A STUDY ON FACTORS INFLUENCING THE OUTCOME OF THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

Dissertation submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600 032.

In partial fulfillment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I, PART - II
GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
KILPAUK MEDICAL COLLEGE
CHENNAI – 600 010.

SEPTEMBER 2006

CERTIFICATE

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ACKNOWLEDGEMENT

I am very much thankful to the Dean, Government Kilpauk Medical College, Chennai and Superintendent, Government Royapettah Hospital, for granting me permission to utilize the facilities of the hospital for the study.

I express my profound thanks to my esteemed Professor and Teacher **Prof. M. PADMANABAN, M.D.,** Professor of Medicine, Government Royapettah Hospital & Kilpauk Medical College, encouraging and extending invaluable guidance to perform and complete this dissertation.

I am deeply indebted to my respected and beloved Former Chief **Prof. S. TAMILVANAN, MD.,** Director (Retd.) Institute of Internal Medicine, Madras Medical College, Chennai, for being a constant Source of Inspiration.

I thank **Prof. K.S.SAIKUMAR, MD.,** Professor and Head of the Department, Department of Internal Medicine, Kilpauk Medical College Hospital, for his guidance and encouragement during this study.

I am also immensely grateful to **Prof. B. RAMAMURTHY, M.D., D.M.,** Head of the Department of Cardiology for his valuable guidance in conducting this study.

I also thankful to Assistant Professors of Cardiology **Dr. G. SUNDRAMURTHY M.D., Dr. C. RAMAKRISHNAN M.D., Dr. E. SURENDER M.D., Dr. S. KASIPANDIAN M.D., Dr. N. JAYAPRAKASH M.D.,** for their valuable suggestions during this study.

I wish to thank **Dr. M. SARAVANABHAVAN, MD., Dr. S. SUNDAR, MD., DCH, Dr. P. PARANTHAMAN, MD, DTCD., and Dr. G. RANJANI, MD.,** Assistant Professors, Department of Medicine, Government Royapettah Hospital, Kilpauk Medical College Hospital for their valuable suggestions.

I sincerely thank **Mr. S. PADMANABAN,** Research Officer (Statistics), ICMR, KMCH for his guidance in analyzing this study.

I thank all our Postgraduates, House Surgeons, Staff of our College for their contribution in this study.

Last, but not the least, I express my gratitude to all the patients, but for whose cooperation this study would not have been successful.

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ABBREVIATIONS

PAI-1	-	Plasminogen activator inhibitor-1
PDGF	-	Platelet derived growth factor
VWF	-	Von Willebrand factor
APSAC activator	-	Anisoylated Plasminogen Streptokinase complex
LBBB	-	Left bundle branch block
RBBB	-	Right bundle branch block
RCA	-	Right coronary artery
LCA	-	Left coronary artery
LCX	-	Left circumflex artery
PTCA	-	Percutaneous transluminal coronary angioplasty
SK	-	Streptokinase
RtPA	-	Recombinant tissue plasminogen activator
LV	-	Left ventricle
RV	-	Right ventricle
AMI	-	Acute myocardial infarction
VF	-	Ventricular fibrillation
VT	-	Ventricular tachycardia
CABG	-	Coronary artery bypass grafting
LAD	-	Left anterior descending artery
BMI	-	Body mass index

INTRODUCTION

Coronary heart disease has been defined as “Impairment of heart function due to inadequate blood flow to the heart compared to its needs, caused by obstructive changes in the coronary circulation to the heart”.

It is the cause of 25-30% of deaths in most of the industrialized countries. In India also it is a major public health problem.

It is aptly called by WHO as the modern epidemic. The increasing incidence of coronary heart disease may be a reflection of increased longevity, adoption of high fat diet, decreased exercise, made possible by increasing affluence.

It is not surprising to note that Sir. William Osler devoted only a few pages in his text book of medicine, published in 1982 to the discussion of Acute myocardial infarction.

It was the brilliant work of Herrick in 1912, who performed autopsy on Acute myocardial infarction patients that put forward the new concept of thrombotic occlusion of coronary artery as the cause of downstream necrosis of heart muscle.

Definite proof for the above said concept came from angiographic studies performed during the early hours of the Acute event.[2]

This prompted scientists to systematically test the thrombolytic strategies to treat Acute myocardial infarction, opening the new era of thrombolytic therapy in acute myocardial infarction.

Scientists have developed many effective thrombolytic drugs like, streptokinase, recombinant tissue plasminogen activator (rt PA) Reteplase (rPA), Urokinase, APSAC (Anisoylated plasminoses streptokinase activator complex), etc.

Evidence for the use of thrombolytic therapy came from large multicentre studies[3]. GISSI and ISIS-2 confirmed reduction in mortality with the early use of streptokinase[5].ISAM (Intravenous streptokinase in Acute myocardial infarction study group) also stands as a proof of efficacy of thrombolytic drugs to reduce mortality.

Success rate of thrombolysis and thus the overall reduction in mortality is different among different agents used[6]. The GUSTO-1 trial showed a 30 days mortality of 6.3% for accelerated t-PA versus 7.4% for streptokinase with intravenous heparin.

But because of the prohibitive cost of tPA, streptokinase became sheet anchor for thrombolytic therapy in Government Royapettah Hospital. Thrombolytic therapy has revolutionised the management of Acute myocardial infarction[7].

GUSTO angiographic substudy showed a success rate of 54% at 90 minutes using strephokinase and Heparin.

Thrombolytic therapy has been consistently proven to reduce the mortality and morbidity. Inspite of this it has been recognized that thrombolytic therapy has failed in a significant population. There is lot of room for improvement. We need to identify the factors that are responsible for failure of thrombolysis.

In this background, we decided to look into over own particulars who receive streptokinase for Acute myocardial infarction, in the coronary care unit of Government Royapettah Hospital.

AIM OF STUDY

1. To find out the overall success rate of thrombolysis in the coronary care unit of Government Royapettah Hospital.

2. To find out whether the following parameters influence the outcome of thrombolysis.

    a. Age

    b. Sex

    c. Body mass Index

    d. Smoking status

    e. Alcohol intake

    f. Diabetes mellitus

    g. Systemic Hypertension

    h. Pre infarction Angina

    i. Time window

    j. Location of myocardial infarction

REVIEW OF LITERATURE

HISTORICAL PERSPECTIVE

Although the anginal syndrome was described in the 1770's it was not until 1912 that Sir James B. Herrick described acute myocardial infarction.

In the landmark paper, Herrick wrote "The clinical manifestation of coronary obstruction will evidently vary greatly… depending on the size, location and number of vessels occluded. The symptoms and end results must also be influenced by blood pressure, by the condition of myocardium not immediately affected by obstruction, and by the ability of the remaining vessels to properly carryout their work as determined by their health or disease"[8].

Most of his observations hold good even after 90 years.

Levine published a book on coronary thrombosis in 1929.

Only after the classic angiographic study of De wood and colleagues from Spotane, who demonstrated thrombotic occlusion of coronary arteries in 87% of patients within 4 hours of symptom onset, medical community was convinced that the proximate cause of Acute myocardial infarction is coronary thrombosis[2].

PATHOPHYSIOLOGY OF ACUTE MYOCARDIAL INFARCTION

Coronary atherosclerosis is the underlying substrate in nearly all patients with Acute myocardial infarction.

The hallmark of atherosclerotic coronary artery disease is the fibrous plaque. It has a fibrous cap, composed of smooth muscle cells and matrix, which covers a variable amount of lipid core, cell debris, macrophages, which may be filled with lipid, often intermixed with variable number of T-lymphocytes.

Plaques are not uniform in their constitution. Plaque heterogeneity is important in that which plaque is prove to fissuring or cracking cannot be determined even by angiography.

Those plaques which have a thin fibrous cap, more number of macrophage and T cells, more lipid content and less number of smooth muscle cells are prove to rupture[9]. Smooth muscle cells appear to protect against plaque disruption, whereas macrophages and mononuclear cells, by elaborating proteolytic enzymes like matrix metallo proteinase, stromelysins, elastases tend to weaken the fibrous cap[10]. Mononuclear cells also elaborate monocyte chemotactic protein (MCP-1) which recruits more number of macrophages and mononuclear cells into the fibrous cap.

WHAT PRECIPITATES PLAQUE DISRUPTION?

It is now proved beyond doubt that acute myocardial infarction occurs as a result of disruption of a coronary artery plaque at a site of high density of inflammatory cells namely macrophages and T lymphocytes. Thus acute myocardial infarction can be thought of as resulting from acute exacerbation of a chronic inflammatory response. Precipitating factors work by exacerbating the inflammatory response and of increasing the physical focus impinging on coronary artery lesion weakened by inflammation, leading to rupture.

1. Infections

An association has been noted between Acute myocardial infarction and antecedent mild respiratory syndromes.

Increased antibody titre to C. pneumoniae have been associated with increased risk of acute myocardial infarctions[11].

Evidence exists for the presence of C. Pneumoniae in atherosclerotic lesions.

2. Emotional or Environmental stress

There was considerable higher incidence of Acute myocardial infarctions during scud missile attacks in the Gulfwar and Los Angeless earth Quake[12,13]. Sudden surges of

epinephrine may be the culprit by increasing the myocardial oxygen demand and also increasing the platelet aggregability.

3. Circadian and seasonal variation

Peak incidence of acute myocardial infarction is between 6 AM and noon. Underlying mechanism is thought to be the diuranal variation in sympathetic nervous system activity and thrombotic tendency.

In the morning hours there is an enhanced platelet aggregability and a trough in intrinsic fibrinolytic activity. Other factors contributing are the increased heart rate and increased coronary artery tone in the morning. PAI-1 levels in blood is highest in the morning hours.

THROMBUS FORMATION

Thrombus formation at the site of plaque disruption is the fundamental pathophysiological mechanism of unstable angina and acute myocardial infarctions.

ROLE OF PLATELETS

This may be reviewed in 3 heading

1. Platelet adhesions
2. Platelet Activation with granular release
3. Platelet aggregation

PLATELET ADHESION

Platelets adhere to the subendothelial collagen immediately. Glycoprotein 1b on the platelet membrane links with Von Willebrand Factor (VWF) in the subendothelial collagen. The membrane receptor complex glycoprotein IIb / IIIa bind a number of relevant protein, including VWF, fibrinogen and fibronection.

PLATELET ACTIVATION AND AGGREGATION

Activated platelets release a number of substances like serotonin, ADP, PDGF (Platelet derived growth factor), thrombospondin, VWF etc.

PDGF Plays a role in the proliferation and migration of smooth muscle cells after vessel damage. Released ADP binds to the specific receptors that change the conformation of Gp IIB/IIIa comoplex so that it binds VWF, fibrinogen, fibronectin, thus linking adjacent platelet into hemostatic plug.

COAGULATION CASEADE

Coagulation caseade plays a critical role in secondary hematosis. Both intrinsic and extrinsic system take part in this process.

