"ANALYSIS OF DEVELOPMENT OF INDEX LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AFTER REVASCULARIZATION IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION"

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF DM IN CARDIOLOGY

DEPARTMENT OF CARDIOLOGY

PSG INSTITIUTE OF MEDICAL SCIENCES AND RESEASRCH

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY, CHENNAI

TAMILNADU, INDIA

AUGUST 2014

CERTIFICATE

PSG Institute of Medical Sciences & Research

Coimbatore

This is to certify that **Dr. PRANAV KUMAR K.V** has prepared this dissertation entitled **"ANALYSIS OF DEVELOPMENT OF INDEX LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AFTER REVASCULARIZATION IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION"**, under my overall supervision and guidance in PSG Institute of Medical Science and Research, Coimbatore in partial fulfillment of the regulations of The Tamil Nadu Dr. M.G.R Medical University for the award of DM Cardiology.

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DECLARATION

I hereby declare that dissertation entitled **"ANALYSIS OF DEVELOPMENT OF INDEX LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AFTER REVASCULARIZATION IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION"** was prepared by me under the guidance and supervision of **Dr. G.Rajendiran MD, DM,** PSG IMS&R, Coimbatore. The dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the University Regulations for the award of DM degree in Cardiology. This dissertation has not been submitted for the award of any Degree or Diploma.

ACKNOWLEDGEMENT

With deep sense of gratitude, I sincerely express my thanks to **Dr. G.Rajendiran**, Professor and Head, Department of Cardiology, PSG Institute of Medical Sciences & Research, Coimbatore, for his valuable guidance and encouragement given at every stage of this project. I would also express my sincere thanks to **Dr.J.S.Bhuvaneswaran, Dr.P.Arun Kumar, Dr.R.Shanmuga Sundharam, Dr.P.Ramasamy, Dr.K.Tamilarasu** and **Dr.M.Lawrence Jesuraj** for guiding me in this study.

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Lastly, I thank God for the wonderful team who helped me in completion of my project.

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October 25, 2013

To
Dr K.V Pranav Kumar
Postgraduate
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Ref.: Proposal titled: *"Analysis of development of Index ventricular systolic dysfunction after revascularization in acute ST elevation myocardial infarction"*

Sub.: Ethics Committee Approval for the study

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 28th August, 2013 in its full board review meeting held at College Council Room, PSG IMS&R, between 2.00 pm and 4.30 pm, and discussed your application to conduct the study entitled:

"Analysis of development of Index left ventricular systolic dysfunction after revascularization in acute ST elevation myocardial infarction"

The following documents were received for review:

1. Duly filled application form
2. Proposal (Ver 1.1)
3. Informed Consent forms in English and Tamil (Ver 1.1)
4. Data Collection Tool
5. Budget
6. CV

The members who attended the meeting at which your study proposal was discussed are as follows:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
2	Mrs. Geetha S Kannan	MA	Lay person	Female	No	Yes
3	Mr Gowpathy Velappan	BA., BL	Legal Advisor	Male	No	Yes
4	Mrs G Malarvizhi	M Sc	Nursing	Female	Yes	No
5	Mr. R. Nandakumar (Vice-Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
6	Dr. G. Rajendiran	DM	Clinician (Cardiology)	Male	Yes	Yes
7	Dr. V. Ramamurthy	Ph D	Biotechnology	Male	Yes	No
8	Dr. M. Ramanathan	M Pharm, Ph D	Non-Medical (Pharmacy)	Male	Yes	Yes
9	Dr. P. Sathyan	DO, DNB	Clinician (Opthalmology)	Male	No	Yes

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10	Dr. Seetha Panicker	MD	Clinician (Obstetrics & Gyanaecology)	Female	Yes	Yes
11	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
12	Dr. Y.S. Sivan	Ph D	Social Scientist (Sociology)	Male	Yes	Yes
13	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
14	Mrs. K. Uma Maheswari	M Sc, M Phil, B Ed	Botany	Female	No	No
15	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

After due consideration, the committee has decided to approve the above proposal.

The approval is valid for one year.

We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

We hereby confirm that neither you nor any of your study team members have participated in the voting/ decision making procedure of the committee. The members of the committee who have participated in the voting/ decision making procedure of the committee do not have any conflict of interest in the referenced study.

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

PIs are required to send progress reports (in the form of an extended abstract with publications if any) to the IHEC every six months (and a month before expiry of approval date, if renewal of approval is being sought).

Request for renewal must be made at least a month ahead of the expiry of validity along with a copy of the progress report.

25.12.13

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

SECRETARY
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COIMBATORE-641 004
INSTITUTIONAL HUMAN ETHICS COMMITTEE

CONTENTS

ABSTRACT

Introduction

Myocardial infarction is the most cause of heart failure. The incidence of heart failure after MI has been reported as high as 23% in various studies. Characteristics of patients in India who develop heart failure after a myocardial infarction are less well studied. Though presence of higher incidence of reduced LV function with delay in revascularization time is established, rates of reduced LV function after different modes of revascularization and correlation with coronary artery lesion is not well established.

Aim and Objectives

To study the incidence of left ventricular dysfunction after the initial episode of myocardial infarction and to determine the difference in rates of development of LV dysfunction depending on time to perform revascularization and based on mode of revascularization and to correlate the development of LV dysfunction with the coronary artery lesion as determined by coronary angiogram.

Methodology

93 patients admitted in PSG Hospital from 1st March 2013 to 31st December 2013 with a diagnosis of Acute ST Elevation Myocardial Infarction and undergoing reperfusion therapy with either streptokinase or by percutaneous coronary intervention were included. Window period and door to needle/door to balloon time are recorded. Left ventricular ejection fraction, as determined by volumetric method, is measured within first 24 hours and on day 5 by a single person to avoid interpersonal variation. Development of heart failure based on Framingham criteria is noted. Use of diuretics is noted. Coronary artery lesion by coronary angiogram is noted.

Results

Out of 93 patients included in the study, 32 underwent primary PCI and 61 underwent thrombolysis. Patients with longer reperfusion time showed a significant reduction in LV ejection fraction. Patients retaining a normal ejection fraction when reperfusion times are between 0-3, 3-6, 6-12 and more than 12 were 70%, 59%, 32% and 0 respectively. Patients who underwent primary PCI had more chance of a preserved LVEF compared to those who underwent thrombolysis (82% Vs 44%. p=0.013). Patients with anterior wall STEMI had less number of patients with normal LVEF when reperfusion times were between 3 to 6 hours (41% Vs 93%. p=0.001) compared to non-anterior wall STEMI patients. No significant associations were found between age, presence of diabetes and the number of vessels involved to LVEF.

Conclusion

Longer reperfusion times are associated with significant reduction in LVEF. Primary PCI leads to better outcome in patients presenting between 3-6 hours when compared with thrombolysis. AW STEMI patients develop significant reduction in LVEF at 3-6 hours compared to non-AW STEMI patients.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and disability in developed and developing countries. As of 2012, CAD is the most common cause of death in the world [1] and also the major cause of hospital admissions [2]. Though high-income countries are seeing a fall in the incidence of CAD, low- and middle-income countries are seeing a very alarming increase in the rates of CAD, and this change is accelerating. In 2001, 75% of all global deaths and 82% of total DALYs (Disability Adjusted Life Years) lost due coronary artery disease occurred in low- and middle-income countries [3].

Mortality from coronary artery disease is expected to increase in developing countries (including India, China, Middle East, sub-Saharan Africa and Latin America), from an estimated 9 million in the year 1990 to a projected 19 million by the year 2020 [4]. It is thought that this projected increase is a consequence of social and economic changes in non-Western countries, which has led to an increased life expectancy, physical inactivity, changing/westernized diets, and an increase in cigarette smoking in these countries [5].

Coronary artery disease affects people at a much younger age in low- and middle-income countries compared to high-income countries. This leads to a greater economic impact on low- and middle-income countries. Effective screening, evaluation, and management strategies for coronary artery disease are well established in developed countries, but these strategies have not been fully implemented in developing countries like India.

Heart failure is the most common complication of coronary artery disease including ST elevation myocardial infarction (STEMI). Coronary artery disease accounts for 50% to 70% of incident cases of heart failure. Coronary heart disease has a relative risk of 8.1 for producing

heart failure. Overall Population Attributable Risk was 62 percent with 68 percent in men and 56 percent in women.

The increasing prevalence of heart failure in the world is in part due to the improved survival after myocardial infarction, successful prevention of sudden cardiac deaths and the ageing population. In the Framingham Heart Study, the prevalence of HF in men was 8 per 1000 at age 50 to 59 years and increased to 66 per 1000 at ages 80 to 89 years. There are an estimated 23 million people with HF worldwide [9]. Heart failure is a major cause of sick leaves, early retirement, hospitalizations and rising health care costs throughout the world.

Despite improvements in therapy of heart failure, the mortality and morbidity rates in patients with HF has remained unacceptably high. Continued efforts are therefore necessary to reduce the incidence of HF. One of the most important variables involved in the incidence of heart failure after a myocardial infarction is the time to reperfusion. Reducing the time to reperfusion, which is assessed by door-to-balloon or door-to-needle time and symptom-to-balloon or symptom-to-needle time is therefore crucial in improving myocardial salvage and preventing heart failure.

Door-to-balloon or door-to-needle time is mostly determined by organizational factors including presentation within regular working hours, rapid diagnosis, activation of catheterization laboratory both during working hours and non-working hours. Symptom-to-balloon or symptom-to-needle time is mainly dependent on patient factors. Current 2013 ACC guidelines give a value of 30 minutes for door-to-needle time and 90 minutes for door-to-balloon time with the aim of reducing the total ischemia time to less than 120 minutes.

However, the times given in guidelines are most often impossible to achieve in the current Indian hospital setting due to many factors including poor awareness among the population about the symptoms of myocardial infarction, lack of rapid transportation/ambulance facilities, shortage of trained staff in hospitals and lack of catheterization laboratories except in tertiary care centers.

Reduction in the time to reperfusion has not only shown to reduce the mortality due to myocardial infarction but several studies have also shown that it can reduce the incidence of heart failure after myocardial infarction. The difference in incidence of heart failure among patients who undergo percutaneous intervention and those who undergo thrombolysis is less well established. Also, the relationship of other variables like age, sex and presence of risk factors and their association with the incidence of reduced LVEF and heart failure after myocardial infarction in the Indian setting have not been well documented.

AIMS AND OBJECTIVES

- To determine the incidence of reduced left ventricular ejection fraction after acute STEMI in patients undergoing reperfusion.
- To analyze the characteristics of patients developing reduced left ventricular ejection fraction and heart failure with respect to time from onset of symptoms to start of therapy, presence of risk factors and number of coronary vessels involved.
- To analyze if there is any difference in incidence of reduced left ventricular function between patients who undergo thrombolysis versus those who undergo primary PCI.

REVIEW OF LITERATURE

History of Coronary Artery Disease

Death from coronary artery disease was relatively rare before 1900. The industrial revolution and the present day modern comfort are believed to have contributed significantly to the rise of coronary artery disease. Leonardo da Vinci is among the earliest scientists documented to have studied coronary arteries and their purpose. In 1628, an English doctor, William Harvey, described the circulation of blood. In the 1700s, cardiologist Friedrich Hoffmann established the link between coronary artery disease and decreased blood flow through the coronary arteries.

In 1768, William Heberden, an English physician, published his observations about the relationship of ischemic heart disease and coronary vascular anatomy. Since then, up to 19th century the disease was called the ‘Heberden’s disease’. In 1879, Ludwig Hekben, by his studies concluded that myocardial infarction was due to coronary obstruction which was secondary to thrombosis. William Osler played a large role studying angina and giving an accurate description of the coronary vessels. James Herrick is credited with coining the phrase "heart attack."

According to Cournand, the first catheterization was done by Claude Bernard in 1844 in a horse. In 1929, Werner Forssmann conducted the first coronary heart catheterization on himself. Forssmann, a urologist, while working on his experiments introduced a catheter into his jugular vein and took an X-ray and found it to be inside the right atrium. This groundbreaking work sparked other advances in this field and by the 1950s physicians were developing angiography, which is a process of making blood vessels viewable by X-ray.

In 1941, André Cournand and Dickinson Richards successfully repeated the trial of Forssmann. With their repeated attempts and experiments, they were finally able to push the catheter into right ventricle and take right ventricular angiograms. In 1950's the forthcoming experiments by them were a milestone in history towards the present day cardiac interventions.

