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Role of thrombolysis in reperfusion therapy for management of AMI: Indian scenario

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1. Introduction

Cardiovascular disorders are the major cause of morbidity & mortality globally as well in India. In 2008, out of the 57 million deaths globally; around 63% (i.e., nearly 30 million deaths) were due to non-communicable diseases.[1] Cardiovascular diseases accounts for nearly half of the deaths due to non-communicable diseases worldwide, thus becoming the leading cause of death due to non-communicable diseases. Approximately, 80% of these deaths have been reported to occur in low and middle-income countries.[1]

Moreover, out of nine million premature deaths due to non-communicable diseases (*viz.* age < 60 years); around eight million occurred in low and middle-income countries. With 6.8% and 5.0% of disability-adjusted life-years (DALYs) lost, CAD is the second largest causes of disease burden in population aged 15 years and older globally.[1]

1.1. *Trends of cardiovascular diseases in India*

Cardiovascular diseases have assumed epidemic proportions in India as well. The Global Burden of Diseases (GBD) study reported the estimated mortality from coronary heart disease (CHD) in India to be 1.6 million in the year 2000 which is estimated to increase to ~64 million by the year 2015.[2] The projected rise in disease burden due to CVD is expected to make it the prime contributor of total mortality and morbidity.[2]

Reports on CAD in Indians have shown that Asian Indians are at 3–4 times higher risk of CAD than white Americans, 6 times higher than Chinese, and 20 times higher than Japanese.[3] Various independent epidemiological studies conducted in North India suggest that the prevalence of CAD has increased from 1% in 1960 to 10.5% in 1998 in the urban population.[3] A higher prevalence of CAD, ranging from 11.0% to 14.2%, has been reported from South India.[3] Taking into account the size of the Indian population, these prevalence rates indicate that a large number of deaths can be attributed to CAD.[3]

1.2. *Premature CAD in Indians*

Cardiovascular diseases are characterized by early age of onset and greater mortality in developing countries like India.[4] In India, the high burden of CVD is not only the prime concern, but also the effect of CVD on productive workforce aged between 35 and 65 years is more worrisome.[5] CHD in Indians is reported to occur a decade or two earlier than their counterparts in developed countries.[5] Since it manifests at a younger age it can have devastating consequences for an individual, the family and society. Moreover, this being individual's working period of life results in loss of potentially productive years of life in India. Among working-age adults (35–64 years old), nearly 18 million productive years of life are expected to be lost from CAD by 2030, a number which is more than nine times higher than expected in the USA.[6] This pattern of disease has substantial implications on India's growing workforce and economy (Table 1).[6]

Table 1 – Salient features of the coronary artery disease (CAD) epidemic in India.

- India topped the world with 1,531,534 cardiovascular disease-related deaths in 2002.[2]
- Incidence of CAD in young Indians is about 12%–16%, which is higher than any other ethnic group.[2]
- According to the INTERHEART study, median age of first heart attack in Indians is 53 years whereas that in Western Europe, China, and Hong Kong is 63 years, with more men affected than women.[3]
- Half of the CVD-related deaths (i.e., 52% of CVDs) in India occur below the age of 50 years, and about 25% of acute myocardial infarction (AMI) in India occurs below the age of 40 years.[2]
- Age-standardized estimates for disability-adjusted life-years lost due to CAD per 1000 population in India are three times higher than in developed countries.[2]

1.3. *A comparison of AMI scenario in India vs developed countries.*

	Syndrome		Mean age (years)	Time (min)		Practice		30 day mortality	
	STEMI	Non-STEMI		Onset of symptoms to admission hospital	Admission to thrombolysis	Primary percutaneous coronary intervention (STEMI vs non-STEMI)	Thrombolytic treatment (proportion streptokinase)	STEMI	Non-STEMI
CREATE	61%	39%	57	300	50	8% vs 7%	59%	9%	4%
Global Registry of Acute Coronary Syndromes[8-10]	30-40%	60-70%	64-69	140		40% vs 28%	47%	8%	3%
European Heart Surveys 1[15]	42%	51%	63	170	40	40% vs 25%	37%	7%	1%
European Heart Surveys2[16]	47%	48%	63	145	37	58% vs 37%	41%	6%	3%
*US national registry of myocardial infarction[12,13]	"	"	68	128	32-38	36%†	21%	8%	"

STEMI=myocardial infarction with ST elevation. Non-STEMI=myocardial infarction with no ST elevation or unstable angina. *This study included only patients with acute myocardial infarction. † In hospitals with interventional facilities.

Comparison of acute coronary syndromes in developed and developing countries

The most comprehensive data about contemporary trends in STEMI patients come from CREATE, a large clinical registry of acute coronary syndrome patients regularly from 89 large hospitals in 10 regions and cities across India.[7]

- About 60% of patients who were assessed had STEMI, whereas in reports from developed countries including the European Heart Surveys, <40% had STEMI. This suggests that patients admitted to Indian hospitals with ACS are

likely to have worse prognoses than those in other countries.[7]

- Three-quarters of the patients were from lower middle class and poor backgrounds and were less likely to be able to afford routine treatments in hospitals and for secondary prevention.
- Patients with STEMI took much longer to reach hospital (median 300 min) than did patients in developed countries (range from 140 to 170 min).[7]
- Patients with non-STEMI or unstable angina took even longer to reach hospital (median 420 min). Few patients used an ambulance to reach the hospital; most used private or public transport.[7]
- The reasons patients reached hospital late include economic reasons, a lack of awareness about the importance of the symptoms and different types of healthcare providers that prevent rapid access to secondary and tertiary care hospitals.[7]
- Rates of primary PCI were lower while that of thrombolytic treatment was higher than in developed countries. This is probably because around three-fourth of patients in India have to pay directly for their own treatments. Moreover, around 25% of the patients had coronary angiography as compared to 50% of the patients in developed countries. Similarly, the rate of PCI in STEMI patients was much lower than in developed countries.[7]
- The equivalent rate of PCI in patients who had non-STEMI or unstable angina was 7%, whereas in developed countries it was higher (around 25%–37%).[7]
- The rates of coronary artery bypass graft were even lower in our patients.[7]
- Although STEMI patients were about a decade younger than those in other registries, their 30-day mortality (9%) was higher than in developed countries (range 6–8%). The mortality in patients with non-STEMI was 3·7%, which was also higher than mortality in developed countries.[7]

1.4. *The current status of treatment of AMI in India*

Primary angioplasty in acute myocardial infarction (PAMI) is the gold standard treatment for management of AMI due to its profound ability to achieve high percentage of reperfusion.[8] Nearly all patients are eligible for PAMI and a complete evaluation of coronaries is possible with confirmation of the acute occlusion. It leads to prompt revascularization under vision with >90% TIMI 3 flow and with stent placement the residual stenosis is eliminated.[9]

However, this treatment modality is available only to less than 10% of STEMI patients in India (CREATE registry) whereas in the developed countries where good transfer facilities exist ≥28% of STEMI patients receive the benefit of PAMI. In Indian conditions, even small towns have a population above 100,000 people.[8] Moreover, lack of awareness, inappropriate transfer facilities, traffic congestion and consultation with family physicians are some of the factors that delays the time to treatment. In small towns where reaching a hospital quickly may be possible, hospital with PAMI capabilities are not available. At the tertiary care hospital where the time from reaching the casualty to establish TIMI 3 flow has its own delay of formalities, round the clock availability of skilled manpower and availability of cath lab in busy hours.[8] All these situations are expected to get worse in India in the future.[8]

1.5. *Hurdles in PAMI… role of thrombolysis*

In smaller cities of India, thrombolysis continues to be a vogue as the facilities for primary angioplasty in myocardial infarction (PAMI) are not available and transport facilities are limited. Also in India the ambulance facilities are poor and those available are often not up to the mark.[10] Most of the times, patients with STEMI condition present late after the onset of symptoms and the desired goals like, door-to-needle time and door-to-balloon time, as specified in guidelines, are rarely met. In CREATE registry, only 41.6% of patients with STEMI presented within 4 h of the onset of chest pain and 31% of patients presented after 12 h.[10]

Presently, there are over 500 centers with facilities for coronary angiography in India[10]; however, the number is quite disproportionate to the size of CAD patient burden in the country. Extrapolation of the Global Burden of Diseases (GBD) study showed that current burden of CAD in India is as high as >32 million patients with a sizeable proportion in rural (3–5%) and urban (7–10%) population.[10] Hence, in Indian conditions with delayed access to the limited number of catheter laboratories and insurance benefits being a rarity, pre-hospital or in-hospital thrombolysis should be the treatment of choice for patients with AMI similar to what the latest review by Kunadian V. and Gibson M. concluded.[11,12]

Approval of third generation thrombolytics by the Drug Controller of India (DCGI) was a major step towards developing viable STEMI systems of care in the country. These new generation fibrinolytic drugs improve reperfusion rates and relative clinical outcomes in STEMI patients. The ability of third generation thrombolytics to be administered as a bolus has made it possible to consider pre-hospital treatment in certain settings.[6] New data on adjunctive therapy with Clopidogrel may also expand the benefits of fibrinolytic therapy.[6] Finally, an improved understanding of the role of pharmacoinvasive approach, i.e., the combination of immediate pharmacological reperfusion with invasive cardiac procedures, suggests the possibility of targeting PCI in high-risk patients.[6]

2. Management of AMI: the current scenario

In the successful management of AMI, timely reperfusion therapy (either pharmacologic or catheter-based) is essential in order to rapidly restore the coronary blood flow and limit myocardial necrosis. The optimal goal of any system is to facilitate rapid recognition of symptoms and treatment of patients with STEMI such that the medical contact-to-needle (door-to-needle) time for initiation of fibrinolytic therapy is ideally achieved within 30 min (or) the medical contact-to-balloon (door-to-balloon) time for PCI is achieved within 90 min.[13] In India, the CREATE registry reported that the median time to reach a hospital was 300 min and the proportion

of STEMI patients undergoing PCI was only 8%.[7] Therefore, as per the ACC guidelines on STEMI management, the patients with acute MI who are suitable candidates for fibrinolytic therapy, should be thrombolysed as soon as possible, ideally within 30 min of first medical contact.[13]

In pharmacological reperfusion therapy, fibrinolytic agent is the key component of pharmacological "cocktail" administered for the treatment of STEMI. Fibrinolytic therapy has been a cornerstone in treatment of patients presenting early; however, adjunct antithrombotic agents (Anticoagulants [viz. Heparin/Enoxaparin] and Anti-platelet drugs [viz. Aspirin, Clopidogrel]) are of utmost importance for maximizing and maintaining the benefit of drug dissolving the occlusive thrombus in the Infarct Related Artery (IRA).[14] The inability to achieve microvascular reperfusion with fibrinolysis (in around 40% of patients) and primary PCI (in around 25% of patients) prompts the use of adjunctive therapy before and combined with invasive strategies.[15]

2.1. *Approaches to treatment of AMI*

The absolute goal of AMI treatment is to achieve earliest possible reperfusion.

