm and 23.6mm, respectively. Independent sample t-test showed that there was no significant difference between the mean lesion length between these groups (p=0.069).

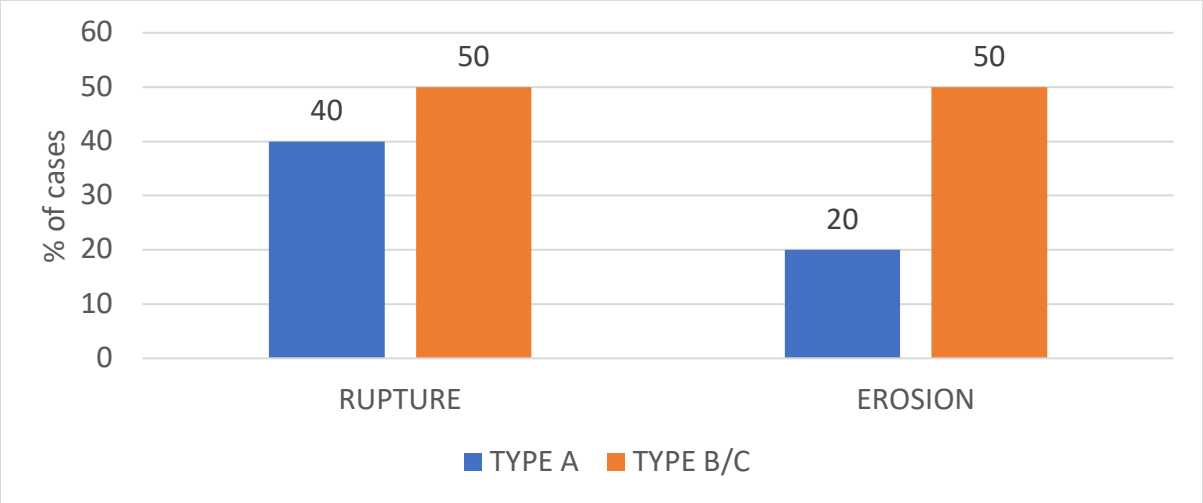

Figure 38. Distribution of lesion complexity on CAG according to mechanism of ACS.

Angiographic lesion complexity was evaluated amongst the study participants. Chi-square test showed that there was no association between angiographic lesion complexity and OCT findings of plaque rupture/erosion (p=0.343).

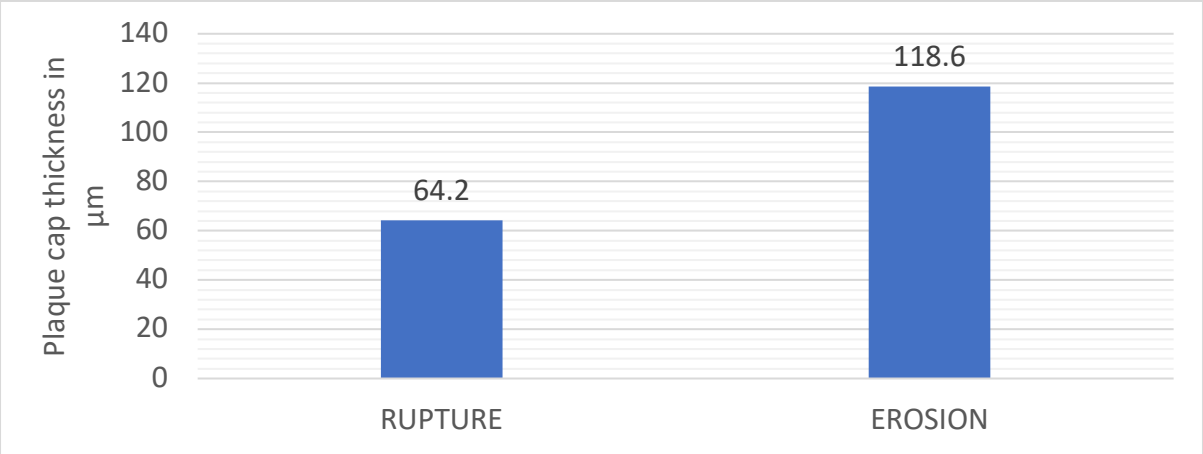

Figure 39. Distribution of plaque cap thickness according to mechanism of ACS.

Analysis of minimum plaque cap thickness on OCT was done. Mean plaque cap thickness amongst plaque rupture patients was 64.2 µm whereas plaque cap thickness amongst plaque erosion patients was 118.6 µm. Independent sample t-test showed that there was a significant difference in the mean plaque cap thickness between the 2 groups (p= 0.001).

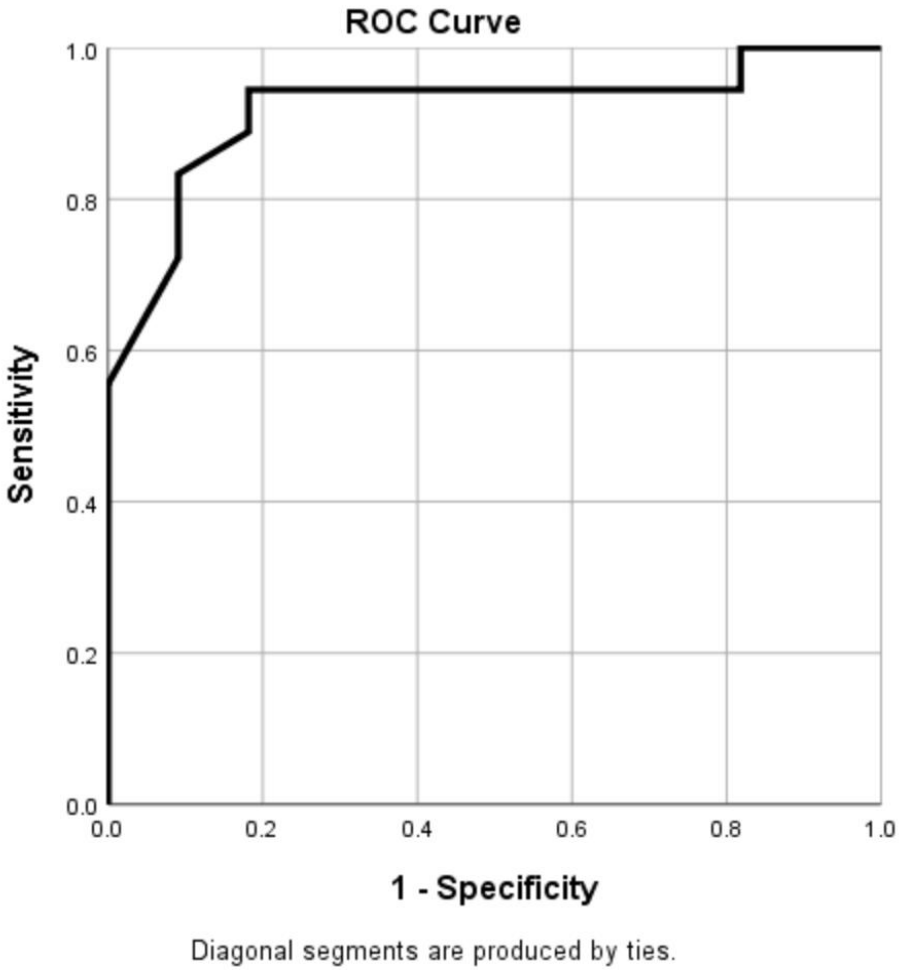

Figure 40. ROC curve showing predictive accuracy of plaque cap thickness for plaque cap integrity.

ROC analysis was performed to detect the accuracy of plaque cap thickness in predicting plaque integrity. A plaque cap thickness of 82.5 μm could predict integrity of plaque cap with a sensitivity of 83% and specificity of 91%. (AUC = 0.919)

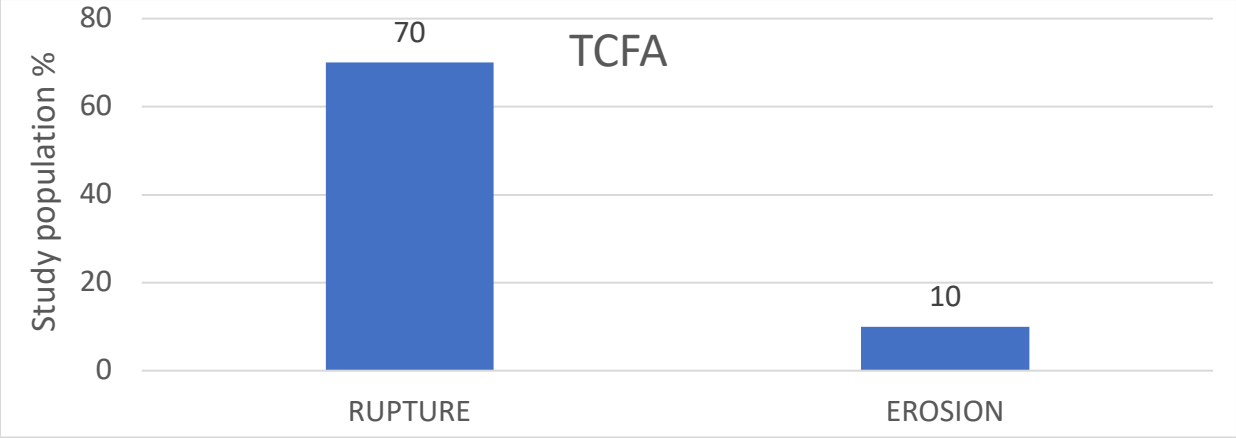

Figure 41. Distribution of TCFA in patients according to mechanism of ACS.

