

ORIGINAL ARTICLE

2013 Consensus Statement for Early Reperfusion and Pharmaco-invasive Approach in Patients Presenting with Chest Pain Diagnosed as STEMI (ST elevation myocardial infarction) in an Indian Setting

Developed in collaboration with STEMI India

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Abstract

In India, the prevalence of ST elevation myocardial infarction (STEMI) is rising exponentially leading to cardiovascular morbidity and mortality. Despite advancement in reperfusion therapy (pharmacologic and interventional), the overall utilization, system of care and timely reperfusion remains suboptimal.

Justification and Purpose: Alarming treatment delays exist in patients presenting with chest pain observed in real-world and published evidences. Time to diagnose STEMI and initiation of reperfusion therapy at various first medical contacts in India is variable mandating immediate attention. We intend to provide evidence based explicit recommendations for practicing clinicians about time-dependent early management and the concept of pharmaco-invasive (PI) approach, contextualized to the situation in India.

Process: Pre-prepared guidance document by expert steering committee was discussed and commented by over 150 experts representing from 16 states in India at regional level. The moderators of these meetings arrived at a consensus on the evaluation and management of STEMI patients by PI approach to improve clinical outcomes.

Recommendations: In addition to patient awareness and education for early symptom identification, education is required for general practitioners and physicians/intensivists to implement early time dependent STEMI management. Percutaneous Coronary Intervention (PCI) is the gold standard, yet it remains inaccessible to majority of patients, hence early reperfusion by initial use of fibrinolytics is recommended followed by coronary intervention. Fibrinolytics are easily available, economical and evaluated in several clinical studies and hence we recommend a PI approach (early fibrinolysis followed by PCI 3-24 hours later). We recommend a time guided 'Protocol/ Plan of Action' for early fibrinolysis and implementing a PI approach at the level of general practitioners, non-PCI hospitals/nursing homes with intensive care facility and in PCI capable centers. For STEMI patients with symptom duration ≤ 6 hours, we suggest administration of fibrinolytics either tenecteplase (Grade1A), reteplase (Grade1B), alteplase (Grade1C) or streptokinase (Grade 2B) alongside contemporary adjunctive medical therapy for PI approach.

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The aim of this Consensus Statement is

- To provide explicit recommendations for practicing clinicians about the early management of STEMI and concept of pharmaco-invasive approach
- To provide recommendations based on the best available evidences, contextualized to the situation in India

It must be recognized that even when randomized clinical trials have been undertaken, treatment options may be limited by resources. The Cardiocare STEMI experts realize that the recommended diagnostic examinations and treatment options may not be available or affordable in all parts of India. Cost-effectiveness is becoming an increasingly important issue when deciding upon therapeutic strategies. As always with guidelines/consensus statement, they are not prescriptive. Clinical scenario and patients vary so much from one another that individual care is paramount, and there is still an important place for clinical judgment, experience, and common sense.

The mandate of the Cardiocare STEMI expert consensus is to recommend evidence-based standards of care, related targets and strategies for implementation of standards in the management of STEMI.

Context and Use

This document should be taken as consensus recommendations by qualified experts, not as rigid rules. It comprises of published evidence and may not cover every eventuality; new evidence is published every day.

Furthermore, this should not be used as a legal resource, as the general nature cannot provide individualized guidance for all patients under all clinical circumstances.

Introduction

Coronary artery disease (CAD) is currently the most common, non-communicable disease in India and will affect over 65 million of its people by the year 2015.¹ One of the gravest complications of CAD is ST-elevation myocardial infarction (STEMI).¹ Acute ST-segment elevation myocardial infarction is caused by coronary plaque disruption with exposure of substances that promote platelet activation, adhesion, and aggregation, thrombin generation, and thrombus formation leading to an occluded epicardial infarct-related artery (IRA).²

Reperfusion is the key strategy in acute STEMI care,³ and it is time-dependent. Shortening the time from symptom to reperfusion and choosing the optimal reperfusion strategy for STEMI patients are great challenges in practice.⁴ Although extensive efforts have been taken by American College of Cardiology/American Heart Association (ACC/AHA),⁵⁻⁷ European Society of Cardiology (ESC)⁸ and Association of Physicians of India (API)⁹ in development of STEMI management guidelines to minimize mortality and benefit STEMI patients, a gap between the guidelines and implementation in the clinical setting still exists.

Plight of Reperfusion : What happens in the real world?

