Pharmaco-invasive Therapy with Fibrinolytic Agents: A Potent Lifesaving Reperfusion Strategy in STEMI Patients in Metro/Tier-I Cities in India

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Abstract

Background: Prompt reperfusion of ischemic myocardium is the focus of acute treatment of patients with ST-segment elevation myocardial infarction (STEMI). The reperfusion approaches include fibrinolytic therapy and primary percutaneous coronary intervention (PCI) which are conventionally considered as mutually exclusive therapeutic modalities. Although primary PCI has been considered as the gold standard, it is not a feasible choice in a large number of patients in India. Despite the availability of PCI capable facilities in metro and tier-I cities in India, STEMI management in these cities pose peculiar challenges. Therefore, fibrinolytic therapy followed by systematic angiography and PCI of the infarct related artery, if indicated, within 2–24 hours (pharmaco-invasive strategy) might hold tremendous practical significance in these locations in India as also in semi-urban and rural areas.

Aim: To generate a consensus on the importance of pharmaco-invasive therapy for STEMI patients when primary PCI cannot be expeditiously performed in metro and tier-I cities in India.

Methodology: A total of 8 expert panel groups comprising 48 experts from Cardiology specialty in India were convened. These groups individually reviewed the evidence on various types of fibrinolytic agents, their importance in STEMI management in general and in India and finally shared their experience and views on the importance of pharmaco-invasive therapy during STEMI management in metro and tier-I cities in India. Individual group opinions were compiled into one document and the consensus was finalized after it was approved by all panel members.

Results: The board concluded that in metro and tier-I cities, pharmaco-invasive therapy, preferably using third generation fibrinolytic agents such as Reteplase and Tenecteplase, should be instituted to all patients for whom a delay in primary PCI of greater than 120 minutes from the time of ECG confirmation is anticipated. This will enhance the time window to preserve the myocardium from further damage arising due to patient related, transportation related or in- hospital delays. The present article also highlights the importance of third generation fibrinolytics in pharmaco-invasive therapy and looks at strategies to augment their use.

Conclusion: Pharmaco-invasive therapy is recommended in STEMI patients even in metro and tier-I cities of India, where delay in access to PCI is anticipated, in place of a strategy of promoting only primary PCI from CVDs in 2012, representing 31% of all global deaths. Cardiovascular disease burden has been increasing at an exponential pace in low and middle-income countries such as India. At least three quarters of the world’s deaths from CVDs occur in low- and middle-income countries. Indeed, India is estimated to have one of the largest burden of acute coronary syndrome (ACS) patients on the globe. ST segment Elevation Myocardial Infarction (STEMI) is one of the most critical forms of ACS, which must be treated quickly and appropriately for optimum results.

There are no accurate epidemiological data on STEMI in India. However, it is estimated that more than 3 million STEMI occurs every year in India. Ischemic heart disease (IHD) and stroke constitute the majority of CVD mortality in India (83%). It is also important to note that in India, the economic burden of STEMI would be more than in the western world, because STEMI patients are relatively younger (by around 5–10 years). These differences could be attributed to genetic predisposition along with abnormal lipid patterns such as elevated Lpa, increased prevalence of metabolic syndrome and lifestyle factors. Apart from this infrastructure and medical manpower deficiencies exist in large parts of the country. Because of these disparities, treatment guidelines and recommendations for the western patients may be inappropriate for Indian patients. Therefore, there is an urgent need to explore appropriate approaches to manage STEMI patients in the Indian scenario.

Introduction

Cardiovascular disease is the leading cause of mortality across the globe; more people die annually from CVDs than from any other cause. An estimated 17.5 million people died...
Hurdles for STEMI Management in Metro and Tier-I Cities in India: Need for Pharmaco-invasive Therapy

Reperfusion therapy is the backbone of STEMI management; indeed Indian consensus document on STEMI care recommends swift initiation of reperfusion either with thrombolytic therapy or primary PCI. For effective care, reperfusion must be instituted in all patients presenting within 12 hours of onset of symptoms. Among the various approaches, primary PCI is the most effective reperfusion therapy, if it can be performed in a timely manner.

