ANALYSIS OF TIME DELAY FOR THROMBOLYTIC THERAPY IN ST-ELEVATION MYOCARDIAL INFARCTION

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CERTIFICATE

This is to certify that the dissertation titled "**Analysis of time delay for thrombolytic therapy in ST-elevation myocardial infarction**" is the bonafide original work of **DR. P.Suresh Kumar** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in SEPTEMBER 2006. The Period of study was from June 2004 to October 2004..

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DECLARATION

I, **DR. P.SURESH KUMAR ,** solemnly declare that dissertation titled **"Analysis of time delay for thrombolytic therapy in ST-elevation myocardial infarction"** is a bonafide work done by me at Govt. Stanley Medical College and Hospital during 2004 under guidance and supervision of my unit chief **Prof.S.NATARAJAN**., Professor and head of the department of medicine.

This dissertation is submitted to Tamilnadu DR. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine.**

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CONTENTS

		Page No.
I	INTRODUCTION	1
II	AIM OF THE STUDY	3
III	REVIEW OF LITERATURE	4
IV	MATERIALS AND METHODS	38
V	RESULTS	41
VI	DISCUSSION	50
VII	CONCLUSION	54
VIII	BIBLIOGRAPHY	55
IX	PROFORMA	64
X	MASTER CHART	66

INTRODUCTION

Coronary Artery Disease(CAD) has been defined as impairment of heart function due to inadequate blood flow to heart (WHO 1982) [1].

CAD has become an important epidemiological significant disease in developed as well as developing countries. There has been a large increase in incidence of cardiovascular disease in recent past in Indian subcontinent. A recent study by ICMR shows the prevalence rate has been found to be 80-120/1000. By the year 2015, It is predicted that CAD would replace the infectious disease as the major cause for mortality. An increase in mortality by 103% in males &about 90% in females from 1985-2015 is expected [2].

Acute Myocardial Infarction results from prolonged Myocardial ischemia precipitated in most cases by occlusive thrombus at the site of preexisting Atherosclerotic plaque.

A steady decline in the mortality rate from ST Elevation Myocardial infarction (STEMI) has been observed across several population group since1960[3]. Several phases in management of patients have contributed to decline in mortality from STEMI [4]. The “clinical observation phase” in first half of twenth century focused on physical and laboratory finding where as treatment is bed rest and sedation. Subsequently “coronary care unit phase” in mid 1960 was noted for detailed analysis and vigorous management of cardiac arrhythmia . “The high technology phase” setting the stage of bed side haemodynamic monitoring. The “Modern reperfusion era” of coronary care was introduced by intracoronary and then intravenous fibrinolysis and development of PCI which revolutioned the management and declined the mortality of STEMI.

Large clinical trials have definitively shown the value of thrombolysis in acute

myocardial infarction [5-7]. Thus attention shifted to increase the use of this therapy. Furthermore ,there and other trails have shown that benefit of this therapy can be maximized with earlier treatment [8,9], that is benefit of thrombolytic therapy are greater in first hour after onset of symptoms. Important delay in administration of this treatment have been observed [10-13]. These delay may reduce the efficacy of thrombolysis by increasing not only mortality [14] but also morbidity [15]. The Goal for the patient with STEMI should be to achieve a door to needle time with in 30 min and a door to balloon time within 90 min [16]

The present study is to analyze the delay in thrombolytic therapy in myocardial infarction.

AIM

1. To determine the Prehospital and Door to needle time in thrombolytic therapy in ST-elevation Myocardial Infarction(STEMI).
2. To evaluate the influence of patient's clinical characteristic in delay in thrombolytic therapy in ST-elevation Myocardial Infarction.

REVIEW OF LITERATURE

ACUTE CORONARY SYNDROMES

Acute coronary syndromes (ACS) is a term used to encompass the spectrum of clinical disorders caused by acute ischemic heart diseases, including unstable angina, non -ST -elevation myocardial infarction, and ST- elevation myocardial infarction.

Initial classification:

Therapeutic decisions are required before patients with Acute coronary syndromes can be categorized into unstable angina or acute MI based on serum cardiac markers and serial ECGs. To facilitate early management, patients are classified into

1. **ST-elevation ACS** :

Also been labeled as “reperfusion eligible” ACS , since prognosis is improved by early reperfusion with percutaneous coronary intervention (PCI) or thrombolytic therapy.

This consist of ST elevation>1mm in 2 or more contagious leads in ECG. Patients with left bundle branch block (LBBB) or isolated posterior MI also included in these as they also benefit from reperfusion therapy.

2. **Non- ST-elevation ACS:**

This consist of unstable angina and Non- ST- elevation MI

They are not benefited by Thrombolytic therapy.

Overall view of Acute Coronary Syndromes

Features	ST-elevation ACS	Non-ST-elevation ACS
Initial therapy	Primary PCI with stents. Thrombolytic therapy if a cath lab with a skilled interventionalist and team is not available in a timely fashion.	PCI with stents plus antithrombin therapy and a GP IIb/IIIa inhibitor for high risk and some intermediate risk patient. Antithrombin therapy for all other hospitalized patient followed by cath/PCI for recurrent ischemia or high risk finding on noninvasive testing.
Prognosis	Acute mortality 25-30%. Inhospital survival depends on speed and adequacy of reperfusion.	In-hospital MI or death in unstable angina varies from 1-5%, depending on risk class. Non-ST-elevation MI has lower hospital mortality than ST-elevation MI but similar 1 year mortality due to more late events.

ATHEROTHROMBOSIS

Atherosclerosis

Atherosclerosis is a chronic immunoinflammatory, fibroproliferative disease fueled by lipids[17]. Coronary atherosclerosis is the underlying cause of nearly all cases of ischemic heart disease , and superimposed thrombosis is the proximate cause of the great majority of the life threatening acute coronary syndrome(unstable angina, myocardial infarction, and sudden death)[18,19] Atherosclerosis affects primarily the intima of medium sized and large arteries, resulting in intimal thickening ,and leads to narrowing and inadequate blood supply.

The earliest lesion of atherosclerosis is the fatty streak, which is a pure immunoinflammatory reaction within intima, consisting of lipid filled macrophage (foam cell) and T lymphocytes. There is no extracellular lipid and so as B cells and neutrophils.

In advanced atherosclerotic lesion (plaques), lipids begin to accumulation extracellularly There is also accumulation of connective tissue produced by smooth muscle cells which gives rise to very heterogeneous atherosclerotic plaque. Because of leaky endothelium ,not only lipoproteins but also many other blood derived components including albumin and fibrinogen, are present in evolving lesion.

The flow limiting potential of an intimal plaques maybe modified by reactive changes in the underlying media and adventitia that may attenuate (positive remodeling) or accentuate (negative remodeling) luminal obstruction and consequent haemodynamic impact of the plaque.

Rupture prone plaques

The risk of plaque rupture depend more on plaque composition than on the degree of stenosis produced by the plaque. Many rupture prone plaques are invisible angiogrphically (and also missed by stress testing) due to their small size and compensatory vascular remodeling .Studies have identified three major determinant of plaque's vulnerability to rupture[20]:

1. The size of lipid core,
2. Inflammation with plaque degradation and
3. Lack of smooth muscle cells with impaired healing.