The most complete data about contemporary trends in STEMI patients in India comes from CREATE¹⁰ a large prospective clinical registry of acute coronary

syndrome (ACS) patients from 89 large hospital centers from 10 regions and 50 cities across India and Kerala ACS Registry which prospectively collected data on 25,748 consecutive ACS admissions from 2007 to 2009 in 125 hospitals in Kerala.¹¹

Among the 20,468 patients enrolled in CREATE, over 60% (12,405) patients had STEMI, a proportion that is substantially higher than registry from developed countries which documented around 40 percent. The median time from the onset of symptoms to hospital arrival was 300 min in STEMI patients, again more than double the delay reported in developed countries (range from 140 to 170 min). In hospital it took a further 50 min to undergo fibrinolysis, compared with a range of 32-40 min in developed countries. Only 5% of the patients utilized ambulance and majority came to the hospital by private transportation. Clinical outcomes were worse in patients with STEMI as compared to patients with NSTEMI, with a lower rate of death (3.7% vs 8.6%), reinfarction (1.2% vs 2.3%), and stroke (0.3% vs 0.7%, $p < 0.0001$ for all). Approximately 59% received fibrinolytic therapy and only 9% underwent primary percutaneous coronary intervention (PCI) during their hospitalization, suggesting substantial room for improvement in the use of acute reperfusion therapy in STEMI patients in India.¹⁰

Even the Kerala ACS Registry documented that STEMI was the most common ACS admission diagnosis and had the highest in-hospital mortality and non-fatal event rates. STEMI patients were less likely to have any formal education and more likely to present more than 6 hours after symptom onset.

In-hospital medical therapy was relatively high overall, 90% received anti-platelet therapy while thrombolytics were used in 41% of STEMI patients. Primary PCI and CABG were performed relatively infrequently and inappropriate thrombolysis was relatively high. Patient-level variables such as STEMI diagnosis and delayed symptom-to-door time were associated with increased risk of mortality.¹¹

Challenges for STEMI System of Care in India^{1,10}

Primary PCI in acute myocardial infarction is proven world over as the gold standard of treatment by way of establishing high percentage of complete and lasting reperfusion. But this treatment modality is available to less than 10% STEMI patients in India.

In Indian context, even small towns are densely populated, traffic congestions and transfer to hospitals take a long time causing delay in time to treatment. Initial delay is by the patient due to lack of awareness. Next delay is due to lack of transfer facilities or unavailability of hospital with PCI capabilities. The third delay is possible within a tertiary care PCI capable hospital where reaching from casualty/emergency department to establishing Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow has delays due to various factors viz. finances, obtaining consent, round the clock man power (cardiologist and staff) and availability of PCI lab in busy hours.

Several challenges largely arise in India due to the distinctive structure of its healthcare system, which is one of the most privatized in the world. The first concern is overall low healthcare spending per person which has led to poor infrastructure for managing medical emergencies and lesser PCI capable hospitals at the population level, especially in rural districts. This gap has been most apparent for pre-hospital emergency medical systems. Second, inadequate public and private health insurance programmes places STEMI patients and their families at great personal financial risk from treatments, contributing to the underutilization of evidence-based therapies. Finally, public education and awareness on identifying early signs and symptoms of myocardial infarction is a substantial challenge given India's low rates of literacy and diverse society.¹

Unfortunately, the overall use and quality of acute reperfusion therapy in India is lagging.^{1,10,11} The consensus statement therefore attempts to guide clinicians for early reperfusion that can easily be translated into clinical practice while focusing on the choice of fibrinolytic agent, plan of action for early reperfusion and pharmaco-invasive approach to bridge the gap in STEMI early reperfusion strategy.

Early patient presentation, rapid diagnosis and early reperfusion in patients presenting with acute chest pain constitute the pillars of success in STEMI management.

Fibrinolytic therapy and primary PCI are two commonly used reperfusion strategies in its management and they are conventionally viewed as mutually exclusive alternative therapeutic modalities". However, well established principles and a great deal of recently acquired clinical evidences support the view that the two in combination are synergistic and their combination is referred as "pharmaco-invasive therapy".¹²⁻¹⁴

Pharmaco-invasive Approach¹²⁻¹⁴

Definition: Pharmaco-invasive therapy means first administering early fibrinolysis and then systematically performing an angiography (and a PCI if needed) within 3 to 24 hours after the start of fibrinolytic therapy, regardless of whether fibrinolysis results in successful reperfusion or not. In the event of fibrinolytic failure, a rescue PCI should be immediately performed where one need not wait for the initial 3 hour window.

Need for pharmaco-invasive approach

Outcome of patients with STEMI is strongly influenced by the time from symptom onset to successful reperfusion.

