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Overview of Reteplase, A Novel Thrombolytic Agent in Indian Context

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Abstract

Cardiovascular disorders are the major cause of concern in India with estimated mortality reaching approximately 64 million by 2015. Though two major treatment options i.e. primary angioplasty (PAMI) and intravenous thrombolysis are available for the management of ST elevation myocardial infarction (STEMI), primary angioplasty is not feasible for majority of STEMI patients in India, hence early reperfusion therapy is critical for rapidly restoring coronary blood flow and limit further myocardial necrosis in these patients. Early/prehospital administration of thrombolytic agent results in better outcome in STEMI. Reteplase, a third generation thrombolytic, because of the possibility of bolus administration provides this opportunity. In this review article, important clinical aspects regarding use of reteplase in the treatment of STEMI are summarized.

Keywords: Reteplase; ACS; STEMI; Double bolus

Introduction

Cardiovascular disorders are the major cause of morbidity and mortality worldwide, including in India [1]. According to the Global Burden of Diseases (GBD) study, mortality from coronary heart disease (CHD) in India is projected to increase from 1.6 million in 2000 to approximately 64 million by 2015 [2]. Two major treatment options for acute myocardial infarction include primary angioplasty (PAMI) and intravenous thrombolysis. Though the first option is superior to intravenous thrombolysis, it is not feasible option for many STEMI patients in India [3]. Timely reperfusion therapy is critical for rapidly restoring coronary blood flow and limit further myocardial necrosis in acute myocardial infarction (AMI) [4]. Unfortunately, the median time to reach a hospital in India is 300 minutes and only 8% of STEMI patients undergo PCI [5]. A South Indian study has also showed that only 10.7% patients underwent primary PCI while 14% patient did not receive reperfusion therapy [6]. It has been recommended that patients with acute MI requiring fibrinolytic therapy should be thrombolysed at the earliest, ideally within 30 minutes of the first medical contact [4].

Early or pre-hospital intravenous thrombolysis to all and early angiography within 3 to 24 hours should be practiced in countries like India [3]. Pharmacoinvasive strategy i.e use of thrombolytic therapy followed by invasive cardiac procedure should be practiced in cases of STEMI patients. If PCI facility is not available then the patient may be transferred immediately after the thrombolytic therapy to center where such facility is available. Similarly, prehospital thrombolytic therapy may be used before the patient is sent for early coronary angiography [1]. Pre hospital thrombolysis will help to reduce the health costs as well as limit the loss of myocardium [1].

The objective of using thrombolytic agent is to produce, rapid, complete and stable thrombolysis [7]. The options of bolus injection and infusion both are available in India. The choice of thrombolytic may make a difference, because continuous intravenous infusion complicates the administration in hospital setting and prehospital administration may not be possible. In such situations bolus-injection of thrombolytic agent is convenient[7] and should be preferred. However, in India, still the use of first generation thrombolytic, streptokinase seems to be common as shown in the South Indian study. Only 10% patients received third generation thrombolytic [6]. Use of more efficient thrombolytic which can be administered without body weight consideration should be the treatment of choice, in countries like India [1].

Reteplase: A novel thrombolytic agent

Reteplase is a single-chain, non-glycosylated peptide, fibrin-specific recombinant plasminogen activator derived from t-PA [7,8] which is designed primarily for bolus thrombolysis in patients with STEMI [9]. It is a mutant of alteplase tissue plasminogen activator [10].

Reteplase preferentially activate fibrin-bound plasminogen rather than fluid-phase plasminogen indicating their fibrin-selectivity. The selectivity is proved by pronounced stimulation of plasminogenolytic activity in the presence of fibrin [7]. The starting dose is calculated based on the target AUC which provides sufficiently high patency rate of about 70% with acceptable low risk of bleeding.

In 1996, reteplase has been approved in Europe as well as United States. In India, reteplase is available as single use vial containing 10 units (18 mg) costing about 29750 rupees.