Chi-square test showed that there was a significantly higher incidence of thin cap fibroatheroma in plaque rupture (70%) as compared to plaque erosion (10%) (p=0.001).

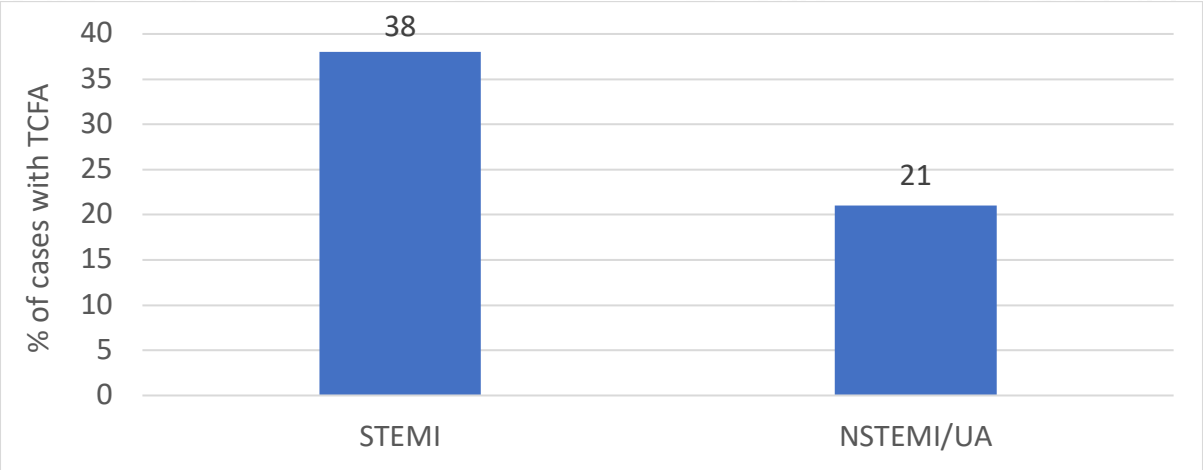

Figure 42. Distribution of TCFA according to clinical presentation.

Chi-square test showed that there was no difference in incidence of TCFA between the STEMI and NSTEMI/UA population in the current study (p=0.282).

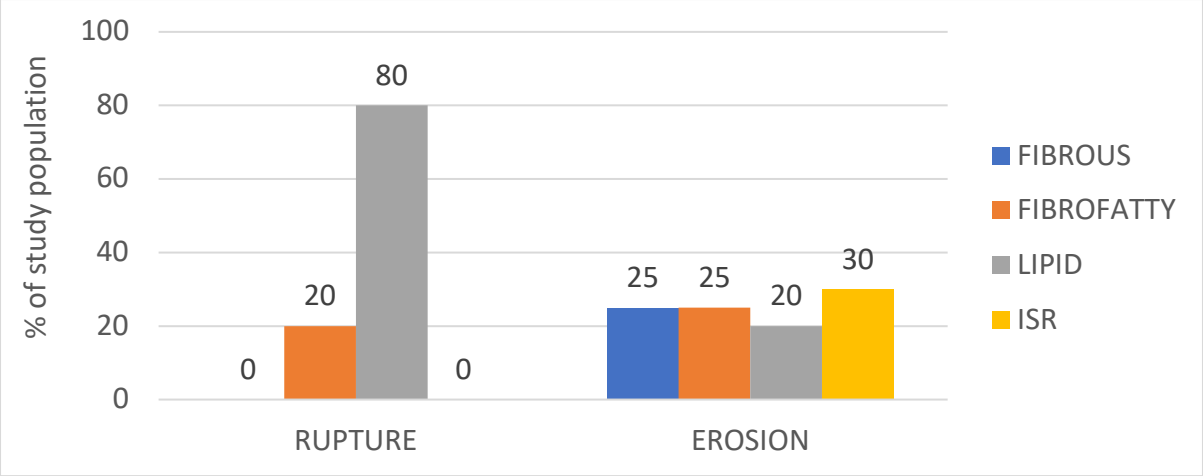

Figure 43. Distribution of plaque type according to mechanism of ACS.

Analysis of plaque morphology using chi-square test revealed that there was significant difference in the distribution of plaque morphology across both groups. Incidence of lipid rich plaque was significantly higher in plaque rupture group (p=0.009).

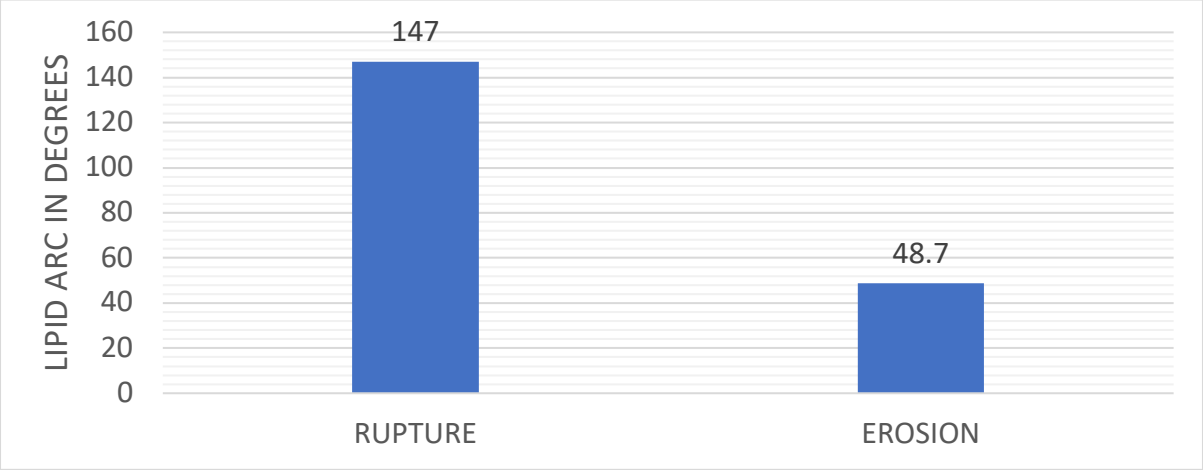

Figure 44. Distribution of lipid arc according to mechanism of ACS.

Chi-square test revealed that the lipid arc was significantly higher in plaque rupture group (147 degrees) as compared to the plaque erosion group (48.7 degrees) ($p<0.001$). This signifies the presence of higher lipid content in plaques which had rupture.

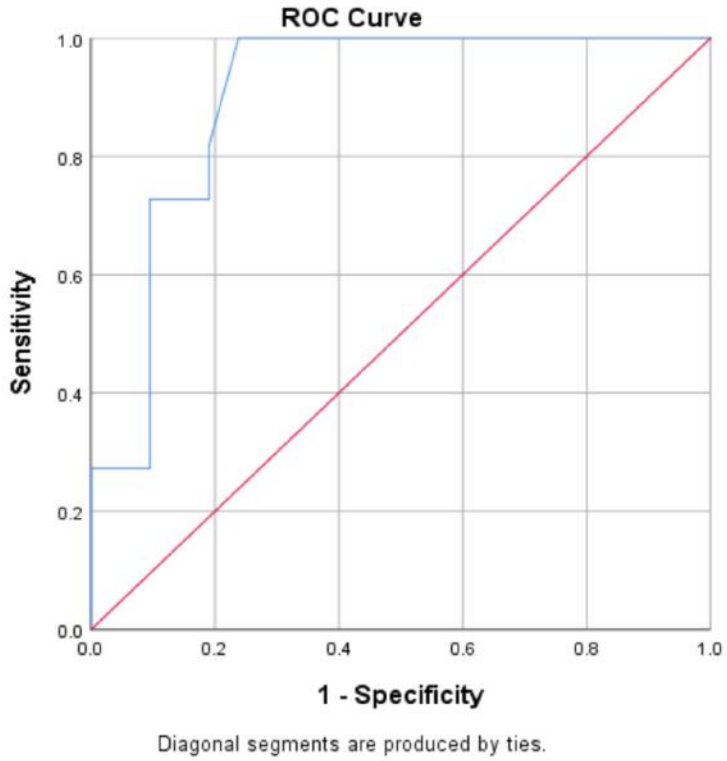

Figure 45. ROC curve showing predictive accuracy of lipid arc in detecting plaque cap rupture.

ROC analysis was done to detect the accuracy of lipid arc in predicting plaque cap rupture. A plaque lipid arc of 110 degrees can predict plaque cap rupture with a sensitivity of 73% and specificity of 91% (AUC = 0.900).

