A STUDY OF ATEROGENIC INDEX OF PLASMA IN MALE ACUTE CORONARY SYNDROME PATIENTS WITH NORMAL SERUM LIPID PROFILE

DISSERTATION SUBMITTED FOR

M.D., BRANCH-V (PHYSIOLOGY)

MAY 2018

THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY,

CHENNAI, TAMILNADU.
BONAFIDE CERTIFICATE

This is to certify that the dissertation titled “A STUDY OF ATHEROGENIC
INDEX OF PLASMA IN MALE ACUTE CORONARY SYNDROME PATIENTS
WITH NORMAL SERUM LIPID PROFILE” is a bonafide record work done by
DR.S.PREETHI, under my direct supervision and guidance, submitted to The Tamilnadu
Dr. M. G. R. Medical University in partial fulfillment of University regulation for
M.D., Branch-V (Physiology).

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DECLARATION

I, **DR. S. PREETHI**, solemnly declare that the dissertation titled “**A STUDY OF Atherogenic Index of Plasma in Male Acute Coronary Syndrome Patients with Normal Serum Lipid Profile**” has been prepared by me. I also declare that this work was not submitted by me or any other, for any award, degree, diploma to any other University board either in India or abroad. This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of **M.D degree Branch-V (Physiology)** to be held in May-2018.

Place: Madurai

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INTRODUCTION
INTRODUCTION

American Heart Association (AHA) has stated that the term ‘Acute Coronary Syndrome’ (ACS) denotes a range of conditions associated with sudden, reduced blood flow to the heart.

This includes

1. Unstable angina
2. Non ST wave Elevated Myocardial Infarction (NSTEMI)
3. ST wave Elevated Myocardial Infarction (STEMI)

The root cause behind these varied clinical manifestations is unpredictable and abrupt disruption in the stable atherosclerotic plaque, that develops in coronary vasculature. This atheroma can lead to catastrophic vessel thrombus, can weaken the underlying media, can form emboli etc. at the expense of blood supply to cardiac tissue. Thus the determinant for incidence of ACS is degree of atherosclerosis.

Atherogenesis is multifactorial. Framingham Heart Study and Atherosclerosis Risk in Communities Studies have identified the major risk factors for atherosclerosis. They are categorized as listed below

1. Constitutional risk factors
   - Age > 40 years
   - Gender – premenopausal females are less vulnerable
Genetics - people with family history are highly prone.

2. Modifiable risk factors

- Hyperlipidemia
- Hypertension
- Diabetes mellitus
- Cigarette smoking
- Stress
- Metabolic syndrome

All these risk factors end up in abnormalities in lipoprotein metabolism especially elevated small oxidized LDL and reduced small HDL 2 particles, and this remains the standalone reason precipitating atherosclerosis. Thus in clinical outpatient setup, as simple, person with altered lipid profile are considered high risk.

Estimation of lipid profile was an excellency in screening cardiovascular risk until prevalence of ACS among persons with normal lipid profile starts to rise. Hence a normal lipid profile never rule out atherosclerosis and this fact kindled the evolution of better markers.

The Atherogenic Index of Plasma (AIP) can be defined as logarithm of ratio of concentration of TGL to HDL cholesterol and it correlates well with size of HDL and LDL particles and with fractional esterification rate of HDL cholesterol.
So apart from formal quantification of lipoproteins, AIP acts as an index that indirectly depicts the quality of lipoproteins indulged in atherogenesis.

Atherogenic Index of Plasma (AIP) can be calculated by

\[
AIP = \log \left( \frac{TGL}{HDL - C} \right) \text{expressed in mmol/lit.}
\]

Recently Dobiasova et al. proposed AIP as a marker for cardiovascular risk. It can be easily calculated from standard lipid profile. It is noninvasive, cost effective, easily practiced in outpatient setup to screen high risk individuals.

Hence estimation of risk in cardiovascular disease remains incomplete without estimating Atherogenic Index of Plasma (AIP).
AIM AND OBJECTIVES
AIMS AND OBJECTIVES

- To study Atherogenic Index of Plasma (AIP) in male Acute Coronary Syndrome patients with normal serum lipid profile.
- To study Atherogenic Index of Plasma (AIP) in apparently healthy male volunteers.
- To compare Atherogenic Index of Plasma (AIP) between male Acute Coronary Syndrome patients with normal serum lipid profile and in apparently healthy male volunteers.
REVIEW OF
LITERATURE
REVIEW OF LITERATURE

HISTORICAL ASPECTS

- Over centuries, **Myocardial infarction** is the most leading cause of mortality and morbidity in the world.

- Pathophysiological studies have unravelled the interaction that happens at histopathological level, leading to the introduction of the term ‘**ATHEROSCLEROSIS**’.

- Atherosclerosis derives its name from Greek words ‘**ather**’ and ‘**sclerosis**’.

- The word ‘**ather**’ means *gruel* that indicates accumulation of lipids.

- The word ‘**sclerosis**’ means **hardening of tunica intima** that indicates thickening of vessel wall layers.

- Years later the interactions of molecular and cellular elements involved in atherosclerosis became evident and focus was shifted on digging out the novel risk factors that aid in formation of atherosclerosis, characteristics and stability of plague, gene influence and so on.

- In 1996, **Milda Dobiasova, Jiri Frohlich et al** made research over Association of metabolic and genetic factors with cholesterol esterification rate in High Density Lipoprotein (HDL).

- In 1998, **Dobiasova et al**, introduced a term called Atherogenic Index of Plasma (AIP), a mathematical value that can be calculated easily from estimated serum or plasma triglyceride and serum or plasma HDL value using the formula
AIP = Log (TGL / HDL – C) expressed in mmol / litre.

- **In 2001, Adult Treatment Panel III (ATP III)** considered adding drugs that can lower triglycerides to achieve HDL goals.
- **In 2004, Dobiasova et al** Risk of the patient towards developing Acute Coronary syndrome (ACS) can be graded, depending upon the value of Atherogenic Index of Plasma (AIP).

<table>
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<th>Value of Atherogenic Index of Plasma (AIP)</th>
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<td>-0.3 - 0.10</td>
<td>Low risk</td>
</tr>
<tr>
<td>0.11 – 0.21</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>&gt; 0.21</td>
<td>Increased risk</td>
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- **In 2007, Beatriz et al**, identified **Hypertriglyceridemia** as a high risk in the causation of coronary artery disease.
**CHOLESTEROL**

Cholesterol and stereos (solid) followed by the chemical suffix -ol for an alcohol, is an organic molecule. It is a sterol (or modified steroid) a type of lipid molecule and is biosynthesized by all animal cells because

1. It is an essential structural component of all animal cell membranes

2. Essential to maintain both structural integrity and fluidity of the membrane.

3. Cholesterol enables animal cells to dispense with a cell wall allowing animal cells to change shape rapidly and to move unlike bacteria and plant cells which are restricted by their cell walls.

4. Cholesterol also serves as a precursor for the biosynthesis of steroid hormones, bile acid and vitamin D. Cholesterol is the principal sterol synthesized by all animals.

**STRUCTURE OF CHOLESTEROL**
In vertebrates, hepatic cells typically produce the greatest amounts. It is absent among prokaryotes (bacteria and archaea) although there are some exceptions, such as Mycoplasma, which require cholesterol for growth.

François Poulletier de la Salle first identified cholesterol in solid form in gallstones in 1769. However, it was not until 1815 that chemist Michel Eugène Chevreul named the compound "cholesterine".

Since cholesterol is essential for all animal life, each cell is capable of synthesizing it by way of a complex 37-step process, beginning with the mevalonate pathway and ending with a 19-step conversion of lanosterol to cholesterol. Furthermore, it can be absorbed directly from animal-based foods.

A human male weighing 68 kg (150 lb) normally synthesizes about 1 gram (1,000 mg) per day, and his body contains about 35 g, mostly contained within the cell membranes. Typical daily cholesterol dietary intake for a man in the United States is 307 mg (above the upper limit recommended by the Dietary Guidelines Advisory Committee).

Most ingested cholesterol is esterified and esterified cholesterol is poorly absorbed. The body also compensates for any absorption of additional cholesterol by reducing cholesterol synthesis. For these reasons, cholesterol in food, seven to ten hours after ingestion, has little, if any effect on concentrations of cholesterol in the blood. However during the first seven hours after ingestion of cholesterol absorbed fats are
being distributed around the body within extracellular water by the various lipoproteins and increase their concentration.

Cholesterol is recycled in the body. The liver excretes it in a non-esterified form (via bile) into the digestive tract. Typically, about 50% of the excreted cholesterol is reabsorbed by the small intestine back into the bloodstream.

Plants make cholesterol in very small amounts.

Plant manufacture phytosterols (substances chemically similar to cholesterol), which can compete with cholesterol for reabsorption in the intestinal tract, thus potentially reducing cholesterol reabsorption. When intestinal lining cells absorb phytosterols, in place of cholesterol, they usually excrete the phytosterol molecules back into the GI tract, an important protective mechanism.

**FUNCTION**

30% of cholesterol present in animal cell membranes is required to build and maintain membranes and modulates its fluidity over the range of physiological temperatures.

The hydroxyl group on cholesterol interacts with the polar heads of the membrane phospholipids and sphingolipids, while the bulky steroid and the hydrocarbon chain are embedded in the membrane, alongside the nonpolar fatty-acid chain of the other lipids.
Through the interaction with the phospholipid fatty-acid chains, cholesterol increases membrane packing, which alters both membrane fluidity and maintains its integrity so that animal cells do not need to build cell walls (like plants and most bacteria). The membrane remains stable and durable without being rigid, allowing animal cells to change shape and to move.

The structure of the tetracyclic ring of cholesterol contributes to the fluidity of the cell membrane, as the molecule is in a transconformation making all but the side chain of cholesterol rigid and planar. In this structural role, cholesterol also reduces the permeability of the plasma membrane to neutral solutes, hydrogen ions and sodium ions.

Within the cell membrane, cholesterol also functions in intracellular transport, cell signalling and nerve conduction. Cholesterol is essential for the structure and function of invaginated caveolae and clathrin-coated pits, including caveola dependent and clathrin dependent endocytosis. The role of cholesterol in endocytosis of these types can be investigated by using methyl beta cyclodextrin (MβCD) to remove cholesterol from the plasma membrane.

Recent studies show that cholesterol is also implicated in cell signalling processes, assisting in the formation of lipid rafts in the plasma membrane which brings receptor proteins in close proximity with high concentrations of second messenger molecules. In multiple layers, cholesterol and phospholipids act as electrical insulators and facilitate speed of transmission of electrical impulses along nerve tissue.
For many neuron fibers, a myelin sheath, rich in cholesterol since it is derived from compacted layers of Schwann cell membrane, provides insulation for more efficient conduction of impulses. Demyelination is believed to be part of the basis for multiple sclerosis.

Within cells, cholesterol is also a precursor molecule for several biochemical pathways such as for the synthesis of vitamin D and all steroid hormones and their derivatives. The liver excretes cholesterol into biliary fluids, which is then stored in the gallbladder. Bile contains bile salts, which solubilize fats in the digestive tract and aid in the intestinal absorption of fat molecules as well as the fat-soluble vitamins A, D, E, and K.

**BIOSYNTHESIS**

All animal cells manufacture cholesterol based on their cell type and organ function. About 20% of total daily cholesterol production occurs in the liver; other sites of higher synthesis rates include the intestines, adrenal glands and reproductive organs.

Synthesis within the body starts with the mevalonate pathway where two molecules of acetyl CoA condense to form acetoacetyl-CoA. This is followed by a second condensation between acetyl CoA and acetoacetyl-CoA to form 3-hydroxy-3-methylglutaryl CoA (HMG-CoA).

This molecule is then reduced to mevalonate by the enzyme HMG-CoA reductase. Production of mevalonate is the rate-limiting and irreversible step in cholesterol synthesis and is the site of action for statins (a class of cholesterol lowering drugs).
Mevalonate is finally converted to isopentenyl pyrophosphate (IPP) through two phosphorylation steps and one decarboxylation step that requires ATP.

Three molecules of isopentenyl pyrophosphate condense to form farnesyl pyrophosphate through the action of geranyl transferase.

Two molecules of farnesyl pyrophosphate then condense to form squalene by the action of squalene synthase in the endoplasmic reticulum.

Oxidosqualene cyclase then cyclizes squalene to form lanosterol. Finally, lanosterol is converted to cholesterol through a 19-step process.

The final 19 steps to cholesterol contain NADPH and Oxygen to help oxidize methyl groups for removal of carbons, mutases to move alkene groups and NADH to help reduce ketones.

**Konrad Bloch and Feodor Lynen** shared the Nobel Prize in Physiology or Medicine in 1964 for their discoveries concerning some of the mechanisms and methods of regulation of cholesterol and fatty acid metabolism.

**REGULATION OF CHOLESTEROL SYNTHESIS**

Biosynthesis of cholesterol is directly regulated by the cholesterol levels present in blood.

A higher intake from food leads to a net decrease in endogenous production, whereas lower intake from food has the opposite effect.
The main regulatory mechanism is the sensing of intracellular cholesterol in the endoplasmic reticulum by the protein SREBP (sterol regulatory element-binding protein 1 and 2). In the presence of cholesterol, SREBP is bound to two other proteins: SCAP (SREBP cleavage-activating protein) and INSIG-1.