Although primary PCI is regarded as a golden standard for reperfusion therapy, in India it is accessible to less than 10% STEMI patients. This is not limited to geographies with no access to PCI facilities, but also in regions where cardiac catheterisation laboratories are available. Various factors lead to delay in the institution of primary PCI of which patient delay and health-care system delay are the prominent ones. Time from symptom onset to the first medical contact is considered as patient delay, and health-care system delay is the time from medical contact to reperfusion. Initially, patient delay may occur due to lack of awareness. Healthcare delay may occur due to lack of transfer facilities or inaccessibility of hospital with PCI capabilities. Treatment delays may also occur due to several other factors such as traffic congestion, delay in shifting the patient from casualty/emergency department to cath lab, lack of 24/7 availability of healthcare team and non-availability of PCI lab during busy times.

Delayed presentation is one of the major problems in accessing early reperfusion therapy. Furthermore, public education and awareness in recognizing early signs and symptoms of myocardial infarction is a significant challenge in India, due to low rates of literacy and diverse society. Prolonged transportation time is another major problem. For instance, majority of hospital ambulances in a metro city such as Hyderabad are equipped with paramedics, however, they are unable to reach the desired location due to huge traffic congestion. In the CREATE registry, which included majority of patients from cities in India with PPCI facilities available, median time from symptom onset to reach hospital was 300 minutes. In addition, delay may occur due to financial issues and while getting consent for doing primary PCI. In many of these cases, the imminent myocardial damage which occurs due to the delay in instituting primary PCI, can be prevented by using fibrinolytic therapy. Therefore, in the Indian context pharmaco-invasive approach is a golden opportunity for the management of STEMI patients. This prolongs the window of opportunity to 24 hours and provide breathing space to relatives of the patient to choose doctor of their choice, arrange finances, gather manpower, complete insurance formalities; all of them are very important in Indian context.

Therefore, pharmaco-invasive therapy could be a better approach, especially when delay in PPCI is anticipated. This approach may be appropriate not just in rural and semi-urban regions where PPCI is not readily available, but also in metro and tier-I cities in India where PCI facilities already exist. Data from the STEMI INDIA program has clearly shown a roadmap on the effective management of STEMI patients with the application of pharmaco-invasive approach.

**Pharmaco-invasive Reperfusion Therapy**

The pharmaco-invasive approach involves initially administering fibrinolytic agents, and then systematically performing an angiography within 2 to 24 hours after the start of fibrinolytic therapy, regardless of whether fibrinolysis results in successful reperfusion or not (Figure 1). In several clinical studies, performing initial fibrinolysis and then initiating angiography/PCI has shown 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. These studies report that early fibrinolysis before PCI compared to standard therapy resulted in nearly 50% reduction in recurrent MI and recurrent ischemia that was statistically highly significant, with no substantial increase in bleeding.

Findings from the pioneering studies done by STEMI-INDIA on Indian patients has given an impetus to the concept of pharmaco-invasive therapy. The initial pilot Kovai Erode Study and the subsequent Tamil Nadu STEMI program have demonstrated the feasibility of linking the two strategies of primary PCI and the pharmaco-invasive strategy. Furthermore, the STEPP-AMI, a prospective, observational, multicentric study evaluated the efficacy and safety of a strategy of pharmaco-invasive therapy with primary PCI. In this study, tenecteplase was given as the lytic agent 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. The primary endpoint of 30-day incidence of death, cardiogenic shock, reinfarction, repeat revascularization, and congestive heart failure, was similar in both groups, although there was a trend toward benefit in the primary PCI group (11.1% vs. 3.9%, p = 0.07, RR = 2.87; 95% CI: 0.92–8.97). At the end of 2-year follow-up, the initial benefit from primary PCI seemed to be narrowed as more events have occurred in the primary PCI group vs pharmacoinvasive group (17.8% vs. 13.6%, p = 0.47, RR = 1.31; 95% CI: 0.62–2.76). Overall, the study concluded that fibrinolysis followed by an early coronary angiogram within 3–24 h with PCI, if appropriate, resulted in similar outcomes when compared to primary PCI in patients with STEMI at 2-year follow-up.26,37,38

The pharmaco-invasive approach has also been recommended by the recent guidelines. The Indian consensus recommends a time guided fibrinolysis either with reteplase, tenecteplase, alteplase or streptokinase alongside contemporary adjunctive medical therapy for pharmacoinvasive