Way back in 1980, it was demonstrated that occluding thrombosis of a coronary artery is the most frequent cause of AMI. Since then, a number of authors have hypothesized that early reperfusion of the IRA may potentially limit infarct size, preserve left ventricular function and ultimately reduce morbidity and mortality.[16]

Primary PCI (angioplasty and/or stenting without prior use of concomitant fibrinolytic therapy) is the preferred therapeutic option when it can be performed within 90 min after the first medical contact. The procedure demands a high degree of expertise in terms of an experienced team, which includes not only interventional cardiologists, but also skilled supporting staff. Therefore, only the hospitals with an established interventional cardiology programme can use primary PCI as a routine treatment option for patients presenting with AMI.[18]

The therapeutic goal in AMI is to retard coagulation and platelet function and open the infarct related coronary artery to achieve the greatest degree of myocardial reperfusion in the shortest possible time. The clinical approaches usually available to achieve myocardial reperfusion include some combination of thrombolysis, angioplasty, anticoagulation, platelet inhibition and β-adrenergic blockade.[16]

The most common approaches considered by the clinicians are as follows:[17]

- **Facilitated PCI** – a strategy of full- or half-dose fibrinolysis, with or without administration of a glycoprotein (GP) IIb/IIIa receptor antagonist, with immediate transfer for planned PCI within 90–120 min.
- **Rescue PCI** refers to the transfer for PCI of patients who demonstrate findings of failed reperfusion with fibrinolysis.
- **Pharmacoinvasive strategy** – the administration of fibrinolytic therapy either in the prehospital setting or at a non-PCI-capable hospital, followed by immediate transfer to a PCI-capable hospital for early coronary angiography and PCI when appropriate.

2.1.1. *Primary PCI (angioplasty and/or stenting without prior use of concomitant fibrinolytic therapy)*

ACC/AHA guidelines recommend primary PCI in equipped settings as it offers several important potential advantages over pharmacologic reperfusion.[19]

2.1.1.1. Advantages of primary PCI[19,20]. Primary PCI is suitable for ≥90% of patients, establishes initial Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in 70–90% of patients.

1. Nearly eliminates the risk of intracranial hemorrhage,
2. Preferable to alternative treatments in high-risk patients, such as those with cardiogenic shock, severe congestive heart failure, or hemodynamic or electrical instability.
3. Appropriately selected patients undergoing primary PCI were shown to have lower rates of nonfatal reinfarction, stroke, and short-term mortality than fibrinolytic recipients in a meta-analysis of data from 23 randomized trials enrolling fibrinolytic-eligible patients with STEMI.[20]

The short-term and long-term clinical outcomes for the 23 trials were evaluated to compare primary percutaneous transluminal coronary angioplasty (PTCA) with thrombolytic therapy for acute ST-segment elevation myocardial infarction (AMI). Overall, patients assigned to primary PTCA were less likely to die, have a non-fatal reinfarction, or fall within the group who had a combined endpoint of death, non-fatal reinfarction, and stroke, than those assigned thrombolytic therapy. These outcomes were significantly decreased not only in the short-term, but also over long-term follow-up.[20] Hence it was concluded that Primary PTCA is more effective than thrombolytic therapy for the treatment of ST-segment elevation AMI.[20] (See Annexure Table).

2.1.1.2. Limitations of primary PCI and place of thrombolysis in the treatment of AMI (Indian context). Clinical studies indicate that the speed of reperfusion after infarct onset may be more important than whether pharmacologic or mechanical intervention is used. Therefore, Primary PCI would have become the universally dominant strategy for achieving early reperfusion if resource and logistical constraints had not limited its broad-based adoption. As discussed earlier, time to reperfusion is the most critical variable in STEMI management and is particularly important for PCI. Availability of invasive facilities is another important determinant of the feasibility of PCI.[19]

Unless rapid transfer to an appropriately staffed facility is available and systems are in place to make it possible, PCI generally involves variable delays. Door-to-balloon times of <90 min are achieved in only approximately one-third of patients who do not require transfer and in a much smaller proportion of patients presenting to hospitals without ready access to primary PCI.[19] Real-world data from the National Registry of Myocardial Infarction (NRMI-3 and -4) databases (n = 4278) shows that the total door-to-balloon times of <90 and <120 min were achieved in only 4.2% and 16.2%, respectively, of STEMI patients transferred for PCI (median 180 min).[19]

Because up to 70% of STEMI patients present to hospitals without on-site PCI facilities, and prolonged door-to-balloon times commonly limit the benefit of PCI, the continued role

and importance of the prompt, early use of fibrinolytic therapy should be emphasized.[19] Logistical complexities such as triage or transportation delays must be considered when a reperfusion strategy is selected, because prompt fibrinolysis may achieve greater benefit, especially if the fibrinolytic-to-PCI time delay associated with transfer exceeds >1 h.[19]

2.1.2. *Thrombolytic agents*

2.1.2.1. Historical perspective. Dr. William Tillett in 1933 discovered "Streptokinase" (SK) when he observed that streptococci agglutinated with plasma but not with serum, which is another great example of serendipity. He concluded that any plasma containing streptococci would not clot and this laid the foundation for thrombolysis in various settings. In 1945, the term "streptokinase" was coined.[11]

Due to non-specificity, side-effects like allergic reactions and hypotension occurred with SK. The initial description of a prolonged infusion of SK for patients with AMI appeared in 1958, followed by several smaller studies, but no definitive benefit was discernible until a meta-analysis of these early studies suggested a significant mortality benefit with first generation fibrinolytics. It was soon recognized that intracoronary fibrinolytic therapy could salvage jeopardized ischemic myocardium, and that early restoration of patency of the IRA resulted in better preserved left ventricular function. Thereafter, a significant mortality benefit with IV fibrinolysis was demonstrated and confirmed. This has led to worldwide adoption of IV fibrinolysis for acute STEMI.[12] Since, SK is derived from streptococcus source and is non-fibrin specific in nature, various side effects like systemic bleeding complications, allergic reactions and hypotension occur with streptokinase. To address these issues, the newer fibrinolytic agents evolved subsequently.

In 1952, Macfarlane and Pilling isolated another fibrinolytic, "Urokinase" (UK) which unlike SK, was non-antigenic. But since it was isolated from human urine, it was presumed that it may transmit infections.

The advent of recombinant DNA technology sparked a revolution in biology and spurred the development of the biotechnology industry. Recombinant technology was then the method of development of all thrombolytics that followed. The first thrombolytic molecule to be developed was Alteplase – a recombinant form of natural tPA (a second generation agent) that showed marked benefits in terms of safety and efficacy profile over earlier generation drugs. However, due to its shorter half life it has to be administered as a continuous infusion making its administration process more complex. Anistreplase belonging to the same class has an advantage of a single bolus due to longer half-life. Later it was hypothesized that genetic modification of the molecule to delete specific domains could create an improved thrombolytic with a longer half-life and rapid onset of action, permitting bolus administration. Moreover, it would be capable of achieving normal TIMI 3 flow in a large percentage of patients and would have a lower bleeding risk. Tenecteplase and reteplase are the two third generation fibrinolytic drugs that result from the modification of native tPA. These variations substantially decreased their clearance from plasma resulting in longer half-life allowing administration as a single bolus and also conferring higher fibrin specificity. The dose is calculated on the basis of body-weight for tenecteplase whereas for reteplase no weight-based dosing calculations are required. Modifications in molecular structure of reteplase resulted in some of the unique properties of drug including high fibrin specificity, low fibrin affinity (binding), longer half-life and greater thrombolytic potency in comparison to t-PA.

Fibrinolytic agents are the preferred pharmacologic class for the management of STEMI because of their ability to achieve reperfusion and to restore blood flow when administered within 12 h of symptom onset. Thrombolytic trials in AMI over the past decade have shown early achievement of more rapid patency & TIMI grade 3 flow and reduced 24-h mortality.[16,21] In the Myocardial Infarction Triage and Intervention which was a randomized, double blind trial, by Weaver WD et al., administration of thrombolytic therapy within 70 min of symptom onset, whether prehospital or in-hospital, reduced mortality from 8.7% to 1.2% ($p = 0.04$).[22,23]

Large randomized clinical trials (RCTs) as well as the Fibrinolytic Therapy Trialists overview have clearly demonstrated a statistically significant mortality benefit with thrombolytic therapy over placebo in this clinical setting.[12] It demonstrated an overall risk reduction in 35 day mortality of 18% with thrombolytic treatment. The beneficial effect of thrombolysis extends to patients presenting within 12 h of the onset of symptoms, but it is clear that the earlier patients are treated the better their outcome. Thrombolytic treatment saves about 30 lives per 1000 patients presenting within 6 h of symptom onset.[24]

Thrombolytics in AMI – pivotal trials

Although several small studies demonstrated the beneficial effects of SK in terms of reducing 30-day and 1-year mortality, the GISSI and the ISIS trials firmly established the efficacy of intravenous SK in the management of patients with AMI.[11]

In the GISSI trial, at 21 days there was 18% reduction in overall hospital mortality following the administration of SK compared with the control group ($p = 0.0002$). Likewise in randomized trial of intravenous SK, oral aspirin, both, or neither among cases of suspected AMI demonstrated that streptokinase and aspirin alone give significant reduction in 5-week vascular mortality. Also the combination was better than either agent alone. But SK was associated with excess of bleeds requiring transfusion, intracranial hemorrhage and non-fatal reinfarction if used alone.[25]

Newer thrombolytic agents have been developed in order to provide longer half-life to enable bolus administration, fibrin specificity, and to be resistant to natural inhibitors such as plasminogen activator inhibitor-1 (PAI-1). Following the breakthrough discovery of SK in the treatment of patients with AMI and the emergence of novel agents, the attention shifted to determine which thrombolytic agent was the best. The GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries), GISSI-2 and ISIS-3 investigators compared intravenous SK and t-PA in the treatment of AMI.[11]

The GISSI-2 trial consisting of 12,490 patients demonstrated that SK and tPA were equally safe and effective in AMI and did not demonstrate specific differences between the two thrombolytic agents (tPA vs. SK) with regards to the combined endpoint of death and severe left ventricular damage (23.1% vs. 22.5%). Although major bleed was significantly higher in SK

and heparin-treated patients (tPA 0.5% vs. SK 1.0%), the overall incidence of stroke was similar in all treatment groups.[11]