Rationale and advantages of double bolus administration

Administration by intravenous infusion is not associated with rapid thrombolysis, whereas, animal studies indicated that bolus administration of reteplase by intravenous route results in rapid thrombolysis [11]. Bolus administration of reteplase results in rapid reperfusion requiring significantly shorter time to reperfusion compared to alteplase, streptokinase, and urokinase [12]. The starting dose is decided by the target AUC which results in a high patency rate of about 70% with acceptable bleeding risk [7]. A single intravenous bolus injection of reteplase in the dose of 0.14 U/kg was shown to have equal efficacy to that of 90-minute intravenous infusion of about 70 mg alteplase over 90 minutes followed by 30 mg maintenance infusion over

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90 minutes. Experimental data showed that reteplase in the suggested bolus dose of 0.14 U/kg results in about 70% a patency rate at 90 minutes, without major risk of intracranial bleeding. Based on this data, 10 U dose of reteplase bolus injection (0.14 U/kg X 70 kg=9.8 U) was calculated [7].

Animal studies have shown that intravenous heparin is required to be given along with reteplase in order to maintain blood flow in coronary artery after the thrombolysis [13]. In the clinical trials also reteplase has always been studied in combination with heparin. Based on the data, it is recommended that heparin should be used in combination with reteplase. Despite the use of heparin, reocclusion was often seen even after successful thrombolysis by reteplase and alteplase in animal model studies. To avoid the chances of reocclusion after single bolus dose, the concept of double-bolus was developed. Increasing the duration of treatment is important in avoiding decline in the blood flow [7]. This was evident from the result which showed that double bolus regimen of reteplase was superior compared to single bolus in reducing reocclusion while the other strategy of simply doubling the single bolus dose was not successful [14].

The concept has been very well evaluated in many clinical studies. Compared to 15 U single bolus dose, reteplase two bolus regimen of 10+5 U produced longer median plasma antigen and activity levels above 700 ng/ml and 250 aU/ml by 15 min without any change in other pharmacokinetic properties and the pharmacodynamic variables. The double bolus regimen of 10 U + 10 U produced further prolongation of 45 min and 35 min with higher median reteplase activity peaks compared to relative antigen peaks. It seems that this regimen overcomes the residual inhibitory activity against the plasminogen activator. With 10+10 U regimen there is increased consumption of fibrinogen and split-product production leading to better fibrinolysis [9]. Ease of administration with bolus dosage may help in more rapid treatment of patients with acute MI [15].

Fibrin specificity and affinity

Reteplase is a fibrin-specific recombinant plasminogen activator lacking fibronectin finger which acts by mimicking the actions of endogenous tPA [8]. Lacks of fibronectin like F (finger) domain is responsible for high binding of t-PA to fibrin [16].

Reteplase preferentially activate fibrin-bound rather than fluid-phase plasminogen [7]. By catalyzing the conversion of endogenous plasminogen to plasmin, reteplase degrades fibrin and results in lysis of the thrombus. It has fibrin specificity, however, its plasminogenolytic activity is lower than alteplase due to absence of lack of fibrin binding finger domain [8]. However, the reteplase has been shown to be more potent thrombolytic than alteplase [7] and produced significantly faster reperfusion compared to alteplase, streptokinase, or urokinase in an animal model [12]. The thrombolysis produced by reteplase is more rapid, complete and stable compared to alterplase infusion in AMI [16]. The higher potency of reteplase for clot lysis can be explained by its pharmacodynamic property. Reteplase penetrates the clot and activates the plasminogen within whereas alteplase accumulates on the surface of clot. In case of alteplase, further lysis of clot depends on plasminogen supply from the plasma [17]. The lower fibrin affinity may be responsible for more efficient clot penetration and lysis [18].

Fewer bleeding complications with reteplase are due to its less effect on aged clots and preservation of haemostatic plugs. Dosing of reteplase is not dependent on patient's body weight [17].

Other advantages of reteplase

The pharmacokinetics of reteplase supports the use of fixed dosage. Similarly, analysis of clinical trial data does not show any effect of body weight on parameters such as patency, mortality or other complications.[7] Reduction in the treatment errors may be another advantage of non-weight based dosing because dosage errors may occur due to visual estimation patient's body weight [19]. Some of the important differences between thrombolytics are listed in Table 1.

Therapeutic efficacy and safety of reteplase

The efficacy and safety of reteplase in patients with acute myocardial infarction has been evaluated in many other landmark studies including INJECT, RAPID 1 and RAPID 2 study [18].