Sudden rupture of plaque may occur spontaneously, But triggers like severe exertion also play a role and thus explain the nonrandom onset of acute coronary syndrome.

Thrombosis

Rupture of plaque leads to thrombosis. In coronary thrombosis,the initial flow obstruction is usually caused by platlet aggregation, but fibrin is important for subsequent stabilization of the early and fragile platelet thrombus [21]

There are three major determinants of the thrombotic response to plaque rupture or the amount of thrombosis formed on top of an eroded plaque[22]:

1. Local thrombogenic substrate
2. Local flow disturbance, and
3. The systemic thrombotic property.

The exposure of the highly thrombogenic lipid rich core to circulating blood, resulting in activation of primary and secondary hemostasis.

Primary hemostasis(platelet plug formation):

Plaque rupture induces platelets to proceed through adhesion, activation, and aggregation.

Platelet adhesion:

It is initiated by the binding of Von Willibrand factor , an adhesive glycoprotein released from the injured vessel wall, to the platelet glycoprotein Ib receptor.

Platelet activation:

Platelet are exposed to multiple agonist at the same time (e.g.,ADP, Thromboxane A2,Epinephrine,Thrombin),which triggers a series of events within the platelet ,including increased cytosolic calcium, cell shape change, phosphorylation of proteins, release of granules and lysosomes, arachidonic acid metabolism, and conformational change in GP IIb/IIIa receptor

Complex so that it becomes expressed and activate on the platelet surface.

Platelet aggregation:

50,000-80,000 GP IIb/IIIa receptors resides on the surface of activated platelets. Fibrinogen is the most important ligand of GP IIb/IIIa receptor which can bind to two GP IIb/IIIa receptors simultaneously, creating a molecular platelet-to-platelet bridge.

Secondary hemostasis:

The principal mechanism for thrombin generation and fibrin deposition following plaque rupture is exposure of tissue factor , a low –molecular weight glycoprotein concentrated in vessel wall macrophage and vulnerable plaque. Tissue factor initiates the extrinsic pathway of coagulation by forming a high-affinity complex with clotting factors VII/VIIa.

Thrombin plays a critical role in clot formation: it converts fibrinogen to fibrin,

activates clotting factors V and VIII and protein C, and is a potent stimulus for platelet activation and aggregation. The formation and polymerization of fibrin is crucial to clot stabilization and propagation,converting the unstable primary platelet plug into an adherent "red" thrombus.

REPERFUSION THERAPY

Although reperfusion occurs spontaneously in some patients, persistent thrombotic occlusion is present in the majority of patients with AMI while the myocardium is undergoing necrosis[23]. Timely reperfusion of jeopardized myocardium represents the most effective way of restoring the balance between myocardial oxygen supply and demand. The extent of protection appears to be related directly to the rapidity with which reperfusion is implemented after the onset of coronary occlusion[23].

The reperfusion can be made out by

1. Fibrinolytic therapy
2. Percutaneous Coronoray Intervention.

In some patients, particularly those with cardiogenic shock, tissue damage occurs in a "stuttering" manner rather than abruptly, a condition that might more properly be termed subacute infarction. This concept of the nature of the infarction process, as well as the observation that the incidence of complications of AMI in both the early and late postinfarction periods is a function of infarct size,underscores the need for careful history-taking to ascertain whether the patient appears to have had repetitive cycles of spontaneous reperfusion and reocclusion.

"Fixing" the time of onset of the infarction process in such patients can be difficult. In such patients with waxing and waning ischemic discomfort, a rigid time interval from the first episode of pain should not be used when determining whether a patient is "outside the window" for benefit from acute reperfusion therapy.

PATHOPHYSIOLOGY OF MYOCARDIAL REPERFUSION.

Prevention of cell death by the restoration of blood flow depends on the severity and duration of pre-existing ischemia. Substantial experimental and clinical evidence exists indicating that recovery of left ventricular systolic function, improvement in diastolic function, and reduction in overall mortality are more favorably influenced, the earlier that blood flow is restored[8]. Collateral coronary vessels also appear to play a role in the successful left ventricular function following reperfusion.[24] They provide sufficient perfusion of myocardium to retard cell death and are probably of greater importance in patients having reperfusion later rather than 1 to 2 hours after coronary occlusion.

Pathology of Reperfusion Injury:

The process of reperfusion, although beneficial in terms of myocardial salvage, may come at a cost due to a process known as reperfusion injury . Kloner has summarized the data on the four types of reperfusion injury that have been observed in experimental animals.

These consist of

(1) lethal reperfusion injury—a term referring to reperfusion-induced death of cells that were still viable at the time of restoration of coronary blood flow,

(2) vascular reperfusion injury— progressive damage to the microvasculature such that there is

an expanding area of no reflow and loss of coronary vasodilatory reserve,[25]

(3) stunned myocardium—salvaged myocytes display a prolonged period of contractile dysfunction following restoration of blood flow owing to abnormalities of intracellular biochemistry leading to reduced energy production [26] , and

(4) reperfusion arrhythmias—bursts of ventricular tachycardia and on occasion ventricular fibrillation that occur within seconds of reperfusion. The available evidence suggests that vascular reperfusion injury, stunning, and reperfusion arrhythmias can all occur in patients with AMI. The concept of lethal reperfusion injury of potentially salvageable myocardium remains controversial, both in experimental animals and in patients[27].

Reperfusion Arrhythmias

Reperfusion Arrhythmias seen commonly following successful reperfusion are .

1. Transient sinus bradycardia occurs in patients with inferior infarcts
2. Premature ventricular contractions,
3. Accelerated idioventricular rhythm, and
4. Nonsustained ventricular tachycardia

In experimental animals with AMI, ventricular fibrillation occurs shortly after reperfusion, but this arrhythmia is not as frequent in patients as in the experimental setting.

When present, rhythm disturbances may actually be a marker of successful restoration of coronary flow.

Pathophysiology of Late Establishment of Patency of the Infarct Vessel:

It has been suggested that improved survival and ventricular function after successful reperfusion are not due entirely to limitation of infarct size[28]. Both experimental and clinical evidence indicate that the benefits of a patent artery include a favorable effect on ventricular remodeling (improved healing of infarcted tissue and prevention of infarct expansion), enhancement of collateral flow, improvement in diastolic and systolic function, and increased electrical stability, and reduced long-term mortality.

Late reperfusion of the artery perfusing an infarction provides a vascular scaffolding in the infarct zone and increases the influx of inflammatory cells that participate in the formation of a mature fibrous scar.The vascular scaffold and firmer myocardial scar prevent infarct segment lengthening and decrease the tendency to infarct expansion and aneurysm formation[29]. Poorly contracting or noncontracting myocardium in a zone that is supplied by a stenosed infarct-related artery with slow antegrade perfusion may still contain viable myocytes. This situation is referred to as hibernating myocardium[30] , and its function can be improved by percutaneous transluminal coronary angioplasty (PTCA) to augment flow in the infarct-related artery. Late reperfusion of the infarct-related artery by thrombolysis or late restoration of flow via PTCA enhances the electrical stability of the infarcted zone and is probably related to the reduced incidence of ventricular fibrillation and automatic firing of implantable cardioverter-defibrillator devices.

FIBRINOLYTIC THERAPY

Indication for fibrinolytic therapy[16]

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 admistered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new LBBB.

