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STEMI Care in India and the Real World: Role of Thrombolysis

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INTRODUCTION

The principal clinical syndromes that result are acute ST elevation myocardial infarction (STEMI), deep vein thrombosis, pulmonary embolism, acute ischemic stroke, acute peripheral arterial occlusion, and occlusion of indwelling catheters. Of these, AMI accounts for maximum number of morbidity and mortality. Over the last century, thrombolytic therapy has gained prominence in the management of STEMI and has helped hundreds of physicians in reanalyzing coronary vessel occlusions. This chapter reviews major milestones in the history of thrombolysis in STEMI.

DEVELOPMENT OF THROMBOLYTIC THERAPY

The discovery of streptokinase

The first thrombolytic, streptokinase was discovered by Dr. William Smith Tillett in 1933 by sheer serendipity. He was Associate Professor of Medicine and Director of the Biological Division at Johns Hopkins University, at that time. He observed that streptococci agglutinated in test tubes that contained human plasma but not in those that contained human serum. He hypothesized that the agglutination of streptococci is caused by fibrinogen in plasma that is deficient in serum. The fibrinogen probably is adsorbed onto the surface of streptococci, rendering the plasma devoid of free fibrinogen. In order to prove his hypothesis, Tillett devised a simple experiment. He took oxalated human plasma containing fibrinogen, which would not clot due to calcium depletion. He added calcium to the control test tubes, and hemolytic streptococci and calcium to the rest of the test tubes, hoping that the hemolytic streptococci would adsorb the fibrinogen and prevent the formation of a clot. However, the results of this experiment were uniformly negative: there was clot formation in all the tubes, regardless of the presence of streptococci. Dejected with the results of this experiment, he left the tubes in the tray without cleaning.

After some time, to his surprise, he found that there was clot lysis in the tubes containing streptococcal cultures. This led him to conclude that the streptococci had synthesized a fibrinolytic agent that was responsible for dissolving the clots (Table 1). This was the probable mechanism for clot lysis, rather than adsorption of fibrinogen as he had earlier presumed. He confirmed these findings on larger scale and on 27 June 1933, Tillett and Garner submitted their findings as 'Fibrinolytic activity of hemolytic streptococci'.

The agent was termed as streptococcal fibrinolysin which was crude and impure, thus could not be used clinically.[1,2]

Mechanism of action of streptokinase

In 1941, Milstone reported the existence of a substance, normally present in plasma that was required for dissolution of clot. He termed it the "lytic factor." Christensen and Kaplan independently determined that the lytic factor was a proteolytic enzyme normally present in plasma as an inactive precursor. The streptococcal substance (fibrinolysin) activates the proteinase precursor, converting it to an active enzyme in a manner analogous to the conversion of trypsinogen to trypsin by enterokinase. The active serum proteinase then lyses the fibrin clot. Christensen and MacLeod proposed the term

Table 1: Milestones of Fibrinolysis Research

Year	Investigator	Observation
1933	Tillett & Garner	Fibrinolytic principal in hemolytic Streptococcal broth.
1941-1945	Milstone,Tagnon, Christensen	Precursor of plasmin converted by streptococcal agent to active enzyme.
1948-54	Mullertz, Williams, Sobel et al., Lack, Ratnoff et al	Fibrinolytic inhibitors and activators (t-PA, UK, Staphylokinase).
1949	Sol Sherry	Successfully used fibrinous, purulent, and sanguinous pleural exudations, hemothorax, and tuberculous meningitis
1953	Kline , Mullertz	Purification of plasminogen.
1961	Guest & Celander	Urokinase.
1981	Rijken & Collen	Activator purified from melanoma line.
1983	Pennica et al.	Cloning and expression of rt-PA.
1990s	Meta Analysis	Recombinant mutant derivatives of rt-PA.

"streptokinase" in 1945 to replace the term fibrinolysin originally applied to the streptococcal component of the system. They further suggested the name "plasminogen" for the inactive form of the serum proteinase and "plasmin" for the active enzyme.[2]

The source for streptokinase

Evans reported the discovery of fibrinolytic properties in certain strains of Streptococcus equisimilis.[3] Christensen reported that the strain S. equisimilis H46A can act as a commercial source for streptokinase as it does not produce erythrogenic toxins, is less fastidious in its growth requirements than are most other group A strains and could be grown on semi-synthetic media. This was a discovery of immense importance as till date, the commercial streptokinase used for thrombolytic therapy is derived from S. equisimilis (Lancefield Group C).

