INTRODUCTION

Thrombolytics recanalize thrombotic occlusion associated with ST-segment elevation myocardial infarction (STEMI) and restoration of coronary flow reduces infarct size and improves myocardial function and survival over the short-term and long-term. Thrombolytic therapy for acute myocardial infarction (AMI) was incorporated into the armamentarium of clinicians over 2 decades ago, and has evolved from first generation thrombolytic—streptokinase (SK) to newer thrombolytics such as alteplase (t-PA), reteplase (rPA) and tenecteplase (TNK). This article provides an overview of the various thrombolytic agents utilized in the management of patients with AMI.

HISTORY OF THROMBOLYTIC AGENTS

In 1933, Dr William Tillett discovered SK through sheer chance when he observed that streptococci agglutinated plasma but not serum. He concluded that any plasma containing streptococci would not clot and this laid the foundation for thrombolysis in various settings. Christensen and MacLeod coined the term “streptokinase” in 1945. Streptokinase was originally utilized in the treatment of patients with tuberculous hemorrhagic pleural effusions and tuberculous meningitis. In 1958, Fletcher first reported the use of thrombolytic therapy for the management of AMI. The breakthrough discovery of SK in the treatment of patients with AMI was followed by a search for ideal thrombolytic agent, which led to the emergence of second and third generation thrombolytics.

THROMBOLYTIC AGENTS IN ACUTE MYOCARDIAL INFARCTION: CLASSIFICATION AND MECHANISM OF ACTION

Thrombolytic agents act by converting the proenzyme, plasminogen to plasmin, the active enzyme. Plasminogen activators that preferentially activate fibrin-bound plasminogen are fibrin-specific. In contrast, nonspecific plasminogen activators do not discriminate between fibrin-bound and circulating plasminogen. Activation of circulating plasminogen results in the generation of unopposed plasmin that can trigger the systemic lytic state (Figure 1).

Thrombolytic agents can be categorized in several ways. Classification schemes can be devised on the basis of the source of the agent, the propensity for enhanced enzymatic activity on fibrin or cell surface or the mechanism of action (enzymatic versus nonenzymatic) or different generation wise. 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). The generational classification of the thrombolytic agents are presented in Table 1 and properties of an ideal thrombolytic agent are presented in Table 2.

Streptokinase

Streptokinase is a nonfibrinogen-specific fibrinolytic agent, produced by hemolytic streptococci that activates plasminogen independent of its association with fibrin. It is not an enzyme and therefore does not exhibit plasmin activity by proteolytic cleavage of plasminogen. Instead, it binds noncovalently to plasminogen in a 1:1 equimolar fashion and thereby confers plasmin activity (Figure 2).

The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) and the International Study of Infarct Survival (ISIS) trials firmly established the efficacy of intravenous SK in the management of patients with AMI. 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. The extent of the beneficial effect appeared to be related to the time of onset of symptoms.

Figure 1: Consequences of activation of fibrin-bound or circulating plasminogen. Plasminogen activators with little or no affinity for fibrin do not distinguish between fibrin-bound and circulating plasminogen. Activation of circulating plasminogen results in systemic plasminemia and subsequent degradation of fibrinogen and other clotting factors.

Figure 2: Various thrombolytic agents and their mechanism of action.
Mechanism of action of streptokinase. Streptokinase binds to fibrin among patients with AMI. Accelerated t-PA group resulted in significant reductions in death and disabling strokes (GUSTO), GISSI-2, and ISIS-3 Investigators compared intravenous SK and aspirin compared with neither treatment resulted in significant reduction not only in death (8% versus 13.2%), but also stroke (0.6% versus 1.1%) and reinfarction (1.8% versus 2.9%). The early survival benefit obtained with SK and aspirin persisted up to 10 years during follow-up. Allergic reaction manifesting as rash, fever, chills, rigors and rarely, anaphylaxis occurs in about 5% of patients treated with SK. Transient hypotension is common with SK and reflects plasmin-mediated release of bradykinin. Patients given SK invariably develop antistreptococcal antibodies, precluding readministration.