1. Time is a crucial factor in STEMI care. "Time is myocardium" is a familiar adage. The risk of 1-year mortality is increased by 7.5% for each 30-minute delay in treatment.^{12,15} A delay in undergoing primary PCI greatly reduces the benefits from the invasive procedure. Nallamothe et al. showed that the mortality benefit associated with primary PCI was lost if PCI-related delay exceeded 60 min.¹⁶ In theory, early fibrinolytic therapy can compensate for PCI-related delay.
2. Concept of Golden Hours : Early fibrinolytic therapy have documented benefits of 65, 37, 26 and 29 lives saved per 1000 treated patients in the 0-1hour, 1-2hr, 2-3hr, and 3-6 hr intervals, respectively. Proportional mortality reduction was significantly higher in patients treated within 2 hours with fibrinolytics compared to those treated later.¹⁷ Prompt fibrinolytic treatment improved the likelihood of aborted myocardial infarction and the greatest incidence occurred in those patients treated within 1 hour of symptom onset, with a sharp drop off after 3 hours.¹⁸
3. As mentioned earlier, data from CREATE registry¹⁰ and Kerala ACS Registry¹¹ indicate alarming delays exist in patient presentation and delays in initiating timely reperfusion hence

Table 1 : Trials comparing routine early PCI after fibrinolysis to standard therapy and some versus Primary PCI alone in STEMI patients

Study (year)	Inclusion criteria	Lytic agent (type) ^f	Strategy	Symptom to lytic/reperfusion therapy (min)	Primary end point
SIAM-III (2003)	STEMI patients presenting <12 h from symptom onset.	Retepase	Standard therapy (81 patients) (rescue PCI in 12%)	216	Combined death, reinfarction, recurrent ischaemia, target lesion revascularization at 6 months
			Early PCI < 6 h from lysis (82 patients) (PCI in 100%)	192	
CARESS-IN-AMI (2008)	High-risk STEMI patients presenting <12 h from symptom onset	Retepase (HALF dose) ^a	Standard therapy (301 patients) (rescue PCI in 31%)	165 ^b	Combined death, reinfarction and recurrent ischaemia at 30 days
			Immediate PCI after lysis (299 patients) (PCI in 86%)	161 ^b	
GRACIA-1 (2004)	STEMI patients presenting <12 h from symptom onset	Alteplase (accelerated)	Standard therapy (251 patients) (rescue PCI in 12%)	187	Combined death, reinfarction, ischaemic-induced revascularization at 12 months
			Early PCI < 6–24 h from lysis (248 patients) (PCI in 80%)	180	
CAPITAL-AMI (2005)	High-risk STEMI patients presenting ≤ 6 h from symptom onset	Tenecteplase	Standard therapy (84 patients) (rescue PCI in 9.5%)	120 ^b	Combined death, reinfarction, ischaemic events or stroke at 6 months
			Early PCI <3 h from lysis (86 patients) (PCI in 89%)	120 ^b	
WEST (2006) ^e	STEMI patients presenting < 6 h from symptom onset	Tenecteplase	Standard therapy (100 patients) (rescue PCI in 14%)	113 ^b	Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock, and major ventricular arrhythmia at 30 days
			Early PCI < 24 h from lysis (104 patients) ^d (PCI in 86%)	130 ^b	
TRANSFER-AMI (2009)	High-risk STEMI patients presenting <12 h from symptom onset	Tenecteplase	Standard therapy (522 patients) (rescue PCI in 25%)	115 ^b	Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock at 30 days
			Early PCI <6 h from lysis (537 patients) (PCI in 85%)	113 ^b	
NORDISTEMI (2010)	STEMI patients presenting <6 h from symptom onset	Tenecteplase	Standard therapy (132 patients) (rescue PCI in 27%)	126 ^b	Combined death, reinfarction, recurrent ischaemia, or stroke at 12 months
			Immediate PCI after lysis (134 patients) (PCI in 86%)	117 ^b	

Contd. 2...

Table 1 : Trials comparing routine early PCI after fibrinolysis to standard therapy and some versus Primary PCI alone in STEMI patients (Contd...)

Study (year)	Inclusion criteria	Lytic agent (type) ^f	Strategy	Symptom to lytic/reperfusion therapy (min)	Primary end point
STREAM (2013) ⁶	STEMI patients presenting <3 h from symptom onset	Tenecteplase (only in age>75yrs, HALF dose)	Early fibrinolysis (<3h symptom) followed by PCI (6-24h) (944 patients) (rescue PCI in 36%)	100 ^b	30-day composite of death from any cause, shock, congestive heart failure, or reinfarction
			Primary PCI (948 patients)	178 ^b	
STEPP AMI ⁸ (2013) Indian patients ⁴⁸	STEMI patients presenting <12 h from symptom onset	Tenecteplase (innovator)	Fibrinolysis + PCI (<12h symptom) (rescue PCI 12%)	245 ^b	Composite of death, reinfarction, repeat revascularization, CHF
			Primary PCI (155 patients)	260 ^b	