Human studies on Streptokinase

In late 1949, Tillett and Sherry successfully used streptokinase to treat fibrinous, purulent, and sanguineous pleural exudations, hemothorax, and tuberculous meningitis.[4,5] In these studies, streptokinase was associated with few side effects such as a pyrogenic reaction with associated malaise, headache, arthralgia, and occasionally nausea and febrile responses.[6] This was probably due to impurities in the existing formulation. Later on, further purification of streptokinase was taken up by Lederle Laboratories. The first report on intravascular thrombolysis in humans came up in 1956 by E. E. Cliffton at the Cornell University Medical College, New York, who used streptokinase in 40 patients with intravascular thrombosis of diverse etiology. His study was associated with non-uniform canalization results and frequent bleeding complications. Despite this fact, he must be credited with the first use of thrombolytic agents for the treatment of pathological thrombi, as well as with the first catheter-directed administration of a thrombolytic agent.

In late 1958, Fletcher and associates performed new studies regarding an intravenous approach to the treatment of STEMI patients. Their patients were infused with streptokinase in massive doses and for prolonged periods after MI. Except for the development of a hemorrhagic diathesis in a few patients, there were no significant complications, and the mortality rate was significantly lower in patients who had received streptokinase, in comparison with other treatments. This proved that streptokinase infusion via the intravenous route was a promising therapeutic approach to STEMI.[7, 8]

After the success of intravascular thrombolysis with streptokinase, Ruegsegger and colleagues successfully dissolved intracoronary clots for the 1st time in various animal models. With serial angiography, they clearly showed dissolution of clots in high proportion of animals. An important finding of this study was that the heart muscle could not be saved from death if more than a few hours passed between clotting and lysis which has now emerged as the concept of golden hour in the management of STEMI. The earlier thrombolysis resulted in smaller area of infarction as compared to controls in this study.[9]

In spite of the success spurts, the production of streptokinase in US was stopped due to the inefficiency in production of less pyrogenic preparations. It still remained the drug of choice in Europe and Australia for several decades. However, in US the focus was shifted to another thrombolytic molecule, urokinase.

Several small scale trials conducted on streptokinase during 1960s and 1970s failed to establish the therapeutic superiority of streptokinase till 1979 when European Cooperative Study Group for Streptokinase Treatment in Acute Myocardial Infarction published its findings from a large scale trial. The trial conducted in 2,388 patients found that the overall mortality rates within 6 months of streptokinase therapy after AMI were significantly lower ($P < 0.01$) in the streptokinase group (15.6%) than in the control group (30.6%).[10] In 1980s, several trials demonstrated that use of streptokinase within 1.5 to 3 hours of infarction was associated with high reperfusion rates. Still, these results were not sufficient to establish practice guidelines.

Intracoronary use of Streptokinase: Post 1979 intracoronary streptokinase use in few STEMI patients, which are associated with cardiac complication like reperfusion arrhythmis in 80% patients. Despite the more effective clot lysis, intracoronary administration fell to an equal footing with intravenous administration due to the associated side effects.

There was no clear protocol design for use of streptokinase in STEMI, but the observation made was that when streptokinase was administered within 1.5 to 3 hours of symtom onset, reperfusion rate as high as 90% were achieved,and with delay in treatment the prognosis worsened. Intravenous streptokinase in evolving STEMI was published for the first time from India in a Pilot Observational Study[11].

Finally, in 1986, a landmark trial, GISSI (Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico) in 11,806 patients in 176 coronary care units dissipitated the confusion. There was a significant difference in mortality rates between the streptokinase group and the non-streptokinase group (controls) at 12 months (17.2% in the streptokinase group vs 19.0% in controls, P=0.008; relative risk, 0.90), especially in the 0–3 and 3–6-hr groups (relative risks, 0.89 and 0.87, respectively). Thus, GISSI succeeded in firmly establishing the efficacy of intravenously administered streptokinase.[12] Intravenous Streptokinase in STEMI 6-36 months follow up published in India[13]. This was followed by many clinical trials to reinforce the benefit of streptokinase. Large multicenter trials like GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), GISSI-2 (Gruppo Italiano per so Studio della Sopravvienza nell'Infarto Miocardico), and ISIS-3 (Third International Study of Infarct Survival Collaborative Group) compared the efficacy of tissue plasminogen activator (t-PA) with that of streptokinase. GUSTO shows no difference in mortality at end of 30 days. [14] GISSI-2 reported similar mortality rates at 6 months, while ISIS-3 found no significant difference in mortality

rates in patients treated with t-PA or streptokinase. The development of antibodies against streptokinase is the major concern for reuse of streptokinase. Although, t-PA has become a popular thrombolytic agent today, Streptokinase continues to be choice of thrombolytic agent in millions suffering from AMI due to the cost benefit.