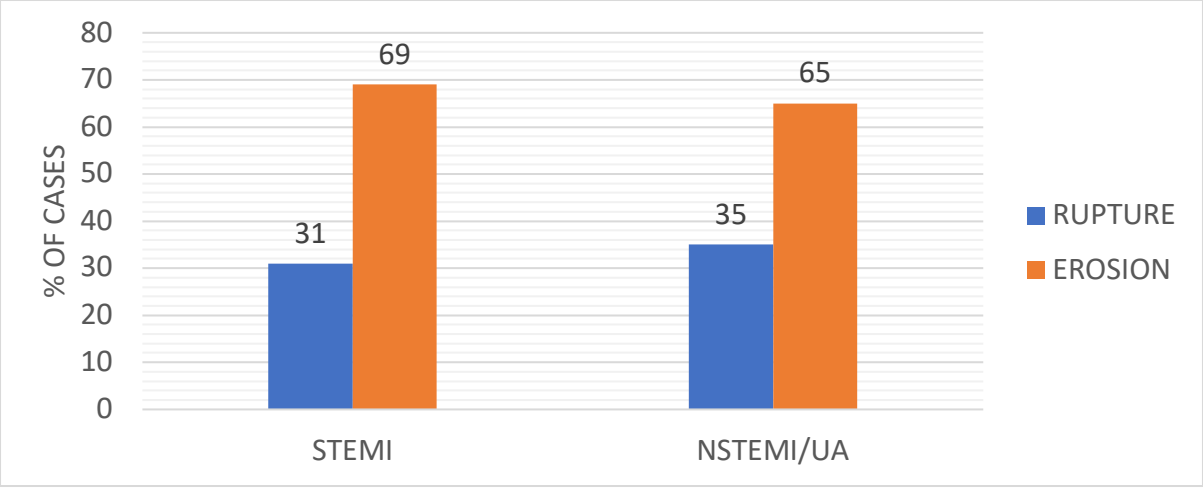

Figure 46. Distribution of mechanism of ACS according to clinical presentation.

Chi-square analysis did not reveal any association between mode of presentation (STEMI vs NSTEMI/UA) and plaque morphology on OCT (rupture/erosion) (p=0.794).

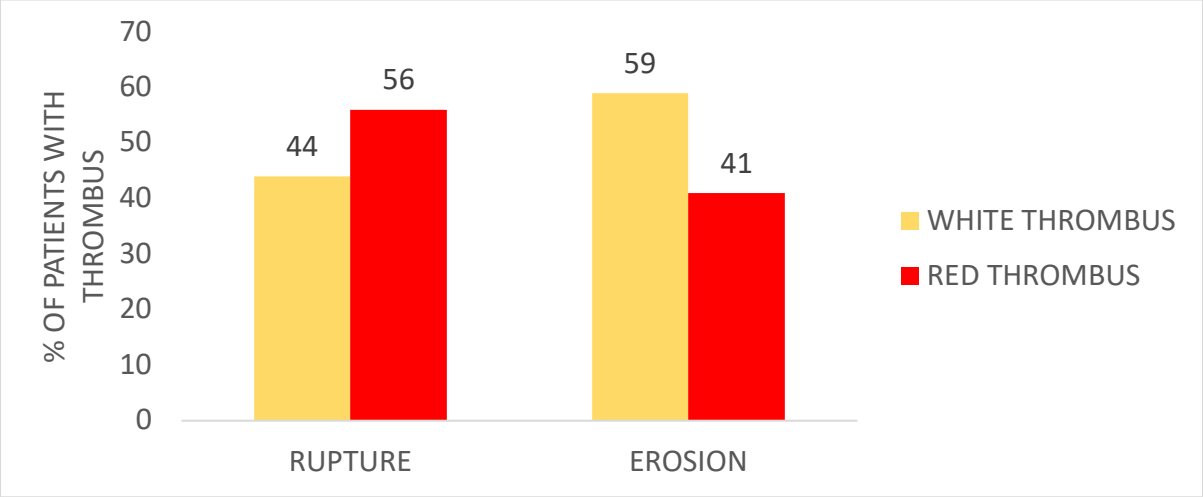

Figure 47. Distribution of thrombus according to mechanism of ACS.

Chi-square test did not reveal any association between the type of thrombus and plaque morphology (p=0.404). Similar incidence of red and white thrombus was noted in both groups.

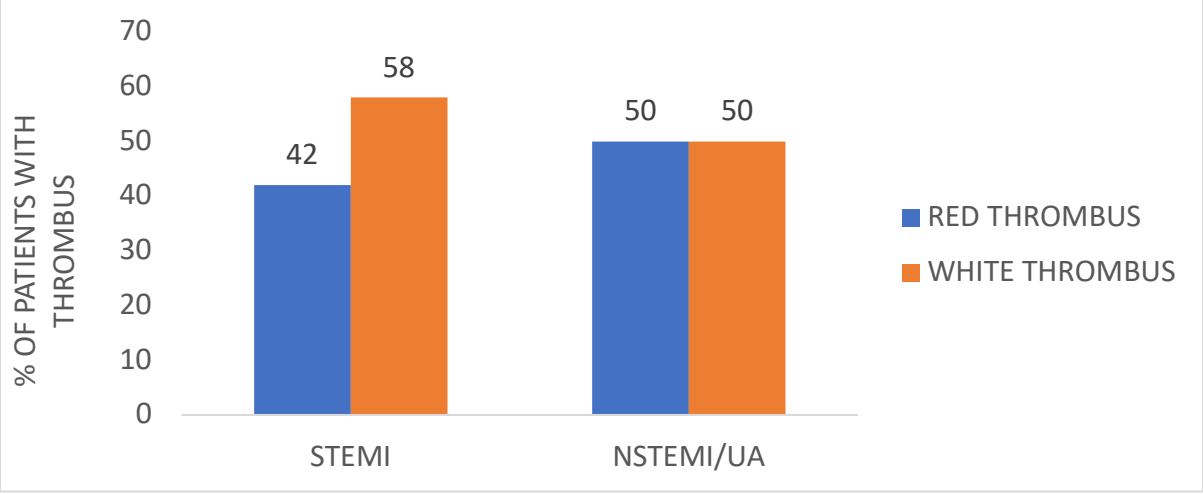

Figure 48. Distribution of thrombus according to clinical presentation.

Chi-square test did not reveal any association between type of thrombus and clinical presentation (p=0.671).

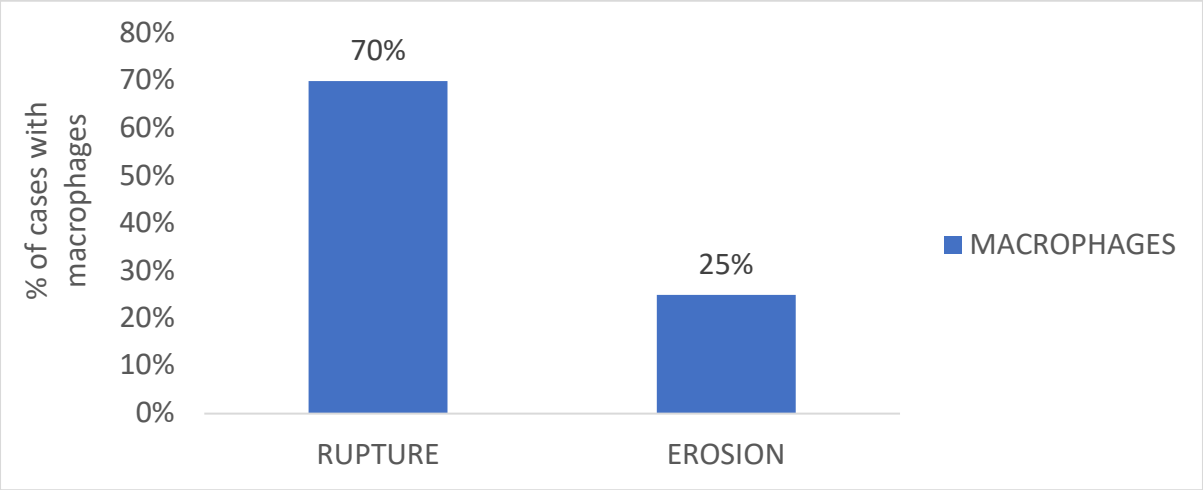

Figure 49. Distribution of macrophages according to mechanism of ACS.

Macrophages were significantly higher in patients with plaque rupture as compared to those with plaque erosion and the difference was statistically significant as shown by chi-square test(p=0.007).

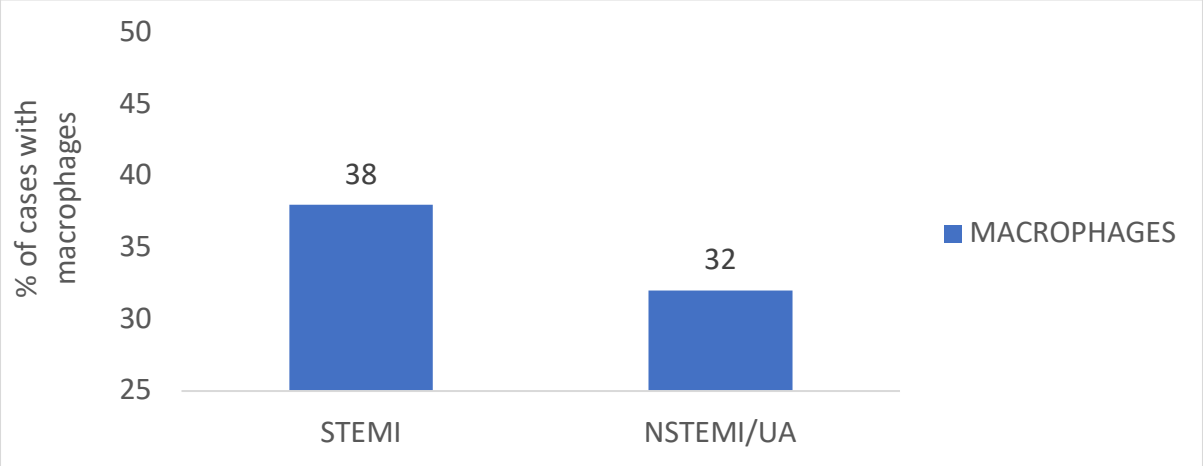

Figure 50. Distribution of macrophages according to clinical presentation.