a-Plus abciximab of 0.25 mg/kg/bolus followed by 0.125 mg/kg/min infusion for 24 h.; b-Expressed as median other times as average; c-Calculated as (time from symptom onset to early PCI) 2 (time from symptom onset to lytic therapy); d-Includes 29 patients referred to rescue PCI; e-Includes also one arm randomized to primary PCI; f-Dose of fibrinolytics are per the full dose in their prescribing information unless mentioned otherwise; g- Trials comparing lysis + PCI versus Primary PCI

pharmaco-invasive approach could theoretically improve myocardial salvage and ultimately improve clinical outcomes.¹⁹

Indications

1. Pharmaco-invasive approach is appropriate for patients with STEMI who are eligible for treatment with fibrinolytic drugs and in whom "transfer time" ≥ 30 min (refer figure 2) or door-balloon time ≥ 90 min [first medical contact to balloon time is ≥ 120 min].
2. PCI related delay: (door-to-balloon) minus (door to needle) > 60 minutes

Thus shortening the time to reperfusion of the IRA by prompt initiation of pharmacological followed by early PCI to consolidate the initial reperfusion process and prevent reocclusion of the IRA may be the optimal reperfusion strategy for patients with STEMI.

Evidence for pharmaco-invasive approach

Early fibrinolysis followed by angiography/PCI has reported more favorable results.²⁰⁻³⁰ The important trials comparing routine early PCI after fibrinolysis to standard therapy and some versus primary PCI alone are summarized in Table 1. The hypothesis of pharmaco-invasive strategy is also supported by meta-analysis²¹ when comparing the combined therapy with the standard ischemia-guided PCI. Compared to routine treatment after fibrinolysis, early PCI within 24 hours of fibrinolysis significantly reduced the composite endpoint of death, re-infarction and ischemia within 30 days. In addition, no more severe bleeding events, which may result from the extended time interval between PCI and fibrinolysis, were observed.²¹

The 2010 European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)²⁵ guidelines on myocardial revascularization also recommended that patients going to a non PCI-capable hospital should receive fibrinolysis immediately and then be transferred to a PCI-capable hospital if the expected Door-to-Balloon time is more than 2 hours. Routine angiography and urgent PCI are indicated after successful fibrinolysis in a time window of 3–24 hours.²⁵

Recent Clinical Evidences on Pharmaco-invasive Strategy

CARESS-in-AMI trial²⁶ was an open label, prospective, multicentre trial which randomized 600 patients aged < 75 years with one or more high-risk features in hospitals who were treated with half-dose reteplase, abciximab, heparin, and aspirin, and randomly assigned to immediate transfer to the nearest interventional centre for PCI, or to management in the local hospital with transfer only in case of persistent ST-segment elevation or clinical deterioration. Rescue PCI was done in 91 patients (30.3%) in the standard care/rescue PCI group. The primary outcome occurred in 13 patients (4.4%) in the immediate PCI group compared with 32 (10.7%) in the standard care/rescue PCI group (hazard ratio 0.40; 95% CI 0.21–0.76, $p=0.004$). There were no significant differences in major bleedings or strokes in immediate PCI group versus standard care/rescue group concluding that immediate transfer for PCI improves outcome in high-risk patients with STEMI treated at a non-interventional centre with half-dose reteplase and abciximab.²⁶

STREAM trial²⁸ was an open-label, prospective, randomized, multicentre, exploratory trial which evaluated the outcome of patients presenting early,

Table 2 : Fibrinolytic Agents for the Treatment of STEMI³¹⁻³³

Characteristics	Streptokinase	Alteplase	Reteplase	Tenecteplase
Allergic reactions	Yes	No	No	No
Plasminogen activation	Indirect	Direct	Direct	Direct
Fibrin specificity	-	++	+	+++
Dose /administration	1.5 MU infusion over 60 min	15 mg bolus plus 90-min infusion up to 85mg	10 + 10 units double bolus given over 2 min with 30 minutes apart	0.53 mg/kg single bolus given over 5 seconds
Plasma half life	18	5	18	20
Resistance to PAI-I	No	No	No	Yes
Activity on platelet rich clot	-	++	+	+++
Patency at 90 min	+	+++	+++(+?)	+++ (+?)
TIMI grade 3 flow (%)	32	54	60	63
Systemic fibrinogen depletion	marked	mild	moderate	minimal

including in a prehospital setting, with ST-elevation myocardial infarction within 3 hours of symptom onset. Almost 2,000 patients were randomized to fibrinolysis with tenecteplase combined with enoxaparin, clopidogrel, and aspirin, and followed by timely angiography within 6 to 24 hours, or rescue coronary intervention if reperfusion fails within 90 minutes of fibrinolysis, versus primary PCI performed according to local standards. Fibrinolysis versus PCI was associated with an increased risk of intracranial bleeding (1.0% vs. 0.2%, P = 0.04; after protocol amendment, 0.5% vs. 0.3%, P = 0.45).²⁸ However, the risk of ICH (1.0%) is expected, non-alarming and similar to reported data on ICH with tenecteplase in landmark clinical trials. The rates of nonintracranial bleeding were similar in the two groups. The study concluded that pre-hospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early STEMI who could not undergo primary PCI within 1 hour after the first medical contact.²⁸