### Table 1: Trials comparing routine early PCI after fibrinolysis to standard therapy in STEMI patients

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Inclusion criteria</th>
<th>Lytic agent (type)</th>
<th>Strategy</th>
<th>Symptoms to lytic therapy/early PCI (min)</th>
<th>Primary endpoint</th>
</tr>
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<tbody>
<tr>
<td>STEPP AMI (2016)</td>
<td>STEMI patients presenting &lt;12 h from symptom onset</td>
<td>Tenecteplase (innovator)</td>
<td>Fibroinolysis + PCI (&lt;12h symptom) (rescue PCI 12%)</td>
<td>245&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Composite of death, reinfarction, repeat revascularization, CHF</td>
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<tr>
<td>STREAM (2010)</td>
<td>STEMI patients presenting &lt;3 h from symptom onset</td>
<td>Tenecteplase (only in age&gt;75yrs, HALF dose)</td>
<td>Early fibrinolysis (&lt;3h symptom) followed by PCI (6-24h) (944 patients) (rescue PCI in 36%)</td>
<td>100&lt;sup&gt;p&lt;/sup&gt;</td>
<td>30-day composite of death from any cause, shock, congestive heart failure, or reinfarction</td>
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<tr>
<td>NORDISTEMI (2010)</td>
<td>STEMI patients presenting &lt;6 h from symptom onset</td>
<td>Tenecteplase</td>
<td>Primary PCI (948 patients)</td>
<td>178&lt;sup&gt;p&lt;/sup&gt;</td>
<td>Combined death, reinfarction, recurrent ischaemia, or stroke at 12 months</td>
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<td>TRANSFER-AMI (2009)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>High-risk STEMI patients presenting &lt;12 h from symptom onset</td>
<td>Tenecteplase</td>
<td>Standard therapy (522 patients) (rescue PCI in 25%)</td>
<td>115&lt;sup&gt;p&lt;/sup&gt;</td>
<td>Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock at 30 days</td>
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<tr>
<td>WEST (2006)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>STEMI patients presenting &lt;6 h from symptom onset</td>
<td>Tenecteplase</td>
<td>Immediate PCI after lysis (134 patients) (PCI in 86%)</td>
<td>117&lt;sup&gt;p&lt;/sup&gt;</td>
<td>Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock, and major ventricular arrhythmia at 30 days</td>
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<tr>
<td>CAPITAL-AMI (2005)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>High-risk STEMI patients presenting &lt;6 h from symptom onset</td>
<td>Tenecteplase</td>
<td>Early PCI &lt;6 h from lysis (537 patients) (PCI in 85%)</td>
<td>113&lt;sup&gt;p&lt;/sup&gt;</td>
<td>Combined death, reinfarction, ischaemic events or stroke at 6 months</td>
</tr>
<tr>
<td>GRACIA-1 (2004)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>STEMI patients presenting &lt;12 h from symptom onset</td>
<td>Alteplase (accelerated)</td>
<td>Standard therapy (251 patients) (rescue PCI in 12%)</td>
<td>187</td>
<td>Combined death, reinfarction, ischaemic-induced revascularization at 12 months</td>
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<tr>
<td>CARESS-IN-AMI (2008)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>High-risk STEMI patients presenting &lt;12 h from symptom onset</td>
<td>Reteplase (HALF dose)</td>
<td>Early PCI &lt;6–24 h from lysis (248 patients) (PCI in 80%)</td>
<td>180</td>
<td>Combined death, reinfarction and recurrent ischaemia at 30 days</td>
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<td>SIAM-III (2003)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>STEMI patients presenting &lt;12 h from symptom onset</td>
<td>Reteplase</td>
<td>Standard therapy (81 patients) (rescue PCI in 12%)</td>
<td>216</td>
<td>Combined death, reinfarction, recurrent ischaemia, target lesion revascularization at 6 months</td>
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<sup>a</sup>Trials comparing lysis + PCI versus Primary PCI; <sup>b</sup> Expressed as median other times as average; <sup>c</sup> Plus abciximab of 0.25 mg/kg/bolus followed by 0.125 mg/kg/min infusion for 24 h; <sup>d</sup> Includes 29 patients referred to rescue PCI; <sup>e</sup> Includes also one arm randomized to primary PCI; <sup>f</sup> Dose of fibrinolytics are per the full dose in their prescribing information unless mentioned otherwise; STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CHF, congestive heart failure; Composite of death, reinfarction, repeat revascularization, target lesion revascularization, and major ventricular arrhythmia at 30 days
Fibrinolytic Options for Pharmaco-Invasive Therapy

Fibrinolytic therapy lyses thrombotic occlusion associated with STEMI and restores the coronary flow. Eventually, fibrinolytic therapy reduces infarct size and improves myocardial function and survival over the short-term and long-term. Fibrinolytic agents act by converting the proenzyme, plasminogen to plasmin, the active enzyme. Plasmin is a serine protease that acts by dissolving fibrin blood clots (Figure 2). A range of fibrinolytic agents are presently available in India. These include the first generation Streptokinase to newer fibrinolytic agents such as the second generation Alteplase, and third generation Reteplase and Tenecteplase. The characteristic features of different fibrinolytic agents are shown in Table 2.

