

PHARMACO-INVASIVE THERAPY IS A CRITICAL OPTION IN NIGERIAN STEMI TREATMENT. A REVIEW

Abstract

Primary percutaneous coronary intervention (PCI) is the preferred re perfusion method in patients with ST-elevation myocardial infarction (STEMI), when performed in a timely manner and by skilled operators. However, this strategy has shown to be limited in environments with lack of PCI facilities and delay in the first medical contact-to-balloon time for logistic reasons. Pre-treatment with fibrinolytic before PCI has the potential to provide early pharmacologic re perfusion before definitive PCI in STEMI patients. Current data suggest that facilitated PCI does not offer any advantage over primary PCI. The role for pharmaco-invasive re-canalization, defined as pharmacological re-perfusion followed by rapid transfer for routine delayed coronary angiography and PCI may still be considered in centers without on-site PCI capability.

Patients presenting with STEMI in Nigeria have a lot of challenges which include delay in decision making, cost of revascularization, religious believes, ignorance and availability of cardiac catheterization and the personnel for the operation. To meet with the demand and challenges of Myocardial infarction in Nigeria, we need the mode of treatment that is beneficial, cost effective and life saving. Hence, pharmaco-invasive is the way for Nigeria and other low income countries of Africa.

Keywords: Percutaneous coronary intervention, myocardial infarction, facilitated, pharmaco-invasive.

Introduction

Coronary artery disease [CAD] is rising in Nigeria.¹⁻⁵ CAD could present as asymptomatic and symptomatic. The symptomatic Coronary artery disease could present as stable angina, unstable angina, non-ST-segment myocardial infarction [NSTEMI] and ST-segment myocardial Infarction [STEMI].⁶ The urgency of treatment depend on the presenting phenotype of CAD. Also, STEMI is the only phenotype that require the use of fibrinolytic drugs. The examples of these drugs include streptokinase, alteplase and tenecteplase.

Nigerian population

The total population in Nigeria was estimated at 211.4 million people in 2021, according to the latest census figures and projections from Trading Economics.⁷ below is the map of Nigeria with the 36 states and the federal capital territory, Abuja. figure 1 showed Nigerian map with states.



Figure 1: Nigeria map.

Definitions

Pharmaco-invasive therapy is the first administration of fibrinolytic agent, then systematically performing an angiography (and PCI if needed) within 3 to 24 hours after the start of fibrinolytic therapy; regardless of whether fibrinolysis results is successful or not.⁸ In the event of fibrinolytic failure, then rescue PCI should be performed immediately and the initial 3-hours window should not be taken into account.^{8,9}

Acute MI trial proved the usefulness of pharmaco-invasive therapy

Time to treat < 90 minutes

Time to fibrinolytic < 30 minutes

These are illustrated in figure 2 and figure 3. The diagnosis of STEMI is from the time 0 clock. The decision for choosing reperfusion strategy in patients presenting via Emergency room form out-of-hospital setting or in a non-PCI center is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion. Target times from STEMI diagnosis represent the maximum time to do specific interventions.