STEPP AMI:^{29,30} Promising data emerges from India for a pharmaco-invasive approach. The results of the first Indian trial, a prospective, observational, multicentric study evaluated the efficacy and safety of a strategy of early fibrinolytic treatment with tenecteplase (innovator product) and additional antiplatelet and antithrombin therapy followed by catheterization (pharmaco-invasive strategy) within 3-24 hours with timely coronary intervention as appropriate versus standard primary PCI in 200 patients with acute myocardial infarction within 12 hours of symptom onset were presented at STEMI INDIA and ACT 2013 conference.³⁰ In an interim presentation ahead of the publication, the STEPP-AMI investigators concluded that pharmaco-invasive strategy was safe and associated with comparable outcomes as primary PCI at 1 year and was associated with more than 80% infarct related artery patency even when the total ischemic time was about 4 hours.³⁰ Significant portion of patients did not require stenting. Patients in pharmaco-invasive arm had lower thrombus burden and better TIMI flows with no

increase in bleeding risk. pharmaco-invasive strategy may successfully alleviate the logistic or geographical barriers of primary PCI in the treatment of AMI in India.³⁰

Choice of Fibrinolytic Agent for Early Reperfusion

A range of options are currently available in India (Table 2)³¹⁻³³

First Generation

Streptokinase: It is still a commonly used thrombolytic agent in India. Streptokinase is isolated from bacteria and hence is antigenic. Potential disadvantages also include i.v. infusion needed, low fibrin specificity, shorter half life, risk of anaphylactic reactions and hemorrhage.

Second Generation

Tissue Plasminogen Activator (t-PA, alteplase): It is a second generation fibrinolytic and produces only mild systemic fibrinogen depletion. t-PA is administered in an accelerated dose regimen over 90 minutes. Although a fibrin specific agent (++) , the use may be limited since an i.v. infusion is required.

Third Generation

They have increased fibrin specificity, increased resistance to inhibition by plasminogen activators and longer half life.

Reteplase is a third-generation variant of the t-PA molecule. It is a fibrin specific agent (+) and administered as a double bolus; each dose consists of 10 units given over two minutes 30 minutes apart.

Tenecteplase: Tenecteplase, most recently approved for the treatment of STEMI, is a third-generation variant of the t-PA molecule. Unlike its predecessors, tenecteplase can be administered as a single bolus over five seconds. It has highest fibrin specificity (+++) and resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1); desirable in a fibrinolytic agent.

It has an advantage of ease of administration,

weight-adjusted, single-bolus administration.³¹ Thus administration of third generation agents (tenecteplase/ reteplase) could be crucial in early fibrinolysis and transfer of a STEMI patient to a tertiary care hospital.

Consensus Statement

The Consensus Development Protocol

Over 150 medical experts from across India and belonging to the specialty of internal medicine, emergency medicine, and interventional cardiology representing reputed medical institutions, hospitals

and clinical practice participated in six regional consensus meetings. The steering committee prepared a draft document ahead of the regional summit, which was presented including historical evidences and data from clinical trials, discussed and commented for changes in all regional meetings. After incorporating the suggestions from each region, the revised regional consensus document was discussed by the moderators. The moderator’s consensus meeting was held at Mumbai on 17th March 2012. The rationale, background, and proposals were discussed by 10 experts/moderators to form the final consensus. The consensus statement therefore attempts to provide clinicians with a set of evidence based recommendations and consensus for early reperfusion that can easily be translated into the practice of caring for STEMI patients in India. It also focuses on the choice of fibrinolytic agent, preferred pathway/plan of action for early reperfusion and pharmaco-invasive approach to bridge the gap in STEMI early reperfusion strategy. The endeavor is to simplify patient flow and provide scientific guidance to optimize early reperfusion to healthcare practitioners who encounter patients presenting with chest pain diagnosed as STEMI.

