"ASSESSMENT OF LEVELS OF APOLIPOPROTEINS IN PATIENTS OF CORONARY ARTERY DISEASES – A CROSS SECTIONAL STUDY"

By

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Dissertation

Submitted to the
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In Partial Fulfillment
of the requirements for the degree of

M. D.
in
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Under the Guidance of

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LIST OF ABBREVIATIONS USED

%	-	Percentage
ABC		ATP-binding cassette
ACCESS		Atorvastatin Comparative Cholesterol Efficacy and Safety Study
ACS		Acute Coronary Syndrome
AMI		Acute Myocardial Infarction
AMORIS		Apolipoproteins Related Mortality Risk
Apo A	-	Apolipoprotein A
Apo A –I		Apolipoprotein A – I
Apo B		Apolipoprotein B
Apo B / Apo A		Apolipoprotein B to Apolipoprotein A ratio
ARIC		Atheroscleosis Risk In Communities
BMI		Body Mass Index
BP		Blood pressure
CAD	-	Coronary artery disease
CBC		Complete Blood count
CETP		Cholesterol ester transfer protein
CHD	-	Coronary Heart Disease
CRP		C-Reactive protein
DM		Diabetes Mellitus
ECAT		European Concerted Action on Thrombosis and Disabilities
ECG		Electrocardiography
HDL	-	High Density Lipoproteins

HERS		Heart and Estrogen /Progestin Replacement Study
HL		Hepatic lipase
Hs-CRP		Highly selective C Reactive protein
HTN		Hypertension
IDL		Intermediate density lipoprotein
IHD		Ischaemic heart disease
IL-1		Interleukin -1
LCAT		Lecithin cholesterol aryl tranferase
LDL	-	Low Density Lipoproteins
LL		Lipoprotein Lipase
Lp(a)		Lipoprotein a
MI		Myocardial Infarction
MMP		Matrix Metalloproteins
NCEP (ATP-III)		National Cholesterol Education Program –Adult Treatment Panel Third
Non – HDLc		Non high density lipoprotein cholesterol
PRIME		Prospective Epidemiological study of Myocardial Infarction
SHARE		Study of Health Assessment and Risk in Ethnic Groups
SMC		Smooth Muscle Cells
TC	-	Total Cholesterol
TNF		Tumour necrosis factor
UKPDS		United Kingdom Prospective Diabetes Study
VLDL		Very low density lipoprotein
WHR		Waist Hip Ratio

ABSTRACT

Background and objectives

Atherosclerotic disease implicates a multitude of risk factors, of which lipid and lipoprotein metabolism assumes central importance. Conventionally, serum lipid profile has been considered to be an important risk factor for development of coronary artery disease. The present study was undertaken to establish Apo AI, Apo B and ApoB/Apo AI as a new marker of atherosclerotic disease in patients with angiographically proven CAD with normal Lipid Profile.

Methodology

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 100 patients with history suggestive of Ischemic heart disease (clinically symptoms of ischemia like chest pain and ECG changes) including MI, Unstable angina and Stable angina were included.during the period of January 2010 to December 2010. Relevant investigations were done and Apo B to A ratio of more than 0.8 in females and 0.9 in males was considered as abnormal.

Results

Males outnumbered females (84% vs 16%) with male to female ratio of 5.25:1. Most of the patients (40%) were in the in the age group of 51 to 60 years Dyslipidemia was found to be the most common risk factor (46%). A large proportion of the patients were in the obese I group (72%). Majority of the patients (88%) had abnormal apo B to A ratio. Significant obstructive CAD was

noted in 87% patients of which 46% had single vessel disease, 23% double vessel disease and 18% had triple vessel disease. Of the 88 patients with abnormal Apo B/ Apo A ratio, 79 had coronary artery disease. Similarly, on the other hand out of 87 patients of CAD, 90.8% had abnormal ratio and 9.19% had normal ratio. This difference was statistically significant ($p<0.001$).

Interpretation and conclusion

Apolipoproteins (A and B) and their ratio may be better risk markers of coronary artery disease than conventional lipid profile.

Keywords

Apolipoprotein A; Apolipoprotein B; Apolipoprotein B to A ratio; Coronary artery disease;

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Chapter 1

Introduction

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in the developed world and is rapidly assuming epidemic proportions in developing countries including India. India has to its discredit the highest number of coronary artery diseases in the world. Previous studies have shown that the overall prevalence of coronary artery disease in India, based on a clinical diagnosis and an electrocardiogram, was 9.0% in the urban and 3.3% in the rural population. The prevalence's was significantly higher in the men, compared with the women in both urban (11.0 vs 6.9%) and rural (3.9 vs 2.6%) populations.[1]

The prevalence of symptomatic coronary artery disease was 2.3% in men and 1.5% in women among rural population, 8.5% in men and 3.4% in the women among urban population. When diagnosed on the basis of electrocardiographic changes alone, the prevalence's was 1.5% and 3.0% in the rural and urban population respectively. Coronary risk factors were two to three times common among urban subjects compared to the rural population in both sexes.[1]

Conventionally, serum lipid profile has been considered to be an important risk factor for development of coronary artery disease. However there are subsets of patients who do not have raised lipid profile and yet develop coronary artery disease.

Extensive research has been done to determine the risk factors unique to this group which may predispose to the elevated risk of this disease. Important

amongst them are lipoproteins, homocysteine, lipoprotein (a), pro-inflammatory cytokines.

Lately, considerable interest arose in apolipoproteins, mainly apolipoprotein B, the major protein in non–HDL-C atherogenic lipoprotein particles (including low-density lipoprotein [LDL], intermediate density lipoprotein, very low density lipoprotein, and Lp(a)) and apolipoprotein A-I, which is the major apolipoprotein constituent of high-density lipoprotein (HDL).

Studies have been undertaken to evaluate the role of the apolipoprotein-B100 (apo-B)/apolipoprotein-AI (apo-AI) ratio as a predictor of CAD risk in the atherosclerosis-prone Indian population, as compared to other conventional lipid ratios.[2]

Atherosclerotic disease implicates a multitude of risk factors, of which lipid and lipoprotein metabolism assumes central importance. Furthermore, lipoprotein cholesterol (particularly low density lipoprotein cholesterol [LDL-C]) constitutes an established risk factor and a primary treatment target for the prevention of coronary heart disease (CHD). The third Adult treatment Panel of the National Cholesterol Education program (NCEP ATP-III) introduced non–high-density lipoprotein cholesterol (HDL-C) as a better risk predictor particularly among hypertriglyceridemic individuals.[3]

Apolipoprotein B,[3,5] apolipoprotein A-I,[6,7] and even more so their ratios[8-10] has been suggested by a number of epidemiological and clinical studies as superior indicators of cardiovascular risk. Numerous studies have been conducted with contrasting results. Various studies reported a similar predictive

power for lipids and apolipoproteins.[11,12] Some argued that apolipoprotein add to prediction of the traditional lipids,[4] whereas others did not find apolipoprotein to have a predictive power beyond that of lipids.[13,14]

Although most of comparative studies of apolipoproteins A-I and B with lipids were conducted among healthy individuals, only a few studied the association between lipoprotein components and prognosis among CHD patients.[6,7,15,16]

Apolipoproteins A-1 and B concentration have been measured in Indians undergoing elective diagnostic coronary arteriography in order to assess the predictive power of apolipoproteins as a 'marker' of coronary artery disease (CAD). This association was also compared to that of other traditional risk factors: age, hypertension, diabetes, family history, smoking and plasma levels of total cholesterol, triglycerides, low and high density lipoproteins.[17]

In various studies national and international, lower levels of plasma apolipoprotein AI (Apo A-I) and higher levels of ApoB, and the ratio of ApoB to ApoA-I have been proved to be independent risk factors for coronary heart disease.[18]

There are very few studies in this regard in our subcontinent and especially our area. No study has been done in this area of the country exploring the association of Apo B/Apo AI ratio with angiographically proven coronary artery disease.

Hence, the present study was undertaken to establish Apo AI, Apo B and ApoB/Apo AI as a new marker of atherosclerotic disease in patients with angiographically proven CAD with normal Lipid Profile.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were;

Primary

To assess the levels of apolipoproteins in patients of CAD.

Secondary

To know the association between serum Apolipoprotein A-I (apoA-I), Apolipoprotein B (Apo B) and its ratio with the severity of CAD.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

With the discovery of antibiotics and the implementation of public health measures to control the spread of communicable diseases, mortality due to infections decreased and life expectancy increased. As a consequence of these changes a non-infectious group of diseases became the main individual cause of mortality: cardiovascular diseases. Around the middle of the last century cardiovascular disease mortality began to increase rapidly, but very little was known about its origins and causes.[19]

Cardiovascular epidemiology began in the 1930's as a consequence of observed changes in the causes of mortality. In 1932, Wilhelm Raab described the relationship between diet and coronary heart disease (CHD) in different regions, and in 1953 an association between cholesterol levels and CHD mortality was reported in various populations.[19]

Coronary artery disease is a progressive disease process that generally begins in childhood and manifests clinically in middle to late adulthood. The word atherosclerosis is of Greek origin and literally means focal accumulation of lipid (athere [gruel]) and thickening of arterial intima (sclerosis [hardening]). Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by endothelial dysfunction, vascular inflammation, buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall. Atherosclerotic buildup results in plaque formation, vascular remodeling, acute and chronic luminal obstruction, abnormalities of blood flow and

diminished oxygen supply to target organs. By impairing or obstructing normal blood flow, atherosclerotic buildup causes myocardial ischemia.

Coronary artery disease is the epidemic of our time and set to remain the single most important disease in the world in the terms of mortality, morbidity, disability and economic loss until 2020 year. This chronic disease has an enormous impact on quality of life. Its risk factors accelerate or modify a complex and chronic inflammatory process that ultimately manifest as fibrous atherosclerotic plaque, the clinical coronary events follow plaque rupturing. The presence and the number of CAD risk factors predict the future cardiovascular events in individuals.[20]

Coronary artery disease is characterized by the presence of atherosclerosis in the epicardial coronary arteries. Atherosclerotic plaques, the hallmark of atherosclerosis, progressively narrow the coronary artery lumen and impair ante grade myocardial blood flow. The reduction in coronary artery flow may be symptomatic or asymptomatic, may occur with exertion or at rest, and may culminate in a myocardial infarction, depending on obstruction severity and the rapidity of its development.[20]

Epidemiology

Global burden

Coronary artery disease is the most common form of cardiovascular disease with an estimated prevalence of CAD in men is 6.9% and 6% among women.[20] It is the most common serious chronic life threatening illness in the

United States where 13 million have CAD, more than six million have angina and more than seven million sustained MI.[21] The estimated direct and indirect costs for coronary heart disease in 2006 is $142.5 billion.[20]

The Incidence of CAD is compatible with the pattern of the distribution of CAD risk factors, CAD occurs when its risk factors are present. According to a case-control study of 52 countries (INTER HEART), nine easily measured and potentially modifiable risk factors accounts for over 90% of the risk of an initial acute myocardial infarction (MI). The effect of these risk factors is consistent in men and women, across different geographic regions, and by ethnic group, making the study applicable worldwide. These nine risk factors include apo B to apo A1 ratio, cigarette smoking, abnormal blood lipid levels, hypertension, diabetes, abdominal obesity, a lack of physical activity, low daily fruit and vegetable consumption, alcohol over consumption, and the psychosocial index. Study found that apo B to apo A1 ratio was the strongest of all risk factors and remained the most important also in multivariate analysis.[20]

Indian scenario

Asian Indians have considerably higher prevalence of premature CAD and standardized mortality rates for CAD compared with Europeans, Chinese. A recent report from the Study of Health Assessment and Risk in Ethnic Groups (SHARE) indicates a significantly higher risk of cardiovascular events among South Asians compared with Europeans and Chinese.[22]

Coronary artery disease is a leading cause of morbidity and mortality in the developed world and is rapidly assuming epidemic proportions in developing countries including India.[23]

Within the Indian subcontinent, a dramatic increase in the prevalence of CAD has been predicted in the next 20 years due to rapid changes in demography and lifestyle consequent to economic development. Earlier studies in Asian Indians have shown that classical risk factors do not explain the excess of CAD seen in this ethnic group.[22]

It is also possible that the risk factors for CAD could differ considerably between native and migrant Indians because of differences in diet, physical activity, body weight and lifestyle changes consequent to affluence and cultural changes consequent to migration.

Studies on Asian Indians, mostly in migrant populations, have reported on the high prevalence of CAD and its occurrence at a young age (premature CAD). The prevalence of CAD in migrant Indians, ranges between 7% to 17%. The overall figure of 11% of CAD in the population represents approximately a 10-fold increase in the prevalence of CAD in urban India during the last 40 years.[22]

Previous study have shown that the overall prevalence of coronary artery disease in India, based on a clinical diagnosis and an electrocardiogram, was 9.0% in the urban and 3·3% in the rural population. The prevalence's were significantly higher in the men compared with the women in both urban (11·0 vs 6·9%) and rural (3·9 vs 2·6%) populations, respectively.[1]

A study[24] compared migrant Indians living in West London with native Indians living in Punjab. The migrant Indians had higher BMI, systolic BP and significantly higher lipid levels. However, both the migrant and native Indians had elevated lipoprotein(a) levels, suggesting that genetic influences may predispose Indians to premature CAD.[22]

It is of interest that, in the SHARE study,[25] while atherosclerosis (carotid intimal medial thickness) was actually higher among Europeans, thrombosis was significantly higher in South Asians, suggesting that a thrombogenic risk factor profile predisposes the latter group to CAD.

Race-associated prevalence of coronary artery disease

The incidence, prevalence, and manifestations of CAD vary significantly with race, as does the response to therapy. Asian Indians exhibit a 2- to 3-fold higher prevalence of CAD than whites in the United States. They also have greater prevalences of hypoalphalipoproteinemia, high lipoprotein(a) levels, and diabetes.

Sex

Men traditionally have a higher prevalence of CAD. Decades of observational studies have verified higher coronary risk in men compared with premenopausal women. After menopause, however, coronary risk accelerates in women. At least part of the apparent protection against CHD in premenopausal women derives from their relatively higher HDL levels compared with those of men. After menopause, HDL values fall in concern with increased coronary risk.

Estrogen therapy lowers LDL cholesterol and raises HDL cholesterol, changes that should decrease coronary risk.[21]

In the Heart and Estrogen/Progestin Replacement Study (HERS), postmenopausal female survivors of acute myocardial infarction were randomized to an estrogen/progestin combination or to placebo. This study showed no overall reduction in recurrent coronary events in the active treatment arm. Indeed, early in the 5-year course of this trial, there was a trend toward an actual increase in vascular events in the treated women.[26,27]

Women, however, follow men by 10 years, especially after menopause. (The value of estrogen supplementation for prevention of CAD has been discredited by the Heart and Estrogen/Progestin Replacement Study [HERS]).[26,27]

The presence of diabetes, as well as tobacco use, eliminates the protection from heart disease associated with female sex. In women, as in men, the most common cause of death is CAD, which accounts for more deaths in women than those related to breast and uterine diseases combined.

Risk factors

From a practical viewpoint, the cardiovascular risk factors that have emerged from such studies fall into two categories: those modifiable by lifestyle and/or pharmacotherapy and those such as age and gender that are immutable. The weight of evidence supporting various risk factors differs. For example, hypercholesterolemia and hypertension certainly predict coronary risk, but other so-called nontraditional risk factors, such as levels of homocysteine, lipoprotein

(a) [Lp(a)], or infection, remain controversial. Moreover, the causality of some biomarkers that predict cardiovascular risk, such as C-reactive protein (CRP), remains uncertain.[21]

Total and LDL cholesterol are considered to be important risk factors for CAD in studies, while hypertriglyceridemia is reported to be the major risk factor in others. Reports show that microalbuminuria, small dense LDL, lipoprotein(a), homocysteine, fibrinolytic and thrombogenenic risk factors like tissue plasminogen activator, plasminogen activator inhibitor and fibrinogen are also associated with CAD.[22]

It is well known that patients with type 2 diabetes have a twofold to threefold increased risk of developing CAD. Recent findings from the United Kingdom Prospective Diabetes Study (UKPDS)[28] show that among type 2 diabetic subjects, a quintet of potentially modifiable risk factors, namely increased concentration of LDL cholesterol, decreased concentration of HDL cholesterol, hypertension, hyperglycemia and smoking confer the risk of CAD.

It is well known that Asian Indians have low HDL cholesterol levels, which could be one of the risk factors for premature CAD in this ethnic group.[22] Studies have confirmed that the mean HDL cholesterol is low in our population (1.03 mmol/l [40 mg/dl]). Low-density lipoprotein cholesterol levels were high in the CAD group, although the actual LDL elevation was only modest. It is possible that in the face of low HDL cholesterol, even modest elevation of LDL with consequent elevation of the LDL/HDL and total cholesterol/HDL cholesterol ratio could contribute to atherogenesis in this population.

Earlier reports in migrant Indians have stressed the role of elevated serum triglycerides as a risk factor for CAD in this ethnic group.[22] However, the role of serum triglycerides as a risk factor for CAD remains controversial.[22]

A recent report generated from the analyses of data from the Multiple Risk Factor Intervention trial and three other trials concluded that triglyceride measurements do not provide clinically meaningful information about coronary heart disease risk beyond that obtained by cholesterol measurements.[29]

Pathophysiology

Initially thought to be a chronic, slowly progressive, degenerative disease, atherosclerosis is a disorder with periods of activity and quiescence. Although a systemic disease, atherosclerosis manifests in a focal manner and affects different organ systems in different patients for reasons that remain unclear.

Plaque growth and vascular remodeling

Atherosclerotic plaques (or atheromas), which may require 10-15 years for full development, characteristically occur in regions of branching and marked curvature at areas of geometric irregularity and where blood undergoes sudden changes in velocity and direction of flow. Decreased shear stress and turbulence may promote atherogenesis at these important sites within the coronary arteries, the major branches of the thoracic and abdominal aorta, and the large conduit vessels of the lower extremities.

A study[30] suggests low shear segments in the coronary arteries develop greater plaque and necrotic core progression and constrictive remodeling,

whereas high shear segments develop greater necrotic core and calcium progression, regression of fibrous and fibrofatty tissue, and excessive expansive remodeling. This suggests a transformation to a more vulnerable phenotype.

The earliest pathologic lesion of atherosclerosis is the fatty streak. The fatty streak is the result of focal accumulation of serum lipoproteins within the intima of the vessel wall. Microscopy reveals lipid-laden macrophages, T lymphocytes, and smooth muscle cells (SMCs) in varying proportions. The fatty streak may progress to form a fibrous plaque, the result of progressive lipid accumulation and the migration and proliferation of SMCs.

Platelet-derived growth factor, insulin like growth factor, transforming growth factors alpha and beta, thrombin, and angiotensin II (A-II) are potent mitogens that are produced by activated platelets, macrophages, and dysfunctional endothelial cells that characterize early atherogenesis, vascular inflammation, and platelet-rich thrombosis at sites of endothelial disruption.