Urokinase

The fibrinolytic potential of human urine was first described by Macfarlane and Pilling in 1947. The active molecule was extracted, isolated, and named ''urokinase'' in 1952. Unlike streptokinase, urokinase directly activates plasminogen to form plasmin; prior binding to plasminogen or plasmin is not necessary for activity. The advantage of urokinase over streptokinase is that it is non-antigenic, preformed antibodies are not observed and the untoward reactions of fever or hypotension are rare. The high molecular weight form of urokinase is isolated from urine while the low molecular weight form is derived from tissue culture of kidney cells. The most commonly employed urokinase has been of tissue-culture origin, manufactured from human neonatal kidney cells. A recombinant form of urokinase (rUK) was tested in a single trial of patients with acute myocardial infarction (MI) and in two multicenter trials of patients with peripheral arterial occlusion. It had a higher molecular weight and a shorter half-life than its low molecular-weight counterpart. Despite these differences, however, the clinical effects of the two agents have been quite similar. McNamara and Fischer were the first to describe the use of urokinase for local thrombolytic treatment, using a high-dose protocol featuring graded, stepwise reductions in dose as the infusion progressed.[15]

Tissue-type plasminogen activator: In early 1947 it was reported that Fibrinokinase present in animal tissue can activate plasminogen, many authors tried purification and characterization of plasminogen activators from sources like pig heart, ovaries and human post mortem vascular perfusates. The first highly purified form of t-PA was obtained from uterine tissue (about 1 mg of t-PA from 5 kg tissue). t-PA has been purified from the culture fluid of a stable human melanoma cell line (Bowes, RPMI-7272). D. Pennica (1982) from the Department of Molecular Biology of Genentech Inc. initiated the cloning and expression of the t-PA gene (Sixth Congress on Fibrinolysis in Lausanne, Switzerland). The recombinant t-PA (rt-PA) was shown to be indistinguishable from the natural activator isolated from human melanoma cell culture, with respect to biochemical properties.

Alteplase (tPA and rtPA)

Tissue plasminogen activator (tPA), originally developed in the mid 1980s after molecular cloning techniques were used to express human (tPA) DNA. Alteplase is a naturally occurring fibrinolytic agent produced by endothelial cells and is intimately involved in the balance between intravascular thrombogenesis and thrombolysis. Natural tPA is a single chain (527 amino acid) serine protease, and in contrast to most serine proteases (e.g., urokinase), the single-chain form has significant activity. tPA exhibits significant fibrin specificity. In plasma, the agent is associated with little plasminogen activation. At the site of the thrombus, however, the binding of tPA and plasminogen to the fibrin surface induces a conformational change in both molecules, greatly facilitating the conversion of plasminogen to plasmin and dissolution of the clot. tPA also manifests the property of fibrin affinity, that is, it binds strongly to fibrin. Other fibrinolytic agents, such as prourokinase, do not demonstrate fibrin affinity.

A predominantly single-chain form of rtPA was eventually approved for the indications of acute MI and massive pulmonary embolism. rtPA has been studied extensively in the setting of coronary occlusion.[16]

In the GUSTO-I study of 41,000 patients with acute MI; rtPA was more effective than streptokinase in achieving vascular patency. Alteplase demonstrate statistically significant reduction in 30 days mortality compared with streptokinase. Despite a slightly greater risk of intracranial hemorrhage with rtPA, overall mortality was significantly reduced (GUSTO Investigators, 1993). COBALT trial was carried out to test the hypothesis that double dose Alteplase is equivalent to accelerated dose of Alteplase (n=7169). The 30 days mortality was higher in double bolus group than in accelerated group, therefore accelerated Alteplase over period of 90 min remains the preferred choice.Alteplase is approved by FDA in treatment of STEMI (2002), Pulmonary Embolism (2002), and Ischemic Stroke (1996).

Reteplase (rPA)

Reteplase was developed as a third-generation recombinant tissue type plasminogen activator. It consists of only the kringle-2 and protease domain of the t-PA molecule. Reteplase is similar to Alteplase but the modification provides a longer half life (13-16 min). The fibrin affinity of Reteplase is low compared to Alteplase which improves its penetration into the clot. Due to higher penetration inside the thrombi additional fibrinolytic activity is achieved which helps in rapid reperfusion leading to less bleeding episodes.