Although no significant difference was observed between SK and tPA in GISSI-2 and ISIS-3, the GUSTO trial demonstrated that an accelerated regimen of tPA (administration of tPA over a period of 90 min, with two-thirds of the dose given in the first 30 min instead of the conventional period of 3 h) resulted in significant reductions in death and disabling strokes among patients with AMI. Accelerated tPA group resulted in 14% reduction in mortality at 30 days compared with the SK strategies. There was slight excess of hemorrhagic stroke for accelerated tPA ($p = 0.03$) when compared with the SK strategies. However, the combined endpoint of death or disabling stroke was significantly lower in the accelerated tPA group than in the SK only groups (6.9% vs. 7.8%, $p = 0.006$). Thus accelerated t-PA provided a higher rate of early perfusion and a lower mortality rate.[11]

When the patients receiving SK as the thrombolytic agent were evaluated within GUSTO II, a striking reduction in mortality and other adverse events was evident. These results were consistent with angiographic studies, which showed that a direct thrombin inhibitor in combination with SK results in a substantially higher rate of TIMI grade 3 flow than SK and heparin in combination.[26]

The GUSTO IIb direct angioplasty sub-study was performed to provide a broader perspective on the comparison between direct angioplasty and thrombolysis with accelerated administration of t-PA. Though at 30 days of follow-up, the composite endpoint favored direct PTCA (9.6% vs 13.7%; $p = 0.03$), but by 6 months approximately half of that benefit was lost. This result is consistent with the open artery concept that direct angioplasty was superior to thrombolytic therapy, although the smaller than expected size of the difference raises questions.[26]

In comparison with SK, 'standard' alteplase and accelerated alteplase administration, reteplase has been shown to produce a higher rate of TIMI grade 3 flow at 60 and at 90 min. This enhanced patency rate coupled with the convenience of a bolus administration provided an attractive approach to thrombolysis.[26]

The superior results of catheter-based strategies of reperfusion, as compared with thrombolytic therapy, although not entirely durable over the long term, most likely relate to the fact that there is earlier and more complete restoration of myocardial blood flow than occurs with thrombolytic agents. Substantial increases in speed and persistence of reperfusion require better adjunctive agents such as direct antithrombins, which markedly improved the results obtained with SK, or inhibitors of platelet glycoprotein IIb/IIIa.

The GUSTO IV ACS study indicated that glycoprotein IIb/IIIa receptor blocker abciximab was not beneficial as first-line medical treatment in patients admitted with acute coronary syndromes without early coronary revascularization.[27]

The combination of abciximab in full doses and reteplase in half doses did not significantly reduce the rate of mortality at 30 days in patients with acute STEMI when compared with reteplase in full doses in the GUSTO V trial.[28]

A double dose reteplase (10 + 10 MU) utilized in the RAPID trial resulted in complete, rapid and sustained thrombolysis of IRA at 90 min and 5–14 day (63% vs. 49%, $p = 0.019$; and 88% vs. 71%, $p < 0.001$) compared with alteplase and improved regional and global left ventricular function at discharge. The RAPID II trial further confirmed the advantage of reteplase over accelerated alteplase in achieving higher rates of early reperfusion in the IRA and fewer acute coronary interventions.[11]

The second generation thrombolytic anistreplase was compared in a study, where SK vs tissue plasminogen activator vs anistreplase and aspirin plus heparin vs aspirin alone were analysed in a randomized comparison among 41,299 cases of suspected AMI.[29] The Aspirin–Heparin combination versus aspirin alone showed no significant medium-term survival advantage, slightly fewer deaths during heparin treatment, but may cease when heparin stops. Also no significant difference with respect to total stroke, excess of major non-cerebral bleeds or excess of definite or probable cerebral hemorrhage was observed.[29]

Anistreplase compared to SK showed no significant difference in reinfarction, similar 6 month survival, more allergy and slight excess strokes.[29]

rtPA compared to SK demonstrated no significant difference in mortality but fewer reinfarctions.[29]

In addition to the GUSTO trial, other trials demonstrated that the accelerated alteplase infusion regimen administered over a 90-min period to be the preferred treatment strategy when compared with a double dose alteplase therapy due to slightly increased rate of intracranial bleeding in the latter group (1.12% vs. 0.81%). The phase I TIMI trial demonstrated that the administration of rtPA in patients with AMI resulted in reperfusion in twice as many occluded infarct-related arteries compared with SK during the first 90 min of initiation of treatment.[11]

Another form of t-PA is the TNK mutant, which has both a longer half-life and markedly enhanced fibrin specificity. Angiographic trials had demonstrated an improvement in TIMI grade 3 flow comparing TNK with accelerated alteplase; and a safety study has shown promising evidence that intracranial hemorrhage is unlikely to be increased. In the TIMI 10B trial, TNK-tPA (40 mg) and alteplase produced similar rates of TIMI grade 3 flow at 90 min. Subsequently the ASSENT 1 trial (Assessment of the Safety and Efficacy of a New Treatment) demonstrated that the safety profile of TNK was comparable to alteplase. To examine the impact of modest improvements in perfusion, a large international trial was conducted comparing TNK and accelerated alteplase with an expected sample size of 16,949 patients in the ASSENT-2 trial.[26]

The 30-day mortality rates were almost identical for the two groups – 6.18% for tenecteplase and 6.15% for alteplase. Rates of intracranial hemorrhage were similar but fewer non-cerebral bleeding complications and significantly less need for blood transfusion ($p = 0.0002$) were seen with tenecteplase.[30]

2.1.2.2. Candidates for use of thrombolytics. The eighth ACCP guidelines on management of STEMI states that for patients with ischemic symptoms characteristic of AMI of <12 h duration and persistent STE, reperfusion (primary PCI or fibrinolytic) therapy be implemented promptly after contact with the health-care system (Grade 1A). In patients with AMI who are candidates for fibrinolytic therapy, administration as soon as possible (ideally within 30 min) after arrival at the hospital or first contact with the healthcare system (Grade 1A) is recommended. In healthcare settings where prehospital administration of fibrinolytic therapy is feasible, it should be administered (Grade 1A).[13]

In a country like India where there is a highly disproportionate ratio of patients presenting with ACS and catheter laboratories (approximately 500) available; the recommendations should be highly pragmatic. Fibrinolytics thus prove a very useful rescue option when intervention laboratories are predicted not to be available immediately.

Fibrinolytic Therapy When There Is an Anticipated Delay to Performing Primary PCI Within 120 Minutes of FMC: Recommendations.[32]

- The benefits of fibrinolytic therapy in patients with ST elevation or bundle-branch block MI are well established, with a time-dependent reduction in both mortality and morbidity rates during the initial 12 h after symptom onset.[32]
- Even when interhospital transport times are short, there may be advantages to the immediate delivery of fibrinolytic therapy versus any delay to primary PCI for patients with STEMI and low bleeding risk who present within the first 1–2 h of symptom onset.[32]

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is beneficial, useful, effective. Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Class I

In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 h when it is anticipated that primary PCI cannot be performed within 120 min of FMC. *(Level of Evidence: A)*.

Class IIa

In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or electrocardiographic evidence of ongoing ischemia within 12–24 h of symptom onset and a large area of myocardium at risk or hemodynamic instability. *(Level of Evidence: C)*.

Class III: harm

Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead a VR. *(Level of Evidence: B)*.

Fibrinolysis is recommended for patients with ischemic symptoms characteristic of AMI: **Timing of Fibrinolytic Therapy**.[32]

- Benefit from fibrinolytic therapy in patients who present >12 h after symptom onset has not been established although there remains consensus that consideration should be given to administering a fibrinolytic agent in symptomatic patients presenting >12 h after symptom onset with STEMI and a large area of myocardium at risk or hemodynamic instability if PCI is unavailable.[32]

2.1.2.3. *Generations of thrombolytic drugs*. Though fibrinolytic therapy for AMI was first attempted in the 1950s, significant advances have been made till date with the development of newer agents that serves the purpose more efficiently. Since discovery, the thrombolytic therapy has evolved over the three generations of thrombolytic drugs.

1. First-generation agents[33]

First generation thrombolytic agents (SK and UK) are non-fibrin specific agents which lack fibrin binding capabilities and cause systemic plasminogen activation with concomitant destruction of hemostatic proteins.[34] While effective in thrombolysis, their antigenic profile and propensity to cause hemorrhagic complications led to the development of newer thrombolytic drugs.[35] A primary driving force behind the development of the second generation tissue plasminogen activator (tPA or alteplase) was its ability to bind to fibrin and produce targeted thrombolysis.

(a) Streptokinase[33]

SK is a non-fibrin specific agent that activates both circulating as well as clot-bound plasminogen and leads to systemic lysis of fibrin. (The fibrin-specific agents predominantly lyse clot-bound fibrin). It binds to plasminogen to form a SK–plasminogen complex that converts freely circulating plasminogen in the bloodstream to plasmin, which finally

initiates fibrinolysis. The systemic plasminogen activation with SK results in extensive fibrinogen depletion and concomitant bleeding risks. In patients with AMI who are treated with SK therapy, approximately 30% achieve TIMI grade 3 flow by 90 min, and another 20% achieve TIMI grade 2 flow. The GUSTO-1 study showed a 30-day mortality rate of 7.3% and an intracranial hemorrhage rate of 0.54% with SK.

Besides the risk of bleeding, development of antibodies in some patients (preventing its reuse), allergic reactions and hypotension are some other disadvantages that results from the nonspecific plasminogen binding of SK.

Col et al. treated 128 patients with SK and aspirin and randomized the patients to either an IV bolus of heparin or no heparin; the study reported no difference in coronary patency at 24 h (86% versus 87%). The DUCCS-1 (Duke University Clinical Cardiology Studies) investigators treated 250 patients with anisoylated plasminogen–SK activator complex (APSAC) and aspirin and randomized patients to heparin or no heparin. There was a small difference in coronary artery patency (80% in the heparin group versus 74% in the control group). In both studies, moderate doses of heparin produced marginal benefits at the cost of increased bleeding.[36]

Trials like GISSI-2 with aspirin and several large studies reported in 2005 with clopidogrel have established their use as adjunctive antiplatelets with fibrinolytics. (Class I recommendation, Level of Evidence: A).

The beneficial effects of aspirin and clopidogrel with fibrinolytic therapy are well established. These agents should be given before or with the fibrinolytic. The recommendation that clopidogrel be continued for up to 1 year is extrapolated from the experience with DAPT in patients with non-ST-elevation ACS.