When cholesterol levels fall, INSIG-1 dissociates from the SREBP-SCAP complex, which allows the complex to migrate to the Golgi apparatus. Here SREBP is cleaved by S1P and S2P (site-1 protease and site-2 protease), two enzymes that are activated by SCAP when cholesterol levels are low.

The cleaved SREBP then migrates to the nucleus and acts as a transcription factor to bind to the sterol regulatory element (SRE), which stimulates the transcription of many genes. Among these are the low-density lipoprotein (LDL) receptor and HMG-CoA reductase. The LDL receptor scavenges circulating LDL from the bloodstream, whereas HMG-CoA reductase leads to an increase of endogenous production of cholesterol.

A large part of this signalling pathway was clarified by Dr. Michael S. Brown and Dr. Joseph L. Goldstein in 1970s and won the Nobel Prize in 1985. Their subsequent work shows how the SREBP pathway regulates expression of many genes that control lipid formation, metabolism and body fuel allocation.

Cholesterol synthesis can also be turned off when cholesterol levels are high. HMG-CoA reductase contains both a cytosolic domain (responsible for its catalytic function) and a membrane domain. The membrane domain senses signals for its degradation. Increasing concentrations of cholesterol (and other sterols) cause a change in this domain's
oligomerization state, which makes it more susceptible to destruction by the proteosome. This enzyme's activity can also be reduced by phosphorylation by an AMP-activated protein kinase. Because this kinase is activated by AMP, which is produced when ATP is hydrolyzed, it follows that cholesterol synthesis is halted when ATP levels are low.

**DIETARY SOURCES**

Animal fats are complex mixtures of triglycerides with lesser amounts of both the phospholipids and cholesterol molecules. Major dietary sources of cholesterol include cheese, egg yolks, beef, pork, poultry, fish and shrimp. Human breast milk also contains significant quantities of cholesterol.

From a dietary perspective, plant cells do not manufacture cholesterol and it is not found in plant foods. Some plant foods, such as avocado, flax seeds and peanuts contain phytosterols which compete with cholesterol for absorption in the intestines, reducing the absorption of both dietary and bile cholesterol. However, a typical diet contributes on the order of 0.2 grams of phytosterols, which is not enough to have a significant impact on blocking cholesterol absorption. Phytosterols intake can be supplemented through the use of phytosterol-containing functional foods or dietary supplements that are recognized as having potential to reduce levels of LDL-cholesterol. Some supplemental guidelines have recommended doses of phytosterols in the range of 1.6-3.0 grams per day *(Health Canada, EFSA, ATP III, FDA)*.

A recent meta-analysis demonstrating a 12% reduction in LDL-cholesterol at a mean dose of 2.1 grams per day.
In 2016, the United States Department of Agriculture Dietary Guidelines Advisory Committee recommended that Americans eat as little dietary cholesterol as possible. Increased dietary intake of industrial trans fats is associated with an increased risk in all-cause mortality and cardiovascular diseases.

Trans fats have been shown to reduce levels of HDL while increasing levels of LDL. Health authorities advocate reducing LDL-cholesterol through changes in diet in addition to other lifestyle modifications.

Rats subjected to high-fat or fructose diets became dyslipidemic. However, well designed, adequately powered randomized controlled trials investigating patient-relevant outcomes of low-fat diets for otherwise healthy people with hypercholesterolaemia are lacking. Moreover, for familial hypercholesterolaemia, large, parallel, randomized controlled trials are still needed to investigate the effectiveness of a cholesterol lowering diet and the addition of omega-3 fatty acids, soya protein, plant sterols or stanols.

**PLASMA TRANSPORT AND REGULATION OF ABSORPTION**

As an isolated molecule, cholesterol is only minimally soluble in water. It dissolves into the (water-based) bloodstream only at exceedingly small concentrations.

Cholesterol is transported within lipoproteins, complex discoidal particles with exterior amphiphilic proteins and lipids, whose outward-facing surfaces are water-soluble and inward-facing surfaces are lipid-soluble; i.e. transport via emulsification.
Triglycerides and cholesterol esters are carried internally. Phospholipids and cholesterol, being amphipathic, are transported in the monolayer surface of the lipoprotein particle.

There are several types of lipoproteins in the blood. In order of increasing density, they are chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Lower protein/lipid ratios make for less dense lipoproteins. Cholesterol within different lipoproteins is identical, although some is carried as its native "free" alcohol form (the cholesterol-OH group facing the water surrounding particles), while others as fatty acyl esters, known also as cholesterol esters, within the particles.

Lipoprotein particles are organized by complex apolipoproteins, typically 80-100 different proteins per particle, which can be recognized and bound by specific receptors on cell membranes, directing their lipid payload into specific cells and tissues currently ingesting these fat transport particles. Lipoprotein particles thus include a molecular addresses which play key roles in distribution and delivery of fats around the body in the water outside cells.

Chylomicrons, the least dense cholesterol transport molecules, contains apolipoprotein B-48, apolipoprotein C, and apolipoprotein E (the principal cholesterol carrier in the brain) in their shells. Chylomicrons carry fats from the intestine to muscle and other tissues in need of fatty acids for energy or fat production. Unused cholesterol
remains in more cholesterol-rich chylomicron remnants and taken up from here to the bloodstream by the liver.

VLDL molecules are produced by the liver from triacylglycerol and cholesterol which was not used in the synthesis of bile acids. These molecules contain apolipoprotein B100 and apolipoprotein E in their shells and are degraded by lipoprotein lipase on the blood vessel wall to IDL.

Blood vessels cleave and absorb triacylglycerol from IDL molecules, increasing the concentration of cholesterol. IDL molecules are then consumed in two processes: half is metabolized by HTGL and taken up by the LDL receptor on the liver cell surfaces, while the other half continues to lose triacylglycerols in the bloodstream until they become LDL molecules, with the highest concentration of cholesterol within them.

LDL particles are the major blood cholesterol carriers. Each one contains approximately 1,500 molecules of cholesterol ester. LDL molecule shells contain just one molecule of apolipoprotein B100, recognized by LDL receptors in peripheral tissues. Upon binding of apolipoprotein B100, many LDL receptors concentrate in clathrin-coated pits. Both LDL and its receptor form vesicles within a cell via endocytosis. These vesicles then fuse with a lysosome, where the lysosomal acid lipase enzyme hydrolyzes the cholesterol esters. The cholesterol can then be used for membrane biosynthesis or esterified and stored within the cell, so as to not interfere with the cell membranes.

LDL receptors are used up during cholesterol absorption and its synthesis is regulated by SREBP, the same protein that controls the synthesis of cholesterol de novo,
according to its presence inside the cell. A cell with abundant cholesterol will have its LDL receptor synthesis blocked, to prevent new cholesterol in LDL molecules from being taken up. Conversely, LDL receptor synthesis proceeds when a cell is deficient in cholesterol.

When this process becomes unregulated, LDL molecules without receptors begin to appear in the blood. These LDL molecules are oxidized and taken up by macrophages, which become engorged and form foam cells. These foam cells often become trapped in the walls of blood vessels and contribute to atherosclerotic plaque formation. Differences in cholesterol homeostasis affect the development of early atherosclerosis (carotid intima-media thickness). These plaques are the main causes of heart attacks, strokes and other serious medical problems, leading to the association of so-called LDL cholesterol (actually a lipoprotein) with "bad" cholesterol.

HDL particles are thought to transport cholesterol back to the liver, either for excretion or for other tissues that synthesize hormones, in a process known as reverse cholesterol transport (RCT). Large numbers of HDL particles correlates with better health outcomes, whereas low numbers of HDL particles is associated with atheromatous disease progression in the arteries.

**METABOLISM, RECYCLING AND EXCRETION**

Cholesterol is susceptible to oxidation and easily forms oxygenated derivatives known as oxysterols. Three different mechanisms can form these: autoxidation, secondary oxidation to lipid peroxidation and cholesterol-metabolizing enzyme
oxidation. A great interest in oxysterols arose when they were shown to exert inhibitory actions on cholesterol biosynthesis. This finding became known as the “oxysterol hypothesis”. Additional roles for oxysterols in human physiology include their participation in bile acid biosynthesis, function as transport forms of cholesterol and regulation of gene transcription.

In biochemical experiments radiolabelled forms of cholesterol such as tritiated-cholesterol are used. These derivatives undergo degradation upon storage and it is essential to purify cholesterol prior to use. Cholesterol can be purified using small Sephadex LH-20 columns.

![Diagram showing metabolism of chylomicrons and lipoprotein metabolism](image-url)

*Figure 69-1. Summary of major pathways for metabolism of chylomicrons synthesized in the intestine and very low density lipoprotein (VLDL) synthesized in the liver. Apo B, apolipoprotein B; Apo E, apolipoprotein E; FFA, free fatty acids; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase.*
Cholesterol is oxidized by the liver into a variety of bile acids.[49] These, in turn, are conjugated with glycine, taurine, glucuronic acid or sulfate. A mixture of conjugated and nonconjugated bile acids, along with cholesterol itself, is excreted from the liver into the bile. Approximately 95% of the bile acids are reabsorbed from the intestines and the remainder are lost in the feces. The excretion and reabsorption of bile acids forms the basis of the enterohepatic circulation, which is essential for the digestion and absorption of dietary fats.

Under certain circumstances, when more concentrated, as in the gallbladder, cholesterol crystallises and is the major constituent for most of the gallstones like lecithin and bilirubin gallstones also occur. Every day, up to 1 g of cholesterol enters the colon.

This cholesterol originates from the diet, bile and desquamated intestinal cells, and can be metabolized by the colonic bacteria. Cholesterol is converted mainly into coprostanol, a nonabsorbable sterol that is excreted in the faeces. A cholesterol-reducing bacterium origin has been isolated from human faeces.
ATHEROSCLEROSIS

Atherosclerotic lesions result from a complex interplay between circulating factors and various cell types in the vessel wall, triggered by chronic and repeated exposure to several systemic and local injurious stimuli. A high level of plasma lipids, particularly low-density lipoproteins (LDL) is a major cause of vascular damage.

Apart from epidemiological evidence for the proatherogenic role of lipoproteins, mechanistic studies suggest that they play a role in relevant features for initiation and progression of lesions, as endothelial dysfunction, intimal disorganisation and thickening. In advanced atheromatous plaques, high extracellular and intracellular lipid deposits are associated with a high risk of vulnerability to rupture, causing thrombosis and its clinical complications.

INITIAL CHANGES IN THE PATHOGENESIS OF ATHEROSCLEROSIS

LDL INFILTRATION, RETENTION AND MODIFICATION.

Sustained high plasma levels of LDL cholesterol is thought to be the major determinant for the entry and retention of LDL particles within the subendothelial layer. Yet, other features such as lipoprotein size, cholesterol enrichment, endothelial permeability and endothelial cell-derived biosynthetic activity (i.e. synthesis of the basement membrane and extracellular matrix) also affect LDL entrance and retention.

Once LDL enters the intimal space, several specific regions of the apoB-fraction interact with extracellular proteoglycans, especially with those that contain side chains of chondroitin sulphate such as versican or biglycan. LDL retention within the intimal layer
may also occur, although to a lesser extent, via lipoprotein association with other matrix molecules (such as lipoprotein lipase, sphingomyelinase, and phospholipase A2), collagen and/or elastin.

**LDL’S DRIVE LEUKOCYTE RECRUITMENT, TRANSMIGRATION AND DIFFERENTIATION.**

Once sequestered in this intimal microenvironment, LDL particles become susceptible to modifications including aggregation/fusion, oxidation (via lipoxygenase,
myeloperoxidase, free radicals, etc), enzymatic cleavage (via proteolytic, lipolytic and hydrolytic enzymes) and incorporation in immune complexes rendering LDL particles proatherogenic.

**LDL’S DRIVE LEUKOCYTE RECRUITMENT, TRANSMIGRATION AND DIFFERENTIATION.**

Modified LDL particles induce endothelial secretion of chemotactic substances and the expression of adhesion receptors, including integrins and selectins, which favour leukocyte (monocyte and lymphocyte) recruitment, adhesion and transmigration into the arterial wall.

Transmigration of monocytes preferably occurs in areas where the subendothelial layer is enriched with modified LDL particles and takes place mainly through the junctions between endothelial cells. Junction adhesion molecule (JAM)-A and -C have been shown to be involved in the control of vascular permeability and leukocyte transmigration across endothelial cell surfaces.

Interestingly, recent evidence supports that high LDL-cholesterol levels selectively recruit distinct monocyte and T-cell subsets into the atherosclerotic lesion.

Once monocytes reach the intimal space, colony–stimulating factor induces monocytes to phenotypically transform into macrophages and express scavenger receptors, which uptake many of the cholesterol molecules and cholesterol esters contained in
modified LDL particles, becoming foam cells – a characteristic cell constituent of atherosclerotic lesions.

**PROGRESSIVE DEVELOPMENT OF ATHEROSCLEROTIC PLAQUE**
Scavenger receptor class A (SRA)-I and SRA-II, CD36, LOX-1, or CXCL16 are involved in oxidised LDL internalisation, whereas we have demonstrated that LRP-1 (low-density lipoprotein receptor related protein-1) is mainly involved in the internalisation of aggregated LDLs, in a process regulated by SREBP1 and SREBP2.

Additionally, LRP5 – a receptor that links Wnt signalling and migration of mononuclear cells – is also upregulated by LDL. Once converted, macrophage-derived foam cells release cytokines, growth factors, metalloproteinases (MMP), reactive oxygen species (ROS) and tissue factor perpetuating the inflammatory response, inducing vascular remodelling and increasing plaque susceptibility to rupture and subsequent thrombus formation.