**Tissue Plasminogen Activator (Alteplase)**

The tissue plasminogen activator (t-PA) molecule contains the following five domains: (1) finger, (2) epidermal growth factor, (3) Kringle 1 and (4) Kringle 2 and (5) serine protease (Figure 3). In the absence of fibrin, t-PA is a weak plasminogen activator. Plasma clearance of t-PA is mediated to a varying degree by residues in each of the domains except the serine protease domain, which is responsible for the enzymatic activity of t-PA. Alteplase is a t-PA produced by recombinant deoxyribonucleic acid (DNA) technology. The accelerated dose regimen of t-PA over 90 minutes produces more rapid thrombolysis than the standard 3 hours infusion of t-PA. The recommended dosage regimen for t-PA is a 15 mg intravenous bolus followed by an infusion of 0.75 mg/kg (maximum 50 mg) over 30 minutes, followed by an infusion of 0.5 mg/kg (maximum 35 mg) over 60 minutes. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO), GISSI-2, and ISIS-3 Investigators compared intravenous SK and t-PA in the treatment of AMI. Although no significant difference was observed between SK and t-PA in GISSI-2 and ISIS-3, the GUSTO trial demonstrated that an accelerated regimen of t-PA resulted in significant reductions in death and disabling strokes among patients with AMI. Accelerated t-PA group resulted in 14% reduction in mortality at 30 days compared with the SK strategies. There was slight excess of hemorrhagic stroke for accelerated t-PA when compared with the SK strategies. However, the combined endpoint of death or disabling stroke was significantly lower in the accelerated t-PA group than in the SK only groups (6.9% versus 7.8%, P = 0.006). The Phase-I Thrombolysis in Myocardial Infarction (TIMI) trial demonstrated that the administration of alteplase in patients with AMI resulted in reperfusion in twice as many occluded infarct-related arteries compared with SK during the first 90 minutes of initiation of treatment.

**Reteplase**

Reteplase is a recombinant deletion mutant form of t-PA, and has a longer half-life of 13–16 minutes. It binds fibrin, and has the ability to penetrate into thrombi. Reteplase when compared with accelerated alteplase infusion regimen was demonstrated to offer no significant benefit in terms of reduction in 30 days mortality among patients with AMI. Likewise, rPA in combination with abciximab did not provide significant benefit in terms of 30 days survival. However a double-dose rPA (10 + 10 MU) utilized in the Revitalising Areas by Planning, Investment and Development (RAPID) trial resulted in complete, rapid and sustained thrombolysis of infarct-related arteries (IRAs) at 90 minutes and 5-14 days (83% versus 49%, P = 0.01; and 88% versus 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 rPA over accelerated alteplase in achieving higher rates of early reperfusion in the IRA and fewer acute coronary interventions. This, however, did not translate into improved clinical outcomes in the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial, which demonstrated no significant difference between rPA and SK in reducing 35-day mortality.

**Tenecteplase**

Tenecteplase is a mutant form of t-PA with specific amino acid substitutions in the Kringle 1 domain and protease domain. A single bolus TNK was demonstrated to be associated with increased IRA patency rates (64% TIMI 3 flow with 50 mg bolus...
In the TIMI 10B trial, TNK (40 mg) and alteplase produced similar rates of TIMI grade 3 flow at 90 minutes (62.8% versus 62.7%, respectively, \( P = \text{NS} \)).

Subsequently, the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-1) Trial demonstrated that the safety profile of TNK was comparable to alteplase.

ASSENT-2 compared single-bolus TNK with accelerated dose t-PA and the 30-days mortality rate with TNK was 6.179% and with t-PA 6.151%. The rate of intracranial hemorrhage (ICH) was 0.93% with TNK and 0.94% with t-PA. Major bleeding occurred in 4.66% of TNK-treated patients compared with 5.94% of t-PA-treated patients (\( P = 0.0002 \)).

There was no specific subgroup of patients for whom TNK or t-PA was significantly better, with the exception of patients treated after 4 hours from the onset of symptoms, among whom the mortality rate was 7.0% with TNK and 9.2% with t-PA. Furthermore, the ASSENT-3 Trial demonstrated that the addition of enoxaparin or abciximab to TNK reduced ischemic complications.

Despite the differences observed between the thrombolytic agents in individual studies, a subsequent meta-analysis, however, did not demonstrate significant differences between the various thrombolytic agents (alteplase, SK, rPA and TNK) in reducing mortality (Figure 4) though total stroke and hemorrhagic stroke rates were lower in SK group.

A comparison of approved fibrinolytic agents is shown in Table 3.

Other Fibrinolytic Agents

Derived from cultured fetal kidney cells, urokinase is a two-chain serine protease, which directly converts plasminogen to plasmin. It was used on rare occasions as an intracoronary (IC) infusion [6,000 international unit (IU)/minutes] to an average cumulative dose of 5,000,000 IU to lyse IC thrombi that were believed to be responsible for an evolving STEMI.