The SMCs are responsible for the deposition of extracellular connective tissue matrix and form a fibrous cap that overlies a core of lipid-laden foam cells, extracellular lipid, and necrotic cellular debris. Growth of the fibrous plaque results in vascular remodeling, progressive luminal narrowing, blood-flow abnormalities, and compromised oxygen supply to the target organ. Human coronary arteries enlarge in response to plaque formation, and luminal stenosis may occur only when the plaque occupies more than 40% of the area bounded by the internal elastic lamina.[31]

Plaque rupture

Denudation of the overlying endothelium or rupture of the protective fibrous cap may result in exposure of the thrombogenic contents of the core of the plaque to the circulating blood. This exposure constitutes an advanced or complicated lesion. The plaque rupture occurs due to weakening of the fibrous cap. Inflammatory cells localize to the shoulder region of the vulnerable plaque. T lymphocytes elaborate interferon gamma, an important cytokine that impairs vascular smooth muscle cell proliferation and collagen synthesis. Furthermore, activated macrophages produce matrix metalloproteinases that degrade collagen.

These mechanisms explain the predisposition to plaque rupture and highlight the role of inflammation in the genesis of the complications of the fibrous atheromatous plaque. A plaque rupture may result in thrombus formation, partial or complete occlusion of the blood vessel, and progression of the atherosclerotic lesion due to organization of the thrombus and incorporation within the plaque.

Plaque rupture is the main event that causes acute presentations. However, severely obstructive coronary atheromas do not usually cause ACS and MI. In fact, most of the atheromas that cause ACS are less than 50% occlusive, as demonstrated by coronary arteriography. Atheromas with smaller obstruction experience greater wall tension, which changes in direct proportion to their radii.

T cells that accumulate at sites of plaque rupture and thrombosis produce the cytokine interferon gamma, which inhibits collagen synthesis. Already-formed collagen is degraded by macrophages that produce proteolytic enzymes

and by matrix metalloproteinases (MMPs), particularly MMP-1, MMP-13, MMP-3, and MMP-9. The MMPs are induced by macrophage- and SMC-derived cytokines such as IL-1, tumor necrosis factor (TNF), and CD154 or TNF-alpha.

It is postulated that lipid lowering stabilizes the vulnerable plaques by modulating the activity of the macrophage-derived MMPs.

Histologic composition and structure

A system devised by Stary et al classifies atherosclerotic lesions according to their histologic composition and structure.[32]

In a type I lesion, the endothelium expresses surface adhesion molecules E selectin and P selectin, attracting more polymorphonuclear cells and monocytes in the subendothelial space.

In a type II lesion, macrophages begin to take up large amounts of LDL (fatty streak).

In a type III lesion, as the process continues, macrophages become foam cells.

In a type IV lesion, lipid exudes into the extracellular space and begins to coalesce to form the lipid core.

In a type V lesion, SMCs and fibroblasts move in, forming fibroatheromas with soft inner lipid cores and outer fibrous caps.

In a type VI lesion, rupture of the fibrous cap with resultant thrombosis causes ACS.

As lesions stabilize, they become fibrocalcific (type VII lesion) and, ultimately, fibrotic with extensive collagen content (type VIII lesion).

Diagnosis

CAD diagnosis is based on history, several biochemical investigations, ECG, echocardiography, and coronary angiography.

Routine blood tests include complete blood count (CBC), chemistry panel, lipid profile, and thyroid function tests (to exclude thyroid disorders). Routine measurement of blood glucose and hemoglobin A_{1C} is appropriate in patients with diabetes mellitus.

Measuring any number of parameters that may reflect coagulation, fibrinolytic status, and platelet aggregability is possible. These measurements may prove to be valuable, but how these measurements affect clinical decision-making is unclear.

Conventionally lipid profile, ECG and echocardiography have been proved to be the basis of CAD. Recently inflammatory marker like Hscrp and cardiac markers like Troponin I have gained importance.

Lipid Profile

Fasting lipid profile includes the following:[27,33,34]

- Total cholesterol level
- LDL cholesterol (LDL-C) level
- HDL cholesterol (HDL-C) level

- Triglyceride level

Routine LDL cholesterol is usually calculated from measurements of total cholesterol, triglycerides and HDL cholesterol in fasting blood sample using the Friedewald formula, which is valid only if fasting triglycerides are <4.5 mmol/l.

Calculated LDL cholesterol does not reflect the true value in patients with metabolic syndrome, diabetes mellitus, nephrotic syndrome or liver disease. Moreover, the technical errors of calculating by the Friedewald equation are up to 20%, especially in subjects with LDL cholesterol levels <3.0 mmol/l.[35]

Measurement of HDL cholesterol requires an additional precipitation procedure to remove apoB-containing particles in plasma that is technically problematic. The full lipid profile (cholesterol, triglycerides, HDL cholesterol and LDL cholesterol) requires the subject to fast for at least 12 h. Although there are methods to measure LDL cholesterol and HDL cholesterol directly, these tests are not yet internationally standardized and are expensive.

Specific lipid studies (if necessary) include the following:

- Small, dense LDL-C level
- Lipoprotein (a) level
- Apolipoprotein profile
- Direct measurement of HDL-C

Measurement of apoB does not require fasting. Although there are methods to measure LDL cholesterol and HDL cholesterol directly, these tests are not yet internationally standardized and are expensive. In contrast, the tests for measuring apoB and apoA-I are widely available, internationally standardized and automated.[35] The assay can be performed on frozen or non-fasting samples, with excellent precision of technical errors (usually <5%).

C-Reactive Protein

An accumulation of clinical evidence shows that markers of inflammation correlate with coronary risk. For example, plasma levels of CRP, as measured by a high-sensitivity assay, prospectively predict risk of myocardial infarction. CRP levels also correlate with outcome of patients with acute coronary syndromes. CRP adds predictive information to that derived from established risk factors, such as those included in the Framingham score. Elevated levels of the acute-phase reactant CRP may reflect merely ongoing inflammation rather than a direct etiologic role for CRP in coronary artery disease.[21]

Elevations in acute-phase reactants such as fibrinogen or CRP could reflect overall atherosclerotic burden and/or extravascular inflammation that potentiate atherosclerosis or its complications.

Visceral adipose tissue releases pro-inflammatory cytokines that drive CRP production and may represent a major extravascular stimulus to elevation of inflammatory markers in obese and overweight individuals. Indeed, CRP levels rise with body mass index (BMI), and weight reduction lowers CRP levels. Intriguing evidence suggests that lipid-lowering therapy reduces coronary events

in part by muting the inflammatory aspects of the pathogenesis of atherosclerosis.[21]

CRP appears to provide prognostic information for CAD. Men with CRP levels in the highest quartile had a 3-fold greater risk of MI, according to the Physicians' Health Study.

Serum Markers

Serum markers in patients with suspected acute cardiac events (ACS, MI) include the following:

- Troponins (I or T)
- Creatine kinase with MB isozymes
- Lactate dehydrogenase and lactate dehydrogenase isozymes
- Serum aspartate aminotransferase

Biomarkers

In a 10-year comparison of 10 biomarkers for predicting death and first major cardiovascular events in approximately 3000 individuals, the most informative biomarkers for predicting death were the following:[36]

- B-type natriuretic peptide
- CRP
- Homocysteine
- Renin
- Urinary albumin-to-creatinine ratio

Echocardiography

Transthoracic echocardiography helps to assess left ventricular function, wall-motion abnormalities in the setting of ACS or AMI, and mechanical complications of AMI.

Stress echocardiography can be used to evaluate hemodynamically significant stenoses in stable patients who are thought to have CAD. Treadmill echocardiography stress testing and dobutamine echocardiography stress testing provide equivalent predictive values.

Coronary Angiography

Coronary angiography was the first available in vivo assessment of the coronary arteries. In this technique, an iodinated contrast agent is injected through a catheter placed at the ostium of the coronaries. The contrast agent is then visualized through radiographic fluoroscopic examination of the heart.

Coronary angiography remains the criterion standard for detecting significant flow-limiting stenoses that may be revascularized through percutaneous or surgical intervention.

Apolipoprotein

Lipid and lipoprotein metabolism are at the heart of atherosclerotic disease. Furthermore, lipoprotein cholesterol (particularly low density lipoprotein cholesterol [LDL-C]) constitutes an established risk factor and a primary treatment target for the prevention of coronary heart disease (CHD).

Lipoprotein particles are made up of an insoluble lipid core surrounded by a coat of phospholipid, free cholesterol and apolipoproteins. Each class of lipoprotein particles is associated with distinctive apolipoproteins that, in addition to stabilizing lipoprotein structure, play an essential role in regulating metabolism. Some of the apolipoproteins act as ligands to tissue receptors, whilst others activate or inhibit enzymes involved in metabolic steps in the circulation or tissues.

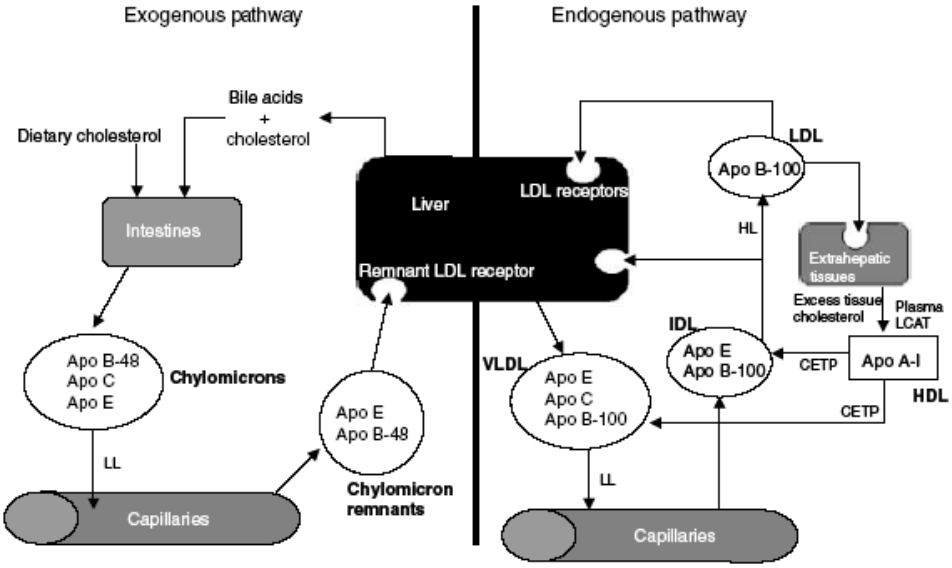


Figure 1. Summary of general pathways of lipoprotein metabolism

For over three decades it has been recognized that a high level of total blood cholesterol, particularly in the form of LDL cholesterol (LDL-C), is a major risk factor for developing coronary heart disease (CHD). However, as more recent research has expanded our understanding of lipoprotein function and metabolism, it has become apparent that LDL-C is not the only lipoprotein species involved in atherogenesis. A considerable proportion of patients with

atherosclerotic disease have levels of LDL-C and total cholesterol (TC) within the recommended range, and some patients who achieve significant LDL-C reduction with lipid-lowering therapy still develop CHD.[37]

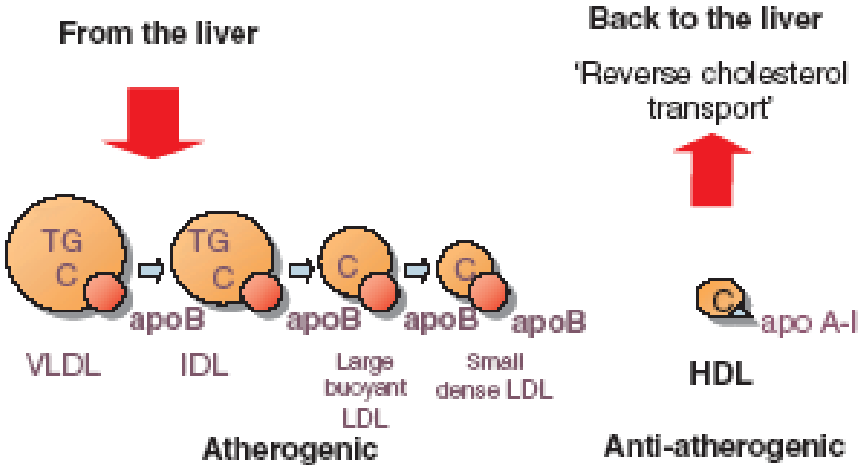


Fig. 2 Atherogenic and anti-atherogenic lipoproteins. Apo B, apolipoprotein B; Apo A-I, apolipoprotein A-I; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; TG, triglyceride; C, cholesterol.

Figure 2. Atherogenic and anti-atherogenic lipoproteins

Other lipid parameters are also associated with elevated cardiovascular risk, and it has been suggested that LDL-C and TC may not be the best discriminants for the presence of coronary artery disease (CAD). Elevated levels of intermediate density lipoprotein (IDL) and very low density lipoprotein (VLDL) are also associated with increased cardiovascular risk, as are low levels of HDL and high levels of plasma triglyceride (TG).[37]

Lately, considerable interest arose in apolipoproteins, mainly apolipoprotein B, the major protein in non–HDL-C atherogenic lipoprotein

particles (including low-density lipoprotein [LDL], intermediate density lipoprotein, very low density lipoprotein, and Lp(a)) and apolipoprotein A-I, which is the major apolipoprotein constituent of high-density lipoprotein (HDL). Apolipoprotein B, apolipoprotein A-I, and even more so their ratio have been suggested by a number of epidemiological and clinical studies as superior indicators of cardiovascular risk. A number of studies reported a similar predictive power for lipids and apolipoproteins. Some argued that apolipoprotein add to prediction of the traditional lipids, whereas others did not find apolipoprotein to have a predictive power beyond that of lipids.[3-14]

Although most of comparative studies of apolipoproteins A-I and B with lipids were conducted among healthy individuals, only a few studied the association between lipoprotein components and prognosis among CHD patients.[6,7,15,16] These studies did not compare men and women[6,7,15] or included a small number of patients.[15]

Apolipoproteins are important components of lipoprotein particles, and there is accumulating evidence that measurement of various forms of apolipoproteins may improve the prediction of the risk of cardiovascular disease.[37]

There is considerable interest in the potential value of measuring circulating concentrations of apolipoproteins to assist in the assessment of the risk of coronary heart disease (CHD), as well as interest in their potential aetiological relevance to disease.

Apolipoprotein B-100 (apoB) is present as a single molecule in low-, intermediate- and very low-density lipoproteins (LDL, IDL and VLDL, respectively) and apoAI is the major apolipoprotein associated with high-density lipoprotein (HDL).

The ratio between the concentrations of apoB and apoAI (henceforth apoB/A) has been proposed to reflect the balance between the opposing processes of arterial internalization of cholesterol and the reverse transport of cholesterol back to the liver. Measurement of apolipoproteins does not require fasting samples, which might help to avoid the compound errors that can arise when using calculated lipid measures (the calculation of LDL cholesterol using the Friedewald formula), and involves internationally standardized methods and reagents.[37]

Such considerations have encouraged investigation of apolipoproteins in a large number of epidemiological studies. A review of retrospective studies, in which blood samples for the assessment of apolipoproteins have been obtained after the diagnosis of CHD (such as in case–control and in crosssectional studies), has reported that raised apo B concentrations were positively correlated with CHD risk in all 27 studies considered, and that patients with CHD had substantially lower apoAI concentrations than did healthy controls in 38 of 41 such studies.[37] More recently, the INTERHEART case control study, which involved approximately 15 000 myocardial infarction (MI) cases and 15 000 controls from 52 countries, reported that apoB/A was one of the strongest correlates of prevalent disease amongst the several anthropometric, psychosocial and established risk factors measured.[37]

Apolipoprotein A

Apolipoprotein a -1 is a polypeptide of 243 amino acids is the principal moiety of hdl cholesterol mainly synthesized in liver and small intestine. The DNA sequence was discovered by Jeffrey J Seilhamer in 1984.

Apolipoprotein A has two major forms, apo A-I and apo A-II. Apo A-I is the major apolipoprotein associated with HDL-C. Levels of apo A-I are strongly correlated with those of HDL-C, and expression of apo A-I may be largely responsible for determining the plasma level of HDL.[38]

Apo A-I also acts as a cofactor for lecithin cholesterol acyl transferase (LCAT) [29], which is important in removing excess cholesterol from tissues and incorporating it into HDL for reverse transport to the liver.[37] Furthermore, apo A-I is the ligand for the ATP-binding cassette (ABC) protein, ABCA1, and hence is involved in the docking procedure by which excess cholesterol in peripheral cells is externalized to HDL for further reverse cholesterol transport either directly or indirectly via LDL back to the liver.[37]

Experiments in transgenic mice have shown that Apo A-II inhibits hepatic and lipoprotein lipase (LL) activity.[39] This effect tends to increase plasma TG and reduce plasma HDL. Thus, although apo A-I is consistently protective against cardiovascular risk, the influence of apo A-II is still unclear.[37]

HDL exists as particles of different sizes, with HDL-2 being the largest and containing the most lipid in its core. HDL-3 particles are smaller and pre-b-

HDL is the smallest, and these may be the most active particles in taking up peripheral cholesterol.[37]

Apolipoprotein composition can be used to separate HDL into subpopulations: HDL containing apo A-I and apo A-II (HDL A-I : A-II), and HDL containing apo A-I but not apo A-II (HDL A-I) [37]. HDL A-I is more effective than HDL A-I : A-II in promoting cholesterol efflux, which is consistent with the atheroprotective effect of apo A-I on LCAT.[37]

The Prospective Epidemiological Study[40] of Myocardial Infarction (PRIME) study examined the association between the incidence of CHD and several HDL related parameters, including HDL-C itself, apo A-I, HDL A-I, and HDL A-I : A-II. All four parameters were related to CHD risk, however, apo A-I was the strongest predictor.[37] In addition, the use of apo A-I for predicting CAD has been confirmed by other studies.[41-43]

Apolipoprotein B

Apolipoprotein B exists in two forms, apo B-48 and apo B-100. Apo B-48 is synthesized in the intestine, where it is complexed with dietary TG and free cholesterol absorbed from the gut lumen to form chylomicron particles. These are metabolized in the circulation and in the liver. Apo B-100 is synthesized in the liver and is present in LDL, IDL and VLDL particles. Only one apo B molecule is present in each of these lipoprotein particles and therefore the total apo B value indicates the total number of potentially atherogenic lipoproteins. Apo B is essential for the binding of LDL particles to the LDL receptor, allowing cells to internalize LDL and thus absorb cholesterol.[37]

An excess of apo B-containing particles is a main trigger in the atherogenic process. Small dense LDL particles are considered more atherogenic than large buoyant LDL molecules, as they are easily internalized into the subintimal space where they adhere to matrix proteoglycans, are oxidized, and increase the risk of atherothrombotic events.[37]

The concentration of plasma apo B particles is highly correlated with the level of non-HDL cholesterol (non-HDL-C), defined as TC minus HDL-C.[37]

As HDL is known to be protective against cardiovascular risk, non-HDL-C reflects the fraction of blood cholesterol that is not contained in atheroprotective lipoproteins. Therefore, non-HDL-C has been recognized by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines[1] as a target for lipid-lowering therapy. Non-HDL-C has been found to predict nonfatal myocardial infarction (MI) and angina pectoris.[37]

However, apo B has been found to be a better predictor of risk than non-HDL-C. Individuals with seemingly low or normal LDL-C levels can still be at increased risk of cardiovascular events. In these patients, the risk of cardiovascular events appears to be more closely related to an increased number of small, dense LDL particles in addition to hypertriglyceridaemia and a low level of protective HDL-C, a combination known as the atherogenic lipid triad. Thus, LDL-C levels are not always a good or adequate indicator of cardiovascular risk, and it has been noted that the level of apo B and/or apo B/apo A-I in the plasma may be a better predictor.[37]

Target levels for apo B have now been included in a table on treatment goals in an update of the NCEP ATP III guidelines.[1] From several perspectives, including pathophysiology, diagnosis, assessment of therapy and methodological soundness, there are powerful arguments to support the routine use of apo B in the clinical setting using apo B and apo A-I, expressed as the apo B/apo A-I ratio, seems to be a very effective way of characterizing cardiovascular risk in any patient irrespective of their lipoprotein abnormality. Patients with diabetes or the metabolic syndrome can have normal LDL-C levels but possess aspects of the atherogenic lipid profile, and these individuals often have a high ratio of apo B/apo A-I, which is a strong indicator of cardiovascular risk.[37]

Apolipoprotein A which is bound to LDL to form lipoprotein(a) [Lp(a)], shares 80% of its amino acid sequence with plasminogen and competitively inhibits the surface binding and activation of plasminogen. It is strongly genetically determined, with large variability in different populations. Elevated Lp(a) has been associated with arterial wall thickening, and high blood concentrations of Lp(a) and apo(a) have been suggested as risk factors for atherosclerosis.[37]

Endothelial function and imaging studies

Apolipoprotein B has been found to be an independent predictor of endothelial vasodilatory function, increased carotid IMT and arterial stiffness in healthy subjects. Furthermore, apo B was also identified as an independent predictor of carotid IMT in patients with familial combined hyperlipidaemia.[44]

A study[45] also reported that the IMT of the common carotid artery was pathologically increased, and levels of apo B and Lp(a) elevated, in young relatives of MI patients.