Class II a

1. In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to STEMI patients with symptom onset within the prior 12 hours and 12-lead ECG finding 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 patients whose initial symptoms of STEMI began more than 25 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.

CONTRAINDICATION AND CAUTIONS FOR FIBRINOLYTIC THERAPY[16].

Absolute contraindications

1. Any prior ICH
2. Known structural cerebral vascular lesion (eg.,AVM)
3. Known malignant intracranial neoplasm (primary or metastatic)
4. Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours.
5. Suspected aortic dissection
6. Active bleeding or bleeding diathesis (excluding menses)
7. Significant closed head or facial trauma within 3 months

Relative contraindications

1. History of chronic severe, poorly controlled hypertension.
2. Severe uncontrolled hypertension on presentation (SBP greater than 180 mm Hg or DBP greater than 110 mm Hg)
3. History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindication.
4. Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (less than 3 weeks).
5. Recent (within 2 to 4 weeks) internal bleeding.
6. Noncompressible vascular punctures.
7. For streptokinase : prior exposure (more than 5 days ago) or prior allergic reaction to these agents.

8. Pregnancy.
9. Active peptic ulcer.
10. Current use of anticoagulants : the higher the INR , the higher the risk of bleeding.

Agents

1. **Streptokinase (SK):**

Dose : 1.5 million units IV over 30-60 minutes

Activates circulating plasminogen to induce a systemic lytic state. Allergic reactions are common (most often hypotension). Least likely to cause intracranial bleeding. Acute IV heparin is not necessary for reduction in mortality or reinfarction, and subcutaneous heparin is of questionable benefit. Heparin is used in high risk setting. Avoid reuse due to persistence of neutralizing antistreptococcal antibodies. Acute patency rate: 50%. Least expensive agent.

2. **Tissue plasminogen activator (tPA)**

Dose : 100 mg IV maximum in 90 minutes: 15 mg bolus, then 0.75 mg/kg (max 50 mg) over 30 minutes, then 0.5 mg/kg (max. 35 mg) over next 60 minutes.

Preferentially activates clot bound plasminogen; does not induce systemic lytic state. No allergic potential. Mortality advantage over SK if accelerated dosing regimen and IV heparin are given within 4 hours of symptom onset despite a slight increase in ICH. Greatest benefit is for patients presenting early with large MI and low risk of ICH. Acute IV heparin is essential to maintain coronary patency. Acute patency rate is 80%. It is expensive.

3. Recombinant plasminogen activator (rPA) (Reteplase):

Dose; 10U IV bolus over 2 minutes, repeated in 30 minutes x 1. Normal saline flush before and after each bolus.

Preferentially activates clot bound plasminogen , but not as fibrin specific as tPA, and fibrinogen is depleted in many patients. No allergic potential. Deletion mutation of wild type tPA with a longer half life and reduced fibrin specificity compared to tPA. Convenient bolus dosing. Mortality and ICH similar to accelerated tPA in GUSTO-III. Acute IV heparin is essential to maintain coronary patency. Acute patency rate is 80%. It is expensive

4. **TNK-tPA (Tenecteplase):**

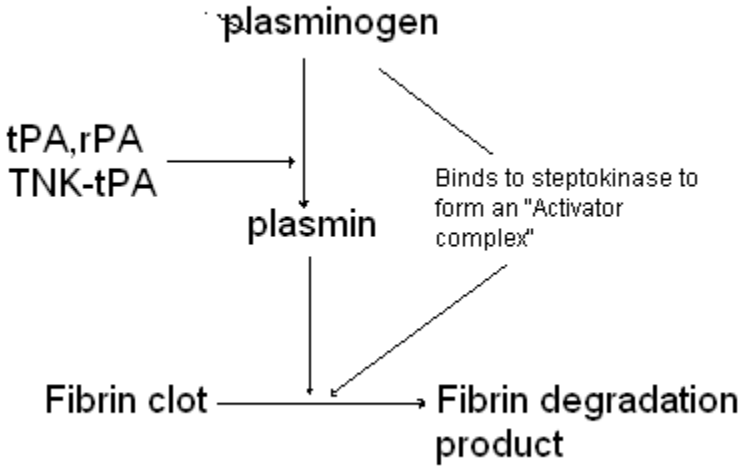
Dose: Single, weight adjusted IV bolus over 5 seconds: < 60 kg (30 mg): 60-69 kg (35 mg); 70-79 kg (40 mg); 80-89 kg (45mg); >90kg (50mg)

Preferentially activates clot bound plasminogen , does not induce systemic lytic state. No allergic potential. Developed by altering amino acids of wild type tPA; Longer half life and increased fibrin specificity compared to tPA. Convenient bolus dosing. Mortality and ICH similar to accelerated tPA in ASSENT-2.. Acute IV heparin is essential to maintain coronary patency. Acute patency rate is 80%. It is expensive.

Adjunctive antithrombin therapy

Fibrinolytic therapy exposes clot bound thrombin, which is a potent stimulus for further platelet aggregation and fibrin generation. To offset this prothrombotic potential , antithrombin therapy is routinely employed particularly with tPA, rPA, and TNK-tPA. There is less need for systemic anticoagulation with streptokinase, as streptokinase results in generation of fibrin degradation products and depletion of clotting factors V and VIII, which confer systemic anticoagulant effects.

Heparin dosing is a balance between the risk of occlusion and the risk of major bleeding,and current recommendation is an IV bolus dose of 60-70 U/kg (max. 5000 units) of unfractionated heparin followed by a continuous IV infusion of 12-15 U/kg/hr (max 1000 U/HR), adjusted to aPTT of 1.5-2.5 times control for 48 hours.



Complication and management of lytic therapy:

Minor bleeding (puncture site, oral, nasal)

Minor bleeding episode are treated by local compression. To minimize the risk of bleeding, compressible vascular access site should be used, vascular line should be left in place for several hours after fibrinolytic therapy (especially after streptokinase),and the number of invasive procedure should be kept minimum.

Major bleeding (GI, intracranial)

The incidence of GI bleeding is 5% and intracranial hemorrhage is 0.5-1.0 % after fibrinolytic therapy. Risk factors for intracranial hemorrhage, which is fatal in 50-60%, include older age (especially >70 years), lower body weight, history of cerebrovascular

events, hypertension on presentation, and use of a fibrin specific fibrinolytic agent. Any focal neurological deficit or significant detoriation in mental status should be treated as an intracranial hemorrhage until excluded by CT scan. Blood investigation (hemoglobin,hematocrit,platelet, PT/PTT, fibrinogen) should be obtained and treatment should be started before CT result is available.

Immediate discontinuation of lytic , heparin, GP IIb/IIIa inhibitors, asprin, and clopidogrel is mandatory.protamine sulphate (20-50 mg IV over 1-3 minutes) can be given to reverse the effect of heparin. Packed RBCs are indicated for bleeding –induced hypotension or hematocrit <25%;platelet transfusions (6-10) are indicated to reverse abciximab effect; and cryoprecipitate (10 units) is indicated to keep fibrinogen levels >150 mg/dl. (Fibrinogen can be low or dysfunctional 6-8 hours after tPA, rPA, and TNK-tPA, and for up to 30 hours after streptokinase).