**VASCULAR REMODELLING**

As atherosclerosis evolves, the presence of LDL and atherogenic cytokines stimulates vascular smooth muscle cells (VSMCs) to alter extracellular matrix (ECM) composition leading to vascular remodelling. Under physiological conditions, VSMCs in the media are known to produce most of the main components of the ECM found in the arterial intima (proteoglycans, collagen and elastin) as well as a large number of enzymes responsible for the equilibrium between ECM synthesis (lysyl oxidase) and degradation (MMP, plasminogen activators).

However, under the effect of atherogenic stimuli, VSMCs undergo phenotypic changes switching from a non-proliferative contractile phenotype (typical in healthy
arteries) into an actively proliferative cell (synthetic phenotype) with the capacity to migrate and increase ECM synthesis.

In fact, migration of VSMCs from the vascular media to the vascular intima is a key process in intimal thickening and vascular remodelling. Circulating bone marrow progenitor cells and progenitor cells present in the vessel adventitia may also be a potential source of VSMCs in the intima.

Once in the intimal layer, VSMC express a variety of receptors for cholesterol uptake thereby participating in the early lipid accumulation process in the atherosclerotic plaque. These include different members of the LDL-receptor family (LDL-R, LRP, VLDL-R) and the scavenger receptor family (CD36, type I and type II scavenger receptors, CXCL16).

The presence of proteoglycan-induced LDL aggregates (agLDL), VSMCs over-express receptors such as LRP-1, which not only facilitates LDL internalisation and the subsequent transformation of VSMC into foam cells, but also acts as a receptor to many other ligands and participates in signalling processes.

Lipid-rich VSMCs show significantly lower migration and repair capacity rendering plaques less able to be populated by VSMCs and therefore, more susceptible to rupture. VSMCs which account for 90–95% of the cell component in initial lesions, decreases to 50% in advanced atherosclerotic lesions making those plaques more vulnerable to rupture.
Indeed, unstable plaques contain a substantial lipid core, little collagen and a small number of VSMCs. We have recently shown, by proteomic approaches, that atherogenic concentrations of LDL particles affect the expression and phenotypic profile of different cytoskeleton and ER-stress proteins of the VSMCs involved in migration and survival thereby mediating the instability and vulnerability of plaques in advanced stages.

FROM FATTY STREAKS TO VULNERABLE PLAQUES

Even in the presence of extensive coronary atherosclerosis, rarely more than a few plaques appear to be at risk of rupture at any given moment. Yet, when ruptured, these plaques precipitate approximately 75% of all fatal coronary thrombi.

The risk of suffering a thrombotic complication depends more on the biochemical and cell composition of the lesions rather than their stenotic severity. Pathological studies performed on patients dying from cardiovascular events have shown the existence of an acute thrombus anchored on the disrupted areas of atherosclerotic lesions in the majority of the patients.

The same evidence has allowed to associate certain plaque features with plaque vulnerability. Indeed, autopsy studies, atherectomy specimens of coronary origin, endarterectomy specimens of carotid origin and intravascular imaging with optical coherence tomography have provided information about ruptured plaques.

However, all these techniques have the same limitation: they provide data on the structure and components of ruptured plaques and only by extrapolation do we learn about
the features of rupture-prone plaques. Undoubtedly an useful animal model, in which the mechanisms leading to spontaneous plaque rupture could be studied prospectively, would overcome some of these problems, but such a model is not yet available.

VULNERABLE PLAQUE ‘PHENOTYPE’

Nonetheless, the human anatomo-pathological studies have revealed, so far, that the main features characterising plaques as ‘vulnerable’ include:

(a) A large necrotic lipid core;
(b) A thin fibrous cap;
(c) Increased inflammation in the fibrous cap;
(d) Reduced collagen and VSMCs amount; and
(e) Neovascularisation.

VULNERABLE PLAQUE ‘PHENOTYPE’
THE LIPID-RICH CORE.

The formation of a lipid-rich core is the essential mechanism in the development of the rupture-prone plaque. It has been suggested that the lipid-rich core is the result of smaller pools of accumulated lipid in the intima combined to a larger lipid pool, which becomes acellular due to apoptosis and necrosis of VSMC and macrophage foam cells.

Therefore, the lipid-rich atheromatous core is hypocellular, totally devoid of supporting collagen and presents high-free cholesterol content in the centre with a low-free to esterified cholesterol ratio at the edges, possibly because of macrophage breakdown and active inflammation.

The lipid core also contains pro-thrombotic oxidised lipids and is impregnated with TF derived from macrophage and VSMC derived foam cells making it highly thrombogenic when exposed to flowing blood.

Studies conducted to evaluate the relative thrombogenicity of the various components of atherosclerotic plaques have demonstrated that the lipid-rich nucleus is up to six times more thrombogenic than all other components. Moreover, inhibition of TF by local administration of TF-pathway inhibitor (TFPI) effectively reduces arterial thrombosis in atherosclerotic lesions.

Besides, LDL-laden foam cells have also shown to release TF increasing the susceptibility of the plaque to thrombus formation. In this regard, we have reported that the interaction between LRP-1 and LDL aggregates is one of the mechanisms that induce VSMC TF expression and the release of microparticles enriched in active TF to the ECM.
THIN FIBROUS CAP.

The fibrous cap is the connective tissue layer covering the lipid-rich core. It consists of VSMCs and the ECM they synthesise (mainly collagen and proteoglycans). The cap also contains inflammatory cells, predominantly macrophage foam cells. Vulnerable plaques tend to have thin fibrous caps and the integrity of this fibrous cap depends, at least in part, on the constituents of the ECM.

Therefore, the balance between collagen synthesis by VSMCs (synthetic phenotype) and breakdown of collagen fibrils by MMPs, collagenases, membrane-type MMPs, gelatinases and stromelysins plays a key role in fibrous cap stability.

Several lines of evidence suggest that inflammatory cytokines are responsible for this balance since these inflammatory mediators not only induce endothelial cells, macrophages and VSMC apoptosis but markedly enhance MMP’s expression and activity in these cells.

Moreover, death of these cells may cause the continuous release of certain MMPs that may be particularly active in destabilising plaques and thus predispose them to rupture.

In fact, quantification of certain MMPs and their inhibitors in blood has been correlated with the degree of atherogenesis in humans. VSMCs apoptosis may also be involved in plaque destabilisation by decreasing the number of collagen-synthesising cells within the atherosclerotic lesion.

INFLAMMATION.

The core of the rupture-prone lipid-rich plaque is essentially hypocellular with little inflammation. In contrast to the plaque core, the ruptured fibrous caps have been found to
be heavily inflamed (26% and 17% macrophage density in the coronary artery and aorta respectively). Accordingly, it is not diffuse inflammation that characterises ruptured plaques but the heavy inflammation of the fibrous cap, specifically, at the shoulders.

CALCIFICATION.

Calcium deposits in the vascular wall occur through all the atherogenic processes, initially as small aggregates, and later as large nodules. Arterial calcification occurs in two distinct forms involving either the atherosclerotic intima or the tunica media. The coronary artery calcium score detected by computed tomography has been proposed to provide prognostic information beyond that provided by traditional risk factor scoring.

As such, clinical observations suggest that culprit plaques in ACS are less calcified and the individual calcifications are smaller compared to culprit plaques in stable angina.

NEOVASCULARISATION.

Plaque angiogenesis may have an important role in the development of severe atherosclerosis. Vasa vasorum angiogenesis provides nutrients to the developing and expanding intima and therefore may prevent cellular death and contribute to plaque growth and stabilisation in early lesions.

However, in more advanced plaques, inflammatory cell infiltration and concomitant production of numerous pro angiogenic cytokines may be responsible for induction of uncontrolled neointimal microvessel proliferation resulting in production of immature and fragile neovessels that may contribute to development of an unstable haemorrhagic rupture-prone environment.
In fact, in rupture-prone and ruptured plaques, the microvessel density is two- to four-fold higher than in stable plaques both in carotid and coronary arteries. In line with these observations, we have reported from coronary atherosclerotic lesions excised from patient’s hearts that the highest neovessel content is associated with the most-advanced stage plaques and in turn is linked with the highest rate of thrombotic episodes. Moreover using laser dissection microscopy, we have deciphered novel angiogenic factors that may contribute to plaque vascularisation and vulnerability.

DIFFERENCES IN PLAQUE VULNERABILITY THROUGHOUT THE VASCULAR BED

CORONARY ARTERY VULNERABLE PLAQUES.

Retrospective analysis of serial angiograms and prospective serial angiographic observations have suggested that coronary occlusion and myocardial infarction most frequently occur in sites that have diameter narrowing less than 70% (often less than 50%). This concept is supported by the demonstration of a mild residual stenosis on angiography after thrombolytic therapy for an acute myocardial infarction. However, it is important to take into account that less severe stenotic plaques are 5–10 times more common than severely stenotic plaques.

Furthermore, severely stenotic plaques are more likely to stimulate collateral circulation to the post stenotic segment; thus, subsequent plaque rupture and thrombosis at such sites may be clinically silent because of the protective effect of collateral recruitment. However, these mild stenotic plaques usually present a large lipid-rich core which after
disruption exposes the thrombogenic gruel to the flowing blood causing about 70–80% of the coronary thrombus formation.

**CAROTID ARTERY VULNERABLE PLAQUES.**

In contrast to coronary plaques, the vulnerable plaques in carotid arteries are severely stenotic and appear to be ulcerated and disrupted. The vulnerable carotid plaques are not necessarily lipid-rich but rather heterogeneous, and they are very stenotic; their rupture or dissection probably relates to the impact of blood during systole against the resistance that they offer by being stenotic.

**AORTIC VULNERABLE PLAQUES.**

Autopsy and transoesophageal echocardiography studies have shown that parameters such as luminal irregularities, plaque composition and non-calcified plaques in the aorta that are greater than 4 mm in thickness are strong predictors of future aortic vascular events.

**THROMBOSIS - ROLE OF PLATELETS IN ATHEROGENESIS**

**RESERVOIR OF ATHEROSCLEROTIC ENHANCERS**

Platelets do not adhere or activate to the intact, non-activated endothelium.

However, inflammatory events such as those observed in the early stages of atherosclerosis lead to endothelial activation which, in turn, may stimulate platelet attachment. Hence, endothelial disruption is not an absolute prerequisite to allow platelet activation and attachment to the arterial wall.

Although the mechanisms that lead to platelet–endothelial interaction remain to be fully described, it has been postulated that platelet activation may be attributed to:
(a) Reduction in the mechanisms implicated in maintaining endothelial antithrombotic properties

(b) Reactive oxygen species (ROS) generated by atherosclerotic risk factors (in fact, the presence of hypertension, hypercholesterolemia, cigarette smoking and diabetes correlates with a higher number of circulating activated platelets) and

(c) An increase in prothrombotic and pro-inflammatory mediators in the circulation.

Activated endothelium allows platelets to roll on even under high shear rates. Platelet rolling, primarily mediated by P-selectin, is followed by firm adhesion mediated by integrin binding.

Thus platelet P-selectin expressed upon activation seems to be essential to allow platelet–endothelium adhesion. Indeed the absence of P-selectin has been shown to protect against the development of atherosclerotic lesions in both low density lipoprotein (LDL) receptor and apoE knock-out mice, especially in the early stages of lesion development.

Platelet attachment to intact but activated/dysfunctional endothelium may also be initiated by interaction of GPIbα and αIIbβ3 (GPIIb/IIIa) with endothelial P-selectin and von Willebrand factor (vWF). Indeed, there is an increased synthesis and subendothelial presence of vWF in atherogenesis, with functional consequences for platelet deposition on the vessel wall.

Therefore blockade of platelet adhesion using either GPIbα or αIIbβ3 antagonists has been shown to decrease platelet adhesion, leukocyte recruitment and lesion size.
Activated platelets in addition to selectin and integrin expression release several mediators retained within their granules that result in cell adhesion, survival and proliferation, coagulation and proteolysis and synthesise chemokines and proinflammatory cytokines all of which accelerate and enhance the inflammatory process promoting plaque development.

Platelets also contain high amounts of micro-RNAs (mRNAs) – small RNA molecules that modulate protein expression by degrading mRNA or repressing translation.

Several reports have documented the role of platelet mRNAs in haematopoiesis including differentiation and lineage commitment to megakaryocytes. In addition certain mRNA levels in platelets have been found to associate with reactivity to specific agonists and to pathological states.

Although their clinical relevance is still under investigation, mRNAs have been suggested as potential biomarkers for platelet reactivity and vascular thrombosis as well as potential delivery vehicles for mRNAs, either as a physiological response to vessel injury or as potential therapeutic approach.

**BRIDGE BETWEEN ATHEROSCLEROSIS AND INFLAMMATION**

A vast amount of platelet-related secretory molecules mediate the interaction between leukocytes and the endothelium in the early stages of atherosclerosis. Indeed, studies performed during recent years bring consistent evidence that platelets, besides driving thrombus formation on plaque rupture, play a key role in the inflammatory response.
For instance, platelet delivery and deposition of Regulation on Activated Normal T cell Expressed and Secreted (RANTES) and platelet factor (PF)-4 to the monocyte and endothelium surface respectively induces activation of monocyte-related integrins and eventually promotes macrophage infiltration in the vascular wall.

