"SIGNIFICANCE OF PLATELET INDICES IN ISCHEMIC HEART DISEASE"

By

Dr. SURAKSHA RAO.B

DISSERTATION SUBMITTED TO THE
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IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE

IN

PATHOLOGY

Under the guidance of

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Acknowledgement

While beginning to write the acknowledgements, one might start feeling happy, relieved and also a bit proud. This thesis is the end of my journey in obtaining my M.D. I have not travelled in a vacuum in this journey. This thesis has been kept on track and has been seen through to completion with the support and encouragement of numerous teachers and friends. In the following, I want to express my gratitude to all of you who made this thesis possible. Thank you so much.

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LIST OF ABBREVIATIONS

ACS – Acute coronary syndrome

CAD – Coronary Artery Disease

CBC – Complete blood test

CHD – Coronary Heart Disease

CKMB – Creatine Kinase – Muscle Brain isoenzyme

cTnT – cardiac Troponin-T

CVD – Cardio Vascular Disease

DALY – Disability Adjusted Life Year

DM – Diabetes Mellitus

DNA – Deoxyribo Nucleic Acid

DVD – Double Vessel Disease

ECG – Electrocardiogram

EDTA – Ethylene Diamine Tetraacetic Acid

HDL – High Density Lipoproteins

H/O – History Of

HTN – Hypertension

IHD – Ischemic Heart Disease

LAD – Left Anterior Descending artery

LCA – Left Circumflex Artery

LDH – Lactate Dehydrogenase

LDL – Low Density Lipoproteins

MI – Myocardial Infarction

MK - Megakaryocyte

MPV – Mean Platelet Volume

NCD – Non communicable disease

NSTEMI – Non-ST Elevation Myocardial Infarction

PC – Platelet count

Pct – Plateletcrit

PDW – Platelet Distribution Width

PTCA – Per Cutaneous Trans-Coronary Angioplasty

RBC - Red blood cell

RCA – Right Coronary Artery

SA – Stable angina

SES – Socio Economic Status

STEMI – ST segment Elevation Myocardial Infarction

SVD – Single Vessel Disease

TVD – Triple Vessel Disease

UA – Unstable Angina

WBC – White blood cells

WHO – World Health Organisation

Yrs - Years

ABSTRACT

Objective:

To determine whether an association exists between platelet volume indices, acute myocardial infarction and other ischemic cardiac events in a predominantly rural / semi rural population.

Materials and Methods:

The study was carried at The Department of Pathology, R.L.Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar in co-ordination with the Department of Medicine between 1st October 2010 to 3Ost April 2012. 420 cases, 140 patients admitted with cardiac Troponin T positive Myocardial infarction (MI), 140 patients with other non-MI ischemic heart conditions and 140 healthy age and sex matched control population who had no features of ischemic heart disease(IHD) were included in the study. Blood (2ml) was collected in dipotassium Ethylene Diamine Tetra acetoacetic acid (EDTA) tubes from all the patients by a clean puncture avoiding froth or bubbles within 2hours of venepuncture and analysed using Beckman Coulter Act5 Diff cell counter. We compared the Platelet indices i.e. Mean platelet volume (MPV) Platelet Distribution Width (PDW) and Plateletcrit (Pct) in these three groups. Clinical data and past history was obtained from each case along with electrocardiogram changes.

Results:

The number of males was 322 (76.66%) and number of females was 98 (23.33%). and age ranged from 23 to95 years. Mean age was 55.44 ± 13.13 years. There were more

number of smokers [59(42.14%)] and alcoholics [09(6.42%)] were seen in the MI group compared to the non-MI group. Diabetes mellitus and hypertension was observed more among the non-MI patients [48(38.28%)] and [57(40.71%)] respectively. The age and sex matched healthy control population had no history of smoking, alcohol intake, diabetes mellitus or hypertension. The platelet count was higher among the MI patients than non-MI and control group [287.92 ± 95.66 $x10^3$ /micL versus 279 ± 94.44 $x10^3$ /micL versus 284.9 ± 85.1 $x10^3$ /micL] with p=0.744. MPV and PDW were significantly higher in MI patients than non-MI patients and healthy controls [8.22 ± 0.762 f L versus 7.84 ± 0.73 f L versus 7.65 ± 0.55 fL] and[13.22 ± 2.4f L versus 12.33 ± 2.45 f L versus 11.66 ±1.87 fL] respectively with p<0.001. Plateletcrit was highest among the non-MI patients 0.82 ± 7.25% than MI patients with 0.233% (±0.071) with p=0.381 followed by MI patients with 0.233 ± 0.071% and healthy controls with 0.21 ± 0.061% with p=0.381.

Conclusion:

Larger and more active platelets which might be causally related to an ongoing thrombus formation leading to myocardial infarction. Platelet indices, mainly Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) are readily available, relatively inexpensive useful markers which were significantly raised among patients admitted with MI in our hospital. Thus these indices should be utilized with other investigative tools to screen patients suspected to have acute coronary syndrome.

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INTRODUCTION

INTRODUCTION

Cardiovascular diseases (CVDs), comprise a major portion of non-communicable diseases. By 2030, about 76% of the deaths in the world will be due to non-communicable diseases (NCDs).[1] By 2030, four fifths of all NCD related mortality is projected to take place in developing nations. In 2010, of all projected worldwide deaths, 23 million are expected to be because of cardiovascular diseases. In fact, CVDs would be the single largest cause of death in the world accounting for more than a third of all deaths.[2]

Both endogenous and exogenous risk factors such as smoking, diabetes mellitus, hypertension, hypercholesterolemia, mental stress, age, male gender and obesity, acting either singly or in combination, significantly increase the chances of developing CVD. However, they only explain part of the cases and other relevant risk factors need to be identified for an accurate calculation of an individual's risk for myocardial infarction.[3]

Platelets are known to have a major effect on the formation of atherosclerotic plaques and therefore play an essential role in the pathogenesis of athero thrombosis. Larger and hyper reactive platelets accelerate the formation of an intracoronary thrombus, leading to a cascade of clinical events, such as acute coronary syndrome (ACS). An increase in platelet aggregability is associated with unstable angina and myocardial infarction. While atherosclerotic plaque rupture starts the thrombogenic phenomenon in ACS, the activity of circulating platelets plays an important role for the progression of thrombus. [4]

Large platelets, that contain more dense granules, are metabolically and enzymatically more active than small platelets and they have a higher thrombotic potential. Platelet size is determined at the level of the progenitor cell (i.e the megakaryocyte), and studies have reported that

cytokines, such as interleukin-3 or interleukin-6, influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets. Thus, platelet volume has been proposed as an indirect marker of increased platelet reactivity. [5]

NEED FOR THE STUDY:

Chest pain is a commonly presented symptom in hospitals. However, a minor group of patients admitted to the emergency department with chest pain are proved to have a cardiac aetiology using electrocardiography and cardiac Troponin T (cTnT) measurement.

Numerous investigations like imaging and laboratory parameters like enzyme markers can confirm the cardiac aetiology and also predict the future risk of the patient. Physicians always search for rapid and independent markers for early and accurate diagnosis of ACS. Now the question need to be addressed whether these required markers are novel and expensive or they are ignored markers that could contribute to cells known to pathogenesis of thromboemboli.

Larger hyperactive platelets play an important role in intracoronary thrombus formation and acute thrombotic events. Platelet indices which reflect platelet activity might be an emerging cardiovascular risk marker. In most laboratories automated cell counters have made the platelet count and platelet indices- Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and Plateletcrit (Pct) routinely available but are underutilised. Hence there is scope to make better use of the platelet parameters generated.

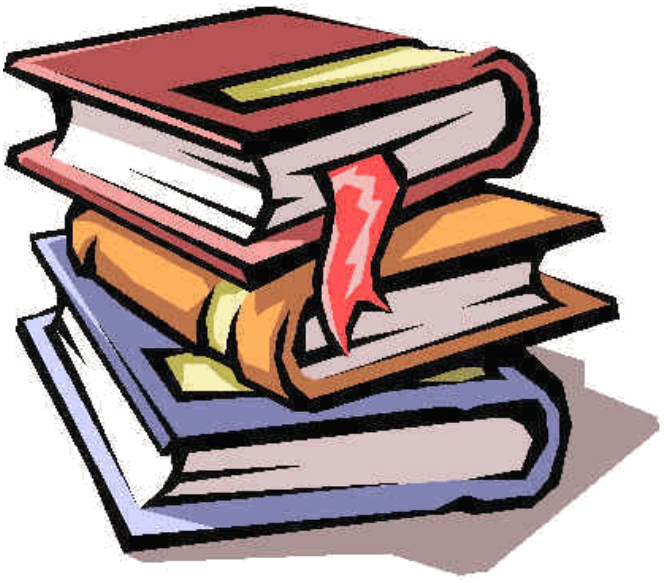
Recently, there has been some focus on platelet count and MPV for aiding the diagnosis of the ACS. The reason is these simple, inexpensive tests available in routine laboratories and used for nearly every patient admitted to emergency room by a routine CBC test.

An increase in Mean MPV and PDW due to platelet activation from platelet swelling and pseudopodia formation is hypothesized. Thus we propose to study the platelet indices in the

spectrum of ischemic heart diseases and determine if an association exists between platelet indices and ischemic heart disease.

AIM OF THE STUDY:

To determine whether an association exists between platelet indices - mean platelet volume (MPV), platelet distribution width (PDW), Plateletcrit (PCt) in acute myocardial infarction and other ischemic cardiac events in a predominantly rural population.



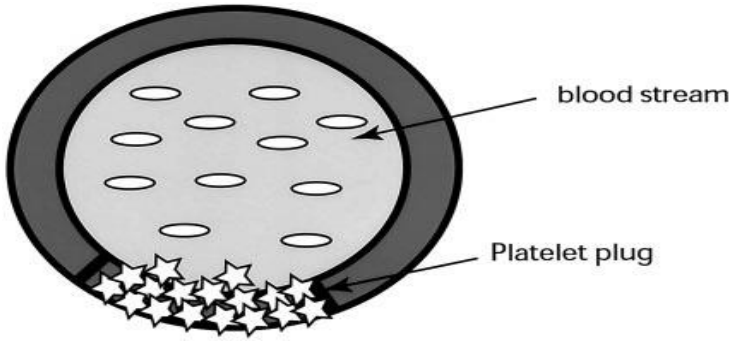
REVIEW OF LITERATURE

REVIEW OF LITERATURE **:**

Platelets are non-nucleated cells produced by megakaryocyte (MK), which are very large cells (50 to 100 μm in diameter) found in bone marrow. The megakaryocyte surface membrane forms proplatelet extensions from which platelets "bud off" and are released into the circulation, where they number approximately 200,000 to 400,000 per microliter of blood.

The platelet surface is coated with hundreds of thousands of receptors for other cells, including activated vascular wall cells and extracellular matrix proteins. [2] However, when challenged by vascular injury, platelets are rapidly activated and aggregate with each other to form a plug on the vessel wall that prevents vascular leakage, functioning as the "band-aids" of the bloodstream.

FIGURE 1 : **PLATELETS FORM A PLATELET PLUG TO STOP BLEEDING FROM AN INJURED BLOOD VESSEL**[6]



Platelets are produced from megakaryocytes and can reduplicate their chromosomes, without undergoing mitosis. This process is called endomitosis. During endomitosis, polyploidal MKs initiates a rapid cytoplasmic expansion phase characterized by the development of a highly developed demarcation membrane system and the accumulation of cytoplasmic proteins and

granules essential for platelet function. During the final stages of development, the MKs cytoplasm undergoes a dramatic and massive reorganization into beaded cytoplasmic extensions called proplatelets. The proplatelets ultimately yield individual platelets. Circulating platelets are heterogeneous in size, density, and reactivity. Therefore, it is suggested that changes in platelet size are determined at thrombopoiesis in the MK [3, 4]

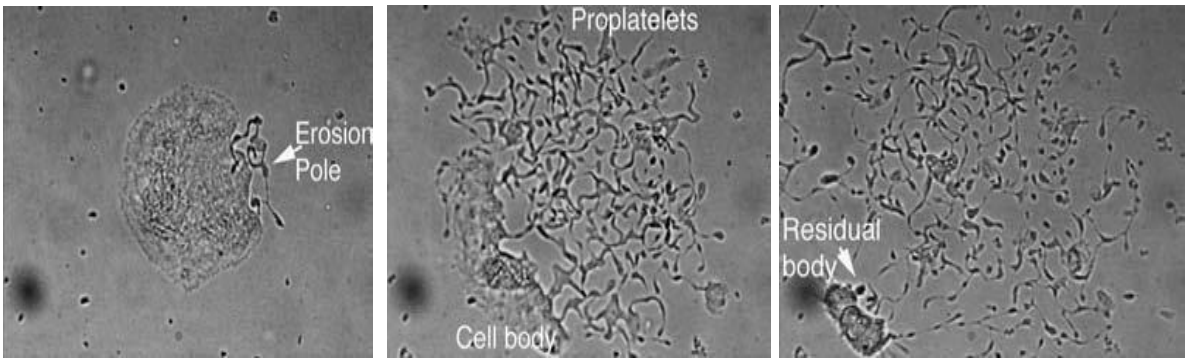


FIGURE 2 : <u>FORMATION OF PROPLATELETS BY A MOUSE MEGAKARYOCYTE</u>.

The bulk of the MK cytoplasm has been converted into multiple proplatelet processes which are highly dynamic and undergo bending and branching. The entire process ends in a rapid retraction that separates the released proplatelets from the residual cell body.[3]

Steady-state megakaryocytopoiesis contributes to the circulating blood platelets measuring 1-2 μm in size, with a lifespan of 8-10 days. [5]

The resting platelets is discoid in shape and this is maintained by a cytoskeleton composed of microtubules, actin filaments, and a spectrin-based membrane skeleton.

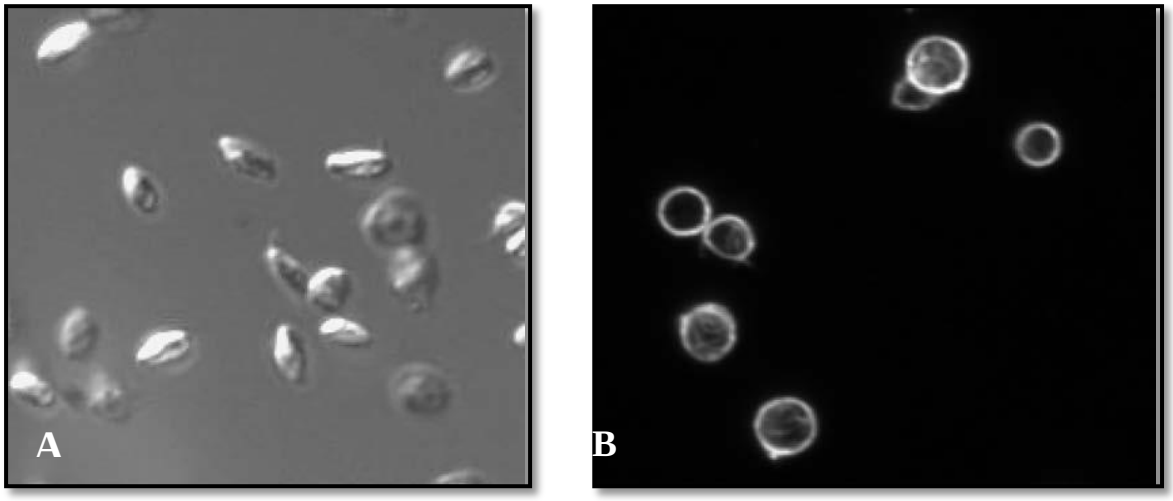


FIGURE 3: <u>THE STRUCTURE OF THE RESTING PLATELET</u>

(A) Differential interference contrast micrograph of a field of human discoid resting platelets.(B) Immunofluorescence staining of fixed, resting platelets with Alexa 488-antitubulin antibody reveals the microtubule coil.[8]

When platelets are exposed to specific agonists, they convert from discs to spheres with pseudopodia in a matter of seconds. This shape change is highly reproducible and follows a sequence of events in which the disc converts into a sphere, after which broad lamellipodia and thin finger-like filopodia extend from the platelet surface. These shape changes are driven by the rapid remodelling of the platelet cytoskeleton.

The conversion of the disc into a rounded shape occurs if cytoplasmic calcium levels rise into the micromolar levels. Resting platelets maintain cytosolic calcium at 10 to 20 nm. The rise in intracellular calcium is then used to activate a filament-severing reaction that powers the disc to sphere transition. This is followed by the rapid protrusion of lamellipodia and filopodia driven by the actin cytoskeleton. Filopodia extended by platelets appear to be used to locate other platelets and strands of fibrin. [6]

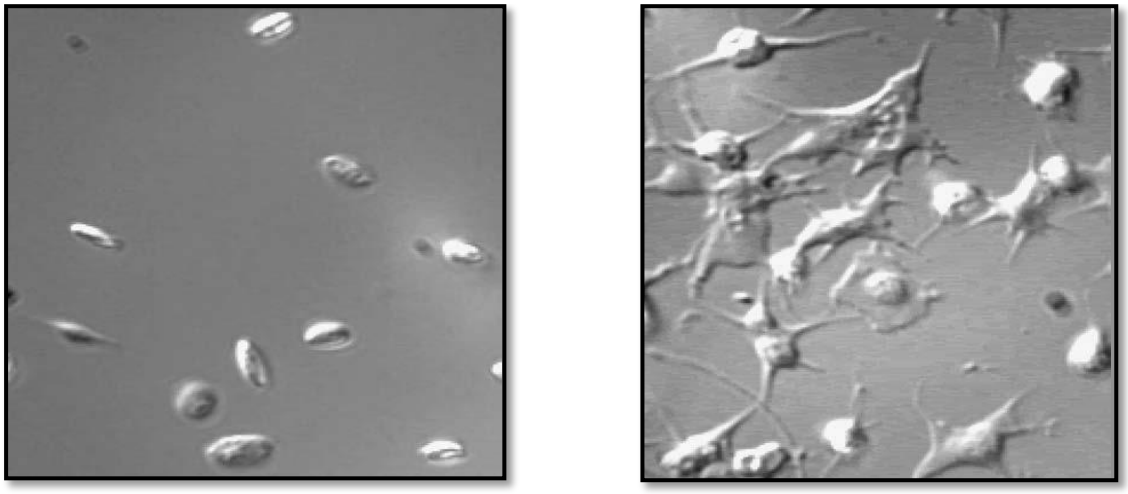


FIGURE 4 : <u>THE RESTING TO ACTIVE TRANSITION OF PLATELETS.</u>

Differential interference contrast micrographs comparing discoid resting platelets in suspension to platelets activated by contact to the glass surface which spread with lamellipodia and form long finger-like filopodia.[8]

The regulation of megakaryocytopoiesis is programmed to meet demands for activated platelets in physiological and pathological conditions, resulting in time-dependent changes of platelet indices. [7]

In other words, the regulation of platelet function and aging, primarily aimed at maintaining platelet mass (platelet count multiplied by MPV) and persistent hemostatic potential, is dependent on the ploidy (ability to reduplicate DNA) and maturity of thrombopoietic progenitors. [8] Some studies have suggested that age is a determinant of platelet functional ability, as evidenced by the fact that young platelets are functionally more active,larger and likely to aggregate more than older platelets. [9] These changes in platelet size are determined at thrombopoiesis in the megakaryocyte and that those changes might precede acute cardiac events.

ISCHEMIC HEART DISEASE :

Ischemic heart disease (IHD) also called coronary artery disease (CAD) or coronary heart disease (CHD) is a syndrome where in more than 90% of the cases are due to late presentation of coronary atherosclerotic arterial obstruction.

Ischemic heart disease is classified as:

- Angina pectoris
- Myocardial infarction (MI)
- Chronic IHD with heart failure
- Sudden cardiac death

In the acute coronary syndrome, the most important predisposing factor is the plaque disruption or acute plaque change in the atherosclerotic vessel which can present as:

- Unstable angina
- Acute myocardial infarction
- Sudden cardiac death.

WORLDWIDE IMPACT OF CHD :

CVD and stroke are the leading causes of death in both economically developed and developing countries. Each year, more than 17 million people die from cardiovascular disease worldwide. Currently, 80% of deaths due to coronary heart disease or stroke take place in developing countries. CVD occurs at a younger age in developing countries like India than in developed countries, thereby resulting in serious loss of productivity. For example, 50% of CVD deaths in India occur before 70 years of age, whereas only about 25% of cardiovascular disease deaths in

developed countries occur before age 70 years. Age-standardized CVD death rates in people 30-69 years old are 180 per 100,000 in Britain, 280 per 100,000 in China, and 405 per 100,000 in India. Traditional risk factors play an important role in the excess risk for cardiovascular disease in developing countries, thereby emphasizing the urgent need to develop cost-effective programs to control these risk factors in these settings with limited resources. [10]

Mortality Associated with CHD

Global CHD Mortality

In 2004, CHD was the leading cause of death worldwide, leading to:

- 7.2 million deaths (12.2% out of a total of 58.8 million deaths)
- 134.0 deaths per 100,000
- 138.6 age-standardized deaths per 100,000
- 22,370,000 DALYs (disability adjusted life-year)
- 222,762 age-adjusted DALYs per 100,000

CHD Mortality in India

In 2004, CHD was the leading cause of death in India, leading to:

- 1.46 million deaths (14% out of a total of 10.3 million deaths)
- 130.7 deaths per 100,000
- 207.7 age-standardized deaths per 100,000
- 15,588,000 DALYs
- 1,931 age-adjusted DALYs per 100,000

(WHO, 2004; WHO, 2009)

FIGURE 5 : MORTALITY ASSOCIATED WITH CHD WORLDWIDE IN COMPARISON TO INDIA [1]

CARDIOVASCULAR DISEASE BURDEN IN INDIAN SUBCONTINENT [12]

- According to the recent WHO statistics (2008) :
  - The most common cause of mortality in the South East Asian region (SEAR) is CVD 2,889,184/12,056,930 (23.96%)
  - Among CVD causes IHD deaths account to 1,521,791/2,889,184 (52.67%)
  - Males are affected predominantly with 942,204 (61.9) deaths and female death numbers to 579,587 (38.1%)

ECONOMIC BURDEN OF CVD IN INDIA:

India is estimated to have lost 8.7 billion international dollars in 2005 because of CHD, stroke, and diabetes. These estimates increase to 54 billion 1998 international dollars by 2015. India's growth of gross domestic product (GDP) is estimated to fall by 1% because of the combined economic impact of CHD, stroke, and diabetes. [1] A 2000 estimate of 9.2 million productive years of lives lost in Indian adults secondary to overall CVD contributes to this economic decline. As CHD (and CVD) rates increase, this estimate increases to 17.9 million by 2030.[13]

Disability adjusted life years (DALYs), a commonly used metric of premature of death and disability, is also estimated to increase at rates comparable or above most other regions throughout the world. Beyond these projections, DALYs lost secondary to CHD in India have been predicted to increase from 7.67 million to 14.4 million in men and 5.6 million to 7.7 million in women from 2000 to 2020. [14]

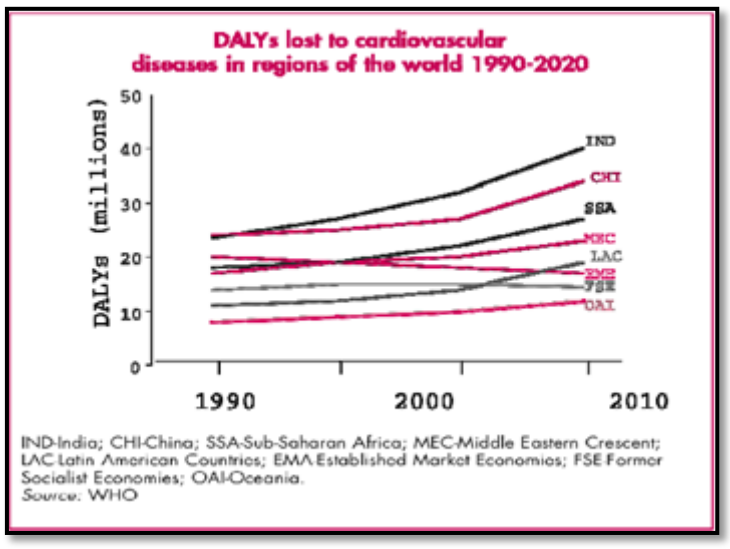


FIGURE 6 : DISABILITY ADJUSTED LIFE YEARS LOST TO CARDIOVASCULAR DISEASE IN REGIONS OF THE WORLD 1990-2020.[14]

PATHOGENESIS OF ACS :

The pathogenesis for ACS among patients can be divided into four groups:[15]

1. Atheromatous CHD
2. Non-atheromatous CHD
3. Hypercoagulable states.
4. MI related to substance misuse.

These conditions are characterized by an imbalance between myocardial oxygen supply and demand. The most common mechanisms involve an imbalance that is caused primarily by a reduction in oxygen supply to the myocardium, the imbalance due to increased myocardial oxygen requirements, usually in the presence of a fixed, restricted oxygen supply.