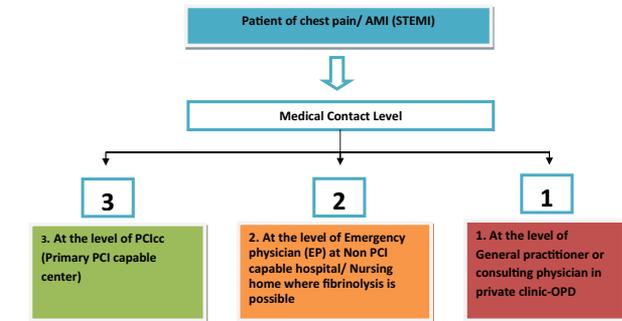


Fig. 1 : An Indian scenario where a STEMI patient approaches a medical contact at different levels

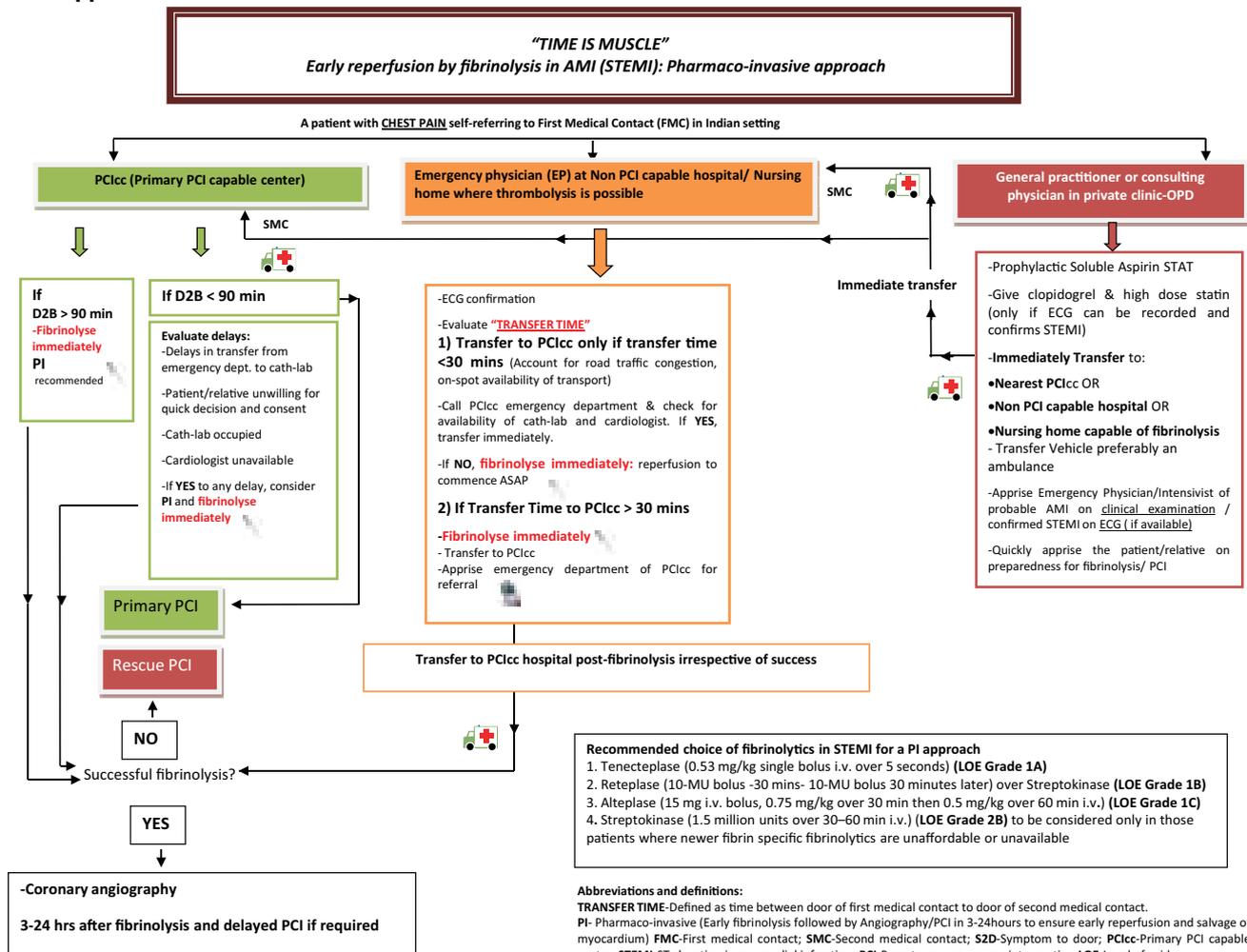


Fig. 2 : Recommended plan of action for early reperfusion and pharmaco-invasive approach