SYSTEMIC FACTORS FAVORING THROMBOGENESIS

1. Catecholamines

Circulating catecholamines increases the platelet aggregability and thrombin generation.

Smoking and emotional factors may be operating by increasing the catecholamines levels in blood.

2. Elevated level of homocysteine

This is toxic to endothelium and it decreases the capacity of endothelium to make nitric oxide and includes endothelial dysfunction.

3. Diabetes mellitus

Apart from accelerated atherosclerosis, platelet activity and coagulation are increased in diabetics suggesting that it is a prothrombotic state. PAI-I levels are also found to be higher in diabetics.

4. Plasminogen activator inhibitor-1 (PAI-1)

High levels of PAI-I levels are associated with increased risk of Acute coronary syndromes.

5. Elevated apoliporpotein (a)

May serve as a competitive inhibitor of plasminogen and cause a prothrombotic stage.

6. Elevated fibrinogen and factor VII

Is yet another risk factor for thrombosis. Interestingly both are found to be elevated in advanced age, obesity, hyperlipidemia, diabetes, smoking and emotional stress.

FIBRINOLYSIS

Fibrinolysis starts at the same time of thrombogenesis because elements of the fibrinolytic system are incorporated into the fibrin thrombus as it forms.

COMPONENTS OF FIBRINOLYTIC SYSTEM

1. Plasminogen and plasmin

Plasminogen is a single chain glycoprotein synthesised primarily by liver. This is the precursor of the chief proteolytic enzyme plasmin. This conversion is facilitated by the binding of plasminogen to fibrin (thrombus). Plasmin is capable of proteolysing not only fibrin but also other proteins like fibrinogen, coagulation factors V, VIII, and extracellular matrix protein.

2. Plasminogen activators

Intrinsic activators of plasminogen are kallikrein and factor XIIa which are direct activators.

Extrinsic activators are tissue type palsminogen activator (t-PA), High molecular weight- two chain urokinase, and low molecular weight two chain urokinase.

Exogenous activators

Are used therapeutically in Acute myocardial infarction, Streptokinase, APSAC, belong to this category.

TISSUE TYPE PLASMINOGEN ACTIVATOR

t-PA is synthesised predominantly by vascular endothelial cells. It is a serine protease.

In the absence of fibrin, t-PA has little activity. Therefore t-PA mediated activation of Plasminogen in plasma is minimal. Both single chain and two chain form of t-PA have proteolytic activity that is enhanced several hundred fold in the presence of fibrin.

Free plasmin in the plasma is rapidly neutralised by CX2 plasmin inhibitor where as fibrin-bound plasmin is protected from X2- plasmin inhibitor.

UROKINASE TYPE PLASMIN ACTIVATORS

Urokinase is a serine protease that is synthesised in the kidney as well as in endothelial cells and initially released as a single chain urokinase or single chain-PA.

Limited proteolysis by plasmin converts single chain-PA to high molecular weight two chain urokinase (HMW two chain UK). Like t-PA, HMW two chain UK also has relative fibrin selectivity but it is enhanced only 10 times by the presence of fibrin.

ENDOGENOUS INHIBITORS OF FIBRINOLYSIS

These inhibitors of plasminogen activators and plasmin belongs to serpin family.

Plasminogen Activator Inhibitor (PAI - 1) Sources

Endothelial cells, hepatocyte, smooth muscle cells and platelets. It is stored in platelet α - granules from which it can be readily released upon platelet activation. PAI-1 is the predominant inhibitor of t-PA and urokinase in human plasma. It accounts for approximately 60% of the total plasminogen activator inhibitory capacity of plasma.

Thrombin induces PAI-1 release from cultured human endothelial cells; so also endotoxin. During inflammatory states PAI-1 levels are increased.

There is a diuranal variation in the circulating levels of PAI-1 concentration which contribute to the clustering of Acute Myocardial Infarction episodes during morning hours as well as morning resistance to thrombolytic therapy.

PAI-2 is found in placental tissue, where it plays a role in hemostasis.

ALPHA2-PLASMIN INHIBITOR

This single chain glycoprotein directly inhibits plasmin. It is synthesised and secreted from hepatocytes. It is also stored in platelet α granules. Alpha 2 plasmin inhibitor rapidly neutralizes free plasmin in plasma. Where as fibrin bound plasmin is protected from its action. Alpha-2 plasmin is incorporated into fibrin clots through cross-linking by factor XIIIa thereby preventing uncontrolled or premature fibrinolysis.

PROTEIN C ACTIONS

It inhibits the release of PAI – 1 from endothelial cells and inactivates PAI – 1, factor Va, VIIa.

REGULATION OF FIBRINOLYSIS

Net activation of plasminogen is the result of a delicate balance among activators and inhibitors and protease receptor on the cell surface. Regulation and control of fibrinolysis occurs at several levels. Secretion of plasminogen activator and also

plasminogen activator inhibitor from endothelium enhancement of plasminogen activation by f-fibrin and plasmin inhibiton by alpha 2 antiplasmin inhibition. In addition certain cell types such as endothelial cells, monocytes and platelets have receptors for plasminogen and plasminogen activators which when occupied enhance plasminogen activation and localize plasmin activity to the cell surface. By modulating the expressing of these cell surface receptors, cellular regulation of fibrinolysis is possible.

ACUTE MYOCARDIAL INFARCTION

Symptoms

Prodromal symptoms are common, most of these symptoms are anginal or anginal like, hours or days before the acute cardiac event.

Retrosternal chest pain, associated with nausea, diaphoresis and dyspnoea is the cardinal symptoms. Pain may radiate to medial aspect of left arm or to both arms, other sites of radiation are neck or lower jaw, to epigastrium and back.

Duration should be more than 15 minutes, occasionally presenting symptoms may be syncope, acute confusion, agitation, stroke or palpitations. Approximately 23% of Acute myocardial infarction go unnoticed by the patient because of

lack of symptoms. Elderly can present as congestive cardiac failure without any history of pain.

Physical Findings

Patient may have an anxious look. Sweating may be excessive.

Pulse rate normal or increased. Persistent sinus tachycardia beyond the initial 12-24 hrs is predictive of high mortality rate.

In patients with acute inferior wall myocardial infarction upto 60% of patients will be having bradycardia in initial hours.

Blood Pressure

Hypotension can occur in acute inferior wall infarction, with right ventricular involvement, and extensive anterior wall infarction with cardiogenic shock. Hypertension may be a feature of anterior wall acute myocardial infarction.

JVP

Elevated JVP is a feature of major RV infarction. Prominent ‘a’ wave may occur because of the decreased compliance of right ventricle. Kussmaul sign may also be seen in right ventricular infarction.

PRECORDIAL EXAMIANTION

Palpation

Palpation in the left lateral position may reveal a diffuse apical impulse rather than a localized impulse. Apex may be dyskinetic also. Decreased compliance of left ventricle may give rise to presystolic expansion of apex corresponding to the auscultatory S_4.

Auscultation

First and second heart sounds are often very soft because of decreased contractility, prolonged PR interval or both.

A fourth heart sound is often audible. Third heart sound is heard in probably only about 15-20% of acute myocardial infarction patients.

Ischemia of posteromedial papillary muscle can manifest as a crescendo decrescendo mid systolic murmur of mitral regurgitation. This murmur usually disappear after the first 12-24 hrs if it is soft. But a loud or moderate intensity murmur may persist much longer or may be permanent

DIAGNOSIS

Electrocardiography

Electrocardiographic criteria for diagnosing acute myocardial infarction are, in presence of chest pain any one of the following.

(i) New or presumably new Q waves (atleast-30ms wide and 0.20 mV deep) in atleast two leads in any of the following groups a) lead II, III, avF b) leads V_1-V_6 C) leads I & avL.

(ii) New or presumably new ST segment elevation or depression ≥ 0.10 mV measured 0.02 sec. after J point in two contiguous leads of the above mentioned lead combination.

(iii) New or presumably new complete LBBB.

Enzymatic Criteria

1. Serial increase and then decrease of plasma CK-MB with change of > 25% between two values.
2. CK-MB > 10-13 U/L or > 5% of total CK activity.
3. Increase in CK-MB activity > 50% between any two samples separated by atleast 4 hours.
4. If only a single sample available, CK-MB elevation > two fold.
5. Beyond 72 hours, an elevation of Troponin T or Troponin I or LDH-1 > LDH-2.

HEMODYNAMIC CLASSIFICATION OF AMI (KILLIP)

Killip classification is the most useful simple method to assign patients into hemodynamic classes.

Class I

No evidence of heart failure. 85% of Acute myocardial infarction patients present in this class.

Class II

Early evidence of heart failure manifested by, bibasilar rales (less than 50% of lung fields) 10% of people present in this category.

Class III

Frank pulmonary odema.

Class IV

Cardiogenic shock. Only 5% of people with Acute myocardial infarction presents in class III or IV category.

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

Immediately begin continuous cardiac monitoring for patients with suspected ischemic type of chest pain and obtain intravenous access.

Administer morphine, oxygen, nitroglycerine and aspirin to patients without contraindication.

THROMBOLYTIC THERAPY : INDICATIONS

Class I

1. In the absence of contraindications fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads.

2. In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new LBBB.

Class IIa

1. In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to STEMI patients with symptoms onset within the prior 12 hours and 12 lead ECG findings consistent with a true posterior MI.

2. In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to patients with symptoms of STEMI beginning within the prior 12 to 24 hours who have continuing ischemic symptoms and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads.

Class III

1. Fibrinolytic therapy should not be administered to asymptomatic patients whose initial symptoms of STEMI began more than 24 hours earlier.

2. Fibrinolytic therapy should not be administered to patients whose 12-lead ECG shows only ST-segment depression except if a true posterior MI is suspected.

CONTRAINDICATIONS

Absolute Contraindications

- Any prior intracranial Haemorrhage.
- Known structural cerebral vascular lesions (eg. Arterio venous malformation).
- Known malignant intracranial neoplasm (Primary or metastatic).
- Ischemic stroke with in 3 months EXPECT acute ischemic stroke with in 3 hours.
- Suspected aortic dissection.
- Active bleeding or bleeding diathesis (excluding menses).
- Significant closed head or facial trauma within 3 months.

Relative Contraindications

- History of chronic severe poorly controlled hypertension.
- Severe uncontrolled hypertension on presentation (SBP > 180 or DBP > 110 mmHg).
- History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications.
- Traumatic or prolonged (> 10 min). CPR or major surgery (less than 3 week).
- Recent (within 2-4 weeks) internal bleeding.
- Non compressible vascular punctures
- For streptokinase / anistreplase prior exposure (> 5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulant the higher the INR, the higher the risk of bleeding.

HISTORY OF THROMBOLYSIS

Human blood has long been known to contain fibrinolytic activity. Well over 110 years ago Denys and Zimmerman observed that the fibrin of human blood obtained from wet cupping dissolved in 12 to 24 hours. Dastre coined the term fibrinolysis.