The INJECT Trial

The objective of INJECT trial was to establish equivalence of reteplase with streptokinase in the reduction of mortality after acute myocardial infarction [20]. This was a large randomized, double blind clinical trial involving a total of 6010 patients with acute myocardial infarction. Reteplase double-bolus (10 U + 10 U; n=2965) was compared with standard dose of streptokinase (1.5 U infusion over 60 minutes; n=2971) [21]. Standard doses of aspirin and heparin were also given to all the patients. The INJECT trial results showed that reteplase was as effective as streptokinase in reducing mortality risk. The mortality rates at 35 days were 9% and 9.5% for reteplase and streptokinase respectively [20]. Though, not statistically significant, reteplase use was associated with positive trend toward improvement in mortality rates. The incidence of recurrent MI or extension of infarction was seen in 5% patients with reteplase and 5.4% in streptokinase group [20]. Thus the INJECT trial established that reteplase use results in similar mortality and clinical benefits like streptokinase. Reteplase was associated with higher incidence of hemorrhagic stroke compared to streptokinase (0.77% vs 0.37%). However, there was no difference in the incidence, severity or the site of other bleeding events. Incidence of bleeding requiring transfusion was 0.7% versus 1% in reteplase versus streptokinase group respectively [21].

The RAPID 1 and RAPID 2 studies assessed angiographic patency after acute myocardial infarction after the treatment with reteplase and alteplase.

The RAPID 1 Study

The RAPID 1 was a dose finding study. The purpose of RAPID 1, an open label, parallel group trial involving 606 patients was to find out best regimen of reteplase for further studies [16]. The study evaluated three regimens of reteplase which were compared to alteplase infusion. The patients in RAPID 1 study received one of the following regimens of reteplase: a 15 U given as a single bolus, a 10 U bolus followed by 5 U 30 min later , a 10 U bolus followed by a 10 U bolus 30 min later. Alteplase was administered as100 mg in the 3 hour dosing regimen. The 100 mg dose was divided as 60 mg over the first hour with an initial bolus of 6-10 mg, followed by 20 mg per hour for an additional 2 hour. All the patients received intravenous heparin and aspirin. The analysis showed that 10 U+10 U double bolus regimen produces highest 60 and 90 minute patency rates of all the treatment regimens. TIMI 3 flow percentage at 90 minutes was significantly higher with r-PA 10 U+10U compared to alteplase. The incidence of reocclusion was 2.9% versus 7.8% in these two groups respectively. Mortality and reinfarction rates were 2.6%, 1.9% respectively with double bolus of 10+10 U compared to 4.5% and 3.9% with alteplase. Major bleeding with reteplase 10+10 U was seen in 13.6% versus 9.1% patients with alteplase while the

incidence of stroke was 3.9% with alteplase compared to no occurrence in reteplase double bolus group [22].

The RAPID 2 Study

The RAPID 2, a multicentre, open label, randomized study conducted in United States and Germany involved 324 patients with acute myocardial infarction. The objective of this study was to compare thrombolytic efficacy of reteplase double bolus regimen with a 90 minute infusion of alteplase. This study compared the 10 MU+10MU double bolus regimen of reteplase with 90 min infusion of alteplase. Similar to RAPID-1, in this study also, all patients received aspirin and intravenous heparin [22]. RAPID 2 trial demonstrated superior efficacy of reteplase versus alteplase with less coronary artery interventions during first six hours (13.6% versus 26.5%; p=0.004). The patency rates after 60 minutes of therapy were higher with reteplase (82% versus 66%; p=0.006).

No significant difference was seen in safety parameters such as major bleeding (12.4% versus 9.7%) or haemorrhagic stroke (1.2% versus 1.8%) between reteplase and alteplase. The respective 35 days mortality rate was 4.1% versus 8.4%.

In both the studies, TIMI 3 flow rates were significantly higher ($p<0.05$) with reteplase compared to alteplase (RAPID 1; TIMI 3 flow rate at 90 minutes were 62.7% for reteplase compared to 49% for alteplase; $p<0.05$ Figure 1; RAPID 2, TIMI 3 flow were 60% vs 45%, respectively; $p<0.05$ Figure 2)

RAPID 1 and RAPID 2 studies demonstrated that reteplase has potential advantages over alteplase. Reteplase can result in earlier and more complete coronary patency [22].