Chi-square test showed that there was no significant difference in prevalence of macrophages on OCT amongst STEMI and NSTEMI/UA population (p=0.599).

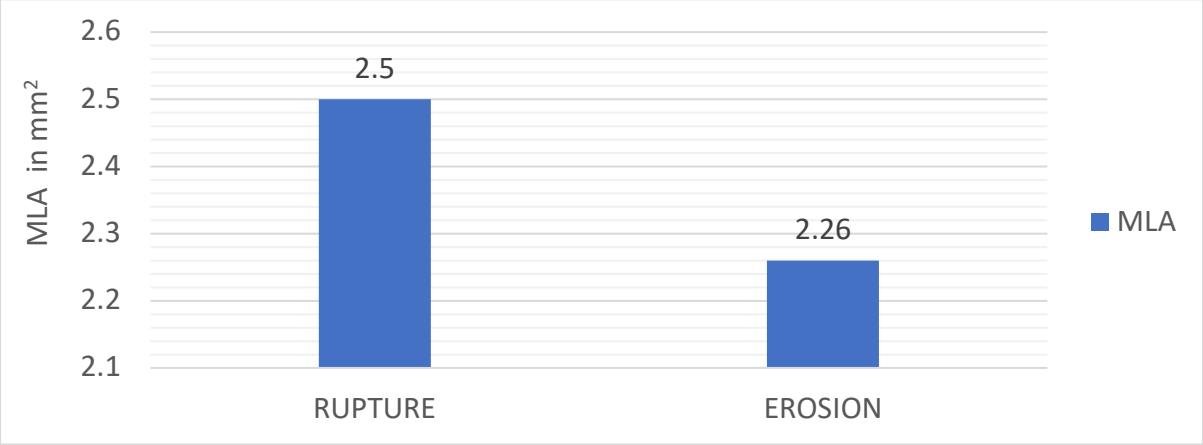

Figure 51. Distribution of minimum luminal area according to mechanism of ACS.

Independent sample t-test showed that there was no difference in the mean minimal lumen area (MLA) in patients with plaque rupture (2.5mm^2) and plaque erosion (2.26 mm^2) (p=0.592).

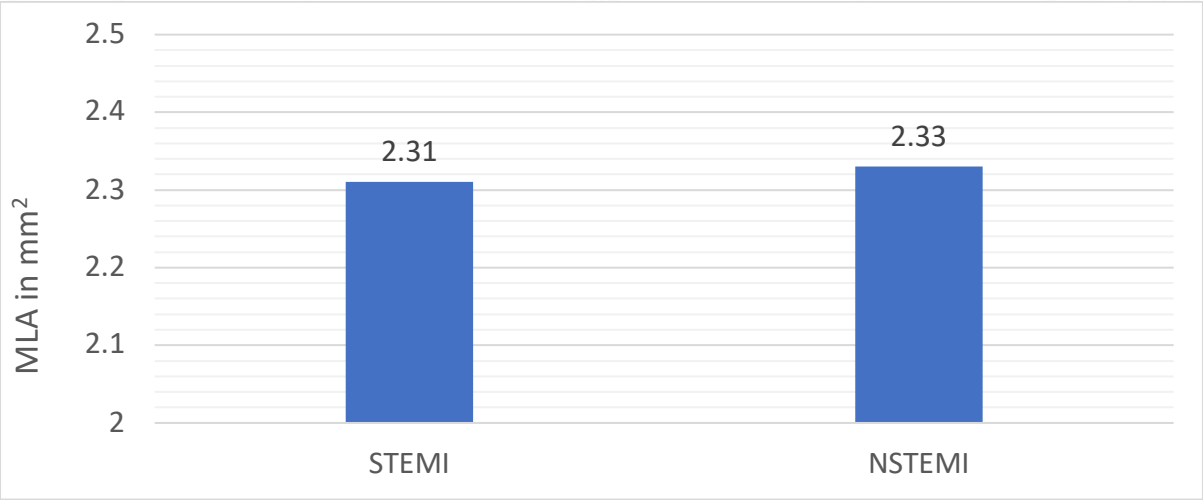

Figure 52. Distribution of MLA according to clinical presentation.

No difference in mean MLA was noted between STEMI and NSTEMI patients by independent sample t-test (p=0.952).

There was no significant difference between area stenosis % on OCT between patients with plaque rupture and plaque erosion (p = 0.948).

Outcome analysis:

The patients were followed up for a period of 1 year. Event rates of death, MI, all cause hospitalisation, any revascularisation and angina on follow up were noted. At the end of 1 year, a total of 26 patients (81%) were on regular follow up.

	Total (n=26)	**RUPTURE (n=8)**	**EROSION (n=16)**	**P-value**
Death, n (%)	0	0	0	-
MI, n (%)	3 (11.5)	2(25)	1(6.2)	0.424
TVR, n (%)	2 (7.7)	0	2(12.5)	0.580
TLR, n (%)	1 (3.8)	0	1(6.2)	0.662
Revascularisation of other vessels, n (%)	3 (11.5)	1(12.5)	2(12.5)	1.0
All-cause hospitalisation events, n (%)	4 (15.4)	2 (25)	2(12.5)	0.741
Angina, n (%)	10 (38.5)	5 (62.5)	5 (31.2)	0.343

Table 7. Clinical outcomes at 1 year follow up.

None of the patients died during the one year follow up period. Around 11% of study population had MI events during the follow up period. 15% patients had all cause hospitalisation events during follow up. Target lesion revascularisation was done in 1 patient (3.8%) whereas target vessel revascularisation was done in 2 patients (7.7%). Revascularisation of other vessels was done in 3 patients (11.5%) over the follow up period. During the period of one year, about 39% patients reported anginal events at different instances in time.

The clinical outcomes were evaluated separately in patients with plaque rupture and plaque erosion. Similar rates of MI were seen in the two groups during the follow up period (p=0.424). Revascularisation rates were numerically higher in patients with plaque erosion but the difference was not statistically significant (p=0.662). Similar all cause hospitalisation rates were noted between the two groups. Reporting of anginal events was also similar between the two groups.

The patients who were kept on medical management (n=6) were also evaluated for clinical endpoint at the end of one year follow up.

Clinical outcomes at 1 year, n (%)	**N = 6**
Angina	**2 (33)**
Death	**0**
MI	**0**
Revascularisation	**0**
All cause hospitalisation	**0**

Table 8. Clinical outcomes at 1 year in patients on medical management.

None of the patients on medical management had any MI, revascularisation or hospitalisation events. No death was reported in this group of patients. 2 out of 6 patients reported anginal events over a period of one year.

Multivariate analysis:

Multivariate analysis was done for predicting the presence of thrombus and plaque cap rupture on OCT.

	ODDS RATIO	**95% C.I.**	**p - value**
Age (per 10 years)	0.434	0.094-1.99	0.284
LDL (per 10 mg/dl)	1.018	0.795-1.30	0.887
Female sex	2.4	0.113-50.79	0.574
STEMI at presentation	0.372	0.011-13.15	0.587
Diabetes	0.650	0.047-9.09	0.749
Hypertension	0.752	0.056-10.06	0.829
Lipid arc (every 30 degrees)	3.775	1.26-11.29	0.018
Presence of macrophages	0.272	0.01-5.54	0.397

Table 9. Multivariate analysis for prediction of plaque rupture.

Multivariate analysis for plaque cap rupture showed that for every 30 degrees increase in lipid arc, there was 3.7-fold increased risk of having a plaque rupture. None of the other baseline variables could predict presence of plaque rupture.

	ODDS RATIO	**95% C.I.**	**p - value**
Age (per 10 years)	0.630	0.18-2.12	0.456
LDL (per 10 mg/dl)	0.914	0.72-1.17	0.478
Female sex	0.744	0.04-15.55	0.849
STEMI at presentation	6.485	0.46-90.62	0.165
Diabetes	11.238	0.82-15.78	0.070
Presence of macrophages	1.057	0.09-12.15	0.965

Table 10. Multivariate analysis for prediction of thrombus on OCT.

Multivariate analysis for prediction of thrombus on OCT showed that none of the baseline variable could predict the presence of thrombus on OCT.

The clinical outcomes at one-year follow up were also evaluated using multivariate analysis. The primary endpoint was composite of death, MI, all cause hospitalisation and any revascularisation events.