Importance of Early Pharmaco-Invasive Therapy

Clinical outcomes of STEMI management is critically dependent on the time from symptom onset to successful reperfusion. Time is the most critical factor in STEMI management. It has been shown that the 1-year mortality increases by 7.5% for each 30-minute delay in treatment. Any delay in performing primary PCI significantly brings down the benefits of reperfusion. Furthermore, a meta-analysis comparing catheterization and PCI after lysis showed that compared to deferred PCI or standard ischemia-guided treatment, planned immediate or early invasive angiography after fibrinolytic therapy was associated with a significant reduction in reinfarction and recurrent ischemia. However, for the most effective salvage of myocardium even while using the pharmaco-invasive strategy, it is essential to start fibrinolytic therapy as early as possible from the onset of symptoms. Indeed, in several studies early fibrinolytic therapy resulted in greater mortality benefit particularly in the patients treated with fibrinolytics within 2 hours of symptoms onset.

First Generation

Streptokinase: It is a very widely used fibrinolytic agent in India, because of its easy availability and low cost. Streptokinase is a non-fibrinogen specific fibrinolytic agent, produced by hemolytic streptococci, that activates plasminogen independent of its association with fibrin. Potential drawbacks of streptokinase include the need for IV infusion, its low fibrin specificity, shorter half-life, hemorrhage and risk of anaphylactic reactions due to its antigenicity.

Second Generation

Tissue Plasminogen Activator (t-PA, Alteplase): It produces only mild systemic fibrinogen depletion. t-PA has to be given in an accelerated dose regimen over 90 minutes. Although it is a fibrin specific agent, its use is limited as it needs to be administered as an intravenous infusion.

Third Generation

The third generation fibrinolytic agents have increased fibrin specificity, increased resistance to inhibition by plasminogen activators and longer half-life. Tenecteplase and Reteplase are the two third generation fibrinolytic agents.

Tenecteplase

Tenecteplase, a variant of the t-PA molecule is an approved agent for the...
Reteplase is a fibrin-specific recombinant plasminogen activator derived from t-PA. It is a single chain deletion variant of Alteplase that is expressed in Escherichia coli. It is specifically designed for bolus thrombolysis in patients with STEMI. Furthermore, there is evidence of dose related bleeding or intracranial hemorrhage. Therefore it is important that the dose of the Tenecteplase should be accurately calculated before administration in STEMI patients.

### Reteplase

Reteplase can be effective and safe in the treatment of STEMI. 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. Furthermore, there is evidence of dose related bleeding or intracranial hemorrhage. Therefore it is important that the dose of the Tenecteplase should be accurately calculated before administration in STEMI patients.

### Advantages of Reteplase

- Feasibility to administer a double dosing regimen results in rapid reperfusion when compared to other fibrinolytic agents
- Dose adjustment on the basis of body weight is not required
- Proven superiority in patency rates when compared to other agents
- Actively penetrates the clot rather than accumulating on the top, leading to effective clot lysis activity
- Comparatively greater ease of administration
- Less chances of dosing errors as infusion is not required during administration