The property of spontaneous thrombolysis was used by Yudin of Russia who used blood from fresh corpses (who were previously healthy; but died of accidents) for transfusion.

In 1933 Tillet and Garner at the John Hopkin's medical school demonstrated that filtrates of broth cultures of certain strains of hemolytic streptococcus contained a substance capable of inciting rapid fibrinolysis of human plasma clots. They named it streptococcal fibrinolysis.

Christensen renamed it streptokinase in 1945. He demonstrated that SK activates an inactive precursor of a proteolytic enzyme, later found to be plasminogen.

Streptokinase was clinically used first in 1947 by Tillet and Sol sherry in a young man who developed loculated bloody effusion in the left pleural cavity following pneumonectomy. The response was dramatic in that all the loculation were broken down and a lysed coagulum was drained.

First clinical trial for acute myocardial infarction recruited 24 patients and they found those treated early alter the onset of infarction did better than those treated late[16].

But only in 1977 FDA approved streptokinase and urokinase for clinical use in USA. Which opened the new era of reperfusion therapy.

THROMBOLYTIC DRUGS

NON FIBRIN SELECTIVE AGENTS

Streptokinase

It is a single chain polypeptide that lacks the serine residue required for enzymatic activity but it can activate plasminogen to plasmin after forming an equimolar complex with it.

Since it is not fibrin selective, extensive conversion of circulating plasminogen to plasmin occurs with subsequent depletion of fibrinogen, plasminogen and factors V and VIII from blood stream.

The accumulation of fibrin degradation products, depletion of circulating alpha 2 antiplasmin and hyperplasminemia that occur constitute a systemic lytic state.

Circulating half life of SK is 18-25 minutes. However the level of fibrinogen to less than 50% of baseline values persists for approximately 24 hours.

Antibodies to SK appear quickly and reaches high value by 5 days and remains above baseline for upto 30 months. So repeated administration is not recommended.

Adverse Effects

Hypotension is the most common adverse effect which ranges from 10-40% of SK administrations.

Allergic reactions reported included fever, chills, urticaria, rash, flushing and muscle pain.

Minor bleeding can occur especially from vascular puncture and access site. Manual compression for 30 minutes or until bleeding stops is usually effective.

Intracranial bleeding is the dreaded complication.

Total stroke incidence in GISSI / International Trial was 0.9%. In ISIS 3 trial it was 1%.

Mode of Administration and Dosage

1.5 million units of SK administrated over 1 hour is the standard regimen. More rapid administration can lead to hypotension and should be avoided.

UROKINASE

This is an endogenous trypsin like enzyme. It is a direct plasminogen activator. It is present in urine and occurs in two forms in blood and tissues as a high molecular weight form and low molecular weight form. It is non fibrin selective, producing a systemic lytic state similar to that produced by SK. It is non

immunogenic and can be administrated as an intravenous bolus or by infusion.

The recommended dose for Acute myocardial infarction is 1,500,000 unit bolus followed by 1,500,000 units given over 90 minutes.

RELATIVELY FIBRIN SELECTIVE AGENTS

Tissue plasminogen Activator (t-PA)

t-PA is an endogenous serine protease synthesised and secreted by human vascular endothelium and numerous other types of cells. Cloning and expression of t-PA gene in E-coli lead to the large scale production of recombinant t-PA since 1984.

Plasma T½ is only 5 minutes but fibrinolytic activity persists on and within clots for 7 hours. rt-PA is metabolised by liver. Plasminogen activator inhibitor-1 (PAI-1) rapidly inactivates t-PA. Infused rtPA rapidly saturates PAI-1 levels seen in blood. Other slow inhibitors of rtPA in blood are C_1 esterase inhibitor and alpha 2 antiplasmin.

rtPA is relatively fibrin specific, it has an affinity for fibrin bound plasminogen. But rtPA is also capable of depleting blood fibrinogen levels to as low as an 50% and elevating fibrinogen degradation products. It has no immunogenisity.

Adverse Effects

Incidence of intracranial hemorrhage and stroke is slightly higher with rtPA than with SK. In GISSI / International trial it was 1.2%. In ISIS-3 it was 1.4% (Total stroke incidence)

Dosage

Front loaded regimen is associated with 91%. Patency rate at 90 minutes and it is now approved by FDA. Here 15 mg IV bolus followed by 50mg IV infusion over 30 minutes followed by 35 mg over next 60 minutes is given.

EFFECTS OF THROMBOLYTIC THERAPY ON MORTALITY

Thrombolytic therapy reduces 35 day mortality by 21% compared with conventional therapy.

When used within the first hour of symptoms it serves 34 lives per 1000 treated patients but it is reduced to 16 lives per 1000 treated cases when used 7-12 hours after the onset of symptoms.

CHOICE OF DRUG

(30 day mortality rate from GUSTO Trial)

S.No.	Regimen	Mortality %
1.	SK and Subcutaneous heparin	7.2%
2.	SK and Intravenous heparin	7.4%
3.	Accelerated rt-PA and Intravenous heparin	6.3%
4.	Combination rt-PA and SK without Heparin	7%

14% reduction in mortality rate was achieved with accelerated rtPA regimen versus SK strategies (p=0.001).

1 year follow up of GUSTO-1 trial showed that the 1% lower mortality rate compared with SK was maintained, which provided further evidence that rt-PA is more effective than SK.

Alteplase (rt-PA) may have the greatest benefit in patients with large infarction and appears to be a low risk of intracranial haemorrhage in younger patients who present early. SK appears to provide greater benefit in older patients with as smaller amount of myocardium at risk, who present later and those with a greater risk to intracranial haemorrhage.

PATENCY OF INFARCT RELATED ARTERY

Angiography assessment

TIMI grading is used to assess the angiographic patency[17].

Grade of Flow	Definition
0	Complete occlusion
1	Penetration without perfusion. Coronary bed distal to occlusion fails to opacify completely.
2.	Partial perfusion. Full but slow opacification of coronary bed distal to occlusion
3.	Complete perfusion

The 90 minutes patency rate from GUSTO angiographic substudy was as follows; accelerated t-PA 81%. (54% grade III flow), combination treatment t-PA-SK 73% (38%- grade III flow) SK-IV Heparin 60% (32%-Grade III flow), SK- Subcutaneous heparin 54% (29% grade III flow)[6,7].

This clearly shows rt-PA is more effective than SK in bringing out a successful thrombolysis.

CLINICAL DETECTION OF REPERFUSION

Sudden disappearance of chest pain is associated with successful thrombolysis. But this is difficult to assess in the CCU setup when most of the patients receive opioid analgesics.

ECG : A BETTER PREDICTOR OF PERFUSION AT MICROVASCULAR LEVEL

Recent studies have suggested that achievement of TIMI grade 3 flow in infarct related artery is not in itself indicative of successful myocardial reperfusion[18].

Myocardial contrast echocardiography has shown that even in the presence of normal epicardial flow after PTCA, impaired myocardial perfusion at tissue level can occur and is associated with poor recovery of LV function.

Resolution of ST-segment elevation on the surface ECG correlated closely with findings at contrast echocardiography[18]. Less than 50% resolution of ST-segment elevation in the chest lead and no accelerated idioventricular rhythm has a sensitivity of 81%. Specificity of 88% and overall accuracy of 85% in predicting < TIMI 3 flow in infarct related vessels[20].

PROGNOSTIC SIGNIFICANCE OF ST RESOLUTION

James A-de-Lemos et al. reported that 30 days mortality was 2.4% among patients who attain < 70% ST resolutions at 90 minutes where as it was 8.1% in those with < 30% ST resolution[21].

Early and stable ST segment recovery is also associated with improved infarct zone wall motion at 48 hours[22].

FACTORS INFLUENCING THE SUCCESS OF THROMBOLYSIS

1. Time interval between pain onset to initiation of thrombolytic therapy

This is the most important variable affecting the success of thrombolysis.

As time window broadens not only more and more myocardium gets necrosed but also the thrombus gets organized and become more resistant to lysis.

2. Structure of thrombi

Thrombi rich in platelets are more resistant to lysis than fibrin rich thrombi.

3. Circadian fluctuations

A morning resistance to thrombolytic therapy was observed by Braunwald et al.[23]. where as better success rate of thrombolysis was found by E Gold Hammer et al. when SK was administered between 16.00-20.00 hours.

4. Pre infarction Angina

Patients with acute myocardial infarction who have intermittent infarct related pain or unstable angina in the seven days preceding the infarction have faster coronary artery

perfusion and smaller infarcts after thrombolytic therapy than patients without pre infarction angina[24].

This may be an additional mechanism for the better prognosis in these patients, the other proposed mechanism being ischemic preconditioning.

5. Sex

Even though mortality is high among women who develop acute myocardiac infarction. Compared to men, the rate of induction of coronary patency with thrombolytic drugs are comparable in women.

Menstruation is not a contraindication for thrombolysis therapy because menstrual bleeding is related more to sloughing of tissue than active bleeding.

6. Congestive heart failure and cardiogenic shock

No significant reduction in mortality occurs when Killip class IV patients are treated with SK. This may partly be due to low rate of adequate recanalisation.

7. Elderly patients

Risk of hemorrhagic complications are high in those aged above 75 years. But the relative benefit seen with coronary thrombolysis is greatest for the elderly.

REPERFUSION INJURY

Refers to detrimental metabolic, functional or structural consequence of restoring coronary flow that might be reduced, avoided or reversed by modifying the condition of reperfusion.

LETHAL REPERFUSION INJURY

Refers to the death of myocardium that were still alive at the initiation of reperfusion. The mechanisms underlying the lethal reperfusion injury may be.

1. Ischemia causes an intracellular osmotic load of accumulated metabolites like lactate inside the cardiac myocytes leading to an increase in the osmolality of cytosol. After reperfusion enough plasma water bathes these cells. Osmotic diffusion of water into the cell causes rupture of cells.

2. Cellular acidosis increases the intracellular excess of calcium, via Na-H+ exchange and Ca-Na+ exchange. This calcium overload causes myofibrillar hypercontraction and rupture of sarcolemma.

3. Excess free radical formation may damage the myocyte structure including sarcolemma.

NON LETHAL REPERFUSION INJURY

Stunning

It is a form of reversible post ischemic contractile dysfunction.

Reperfusion arrhythmia

It also considered a form of non lethal reperfusion injury.

EFFECT OF REPERFUSION ON INFARCT REPAIR

Clinical studies has revealed that thrombolytic reperfusion performed more than 6 hours after symptom onset could still improve ventricular function and survival even though myocardial salvage need not be responsible for this effect.

This has been attributed to faster healing, reducing the complication like infarct expansion, aneurysm, as well as cardiac rupture.

Reperfusion gives inflammatory cells access to the infracted region, with resultant degradation of dead cells which must be removed in order for repair to occur.

PATIENTS AND METHODS

PLACE OF STUDY

This study was conducted in the coronary care unit of Government Royapettah Hospital, Chennai.