Reteplase was developed with the goal of avoiding the necessity of a continuous intravenous infusion, thereby simplifying ease of administration. Reteplase produced in Escherichia coli cells, is nonglycosylated, demonstrating a lower fibrin-binding activity and a diminished affinity to hepatocytes. This latter property accounts for a longer half-life than rtPA, potentially enabling bolus injection versus prolonged infusion. Reteplase has been studied in several small trials, and its safety and efficacy appear to be similar to alteplase.[17] Reteplase was approved by FDA in year 1996 for treatment of STEMI.

Several trials have been conducted to prove the efficacy of the Reteplase in management of AMI. GUSTO-III trial compared the double bolus Reteplase against accelerated infusion of Alteplase. The observation proves Reteplase efficacy as equal to accelerated Alteplase. In RAPID- 1, 2 trials the angiography patency was assessed post AMI. The angiography findings shows higher rate of patency and greater TIMI 3 flow with Reteplase than Alteplase. INJECT trial (The International Joint Efficacy Comparison of Thrombolytics) compared the mortality rate following

randomization with Reteplase vs Streptokinase. The mortality rate was lower with Reteplase compared with Streptokinase. Reteplase has longer half life, higher and faster thrombolytic patency than alteplase, lower hemorrhagic risk than alteplase. It is given as a bolus without weight adjustment.

Tenecteplase (TNK-tPA)

This molecule was bioengineered in an effort to lengthen the duration of bioavailability of tPA. Three regions in kringle-1 and the protease portion of tPA which mediated hepatic clearance, fibrin specificity, and resistance to plasminogen activator inhibitor were identified. These three sites were modified to create TNK-tPA, a novel molecule with a greater half-life and fibrin specificity. The longer half-life of TNK-tPA allowed successful administration as a single bolus, in contrast to the infusion required for rtPA. In addition, TNK-tPA manifests greater fibrin specificity than rtPA, resulting in less fibrinogen depletion. In studies of acute coronary occlusion, TNK-tPA performed at least as well as rtPA, concurrent with greater ease of administration.[17] It received US FDA approval for the management of acute MI in the year 2000. The first biosimilar tenecteplase (Elaxim) was indigenously developed in India by Gennova Biopharmaceuticals at Pune. Several clinical trials have been conducted to establish efficacy of Tenecteplase. Efficacy for clot lysis of single bolus Tenecteplase was studied in Thrombolysis in Myocardial Infarction (TIMI) 10 A and 10 B trials while safety was assessed in ASSENT 1(Assessment of the Safety of a New Thrombolytic). The results of these studies suggest that body weight adjusted single bolus dose of Tenecteplase is equivalent to 90 min regime of Alteplase.

Indigenous tenecteplase has convincing evidence supporting its utility in Indian STEMI patients. In STEPP-AMI study, the primary end point occurred in 11.1% in pharmacoinvasive (PI) group and in 3.9% in primary PCI (PPCI) group, p=0.07 (RR=2.87; 95% CI 0.92 to 8.97). The infarct-related artery patency at angiogram was 82.2% in PI group and 22.6% in PPCI group (p<0.001).[15] The Indian registry on use of indigenous tenecteplase in 15222 STEMI patients revealed that overall rate for achieving clinically successful thrombolysis (CST) by TNK was 95.43%.[18]

Pre-hospital Thrombolysis (PHT): PHT plays important role in early and effective management of STEMI. The American Heart Association (AHA) and the American College of Cardiology (ACC) favours the use of pre-hospital thrombolysis over percutaneous coronary intervention (PCI).[20] CAPTIM trial reports that pre-hospital thrombolysis within 2 hours of symptom onset is superior to PCI.[21]

Advantages of newer agents over the older agents

Alteplase was found to have a more favorable mortality results than streptokinase in GUSTO study. It had better thrombolytic/fibrinolytic action than urokinase. The disadvantages were higher bleeding risk and lack of resistance to plasminogen activator inhibitor (PAI-1). Reteplase although was more potent than alteplase was associated with higher bleeding risk. The advantage associated with reteplase was that it could be given in form of bolus injection rather than continuous infusion. With the introduction of tenecteplase, we now have a thrombolytic that can be given as a bolus injection, is more fibrin specific and resistant to plasminogen activator inhibitor.