Coronary arteriography and ventriculography became the gold standard for studying the cardiac and vessel anatomy and left ventricular pump function. They gave valuable information which made the way for surgical treatment for coronary revascularizations. Dotter, Judkins and Andreas Gruntzig conducted many experiments which led to the advances in invasive cardiology.

The first coronary bypass surgery was done in Cleveland Clinic in 1967. Dr. Rene Favaloro was the pioneer of the open-heart techniques, which involved the removal of a vein from one part of a patient's body and using it to connect the aorta and coronary arteries, creating a "bypass" around blocked coronary arteries. Dr. Andreas Gruentzig performed the first coronary angioplasty in 1977 in Switzerland. Dr. Gruentzig inserted a catheter into a coronary artery that was blocked and inflated a tiny balloon made at his kitchen table and compressed the buildup of plaque against the walls of the artery according to The Society for Cardiovascular Angiography and Interventions.

1986 saw the development of tiny metal stents that serve to prop open the artery and keep it from closing again after balloon angioplasty. Need for invasive, higher-risk surgeries was reduced due to the usage of stents which became commonplace. By 2002, more than 2 million coronary angioplasties were performed annually across the globe and drug eluting stents were developed.

Definition of Myocardial Infarction

The definition of myocardial infarction is given by ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction.

Criteria for Acute, Evolving, or Recent MI
Either of the following criteria satisfies the diagnosis for acute, evolving, or recent MI: 1 Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following: a Ischemic symptoms b Development of pathologic Q waves in the ECG c Electrocardiographic changes indicative of ischemia (ST-segment elevation or depression) d Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality 2 Pathologic findings of an acute myocardial infarction
Criteria for Healing or Healed Myocardial Infarction
Any one of the following criteria satisfies the diagnosis for healing or healed myocardial infarction: 1 Development of new pathologic Q waves in serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarction developed. 2 Pathologic findings of a healed or healing infarction

Classification of Myocardial Infarction

This is also given by ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction.

TYPE	FEATURES
1	Spontaneous myocardial infarction related to ischemia caused by a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
2	Myocardial infarction secondary to ischemia caused by increased oxygen demand or decreased supply (e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, hypotension)
3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or presumably new major obstruction in a coronary artery by angiography and/or pathology, but death occurring before blood samples could be obtained, or before the appearance of cardiac biomarkers in the blood
4a	Myocardial infarction associated with PCI
4b	Myocardial infarction associated with stent thrombosis, as documented by angiography or autopsy
5	Myocardial infarction associated with CABG

Epidemiology

Global Trends in Cardiovascular Disease

85% of the world's population lives in low and middle-income countries. Cerebro vascular disease (CVD) incidence rates in these countries largely accounts for global rates of CVD. Though CVD rates are falling in high-income countries, CVD rates worldwide are increasing because most low and middle-income countries are entering the second and third

phases of the epidemiologic transition, featured by rising CVD rates. CVD will be the dominant factor in economic impact of chronic diseases. Countries such as China, India, and Russia would be spending between $200 and $550 billion in national income as a result of heart disease, stroke, and diabetes [9].

In 1990, CVD accounted for 28% of the 50.4 million deaths worldwide and 9.8% of the 1.4 billion lost DALYs. By 2030, WHO predicts that worldwide, CVD will be responsible for nearly 24 million deaths. Of these CAD will cause 14.9% deaths in men and 13.1% deaths in women and stroke will be the cause of 10.4% of deaths in men and 11.8% of deaths in women.

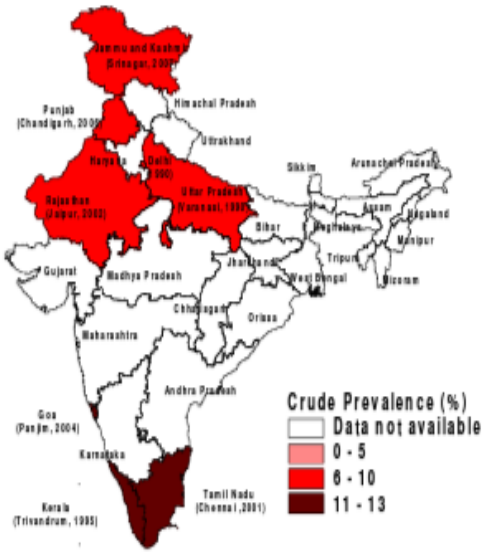
Prevalence of CAD in India

In India, coronary artery disease rates have increased during the last 30 years in contrast to declining trends that have been noticed in developed Western countries. The high prevalence of CAD in Indians came to light after the detection of increased incidence of CAD and MI in Indians living abroad. More than 20 million Indians live abroad and nearly 1.7 million of them in the USA. The Kaiser study [10] showed a prevalence of CAD in Indians in the US to be nearly 3 to 4 times than that of the American population, 6 times higher than Chinese population [17] and 20 times higher than the Japanese [16]. Indians develop heart disease 10 years earlier than other populations.

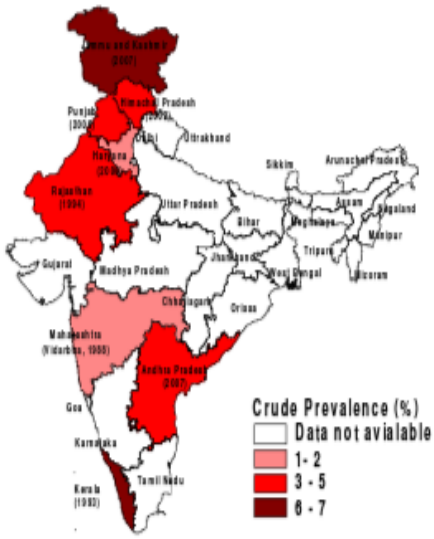
The prevalence of CAD in North India has increased from 1% in 1960 to 10.5% in 1998[12] and that in south India is 11% to 14.3% [13], slightly more than in north India and in Indians in the US. A study from Calicut Medical College in Kerala [15] showed that first heart attacks in patients aged less than 40 have increased 20-times between 1971 and 1991.

According to the WHO, in 1990 nearly 1.2 million died from heart disease and by 2020, 100 million Indians will have CAD (nearly 25% of world's CAD patients). Hence India is set to become the 'CAD capital of the world' as well, in addition to Diabetes and sooner still the Hypertension capital of the world as 1 in 5 people in Chennai have been found to be hypertensive.

CAD occurs equally in both vegetarians and non-vegetarians. The prevalence of CAD in urban population is twice that in rural population though smoking is more prevalent in the rural areas and in the face of the fact that CAD has doubled in rural areas as well [14].



(A)
Urban CHD Prevalence
(1990 – 2007)



(B)
Rural CHD Prevalence
(1988 – 2007)

Special Features of CAD in Indians

Many studies came upon some salient features of coronary artery disease epidemic among Indians [15] [18] [19] [20]

- India led the world with 1,531,534 cardiovascular disease related deaths in 2002
- Median age of first heart attack is 53 years in Indians compared to 63 in other groups
- Incidence of CAD in young Indians is about 12%–16%, which is the highest among any other ethnic group
- About 5%–10% of heart attacks occur in Indian men and women younger than 40 years
- Left main and triple vessel disease is twice as common than in whites not only in males but also in females
- Pre-hospital cardiac arrest is more common than in other ethnic groups.

Risk Factors for CAD in Indians

Indians have a higher prevalence of CAD in presence of low cardiac risk factors like obesity, smoking, cholesterol and hypertension as was seen in the CADI study. This feature has been called the **Indian paradox**. Other factors like DM, physical inactivity, low HDL levels are more prevalent in Indians. A number of other risk factors like lipoprotein (a), metabolic syndrome, homocysteine, fibrinogen, C-reactive protein (CRP) are also more common in the Indians [28].

If any three of the conventional risk factors are present the risk of CAD increases 13 fold, but the addition of increased lipoprotein (a) levels increases the risk 43-fold [25]. Lipoprotein(a) is

genetically inherited and makes Indians more susceptible to heart disease at a young age. It amplifies the effect of high LDL and low HDL cholesterol, and hastens atherosclerosis.

High homocysteine levels occur with improper diet and cooking methods. High levels of CRP are associated with abdominal obesity and sedentary life. Diabetes is 2-4 times more common among Indians than other ethnic groups [24]. Incidence of diabetes mellitus has doubled in the rural population and tripled in urban population over the past three decades. Indians develop diabetes mellitus earlier (10- 15 years) and at a lower body weight (9.1 to 13.6 kg) than other ethnic groups.

Between 2000 and 2030, diabetic population in India is projected to go up from 32 million to 79 million. Diabetes mellitus and CAD are inextricably intertwined [24]; one causes the other within 10 to 20 yrs. The incidence of CAD among diabetics is 14-times higher in those below 45 years and 2-3 times more in those older.

Use of stricter Asia Pacific Criteria for abdominal obesity resulted in a 50% increase in prevalence of metabolic syndrome from 22% to 32% in Indian men and from 20% to 29% in Indian women in Singapore [23]. Metabolic syndrome is typically associated with atherogenic phenotype B characterized by hypertriglyceridemia, low HDL-C, high small dense LDL, high apolipoprotein B and low apolipoprotein A-1. This explains the very high risk of CAD in metabolic syndrome.

About 20% of diabetics do not have metabolic syndrome and have a greatly reduced risk of CAD. Conversely, people with metabolic syndrome have a substantially increased risk of CAD even in absence of diabetes [22].

CURES study by Mohan et al [21] clearly shows every fifth individual is hypertensive in Chennai which is equal to or greater than the incidence of diabetes. Prevalence of hypertension in the study population was 20%, (23.2% in men and 17.1% in women). Even in the young (20-29 years), the incidence of hypertension was 3.8% in men and 3.1% in women. At the age of >60 years the incidence was 50.8% in men and 51% in women. The number of people with hypertension may overtake diabetics in our subcontinent.

INTERHEART study [20] was done by Yusuf et al in 2004 showed that the risk factors among Indians to be slightly different from other ethnic groups. It showed hypertension (OR 2.89), diabetes (OR 2.48) and abdominal obesity (OR 2.43) had more severe effects in South Asia, whereas psychosocial factors had a lesser OR of 2.15, compared with 2.67 worldwide. It also showed hypertension and diabetes were more important risk factors in younger women than men in India. Factors peculiar to the South Asian population such as truncal obesity, high TGL and low HDL-C were also found.

North Indians manifest coronary artery disease at lower levels of total cholesterol than South Indians. Lower HDL-C and higher TGL levels in both younger and older coronary artery disease patients appear to be a hallmark of the Indian population. There was also a greater association of smoking with CAD in younger individuals especially young men than young women. Prevalence of smoking in South Indian males (44.6%) and the prevalence of passive smoking in South Indian females (45.3%) has been found out to be significantly higher than in North Indians.

Process of Atherosclerosis

Atherosclerosis is a process that starts soon after birth as soon as the infant starts feeding diet that contains fat. Low-density lipoprotein (LDL) particles begin adhering to the vessel wall and accumulating in the intima. These get oxidized and become oxidized LDL. These oxidized lipoprotein particles releases cytokines which attracts the monocytes. The next process starts with the adherence of circulating blood monocytes to the endothelium. This is favored by the expression of molecules like vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and selectins (includes both E-Selectin and P-Selectin).

These monocytes then start to migrate to the subendothelial space and start accumulating. This process is mediated by the action of protein molecules known as chemoattractant cytokines or chemokines like monocyte chemoattractant protein 1 (MCP-1), Interleukin-8 (CXCL8), Interferon-γ, etc. These monocytes take up the lipids present in the intima and become a foam cell or lipid-laden macrophage. These foam cells start to replicate due to the presence of macrophage colony-stimulating factor (M-CSF).

The macrophage foam cells which are present in the artery wall serve not only as a reservoir for excess lipid but also as a source of proinflammatory mediators like cytokines and chemokines and various eicosanoids and lipids such as platelet-activating factor. They also serve as a source of large quantities of oxidant species. These processes constitute the innate immunity which is an amplification of inflammation without the presence of an antigen. Dendritic cells in atherosclerotic lesions can present antigens to the T cells. These antigens include modified lipoproteins, beta2-glycoprotein Ib, heat shock proteins and infectious agents.