PERIOD OF STUDY

From January 2005 to August 2005.

DESIGN

Observational prospective cohort study of patients receiving streptokinase for acute myocardial infarctions. A total of 115 patients were included in the study.

METHODOLOGY

A. Subject selection

1. Inclusion criteria

a. Presence of typical chest pain suggestive of Acute myocardial infarction along with ECG evidence of Acute myocardial infarction. Criteria for thrombolysis being 2mm or more ST elevation in two contiguous pericardial leads or 1mm or more ST elevation in two contiguous limb leads. ECG were recorded using Hewlett. Packard Page write 100 machine.

b. Time window of 12 hrs from the onset of pain to the initiation of thrombolysis.

2. Exclusion criteria

a. Late thrombolysis (more than 12 hrs from the onset of pain)

b. Recurrent myocardial infarction

c. Presence of bundle branch block

d. Development of pericarditis

DRUG THERAPY

- All patients received streptokinase 1.5 million units in 100ml of normal saline over 60 minutes.
- Aspirin was given to all patients.
- Use of heparin, β blockers, ACE inhibitors was according to CCU protocols, which was in accordance with ACC/AHA recommendations.

CRITERIA FOR SUCCESSFUL THROMBOLYSIS

Success was defined by

Clinical complete subsidence of chest pain.

Electrocardiographically – more than 50% ST resolution in a lead which showed maximum ST elevation initially. ST Elevation is measured manually, 80ms after J point from isoelectric line. Preceding PR segment is taken as isoelectric line.

Patients were analysed for success at thrombolytic therapy at 90 minutes after initiation of thrombolytic therapy, applying the above mentioned criteria.

The following parameters were analysed among them to know whether they influenced the outcome of thrombolysis.

- Age
- Sex
- Body mass index
- Smoking status
- Alcohol intake
- Diabetes mellitus
- Systemic hypertension
- Pre infarction Angina
- Time window
- Location of myocardial infarction

DEFINITIONS

Body Mass Index

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height}^2 \text{ (meter)}}$$

S.No.	Body Mass Index (Kg/m^2)	Grade
1.	< 18.5	Under weight
2.	18.5 to 24.9	Normal weight
3.	25.0 to 29.9	Over weight
4.	30.0 to 34.9	Class 1 Obesity
5.	35.0 to 39.9	Class II Obesity
6.	≥ 40.0	Class III Obesity

A BMI between 25 and 30 should be viewed as medically significant and worthy of therapeutic intervention, especially in the presence of risk factors that are influenced by adiposity, such as hypertension and glucose intolerance.

Smoking

Patients are considered smokers if they were using tobacco for smoking in any form currently. Ex. Smoker were defined as those who quitted smoking for more than 1 year back from the date of admission.

Diabetes mellitus

Patients were considered to be diabetic when

1. Currently on oral hypoglycemic drugs and/or insulin or
2. Fasting plasma glucose > 126 mg% or 2 hr post prandial plasma shows > 200mg on more than 2 occasions.

Hypertension

Patients were considered hypertensives when

They are already on antihypertensive medications

Medically documented history of blood pressure elevation more than 140/90 mmHg, on two occasions in the past.

Pre infarction angina

Was defined as history of anginal pain during the preceding 7 days of the active event causing hospital admission.

Location of myocardial infarction

Inferior wall infarction

Patients with ST elevation, with or without Q wave in Leads II; III; aVF are considered to have inferior wall infarction.

Anterior wall infarction

Those people showing ST elevation with or without Q wave in any two contiguous leads from V_1-V_6 and L1 and aVL are considered to have anterior wall infarction.

FOLLOW UP

Patients were followed by until they were discharged from the hospital. ECHO was done whenever possible.

STATISTICAL METHOD

Univariate analysis was done by chi-square test and multivariate analysis by logistic regression, was done using SPSS windows computer software.

OBSERVATIONS

A total of 115 patients were studied. Their age ranged from 31-76 years (mean 53.44). 94 of them were males (81.74%) and 21 females (18.26%). 60 of them were hypertensives (52.17%) 46 were diabetic (40%). 67 people were smokers (58.26%) and 38 (33.04) used to consume alcohol. 68 (59.13%) of them were overweight BMI ≥ 25. 28 patients experienced pre infarction angina (24.35%). 66 patients had anterior wall infarction (57.39) and 49 patients (42.61) had inferior infarction.

DETAILS OF STUDY POPULATION

Total Number of Patients - 115

TABLE – 1

SEXWISE DISTRIBUTION

S.No.	Sex	Number	Percentage
1.	Male	94	81.74%
2.	Female	21	18.26%

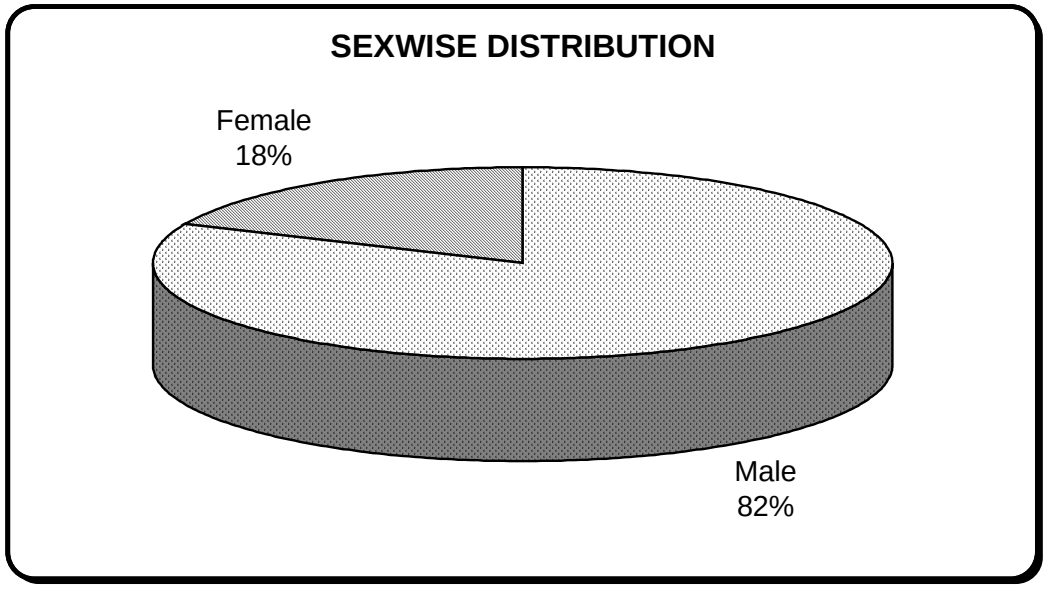


TABLE – 2

AGEWISE DISTRIBUTION

S.No.	Sex	Number	Percentage
1.	< 60 years	76	66.09%
2.	≥ 60 Years	39	33.91%

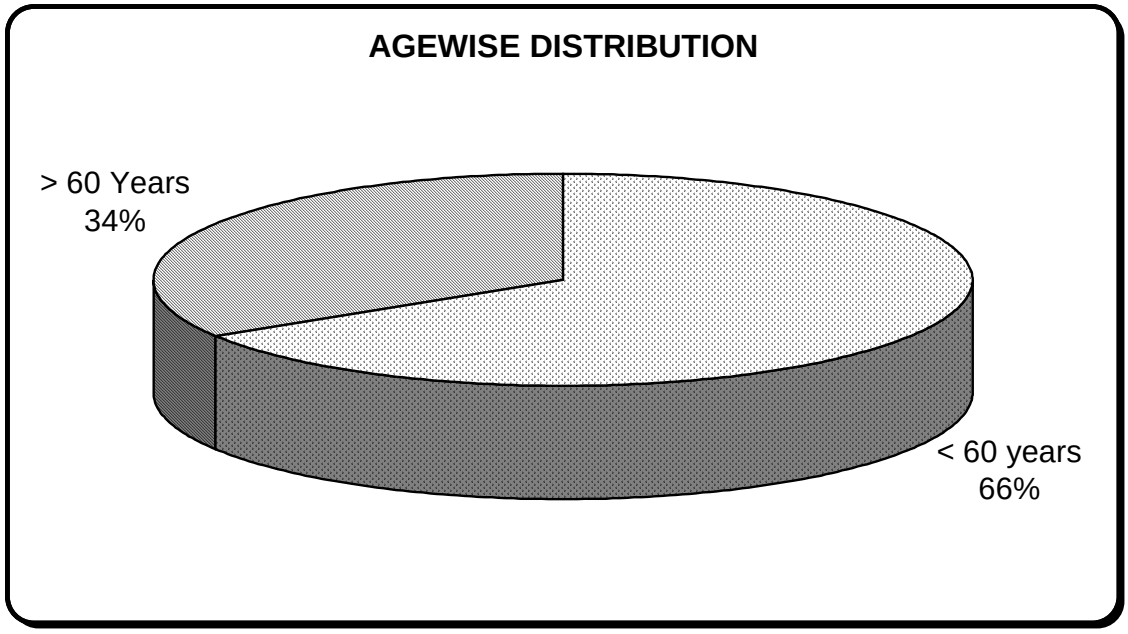


TABLE – 3

SOCIO ECONOMIC STATUS

S.No.	Family Income	Number	Percentage
1.	< 1500	71	61.74%
2.	1501 – 3000	40	34.78%
3.	3001 – 5000	4	3.48%