Indian Evidence on Reteplase

A phase-III, multi-centric, open-label study was conducted in 80 Indian patients with STEMI who were admitted within six hours of symptom. The objective of the study was to evaluate the safety and efficacy of reteplase in STEMI patients. The patients were treated with reteplase standard dose i.e. 10 + 10 units intravenously. Each dose was give over two minutes and not more than 30 minutes apart. The post-marketing retrospective study involving 204 patients also used similar dosage of reteplase. The mortality rate in phase III study was 6.25%, however, none was related to the study drug. Compared to baseline, reteplase use resulted in significant increase (44.3% vs 48.7%; p=0.0002) in left ventricular ejection fraction at the end of 30 days and 50% resolution of ST-segment was observed in 51.25%, 55% and 73.75% patients at 90 minutes, 120 minutes and 6 hours respectively after the dosing. In post-marketing study, mortality rate was 3.92% while bleeding was reported in only 0.98% patients. These two studies confirmed the efficacy and safety of reteplase in Indian population [23].

In another post-marketing study (PRECISE-IN trial), when 20 units reteplase (two 10 unit IV bolus each over two minutes and 30 minutes apart) were given within 6 hours after the onset of AMI symptoms, resolution of 50% of ST elevation was reported in 90.50% patients. Out of 228 patients in this trial, 61.40% had diabetes mellitus. No significant difference was seen between diabetes versus non-diabetes patients for resolution of ST elevation (p=0.15).The incidence of adverse event in this study was 5.3% [24].

Concomitant Medications

Though fibrinolytic is the main component of pharmacological reperfusion therapy in STEMI patients, adjunct antithrombotic drugs

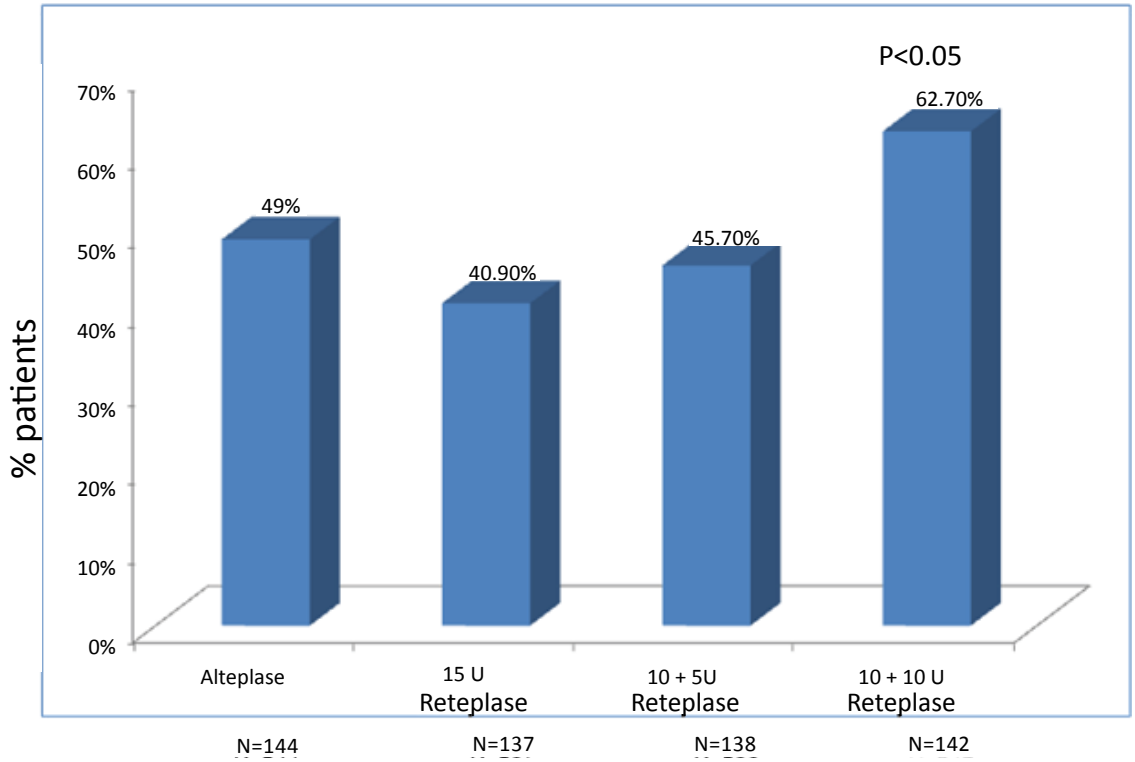

Figure 1: TIMI 3 flow rate at 90 minutes in RAPID 1 study.