For persistent bleeding, fresh frozen plasma (2-3 units) and repeat cryoprecipitate transfusion are indicated. For continued bleeding despite these measures, additional platelet transfusion (even the platelet count is normal) is recommended to reverse the effect of asprin and fibrin split products. Aminocapraoic acid may counteract the effect of plasmin but at a risk of severe thrombosis

Fever

Fever occur in 5% of patients receiving streptokinase and is treated with asprin or acetaminophen.

Hypotension

Hypotension occurs in 10-15% of patients during streptokinase infusions and is treated with IV fluids and by slowing or temporarily discontinuing the streptokinase infusion until BP> 90 mm Hg, then resuming the normal infusion rate. Hypotension is not an allegic reaction unless it is associated with anaphylaxis

Rash:

Rash occurs in 2-3% of patients receiving streptokinase and is treated by discontinuing the streptokinase infusion and giving benadryl 50 mg (IV or PO) and hydrocortisone 100 mg (IV) q 6h (if severe). If a full lytic dose was not received, 50 mg tPA or acute PCI should be considered.

Anaphylaxis :

Anaphylaxis occurs in 0.1% of patients receiving streptokinase and is treated by discontinuing the streptokinase infusion, securing an airway, and giving epinephrine 1-5 cc of 1:10000 solution IV, hydrocortisone 100-200 mg IV q 4-6 h, and IV fluids. IV dopamine is indicated for persistent hypotension.

Rigors

Rigors can occur during plasminogen breakdown.

Reperfusion Arrhythmias:

Bradycardia, third degree AV block

Occurs most often with acute reperfusion of the right coronary artery and usually resolves within minutes. Symptomatic episodes are treated with atropine. Transcutaneous pacing is rarely needed.

Bezold-jarish reflex:

Presents as profound hypotension with bradycardia in response to activation of vagal afferent fibers following acute reperfusion of RCA. Treated with atropine every 3-5 minutes, IV fluids, and possibly temporary pacing. Persistent episodes may require norepinephrine IV.

Idioventricular rhythm:

No treatment is required for rates<120 bpm in the absence of hypotension.

Ventricular tachycardia:

No treatment is required for runs of nonsustained VT, which are common and usually abate over time. For pulseless VT or ventricular fibrillation, immediate defibrillation is required.

CHOICE OF AGENT.

For choosing the thrombolytic agent between streptokinase , tPA, rPA, and TNK-tPA it is better to categorize patients into those that are at (Simoons and Arnold[31])

1. High risk of death

Advanced age, female gender, depressed left ventricular function, anterior MI, bundle branch block, total magnitude of ST-segment elevation, diabetes, heart rate greater than 100 beats/min, systolic pressure less than 100 mm Hg, long delay since onset of ischemic discomfort.

2. High risk of intracranial hemorrhage

Age greater than 65 years.

In the subgroup of patients presenting within 4 hours of symptom onset, the speed of reperfusion of the infarct vessel is of paramount importance and a high-intensity thrombolytic regimen such as accelerated t-PA is the preferred treatment, except in those

individuals in whom the risk of death is low (e.g., a young patient with a small inferior MI) and the risk of intracranial hemorrhage is increased (e.g., acute hypertension), in whom streptokinase and accelerated t-PA are approximately equivalent choices.

For those patients presenting between 4 and 12 hours after the onset of chest discomfort, the speed of reperfusion of the infarct vessel is of lesser importance, and therefore streptokinase and accelerated t-PA are generally equivalent options, given the difference in costs

Patients with low mortality risk but an increased risk of intracranial hemorrhage (e.g., elderly patients with inferior MI, blood pressure greater than 100 mm Hg, and heart rate less than 100 beats/min), streptokinase is probably preferable to t-PA because of cost considerations if thrombolytic therapy is prescribed at all in such a patient[4].

In those patients considered appropriate candidates for fibrinolysis and in whom tPA would have been selected as the agent of choice in the past, now it is better to consider using a bolus thrombolytic such as reteplase or tenecteplase. The rationale for this recommendation is that these agents has the advantage of ease of administration, a lower chance of medical errors, and less noncerebral bleeding and also offers the potential for prehospital treatment[32].

LATE THERAPY.

No mortality benefit was demonstrated in the LATE and EMERAS trials when thrombolytics were routinely administered to patients between 12 and 24 hours,[33,34] but it is still reasonable to consider thrombolytic therapy in appropriately selected patients with persistent symptoms and ST elevation on ECG beyond 12 hours . Persistent chest pain late after the onset of symptoms correlates with a higher incidence of collateral or antegrade flow

in the infarct zone and is therefore a marker for patients with viable myocardium that might be salvaged.

Because elderly patients treated with thrombolytics more than 12 hours after the onset of symptoms are at increased risk of cardiac rupture, it is our practice to restrict late thrombolytic administration to younger patients (<65 years) with ongoing ischemia, especially those with large anterior infarctions.

The elderly patient with ongoing ischemic symptoms but presenting late (>12 hours) is probably better managed with direct (primary) PTCA (see below) than with thrombolytic therapy.

Angiographic assessment

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the TIMI grading system: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow.

Early reports frequently lumped TIMI grades 2 and 3 under the general category of patency, but it is now recognized that grade 3 flow is the goal of reperfusion therapy, because full perfusion of the infarct-related coronary artery yields far better results in terms of infarct size, maintenance of left ventricular function, and reduction of both short- and long-term mortality rates. Relatively new methods of angiographic assessment of the efficacy of thrombolysis include counting the number of frames required on the cine film for dye to flow

from the origin of the infarct-related artery to a landmark in the distal vascular bed (TIMI frame count) and determining the rate of entry and exit of contrast dye from the microvasculature in the myocardial infarct zone (TIMI Myocardial Perfusion Grade)[35,36]

Time as a determinant for success of thrombolytic therapy

Mordern in-hospital care of the STEMI has resulted in a substantial reduction in mortality. Some 40 to 65 percent of death from AMI , however , occur within an hour of the onset of symptoms and prior to arrival at a hospital. Most death are attributed to ventricular fibrillation . To achieve a further substantial decrease in mortality rate, it will be necessary to reduce the incidence of deaths outside the hospital. The earlier the thrombolytic therapy can be initiated in eligible patients, the better the outcome, it is also essential to bring patients with chest pain into the medical care system as soon as possible because of the need to shorten the time between the onset of symptoms and the initiation of thrombolytic therapy.

Thrombolytic therapy can reduce the relative risk of in-hospital death by up to 50% when administered within the first hour of the onset of symptoms of AMI, and much of this benefit is maintained for at least 10 years. Appropriately used thrombolytic therapy appears to reduce infarct size, limit Left ventricular dysfunction, and reduce the incidence of serious complications such as septal rupture, cardiogenic shock, and malignant ventricular arrhythmias. Since myocardium can be salvaged only before it has been irreversibly injured, the timing of reperfusion therapy, by thrombolysis or a catheter-based approach, is of extreme importance in achieving maximum benefit.

While the upper time limit depends on specific factors in individual patients, it is clear that "**every minute counts**" and that patients treated within 1 to 3 h of the onset of

symptoms generally benefit most. Although reduction of the mortality rate is more modest, the therapy remains of benefit for many patients seen 3 to 6 h after the onset of infarction, and some benefit appears to be possible up to 12 h, especially if chest discomfort is still present and ST segments remain elevated in ECG leads that do not yet demonstrate new Q waves[37].