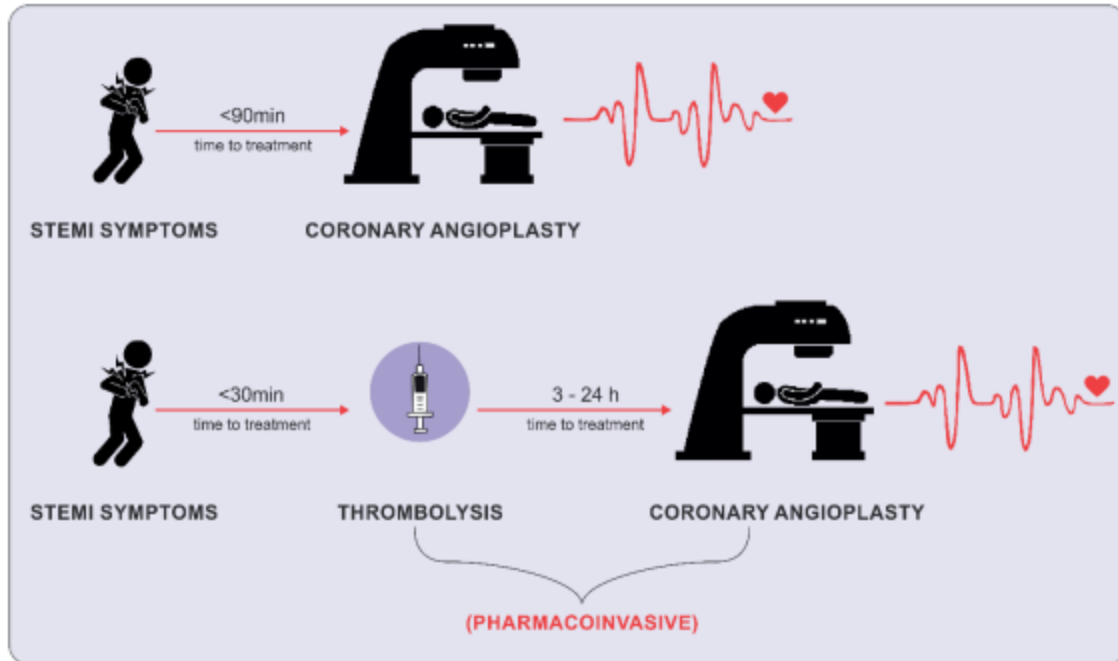


Figure 2: Pharmacoinvasive approach of STEMI care (adapted from⁹)

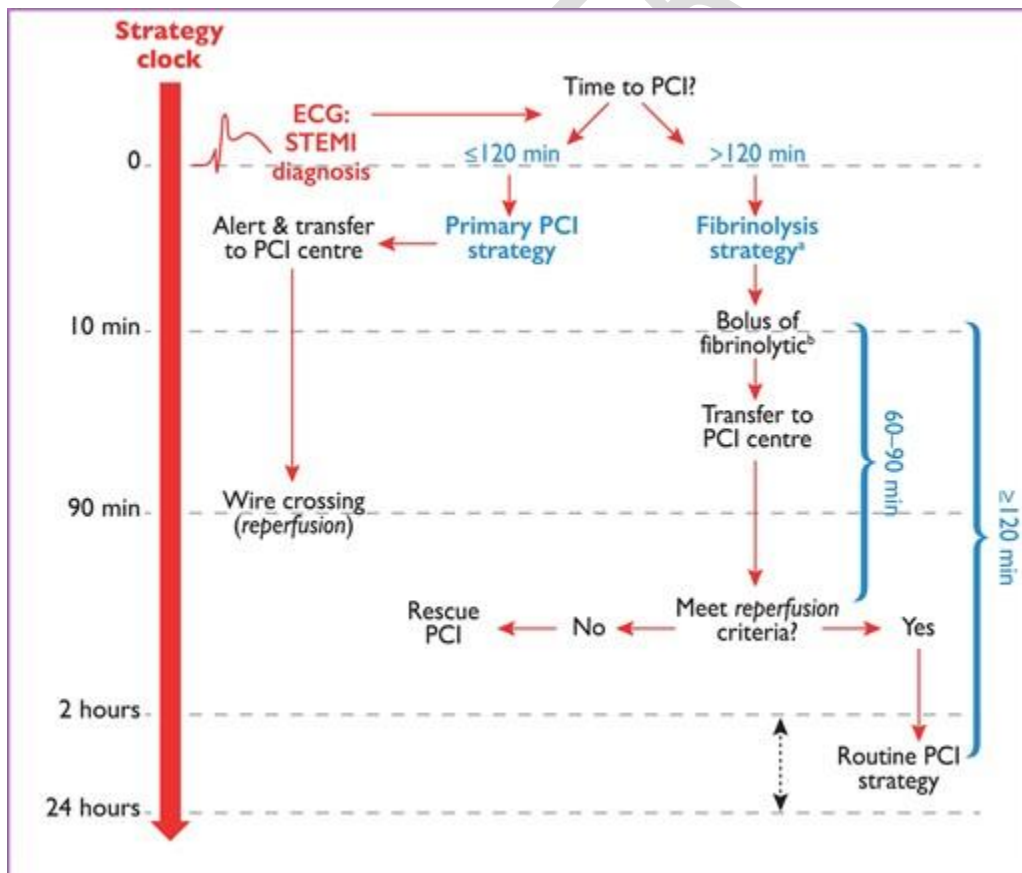


Figure 3: Target times according to reperfusion strategy selection in patients presenting via Emergency room or in a non-PCI center. ECG = electrocardiogram; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction.¹⁰ Adapted from ESC 2017 guideline.¹⁰