Moreover, both activated platelets and endothelial cells actively secrete pro-inflammatory cytokines such as CD40L and IL-1β, which further stimulate the endothelium and promote the activation of endothelial nuclear factor-B (NFκB). Activation of NFκB in turn triggers the transduction and translation of key genes such as MCP-1, αvβ3, ICAM-1 and VCAM-1 crucial for monocyte attachment and transmigration.

On the other hand, platelet–leukocyte interactions also occur via P-selectin or P-selectin glycoprotein (PSGL)-1 or integrin Mac-1/GPIb and/or fibrinogen-αIIbβ3 binding. Such interactions facilitate firm leukocyte adhesion to endothelial-adhered platelets or directly to the endothelium supporting plaque formation. Leukocytes however are not the only cells that are recruited by platelets into a vascular lesion.

Platelets have recently been shown to contribute to progenitor cell recruitment for vascular regeneration. Platelets store an abundant amount of stromal derived factor-1 (SDF-1; a potent chemokine for progenitor cells) in their granules that supports the adhesion of progenitor cells to either the endothelium or thrombus surface. In addition, platelets are able to regulate progenitor cell differentiation into foam cells or endothelial cells depending on the conditions.
Finally, platelets may also contribute to atherogenesis by mediating cholesterol uptake in the vascular wall. Free-cholesterol retention in cells and tissues can not only originate from endocytosed cholesterol esters that are hydrolysed in phagolysosomes but also directly from free cholesterol of cell membranes.

Membranes of circulating cells, including activated platelets and probably dead leucocytes, can release free cholesterol. It has been shown that focal intraplaque microhaemorrhages initiate platelet and erythrocyte phagocytosis, leading to iron deposition, macrophage activation, ceroid production and foam-cell formation. Interestingly, the cholesterol content of erythrocyte membranes exceeds that of all other cells in the body with lipids constituting 40% of their weight.
ACUTE CORONARY SYNDROME

The term *Acute Coronary Syndrome* (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina (UA) to non ST segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI).

Unstable angina and NSTEMI are closely related conditions. They are similar in pathophysiologic origin and clinical presentations but differ in their severity. A diagnosis of NSTEMI can be made when the ischemia is sufficiently severe to cause myocardial damage that results in the release of a biomarker of myocardial necrosis into the circulation (cardiac-specific troponins T or I, or muscle and brain fraction of creatine kinase [CK-MB]). In contrast, the patient is considered to have experienced UA if no such biomarker can be detected in the bloodstream hours after the initial onset of ischemic chest pain.

**Unstable angina** exhibits 1 or more of 3 principal presentations:

1. Rest angina (usually lasting >20 minutes)
2. New-onset (<2 months previously) severe angina
3. A crescendo pattern of occurrence (increasing in intensity, duration, frequency or any combination of these factors).
Approximately 1.36 million hospitalizations are required for ACS in India every year, out of which 0.81 million are for myocardial infarction (MI) and the remainder are for Unstable Angina. Roughly two-thirds of patients with MI have NSTEMI and the rest have STEMI.

**PLAQUE DISRUPTION, THROMBOSIS AND ACS**

The pathogenesis of ACS involves an intricate interplay among the endothelium, inflammatory cells and the thrombogenicity of the blood.

Angiographically, noncritical coronary lesions (<50% stenosis in the diameter of the vessel) may be associated with abrupt progression to severe or total occlusion and may eventually account for as many as two-thirds of cases of ACS.

Factors such as the lipid and tissue factor content of the plaque, the severity of the plaque rupture, the degree of inflammation at the site, the blood flow in the area and the patient's antithrombotic and prothrombotic balance are important in controlling the degree of thrombus formation and determining whether a given plaque rupture will result in ACS.

Autopsy studies have shown that plaque rupture causes approximately 75% of fatal MIs, whereas superficial endothelial erosion accounts for the remaining 25%.
ACUTE CORONARY SYNDROME

NORMAL

Atherosclerosis

FIXED CORONARY OBSTRUCTION
(Typical angina)

PLAQUE DISRUPTION

SEVERE FIXED CORONARY OBSTRUCTION
(Chronic ischemic heart disease)

Healing

Platelet aggregate

Thrombus

MURAL THROMBUS WITH VARIABLE OBSTRUCTION / EMBOLI
(Unstable angina or acute subendocardial myocardial infarction or sudden death)

OCCLUSIVE THROMBUS
(Acute transmural myocardial infarction or sudden death)
After the rupture of plaque or erosion of endothelial, the subendothelial matrix (which is rich in tissue factor, a potent procoagulant) is exposed to the circulating blood. This exposure leads to platelet adhesion followed by platelet activation and aggregation and the subsequent formation of a thrombus.

Two types of thrombi can form: a platelet-rich clot referred to as a white clot that forms in areas of high shear stress and only partially occludes the artery, or a fibrin-rich clot referred to as a red clot that is the result of an activated coagulation cascade and decreased flow in the artery.

Red clots are frequently superimposed on white clots, leading to total occlusion. Several lines of evidence support the central role of thrombosis in the pathogenesis of ACS.

**THERAPEUTIC GOALS AND APPROACHES FOR ACS**

The severity of findings on coronary angiography and angioscopy parallels the clinical severity of ACS. Although only white clots are found in patients with UA/NSTEMI, red clots form in patients with STEMI.

The differences in the underlying pathophysiology of UA/NSTEMI and STEMI call for different therapeutic goals and approaches. In UA/NSTEMI, the goal of antithrombotic therapy is to prevent further thrombosis and to allow endogenous fibrinolysis to dissolve the thrombus and reduce the degree of
coronary stenosis. Revascularization is frequently used to increase blood flow and prevent reocclusion or recurrent ischemia.

In contrast, in STEMI the infarct-related artery is usually totally occluded, and immediate pharmacological or catheter-based reperfusion is the initial approach, with the goal of obtaining normal coronary blood flow. Other therapies such as anti-ischemic and lipid-lowering therapies are used in all cases to stabilize plaques over long term.

**EARLY ASSESSMENT**

The symptoms of UA/NSTEMI and STEMI are similar, and differentiating the two requires medical evaluation and 12-lead electrocardiography (ECG). The 2007 guidelines for managing UA/NSTEMI, released by the American College of Cardiology (ACC) and the American Heart Association (AHA) state that patients with symptoms suggestive of ACS should be referred to a facility that has capabilities for 12-lead ECG recording, biomarker determination and evaluation by a physician (eg, an emergency department [ED]).

Patients who have previously been given a prescription for nitroglycerin should be instructed promptly to take 1 dose of nitroglycerin sublingually for chest discomfort or pain. If no relief occurs, or if symptoms worsen 5 minutes after 1 dose of nitroglycerin has been taken. Patients at increased risk of ACS such as
those with known coronary artery disease (CAD), peripheral vascular disease, cerebral vascular disease, diabetes or a 10-year Framingham risk of CAD of 20% or higher should be targeted by health care professionals and should be educated about recognizing the symptoms of ACS.

All patients presenting to the ED with chest discomfort or other symptoms suggestive of ACS should be considered high-priority triage cases. Evaluation and treatment should follow a predetermined, institution-specific protocol for chest pain. If the initial diagnosis and treatment plan are unclear to the ED physician, immediate cardiology consultation is advisable. 6 to 7 million persons present to EDs with the symptom of chest pain or other symptoms suggestive of possible ACS in US annually. Out of them approximately 20% to 25% receive a final diagnosis of UA or MI.

The 2007 ACC/AHA guidelines for managing UA/NSTEMI state that the first step in assessing patients with chest discomfort or other symptoms suggestive of ACS is determining the likelihood that the symptoms and signs represent ACS secondary to obstructive CAD. The second step is determining the risk of an adverse clinical outcome for those patients with an intermediate or high likelihood of ACS risk stratification. Early risk assessment is based on initial findings from the history, physical examination and the results of ECG and cardiac biomarker measurements.

**CLINICAL PRESENTATION**
HISTORY FINDINGS

Careful and focused history taking and physical examination are essential to assess the likelihood of ACS and to determine the risk of an adverse outcome.

Although patients typically describe stable angina as deep, poorly localized chest or arm discomfort that is exacerbated by activity or emotional stress and relieved by rest, nitroglycerin, or both, the discomfort associated with UA is more severe, occurs at rest and is usually described as frank pain. Often located in the substernal region (sometimes the epigastric area), the pain or pressure frequently radiates to the neck, jaw, left shoulder and left arm. Some patients may present with symptom other than chest discomfort; such “angina equivalent” symptoms include most commonly dyspnea, nausea, vomiting, diaphoresis and unexplained fatigue.

Atypical presentations are more common among women and elderly people. Rarely syncope may be the presenting symptom of ACS. Pain that is sharp, stabbing or pleuritic reproducible with palpation or with movement, or able to be localized at the tip of 1 finger is usually not ischemic.

The 5 most important history-related factors that helps in identifying ischemia due to CAD ranked in order of importance are

- The nature of the angina symptoms
- A history of CAD
• Male sex

• Older age and

• Number of traditional risk factors present.

Traditional cardiac risk factors (like hypertension, hypercholesterolemia, cigarette smoking, diabetes and family history of premature CAD) have actually been found to be weak predictors of the likelihood of acute ischemia although their presence relates to poor outcomes for patients with established ACS.

**PHYSICAL EXAMINATION:**

The primary goals of the physical examination are to identify any precipitating causes of myocardial ischemia and to assess the hemodynamic consequences of the acute ischemic event.

Physical examination findings that indicate a large area of ischemia and high risk include diaphoresis, pale, cool skin, sinus tachycardia, a third or fourth heart sound, basal rales and hypotension.

**ELECTROCARDIOGRAPHY**

The ACC/AHA guidelines state that an experienced emergency physician should review the results of 12-lead ECG within no more than 10 minutes after the
arrival in the ED of a patient with chest discomfort or other symptoms suggestive of ACS.

**ST ELEVATION MYOCARDIAL INFARCTION**

Findings on ECG associated with UA include ST-segment depression, transient ST-segment elevation, T-wave inversion or some combination of these factors. Depending on the severity of the clinical presentation, these findings are present in 30% to 50% of patients.

New ST-segment deviation, even of only 0.05 mV, is an important and specific measure of ischemia and prognosis. T-wave inversion is sensitive for...
ischemia but is less specific unless it is marked ($\geq 0.3 \text{ mV}$). A ST-segment elevation of $0.1 \text{ mV}$ or more, if present in at least 2 contiguous leads indicates acute MI in 90% of patients as confirmed by serial measurements of cardiac biomarkers.

Because the process of myocardial ischemia is quite dynamic and a single 12-lead ECG provides only a snapshot view of this process, the ACC/AHA guidelines recommend that patients hospitalized for UA/NSTEMI undergo serial ECG tracings or continuous ST-segment monitoring.

**CARDIAC BIOMARKERS OF NECROSIS**

Cardiac biomarkers should be measured for all patients who present with chest discomfort or other symptoms suggestive of ACS. Measurements of the cardiac-specific troponins T and I allow for highly accurate, sensitive and specific determination of myocardial injury in the context of ischemic symptoms. These troponins have replaced CK-MB as the preferred marker for the detection of myocardial necrosis.

However, troponin measurements have some drawbacks. Troponin levels usually do not increase until at least 6 hours after the onset of symptoms. Therefore, a negative result obtained within this period should prompt a repetition of the assay 8 to 12 hours after the onset of symptoms. Because troponin levels remain elevated for a prolonged period (5 to 14 days) after myocardial necrosis, their usefulness in detecting recurrent myocardial damage is limited.
However, they are helpful in detecting myocardial damage in a patient who presents for assessment several days after the onset of symptoms. Because of the shorter half-life of CK-MB, the levels of this isoenzyme are useful for diagnosing infarct extension (reinfarction) and periprocedural MI.
Point-of-care assays for bedside detection of biomarkers are being developed so that the time delay can be minimized and treatment decisions can be made quickly but the use of such assays is currently limited.

**OTHER LABORATORY TEST**

A chest radiograph is usually obtained at the time of admission so that the patient can be evaluated for other causes of chest pain and screened for Pulmonary congestion which implies an adverse prognosis.

A full lipid profile should be obtained within 24 hours of the onset of ACS, as recommended by the National Cholesterol Education Program Adult Treatment Panel III and by the 2007 ACC/AHA guidelines.

Selected patients should be assessed for secondary causes of ACS also. Thyroid function should be evaluated when a patient presents with symptoms of ACS and has persistent tachycardia.

**DIAGNOSTIC PATHWAYS IN THE ED**

The current ED pathways for assessing and managing patients who may have ACS rely on 4 main diagnostic tools: clinical history, ECG results, levels of cardiac markers and the results of stress testing.

On the basis of the initial information, patients are assigned to one of 4 categories:
• a noncardiac diagnosis,
• chronic stable angina,
• possible ACS or
• definite ACS.

EARLY INVASIVE STRATEGY OR INITIAL CONSERVATIVE STRATEGY

An early invasive strategy involves routine cardiac catheterization generally within 4 to 24 hours after admission, followed by revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) depending on the coronary anatomy.

ANTI-ISCHEMIC THERAPY

A conservative strategy in contrast, consists of initial medical management followed by catheterization and revascularization only if ischemia recurs despite vigorous medical therapy, either when the patient is at rest or during a noninvasive stress test.

NITROGLYCERIN

Nitroglycerin is a vasodilator that reduces myocardial oxygen demand by decreasing ventricular preload via venodilation. It enhances myocardial oxygen delivery by dilating large coronary arteries and improving collateral flow to ischemic areas.