	ODDS RATIO	**95% C.I.**	**p - value**
Age (per 10 years)	1.970	0.518-7.49	0.32
LDL (per 10 mg/dl)	1.15	0.91-1.45	0.239
STEMI at presentation	2.31	0.14-37.32	0.555
Diabetes	6.58	0.37-11.43	0.199
Plaque rupture	0.59	0.037-9.74	0.72

Table 11. Multivariate analysis for prediction of primary endpoint on follow up.

None of the baseline variables could predict the primary end point at the end of one year follow up. None of the patients in the medical management group reached the primary endpoint at the end of one year follow up.

DISCUSSION

The present study aimed to characterize the culprit lesion morphology in patients presenting with acute coronary syndrome using optical coherence tomography. Our study included patients with acute coronary syndrome who directly presented to our center as well as those who were referred for further management from other hospitals, within a period of 6 weeks of index event. The broad inclusion used in our study is in contrast to the previous OCT studies in ACS patients. Majority of the patients in our study group were middle aged and females comprised about one-tenth of the study population. Other studies of OCT in ACS patients have reported that females comprised about one-fourth of their study group[2]. STEMI patients comprised about 40% of the study population while the rest of the patients had NSTEMI and unstable angina. Similar prevalence of STEMI patients (43%) has been reported in other studies[2,35]. About one-fifth of our patients had undergone fibrinolysis at the primary care hospitals and were subsequently referred as part of the pharmacoinvasive strategy. Due to fibrinolysis, the morphology of the culprit lesion may have been altered in these patients which would preclude accurate identification of various features of the culprit lesion. Primary PCI was done in 12.5% of our study population. The patients in our study population had a higher rate of previous MI as compared to Western studies (44% vs 12%, respectively)[35]. Around two-fifth of our study population has history of prior revascularization with either PCI or CABG. This is in contrast to the prior revascularization rates of 10% noted in a study by Ino et al.[2]. The higher incidence of previous MI and past revascularization in our study group may indicate that these patients have more severe disease and are at higher risk of adverse events in future.

Two-fifth of our study population was diabetic whereas hypertension and dyslipidemia was noted in 62% patients, respectively. About half (47%) of the patients were current or reformed smokers. Similar prevalence of risk factors was seen in study groups of Hu et al. and Ino et al.[2,35]. However, in a study by ElFaramawy et al., prevalence of hypertension in the ACS group was only 11% with higher prevalence of smokers (70%)[36]. Clinical features of heart failure were noted in 6% of our study population whereas mean cardiothoracic ratio on chest x-ray was 0.52. Mean LV ejection fraction in our study group was 57.8% suggestive of normal ventricular function, which is in concordance with other studies[2,35]. This suggests that the patients in our study group had good functional class at baseline. Mean hemoglobin levels in the participants was 13.6 gm/dl and was associated with normal ESR levels in majority of the population. Renal function parameters were normal. Patients had an average LDL cholesterol and total cholesterol levels of 97.9 mg/dl and 161.35 mg/dl which are similar to those noted in previous studies indicating that majority of patients had normal lipid profiles[35]. However, lipid profile values in post MI settings are highly dependent on the time period of analysis as cholesterol levels starts decreasing after 24-48 hours after index events and returns back to baseline levels by 6-8 weeks[37]. The near normal lipid profiles in these patients could be the result of delay in analysis or late presentation post an index event.

Majority of patients in our study population had multivessel disease whereas 34% had single vessel disease. OCT studies in ACS by Ino et al. and Hu et al. showed a multivessel disease prevalence of 30% and 53%, respectively. LAD was the most common culprit vessel in our study group followed by RCA, similar to the study by Hu et al. and ElFaramawy et al.[35,36]. However, in the study by Ino et al., RCA was the most common culprit vessel followed by LAD[2]. Majority of the culprit lesions in our study were located in the mid-segment of the vessel. In the study by Hu et al., culprit lesions were

most commonly located in the proximal segment[35]. Average reference vessel diameter (QCA derived) in our study was similar to previous studies. In our study group, all culprit lesions produced significant lumen stenosis with an average diameter stenosis of 77% which was similar to the lesion severity seen in similar studies. Majority of the lesions were angiographically complex, belonging to Type B, as per ACC/AHA lesion classification. In-stent restenosis and spontaneous coronary artery dissection was also noted in a small subset of our group (25%). Other studies do not provide information about patients with in-stent restenosis as they were probably excluded.

Mean plaque cap thickness on OCT in our study population was 99.87 μm. Mean plaque cap thickness was similar in STEMI and NSTEMI patients in our study. 28% patients in the study population had thin cap fibroatheroma. An OCT study in acute myocardial infarction patients showed higher prevalence of TCFA in the study population (75%)[18]. TCFA were more commonly seen in STEMI patients as compared to NSTEMI patients in the study by Ino et al.[2]. However, there was no difference in prevalence of TCFA amongst STEMI and NSTEMI/UA patients in our study. Lipid content of plaque, as estimated by lipid arc on OCT, was similar in patients with STEMI and NSTEMI in our study group. Lipid plaque was most common in our study group, which is similar to results of other studies by Ino et al. and Kubo et al. [2,18]. Similar proportion of lipid plaques were found in STEMI and NSTEMI patients. Amongst our study patients with ISR, homogenous ISR was the most common morphology. OCT studies in in-stent restenosis have shown that heterogenous pattern of ISR is more common in 2nd generation stents whereas the frequency of neoatherosclerotic lesions tend to increase with time[38].

Plaque rupture was noted in 34% of the study population. In the OCT study by ElFaramawy et al, plaque rupture was noted in 53% of the study population whereas Ino et al. reported an incidence of 51% in their study[2,36]. 82% of the

study population had thrombus on OCT amongst which majority had white thrombus (44%). Ino et al. showed that incidence of red thrombus was higher and patients with STEMI had significantly higher red thrombus burden as compared to NSTEMI[2]. The study by ElFaramawy et al. showed that thrombus was seen in 92% of patients in the ACS group[36]. Another OCT study on patients with ACS revealed prevalence of thrombus in about 85% of patients with red thrombus being more common than white thrombus[21]. The higher prevalence of NSTEMI patients in our study may have led to higher number of patients with white thrombus on OCT. In our study group, macrophages were noted in plaque caps of 34% of study population. The high resolution of OCT helps in detection of macrophages thus helping in identification of vulnerable plaques[39]. Presence of macrophages are a marker of inflammation and increased disease activity. Studies have shown higher macrophage densities in unstable patients whereas sites of plaque rupture are also noted to have higher macrophage densities[20]. In the study by ElFaramawy et al., macrophages were noted in 44% patients in the ACS group. Reference vessel are and minimum lesional area were similar between all three vessels in our study group.

The causes of acute coronary syndrome, as detected by OCT, were plaque erosion (PE), plaque rupture (PR) and spontaneous coronary artery dissection (SCAD) in 62%, 32% and 6% patients, respectively in our study group. Previous OCT studies in ACS have shown plaque rupture to be the most common cause of ACS with STEMI patients having higher incidence of plaque rupture [2,36]. No difference was noted in occurrence of plaque rupture between STEMI and NSTEMI patients in our group (31% vs 35%, respectively). This difference in findings in our study group could be attributed to the broader inclusion criteria adopted in our study. We included all patients within 6 weeks of index event including those who have undergone fibrinolysis/primary PCI. Administration of drugs including fibrinolytics have the potential to change the

morphology of the lesions. As time progresses, the underlying ruptured plaque may heal and may be difficult to heal. Thus, imaging done at a later time may also cause difficulty in detection. Presence of healed plaques in non-culprit segments has been predicted to be a protective marker against major adverse cardiovascular events in future[40].

Culprit lesion morphology (plaque rupture/erosion) in our study group did not differ with culprit vessels, multivessel involvement or site of culprit lesion within the vessel segment. Angiographic characteristics of culprit lesion like lesion length, percentage diameter stenosis and lesion complexity (ACC/AHA) did not differ between those with plaque rupture and plaque erosion. In the study by Hu et al. which compared patients with plaque rupture and erosion, lesion morphology differed according to the culprit vessel and presence of multivessel involvement[35]. Plaque rupture was associated with higher diameter stenosis, lower minimum lumen area and more angiographically complex lesion as compared to plaque erosion.

Patients with plaque erosion in our study group had significantly higher plaque cap thickness as compared to those with plaque rupture. This was similar to the OCT findings noted in study on ACS patients by Jia et al.[21]. OCT has been used to detect plaque cap thickness which forms an integral part of determining the plaque morphology. Plaques with thin caps have been associated with positive remodeling and higher inflammatory markers which makes them vulnerable to rupture [41]. This explains the higher incidence of thin cap fibroatheroma in patients with plaque rupture as compared to plaque erosion in our study. Previous studies have shown that a fibrous cap thickness of 67μm has a sensitivity of 83% and specificity of 77% for prediction of plaque rupture in vivo[42]. Even patients with thick fibrous cap can undergo rupture under stressful conditions like exercise. Exercise induced shear stress can plaque disruption at the region of the plaque shoulder[3]. In our study, we propose a

fibrous cap thickness of 82.5 μm which can predict plaque rupture with a sensitivity of 83% and specificity of 91%. This may help to better predict the vulnerable plaques at risk of rupture. Multivariate analysis in our study showed that increasing lipid content of plaque is associated with about three-fold risk of developing plaque rupture.