The coadministration of other P2Y12 antagonists like prasugrel and ticagrelor with fibrinolytic therapy has not been prospectively studied, hence not recommended.[32]

In the GISSI-2 trial, a comparison of SK (SK, 1.5 MU IV infusion over 30–60 min) and alteplase (tPA, 100 mg IV infusion over 3 h) administered with heparin (12,500 U s.c. twice daily until discharge from hospital, starting 12 h after beginning the tPA or SK infusion) was carried out in patients with AMI admitted to coronary care units within 6 h from onset of symptoms. The incidence of major bleeds was significantly higher in SK and heparin treated patients compared to alteplase (respectively, tPA 0.5%, SK 1.0%).[37]

(b) 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" (UK) in 1952. Unlike SK, UK directly activates plasminogen to form plasmin and prior binding to plasminogen or plasmin is not necessary for activity.[33] The agent is nonantigenic, and untoward reactions of fever or hypotension are rare. In AMI patients receiving UK, the patency rate at 60 min is around 60%.[33] However, after the manufacturer could not prove that because of the drug being derived from the human source material, there is no risk of transmitting infections, UK was not approved by the FDA and production was suspended. Nevertheless, the drug is widely used in Korea and the Asian-Pacific area, where the Thrombolysis in Myocardial Infarction in Korea (TIMIKO) trial compared alteplase and UK in patients presented with AMI.[33] The 30-day mortality rate was not significantly different between the two treatment groups: 4.6% in the UK group and 4.4% in the alteplase group. Moreover, the incidence of ICH was 0.3% in the UK group and 1.1% in the alteplase group. The risk of major bleeding was 10% with UK and 9.7% with alteplase.[33]

2. Second-generation agents

(a) Alteplase

Alteplase or recombinant tissue plasminogen activator (rtPA) is a second generation thrombolytic agent developed after molecular cloning techniques were used to express human tPA DNA. Alteplase is a fibrin specific agent which converts plasminogen to plasmin in the presence of fibrin. It is a predominantly single-chain form of rtPA, which has been studied extensively in the setting of coronary occlusion.[33] Alteplase helps to achieve TIMI grade 3 flow in 50–60% of patients at 90 min. In the GUSTO-I study of 41,000 patients with AMI, alteplase was found to be more effective than SK in achieving vascular patency. Despite a slightly greater risk of intracranial hemorrhage with rtPA, overall mortality was significantly reduced. The patients who received alteplase had a 6.3% mortality rate at 30 days and a 0.72% incidence of intracranial hemorrhage. Compared with SK, alteplase resulted in a 1% absolute reduction in death or nonfatal stroke.[33] Clinically, recombinant t-PA (or alteplase) is capable of more rapid thrombolysis and superior reperfusion compared with SK. However, alteplase produces a significant amount of fibrinogenolysis – although considerably less than either SK or UK and there is no difference between alteplase and fibrin-nonselective plasminogen activators in bleeding complications.[38] Other limitations of alteplase therapy include a delay in the time to patency in many patients and a substantial risk of re-occlusion. There are also practical issues with the administration of alteplase: because of its extremely short half-life (3–6 min) because of which it has to be administered as a continuous infusion over a period of 30–60 min. (*15 mg bolus over 1–2 min, then 0.75-mg/kg infusion (50-mg maximum) over 30 min, followed by 0.5-mg/kg infusion (35-mg maximum) over 60 min; †15 mg over 1–2 min, then 50 mg over 30 min and 35 mg over 60 min. In addition, two intravenous access sites are required, one for heparin and one for alteplase. This complex infusion protocol makes alteplase administration relatively cumbersome.[38]

(b) Anistreplase

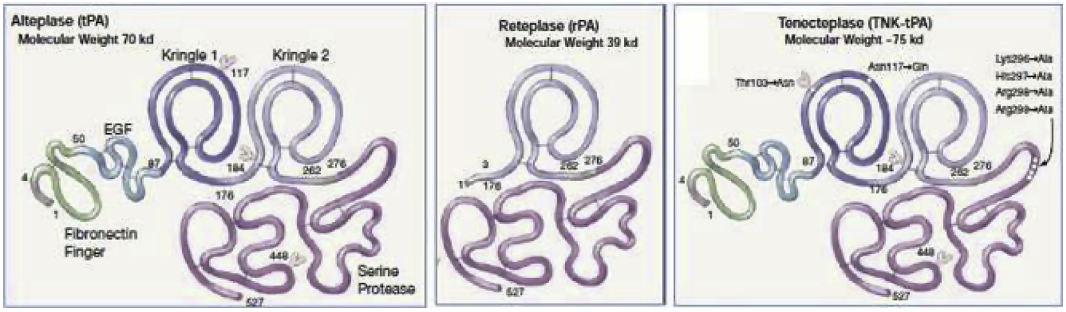
Anistreplase is a second generation thrombolytic agent, which results in a combined TIMI grade 2 and TIMI grade 3 flow rate of 50%–60% at 90 min. It has a side effect profile similar to that of SK, but has the advantage of single-bolus administration. The International Study of Infarct Survival (ISIS)-3 showed a 10.5% mortality rate at 35 days with anistreplase and an ICH rate of 0.6%.

3. Third-generation agents

The third-generation fibrinolytic agents were developed with an objective to improve safety, efficacy and ease of administration of previous generations of thrombolytic drugs.[38] In an attempt to achieve better lytic characteristics and less bleeding risk, genetic engineering techniques were used to modify the wild-type t-PA molecule, which consists of several distinct domains which are known to be associated with specific functional properties. (See Table below). Thus, it was thought that genetic modification of the molecule to delete specific domains could be a viable method of creating an improved plasminogen activator. This improved

thrombolytic would optimally have a longer half-life, permitting bolus administration, and would have a rapid onset of action. It would be capable of achieving normal TIMI 3 flow in a large percentage of patients and would have a lower potential for bleeding complications.[38]

required for alteplase. In addition, TNK-tPA manifests greater fibrin specificity than alteplase, resulting in less fibrinogen depletion. In studies of acute coronary occlusion, TNK-tPA performed at least as well as alteplase, concurrent with greater ease of administration. The efficacy and dosing of tenecteplase in the



Structure: Second and third generation fibrinolytics.[39]

(a) Tenecteplase (TNK-t-PA; TNKase)

Tenecteplase is a novel third generation fibrinolytic drug that results from the modification of native tPA at 3 sites. These variations substantially decrease the clearance of TNK-tPA from plasma which results in longer half-life and higher fibrin specificity of the drug. Longer half-life of TNK-tPA allows the successful administration of drug as a single bolus, the dose being calculated on the basis of body-weight, in contrast to infusion treatment of acute MI were evaluated in the TIMI 10A, TIMI 10B, ASSENT-1, and ASSENT-2 trials. Tenecteplase demonstrated 90-min TIMI grade 3 flow rates of 59%–64%. The primary endpoint of 30-day all-cause mortality occurred in 6.18% of the tenecteplase group and 6.15% of the alteplase group. The incidences of ICH were similar to alteplase in majority of the trials.

(b) Reteplase (r-PA)

It is a 1st third generation recombinant form of t-PA that operates in the presence of fibrin (i.e. it is fibrin specific).[33]

Characteristics of commonly used fibrinolytics in the treatment of STEMI[a-d]. There are several fibrinolytic agents currently approved for the management of STEMI.

Characteristic (units)	Streptokinase	Altepase	Tenecteplase	Reteplase
Generation	I	II	III	III
Plasma half-life (min)[a]	18–23	3–8	18–20	15–18
Metabolism[a]	Hepatic	Hepatic	Hepatic	Renal
Mechanism of action[a]	Activator complex	Direct	Direct	Direct
Fibrin specificity[a]	Non-specific	++ (high)	+++ (very high)	+ (moderate)
Fibrin affinity[c]	–	++	+++	+
Antigenic[c]	Yes	No	No	No
Allergic reaction (hypotension most common)[c]	Yes	No	No	No
Method of administration[a]	1 h Infusion	Bolus +90 min infusion	Single Bolus	Double bolus
Weight-based dosing[b]	No	Yes	Yes	No
Dose[c]	1.5 MU over 30–60 min	Up to 100 mg in 90 min	30–50 mg based on weight	10 U × 2 (30 min apart), each over 2 min
90-min Patency rates (~ %)[d]	50	75	75	80
TIMI Flow grade 3 (~ %)[c]	30	50	~60	~60
Rate of ICH (~ %)[c]	0.4	0.4–0.7	0.9	0.8

* Kunadian V & Gibson CM. Thrombolytics and Myocardial Infarction. Cardiovas Ther. 2012;30:e81–e88.
Adapted and modified from;

[a] Menon V, Harrington RA, Hochman JS, Cannon CP, Goodman SD, Wilcox RG, Schünemann HJ, Ohman EM. Thrombolysis and adjunctive therapy in acute myocardial infarction: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.Chest 2004;126;549S–575S.
[b] Hilleman DE, Tsikouris JP, Seals AA, et al. Fibrinolytic agents for the management of ST-segment elevation myocardial infarction. Pharmacotherapy 2007;27(11):1558–1570.
[c] Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. JACC 2007;50(10):917-929.
[d] Pollack CV, Antman EM, Hollander, JE. Management of Patients With ST-Segment Elevation Myocardial Infarction: Implications for Emergency Department Practice. Ann Emerg Med. 2008;52:344-355

Reteplase is a non-glycosylated thrombolytic agent engineered by means of recombinant DNA technology, derived from tissue plasminogen activator (t-PA). Reteplase mimics the endogenous tissue plasminogen activator (t-PA), a serine protease, converting plasminogen to plasmin and thereby precipitating thrombolysis. Modifications in molecular structure of Reteplase results in some of the unique properties of drug including high fibrin specificity, low fibrin affinity (binding), longer half-life and greater thrombolytic potency in comparison to t-PA. A double bolus reteplase (10 + 10 MU) utilized in the RAPID trial resulted in complete, rapid and sustained thrombolysis of IRA at 90 min and 5–14 day (63% vs. 49%, $p = 0.019$; and 88% vs. 71%, $p < 0.001$) compared with alteplase and improved regional and global left ventricular function at discharge.[11]

2.1.2.4. Rationale for the utilization of bolus thrombolytic agent with a relevance to conditions in India. Evidence from many clinical trials now indicates that two characteristics of a thrombolytic drug determine its efficacy: (1) the ability to achieve early and complete reperfusion (2) the ease of administration to ensure the earliest initiation of treatment.[16] Despite the lack of clinical benefit over conventional agents, bolus agents have number of potential treatment advantages that favor their clinical utilization.[12] These benefits are summarized below.