MORPHINE AND OTHER ANALGESICS
Morphine is recommended when ischemia-related symptoms are unrelieved after 3 doses of nitroglycerin or when such symptoms recur during treatment. In such cases, 1 to 5 mg of morphine sulfate can be administered intravenously every 5 to 30 minutes as needed, with careful monitoring of blood pressure and respiratory rate.

Morphine acts as a potent analgesic and anxiolytic. Hemodynamic effects may be beneficial in treating UA/NSTEMI.

**BETA BLOCKERS**

β-Blockers inhibit β-1 adrenergic receptors in the myocardium and decrease myocardial contractility and heart rate, thereby reducing myocardial oxygen demand.

The 2007 ACC/AHA guidelines state that, in the absence of contraindications, therapy with oral β-blockers should be initiated within the first 24 hours after onset of ACS (class I recommendation).

**CALCIUM CHANNEL BLOCKERS**

Calcium channel blockers inhibit the contraction of both the myocardium (thereby reducing myocardial oxygen demand) and vascular smooth muscle (thereby causing coronary vasodilatation and improving myocardial blood flow).

**INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM**
The 2007 ACC/AHA guidelines recommend that, in the absence of hypotension or other known contraindications, an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin II receptor blocker for patients who cannot tolerate ACE inhibitors) should be administered orally within the first 24 hours to patients with pulmonary congestion or an LV ejection fraction of 40% or lower (class I recommendation) and should be considered for administration to patients without these features (class IIa recommendation).

ANTITHROMBOTIC THERAPY

Antithrombotic therapy is the cornerstone of treatment for patients with UA/NSTEMI. It has 2 components:

(1) Antiplatelet therapy reduces platelet activation and aggregation has integral steps in the formation of a thrombus after plaque disruption,

(2) Anticoagulant therapy targets the clotting cascade to prevent the deposition of fibrin strands in the clot.

ANTIPLATELET THERAPY

ASPIRIN.

Aspirin blocks the synthesis of thromboxane A2 by irreversibly inhibiting cyclooxygenase 1, thereby diminishing platelet aggregation.
Four randomized trials have each demonstrated that, compared with placebo, aspirin reduces the risk of death or MI by more than 50% for patients presenting with UA/NSTEMI.

**CLOPIDOGREL**

Clopidogrel is a thienopyridine derivative that blocks the P2Y12 adenosine diphosphate receptor on platelets. This action decreases platelet activation and aggregation, increases bleeding time and reduces blood viscosity.

Therapy with clopidogrel and aspirin is recommended for essentially all patients with UA/NSTEMI.

**NEWER P2Y12 ADP INHIBITORS.**

A high rate of recurrent atherothrombotic events despite the administration of dual-antiplatelet therapy with aspirin and clopidogrel has sparked great interest in finding more potent inhibitors of the P2Y12 ADP receptor.

Prasugrel is an irreversible P2Y12 ADP receptor antagonist that was recently approved by the US Food and Drug Administration.

Ticagrelor (AZD6140) is a reversible oral P2Y12 receptor antagonist with a half-life of approximately 12 hours.
GP IIb/IIIa INHIBITORS.

The platelet GP IIb/IIa inhibitors are potent and specific inhibitors of platelet aggregation. They act by interrupting the final common pathway of fibrinogen-mediated cross-linkage of platelets.

ANTICOAGULANT THERAPY

The 2007 ACC/AHA UA/NSTEMI guidelines recommend the initiation of anticoagulant therapy for all patients (without contraindications) as soon as possible after presentation.

The guidelines recommend 4 agents as options:

- unfractionated heparin (UFH),
- low molecular weight heparin
- enoxaparin,
- fondaparinux, and
- bivalirudin

UNFRACTIONATED HEPARIN.

The ACC/AHA guidelines recommend weight-adjusted dosing of UFH (60 U/kg bolus and 12 U/kg/hr infusion), frequent monitoring of activated partial thromboplastin time (every 6 hours until 2 consecutive values are within the target range,
and every 24 hours thereafter. Administration of UFH should continue for at least 48 hours after presentation with UA/NSTEMI. Complete blood cell counts should be determined at least daily during therapy with UFH. Autoimmune heparin-induced thrombocytopenia in association with thrombosis is a rare but dangerous complication of UFH administration.

**LOW MOLECULAR-WEIGHT HEPARIN.**

Because the rates of recurrence of ischemic events remain high when UFH is administered, low molecular weight heparins (LMWHs) were developed with the goal of providing improved anticoagulation.

They are active against both factor Xa and factor IIa and inhibit the action and generation of thrombin. Their other advantages over UFH include a lower rate of thrombocytopenia, more bioavailability and less binding to plasma proteins, a factor that renders monitoring the level of anticoagulation unnecessary.

**DIRECT THROMBIN INHIBITORS.**

Direct thrombin inhibitors have several potential advantages over indirect thrombin inhibitors (such as UFH or LMWH) as they do not require a cofactor for their action and can directly inhibit clot-bound thrombin; they do not interact with plasma proteins and do not cause thrombocytopenia.

**FACTOR XA INHIBITORS.**
Fondaparinux is a synthetic pentasaccharide that is an indirect factor Xa inhibitor and requires antithrombin for its action.

The 2007 ACC/AHA guidelines contain a class I recommendation for fondaparinux as treatment for patients with UA/NSTEMI who will be managed by either a conservative strategy or an early invasive strategy, unless CABG is planned within 24 hours.

**ORAL ANTICOAGULATION.**

Trials of oral anticoagulation with Warfarin after ACS have demonstrated the benefit of the combination of warfarin plus aspirin over aspirin alone, provided a sufficient degree of anticoagulation was achieved.

**DISCHARGE ANTITHROMBOTIC THERAPY.**

The 2007 ACC/AHA guidelines provide clear recommendations for antithrombotic therapy at the time of discharge; these recommendations are based on the management strategy.

**LIPID-LOWERING THERAPY**

In the absence of contraindications, lipid-lowering therapy with statins should be initiated for all patients with UA/NSTEMI, regardless of baseline LDL cholesterol levels. If the LDL cholesterol concentration is 100 mg/dl (to convert to mmol/L, multiply by 0.0259) or higher, cholesterol-lowering therapy should be initiated or intensified with the goal of achieving an LDL cholesterol concentration lower than 100 mg/dl.
An update to both the Adult Treatment Panel III guidelines and the 2007 ACC/AHA guidelines states that further titration to a dose necessary to sustain an LDL cholesterol concentration of 70 mg/dl or lower is reasonable (class IIa recommendation)

**RISK STRATIFICATION**

The ACC/AHA guidelines state that risk stratification is an integral prerequisite to decision-making. The outcomes of patients with ACS span the entire risk spectrum: data from a global registry indicate that the 30-day mortality rate ranges from 1.7% for patients with UA to 7.4% for patients with NSTEMI to 11.1% for those with STEMI. Early risk stratification is useful for selecting the site of care (coronary care unit or monitored step-down unit), selecting therapy (such as glycoprotein [GP] IIb/IIIa inhibitors and early invasive strategy) and estimating prognosis.

**HIGH-RISK CLINICAL SUBGROUPS**

Certain clinical characteristics are associated with a substantial increase in adverse outcomes for patients with ACS: older age, diabetes (diabetic patients with UA/NSTEMI are at an approximately 50% higher risk of adverse outcomes than nondiabetic patients), extracardiac vascular disease, evidence of congestive heart failure (CHF; Killip class II or higher) and presentation with ACS despite long-term aspirin therapy.

**ELECTROCARDIOGRAPHY**
The admission ECG is a strong predictor of both early and long-term prognosis. In the Thrombolysis in Myocardial Infarction (TIMI) III Registry of patients with UA/NSTEMI, a ST deviation of as little as 0.05 mV increased the risk of death or MI by approximately 2-fold both at 30 days and at 1 year.

TROPONINS AND OTHER MARKERS

Troponin is a powerful instrument for risk stratification across the spectrum of patients presenting with symptoms of acute cardiac ischemia. Even a minor elevation of troponin signifies an adverse prognosis and permits the determination of high-risk patients who will benefit from specific therapies, such as GP IIb/IIIa inhibitors, an early invasive strategy or both. In addition, a quantitative relationship exists between the degree of elevation of troponin levels and the risk of death.

Plasma markers of inflammation as risk predictors for patients with ACS. Of these markers, CRP has been the most extensively studied. Elevated CRP levels detected by a high-sensitivity CRP test relate to an increased risk of mortality.

B-type natriuretic peptide (BNP) provides powerful prognostic information across the entire spectrum of patients with ACS.

A multimarker approach using several biomarkers has been advocated for improving risk stratification and enhancing patient outcomes. One study used a combination of Troponin I, CRP and BNP to assess risk and found that each marker was
an independent predictor of the composite of death, MI or heart failure. Notably, the mortality risk nearly doubled as the number of elevated markers increased.

**ROLE OF LIPOPROTEIN RATIOS IN RISK STRATIFICATION:**

Efforts have been made in seeking emergent or new cardiovascular risk factors to improve cardiovascular disease prediction. However, it must be emphasized that in an attempt to optimize the predictive capacity of the lipid profile, several lipoprotein ratios have been defined.

These ratios can provide information on risk factors difficult to quantify by routine analyses and could be a better mirror of the metabolic and clinical interactions between lipid fractions. The rationale for using these lipoprotein ratios as cardiovascular risk factors in clinical practice, specifying their cut-off risk levels and a target lipid lowering therapy.

**TOTAL CHOLESTEROL/HDL CHOLESTEROL AND LDL/HDL CHOLESTEROL RATIOS**

The total/high-density lipoprotein (HDL) cholesterol ratio, known as the atherogenic or Castelli index and the LDL/HDL cholesterol ratio are two important components and indicators of vascular risk, the predictive value of which is greater than the isolated parameters.
An increase in total cholesterol concentration and specifically LDL cholesterol, is an atherogenic lipid marker, whereas reduced HDL cholesterol concentration is correlated with numerous risk factors, including the components of the metabolic syndrome and probably involves independent risk.

**APOB/APOA-I RATIO**

Apolipoprotein (apo) B represents most of the protein content in LDL and is also present in intermediate-density lipoproteins (IDL) and VLDL. ApoA-I is the principal apolipoprotein in HDL. Both apolipoproteins, therefore, separately provide information for detecting high-risk individuals.

ApoA-I is also believed to be a more reliable parameter for measuring HDL than cholesterol content since it is not subject to variation.

Therefore, the apoB/apoA-I ratio is also highly valuable for detecting atherogenic risk and there is currently sufficient evidence to demonstrate that it is better for estimating vascular risk.

**ATHEROGENIC INDEX OF PLASMA**

Atherogenic index of plasma \([\log (\text{TGL}/\text{HDL-C})]\) (AIP) reflect the size of LDL and HDL subpopulations and closely correlate with each other over a wide range of plasma lipid values.
AIP is a transformation of triglyceride (TGL) / HDL-C that better meets the assumption of normality of the errors in the statistical model being used to describe the treatment effects than does the untransformed variable.

We have identified an inverse relation between the relative plasma HDL a content and FERHDL. This indicates that the cholesteryl ester generating capacity of the HDL pool may be a function of the relative HDL particle size distribution.

*Barter et al* suggest that esterification rates may be independent of HDL cholesteryl ester content and may instead be directly related to HDL particle size. Investigations by *Fielding et al*, however, have suggested that cholesteryl ester may be a feedback inhibitor of LCAT.

The increased FERHDL observed in hyperlipidemic subjects was shown to be associated with a change in particle size distribution of HDL, caused by a reduction in the number of HDL particles and an increase in the number of very small HDL particles. It is unclear whether this increased esterification rate is entirely due to the lack of HDL2, which is capable of inhibiting LCAT or to the presence of a small subset of HDL 3, which is an excellent substrate for LCAT.

Studies by *Barter et al* suggest that a combined effect may have resulted in the elevated esterification rates we have observed. Investigations in their laboratory have shown that HDL2 may be a competitive inhibitor of LCAT and that plasma of hypertriglyceridemic subjects may have an increased content of small HDL3, which have a greater-than-normal reactivity with LCAT.
The consensus of these studies is that the smaller (HDL3) particles are the best substrate for the enzyme and that HDL2 is a competitive inhibitor of this reaction.

While studies have recently shown that small HDLs are preferred LCAT substrates in vitro and that an inverse, linear relation exists between the size of an HDL particle and its ability to interact with LCAT, it is still unclear which factors lead to changes in HDL particle size distribution.

Subjects with the highest FERHDL had practically no HDL a particles. Low levels of HDL2 impaired synthesis or to increased catabolism. Eisenberg has suggested that the interconversion of HDL2 and HDL3 probably requires the coordinated action of LCAT, cholesteryl ester transfer protein, and the triglyceride.

However numerous studies have shown that HDL2 can be generated from HDL3 and can also be converted back to HDL, the factors that regulate their interconversions and determine the level of HDL2, relative to HDL3 remain unclear. Some studies have suggested the HDL2 levels may be directly affected by the duration and magnitude of triglyceridemia.

HDL2 levels have been shown to be strongly correlated with the activity of lipoprotein lipase and inversely related to the activity of hepatic lipase.

Therefore, since we have observed that elevated triglyceride levels are associated with a decrease in HDL2 cholesterol levels and with an increase in the rate of cholesterol esterification in HDL, it seems possible that the low HDL2 levels observed in hypertriglyceridemia may be partially due to an increased transfer of cholesteryl esters from the HDL pool to lower-density lipoproteins. This is, in fact, what we have observed
in other investigations in which hyperlipidemic patients had impaired equilibration of cholesteryl esters within their HDL pool, resulting in their increased transfer to apo B-containing lipoproteins.