Figure 1: Pathogenesis of atherosclerosis

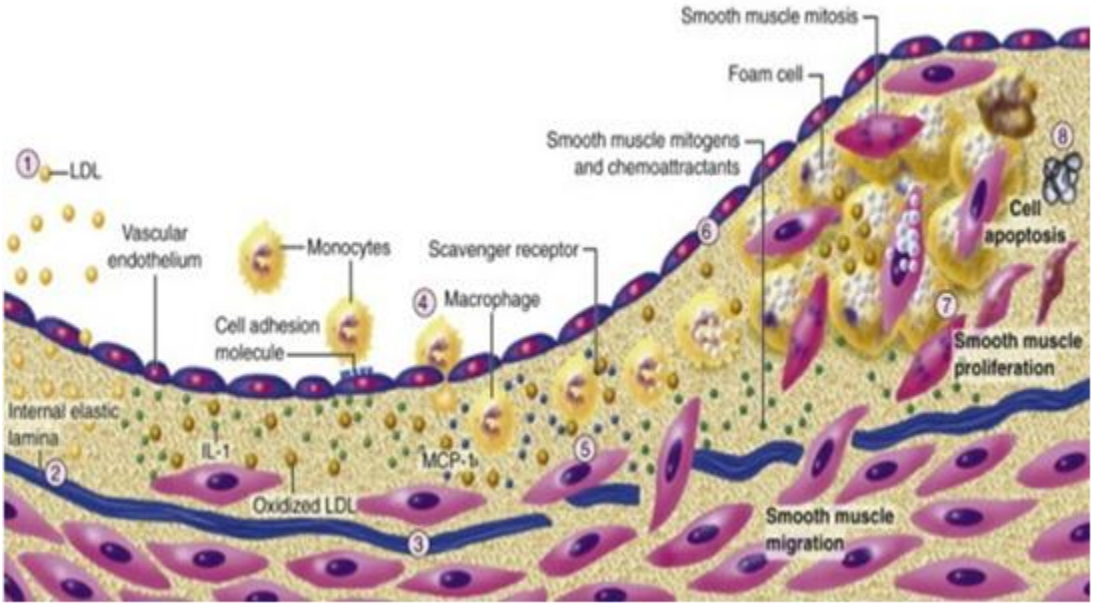
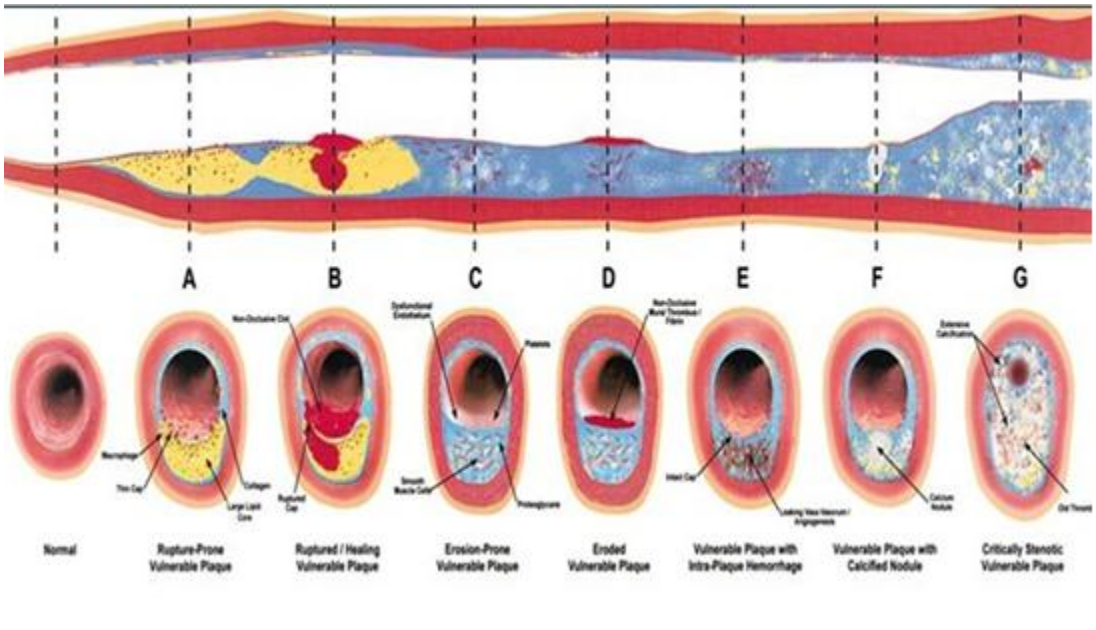


Figure 2: Plaque formation



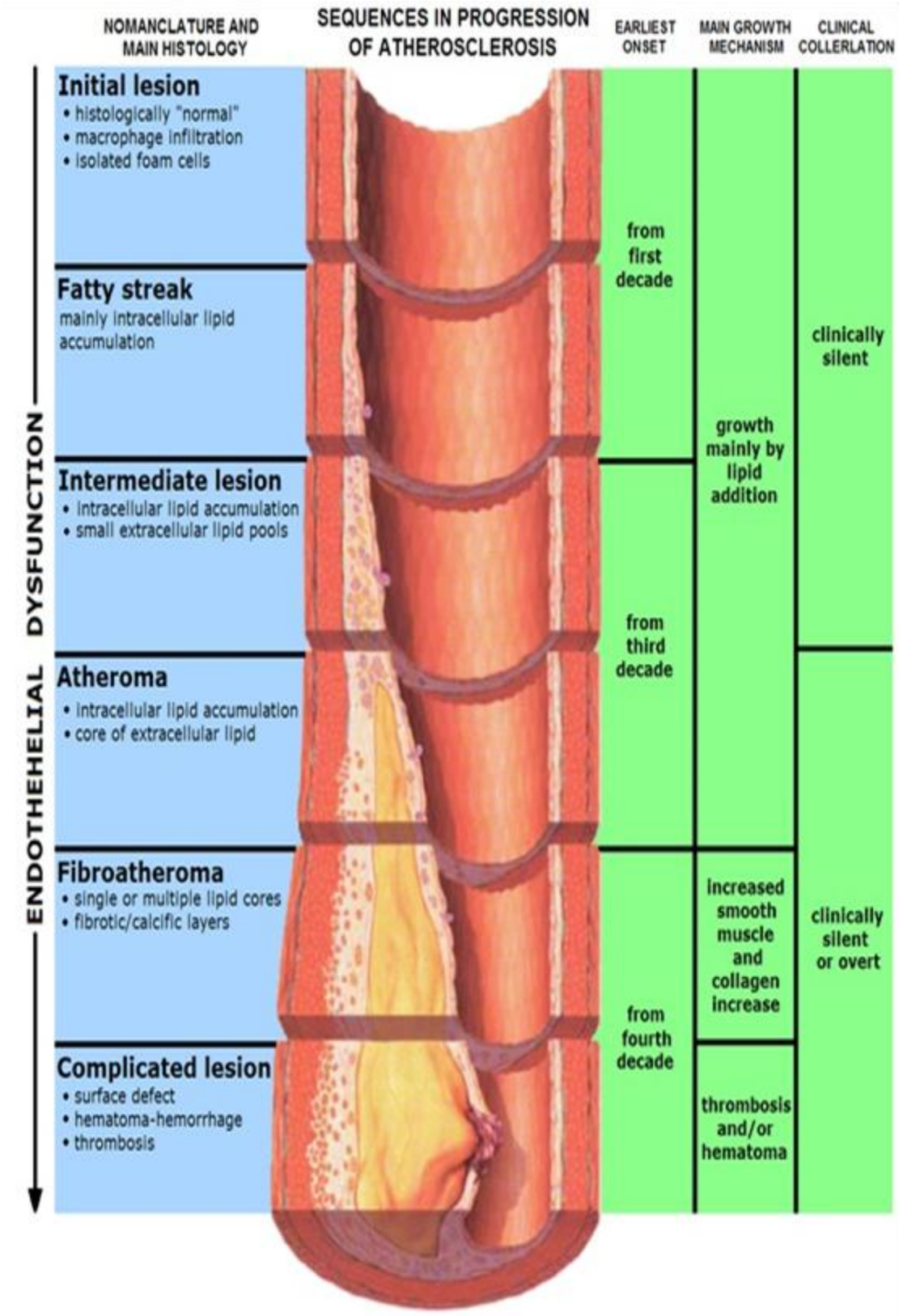
The next process involves the smooth muscle cells (SMCs). These smooth muscle cells migrate from the tunica media to the tunica intima. This process is facilitated by the presence of factors like platelet derived growth factor (PDGF). There is proliferation of smooth muscle cells in the intima. These SMCs in the atherosclerotic intima also exhibit a less mature phenotype than the quiescent SMCs in the normal arterial medial layer. This SMC replication causes the formation of a fibrous capsule covering the fatty streak.

Extracellular matrix itself makes up much of the volume of an advanced atherosclerotic plaque. The majority of extracellular matrix macromolecules that accumulate in atheroma include interstitial collagen type I, collagen type III, proteoglycans such as versican, biglycan, aggrecan, decorin and elastins. These macromolecules are broken down by matrix metalloproteinases (MMPs). Dissolution of extracellular matrix macromolecules will lead to migration of SMCs as they migrate into the tunica intima from the media through a dense extracellular matrix and the internal elastic lamina. Overexpression of proteinase inhibitors (known as tissue inhibitors of metalloproteinases, or TIMPs) can delay SMC accumulation in the intima of a plaque [26].

Atheroscerotic plaques develop their own microcirculation which is mediated by vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). The abundant microvessels in plaques will lead to a relatively large surface area through which leukocytes will migrate into the plaque. Some plaques can become calcified due to deposition of calcium.

As time goes on, enzymatic degradation can cause erosion of the fibrous cap. The endothelial cap separating the plaque and blood flow becomes thin and fragile. Rupture of the plaque may be due to the mechanical stress on the arteries or due to reduced collagen secretion

Figure 3: Evolution of Atherosclerosis

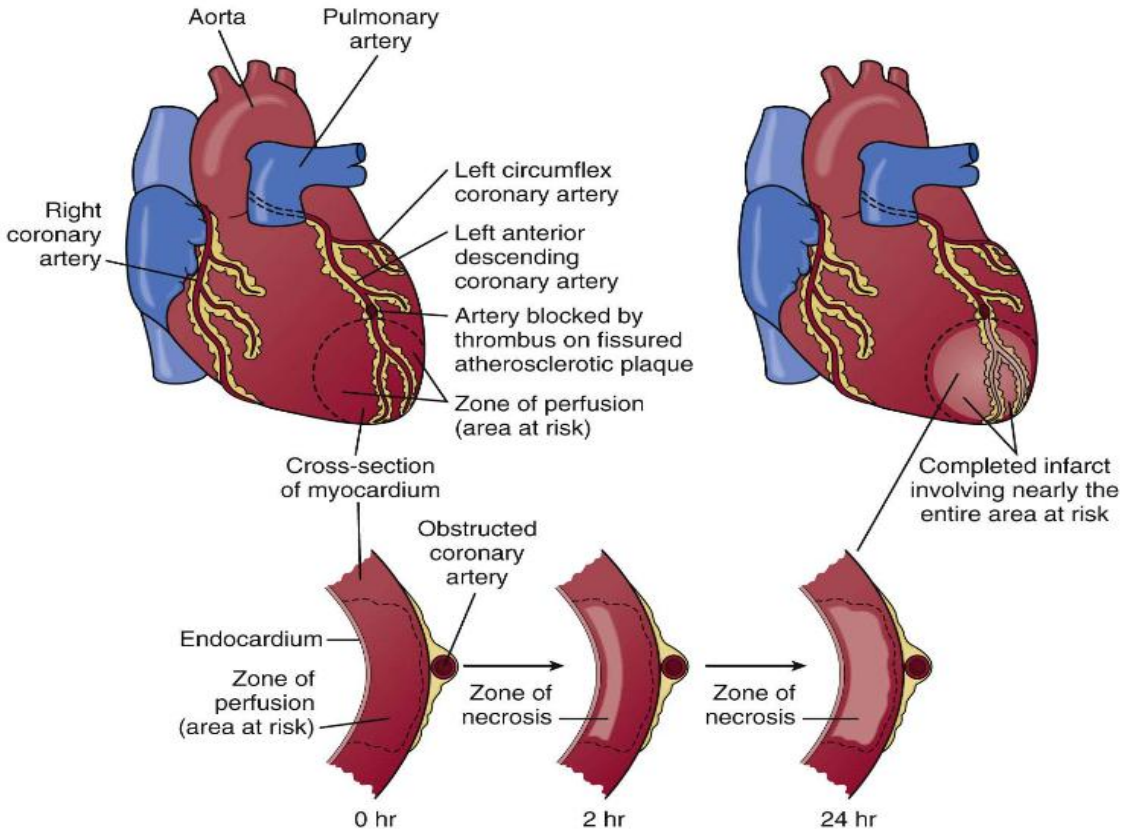


by the smooth muscle cells leading to rupture of the cap. This causes spilling of highly atherogenic plaque contents into blood stream which triggers the formation of thrombus.