An angiographic study demonstrated that women with significant CAD, defined as stenosis of more than 60% in at least one coronary artery, had higher levels of apo B, LDL-C, TG and TC and lower levels of HDL-C than women without CAD.[46]

The apo B level was found to be the best predictor of the extent of CAD after correction for age, as assessed by the number of stenotic arteries, and was the only statistically significant predictor of the presence of CAD in patients without dyslipidaemia.[46]

Similarly, a study[47] found that apo B and apo A-I were more common and strongly related to the presence of angiographically proven CHD than LDL-C in Asian Indians with diabetes. In addition, in male survivors of MI under 45 years of age.

Another study[48] found that 18% of the variation in atherosclerosis score, based on angiography and adjusted for age, smoking habits and body weight, was related to the level of apo B.

CHD events related to apolipoprotein B and apolipoprotein A-I levels

In the Bogalusa Heart Study, children of parents with a history of MI had high apo B and low apo A-I levels, and thus a high apo B/apo A-I ratio, whereas their LDL-C and HDL-C levels were not outside normal limits.[49] Subsequent

clinical studies have investigated the predictive value of apolipoprotein levels in cardiovascular risk.

In patients with unstable angina in the European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris study, baseline levels of HDL-C and apo A-I were found to be the strongest predictors of MI, independent of other coronary risk factors and lipid measurements. Apo B was also associated with coronary events, but in this study the association was not independent of HDL-C.[50]

In addition, another study[51] reported that low levels of apo A-I and HDL-C were significantly related to an increased risk of total or cardiac mortality in patients who had previously developed angiogram-positive angina pectoris.

A prospective study[52] results from QUEBEC Cardiovascular study in 1997 reported that, an increased proportion of small, dense LDL particles has also been associated with marked alterations in plasma lipoprotein and lipid levels, such as elevated TG and apo B concentrations and reduced HDL cholesterol levels, all of which are highly predictive of an increased risk for IHD.

Apolipoprotein B was also found to be an independent predictor of ischaemic heart disease (IHD) in the prospective Quebec Cardiovascular Study[4] in 1996. Subjects in this study were stratified according to baseline apo B level, and men in the highest tertile for apo B were found to be at greater risk of IHD than men in the lowest tertile ($P < 0.0005$). The relationship between baseline apo B level and IHD risk was found to be independent of TG and HDL-C, and apo B level was a better predictor of IHD than the TC/HDL-C ratio.

The large prospective AMORIS study,[53] which published its first report of the relationship between lipid levels and cardiovascular events in 1992, was designed specifically to assess the power of apo B, apo A-I and the apo B/apo A-I ratio for predicting fatal acute MI or sudden death, and whether apo B and apo A-I added predictive power over and above that of TG, TC and LDL-C levels [11]. Raised apo B levels, an increased apo B/apo A-I ratio and low levels of apo A-I were highly predictive of risk of fatal MI in univariate analyses. Compared with subjects in the lowest quartile, those in the highest quartile for apo B had almost a threefold increase in risk; for the apo B/apo A-I ratio the increase in risk was almost fourfold in men and threefold in women.

Risk for subjects in the highest quartile of apo A-I was less than half that of subjects in the lowest quartile. The results were similar for males and females, and in patients above and below 70 years of age.

Furthermore, in multivariate analyses, high apo B levels, high apo B/apo A-I ratio and low levels of apo A-I were stronger predictors of risk than LDL-C, TC and TG levels.[37] When adjusting for TC, TG and age there was a dose–response relationship showing that the highest risk for both males and females is found in those patients with the highest apo B and lowest apo A-I levels.[37] Follow-up has now exceeded 99 months with results based on 1267 acute MI deaths in males and 586 in females.

Based on all these findings, the ratio of apo B/apo A-I, i.e. the balance between potentially atherogenic cholesterol-rich apo B-containing particles and

the anti-atherogenic apo A-I rich particles, is proposed as the best integrated measure of cardiac risk related to lipoprotein profiles.

AMORIS study,[53] indicated that the apoB/apoA-I ratio, which indicates the 'cholesterol balance', is a robust and specific marker of virtually all ischaemic events.

Furthermore, the apo B/apo A-I ratio has also been shown to be superior to the LDL-C/HDL-C and TC/HDL-C ratios in predicting cardiac risk.[37] The apo B/apo A-I ratio is preferred as the apolipoprotein determinations are independent measures compared with the conventionally used lipid ratios that are based on calculated numbers. The risk of fatal MI in subjects with LDL-C (<3 mmol/L) (115 mg/dL) was related to elevated TG values, and especially to a high apo B/apo A-I ratio, but not to LDL-C values. Again, this strengthens the use of the apo B/apo A-I balance as an integrated risk ratio irrespective of the levels of TC and LDL-C.[37]

A study[6] analysed the predictive role of multiple thrombotic/fibrinolytic risk variables as well as several lipoprotein-related variables in a 4-year prospective study of 1045 post-MI patients, and reported that apo B was a stronger predictor of cardiac risk than LDL-C. In multivariate analyses, apo B as well as apo A-I and D-dimer remained significant predictors of cardiac risk.

In the Scandinavian Simvastatin Survival Study (4S),[54] both apo B and LDL-C predicted CHD risk for patients in the placebo group with similar statistical strengths.

In another secondary prevention study, [55] on-treatment levels of TC, LDL-C and TG did not predict cardiovascular events for 848 patients with angiographically proven CAD responding to statin treatment with at least a 30% reduction in TC. In contrast, on-treatment levels of apo A-I were predictive of future CAD risk in both men and women, and on-treatment apo B levels were predictive of risk when the study population was analysed as a whole.

Recent study[8] confirmed the results from the AMORIS study. These investigators followed 2508 middle-aged men, free of coronary disease at baseline, for 6 years. The study found that apo B was a better predictor of cardiac risk than LDL-C, and that both apo B with TG and the apo B/apo A-I ratio had the strongest associations with CHD.

The EPIC-Norfolk study[56] assessed whether apoB and apoA-I are superior to LDL C and HDL C and lipid ratios in CAD. ApoB/apoA-I ratio remained a highly significant predictor (OR ¼ 2.09, 95% CI: 1.24–3.51). Authors also found that the predictive value of the apoB/ apoA-I ratio was preserved although it added only marginally to the predictive power of the Framingham risk score (<10%, 10–20% or >20%). The study concluded that, the apoB/apoA-I ratio is a strong predictor of the risk of future CAD, even after adjustment for traditional CV risk factors including LDL C and HDL C. Based on the many advantages of the apoB/apoA-I ratio (independent risk factor, physiological aspects, methodological – fasting not needed) the authors recommend that the apoB/ apoA-I ratio is incorporated into routine clinical practice.

The MONICA/Kora Augsburg study[12] was performed in 1414 men and 1436 women aged 35–64 years without a prior MI. The main result was the strong direct relationship between high apoB levels and increased risk for MI. By contrast, high apoA-I concentrations were not significantly associated with low risk for MI. The results for apoB levels and the apoB/apoA-I ratio remained significant even when adjusted for age, smoking, alcohol, BMI, diabetes and hypertension.

In an Iranian study[57] on 251 subjects with angiographically defined CAD found that apoB, apoA-I and the apoB/apoA-I ratio were all significantly better than lipids and lipoproteins in discriminating atherosclerosis. Highest apoB/apoA-I ratio was found in those with clinically manifest coronary and atherosclerotic disease and diabetes mellitus.

In a Dutch angiographic study,[58] found that apoB was the best single lipid-related determinant of the extent of coronary stenosis in women with dyslipidaemia and also in those with normal lipids.

Second Northwick Park Heart Study[8] (NPHSII) on 2508 healthy middle-aged UK men to examine the relative values of apoB and other lipid variables in predicting CHD risk over 6 years of follow-up 15 showed that, apoB/apoA-I ratio conferred the highest relative risk of CHD.

Health Professionals Follow-up prospective Study[59] compared the predictive value of apoB with that of LDL cholesterol in 746 diabetic men followed-up for 6 years.17 In both univariate and multivariate hazard models, the risk ratio for apoB was higher than those for LDL cholesterol.

A recent study[60] compared the validity of plasma apoB, non-HDL cholesterol and LDL cholesterol concentrations in predicting cardiovascular risk, defined by Framingham Risk Score, and subclinical atherosclerosis, defined as presence of extra-coronary plaques and high coronary calcium deposit. The authors reported that apo B was consistently a stronger predictor of CHD risk (and peripheral and coronary atherosclerosis) than either non-HDL cholesterol or LDL cholesterol.

A study[2] from Delhi suggested that the apo-B/apo-AI ratio is a better discriminator of CAD risk in the atherosclerosis-prone Indian population, than any of the conventional lipid ratios. The reduction of value of the apo-B/apo-AI ratio may drastically decrease the risk for CAD. Hence, the apo-B/apo-AI ratio may be suggested as an alternative to other lipid ratios of risk assessment in patients with CAD.

Apolipoproteins A-1 and B concentration were measured in 201 Indian patients (32 females; 169 males) undergoing elective diagnostic coronary arteriography in order to assess the predictive power of apolipoproteins as a 'marker' of coronary artery disease (CAD). The results indicated that, the measurement of apolipoproteins A-1 and B provide a better marker for predicting the presence of coronary artery disease as compared to traditional lipid measures. Overall the levels of these apolipoproteins seem to be lower in Indian population as compared to those reported from the West.[17]

Apolipoprotein metabolism is closely associated with the development of atherosclerosis, and the roles played by the various apolipoprotein types are

beginning to be delineated. Elevated levels of apo B and/or low levels of apo A-I have consistently been associated with an elevated risk of cardiovascular events in clinical studies, and baseline apo B level has been demonstrated to be a better predictor of cardiovascular risk than LDL-C. Apo B and apo A-I also retain their predictive power in patients receiving lipid-modifying therapy. As apo B and apo A-I appear to have opposing effects on atherogenic risk, the ratio between the two, indicating the balance between potentially atherogenic versus atheroprotective cholesterol-rich particles, may be a more useful measure of risk than either parameter alone.[37]

Apolipoprotein levels are also straightforward to measure, do not require fasting blood samples, and the analyses are standardized and are easily automated. Apo B and apo A-I may thus have methodological advantages over LDL-C and HDL-C as measures of cardiovascular risk, in addition to their greater predictive power. It has been suggested that measurement of apo B and apo A-I could significantly improve the assessment of cardiovascular risk, especially in patients without elevated LDL-C, and these markers should be included in revisions to the international guidelines for lipid-modifying treatment. Thus, instead of having to measure TC, TG, LDL-C, HDL-C, non-HDL-C and lipid ratios as recommended by the NCEP ATP III guidelines,[1] it may suffice to measure apo B/apo A-I, to effectively evaluate cardiac risk and to monitor the effects of lipid-lowering therapy.

The apolipoprotein profile is clearly a valuable indicator of cardiovascular risk, and provides information that may be used to guide the treatment of individual patients in clinical practice. Treatment regimens should be assessed

according to their effects on apolipoproteins, as well as on the established lipoprotein measures. New guidelines should be developed including apo B and apo A-I as important predictors of cardiac risk and as markers of lipid-lowering therapy.[37]

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 100 patients during the period of January 2010 to December 2010.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2010 to December 2010.

Method of collection of data

Source of Data

Patients admitted in wards of Department of Medicine and Cardiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum with history suggestive of Ischemic heart disease (clinically symptoms of ischemia like chest pain and ECG changes) including MI, Unstable angina and Stable angina were included.

Sample size

Hundred (100) patients were selected for the study.

Sampling procedure

The sample size was calculated based on the formula as mentioned below.

$n = 4 X p X q / d^2$

Where p = Prevalence (Prevalence of the disease which was taken as 50% as no records were available regarding the study).

q = 100 – p

d = Absolute error taken as 10%

$n = 4 X 50 X 50 / 10^2$

n = 100

Selection criteria

Inclusion Criteria

- All patients admitted in Medicine and Cardiology wards in KLES Dr. Prabhakar Kore with history suggestive of Ischemic heart disease (clinically symptoms of ischemia like chest pain and ECG changes) including MI, Unstable angina and Stable angina will be included.

Exclusion Criteria

- Patients with liver disease and renal disease.

Procedure

The study was approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College, Belgaum. Patients Admitted in the wards of

Department of Medicine and Cardiology at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were evaluated based on selection criteria. The selected patients were briefed about the nature of the study and a written informed consent was obtained (Annexure–I).

Demographic data like gender and age were collected along with relevant history and recorded on predesigned and pretested proforma (Annexure-II). A thorough clinical examination was conducted and the findings were also recorded.

Physical examination was conducted to assess body mass index and waist hip ratio. Body mass index was calculated based on formula;

$$\text{Body Mass Index} = \frac{\text{Weight (Kg)}}{\text{Height}^2 \text{ (m)}}$$

Body mass index was classified according to Overweight and obesity by BMI in adult Asians as below.[61]

Classification	BMI (Kg/m^2)	Risk of co-morbidities
Underweight	< 18.5	Low (But increased risk of other clinical problems
Normal range	18.5 to 22.9	Average
Overweight	≥ 23	
At risk	23.0 to 24.9	Increased
Obese I	25.0 to 29.9	Moderate
Obese II	≥ 30.0	Severe

The WHR was calculated as;

$$\text{WHR} = \frac{\text{Waist circumference (Cms)}}{\text{Maximum hip circumference (Cms)}}$$

Waist hip ratio of less than 0.9 in males and 0.85 in females was considered as normal.[62]

Routine investigations such as haemogram (haemoglobin, total count, differential count, erythrocyte sedimentation rate), mini renal, liver function test, urine routine and microscopy were done. Others tests like fasting blood sugar, electrocardiogram were carried out.

Special tests such as cardiac enzymes, fasting lipid profile, apolipoprotein A (by Turbidimetry method), apolipoprotein B (by Turbidimetry method), HsCRP (by PETIA method) and coronary angiography were conducted and recorded.

The results of the angiography were divided into four subgroups depending on the number diseased vessels.[63]

- Normal
- Single vessel disease
- Double vessel disease
- Triple vessel disease

Based on NCEP (National Cholesterol Education Program) guidelines[3] normal values of lipid parameters were;

- Low density lipoprotein < 100 mg/dL
- High density lipoprotein
    - Female > 50 mg/dL
    - Males > 40 mg/dL
- Total Cholesterol < 200 mg/dL.
- HsCRP < 3 mg/dL.

Apo B to A ratio

Although clinical evidence clearly demonstrates that apoB and apoA-I are significantly associated with CAD risk, they have not been generally accepted as therapeutic targets by the various bodies providing lipid-regulating guidelines.[37] However, a target apoB level of <90 mg/dl for patients with CAD or at high risk of CAD has been suggested by the Canadian Cardiovascular Society.[64] Based on the known strong positive relationship between non-HDL cholesterol and apoB, a target levels for apoB has been proposed by Grundy as an updated revision of the NCEP ATPIII guidleines.[3] Regarding cut-off values for apoA-I, a study[37] defined cutoff apoA-I levels of 115 mg/dl for males, and 125mg/dl for females, corresponding to apoB/apoA-I ratios of 0.9 and 0.8, respectively. Hence, for apo B to A ratio of more than 0.8 in females and 0.9 in males was considered as abnormal.

Statistical analysis

The data obtained was tabulated and analysed using rates, ratios and percentages. The data was analysed using Fisher exact test, chi-square test with

Yate's correction wherever indicated and Odd's ratio. A 'p' value of less than 0.05 was considered as statistically significant.

Chapter 5

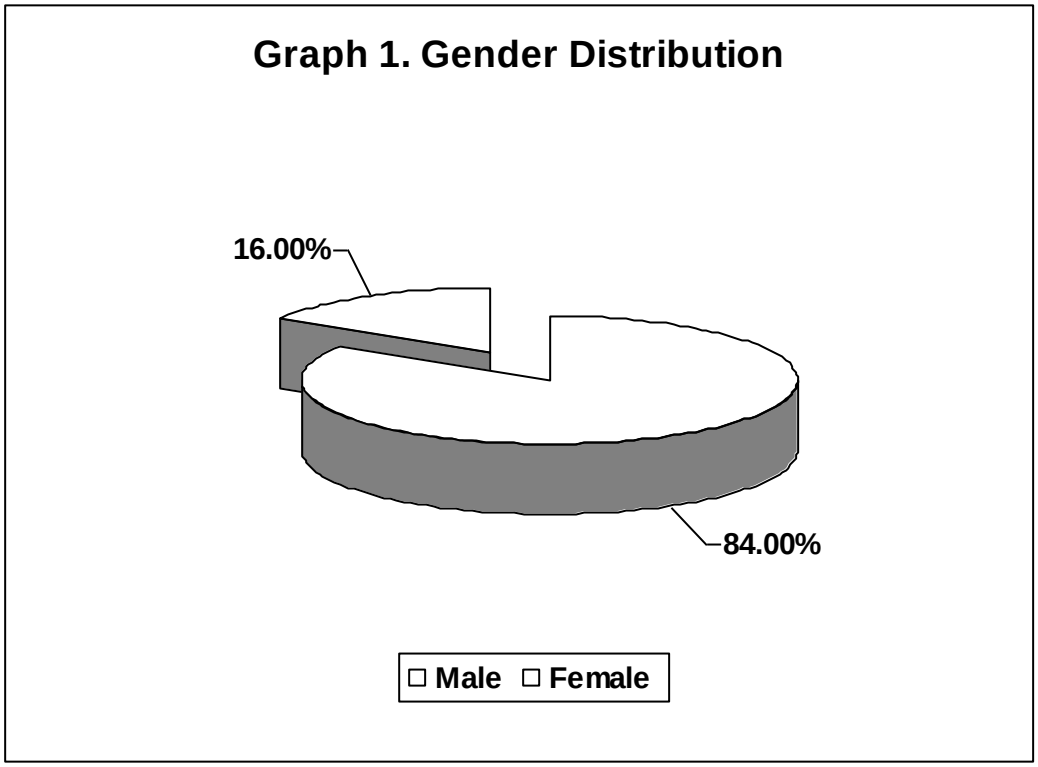
Results

RESULTS

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 100 patients with history suggestive of Ischemic heart disease (clinically symptoms of ischemia like chest pain and ECG changes) including MI, Unstable angina and Stable angina during the period of January 2010 to December 2010. The data obtained was tabulated and analysed as below.