(1) Ease of treatment
- Utilization of bolus fibrinolytics treatment could aid in more rapid treatment of AMI, since there is unequivocal evidence that earlier delivery of therapy is associated with greater myocardial salvage and improved prognosis to improve survival.[40]
- Reducing the time to treatment, particularly the "door-to-drug" time, has been identified as a critical target. An increased door-to-drug time has been shown to relate directly to increased mortality. The time from "the decision" to "the start of drug" can be reduced if a simple, bolus fibrinolytic agent is available.[12]
- The advantage of single-bolus therapy in relationship to compliance was established in ISIS-3, in which 95% of patients assigned to anistreplase actually received the drug compared with only 89% and 90% of patients in the alteplase and SK groups, respectively.[12]
- Further, patients administered double-bolus reteplase therapy received the drug 15 min sooner than did those treated with alteplase infusion in a study by Hilleman and colleagues.[12]

(2) Prehospital treatment
- Time from symptom onset to initial treatment with fibrinolysis has not improved over the last 2 decades.[12]
- Although some success has been achieved in abbreviating the door-to-needle time as it relates to the administration of fibrinolytic therapy, the same cannot be said for the delay that persists between symptom onset and hospital arrival. Indeed, despite an understanding of the demographic, cultural, and other barriers that exist and an effort through intense public education programs to abbreviate the time from symptom onset to presentation for appropriate therapy among patients with chest pain syndromes, no improvement in time to arrival to hospital has been achieved.[40]
- Hence, among regions and countries (true for India) where these delays are an important factor, and especially where emergency medical services transport times exceed 1 h, there is now substantial motivation to move toward pre-hospital bolus fibrinolysis in the ambulance or home. Bolus fibrinolytic therapy may be even more advantageous in this setting, where simplicity and lack of need for multiple intravenous lines is at a premium.[40]
- In an overview of six randomized trials involving 6434 patients, the utilization of a pre-hospital thrombolysis resulted in significantly earlier treatment of patients, compared to a conventional in-hospital strategy (104 min vs 162 min; $p = 0.007$). A significant improvement in in-hospital mortality was also evidenced by this approach. In the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial, a prehospital thrombolysis strategy compared favorably to primary angioplasty. Utilization of bolus fibrinolytics therapy enhances the feasibility of this promising strategy.[12]
- In the Early Reteplase-Thrombolysis in Myocardial Infarction (ER-TIMI) 19 study, utilization of prehospital reteplase decreased the time to initial treatment by 32 min compared to conventional in-hospital administration. As a result 49% of patients received initial therapy within 30 min of health-care contact (compared to only 5% in the classically treated group; $p < 0.0001$).[12]

(3) Decrease in medication errors
- The "therapeutic window" for thrombolytic therapy is small, and the potential for adverse outcome from dosing errors is high.[41] Incorrect dosing of fibrinolytic therapy has been reported to occur 5%–12% of the time. Several studies have reported higher mortality, stroke, and major hemorrhagic event rates in patients who received incorrect doses of fibrinolytic agents.[42]
- The ease of administration with bolus fibrinolytic agents can reduce medication errors. These errors have been associated with adverse outcomes and longer hospital stays in this population. A surprisingly high percentage of medication errors (that is, an incorrect dose or infusion duration) have been documented with traditional bolus followed by infusion alteplase therapy.[12] In GUSTO-I, 12% of the 41,021 patients treated with alteplase or SK infusion had a medication error. 13.5% of patients treated with streptokinase and 11.5% of patients treated with t-PA were subjected to a medication error (e.g., incorrect dose or infusion length).[12]
- Most importantly, 30-day mortality was significantly higher in patients with medication errors: For t-PA dosing errors, mortality was 7.7% versus 5.5% for patients who received the correct t-PA dose ($p < 0.001$); findings were similar for streptokinase.[41]
- In a Registry of Myocardial Infarction, >71,000 patients who received a dose of alteplase >1.5 mg/kg had a 2.3-fold increase in ICH, suggesting that medication errors with bolus and infusion fibrinolytic therapy may be important.

- In the Intravenous NPA for Treatment of Infarcting Myocardium Early (InTIME)-II trial, there were more dosing errors in the alteplase group than in the single bolus third generation group 7.3% vs. 5.7%, $p < 0.001$).[12]
- Mortality was higher among alteplase treated patients with medication errors vs. those receiving the correct Alteplase dose (12.5% vs. 5.9%, $p < 0.001$).
- ICH also was significantly increased among alteplase-treated patients with medication errors (1.4% vs. 0.6% with the correct alteplase dose).[12] In the ASSENT-3 PLUS (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 Plus) study, approximately 20% of patients received >105% of the correct dosage of weight-based single-bolus tenecteplase administered prehospital; this was associated with an approximately 2-fold rate of intra-cerebral hemorrhage versus lower doses among patients receiving unfractionated heparin as the concomitant antithrombin agent.
- More recent data studies showed that use of a bolus thrombolytic agent reduced the rate of medication errors. Thus, use of the simpler bolus thrombolytic agents may improve overall clinical outcome by ensuring accurate dosage.[41] For the double-bolus agent reteplase, the rate of medication errors also has been low; only 1% of patients did not receive the full reteplase dose in one study, compared with 4% for alteplase ($p < 0.03$).[12]
- Within contemporary emergency departments, physicians and nurses are required to deal with a growing and increasingly complicated array of available therapies for acute coronary syndromes. These demands are often accented by resource constraints; hence, simple bolus fibrinolytic regimens are a welcome innovation, and such regimens are less likely to engender medication errors.[40]

2.1.3. *Thrombolyse now and stent later (pharmacoinvasive approach)*

Acute ST-Elevated Myocardial Infarction (STEMI) is a medical condition caused by the coronary plaque rupture/erosion and resultant thrombosis leading to an occluded epicardial infarct-related artery (IRA).[12] Myocardial reperfusion therapy (Fibrinolysis/PCI) is based on the concept that after a coronary vessel is occluded, myocardial cell death starts from the endocardium (inner layer) outward to the epicardium (outer layer). When the occlusion is released and myocardial blood flow is restored, the size of the final MI is determined by the amount of myocardium supplied by the infarct-related artery (IRA), the time from occlusion to reperfusion and the extent of collateral blood supply.[43]

Prehospital thrombolysis appears safe and effective and is associated with a substantial gain in time to treatment. A meta-analysis of studies comparing prehospital and inhospital thrombolysis has shown a relative reduction in short-term mortality of 17% with prehospital thrombolysis. Therefore, the Comparison of Angioplasty and Prehospital Thrombolysis in acute Myocardial infarction (CAPTIM) trial was set up to compare prehospital thrombolysis and primary PCI in more than 800 patients with STEMI. Patients randomized <2 h after symptom onset had a strong trend toward lower 30-day mortality with prehospital thrombolysis compared with those randomized to primary PCI (2.2% versus 5.7%, $p = 0.058$).[44]

All-cause mortality at 5 years in CAPTIM trial was 9.7% in the prehospital fibrinolysis group when compared with 12.6% in the primary angioplasty group. For patients included within 2 h, 5 year mortality was 5.8% in the prehospital fibrinolysis group when compared with 11.1% in the primary angioplasty group.[45]

The 5-year follow-up was consistent with the 30-day outcomes of the trial, showing similar mortality for primary PCI and a policy of prehospital lysis followed by transfer to an interventional center.[45]

The CAPTIM trial confirms that the benefit of intravenous thrombolysis is extremely time sensitive and when treatment is established in the first 2 h after symptom onset, the so-called "golden hour," survival dramatically increases.[44]

The PRAGUE trial showed that although angioplasty was performed within 1 h after the beginning of the SK infusion and opened more than twice as many vessels than with the SK infusion, this did not result in better patient outcome. More bleeding complications were observed when SK was combined with heparin given in the cath lab, hence could be one among many factors to offset the mortality benefit with SK compared to the policy of thrombolysis followed by transfer to PCI centre or direct transfer to the PCI centre.[46]

Based on the evidence so far, the 2013 ACC/AHA focused update for the management of patients with acute STEMI states that patients presenting to the non-PCI centers, receive fibrinolytic therapy as a primary reperfusion therapy and to should be transferred as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy.[11] Early catheterization after thrombolysis is to be preferred to conservative management. At 12 months, patients in the invasive group had a lower rate of death, reinfarction, or revascularization, and trended toward reduced death or reinfarction. Thus, results from the GRACIA study support a strategy of "lyse now, stent later".[47]

Intravenous thrombolysis although one of the accepted modes of treatment for ST-elevation myocardial infarction, carries a higher risk of reinfarction than primary PCI. There are few data comparing PPCI with thrombolysis followed by routine angiography and PCI. The pharmacoinvasive strategy (thrombolysis followed by routine angiography) with PPCI was analyzed from a nationwide registry which included 223 centers and 1714 patients over a 1-month period at the end of 2005, with 1-year follow-up. Sixty percent of the patients underwent reperfusion therapy, 33% with PPCI and 29% with intravenous thrombolysis (18% prehospital). At baseline, the Global Registry of Acute Coronary Events score was similar in thrombolysis and PPCI patients. Time to initiation of reperfusion therapy was significantly shorter in thrombolysis than in PPCI (median 130 versus 300 min). After thrombolysis, 96% of patients had coronary angiography, and 84% had subsequent PCI (58% within 24 h).[48] In-hospital mortality was 4.3% for thrombolysis and 5.0% for PPCI. In patients with thrombolysis, 30-day mortality was 9.2% when PCI was not used and 3.9% when PCI was subsequently performed. One-year survival was 94% for thrombolysis and 92% for PPCI ($p = 0.31$). Thus when used early after the onset of symptoms, a pharmacoinvasive strategy that combines thrombolysis with a liberal use of PCI yields early and 1-year survival rates that are comparable to those of PPCI (Fig. 1).[48]

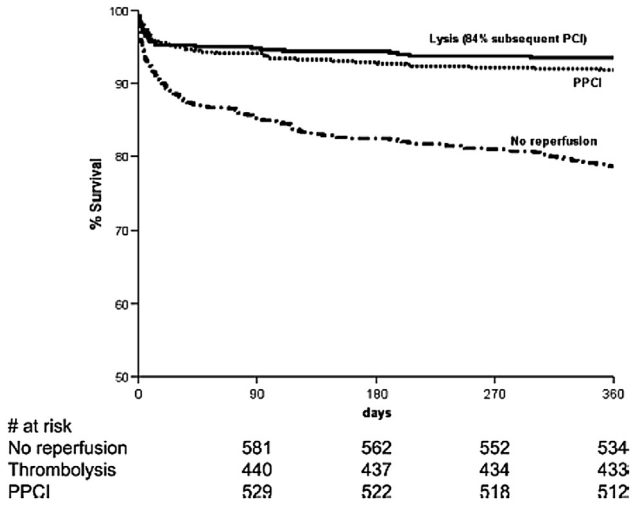


Fig. 1 – One-year survival according to use and type of reperfusion therapy. Adapted from – Circulation 2008;118:268–276.