TRENDS IN THROMBOLYSIS FOR STEMI

Although the first thrombolytic was discovered in 1933. The clinical use of thrombolytics in the management of acute MI was delayed till 1980s. This was due to the controversies in the pathogenesis of MI. It was earlier thought that coronary thrombosis is a consequence rather than cause of myocardial infarction. This confusion was resolved in 1980, when DeWood and his colleagues showed that 87% of patients presenting within 4 hours of acute MI had total coronary occlusion. He showed the angiographic evidence for coronary thrombosis in STEMI patients for the first time and was able to retrieve the thrombus using Fogarty catheter in 88% of these patients. DeWood's paper led to credence to the concept of endogenous fibrinolysis and ushered the era of fibrinolytics.[22]

By the end of 1980s, large randomized trials had been conducted in this area. The meta-analysis of these trials suggested that the sooner the thrombolytic given after the onset of chest pain, the greater the survival benefit. This led to the concept of 'golden hour' in myocardial thrombolysis which was later lengthened to a period of three hours. The findings of GREAR trial suggested that modest delays in the treatment may be detrimental as myocardial cell death starts within minutes of symptom onset and pre-hospital thrombolysis is effective in saving lives.[23]

Pre-hospital thrombolysis: Although, primary PCI within first 6 hours of chest pain is suggested as the most preferred therapy for STEMI, it is not feasible in routine clinical settings due to delays in transfer, unavailability of catheterization facility and scarcity of skilled personnel (Kushner et al, 2009). Five year follow-up of a multi-centric trial CAPTIM shows that pre-hospital fibrinolysis with immediate transfer for rescue angioplasty if needed is associated with similar mortality as compared to P-PCI if managed within 6 hours of onset of chest pain and pre-hospital thrombosis improved long term mortality when administered within first 2 hours.[20] Major breakthroughs in treatment of STEMI have been summarized in Table 2.

Thrombolytic therapy followed by PCI

Thrombolytic therapy despite its convenience has certain limitations owing to the risk of reocclusion, failure of thrombolysis which can increase the mortality in STEMI patients. Thrombolysis at the site of a ruptured atherosclerotic plaque provides a further nidus for rethrombosis and occlusion. Immediate thrombolysis followed by angioplasty is likely to reduce the chances of reocclusion due to rethrombosis or residual thrombus. This hypothesis led to emergence of pharmacoinvasive therapy that combined the benefits of both thrombolysis and PCI.

Table 2: Major Breakthroughs in the Treatment of STEMI

Year	Author	Treatment
1912	James Herrick	Importance of Rest in MI management
1923	Wearn	Rest, hydric restriction, digitalis use for pulmonary congestion
1928	Parkinson and Bedford	Morphine use to relieve pain, rest for long time
1946 1949 1957 1958 1959	Wright IS Tillett & Sherry Cliffton Fletcher et al. Ruegsegger and colleague	Use of warfarin in treatment of coronary thrombosis with MI Streptokinase use in humans (fibrinous pleural adhesions) Plasmin (fibrinolysin) in human thrombotic disease Streptokinase in patients with acute MI Lysis of artificial clots in man by streptokinase
1959	McLean J.	The discovery of Heparin
1960	Bernard Lown	Intense fluid replacement, use of O2, early mobility
1961	Desmond Julian	Coronary Care Unit
1963,1967	Shumway NE, et al	Heart Transplant
1965 1966	James Black Schmutzler et al	Described Beta blocker Propranolol IV Streptokinase in AMI
1971 1979 1981 1981 1984 1984 1984 1985 1986-88	John Vane Rentrop et al. Schroder et al. Weimar et al. Chazov E, et al Willam Ganz et al Chopra HK et al van de Werf et al. William Ganz et al GISSI, ISIS-2, ASSET, AIMS	Discovery of antiplatelet activity of aspirin Intracoronary and intravenous streptokinase for acute MI t-PA for human thrombosis (deep vein thrombosis) Administration of fibrinolysin in AMI Intravenous streptokinase in evolving acute myocardial infarction Intravenous Streptokinase in AMI Recombinant t-PA in acute MI The Effect of rate of IV STK in AMI Survival benefit with IV streptokinase, rt-PA vs. placebo in acute MI
1988	ISIS-2	Aspirin became mainstay treatment
1988	Pfeffer MA, et al	Development of ACE inhibitors
1988	TIMI trial	Early open artery theory
1988 1990 1993	Sabatine MS, et al, ISIS-2 Chopra HK et al Braunwald E, et al, GUSTO	Anticoagulants to fibrinolytics IV Streptokinase in AMI 6-36 month follow up Thrombolytic trials
1994	Grines CL, et al	Primary PCI
2002 2008	Zhao Z-Q et al NINDS [80], Hacke et al. [83]	Postconditioning Recombinant t-PA in ischemic stroke
2011	Shah VK, et al	Stem cell therapy
2011	Ishikawa K, et al	Gene Therapy
2012	Brodie BR, et al	Aspiration thrombectomy prior to coronary stenting
2012 2013 2014	Soler-Botija C et al Iyengar SS et al Dalal JJ et al	Tissue engineering Pharmacologic reperfusion therapy with TNK in STEMI Consensus Statement of Pharmaco invasive approach in STEMI
2015	Thomas Alexander et al	CSI Forum: Consensus Statement Framework for a National STEMI Program: Consensus document developed by STEMI INDIA, Cardiological Society of India and Association Physicians of India