There is reduced myocardial perfusion that results from coronary artery narrowing caused by a thrombus that developed on a disrupted atherosclerotic plaque and is usually non-occlusive.

Microembolization of platelet aggregates and components of the disrupted plaque are believed to be responsible for the release of myocardial markers in many of these patients.

The most common underlying molecular and cellular pathophysiology of disrupted atherosclerotic plaque is arterial inflammation, caused by non-infectious (e.g., oxidized lipids) and possibly, infectious stimuli, which can lead to plaque expansion and destabilization, rupture or erosion, and thrombogenesis. Activated macrophages and T lymphocytes located at the shoulder of a plaque increase the expression of enzymes such as metalloproteinase that cause thinning and disruption of the plaque. A less common cause is dynamic obstruction, which may be triggered by intense focal spasm of a segment of an epicardial coronary artery.

- Secondary unstable angina is precipitated by conditions that:[16]

1) Increase myocardial oxygen requirements, such as fever, tachycardia, or thyrotoxicosis.

2) Reduced coronary blood flow, such as hypotension or

3) Reduced myocardial oxygen delivery, such as anemia or hypoxemia.

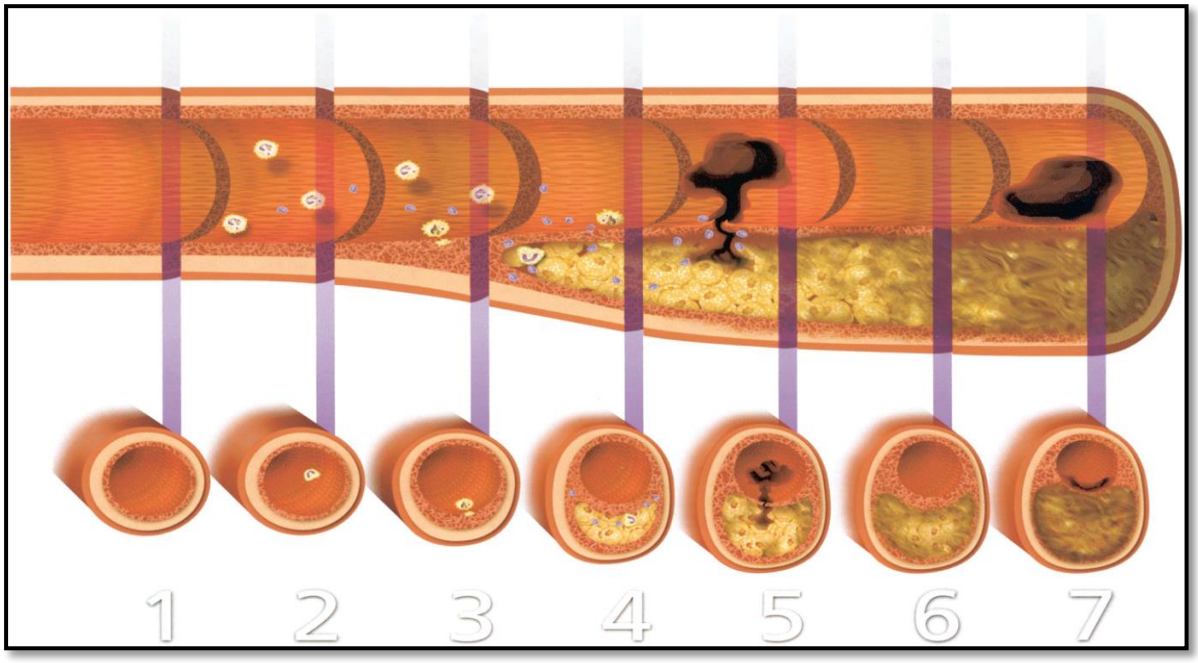


FIGURE 7: <u>INITIATION, PROGRESSION, AND COMPLICATION OF HUMAN CORONARY ATHEROSCLEROTIC PLAQUE.</u>[17]

Longitudinal section of artery depicting "timeline" of human atherogenesis from normal artery to atheroma that caused clinical manifestations by thrombosis or stenosis .Bottom, Cross sections of artery during various stages of atheroma evolution.

1) Normal artery.

2) Lesion initiation occurs when activated endothelial cells, express adhesion and chemo attractant molecules that recruit inflammatory leukocytes. Extracellular lipid begins to accumulate in intima at this stage.

3) Evolution to fibrofatty stage: Macrophages become lipid-laden foam cells by engulfing modified lipoproteins. Leukocytes and resident vascular wall cells can secrete inflammatory cytokines and growth factors that amplify leukocyte recruitment and cause smooth muscle cell migration and proliferation.

4) As lesion progresses, inflammatory mediators cause expression of tissue factor, a potent procoagulant, and of matrix-degrading proteinases that weaken fibrous cap of plaque.

5) If fibrous cap ruptures at point of weakening, coagulation factors in blood gain access to thrombogenic, tissue factor–containing lipid core, causing thrombosis on non-occlusive atherosclerotic plaque. If balance between prothrombotic and fibrinolytic mechanisms prevailing at that particular region and at that particular time is unfavourable, occlusive thrombus causing acute coronary syndromes may result.

6) When thrombus resorbs, products associated with thrombosis such as thrombin and mediators released from degranulating platelets, including PDGF and TGF-b, can cause healing response, leading to increased collagen accumulation and smooth muscle cell growth. In this manner, the fibro fatty lesion can evolve into advanced fibrous and often calcified plaque, one that may cause significant stenosis, and produce symptoms of stable angina pectoris.

7) In some cases, occlusive thrombi arise not from fracture of fibrous cap but from superficial erosion of endothelial layer. Resulting mural thrombus, again dependent on local prothrombotic and fibrinolytic balance, can cause acute myocardial infarction. Superficial erosions often complicate advanced and stenotic lesions, as shown here. However, superficial erosions do not necessarily occur after fibrous cap rupture, as depicted in this idealized diagram.

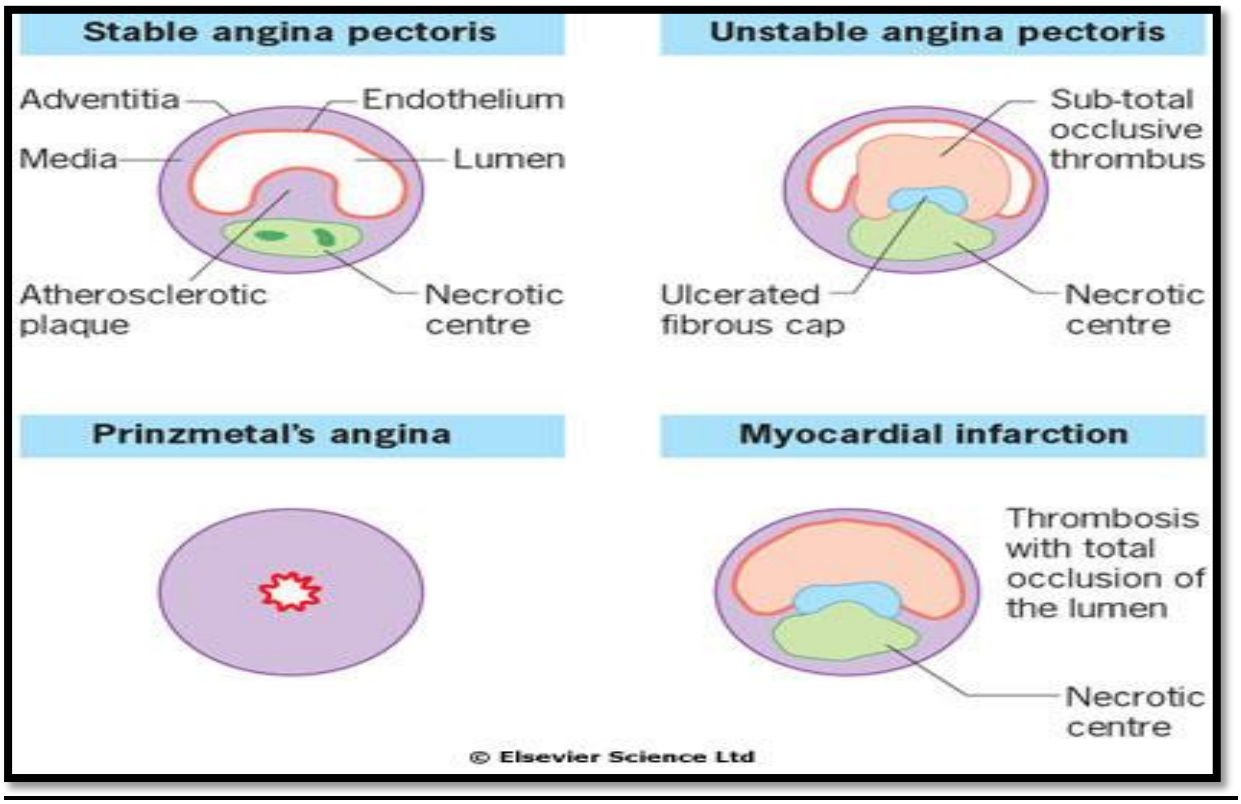


FIGURE 8: PATHOPHYSIOLOGY OF THROMBUS FORMATION AND VESSEL OCCLUSION.[18]

RISK FACTORS FOR CARDIOVASCULAR DISEASE:

Atherosclerotic disease in the arteries of the heart is the most common cause of clinically apparent coronary heart disease. Heart failure most commonly occurs as a result of coronary heart disease or hypertension, although valvular heart disease and cardiomyopathy also can lead to heart failure.

Risk factors for cardiovascular disease can be categorized as traditional (i.e., those identified in the Framingham Heart Study) or novel. Risk factors can also be grouped as modifiable and non-modifiable.

	TRADITIONAL (OR ESTABLISHED)*	NOVEL (OR LESS ESTABLISHED)
Modifiable	Hypertension Diabetes Dyslipidemia† Smoking Obesity Physical inactivity Kidney dysfunction/damage Left ventricular hypertrophy Alcohol Atrial fibrillation‡	Socioeconomic status Psychological factors Inflammatory markers Infection Homocysteine Thrombotic factors Natriuretic peptide Troponin†
Nonmodifiable	Age Gender Ethnicity Family history	Genetic polymorphism Coronary artery calcification†

*Factors incorporated in multiple risk scoring systems or dealt with in clinical guidelines and potentially affecting clinical decisions for cardiovascular disease prevention.
†Risk factor mainly for coronary heart disease.
‡Risk factor mainly for stroke.

TABLE 1: **RISK FACTORS FOR CORONARY HEART DISEASE** [19]

GENDER :

Before age 60, men have a 1.5- to 2-fold higher risk of coronary heart disease and stroke than do women. After 60 years of age, however, the risk of coronary heart disease and stroke in women increases at a faster rate than men, and the risk becomes equivalent in both sexes at 80 years of age. This gender difference at younger ages is thought to be primarily due to differences in levels of estrogen and other endogenous sex hormones.[20]

RACE AND ETHNICITY :

The incidence and prevalence of cardiovascular disease vary substantially across ethnic groups. Asians are less prone to developing coronary heart disease than whites or blacks. Ethnic

differences in CHD prevalence within India are not consistent across studies. A study conducted showed that Muslim men have the highest CHD prevalence rates and Christian men have been shown to have the lowest CHD prevalence rates. [21]

CHD prevalence appears to be worsening in India. In developed countries, ischemic heart disease is predicted to rise 30-60% between 1990 and 2020. In developing countries, rates are predicted to increase by 120% in women and 137% in men from 1990 to 2020.[22] Thus, lifestyle and other environmental factors appear to be more important than ethnicity in influencing the risk of cardiovascular disease. There are also ethnic differences in awareness of traditional modifiable risk factors. Individual ancestry, as estimated by genetic markers, may provide better information for differentiating the genetic and environmental contributions to ethnic differences.

CHD AND SOCIO-ECONOMIC STATUS :

Patients with a lower SES were less likely to be diagnosed to have diabetes or hypertension, were more likely to use tobacco and to present with STEMI. Patients with a lower SES were also less likely to undergo coronary angiography, percutaneous coronary intervention (PCI), and CABG surgery and were less likely to receive medications for CHD secondary prevention, excluding anti-platelet therapy. However, AMI mortality rates were similar between low and high SES after adjusting for CHD risk factors, location of infarct, and treatments.[14]

HYPERTENSION :

Hypertension, defined as systolic/diastolic blood pressure of 140/90 mm Hg or higher, is the most prevalent modifiable risk factor for coronary heart disease, stroke, and heart failure. Systolic pressure is a stronger risk predictor than diastolic blood pressure, and each 20-mm Hg increase in systolic blood pressure is associated with two-fold increased risk of coronary heart disease in

middle-aged populations.[23] Adoption of a diet that is rich in potassium, magnesium, calcium, protein, and fibre can reduce blood pressure to a degree equivalent to using one antihypertensive medication, and substituting additional protein or unsaturated fats leads to additional improvement in blood pressure and the lipid profile. [24]

DIABETES MELLITUS:

Diabetes mellitus, which is defined as fasting plasma glucose of 126 mg/dL or higher, a non-fasting plasma glucose or a plasma glucose 2 hours after an oral glucose tolerance test of 200 mg/dL or higher, or a haemoglobin A_{1c} level of 6.5% or higher, is associated with a two-fold increased risk for cardiovascular disease. Diabetes is often considered as equivalent to a history of coronary heart disease in terms of predicting the risk for coronary heart disease events.[25] By comparison; aggressive blood pressure reduction in persons with diabetes prevents both micro vascular and macro vascular disease. [26]

DYSLIPIDEMIA :

Elevated LDL-C is a strong risk factor, particularly for coronary heart disease. Each 1-mg/dL increase in the LDL-C level is associated with approximately a 1% higher risk of coronary heart disease. Decreased HDL-C levels and elevated triglyceride levels are also associated with the risk of coronary heart disease. Current clinical guidelines for treatment of hyperlipidemia are based mainly on LDL-C levels, but the non-fasting non-HDL cholesterol level (total cholesterol minus HDL-C) and the HDL cholesterol level are sufficient to estimate the risk of coronary heart disease.[19]

SMOKING :

Current smokers have an approximately two-fold higher risk of cardiovascular disease compared with former and never smokers. Second-hand smoke is also associated with a 30% or greater increase in the risk of coronary heart disease.

In patients with coronary heart disease, the risk for recurrent coronary heart disease events is substantially reduced by smoking cessation, and the risk in former smokers returns to the level of non-smokers within 3 years.[19]

OBESITY :

Obesity is closely associated with hypertension, dyslipidemia, and diabetes. Even accounting for these traditional cardiovascular risk factors, obesity may be an independent predictor of CHD and heart failure. Each 5-kg/m2 higher body mass index (BMI) is associated with 40% increased risk for cardiovascular mortality in middle-aged populations. Among individuals with morbid obesity (BMI $\geq$ 35 kg/m2), weight reduction through bariatric surgery may reduce the risk of coronary heart disease by more than 50%.[19]

PHYSICAL INACTIVITY :

Physical inactivity and sedentary lifestyle are associated with increased risk for cardiovascular disease. In patients who have survived an acute myocardial infarction, exercise-based cardiac rehabilitation is associated with reduction of mortality but not of recurrent myocardial infarction.[27]

PSYCHOLOGICAL FACTORS :

Acute and chronic stress, in daily life or due to a natural disaster, is associated with an increased risk for cardiovascular disease. Acute or chronic stress may raise blood pressure, alter glucose or lipid metabolism, and increased blood viscosity.[28]

INFLAMMATION :

Higher levels of inflammatory markers are associated with a higher risk of cardiovascular disease, consistent with the concept that atherosclerosis is an inflammatory process.[19,29]

ALCOHOL :

An association between alcohol consumption and the risk of incident coronary heart disease has been noted in both primary and secondary prevention settings, with the lowest risk at light (<3 drinks per week) to moderate (3 to 7 [for female] or 14 [for male] per week) alcohol consumption. Alcohol use is also associated with injuries and other harmful outcomes, including hypertension and atrial fibrillation.[19]

FAMILY HISTORY :

Premature coronary heart disease in a first-degree relative (male relative <55 years and female <65 years or <60 years in both genders) is associated with increased risk of coronary heart disease. Family history of premature coronary heart disease likely integrates genetic predisposition to cardiovascular disease or cardiovascular risk factors, lifestyle preferences, and environmental factors. [19]

GENETIC FACTORS :

Numerous single nucleotide polymorphisms have been associated with cardiovascular disease risk factors or the incidence of cardiovascular disease.

THROMBOTIC AND FIBRINOLYTIC FACTORS :

Various thrombotic and fibrinolytic factors, such as fibrinogen and plasminogen activator inhibitor, have been associated with incident cardiovascular disease. Whether such information

improves the prediction of prognosis over prediction based on traditional risk factors alone and, if so, whether such factors provide targets for prevention, are not yet clear.[19]

NEW ASPECTS OF TRADITIONAL RISK FACTORS :

Global risk prediction and the management of traditional risk factors in clinical practice are generally based on the most recent assessments of risk factors or the average of multiple measurements over a short period of time. However, change over time or the duration of an abnormal risk factor level may be associated with future risk independent of baseline values. The association of traditional risk factors with cardiovascular disease risk is generally graded and continuous, such that higher levels of the risk factors impart greater risk; as a result, cut offs to define elevated levels of risk factors are somewhat arbitrary. In general, the definition of normal is becoming stricter with increasing recognition that "borderline" levels of risk factors are associated with cardiovascular risk, that the greatest population burden may be in persons with lower elevations of risk because they are much more numerous than persons with very high levels of risk, and because interventions are becoming safer and more effective. For example, diabetes is now defined as a fasting glucose level of 126 mg/dL rather than 140 mg/dL. [19]

BIOMARKERS OF SUBCLINICAL DAMAGE OR DISEASE :

The diagnostic approach to ACS remains one of the most difficult and controversial challenges facing emergency physicians. In recent years, cardiac troponins have emerged as the biochemical "gold standard" for diagnosis of patients with acute chest pain, enhancing our ability to recognize ACS. Early diagnosis and treatment of myocardial ischemia improve patient outcomes, but conventional markers are often non-diagnostic at the time of arrival at the emergency department. Promising new biomarkers, which appear earlier after the onset of ischemia, are being studied and

integrated into clinical practice. Some are markers of myocyte necrosis, but others, including ischemia-modified albumin and natriuretic peptides, detect myocardial ischemia and myocardial dysfunction.[30]

Ideal markers are not normally present in serum, become rapidly and markedly elevated during acute MI, and are not released from other injured tissues. The increasing sensitivity and specificity of serum cardiac markers, which are macromolecules (proteins) released from myocytes undergoing necrosis, have made them the "gold standard" for detection of myocardial necrosis.

What we have now are :

1. Troponins
2. Creatine kinase – MB isoenzyme
3. Myoglobin
4. Brain Natriuretic Peptide (BNP)
5. Pro BNP
6. Lactate Dehydrogenase

All markers of myocardial injury or necrosis but what has always been used are the cardiac Troponins and creatine kinase.

TROPONINS:

The troponins together form a complex of three proteins. This complex consists of troponin T (TnT; Tropomyosin binding), troponin I (TnI, Inhibitory component) and troponin C (TnC, Calcium binding component). Upon cell death, these, and all other proteins constituting the cell, are released into the circulation. After acute myocardial infarction it has been shown in serum of patients with AMI that the predominant forms in blood are free cTnT and the cTnI-TnC binary complex. Troponins have replaced other markers because they are more specific in the setting of

injuries to skeletal muscle or other organs and also are more sensitive in the setting of minimal myocardial injury.

Cardiac-derived TnI (cTnI) and TnT (cTnT), proteins of the sarcomere, are not normally present in the blood with standard sensitivity assays and have amino acid sequences distinct from their skeletal muscle isoforms.

Troponin T is a cardio-specific polypeptide mostly bound to contractile elements of myocardial cells, but with small amounts also present free in the cytoplasm. Cytosolic cardiac troponin T is released within the first few hours after infarction. Release of myofibrillar cTnT occurs more slowly, over a period of days. This biphasic release results in an early rise in serum levels (3-4 hours after the infarct) which is sustained for 10 days or more. This makes it a very useful marker. Minor elevations occur in unstable angina.

With even small acute MIs, troponins increase to 20-fold or more above the lower limits of the assay, and elevations persist for several days.

The troponins generally are first detectable 2 to 4 hours after the onset of acute MI, are maximally sensitive at 8 to 12 hours, peak at 10 to 24 hours, and persist for 5 to 14 days. Their long persistence has allowed them to replace other markers for the diagnosis of acute MI in patients presenting late (>1 to 2 days) after symptoms. However, this persistence can obscure the diagnosis of an early recurrent MI, for which more rapidly cleared markers (i.e., CK-MB) are more useful.[31]

CREATINE KINASE AND ISO-ENZYMES :

Creatine kinase is a cytosolic enzyme (81 kDa) expressed in various tissue types. The two subunits of this dimeric enzyme can either be B-type (brain) or M-type (muscle), yielding three possible isoenzymes (MM, BB and MB), which are all present in tissue, but the composition varies. Skeletal muscle expresses CK-MM at high levels (99%) and CK-MB at low levels (1.1%),

whereas cardiac muscle, in contrast, expresses CK-MM at 79% and CK-MB at 20%.46 It is important to realize that the total CK activity in skeletal muscle is about 5-10 fold higher than in cardiac muscle, so that in absolute values (activity per gram wet weight tissue), skeletal muscle contains approximately equal amounts of CK.MB.

However, because cardiac muscle contains the largest proportion of CK-MB, this was the first biochemical marker for AMI that was relatively specific for necrotic myocardium. [31,32]

Total CK starts to rise within 3 to 8 hours after MI, peaks at 10 – 24 hours and returns to normal by 3 – 4 days. It can be markedly elevated with skeletal muscle trauma or brain injury.