Table 1. Gender Distribution

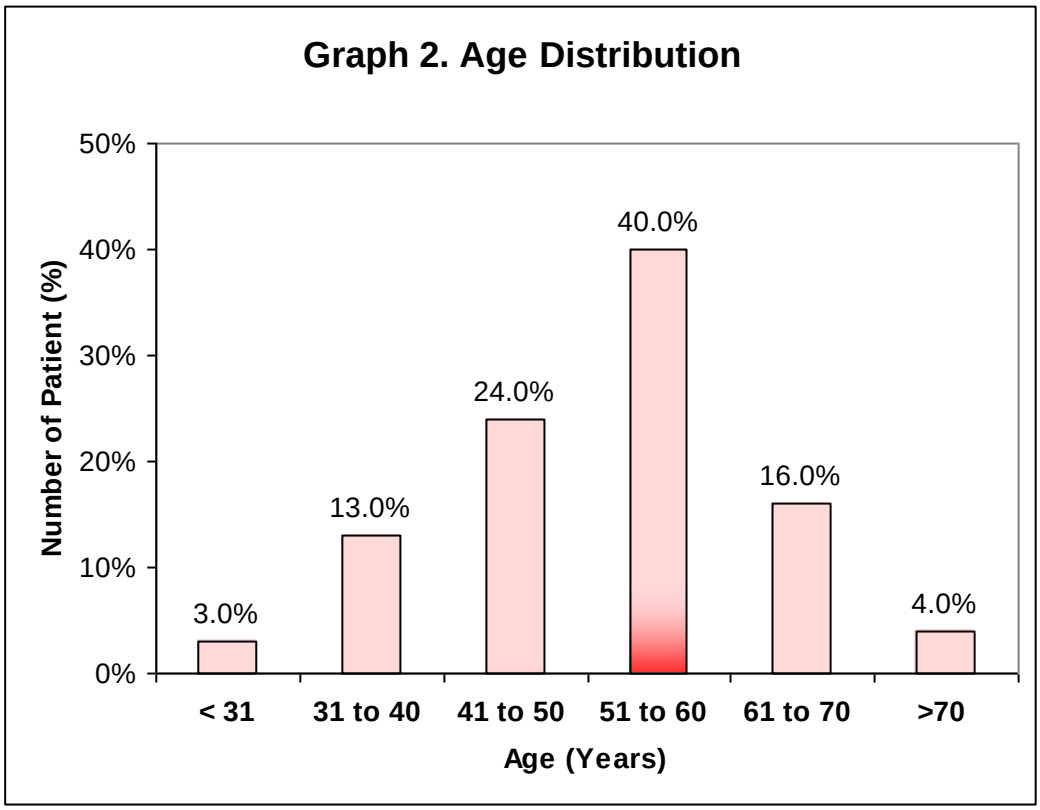
Gender	Distribution (n=100)	
	Number	**Percent**
Male	84	84.00
Female	16	16.00
Total	**100**	**100.00**



In this study males outnumbered females (84% vs 16%) with male to female ratio of 5.25:1.

Table 2. Age Distribution

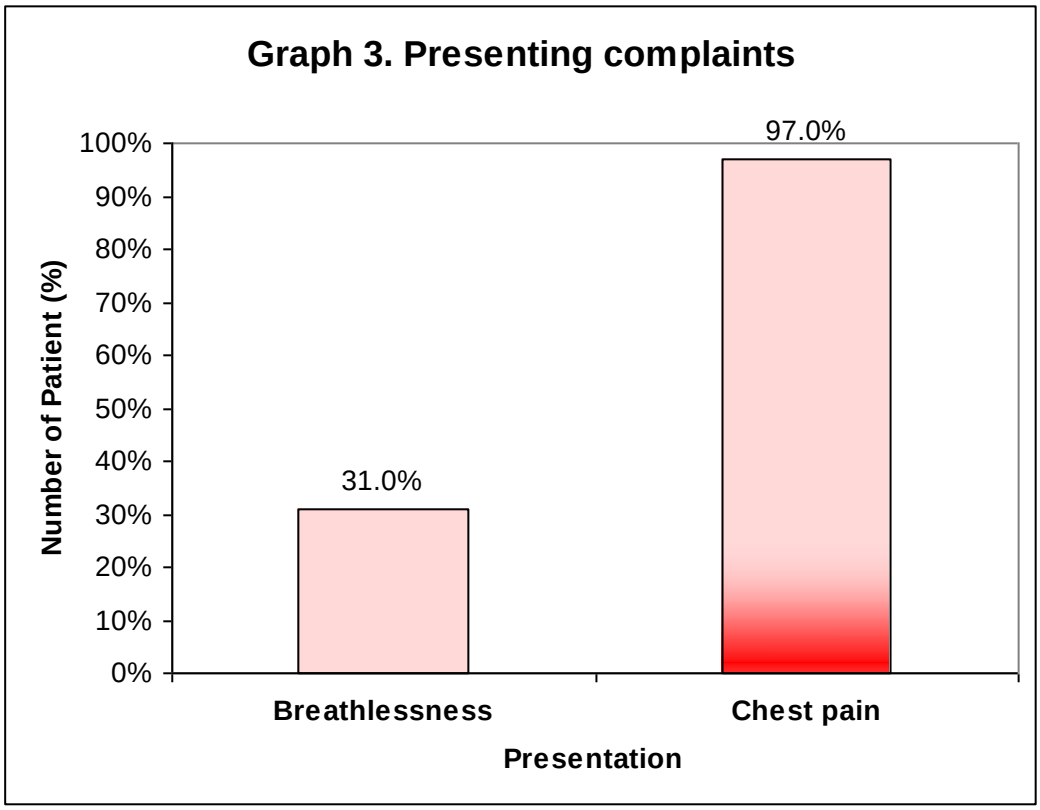
Age group (Years)	Distribution (n=100)	
	Number	**Percent**
< 31	3	3.00
31 to 40	13	13.00
41 to 50	24	24.00
51 to 60	40	40.00
61 to 70	16	16.00
> 70	4	4.00
Total	**100**	**100.00**



In age distribution most of the patients (40%) were in the in the age group of 51 to 60 years followed by 24% in 41 to 50 years and 16% in 61 to 70 years.

Table 3. Presenting complaints

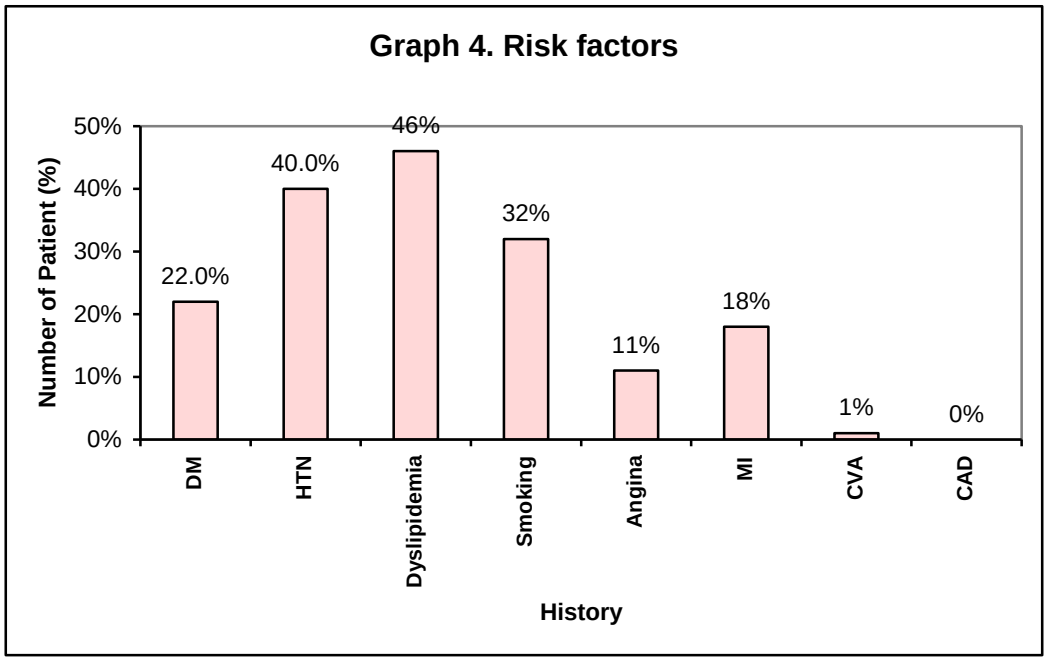
Complaints	Distribution (n=100)	
	Number	**Percent**
Breathlessness	31	31.00
Chest Pain	97	97.00



Majority of the patients (97%) presented with complaints of chest pain and breathlessness was noted in 31%. However, both complaints were seen in most of the patients.

Table 4. Risk factors

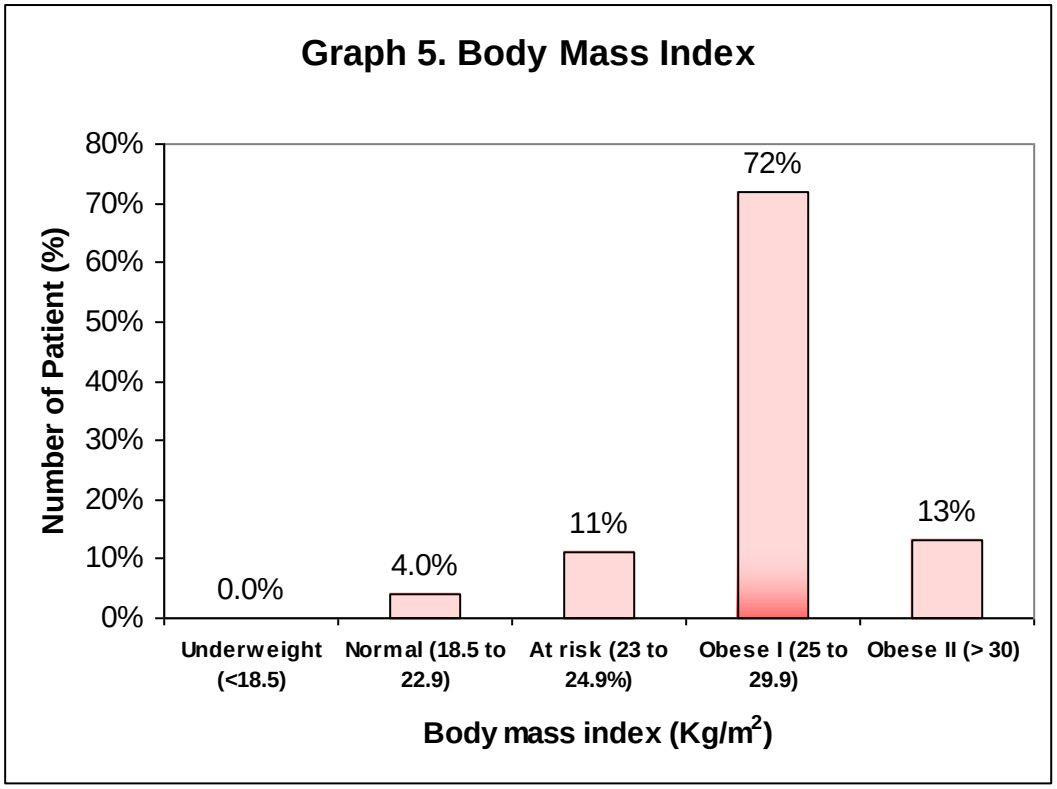
Risk factors	Distribution (n=100)	
	Number	**Percent**
Diabetes	22	22.00
Hypertension	40	40.00
Dyslipidemia	46	46.00
Smoking	32	32.00
Angina	11	11.00
MI	18	18.00
CVA	1	1.00
CAD	0	0.00



Among the patients of CAD most of the patients had multiple risk factors. Dyslipidemia was found to be the most common among them (46%) followed by history of hypertension, smoking, and diabetes (40%, 32% and 22%). Most of the patients which were admitted in the hospital were already initiated on lipid lowering agent.

Table 5. Body Mass Index

BMI (kg/m^2)	Distribution (n=100)	
	Number	**Percent**
Underweight (< 18.5)	0	0.00
Normal range (18.5 to 22.9)	4	4.00
At Risk (23 to 24.9)	11	11.00
Obese I (25 to 29.9)	72	72.00
Obese II (> 30)	13	13.00
Total	**100**	**100.00**



A large proportion of the patients were in the obese I group (72%). However 13% of patients were in obese II group and 11% were at risk. The mean waist circumference was 84.66 ±8.38 cms. The mean BMI was 27.21 ± 2.41 Kg/m^2

Table 6. Vitals and BP

Vital parameters	Mean	SD
Pulse rate (beats/min)	80.2	8.56
Systolic blood pressure (mm Hg)	133.2	18.29
Diastolic blood pressure (mm Hg)	82.2	9.70

In the present study mean pulse rate was 80.20 ± 8.56 beats per minutes. The mean systolic and diastolic blood pressure was 133.20 ± 18.29 and 82.20 ± 9.70 mm Hg respectively.

Table 7. Investigations

Investigation	Mean	SD
Fasting blood sugar (mg/dL)	128.7	55.56

In this study mean fasting blood sugar levels were 128.70 ± 55.56 mg/dL.

Table 8. Lipid profile

Parameters	Mean value	
	Mean	**SD**
Total cholesterol (mg/dL)	170.24	32.51
Triglycerides (mg/dL)	131.20	51.75
HDL (mg/dL)	43.55	15.11
LDL (mg/dL)	91.72	32.93
Hs-CRP (mg/dL)	5.06	4.58

The mean parameters of the study population is as shown in table 9.

Table 9. Overall mean apolipoprotein (n=100)

	Mean	**SD**
Apo A (mg/dL)	107.3	23.5
Apo B (mg/dL)	72.1	21.14
Apo B to Apo A ratio	1.61	0.56

Overall mean Apo A was 107.3 ± 23.5 mg/dL and Apo B was noted as 72.1 ± 21.14 mg/dL. The mean Apo B to Apo A ratio was 1.61 ± 0.56.

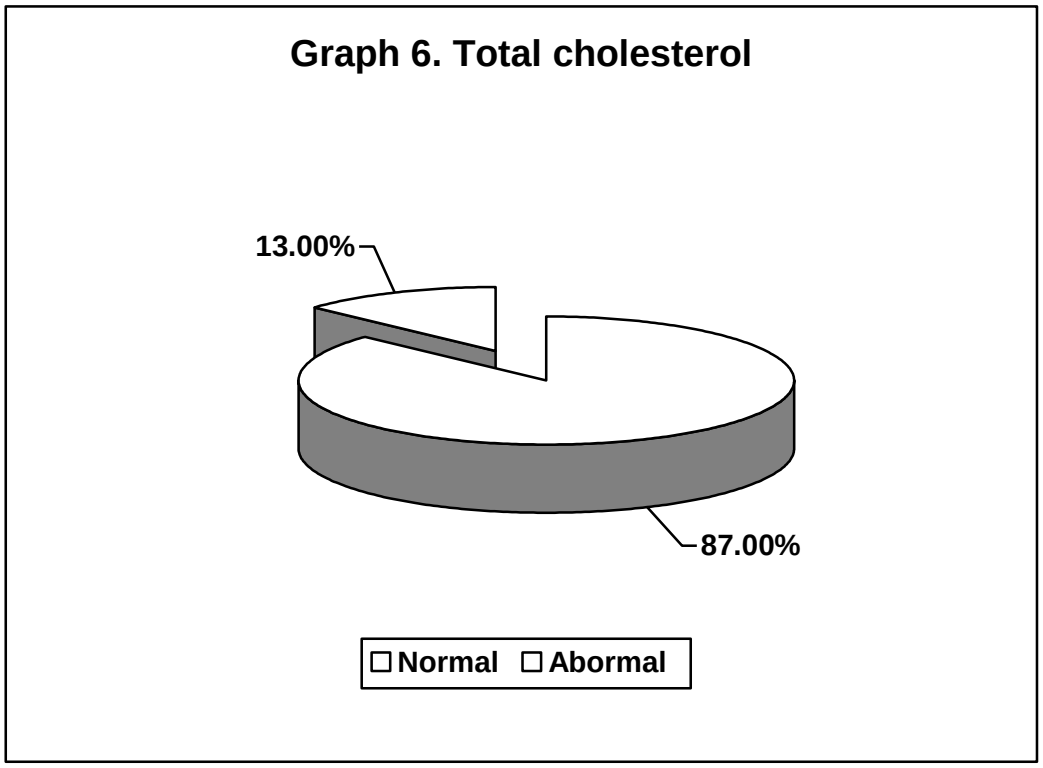
Table 10. Characteristics and biochemical profile of 84 male and 16 females

Parameters	Males		Females	
	Mean	**SD**	**Mean**	**SD**
Age (Years)	52.23	10.98	56.25	10.15
BMI (Kg/m^2)	26.97	2.35	28.47	2.41
Waist circumference (Cms)	83.96	8.13	88.31	8.97
Total cholesterol (mg/dL)	171.12	31.42	165.63	38.56
Triglycerides (mg/dL)	132.65	51.94	123.56	51.70
HDL (mg/dL)	43.57	16.10	43.44	8.59
LDL (mg/dL)	90.32	31.83	99.06	38.51
HDL to Total cholesterol ratio	0.26	0.08	0.28	0.08
Hs-CRP (mg/dL)	5.01	4.67	5.31	4.21
Apolipoprotein A (mg/dL)	71.64	21.50	74.50	19.58
Apolipoprotein B (mg/dL)	105.40	22.58	117.00	26.52
Apo B to Apo A ratio	1.59	0.56	1.68	0.55

The mean characterstics and biochemical profile of males and females are as shown in table 11.