Compared with PCI for STEMI , fibrinolysis is generally the preferred reperfusion strategy for patients presenting in the first hour of symptoms, if there are logistical concerns about transportation of the patients to suitable PCI center, or there is an anticipated delay of at least 1 hr between the time that fibrinolysis could be started versus implementation of PCI. Although patients < 75 years achieve a greater relative reduction in the mortality rate with fibrinolytic therapy than do older patients , the higher absolute mortality rate (15 to 25%) in the latter results in similar absolute reductions in the mortality rates for both groups.

Time loss between onset of symptoms and initiation of therapy

Prolonged delay time in responding to patient's symptoms is the rate limiting step in defining the prehospital phase of myocardial infarction. Mean time in such response is 3 hours [38] . Most of the time is consumed in decision making , while failing to recognize or acknowledge the seriousness of the problem.

Many factors influence the delay in receiving the thrombolytic therapy.

Diabetic:

Prehospital delay has been shown to be prolonged for patients with diabetic [40-42]. Diabetic patients frequently present with atypical symptoms due to the presence of diabetic autonomic neuropathy. This atypical presentation reduces the intention of patients to come to hospital and also the diagnostic delay in hospital[43]

Age:

Due to multiple compounding factors like presence of other disease, atypical pain, presence of attender to take care, older age persons have prolonged prehospital delay when compared to younger age group

It is possible that older people have more atypical symptoms with pathological ECG changes from previous myocardial damage. This combination create problems in interpreting ECG and thereby increased door to needle time[12].

Women :

Some studies show significant delay in women and in others there is no gender difference in the time lag. This delay is attributed to reduced care and more atypical presentation.[44,45]

There is tendency for physicians to show less concern for women's ST elevation than men's. Jackson et al [46] found longest delay for women in this aspect.

Coronary Artery Disease:

CAD patients would attribute the chest pain to the anginal pain they usually get on excertion and try to self medicate them which is cause of delay.

But studies shows conflicting reports in the delay in these group of patients[47].

Other factors determining the delays are education level and blacks wait longer time than white.

Delay in transport to hospital

Ambulance transportation time in most industrialized countries is of a short duration.

Ambulance have priority in traffic and are well identified. In medium sized town without regular traffic jams , a major gain in time in this link of the chain is not likely. In rural areas, as well as in a metropole, the situation may be different, but even then the the loss of time due to transport is limited. In Nottingham registry, the median time time from the patient's call for the ambulance to its hospital arrival was 29 minutes(Rowley,1992).

There is a striking difference in delay in delay of hospital admission between patients who choose to call a general practitioner compared to those who choose to call an emergency ambulance. If a general practitioner referred the patient to the hospital, median delay was 247 minutes, compared with 100 minutes when the patient called an ambulance directly .

Strategy to reduce the time from onset of symptoms to treatment

Health care professionals should heighten the level of awareness of patients at risk for AMI (e.g., those with hypertension, diabetes, history of angina pectoris, old age). They should review and reinforce with patients and their families the need for seeking urgent medical attention for a pattern of symptoms including chest discomfort, extreme fatigue, and dyspnea, especially if accompanied by diaphoresis, lightheadedness, palpitations, or a sense of impending doom.[48]

This education should be continuous. Information of the public to reduce time from symptom onset to medical service call have shown success only during the time the continuous publicity was maintained. Soon after the end of such activities the prehospital delay again reached the initial duration[49].

Patients should also be instructed in the proper use of sublingual nitroglycerin that should be taken as one tablet at the onset of ischemic-type discomfort and repeated at 5-minute intervals for a total of three doses. If the symptoms have not dissipated within 15 minutes, the

patient should be rapidly transported to a medical facility that has the capability of recording and interpreting an electrocardiogram, providing advanced cardiac life support and cardiac monitoring, and initiating reperfusion therapy with either thrombolysis or angioplasty if indicated. Primary care physicians need to take a larger role in helping implement strategies to facilitate early treatment.[48]

Well-equipped ambulances and helicopters staffed by personnel trained in the acute care of the infarction victim (mobile CCUs) allow definitive therapy to commence while the patient is being transported to the hospital.

Trained paramedics can reliably diagnose myocardial infarction by ECG. The use of a direct admission procedure, by a radio link to the CCU, substantially reduces the time interval for thrombolytic treatment after acute myocardial infarction[50]

PREHOSPITAL THROMBOLYSIS.

The potential benefits of prehospital thrombolysis have been evaluated in several randomized trials . Although none of the individual trials showed a significant reduction in mortality with prehospital initiated thrombolytic therapy, there was a generally consistent observation of benefit from earlier treatment, and a meta-analysis of all the available trials demonstrated a 17 per cent reduction in mortality [51].

The CAPTIM trial reported a trend toward a Lower rate of mortality among STEMI patients receiving prehospital fibrinolysis as compared with primary PCI, especially if the patient was treated with in 2 hours of the onset of symptoms. Additional benefit from prehospital benefit is found in a report of French registry of STEMI patient treated less than 12 hours from the onset of symptoms; the 1 month mortality rate was 14.7 percent in patients

who do not receive reperfusion, 9 percent in those treated with in-hospital fibrinolysis, 7.9 percent in those treated with primary PCI and 3.2 percent in those receiving prehospital fibrinolysis[52].

Several factors must be weighed when communities consider whether their ambulances and emergency transport vehicles should have capabilities of initiating thrombolytic therapy. The greatest reduction in mortality is observed when reperfusion can be initiated within 60 to 90 minutes of the onset of symptoms.

It has been suggested that the streamlining of emergency department triage practices so that treatment can be started within 30 minutes, when coupled with the 15 to 30 minute transport time that is common in most urban centers, may be more cost effective than equipping all ambulances to administer prehospital thrombolytic therapy. The latter would require extensive training of personnel, installation of computer-assisted electrocardiographs or systems for radio transmission of the ECG signal to a central station, and stocking of medicine kits with the necessary drug supplies.

However, in selected communities where transport delays may be 90 minutes or longer and experienced personnel or physicians are available on ambulances, prehospital thrombolytic therapy is probably beneficial [53].

A thrombolysis nurse produced a dramatic improvement in median door-to-needle and pain-to-needle times in patients presenting with definite MI. This would lead to an additional 41 lives saved at 30 months per 1,000 patients treated[54]. Emergency department staff may be alerted to the sudden development of ST segment elevation by periodic visual inspection of the bedside ECG monitor, by continuous ST-segment recording, or by auditory

alarms when the ST-segment deviation exceeds programmed limits.

In a study done at department of cardiology, oxford , UK, an aggressive policy is used to reduce the door to needle time. This lead to increased propotion of eligible patients to receive thrombolysis early. However, greater pressure on medical staff to make rapid management decisions increased the proportion of patients being thrombolysed inappropriately[55] The time taken to administer thrombolysis to patients admitted with acute myocardial infarctions can be reduced by focusing on the delay by Registration of hospital time[56]

Physicians evaluating patients in the emergency department must confront the difficult task of rapidly identifying patients who require urgent reperfusion therapy, triaging lower risk patients to the appropriate facility within the hospital, and not discharging patients home inappropriately while avoiding unnecessary admissions.

MATERIALS AND METHODS

Study sample.