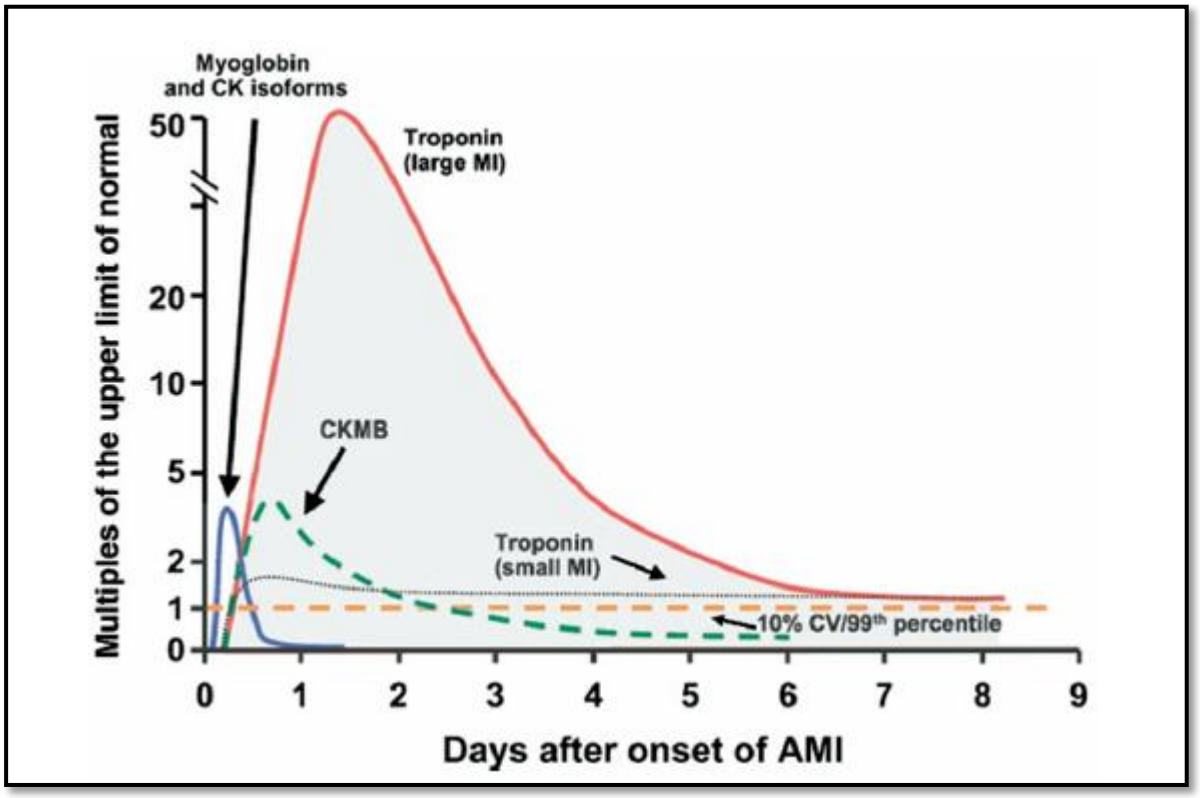


FIGURE 9 : ELEVATION OF CARDIAC MARKERS AFTER MI.[16]

PLATELETS ROLE IN CARDIOVASCULAR DISEASE :

Platelets play a substantial role in atherothrombosis, and platelet activation is implicated in the genesis of acute coronary syndromes (ACS)

PLATELET ACTIVATION :

The initial tethering of platelets at sites of vascular injury is mediated by glycoprotein Ib/V/IX, a structurally unique receptor complex expressed in megakaryocytes and platelets. Von Willebrand factor is the major ligand for one component of this complex, glycoprotein Ib, and the absence of the factor causes defects in primary hemostasis and coagulation.

After the initial adhesion of platelets to the extracellular matrix, the repair process requires a rapid response to autocrine and paracrine mediators, including adenosine diphosphate (ADP), thrombin, epinephrine, and thromboxane A2. These mediators amplify and sustain the initial platelet response, and they recruit circulating platelets from the flowing blood to form a growing hemostatic plug.

The final pathway for all agonists is the activation of the platelet integrin glycoprotein IIb/IIIa ($\alpha IIb\beta 3$), the main receptor for adhesion and aggregation.[33]

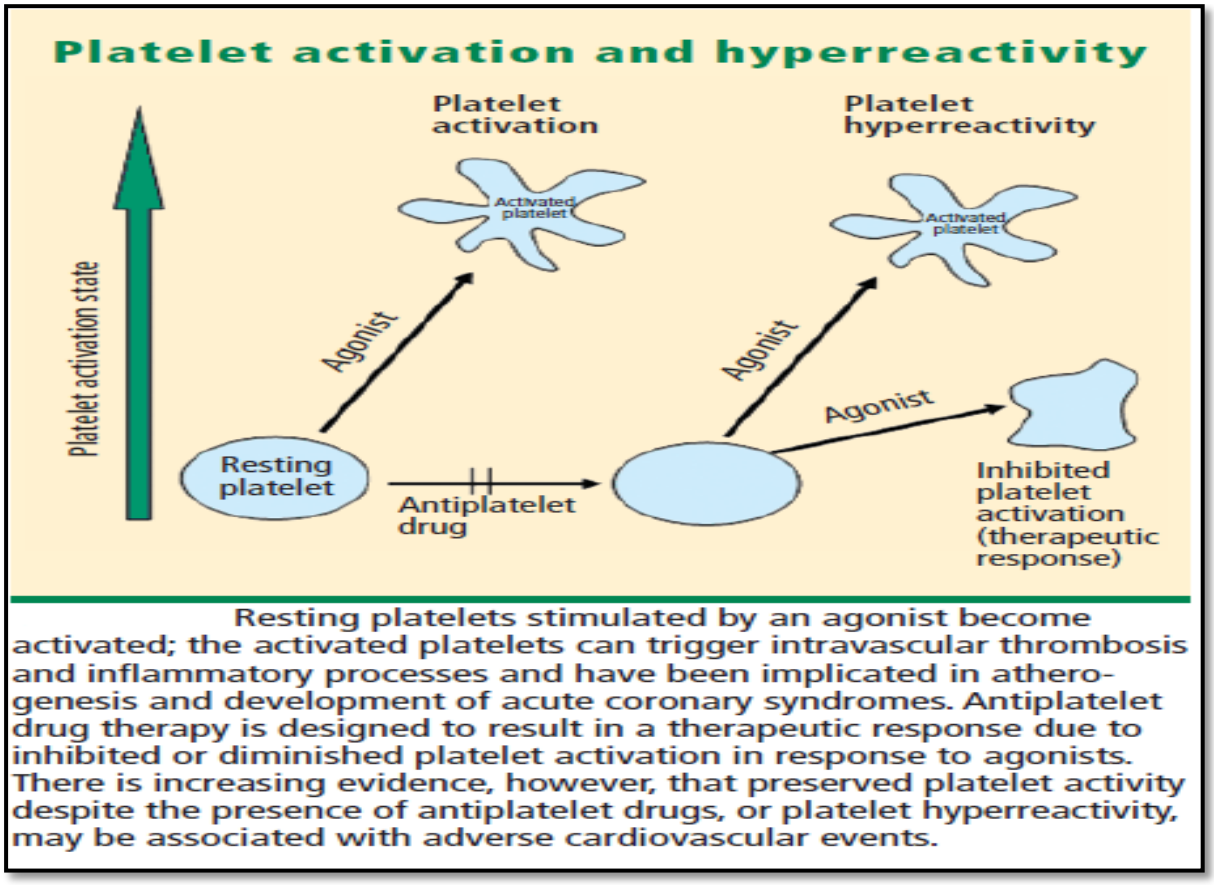


FIGURE 10 : **PLATELET ACTIVITY AND HYPERACTIVITY** [33]

Fibrinogen plays an important role in maintaining the stability of a thrombus, by bridging glycoprotein IIb/IIIa integrins between platelets; von Willebrand factor (vWF) is necessary to facilitate interplatelet bridges at low shear rates in vitro. Quiescent platelets contain the pre-mRNA of the molecule termed tissue factor, the primary initiator of the coagulation cascade that leads to the conversion of Prothrombin to thrombin and fibrinogen to fibrin.

The vascular endothelium controls platelet reactivity by means of three pathways: the arachidonic acid–prostacyclin pathway, the L-arginine– nitric oxide pathway, and the endothelial ectoadenosine diphosphatase (ecto-ADPase) pathway.

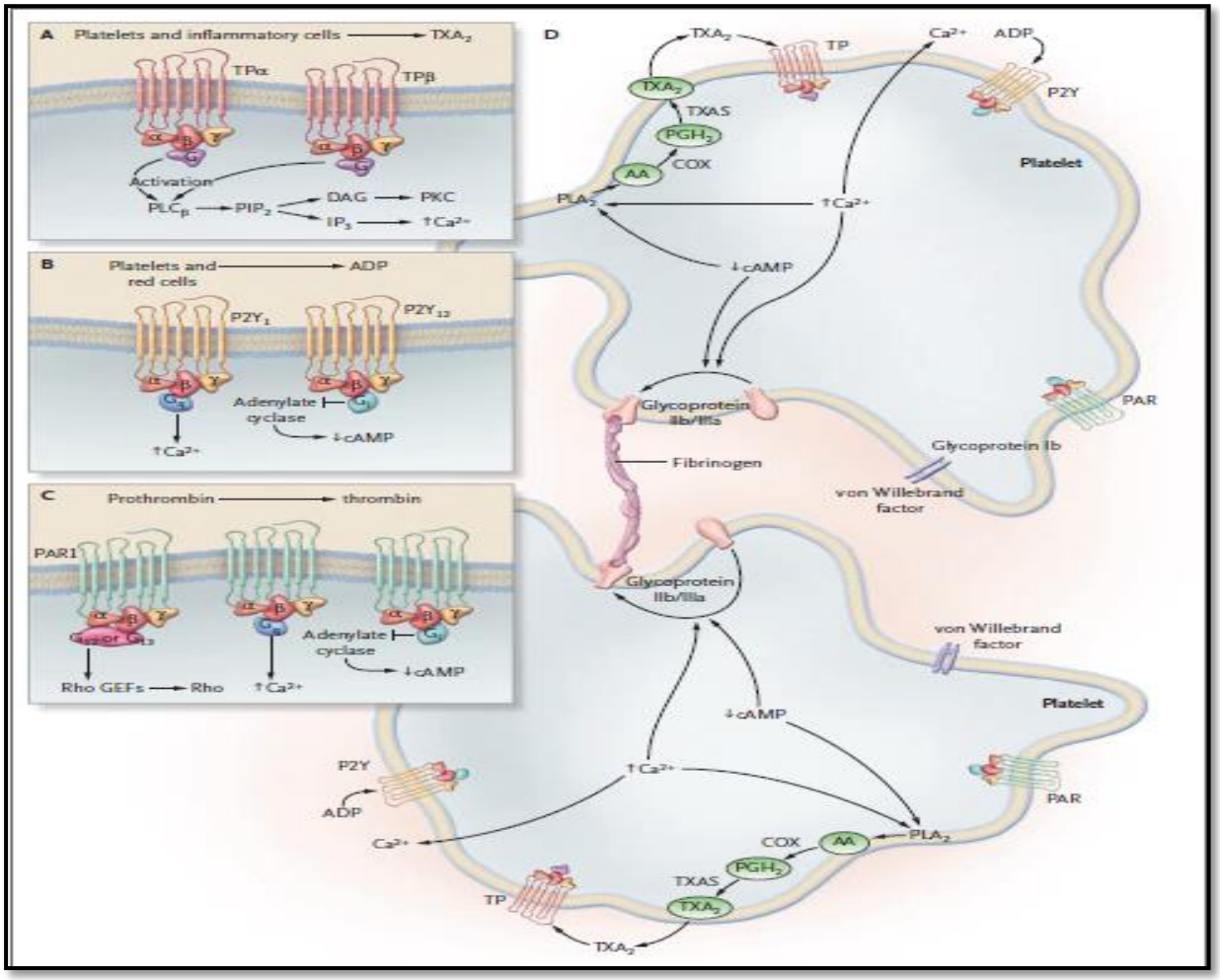


FIGURE 11: **AGONISTS, RECEPTORS, AND EFFECTOR SYSTEMS IN PLATELET ACTIVATION** A, B, and C depict outside-in signalling mediated by thromboxane A2 (TXA2), adenosine diphosphate (ADP), and thrombin, respectively.[34]

Platelets are engaged through receptors for collagen (ie, glycoprotein Ia/IIa or integrin α2β1) and glycoprotein VI, leading to intracellular signaling and activation of the platelets. Platelet activation is followed by firm adhesion through engagement of another integrin, αIIAbβ3 (glycoprotein IIb/IIIa) receptor, on platelet surfaces for fibrinogen. The glycoprotein IIb/IIIa receptor is involved in a homotypic platelet–platelet interaction with an αIIAbβ3 receptor on another platelet, which attracts further platelets and results in platelet–platelet adhesion, called platelet aggregation.[33,34]

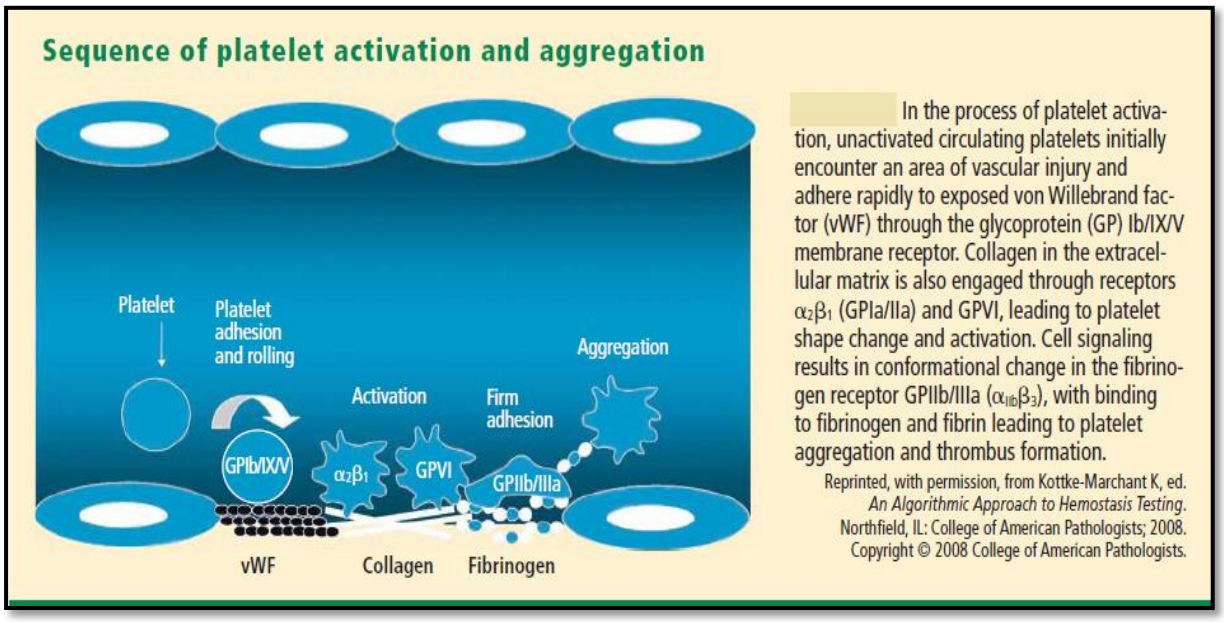


FIGURE 12: SEQUENCE OF PLATELET ACTIVATION AND AGGREGATION[33]

PLATELETS AND DEVELOPMENT OF ATHEROSCLEROTIC LESIONS :

ATHEROGENESIS :

Platelets play a pivotal role in atherogenesis. They contain and release chemokines and growth factors, including:

• RANTES, a chemokine that stimulates monocytes and T cells to increase the production of monocyte infl ammatory mediators.

• Platelet-derived growth factor, which stimulates the migration and proliferation of smooth muscle cells

• Transforming growth factor–β, which also stimulates proliferation of smooth muscle cells.

Platelets that adhere to the vessel wall at sites of endothelial-cell activation contribute to the development of chronic atherosclerotic lesions, and when these lesions rupture, they trigger the acute onset of arterial thrombosis.

The interaction between glycoprotein Ib and von Willebrand factor allows platelets to roll on endothelial cells.

Activated platelets can also influence the progression of plaque formation by releasing adhesive ligands, such as P-selectin, that become expressed on the platelet membrane and mediate platelet–endothelium interactions. Signaling by P-selectin stimulates monocytes and macrophages to produce chemoattractants or growth factors.

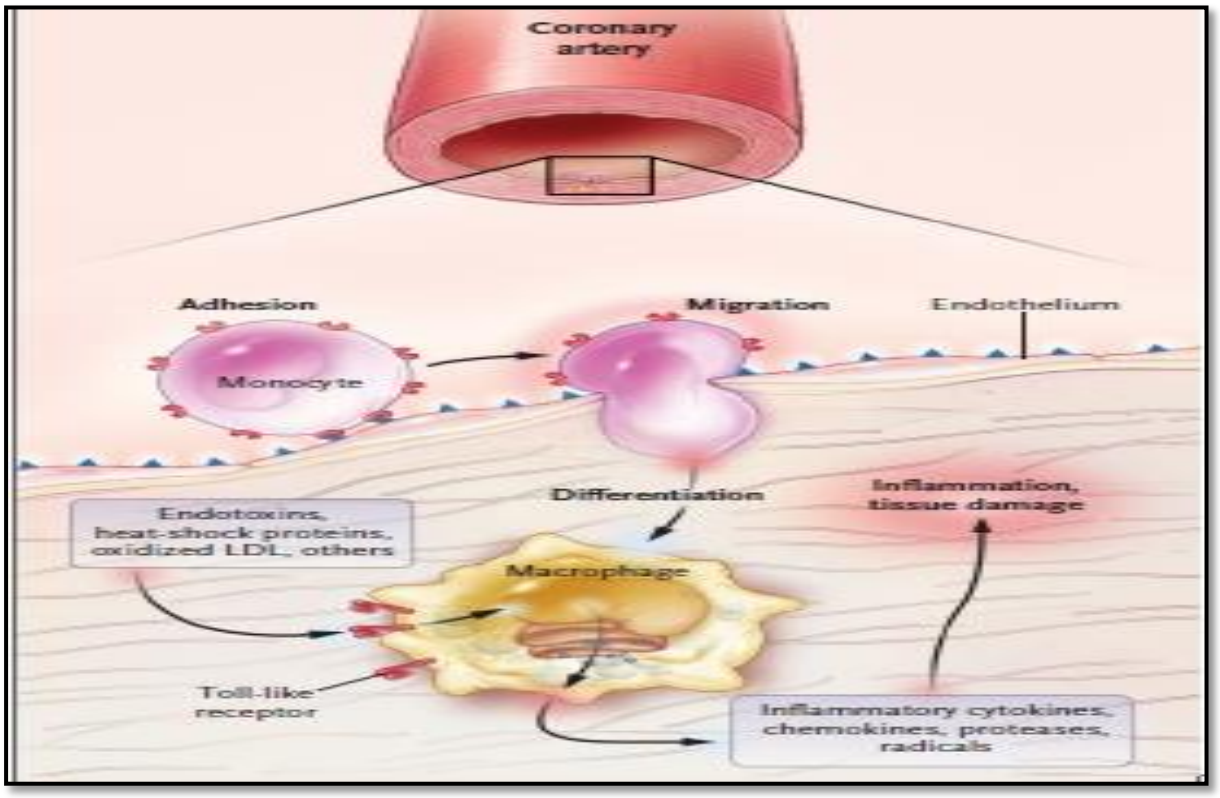


FIGURE 13 : MONOCYTES RECRUITMENT TO ENDOTHELIUM BY PLATELETS [35]

PLATELET-DERIVED MEDIATORS OF INFLAMMATION

Activated platelets release inflammatory and mitogenic mediators into the local microenvironment, thereby altering the chemotactic and adhesive properties of endothelial cells.

These platelet induced alterations of endothelial-cell function support the chemotaxis, adhesion, and transmigration of monocytes to the site of inflammation. CD40 ligand released from platelets induces inflammatory responses in the endothelium.

CD40 ligand is stored in the cytoplasm of resting platelets and rapidly appears on the surface after platelet activation. Platelet derived CD40 ligand can induce endothelial cells to produce reactive oxygen species, adhesion molecules, chemokines, and tissue factor, all of which are components of an inflammatory response.[35]

A prospective study of healthy women found that high plasma levels of soluble CD40 ligand are associated with an increased risk of vascular events.[36]

Moreover, several cardiovascular risk factors, including cigarette smoking[37] and type 2 diabetes mellitus[38], are associated with platelet activation and increased release of the CD40 ligand. The combination of hyperinsulinemia and hyperglycemia up-regulates the release of platelet CD40 ligand and monocyte-derived tissue factor. [39]

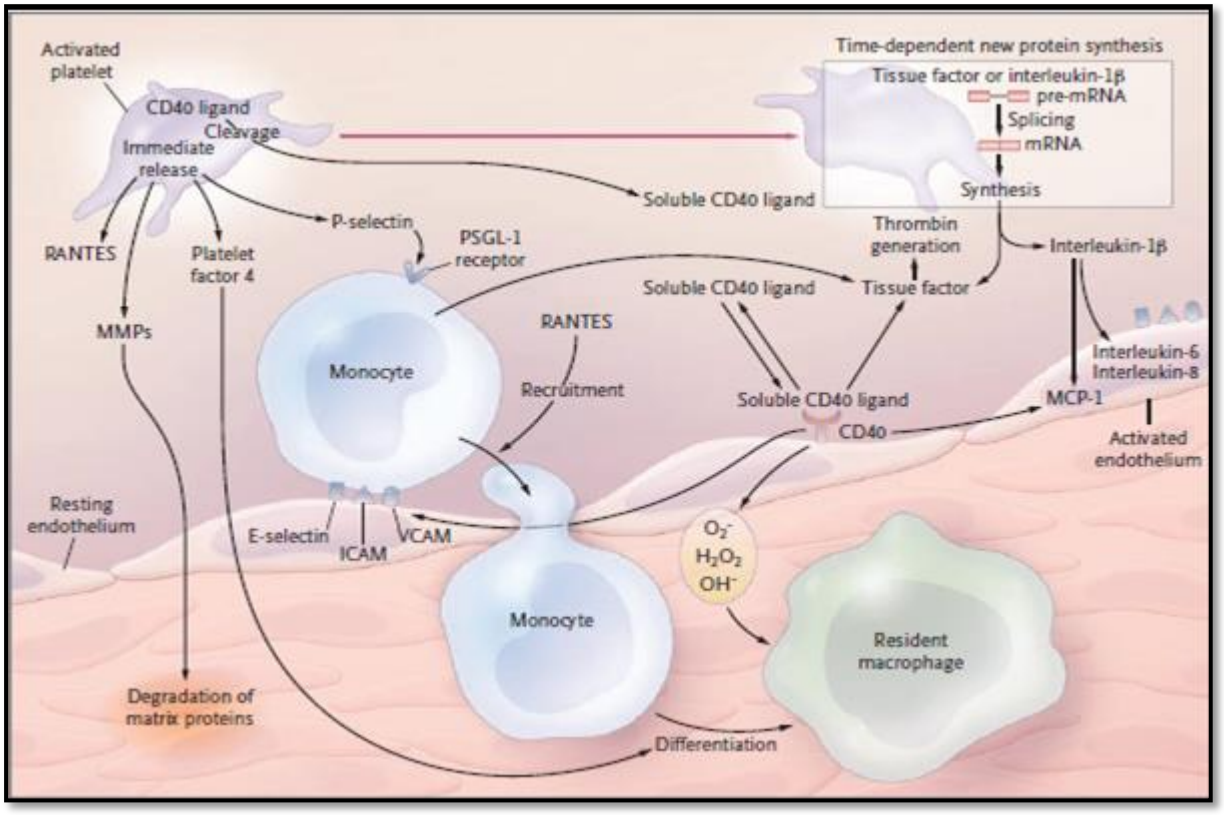


FIGURE 14 : <u>PLATELET DERIVED MEDIATORS OF INFLAMMATORY RESPONSE</u>[34]

The stimulation of platelets by strong agonists can cause the shedding of small membrane vesicles from the platelet surface known as microparticles. Activated platelets or platelet microparticles also release chemokines that can trigger the recruitment of monocytes or promote their differentiation into macrophages. Activated platelets also release the matrix-degrading enzymes matrix metalloproteinases 2 and 9.

REACTIVE OXYGEN SPECIES AND PLATELET ACTIVATION :

The enhanced release of reactive oxygen species (e.g., O2 −) from the vessel wall (where endothelial and smooth-muscle cells express a variety of enzymes that generate these species) indirectly affects the activation of platelets because the species scavenge nitric oxide.