Table 11. Total cholesterol

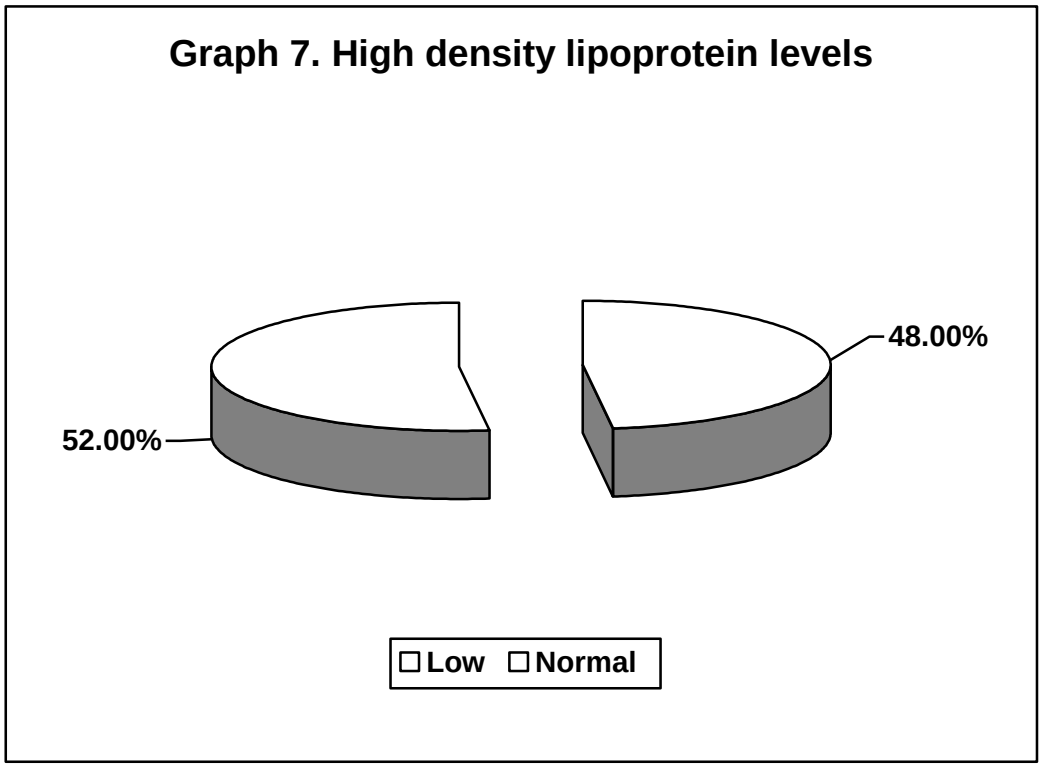
Total cholesterol (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
Normal (< 200)	87	87.00
Abnormal (> 200)	13	13.00
Total	**100**	**100.00**



In this study, based on total cholesterol levels < 200 mg/dL, 87% patients had normal total cholesterol levels compared to 13% patients who had raised total cholesterol levels. The mean total cholesterol levels were 170.24 ± 32.51 mg/dL.

Table 12. High density lipoprotein levels

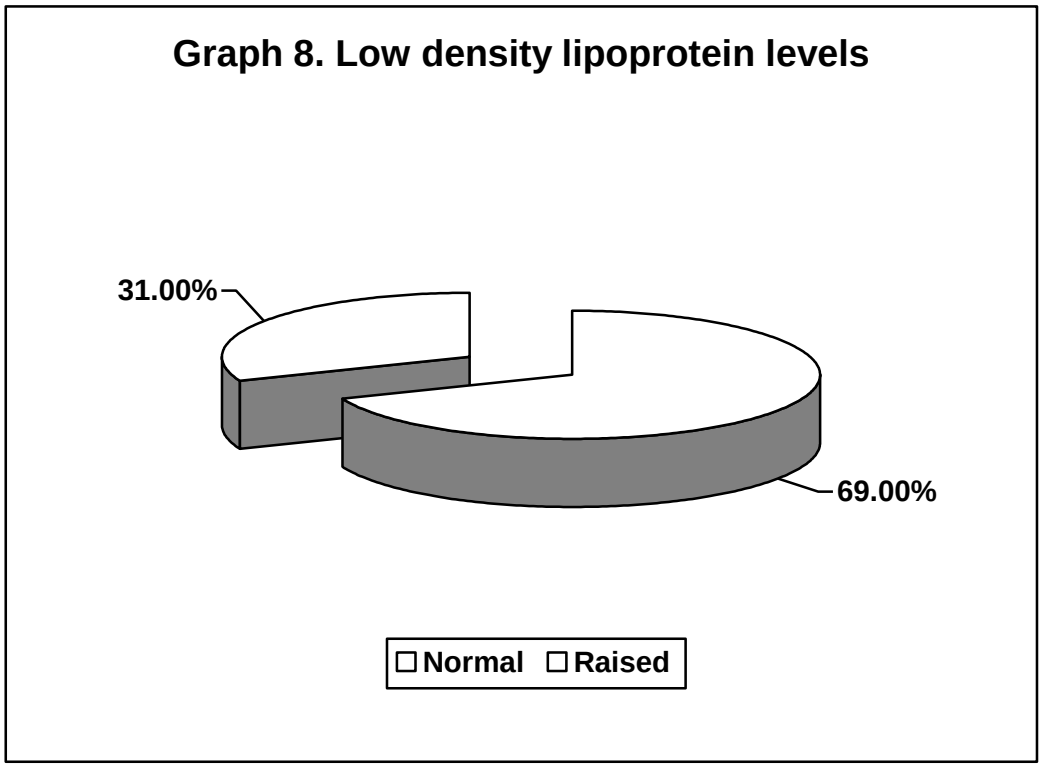
High density lipoprotein levels (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
Low (Males < 40; Females < 50)	48	48.00
Normal (Males > 40; Females > 50)	52	52.00
Total	**100**	**100.00**



In this study, based on HDL levels < 40 mg/dL in males and < 50 mg/dL in females, 52% patients had normal HDL levels compared 48% patients who had low HDL levels. The mean HDL levels were 43.55 ± 15.11 mg/dL

Table 13. Low density lipoprotein levels

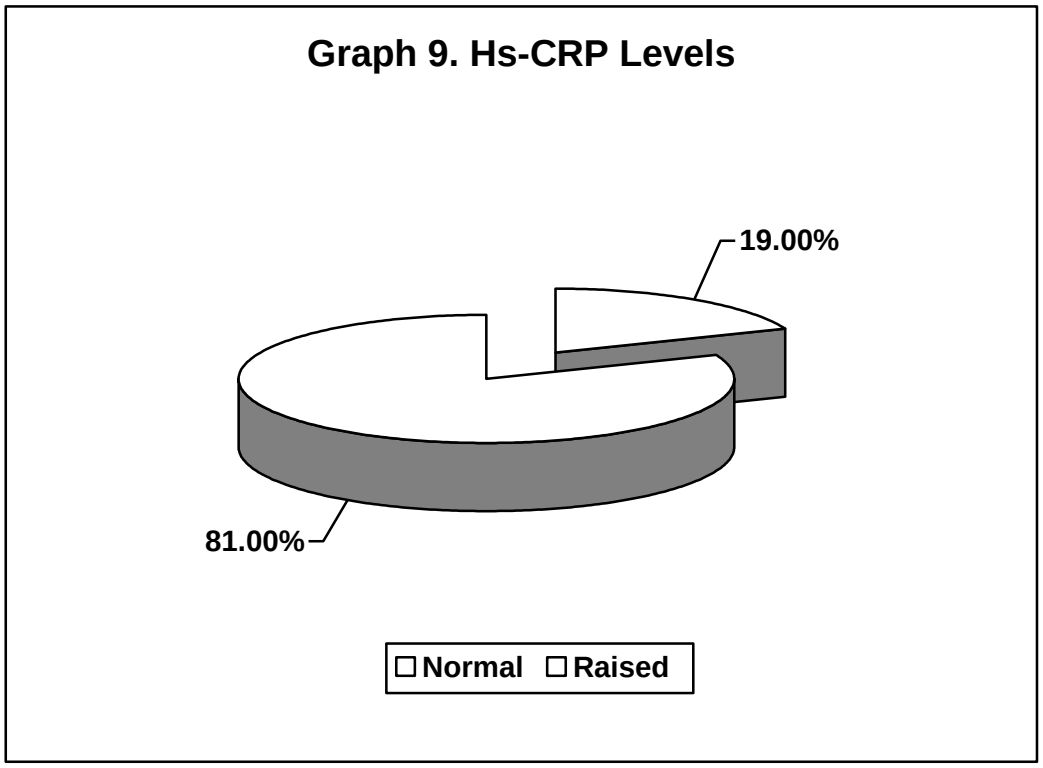
Low density lipoprotein levels (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
Normal (< 100)	69	69.00
Raised (> 100)	31	31.00
Total	**100**	**100.00**



In the present study, 69% patients had LDL levels < 100 mg/dL and in 31% of the patients LDL levels were > 100 mg/dL. The mean LDL levels were 91.72 ± 32.93 mg/dL.

Table 14. Hs-CRP levels

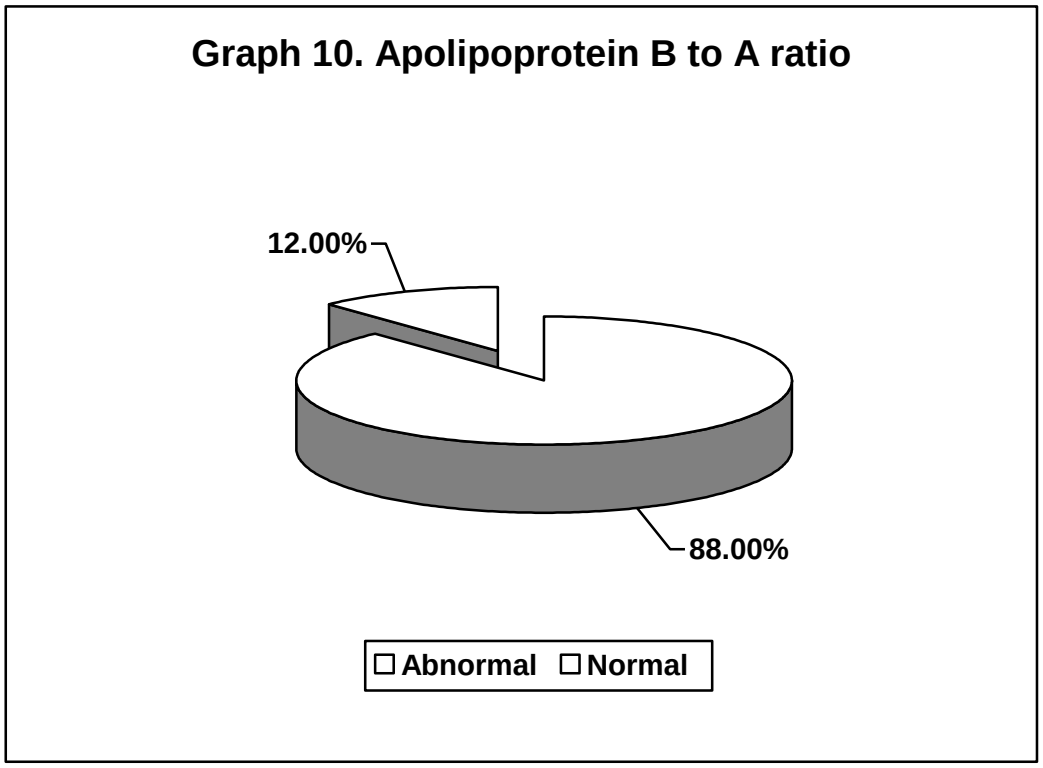
Hs-CRP Levels (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
Normal (< 3)	19	19.00
Raised (> 3)	81	81.00
Total	**100**	**100.00**



In this study, majority (81%) patients had high Hs-CRP levels (> 3) and in the remaining (19%) Hs-CRP levels were normal (< 3). The mean LDL levels were 5.06 ± 4.58 mg/dL.

Table 15. Apolipoprotein B to A ratio

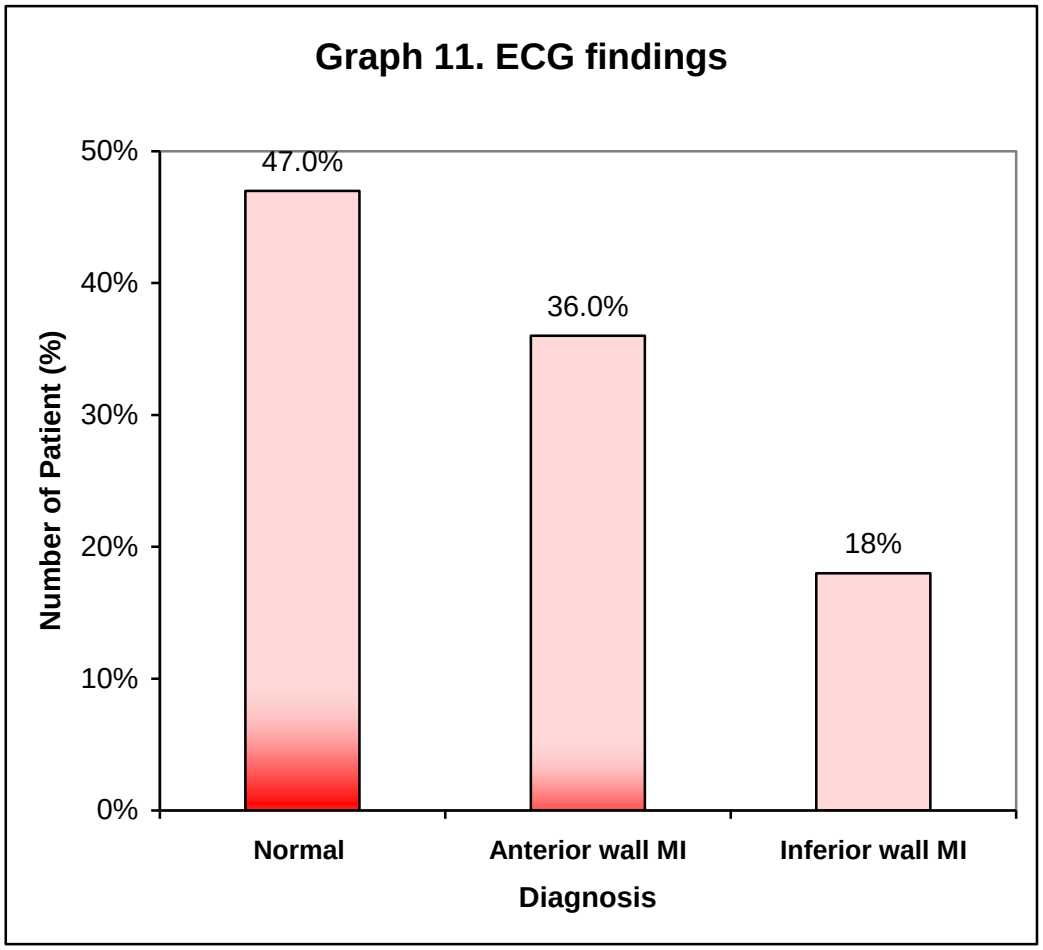
Apolipoprotein B to A Ratio	Distribution (n=100)	
	Number	**Percentage**
Abnormal (> 0.9 males; > 0.8 females)	88	88.00
Normal (< 0.9 males; < 0.8 females)	12	12.00
Total	**100**	**100.00**



In this study, majority of the patients (88%) had abnormal apo B to A ratio and in 12% it was normal.

Table 16. ECG findings

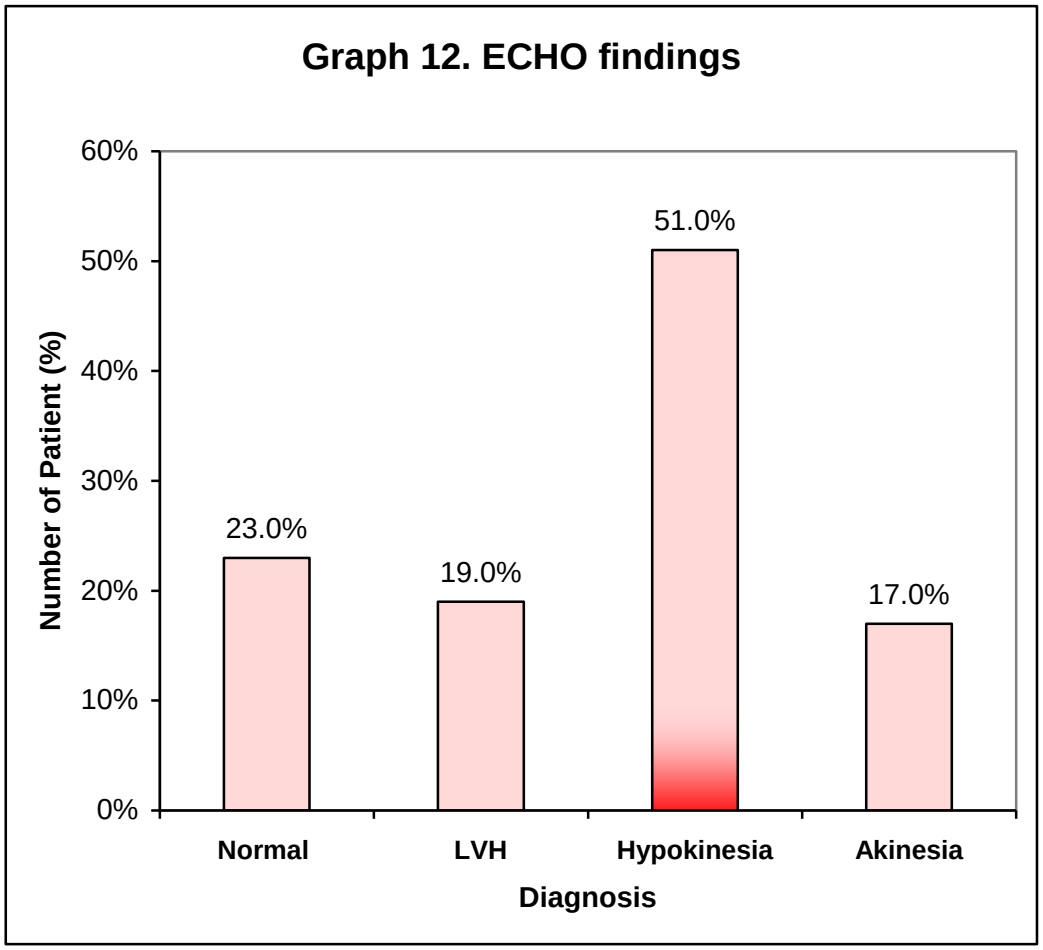
ECG Findings	Distribution (n=100)	
	Number	**Percentage**
Normal	47	47.00
Anterior wall MI	36	36.00
Inferior wall MI	18	18.00



The ECG was found normal in 47% patients, anterior wall MI in 36% and inferior wall MI was noted in 18% of the patients.

Table 17. ECHO findings

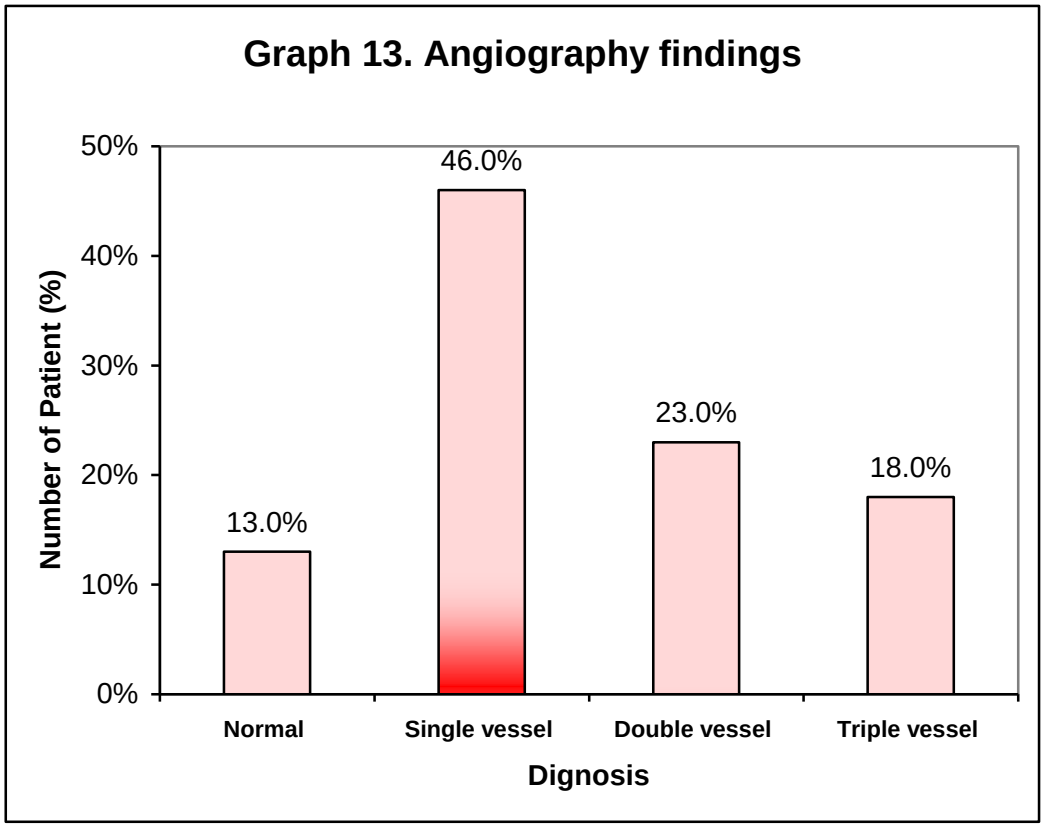
ECHO	Distribution (n=100)	
	Number	**Percentage**
Normal	23	23.00
LVH	19	19.00
Hypokinesia	51	51.00
Akinesia	17	17.00



The echocardiography showed hypokinesia in 51% and akinesia in 17% patients. LVH was noted in 19% and 23% patients had normal echocardiography.