For the present investigation the sample includes 107 patients with STEMI consecutively admitted to intensive coronary care units in Stanley medical college during period of June 2004 to October 2004 .

Patients included in the study are the one who had a typical electrocardiogram changes including ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads or new or presumably new LBBB. with a typical changes in the levels of serum enzyme

with or without chest pain lasting > 30 minutes.

Patients with symptoms of acute coronary syndrome with NSTEMI , unstable angina were excluded .

Study variables.

On admission patient's clinical profile, electrocardiographic data, information on administration of thrombolytic agents and complication if any were noted and investigation for cardiac enzymes and plasma sugar were taken and noted

During the hospital stay the patients were interviewed and completed a standard record form covering details of their past medical history. The time of onset of AMI symptoms was recorded as accurately as possible. For some patients (i.e., patients with cardiogenic shock, signs of dementia,etc.) this information was obtained from family members. The time of entry to hospital was recorded. The time of admission to the coronary care unit was recorded and so is the time of start of thrombolytic therapy .The pre-hospital time interval was defined as the time interval from the beginning of the most recent onset of chest pain or the latest episode of intensified or prolonged pain to entry to hospital.

Study variables included: age, gender, alcohol consumption, cigarette smoking, hypertension, diabetes mellitus, history of coronary artery disease (documented history of angina and/or myocardial infarction), location of MI,.

Statistical analysis.

The time delays were expressed in minutes. Treatment delay data had a skewed distribution(Fig1,2); therefore all data are processed with medians and range. The significance of differences in median times was determined using a Mann–Whitney U-test. Two-tailed *P*-values <0·05 were considered statistically significant. For better understanding data are presented as medians (range) and mean (SD).

RESULTS

One hundred and seven consecutive STEMI patients were studied with mean age of 53.80. Out of this 89 received thrombolytic therapy. The patients characteristic are presented in Table 1.

Table 1

The Median time from onset of symptoms to arrival at emergency department was 155 minutes and Median time from hospital arrival to thrombolysis was 40 minutes . The various delay were shown in median as there is skewed distribution (Table 2)

Table 2

	Time Median (range)
Onset of chest pain to patient's initiation to go to hospital	45 (5-1120)
Transportation time	45 (15-430)
Delay due to private consultation (74/107)	35 (10-1185)
Prehospital delay	155 (40-1260)
Door to needle time in thrombolysed (89/107)	40 (15-685)
Total delay	200 (70-1340)

ANALYSIS OF PATIENT'S CHARACTERISTIC ON DELAY

1.Age

Prehospital time **Table 3**

. Door to needle time :

89 patients are thrombolysed and analysed for door to needle time

Table 4

2. **Sex**

Prehospital time **Table 5**

Door to needle time: **Table 6**

3. Diabetic

Prehospital time **Table 7**

Test Statistics(a)

Mann-Whitney U **P-value = 0.033**

Door to needle time **Table 8**

4. Hypertension

Prehospital time **Table 9**

Door to needle time **Table 10**

P value <0.001

5.Previous history of CAHD

Pre hospital time **Table 11**

Door to needle time **Table 12**

6. Smokers

Prehospital time **Table 13**

Test Statistics

Mann-Whitney U p value = 0.028

Door to needle time **Table 14**

7. Alcoholic

Prehospital time **Table 15**

Door to needle time **Table 16**

8. Location of MI

Prehospital time **Table 17**

Door to needle time **Table 18**

Patients seeking treatment from private practitioner delayed longer than who came directly to tertiary hospital.

Table 19

P value <0.05

DISCUSSION

This study is to describe the various time intervals leading to delay in thrombolytic therapy and to describe the influence of patient's clinical characteristics to delay in thrombolytic therapy in the sample of patients admitted to coronary care unit for STEMI from June 2004 to October 2004.

Of 107 STEMI patients studied 91 were male and 16 were females with mean age of 53.80 with a SD of 11.50. 15.9% (17) of patients were above 65 years age group.

89 patients (83.2%) were thrombolysed out of total 107 patients. 18 of them did not receive thrombolytic therapy. Prehospital delay was the cause for 11 of 18 patients not receiving thrombolytic therapy, remaining are due to contraindications like accelerated hypertension in 4, previous use of streptokinase in 1 , stroke in 1, and bleeding complication in 1 leading to termination of thrombolysis

In this study group 19.6% (21/107) of patients were diabetic , 23.4% (25/107) were hypertensive and 9.3% (10/107) of them had previous history of angina and/or myocardial infarction.

61 of the patients had anterior wall MI and 46 of them had inferior wall MI.

In this study the median prehospital time was155 minutes and the door to needle time was 40 minutes.. Prehospital time was calculated for all the 107 patients and door to needle time was calculated for the 89 patients who were thrombolysed.

A review of data from various studies published through out the world vary from 83

min to 300 min (median time) for prehospital delay and for Door to needle time it is between 30 to 95 minutes(median time). These differing delay are likely attributable to varying demographic and clinical characteristics of samples under study, definition of symptom onset used and period during which study is conducted. In an Indian study done in PGI, Chandigar median prehospital delay was 5.2 hours and Door to needle time was 60 minutes[57].

Extract of various studies are as follows

Median Delay (min)

	Pre-hospital	In-hospital	Total
Birkhead *et al*.[58]	103	31*	na
Gonzalez *et al*.[59]	na	50	155
Herlitz *et al*.[60]	98	50	200
Porter *et al*.[61]	150	40	na
Newby *et al*.[14]	92	64	168
Rustige *et al*.[62]	na	30	160
Anne- Maree Kelly et al [12]	83	37	na
Di Chiara Aet al [13]	129	45	na
Abba AA et al [63]	300	95	na
Constantine et al [64]	130	85	na

*Thrombolysis given in the Accident and Emergency department.

On analyzing the patient's characteristics it was found that diabetic presented to hospital 260 minutes(median time) after the onset of symptoms of Myocardial infarction when compared to nondiabetic who came with median time of 150 minutes . This shows that there was a significant pre hospital delay in diabetics ($p<0.05$) and suggest that diabetic sensory neuropathy causing attenuation of symptoms was responsible. This finding is almost universal and found in all studies [40-43]

When Age is considered, older persons have a mean door to needle time of 99.33

minutes when compared to the younger who have a mean delay of 50 minutes .This is due to atypical presentation and difficulties in eliciting proper history. [65]

The median door to needle time in hypertensives was 70 minutes when compared to normotensives whose door to needle time was 40 minutes ($p<0.001$) A higher prevalence of previous myocardial damage and myocardial hypertrophy might have induced ECG abnormalities , creating problems in the early interpretation of the ECG along with the fear of increased risk for Intracerebral hemorrhage caused unnecessarily long delay times in hospital [41].

Non Smokers have significant prehospital delay when compared to smoker ($p< 0.05$). This may probably due to increased awareness among the smoker . Delay was not significant for female sex, previous history of CAD, which was same as of North Indian study [57] but other western study shows significant delay in them [41,42].

The location of MI does not significantly alter the prehospital delay or Door to needle time similar to western study. (Giuseppe Berton et al) [65].