Activated platelets can also generate reactive oxygen species. The metabolism of arachidonic acid by means of the COX-1 pathway contributes to the production of reactive oxygen species. [40]

Agonists that induce platelet activation also activate the platelet isoform of NADPH oxidase. The production of O2 − by platelets through the pathway dependent on these oxidases enhances the recruitment of platelets to a growing thrombus.[41, 42]

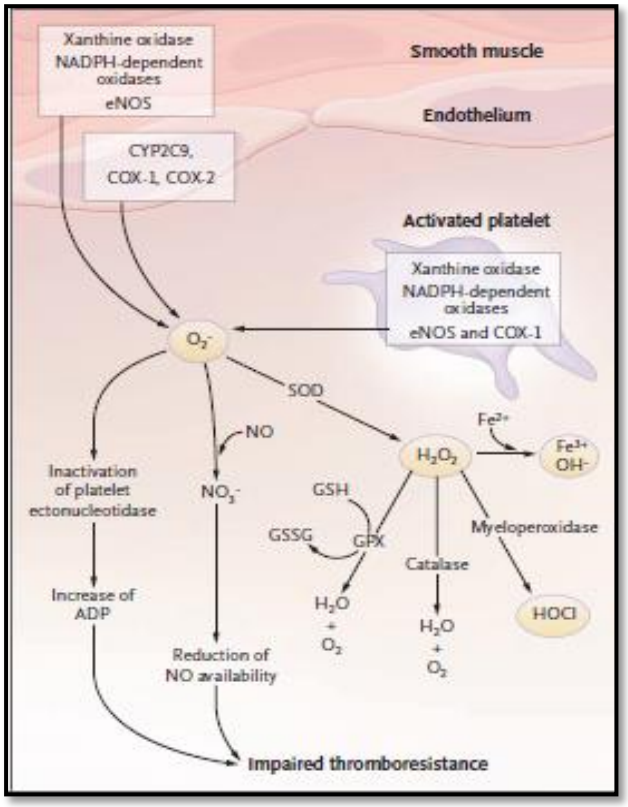


FIGURE 15 : <u>ROLE OF REACTIVE OXYGEN SPECIES IN PLATELET ACTIVATION.</u>[34]

The production of reactive oxygen species is promoted in vascular endothelial cells and smooth-muscle cells in response to injury through several enzymatic pathways and by the expression of enzymes by activated platelets. O2 can scavenge nitric oxide (NO) to form peroxynitrate (NO3 −), thereby impairing the antiplatelet activity of NO.

The increased generation of reactive oxygen species can induce enhanced lipid peroxidation of cell-membrane phospholipids or circulating LDL, leading to the increased generation of F2-isoprostanes, a family of prostaglandin isomers reduced from arachidonic acid by a mechanism catalyzed by free radicals. [43,44] F2-isoprostanes can modulate the adhesive reactions and activation of platelets induced by low levels of other agonists.

The consistent relationship between the rates of formation of F2-isoprostanes and thromboxane in obese women[45] and in patients with hypercholesterolemia, type 2 diabetes mellitus, or homozygous homocystinuria [46] suggests that a low-grade inflammatory state associated with these metabolic disorders may be the primary trigger of thromboxane-dependent platelet activation that is mediated, at least in part, by enhanced lipid peroxidation.

PLATELETS IN ATHEROGENESIS IN HUMANS:

The evidence for a role of platelets in atherogenesis in humans is limited and largely indirect. Several platelet-derived chemokines and growth factors are detectable in atherosclerotic plaques.[47] Moreover, platelet activation is associated with increased wall thickness of the carotid artery and with progressive thickening of the artery in patients with type 2 diabetes mellitus.[48] Persistent platelet activation, as reflected by enhanced excretion of thromboxane metabolites, has been reported in association with major cardiovascular risk factors that accelerate atherogenesis.[49]

PLATELETS AND ARTERIAL THROMBOSIS

Atherosclerosis without flow-limiting thrombosis is a slowly progressive disease. The usual mechanism responsible for the sudden transition from a stable, often clinically silent, disease to a symptomatic life-threatening condition is the denudation and erosion of the endothelial surface or plaque disruption followed by thrombosis.

A break in the endothelial permeability barrier facilitates the recruitment of circulating monocytes and plasma lipids into the arterial wall as well as platelet deposition at the sites of endothelial denudation. Damaged endothelial cells, monocytes, and aggregated platelets, through the release of mitogenic factors, potentiate the migration and proliferation of smooth muscele cells (SMCs), which, together with increased receptor mediated lipid accumulation and increased connective tissue synthesis, shape the typical atheromatous plaque. Repeated cycles of this process result in hyperplasia of the intima–media layer of the vessel wall and the development of an atherosclerotic plaque.

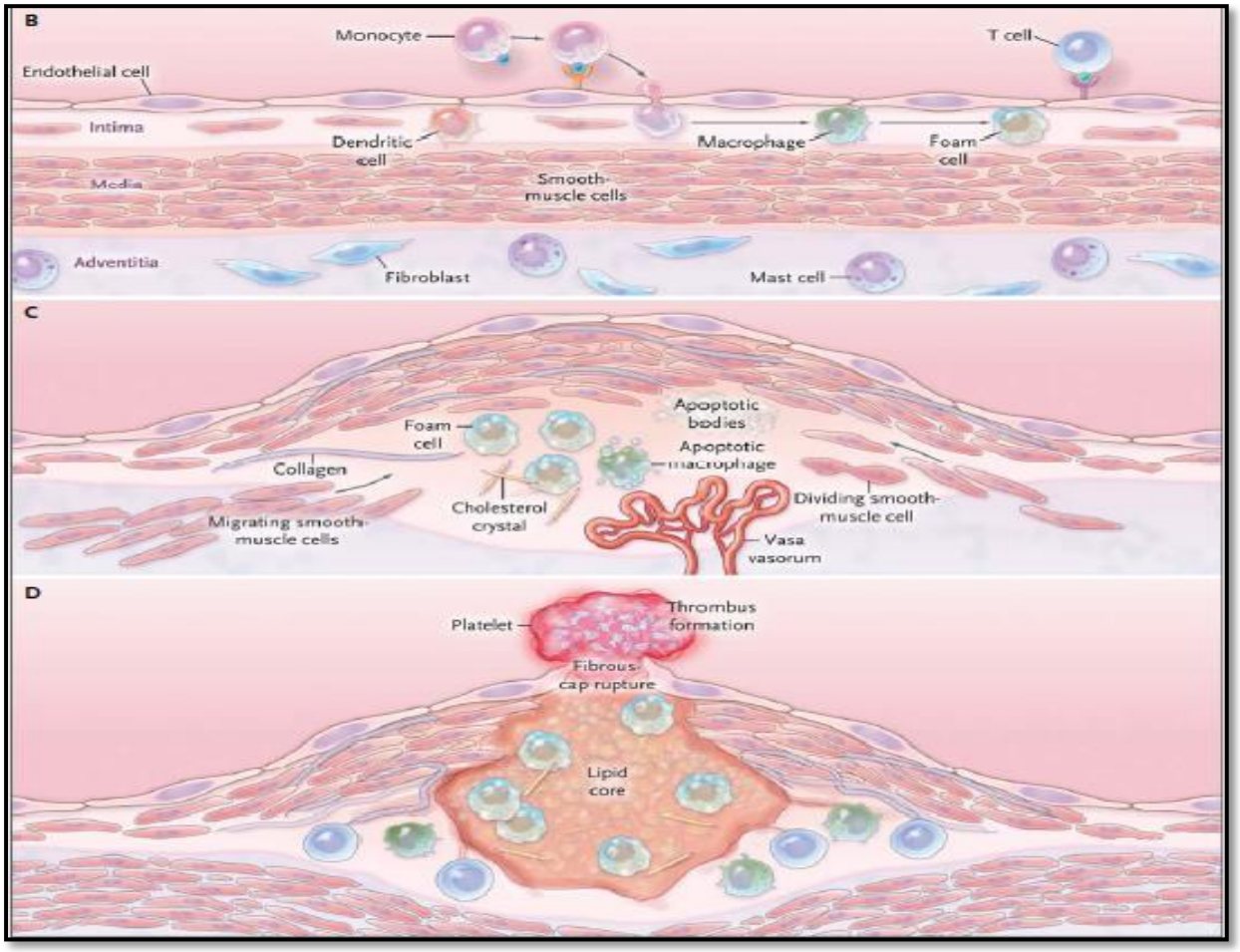


FIGURE 16 : DYSFUNCTIONAL ENDOTHELIUM AND SUBSEQUENT ATHEROSCLEROTIC LESION

In some instances a much faster development is observed; thrombosis associated with vulnerable disrupted plaques seems to be responsible for the accelerated process of clinical syndrome presentation. Although the exact triggering factors of the vulnerable plaque rupture are unknown, inflammation is accepted to be a pivotal chronic event. Culprit coronary plaques are characterized by greater lipid content, macrophage count, apoptosis, angiogenesis, and internal elastic lamina dilatation. [50,51,52]

Human atherectomy specimens and necropsy studies have revealed that the main intrinsic features that characterize plaques as "vulnerable" are:

(1) A large necrotic lipid core occupying more than 40% of the total plaque volume;

(2) A thin fibrous cap;

(3) An increased macrophage, foam cell, and T-lymphocyte content at the margins or so-called shoulders of the plaque;

(4) Reduced amounts of collagen and SMCs;

(5) Thrombotic material with the deposition of platelets and fibrin.

EVALUATION OF PLATELET INDICES:

Traditionally, platelet function and size correlate because larger platelets, produced from activated megakaryocytes in the bone marrow, as explained are likely to be more reactive than normal platelets. Consequently, larger and hyperactive platelets play a pivotal role in accelerating the formation and propagation of intracoronary thrombus, leading to the occurrence of acute thrombotic events. These observations led to the hypothesis that increased consumptions of platelets thereby reducing the platelet count and increased MPV, which is an index of platelet size that acts as a reliable index of platelet activation, may be a potentially useful marker in cardiovascular risk stratification. [54]

The frequently described inverse relationship between platelet count and MPV in physiological and some pathological conditions reflects the tendency to maintain hemostasis by preserving a constant platelet mass. This inverse relationship is often seen in inflammatory disorders, where enhanced thrombopoiesis increases the quantity of circulating platelets, and large amount of highly reactive large-sized platelets migrate to inflammatory sites, where they are intensely consumed. Importantly, defective thrombopoiesis and enhanced destruction and swelling of circulating platelets in an environment rich in activating agents can affect the relationship between platelet count and MPV. Circulating platelets contain matrix ribonucleic acid, mitochondria, alpha- and dense granules which provide mechanisms of self regulation by shape-change and release of biologically active substances . Rapid (minutes-hours) shifts in platelet indices, including an increase of MPV, may take place as a result of the synthesis of prothrombotic and

pro-inflammatory agents in platelets, degranulation of alpha-granules, and release of highly reactive platelets from stores (the spleen).[55]

MPV is measured by cell counters employing impedance an optical effects . The discordance between the results of different and even the same cell counters limits the interchangeable use of MPV. This can explain, at least partly, why haematological laboratories sometimes do not display the MPV and some other indices of platelet function.

Inaccurate measurement of platelet indices may be due to inappropriate blood sampling and storing. The platelet indices have been shown to be sensitive to the differences in blood sample anticoagulation, storage temperature and delays in processing. In particular, the time-dependent swelling of platelets in samples anticoagulated with ethylenediaminetetraacetic acid (EDTA) can result in an artefactual increase of MPV and misinterpretation of prethrombotic changes . Storage-dependent changes are also characteristic for other simultaneously measured indices, such as mean platelet component (MPC; reflects density and platelet degranulation) and platelet distribution width (PDW; relates to the platelet pseudopodia and shape change). One recent study suggested recording both MPV and PDW to provide more reliable information.[56]

Understanding of the role of platelets in a variety of thrombotic and inflammatory disorders has substantially improved, owing to the recent advances in the quantification of laboratory markers of platelet function. MPV has emerged as a relatively reliable marker of thrombopoiesis and platelet function. PDW and Plateletcrit are yet to be explored fully with respect to its significance.

Established cardiovascular risk factors, such as smoking, hypertension, diabetes, as well as age, sex, and possibly ethnicity can modify shifts of MPV, affecting the expected inverse relationship between MPV and platelet count seen in inflammatory thrombocytosis.

But A few studies which investigated the effects of therapeutic interventions on MPV in various clinical conditions showed that Aspirin, with its specific action on the arachidonic acid cascade in

megakaryocytes and platelets, exerted little, if any, effect on MPV . The failure to affect platelet size was also reported in the case of dual (aspirin + clopidogrel) therapy [57, 58]

MATERIALS AND METHODS:

SOURCE OF DATA (SAMPLE):

A hospital based study carried out over a period of one and half year comprising of 420 cases beginning from October 2010 at R.L.Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

METHOD OF DATA COLLECTION:

It is a study conducted in the Department of Pathology, of Sri Devaraj Urs Medical College, from October 2010.

- Blood (2ml) was collected in dipotassium EDTA tubes from all the patients by a clean puncture avoiding froth or bubbles after obtaining informed consent.
- The sample collected was run within 2 hours of venepuncture using Beckman Coulter Act 5Diff automated cell counter.
- Platelet count, Mean platelet volume (MPV), Plateletcrit (Pct), Platelet distribution width (PDW) and Plateletcrit was calculated.
- Clinical data was obtained from each case with respect to name, age, clinical history, associated co-morbidities like Diabetes mellitus, hypertension, smoking alcohol intake and history of any drug intake.

Strips manufactured by Roche for specific detection of cardiac TnT through quantitative imunological tests were used. This test contains two monoclonal antibodies specific for cardiac

TnT: one gold-labelled, the other biotinylated. Test strips were analyzed by using optical system of cardiac reader provided by Roche. The quantitative range for cardiac TnT detection extends from 0.1ng/ml to 2ng/ml. The reader interprets TnT concentration below or above this range qualitatively (low or high respectively). The cutoff used in our study for positive TnT assay was 0.1ng/ml.

- Internal and external quality control will be strictly followed.

STATISTICAL ANALYSIS:

Statistical analysis will be carried out using descriptive measures like Mean Standard Deviation and proportion. ANOVA test will be used to test the variation of mean in three groups and its significance.

INCLUSION CRITERIA:

1. Patients admitted for intensive care with unstable angina or acute myocardial infarction.
2. Patients with stable coronary artery disease or with a history of previous Ischemic event attending routine follow up.
3. Age and sex matched control group who have no features of ischemic cardiac disease, alcohol / smoking, diabetes mellitus, hypertension, anemia.

EXCLUSION CRITERIA:

1. Patients with musculoskeletal chest pain, acid peptic disease with no evidence of ischemic heart disease by ECG.
2. Patients with other thrombotic diseases like stroke, vasculitis.

RESULTS

RESULTS:

The total number of cases that were studied: 420.

The total number of patients with cardiac Troponin-T positive acute myocardial infarction and grouped as MI: 140.

The total number of patients with cardiac Troponin-T negative acute coronary syndrome other than acute MI and grouped as non- MI: 140.

The total number of age and sex matched healthy controls with no history or symptoms of ischemic heart disease and grouped as controls: 140.

TABLE 2 : DISTRIBUTION OF RISK FACTORS IN ALL PATIENTS

GROUPS (n=140)	MI GROUP (%)	NON-MI GROUP (%)	HEALTHY CONTROLS (%)
AGE,YEARS MEAN (SD)	54.47 (12.9)	60.43 (12.33)	51.37 (12.66)
MALES	116 (82.85)	91 (65)	115 (82.14)
FEMALES	24 (17.14)	49 (35)	25 (17.85)
DIABETES MELLITUS	44 (31.42)	48 (34.28)	0 (0)
HYPERTENSION	50 (35.71)	57 (41)	0 (0)
SMOKERS	59 (42.14)	37 (26.42)	0 (0)
ALCOHOLICS	09 (06.42)	07 (05)	0 (0)
H/O IHD	05 (03.57)	06 (04.28)	0 (0)
H/O PREVIOUS MI	09 (06.42)	12 (08.57)	0 (0)

Patients with MI had a higher male preponderance with 82.85% and more smokers (42.14%) than non-MI patients.

The non-MI patients showed a higher prevalence of Diabetes Mellitus and Hypertension than MI patients.

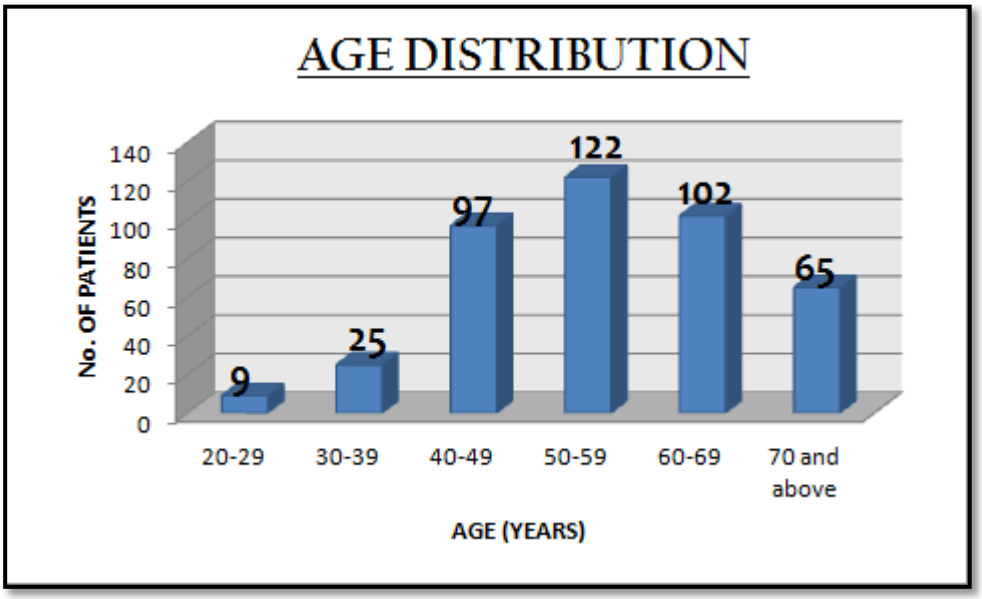
AGE:

In the present study, the ages ranged from 23 to 95 years. Mean age was 55.44 ± 13.13 years. Majority of patients belonged to the 6th decade of life (29.04%), followed by 7th decade (24.28%) and 5th decade (23.09%) of life.

TABLE 3 : AGE DISTRIBUTION AMONG ALL PATIENTS

AGE GROUPS (Years)	NUMBER	PERCENT (%)
20-29	09	2.14
30-39	25	5.95
40-49	97	23.09
50-59	122	29.04
60-69	102	24.28
70 AND ABOVE	65	15.47
TOTAL	420	100

CHART 1 : AGE DISTRIBUTION AMONG ALL PATIENTS

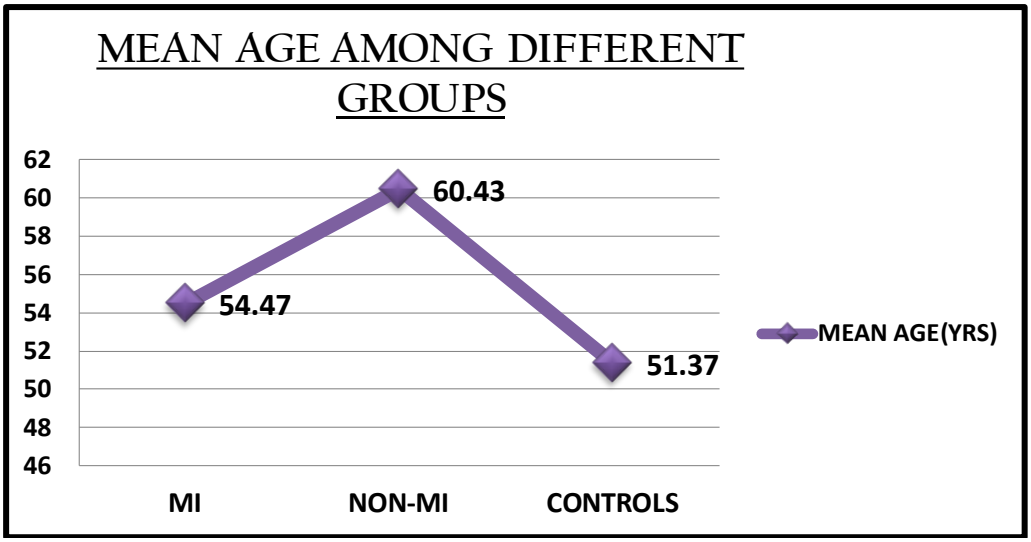


The mean age among patients in the MI group was 54.47 (± 12.9) years.

The mean age among patients in the non- MI group was 60.43 (± 12.3) years.

The mean age among patients in the healthy control group was 51.37 (± 12.66) years.

CHART 2 : MEAN AGE AMONG DIFFERENT GROUPS



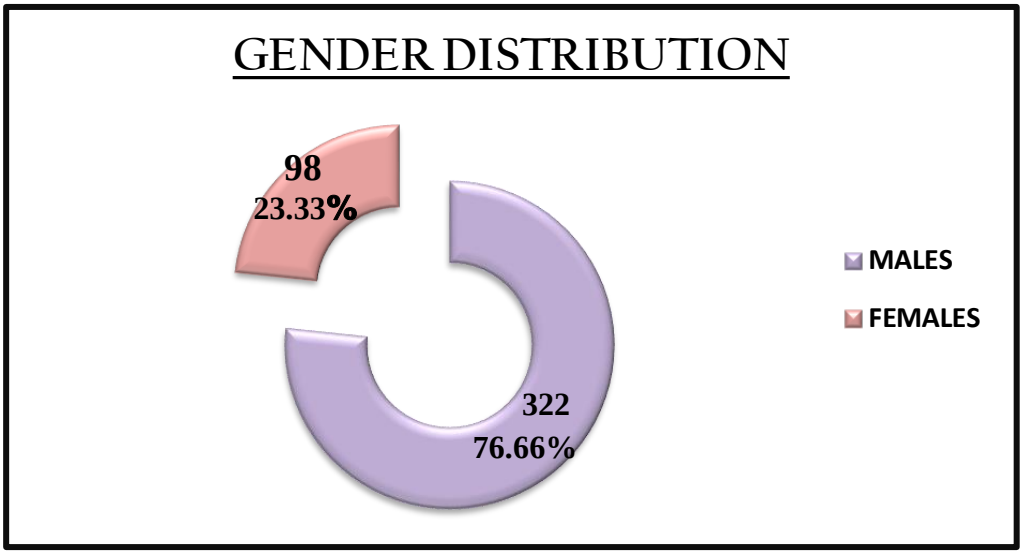
Between the MI and NON MI patients, the mean age was higher in the non-MI patients.

GENDER:

In the present study, number of males was 322 (76.66%) and number of females was 98 (23.33%).

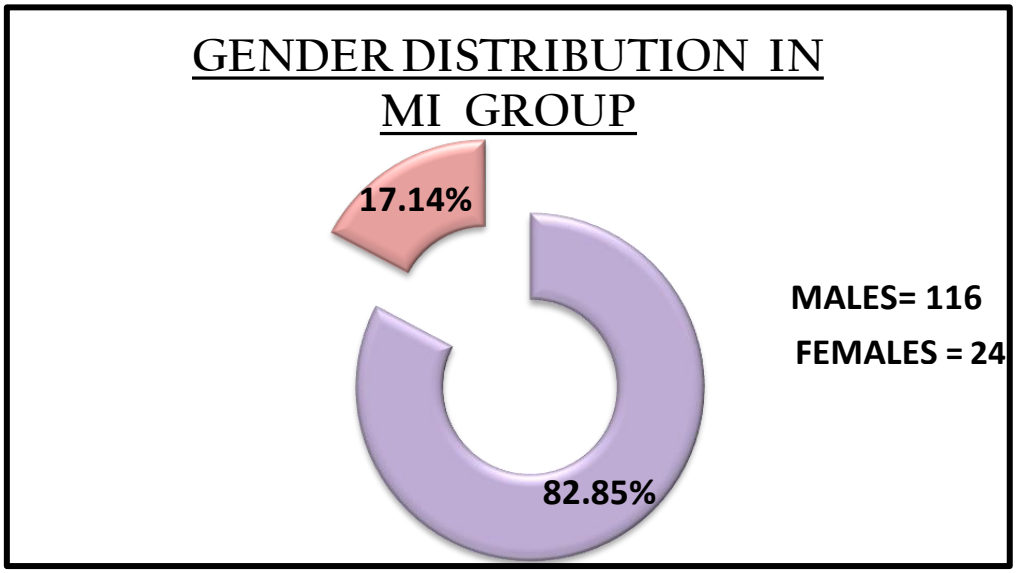
Male: female ratio was 3.28.