Table 18. Angiographic findings

Angiographic findings	Distribution (n=100)	
	Number	**Percent**
Normal	13	13.00
Single vessel	46	46.00
Double vessel	23	23.00
Triple vessel	18	18.00
Total	**100**	**100.00**



In the present study the angiographic findings were normal in 13% and CAD was noted in 87% patients of which 46% had single vessel disease, 23% double vessel disease and 18% had triple vessel disease.

Table 19. Comparison of Apo B to Apo A ratio with CAD

Angiographic findings	Apo B to A ratio			
	Abnormal (n=88)		Normal (n=12)	
	Number	Percent	Number	Percent
Normal coronaries	9	69.23	4	30.76
Coronary artery disease	79	90.8	8	9.19
x^2_{YC}=16.407				p<0.001
OR = 14	95% CI; 3.60 – 54.46			p<0.001

In this study of the 88 patients with abnormal apo B to A ratio, 90.8% had coronary artery disease and in 9.19% of patients with CAD apo B to apo A ratio was normal. This difference was statistically significant (p<0.001).

Table 20. Correlation of History of dislipidemia with Apo B/A ratio

Angiographic findings	Abnormal Apo B/A (n=88)				Normal Apo B/A (n=12)			
	H/o of dyslipidemia (n=43)		No history (n=45)		H/o of dyslipidemia (n=3)		No history (n=9)	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Normal	0	0.00	9	20.00	0	0.00	4	44.44
Single	16	37.21	25	55.56	1	33.33	4	44.44
Double	15	34.88	6	13.33	2	66.67	0	0.00
Triple	12	27.91	5	11.11	0	0.00	1	11.11
Total	**43**	**100**	**45**	**100**	**3**	**100**	**9**	**100**

x^2=13.679 p<0.001

In this study of the 88 patients with abnormal apo B to A ratio, 43 patients had history of dyslipidemia. Among them 27.91% patients had triple vessel disease, 34.8% had double vessel disease, and 37.21% had single vessel disease whereas in those with no history of dislipidemia (45 patients) 11.11% had triple vessel disease, 13.33% had double vessel disease and 55.5% had single vessel disease. This difference statistically significant (p<0.001).

Table 21. Correlation of Apo B/A ratio with BMI

BMI	Apo B to A ratio			
	Abnormal (n=88)		Normal (n=12)	
	Number	Percentage	Number	Percentage
Underweight (< 18.5)	0	0.00	0	0.00
Normal range (18.5 to 22.9)	0	0.00	4	33.33
At Risk (23 to 24.9)	5	5.68	6	50.00
Obese I (25 to 29.9)	70	79.55	2	16.67
Obese II (> 30)	13	14.77	0	0.00
Total	**88**	**100.00**	**12**	**100.00**

x^2=55.680 p<0.001

In this study, out of the 88 patients with abnormal apo B to apo A ratio, 79.55% patients had obese I category and 14.77% had obese II category whereas in patients with normal apo B to apo A ratio 33.33% had normal BMI and 50% were at risk and this difference statistically significant (p<0.001).

Table 22. Correlation of abnormal Apo B/A ratio with BMI and CAD

Angiographic findings	Abnormal Apo B/A ratio (n=88)									
	Underweight (n=0)		Normal (n=0)		At Risk (n=5)		Obese I (n=70)		Obese II (n=13)	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Normal	0	0.0	0	0.0	5	100	7	10.00	2	15.38
Single	0	0.0	0	0.0	0	0.0	29	41.43	7	53.85
Double	0	0.0	0	0.0	0	0.0	20	28.57	1	7.69
Triple	0	0.0	0	0.0	0	0.0	14	20.00	3	23.08
Total	**0**	**00**	**0**	**00**	**5**	**100**	**70**	**100**	**13**	**100**

x^2=28.250 p<0.001

In the present study among patients (n=88) with abnormal apo B to apo A ratio, 70 had obese I category. Among them 41.43% had single, 28.57% had double and 20% had triple vessel disease. Of the 13 obese II patients, 53.85% had single, 7.69 had double and 23.03% had triple CAD. However all the five patients with at risk obesity had normal coronaries. This difference was statistically significant (p<0.001).

Table 23. Correlation of Apo B/A ratio with total cholesterol and CAD

Angiographic Findings	Abnormal Apo B/A (n=88)				Normal Apo B/A (n=12)			
	TC < 200 (n=78)		TC > 200 (n=10)		TC < 200 (n=9)		TC > 200 (n=3)	
	No	%	No	%	No	%	No	%
Normal	5	6.41	4	40.00	4	44.44	0	0.00
Single	39	50.00	2	20.00	4	44.44	1	33.33
Double	19	24.36	2	20.00	1	11.11	1	33.33
Triple	15	19.23	2	20.00	0	0.00	1	33.33
Total	**78**	**100.00**	**10**	**100.00**	**9**	**100.00**	**3**	**100.00**

$x^2 = 11.564$ p=0.009

In this study abnormal apo B to A ratio was found in 88 patients among them 78 had normal total cholesterol levels (less than 200 mg/dL). Among these patients with normal total cholesterol levels single vessel disease was seen in 50%, double in 24.36% and triple in 19.23%. This difference was statistically significant (p=0.009).

Table 24. APO B/A ratio in CAD Vs Normal coronary arteries with normal LDL (<100 mg/dL) (n=69)

	Abnormal APO B/A		Normal APO B/A	
	Number	**Percent**	**Number**	**Percent**
Normal coronaries	6	54.5	5	45.5
Coronary artery disease	52	89.7	6	10.3
x^2_{YC}=6.087				p=0.014
OR = 7.22		95%CI 1.68-31		p=0.008

In the present study among the patients with normal LDL (n=69) 58 patients had abnormal apo B to A ratio. Among these, 89.7% patients had coronary artery disease and this difference was statistically significant ($p<0.05$).

Table 25. Correlation of Apo B/A ratio with HsCRP

HsCRP	Apo B to A ratio			
	Abnormal (n=88)		Normal (n=12)	
	Number	Percentage	Number	Percentage
Normal (< 3)	12	13.64	7	58.33
Raised (> 3)	76	86.36	5	41.67
Total	**88**	**100.00**	**12**	**100.00**

x^2=13.708 p<0.001

In the present study among the patients with raised Hs-CRP (n=81), 76 (86.36%) patients had abnormal apo B to apo A ratio and this difference was statistically significant (p<0.001).

Chapter 6

Discussion

DISCUSSION

Although studies of lipids and the degree of coronary atherosclerosis began in the late 1960s, uncertainty remains on which lipid measurement best discriminates the degree of CAD. Discussions on which is the "most influential" lipid parameter have been particularly unrewarding. Epidemiological and clinical studies have consistently demonstrated that an elevated concentration of LDL-C in plasma is associated with an increased risk of CAD. Increased LDL-C concentration levels are a well-established risk factor for CAD and are currently recommended as the primary target for lipid-lowering therapy for the prevention and treatment of cardiovascular disease, although its unique superiority over other circulating predictors of CAD is unclear.[63]

However, there is considerable interest in the potential value of measuring circulating concentrations of apolipoproteins to assist in the assessment of the risk of CAD, as well as in their potential aetiological relevance to the disease. Apolipoproteins are important components of lipoprotein particles, and there is accumulating evidence that the measurement of various forms of apolipoproteins may improve the prediction of the risk of cardiovascular disease.[63]

Clinical trials using softer end-points, like coronary angiography, angina pectoris and nonfatal myocardial infarction, have been published and reviewed, with most pointing to the importance of Apo B and Apo A-I as risk indicators. Apo B is present as a single molecule in LDL, IDL and VLDL, while Apo A-I is the major apolipoprotein associated with HDL.[63]

Also, the prevalence of dyslipidaemia, especially low levels of HDL-C, is high in south asian population. There is abundant evidence that the risk of coronary atherosclerotic cardiovascular disease is directly related to plasma lipid and apolipoprotein levels, but the relationships between the serum Apo A-I and Apo B levels and the extent of CAD have not been consistently shown.[63]

The present study was an attempt to investigate the possible relationship of the serum levels of Apo B, Apo A-I, and lipids with the severity of coronary lesions and number of vessels diseased, these parameters were examined in 100 patients in this region of India.

In this study, the utility of apolipoproteins as a marker for cad and their superiority over lipid profile was explored. 100 patients were taken all of whom underwent coronary angiography to determine the atherosclerotic burden.

In the study of the 100 subjects 84% were males and 16% were females indicating male preponderance with male to female ratio of 5.25:1. In various studies[17,65,66] similar findings have been noted. This might be due to the increased prevalence of risk factors of CAD in males.

Majority of the patients, 40 were found to be between 51 to 60 years old with 24 between 41 to 50 and 16 from 61 to 70 years. Overall, the mean age was was 52.87 ± 10.89 years. Among males the mean age was 52.23 ± 10.98 years and in females it was 56.25 ± 10.15 years. Similar findings were reported in a study[67] done in South Asian Countries which showed the mean age for CAD in Indian as 53.0 ± 11.4 years, in males the mean age was 51.0 ± 10.4 and in

females 57.3 ± 11.6. Other studies similar mean age of males and females were noted.[63,65.66]

In this study, the patients had multiple risk factors. Dyslipidemia was the most common among them (46%) followed by hypertension, smoking and diabetes (40%, 32% and 22%). Similar distribution of risk factors was also noted in similar studies done earlier except smoking which was found to be 18.1% in males and 12.8 in females. [63,65.66]

In the present study, patients which were admitted in the hospital had either history of dyslipidaemia in the family (35%) or had been already initiated on lipid lowering agents by primary health care physicians (65%) because of deranged lipid parameters. It has been proven beyond doubt that lipid lowering agents decrease the levels of LDL but their effects on Apo B has been controversial as proved by ACCESS study.[69] This study has shown that statins have been effective in lowering LDL, but have not shown commensurate changes in Apo B levels.

In this study, most of the patients were in the obese I group reiterating the fact that CAD is intimately related to BMI. The mean BMI in the study was 27.21 ± 2.41 Kg/m^2. In males the mean BMI was 26.97 ± 2.35 and in females it was 28.47 ± 2.41 Kg/m^2. The mean total cholesterol was found to be 170.24 ± 32.51 mg/dL. In males the mean total cholesterol was 171.12 ± 31.42 mg/dL and in females it was 165.63 ± 38.56 mg/dL. This finding was similar to previous studies.[65,66]

NCEP guidelines regard total cholesterol cut off value of less than 200 mg/dL as within the normal limits. In this study 87% were found to have total cholesterol < 200 and 13% mg/dL. The mean total cholesterol was found to be 171.12 ± 31.42 mg/dL in males and in females it was 165.63 ± 38.56 mg/dL. In previous study[65] done in Israel mean total cholesterol among males was 219 ± 30 mg/dL and females it was 230 ± 30 mg/dL. Variation in the present study can be attributed to patients being on lipid lowering agents like statins.

In the present study, large number of patients were found to have HDL levels in the normal range. HDL levels were found to be more than normal range (>40 in males and >50 in females) in 52% of the patients with CAD. Overall, the mean HDL was 43.55 ± 15.11 mg/dL and in males the HDL levels were 43.57 ± 16.10 mg/dL and in females it was 43.44 ± 8.59 mg/dL which was similar to previous studies.[65,66]

Conventionally it was been proven that lipid profile plays a vital role in the determination of CAD. High HDL has always been stated as a protective marker for CAD. More than half the patients in this study having HDL more than normal range were found to have CAD, obviating the need for a better risk factor and prognostic marker for atherosclerotic disease.

In this study 69% of the patients with CAD had LDL less than 100 mg/dL. The mean LDL was found to be 91.72 ± 32.93 mg/dL. In males the mean LDL levels were 90.32 ± 31.83 mg/dL and in females 99.06 ± 38.51 mg/dL whereas a study from Israel[1] showed high levels of mean LDL that is 154 ± 27.7 mg/dL in males and 160 ± 28 mg/dL in females. Similar values of high LDL were

found in the other study done in UK.[66] Low density lipoproteins have been the standard marker for determination of the risk of CAD. LDL levels more than 100 mg/dL in patients have been known to be associated with higher risk of CAD. The disparity in the levels of LDL in the present study and other studies can be explained by the fact that most of the patients in this study were on lipid lowering agents like statins. Also, these findings suggest that determination of the risk for CAD may not entirely be associated with the levels of LDL and it may not be the gold standard determinant for the risk of CAD thus, necessitating the need for newer markers to assess risk of CAD.

Hs-CRP has been a quintessential marker of inflammation with newer models of the pathophysiology of CAD focusing on inflammation as a major culprit for risk of ACS. Hs-CRP assumes paramount importance as a prognostic marker in patients with CAD which has been known to be associated with increase in the levels of this inflammatory marker. In the study this fact was proven with 81% of all patients with CAD were associated higher Hs-CRP. Overall, the mean Hs-CRP was found to be 5.06 ± 4.58 mg/dL. Among males the mean Hs-CRP levels were 5.01 ± 4.67 mg/dL and in females it was 5.31 ± 4.21 mg/dL mean crp values were 0.39+_0.7 with males mean crp levels of 0.35+_0.7 and females 0.44+_0.7.these values were similar to found in this study.

Apo A-I is the major apolipoprotein constituent of the antiatherogenic high-density lipoproteins (HDL). Levels of Apo A-I are strongly associated with those of HDL cholesterol. Apo A-I is critically involved in removing excess cholesterol from tissues and incorporating it into HDL for reverse transport, either directly or indirectly via LDL to the liver.

In the present study, the mean Apo A -1 was found to be 72.10 ± 21.14 mg/dL. The mean Apo A in males was 71.64 ± 21.50 mg/dL and in females it was 74.50 ± 19.58 mg/dL. A study[17] done on Indian population in AIIMS had showed Apo A -1 levels of 76.0 ± 18.1 mg/dL which were similar to findings seen in a study[65] done in Israel where mean Apo A -1 in males was 1.06 ± 0.16 g/L and in females mean Apo A-1 was 1.16 ± 0.16 g/L and a study[66] in Caucasian population showed mean apoa-1 in males as 1.36 ± 0.30 g/l and 1.26 ± 0.25 g/l in females suggesting lower apolipoproteins levels among Indian population compared to Caucasians.

Apolipoprotein B-100 (Apo B) is the chief protein component constituent of the atherogenic very-low-density lipoprotein (VLDL), of intermediate-density lipoprotein (IDL) and of LDL particles, each particle including one Apo B molecule. Hence, plasma Apo B levels reflect the total numbers of atherogenic particles. Apo B is also essential for the binding of LDL particles to the LDL receptor for cellular uptake and degradation of LDL particles.

In the present study the mean Apo B was 107.26 ± 23.50 mg/d. Among the males mean Apo B was 105.40 ± 22.58 mg/dL and in females it was 117.00 ± 26.52 mg/dL. Wide variations have been reported in Apo B levels in previous studies.[17,65,66] A study[17] in Indian population at AIIMS mean Apo B levels in CAD patients were 78.9 ± 19.5 mg/dl. In another study[65] from Israel reported mean Apo B was 1.03 ± 0.17 g/l in males and 1.04 ± 0.16 g/L in females whereas study[66] from UK reported 0.61 ± 0.214 g/L in males and 0.616 ± 0.254 g/L in females.

Apo B, Apo A-I and the Apo B/Apo A-I ratio reflect the status of the major atherogenic and anti-atherogenic pathways of lipoprotein metabolism. Accordingly, high Apo B/Apo A-I ratio indicates a high risk for CVD.

Apolipoprotein B/A ratio was found to be significantly higher (>0.9 in males and >0.8 in females) in 88% of the patients who were found to have CAD on coronary angiography. Overall the mean Apo B /Apo A ratio was 1.61 ± 0.56. Among males the mean ratio was 1.59 ± 0.56 and in females it was 1.68 ± 0.55. A study[66] from UK found Apo B to Apo A ratio of 0.16 ± 0.029. Another study[65] from Israel found the Apo B /Apo A ratio of 1.0 ± 0.2 in males and 0.9 ± 0.2 in females.

The significant number of patients in this category reiterated Apolipoprotein B/Apolipoprotein A ratio as a predictor for risk of CAD. These were similar to the findings in this study.

Out of 100 patients who underwent coronary angiography 46 were found to have single vessel coronary artery disease 23 had double vessel, 18 triple vessel and 13 were found to be normal coronaries.

A significant relationship was found between ratio of Apo B / Apo A and coronary artery disease. Significantly more number of patients (90.8%) with Apo B / Apo A in the abnormal range (>0.9 in males and >0.8 in females) were found to have CAD and only 8 had normal coronary arteries ($p<0.001$). With regard to patients with normal Apo B / Apo A ratio only 8 patients had CAD whereas 4 had normal coronaries. In an Indian study[23] from Delhi where Apo B / Apo A ratio was measured in patients with acute MI, it was found to be 0.96 ± 0.30.

Low density lipoprotein has been established as a risk factor and the primary treatment target for prevention of heart disease. In the study, 69 patients were found to have normal LDL (<100 mg/dL). Among these patients, 58% patients were found to have abnormal Apo B /Apo A ratio; out of which 52% had proven CAD on angiography. This value was statistically significant (p=0.014). These finding were consistent with amoris study[9] which postulated that Apo B was more significant than LDL cholesterol in prediction of risk of MI in both men and women but especially in those having normal / low LDL-C levels. Similar study[63] examined the levels of LDL-C with severity of CAD and found no differences among the subgroup of the patients. The authors examined whether levels of LDL-C, were related to CAD, but did not find an association with CAD. Study revealed strong relations between Apo A-I and Apo B levels and the presence of CAD as defined by the observation of vessel stenosis. These findings were similar to the present study. This suggests that the traditional thought about risk for CAD being less in patients with normal LDL does not hold weightage.

Hence, a new marker for determination of CAD is required. Apo B / Apo A ratio seems to be the much needed answer.