A STEMI patient should have PIC with stent within 90 minutes of the onset of symptoms. If patient cannot get to the Cath lab within 120 minutes, then fibrinolytic agents such streptokinase, Alteplase, tenecteplase should be given, and move patient to the cath lab for coronary angiogram with or without PCI + stent within 3-24 hours.^{8,9}

PCI CENTERS IN NIGERIA

The PCI centers are in some cities in Nigeria. These include Lagos, Yenegoa, Port Harcourt, Abuja, Enugu, Ekiti, etc. There are many cities in Nigerian 6 geopolitical regions. Most of these cities have no functional cardiac catheterization laboratory. Also, many of the hospitals with cath labs cannot perform coronary artery by-bass surgery hence they are stand alone PCI centers without surgical back up.

Challenges of STEMI Management in Nigeria

Re-perfusion therapy is the pillar of STEMI management. Among the various approach to re-perfusion, primary PCI is preferred if it can be done timely. If that is not available [within 120minutes from time 0 clock] then fibrinolytic drugs should be given and followed with urgent PCI within 24 hours in PIC-capable center.

Although primary PCI is regarded as a golden standard for re-perfusion therapy,⁷ in Nigeria it is not readily accessible due to many challenges which may include the following:

1. Accessibility: This is not limited to geographies with no access to PCI facilities, but also in regions where cardiac catheterization laboratories are available. Among those that will be available for PCI, the distance of the PCI capable center from the city where the patient lives may take several hours to get there.
2. Finance: this is one of the key challenges in STEMI treatment in Nigeria. the cost of the treatment is expensive and the patient pay from his/her pocket most time. Once patients are informed of the cost, some will give off hope, other will tell you that they will look for the money first. Only few will proceed for the therapy to meet with timing of PCI.
3. Delay within the PCI capable hospital may result from patient or Health-care system delay. Patient delay is the time from symptom onset to the first medical contact. The common cause of patient delay include finance, denial of diagnosis, wrong advise from relatives or friends, religion and ignorance and lack of awareness.

Health-care system delay is the time from medical contact to reperfusion. This may result from lack of transfer facilities or inaccessibility of hospital with PCI capabilities. Other causes of health system delay include factors such as traffic congestion, delay in shifting the patient.

4. Delayed presentation: This is one of the major problems in accessing early reperfusion therapy. Lack of public education and awareness in recognizing early signs and symptoms of myocardial infarction is a significant challenge in Nigeria. This is due to low rates of literacy and diverse society. Delay in transportation time is another major problem. For example, majority of hospitals ambulances are not equipped with paramedics. The services of paramedics in Nigeria is still far from optimal. Our roads are bad with multiple pot holes that slow than vehicle movement

While in this delay, imminent myocardial damage has occurred and the timing of primary PCI has elapsed. This can be prevented by using fibrinolytic therapy. Therefore, in the Nigerian context, pharmaco-invasive approach is a golden opportunity for the management of STEMI patients. This help in prolonging the prolongs the window of opportunity to 24 hours and provide breathing space to overcome some of the challenges listed above.

These points above highlighted the critical need of pharmaco-invasive therapy in Nigeria. This approach may cover many cities, suburban and villages in Nigeria where PCI is not readily available.

The geography and logistics of transport and cost of the procedure

The advantage of pharmaco-invasive system and any long term follow up are dependent on factors like the type of fibrinolytic agent used. In Nigeria, we must give room for pharmaco-invasive therapy. This can prove a wide time window for PCI if pharmaco-invasion is followed.

Pharmaco-invasive Reperfusion Therapy

In several clinical studies, performing initial fibrinolysis and then initiating angiography/PCI showed potential favorable effects. Table 1 represents a brief summary of studies between routine early PCI after fibrinolysis to standard therapy in STEMI patients. The concept of pharmaco-invasive therapy has also been backed by the meta-analyses, which compared ischemia-guided angioplasty after thrombolysis versus routine early coronary angioplasty.