It is of interest that low levels of HDL2 cholesterol have also been associated with the increased ratio of waist-to-hip circumference, plasma insulin levels, and glucose intolerance.

These findings agree with our observations of increased FER values in patients with an increased number of risk factors for CAD.

This study suggests that the FERHDL value may reflect the capacity of the HDL pool to synthesize cholesteryl esters and that this may be related to the ratio of HDL2 to HDL3. Thus, the determination of FERHDL may have important diagnostic merit since the low ratio of HDL2 to HDL3 appears to be the best indicator of the presence of coronary atherosclerosis.

The Atherogenic Index of Plasma been successfully used as an additional index when assessing cardiovascular (CV) risk factors.

Indeed, it has been suggested that AIP values of −0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high CV risk, researchers have shown that the logarithmically transformed TGL/HDL-C ratio is the best determinant for (FERHDL) and thus a better predictor of cardiovascular risk than other previously used lipid parameters. Furthermore, in situations where other atherogenic risk parameters appear normal, AIP may be the diagnostic alternative.
This concludes that Atherogenic Index of Plasma was an index of highest sensitivity for predicting the acute coronary events and combined with the fact that it is available and easy to calculate candidates it as a better screening tool for evaluating the cardiac risk and therefore it is recommended that

1- AIP is recommended to be used as a predictor of CHD.

2- It should be used as a monitoring index for any lipid lowering intervention.

3- Further studies required to improve these results in a larger sample size and correlating AIP with angiographically proven CHD.
MATERIALS AND METHODS
MATERIALS AND METHODS

PLACE OF STUDY

Study was conducted in the Department of Cardiology and Department of Medicine, Government Rajaji Hospital and Department of Biochemistry, Madurai Medical College, Madurai in co-ordination with the Institute of Physiology, Madurai Medical College, Madurai for a period of one year.

ETHICAL COMMITTEE

Approval obtained from the ethical committee of Government Rajaji Hospital, Madurai.

STUDY DESIGN

Observational case control study

SAMPLE SIZE

Total subjects - 100

Study population - 50

Controls - 50

STUDY POPULATION

Male Patients admitted in Medicine or Cardiology ward following first episode of acute coronary syndrome.
INCLUSION CRITERIA:

1. Age between 45 – 60 years

2. Serum lipid profile within normal limits.
   
   Total Cholesterol < 200 mg/dl
   
   Triglyceride < 150 mg/dl
   
   LDL Cholesterol < 130 mg/dl
   
   HDL Cholesterol > 27 - 60 mg/dl

EXCLUSION CRITERIA:

1. Previous history of Coronary Artery Disease.

2. On long term lipid altering drugs like
   
   • Hypolipidemic drugs
   
   • Steroids
   
   • Immunosuppressants
   
   • Antiretroviral drugs etc.

3. H/o systemic diseases like
   
   • Hypertension
- Diabetes mellitus
- Thyroid disorders and other endocrine abnormalities
- Liver disease
- Renal disease
- Dyslipidemia
- Peripheral vascular diseases
- Cardiovascular events other than ACS etc.

4. Nicotine dependence or alcohol use disorder.

5. Family history of CAD

CONTROL GROUP

Apparently healthy age matched male volunteers attending Master health check up or Medicine OPD.

MATERIALS USED FOR STUDY

1. Proforma – to record the anthropometric measurements and the clinical findings of the subjects.

2. Portable weighing machine – to record the body weight in kilograms.

3. Inch tape – to measure the standing height in centimeters.

4. Standardized mercury sphygmomanometer – to record the Blood Pressure in mmHg.
METHODOLOGY:

The study was initiated after obtaining permission from Department of Cardiology and Department of Medicine, Government Rajaji Hospital, Madurai.

Hemodynamically stable patients on day 2 of admission following Acute Coronary Syndrome confirmed by ECG changes or elevated cardiac biomarkers or both and treated was selected.

After getting informed written consent, detailed history was taken. General and Systemic examination was done. Blood sample was collected following fasting.

For control group male persons attending Master health checkup or Medicine OPD were selected according to inclusion and exclusion criteria. Lipid profile was done and those people with normal values were taken as control group.

The experimental protocol includes

1) RECORDING OF A DETAILED HISTORY including history of present illness

- Nature of chest pain
- Duration
- Site
- Any radiation
- Aggravated by exertion
- Difficulty in breathing
• Palpitations
• Giddiness
• Loss of consciousness

HISTORY OF PAST ILLNESS

1. H/o similar episodes before
2. On long term lipid altering drugs
3. H/o systemic diseases like
   • Hypertension
   • Diabetes mellitus
   • Thyroid disorders and other endocrine abnormalities
   • Liver disease
   • Renal disease
   • Dyslipidemia
   • Peripheral vascular diseases
   • Cardiovascular events other than ACS etc.

Nicotine dependence or alcohol use disorder, Family history of CAD etc.

2. MEASUREMENT OF ANTHROPOMETRIC INDICES:

The subjects were asked to stand erect with their arms relaxed at their side
and feet together.

The following were measured:

- **Weight** (in kilograms) was recorded using a portable standard weighing machine.
- **Height** (in centimeters) was measured to the nearest 0.5 cm using an inch tape.
- **Body Mass Index (BMI)** was calculated using Quetelet Index.

\[
\text{BMI} = \text{Weight (Kg)/ Height (m}^2)\.
\]

3. **RECORDING OF VITAL SIGNS** viz. pulse rate, respiratory rate and measurement of blood pressure were done and documented.

4. **GENERAL EXAMINATION** was done to elicit Pallor, Cyanosis, Icterus, Clubbing, Pedal edema, Jugular venous pulse.

3. **EXAMINATION OF CARDIOVASCULAR SYSTEM** was done to assess the health of the subject.

4. **BLOOD INVESTIGATIONS:**

   Fasting blood samples were collected in the morning between 7 a.m. and 8 am by venopuncture with all aseptic precautions, using a dry disposable syringe under sterile conditions in a sterile plain vial. Serum was separated by centrifugation at 3000 rpm for 15 minutes and is used for estimation of lipid profile.

**Serum lipid profile** includes

- Total Cholesterol
- Triglyceride
• LDL Cholesterol
• HDL Cholesterol
• VLDL Cholesterol

ESTIMATION OF SERUM LIPID PROFILE:

TRIGLYCERIDE:

METHOD:

Enzymatic calorimetric quantification of triglyceride was done using GPO-PAP method.

PRINCIPLE:

In enzymatic calorimetric method, Triglycerides are hydrolysed to release glycerol by use of lipase. Glycerol is converted to coloured complex and absorbance of colored complex is proportionate to triglyceride concentration.

\[
\begin{align*}
\text{Triglyceride} + 3\text{H}_2\text{O} & \xrightarrow{\text{lipoprotein lipase}} \text{Glycerol} + 3 \text{R – COOH} \\
\text{Glycerol} + \text{ATP} & \xrightarrow{\text{Glycerokinase}} \text{Glycerol 3 phosphate} + \text{ADP} \\
\text{Glycerol 3 phosphate} + \text{O}_2 & \xrightarrow{\text{GPO}} \text{Dihydroxyacetone} + \text{phosphate} + \text{H}_2\text{O}_2 \\
\text{H}_2\text{O}_2 + 4 – \text{amino phenazone} + 4- \text{chlorophenol} & \xrightarrow{\text{POD}} 2\text{H}_2\text{O} + \text{HCl} + \text{dye}
\end{align*}
\]

GPO – Glycerol phosphate oxidase
POD - Peroxidase

PROCEDURE:

- 10µL of sample and 10µL of control were pipetted into the cuvette.
- For blank 10µL of distilled water was taken in cuvette.
- All 3 cuvette marked blank, standard and sample were made added with 1000µL of working reagent.

ASSAY:

<table>
<thead>
<tr>
<th></th>
<th>Blank</th>
<th>Standard</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>S</td>
<td>T</td>
</tr>
<tr>
<td>Distilled water</td>
<td>10µL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Standard</td>
<td>-</td>
<td>10µL</td>
<td>-</td>
</tr>
<tr>
<td>Sample</td>
<td>-</td>
<td>-</td>
<td>10µL</td>
</tr>
<tr>
<td>Working reagent</td>
<td>1000µL</td>
<td>1000µL</td>
<td>1000µL</td>
</tr>
</tbody>
</table>

Here working reagent is a liquid mono reagent which has the following constituents.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPES [Piperazine-1.4-bis (2-ethane-sulfonic acid)]</td>
<td>50.0 mmol/L</td>
</tr>
<tr>
<td>EDTA</td>
<td>0.13 mmol/L</td>
</tr>
<tr>
<td>ATP (Adenosine-tri-phosphate)</td>
<td>1.65 mmol/L</td>
</tr>
<tr>
<td>Magnesium ions</td>
<td>0.5 mmol/L</td>
</tr>
<tr>
<td>4-Aminophenazone</td>
<td>0.6 mmol/L</td>
</tr>
<tr>
<td>4-Chlorophenol 1.55 mmol/L</td>
<td></td>
</tr>
<tr>
<td>GPO (Glycerophosphate-Oxidase) ≥ 2.5 KU/L</td>
<td></td>
</tr>
<tr>
<td>Glycerokinase ≥ 1.0 KU/L</td>
<td></td>
</tr>
<tr>
<td>POD (Peroxidase)</td>
<td>≥ 5.0 KU/L</td>
</tr>
<tr>
<td>LPL (Lipoprotein lipase)</td>
<td>≥ 2.0 KU/L</td>
</tr>
<tr>
<td>Detergent, Stabilizer, preservative</td>
<td></td>
</tr>
</tbody>
</table>

After mixing the working reagent with blank, sample and standard, they were incubated for 5 minutes at 37°C. The reaction was taken as end point and the absorbance (A) were read using spectrophotometer.

**CALCULATION:**

**Concentration of triglyceride is calculated using the formula**

\[
\text{Concentration of Triglycerides (mg/dl)} = \frac{A_{\text{sample}} \times \text{Concentration Calculated/Standard}}{A_{\text{standard}}}
\]

**Linearity** up to 1000 mg/dl.
If the result exceeds 1000 mg/dl, repeat the test using diluted serum (1+4) with 0.9 % sodium chloride solution and multiply the result by 5.

**REFERENCE VALUE:**

<table>
<thead>
<tr>
<th>Value in mg/dl</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>Normal</td>
</tr>
<tr>
<td>151 – 199</td>
<td>Borderline high</td>
</tr>
<tr>
<td>&gt;200</td>
<td>High</td>
</tr>
</tbody>
</table>

**ESTIMATION OF TOTAL CHOLESTEROL:**

**METHOD:**

Enzymatic calorimetric quantification of total cholesterol was done using CHOD – POD method (cholesterol oxidase and peroxidase method).

**PRINCIPLE:**

Esterified cholesterol were hydrolysed by cholesterol esterase to free cholesterol. The free cholesterol is oxidised to form hydrogen peroxide. This further reacts with phenol and 4-aminoantipyrine to form a red coloured quinoneimine dye complex. Intensity of the colour formed is directly proportional to the amount of cholesterol present in the sample.

\[
\text{Cholesterol esters} + \text{H}_2\text{O} \xrightarrow{\text{cholesterol esterase}} \text{Cholesterol} + \text{Fatty Acids}
\]

\[
\text{Cholesterol} + \text{O}_2 \xrightarrow{\text{Cholesterol Oxidase}} \text{Cholestenone} + \text{H}_2\text{O}_2
\]

\[
\text{H}_2\text{O}_2 + 4 \text{Aminoantipyrine} + \text{phenol} \xrightarrow{\text{Peroxidase}} \text{Red Quinoneimine Dye} + \text{H}_2\text{O}
\]
PROCEDURE:

- 1 ml of working reagent was taken in three tubes named blank (B), standard (S) and test (T).
- Distilled water of 0.01 ml was added to blank test tube. For standard 0.01 ml of standard solution and for test 0.01 ml of sample were added.
- After mixing they were incubated for 5 minutes at 37°C. The reaction was taken as end point and the absorbance (A) were read using spectrophotometer

ASSAY:

<table>
<thead>
<tr>
<th></th>
<th>Blank B</th>
<th>Standard S</th>
<th>Sample T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working reagent</td>
<td>1 ml</td>
<td>1 ml</td>
<td>1 ml</td>
</tr>
<tr>
<td>Distilled water</td>
<td>0.01 ml</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Standard</td>
<td>-</td>
<td>0.01 ml</td>
<td>-</td>
</tr>
<tr>
<td>Sample</td>
<td>-</td>
<td>- 0.01 ml</td>
<td>0.01 ml</td>
</tr>
</tbody>
</table>

COMPOSITION OF WORKING REAGENT:
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol esterase</td>
<td>&gt;100 U/L</td>
</tr>
<tr>
<td>Cholesterol oxidase</td>
<td>&gt;100 U/L</td>
</tr>
<tr>
<td>Peroxidase</td>
<td>&gt;1000 U/L</td>
</tr>
<tr>
<td>4 amino antipyrine</td>
<td>0.3 mM</td>
</tr>
<tr>
<td>Phenol</td>
<td>4 mM</td>
</tr>
</tbody>
</table>

**CALCULATION:**

Concentration of Cholesterol is calculated using the formula

\[
\text{Cholesterol in mg/dl} = \frac{\text{Absorbance T}}{\text{Absorbance S}} \times \text{Concentration of standard in mg/dl}
\]

**REFERENCE VALUE:**

<table>
<thead>
<tr>
<th>Value in mg/dl</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>Normal</td>
</tr>
<tr>
<td>200–239</td>
<td>Borderline high</td>
</tr>
<tr>
<td>240 and above</td>
<td>High</td>
</tr>
</tbody>
</table>

**ESTIMATION OF HIGH DENSITY LIPOPROTEIN – CHOLESTEROL**
(HDL –C):

METHOD:

Quantification of High Density Lipoprotein Cholesterol was done using Immunoinhibition method.