CHART 3 : GENDER DISTRIBUTION AMONG ALL PATIENTS



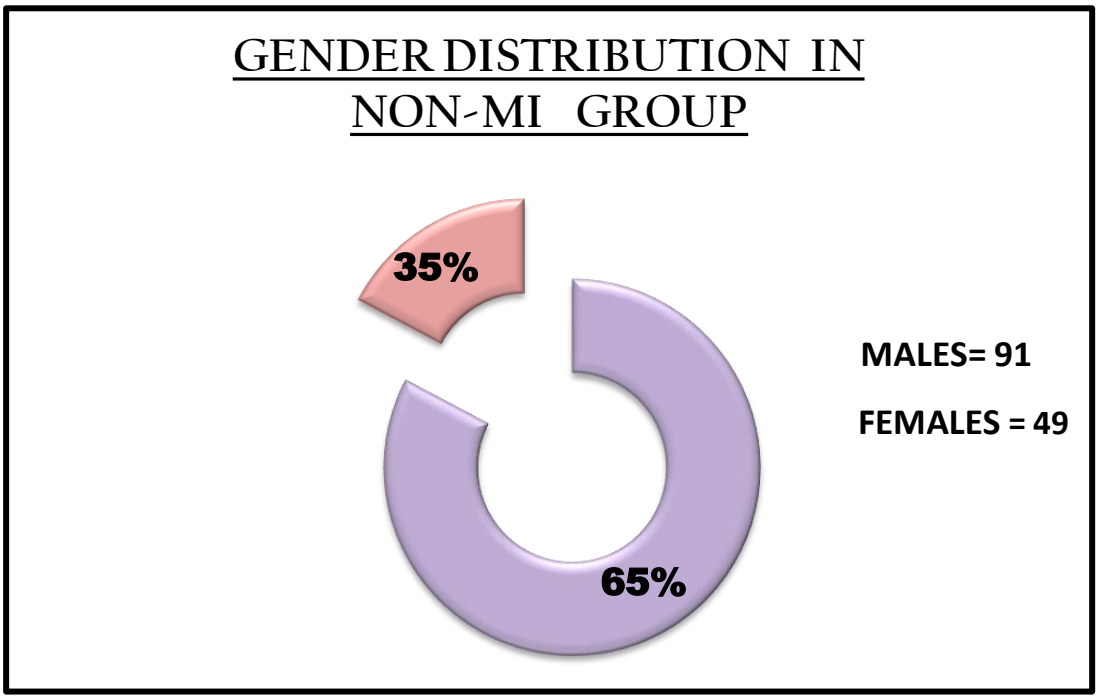
The number of males in the MI group was 116 (82.85%) and the number of females were 24 (17.14%)

CHART 4 : GENDER DISTRIBUTION IN MI GROUP



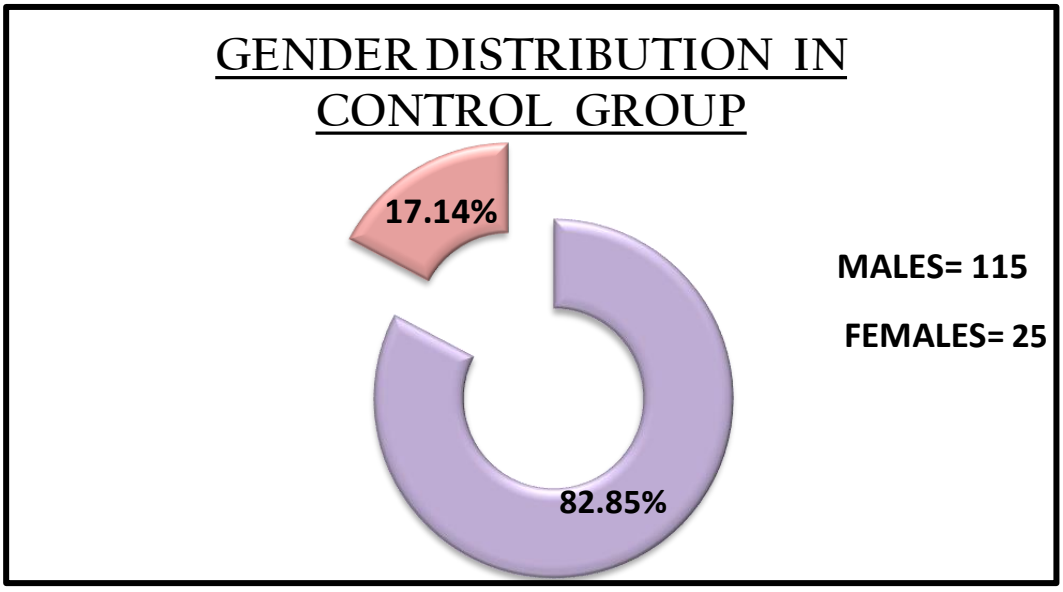
The number of males in the Non - MI group was 91 (65%) and the number of females was 49 (35%)

CHART 5 : GENDER DISTRIBUTION IN NON-MI GROUP



The number of males in the healthy control group were 115 (82.14%) and the number of female were 25 (17.85%).

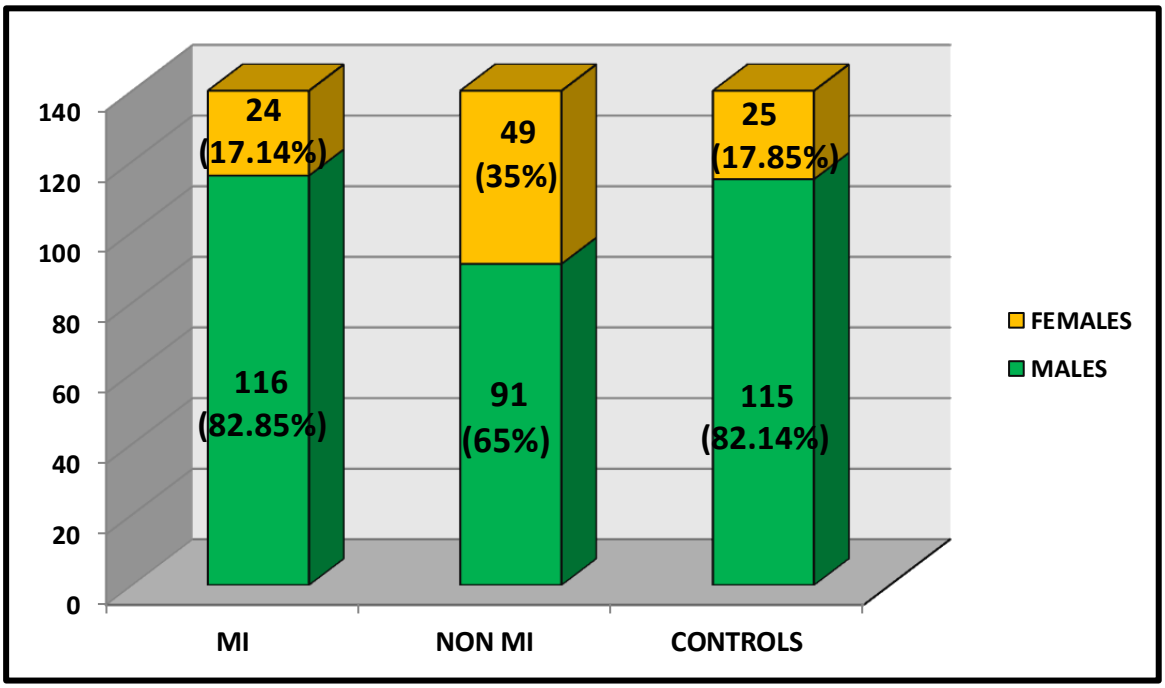
CHART 6 : GENDER DISTRIBUTION IN CONTROL GROUP



GENDER DISTRIBUTION AMONG ALL GROUPS

In the study males were more in number than females among the patients of both MI and non MI groups.

CHART 7: COMPARISON OF GENDER DISTRIBUTION AMONG INDIVIDUAL GROUPS



RISK FACTORS ASSESSMENT AMONG PATIENTS

SMOKING :

Among the patients of the study, total number of smokers were 96 (22.85%) and 324 (77.14%) non-smokers.

59(42.14%) smokers belonged to the MI group and 37(26.42%) to the non-MI group.

CHART 8 : SMOKING PREVALENCE AMONG ALL PATIENTS

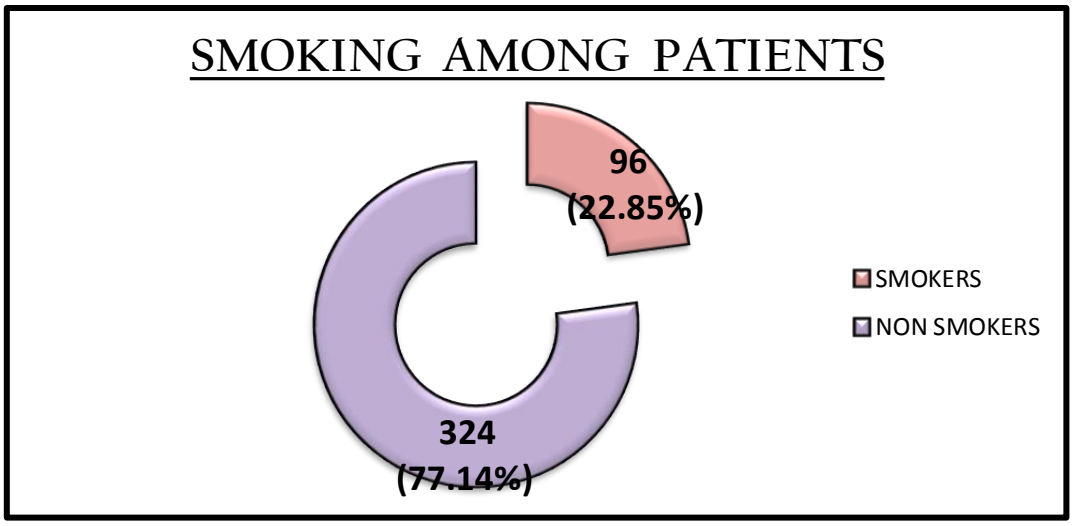
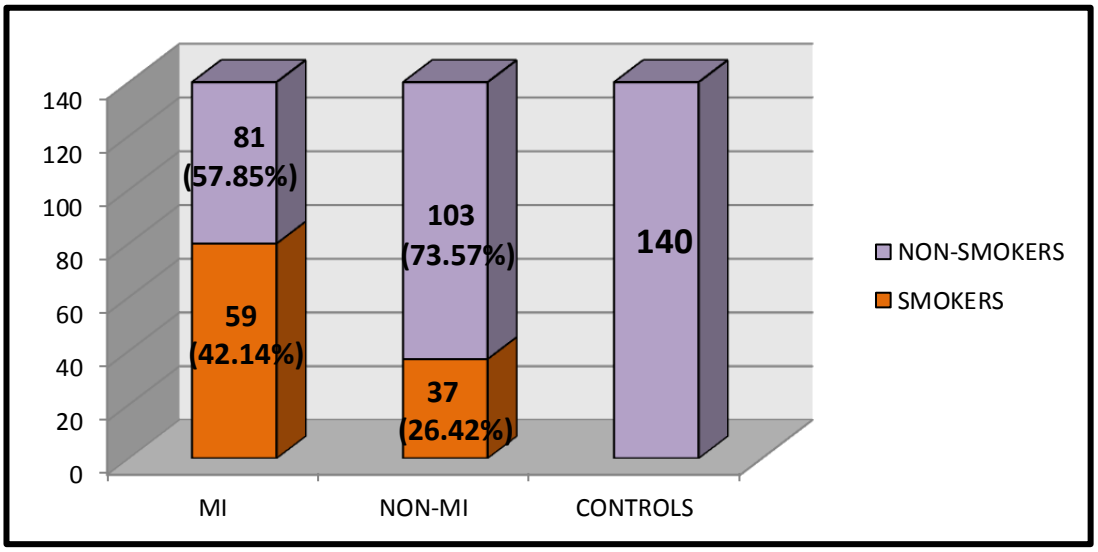


CHART 9 : COMPARISON OF SMOKING PREVALENCE AMONG INDIVIDUAL GROUPS



ALCOHOL :

There were only 16 (3.80%) patients with history of alcohol intake.

09 of them were patients of MI and 07 belonged to the non-MI group.

CHART 10 : **ALCOHOL INTAKE AMONG ALL PATIENTS**

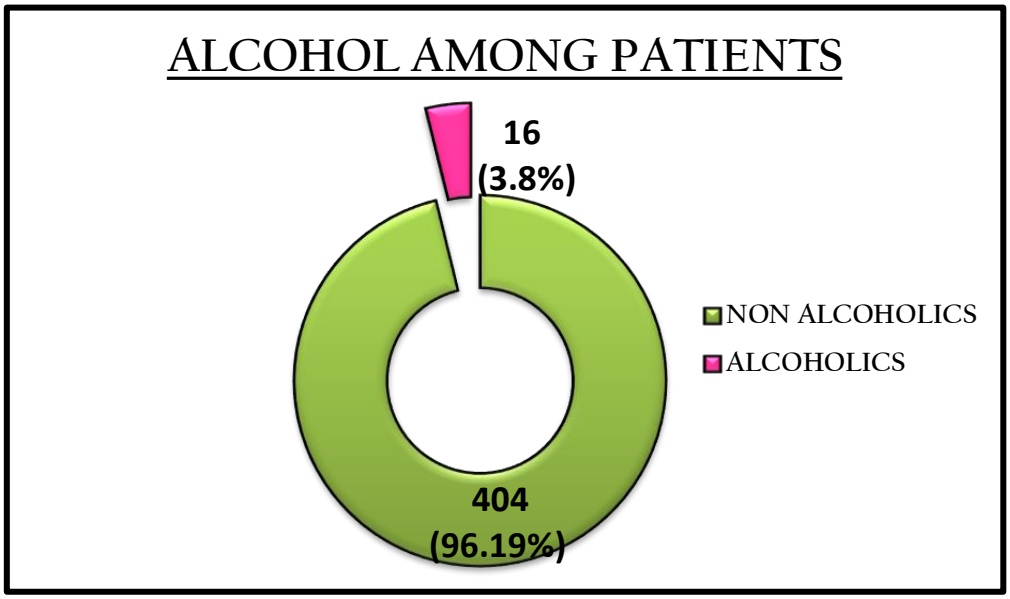
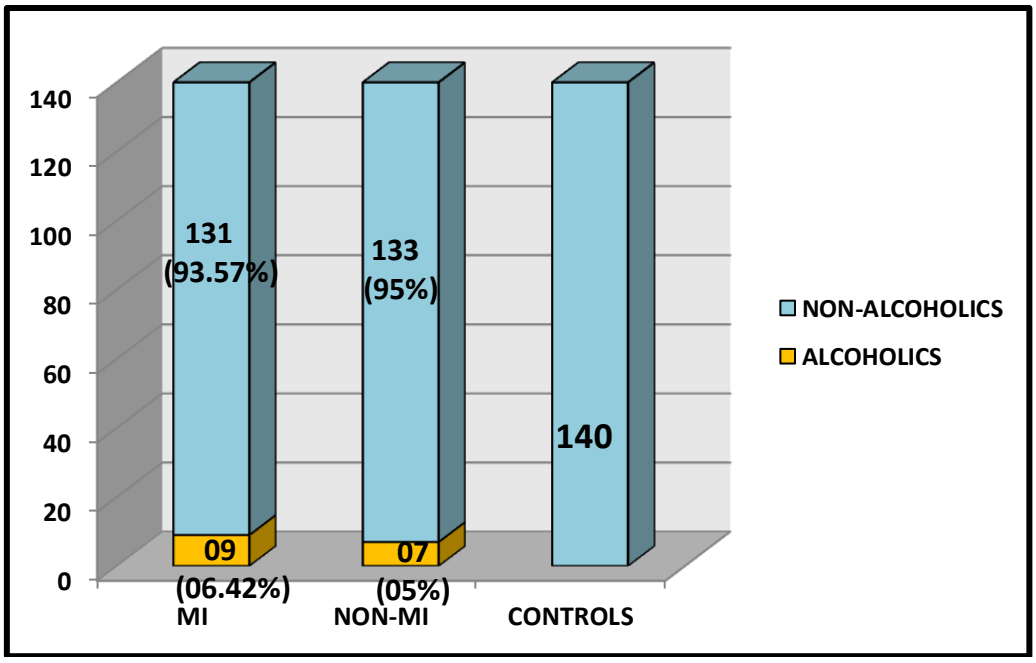


CHART 11 : **COMPARISON OF ALCOHOL INTAKE AMONG INDIVIDUAL GROUPS**



DIABETES MELLITUS:

Of all the 420 patients 92(21.9%) were diabetic with 66(71.73%) males and 26(28.26%) females among them.

CHART 12 : PREVALENCE OF DIABETES MELLITUS AMONG ALL PATIENTS

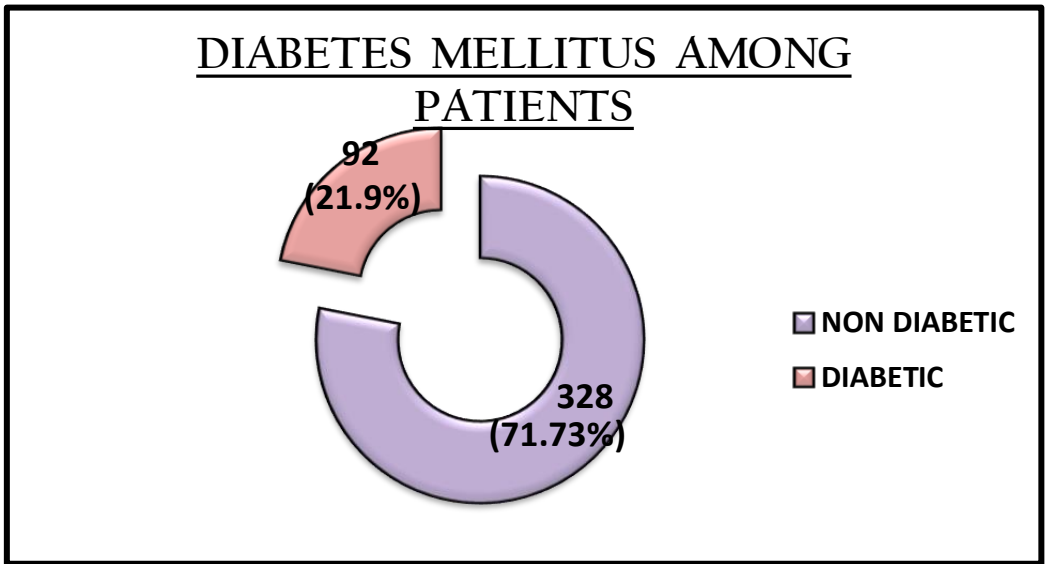


CHART 13 : **GENDER DISTRIBUTION AMONG DIABETIC AND NON-DIABETIC PATIENTS**

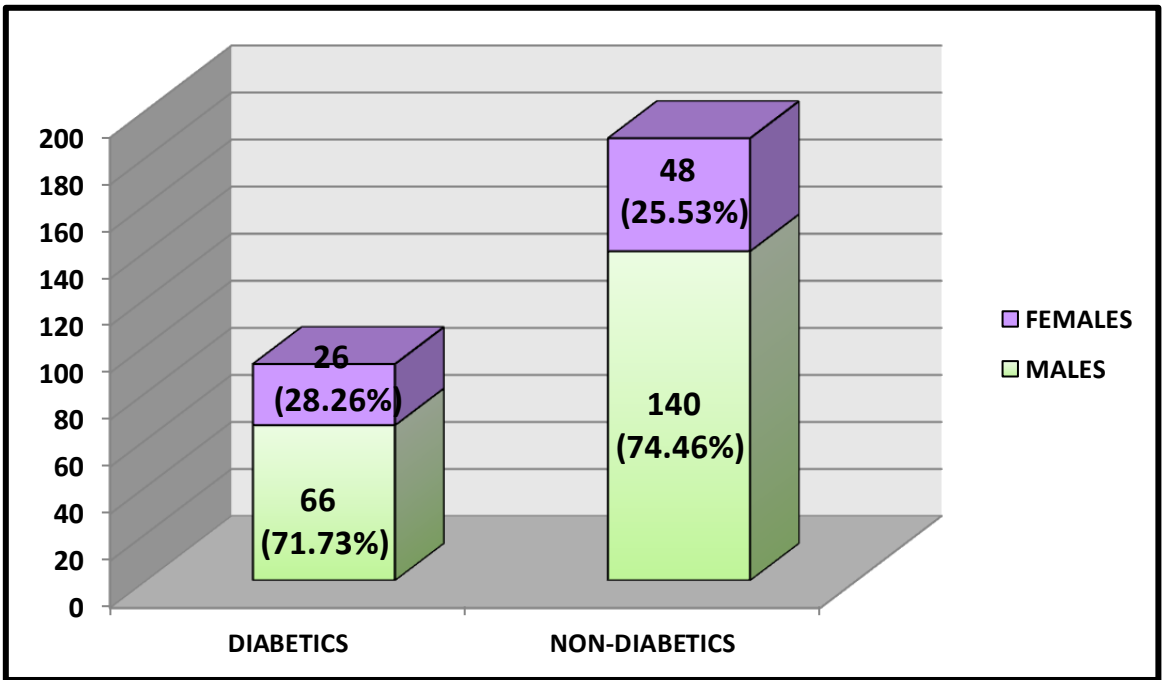
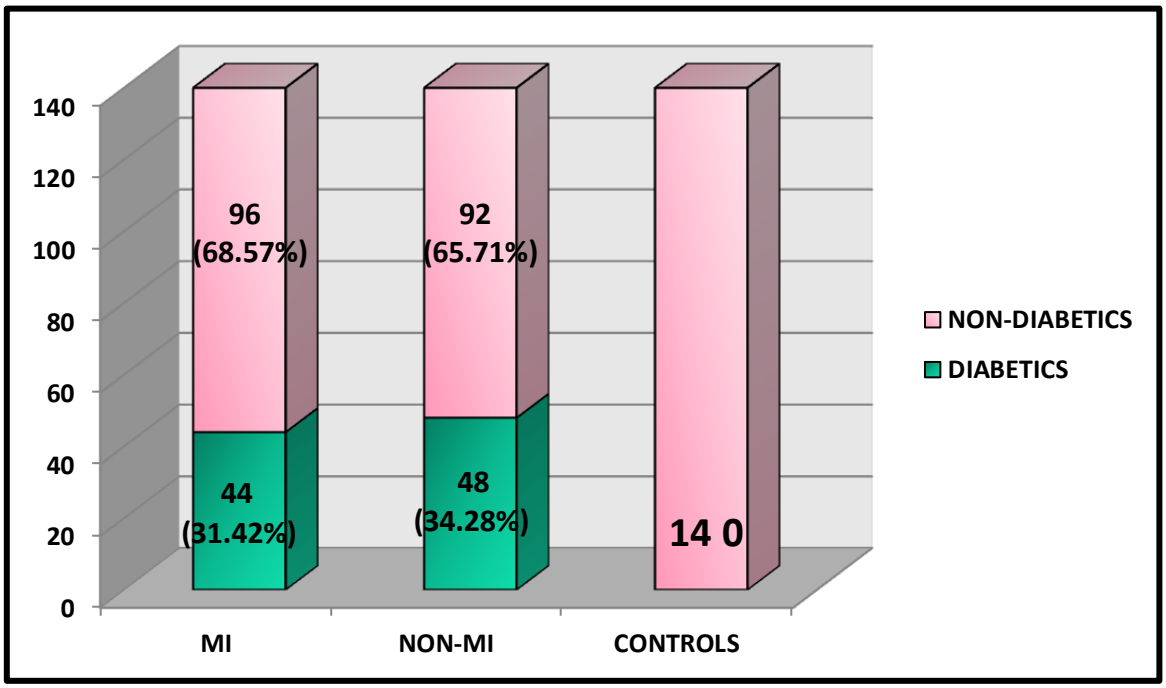


CHART 14 : **COMPARISON OF DIABETES MELLITUS PREVALENCE AMONG INDIVIDUAL GROUPS**



Non-MI group had more diabetics 48(34.28%) than MI patients 44(31.42%).