Facilitated PCI: The initial trials of facilitated PCI (i.e. preceded by thrombolytics) (ASSENT-4 and FINESSE) evaluated the benefits of thrombolysis immediately followed by PCI. However, these were not associated with consistent mortality benefits in all patient groups. Full dose tenecteplase followed by immediate PCI in ASSENT-4 was associated with increased risk of thrombosis. This was probably due to restricted use of clopidogrel and GpIIb/IIa inhibitors in ASSENT-4 trial. On the other hand, FINESSE trial was associated with increase in the bleeding events as compared to PPCI despite using similar dose of heparin.[23]

Pharmacoinvasive approach: Multiple trials evaluated the effect of immediate thrombolysis followed by PCI after a gap of 2- 24 hours. This enabled PCI at a later stage with full dose GpIIb/IIIa inhibitors, heparin and antiplatelet

without increased risk of bleeding. These trials include GRACIA-2, FAST-MI, TRANSFER-AMI and WEST. The largest randomized clinical trial so far, TRANSFER-AMI (n=1059) showed that thrombolysis using tenecteplase, aspirin and LMW heparin followed by PCI within 6 hours was associated with lower ischemic complications as compared to standard thrombolysis followed by rescue PCI if necessary. The other three trials have shown efficacy of pharmacoinvasive strategy as comparable to PPCI. [22]

The 1-year results from STREAM confirm that mortality rates were low, and that a PI strategy resulted in a similar mortality as PPCI. The composite end point of death, shock, congestive heart failure, and reinfarction was numerically lower in the PI arm at 30 days. [25]

The 5 year survival data from FAST-MI study shows that crude five-year survival rate was 65% in patients without reperfusion therapy, 88% for patients with fibrinolysis and 84% for those with PPCI. Direct comparison of the two reperfusion techniques showed a nonsignificant trend favouring fibrinolytic treatment (HR 0.73, 0.50-1.06; P=0.10).[26]

Reasons for superiority of Pharmacoinvasive approach:

- Most feasible and effective reperfusion strategy in clinical settings with lack of immediate availability of PCI
- Immediate thrombolysis in this strategy can be more conveniently achieved now with the availability of newer thrombolytics like Tenecteplase
- Widens the window between thrombolysis and PCI that allows greater time for transfer of patients to PCI-capable hospitals
- The time gap between thrombolysis and PCI allows liberal use of GP IIb/IIIa inhibitor, clopidogrel and heparin without inadvertent increased risk of bleeding

Hence, pharmacoinvasive strategy has been recommended more strongly for high risk STEMI patient than non-high risk AMI patient in STEMI guidelines.

A scenario not infrequently encountered in our practice is given below. A 45-year-old normotensive and non-diabetic male shopkeeper had chest and upper abdominal pain beginning early in the morning. The pain initially was intermittent and temporarily subsided. Our patient attributed the discomfort to upper gastro-intestinal discomfort and he had some home available remedies for gastric discomfort. Four hours later, after reaching his workplace, the pain returned in a severe form and associated with vomiting. He reached out to the local general practitioner, who evaluated him and administered injectable ranitidine and antiemetics. There was temporary improvement and he went back to his office. He applied for leave and reached home. On the way home, he had an episode of fainting and was rushed to the hospital in the nearby town which was 40 km away. He was admitted and evaluated to have extensive ST Elevation anterior wall myocardial infarction (STEMI) with qRBBB. He was thrombolysed with streptokinase with a window period of 14 hours. He seemed to be stable. Later in the night, the patient developed acute pulmonary edema and required intravenous diuretics, nitroglycerine and morphine. Next day morning the patient was referred to a PCI capable centre, which was 50 km away. He underwent an angiogram that showed an occluded proximal left anterior descending artery and an ejection fraction of 20-25%. He underwent rescue PCI and stenting to proximal LAD with non medicated stent. The procedure was complicated by no flow and hypotension, for which adjunctive pharmacotherapy along with intra-aortic balloon pump were used. He remained in CCU for 7 days and was later discharged with an ejection fraction of 20-25%. The patient was discharged on multiple medications. One month after his acute MI, the patient continued to have class III dyspnea with exertion and was unable to return to work. A follow-up echocardiogram demonstrated impaired left ventricular systolic function (EF 25%) with severe apical hypokinesis. He was advised an implantable cardiac defibrillator, which he could not afford.