Saruplase or prourokinase (scuPA), a naturally occurring glycoprotein, is converted by plasmin into urokinase, and seems to have intrinsic plasminogen activating potential. Saruplase was compared with SK in the Prourokinase in Myocardial Infarction (PRIMI) and Comparative Trial of Saruplase versus Streptokinase (COMPASS) and with alteplase in Study in Europe with Saruplase and Alteplase in Myocardial Infarction (SESAM) Trial. Although the mortality rates were comparable between scuPA and other agents,
Cardiology

Section 4

Figure 4: Meta-analyses: No difference in mortality when all alteplase (including accelerated and nonaccelerated alteplase regimens) compared with streptokinase. t-PA, alteplase; SK, streptokinase

<table>
<thead>
<tr>
<th>Study</th>
<th>Alteplase n/N</th>
<th>Streptokinase n/N</th>
<th>Or (95% CI Random)</th>
<th>Weight %</th>
<th>Or (95% CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL ILLINOIS</td>
<td>6/123</td>
<td>9/130</td>
<td></td>
<td>0.9</td>
<td>0.69 (0.24, 2.00)</td>
</tr>
<tr>
<td>CHERNG</td>
<td>2/59</td>
<td>5/63</td>
<td></td>
<td>0.4</td>
<td>0.41 (0.08, 2.18)</td>
</tr>
<tr>
<td>ECGS</td>
<td>3/64</td>
<td>3/65</td>
<td></td>
<td>0.4</td>
<td>1.02 (0.20, 5.23)</td>
</tr>
<tr>
<td>HISSI</td>
<td>929/10372</td>
<td>887/10395</td>
<td></td>
<td>30.8</td>
<td>1.05 (0.96, 1.16)</td>
</tr>
<tr>
<td>GUSTO-I</td>
<td>652/10344</td>
<td>1472/20173</td>
<td></td>
<td>30.9</td>
<td>0.85 (0.78, 0.94)</td>
</tr>
<tr>
<td>ISIS-3</td>
<td>1418/13746</td>
<td>1455/13780</td>
<td></td>
<td>34.1</td>
<td>0.97 (0.90, 1.05)</td>
</tr>
<tr>
<td>PAINS</td>
<td>4/86</td>
<td>7/85</td>
<td></td>
<td>0.6</td>
<td>0.54 (0.15, 1.93)</td>
</tr>
<tr>
<td>TIMI-1</td>
<td>7/143</td>
<td>12/147</td>
<td></td>
<td>1.1</td>
<td>0.58 (0.22, 1.52)</td>
</tr>
<tr>
<td>WHITE</td>
<td>5/135</td>
<td>10/135</td>
<td></td>
<td>0.8</td>
<td>0.48 (0.16, 1.45)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3026/35072</td>
<td>3860/44974</td>
<td></td>
<td>100.0</td>
<td>0.94 (0.85, 1.04)</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 14.19 df=8 p=0.0747
Total for overall effect z=-1.23 p=0.2

TABLE 3 | Comparison of approved fibrinolytic agents17

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Streptokinase (SK)</th>
<th>Alteplase (t-PA)</th>
<th>Retepase (rPA)</th>
<th>TNK t-PA (US $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1.5 MU in 30–60 min</td>
<td>Up to 100 mg in 90 min (based on weight)</td>
<td>10 U X 2 (30 min apart each over 2 min</td>
<td>30–50 mg based on weight</td>
</tr>
<tr>
<td>Bolus administration</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antigenic</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Allergic reactions (hypotension most common)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Systemic fibrinogen depletion</td>
<td>Marked</td>
<td>Mild</td>
<td>Moderate</td>
<td>Minimal</td>
</tr>
<tr>
<td>90-min patency rates (%)</td>
<td>=50</td>
<td>=75</td>
<td>=75</td>
<td>=75</td>
</tr>
<tr>
<td>TIMI grade 3 flow (%)</td>
<td>32</td>
<td>54</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>Cost per dose (US $)</td>
<td>568</td>
<td>2,750</td>
<td>2,750</td>
<td>2,750 for 50 mg</td>
</tr>
</tbody>
</table>

Abbreviations: TNK t-PA, Tenecteplase tissue plasminogen activator; TIMI, Thrombolysis in myocardial infarction; US, United States

ScuPA was overcome by other adverse events such as increased reinfarction rates and hemorrhagic strokes.1