HYPERTENSION :

Hypertension was overall seen in 107(25.47%) patients and 313(74.52%) patients were non-hypertensive. Among the hypertensives, 67(62.61%) were males and 40(37.38%) were females.

CHART 15 : **PREVALENCE OF HYPERTENSION AMONG ALL PATIENTS**

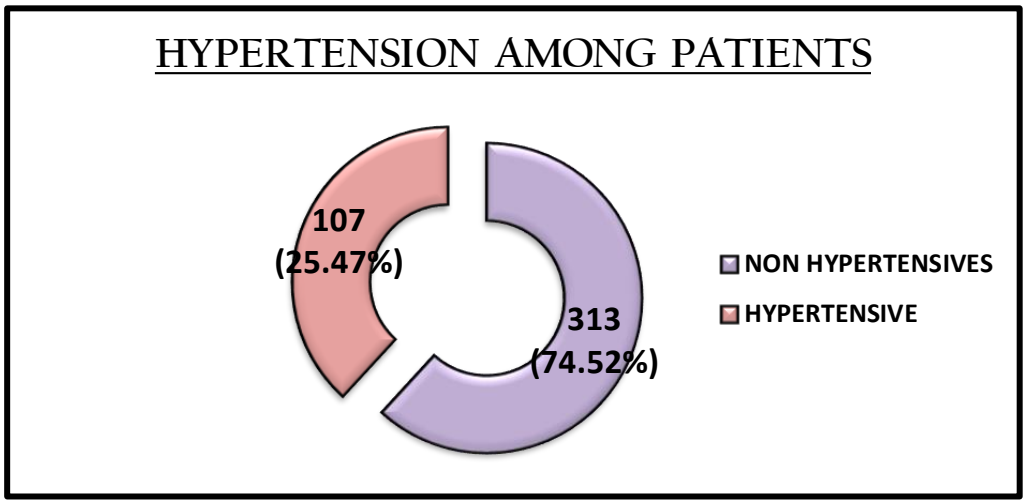
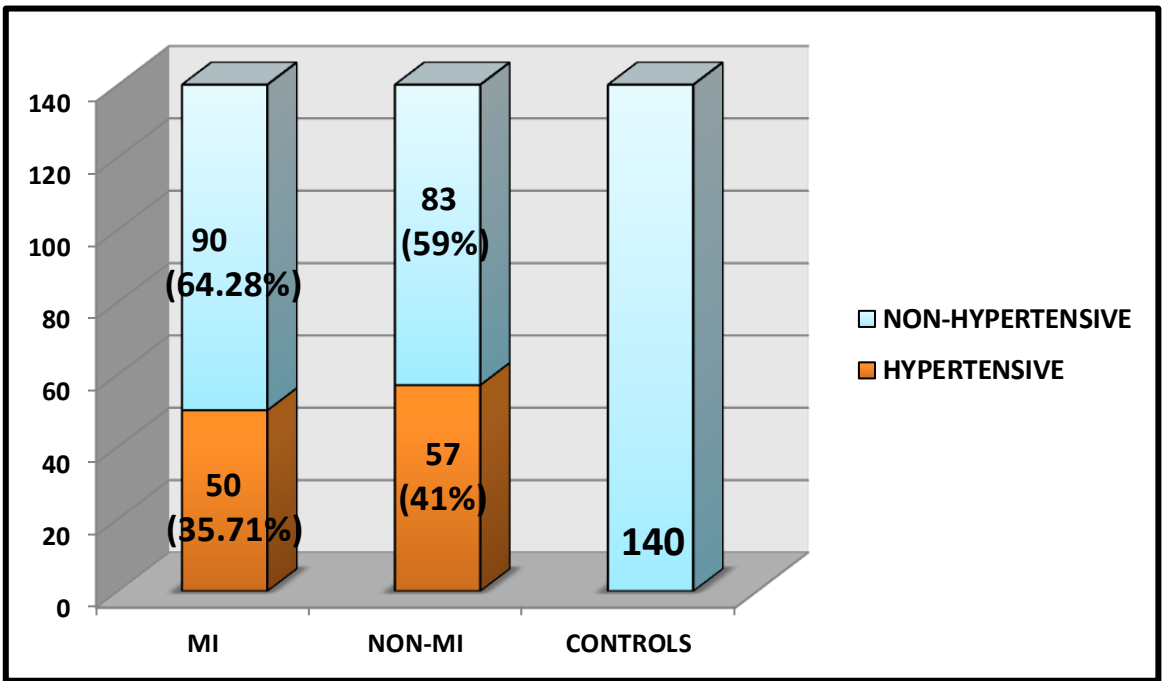


CHART 16 : **COMPARISON OF HYPERTENSION PREVALENCE AMONG INDIVIDUAL GROUPS**



Non-MI group showed more hypertensives 57 (41%) than MI group 50 (35.71%)

FAMILY HISTORY OF ISCHEMIC HEART DISEASE (IHD) :

Family history of IHD was noted only among 11(2.61%) patients.

CHART 17 : **INCIDENCE OF FAMILY HISTORY OF IHD AMONG PATIENTS**

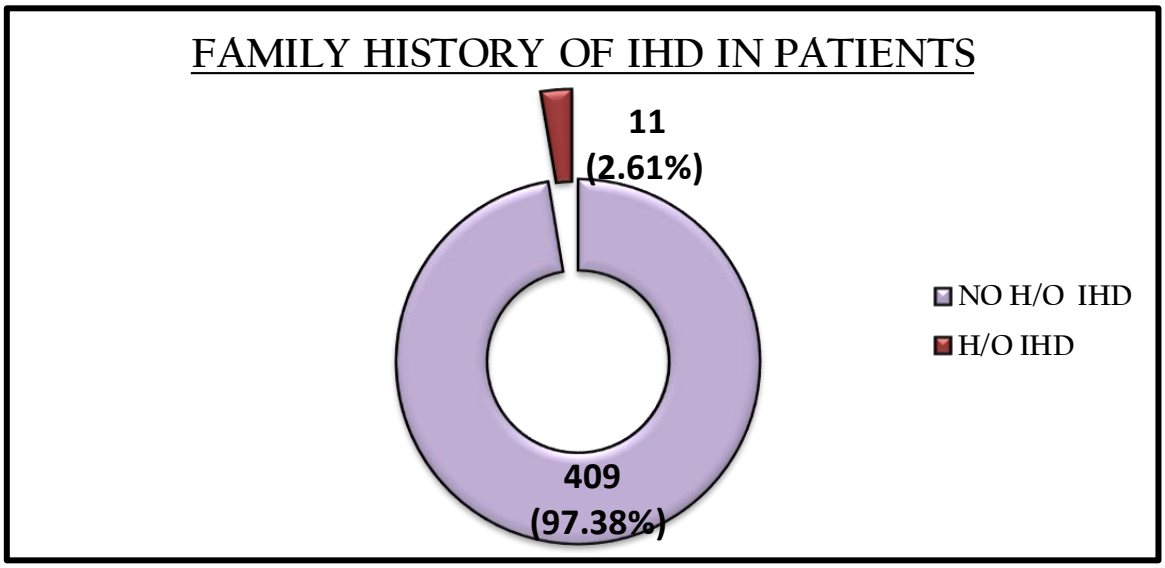


CHART 18 : **GENDER DISTRIBUTION IN PATIENTS WITH FAMILY H/O IHD**

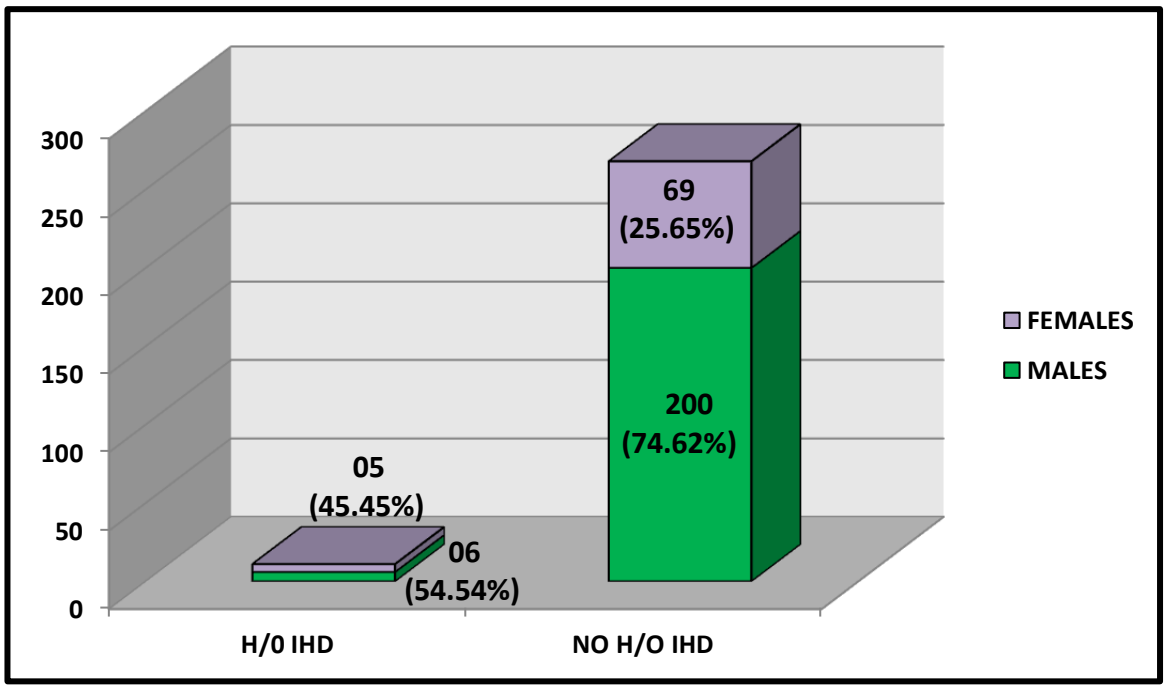
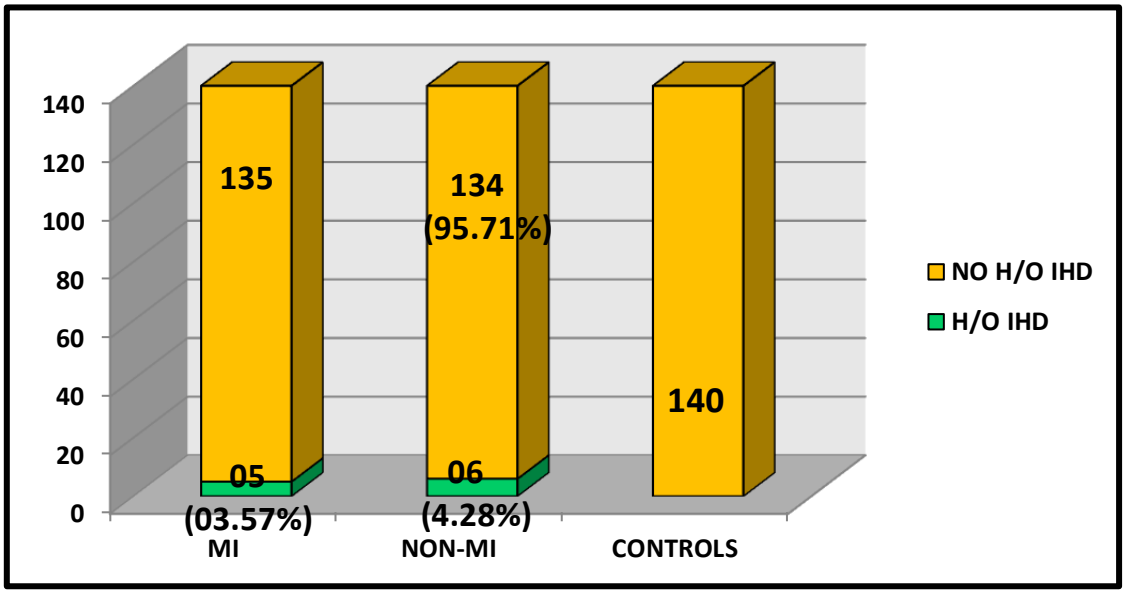


CHART 19 : **COMPARISON OF FAMILY HISTORY OF IHD AMONG INDIVIDUAL GROUPS**

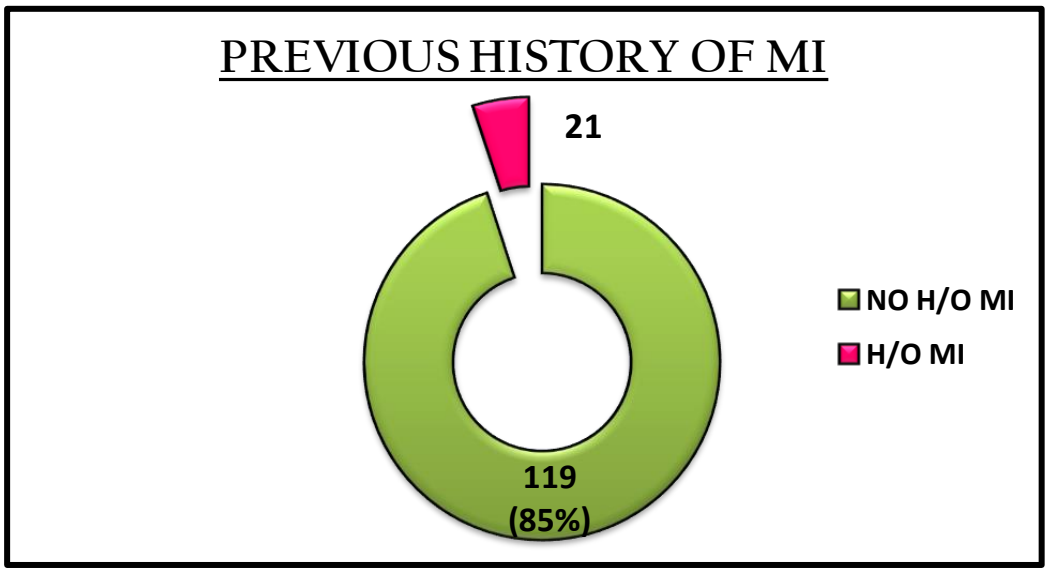


06 belonged to the non-MI category and 05 were patients with MI.

PREVIOUS HISTORY OF MYOCARDIAL INFARCTION :

Among the MI patients under study 21(15%) had previous history of myocardial infarction. 15 of them were males and 06 were female patients.

CHART 20 : **INCIDENCE OF PREVIOUS HISTORY OF MI AMONG PATIENTS**

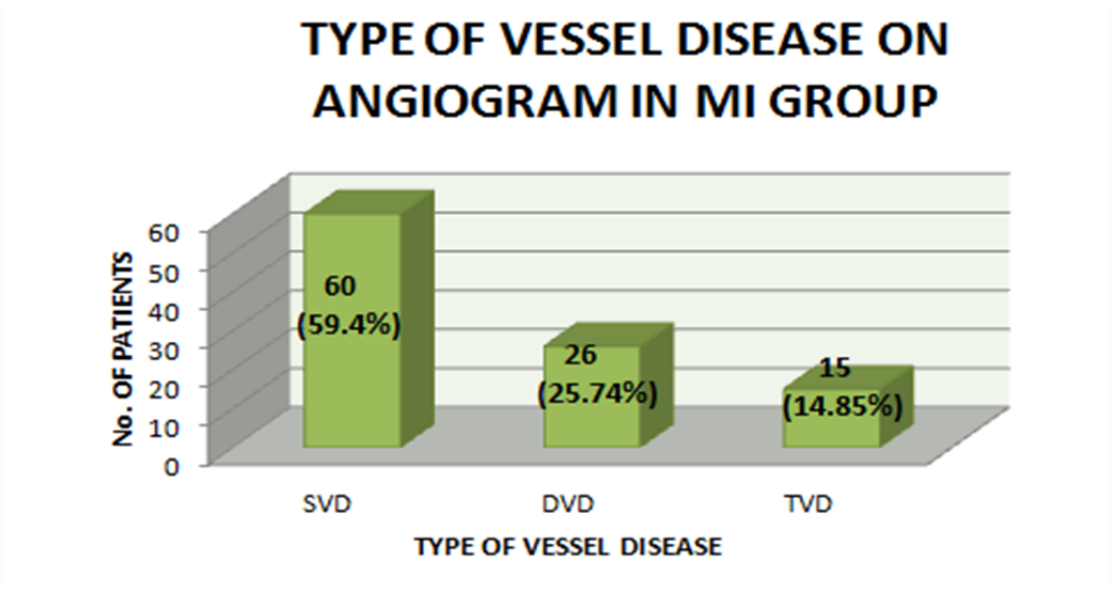


NUMBER OF AFFECTED VESSELS ON CORONARY ANGIOGRAM IN MI PATIENTS :

Among the 140 patients who had MI, 101 (72.14%) patients underwent a coronary angiogram which evaluated the number of vessels affected.

Single vessel disease (SVD) was observed in 60 (59.4%) patients, double vessel disease (DVD) was noted in 26 (25.74%) patients and 15(14.85%) patients had triple vessel disease (TVD).

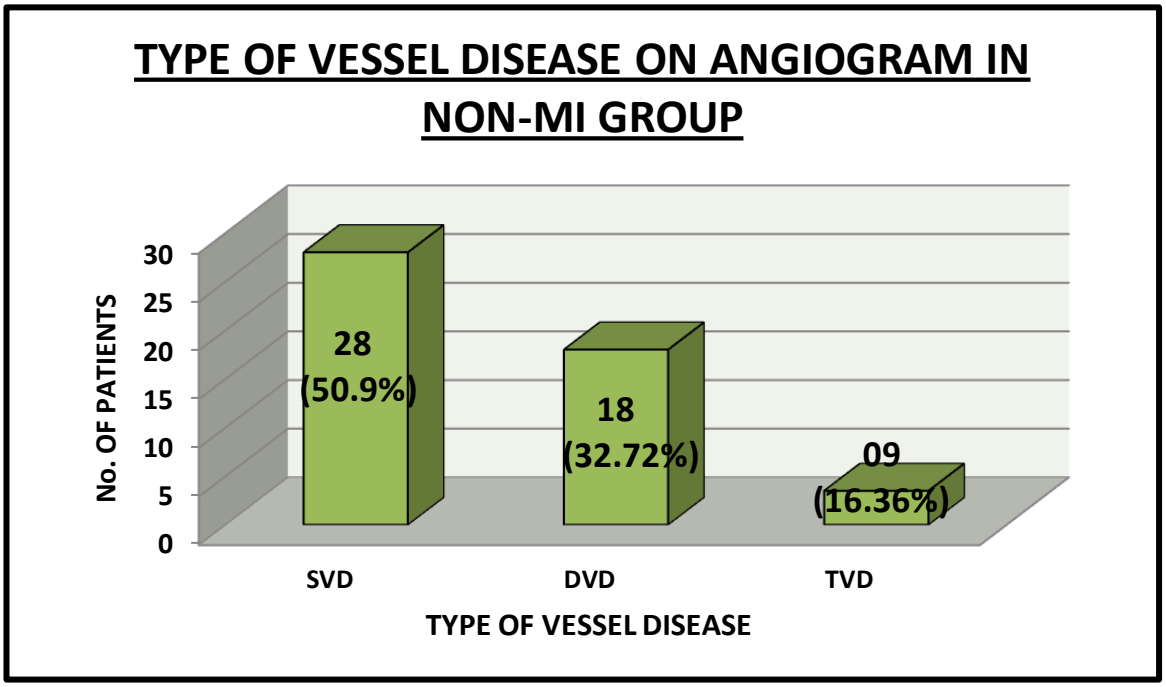
CHART 21 : TYPE OF VESSEL DISEASE AMONG PATIENTS WITH M



NUMBER OF AFFECTED VESSELS ON CORONARY ANGIOGRAM IN NON - MI PATIENTS :

In the patients among the non-MI group, 55(39.28%) underwent angiogram and 28(50.90%) had SVD, 18 (32.72%) of them had DVD and 09 (16.36%) patients had TVD.

CHART 22 : **TYPE OF VESSEL DISEASE AMONG PATIENTS IN NON-MI GROUP**

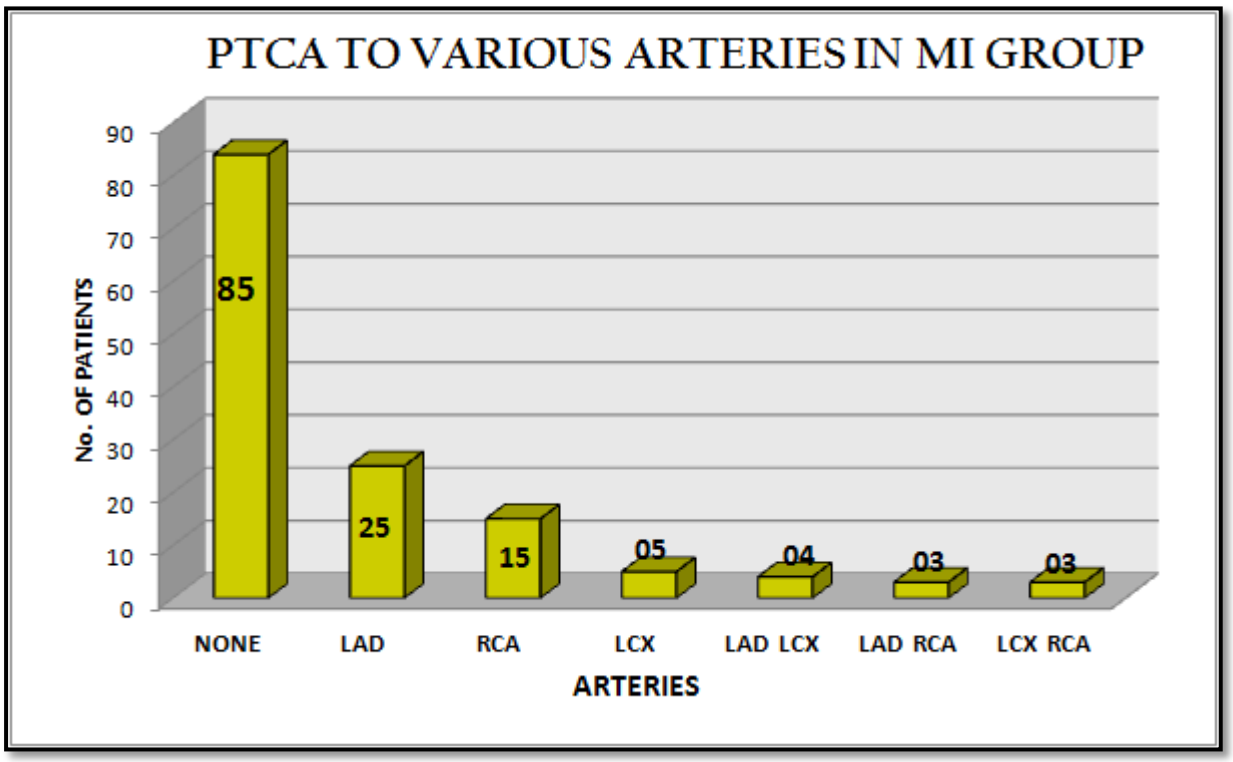


PRIMARY TRANSCUTANEOUS CORONARY ANGIOPLASTY IN MI PATIENTS

Among the 140 patients of the MI group 55(39.28%) patients underwent primary transcutaneous coronary angioplasty (PTCA) to various arteries as shown below.