Pathophysiology of Myocardial Infarction

Plaque disruption leads to exposure of highly atherogenic plaque content to blood stream which leads to formation of a thrombus. Occlusion of the entire vessel will lead to ST elevation myocardial infarction. This transmural injury and infarction leads to change in the sequence of depolarization producing the characteristic ECG changes. Size of the infarct depends largely on the magnitude of coronary collateral flow which if present may minimize the area of infarction. The location of infarct depends on the vessel that is involved.

Figure 4: Evolution of Myocardial Infarction



As time progresses, certain characteristic changes take place in the infarcted zone of the heart. The various gross changes and histological changes are given below

Time	Gross Examination	Histopathology
0 - 0.5 hours	None	None
0.5 – 4 hours	None	Glycogen Depletion, as seen with a PAS Stain Possibly waviness of fibers at border
4 – 12 hours	Sometimes dark mottling	Initiation of coagulation necrosis Edema Hemorrhage
12 – 24 hours	Dark mottling	Ongoing coagulation necrosis Karyopyknosis Hypereosinophilia of myocytes Contraction band necrosis in margins Beginning of neutrophil infiltration
1 – 3 days	Infarct center becomes yellow-tan	Continued coagulation necrosis Loss of nuclei and striations Increased infiltration of neutrophils to interstitium
3 – 7 days	Hyperemia at border Softening yellow-tan center	Beginning of disintegration of dead muscle fibers Necrosis of neutrophils Beginning of macrophage removal of dead cells at border
7 – 10 days	Maximally soft and yellow-tan Red-tan margins	Increased phagocytosis of dead cells at border Beginning of granulation tissue formation at margins
10 – 34 days	Red-gray and depressed borders	Mature granulation tissue with type I collagen
2 – 8 weeks	Gray-white granulation tissue	Increased collagen deposition Decreased cellularity
More than 2 months	Completed scarring	Dense collagenous scar formed

Pathophysiology of Myocardial Infarction

LV Function

Interruption of antegrade flow in a coronary vessel leads to abnormal or loss of contractile function in the myocardium that is supplied by that vessel. Four abnormal patterns of contraction can develop. Dyssynchrony causes dissociation in time between the contraction in

the affected myocardium and surrounding myocardium. Hypokinesis is reduction in the length of shortening. Akinesis is cessation of shortening. Dyskinesis causes paradoxical expansion and bulging. There is hyperkinesis of the surrounding myocardium to maintain the cardiac output but it subsides within two weeks.

If a large portion of the left ventricular myocardium is involved, LV pump action becomes decreased leading to low cardiac output and stroke volume, reduced blood pressure and elevated end systolic volume. Initially, the LV dilates as necrotic myocytes slip past each other. The infarct zone thins and elongates leading to infarct expansion. Later fibrous tissue is formed which leads to increased stiffness of the myocardium.

Left ventricular function is reduced when more than 15% of the myocardium is involved. Clinical signs of heart failure develop at 25% and cardiogenic shock occurs at 40%. Diastolic dysfunction also occurs in MI as a result of decrease in the peak rate of decline in LV pressure, an increase in the time for the fall in LV pressure, and an initial rise in LV end-diastolic pressure.

LV Remodeling

As a consequence of myocardial infarction, certain changes take place in the size, shape and thickness of the infarcted and the non-infarcted myocardium. These are called Ventricular Remodeling. Other than the size of infarct, there are two other major factors which determine the process of remodeling. First is the elevated ventricular pressure which leads to increased wall stress and infarct expansion. Other is the patency of the infarct artery which can accelerate scar formation and prevent remodeling.

Infarct expansion is defined as “acute dilation and thinning of the area of infarction not explained by additional myocardial necrosis.” [27]. This can be explained by mechanisms like

slippage of muscle bundles, disruption of normal cardiac cells and due to tissue loss within the infarct zone. The apex is the thinnest region and is especially prone for infarct expansion. Infarct expansion is associated with increased incidence of heart failure, aneurysm formation and increased mortality.

Dilatation of the non-infarcted zone of the myocardium occurs as a result of a compensatory mechanism to maintain the normal cardiac output. Also the increased pressure load on the non-infarcted myocardium leads to hypertrophy of those areas which helps maintain a normal cardiac output.

Ventricular remodeling after an acute myocardial infarction can be modified by a number of therapeutic interventions. Acute reperfusion restricts the area of myocardial infarction and prevents dilatation of the left ventricle. Treatment with angiotensin II inhibitors provides cardiac protection by reducing the endothelial dysfunction and reducing ventricular remodeling in addition to its direct antiatherogenic effects. Aldosterone inhibition also reduces collagen deposition and decreases the development of ventricular arrhythmias.

Incidence of Heart Failure after Myocardial Infarction

There are several studies that have studied the relationship between door to balloon time and symptom to balloon time. Several of these studies found that prolongation in these times lead to a reduced index left ventricular function. These studies include the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial that included 2639 patients and found that left ventricular ejection fraction was inversely associated with the door to balloon time [29].

Ng and el [30] found that after myocardial infarction, LVEF was significantly highera mong patients with shorter symptom to balloon time when compared with those who had longer times (n=2,529, P=.029). Also a study done on 1723 Polish patients [31] showed a significant difference in the mean LV ejection fraction among patients with the shortest symptom to balloon time (<1.5hours, 48% ± 13.4%) compared to those with the longest reperfusion time (>6hours, 31.4% ± 11.3%, P=.05).

Some studies such as Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial [32], Stent Primary Angioplasty in Myocardial Infarction (PAMI) trial [33], Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial [34] and a few more studies found no association between reduced LV ejection fraction and the symptom to balloon time. The explanation offered was that the early reduced LV ejection fraction could possibly be due to myocardial stunning or due to hibernating myocardium rather than denoting the size of the infarct. This could also be explained by the improvement in the LV ejection fraction on follow up.

Most of the trials which included LV ejection fraction at follow up as a parameter reported a significant improvement in LVEF on follow up compared to the index LVEF in patients who had shorter reperfusion times. One randomized study [35] found that longer reperfusion time was an independent predictor of worsening of LV function in 43% of the subjects at 6 months (HR 1.43, 95% CI 1.06-1.94). The PAMI trial noted an improvement in LVEF of 12% on follow up in patients with reperfusion time of < 2 hours as compared to an improvement of 4% in patients with reperfusion time of > 2 hours. The final LVEF at 6 months depended more on vessel patency than on reperfusion time in these trials.

List of trials studying time to reperfusion and index LVEF [36]

Study and year	Country of study	Type of study	No. of patients	Patient characteristics	Time to reperfusion	Main results	Conclusions
Symptom-to-balloon time							
van't Hof et al 1998[36]	Netherlands	Subanalysis of RCT (1990-1995)	358	Mean age: 59-61 y; male: 67%-86%	Ischemic time = symptom-to-balloon time (mean 212 ± 92 min); LVEF measured by RNV	In 3 groups of symptom-to-balloon time of <3, 3-6, and >6 h, predischarge LVEF was not significantly different among the groups (46%, 46%, and 44%; $P = .35$).	No effect of early reperfusion was noted on acute LVEF
Brodie et al 1998[18]	USA (North Carolina)	Cohort study (1984-1996)	1352	Mean age: ~60 y; female 25%-30%	Time to reperfusion = symptom-to-balloon; LVEF measured by ventriculograms	LVEF during hospitalization was higher in the patients with time to reperfusion <2 h (54.7 ± 13) vs those ≥2 h (52.0 ± 13, $P = .02$).	Shorter symptom-to-balloon time is associated with better EF at admission.
Brodie et al 2001[33] (Stent PAMI trial)	Multicenter RCT	Subanalysis of RCT	1232	Mean age: 60 y; female: 14%-29.9%	Time to reperfusion = symptom-to-balloon; LVEF measured by ventriculograms	In 4 groups of symptom-to-balloon time of <2, 2-<4, 4.0-<6, and ≥6 h, acute LVEF was not significantly different (49.8 ± 12.8, 55.8 ± 11.4, 53.9 ± 12.4, and 52.7 ± 11.1; $P = .15$).	No association was found between acute LVEF and symptom-to-balloon time.
De Luca et al 2004[10]	Netherlands	Cohort study (1994-2001)	1143	Mean age: 60 y; male: 59%-80%	Ischemic time = symptom time to balloon; LVEF measured by radionuclide ventriculography	Ischemic time had an inverse correlation with predischarge ejection fraction ($r = 0.068$, $P = .022$).	Symptom-to-balloon time had an inverse correlation with LVEF at the time of hospitalization.
Brodie et al 2006[27] (CADILLAC trial)	76 sites in 9 countries	Subanalysis of RCT	2082	Mean age: 60 y; male: 70%	Time to reperfusion = symptom-to-balloon time; LVEF measured by ventriculograms	Index LVEF was similar in patients with symptom-to-balloon times of <3<3, 3-6, and >6 h (56%, 55.9%, 56.3%; $P = .78$).	Symptom-to-balloon time does not correlate with index LVEF.
Trzos et al 2007[29]	Poland	Retrospective study (2001-2004)	1723	Mean age: 52.3-67.2 y; female: 29.5%-56.2%	Symptom-to-balloon time (median 268.5 ± 206 min); LVEF measured by echocardiography	In 4 groups of symptom-to-balloon time of <90 min (group1), 90-180 min (group 2), 180-360 min (group 3), and >360 min (group 4), mean LVEF was significantly higher in group 1 (48% ± 13.4%) as compared with group 4 (31.4% ± 11.3%, $P = .05$). No significant differences were noted as compared with group 3 (43.3% ± 15.6%) and group 4 (40.4% ± 10.2%). Killip class III/IV was significantly worse in group 4 ($P < .05$). Significantly higher incidence of cardiogenic shock was noticed in group 4 (18.4%).	Patients who undergo reperfusion after 6 h of symptoms onset have significantly higher incidence of cardiogenic shock, but have a lower index LVEF.

Study and year	Country of study	Type of study	No. of patients	Patient characteristics	Time to reperfusion	Main results	Conclusions
Brodie et al 2007[34] (EMERALD trial)	USA	Subanalysis of multicenter RCT	501	Mean age: 58 y; female: 12.6%-23.1%	Time to reperfusion = symptom-to-balloon time; LVEF measured by sestamibi scan	Index LVEF in the time-to-reperfusion groups (<2, 2-3, >3-4, and >4 h) was not significantly different (66%, 65%, 61.5%, and 62%; $P = .21$.)	No association was found between index LVEF and symptom-to-balloon time.
Aquaro et al 2007[35]	Italy	Prospective study	60	Mean age: 64 y; male: 66%	Pain-to-balloon time (mean 259 ± 157 min); LVEF measured by cardiac magnetic resonance imaging.	In 4 groups of pain-to-balloon of <168, 160-222, 223-300, and >300 min, index LVEF was not significantly different (44.8 ± 7.7, 49.8 ± 7.8, 47.5 ± 8.1, and 40.0 ± 15.2; P, not significant).	Index LVEF was similar in patients with short or longer symptom-to-balloon times.
Hahn et al 2008[37]	Korea	Retrospective study	73	Mean age: 54-57 y; male: >83%	Symptom-to-balloon time (mean); LVEF measured by contrast-enhanced MRI	Symptom-to-balloon times of (≤180, 180-360, and >360 min) were not associated with LVEF (52 ± 11, 54 ± 11, and 48 ± 14; $P = .34$). LVEF was similar for 3 groups of door-to-balloon time as well.	Symptom-to-balloon time determined the transmurality of myocardial injury, but was not associated with index LVEF.
Francone et al 2009[32]	Italy	Prospective study	70	Mean age: 57-58 y; male: 53%-78%	Time to reperfusion = symptom-to-balloon time (mean); LVEF measured by cardiac MR at 3 d and 6 mo	Symptom-to-balloon time of ≤90, >90-150, >150-360, and >360 min was associated with LVEF immediately after discharge (47 ± 10, 46 ± 9, 47 ± 6, and 38 ± 7; $P = .06$)	Salvaged myocardium is markedly reduced when reperfusion occurs after >90 min of symptom onset. There was a trend, but no difference was noted between LVEF postdischarge and different times to reperfusion.
Wierzbicka et al 2009[12]	Poland	Single-center prospective study	207	Mean age: 60 y; male: 72%-80%	Time to treatment = start of first symptoms of acute MI to time of an artery puncture	LVEF (median of 3-5 d) was not significantly different in those with symptom-to-needle time ≤6 h (55 ± 10) as compared with >6 h (52 ± 11, $P = .6959$)	Symptom-to-needle time was not associated with index LVEF during the hospitalization for acute MI.
Bertini et al 2009[31]	Netherlands	Retrospective study	157	Mean age: 60 y; male: 78%	Symptom-to-balloon time (mean 212±92 min); LVEF measured by 2-dimensional echo	In 3 groups of symptom-to-balloon time of <170, 170-215, and >215 min, index LVEF was significantly higher in the early reperfusion group (50 ± 6, 47 ± 8, and 45 ± 7; $P < .05$)	Symptom-to-balloon time was directly associated with index LVEF.