Lipid content was significantly higher in plaques which had evidence of rupture in our study. Previous work has shown that plaque ruptures are usually found in lesions with a large necrotic lipid core whereas plaque erosion is seen in lesions which have a smaller necrotic core and are rich in proteoglycan matrix[43]. Similar findings were noted in study by Jia et al. where the lipid content was higher in plaque rupture[21]. However, the lipid content of the ruptured plaque in their study was much higher as compared to our study as denoted by the mean lipid arc (275.8 ± 60.4° vs. 145 ± 65.2°, respectively). This indicates a higher atherosclerotic burden. Lipid plaques were more common in our patients with plaque rupture, which is in accordance with previous studies. In our study, red thrombus was more commonly found in patients with plaque rupture as compared to plaque erosion. However, the difference was not statistically significant. This is in discordance with other studies which have shown significantly higher prevalence of red thrombus in plaque rupture[21]. This difference is likely attributed to the characteristics of patients studied. Our study included a wide variety of ACS patients, including those who had undergone fibrinolysis and were subsequently referred. Clot lysis due to fibrinolytic agents may have led to underestimation of red thrombus burden in our study. In our study, macrophages were more commonly seen in lesions with plaque rupture as opposed to erosion. This depicts the higher inflammatory activity present in plaques which undergo rupture, as shown in previous studies[20]. There were no independent predictors of presence of thrombus on OCT in the current study.

In the current study, minimum lumen area, as measured on OCT, was similar at the site of plaque with rupture and erosion. Previous studies have demonstrated that minimum luminal diameter, as measured by QCA, was smaller in patients with plaque rupture[35]. However, QCA may have inherent fallacies in accurate measurement of diameter stenosis and minimum luminal diameter. This problem can be likely overcome by using intracoronary imaging like OCT, which on account of its high resolution, can detect the various layers of the arterial wall and give an accurate estimation of the minimum luminal area and diameter stenosis[44]. In the study population, patients with history of prior revascularization had similar lesion morphology as those who did not have any revascularization.

With the development of OCT technique, it has been possible to classify the ACS patients into those with plaque rupture and plaque erosion. This helps in evaluating the clinical outcomes in these groups of patients and whether they should be managed differently. In the current study, patients were followed up for one year. There was no significant difference in the occurrence of myocardial infarction, all-cause hospitalization and target lesion revascularization between patients with plaque rupture and plaque erosion. There were no independent predictors of adverse events at follow up in the current study. Hu et al. followed up ACS patients with plaque rupture and erosion for one-year period and showed that there was no significant difference in between the two groups in terms of adverse events like death, MI and revascularization[35]. These outcomes were in accordance with the outcomes noted in the current study. Plaque rupture patients, who underwent PCI, had higher incidence of stent malapposition, in-stent dissection and thrombus in the study by Hu et al[35]. However, another study by Niccoli et al. showed that patients with plaque rupture had higher incidence of adverse events, in the form

of unstable angina and repeat revascularization, over a three year follow up period[45].

Culprit lesions with cap erosion have different morphology than those with fibrous cap rupture as they have predominantly white thrombus burden, higher minimum lumen area and lower lipid content. All these qualities have led to the hypothesis that all patients with ACS do not warrant stent placement. Patients with plaque erosion can be managed conservatively with dual anti-platelet therapy. In the current study, majority of patients with plaque erosion underwent stenting. EROSION study has demonstrated that patients with plaque erosion can be managed with dual antiplatelet agents without any significant adverse events over a one-year follow up period[46]. There was reduction in residual thrombus burden while the minimum luminal area remained constant over the one-year follow up period. With the widespread use of statins, plaque stability will improve thus reducing the incidence of plaque rupture. Subsequently, increasing number of patients with plaque erosion will be encountered in daily clinical practice. The encouraging results shown in previous studies of conservative management in plaque erosion call for larger scale studies in this regard. This will indeed be a paradigm shift in management of patients presenting with ACS. This can be made possible only by more robust use of intravascular imaging, especially OCT, in patients with ACS. Intravascular imaging can help determine the culprit lesion morphology which will guide the management strategy. This will prevent patients from the potential complications associated with PCI and stents. However, we need more data regarding longer term follow up in this subset before a change in current clinical practice can be advocated.

LIMITATIONS

1. It was a single center study with a small sample size and the results cannot be generalized to a larger population.

2. The current study had a very broad inclusion criteria which included ACS patients presenting till six weeks from the index events. There was higher prevalence of NSTEMI patients and ISR patients were also included. Patients who underwent fibrinolysis were also included in the current study. These factors may have influenced the final results.

3. Sicker patients with STEMI and NSTEMI were excluded from the study. This will introduce a bias and will thus influence the final outcomes.

4. Healed plaque rupture could have been missed which could underestimate the incidence of plaque rupture in the study population.

5. It is difficult to distinguish between spontaneous plaque rupture from iatrogenic plaque rupture caused during thrombus aspiration.

CONCLUSION

1. Patients with plaque rupture have higher atherosclerotic and inflammatory burden characterized by larger lipid pool, higher incidence of macrophages and thin-cap fibroatheroma.

2. Plaque characteristics like plaque cap thickness and lipid arc can be used to predict plaque stability.

3. Clinical outcomes at one-year follow up were similar in patients with plaque rupture and plaque erosion in terms of death, myocardial infarction and repeat revascularisation.

4. Patients with plaque erosion, who were managed conservatively, had good outcomes at the end of one year. Large randomized studies are required to evaluate long term outcomes in patients with plaque rupture and plaque erosion.

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APPENDIX 1: PROFORMA

Case number - Age - Sex –
Weight - Height –

Chief complaints : - i) Angina – effort angina/rest angina
ii) SOB
iii) Palpitation
iv) Syncope
v) Pedal swelling
vi) Others –

PAST H/O MI –

Significant past history –

H/o PCI/CABG –

Risk factors – DM/HTN/DLP/SMOKER/THYROID DISEASE/ PERIPHERAL ARTERIAL DISEASE

Current Medications –

Classification – Chronic stable angina/ Unstable angina/ NSTEMI / STEMI

<u>Clinical Examination</u>
PR = , Distal pulses palpable Y/N
BP =
JVP - Pedal Edema -

Cardiovascular examination –

Chest –

Any other relevant findings –

Investigations

X- Ray –

2D ECHO - LV dimensions
Ejection fraction
RWMA
MR/AR
Pericardial effusion

TROP T –

PRO BNP –

S. CREATININE –

FASTING LIPID PROFILE –

THYROID PROFILE –

ESR –

CORONARY ANGIOGRAPHY FINDINGS

NO. OF VESSEL INVOLVED –

SITE OF LESION –

TYPE OF LESION (ACC / AHA) - TYPE A/B/C

QUANTITATIVE CORONARY ANGIOGRAPHY :-
LESION LENGTH –
MINIMAL LUMINAL DIAMETER –
DIAMETER STENOSIS –
REFERENCE VESSEL DIAMETER –

OPTICAL COHERENCE TOMOGRAPHY(OCT) EVALUATION

PLAQUE MORPHOLOGY :–

TYPE – FIBROUS/LIPID RICH/FIBROFATTY
MINIMUM PLAQUE CAP THICKNESS –
TCFA – Y/N
LIPID ARC –
PLAQUE CAP INTEGRITY – RUPTURE/EROSION
CALCIFICATION – Y/N
MICROCHANNELS – Y/N
INTRALUMINAL THROMBUS – RED/WHITE
MACROPHAGES – Y/N
NEOATHEROSCLEROSIS – Y/N

QUANTITATIVE ASSESSMENT:-

MINIMUM LUMINAL DIAMETER –
REFERENCE VESSEL DIAMETER –
AREA STENOSIS –

FOLLOW UP ASSESSMENT
ANGINA –
ALL CAUSE DEATH –
DEATH FROM CARDIOVASCULAR CAUSE –
ANY MI –
TARGET LESION REVASCULARISATION –
TARGET VESSEL REVASCULARISATION –

APPENDIX 2 : CONSENT FORM

Title of the study:
Optical coherence tomography based characterisation of culprit lesions in acute coronary syndrome

Participant's name:
Age (in years):

I_____, son/daughter/husband/wife of
_____ declare that (Please tick boxes)

• I have read the above information provided to me regarding the study. **[ ]**
• I have clarified any doubts that I had. [ ]
• I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal Rights [ ]
• I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access. [ ]
• I understand that my identity will not be revealed in any information released to third parties or in publication of study results. [ ]
• I voluntarily agree to take part in this study [ ]

- I understand that participation in the study means that I am willing to undergo the said procedure as already explained and my health records shall be accessed by the investigators for the purpose of the study. [ ]
- I understand that I do not have to bear any extra expense for the purpose of this study. No financial support will be provided to me for participation in the study. [ ]

• I have been provided with the contact numbers of the principle investigator, in case I want to know more about the study and participants rights [ ].
• I have received a copy of this signed consent form [ ]

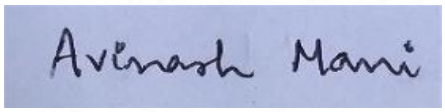
Name:
Signature:
Name of witness:
Signature:
Relation to participant:

<u>Person Obtaining Consent</u>

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her
, in nontechnical terms, all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and all questions asked were answered.