Anistreplase or anisoylated plasminogen-SK activator complex (APSAC) is another form of SK, an equimolar acylated complex of human lys-plasminogen and SK. This complex acts on plasminogen upon deacylation spontaneously in plasma. Usually administered in a dose of 30 mg over 2 to 5 minutes intravenously, it has a side effect profile similar to that of SK, a patency profile similar to that of conventional dose t-PA and a mortality benefit similar to that of SK or t-PA (ISIS-3).8

Staphylokinase, a highly fibrin-specific plasminogen activator requires priming on the surface of a clot. Recombinant staphylokinase in STAR Trial achieved TIMI flow grade 3 (TFG3) at 90 minutes in 62% of STAR patients versus 58% of t-PA patients.
Study of Tamoxifen and Raloxifene therapy was not associated with increased mortality, hemorrhagic or allergic complications. However, there was an occurrence of antibody-mediated STAR-neutralizing activity from the 2nd week following treatment. The pegulated-staphylokinase (PEG-Sak) evaluated in the Collaborative Angiographic Patency Trial of Recombinant Staphylokinase (CAPTORS) II Trial demonstrated comparable TFG3 rates to that with t-PA. Lanoteplase (nPA), a variant of t-PA with greater fibrinolytic activity and slower clearance from the plasma, resulted in equivalent thrombolytic efficacy to alteplase (InTIME). However, nPA was associated with an increased risk of hemorrhagic strokes.

### LIMITATIONS OF THROMBOLYSIS

#### Contraindications to Thrombolysis

Although the use of fibrinolytic therapy was associated with significant reduction in mortality, it was soon demonstrated to be overcome by a number of limitations. An analysis from the TIMI-9 registry demonstrated that 10.3% of patients have contraindications to thrombolysis, which consisted of prior stroke or transient ischemic attack, recent cardiopulmonary resuscitation (CPR), trauma, surgery, recent bleeding and persistent hypertension (Table 4).

#### Timing of Thrombolytic Treatment

The benefit of fibrinolytic therapy decreases as time progresses following the onset of symptoms (Figure 5). Prehospital administration of thrombolysis was beneficial if administered within 70 minutes in terms of reduction in the composite score of death, stroke, serious bleed and infarct size (P = 0.009). A meta-analysis by Morrison demonstrated that prehospital thrombolysis resulted in significant decrease in time to thrombolysis and all-cause mortality. The Comparison of Primary Angioplasty and Prehospital Fibrinolysis in Acute Myocardial Infarction (CAPTIM) Trial reported a trend toward a lower rate of mortality among STEMI patients receiving prehospital fibrinolysis as compared with primary percutaneous angioplasty.

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**Table 4** Contraindications and cautions for fibrinolytic use in ST-segment elevation myocardial infarction (STEMI)

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Any prior intracranial hemorrhage</td>
</tr>
<tr>
<td>- Known structural cerebral vascular lesion (e.g. arteriovenous malformation)</td>
</tr>
<tr>
<td>- Known malignant intracranial neoplasm (primary or metastatic)</td>
</tr>
<tr>
<td>- Ischemic stroke within 3 months except acute ischemic stroke within 3 hours</td>
</tr>
<tr>
<td>- Suspected aortic dissection</td>
</tr>
<tr>
<td>- Active bleeding or bleeding diathesis (excluding menses)</td>
</tr>
<tr>
<td>- Significant closed head or facial trauma within 3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History of chronic severe poorly controlled hypertension</td>
</tr>
<tr>
<td>- Severe uncontrolled hypertension on presentation (SBP &gt;180 mm Hg or DBP &gt;110 mm Hg)³</td>
</tr>
<tr>
<td>- History of prior ischemic stroke &gt; 3 months, dementia, or known intracranial pathology not covered in contraindications</td>
</tr>
<tr>
<td>- Traumatic or prolonged (&gt;10 min) CPR or major surgery (&lt;3 wk)</td>
</tr>
<tr>
<td>- Recent (within 2-4 wk) internal bleeding</td>
</tr>
<tr>
<td>- Noncompressible vascular punctures</td>
</tr>
<tr>
<td>- For streptokinase, anistreplase: Prior exposure (&gt;5 days ago) or prior allergic reaction to these agents</td>
</tr>
<tr>
<td>- Pregnancy</td>
</tr>
<tr>
<td>- Active peptic ulcer</td>
</tr>
<tr>
<td>- Current use of anticoagulants: The higher the INR, the higher the risk of bleeding</td>
</tr>
</tbody>
</table>

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CPR, Cardiopulmonary resuscitation; INR, International normalized ratio