PRINCIPLE:

It involves two steps

1. Antihuman B lipoprotein antibodies were made to bind lipoproteins other than HDL such as LDL, VLDL and Chylomicrons.

2. HDL cholesterol were hydrolysed and oxidised to form hydrogen peroxide which inturn reacts with 4-aminoantipyrine to form a blue coloured complex.

Intensity of the colour formed is directly proportional to the amount of HDL cholesterol present in the sample.

HDL Cholesterol esters + H₂O $\xrightarrow{\text{cholesterol esterase}}$ cholesterol + Fatty Acids

HDL Cholesterol + O₂ $\xrightarrow{\text{Cholesterol Oxidase}}$ Cholestenone + H₂O₂

H₂O₂ + 4 Amino antipyrine + fluroaniline $\xrightarrow{\text{peroxidase}}$ blue color complex + H₂O

PROCEDURE:

➢ 300 µl of working reagent 1 was taken in three tubes named blank (B), standard (S) and test (T).
Distilled water of 4µl was added to blank test tube. For standard 4µl of standard solution and for test 4µl of sample were added.

After mixing they were incubated for 5 minutes at 37°C, 100µl of working reagent 2 was added.

The reaction was taken as end point and the absorbance (A) were read using spectrophotometer

**ASSAY:**

<table>
<thead>
<tr>
<th></th>
<th>Blank (B)</th>
<th>Standard (S)</th>
<th>Sample (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working reagent 1</td>
<td>300µl</td>
<td>300µl</td>
<td>300µl</td>
</tr>
<tr>
<td>Distilled water</td>
<td>4µl</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Standard</td>
<td>-</td>
<td>4µl</td>
<td>-</td>
</tr>
<tr>
<td>Sample</td>
<td>-</td>
<td>-</td>
<td>4µl</td>
</tr>
</tbody>
</table>
Composition of working reagent 1:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxidase (Horseradish)</td>
<td>2400 U/L</td>
</tr>
<tr>
<td>4-aminoantipyrine</td>
<td>0.9 mM</td>
</tr>
<tr>
<td>Anti human (b)-lipoprotein antibody(sheep)</td>
<td></td>
</tr>
</tbody>
</table>

Composition of working reagent:
Cholesterol oxidase (Nocardia) | 20,000 U/L
---|---
Cholesterol esterase (Psuedomonas) | 4,000 U/L
(N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3- 5-dimethoxy-4-fluoraniline FDAOS | 0.8 Mm

**CALCULATION:**

*Concentration of Cholesterol is calculated using the formula*

\[
\text{HDL Cholesterol in mg/dl} = \frac{\text{Absorbance} \cdot T}{\text{Absorbance S}} \times \text{Concentration of standard in mg/dl}
\]

**REFERENCE VALUE:**

<table>
<thead>
<tr>
<th>Value in mg/dl</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 – 60</td>
<td>Normal</td>
</tr>
</tbody>
</table>
CALCULATION OF LOW DENSITY LIPOPROTEIN – CHOLESTEROL & VERY LOW DENSITY LIPOPROTEIN – CHOLESTEROL:

LDL and VLDL values were calculated using Friedewald’s formula as their estimation is onerous.

\[
\text{LDL} = \text{TC} - \text{HDL} - (\text{TGL} / 5)
\]

\[
\text{VLDL} = \text{TGL} / 5
\]

Here TC – Total Cholesterol

HDL - High Density Lipoprotein and TGL – Triglyceride.

<table>
<thead>
<tr>
<th></th>
<th>Desirable Values in mg/dl</th>
<th>High Risk values in mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride</td>
<td>&lt;150</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>&lt;200</td>
<td>&gt;240</td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>40 – 60</td>
<td>35 - 45</td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>60 – 130</td>
<td>&gt;160</td>
</tr>
</tbody>
</table>

After obtaining the values of lipid profile,

Atherogenic Index of Plasma (AIP) was calculated using the formula below after converting

TG and HDL – C values to mmol / lit.
**AIP** = Log \((\text{TG} / \text{HDL} - C)\) expressed in mmol / lit.

Risk of the patient towards developing Acute Coronary syndrome (ACS) can be graded depending upon the value of Atherogenic Index of Plasma (AIP).

<table>
<thead>
<tr>
<th>Value of Atherogenic Index of Plasma (AIP)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.3 - 0.10</td>
<td>Low risk</td>
</tr>
<tr>
<td>0.11 – 0.21</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>&gt; 0.21</td>
<td>Increased risk</td>
</tr>
</tbody>
</table>

Other lipid ratios can also be calculated using the formula.

- Total cholesterol / High Density Lipoprotein ratio.
  Ratio more than 4 is considered high risk.

- Low Density Lipoprotein / High Density Lipoprotein ratio.

<table>
<thead>
<tr>
<th>Value of LDL / HDL ratio</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.3</td>
<td>Low risk</td>
</tr>
<tr>
<td>3.3 - 3.7</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>&gt;3.7</td>
<td>Increased risk</td>
</tr>
</tbody>
</table>
RESULTS AND OBSERVATION
RESULTS AND OBSERVATION

The association of Atherogenic Index of Plasma (AIP) in incidence of Acute coronary syndrome was analysed using Chi-Square test and student t test.

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) software version 16. The statistical significance was made at ‘p’ value < 0.05.

1. AGE DISTRIBUTION
## 1. AGE DISTRIBUTION

<table>
<thead>
<tr>
<th>AGE in years</th>
<th>CASE</th>
<th>CONTROL</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 – 45</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>46 – 55</td>
<td>32</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>56 – 60</td>
<td>15</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Mean ± SD

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 ± 3.86</td>
<td>45</td>
<td>47 ± 3.21</td>
</tr>
</tbody>
</table>

p value

| p value | 0.75 |
Table – 1 showing age distribution among cases and controls

Analysis of data using chi square test is not significant.

2. BODY MASS INDEX
2. **BODY MASS INDEX**

<table>
<thead>
<tr>
<th>BMI</th>
<th>CASE</th>
<th>CONTROL</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>in Kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing BMI distribution](attachment:image.png)
Table – 2   showing BMI of study and control groups

Mean BMI for developing Acute coronary syndrome is 26.36.

3. MEAN VALUE OF LIPID PROFILE
### 3. MEAN VALUE OF LIPID PROFILE

<table>
<thead>
<tr>
<th>Lipid profile (mg/dl)</th>
<th>Cases</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>186.58</td>
<td>13.98</td>
<td>168.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>128.96</td>
<td>12.19</td>
<td>107.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>41.27</td>
<td>4.62</td>
<td>50.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>119.1</td>
<td>14.05</td>
<td>83.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Low Density Lipoprotein</td>
<td>119.8</td>
<td>8.99</td>
<td>92.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table - 3 showing mean value of Lipid profile
When comparing the Lipid profile level between cases and controls it was found that there was a significant increase in the Triglyceride, Total Cholesterol, Low Density Lipoprotein cholesterol (LDL), Very Low Density Lipoprotein cholesterol (VLDL) and decrease in High Density Lipoprotein cholesterol (HDL) value in the study group than in the control group.

Results analysed using student t test disclosed a statistically significant ‘p’ value.
4. MEAN VALUES OF ATHEROGENIC INDEX OF PLASMA
### 4. MEAN VALUES OF ATEROGENIC INDEX OF PLASMA

<table>
<thead>
<tr>
<th>AIP (mmol/ l)</th>
<th>Cases</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>&lt; - 0.3 (no risk)</td>
<td>- 0.4</td>
<td>0.04</td>
<td>- 0.43</td>
</tr>
<tr>
<td>- 0.3 to 0.10 (low risk)</td>
<td>0.9</td>
<td>0.08</td>
<td>0.079</td>
</tr>
<tr>
<td>0.11 to 0.21 (intermediate risk)</td>
<td>0.18</td>
<td>0.005</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;0.21 (high risk)</td>
<td>0.23</td>
<td>0.04</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Table - 4 showing mean value of Atherogenic Index of Plasma

When comparing the Atherogenic Index of Plasma between cases and controls using student t test, it showed a statistically **significant ‘p’ value.**
5. LIPID RATIOS

<table>
<thead>
<tr>
<th></th>
<th>CASES</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>0.39</td>
<td>0.09</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>4.48</td>
<td>3.8</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>2.93</td>
<td>1.9</td>
</tr>
</tbody>
</table>
5. LIPID RATIOS

<table>
<thead>
<tr>
<th>Lipid ratios</th>
<th>Case</th>
<th>Control</th>
<th>p  value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>0.39 ± 0.03</td>
<td>0.09 ± 0.02</td>
<td>0.018 Significant</td>
</tr>
<tr>
<td>TC / HDL</td>
<td>4.48 ± 0.36</td>
<td>3.80 ± 0.5</td>
<td>0.038 Significant</td>
</tr>
<tr>
<td>LDL / HDL</td>
<td>2.93 ± 0.51</td>
<td>1.90 ± 0.31</td>
<td>0.028 Significant</td>
</tr>
</tbody>
</table>

Table – 5 showing the Lipid ratios among study and control groups.

When comparing the Lipid ratios between controls and study population it was found that there was a remarkable increase in the lipid ratios among people of study group.

Results analysed using student t test disclosed a statistically significant ‘p’ value.
6. AIP DISTRIBUTION

[Bar chart showing the distribution of AIP in cases and controls across different AIP ranges: < - 0.3, 0.3 to 0.10, 0.10 to 0.20, >0.21.]
6. AIP DISTRIBUTION

AIP STATUS AMONG STUDY GROUP AND CONTROL GROUP

<table>
<thead>
<tr>
<th>AIP</th>
<th>CASE</th>
<th>CONTROL</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; - 0.3</td>
<td>6</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>-0.3 to 0.10</td>
<td>5</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>0.10 to 0.20</td>
<td>17</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>&gt;0.21</td>
<td>22</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>TOTAL</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Chi square : 14.26  
P value : 0.00257  
Significant

Table – 6 showing AIP status among study group and control group.

When comparing the AIP between controls and study population it was found that people with raised AIP are associated with acute coronary syndrome.
7. AIP ANALYSIS

![Bar chart showing the number of persons in AIP cases and controls.

AIP: AIP (Anatomically Interpretable Pedigree) values.

- Cases: Blue bars
- Control: Orange bars

Bar heights indicate the number of persons, with > - 0.3 on the x-axis and < - 0.3 on the x-axis.
7. AIP ANALYSIS

ODD’S RATIO: STRENGTH OF ASSOCIATION BETWEEN AIP AND ACUTE CORONARY SYNDROME.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Control</th>
<th>Total</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP &gt; -0.3</td>
<td>38</td>
<td>10</td>
<td>48</td>
<td>Odds ratio is 17.87 (CI 95% 2.7 – 116.88)</td>
</tr>
<tr>
<td>AIP &lt; -0.3</td>
<td>12</td>
<td>40</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Table – 7 showing strength of association between AIP and acute coronary syndrome
8. DISTRIBUTION OF PARAMETERS AMONG STUDY AND CONTROL GROUP

![Graph showing distribution of parameters among study and control group.](image-url)
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CASE</th>
<th>CONTROL</th>
<th>p  Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>54 ± 6</td>
<td>53 ± 2</td>
<td>0.955</td>
</tr>
<tr>
<td>BMI</td>
<td>26.36 ± 0.65</td>
<td>24.80 ± 0.47</td>
<td>0.010</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>186.58 ± 13.98</td>
<td>168.44 ± 12.16</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>128.96 ± 12.19</td>
<td>107.84 ± 11.51</td>
<td>0.003</td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>41.27 ± 4.62</td>
<td>50.51 ± 6.78</td>
<td>0.002</td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>119.1 ± 14.05</td>
<td>83.59 ± 11.98</td>
<td>0.003</td>
</tr>
<tr>
<td>Very Low Density Lipoprotein</td>
<td>119.8 ± 8.99</td>
<td>92.3 ± 6.67</td>
<td>0.004</td>
</tr>
<tr>
<td>AIP</td>
<td>0.39 ± 0.03</td>
<td>0.09 ± 0.02</td>
<td>0.018</td>
</tr>
<tr>
<td>TC / HDL</td>
<td>4.48 ± 0.36</td>
<td>3.80 ± 0.5</td>
<td>0.038</td>
</tr>
<tr>
<td>LDL / HDL</td>
<td>2.93 ± 0.51</td>
<td>1.90 ± 0.31</td>
<td>0.028</td>
</tr>
</tbody>
</table>
DISCUSSION
DISCUSSION

Coronary atherosclerosis is the major cause of Acute coronary syndrome, which is the chief single cause of death both in developed and developing countries Dr. Ganesh D Ghuge 2012. Early diagnosis of coronary atherosclerosis can reduce the mortality and morbidity. As a search of the risk factor responsible for the Coronary artery disease goes on, many ratio of the lipid have been described as better predictor of CAD.

Result of Lipid Research Clinics prevalence study showed that the ratio of Total cholesterol and HDL was better predictor of CAD.