According to NCEP guidelines total cholesterol is considered a risk factor for CAD with cutoff values of >200 mg/dL. In this study we compared patients having abnormal Apo B / Apo A ratio and their total cholesterol values with CAD. Out of 88 patients with abnormal Apo B / Apo A, 78 had total cholesterol < 200 mg/dl. In the group of 78 patients with total cholesterol <200 mg/dL 73 had significant cad (p<0.009). These findings were inconsistent with other

study[63] which did not find any differences in total cholesterol levels with severity of CAD.

This finding in the present study brought to light the importance of the Apo B / Apo A ratio in comparison to total cholesterol as a marker of CAD and the severity of CAD. Thus the findings reemphasized that Apo B / Apo A ratio has a better predictive value than total cholesterol for CAD.

Hs-CRP has been documented in literature as the marker for inflammation. In the study we found a significant correlation (p=0.000) between HsCRP and Apo B/A ratio. In the present study among the patients with raised Hs-CRP (n=81), 76 (86.36%) patients had abnormal Apo B to Apo A ratio and this difference was statistically significant (p<0.001). Endothelial injury causes inflammatory changes in the vessel wall and this increases the inflammatory mediators like HsCRP. This vessel injury is responsible for disruption of plaque leading to ACS. Hence, Apo B/A ratio not only defines the risk for CAD but also can be used in prognostication of CAD in parallel with inflammatory markers like Hs-CRP.

BMI has been known to be in directly related to CAD in all previously published literature.[65,66] In this study we tired to find a correlation between Apo B/A ratio and BMI. In the present study among patients (n=88) with abnormal Apo B to Apo A ratio, 70 had obese I category. Among them 41.43% had single, 28.57% had double and 20% had triple vessel disease. Of the 13 obese II patients, 53.85% had single, 7.69 had double and 23.03% had triple CAD. However all the five patients with at risk obesity had normal coronaries. This difference was

statistically significant ($p<0.001$) thus proving that the ratio of the apoliproprotein were correlated to BMI. The higher the BMI, the more was the risk of CAD indicating importance of Apo B/A ration as a predictive marker. These findings were consistent with previous studies.[65,66]

In this study many patients had dyslipidemia as a risk factor. These patients had either history of dyslipidemia or were already on lipid lowering agents like statins. Of the 88 patients with abnormal Apo B to A ratio, 43 patients had history of dyslipidemia. Among them 27.91% patients had triple vessel disease, 34.8% had double vessel disease, and 37.21% had single vessel disease whereas in those with no history of dyslipidemia (45 patients) 11.11% had triple vessel disease, 33.33% had double vessel disease and 55.5% had single vessel disease. This difference statistically significant ($p<0.001$). Thus having established that single vessel disease was still seen (55.5%) with no history of dyslipidemia but abnormal Apo B to Apo A ratio. Previously no other study has observed this correlation which is statistically significant among dyslipidemia Apo B to Apo A ratio and severity of CAD. This findings confirmed that Apo B to Apo A ratio and dyslipidemia are reliable and important factors for CAD.

Chapter 7

Conclusion

CONCLUSION

The present study was done to determine the levels of Apolipoproteins B and A1 in patients of Ischemic heart disease to find out their significance in predicting risk of coronary artery disease and its severity. On the basis of results obtained from this study, it can be concluded that Apolipoproteins (A and B) and their ratio may be better risk markers of coronary artery disease than conventional lipid profile. Study also demonstrated a relationship between abnormality of apolipoproteins and the severity of coronary artery disease as judged by number of involved vessels. Even in an asymptomatic individual with high Apo B or high Apo B/Apo A ratio, steps should be taken to reduce the risk of developing CAD by controlling other coronary risk factors. Study may also suggest that the measurement of Apo B and Apo A should be added to the routine lipid profile assessment in order to know the atherogenic potential of lipid disorders in a particular case.

Chapter 8

Summary

SUMMARY

Coronary artery disease is a leading cause of morbidity and mortality in the developed world and is rapidly assuming epidemic proportions in developing countries including India. Although abnormal lipids are the most important risk factors for causation of this disease worldwide, there is large proportion of patients, particularly in India who manifest significant CAD and have normal or near normal conventional lipid profile. Extensive research has been done to determine the risk factors unique to this group. Important amongst them are Apolipoproteins, homocysteine, lipoprotein (a), pro-inflammatory cytokines etc. The present study was undertaken to measure Apo AI, Apo B and Apo B/Apo AI ratio in patients with Ischemic heart disease undergoing diagnostic coronary angiography and to find correlation of Apolipoprotiens levels with severity of disease and with conventional lipid profile.

The study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 100 patients with Ischemic heart disease diagnosed on the basis of clinical evaluation and who were subjected to diagnostic coronary angiography.

Dyslipidemia was found to be the most common risk factor (46%). A large proportion of the patients were in the obese I group (72%). majority of the patients (88%) had abnormal apo B to A ratio. Significant obstructive CAD was noted in 87% patients of which 46% had single vessel disease, 23% double vessel disease and 18% had triple vessel disease. Of the 88 patients with abnormal Apo B/ Apo A ratio, 79 had coronary artery disease. Similarly, on the other hand out

of 87 patients of CAD, 90.8% had abnormal ratio and 9.19% had normal ratio. This difference was statistically significant ($p<0.001$).

Out of 69 patients of normal LDL (<100 mg/dl), 58 had abnormal Apo B/Apo A ratio of which 52 (89.7%) had angiographically proven CAD. In these patients with normal LDL Apo B/Apo A ratio was found abnormal with statistically significant correlation to severity of CAD on angiography ($p=0.008$). This finding reiterated that Apo B, Apo A and their ratio are better markers of coronary artery disease than conventional lipid profile.

Study also demonstrated a relationship between the severity of coronary artery disease as judged by number of involved vessels and abnormal Apo B/Apo A ratio. Study also showed correlation between Apo B / Apo A ratio and severity of CAD in patients with normal LDL levels (< 100 mg/dL) and also correlation was found between Apo B/ Apo A ratio and CAD in patients with history of dyslipidemia on lipid lowering agents. This suggests that the measurement of Apo B and Apo A should be routinely added to the routine lipid profile in order to assess the atherogenic potential of lipid disorders.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

"ASSESSMENT OF LEVELS OF APOLIPOPROTEINS IN PATIENTS OF CORONARY ARTERY DISEASES"

Objective and purpose of the study

This research is intended to study the assessment of apolipoproteins in patients of coronary artery diseases .The principal investigator of the study is Dr. Ranjan Modi under the guidance of Dr. V.A. Kothiwale.

Procedure

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future

health care or other services that you receive. The study doctor or sponsor may stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about me during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify me in this research record. Information from this study may be published but my identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant you may call Dr. V. D. Patil, Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number 0831-2471350.

In case of the queries during study or in future you may contact following person

Principal investigator : Dr. Ranjan Modi

Guide : Dr. V. A. Kothiwale

Consent Statement

You voluntarily agree to take part in this study by signing below. You may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read, or it has been read to you, this entire consent form, and have had all your questions answered.

Name of the Participant or legally authorized representative: _____

Signature / Thumb print _____

Name of the Witness : _____

Signature _____

Investigator Name : _____

Signature _____

Date: Place:

Annexures

Annexure II

ANNEXURE II – PROFORMA

Case No:

NAME: AGE/SEX:

IP No. ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

HISTORY OF PRESENTING ILLNESS:

PAST HISTORY:

k/c/o Type 2 diabetes mellitus yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment –

Family History

k/c/o Hypertension yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment –

Family History

k/c/o Dyslipidemia yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment-

Family History

Past H/o Angina yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment-

Family History

Past H/o Myocardial Infarction yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment-

Family History

Past H/o Cerebrovascular events yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment-

Family History

Past H/o Coronary artery disease yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment-

Family History

Any other relevant past history

ON EXAMINATION:

- NUTRITION :

HEIGHT:

WEIGHT:

BMI :

WAIST CIRCUMFERENCE:

- VITALS:

Pulse Rate:

Blood Pressure:

SYSTEMIC EXAMINATION

Cardiovascular system:

Respiratory System:

Per Abdomen:

Central Nervous System:

INVESTIGATIONS:

- FBS –
- TOTAL TRIGLYCERIDES –
- TOTAL HDL –
- TOTAL CHOLESTEROL-
- ESTIMATED LDL -
- HsCRP LEVELS –
- APOLIPOPROTEINS A
- APOLIPOPROTEINS B –
- ECG-
- Angiography
- Any other relevant investigation-

Signature of Patient Signature of Examiner

Signature of Guide

ANNEXURE III - MASTER CHART

Sl. No.	IP. No.	Sex	Age (Years)	Breathlessness	Chest pain	Smoking	Diabetes mellitus	Hypertension	Dyslipidemia	Angina	MI	CVA	CAD	Body mass index (Kg/m2)	Waist circumference (Cms)	Systolic	Diastolic	Pulse Rate (/Min)	CVS	Respiratory system	Per abdomen	Central Nervous System	Fasting blood sugar (mg/dL)	Total cholesterol (mg/dL)	Total Triglycerides (mg/dL)	High density Lipoprotein (mg/dL)	Low density lipoprotein (mg/dL)	HsCRP	Apolipoprotein B	Apolipoprotein A	HDL / Total cholesterol ratio	Apo B / Apo A Ratio	Normal	Anterior wall	Inferior wall	Normal	LVH	Apex	Anterior Wall	Inferior wall	Apex	Anterior Wall	Inferior wall	Normal	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex
1	372466	M	54	-	+	-	-	-	+	+	-	-	-	31.2	88	120	70	80	-	-	-	-	97	244	136	42	160	3.0	102	58	0.2	1.76	N	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
2	372853	M	27	-	+	-	-	-	-	+	-	-	-	29.2	80	100	70	80	-	-	-	-	85	129	114	30	76	10.1	62	113	0.2	0.55	-	-	+	N	-	-	-	-	-	-	-	N	+	-	-	-	-	-	-	-
3	372272	M	65	-	+	-	-	-	-	-	-	-	-	23.4	70	120	80	90	-	-	-	-	88	129	269	33	42	2.5	62	72	0.3	0.86	N	-	-	-	+	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
4	372236	M	36	+	+	-	-	+	+	-	-	-	-	24.2	80	120	80	80	-	-	-	-	73	135	241	33	54	3.9	82	98	0.2	0.84	N	-	-	N	-	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
5	370227	M	60	-	+	+	-	-	-	-	-	-	-	35.6	96	119	70	80	-	-	-	-	81	161	121	30	101	3.1	87	46	0.2	1.89	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	+	+	-	-	-	-
6	372838	M	45	+	+	+	-	+	+	-	+	-	-	32.0	85	170	60	80	-	-	-	-	97	153	207	39	72	2.7	101	92	0.3	1.10	N	-	-	-	+	-	-	-	-	-	-	N	-	-	+	-	-	-	-	-	-
7	372842	M	51	+	+	-	-	+	-	-	+	-	-	21.4	62	130	80	86	-	-	-	-	106	125	112	41	61	2.9	92	96	0.3	0.86	N	-	-	-	+	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
8	372241	M	45	-	+	-	-	+	+	-	-	-	-	27.9	70	124	90	86	-	-	-	-	91	179	130	36	117	5.0	97	55	0.2	1.76	N	-	-	N	-	-	-	-	-	-	-	N	-	+	-	-	+	+	-	-	-
9	372168	M	42	-	+	+	-	-	-	-	-	-	-	27.9	75	160	100	80	-	-	-	-	173	169	110	35	112	17.1	110	60	0.2	1.83	-	+	-	-	-	-	-	-	-	+	N	-	-	-	-	-	-	+	+	+
10	370404	M	60	-	+	-	-	-	-	-	-	-	-	22.8	75	130	80	80	-	-	-	-	99	205	247	44	106	2.5	93	107	0.2	0.87	N	-	-	N	-	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
11	373233	M	32	+	+	-	-	-	-	-	-	-	-	26.6	78	118	70	80	-	-	-	-	144	180	136	32	100	3.5	99	63	0.2	1.57	N	-	-	N	-	-	-	-	-	-	-	N	+	-	-	-	-	-	-	-	-
12	372665	M	40	+	+	+	+	+	+	-	-	-	-	25.2	90	110	70	80	-	-	-	-	159	206	150	42	90	5.1	114	51	0.2	2.24	-	+	-	-	-	-	-	-	+	+	+	N	-	-	-	-	-	-	+	+	+
13	372588	M	47	+	+	-	-	-	+	-	-	-	-	25.6	86	120	90	84	-	-	-	-	70	91	65	28	50	5.6	77	45	0.3	1.71	N	-	-	-	-	-	-	-	-	+	+	N	-	-	-	+	+	-	-	-	-
14	366060	M	70	-	+	-	-	-	-	-	-	-	-	25.4	89	130	80	80	-	-	-	-	90	121	139	31	62	4.2	88	55	0.3	1.60	N	-	-	-	+	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
15	372208	M	51	+	-	+	-	-	-	-	-	-	-	24.8	80	130	90	86	-	-	-	-	102	96	126	25	46	4.0	81	66	0.3	1.23	-	+	-	-	-	-	+	+	-	-	-	N	-	+	-	-	-	-	-	-	-
16	369550	M	51	-	+	-	-	-	-	-	-	-	-	24.6	79	126	80	80	-	-	-	-	114	190	97	47	124	8.7	89	97	0.2	0.86	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
17	369768	M	30	-	+	-	+	-	+	-	-	-	-	25.0	81	150	100	80	-	-	-	-	335	166	321	30	180	35.1	93	72	0.2	1.29	-	+	-	N	-	-	-	-	-	+	-	N	-	-	-	+	+	-	-	-	-
18	368663	M	40	-	+	-	-	-	-	-	-	-	-	22.6	74	130	80	80	-	-	-	-	90	113	134	33	53	2.9	50	52	0.3	0.89	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
19	372218	M	38	-	+	+	-	-	-	-	+	-	-	24.6	82	170	80	80	-	-	-	-	127	118	114	27	68	9.3	97	68	0.2	1.43	-	+	-	N	-	-	-	-	+	+	-	N	-	+	-	-	-	-	-	-	-
20	372210	M	55	-	+	-	-	-	-	-	+	-	-	23.6	85	148	80	72	-	-	-	-	99	185	200	37	108	2.6	99	87	0.2	1.14	-	-	+	N	-	-	-	-	-	-	+	N	+	-	-	-	-	-	-	-
21	372290	M	38	-	+	+	-	+	-	+	-	-	-	29.9	90	150	100	70	-	-	-	-	84	210	219	34	132	3.3	110	63	0.2	1.75	N	-	-	-	+	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
22	372426	M	82	+	-	-	-	+	-	-	-	-	-	26.5	86	110	80	60	-	-	-	-	102	143	51	45	88	25.0	90	55	0.3	1.64	N	-	-	-	+	-	-	-	-	-	-	N	+	-	-	-	-	-	-	-	-
23	372275	M	38	-	+	-	-	-	-	+	-	-	-	26.7	88	100	80	60	-	-	-	-	89	88	73	28	45	5.4	90	60	0.3	1.50	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
24	358070	M	48	+	+	+	-	-	+	+	-	-	-	28.3	92	130	100	96	-	-	-	-	72	200	170	50	90	3.0	97	60	0.3	1.62	N	-	-	-	+	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
25	358707	M	63	+	+	-	+	-	-	-	+	-	-	29.0	90	135	90	90	-	-	-	-	100	210	154	60	180	5.0	97	55	0.3	1.76	-	+	-	-	-	-	-	-	-	+	-	N	-	-	-	+	+	-	-	-	-
26	372465	F	40	+	+	-	-	-	+	-	-	-	-	26.0	87	120	80	80	-	-	-	-	89	157	121	40	93	3.6	90	70	0.3	1.29	N	-	-	-	+	-	-	-	-	-	-	N	-	-	-	+	+	-	-	-	-
27	358351	M	58	-	+	-	+	+	-	-	-	-	-	29.7	95	130	80	90	-	-	-	-	191	220	150	88	60	4.8	110	50	0.4	2.20	-	+	+	-	-	-	-	-	+	-	+	-	N	-	-	-	-	-	-	-	-	-
28	358766	M	49	-	+	+	-	-	+	-	-	-	-	27.6	89	130	80	80	-	-	-	-	77	170	98	50	70	3.1	89	50	0.3	1.78	-	+	-	-	-	-	-	-	-	+	-	N	-	+	-	-	-	-	-	-	-
29	358681	M	60	-	+	-	+	+	+	-	+	-	-	29.4	93	110	70	60	-	-	-	-	122	200	200	42	160	4.7	110	50	0.2	2.20	N	-	-	-	-	-	+	-	+	-	-	N	-	-	-	-	-	-	+	+	+
30	370286	F	65	+	-	-	+	-	+	-	-	-	-	31.0	100	120	80	76	-	-	-	-	151	124	96	40	65	8.9	107	44	0.3	2.43	-	+	-	-	-	-	-	-	-	+	-	N	-	+	-	-	-	-	-	-	-
31	358352	F	61	-	+	-	-	-	-	-	-	-	-	34.0	108	120	80	90	-	-	-	-	125	215	162	54	209	3.8	100	60	0.3	1.67	-	-	+	N	-	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-