Of the prehospital time, time interval between the onset of chest pain to patient's initiation to go to hospital was 45 minutes and this timing is not studied in detail in previous studies Hirvoven,T.P.J et al [66]shows the median time interval between the onset of chest pain to patient's initiation to go to hospital was 60 minutes . Transportation to hospital consumes a median time of 45 minutes

69.15% (74/107) of the patients consulted the local practitioner before coming to tertiary hospital. Prehospital delay was significantly higher in patients (167.5 Vs 90 min $p<0.05$) who had visited a local practitioner than those who came straightaway to the emergency unit of the

hospital. This finding is similar with the Indian study [57]

Limitations of the study: patient who died of AMI outside the hospital and those with silent MI who are not presented to hospital were not studied.

CONCLUSION

The present study shows that in case of STEMI, the time interval between onset of symptoms and patient's arrival is still far from optimal and Door to needle time is comparable with other countries.

Diabetic patients present to hospital late and Door to needle time was higher for hypertensives.

The other main factors contributing to prehospital delay are prior consultation with the local practitioner and unavailability of rapid transport facilities.

The best way to minimize delay is probably by a public education campaign with a correctly designed message, (particularly Diabetics and Elderly persons should be explained about the symptoms of AMI) and to increase public awareness to use ambulance transport to hospital. The emergency department should constantly develop protocol and guidelines to assure rapid identification of AMI patients.

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PROFORMA

NAME: IP NO:

AGE: ADDRESS:

SEX:

OCCUPATION

EDUCATION: EARNING:

PAST HISTORY

1. Hypertension
2. Diabetes mellitus
3. coronary heart disease
4. other illness

PERSONAL HISTORY:

1. Smoking No of cigarettes /day: Duration in years:
2. alcohol

Time of onset of chest pain or anginal eqvualent:

Time of initiation to go to hospital:

Time interval between starting of chest pain

to patient's initiation to go to hospital:

Reason's if any for patient's time delay :

Time taken to arrange for transport:

Duration of transport:

Total delay for transport:

Mode of transport:

Distance of the place from Stanley:

Consulting time with local practitioner:

Immediate referral to tertiary hospital:

ECG taken and referred:

Time of entry into emergency department:

Time at which the ECG taken(printed in ECG):

Time of entry into cardiac care unit:

Time of starting of thrombolytic therapy:

Reason for delay or reason for not thrombolysing:

CLINICAL EXAMINATION:

Pulse rate Blood pressure JVP:

CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATION:

Plasma sugar (Fasting):

S- CPK MB:

Electrocardiogram: Location of MI:

S .No	Age	Sex	Diabetes	Hyper-tension	CAHD	Smokin	Alcohol
46	51	Male	No	No	No	Yes	Yes
47	45	Male	No	No	No	Yes	Yes
48	65	Male	No	No	No	Yes	No
49	75	Female	Yes	Yes	No	No	No
50	44	Male	No	No	No	Yes	Yes
51	39	Male	No	No	No	Yes	Yes
52	60	Female	No	Yes	No	Yes	Yes
53	46	Male	No	Yes	No	Yes	Yes
54	50	Female	Yes	Yes	No	No	No
55	55	Male	Yes	No	No	Yes	No
56	72	Male	No	Yes	No	Yes	No
57	42	Male	No	No	No	Yes	No
58	70	Female	No	No	No	No	No
59	70	Male	No	No	No	Yes	No
60	75	Male	No	No	No	Yes	Yes
61	63	Male	No	No	No	Yes	No
62	70	Male	No	No	No	Yes	Yes
63	70	Male	No	No	No	No	No
64	47	Male	No	No	Yes	Yes	Yes
65	69	Male	No	No	Yes	No	No
66	50	Male	No	Yes	No	Yes	Yes
67	57	Male	No	Yes	No	No	No
68	71	Male	No	No	No	No	No
69	33	Male	No	No	No	Yes	No
70	56	Male	No	Yes	No	Yes	No
71	62	Male	No	Yes	No	Yes	Yes
72	57	Male	Yes	Yes	No	No	Yes
73	48	Male	No	No	No	No	No
74	47	Male	Yes	No	No	Yes	Yes
75	60	Male	No	Yes	No	No	No
76	50	Male	No	No	No	Yes	No
77	65	Female	No	No	No	No	No
78	47	Male	No	No	No	Yes	No
79	60	Female	No	Yes	No	No	No
80	46	Male	No	No	No	No	No
81	40	Male	No	No	No	Yes	Yes
82	28	Male	No	No	No	Yes	Yes
83	33	Male	Yes	No	No	No	No
84	59	Male	Yes	No	No	Yes	Yes
85	50	Male	Yes	No	No	No	No

S .No	Age	Sex	Diabetes	Hyper-tension	CAD	Smokin	Alcohol
86	52	Male	Yes	No	No	No	No
87	56	Female	Yes	No	No	No	No
88	38	Male	No	No	No	Yes	Yes
89	35	Male	No	Yes	No	No	Yes
90	59	Female	No	No	No	No	No
91	41	Male	Yes	Yes	No	Yes	Yes
92	80	Male	Yes	No	No	Yes	No
93	45	Male	No	No	No	Yes	Yes
94	40	Male	No	No	No	Yes	No
95	57	Male	No	No	Yes	Yes	No
96	47	Male	Yes	No	No	No	No
97	36	Male	No	No	Yes	Yes	Yes
98	45	Male	No	No	No	Yes	Yes
99	71	Male	No	No	No	No	No
100	65	Male	No	No	No	Yes	No
101	60	Male	No	No	No	Yes	Yes
102	55	Male	No	No	No	Yes	Yes
103	55	Female	No	Yes	No	No	No
104	46	Male	No	No	No	Yes	No
105	53	Male	Yes	No	No	No	No
106	67	Female	No	No	No	No	No
107	45	Male	No	No	No	Yes	No

CAD- Coronary Artery Disease

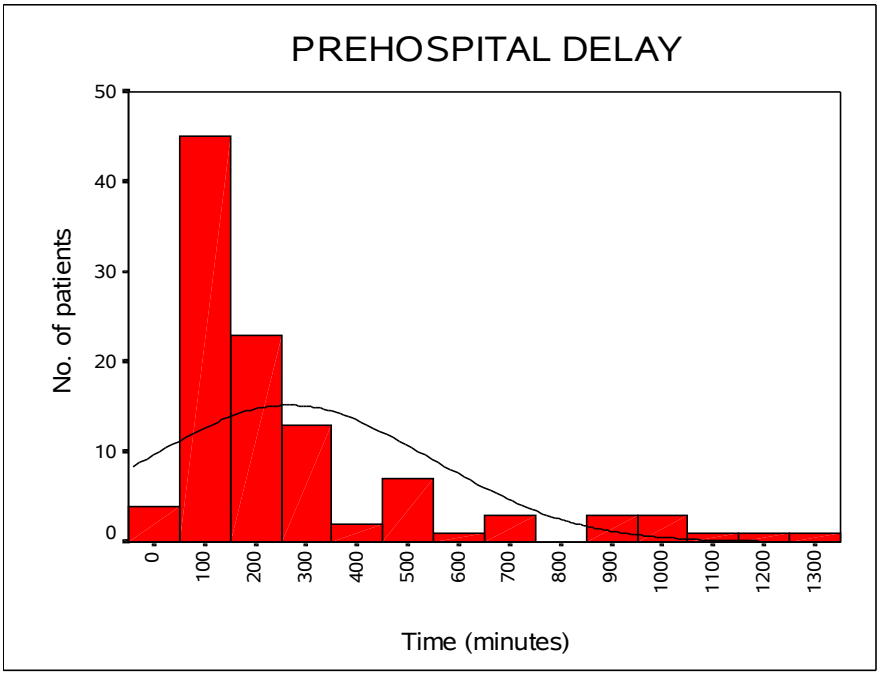
Patient time - Time interval between starting of chest pain to patient's initiation to go to hospital