The emerging modality of pharmacoinvasive therapy combines the benefits of mechanical and pharmacologic reperfusion.[19] Thus to ensure maximum benefit of the pharmacoinvasive approach which best suits a vast country like India, where infrastructure is not developing with the speed of population, the use of more efficient thrombolytic agents which can be administered without weight based calculation (viz. reteplase) should be the treatment of choice. First medical contact (small nursing homes, satellite hospitals, casualty of bigger hospitals) should be "pre hospital" areas of thrombolysis which will not only reduce the health costs but more importantly results in loss of myocardium. Early thrombolysis and early angiography to all should be the future of managing STEMI in Indian context.[8] More importantly, physician-based smaller hospitals (in villages, smaller towns or suburbs of cities) can play a crucial role, by administering thrombolytic agent to these patients at the time of first medical contact with agents like third generation thrombolytics, which are characterized by the ease of administration and lack of anaphylactic reactions. The patient thus gets enough time to move to a catheter lab facility in next 3–24 h. This time also allows them to arrange for finances, gather manpower, and complete insurance formalities (all very important in Indian context). In addition, this breathing period has not done the myocardium any harm, due to early thrombolysis and recanalised culprit artery. Since this population comprises of very young STEMI patients where the predominant pathology in the coronary artery is a thrombus rather than the traditional atherosclerotic plaques; such patients if treated early with effective thrombolysis, can have practically normal coronaries. In future for this special Indian subset, every attempt should be made for early thrombolysis because that could be the only therapy required for these young individuals and unnecessary stenting would get avoided.[8] Public awareness should be increased about early detection (symptoms) of AMI, importance of confirmed diagnosis of AMI, early treatment and the concept of golden hour.

The earlier ACC/AHA and ESC STEMI guidelines recommended PCI as the initial approach to management of STEMI, contingent upon treatment at centers with a skilled PCI laboratory and rapid initiation. Appropriately selected patients undergoing primary PCI were shown to have lower rates of nonfatal re-infarction, stroke, and short-term mortality than thrombolytic recipients in a meta-analysis of data from 23 randomized trials enrolling thrombolytic-eligible patients with STEMI. However, for many patients these criteria for primary PCI to be preferred will not be met and it was important to note that the guidelines also state that there is no strong preference between PCI and thrombolysis as the choice of initial reperfusion therapy in patients who present within 3 h after symptom onset.[49]

Several randomized trials and three contemporary meta-analyses have shown that early routine post-thrombolysis angiography with subsequent PCI (if required) reduced the rates of reinfarction and recurrent ischemia compared with a 'watchful waiting' strategy, in which angiography and revascularization were indicated only in patients with spontaneous or induced severe ischemia or LV dysfunction. The benefits of early routine PCI after thrombolysis were seen in the absence of increased risk of adverse events (stroke or major bleeding).

Thus, early referral for angiography with subsequent PCI (if indicated) should be the standard of care after thrombolysis: the so-called 'pharmacoinvasive' strategy. A crucial issue is the optimal delay between lysis and PCI: there was a wide variation in delay in trials, from a median of 1.3 h in the Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction (CAPITAL-AMI) trial to 16.7 h in the GRACIA-1 trial. Based on the three most recent trials, all of which had a median delay between start of lysis and angiography of 2–3 h, a time window of 3–24 h after successful lysis is recommended.[50]

The ESC 2012 guidelines have summarized important delays and treatment goals in the management of acute STEMI.[50]

Delay	Target
Preferred for FMC to ECG and diagnosis	≤10 min
Preferred for FMC to fibrinolysis ('FMC to needle')	≤30 min
Preferred for FMC to primary PCI ('door to balloon') in primary PCI hospitals	≤60 min
Preferred for FMC to primary PCI	≤90 min (≤60 min if early presenter with large area at risk)
Acceptable for primary PCI rather than fibrinolysis	≤120 min (≤90 min if early presenter with large area at risk) if this target cannot be met, consider fibrinolysis.
Preferred for successful fibrinolysis to angiography	3–24 h

In a pilot initiative conducted in India during approximately the first 6 months, 84 patients received care within this quality improvement programme. The mean time of arrival from symptom onset was 170 min, with 77% of patients arriving by ambulance with a mean transport time of 44 min (5–99 min). The mean time from hospital arrival to PCI was 69 min for patients undergoing primary PCI while the mean time to PCI after fibrinolytic therapy with the pharmacoinvasive strategy was 480 min.[6]

2.1.4. *Comparison of various thrombolytic agents*

2.1.4.1. *Bolus vs. prolonged infusion.* The GUSTO angiographic substudy demonstrated that delayed (>90 min) restoration of TIMI 3 flow was not associated with an improved outcome compared with restoration of TIMI 3 flow at 90 min. Hence for optimal treatment of AMI, normal blood flow (TIMI 3) in the infarct-related artery should be reestablished as rapidly as possible and maintained.[51]

Intravenous standard-dose alteplase was superior to intravenous SK in achieving early reperfusion, as confirmed by the GUSTO angiographic substudy using accelerated alteplase administration. The 90-min TIMI 3 flow rate in the GUSTO angiographic substudy was 54% with accelerated alteplase administration, which was slightly higher than the 90-min TIMI 3 flow rate with standard dose alteplase (49.0%).[51]

Tenecteplase also offers a simple, efficient, 5-s administration over a single bolus. TIMI 10B compared 40-mg doses of tenecteplase and an accelerated alteplase regimen. The rate of TIMI grade 3 flow at 90 min, was 62.7% in the accelerated alteplase group and 62.8% in the tenecteplase 40-mg group.[33]

RAPID 1 evaluated three bolus regimens of reteplase in comparison with a 3 h infusion of alteplase. RAPID 2 compared the 10 MU + 10 MU double bolus regimen of reteplase with the accelerated regimen (90 min infusion) of alteplase. The results of these studies showed that reteplase opened more arteries more quickly than did alteplase. Angiography at both 60 and 90 min evinced a higher rate of patency and greater TIMI 3 flow rates with reteplase than with alteplase. In RAPID 1, at 90 min, TIMI 3 flow rates were 63% for reteplase compared to 49% for alteplase ($p < 0.05$). Thus the reteplase resulted in a higher TIMI 3 patency rate compared with standard-dose alteplase (87.8% vs. 70.7%, $p < 0.01$). In RAPID 2, TIMI 3 flow was 60% vs. 45%, respectively, ($p < 0.05$).[52]

Very early administration of thrombolytics, within 70–90 min of onset of chest pain, is associated with improved survival and left ventricular function. Completeness of thrombolysis is also critical for achieving optimal outcomes.[51]

A practical advantage of reteplase 10 + 10 U regimen is the ease of bolus administration compared with the relative complexity of infusions of varying doses of alteplase. TIMI 3 flow appears to occur earlier after bolus administration of reteplase than with standard-dose alteplase, which was not the case with.

Tenecteplase in TIMI 10B trial. Reteplase thus achieves more rapid, complete, and sustained thrombolysis of the infarct related artery than standard-dose alteplase. The early and improved infarct-related artery patency was associated with improved global and regional function at hospital discharge in reteplase treated patients.[51]

2.1.4.2. *Non-weighted bolus vs weighted bolus.* AMI is an emergency and every minute is crucial. Dramatic reductions in mortality can be achieved if treatment is obtained during the first golden hour.[53] The dosing of intravenous regimens is based on body weight. Reteplase is a simpler alternative since it is administered as a bolus and dosing is not based on weight. Therefore with reteplase fibrinolytic administration is simplified, which may be especially important in the prehospital setting.[19]

The use of bolus fibrinolytic therapy, such as reteplase or tenecteplase, is appealing to emergency personnel and may enable treatment to be initiated more quickly than with an agent administered by infusion.[19]

Non-weight based dosing may have the potential to decrease treatment errors, because visual approximation of a patient's weight is subject to substantial dosage errors.[19]

In the ASSENT-3 PLUS study, approximately 20% of patients received >105% of the correct dosage of weight-based single-bolus tenecteplase administered prehospital; this was associated with an approximately 2-fold rate of intra-cerebral hemorrhage versus lower doses among patients receiving unfractionated heparin as the concomitant antithrombin agent.

Mortality was also shown to be increased in patients receiving an incorrect dosage of SK or alteplase, which are dosed by intravenous infusion based on body weight.[19] Reteplase which is a fixed dose double-bolus injection can be administered irrespective of age or weight, which can be safe and conveniently done by paramedics in prehospital or ambulance setting.[19]

2.1.4.3. *Molecular structural and functional differences among thrombolytic agents.* Alteplase, was the first fibrin specific agent classified as a second generation fibrinolytic to be synthesized through genetic modification of wild-type tissue plasminogen activator by using recombinant DNA technology. Both the wild-type tPA and alteplase consist of several domains, each of which is associated with a specific function.

Protease domain is responsible for the conversion of plasminogen to plasmin. The protease domain contains a binding site for plasminogen activator inhibitor type 1 (PAI-1), and the molecule contains carbohydrate side chains that serve as mediators of plasma clearance.

Kringle 2 domain, associated with low-affinity fibrin binding, accelerates conversion of fibrinogen to fibrin.

Fibronectin finger-like domain, which is associated with high affinity fibrin binding; an epidermal growth factor domain that accelerates clearance in the liver Kringle 1 domain associated with receptor binding.[54]

Function of different domains are explained in the following table.

Function of different domains in wild-type t-PA.[38]

Region of molecule	Function
Fibronectin finger	High fibrin binding
Epidermal growth factor	Receptor binding (liver)
Kringle 1	Receptor binding
Kringle 2	Low fibrin binding (stimulation)
Protease domain	Plasminogen-specific, PAI-1binding site
Carbohydrates	Mediators of plasma clearance

Reteplase is a genetically engineered variant of wild-type tPA. The molecular structure of Reteplase differs from wild-type t-PA in the lack of three domains (finger, epidermal growth factor (EGF) and kringle-1) and because it is produced in *Escherichia coli* cells, reteplase also lacks carbohydrate side chains (unglycosylated). These differences in molecular structure between reteplase and alteplase account for their different pharmacological profiles.[16] A major difference between reteplase and alteplase, is the deletion of kringle-1 and epidermal growth factor domains in reteplase.

These domains facilitate binding to receptors in the liver and enhance hepatic clearance of alteplase. Therefore deletion of the kringle-1 and EGF domains contributes to the longer half-life of reteplase (13–16 min vs 3–6 min with alteplase). This longer half-life of reteplase allows maintenance of therapeutic plasma concentrations and permits an intravenous bolus-dosing regimen.[16]

Unlike reteplase, which is a deletion mutant of wild-type tPA, tenecteplase is derived from wild-type tPA by introducing a point mutation in the carbohydrate side chain that reduces the clearance of the molecule and results in its longer half-life.[38]

- Fibrin Affinity and Hemostatic plugs:

The finger domain, a fibronectin-like projection promotes high-affinity fibrin binding in alteplase. In reteplase this domain is deleted hence at therapeutic concentrations, the fibrin-binding affinity of reteplase is approximately 30% that of alteplase. Although fibrin specificity is desirable to minimize the occurrence of plasminemia which occurs with SK, very high-affinity fibrin binding may cause high concentrations of t-PA to accumulate at surface receptors on the fibrin clot. As a result, fibrinolysis may occur more slowly, since the fibrinolytic activity must progress from the surface to the interior of the clot.