Name:
Signature:
Date:
Place:SCTIMST, Thiruvananthapuram

Principal investigator



Dr. Avinash Mani
SreeChitra Quarters, Kumarapuram
Trivandrum
Mobile. 08820311853
Date -

Study Independent Contact Person
Dr. K Shivakumar
0471-2524593

APPENDIX 3: TAC APPROVAL

Technical Advisory Committee (Clinical Studies)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
THIRUVANANTHAPURAM – 695011, INDIA

TAC Registration No: SCT-/S/2018/764

Date: 04.08.2018

Project title: OPTICAL COHERENCE TOMOGRAPHY (OCT) BASED CHARACTERISATION OF CULPRIT LESIONS IN ACUTE CORONARY SYNDROME

Principal Investigator:	
Dr. Avinash Mani , Resident, Department of Cardiology, SCTIMST	Degree: MBBS, MD (GENERAL MEDICINE)
Co-Principal Investigator(s)	
Dr. Ajit Kumar V.K. Professor and Head, Department of Cardiology, SCTIMST	Degree: MBBS, MD, DM
Dr. Abhilash S.P., Associate Professor, Department of Cardiology, SCTIMST	Degree : MBBS, MD,DM

Members who participated in the TAC meeting on 16/06/2018
Dr. Rupa Sreedhar (Chairperson)
Dr. Prasantakumar Dash
Dr. Krishna Kumar K
Dr. Sankara Sarma P
Dr. Bijulal S
Dr. Jayadevan ER
Dr. Syam K
Dr. Varghese T. Panicker
Dr. K. Shivakumar (Member Secretary)

Dr. Varghese T Panicker, Dr. Rupa Sreedhar, Dr. Jayadevan ER, Dr. Syam K, Dr. Krishna Kumar K, and Dr. Bijulal S stayed away from the proceedings when the projects in which they are involved as investigator were discussed (#762, 768, 769, 772, 775, 776, 778, 782, 784, 785).

Risk Classification of the project (Minimum/ Moderate/ High): Minimum

Requirement of DSMB: No

Recommended members of DSMB: Not applicable

Recommendations of TAC:
Recommended for consideration of IEC in the light of the responses received from the investigator

The PI may note that there can be no additions / alterations in the documents approved by TAC when they are submitted to the IEC.

Signature of the Member Secretary, TAC (Clinical Studies)

Note for IEC
Copy of the investigator's responses to questions/suggestions from TAC is attached (Appendix-1).

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APPENDIX 4: IEC APPROVAL

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1297/OCTOBER-2018 19.11.2018

Dr. Avinash Mani
Resident
Department of Cardiolog y
SCTIMST, Thiruvananthapuram

Dear Dr. Avinash Mani,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "OPTICAL COHERENCE TOMOGRAPHY BASED CHARACTERISATION OF CULPRIT LESIONS IN ACUTE CORONARY SYNDROME *(IEC/1297)*" *on 26th October, 2018.*

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 27.09.2018 with check list*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 27.09.2018 with check list*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 26th October, 2018 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
5.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
8.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
9.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
10.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
11.	Dr. Anand Kumar A	MD, DM	Male	Clinician	No
12.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
13.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

APPENDIX 5: MASTER CHART

DATE	CASE NO	SEX	AGE	DIAGNOSIS	LYSED	PRIMARY PCI DM	HTN	DLP	SMOKER	PAST ACS	PAST REVAS	CLINICAL HF	CTR	LVIDd	LVIDs	EF	MR (GRADE)	TROPT	BNP	Hb	ESR	S.CREAT	TC	LDL	HDL	TG	TSH
21/04/15	1	F	37	STEMI	Y	N	N	Y	N	N	N		0.51	46	31	62	0			112	78	0.6	261	129	34	98	1.4
11/02/15	2	M	42	STEMI	Y	N	Y	Y	N	N	N		0.57	51	30	70	2			146	5	0.9	191	112	43	177	2.2
17/07/15	3	M	30	STEMI	Y	N	Y	Y	N	N	N		0.52	48	32	44	1			151	30	0.9	97	41	41	77	3.4
11.01.2016	4	F	63	STEMI	N	Y	N	N	N	N	N		0.52	44	30	62	0			141	7	0.8	160	94	46	88	1.39
21.08.2016	5	M	50	STEMI	N	Y	Y	Y	Y	Y	Y		0.58	52	26	30	1			18	4	0.57	206	150	42	71	1.03
07.09.2016	6	M	47	STEMI	Y	N	N	N	Y	N	N		0.54	43	28	63	0			153	14	1.08	136	75	26	176	1.8
11.03.2017	7	M	60	STEMI	N	N	N	N	N	N	N		0.46	42	29	35	2			135	11	0.94	189	121	42	132	
17.4.2017	8	M	54	UA	N	N	Y	Y	Y	N	N		0.55	49	32	63	2			151	35	1.14	134	70	33	138	
03.11.2017	9	M	64	STEMI	N	Y	Y	Y	Y	N	Y		0.51	35	24	60	2	1.950		159	2	1.22	59	37	24	103	0.8
30.11.2017	10	M	58	STEMI	Y	N	N	N	N	N	N		0.52	51	41	39	0			148	25	1.05	122	91	32	92	
04.06.2018	11	M	23	STEMI	Y	N	N	N	Y	N	N		0.51	51	36	48	0	4.3	5370	139	10	0.9	140	80	34	130	1.69
27.10.2018	12	M	72	UA	N	N	Y	Y	Y	N	N		0.52	43	28	68	0			164	5	1.01	120	60	61	50	0.7
18.11.2018	13	M	56	NSTEMI	N	N	Y	Y	Y	Y	N		0.51	51	38	80	0			155	10	1.22	131	59	59	120	2.3
26.06.2019	14	M	63	UA	N	N	Y	Y	Y	Y	N		0.52	42	26	67	0			15	3	1.04	201	139	42	102	0.95
17.03.2015	15	M	47	NSTEMI	N	N	N	Y	Y	Y	N		0.46	50	35	54	1			144	46	1.07	259	162	36	288	
24.03.2015	16	M	47	STEMI	N	N	Y	N	N	N	N		0.5	44	27	68	2			149	3	1	167	103	37	135	
06.07.2015	17	M	63	UA	N	N	Y	Y	N	Y	N		0.55	53	32	70	0			119	9	0.8	173	122	37	68	
31.07.2015	18	M	60	STEMI	N	Y	Y	Y	N	N	N		0.5	44	29	64	1			108	15	1.1	324	269	37	93	
20.11.2015	19	F	73	NSTEMI	N	N	Y	N	Y	N	N		0.65	56	34	30	3	0.28	9000	94	8	1.7	187	136	32	96	
03.03.2016	20	M	60	UA	N	N	Y	N	N	Y	N		0.55	58	32	32	1			135	45	1	230	158	48	120	
09.03.2016	21	M	62	UA	N	N	Y	N	N	Y	N		0.55	46	31	61	0			164	24	1.5	194	104	42	239	
01.04.2016	22	M	60	UA	N	N	N	N	Y	N	Y		0.6	68	53	43	2			94	10	1.4	148	101	33	69	
02.10.2016	23	M	55	NSTEMI	N	N	Y	Y	Y	N	N		0.5	47	31	62	1			124	45	1.4	111	56	34	106	
04.08.2016	24	M	56	NSTEMI	N	N	Y	Y	N	Y	N		0.47	45	29	64	0	0.23		144	7	0.91					
12.06.2018	25	M	46	UA	N	N	N	Y	Y	N	N		0.52	55	37	59	0			132	7	1.08	126	81	20	125	
17.03.2015	26	M	75	UA	N	N	N	Y	N	N	N		0.55	45	24	62	0			128	24	1.3	197	131	38	138	
18.03.2015	27	M	50	UA	N	N	N	Y	Y	N	N		0.48	52	30	75	1			126	5	1.1	270	185	47	191	
01.04.2015	28	M	49	UA	N	N	Y	Y	Y	Y	N		0.45	55	33	69	0			126	22	0.9	159	99	47	66	
10.04.2017	29	M	42	UA	N	N	Y	Y	N	Y	N		0.5	41	27	65	0			137	11	0.8	110	59	29	110	
08.02.2018	30	M	64	NSTEMI	N	N	Y	Y	N	Y	N		0.51	47	31	63	0	0.01		125	10	1.35	86	35	36	76	
27.05.2020	31	M	50	STEMI	Y	N	Y	N	Y	N	N		0.5	44	28	55	0			131	4	1.02	127	64	47	61	
25.02.2020	32	F	62	UA	N	N	Y	Y	N	Y	N		0.49	40	23	63	0			9.9	40	0.82	125	53	52	98	