Improvement of STEMI Care in India

Patient - Awareness, Education and Plan of Action

- Early identification of symptoms and early presentation to registered medical practitioner/ STEMI designated hospitals
- Importance of early presentation and reperfusion strategies including availability of treatment for AMI at nearby hospitals.
- Encourage the patients to carry baseline ECG during transfer to PCI/Non PCI Hospitals

Physician education

- Time dependant decision taking
- Immediate ECG in patients of suspected AMI and confirmation of STEMI
- To avoid delay in reperfusion and importance of early reperfusion
- Systematic protocol, guideline adherence and knowledge of newer fibrinolytic agents and their advantages
- Pharmaco-invasive concept in STEMI management

Preferred Plan of Action/ Protocol for Early Reperfusion and Pharmaco-invasive strategy in STEMI patients in INDIA

Based upon the opinion of experts, Figure 1 represents the various scenarios in which STEMI patients with chest pain present to medical contact points. While Figure 2 illustrates the preferred plan of action and pathway for achieving early reperfusion. Clinicians are recommended to follow Figure 2 in order to streamline and improve the management of STEMI care in India.

Plan of Action / Protocol Flow Chart

Early Reperfusion and Pharmaco-invasive Approach

1. First Medical Contact (FMC) at the level of General Practitioner or Consulting Physician in private clinic /OPD

- All patients of chest pain / suspected of AMI on clinical diagnosis should receive prophylactic dose of 350 mg soluble /chewable aspirin (non enteric-coated) immediately.
- Immediate ECG recording (if available) and confirm the diagnosis of STEMI (if possible).
- Clopidogrel (300 mg if patient age \leq 75 years or 75mg if age $>$ 75 years) and Statins (Atorvastatin 40 -80 mg) should be administered after confirmation of STEMI by ECG.
- In order to achieve early reperfusion and obtain best benefit outcomes, it is very important for the GP/Physician to take time

dependent decision and transfer immediately (preferably by ambulance) to the nearest reperfusion capable centre (PCI Capable centers/ hospitals where fibrinolysis is possible) to avoid any further delay in STEMI treatment.

(Note: GP to avoid referring the patients to diagnostic centers as they take 3-4 hours of precious time for ECG reporting that may add to delay in timely intervention)

- GP/Physician needs to maintain a list and contact details of nearby PCI Capable centers/ Non PCI hospitals for quick and immediate plan of action and to avoid delays in transfer. Also, encourage the patients to carry baseline ECG if recorded.
 - GP/Physician should quickly apprise the patient/relatives regarding condition of the patient and gain their confidence towards preparedness for fibrinolysis/ primary PCI. This aids in patient information, reduces the apprehension and time for decision and avoids further delay in treatment.
- #### 2. First / Second Medical Contact at the level of Emergency physician at Non PCI capable hospital/ nursing home capable of fibrinolysis
- All suspected cases of chest pain or AMI on clinical evaluation, immediate ECG recording is mandatory to confirm the diagnosis of STEMI.
 - To achieve early reperfusion and obtain best benefit outcomes, it is also very important for the emergency physician at non PCI capable hospital / Nursing home capable of fibrinolysis to take time dependent decision and evaluate the transfer time for invasive therapy in STEMI treatment.
 - Evaluate the TRANSFER TIME
 - Transfer Time is defined as time between first medical contact (FMC) to PCI capable hospital
 - Transfer to primary PCI capable center only if 'transfer time' is $<$ 30 minutes.
 - Emergency physician also needs to anticipate the transfer time taking in account road traffic congestion, on-spot availability of transport and distance of the PCI center from the current setup.
 - The emergency physician should call emergency department of PCI capable hospital and check for availability of cath-lab and cardiologist. If available, only then transfer the patient immediately to the primary PCI capable hospital/center. (Preferably in a cardiac care ambulance)
 - If cath-lab and cardiologist are occupied/

Table 3 : Adjunctive therapyWith fibrinolytic therapy^{5,8,35}**1 Antiplatelet co-therapy**

If not already on oral Aspirin, 350 mg soluble or chewable (non enteric coated) Aspirin PLUS Clopidogrel oral loading dose (300mg) if age ≤ 75 years
If age > 75 years start with maintenance dose of Clopidogrel (75 mg)

2.1 Antithrombin co-therapy

With alteplase, reteplase and tenecteplase :

In patients < 75 years Enoxaparin i.v. bolus of 30 mg followed 15 min later by s.c. dose of 1 mg/kg. The first two s.c. doses should not exceed 100 mg.