Reteplase lacks the fibronectin like F (finger) domain, which accounts for the high binding of t-PA to fibrin. Yet, the kringle 2 domain common to reteplase and t-PA also contributes to fibrin interaction (although not with such high affinity as the finger domain). Therefore, reteplase does not bind as highly to fibrin compared to native t-PA.[38] Due to lower fibrin binding affinity, Reteplase binds loosely to fibrin and has the ability to penetrate into thrombi which allow for more efficient clot penetration and lysis.

The concentration-dependent lysis of plasma clots by reteplase and alteplase, after 4 h of incubation, has shown that reteplase has the same maximal lytic efficacy as Alteplase at equipotent concentrations. However, reteplase has less lytic efficacy in platelet-rich plasma clots and aged clots, suggesting that reteplase preserves hemostatic plugs and may thus produce fewer bleeding complications than does alteplase.[16]

In humans, following intravenous bolus doses of reteplase, plasma fibrinogen concentrations remain unchanged except at higher doses; however, α-antiplasmin and fibrin-D dimer levels exhibited dose-related decreases. In patients with AMI, reteplase results in significantly decreased levels of fibrinogen, plasminogen, α-antiplasmin, fibrinogen degradation products, and fibrin D-dimers.

Compared with other molecules used in clinical practice, TNKase has the highest degree of fibrin specificity and binding.[55] However, the increased fibrin specificity may not necessarily produce a dramatic increase in the rate of clinical reopening of occluded arteries, as tenecteplase was not significantly better than alteplase in terms of maximal speed of clot lysing.[56]

- Antigenicity

Alteplase have not demonstrated presence of any antigenicity.[57] Like Alteplase (tPA), the varients of wild-type tPA, reteplase has been shown to have low antigenic activity; antibodies to reteplase have not been observed in any of 2400 patients tested for antibody formation. This property has a clinically significant advantage over the first generation agent streptokinase and its derivatives.[16] Tenecteplase too has a antigenic profile similar to that of t-PA.[39]

2.1.4.4. *Ease of administration is important especially in emergency settings*. The complicated regimens of the second-generation drugs may partly account for their underuse. For instance, Alteplase, has to be given as an accelerated intravenous infusion regimen involving a bolus followed by two timed infusions whereas, Reteplase can be administered a double bolus and dosing does not depend on the patient's weight[16] whereas for tenecteplase though it can be given as a single bolus, the dose needs to be calculated based on the patient's body-weight which is cumbersome in an emergency setting. With Tenecteplase, the entire dose can be delivered over a single 5-s bolus—no infusion or second bolus is necessary.[58]

Reteplase treatment reduced the median door-to-needle time by 32 min in the ER-TIMI (Early Retavase-Thrombolysis In Myocardial Infarction) 19 study, which also led to earlier ST-segment resolution.[59] Adherence to the ACC-AHA guidelines, as well as knowledge about the available fibrinolytic agents, is essential for physicians and pharmacists to make informed decisions regarding appropriate pharmacologic reperfusion strategies.[54]

2.1.4.5. *Reinfarction rates*. Reinfarction is the visible sign of coronary reocclusion. This is supported by the association of angiographically proved IRA reocclusion with symptomatic reinfarction.[60] A moderate hypercoagulative state, characterized by increased thrombin and plasmin activation, is known in patients with AMI. The administration of thrombolytic agents in these patients causes an additional pro-coagulant effect besides the desired activation of the plasminogen-plasmin system.[61]

Both tenecteplase and teteplase thrombolytic regimens have a pro-coagulant action in addition to the preexisting hyper-coagulative state of patients with AMI. This effect is associated with a significant increase in kallikrein activity. The amount of the pro-coagulant effect, however, is only moderate compared with other non-clot-specific thrombolytic agents like streptokinase.[61] Tenecteplase and reteplase, having plasma half-lives of less than 25 min, require effective immediate adjunctive antithrombotic support at a time of intense thrombotic and inflammatory activity at the site of the plaque.[60]

Antithrombotic treatment as an adjunct to thrombolytic and antiplatelet (aspirin) therapy was evaluated in the GISSI-2 and ISIS-3 trials with strong indications from angiographic studies that intravenous heparin considerably contributes to sustained IRA patency.[62]

If the delay between fibrinolysis and PCI is too long, patients are exposed to the risk of reinfarction and recurrent ischemia while they await PCI, and patients in whom reperfusion after fibrinolysis is not successful may not be able to undergo rescue PCI quickly enough to salvage myocardium. Therefore, catheterization and PCI should be performed a few hours after fibrinolysis (within 6 h).[63]

The re-infarction rates were significantly greater for tenecteplase (9.3%) than reteplase (4.2%).[60] High rates of re-infarction reflect variation in the precise method of administration of the fibrinolytic agents and associated antithrombotic treatment within the prehospital environment. Maintenance of heparin levels by heparin infusion is critical at a time of intense thrombotic and inflammatory activity (AMI).

The effect of the lack of a heparin infusion was reduced for reteplase by the administration of its second dose within the recommended limit of 30 min. For tenecteplase a treatment to hospital arrival time of under 30 min was associated with a very high, re-infarction rate of 9.3%, indicating that even within this interval a heparin infusion is vital. Though in the ASSENT-3 PLUS trial, unfractionated heparin was administered in the ambulance where the reinfarction rate was 5.8% after prehospital tenecteplase, the difference in the reinfarction rates was non-significant (4.0% vs 5.9%), compared to those for whom it was started in hospital.[60]

2.1.4.6. Bleeding risks of thrombolytics. As the first generation thrombolytic agents are not fibrin specific, they convert circulating plasminogen to plasmin. As there is a constant equilibrium between circulating plasminogen and plasminogen in thrombus, there is depletion of circulating plasminogen reducing clot lysis and efficacy of the thrombolytic agents. This is known as Plasminogen steal. Moderately fibrin specific agents like reteplase overcome this limitation and are also more effective than first generation agents, namely SK.[19,64]

Higher binding affinity for fibrin also decreases the amount of circulating unbound Alteplase and decreases its interaction with the thrombus. In contrast, Reteplase has a lower fibrin binding affinity for fibrin in vitro, which may increase the amount of unbound drug available to act elsewhere on the clot and improve penetration into the clot.[65]

Very high fibrin-affinity may cause high concentrations of t-PA to accumulate at surface receptors on the fibrin clot. As a result, fibrinolysis may occur more slowly, since the fibrinolytic activity may progress from the surface to the interior of the clot. Due to lower fibrin binding affinity compared to alteplase (+++) and tenecteplase (++++).

Reteplase (+) binds loosely and irreversibly to the fibrin by virtue of which it gets an ability to penetrate into thrombi and allows for more efficient clot penetration and lysis. The concentration-dependent lysis of plasma clots by reteplase and alteplase, after 4 h of incubation, has shown that reteplase has the same maximal lytic efficacy as alteplase at equipotent concentrations. However, reteplase has less lytic efficacy in platelet-rich plasma clots and aged clots, suggesting that it preserves hemostatic plugs and may thus produce fewer bleeding complications than those with higher fibrin affinity.[16]

3. Pearls for clinical use[12,13,66]

3.1. *Dosage and method of administration of various thrombolytics*

Agent	Dosing and administration
Streptokinase	1,500,000 IU i.v. infusion over 30–60-min
Reteplase	Two 10-U boluses, each administered over 2 min, 30 min apart
Alteplase	90-min infusion: 15-mg i.v. bolus, followed by 0.75 mg/kg (maximum dose 50 mg) infused over 30 min, followed by 0.50 mg/kg (maximum dose 35 mg) infused over 60 min 3-h infusion: total dose of 100 mg, with 60 mg administered within the first hour, and 20 mg administered during second and third hour
Tenecteplase	Single bolus administered over 5 s; dose based on patient weight (maximum dose 50 mg): <60 kg: 30 mg; 60–69 kg: 35 mg; 70–79 kg: 40 mg; 80–89 kg: 45 mg; and ≥90 kg: 50 mg

Concomitant use of antithrombin therapy

Is anticoagulant therapy required with thrombolytics?

Parenteral anticoagulation has been used extensively during and after fibrinolysis and should preferably be given until revascularization (if performed). Otherwise it should be given for at least 48 h or for the duration of hospital stay, up to 8 days. UFH was found to improve coronary patency after alteplase but not after streptokinase. Careful dosing and close monitoring of intravenous UFH therapy is mandatory; aPTT values >70 s are associated with a higher likelihood of bleeding, reinfarction and death.[50]

In spite of an increased risk of major bleeding, the net clinical benefit favored enoxaparin over UFH in more recent studies namely in the ASSENT 3 trial ($n = 6095$), where a standard dose of enoxaparin given in association with tenecteplase for a maximum of 7 days reduced the risk of in-hospital reinfarction or in-hospital refractory ischemia when compared with UFH.[50]

In the large ExTRACT–TIMI 25 trial, a lower dose of enoxaparin associated with a reduction in the risk of death and reinfarction at 30 days when compared with a weight-adjusted UFH dose.

Tenecteplase, aspirin, enoxaparin and clopidogrel comprise the antithrombotic combination that has been most extensively studied as part of a pharmacoinvasive strategy, viz. Trial of Routine.

ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in acute myocardial infarction (TRANSFER), NORwegian study on DIstrict treatment of ST-Elevation

Myocardial Infarction (NORDISTEMI), GRACIA-2, and GRACIA-3.[50]

- For patients with acute STEMI, in addition to aspirin and other antiplatelet therapies, we recommend the use of antithrombin therapy over no antithrombin therapy (Grade 1A), including for those patients receiving fibrinolysis (and regardless of which lytic agent is administered), primary PCI, or patients not receiving reperfusion therapy.[13]
- UFH[13]
  - For patients receiving streptokinase, we suggest administration of either IV UFH. (5000-U bolus followed by 1000 U/h for patients >80 kg, 800 U/h for <80 kg) with a target activated partial thromboplastin time (APTT) of 50–75 s or subcutaneous UFH (12,500 U q12h) over no UFH therapy for 48 h (both Grade 1B).
  - For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis in AMI, we recommend administration of weight-adjusted heparin (60 U/kg bolus for a maximum of 4000 U, followed by 12 U/kg/h [1000 U/h maximum]) adjusted to maintain an APTT of 50–70 s for 48 h (Grade 1B).
  - For patients with STEMI undergoing primary PCI, we recommend administration of IV UFH over no UFH therapy (Grade 1C). The recommended periprocedural dosing in patients receiving a glycoprotein (GP) IIb/IIIa inhibitor is 50–70 U/kg (target activated clotting time [ACT] > 200 s); in patients not receiving a GP IIb/IIIa inhibitor, the recommended periprocedural dosing is 60–100 U/kg (target ACT, 250–350 s).
- Low-Molecular-Weight Heparin (Enoxaparin)[50]
  - In patients <75 years of age: 30 mg intravenous bolus followed 15 min later by 1 mg/kg s.c. every 12 h until hospital discharge for a maximum of 8 days. The first two doses should not exceed 100 mg.
  - In patients >75 years of age: no intravenous bolus; start with first subcutaneous dose of 0.75 mg/kg with a maximum of 75 mg for the first two s.c. doses.
  - In patients with creatinine clearance of <30 mL/min, regardless of age, the subcutaneous doses are given once every 24 h.
- Fondaparinux[50]
  - 2.5 mg i.v. bolus followed by a subcutaneous dose of 2.5 mg once daily up to 8 days or hospital discharge.