Table 1: Trials comparing fibrinolysis plus PCI versus Primary PCI

Study (year)	Inclusion criteria	Lytic agent (type)	Strategy	Symptoms to lytic therapy/early PCI (min)	Primary endpoint
SIAM-III (2003) ¹¹	STEMI patients presenting <12 h from symptom onset.	Retepase	Standard therapy (81 patients) (rescue PCI	216	Combined death, reinfarction, recurrent ischaemia, target

			in 12%) Early PCI < 6 h from lysis (82 patients) (PCI in 100%)	192	lesion revascularization at 6 months
CARESS-IN-AMI (2008) ¹³	High-risk STEMI patients presenting <12 h from symptom onset	Reteplase (HALF dose)	Standard therapy (301 patients) (rescue PCI in 31%) Immediate PCI after lysis (299 patients) (PCI in 86%)	165 161	Combined death, Reinfarction and recurrent ischaemia at 30 days
GRACIA-1 (2004) ¹⁷	STEMI patients presenting <12 h from symptom onset	Alteplase (accelerated)	Early PCI <3 h from lysis (86 patients) (PCI in 89%) Standard therapy (251 patients) (rescue PCI in 12%)	120 187	Combined death, reinfarction, ischaemic induced revascularization at 12 months
CAPITAL-AMI (2005) ¹⁶	1 High-risk STEMI patients presenting < 6 h from symptom onset	Tenecteplase	Early PCI < 24 h from lysis (104 patients)d (PCI in 86%) Standard therapy (84 patients) (rescue PCI in 9.5%)	120 120	Combined death, reinfarction, ischaemic events or stroke at 6 months
WEST (2006) ¹⁵	STEMI patients presenting < 6 h from symptom onset	Tenecteplase	Early PCI <6 h from lysis (537 patients) (PCI in 85%) Standard therapy (100 patients)	113 113	Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock, and major ventricular

			(rescue PCI in 14%)		arrhythmia at 30 days
TRANSFER-AMI (2009) ¹⁴	High-risk STEMI patients presenting <12 h from symptom onset	Tenecteplase	Immediate PCI after lysis (134 patients) (PCI in 86%) Standard therapy (522 patients) (rescue PCI in 25%)	117 115	Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock at 30 days
NORDISTEMI (2010) ¹³	STEMI patients presenting <6 h from symptom onset	Tenecteplase	Primary PCI (948 patients) Standard therapy (132 patients) (rescue PCI in 27%)	178 126	Combined death, reinfarction, recurrent ischaemia, or stroke at 12 months
STREAM (2010) ¹²	STEMI patients presenting <3 h from symptom onset	Tenecteplase (only in age>75yrs, HALF dose)	Primary PCI (155 patients) Early fibrinolysis (<3h symptom) followed by PCI (6-24h) (944 patients) (rescue PCI in 36%)	260 100	30-day composite of death from any cause, shock, congestive heart failure, or reinfarction
STEPP AMI (2016) ¹¹	STEMI patients presenting <12 h from symptom onse	Tenecteplase	Fibrinolysis + PCI (<12h symptom) (rescue PCI 12%) Primary PCI (155 patients)	245 260	Composite of death, reinfarction, repeat revascularization, CHF

Note: STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CHF, congestive heart failure.

Fibrinolytic Options for Pharmaco-Invasive Therapy

Fibrinolytic agent lyses thrombotic occlusion associated with STEMI and restores the coronary flow. These drugs reduce infarct size and improves myocardial function and survival over the short-term and long-term. These drugs work by converting plasminogen to plasmin, the active enzyme. Plasmin is a serine protease that works by dissolving fibrin blood clots. A range of fibrinolytic agents are present in Nigeria.

These include the first generation Streptokinase to newer fibrinolytic agents such as the second generation Alteplase, and third generation Reteplase and Tenecteplase. The table 2 detail the characteristics of the commonly used fibrinolytic agents.

The characteristic features of different fibrinolytic agents are

Table 2: Characteristic features of fibrinolytic agents.¹⁹⁻²²

characteristics	Streptokinase	Alteplase	Reteplase	tenecteplase
Plasminogen activation	Indirect	Direct	Direct	Direct
Allergic reactions	Yes	No	No	No
Fibrin specificity	No	Yes	Yes	Yes
Dose /administration	1.5M	15 mg bolus plus 90-min infusion up to 85mg	10 + 10 units double bolus given over 2 min with 30 minutes apart	< 60 kg - 30 mg (6 mL) 60 to 69 kg - 35 mg (7 mL) 70 to 79 kg - 40 mg (8 mL) 80 to 89 kg - 45 mg (9 mL) ≥90 kg - 50 mg (10 mL)
Plasma half life	18mins [fast half] 83mins [slow half life]	5 mins	18 mins	20 mins
Activity on platelet rich clot	+	++	+	+++
Patency at 90 min	+	+++	+++	+++
TIMI grade 3 flow	32	54	60	63