In patients > 75 years: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg for the first two s.c. doses

If enoxaparin is not available, a weight-adjusted bolus of i.v. heparin followed by a weight-adjusted i.v. infusion with first aPTT control after 3 hours

2.2 With streptokinase

Fondaparinux 2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge OR

Enoxaparin i.v. bolus followed 15 minutes later first s.c. dose, if age > 75 years, no i.v. bolus and start with reduced first s.c. dose OR

A weight-adjusted dose of i.v. heparin followed by a weight adjusted infusion

Note: Prasugrel and Ticagrelor have not been clinically evaluated along with fibrinolysis and should be avoided until data is available.

unavailable at the PCI capable hospital, then immediately fibrinolyse the patient and administer contemporary adjunctive therapy (reperfusion to commence as soon as possible)

- ii. If 'transfer time' to primary PCI capable center is > 30 minutes then fibrinolyse the patient immediately, administer contemporary adjunctive therapy including anti-platelets and anti-thrombotic agents (Table 3) and then transfer to primary PCI capable center irrespective of reperfusion status (preferably in a cardiac care ambulance)

3. Medical contact at the level of Primary PCI capable hospital/Center

A time dependant approach and decision has to be taken for early reperfusion upon diagnosis of STEMI. Delays in reperfusion strategy occurring at the Primary PCI capable hospital need to be accounted namely:

- Patient counselling regarding the condition and PCI procedure
- Delays in transfer from emergency dept. to cath-lab
- Patient/relative unwilling for quick decision, consent and arrangement of finance
- Cath-lab occupied
- Cardiologist unavailable

- i. If the Door to Balloon time is expected

to be < 90 minutes, then Primary PCI is recommended

- ii. If the Door to Balloon time is expected to be > 90 minutes, (for any of the above cited reasons) then fibrinolyse immediately, administer adjunctive therapy including anti-platelet and antithrombotic agents and perform intervention as recommended 3–24 hours after fibrinolysis.

Choice of Fibrinolytic Agents for Early Reperfusion and Pharmacoinvasive Approach

Almost all of the pharmacoinvasive strategies have been clinically evaluated with i.v. bolus agents only. In an Indian scenario, for all eligible STEMI patients, immediate fibrinolytic therapy alongside contemporary adjunctive medical therapy must be administered in patients presenting with symptom onset < 6 hours. This facilitates early reperfusion and in adopting a pharmacoinvasive approach.

We recommend one of the following lytics in a pharmacoinvasive approach with a level of evidence (LOE)³⁴

1. Tenecteplase (0.53 mg/kg single bolus i.v. over 5 seconds) [LOE Grade 1A]
2. Reteplase (10-MU bolus -30 mins + 10-MU bolus 30 minutes later) over Streptokinase [LOE Grade 1B]
3. Alteplase (15 mg i.v. bolus, 0.75 mg/kg over 30 min then 0.5 mg/kg over 60 min i.v.) [LOE Grade 1C]
4. Streptokinase (1.5 million units over 30-60 minutes i.v.) [LOE Grade 2B] To be considered only in those patients where newer fibrin specific fibrinolytics are unaffordable or unavailable

Note: Due to limited data on streptokinase, it is suggested that angiography and PCI should be performed in later half of time window of 3–24 hours post-streptokinase as fibrinolytic agent. For PI approach and rescue PCI, radial approach should be preferred.

Adjunctive Therapy^{5,8,35}

Alongwith thrombolytic therapy, the use of adjunctive medicines like antiplatelets and antithrombin therapy is extremely important in clinical management of STEMI. With each fibrinolytic, it is recommended to use specific therapies as described in Table 3.

Consensus Summary

Addressing appropriate STEMI care in India is the need of the hour. In addition to patient awareness and education for early symptom identification, extensive education is required for general practitioners and physicians/intensivists to implement early time dependent STEMI management. Primary PCI is the gold standard, yet it remains inaccessible to majority patients, hence early reperfusion by initial use of fibrinolytics is recommended followed by coronary intervention. Fibrinolytics are easily available, economical and evaluated in several clinical studies and hence we recommend a Pharmaco-invasive approach.

Pharmaco-invasive therapy means first administering early fibrinolysis and then systematically performing an angiography (and a PCI if needed) within 3 to 24 hours after the start of fibrinolytic therapy, regardless of whether fibrinolysis results in successful reperfusion or not. In the event of fibrinolytic failure, a rescue PCI should be immediately performed where one need not wait for the initial 3 hour window.

We recommend a time guided 'Protocol/ Plan of Action' (Figure 2) for early fibrinolysis and implementing a Pharmaco-invasive approach at the level of general practitioners, non-PCI hospitals/nursing homes with intensive care facility and in PCI capable centers. Fibrinolysis should be performed either with tenecteplase (Grade1A), reteplase (Grade1B), alteplase (Grade1C) or streptokinase (Grade 2B) alongside contemporary adjunctive medical therapy for Pharmaco-invasive approach.

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