Study and year	Country of study	Type of study	No. of patients	Patient characteristics	Time to reperfusion	Main results	Conclusions
Ray et al 2010[30]	India	Prospective pilot study	48	Mean age: 57.6 y; male: 80%	Ischemic time = symptom-to-balloon time; LVEF assessed by Echo-Doppler	1-h delay in ischemic time was associated with LVEF reduction of 0.63%, in multivariate analysis.	Ischemic time is an important predictor of LVEF after primary PCI.
Maeng et al 2010[13] (DANAMI trial)	Denmark	Subanalysis of RCT in 29 hospitals (1997-2001)	686	Mean age: 62-64 y; male: >72%-74%	Symptom-to-balloon (median 95 min); LVEF by echocardiography before discharge	Symptom-to-balloon times of <3, 3-5, and ≥5 h was significantly associated with predischarge LVEF (54%, 50% and 50%; $P < .001$); significantly associated with LVEF >40% (80.3%, 77.2%, and 66.9%; $P = .006$).	Shorter symptom-to-balloon time was associated with an increased likelihood of subsequent LVEF >40% and index LVEF.
Ng et al 2011[14]	Netherlands	Prospective cohort study (1994-2004)	2,529	Mean age: 60 ± 12 y; female: 21%	Ischemic time = symptom-to-balloon time (median 4 h, range 3-5 h); LVEF measured by radionuclide ventriculography or echocardiogram before discharge	Ischemic time expressed as a continuous variable significantly correlated with LVEF, but the correlation was weak ($P = .002$, $r = -0.062$). LVEF was significantly higher with shorter symptom-to-balloon time (≤3 h, 45.1 ± 11.7; 3-6 h, 44.6 ± 11.9; ≥6 h, 43.2 ± 12.1; $P = .029$)	Symptom-to-balloon time was associated with postinfarction LVEF in patients under going primary PCI.
Door-to-balloon time							
Rochitte et al 2001[26]	Brazil	Retrospective study	67		Door-to-balloon time (median 132 min); LVEF measured by echocardiogram	LVEF during hospitalization was higher in the group with door-to-balloon time <120 min (53.1% ± 9%) vs those with door-to-balloon time ≥120 min (46.1% ± 13%, $P = .059$).	Door-to-balloon time more than 2 h was associated with a lower LVEF early after MI, but with borderline significance.
Brodie et al 2006[16]	USA (North Carolina)	Cohort study (1984-2003)	2322	Mean age: ~60 years; female gender: 25%-30%	Door-to-balloon time; LVEF measured by ventriculograms	In 4 groups of door-to-balloon time of <1.4, 1.5-1.9, 2.0-2.9, and ≥3 h, index LVEF was significantly higher in the early reperfusion group (52.6 ± 12.3, 51.4 ± 12.3, 50.7 ± 12.9, and 48.8 ± 13.1; $P < .0001$).	Door-to-balloon time was inversely associated with LVEF during the hospitalization for STEMI.
Brodie et al 2006 (CADILLAC trial)[27]	76 sites in 9 countries	Subanalysis of RCT	2082	Mean age: 60 y; male: 70%	Time to reperfusion = door-to-balloon time; LVEF measured by ventriculograms	Index LVEF was similar in patients with door-to-balloon times of <1.5, 1.5-2, 2-3, and >3 h (58%, 59%, 56%, and 57%; $P = .39$).	Door-to-balloon time does not correlate with index LVEF.

Study and year	Country of study	Type of study	No. of patients	Patient characteristics	Time to reperfusion	Main results	Conclusions
Brodie et al 2007 (EMERALD trial)[24]	USA	Subanalysis of Multicenter RCT	501	Mean age: 58 y; female: 12.6%-23.1%	Time to reperfusion = door-to-balloon time; LVEF measured by sestamibi scan	Index LVEF in the door-to-balloon time groups (<1, 1-1.5, >1.5-2, and >2 h) was not significantly different (66.5%, 63.0%, 65%, and 61.5%; $P = .22$).	No association was found between index LVEF and door-to-balloon time.
Ortiz-Pérez et al 2010[28]	USA and Spain	Prospective study	172	Mean age: 58-59 y; male: 82%-85%	Door-to-balloon time; LVEF was assessed using cardiac magnetic resonance.	LVEF was not significantly different between the early (<90 min, 43% ± 10%) and late (≥90 min 41% ± 11%), reperfusion groups ($P = .3$).	Early reperfusion after STEMI was associated with significantly increased myocardial salvage; however, there was no effect on index LVEF.
Maeng et al 2010[13] (DANAMI trial)	Denmark	Subanalysis of RCT in 29 hospitals (1997-2001)	686	Mean age: 62-64 y; male: >72%-74%	Door-to-balloon time (median 111 min); LVEF measured by echocardiography before discharge	No differences were noted in the predischarge LVEF (50, 50, and 50) or LVEF >40 (78%, 71.3%, and 75.8%) in 3 groups of door-to-balloon time (early [<90 min], intermediate [90-105 min], and late [>105 min]).	No association was observed with door-to-balloon time and index LVEF.
Blankenship et al 2010[25] (HORIZONS-AMI trial)	123 hospitals in 11 countries—USA, Europe, South America, and Israel	Subanalysis of RCT (2005-2007)	2639	Mean age: 60.1 y; male: 77.2%	Door-to-balloon time; LVEF measured by ventriculograms	In univariate analysis, LVEF was inversely associated with door-to-balloon time (−0.21 [SE 0.10], $P = .03$). In multivariate analysis (adjusted for previous CHF, daytime presentation, DM, previous angina, male gender, infarct-related artery, and presentation to no-angioplasty hospital), LVEF had inverse association with door-to-balloon time (−0.25 [SE 0.09], $P = .003$).	Door-to-balloon time has an inverse association with LVEF measured at the time of angiography.

A total of 12 studies were done to establish a relationship between reperfusion time and index heart failure. 11 of these studies showed significant association between these 2 variables. The largest trial by American College of Cardiology National Cardiovascular Data Registry [37] showed an absolute increase in heart failure by 5.3% in patients with door to balloon time of >120 minutes compared to a time of <60 minutes. The largest study done by Ng S et al [30] showed that for every 1 hour increase in reperfusion time, there was an increase in incidence of heart failure by 4%.

Many trials including Danish Acute Myocardial Infarction 2 (DANAMI-2) study have shown that primary angioplasty has better outcome compared to intra venous thrombolysis in terms of 30 days mortality. Another trial done by Henriques et al [38] has established that primary angioplasty has better outcome in terms of LVEF in patients who have anterior wall myocardial infarction compared to intra venous thrombolysis.

MATERIALS AND METHODS

Source of Data

This study was done in PSG Hospitals which is affiliated to PSG Institute of Medical Sciences and research in Coimbatore, Tamil Nadu. All patients presenting to the hospital with acute STEMI and undergoing thrombolysis or primary PCI were included in the study between the period of March to December 2013. A total of 93 patients were included out of which 32 underwent primary PCI and 61 underwent thrombolysis with streptokinase. 40 of 61 patients who were thrombolysed underwent coronary angiogram for risk stratification and further management.

Methodology

A total of 93 consecutive patients with STEMI undergoing either primary PCI or thrombolysis were included in the study after obtaining proper consent from the patients. Age, sex, time of onset of chest pain and the time of start of thrombolysis or time of balloon dilatation were noted. Presence or absence of diabetes mellitus, hypertension and smoking history were recorded. The left ventricular ejection fraction within 24 hours of admission and before discharge were recorded by a single operator to avoid inter observer variability using Simpson's Method. Presence of heart failure was monitored during the hospital stay based on the Framingham Criteria for Heart Failure. Number of vessels with 50% or more stenosis was noted either during primary PCI or during elective coronary angiogram. Statistical analysis was done using Pearson's correlation coefficient, Chi square test and Multivariate analysis using SPSS software.

Inclusion Criteria

- All patients presenting to PSG hospitals with diagnosis of acute STEMI, who underwent reperfusion with either thrombolysis or primary PCI during the time period of March 2013 and December 2013.

Exclusion Criteria

- Patients with previous history of coronary artery disease were excluded.
- Patients with previous history of heart failure were excluded.
- Patients with structural heart disease like valvular heart disease or any congenital heart disease were excluded.

Protocol of the Study

Entry Point

Patients presenting with acute STEMI who are undergoing revascularization

History

Time of onset of chest pain

Past history of diabetes, hypertension, smoking

Past history of CAD, heart failure, structural heart disease

Management

Patient undergoes either thrombolysis or primary PCI

Time from onset of chest pain to start of thrombolysis or start of balloon dilation is noted

Follow Up

Patient followed up for signs of heart failure

LV ejection fraction by echocardiography using Simpson's method is determined during the first 24 hours and on discharge

Number of vessels with 50% or more lesions is noted during primary PCI or elective coronary angiogram

Definitions

Definition of MI

(ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction)[6]

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin(cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia
- New or presumed new significant ST segment and T wave (ST–T) changes or new left bundle branch block(LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

ECG Criteria for STEMI

(ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction)[6]

- New ST segment elevation at the J point in two contiguous leads with elevation >0.1 mV in all leads other than leads V2-V3
- For leads V2-V3, ST elevation should be ≥0.2 mV in men ≥40 years, ≥0.25 mV in men <40 years, or ≥0.15 mV in women

Diagnostic criteria for heart failure [7]

Framingham Criteria		
MAJOR CRITERIA	**MINOR CRITERIA**	**MAJOR OR MINOR CRITERIA**
Paroxysmal nocturnal dyspnea or orthopnea Neck-vein distention Rales Cardiomegaly Acute pulmonary edema S_3 gallop Increased venous pressure, >16 cm H_2O Hepatojugular reflux	Ankle edema Night cough Dyspnea on exertion Hepatomegaly Pleural effusion Vital capacity decreased by one third from maximal capacity Tachycardia (rate > 120 beats /min)	Weight loss > 4.5 kg in 5 days in response to treatment