The above scenario is fairly frequently seen by Indian cardiologists even in 2016. The case brings out glaring deficiencies at various levels in STEMI care in India. Individually, we have excellent hospitals, physicians, clinical cardiologists, and cardiac interventionists. Of late we are having good ambulance services, at least in some states. However, we do not have ANY system in place for STEMI care across the country. The world-over dedicated STEMI programs are successfully implemented in many Western countries for nearly three decades. This commentary focuses on the possible systems that may be put in place to improve the acute care of STEMI across India. Most of the improvement in outcomes in Indian patients could be achieved by timely implementation of the proven therapies focusing the time window.

Problems in STEMI care in India

Indian ACS patients, for reasons not exactly clear, seem to present with higher percentage of STEMI. They are less likely to receive timely reperfusion therapy, invasive therapy and evidence based medicines [27]. The above patient scenario brings forth a few major lacunae in STEMI care that include lack of dedicated STEMI care systems, lack of instantaneously available ECG facility at first point of medical contact, lack of patient awareness, lack of physician readiness, lack of equipped ambulance systems network for patient transport (Emergency Cardiac Services : ECS) and pay from pocket for even Emergency Medical Services (EMS). These are the major reasons for the excess mortality and poorer outcomes seen in Indian patients with STEMI[27].

In a registry involving 50 cities, only 58·5% of patients with STEMI were thrombolysed mostly with streptokinase and a minority received percutaneous coronary intervention (PCI). The average delay in presentation was > 6 hours. The real situation in most parts of India is likely to lower as these registries have sampled data from tertiary care centres and some of the better developed states. The reported 30-day outcomes for patients with STEMI in the

Create registry were death (8·6%), reinfarction (2·3%), and stroke (0·7%). Mortality benefits of PPCI lost if it is delayed more than 60 minutes as depicted in the Global Registry of Acute Coronary Event [28]. Importantly, the poor are marginalized in STEMI care and are less likely to receive thrombolytics, percutaneous coronary intervention and even lipid-lowering drugs. Consequently, the mortality was also higher for poor patients[29]

In the Italian Registry of TNK in STEMI of 27,000 patients[30]. It has been shown the thrombolysis with TNK is easily n, accessible, and available everywhere. Door to balloon time in PPCI exceeds 90 minutes practically. Then, PPCI does not reduce mortality consistently. Rapid diagnosis and early reperfusion are pillars of success in STEMI Care. TNK is Class 1A recommendation for STEMI ACCP Guideline[31] and is recommended in Pre- Hospital Thrombolysis Protocol (Vienna STEMI Registry[32] The Mayo Clinic STEMI Protocol[33] and The French FAST-MI registry[34]). The potential of TNK cannot be overemphasized. It is given a bolus dose with no hypertension, no allergic reactions, longer half life, high fibrin specificity and simplified weight adjusted dose, with mostly very minor manageable bleeding. It is an agent of first choice for pre-hospital thrombolysis in STEMI. It has been shown in one of the study that only 4% of transferred patients received PPCI within 90 Min.[35] Pre-hospital thrombolysis is the strongest independent predictor of in-hospital survivor in UK[36].

In the recently published Indian registry on STEMI consisting of 15,222 patients 722 centres treated with indigenous tenecteplase (TNK) has shown clinically successful thrombolysis in 96.5% of patients in less than three hours, 96% in three to six hours and 85.3% in more than six hours of STEMI[37]. Pharmaco invasive therapy including early administration of thrombolysis (TNK) followed by PCI within 3-24 hours after initiation of thrombolytic therapy regardless of success of thrombolysis. However in case of thrombolytic failure, a rescue PCI should be instantaneously performed. Timely guided protocol for early thrombolysis with tenecteplase (Grade IA) at the level of physician, non-PCI capable centres/nursing homes with intensive care facility and subsequent access to PCI capable centres improves STEMI outcome[38]. Such a strategy may be the preferred strategy in India as PPCI possible only in 10% of STEMI patients[39].

STEMI care in India: Problems and Solutions

There are significant barriers to effective STEMI care. They are at public awareness level, patient level, hospital/physician level and at Government and societal levels. Patients often ignore symptoms, self medicate and even when they decide to seek medical attention, they consult non-physicians in India. To overcome these barriers, organized patient education and awareness programs are urgently needed. Cardiological society of India (CSI), Association of physicians of India (API) and the Indian medical association (IMA) should join hands in these awareness programs. Such programs should not only use the traditional methods like public lectures, print materials, but should also focus on television, internet and social media. The public should be educated that for anyone beyond their teens, an ECG is a must for acute pain or discomfort from jaw to umbilicus including upper limbs. Public should be educated about the significance of time, seeking immediate medical attention and timely reaching the 'right' hospital or physician for STEMI care.