(%)				
Systemic fibrinogen depletion	Marked	mild	Moderate	Minimal
Cost	+	++++	++++	++++

Note: TIMI, thrombolysis in myocardial infarction; PAI-1, plasminogen activator inhibitor-1

Retepase

Retepase is a second-generation recombinant tissue-type plasminogen activator. It works more rapidly and to have a lower bleeding risk than the first-generation agent alteplase. It is a synthensized fromnonglycosylated deletion mutein of tPA that contains 355 of the 527 amino acids of native tPA. The drug is produced in Escherichia coli by means of recombinant DNA techniques.²³

Retepase does not bind fibrin as tightly as native Tpa. It can diffuse more freely through the clot rather than bind only to the surface as tPA does. At high concentrations, reteplase does not compete with plasminogen for fibrin-binding sites, allowing plasminogen at the site of the clot to be transformed into clot-dissolving plasmin. These characteristics help explain why clots resolve faster in patients receiving reteplase than in those receiving alteplase.²³

The biochemical modifications also resulted in a molecule with a longer half-life (~13-16 minutes), which allows bolus administration. It is administered as two boluses of 10 U given 30 minutes apart, with each bolus administered over 2 minutes.²³ The result is more convenient administration and faster thrombolysis with reteplase than with alteplase, which is given in a bolus followed by intravenous (IV) infusion.²³ Like alteplase, reteplase may be readministered as necessary; it is not antigenic and almost never is associated with any allergic manifestations.

Tenecteplase: Tenecteplase, a variant of the t-PA. It is 527-amino-acid glycoprotein (GP) and it has modifications in amino acid molecules. These modifications included substitution of asparagine for threonine 103 and glutamine for asparagine 117, as well as a tetra-alanine substitution at amino acids 296-299 in the protease domain. It molecule is an approved agent for the treatment of STEMI.³¹ Unlike the earlier generation lytics, Tenecteplase can be administered as a single bolus over five seconds. It has the highest fibrin specificity and resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1). The weight-based dosing is the main drawback of tenecteplase, as significant dosing errors could occur due to wrong measurements of weight during the emergency situations that are common in STEMI.³¹⁻³³

Streptokinase

Streptokinase is produced by beta-hemolytic streptococci. It is not a plasminogen activator, but when it binds with free circulating plasminogen (or with plasmin), it form a complex that can convert additional plasminogen to plasmin.³⁴ Streptokinase activity is not enhanced in the presence of fibrin. Studies using radioactive streptokinase have documented two disappearance rates: a “fast” half-life (~18 minutes) and a “slow” half-life of (~83 minutes).³⁴

Because streptokinase is produced from streptococcal bacteria, it often causes febrile reactions and other allergic problems.³⁴ It can also cause hypotension that appears to be dose-related. Streptokinase usually cannot be administered safely a second time within 6 months, because it is highly antigenic and results in high levels of antistreptococcal antibodies.

Streptokinase is the least expensive fibrinolytic agent, but unfortunately, its antigenicity and its high incidence of untoward reactions limit its usefulness in the clinical setting.³⁴

Reperfusion strategy in STEMI

Once the diagnosis of STEMI is confirmed, the patient could be taken for primary PCI or pharmaco-invasive therapy. The figure 4 below explain the illustration of the steps approach to management.