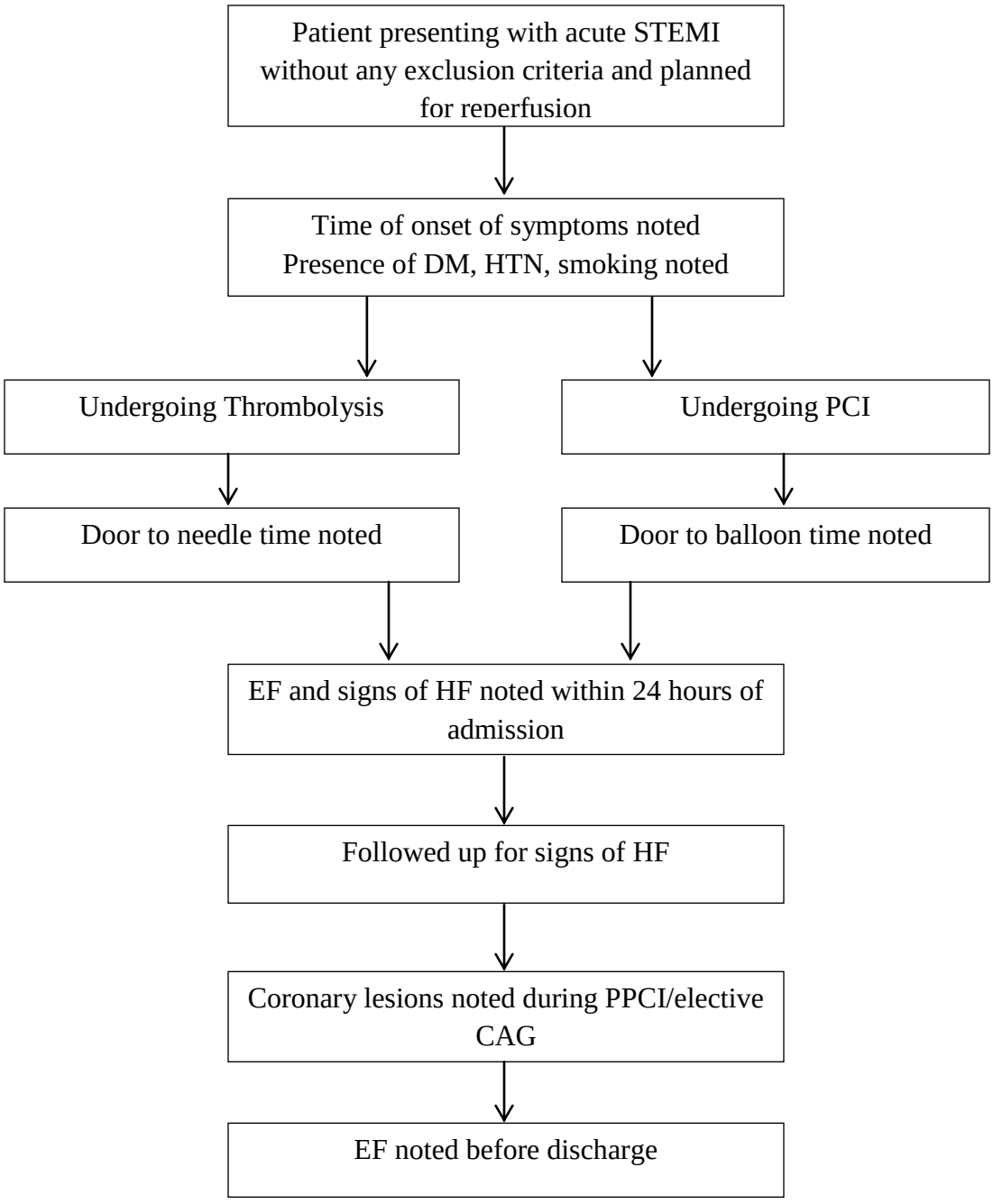
The Framingham criteria requires the simultaneous presence of at least 2 major criteria or 1 major criteria and two minor criteria. Minor criteria are accepted only if they cannot be attributed to another cause (e.g. pulmonary hypertension, nephrotic syndrome, chronic lung disease, cirrhosis, etc.).

Classification of severity of LV dysfunction based on LVEF

(From Feigenbaum's Echocardiography, 7th Edition)

Normal LVEF	>55%
Mild LVD	45 – 54%
Moderate LVD	30 – 44%
Severe LVD	<30%

FLOW CHART OF THE STUDY



RESULTS

Total of 93 patients were included in the study of which 32 underwent primary PCI and 61 underwent thrombolysis with streptokinase.

Table 1: General Characteristics of the study group

Average Age		55
Male / Female		81(87%) / 10 (13%)
Diabetes		42 (45.16%)
AW MI		52 (55.91%)
Time to reperfusion		
	0 – 3 hours	20 (21.5%)
	3 – 6 hours	44 (47.31%)
	6 – 12 hours	25 (26.88%)
	> 12 hours	4 (4.3%)
PCI / Lysis		32 (34.4%) / 61 (65.6%)
Deaths		5 (5.38%)
EF > 55%		48
EF 45 – 54%		19
EF < 45%		26

Figure 5: Graphic representation of LVEF in study group

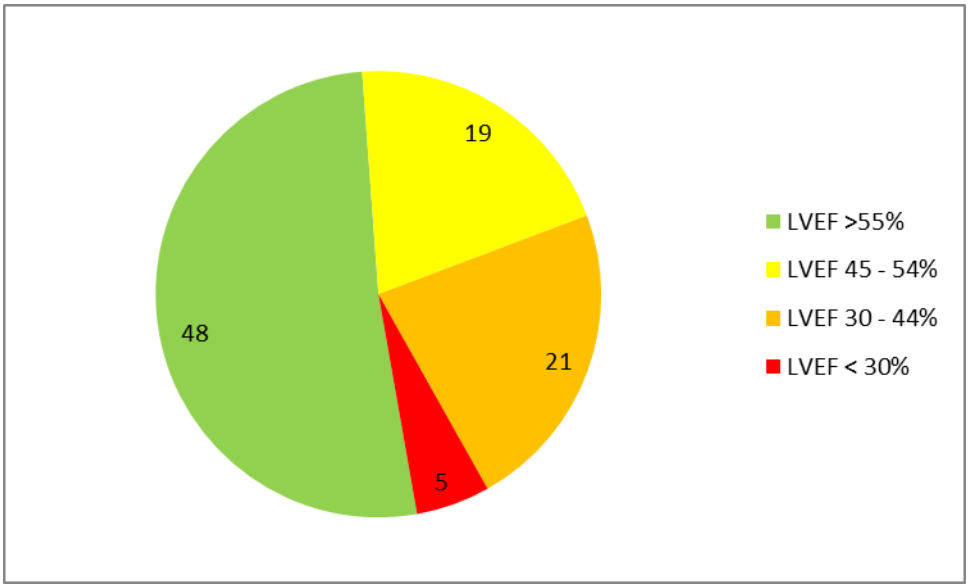


Table 2: Characteristics based on time to reperfusion

Time to reperfusion	<3 hours	3 to 6	6 to 12	> 12	p value
Mean Age	53.7±12.135	52.72±12.79	58.6±8.61	64±10.39	0.087
Male	19(95.0)	35(79.54)	23(92.0)	4(100.0)	0.215
Diabetes	11(55.0)	16(36.36)	12(48.0)	3(75.0)	0.299
Anterior MI	6(30.0)	29(65.9)	15(60.0)	2(50.0)	0.059
Heart failure symptoms	3(15.0)	10(22.72)	4(16.0)	3(75.0)	**0.050**
Normal LV function	14(70.0)	26(59.09)	8(32.0)	0(0.0)	**0.008**
LVEF < 45%	4(20.0)	7(15.9)	11(44.0)	4(100.0)	**0.001**
Death	1(5)	1(2.27)	2(8.0)	1(25.0)	0.24

Significant association was noted between time to reperfusion and patients developing signs of heart failure, patients with normal LVEF and patients with LVEF < 45%.

Graphic representation of LVEF based on time to reperfusion

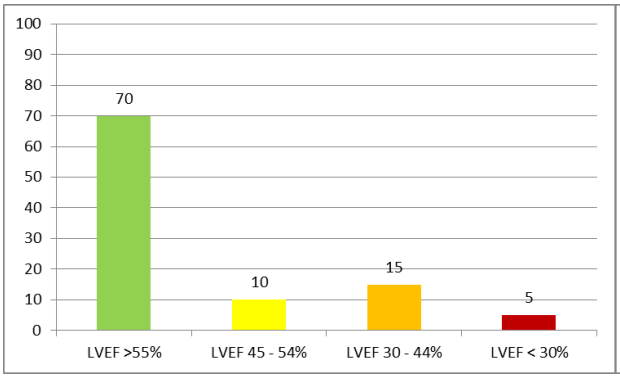


Figure 6: LVEF in patients with reperfusion time < 3 hours

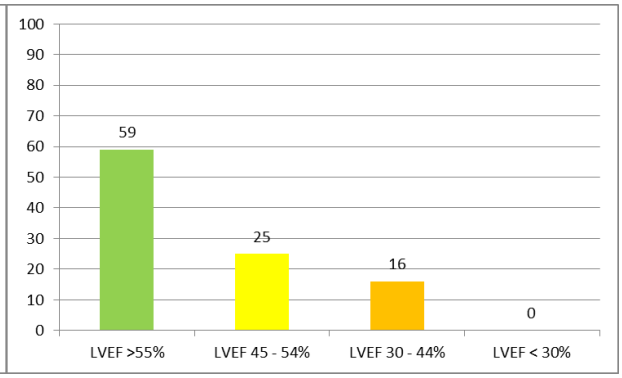


Figure 7: LVEF in patients with reperfusion time 3-6 hours

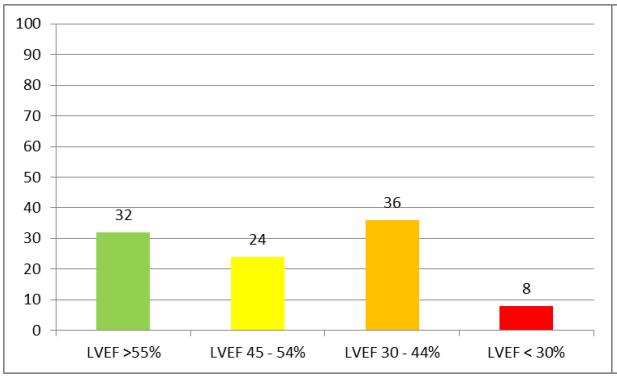


Figure 8: LVEF in patients with reperfusion time 6-12 hours

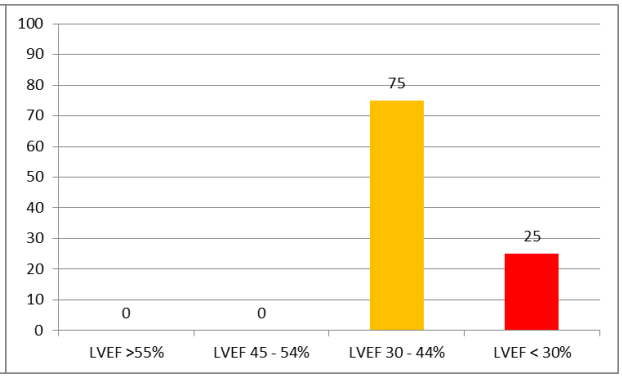


Figure 9: LVEF in patients with reperfusion time > 12 hours

These graphs show that as time to reperfusion gets longer, less number of patients retain a normal left ventricular function and more patients start developing moderate and severe left ventricular systolic dysfunction.

Table 3: Characteristics based on PCI or thrombolysis

Variables		PCI	Thrombolysis	p value
Total Number		32	61	
Mean age		54.59±12.06	55.21±11.78	0.812
Male		29(90.62)	52(85.24)	
Diabetes		12(37.5)	30(49.2)	0.196
Anterior wall MI		20(62.5)	32(52.5)	0.24
Deaths		3(9.4)	2(3.3)	0.221
< 3hours				
	LVEF > 55%	3(75.0)	11(68.75)	0.657
	LVEF < 45%	1(25.0)	3(18.75)	0.624
3-6 hours				
	LVEF > 55%	14(82.35)	12(44.44)	**0.013**
	LVEF < 45%	0(0.0)	7(25.92)	**0.023**
6-12 hours				
	LVEF > 55%	1(12.5)	7(41.17)	0.166
	LVEF < 45%	4(50.0)	7(41.17)	0.504
>12 hours				
	LVEF > 55%	0(0.0)	0(0.0)	-
	LVEF < 45%	3(100.0)	1(100.0)	-

This table shows that there are no significant differences between the general characteristics of the patients undergoing either thrombolysis or PCI.

Significant differences are noted between PCI group and thrombolysis group only in the group of patients who undergo reperfusion between 3 and 6 hours. In this group, patients who undergo PCI have a significantly better LVEF than those who undergo thrombolysis. Patients who undergo reperfusion after 12 hours, irrespective of undergoing PCI or thrombolysis, have an LVEF of < 45%.