Most common vessel was Left Anterior Descending (LAD) artery.

CHART 23 : PTCA TO VARIOUS VESSELS IN PATIENTS WITH MI



The most common artery involved was LAD among 25(45.45%) patients.

TABLE 4 : COMPARISON OF HEMATOLOGICAL PARAMETERS IN ALL PATIENTS:

VARIABLE (SD)	MI GROUP	NON-MI GROUP	HEALTHY CONTROLS	TOTAL
RBC COUNT (x 10^6/micL)	4.74(0.763)	4.42(0.807)	4.75(0.565)	4.64(0.734)
WBC COUNT (x 10^3/micL)	12.76(4.32)	10.85(4.477)	8.45(2.677)	10.69(4.28)
PLATELET COUNT (x 10^3/micL)	287.92(95.66)	279.57(94.44)	284.90(85.10)	284.13(91.703)
HEMOGLOBIN (g/dl)	14.68(10.852)	12.66(2.632)	14.08(1.361)	13.81(6.534)
MEAN CORPUSCULAR VOLUME (fL)	85.07(10.42)	89.97(45.45)	88.50(6.043)	87.85(27.164)

Mean RBC count was 4.64 x 10^6/micL with MI patients showing higher count among the 3 groups with 4.74 x 10^6/micL.

Mean WBC count was 10.69 x 10^3/micL and patients with MI had higher WBC count with 12.76 x 10^3/micL.

Mean platelet count was 284.13 x 10^3/micL with MI patients showing a higher count of 287.92 x 10^3/micL.

Mean haemoglobin was 13.81 g/dl and MI patients had higher haemoglobin of 14.68 g/dl.

Mean corpuscular volume was 87.85f L and non-MI patients had higher MCV of 89.97f L than the MI and control population.

TABLE 5 : COMPARISON OF PLATELET INDICES IN ALL PATIENTS

VARIABLE (SD)	MI GROUP	NON-MI GROUP	HEALTHY CONTROLS	TOTAL
PLATELET COUNT (X 10^3 / micL)	287.92 (95.66)	279.57 (94.44)	284.90 (85.10)	284.13 (91.703)
MPV (fL)	8.22 (0.762)	7.84 (0.735)	7.65 (0.554)	7.90 (0.728)
PDW (fL)	13.22 (2.40)	12.33 (2.456)	11.66 (1.87)	12.40 (2.341)
PCT (%)	0.233 (0.071)	0.82 (7.25)	0.21 (0.061)	0.42 (4.186)

Higher platelet count of 287.92 X 10^3 / micL, MPV OF 8.22f L and PDW of 13.22f L was observed among the patients with MI than the non-MI and control groups.

Plateletcrit was found to be higher among non-MI patients with 0.233%

TABLE 6: **ANOVA F-TEST TO CHECK THE SIGNIFICANCE OF HEMATOLOGICAL PARAMETERS**

PARAMETERS	CONSTANT (F)	SIGNIFICANCE
RBC COUNT ($x 10^6$/micL)	9.487	< 0.001
WBC COUNT ($x 10^3$/micL)	42.520	< 0.001
HEMOGLOBIN (g/dl/)	3.569	0.029
MEAN CORPUSCULAR VOLUME (f L)	1.204	0.301
PLATELET COUNT ($x 10^3$/micL)	0.296	0.744
MEAN PLATELET VOLUME (f L)	24.726	< 0.001
PLATELET DISTRIBUTION WIDTH (f L)	16.879	< 0.001
PLATELETCRIT (%)	0.967	0.381

ANOVA F-Test to check for the significance of hematological parameters shows a $p<0.05$ significance for RBC count, WBC count, Hemoglobin, Mean Platelet Volume and Platelet Distribution Width.

MCV, Platelet count and Plateletcrit show no statistical significance with $p>0.05$

TABLE 7 :MULTIPLE COMPARISONS OF THE PARAMETERS USING BONFERRONI ADHOC TEST

DEPENDENT VARIABLE	(I) GROUP	(J) GROUP	STD ERROR	SIGNIFICANCE
PLATELET COUNT	MI GROUP	NON-MI GROUP	10.979	1.000
		CONTROLS	10.979	1.000
	NON-MI GROUP	MI GROUP	10.979	1.000
		CONTROLS	10.979	1.000
	CONTROLS	MI GROUP	10.979	1.000
		NON-MI GROUP	10.979	1.000
MPV	MI GROUP	NON-MI GROUP	0.082	0.001
		CONTROLS	0.082	0.001
	NON-MI GROUP	MI GROUP	0.082	0.001
		CONTROLS	0.082	0.057
	CONTROLS	MI GROUP	0.082	0.001
		NON-MI GROUP	0.082	0.057
PCT	MI GROUP	NON-MI GROUP	0.500	0.707
		CONTROLS	0.500	1.000
	NON-MI GROUP	MI GROUP	0.500	0.707
		CONTROLS	0.500	0.670
	CONTROLS	MI GROUP	0.500	1.000
		NON-MI GROUP	0.500	0.670
PDW	MI GROUP	NON-MI GROUP	0.270	0.003
		CONTROLS	0.269	0.001
	NON-MI GROUP	MI GROUP	0.270	0.003
		CONTROLS	0.270	0.039
	CONTROLS	MI GROUP	0.269	0.001
		NON-MI GROUP	0.270	0.039

Bonferroni adhoc test showing for multiple comparisons shows significance of $p<0.05$ in MPV and PDW between the 3 groups.

DISCUSSION

DISCUSSION :

AGE :

The average age of onset of CVD is younger (below 55 years) among Indians than in other populations around the world.[59,60,61]

In the present study, the ages ranged from 23 to 95 years. The mean age in our study was 55.44 ± 13.13 years. Majority of patients belonged to the 6^{th} decade of life (29.04%), followed by 7^{th} decade (24.28%) and 5^{th} decade (23.09%) of life.

According to the INTERHEART study by Yusuf.S et al.[62] among regions, striking variations were noted in the age of first presentation of acute myocardial infarction, with the youngest patients in south Asia (median age 53 years) which was almost in accordance to the mean age of our study.

GENDER :

The prevalence of cardiovascular disease is higher in males than females though the mortality due to CVD is higher in females. The Framingham study showed that women have a lower incidence of coronary artery disease than men do up until age 75.In the present study, number of males was 322 (76.66%) and number of females was 98 (23.33%). [59,61,63]

The total number of males with ischemic heart disease in our study was 207 and females affected were 73. The male to female ratio was 2.83.

ASSESSMENT OF RISK FACTORS :

SMOKING :

Smoking has been identified as one on the important risk factor for all CVD. Current smokers have an approximately two-fold higher risk of cardiovascular disease compared with former and never smokers.[64, 65]

Nevertheless the risk of cardiovascular disease is roughly proportional to cigarette consumption and the risk persists even at low level of smoking, that is, one to two cigarettes per day and recent studies have shown that environmental tobacco smoke is a risk factor for ischemic heart disease. Passive smoking increases the coronary death rate among never smokers by 20% to 70%.[66]

TABLE 8: COMPARISON OF PREVALENCE OF SMOKING WITH OTHER STUDIES

	Khandekar MM et al.[67] J Clin Pathol 2006	Ranjith MP et al.[68] J Clin Pathol 2009	Gupta.R et al.[69] World J Cardiol 2012.	PRESENT STUDY
PREVALENCE SMOKING	**40.5%**	**60%**	**35.7%**	**22.85%**

A study done by Khandekar MM et al.[67] showed smoking in 40.5% patients of whom smokers were more 14.8% in the acute coronary events patients than other patients with 14.2%.

Ranjith M.P et al. [68] study showed smoking in 60 % patients with relatively higher incidence of smoking 31.76% in the stable angina group than acute coronary syndrome patients who had 28.23% smokers.

Gupta et al [69] showed 35.7% smoking prevalence and increased relative risk of MI compared to stroke.

In our study the prevalence of smoking was 96 patients (22.85%) with more smokers (42.14%) among patients with MI compared to those (26.42%) with non-MI conditions.

In comparison to other Indian studies, our study showed a lesser prevalence of smoking among patients. This may be due to the habit of arecanut and beetlenut chewing being more common among rural and semi urban population than the urban dwellers.

ALCOHOL CONSUMPTION :

Moderate alcohol consumption is known to be protective against coronary heart disease (CHD). However a study of acute MI patients, revealed that alcohol consumption in South Asians was not protective against CHD.[4] Other studies have shown that regular and moderate alcohol intake is associated with low risk of IHD and heavy or binge drinking was associated with high risk of IHD.[70,71]

Alcohol consumption was observed only among 16 (3.80%) patients in our study. As the exact amount of alcohol intake was not available we could not stratify the patients into moderate or heavy alcohol intake groups.

DIABETES MELLITUS :

Of the risk factors, diabetes, and its predominant form, type 2 diabetes mellitus (T2DM), has a distinctive association with CHD. Those with diabetes have 2-4 fold higher risk of developing coronary disease than people without diabetes.

The age and sex adjusted mortality risk in diabetic patients without pre-existing coronary artery disease has been found to be equal to that of non-diabetic individuals with prior MI. [72, 73, 74]

TABLE 9 : COMPARISON OF PREVALENCE OF DIABETES MELLITUS WITH OTHER STUDIES

	Khandekar MM et al [67] J Clin Pathol 2006	Ranjith MP et al.[68] J Clin Pathol 2009	Assiri A.S *et al.* [75] J Saudi Heart Assoc 2012.	OUR STUDY
DIABETES MELLITUS	**29%**	**60%**	**58.5%**	**21.9%**

Study by Ranjith et al.[68] and Assiri A.S et al. [75] showed a higher prevalence of Diabetes mellitus of 60% and 58.5% respectively while another study done by Khandekar MM et al.[67] on Indian population showed 29% diabetics in their study.

Our study had 92 (21.9%) diabetics.

Male predilection was noted in our study with 66(71.73%) males and 26(28.26%) females being diabetic. This was in accordance to studies like Gupta R et al [59] who quoted ICMR survey which studied risk factor prevalence of Non-communicable Disease among men and women in 8 Indian states showing higher male predilection of DM than female.

Study done by Kodiatte T.A et al.[76] which studied platelets in Type-2 DM showed more male diabetics compared to females with 65% and 35% respectively in their study.

HYPERTENSION :

Hypertension was seen in 107(25.47%) patients, of which 67(62.61%) were males and 40(37.38%) were females.

TABLE 10 : COMPARISON OF PREVALENCE OF HYPERTENSION WITH OTHER STUDIES

	Khandekar MM et al.[67] J Clin Pathol 2006	Ranjith MP et al.[68] J Clin Pathol 2009	PRESENT STUDY
PREVALENCE HYPERTENSION	**25.77%**	**60%**	**25.47%**

Ranjith et al.[68] study showed a higher prevalence of hypertension (60%) compared to Khandekar et al.[67] showing (25.77%) and our study with (25.47%). This variation can be attributed to the regional variation of hypertension as per Gupta et al.[69] which shows higher prevalence of hypertension in North Indian states compared to South India.

In our study hypertension was seen more among the non- MI group (41%) in comparison to MI patients (35.71%) Similar finding was also noted in study by Khandekar et al. [67](28.5% in stable ACS versus 24.4% in acute MI)

FAMILY HISTORY OF IHD:

Premature coronary heart disease in a first-degree relative (male relative <55 years and female <65 years or <60 years in both genders) is associated with increased risk of coronary heart disease.[64] Family history seemed to be slightly more important in young (PAR 14·8% [11·7–18·5]) compared with old individuals (10·4% [8·3–13·0]).[4]

In our study family history of IHD was noted in only 11(2.61%) patients. Mild difference was seen with 05 MI patients having a family history compared to 06 patients without MI.

HISTORY OF PREVIOUS MI :

Any prior episode of MI adds on to the risk of having a subsequent episode of MI in a patient.[62] Among the patients of MI group 21 (15%) of them had a previous episode of MI and the rest 119 (85%) presented with incident episode of MI.

NUMBER OF AFFECTED VESSELS ON CORONARY ANGIOGRAM :

Only 101(72.14%) patients among the 140patients with MI in our study underwent coronary angiogram. Majority of them 60(59.4%) were found to have single vessel disease, 26(25.74%) patients had DVD and TVD was least noted in 15 (14.85%) patients.

Among the 140 patients in the non-MI group,55 (39.28%) patients underwent angiography of whom, again majority of the patients 28 (50.9%) were found to have SVD, 18(32.72%)patients with DVD and TVD was seen in 9(16.36%) patients.

Study conducted by Pizzuli et al.[77] noted no significant difference in platelet count or size with regard to the degree of atherosclerosis or vessel involvement of 1, 2 or 3 vessel disease when compared with people with normal angiogram.

PTCA IN PATIENTS WITH MI :

Among the 140 patients with MI, 55 (39.28%) patients underwent PTCA and the most common artery involved was LAD among 25(45.45%) patients.

HEMATOLOGICAL PARAMETERS :

The various hematological parameters like red blood cell (RBC) and white blood cell (WBC) counts along with hemoglobin (Hb) levels and mean corpuscular volume (MCV) were evaluated with the platelet indices.

RBC COUNTS :

The mean RBC count was 4.64×10^6/micL. The mean RBC count was higher among the MI patients (4.74×10^6/micL) compared to the non-MI patients (4.42×10^6/micL) and almost equal to the mean count of the control group (4.75×10^6/micL).

WBC COUNTS :

The mean WBC count was 10.69x10^3/micL. The mean WBC count was higher among the MI patients (12.76 x10^3/micL) followed by the non-MI patients (10.85 x10^3/micL) and the control group (8.45 x10^3/micL).

HEMOGLOBIN LEVELS :

The mean Hb level was 13.81g/dl. The mean Hb level was higher among the MI patients (14.68 g/dl) than the non-MI patients (12.66 g/dl) and the control group (14.08g/dl). The patients in the non-MI group with other ischemic heart conditions had a relatively lower Hb level. On comparison with all groups, the hemoglobin value was found to be significant with p=0.02.

MEAN CORPUSCULAR VOLUME :

The mean MCV was 87.85%. The mean MCV among all the 3 groups were almost nearly equal with MI group patients having lower MCV (85.07%) followed by the control group (88.5%) and non-MI patients (89.97%)

When all these parameters were compared statistically between the 3 groups of MI, non-MI and control patients using ANOVA test, the RBC count, WBC count and hemoglobin levels were found to be statistically significant with a p-value of < 0.05.

PLATELET INDICES :

The platelet indices studied among patients with IHD and compare with healthy control group were platelet count, mean platelet volume (MPV), platelet distribution width (PDW) and Plateletcrit (Pct).

PLATELET COUNT :

The mean platelet count in our study was 284.13 (± 91.7) x 10^3 /micL . The mean platelet count was higher in the MI group (287.92 x 10^3 /micL) than non-MI patients (279.57 x 10^3 /micL) and also the control group (284.90 x 10^3 /micL)

TABLE 11 : COMPARISON OF PLATELET COUNT WITH OTHER STUDIES

PLATELET COUNT (x 10^3/micL)	Linden MD *et al.* [78] J Thromb Haemostat 2007 (n=677)	Lippi G *et al.* [79] Arch Pathol Lab Med 2009 (n=2304)	Khandekar MM *et al.* [67] J Clin Pathol 2006 (n=210)	Ranjith MP *et al.* [68] J Clin Pathol 2009 (n=180)	OUR STUDY (n=420)
MI GROUP	224.5 (±1.49)	238 (120-455)	232.84 (± 88.8)	201 (±13.07)	287.92 (±95.66)
NON MI GROUP	226.6 (±3.0)	247 (140-389)	240.79 (± 79.0)	267 (±7.91)	279.57 (±94.44)
CONTROLS	237.7 (±6.0)	---	270.77 (± 75.2)	256.65 (±25.49)	284.90 (±85.10)
SIGNIFICANCE (*p* value)	>0.05	0.13	<0.05	<0.001	0.744

( ) = SD

In some of the other studies [67, 68]conducted there was a gradual decline in the platelet count from the control group to the non-MI and the MI group. Least mean platelet count was observed in the MI group. This was attributed to the platelet consumption in the acute phase of clot formation and subsequent thrombosis.[68]

However in studies conducted with a larger sample size by Linden M.D et al.[67], Lippi G et al.[79]and Khode et al.[80] no significant correlation was observed with platelet count between patients with IHD and controls.

Study by Klovaite J et al.[81] done on a sample size of 39,531 participants also did not show any association between platelet count and increased risk of MI. However on dividing the individuals into strata based on tertiles of platelet count and within the strata into quintiles of MPV association was seen in individuals with medium (248-302 $x10^9$/L) and high (>302 $x10^9$/L) platelet count and increasing MPV had increased risk of MI.

Our study similarly showed platelet count did not significantly differ between patients with and without MI or between patients with MI and the control group. (p=1.00)

MEAN PLATELET VOLUME :

The MPV in our study was *7.*90(± 0.728*)* fL. The MPV was highest in the MI group *8.*22 (±0.76) fL than non-MI patients with 7.84(± 0.735)fL and the control group 7.65(± 0.554) fL.

TABLE 12 : **COMPARISON OF MEAN PLATELET VOLUME WITH OTHER STUDIES**

MEAN PLATELET VOLUME (fL)	MI GROUP	NON MI GROUP	CONTROLS	SIGNIFICANCE (p value)
Lippi G *et al.*[79] Arch Pathol Lab Med 2009	**8.0 (6.7-10)**	**7.4 (6.5-9.5)**	**---**	**<0.001**
Khandekar MM *et al.*[67] J Clin Pathol 2006	**10.43 (1.03)**	**9.37 (0.99)**	**9.20 (0.91)**	**<0.001**
Ranjith MP *et al.*[68] J Clin Pathol 2009	**10.97 (0.58)**	**10.03 (0.23)**	**9.12 (0.63)**	**<0.001**
Khode V et al.[80] J Cardiovasc Dis Res 2012	**9.65 (0.9)**	**9.38 (0.8)**	**9.21 (0.6)**	**0.025**
PRESENT STUDY	**8.22 (0.76)**	**7.84 (0.73)**	**7.65 (0.55)**	**<0.001**

( ) = SD

Most of the studies [67,68,79,80] conducted have found a relationship between MPV measured at the time of diagnosis of MI compared to patients without MI but other ischemic heart conditions and healthy controls. The table demonstrates the studies which showed that MPV remained higher in MI group than in others.

TABLE 13 : COMPARISON OF MEAN PLATELET VOLUME BETWEEN ACUTE MI GROUP AND NON-MI GROUP WITH OTHER STUDIES.

PUBLICATION	ACUTE MI		NON-MI	
	N	MPV(f L)	N	MPV (f L)
Yilmaz et al.[82] (2008)	111	10.4	225	9.41
Senaran et al.[83] (2001)	20	8.2	37	7.2
Hendra et al.[84] (1988)	147	10.0	150	9.45
Towbridge et al.[85] (1987)	103	7.3	72	6.56
Kishk et al.[5] (1985)	70	7.3	95	6.7
Erne et al.[86] (1988)	55	10.9	526	9.69
Khandekar et al.[67] (2006)	94	10.43	70	9.37
Khode et al.[80] (2012)	39	9.65	24	9.38
PRESENT STUDY	140	8.22	140	7.65

Our results were in accordance to the studies [5,67,80,82,83,84,85,86] conducted as shown in the table with varying sample size observing that MPV was raised in patients who had suffered an acute MI when compared with patients without MI (r= ,p<0.001).

TABLE 14 : **COMPARISON OF MEAN PLATELET VOLUME BETWEEN ACUTE MI GROUP AND HEALTHY CONTROL GROUP WITH OTHER STUDIES**

PUBLICATION	ACUTE MI		CONTROLS		p VALUE
	N	MPV(f L)	N	MPV(f L)	
O'Brien et al.[87] (1973)	23	8.1	36	7.01	< 0.001
Cameron et al.[88] (1983)	100	9.07	200	8.32	< 0.001
Martin et al.[89] (1983)	15	7.3	22	6.32	0.05
Martin et al.[54] (1991)	126	10.09	1590	9.72	< 0.001
Smyth et al.[90] (1993)	24	8.54	23	8.1	0.04
Pizulli et al.[91] (1998)	108	9.4	97	8.2	< 0.001
Khandekar et al.[67] (2006)	94	10.43	30	9.2	< 0.001
Assiri et al.[75] (2011)	80	8.99	49	8.38	< 0.001
Khode et al.[80] (2012)	39	9.65	65	9.21	0.018
Present study	140	8.22	140	7.65	< 0.001

The MPV was also significantly ($p<0.001$) raised in patients with MI in comparison to healthy control population in our study. This is in agreement with the results of similar studies by other workers. [54,67,75,80,87,88,89,90,91] In these studies increased MPV was found to be associated with coronary artery disease, acute MI, congestive heart failure and hypertensive patients with evidence of target organ damage[92] and cerebrovascular disease,[93] an important complication of atherosclerosis. Substantial evidence indicates that platelets and their interaction with the coronary arterial wall are of pathogenic importance in coronary atherosclerosis and its complications. After erosion or rupture of atherosclerotic plaques in coronary arteries, platelet activation plays a crucial role in the prothrombotic events leading to MI. Increased platelet reactivity are associated with increased platelet volume.[4,94] As mentioned earlier large platelets that contain more dense granules are metabolically and enzymatically more active than small platelets and have higher

thrombotic potential. The size of platelets has been found to associate with an increased number of megakaryocytes. The increased ploidy of megakaryocytes correlated with megakaryocyte and platelet volume.[54,89,96,97] Elevated levels of CD40 ligands, which are expressed by activated platelets, have been found in atheromatous plaques.[98]

Pizulli et al.[77] suggested that because platelets stay in the circulation for 7–11 days, they might be detected days before symptoms appear. Similarly, Martin et al.[54] have been shown a correlation between higher MPV and recurrence or death after the first MI in their prospective study.

PLATELET DISTRIBUTION WIDTH :

The PDW in our study was 12.40(2.341) fL.

The PDW was significantly higher in the patients of MI group 13.22(± 2.4)f L than non-MI patients with *12.33*(± 2.45)fL and the control group 11.66(± 1.87) fL.

TABLE 15 *:* COMPARISON OF PLATELET DISTRIBUTION WIDTH WITH OTHER STUDIES

PLATELET DISTRIBUTN WIDTH (fl) (SD)	Nandwani et al.[95] JIACG 2011	Khode V et al.[80] J Cardiovasc Dis Res 2012	Khandekar MM et al. [67] J Clin Pathol 2006	Ranjith MP et al. 6[8] J Clin Pathol 2009	Present study
MI GROUP	10.17 (±1.30)	10.84 (± 2.2)	10.43 (±1.03)	14.63 (±0.64)	13.22 (±2.40)
NON MI GROUP	10.22 (±0.14)	10.65 (± 1.7)	9.37 (±0.99)	12.43 (±0.62)	12.33 (±2.45)
CONTROLS	7.76 (±1.25)	10.35 (± 1.3)	9.20 (±0.91)	12.01 (±0.55)	11.66 (±1.87)
SIGNIFICANCE (p value)	<0.001	0.376	<0.001	<0.001	<0.001

The role of PDW specifically in patients with CAD and acute coronary events is yet to be explored .[67] Nevertheless our observations were the significantly elevated PDW among the patients with MI followed by the non-MI patients and then the healthy control group.