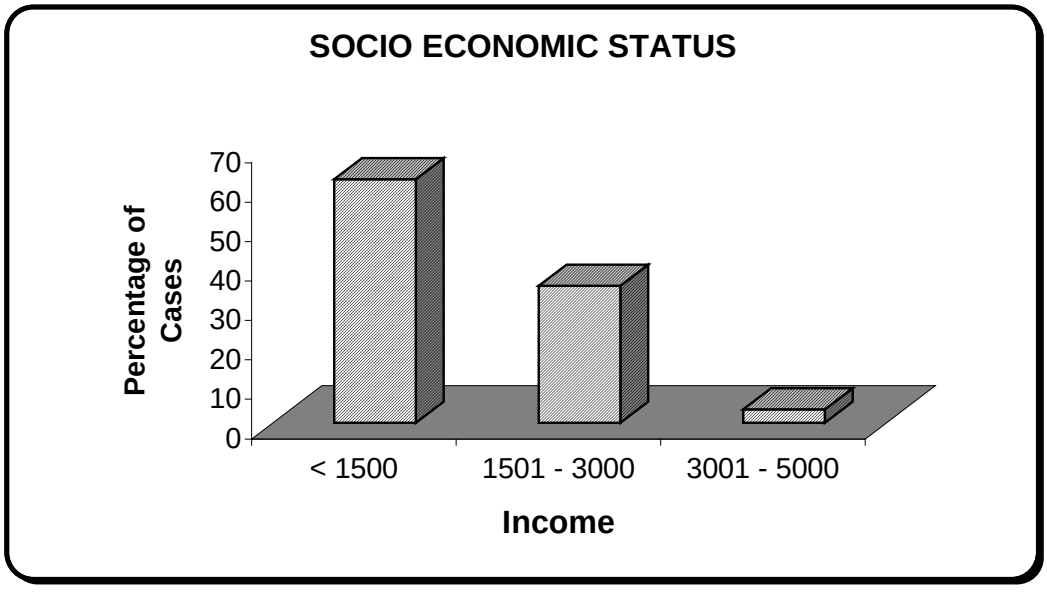


TABLE – 4

BODY MASS INDEX

S.No.	BMI (Kg / M²)	Number	Percentage
1.	< 24.9	47	40.87%
2.	≥ 25	68	59.13%

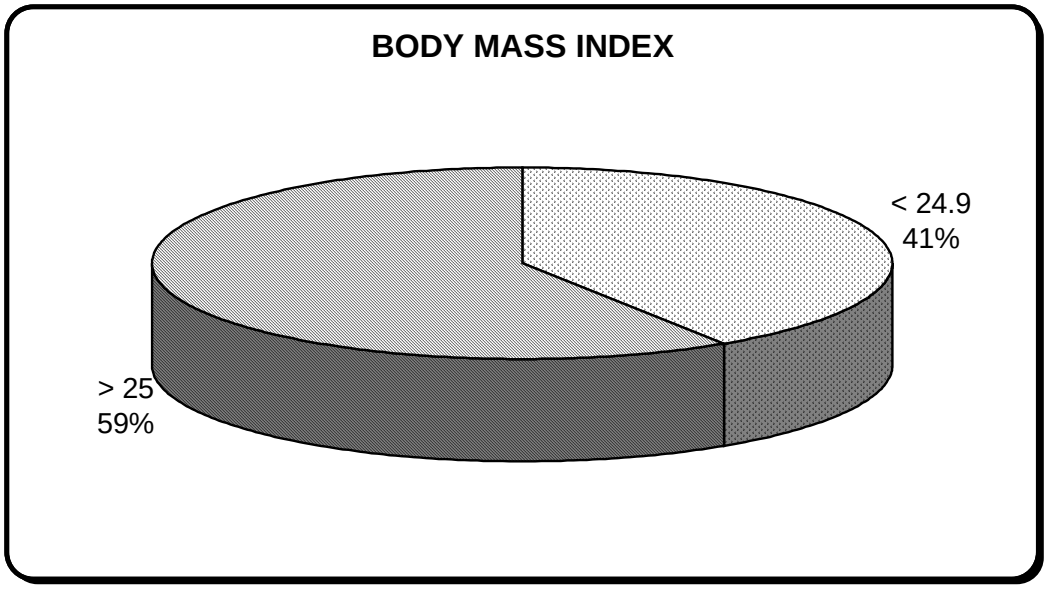


TABLE – 5

RISK FACTORS

S.No.	Risk Factors	Number	Percentage
1.	Smoking	67	58.26%
2.	Alcohol	38	33.04%
3.	Diabetes	46	40%
4.	Hypertension	60	52.17%
5.	Pre infarction angina	28	24.35%

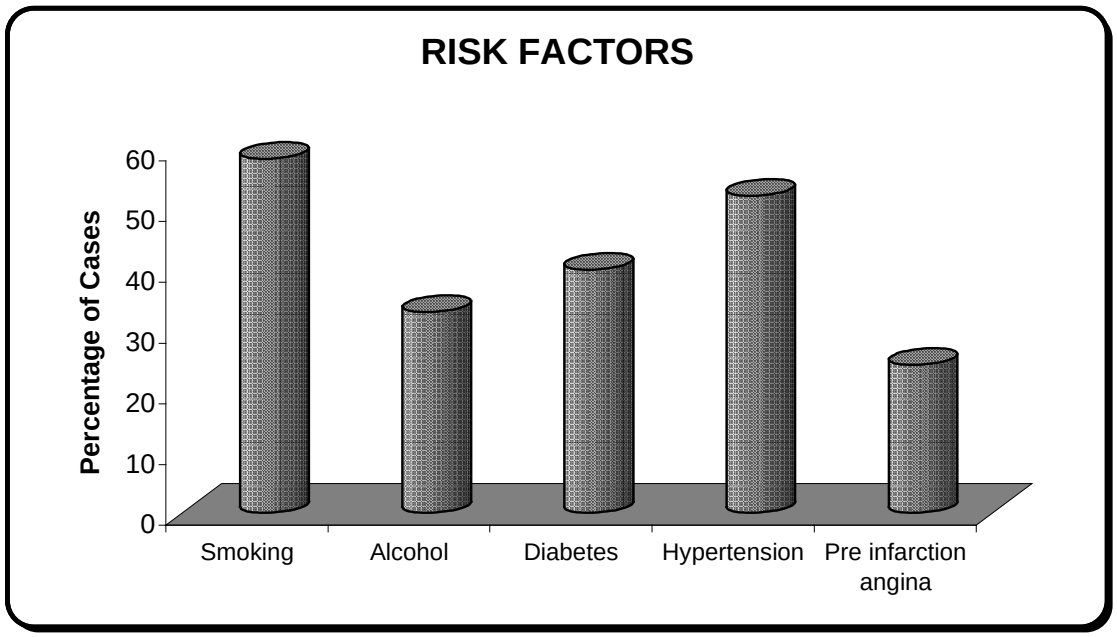


TABLE – 6

TIME WINDOW

S.No.	Time Window	Number	Percentage
1.	0-4 hours	64	55.65%
2.	4-8 hours	33	28.70%
3.	8-12 hours	18	15.65%

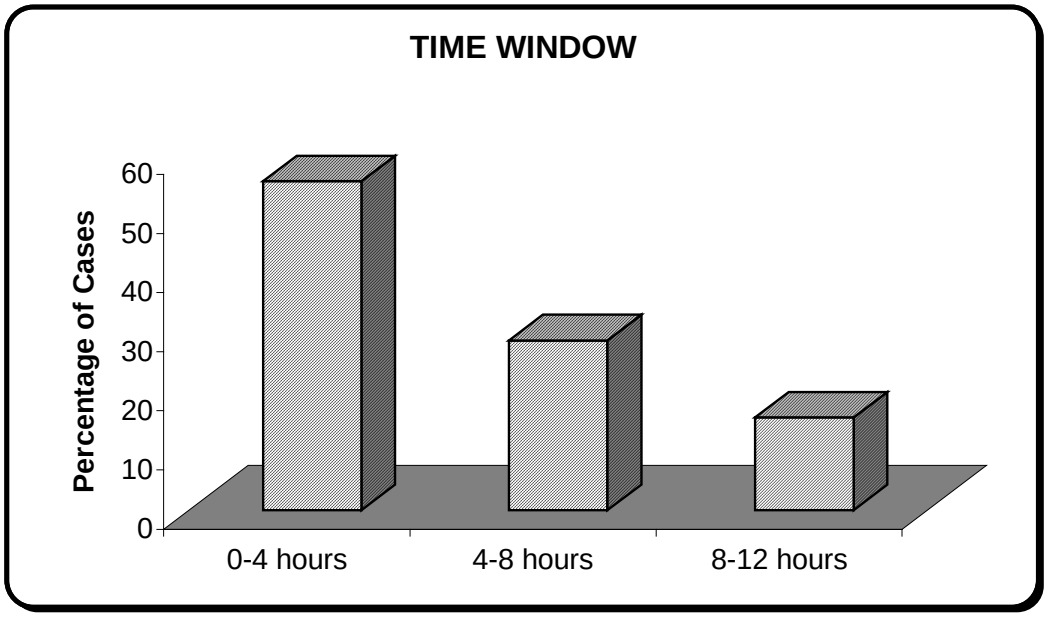
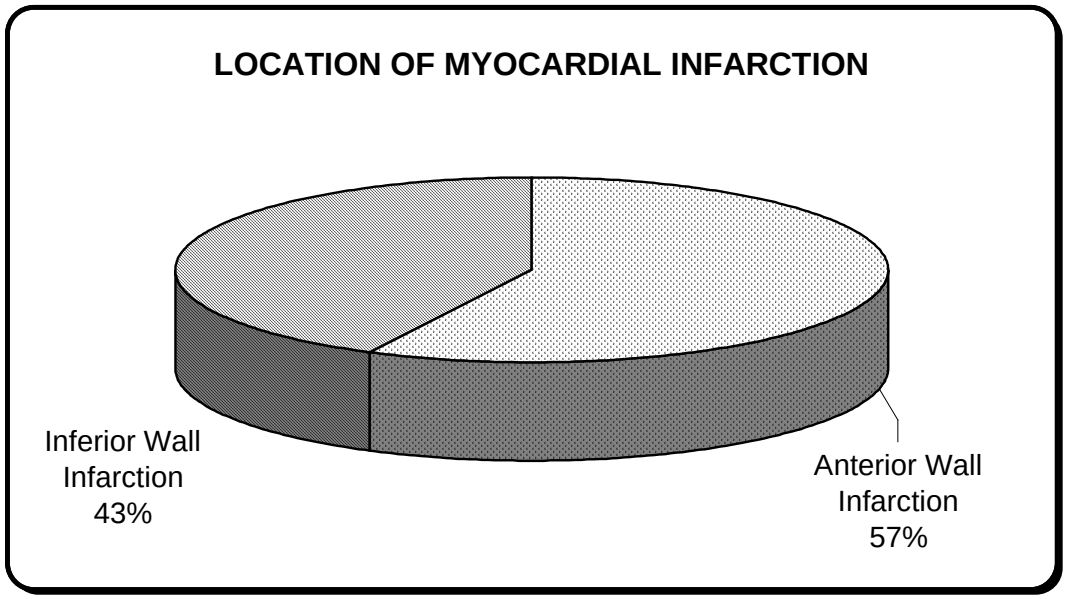