Figure 10: Normal LVEF based on time to reperfusion in PCI and thrombolysis groups

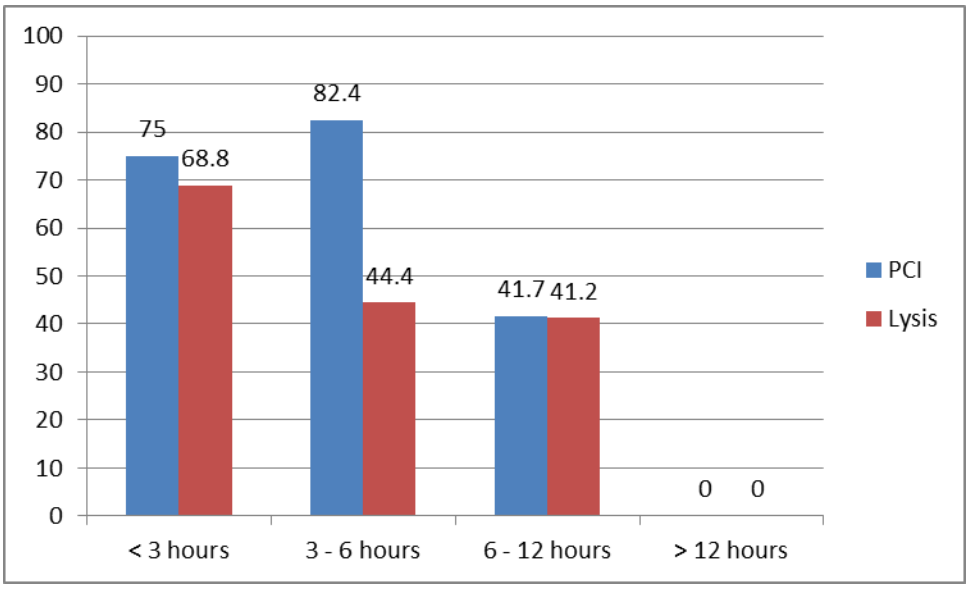


Figure 11: LVEF < 45% based on time to reperfusion in PCI and thrombolysis groups

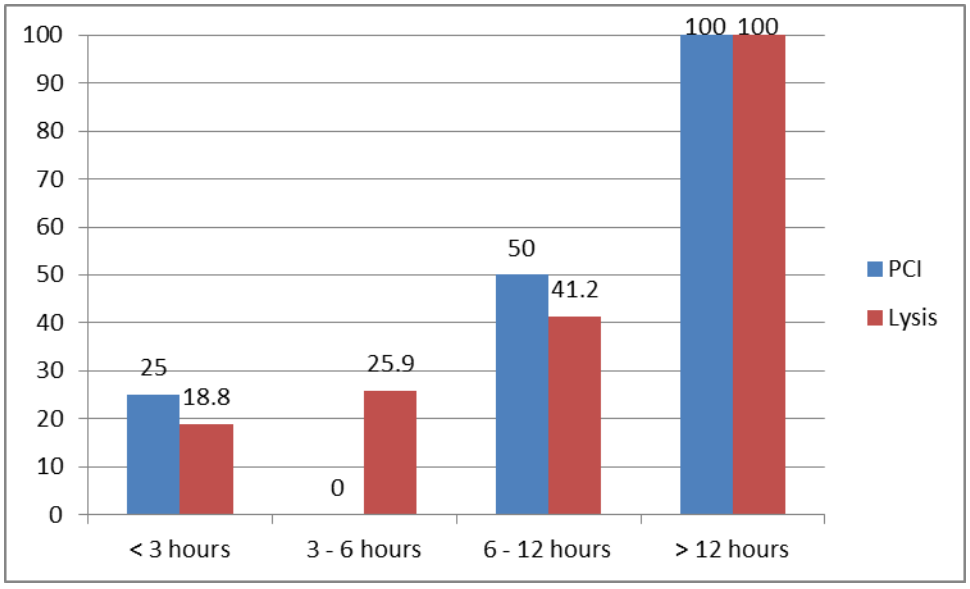


Table 4: Characteristics based on age

Age		**< 30**	**30-40**	**40-50**	**50-60**	**60-70**	**>70**	**p value**
N value		3	8	20	30	24	8	
Diabetes		1(33.33)	2(25.0)	10(50.0)	13(43.33)	10(41.67)	6(75.0)	0.453
AW MI		2(66.67)	5(62.5)	11(55.0)	15(50.0)	13(54.17)	6(75.0)	0.859
Death		0(0.0)	0(0.0)	1(5.0)	2(6.67)	1(4.17)	1(12.5)	0.902
< 3 hours								
	LVEF > 55%	0(0.0)	1(100.0)	4(57.14)	7(100.0)	1(50.0)	1(50.0)	0.215
	LVEF < 45%	1(100.0)	0(0.0)	1(14.28)	0(0.0)	1(50.0)	1(50.0)	0.136
3 - 6 hours								
	LVEF > 55%	2(100.0)	4(66.67)	8(72.72)	6(60.0)	6(46.15)	0(0.0)	0.29
	LVEF < 45%	0(0.0)	1(16.67)	0(0.0)	3(30.0)	2(15.38)	1(50.0)	0.338
6 – 12 hours								
	LVEF > 55%	0(0.0)	0(0.0)	1(50.0)	2(18.18)	4(44.44)	0(0.0)	0.29
	LVEF < 45%	0(0.0)	0(0.0)	1(50.0)	4(36.37)	4(44.44)	2(100.0)	0.46
>12 hours								
	LVEF > 55%	0(0.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	2(100.0)	-
	LVEF < 45%	0(0.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	2(100.0)	-

From this table, age has no significant effect on the left ventricular ejection fraction and the development of left ventricular systolic dysfunction based on time to reperfusion.

Table 5: Characteristics based on anterior wall or non-anterior wall MI

Variables		AW MI	Non AW MI	p value
N value		52	41	
Mean Age		54.67±12.28	55.41±10.55	0.766
Diabetes		26(50.0)	16(39.0)	0.199
Death		3(5.8)	2(4.9)	0.612
< 3 hours				
	LVEF > 55%	4(66.67)	10(71.42)	0.613
	LVEF < 45%	2(33.33)	2(14.28)	0.343
3-6 hours				
	LVEF > 55%	12(41.37)	14(93.33)	**0.001**
	LVEF < 45%	7(24.13)	0(0.0)	**0.041**
6-12 hours				
	LVEF > 55%	3(20.0)	5(50.0)	0.128
	LVEF < 45%	9(60.0)	2(20.0)	0.058
>12 hours				
	LVEF > 55%	0(0.0)	0(0.0)	-
	LVEF < 45%	2(100.0)	2(100.0)	-

Patients with anterior wall myocardial infarction have a more reduced left ventricular ejection fraction than those with non-anterior wall myocardial infarctions. There is significant difference between anterior and non-anterior wall myocardial infarction in the group with a reperfusion time of 3 to 6 hours. After 6 hours, the rate of reduction in LVEF increases in the non-anterior wall myocardial infarction. Therefore, patients with AWMI develop reduced LVEF faster than patients with non-AWMI.

Table 6: Characteristics based on presence of diabetes mellitus

		Diabetics	Non Diabetics	P Value
N value		42	51	
Mean Age		56.45±11.96	53.80±11.46	0.521
AW MI		26(61.94)	26(50.9)	0.199
Death		4(9.5)	1(1.96)	0.126
< 3 hours				
	LVEF > 55%	7(63.63)	7(77.77)	0.426
	LVEF < 45%	3(27.27)	1(11.11)	0.375
3 - 6 hours				
	LVEF > 55%	8(50.0)	18(64.28)	0.271
	LVEF < 45%	4(25.0)	3(10.71)	0.205
6 – 12 hours				
	LVEF > 55%	5(41.67)	3(23.07)	0.286
	LVEF < 45%	7(58.33)	4(30.7)	0.163
>12 hours				
	LVEF > 55%	0(0.0)	0(0.0)	-
	LVEF < 45%	3(100.0)	1(100.0)	-

There was no significant relationship between the presence or absence of diabetes mellitus and left ventricular ejection fraction after ST elevation myocardial infarction based on time to reperfusion.

Table 7: Characteristics based on number of vessels involved

		1 vessel	2 vessel	3 vessel	p value
N Value		34	16	20	
Mean age		51.44±11.33	55.60±9.78	59.95±11.37	0.079
Diabetes		10(29.41)	11(68.75)	8(40.0)	0.038
AW MI		23(67.64)	9(56.25)	45(20.0)	0.324
Death		2(5.9)	1(6.2)	1(5.0)	0.992
< 3 hours					
	LVEF > 55%	1(50.0)	5(62.5)	4(100.0)	0.505
	LVEF < 45%	1(50.0)	1(12.5)	0(0.0)	0.381
3 - 6 hours					
	LVEF > 55%	11(61.11)	1(25.0)	8(80.0)	0.243
	LVEF < 45%	2(11.11)	1(25.0)	0(0.0)	0.16
6 – 12 hours					
	LVEF > 55%	3(23.07)	1(33.33)	3(75.0)	0.24
	LVEF < 45%	5(38.46)	2(66.67)	1(25.0)	0.595
>12 hours					
	LVEF > 55%	0(0.0)	0(0.0)	0(0.0)	-
	LVEF < 45%	1(100.0)	1(100.0)	2(100.0)	-

This study also showed no significant relationship between left ventricular ejection fraction after myocardial infarction and the number of vessels involved with more than 50% stenosis in coronary angiogram based on time to reperfusion.

Table 8: Multiple Regression Analysis

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	R^2	Overall p-value
	B	Std. Error	Beta				
(Constant)	.882	.330		2.676	.009	0.313	0.000
Age	.003	.003	.088	.903	.369		
Gender	-.048	.122	-.039	-.394	.694		
Time period	.000	.012	-.005	-.046	.964		
DM	.073	.077	.089	.946	.347		
SHT	.047	.079	.055	.587	.559		
Smoking	-.073	.084	-.088	-.872	.386		
No. of vessels	.023	.036	.061	.651	.517		
LVEF	-.017	.004	-.468	-4.494	.000		

a. Predictors: (Constant), EF, SHT, vessels, Gender, DM, Age, Time period, Smoking

b. Dependent Variable: HF

This table shows that though all the factors together contribute to heart failure by 31.3%, LVEF has the strongest association.

DISCUSSION

A total of 93 patients were included in this study. All patients presented to the emergency department with acute onset of chest pain and were diagnosed as ST elevation myocardial infarction. Out of 93, 32 patients underwent primary angioplasty and 61 underwent intra venous thrombolysis with streptokinase. All patients were given the option of both thrombolysis and primary PCI. The decision to do thrombolysis or primary PCI was made by the patients and family considering the costs involved.

Age and sex distribution

In this study, the mean age was 57.25. Subjects below 40 years of age constituted 11.8% (N=11) and subjects over 70 years of age constituted 8.6% (N=8). The youngest age encountered was 27 and the oldest age was 77. Males constituted 89.25% (N=83) and females 10.75% (N=10) which again shows that males are more prone to coronary artery disease than females. The sex ratio in this trial was 8.3:1. The lowest age among females was 47 which again shows that coronary artery disease occurs later in age among females.

Time to reperfusion

The reperfusion time depends on two factors. The initial period is the symptom onset to presentation time which depends on the patient and his awareness of symptoms of coronary artery disease and the availability of quick transportation to reach the hospital. The later part is the door to needle time which depends on the availability of trained staff and a fully operational cardiac cauterization lab and an intensive cardiac care unit.

Various studies have shown that the shorter the reperfusion time, the better is the left ventricular function and lower the mortality. The Fibrinolytic Therapy Trialists Collaborative Group did a meta-analysis on 9 randomized trials which included over 58,000 patients and found a significant relationship between mortality benefit and time to reperfusion up to 12 hours. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) Trial has shown that there is mortality benefit up to a period of 12 hours with thrombolysis (5.3% at 2h, 5.9% at 2 to 4h, 8.5% at 4 to 6h and 8.9% at 6h).

The average time to reperfusion, which is the time from the onset of chest pain to start of thrombolysis or balloon dilatation was 5 hours and 30 minutes. Similar to GUSTO and other trials, this study has shown that maximum benefit occurred up to 6 hours after which some benefit was noted up to 12 hours but all patients who had a reperfusion time of more than 12 hours had an LVEF of < 45%.

Most of the patients in this study had a reperfusion time of 3 to 12 hours (N=69, 74.19%). This study shows that time to reperfusion has a significant association with LVEF. As time to reperfusion increases, the LVEF is significantly reduced. LVEF was < 45% in 17.18% of patients who had a reperfusion time of less than 6 hours (N=11, p = .001), 44% of patients with reperfusion time between 6 and 12 (N=11) and 100% of patients with reperfusion time of more than 12 hours (N=4).

Difference between PCI and Thrombolysis

Of the 93 patients in this study, 32 underwent primary PCI and 61 underwent thrombolysis. In patients with reperfusion time of less than 3 hours, 75% in PCI group had normal LVEF compared to 68.75% in thrombolysis group with no statistical significance (p =

0.657). In reperfusion time of 3 to 6 hours, 82.35% in PCI group had normal LVEF compared to 44.4% in thrombolysis group showing statistically significant difference (p=0.013).