Concomitant administration of heparin and reteplase

- Heparin and reteplase are incompatible when combined in solution; hence should not be administered simultaneously in the same intravenous line. If reteplase is to be injected through an intravenous line containing heparin, a normal saline or 5% dextrose solution should be flushed through the line before and after administering the reteplase injection.[66]

3.2. *Concomitant use of antiplatelet drugs*

While the initial goal of reperfusion is to restore flow in the infarct-related artery (IRA) as quickly and completely as possible, the ultimate goal of reperfusion in STEMI is to maintain IRA patency and improve myocardial perfusion in the infarct zone. Despite adequate restoration of flow in the epicardial IRA, perfusion of the infarct zone may still be compromised by a combination of microvascular damage and reperfusion injury. Microvascular damage occurs as a consequence of downstream embolization of platelet microemboli and thrombi followed by release of substances from activated platelets that promote occlusion or spasm. Thus, in order to maintain IRA patency (decreasing thrombus recurrence and preventing reocclusion) and potentially minimize microvascular damage, adjunctive antiplatelet and antithrombotic treatments should be included in the management of acute STEMI, regardless of the reperfusion strategy initially employed.[13]

Convincing evidence of the effectiveness of aspirin in addition to fibrinolysis was demonstrated by the ISIS-2, in which the benefits of aspirin and streptokinase were seen to be additive. The first dose of 150–300 mg should be chewed or given intravenously (though at a lower dose range) and a lower dose (75–100 mg) given orally daily thereafter.

In the CLopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28 (CLARITY-TIMI 28) trial, clopidogrel added to aspirin reduced the risk of cardiovascular events in patients ≤75 years of age who had been treated with fibrinolysis.[50]

Accordingly, there is a good case for the routine use of clopidogrel added to aspirin as an adjunct to lytic therapy. Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis and should not be given.[50]

ACCP recommends

1. Antiplatelet therapy[50]
   Aspirin
   162- to 325-mg loading dose (I A)
   81- to 325-mg daily maintenance dose (indefinite) (I A)
   81 mg daily is the preferred maintenance dose IIa B
2. P2Y12 receptor inhibitors
   Clopidogrel: I A
   Age <75 y: 300-mg loading dose
   Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding I A (14 d)
   Age >75 y: no loading dose, give 75 mg (I A)
   Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding

3.3. *Complications of fibrinolysis*

- The main complication of fibrinolytic therapy is bleeding, with the most dreaded complication being ICH. The dosage of adjunctive IV UFH, the measured aPTT level, as well as the timing of aPTT monitoring appear to have a strong relationship with the risk of ICH[19]
- Predictors of ICH: age, weight, prior cerebrovascular disease, diastolic BP, combination alteplase-SK therapy, hypertension, hypertension × age interaction term, accelerated alteplase treatment, systolic BP[19]
- Adjunctive heparin use in the setting of fibrinolytics agents appears to have a narrow therapeutic window. While the baseline risk of ICH varies between individual studies, there appears to be a consistent association between heparin dosing and risk of ICH.[19]

- The measured activated partial thromboplastin time (APTT) level as well as the timing of APTT monitoring appears to have a strong relationship with the risk of ICH. Early trials recommended initial APTT evaluation at 6 h. In contrast, heparin dose adjustment with 3-h APTT monitoring resulted in the lowest reported ICH rate of 0.64% observed in any megatrial. When this approach was repeated in the ASSENT-3 trial, this heparin-dosing regimen resulted in 0.94% ICH rate.[19]
- Severe bleeding-causing substantial hemodynamic compromise requiring intervention, and moderate bleeding as that requiring transfusion but without associated hemodynamic compromise[19]
- The most common cause of bleeding may be the use of coronary revascularization procedures. The most powerful multivariable predictors of moderate or severe bleeding are advanced age, lighter body weight, and female sex. These variables remained the most potent predictors of bleeding risk even among patients who did not undergo an in-hospital cardiac procedure.
- The other bleeding complications associated with fibrinolysis, usually are only minor (e.g., puncture site bleeding after PCI).[19]
- Rates of hemorrhage other than intracranial as reported in randomized trials of thrombolysis are difficult to interpret because of varying definitions, different intensities of data collection and differences in use of invasive revascularisation procedures. Overall, in the placebo-controlled trials there is a 2- to 3-fold increased incidence of severe hemorrhage after thrombolytic therapy (0.4% among controls vs 1.1% among patients randomized to active treatment).[62]
- That fibrin specificity is associated with bleeding even after adjustment for the aPTT level is suggested by a greater bleeding risk with first generation >second generation >third generation.[19]

3.4. *Management of serious bleeding which occurs in a critical location*

(intracranial, gastrointestinal, retroperitoneal, pericardial)

- Any concomitant heparin should be terminated immediately. Heparin effects can be reversed by protamine
- In addition, the second bolus of reteplase should not be given if the serious bleeding occurs before it is administered.

3.5. *Precautions to be taken for bleeding at external sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites)*

- Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from noncompressible sites.
- Should an arterial puncture be necessary during the administration of reteplase, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 min, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

3.6. *Managing complications other than bleeding that may occur*

- Arrhythmias-Manage with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when reteplase is administered

4. Pharmacoeconomics

Despite the need for the initial investment and the lower diagnostic accuracy of AMI in the prehospital care group, the total cost of the hypothetical cohort of patients followed for one year was lower compared to the inhospital treatment. In spite of the higher cost of the bolus thrombolytic agent when compared to SK, the higher effectiveness of the first in the prehospital environment allows the minimization of the costs resulting from complications that are secondary to the delay in the reperfusion of patients with AMI, such as heart failure, reinfarction and the need for a higher number of high-cost interventions. The benefits of intervention health, i.e., the possibility of early reperfusion, can mean a lower cost in the mid- and long-term, due to the decrease in reinfarction and morbidity of the chronic ischemic cardiopathy.[67]

5. Future trends in thrombolysis

5.1. *Telemedicine*

"Tele-Medicine (TM) is the use of telecommunication and information technologies in order to provide clinical health care at a distance. It helps eliminate distance barriers and can improve access to medical services that would often not be consistently available in distant rural communities. It is also used to save lives in critical care and emergency situations". TM may therefore be extremely useful in reducing time of treatment, especially when time is paramount, such as in cardiovascular emergencies. When treating patients with AMI, the time from the onset of symptoms to reperfusion is crucial for salvaging myocardium; in other words, "time is muscle". Shorter time-to-reperfusion is associated with smaller infarct size and micro-vascular damage and larger salvaged myocardium.[68]

Despite many years of medical advances, the time from symptom onset to thrombolysis has remained at large unchanged, with a median of 2.5–3 h. A prehospital treatment strategy when compared with inhospital thrombolysis has been shown to reduce time to thrombolysis with around 1 h and inhospital mortality by 17% in a meta-analysis of randomized trials.[69]

A nation-wide registry of real-life patients showed that prehospital diagnosis and treatment are associated with reduced time to thrombolysis by almost 1 h and reduced adjusted long-term mortality by 30%. Importantly, prehospital diagnosis established by a physician at the hospital using telemedicine and subsequent Prehospital thrombolysis (PHT) delivered by paramedics in the ambulances

seem as efficient in reducing time delays as physician-staffed ambulances.[69]

Prehospital Electrocardiograms (ECGs) may be useful in improving timeliness of treatments in acute cardiovascular disease, and TM may play a primary role in allowing any patient with a suspected cardiovascular emergency to be examined with prehospital ECG by a cardiologist, wherever the patient is, either in rural or urban areas.[68]

A system with paramedics, who transmit a prehospital ECG using telemedicine to a physician in the hospital for decision-making and then administrating thrombolysis, seems as efficient in reducing treatment delay as a system with physician-staffed ambulances.[69]

5.2. *Nano-thrombolysis*

With regard to thrombolytic therapies, significant advancements have been made in order to increase the efficacy of plasminogen activators. The evolution from fibrin non-specific to fibrin-specific therapeutics was the first step, allowing for a decrease in the activation of circulating plasminogen. This has been followed by the reengineering of the PA in order to modulate its blood half life. Recombinant tPA, which was utilized in this study, is often given as an infusion over the course of 90 min, as its blood half life is 4–6 min.[70]

Third generation agents given as a single bolus, may take 20–24 min to clear from the blood, have higher fibrin specificity, yet still demonstrates similar ICH rates as tPA of ~1% in AMI patients with 55% of ICH patients dying, and 55% of ICH survivors possessing residual neurological deficit.

In fact, 20% of IRA fail to reestablish normal coronary flow following tPA therapy. In addition, another 15 percent of reperfused arteries will reocclude, leading to larger infarct size.[70]

It is therefore vital to develop new thrombolytic agents with potentially increased efficacy and fibrin specificity, greater therapeutic windows, and vastly improved safety profiles.[70]

Nanomaterials are promising modalities for building targeted thrombolytics. For the most part, it is difficult to develop nanoagents that transverse the blood brain barrier (BBB) in the absence of permeabilization. This may be due, in part, to the lack of an endogenous pathway for the particles to translocate into the brain. Thus, covalent attachment of thrombolytics to a targeted nanoparticulate delivery vehicle may lead to the development of agents minimizing the most egregious of side effects, ICH. Nanomaterials may also extend the circulation time of PAs, allowing them to be administered as a bolus as opposed to an infusion, increasing the duration of effect.[70]

Thus, the design of nanoagents with comparable therapeutic efficacy to the free drugs, yet demonstrating superior safety profiles may provide for the easing of the complications often associated with PA therapies, particularly intracerebral hemorrhage, as nanoagents with minimal BBB permeability can be utilized to develop targeted thrombolytics.[70]

Conflicts of interest

All authors have none to declare.

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