### Table 3: Specific advantages of reteplase are listed below

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bolus injections should be 30 minutes; both doses must be administered over two minutes. The specific advantage of Reteplase is that there is no need of dose adjustment based on body weight. Furthermore, administration of Reteplase is easy as it does not require infusion and therefore minimises dosing errors. Specific advantages of Reteplase are listed in Table 3. The safety and efficacy of Reteplase in patients with acute myocardial infarction has been evaluated in few international clinical studies. The INJECT trial was conducted to establish equivalence of Reteplase with Streptokinase in the reduction of mortality after acute myocardial infarction. In this study, Reteplase was at least as effective as streptokinase. Furthermore, a similar trend in terms of recurrent myocardial infarction, in-hospital stroke rates and bleeding events were observed with both treatment groups. However, Reteplase was significantly associated with fewer cases of atrial fibrillation, asystole, cardiac shock, heart failure, and hypotension. Furthermore, the RAPID 1 and RAPID 2 studies validated the potential advantage of Reteplase over Alteplase. Compared to Alteplase, Reteplase can result in earlier and more complete coronary patency. The beneficial effects of Reteplase have been corroborated in the Indian context too. A phase-III prospective, multi-centric trial has found that Reteplase can be effective and safe in the treatment of patients with STEMI. Similarly, in a post-marketing study (PRECISE-IN trial), administration of Reteplase (two 10 units IV bolus each over two minutes and 30 minutes apart) within 6 hours after the onset of AMI symptoms resulted in 50% resolution of ST elevation in 90.5% patients. In addition, the RAPID 1, RAPID 2 and INJECT studies have shown that treatment with Reteplase is not associated with an increase in bleeding complications or adverse events. Moreover, occurrence of intracranial hemorrhage or hemorrhagic stroke was comparable with Alteplase in GUSTO III trial.

### Expert Opinion

**Importance of pharmaco-invasive therapy in metro and tier-I cities in India**

In India, primary PCI facilities are available in several hospitals in metro and tier-I cities. However, pharmaco-invasive therapy, preferably using third generation fibrinolitics, can still be beneficial in many patients as there is significant patient or health-care system delays due to various reasons as elucidated in the preceding section. Furthermore, patients referred from smaller non-PCI centers to PCI centers in metro and tier-I cities should be advised to institute lytic therapy at the first medical facility before early transfer to the PCI center so that the
proven benefits of pharmaco-invasive therapy may be availed of by the patient.

While extending the discussion on the overall STEMI care in India, the panel opined that in order to improve STEMI care in tier-II cities and rural hospital settings, the bigger hospitals with PCI facilities should take the initiative to educate them on the advantages of the pharmaco-invasive strategy and the use of third generation lytics. Hand holding is very important while creating awareness and educating the healthcare personnel from remote areas. Building a STEMI-INDIA like healthcare infrastructure (Hub and Spoke Model; Figure 3) in every state across India would be important and that would ensure appropriate care of STEMI patients. The STEMI-INDIA model has been shown to be a reliable model with clear mortality and economic benefit as proven in the landmark study in Tamil Nadu. Replication of a similar program in other states should be encouraged. Integrating the STEMI system of care with the government sponsored BPL health insurance schemes would make it a more equitable and sustainable program in India. The recent decision of the Union Government to include this in the NHM will ensure that the financial costs will be shared by the Central Government and the State governments. Importantly, the long term viability of the program can be ensured only if each State government is also a stakeholder and there is a public-private collaboration in delivering quick and appropriate reperfusion therapy.

Choice of Fibrinolytic Therapy

The choice of fibrinolytic therapy, most often is decided based on the affordability of the patient and the availability of the lytic agent. However, while choosing an appropriate fibrinolytic agent, the physician has to keep in mind the advantages and disadvantages associated with each agent. It would be preferable to use a third generation thrombolytic agent such as Tenecteplase or Retepase. Both are equally effective with some advantages and disadvantages. Moreover experts advocated that the higher price of the third generation lytics can be brought down drastically by creating systems involving the government, private hospital and the health insurance schemes.

Conclusion

Metro and tier-I cities in India have many hospitals with primary PCI facilities. However, delays in primary PCI are common and result in increased mortality and morbidity. Pharmaco-invasive therapy, preferably using a third generation lytic, can be a critical reperfusion strategy in many patients who present to a PCI centre where delay in PPCI is anticipated. It can be a lifesaving option for the patients presenting to a non PCI centre and for those living in rural and semi-urban regions. In these situations thrombolysis and transfer for pharmaco-invasive management would be the best option. Setting up a STEMI system of care utilizing the ‘STEMI India’ model would optimize reperfusion therapy in STEMI patients and should be implemented across the country.

Disclaimer

This publication was funded by Abbott Healthcare Pvt Ltd. Dr. Vikrama Raja, Medical Affairs has authored this publication in the capacity of employee of Abbott Healthcare Pvt Ltd. Dr Thomas Alexander Dr. Nazir J Juvale, Dr. Arup Dasbiswas, Dr. Samir Dr. Kubba, Dr. RK Singh have co-authored this publication. The authors have declared and confirmed that there is no conflict of interest with respect to this authored publication.

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Journal of The Association of Physicians of India • Vol. 66 • May 2018