UNDER PEER REVIEW

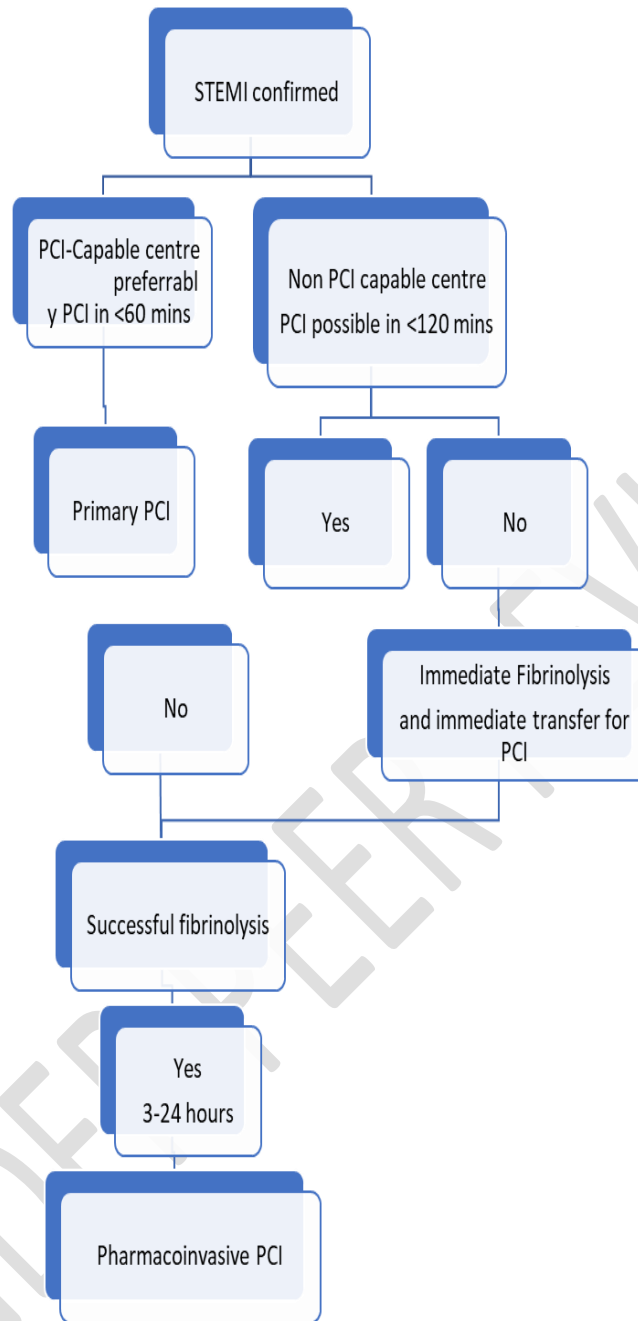


Figure 4. Reperfusion strategy in STEMI

Four types of pharmacoinvasive therapies are being utilized currently.

1. Facilitated PCI: PCI done following thrombolysis for all patients with STEMI who do not have absolute contraindication to thrombolysis.
2. Consolidating PCI: PCI early after thrombolysis that can establish recanalization when lysis has failed, and bolster benefit when it has succeeded.
3. RESCUE PCI: PCI following thrombolysis in patients in whom thrombolysis has failed.
4. DELAYED PCI : This is late PCI post thrombolysis, if needed to improve recurrent ischemia before discharge from the hospital

NEED FOR PHARMACOLOGIC INVASIVE THERAPY⁷⁻⁹

The outcome of STEMI is influenced by the time from symptomatic onset to successful reperfusion. Time is a critical factor in STEMI care. Every 30 minutes delay in treatment presents an increase of 75% mortality per year. Early fibrinolytic therapy saves life. The table 3 shows the various time targets to save the myocardium.

Import targets

Table 3. Shows imported targets in treatment of STEMI⁵⁻⁹

S/N	INTERVALS	TIME TARGET
1.	Maximum time from FMC to ECG and diagnosis	≤10minutes
2.	Maximum delay from STEMI diagnosis to primary PCI (wire Crossing) to choose primary PCI or fibrinolytic agent	≤120 minutes
3.	Maximum time from STEMI diagnosis to wire crossing in patients presenting as primary PCI hospital	≤60 minutes
4.	Maximum time from STEMI diagnosis to wire crossing in transferring patients	≤90 minutes
5	Maximum time from STEMI diagnosis to bolus or infusion of fibrinolyte	≤10 minutes
6.	Time delay from start of fibrinolyte to evaluation of its efficacy (success or failure	60 – 90minutes
7.	Time delay from start of fibrinolytic to angiogram (if fibrinolytic is successful	3 -24 hours

Contraindication of thrombolysis

1. Absolute CI

- Previous ICH or stroke of unknown origin
- Ischemic stroke in the past 6 months
- Recent major trauma/surgery/head injury (within the preceding 3 weeks)
- GI bleeding within the past month
- Known bleeding within past month
- Known bleeding disorder
- Aortic dissection
- Non compressible puncture in the past 24 hours (e.g lung biopsy, lumber puncture)

RELATIVE CI

- Transient ischemic attack in the last 6 months
- Oral anti-coagulant therapy
- Pregnancy or within one week post-partum
- Refractory hypertension > 180/100 mmHg
- Advanced lung disease
- Infective endocarditis
- Acute peptic ulcer
- Prolong traumatic resuscitation

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