Tan et al found Atherogenic Index of Plasma (AIP), to be a suitable and statistically reliable ratio for evaluating the atherogenicity.

The parameter of log (TGL/HDL) as an atherogenic index has correlation with lipoprotein particle size and esterification rate in apo B lipoprotein depleted plasma (FER HDL) Dobiaova M Frohlich 2001.

There is a high significant association between FER HDL and AIP which reflects the delicate metabolic interaction within the whole lipoprotein complex Frohlich 2008.

In this study we have analysed the association of Atherogenic Index of Plasma (AIP) with Incidence of Acute Coronary Syndrome (ACS). We have chosen 100 people, among them 50 constitutes the study group who are all
diagnosed and stabilised patients of Atherogenic Index of Plasma (AIP). Other 50 constitutes the control group who are all age matched apparently normal people attending Master health checkup. Most confounding factors were excluded and values obtained were analysed.

AGE:

Men aged between 35 and 60 years were included. The mean age of study group and control group is 45 ± 3.86 and 47 ± 3.21 respectively. This difference does not show any statistical significance. American Heart Association studies reveal that the mean age for developing Heart disease is 52.73 Austin Ma et al.

BODY MASS INDEX:

In our study, Mean BMI for developing Acute coronary syndrome is 26.36. Third joint task force of European Society of Cardiology Committee for Practice Guidelines and other societies on cardiovascular disease prevention in clinical practice on cardiovascular disease prevention identified Mean BMI for developing Acute coronary syndrome as 27. The incidence of CAD correlates positively with increasing BMI Rauchová H et al.

LIPID PROFILE:

National Institute of Health consensus conference concluded the causal relationship of elevated lipid profile values with cardiovascular disease Reaven GM 1993.
Lipid profile includes estimation of triglyceride, total cholesterol, High Density Lipoprotein (HDL), Very Low Density Lipoprotein (VLDL) and Low Density Lipoprotein (LDL) (Lina Badimon et al 2012). Mean value of Total Cholesterol level among study and control group are 186.58 and 168.44 respectively. It was found that there exists a statistically significant difference with a p value of 0.002 in relation to the mean values of Total Cholesterol i.e., study group has elevated total cholesterol level when compared to control group.

Mean value of Triglyceride level among study and control group are 128.96 and 107.94 respectively. Statistically significant difference with a p value of 0.003 exists in relation to the mean values of Triglyceride i.e., study group has elevated Triglyceride level when compared to control group.

Similarly the mean values of HDL, LDL, VLDL among study and control group are 41.27, 119.1, 119.8 and 50.51, 83.59, 92.3 respectively.

The mean values of HDL, LDL and VLDL exhibits Statistical significance with p value of 0.002, 0.003 and 0.004 i.e, HDL is low among study group whereas LDL and VLDL are high among study group compared to control group.

European Heart Journal states, Atherosclerosis is a diffuse pathological process driven by cholesterol accumulation, aided by high LDL and low HDL.

ATHEROGENIC INDEX OF PLASMA:
Atherogenic Index of Plasma, according to Grover et al, is the index of atherogenicity and is the major predictor of future cardiovascular events. When comparing the AIP between controls and study population using chi square test, the p value of 0.002 remains significant. It was found that people with raised AIP are associated with acute coronary syndrome. The calculated odd’s ratio was 17.87 i.e., patients with raised AIP value may have 17 times more risk of developing Acute Coronary Syndrome, than persons with low AIP value.

LIPID RATIOS:

The analysis based on the lipid ratios total cholesterol to HDL and LDL to HDL shows higher the value of ratios, higher the incidence of Acute Myocardial Infarction William et al 2003.

When comparing the Lipid ratios between controls and study population it was found that there was a remarkable increase in the lipid ratios among people of study group. The mean value of Total cholesterol to HDL ratio is 4.48 and 3.80 among study and control group with a significant p value of 0.038 and the mean value of LDL to HDL ratio is 2.93 and 1.90 among study and control group with a significant p value of 0.028.

There are several biochemical ratios indicating the risk of atherosclerosis. Gaziano et al reported that the ratio of triglyceride to HDL was a strong predictor of MI. As the search for the risk factor responsible for the CAD goes on, many ratio of the lipid such as
Total Cholesterol / HDL, LDL / HDLC and HDLC2 / HDLC3 have been described as better predictor of CAD.

Result of the Lipid Research Clinics Prevalence Study showed that the ratio of Total Cholesterol / HDL was better predictor of CAD. Tan et al found AIP to be a suitable and statically reliable for evaluating the atherogenicity index. Although an independent, inverse relationship between HDL and cardiovascular risk has been demonstrated Austin et al. TGL has also been proposed to be a major determinant of cholesterol esterification, transfer and HDL remodelling in human plasma.

Fraction etherification rate of cholesterol and ratio of TGL / HDL are powerful predictor of positive finding on coronary angiography Dobiosova et al.

The plasma parameter of log (TGL / HDL) as an atherogenic index has correlation with lipoprotein particle size and esterification rate in apo B lipoprotein depleted plasma (FER HDL) Enugu et al.

There is a high significant association between FER HDL and AIP suggesting that AIP reflects the delicate metabolic interaction within the whole lipoprotein complex AIP provides information about the atherogenicity of plasma Bittner et al. Application of AIP to data from earlier trials may offer new insights Humphries Se et al.

**AIP DISTRIBUTION AND AIP ANALYSIS:**

When comparing the AIP between controls and study population using chi square test, the p value of 0.002 remains significant, It was found that people with raised AIP are associated with acute coronary syndrome.
The calculated **odds ratio** was **17.87** i.e., patients with raised AIP value may have 17 times more risk of developing Acute Coronary Syndrome, than persons with low AIP value. Although imprecision in TG measurements, within-individual variability, and complex interactions between TG and lipoprotein levels may obscure the impact of TGL in the development of CHD, data indicate that elevated fasting TGL represent a useful marker for risk of CHD, particularly when HDL levels are considered. The strong association of the ratio of TGL /HDL with risk of CHD suggests a metabolic interaction between the TGL and cholesterol ester rich lipoproteins in increasing risk of MI.
CONCLUSION

Present study shows patients of Acute Coronary Syndrome (ACS) even with normal serum lipid profile has higher values of Atherogenic Index of Plasma (AIP) than healthy volunteers. Thus raised AIP is associated with atherosclerosis thereby associated with cardiovascular risk.

Risk factors for cardiovascular disease were rotten to the core, that Acute Coronary Syndrome remains the leading cause of death worldwide

Thus a sound cardiovascular risk assessment and constitutive preventive therapeutics alone can offer secondary prevention, cutback morbidity and downturn mortality.

Atherogenic Index of Plasma (AIP), a better mirror of metabolic interaction between lipoproteins, predicts individuals at higher risk of cardiovascular disease especially in clinical practices, when the absolute values of lipid profile seem normal or not markedly dearranged or in centres with insufficient resources. Therefore AIP can be advocated for

1. Inclusion in routine lipid profile
2. Application as a monitoring index for any lipid lowering intervention.
3. Classification of patients and to direct needful therapy.

Thus Atherogenic Index of Plasma (AIP) can be readily calculated from routine lipid profile and can be effectively used for disease prevention.
LIMITATIONS:

Further studies can be planned

- With large sample size.
- With the investigation of the valuable outcome following management. This can be achieved by observing them for a long period.
BIBLIOGRAPHY
BIBLIOGRAPHY


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30. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt Np, Rieder Mj, Cooper Gm, Roos C, Voight Bf, Havulinna As, Wahlstrand B, Hedner T, Corella D, Tai Es, Ordovas Jm.


PROFORMA
PROFORMA

Name :                     Age :

Occupation :             Date of Admission :

Address:

H/o presenting complaints :

H/o chest pain –
duration - site - any radiation- aggravated by exertion-

H/o difficulty in breathing, palpitations, giddiness

H/o loss of consciousness

Past history:

H/o similar episodes before

H/o Hypertension, Diabetes mellitus, Thyroid disorders, Liver disease, Renal disease

H/o intake of drugs such as steroids, lipid altering drugs, retinoids, immunosuppressants, antiretroviral drugs, aspirin.

Personal history:

Dietary habits

H/o smoking and alcohol intake if yes

Quantity :              No. of years :

Family history:

H/o Coronary artery disease, hypercholesteremia

General Examination:

Conscious        Oriented          Pallor

Cyanosis         Icterus           Clubbing
Pedal edema

Pulse: rate / minute : rhythm: volume:

Respiratory rate / minute : Temperature in F:

Blood pressure in mmHg:

Jugular venous pulse:

**Anthropometric measurements:**

Height (cm): Weight (kg): BMI (kg/m²):

Waist circumference (cm): Hip circumference (cm):

Waist Hip ratio:

**Systemic Examination:**

Cardiovascular system:

Respiratory system:

Abdomen:

**Investigations:**

Serum Creatine kinase - MB

Lipid profile

  Total Cholesterol in mg/dl :
  Triglyceride in mg/dl :
  LDL Cholesterol in mg/dl :
  HDL Cholesterol in mg/dl :
  VLDL Cholesterol in mg/dl

Electrocardiograph
ABBREVIATION
<table>
<thead>
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<th>Sl.No.</th>
<th>ABBREVIATION</th>
<th>EXPANSION</th>
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<tr>
<td>1.</td>
<td>AIP</td>
<td>Atherogenic Index of Plasma</td>
</tr>
<tr>
<td>2.</td>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>3.</td>
<td>NSTEMI</td>
<td>Non ST wave Elevated Myocardial Infarction</td>
</tr>
<tr>
<td>4.</td>
<td>STEMI</td>
<td>ST wave Elevated Myocardial Infarction</td>
</tr>
<tr>
<td>5.</td>
<td>ACS</td>
<td>Acute Coronary Syndrome</td>
</tr>
<tr>
<td>6.</td>
<td>TC</td>
<td>Total Cholesterol</td>
</tr>
<tr>
<td>7.</td>
<td>TGL</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>8.</td>
<td>LDL - C</td>
<td>Low Density Lipoprotein Cholesterol</td>
</tr>
<tr>
<td>9.</td>
<td>HDL - C</td>
<td>High Density Lipoprotein Cholesterol</td>
</tr>
<tr>
<td>10.</td>
<td>VLDL - C</td>
<td>Very Low Density Lipoprotein Cholesterol</td>
</tr>
</tbody>
</table>
CERTIFICATE - II

This is to certify that this dissertation work titled “A STUDY OF Atherosgenic Index of Plasma in Male Acute Coronary Syndrome Patients with Normal Serum Lipid Profile” of the candidate DR. S. PREETHI with registration Number 201515101 for the award of M.D., in the branch of Physiology. I personally verified the Urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from Introduction to Conclusion pages and result shows 0 percentage of plagiarism in the dissertation.

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(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

<table>
<thead>
<tr>
<th>Prof Dr V Narasajjan MD MNAMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (Neuro) Dsc. (Neurosciences )</td>
</tr>
<tr>
<td>Dsc (Hons)</td>
</tr>
<tr>
<td>Professor Emeritus in Neurosciences, Tamil Nadu Govt Dr MGR Medical University</td>
</tr>
<tr>
<td>Chairman, IEC</td>
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<thead>
<tr>
<th>Dr. M. Shanthy, MD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Member Secretary, Professor of Pharmacology, Madurai Medical College, Madurai</td>
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</tbody>
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<table>
<thead>
<tr>
<th>MEMBERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dr. K. Meenakshi Sundaram, MD (Physiology) Vice Principal, Madurai Medical College</td>
</tr>
<tr>
<td>2. Dr. Sheela Mallika Rani, M.D., Anaesthesiology, Medical Superintendent Govt. Rajaji Hospital, Madurai</td>
</tr>
<tr>
<td>3. Dr. V. T. Premkumar, MD (General Medicine) Professor &amp; H.O.D. of Medicine, Madurai Medical &amp; Govt. Rajaji Hospital, College, Madurai</td>
</tr>
<tr>
<td>4. Dr. D. Muruthupandian, M.S., Professor &amp; H.O.D. Surgery, Madurai Medical College &amp; Govt. Rajaji Hospital, Madurai</td>
</tr>
<tr>
<td>5. Dr. G. Meenkumari, M.D., Professor of Pathology, Madurai Medical College, Madurai</td>
</tr>
<tr>
<td>7. Thiru. Pala Ramasamy, B.A., B.L., Advocate, Palam Station Road, Selur</td>
</tr>
<tr>
<td>8. Thiru. P. K. M. Chelliah, B.A., Businessman, 21, Jawahar Street, Gandhi Nagar, Madurai</td>
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## ETHICS COMMITTEE CERTIFICATE

<table>
<thead>
<tr>
<th>Name of the Candidate :</th>
<th>Dr. S. Preethi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course :</td>
<td>PG in MD., Physiology</td>
</tr>
<tr>
<td>Period of Study :</td>
<td>2015 - 2018</td>
</tr>
<tr>
<td>College :</td>
<td>MADURAI MEDICAL COLLEGE</td>
</tr>
<tr>
<td>Research Topic :</td>
<td>A study of atherogenic index of plasma in male acute coronary syndrome patients with normal serum lipid profile</td>
</tr>
<tr>
<td>Ethical Committee as on :</td>
<td>26.10.2016</td>
</tr>
</tbody>
</table>

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

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Chairman: [Signature]
Dean / Convener: [Signature]
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Student message:

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Preethi Sivakumar <preethi27@gmail.com>
to: Vasanth, manickam_16@gmail.com

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