Similar results were noted by other studies like Khandekar et al.[67] Ranjith et al.[68] Khode, et al.[80] with higher PDW levels among MI patients but this levels were significant only in few studies [67, 68] Nandwani et al. [95] observed that patients with non-MI had a significantly higher PDW compared to MI patients but yet on comparison with the controls PDW of both MI and non-MI group was significantly ($p<0.001$) higher .

Vagdatli E et al.[56] in their study on puerperas in different trimesters, MI, patients and those with phlebothrombosis and healthy people concluded that PDW seemed to be more specific indicator of platelet activation than MPV, since it was not elevated during single platelet distention caused by platelet swelling. And the combined use of MPV and PDW could predict activation of coagulation more efficiently.

PLATELETCRIT :

TABLE 16 : COMPARISON OF PLATELETCRIT WITH OTHER STUDIES

PLATELETCRIT (%)	Khode V et al.[80] J Cardiovasc Dis Res 2012	OUR STUDY
MI GROUP	O.28 (± 0.09)	0.23 (± 0.071)
NON MI GROUP	0.27 (± 0.08)	0.82 (± 7.25)
CONTROLS	0.26 (± 0.07)	0.21 (± 0.061)
SIGNIFICANCE (p value)	0.695	0.381

Plateletcrit is equivalent to hematocrit of the red blood cells and equal to the sum of platelet impulses which are individually detected by the cell counter.

Our study showed mean Plateletcrit *of* 0.42% (± 4.186) The Plateletcrit among non-MI patients [0.82% (± 7.25)] in our study was higher than the patients who suffered MI [0.23 % (± 0.071)]and the healthy control group [0.21% (± 0.061)] No significant correlation was observed between these values (p=0.381) The Plateletcrit of non MI group and MI group, non-MI and controls and MI and controls showed no significant correlation with p value of 0.707, 0.670 and 1.0 respectively.

Only one other study by Khode et al.[80] studied Plateletcrit which showed a gradual decline in the values from MI group to non-MI group and the controls. But there was no significant correlation of the values (p=0.694) However this variable needs more detailed study in larger sample and in patients with different prethrombotic condition to understand its significance.

LIMITATIONS OF THE STUDY :

- Follow up of the patients was not possible to examine the prognostic value of our findings.
- Patients with qualitative disorders and causes of reactive platelets were not assessed.
- Confounding factors for platelets like diabetes mellitus, hypertension, smoking, anemia could not be eliminated in all patients.
- History of anti-platelet therapy in all patients was not available to include in the study. But studies have shown that most of these drugs do not have a significant impact on platelet size or volume.
- Platelet function tests could not be conducted on the sample to substantiate our findings further.

SUMMARY & CONCLUSION

SUMMARY

- This is a study undertaken in Sri Devaraj Urs Medical College, Kolar, Karnataka to determine whether an association exists between platelet indices - mean platelet volume (MPV), platelet distribution width (PDW), Plateletcrit (PCt) in acute myocardial infarction and other ischemic cardiac events in a predominantly rural population..
- A total of 420 cases were studied and were divided further into 3 groups of 140 patients each who were MI group, non-MI group and age and sex matched healthy controls.
- Majority of patients belonged to the 6^{th} decade of life (29.04%), followed by 7^{th} decade (24.28%) and 5^{th} decade (23.09%) of life.
- Out of 420 cases in this study number of males was 322 (76.66%) and number of females was 98 (23.33%).
- Between the MI and non-MI patients, the mean age was higher in the non-MI patients (60.43 yrs versus 54.47yrs.)
- The number of males in the MI group were 115 (82.14%) compared to non - MI group were 91 (65%)
- The total number of smokers were 96 (22.85%) with more smokers were seen in the MI group.
- Alcohol consumption was observed only among 16 (3.80%) patients in our study. MI group had more alcoholics 09 (6.42%) than non-MI group 07 (5%).
- Our study had 92 (21.9%) diabetics showing a male predilection with 66(71.73%) male diabetics. The non-MI group had more number of diabetics 48 (34.28%) than MI group with 44(31.42%)
- Hypertension was seen in 107(38.21%) patients, of which 67(62.61%) were males and 40(37.38%) were females. Hypertension was more prevalent among non-MI [57(40.71%)] than MI patients [50(35.71%)]

- In our study family history of IHD was noted in only 11(2.61%) patients and 21 (15%) patients in MI group had a previous episode of MI.

- Single vessel disease (SVD) was observed in 60 (59.4%) patients, double vessel disease (DVD) was noted in 26 (25.74%) patients and 15(14.85%) patients had triple vessel disease (TVD).

- The mean platelet count was 284.13 ± 91.7 x 10^3 /micL and was higher in the MI group (287.92 x 10^3 /micL) than non-MI patients (279.57 x 10^3 /micL) and also the control group (284.90 x 10^3 /micL).
- The MPV was 7.9 ± 0.728 fL, highest in the MI group 8.22(±0.76)f L than non-MI patients with 7.84(± 0.735)fL and control group7.65(± 0.554) fL, was statistically significant ($p<0.001$)
- The PDW was12.40 ± 2.34 Fl and was significantly higher in the patients of MI group 13.22(± 2.4)f L than non-MI patients with 12.33(± 2.45)fL and the control group 11.66(± 1.87) fL.
- Our study showed mean Plateletcrit of 0.42% (± 4.186) The Plateletcrit among non-MI patients [0.82% (± 7.25)] in our study was higher than the patients who suffered MI [0.23 % (± 0.071)]and the healthy control group [0.21% (± 0.061)] No significant correlation was observed between these values ($p=0.381$)

CONCLUSION

The study was started to determine whether an association exists between platelet indices - mean platelet volume (MPV), platelet distribution width (PDW), Plateletcrit (PCt) in acute myocardial infarction and other ischemic cardiac events in a predominantly rural population.

These indices are useful means of identifying larger and more active platelets which are a risk factor for developing coronary thrombus.

Such patients can easily be identified during routine hematological analysis and possibly benefit from preventive and anti-platelet treatment.

Our study concluded that among the platelet indices, mainly Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) are readily available, relatively inexpensive useful markers which were significantly raised among patients admitted with MI in our hospital. Platelet count and Plateletcrit did not show any significant association among the patients and healthy population. Thus these should be utilized with other investigative tools to screen patients suspected to have acute coronary syndrome.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Preventing Chronic Disease: A Vital Investment. World Health Organization Global Report. 2005.

2. Global Burden of Disease. 2004 update (2008). World Health Organization

3. Jakubowski JA, Adler B, Thompson CB, et al. Influence of platelet volume on the ability of prostacyclin to inhibit platelet aggregation and the release reaction. J Lab Clin Med 1985; 105: 271-276.

4. Endler G, Klimesch A, Sunder-Plassmann H, et al. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol 2002; 117: 399-404.

5 Kishk YT, Trowbridge EA, Martin JF. Platelet volume subpopulations in acute myocardial infarction: an investigation of their homogeneity for smoking, infarct size and site. Clin Sci 1985;68:419–425.

6 Gregg D, Pascal J,Clermont G. Platelets and Cardiovascular Disease Circulation. 2003;108:e88-e90.

7 Marchant KK. Importance of platelets and platelet response in acute coronary syndromes. Cleveland clinic journal of medicine.Volume 76 • supplement 1 april 2009.

8 The structure and production of blood platelets. Joseph E. Italiano, Jr. Chapter 1 Platelets in hematologic and cardiovascular disorders. Cambridge University Press.2008

9 Thompson CB , Jakubowski JA, Quinn PG, Deykin D, Valeri CR. Platelet Size and Age Determine Platelet Function Independently. Blood.1984;63: 1372-1375

10 . Loo BVD, Martin JF. A Role for Changes in Platelet Production in the Cause of Acute Coronary Syndromes. Arterioscler Thromb Vasc Biol. 1999;19:672-679.

11 World Health Organisation. Comparative quantification of health risks. Global and regional burden of disease attributable to major risk factors. Geneva: World Health Organisation, 2004.

12 World Health Organisation . Disease and injury regional estimates for 2004. Geneva,Switzerland.

13 Leeder, S, Raymond S, Greenberg H. A Race Against Time: The challenge of cardio vascular disease in developing economies. 2004. Columbia University. New York City, New York.

14 Xavier D, Pais PP, Devereaux PJ et al. on behalf of the CREATE registry investigators. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet 2008; 371:1435-42.

15 Egred M, Viswanathan G, Davis G K. Myocardial infarction in young adults. Postgrad Med J 2005;81:741–745.

16 Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE et al. 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction. Circulation. 2011; 123:e426-e579.

17 Libby P. Current Concepts of the Pathogenesis of the Acute Coronary Syndromes. Circulation. 2001;104:365-372.

18 Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989, p 63.

19 Klag MJ. Epidemiology of cardiovascular disease. Braunwald's heart disease: a textbook of cardiovascular medicine. 9th Ed.Philadelphia, WB Saunders. 2012,p 256-260

20 Sare GM, Gray LJ, Bath PMW. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. Eur Heart J. 2008;29:2031-2041.

21 Gopianth N, Chandha SL, Jain P, et al. An epidemiological study of coronary heart disease in different ethnic groups in Delhi urban population. J Assoc Physicians India 1995; 43: 30–3.

22 Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. Lancet 1997;349:1498–504.

23 Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362:1527-1535.

24 Appel LJ, Giles TD, Black HR. American Society of Hypertension Writing Group. ASH position paper: dietary approaches to lower blood pressure.J Am Soc Hypertens.2009;5:321-31

25 Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373:1765-1772.

26 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998;317:703-713.

27 . Lavie CJ, Thomas RJ, Squires RW, et al. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. Mayo Clin Proc. 2009;84:373-383.

28 Anyadubalu CC. The Experiences of Coronary Heart Disease Patients: Biopsychosocial Perspective. Intl J of Hum and Soc Sci.2010; 5:614-621.

29 Ross R. Atherosclerosis- An inflammatory disease. NEJM. 1999; 340(2):115-126.

30 Lippi G, Montagnana M, Salvagno GL, Guidi GC. Potential value for new diagnostic markers in the early recognition of acute coronary syndromes. Can J Emerg Med 2006;8(1):27-31.

31 Lewandrowski K,Chen A, Januzzi J. Cardiac Markers for Myocardial Infarction. Am J Clin Pathol 2002;118(Suppl 1):S93-S99.

32 Michielsen E. Implications of cardiac Troponin t degradation. 2008. Department of Clinical Chemistry, University Hospital Maastricht, Maastricht, The Netherlands.

33 Merchant K.K. Importance of platelets and platelet response in acute coronary syndromes.Cleveland clinic Journal of Medicine. 2009; 76.

34 Davi G, Patrono C. Platelet Activation and Atherothrombosis. N Engl J Med 2007;357:2482-94.

35 Hansson GK. Inflammation, Atherosclerosis,and Coronary Artery Disease. N Engl J Med 2005;352:1685-95.

36 Schonbeck U, Varo N, Libby P, Buring J, Ridker PM. Soluble CD40L and cardiovascular risk in women. Circulation 2001; 104:2266-8.

37 Harding SA, Sarma J, Josephs DH, et al. Upregulation of the CD40/CD40 ligand dyad and platelet-monocyte aggregation in cigarette smokers. Circulation 2004; 109:1926-9.

38 Santilli F, Davi G, Consoli A, et al. Thromboxane-dependent CD40 ligand release in type 2 diabetes mellitus. J Am Coll Cardiol 2006;47:391-7.

39 Vaidyula VR, Rao AK, Mozzoli M, Homko C, Cheung P, Boden G. Effects of hyperglycemia and hyperinsulinemia on circulating tissue factor procoagulant activity and platelet CD40 ligand. Diabetes 2006;55:202-8.

40 Pignatelli P, Sanguigni V, Lenti L, et al. gp91phox-Dependent expression of platelet CD40 ligand. Circulation 2004;110: 1326-9.

41 Krotz F, Sohn HY, Gloe T, et al. NAD(P)H oxidase-dependent platelet superoxide anion release increases platelet recruitment. Blood 2002;100:917-24.

42 Krotz F, Sohn HY, Pohl U. Reactive oxygen species: players in the platelet game. Arterioscler Thromb Vasc Biol 2004; 24:1988-96.

43 Morrow JD, Hill KE, Burk RF, Nammour TM, Badr KF, Roberts LJ II. A series of prostaglandin F2-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. Proc Natl Acad Sci U S A 1990;87:9383-7.

44 Morrow JD. Quantification of isoprostanes as indices of oxidant stress and the risk of atherosclerosis in humans. Arteioscler Thromb Vasc Biol 2005;25:279-86.

45 Davi G, Guagnano MT, Ciabattoni G, et al. Platelet activation in obese women: role of inflammation and oxidant stress. JAMA 2002;288:2008-14.

46 Davi G, Di Minno G, Coppola A, et al. Oxidative stress and platelet activation in homozygous homocystinuria. Circulation 2001;104:1124-8.

47 Koyama H, Maeno T, Fukumoto S, et al. Platelet P-selectin expression is associated with atherosclerotic wall thickness in carotid artery in humans. Circulation 2003; 108:524-9.

48 Fateh-Moghadam S, Li Z, Ersel S, et al. Platelet degranulation is associated with progression of intima-media thickness of the common carotid artery in patients with diabetes mellitus type 2. Arterioscler Thromb Vasc Biol 2005; 25:1299-303.

49 Nowak J, Murray JJ, Oates JA, FitzGerald GA. Biochemical evidence of a chronic abnormality in platelet and vascular function in healthy individuals who smoke cigarettes. Circulation 1987; 76:6-14.

50 Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92: 657-71.

51 Davi G, Di Minno G, Coppola A, et al. Oxidative stress and platelet activation in homozygous homocystinuria. Circulation 2001;104:1124-8.

52 Stary H, Blankenhorn D, Chandler A. A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report fromthe Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1992;85:391–405.

53 Nabel EG,Braunwald E. A Tale of Coronary Artery Diseaseand Myocardial Infarction. N Engl J Med 2012;366:54-63.

54 Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after MI. Lancet. 1991;338:1409–1411.

55 Jagroop IA, Clatworthy I, Lewin J, Mikhailidis DP. Shape change in human platelets: measurement with a channelyzer and visualisation by electron microscopy. Platelets 2000;11:28-32.

56 Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I.Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 2010; 14: 28-32.

57 Erhart S, Beer JH, Reinhart WH. Influence of aspirin on platelet count and volume in humans. Acta Haematol 1999; 101: 140-4.

58. Guthikonda S, Alviar CL, Vaduganathan M, et al. Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease. J Am Coll Cardiol 2008;52: 743-9.

59. K. S. Reddy and A. Satija. “The Framingham heart study: impact on the prevention and control of cardiovascular diseases in India,” Progress in Cardiovascular Diseases, vol. 53, no. 1, pp. 21–27, 2010.

60. World Health Organization.Global Status Report of NCD 2010. Geneva: World Health Organization, 2011

61. Grover A, Bahl A, Vijayavergiya R et al. Changing trends of cardiovascular disease in India: Implications for prevention based on 2001 census. Indian J Cariol 2003;6:59-63.

62. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937–52.

63. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. Ann Intern Med.1976;85:447–452.

64. Michael KJ. Epidemiology of cardiovascular disease in Braunwald's heart disease: a textbook of cardiovascular medicine.9th Ed. Philadelphia, WB Saunders. 2012.

65. Huffman M.D. Coronary heart disease in India. Centre for chronic disease control.

66. Otsuka R, Watanabe H, Hirata K, et al. Acute Effects of Passive Smoking on the Coronary Circulation in Healthy Young Adults. JAMA. 2001;286(4):436-441.

67. Khandekar M M, Khurana A S, Deshmukh S D, Kakrani A L, Katdare A D, Inamdar A K . Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario. J Clin Pathol 2006;59:146–149.

68. Ranjith M P, Divya R, Mehta V.K, Krishnan M G, KamalRaj R, Kavishwar A. Significance of platelet volume indices and platelet count in ischaemic heart disease . J Clin Pathol 2009; 62:830–833.

69. Gupta R, Guptha S, Sharma KK, Gupta A, Deedwania P. Regional variations in cardiovascular risk factors in India: India heart watch. World J Cardiol 2012; 4(4): 112-120.

70. Roy A, Prabhakaran D, Jeemon P, Thankappan KR, Mohan V, Ramakrishnan L et al. Impact of alcohol on coronary heart disease in Indian men. Atherosclerosis. 2010 Jun;210(2):531-5.

71. Ruidavets JB, Ducimetière P, Evans A, Montaye M, Bingham A, Yarnell J et al. Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). BMJ 2010;341:c6077

72. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979; 241 : 2035-8.

73. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339 : 229-34.

74. Ali M.K, Narayan K.M.V, Tandon N. Diabetes & coronary heart disease: Current perspectives. Indian J Med Res 2010; 132: 584-597.

75. Assiri A.S, Jamil A, Mahfouz A.A, Mahmoud Z.S, Ghallab M. Diagnostic importance of platelet parameters in patients with acute coronary syndrome admitted to a tertiary care hospital in southwest region, Saudi Arabia. J Saudi Heart Assoc 2012;24:17-21.

76. Kodiatte TA, Manikyam UK, Rao SB, Jagadish TM, Reddy M, Lingaiah HM, Lakshmaiah V. Mean platelet volume in type 2 diabetes mellitus. J Lab Physicians.2012;4:5-9.

77. Pizzulli L, Yang A, Martin JF, et al. Changes in platelet size and count in UA compared to stable angina or non-cardiac chest pain. Eur Heart J 1998;19:80–4.

78. Linden M.D, Furman M.I, Frelinger A.L, Fox M.L, Barnard M.R, Li Y et al. Indices of platelet activation and the stability of coronary artery disease. J Thromb Haemost 2007;5:761-5.

79. Lippi G, Filippozzi L, Salvagno G.L, Montagnana M, Franchini M, Guidi G.C et al.Increased mean platelet volume in patients with acute coronary syndromes. Arch Pathol Lab Med. 2009;133:1441-1443.

80. Khode V, Sindhur J, Kanbur D, Ruikar K, Nallulwar S. Mean platelet volume and oyher platelet volume indices in patients with stable coronary artery disease and acute myocardial infarction : A case control study. J Cardiovasc Dis Res. 2012;3:272-5.

81. Klovaite J, Benn M, Yazdanyar S, Nordestgaard BG. High platelet volume and increased risk of myocardial infarction: 39531 participants from the general population. J Thromb Haemost 2011;9:49-56.

82. Yilmaz MB, Cihan G, Guray Y, Guray U, Kisacik HL, Sasmaz H, Korkmaz S. Role of mean platelet volume in triaging acute coronary syndromes. J Thromb Thombolysis 2008;26:49-54.

83. Senaran H, Ileri M, Altinbas A, Kosar A, Yetkin E, Ozturk M, Karaaslan Y, Kirazli S. Thrombopoietin and mean platelet volume in coronary artery disease.Clin Cardiol 2001;24: 405–8.

84. Hendra TJ, Oswald GA, Yudkin JS. Increased mean platelet volume after acute myocardial infarction relates to diabetes and to cardiac failure. Diabetes Res Clin Pract 1988; 5: 63–9.

85. Trowbridge EA, Martin JF. The platelet volume distribution: a signature of the prethrombotic state in coronary heart disease? Thromb Haemost 1987; 58: 714–17.

86. Erne P, Wardle J, Sanders K, Lewis SM, Maseri A. Mean platelet volume and size distribution and their sensitivity to agonists in patients with coronary artery disease and congestive heart failure. Thromb Haemost 1988; 59: 259–63.

87. O'Brien JR, Etherington M, Jamieron S, et al. Stressed template bleeding-time and other platelet function tests in myocardial infarction. Lancet1973;11778:694–6.

88. Cameron EA, Phillips R, Ibbatson RM, et al. Platelet size in myocardial infarction. BMJ 1983;287:449–51.

89. Martin JF, Plumb J, Kilbey RS, et al. Changes in volume and density of platelets in myocardial infarction. BMJ 1983;287:456–9.

90. Smyth DW, Martin JF, Michalis L, et al. Influence of platelet size before coronary angioplasty on subsequent restenosis. Eur J Clin Invest 1993;23:361–7.

91. Pizzulli L, Yang A, Martin JF, et al. Changes in platelet size and count in UA compared to stable angina or non-cardiac chest pain. Eur Heart J 1998;19:80–4.

92. Nadar SK, Blann AD, Kamath S et al. Platelet indexes in relation to target organ damage in high-risk hypertensive patients:a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) J Am Coll Cadiol. 2004;44:415-422.

93. Valkila EH, Salenius JP, Koivula TA. Platelet indices in patients with occlusive carotid artery disease. Angiology. 1994;45:361-65.

94. Kristensen SD, Milner PC, Martin JF. Bleeding time and platelet volume in acute myocardial infarction – a 2 year follow-up study. Thromb Haemost, 1988; 59: 353–56

95. Nandwani S, Bhatnagar M, Gaur S, Kumar M. Study of platelet volume indices in patients of acute coronary events. Journal of The Indian Academy of Geriatrics. 2011; 7:22-24.

96. Kristensen SD. The platelet-vessel wall interaction in experimental atherosclerosis and ischaemic heart disease with special reference to thrombopoiesis. Dan Med Bull, 1992; 39: 110–27.

97. Threatte GA. Usefulness of the mean platelet volume. Clin Lab Med. 1993; 13: 937–50.

98. Geisler T, Bhatt DL: The role of infl ammation in atherothrombosis: current and future strategies of medical treatment. Med Sci Monit, 2004;10(12): RA308–RA316.

ANNEXURES

PROFORMA

- Name of the patient : OP/IP:
- Age: Sex:
- Clinical diagnosis:
- H/O: Smoking: Y/N Alcohol intake: Y/N
- Family history of IHD: Y/N
- H/O previous MI:
- H/O Diabetes mellitus / Hypertension: Y/N
- H/O Hypercholesterolemia/ Hypertriglyceridaemia: Y/N
- H/O anti coagulant intake: Y/N
- H/O oral hypoglycaemic agents:
- H/O Anti lipidaemics :
- BP:
- ECG: ST elevation/Non ST elevation/Others
- ECHO:
- Angiogram:
- CK-MB= *Troponin-T=
- Haemogram: RBC: WBC: Hb: MCV:

  -Platelet count: -Mean platelet volume:

  -Platelet distribution width: -Plateletcrit :

INFORMED CONSENT FORM

TITLE OF THE PROJECT: SIGNIFICANCE OF PLATELET INDICES IN ISCHEMIC HEART DISEASE.

The blood contains red blood cells, white blood cells and platelets.
This study is being conducted in the Department of Pathology, Sri Devaraj Urs Medical College to determine if there is any association between the size and volume of platelets in patients who suffer from heart disease involving reduced supply of blood to the heart (Ischemic heart disease).

You are being contacted to request you to give consent for using your blood sample for this study. Participation in this study is purely voluntary and does not involve any cost for you. No additional blood sample will be taken from you for this study.
Confidentiality will be maintained and any data collected will be used only for academic purpose.

For any further clarification or information you are free to contact:
Dr. Suraksha Rao. B

CONSENT TO PARTICIPATE IN THE STUDY

I have read / had read to me the purpose of this study. I understand that no additional blood sample will be collected from me apart from that collected for my treatment.
I agree to participate in this study.

Name (Patient): Signature: Date:

Name (Witness): Signature: Date:

Name and signature of the Principal investigator: Date:

KEY TO MASTER CHART

IP / OP No. = Inpatient/ outpatient number

MI = Myocardial infarction

DM = Diabetes Mellitus

HTN = Hypertension

H/O IHD = History of Ischemic Heart Disease

Prev MI= Previous episode of Myocardial Infarction

Angio = Angiogram result

WBC = White Blood Cell count

RBC = Red Blood Cell count

Hb = Haemoglobin

MCV = Mean Corpuscular Volume

Plt = Platelet count

MPV = Mean Platelet Volume

PDW = Platelet Distribution Width

Pct = Plateletcrit