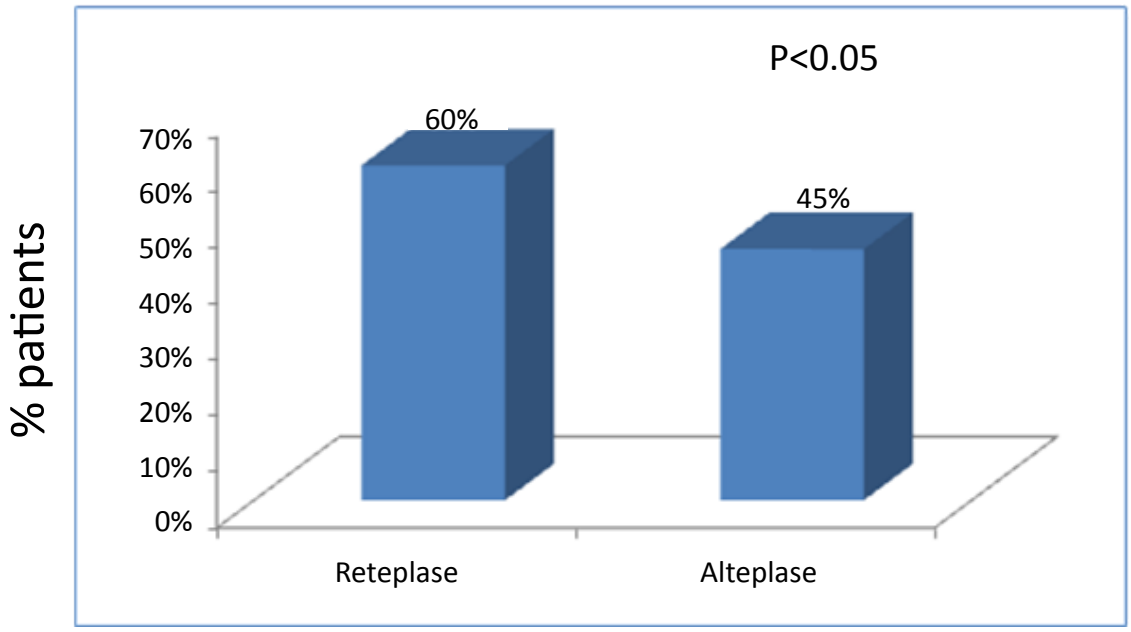

Figure 2: TIMI 3 flow rate at 90 minutes in RAPID 2 study.

such as anticoagulants and antiplatelet agents are also important [1].

Doses of antiplatelet and antithrombin co-therapies with fibrinolytic therapy [25]

- **Aspirin:** Starting dose 150–500 mg orally (250 mg IV if oral dose is not possible)
- **Clopidogrel:** In patients ≤75 years of age, loading dose 300 mg orally, followed by a 75 mg/day as maintenance dose.
- **Unfractionated heparin:** For patients receiving reteplase in AMI, weight-adjusted heparin in the dose of 60 U/kg bolus for a maximum of 4000 U, followed by 12 U/kg/h [1000 U/h maximum] is recommended adjusted to maintain an APTT of 50-70 s for 48 hours
- **Fondaparinux:** 2.5 mg intravenous bolus followed by 2.5 mg subcutaneous dose once daily up to 8 days or hospital discharge
- **Enoxaparin:** In patients with <75 years of age: Intravenous 30 mg bolus followed 15 min later by 1 mg/kg subcutaneously (S.C.)/ 12 hours until hospital discharge for a maximum eight days. The first two doses should not exceed 100 mg. **In patients >75 years:** No intravenous bolus; first s.c. dose of 0.75 mg/kg with a maximum of 75 mg for the first two s.c. doses. In patients with <30 mL/min creatinine clearance, regardless of age, s.c. doses are given once/24 hours.

Heparin should be used in combination with reteplase. However, reteplase should not be mixed with any other drug or given through same intravenous line with other agents. Reteplase is incompatible when given in solution with heparin [26].