TABLE – 7

LOCATION OF MYOCARDIAL INFARCTION

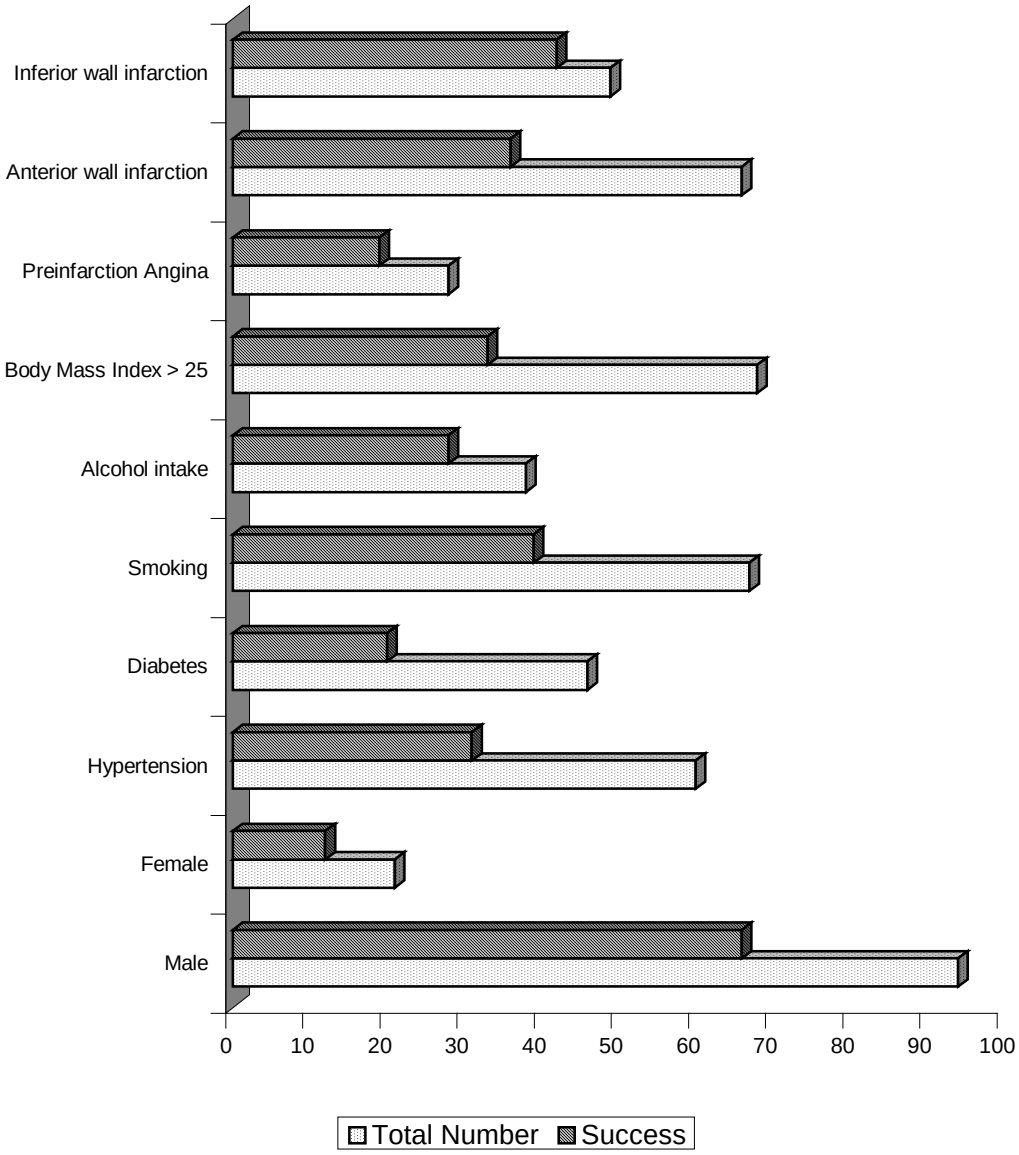
S.No.	Myocardial infarction	Number	Percentage
1.	Anterior wall infarction	66	57.39%
2.	Inferior wall infarction	49	42.61



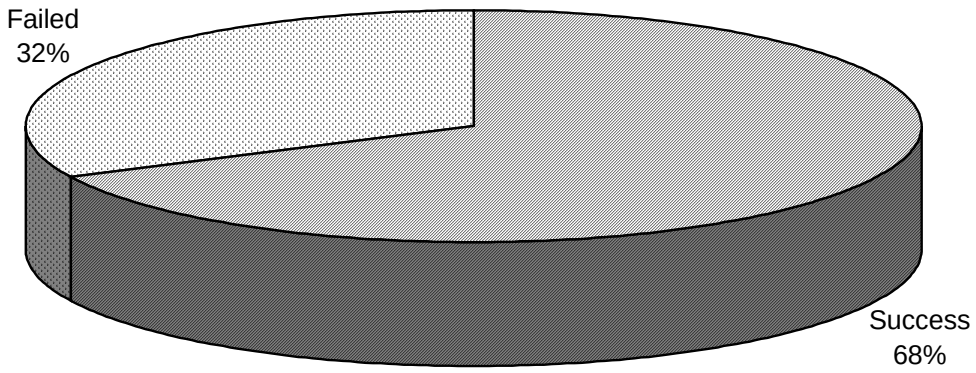
CLINICAL DETAILS OF STUDY POPULATION ACCORDING TO THE OUTCOME OF THROMBOLYSIS

Variables	Success	Failure
Number	78 (67.83%)	37 (32.17%)
SEX		
Male	66	28
Female	12	9
AGE		
< 60 years	52	24
≥ 60 years	26	13
BMI (Kg / m^2)		
< 24.9	45	2
≥ 25	33	35
Smoking	39	28
Alcohol	28	10
Diabetes	20	26
Hypertension	37	23
Pre infarction Angina	19	9
TIME WINDOW		
0 – 4 hours	51	13
4 – 8 hours	20	13
8 – 12 hours	7	11
LOCATION OF MI		
Anterior wall infarction	36	30
Inferior wall infarction	42	7

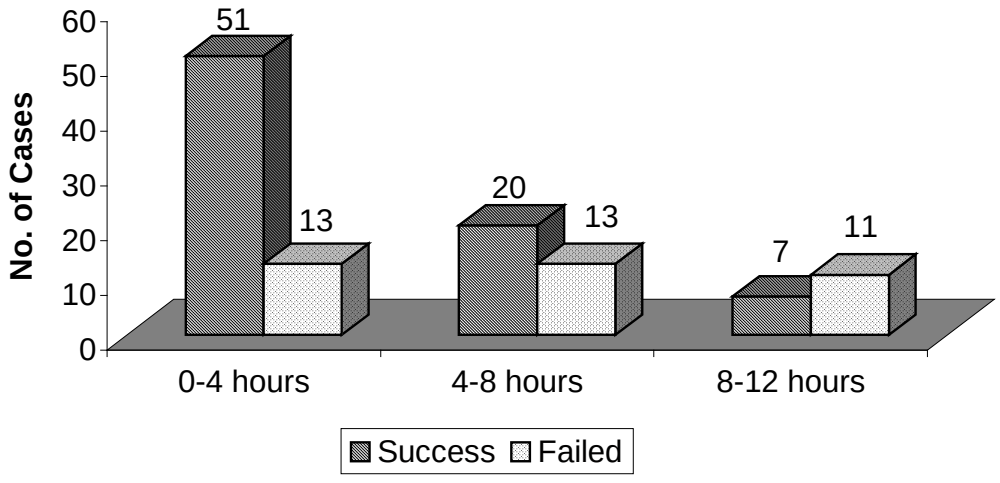
SUCCESS RATE WITH RESPECT TO INDIVIDUAL VARIABLES



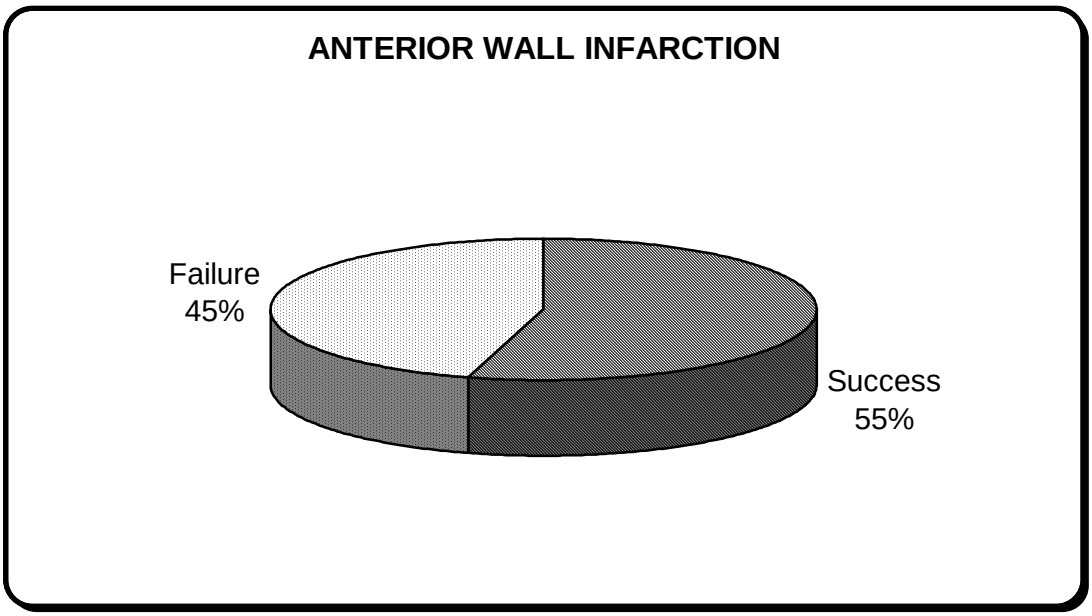
OUTCOME OF THROMBOLYSIS
(Total No. of Patients 115)

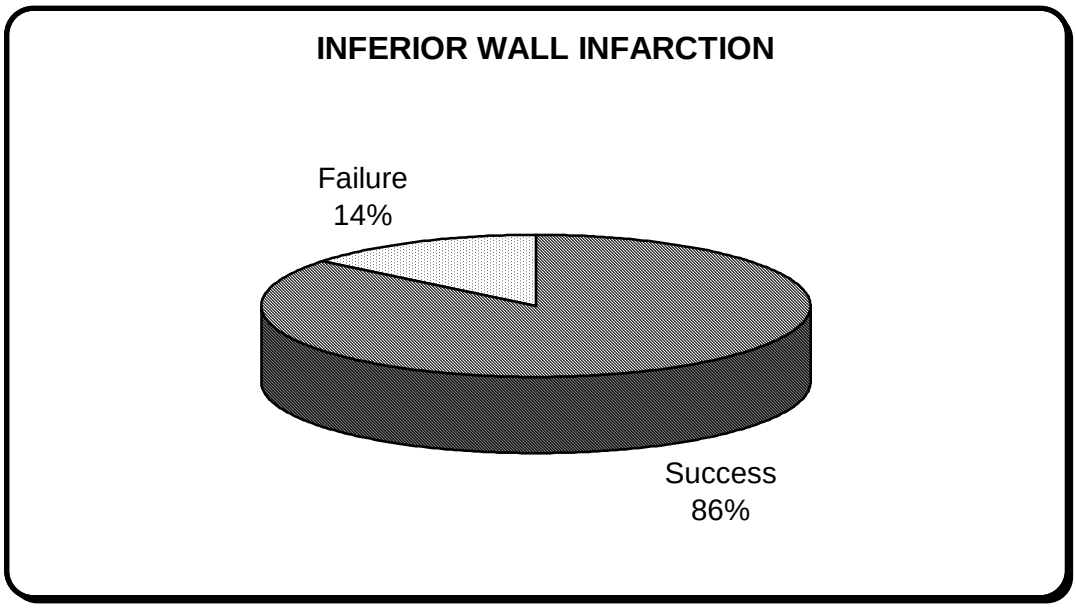


TIME WINDOW VS OUTCOME



SUCCESS RATE OF THROMBOLYSIS IN ANTERIOR AND INFERIOR INFARCTIONS





UNIVARIATE ANALYSIS FOR INFLUENCING

FACTORS

Sl. No.	Variable	Odds Ratio	X_2 chi-square	P value	Comment
1.	Gender	0.57	1.34	0.57	Not Significant
2.	Age	1.08	0.04	0.848	Not Significant
3.	BMI	23.86	28.39	0.000	Significant
4.	Smoking	3.11	6.80	0.009	Significant
5.	Alcohol	0.66	0.89	0.345	Not Significant
6.	Diabetes	6.85	26.83	0.000	Significant
7.	Hypertension	1.82	2.18	0.139	Not Significant
8.	Pre infarction Angina	1.00	0.00	0.996	Not Significant
9.	Time Window				
	0-4 hours	0.29	9.30	0.002	Significant
	4-8 hours	1.57	1.11	0.290	Not Significant
	8-12 hours	4.29	8.19	0.004	Significant
10.	Location of myocardial infarction				
	Anterior wall	5.00	12.52	0.004	Significant
	Inferior wall	0.20			

MULTIVARIATE ANALYSIS OF COMBINATION OF FACTORS INFLUENCING THE OUTCOME OF THROMBOLYSIS

We have individually tested the variables with outcome. Since we have multiple variables we have used logistic Regression Analysis for testing the significance of combination of variables with outcome.