ANNEXURE III - MASTER CHART

Sl. No.	IP. No.	Sex	Age (Years)	Breathlessness	Chest pain	Smoking	Diabetes mellitus	Hypertension	Dyslipidemia	Angina	MI	CVA	CAD	Body mass index (Kg/m2)	Waist circumference (Cms)	Systolic	Diastolic	Pulse Rate (/Min)	CVS	Respiratory system	Per abdomen	Central Nervous System	Fasting blood sugar (mg/dL)	Total cholesterol (mg/dL)	Total Triglycerides (mg/dL)	High density Lipoprotein (mg/dL)	Low density lipoprotein (mg/dL)	HsCRP	Apolipoprotein B	Apolipoprotein A	HDL / Total cholesterol ratio	Apo B / Apo A Ratio	Normal	Anterior wall	Inferior wall	Normal	LVH	Apex	Anterior Wall	Inferior wall	Apex	Anterior Wall	Inferior wall	Normal	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex
32	369270	F	63	+	+	-	-	-	+	-	-	-	-	30.8	95	114	80	84	-	-	-	-	94	145	54	47	87	3.1	103	64	0.3	1.61	N	-	-	N	-	-	-	-	+	+	-	N	-	-	-	-	-	-	+	+
33	373264	M	50	-	+	-	-	-	+	-	-	-	-	25.9	90	140	90	80	-	-	-	-	130	180	110	45	150	6.0	101	65	0.3	1.55	N	+	-	N	-	-	-	-	+	+	-	-	-	-	-	-	+	+	-	-	-
34	373545	M	60	-	+	+	-	+	-	-	-	-	-	29.0	92	140	90	80	-	-	-	-	210	190	150	50	110	4.4	97	43	0.3	2.26	N	-	+	N	-	-	-	+	-	+	-	-	-	-	-	+	-	+	-	-	-
35	392232	M	35	-	+	-	-	-	-	-	-	-	-	24.0	75	130	80	80	-	-	-	-	120	180	100	59	90	4.0	115	98	0.3	1.17	N	-	-	N	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
36	393925	F	70	+	+	-	+	+	-	-	-	-	-	30.0	92	160	90	100	-	-	-	-	210	196	92	42	112	3.6	186	77	0.2	2.42	-	+	-	N	-	-	-	-	+	+	N	-	-	-	-	-	-	+	+	+
37	396274	M	50	+	+	-	-	-	+	-	-	-	-	26.0	92	150	90	90	-	-	-	-	210	170	152	50	88	3.4	112	84	0.3	1.33	N	-	-	-	-	-	-	-	+	+	-	N	-	+	-	-	-	-	-	-
38	4E+06	M	56	+	+	+	-	-	+	-	-	-	-	25.0	85	140	90	80	-	-	-	-	150	180	90	56	80	3.5	96	60	0.3	1.60	N	+	-	N	-	-	-	-	+	+	-	N	-	-	-	-	+	+	-	-	-
39	396650	M	70	-	+	-	-	+	-	-	-	-	-	24.8	78	140	90	80	-	-	-	-	180	200	90	42	90	4.1	89	72	0.2	1.24	N	-	-	N	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
40	396368	M	42	-	+	-	-	-	+	-	-	-	-	27.2	95	150	80	80	-	-	-	-	210	160	140	45	100	2.9	117	79	0.3	1.48	N	+	-	-	-	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
41	396574	M	56	+	+	+	-	-	+	-	-	-	-	28.0	98	160	90	90	-	-	-	-	101	170	130	50	100	3.2	106	82	0.3	1.29	-	-	+	N	-	-	-	-	-	+	N	+	-	-	+	+	-	-	-	-
42	396126	M	45	-	+	-	-	+	-	-	-	-	-	27.8	90	150	90	90	-	-	-	-	92	188	105	41	108	3.0	142	64	0.2	2.22	N	+	-	N	-	-	-	-	+	+	-	N	-	+	-	-	-	-	-	-	-
43	358579	F	50	+	+	-	-	-	+	-	-	-	-	27.8	88	130	80	80	-	-	-	-	90	180	100	51	75	3.6	103	69	0.3	1.49	-	+	-	N	-	-	-	-	+	-	-	N	-	+	-	-	-	-	-	-	-
44	396270	M	35	-	+	-	-	-	-	-	-	-	-	26.0	88	130	80	80	-	-	-	-	120	170	90	40	110	3.2	101	88	0.2	1.15	N	+	-	-	-	-	+	-	+	-	-	N	-	+	-	-	-	-	-	-	-
45	396625	M	50	-	+	+	-	+	-	-	-	-	-	25.9	70	150	90	80	-	-	-	-	95	163	141	45	95	3.1	136	101	0.3	1.35	N	-	-	-	-	-	-	-	-	+	-	N	-	+	-	-	-	-	-	-	-
46	396828	M	42	-	+	-	-	-	+	-	-	-	-	26.9	80	140	90	80	-	-	-	-	99	194	209	32	110	4.1	89	71	0.2	1.25	N	-	-	N	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
47	412411	M	50	-	+	+	-	+	+	-	-	-	-	26.0	79	136	90	80	-	-	-	-	120	186	80	50	112	3.2	137	82	0.3	1.67	N	-	-	N	-	-	-	-	+	-	N	-	+	-	-	-	-	-	-	-
48	412472	M	55	-	+	-	-	-	-	-	-	-	-	26.2	86	140	90	84	-	-	-	-	100	180	120	32	90	2.9	92	70	0.2	1.31	-	-	-	N	-	-	-	-	+	-	N	-	+	-	-	-	-	-	-	-
49	394290	M	64	-	+	-	-	-	+	-	+	-	-	27.0	82	160	90	90	-	-	-	-	98	170	110	41	80	3.7	105	68	0.2	1.54	-	+	-	-	+	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
50	394278	M	52	-	+	+	-	-	+	-	-	-	-	28.0	96	120	80	90	-	-	-	-	101	197	170	40	85	5.1	130	42	0.2	3.10	N	-	-	N	-	-	-	-	+	+	-	N	-	-	-	-	-	-	+	+	+
51	392578	F	60	-	+	-	-	-	+	-	-	-	-	26.0	90	110	70	80	-	-	-	-	75	180	119	30	91	5.0	112	48	0.2	2.33	-	-	+	N	-	-	-	-	-	-	+	N	-	-	-	-	-	-	+	+	+
52	392762	M	57	-	+	-	+	+	-	-	+	-	-	28.0	92	110	80	84	-	-	-	-	104	170	110	30	85	4.1	110	49	0.2	2.24	-	+	-	N	-	-	-	-	+	+	-	N	-	-	-	+	+	-	-	-	-
53	392634	M	64	+	+	-	-	-	-	-	-	-	-	27.0	94	120	70	70	-	-	-	-	92	160	111	39	92	3.5	90	46	0.2	1.96	N	-	-	-	+	-	-	-	-	-	-	N	-	-	-	+	-	-	-	-	-
54	394313	M	60	-	+	+	+	+	-	-	-	-	-	29.0	96	130	80	60	-	-	-	-	148	180	120	40	90	3.1	94	49	0.2	1.92	-	-	+	N	-	-	-	-	-	-	-	N	-	-	-	+	-	+	-	-	-
55	392889	M	55	-	+	-	-	+	+	-	-	-	-	26.0	92	130	80	70	-	-	-	-	119	126	248	28	48	4.0	120	52	0.2	2.31	N	-	-	N	-	-	-	-	-	-	N	-	-	-	+	+	-	-	-	-
56	394250	M	57	-	+	-	+	+	+	-	+	-	-	26.0	90	110	80	90	-	-	-	-	73	190	110	57	83	3.5	110	72	0.3	1.53	-	-	+	N	-	-	-	-	-	-	+	N	-	-	-	+	+	-	-	-	-
57	391481	M	52	-	+	-	-	+	-	-	+	-	-	22.1	75	149	80	60	-	-	-	-	104	205	170	57	90	3.0	119	131	0.3	0.88	-	-	+	N	-	-	-	-	+	-	+	N	-	-	-	-	-	-	+	+	+
58	391485	M	50	-	+	+	+	+	-	-	-	-	-	30.0	90	150	90	80	-	-	-	-	169	160	100	40	78	3.1	146	97	0.3	1.51	-	+	-	N	-	-	-	-	+	+	-	N	-	+	-	-	-	-	-	-	-
59	395427	M	49	-	+	+	-	-	+	-	+	-	-	27.0	85	130	70	80	-	-	-	-	212	120	61	40	65	4.1	110	44	0.3	2.50	-	+	-	-	-	-	-	-	+	+	-	N	-	-	-	+	+	-	-	-	-
60	393970	M	56	-	+	-	-	-	-	+	-	-	-	30.0	92	130	80	80	-	-	-	-	271	200	100	42	145	5.1	140	42	0.2	3.33	N	-	-	-	-	-	-	-	+	+	-	N	-	-	-	-	-	-	+	+	+
61	395379	M	54	+	+	+	-	+	+	-	+	-	-	29.0	96	140	80	90	-	-	-	-	100	190	90	35	90	4.7	114	38	0.2	3.00	-	-	+	N	-	+	+	-	-	-	-	N	-	-	-	-	-	-	+	+	+
62	395480	F	68	-	+	-	-	-	+	-	+	-	-	28.0	87	140	80	80	-	-	-	-	212	200	92	30	100	3.5	107	40	0.2	2.68	N	-	+	-	-	-	-	-	-	-	+	N	-	-	-	-	-	-	+	+	+

ANNEXURE III - MASTER CHART

Sl. No.	IP. No.	Sex	Age (Years)	Breathlessness	Chest pain	Smoking	Diabetes mellitus	Hypertension	Dyslipidemia	Angina	MI	CVA	CAD	Body mass index (Kg/m2)	Waist circumference (Cms)	Systolic	Diastolic	Pulse Rate (/Min)	CVS	Respiratory system	Per abdomen	Central Nervous System	Fasting blood sugar (mg/dL)	Total cholesterol (mg/dL)	Total Triglycerides (mg/dL)	High density Lipoprotein (mg/dL)	Low density lipoprotein (mg/dL)	HsCRP	Apolipoprotein B	Apolipoprotein A	HDL / Total cholesterol ratio	Apo B / Apo A Ratio	Normal	Anterior wall	Inferior wall	Normal	LVH	Apex	Anterior Wall	Inferior wall	Apex	Anterior Wall	Inferior wall	Normal	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex
63	395618	M	55	+	+	-	-	+	-	-	+	-	-	29.0	91	160	100	80	-	-	-	-	191	170	110	37	98	3.7	142	71	0.2	2.00	N	-	-	N	+	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
64	394298	M	60	-	+	-	-	-	-	-	-	-	-	30.0	92	110	80	80	-	-	-	-	300	190	110	32	90	3.2	110	32	0.2	3.44	-	+	-	N	-	+	+	-	-	-	N	-	+	-	-	-	-	-	-	-
65	393412	M	62	+	+	+	-	+	-	-	-	-	-	29.0	90	210	120	90	-	-	-	-	122	180	125	92	113	2.9	78	65	0.5	1.20	-	+	-	N	-	+	-	-	-	-	N	-	+	-	-	-	-	-	-	-
66	394182	M	46	+	+	-	-	-	+	-	-	-	-	31.0	94	140	80	70	-	-	-	-	99	170	90	50	70	3.9	92	70	0.3	1.31	N	+	-	N	-	-	-	-	+	+	-	N	-	+	-	-	-	-	-	-	-
67	394636	F	47	-	+	-	-	-	-	-	-	-	-	30.0	85	110	80	70	-	-	-	-	78	210	150	40	110	3.0	130	85	0.2	1.53	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
68	395587	M	58	-	+	-	-	+	-	-	-	-	-	27.0	84	130	80	80	-	-	-	-	141	160	100	51	72	4.0	104	72	0.3	1.44	N	-	-	N	-	-	-	-	+	-	-	N	-	+	-	-	-	-	-	-	-
69	394636	M	29	-	+	+	-	-	-	-	-	-	-	26.0	92	130	80	84	-	-	-	-	73	160	90	42	60	2.5	115	69	0.3	1.67	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
70	395498	F	52	+	+	-	-	-	+	-	-	-	-	29.0	90	170	90	70	-	-	-	-	99	190	110	52	70	3.5	125	92	0.3	1.36	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	+	+	+
71	385322	M	55	-	+	-	-	+	-	-	-	-	-	30.0	90	140	80	90	-	-	-	-	92	209	83	148	44	3.2	121	88	0.7	1.38	N	+	-	N	-	+	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
72	388142	M	40	-	+	+	-	-	+	-	-	-	-	29.0	92	120	70	90	-	-	-	-	100	180	144	37	114	13.7	147	111	0.2	1.32	N	+	-	N	-	-	+	-	-	-	-	N	-	+	-	-	-	-	-	-	-
73	386180	F	51	-	+	-	-	+	+	-	-	-	-	28.0	90	140	80	80	-	-	-	-	84	73	216	36	152	10.2	136	92	0.5	1.48	N	+	-	N	-	+	+	-	-	-	-	N	-	+	-	-	-	-	-	-	-
74	379310	M	72	+	+	+	-	-	-	-	-	-	-	25.0	80	110	60	72	-	-	-	-	93	117	274	39	23	2.5	96	92	0.3	1.04	N	-	-	N	-	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
75	373364	M	57	-	+	-	+	+	+	-	-	-	-	25.0	79	130	80	80	-	-	-	-	193	210	160	32	53	3.1	99	102	0.2	0.87	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	+	+	-	-	-	-
76	373515	M	60	-	+	-	-	-	-	-	-	-	-	29.0	84	130	70	70	-	-	-	-	120	190	110	42	70	3.1	112	87	0.2	1.29	N	+	-	N	-	+	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
77	374044	M	48	+	+	-	+	+	-	-	+	-	-	26.0	80	120	80	84	-	-	-	-	140	182	91	40	174	5.2	104	57	0.2	1.82	N	+	-	N	-	-	-	-	+	+	-	N	-	-	-	-	-	-	+	+	+
78	374045	F	58	-	+	-	-	-	+	-	+	-	-	24.0	72	140	90	90	-	-	-	-	82	117	64	39	65	19.0	80	101	0.3	0.79	N	-	+	N	-	-	-	-	-	-	+	N	-	-	-	+	+	-	-	-	-
79	374043	M	52	-	+	+	+	-	-	-	-	-	-	27.0	78	110	80	80	-	-	-	-	219	181	207	32	108	3.5	72	48	0.2	1.50	N	-	-	N	+	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
80	373752	M	54	-	+	-	-	-	-	-	-	-	-	26.5	80	140	80	60	-	-	-	-	91	200	120	40	70	3.7	88	62	0.2	1.42	N	-	-	N	+	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
81	373751	M	48	-	+	-	+	+	-	+	-	-	-	27.0	85	130	80	80	-	-	-	-	110	190	104	40	82	3.2	102	74	0.2	1.38	N	-	-	N	+	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
82	373727	M	42	+	+	-	-	+	-	-	-	-	-	24.0	68	150	90	80	-	-	-	-	150	184	120	43	91	2.5	91	97	0.2	0.84	N	-	-	N	+	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
83	373762	M	38	-	+	-	-	-	+	-	-	-	-	28.0	75	110	70	70	-	-	-	-	101	160	90	52	70	3.2	86	56	0.3	1.54	N	-	+	N	-	-	-	-	-	-	+	N	+	-	-	-	-	-	-	-	-
84	373958	M	60	-	+	+	-	+	+	-	+	-	-	28.0	80	110	60	60	-	-	-	-	99	192	84	50	66	3.4	108	71	0.3	1.52	N	+	+	N	-	+	-	-	-	-	+	N	-	-	-	-	-	-	+	+	+
85	373616	M	54	+	+	-	+	+	-	+	-	+	-	29.0	82	190	110	94	-	-	-	-	88	95	172	34	26	7.4	123	42	0.4	2.93	N	-	-	N	+	-	-	-	-	-	+	N	-	-	-	-	-	-	+	+	+
86	390875	M	70	+	+	+	-	-	+	-	-	-	-	25.0	74	130	90	60	-	-	-	-	87	180	100	60	70	4.8	124	92	0.3	1.35	N	+	-	N	+	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
87	391261	F	35	-	+	-	-	-	-	-	-	-	-	26.0	72	130	80	80	-	-	-	-	82	132	248	36	46	2.9	127	104	0.3	1.22	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
88	391437	M	75	-	+	-	-	+	-	-	-	-	-	27.0	78	130	80	80	-	-	-	-	201	158	80	44	98	10.1	163	84	0.3	1.94	N	-	+	N	-	-	-	-	-	-	+	N	-	-	+	-	-	-	-	-	-
89	391324	F	68	+	+	-	+	-	+	-	-	-	-	28.0	80	130	70	80	-	-	-	-	270	183	153	46	106	4.1	158	76	0.3	2.08	N	+	-	N	+	-	-	-	-	-	+	N	-	-	-	-	-	-	+	+	+
90	391576	M	55	-	+	+	+	-	+	-	+	-	-	26.0	82	140	80	80	-	-	-	-	309	166	160	36	98	8.9	179	82	0.2	2.18	N	+	-	N	-	-	-	-	+	+	-	N	-	-	-	-	-	-	+	+	+
91	391752	M	45	-	+	-	+	+	+	-	-	-	-	25.2	72	140	80	80	-	-	-	-	131	176	162	36	108	5.9	136	124	0.2	1.10	N	-	+	N	-	-	-	-	-	-	+	N	-	-	-	+	+	-	-	-	-
92	391850	M	58	-	+	-	+	+	-	+	-	-	-	27.6	76	130	80	80	-	-	-	-	175	129	92	41	70	4.4	117	85	0.3	1.38	N	-	-	N	-	-	-	+	+	-	-	N	-	-	+	-	-	-	-	-	-
93	391661	M	72	-	+	+	-	+	+	+	-	-	-	28.2	80	110	70	70	-	-	-	-	120	180	110	56	80	5.5	164	101	0.3	1.62	N	+	-	N	-	-	-	-	-	-	+	N	-	-	-	-	-	-	+	+	+

ANNEXURE III - MASTER CHART

Sl. No.	IP. No.	Sex	Age (Years)	Breathlessness	Chest pain	Smoking	Diabetes mellitus	Hypertension	Dyslipidemia	Angina	MI	CVA	CAD	Body mass index (Kg/m2)	Waist circumference (Cms)	Systolic	Diastolic	Pulse Rate (/Min)	CVS	Respiratory system	Per abdomen	Central Nervous System	Fasting blood sugar (mg/dL)	Total cholesterol (mg/dL)	Total Triglycerides (mg/dL)	High density Lipoprotein (mg/dL)	Low density lipoprotein (mg/dL)	HsCRP	Apolipoprotein B	Apolipoprotein A	HDL / Total cholesterol ratio	Apo B / Apo A Ratio	Normal	Anterior wall	Inferior wall	Normal	LVH	Apex	Anterior Wall	Inferior wall	Apex	Anterior Wall	Inferior wall	Normal	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left anterior descending	Left circumflex
94	412501	M	67	-	+	-	-	+	+	-	-	-	-	25.5	78	140	90	84	-	-	-	-	135	200	160	42	120	4.1	102	76	0.2	1.34	N	+	-	N	-	-	-	-	+	-	-	N	-	-	-	+	+	-	-	-	-
95	412194	M	55	-	+	-	-	+	+	+	-	-	-	27.5	80	130	90	80	-	-	-	-	189	191	120	52	110	3.8	113	69	0.3	1.64	N	-	+	N	-	-	-	+	-	+	-	N	-	-	-	+	+	-	-	-	-
96	412350	M	65	-	+	+	+	-	+	-	-	-	-	28.5	90	150	90	92	-	-	-	-	102	201	98	44	100	3.2	120	93	0.2	1.29	N	+	-	N	-	-	+	-	-	-	-	N	-	-	-	-	+	+	-	-	-
97	412468	F	52	-	+	-	-	+	-	-	-	-	-	28.7	89	130	80	82	-	-	-	-	98	178	100	55	92	3.6	110	89	0.3	1.24	N	-	-	N	-	-	-	-	-	-	-	N	-	+	-	-	-	-	-	-	-
98	413539	M	46	+	+	-	-	-	-	-	-	-	-	26.5	79	120	70	90	-	-	-	-	140	169	89	48	78	3.5	77	54	0.3	1.43	N	-	-	N	-	-	-	-	-	-	+	N	+	-	-	-	-	-	-	-	-
99	413874	M	48	-	+	-	-	-	-	-	-	-	-	24.5	62	130	80	90	-	-	-	-	126	189	97	50	90	2.9	83	107	0.3	0.78	N	-	-	N	-	-	-	-	-	-	-	N	-	-	-	-	-	-	-	-	-
100	413866	F	60	-	+	-	+	-	+	-	-	-	-	28.2	88	140	90	90	-	-	-	-	110	170	100	57	112	3.6	98	81	0.3	1.21	N	+	-	N	-	+	+	-	-	-	-	N	-	-	-	+	+	-	-	-	-

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

Angio	-	Angiography
Apo A	-	Apolipoprotein A
Apo B	-	Apolipoprotein B
Apo B / Apo A	-	Apolipoprotein B to Apolipoprotein A ratio
BMI	-	Body Mass Index
BP	-	Blood Pressure
CAD	-	Coronary Artery Disease
CVA	-	Cerebrovascular accident
CVS	-	Cardiovascular System
ECG	-	Electrocardiography
Echo	-	Echocardiography
HDL	-	High Density Lipoproteins
Hs-CRP	-	Highly selective C Reactive protein
IP	-	In Patient
LDL	-	Low Density Lipoproteins
LVH	-	Left ventricular hypertrophy
MI	-	Myocardial Infarction
PR	-	Pulse Rate
TC	-	Total Cholesterol
TG	-	Triglycerides
WC	-	Waist Circumference