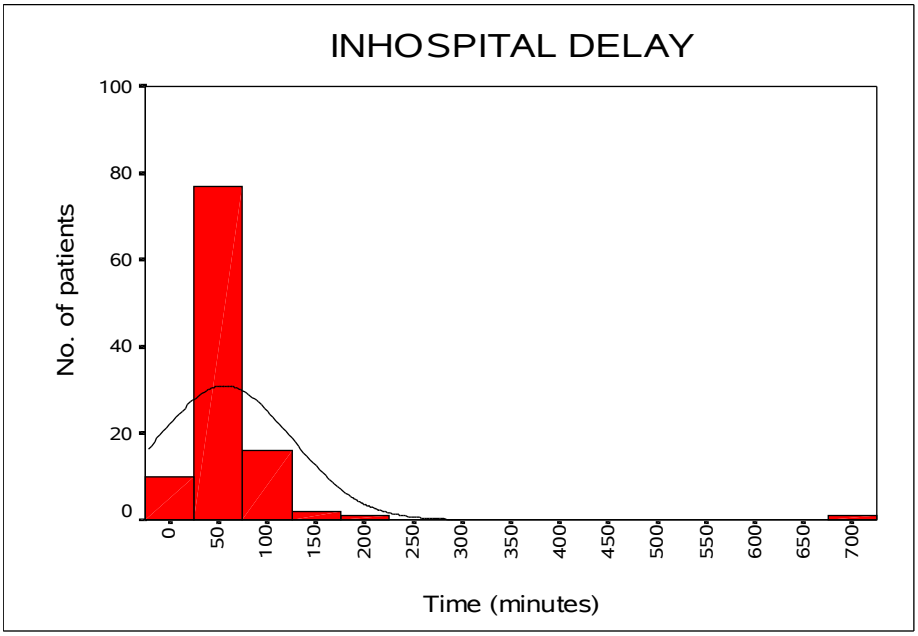
Local consult – time delay due to consultation with local practitioner

Prehosp - Time interval between starting of chest pain to entry into hospital.

DTN – Door To Needle time.

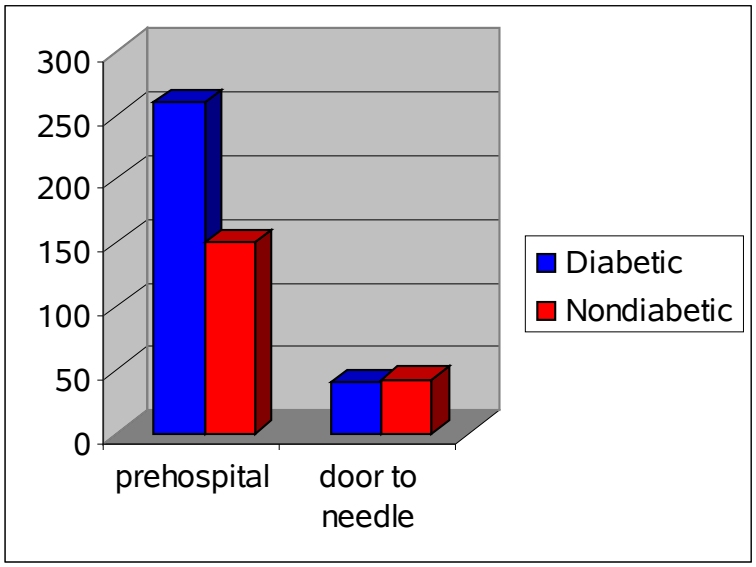
Thromb - weather patient was thrombolysed or not.





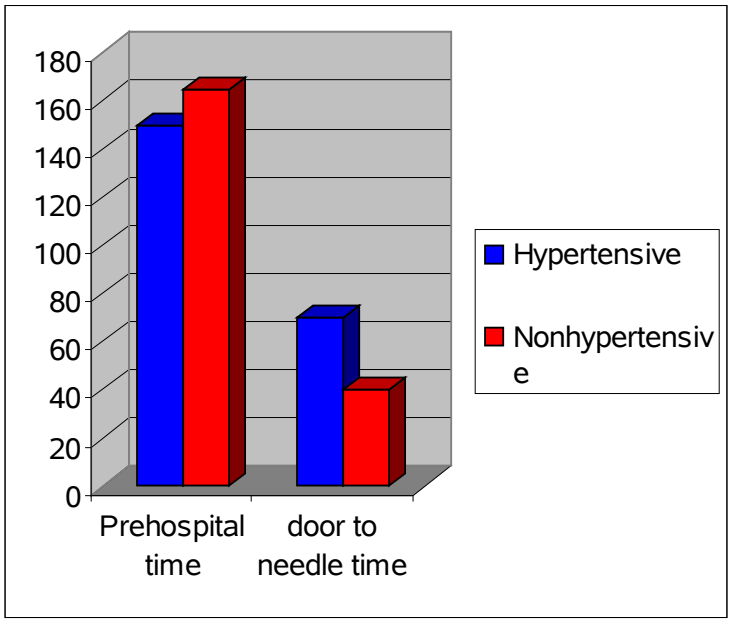
Diabetes and time interval

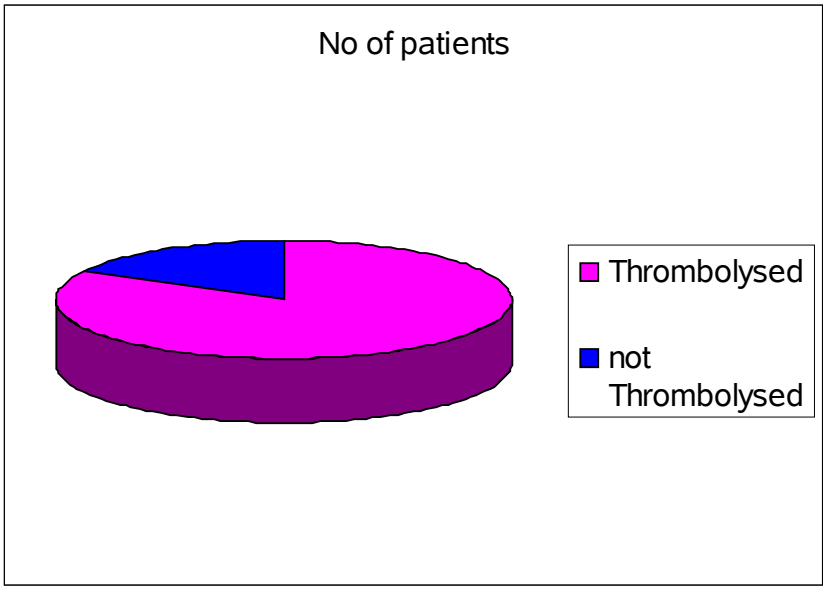
Time in minutes



Hypertension and time interval

Time in minutes





Prehospital time and delay due to prior local consultation

Time in minutes