LOGISTIC REGRESSION ANALYSIS

S.No.	Variable	Significant (P Value)	Odds ratio (Multivariate)
1	BMI ≥ 25	0.001	33.049
2	Smoking	0.000	0.071
3	Diabetes	0.001	12.206
4	Time Window (4 to 12 hrs)	0.072	3.112
5	Anterior wall infarction	0.001	0.067

We have found only the above five variables were statistically significant in deciding the outcome of the thrombolysis. Of these patient with BMI ≥ 25 have 33 times more chance of failure than patient with BMI < 24.9. Diabetes have 12 times more chance of failure than non diabetics. Patients presented late > 4 hrs have 3 times chance of failure than those presented ≤ 4 hrs.

DISCUSSION

The major finding of this study is that the location of the infarct significantly affects the outcome of thrombolysis. Those with anterior wall myocardial infarction have a 5 times chance of undergoing failure of thrombolysis compared to inferior wall myocardial infarction (P=0.004) This is after adjustment for all confounding variables like time window, age, smoking status, index, diabetes and hypertension.

Similar[25] observations were made by Gibson, Murphy and Braunwald et al. (TIMI Study group). Then found that TIMI grade III flow rates were lower for left coronary and circumflex artery compared to right coronary artery after thrombolytic therapy.

The reason for this differential response will be evident when we look into physiology of coronary circulation in right and left coronary arteries.

Blood flow in right coronary artery is relatively independent of phases of cardiac cycle, being present in both systole and diastole. Where as flow in left coronary artery is almost absent during systole and may even be reversed in

conditions of heightened microvascular tone and left ventricular hypertrophy[26].

The relatively thicker wall, the increased wall thickening during systolic contraction and higher intracavitary pressure of left ventricle may all produce higher intramyocardial pressure that is observed in the thinner walled right ventricle, which is also subjected to lower filling pressures.

Moreover the extent of necrosis in anterior wall is more resulting in increased myocardial edema compared to inferior infarctions. This may further decrease the reperfusion rates in anterior infarctions. Yet another mechanism may be, better drug delivery to right coronary artery and prolonged contact of streptokinase with the thrombus, resulting in more efficient fibrinolysis.

ALCOHOL AND THROMBOLYSIS

Alcohol consumption has no influence in the outcome of thrombolytic therapy in our study. OR = 0.66, X_2= 0.89, P= 0.345, which is statistically not significant.

Alcohol is known to reduce coronary artery disease related mortality. In a meta analysis of all experimental studies that assessed the effects of moderate alcohol intake on concentrations of HDL cholesterol, apolipoprotein A1, fibrinogen, triglycerides and other biological markers, Rimm,

William, Fosher et al.[27]. Concluded that 30g of alcohol per day would cause an estimated reduction of 24.7% in risk of coronary artery disease.

INFLUENCE OF AGE OF THE PATIENT ON THROMBOLYSIS

Age has got no influence in the outcome of thrombolysis in our study X_2=0.04, OR=1.08, P= 0.848, which is statistically not significant.

This shows that with respect to fibrinolysis elderly people do not behave differently from younger people. This is reflected in reduction mortality rate among elderly with thrombolysis. In patients aged more than 75 years who were treated with streptokinase in GISSI-2 trial, there was a reduction of 4.2 fewer deaths per 100 patients than in controls. In ISIS-2 there was 3.3 fewer deaths per 100 patients in those over 70 years of age who were treated[4].

GENDER

No statistically significant difference was noticed based on gender. Wood field, Lunderberg, Topol et al.[30], performed as angiographic study to findout the patency rate at 90 minutes in men versus women.

At 90 minutes TIMI-3 flow rate was 39% in women and 38% in men, which was not statistically significant. But 30 day mortality was 13.1% in women versus 4.8% in men (p= 0.001)

Thus even though females have a poor outcome after myocardial infarction, they do not behave differently to thrombolytic therapy.

BODY MASS INDEX

Patients with BMI ≥ 25 have more chance of failure of thrombolysis than patient with BMI < 24.9. OR = 23.86, X_2 = 28.39, P = 0.000 which is statistically highly significant.

Similar observations made by Lundergan CF, Reiner JS, McCathy WF, et al. They described the increasing the body weight is associated with a reduced likelihood of successful (TIMI grade 3 flow) infarct related artery reperfusion 90 minutes after thrombolysis[35].

The higher the BMI group, the higher the prevalence of hypertension, diabetes mellitus, history of familial coronary disease and hyperlipidemia.

DIABETES MELLITUS

In this study success rate of thrombolysis in diabetics is found to be different from non diabetic population.Univariate

analysis shows Odds ratio=6.85,X2=26.83,P value=0.000, which is statistically significant.

Gray, Yudkin et al. found a reduction in reperfusion rates in thrombolysed diabetic patients[31].

Diabetes is a prothrombotic state as reflected by the increased blood levels of fibrinogen, factor VII, and Von Willebrand factor. These changes are even more increased if diabetic people happened to be smokers.

Platelet function is also impaired in diabetics. They aggregate more readily to stimuli like ADP and collagen. Glycation of membrane proteins due to chronic exposure to high blood glucose levels[32], change in fluidity of platelet membrane brought out by high concentration of cholesterol and triglycerides are the proposed mechanisms for these abnormalities.

On the otherhand patients with type II diabetes have profound suppression of fibrinolysis. Plasminogen activator inhibitor-1 levels are high in type II diabetic people which is responsible for this effect.

Nevertheless thrombolytic therapy should be administered to diabetics with Acute myocardial infarction, because for every 100 diabetic patients treated with thromoblytic drugs four lives are saved.

PRE INFARCTION ANGINA

Andreoti; Vincenzo et al. had demonstrated by angiographic method that those acute myocardial infarction patients who experienced preinfarction angina within seven days preceding the acute event had a more rapid thromoblysis. Potency rates were higher at 35 minutes but at 90 minutes both were same[33].

In this study success rate was same at 90 minutes in both groups. This is because ECG monitoring was not continuous in this study. Continuous ST segment monitoring may be needed to demonstrate the early achievement of patency in pre infarction angina patients.

SMOKING

Outcome of thrombolysis is affected by smoking. In this study there is a statistically significant trend towards a bad out come[34]. Odds ratio=3.11,X2=6.80,P=0.009 which is statistically significant. Smoking increases blood hematocrit, fibrinogen levels and platelet levels contributing to the hypercoagulable state promoting coronary thrombosis, smokers are also found to have lesser fibrinolytic activity than non smokers.

CIRCADIAN VARIATION

Eugene[23] Braunwald et al. noticed a circardian variation in efficacy of thrombolytic therapy, with better patency rates in the evening hours. This is due to circadian variation in the blood levels of PAI-1, which is highest in the morning hours.

In this study no such circadian variation was observed. Probable reasons for this discrepancy may be the shorter time window observed in patients presenting in morning homes as well as smaller sample size.

PAIN TO STREPTOKINASE INTERVAL (TIME WINDOW)

This is the most powerful predictor of success rate. In this study also it is evident. Success rate was 55.65% those patients thromoblysed within 4 hrs from the onset of symptoms, the success rate decreased to 28.70% when they were thrombolysed after 4 hrs but within 8 hrs of onset of symptoms. Success rate came down to 15.65% when streptokinase was administered after 8 hours but within 12 hours.

CONCLUSION

- In this study the overall success rate of thrombolysis was 68%
- Age, Gender, Alcohol intake, Hypertension, pre infarction Angina have no influence in the outcome of thrombolysis.
- Patient with BMI ≥ 25, Smoking, Diabetes were affect the outcome of thrombolysis in unfavourable way.
- Pain to streptokinase interval (Time Window) affect the outcome of thrombolysis in favourable way. Earlier they came, they had better outcome.
- Anterior wall myocardial infarction 5 times more chance of failure than inferior wall myocardial infarction.

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PROFORMA

Case No.

Name : Age : Sex :

IP No. : DOA : ICCU No. :

Address : Occupation :

PRESENTING HISTORY

Anginal Chest Pain ☐ Radiation ☐ Dyspnea ☐

Atypical Chest Pain ☐ Sweating ☐ Syncope ☐

Palpitations ☐ Fatigability ☐ Cold Extremities ☐

Others ☐

PREVIOUS & PERSONAL HISTORY

IHD ☐ HTN ☐ DM ☐ COPD/BA ☐ Alcohol ☐

Smoking ☐ Hypercholesterolemia ☐ Others ☐

EXAMINATION

Cold Peripheries ☐ Pedal Odema ☐ Cyanosis ☐

BMI < 24.9 ☐ ≥ 25 ☐

PR : BP : JVP :

CVS : S_1S_2 ☐ LV S_3/S_4 ☐

RV S_3/S_4 ☐ Others ☐

RS : Breath Sounds ☐ Rhonchi ☐

Basal Creps ☐ Others ☐

Emphysematous changes ☐

ABDOMEN :

Hepatomegaly ☐

CNS :

Signs of Cardiac Failure :

Killip Stage :

Investigations :

Blood Sugar : SGOT :

Serum Cholesterol : CXR PA :

ECG :

Admission ECG :

90 min ECG after Inj. SK :

ST. Resolution < 50% ☐

> 50% ☐

Pain reduction after Inj. SK : Yes ☐ No ☐

Echo :

Outcome :