When reperfusion time was 6 to 12 and more than 12 hours, 12.5% and 0% in PCI group and 41.17% and 0% in thrombolysis group respectively had normal LVEF with no statistical significance between the groups (p=0.166). This shows that maximum benefit of primary PCI over thrombolysis is obtained in those who have a reperfusion time of 3 to 6 hours. Similar results were obtained in the study done by Brodie et al which showed no significant difference between PCI and thrombolysis groups up to 6 hours but showed better outcome in PCI group from 6 to 12 hours. This was attributed to limitation of thrombolysis to first 6 hours previously when the trial was done.

The reason for presence of reduced LVEF as time to reperfusion increases may be due to the larger area of myocardium that is involved as the time of vessel non patency increases and also because of the fact that infarction zone expands as the previously stunned myocardium also begins to undergo necrosis as the duration of ischemia increases.

Difference between AW STEMI and non-AW STEMI

52 of the 93 patients who presented with STEMI had AW STEMI while the remaining 41 patients had lateral wall, inferior wall or posterior wall STEMI. When reperfusion time was less than 3 hours, 66.67% of AW STEMI patients and 71.42% of non-AW STEMI patients had normal LVEF showing no statistical significance (p=0.613). In those with reperfusion time of 3 to 6 hours, only 41.37% of patients with AW STEMI had normal LVEF compared to 93.3% of patients in non-AW STEMI group who had normal LVEF and was statistically significant (p=0.001).

When the reperfusion time was 6 to 12 hours, only 20% of AW STEMI and 50% of non-AW STEMI had normal LVEF and there was no statistical difference (p=0.128). None of the patients who presented after 12 hours in both groups had normal LVEF. This shows that AW STEMI patients develop reduced LVEF faster than non-AW STEMI patients and this difference is observed up to 6 hours. After 6 hours, non-AW STEMI patients also start developing reduced LVEF and as time progresses, have no statistical difference from those who have AW STEMI. The reason for higher incidence of reduced LVEF in AW STEMI may be due to the fact that AW STEMI puts a larger area of myocardium at risk.

Effect of Age on LVEF

53.76% of the patients in this study (N=50) were in the age group of 40 to 60 years. Subjects below 40 years of age constituted 11.8% (N=11) and subjects over 60 years of age constituted 34.4% (N=32). There was no statistical difference between various age groups and the development of LVEF. However, it was noted that older individuals had longer reperfusion times. All 4 of the patients who were above 70 years of age had a reperfusion time of over 12 hours. The reasons for this delay need to be evaluated.

Role of Diabetes in LVEF

Of the 93 patients enrolled in this study, 42 patients (45.16%) had diabetes mellitus which is higher than the 30% described in other trials. Statistical analysis of the data showed that there was no significant association between the presence of diabetes mellitus and the presence of normal LVEF or development of reduced LVEF. A study done by Alegria et al [39] showed that patients with diabetes only had a modestly increased size of the infarct and reduced LVEF

than non-diabetics. Diabetics are known to do poorly even after reperfusion with higher mortality compared to non-diabetics. The increased mortality among diabetics could not be explained by these moderate changes after MI in diabetics.

Symptomatic Heart Failure

Though 45 of the 93 patients (48.38%) had reduction in LVEF, only 20 of the 93 patients (21.5%) developed signs of heart failure based on the Framingham's criteria. To find out the reasons for development of signs and symptoms of heart failure in some but not all patients with reduced LVEF, a multiple regression analysis of the data was done.

Multiple regression analysis showed that factors such as age, sex, diabetes, hypertension, smoking, reperfusion time, number of vessels involved and LVEF were all together contributing to the development of signs and symptoms of heart failure. Among these, LVEF had the strongest correlation with the development of symptoms of heart failure. Some studies[40] have shown that time to reperfusion does not correlate strongly with development of heart failure since a significant part of the myocardium may only be stunned and not necrosed during the initial few hours.

LIMITATIONS

- Number of subjects enrolled in the study was small. Larger number may have shown statistical significance among the variables.
- The study did not include follow up left ventricular ejection fraction assessment even though it has been shown that LVEF improves at 6 months.
- Left ventricular ejection fraction assessment by echocardiography, though assessed by a single observer to avoid bias, is still not a very accurate method.
- Exact time of onset of chest pain is difficult to obtain from history. Incorrect data can lead to errors in statistical analysis of variables.

CONCLUSION

1. LVEF strongly depends on the reperfusion time. Longer reperfusion times lead to a significant reduction in LVEF
2. Primary PCI is superior to thrombolysis with streptokinase in terms of retaining a normal LVEF. This is very significant in those undergoing reperfusion between 3 and 6 hours of symptom onset.
3. Patients with reperfusion times of over 12 hours, irrespective of mode of revascularization or any other variables, have a significant reduction in LVEF.
4. AW STEMI patients tend to have higher incidence of reduced LVEF compared to non-AW STEMI. The percentage of patients with AWMI who had reduced LVEF was significantly higher than non AW STEMI group when time to reperfusion was between 3 and 6 hours.
5. Non-AW STEMI had better maintained LVEF compared to AW STEMI patients but this difference becomes insignificant when time to reperfusion exceeds 6 hours.
6. Even though older patients showed higher incidence of reduced LVEF, this was not significant.
7. Reason for longer reperfusion times in older individuals needs to be studied.
8. Presence or absence of diabetes had no significant relationship to the development of reduced LVEF after acute STEMI.
9. The number of vessels with more than 50% stenosis as seen during angiogram had no association to the development of reduced LVEF after acute STEMI.

10. Not all patients with moderate to severe reduction in LVEF developed signs of heart failure. Multiple regression analysis showed that there was significant association between developing signs of heart failure and other variables like age, sex, diabetes, hypertension, smoking, family history and number of vessels involved with the most significant variable being LVEF.
11. This study stresses the need for creating patient awareness about coronary heart disease to reduce symptom to door time and the need for hospitals with PCI facilities and a well-organized staff to reduce the door to balloon time thereby reducing the overall symptom to balloon time and preventing the development of reduced LVEF which is the most common cause of morbidity and mortality after an acute myocardial infarction.

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ANNEXURE I

List of Abbreviations Used

CAD	: Coronary Artery Disease
DM	: Diabetes Mellitus
SHT	: Hypertension
CVD	: Cardio Vascular Disease
ACS	: Acute Coronary Syndrome
MI	: Myocardial infarction
PCI	: Percutaneous coronary intervention
ECG	: Electro cardiogram
SMC	: Smooth muscle cell
CHD	: Coronary heart disease
STEMI	: ST elevation myocardial infarction
IHD	: Ischemic heart disease
AW	: Anterior wall
LVEF	: Left ventricular ejection fraction
LVD	: Left ventricular dysfunction
DALY	: Disability Adjusted Life Years

ANNEXURE II

Case Proforma

Name: Age: Sex:

IP No: OP No:

Diagnosis: AW / LW / IW / PW / RV STEMI Killip Class: I / II / III / IV

Risk Factors: DM / SHT / Smoker / Family History

Plan: PCI / Thrombolysis

Onset of Chest pain :

Time of presentation to EMD :

Time of start of thrombolysis/Balloon dilation :

Total symptom to needle/balloon time :

Presence of signs of HF during hospital stay: Yes / No

Use of diuretics during hospital stay : Yes / No

LVEF

Day 1: Day 5:

Vessels with >50% lesion: LAD LCX RCA RI

Complications:

Death: Yes / No

Master Chart:

S. No	Age	Sex			MI			Lysis	Onset to N/B	Killip	HF	Diu Retic	EF	EF	DM	SHT	Smoker	FH	Vessels			Death
			AW	LW	IW	PW	RV						D1	D5					LAD	LCX	RCA	
1	31	1	1	0	0	0	0	1	3.15	1	0	1	40	36	1	1	1	1	1	0	0	0
2	59	1	1	0	0	0	0	1	8.15	1	0	2	40	40	1	1	1	0	1	0	1	0
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76	56	1	1	0	0	0	0	0	5.58	1	0	0	60	63	0	0	1	0	1	1	1	0
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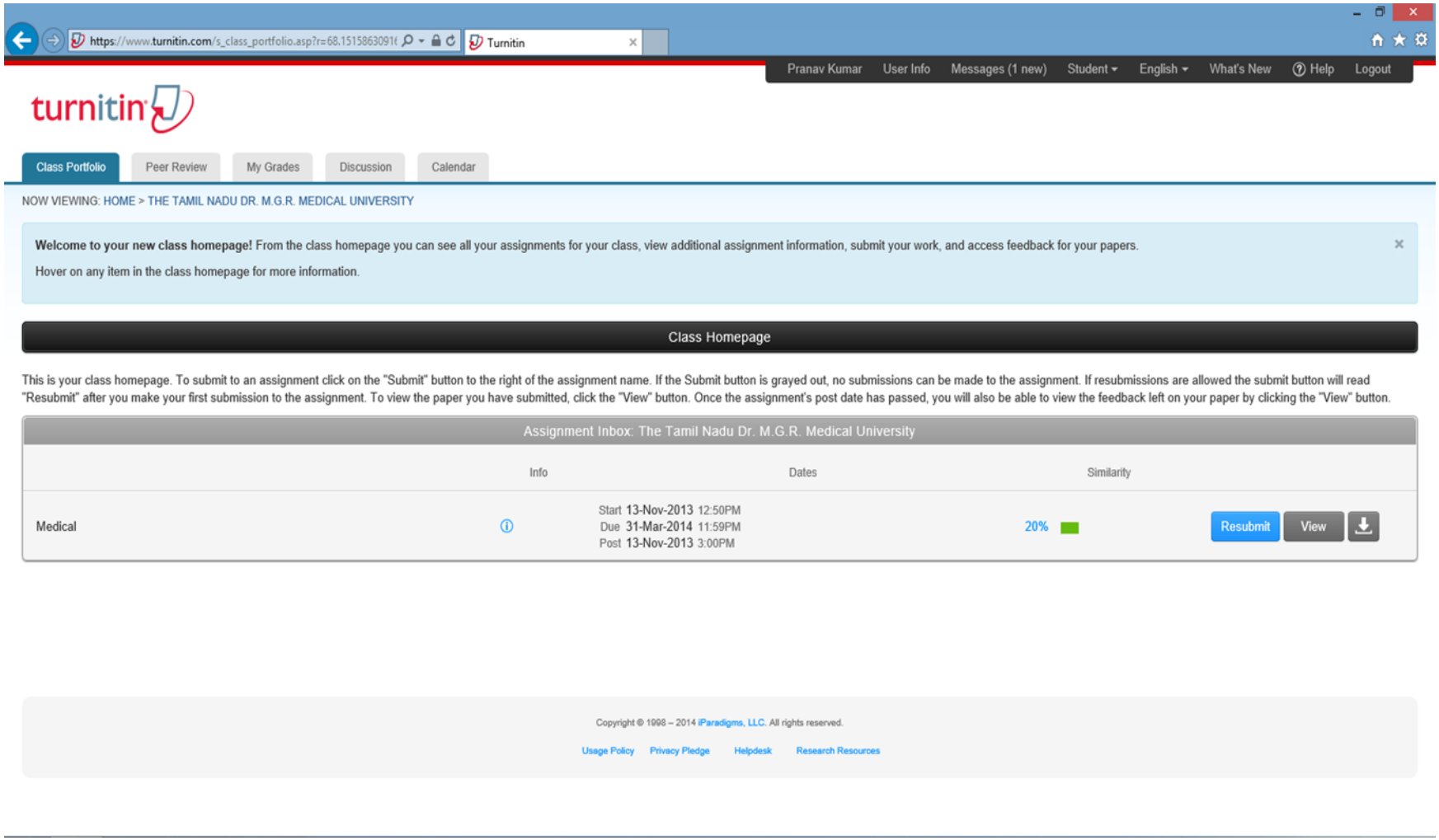
INTRODUCTION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INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and disability in developed and developing countries. As of 2012, CAD is the most common cause of death in the world [1] and also the major cause of hospital admissions [2]. Though high-income countries are seeing a fall in the incidence of CAD, low- and middle-income countries are seeing a very alarming increase in the rates of CAD, and this change is accelerating. In 2001, 75% of all global deaths and 82% of total DALYs lost due coronary artery disease occurred in low- and middle-income countries [3].

Mortality from coronary artery disease is expected to increase in developing countries (including India, China, Middle East, sub-Saharan Africa and Latin America), from an estimated 9 million in the year 1990 to a projected 19 million by the year 2020 [4]. It is thought that this projected increase is a consequence of social and economic changes in non-Western countries, which has led to an increased life expectancy, physical inactivity, changing/westernized diets, and an increase in cigarette smoking in these countries [5].