NO OF VSL	LMCA	LAD	LCX	RCA	CULPRIT	VES	LOCATION	O	LENGTH(mm)	%STENOSIS	RVD(mm)	LESION COM	MIN.	PLAQUE	LIPID ARC	PLAQUE TYP	plaque cap	ri	THROMBUS	CALCIFICATI	K	MACROPHAG	NEOATHERO	RVA(OCT)	(n	MLA(OCT)	(n	AREA-STENOSI	CAUSE - LESI	PROCEDURE	VESSEL	NO OF STEN	ANGINA	RE-HOSPITAL	MI	REVASCULAI	TVR	TLR	DEATH	COMPOSITE
SVD		0	1	0	0 LAD		PROXIMAL		13	60	2.75	A		80	70	FIBROFATTY	RUPTURE		WHITE	N		Y	N	8.6		2.9		66.28%	RUPTURE	PCI	LAD	1	N	N	N	N	N	N	N	N
SVD		0	1	0	0 LAD		PROXIMAL		20	90	3	B		95	0	FIBROUS	INTACT		WHITE	N		N	N	7.1		1.86		73.80%	EROSION	PCI	LAD	1	N	N	N	N	N	N	N	N
SVD		0	1	0	0 LAD		MID		20	80	3	A		58	90	LIPID	RUPTURE		WHITE	N		Y	N	8.28		3.4		58.94%	RUPTURE	PCI	LAD	1	N	N	N	N	N	N	N	N
SVD		0	1	0	0 LAD		MID		21	80	2.75	A		150	0	FIBROUS	INTACT		WHITE	N		N	N	4.8		1.3		72.92%	EROSION	PCI	LAD	1	N	N	N	N	N	N	N	N
TVD		0	1	1	1 RCA		PROXIMAL		26	75	3.5	B		80	60	FIBROFATTY	INTACT		RED	N		N	N	5.6		1.7		69.64%	EROSION	PCI	RCA	2								
DVD		0	1	0	1 LAD		PROXIMAL		30	80	2.75	B		60	120	LIPID	RUPTURE		WHITE	N		N	N	4.1		1.18		71.22%	EROSION	PCI	LAD	1	N	N	N	N	N	N	N	N
DVD		0	1	1	0 LAD		MID		35	80	3	B		110	156	LIPID	INTACT		RED	N		Y	N	8.24		1.19		85.56%	EROSION	PCI	LAD	1								
SVD		1	1	0	0 LAD		PROXIMAL		18	90	3.5	B		52	170	LIPID	RUPTURE		RED	N		Y	N	7.23		3.75		48.13%	RUPTURE	PCI	LM-LAD	2								
DVD		0	1	1	0 LCX		MID		36	99	2.5	C		130	0	HETEROGEN	INTACT		RED	N		N	Y	5.5		2.03		63.09%	EROSION	PCI	LCX	1	N	N	N	Y	N	N	N	Y
SVD		0	1	0	0 LAD		MID		14	80	3	B		60	290	LIPID	RUPTURE		WHITE	N		Y	N	7.32		2.7		63.11%	RUPTURE	PCI	LAD	1								
SVD		0	1	0	0 LAD		MID		20	60	3.5	A		130	0	FIBROUS	INTACT		RED	N		N	N	8.7		6.03		30.69%	EROSION	NIL	NIL	0	N	N	N	N	N	N	N	N
SVD		0	0	1	0 LCX		PROXIMAL		15	60	3	A		100	0	FIBROUS	INTACT		RED	N		N	N	8.4		3.2		61.90%	EROSION	NIL	NIL	0	N	N	N	N	N	N	N	N
DVD		0	1	0	1 RCA		MID		14	50	3	A		85	50	FIBROFATTY	INTACT		WHITE	N		N	N	7		1.44		79.43%	EROSION	PCI	RCA	1								
SVD		0	0	0	1 RCA		MID		26	95	3.5	ISR		60	155	LIPID	RUPTURE		RED	N		N	Y	9.1		2.1		76.92%	RUPTURE	PCI	RCA	1	N	N	N	N	N	N	N	N
TVD		0	1	1	1 LAD		PROXIMAL		25	70	3	ISR		150	0	HOMOGENO	INTACT		NIL	N		N	Y	8.5		1.9		77.65%	EROSION	CABG	MV	0	Y	N	N	N	N	N	N	N
TVD		1	1	1	1 LAD		PROXIMAL		30	99	3.5	B		54	100	LIPID	INTACT		NIL	N		Y	N	7.9		2.46		68.86%	EROSION	CABG	MV	0								
TVD		0	1	1	1 RCA		MID		26	90	3	ISR		170	0	HOMOGENO	INTACT		WHITE	N		N	Y	8.1		2.2		72.84%	EROSION	PCI	RCA	1	Y	Y	Y	N	Y	Y	N	Y
DVD		0	1	1	0 LAD		MID		25	90	2.25	B		55	155	LIPID	RUPTURE		RED	N		N	N	7.3		1.8		75.34%	RUPTURE	PCI	OM/LAD	2	Y	Y	Y	Y	N	N	N	Y
TVD		0	1	1	1 LAD		PROXIMAL		14	70	3	B		100	60	FIBROFATTY	INTACT		WHITE	N		N	N	8.3		2.1		74.70%	EROSION	PCI	LAD	1	N	N	N	N	N	N	N	N
DVD		0	1	0	1 RCA		MID		28	70	3.5	SCAD		120	0	FIBROUS	INTACT		NIL	N		N	N	7.7		2.7		64.94%	SCAD	PCI	RCA	1	N	N	N	N	N	N	N	N
TVD		1	1	1	1 SVG-OM		MID		14	70	3	C		52	130	LIPID	RUPTURE		RED	N		Y	N	7.5		2.7		64.00%	RUPTURE	PCI	SVG-OM	1	Y	Y	Y	N	N	N	N	Y
DVD		0	1	0	1 RCA		MID		45	60	3	SCAD		85	0	FIBROUS	INTACT		NIL	N		N	N	6.7		1.9		71.64%	SCAD	PCI	RCA	3	N	Y	Y	Y	N	N	N	Y
DVD		0	1	0	1 RCA		MID		12	80	4	B		70	160	LIPID	INTACT		WHITE	N		Y	N	8.9		1.79		79.89%	EROSION	PCI	RCA	1	Y	N	N	N	N	N	N	N
DVD		0	1	0	1 LAD		PROXIMAL		15	60	3.75	B		140	0	FIBROUS	INTACT		RED	N		N	N	7.6		4.3		43.42%	EROSION	NIL	NIL	0	N	N	N	N	N	N	N	N
TVD		0	1	1	1 LAD		PROXIMAL		14	80	2.75	B		56	190	LIPID	RUPTURE		RED	N		Y	N	8.4		1.4		83.33%	RUPTURE	PCI	LAD	1	Y	N	N	N	N	N	N	N
SVD		0	1	0	0 LAD		PROXIMAL		10	50		A		69	150	LIPID	RUPTURE		NIL	N		Y	N	7.6		3.5		53.95%	RUPTURE	NIL	NIL	0	Y	N	N	N	N	N	N	N
DVD		0	1	1	0 LCX		MID		10	80	2.3	ISR		85	0	HOMOGENO	INTACT		WHITE	N		N	N	6.2		3.3		46.77%	EROSION	POBA	LCX	0	Y	N	N	N	N	N	N	N
DVD		0	0	1	1 RCA		MID		38	100	2.5	ISR		140	100	NEOATHERO	INTACT		WHITE	N		Y	Y	6.4		1.9		70.31%	EROSION	PCI	RCA	2	Y	Y	N	Y	Y	N	N	Y
TVD		0	1	1	1 RCA		DISTAL		50	80	2.75	ISR		210	0	HETEROGEN	INTACT		RED	N		N	N	3.8		0.8		78.95%	EROSION	PCI	RCA	2	N	N	N	N	N	N	N	N
DVD		0	1	1	0 LAD		PROXIMAL		14	70	3	A		100	70	FIBROFATTY	RUPTURE		WHITE	N		N	N	7.2		0.8		88.89%	RUPTURE	PCI	LAD	2	Y	N	N	N	N	N	N	N
DVD		0	1	0	1 LAD		MID		25	80	2.5	Myocardial br		190	50	FIBROFATTY	INTACT		WHITE	N		N	N	4.9		1.5		69.39%	EROSION	PCI	LAD/RCA	2	N	N	N	N	N	N	N	N
SVD		0	0	1	0 LCX		PROXIMAL		10	60	2.5	B		100	70	FIBROFATTY	INTACT		NIL	N		N	N	6.5		2.6		60.00%	EROSION	POBA	LCX	0	N	N	N	N	N	N	N	N

RESULTS

100% Completed: 100% Checked

4% Plagiarism 96% Unique

Sentence Wise Result | Matched Sources | Document View

Unique	Optical coherence tomography (OCT) is a new type of imaging modality which helps to obtain cross s...
Unique	OCT images are two dimensional datasets which show the backscattering of light in a particular cross...
Unique	OCT tries to achieve balance between imaging resolution and tissue penetration thus lying in between...
Unique	OCT imaging was independently developed by two independent researchers around 1990 – Naohiro T...
Unique	Fujimoto of Massachussets Institute of Technology (MIT), United States.
Unique	Invitro imaging of human retinal tissue and coronary artery was first performed in 1991.
Unique	It was done to demonstrate the use of this new technique in transparent and turbid media5.
Unique	OCT imaging was first utilized in ophthalmology and has had a very large clinical impact.
Unique	The first in vivo studies of human macula and optic disc were done in 19936.