Successful ☐

Failed ☐

MASTER CHART

S. No.	IP No.	Age	Sex	Socio Economic status	BMI	Smoking	Alcohol	DM	HT	Preinfarction Angina	Time Window			Type of MI		Outcome
											0-4 Hrs.	4-8 Hrs.	8-12 Hrs.	AWMI	IWMI	
1	807402	48	M	1	21.9	1	0	0	0	0	1	0	0	1	0	1
2	807569	78	M	1	24.6	0	0	1	1	0	0	1	0	0	1	0
3	807600	48	M	1	23.8	1	0	1	0	1	1	0	0	0	1	0
4	807771	81	M	2	22.7	0	0	0	0	0	1	0	0	0	1	0
5	807772	30	M	1	24.3	1	0	1	0	1	0	1	0	1	0	0
6	807974	42	M	2	31.3	1	1	0	0	1	0	1	0	1	0	1
7	808064	52	M	1	25	1	0	0	0	0	1	0	0	1	0	0
8	807984	52	F	1	27.3	0	0	1	1	0	0	1	0	0	1	0
9	808411	60	F	1	24.8	0	0	0	0	0	1	0	0	0	1	0
10	808481	62	M	2	30.3	1	0	0	1	0	0	0	1	1	0	1
11	808492	60	M	2	32.8	1	0	0	0	1	1	0	0	0	1	0
12	808596	55	F	1	28	0	0	1	1	0	1	0	0	1	0	1
13	808730	54	M	1	27	1	1	1	0	0	0	1	0	1	0	1
14	809025	60	F	1	24.2	0	0	0	1	0	0	1	0	1	0	0
15	809026	65	M	2	33.8	1	1	0	0	1	1	0	0	1	0	0
16	809137	68	M	1	34	1	1	1	0	0	1	0	0	0	1	1
17	809146	54	F	2	34.6	0	0	1	0	0	0	1	0	1	0	1
18	809289	50	M	2	36.5	1	0	0	1	0	1	0	0	1	0	1
19	809349	60	M	1	28.3	1	0	1	1	0	1	0	0	0	1	0
20	809360	56	M	2	23.8	1	0	0	1	1	1	0	0	0	1	0
21	809681	62	M	1	24.9	1	1	0	0	0	0	1	0	0	1	0
22	809779	53	F	1	30	0	0	1	0	0	0	1	0	0	1	0
23	809980	46	M	1	27.7	1	1	0	1	0	1	0	0	1	0	0
24	809984	48	M	1	24.1	1	0	0	1	0	0	1	0	0	1	0
25	810026	50	M	2	26.9	0	1	1	0	0	0	0	1	1	0	0
26	810139	60	M	1	22	0	0	0	1	0	1	0	0	1	0	0
27	810163	40	M	2	32.4	1	0	1	1	0	0	1	0	1	0	1
28	810176	45	M	1	23	1	1	0	0	0	1	0	0	1	0	0
29	810260	49	M	2	31.5	0	0	0	0	0	1	0	0	1	0	0

30	810288	58	M	1	23.9	0	1	0	1	0	0	1	0	0	1	0
31	810575	58	M	2	26	1	0	0	1	0	1	0	0	0	1	0
32	810585	55	M	1	26.4	0	1	0	0	0	0	1	0	1	0	0
33	810684	61	M	1	23.9	0	0	0	1	0	1	0	0	0	1	0
34	810857	50	M	3	28.8	1	1	0	1	0	1	0	0	0	1	0
35	810870	44	M	1	24.4	1	1	0	0	0	1	0	0	0	1	0
36	811042	43	F	1	26.7	0	0	0	1	0	0	1	0	1	0	0
37	811138	68	F	1	25.6	0	0	0	0	0	1	0	0	1	0	0
38	811542	47	M	2	34.6	1	1	1	1	0	1	0	0	1	0	1
39	811630	57	M	1	24.8	0	0	0	1	0	1	0	0	1	0	0
40	811748	36	F	2	37.7	0	0	1	1	0	0	1	0	1	0	1
41	812044	60	M	2	36.3	1	1	0	1	0	0	0	1	1	0	1
42	812104	38	M	1	24.8	0	0	0	0	0	0	1	0	1	0	0
43	812402	43	M	2	25	1	0	0	0	0	1	0	0	0	1	0
44	812455	60	M	1	24.8	0	0	0	1	0	1	0	0	1	0	0
45	812459	49	M	1	26.2	0	0	0	0	0	0	1	0	1	0	0
46	812582	71	M	3	38	1	1	1	1	1	1	0	0	0	1	1
47	812586	45	M	2	31	0	0	0	0	0	0	1	0	1	0	0
48	812661	50	M	3	24	1	0	0	1	0	1	0	0	0	1	0
49	812786	54	M	1	27	0	0	0	0	0	0	1	0	1	0	0
50	812911	65	M	2	36.3	1	1	1	1	0	0	1	0	0	1	1
51	812961	60	M	2	29	0	0	0	0	0	1	0	0	1	0	0
52	813053	63	M	2	26.4	0	0	0	1	0	1	0	0	0	1	0
53	813211	40	M	1	24.7	0	1	0	0	0	0	1	0	1	0	0
54	813146	40	M	1	23.8	0	0	0	1	0	1	0	0	1	0	0
55	813204	52	M	1	34.3	1	0	1	1	0	0	0	1	0	1	1
56	813284	32	M	2	31	0	1	0	1	0	0	1	0	1	0	0
57	813361	60	F	2	38.9	0	0	1	0	0	0	0	1	0	1	1
58	813529	55	M	1	24.1	0	1	0	1	0	0	1	0	1	0	0
59	813619	57	M	1	33	1	1	1	1	1	1	0	0	0	1	0
60	813696	60	F	1	28	0	0	1	1	1	1	0	0	0	1	0
61	813800	38	M	1	24.4	1	1	0	1	1	1	0	0	0	1	0
62	813820	52	M	2	34.2	1	0	0	1	1	1	0	0	1	0	1
63	813815	72	F	2	37	0	0	1	1	0	0	1	0	1	0	1

64	813828	72	M	2	34.5	1	0	1	1	1	0	0	1	1	0	1
65	814140	60	M	1	23	1	1	0	1	1	1	0	0	1	0	0
66	814165	40	M	2	28	1	0	1	0	0	1	0	0	1	0	1
67	814263	49	M	1	27.3	1	1	0	0	0	1	0	0	0	1	0
68	814301	60	M	2	35	1	0	1	1	0	0	1	0	0	1	1
69	814364	50	F	2	28.6	0	0	0	1	1	0	0	1	1	0	1
70	814424	48	M	2	27.5	1	0	1	0	0	1	0	0	1	0	1
71	814624	40	M	2	23.9	1	1	0	0	0	1	0	0	0	1	0
72	814648	48	M	3	24.9	1	1	0	1	1	1	0	0	0	1	0
73	814653	50	M	1	31	1	1	0	1	0	1	0	0	1	0	0
74	814686	44	F	1	36	0	0	1	0	0	0	1	0	1	0	1
75	815074	42	M	2	31.4	1	0	1	0	0	0	0	1	1	0	1
76	815092	64	M	1	24.6	1	1	0	0	1	1	0	0	1	0	0
77	815205	68	F	2	30.5	0	0	1	1	0	1	0	0	1	0	0
78	815094	78	F	1	31	0	0	0	1	0	1	0	0	0	1	0
79	815291	55	F	2	29.3	0	0	1	0	1	1	0	0	1	0	1
80	815319	44	M	1	23	1	1	0	0	0	0	1	0	0	1	0
81	815332	42	M	1	24.3	1	0	0	1	0	1	0	0	0	1	0
82	815555	64	M	2	32.4	1	0	1	0	1	0	1	0	1	0	0
83	815706	68	M	1	24	1	1	0	1	0	1	0	0	1	0	0
84	815782	65	F	2	33	0	0	0	1	0	0	0	1	0	1	0
85	815783	52	M	1	24.3	1	0	1	0	1	0	0	1	0	1	0
86	815813	77	M	1	24.7	0	1	0	0	0	1	0	0	1	0	0
87	815936	49	M	1	33	1	0	0	1	0	0	1	0	1	0	1
88	816013	42	M	1	26	1	0	1	1	1	0	0	1	0	1	0
89	816031	82	M	1	33	0	1	1	0	0	1	0	0	0	1	0
90	816242	50	M	2	32.6	1	0	0	1	1	0	0	1	1	0	1
91	816463	44	M	1	23.7	0	0	0	0	0	1	0	0	0	1	0
92	816942	55	M	1	32	1	1	0	1	0	1	0	0	1	0	1
93	816977	45	M	1	24.3	1	0	1	0	1	1	0	0	1	0	0
94	817082	50	M	1	34.7	1	0	0	1	1	0	1	0	1	0	1
95	817131	60	M	1	37	1	0	1	0	0	0	0	1	1	0	1
96	817135	46	M	1	36.7	1	0	1	1	1	1	0	0	0	1	1
97	817194	50	M	1	27.5	1	1	1	1	0	0	1	0	1	0	1

98	817200	55	M	1	24.1	1	0	0	0	0	1	0	0	0	1	0
99	817218	47	M	1	23.8	1	0	1	1	1	0	0	1	0	1	0
100	817615	41	M	1	24.7	1	0	1	1	0	1	0	0	1	0	0
101	818019	57	M	1	24.2	1	0	0	0	0	1	0	0	0	1	0
102	818109	60	M	2	36	1	1	1	1	0	0	0	1	1	0	1
103	818140	60	M	1	22.7	1	0	0	0	0	1	0	0	0	1	0
104	818312	61	M	1	24	1	0	1	0	0	1	0	0	1	0	1
105	818321	31	M	1	22	0	1	0	0	0	1	0	0	1	0	0
106	818338	60	F	2	31	0	0	1	0	0	0	1	0	1	0	1
107	818584	48	M	2	30.9	1	0	1	1	0	0	0	1	1	0	1
108	818580	52	M	1	23.9	0	0	0	1	0	1	0	0	1	0	0
109	818730	55	M	1	29.2	1	1	0	0	1	0	0	1	0	1	0
110	818821	45	M	1	22.9	1	0	1	0	0	1	0	0	0	1	0
111	818862	35	M	1	24.1	0	1	0	0	0	0	1	0	0	1	0
112	819071	51	M	1	24.5	1	0	0	0	1	1	0	0	1	0	0
113	819364	44	M	1	28.6	0	1	1	1	0	1	0	0	0	1	0
114	819376	50	F	1	24.6	0	0	0	0	0	0	0	1	0	1	0
115	819563	60	F	2	32.3	0	0	1	1	1	1	0	0	1	0	0

Socio economic Status : 1 - Income < 1500; 2 - Income 1501 - 3000; 3 - Income 3001 - 5000
Smoking : 0 - No; 1 - Yes
Alcohol : 0 - No; 1 - Yes
Diabetes : 0 - No; 1 - Yes
Hypertension : 0 - No; 1 - Yes
Pre-infarction angina : 0 - No; 1 - Yes
Time Window : 0 - No; 1 - Yes
Type of MI : 0 - No; 1 - Yes
Outcome : 0 - Successful; 1 - Failed
M - Male
F - Female