Contraindications

Reteplase should not be given in patients with known hemorrhagic diathesis, patients receiving concomitant therapy with oral anticoagulants (e.g. warfarin sodium), history of cerebrovascular accident, recent history of severe bleeding, major trauma or major surgery, obstetrical delivery, organ biopsy, puncture of non-compressible vessels, neoplasm with increased bleeding risk, severe uncontrolled hypertension, oesophageal varices, severe hepatic or kidney, dysfunction, active peptic ulcer, acute pancreatitis, pericarditis or bacterial endocarditis [26].

Safety of Reteplase

Bleeding is the most common adverse event with thrombolytic agents [8]. The safety of reteplase has been well established in several clinical trials. Similar to any other systemic thrombolytic agent, bleeding is the most common adverse effect of reteplase administration. The percentage of patients with STEMI having minimum of one bleeding episode were similar for reteplase (10U + 10U) and comparator thrombolytic agent as seen in INJECT study, GUSTO III study, and RAPID I and II trials. Generally, puncture site is the most common bleeding site with double bolus dose of reteplase (10 + 10 U) and such bleeding incidences are often mild in nature [8].

The results of RAPID 1, RAPID 2 and INJECT studies showed that treatment with reteplase is not associated with an increase in bleeding complications (Table 2) or other adverse events [18]. Incidence of intracranial hemorrhage or hemorrhagic stroke was similar with reteplase and alteplase in GUSTO III trial [10].

Reteplase has safety advantages over streptokinase. Reteplase use in INJECT trial has shown to have significantly lower incidence of cardiac adverse events including atrial fibrillation, asystole, cardiogenic shock, congestive heart failure and hypotension. Similarly, allergic reactions with streptokinase were higher compared to reteplase [21]. The clinical experience in Indian patients has shown similar safety as reported in other clinical trials.

Though there are no cost effectiveness studies comparing reteplase with other thrombolytic therapy, because of ease of administration pre hospital thrombolysis with reteplase may help to reduce the total health cost in patients with AMI [1].

	Reteplase	Stroptokinase	Alteplase	Tenecteplase
Generation [1]	**Third**	First	Second	Third
Fibrin specificity [1]	**Moderate**	Non-specific	High	Very high
Antigenic [19]	**No**	Yes	No	No
Can be given by bolus route [19]	**Yes**	No	No	Yes
Dosage is based on body weight [19]	**No**	No	Yes	Yes
Dose [1,15]	**Double bolus**	One hour infusion	Infusion	Single bolus

Table 1: Comparison of thrombolytic agents.

INJECT study [21]		RAPID trials* [8]		GUSTO III [10]	
Reteplase (10 U + 10 U)	**Streptokinase**	**Reteplase (10 U + 10 U)**	**Alteplase**	**Reteplase (10 U + 10 U)**	**Alteplase**
15.8%	16.6%	47.4%	47.9%	30.5%	30.8%

*pooled results of the angiographic RAPID trials

Table 2: Comparative rates of STEMI patients with at least one bleeding episode (Simpson).

Clinical Pearls for Use of Reteplase Based on its Pharmacokinetics and Pharmacodynamic Profile

1. Initial dosage of reteplase is 10 IU. Bolus use is possible due to long half-life of reteplase [7].
2. Double bolus regimen (10 U + 10 U) of reteplase is preferred over doubling single bolus dose [7].
3. Time interval between two bolus injections is 30 minutes; both doses should be administered over two minutes [7].
4. There is no need of dose adjustment based on body weight [8].
5. Use of intravenous heparin is recommended with reteplase [27].
6. Lesser drug is required to maintain therapeutic level [28].
7. Easy administration as no infusion required.
8. The recommended dosage for reteplase is two IV bolus doses of 10 U over 2 min, 30 min apart [7].
9. Unlike tentactaplase [29], the dosing is non body weight based.
10. Simple dosing regimen may reduce dosing errors resulting in improved outcome.

Summary

Patients with STEMI requiring fibrinolytic therapy should be thrombolysed within 30 minutes of the first medical contact. Reteplase is a unique thrombolytic agent having high affinity fibrin binding and longer half life compared to alteplase. Bolus administration due to loner half life makes administration of reteplase simpler and possible for prehospital initiation in patients with STEMI. Reteplase use results in rapid, complete and sustained thrombolysis. Due to these advantages, early use of third generation thrombolytic agents such as reteplase should be increased in India.

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