Another most important barrier is at the level of hospital systems. For a country like India, wherein only less than 10% of STEMI patients receive PCI, primary PCI cannot and will not be the answer for every patient of STEMI. We should rely on thrombolysis, especially bolus agents like Tenecteplase (TNK), and promptly shifting the patients to a PCI capable centre. Considering the efficacy, a strategy of prehospital thrombolysis should be ideally suited for Indian conditions. Considering the diverse Indian conditions, a combination of strategies could be more appropriate. For instance, primary PCI should be the preferred strategy in most of the hospitals, who are already offering 24 x 7 emergency PCI services and the patient can reach the available STEMI Care PPCI capable centres less than 90 min[40]. In case there is a delay in access to PPCI capable centre due to lack of transfer facility, densely populated cities, traffic congestions etc. Other cities and small district towns would have certified STEMI care physicians and hospitals. These hospitals should do the initial care, thrombolysis with TNK, management of complications and then should have an organized way of early transfer to nearby cities wherein early angiogram and PCI are possible. For rest of rural India, pre-hospital thrombolysis with TNK could be the ideal strategy. For these to become practical, we need to have "Integrated STEMI Care Systems". We need to have emergency (108) ambulances, equipped with a facility to do an ECG and transmit to a central station, wherein a cardiologist can ascertain STEMI. Upon confirmation of STEMI, the patient should receive aspirin and statin. These ambulances should also have medical and paramedical personnel who can assess sickness, administer a questionnaire to assess the suitability for thrombolysis with TNK. The patient should be taken in the ambulance that has facility to monitor rhythm and defibrillator. Automated algorithms can decide, based on the place, distance to a STEMI hospital or a PCI capable centre, whether to shift for primary PCI or to a hospital for thrombolysis or pre-hospital thrombolysis in the ambulance itself. Accordingly the hospital should be activated and no time should be wasted at the hospital emergency. If pre-hospital thrombolysis is decided, the patient or relative may talk to a centrally stationed cardiologist and the medical personnel get a consent and administer the agent under cardiac monitoring inside the ambulance, while the patient is being shifted to a nearby hospital.

The above ambitious plan could only work if there is governmental participation and the STEMI care is integrated to the existing emergency care systems in India. The government should make emergency STEMI treatment at subsidized cost to all Indians, may be through medical insurance schemes. The Government should identify STEMI care centres in each city, district and rural areas and certify them. The information on the list of PCI

capable and other STEMI care centres should be widely and easily available. Government should also ensure the availability of thrombolytic, especially bolus agents like TNK at subsidized cost to the poor. Recently published STREAM Trial 2014 with 1 year mortality follow up data has shown that PPCI less than 60 minutes is not practical in most of the STEMI patients, thus, TNK followed by PCI in 24 Hours is strongly recommended protocol[40]

Therefore, Golden time window intervention of < 2 hours is most powerful predictor of salvaging jeopardized myocardium in STEMI and significantly reduce STEMI inflicted morbidity and mortality. If TNK is given in <60 minutes, it may reduce infarct size from larger to smaller, transmural to subendocardial or may even abort MI, thus help improving subsequent PCI outcome by reducing thrombus burden and better TIMI flow. Time delay > 90 minutes reduce the benefit of PPCI. Thus the objective of Integrated TIMI Care is to minimize time from chest discomfort to ECG < 30 minutes ((FMC), ECG to drug intervention <60 minutes, drug intervention to PCI < 90-120 minutes will definitely have STEMI inflicted morbidity and mortality benefit in our country to create global impact. We must act locally to impact globally.

Future Directions for STEMI Programme in India

CSI Forum: Consensus Statement: Framework for a National STEMI Program: Consensus document developed by STEMI INDIA, Cardiological Society of India and Association Physicians of India[41]: Addressing some of these issues, STEMI India, a not-for-profit organization, Cardiological Society of India (CSI) and Association Physicians of India (API) have developed a protocol of "systems of care" for efficient management of STEMI, with integrated networks of facilities. Leveraging newly-developed ambulance and emergency medical services, incorporating recent state insurance schemes for vulnerable populations to broaden access, and combining innovative, "state-of-the-art" information technology platforms with existing hospital infrastructure, are the crucial aspects of this system. A pilot program was successfully employed in the state of Tamilnadu. The purpose of this statement is to describe the framework and methods associated with this programme with an aim to improve delivery of reperfusion therapy for STEMI in India. This programme can serve as model STEMI systems of care for other low-and-middle income countries.

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