1 Viewed as advisory for clinical decision-making, and may not be all-inclusive or definitive.

2 Could be an absolute contraindication in low-risk patients with myocardial infarction (MI).
coronary intervention (PCI), especially if patients were treated within 2 hours of the onset of symptoms. Boersma evaluated the relation between treatment delay and short-term mortality (up to 35 days) and greater benefit was observed among patients who received fibrinolytic therapy at 0–1 hours’ time-interval from symptom onset (65, 37, 26 and 29 lives saved/1,000 treated patients in the 0–1, 1–2, 2–3 and 3–6 hours intervals, respectively). In the GUSTO-I trial, females, elderly, diabetics and patients with previous infarction or bypass surgery were associated with longer presentation and treatment delays.

Cerebrovascular Events
The Fibrinolysis Therapy Trialists (FTT) collaborators analysis demonstrated that thrombolysis was associated with an increase in stroke rate compared to control patients (1.2% versus 0.8%,  \( P < 0.00001 \)). An analysis from the GUSTO-I Study demonstrated that the overall incidence of stroke following fibrinolytic therapy was 1.4% (95% of stroke occurred within 5 days). Combination treatment with SK and t-PA was associated with significantly more stroke than SK alone (1.64% versus 1.19%,  \( P < 0.007 \)). Of these, among 41% of the cases, the stroke was fatal. Intracranial hemorrhage occurred in 0.46% of cases who received SK and 0.88% of cases who received combination therapy ( \( P < 0.001 \)). Another analysis demonstrated a slight increase in ICH among patients receiving t-PA (0.95%). Intracranial hemorrhage is the most serious complication of fibrinolytic therapy; its frequency varies with the clinical characteristics of the patient (low bodyweight, increased age and hypertension at presentation associated with increased risk) and the fibrinolytic agent prescribed (Figure 6).

Patency of Infarct Arteries
Early patency of the IRAs is not demonstrated in all patients treated with fibrinolytic therapy. Angiography following fibrinolytic therapy demonstrates that TFG3 is achieved in only approximately 40–60% of cases. In an analysis from the GUSTO Trial, the patency of infarct artery (TFG 2/3) at 90 minutes was achieved in 81% of cases in the accelerated t-PA group compared to only 54% in the SK group ( \( P < 0.001 \)). Normal flow (TFG3) was achieved in 54% of patients who received t-PA compared to 40% among those who received the other treatments (SK + subcutaneous heparin, SK + intravenous heparin, combination of SK, t-PA and heparin). The mortality at 30 days was significantly increased among those who had reduced flow compared to those who had normal flow (8.9% versus 4.4%,  \( P = 0.009 \)).

Even patients with TFG3 may not achieve adequate myocardial perfusion, especially if there is a great delay between the onset of symptoms and restoration of epicardial flow. Myocardial no-reflow may occur due to microvascular damage and reperfusion injury. Fibrinolysis may actually exacerbate microembolization of platelet aggregates because of the exposure of clot-bound thrombin, an extremely potent platelet agonist.

Reinfarction and Recurrent Ischemia
Thrombolysis is also overcome by frequent occurrence of recurrent ischemia, reocclusion of the infarct artery (reocclusion within 5–7 days occurred in 4.9–6.4% cases in the GUSTO analysis) and reinfarction. Reinfarction occurred in 4.3% of cases following thrombolysis at a median of 3.8 days after thrombolysis. The 30 days and mortality from 30 days to 1 year was significantly increased among those who had reinfarction (11.3% versus 3.5% and 4.7% versus 3.2%, respectively,  \( P < 0.001 \)).

Age
Several studies have demonstrated that short-term and long-term mortality increases with age. In the GUSTO-I subanalysis, there was not only an increase in 30-day mortality with age [3.0% (< 65 years), 9.5% (65–74 years), 19.6% (75–85 years), and 30.3% (> 85 years)], there was also an increase in stroke, cardiogenic shock, bleeding and reinfarction. Accelerated t-PA was associated with fewer combined death or disabling stroke in all but the oldest patients, who showed a weak trend toward a lower incidence with SK plus subcutaneous
heparin. Likewise, accelerated t-PA treatment resulted in lower 1 year mortality in all but the oldest patients (47% t-PA versus 40.3% SK). Weaver and colleagues demonstrated that 28% of patients hospitalized for AMI were greater than or equal to 75 years of age and only 5% of patients were administered a systemic thrombolytic agent. Though, there was an increase in mortality with increasing age, the relative and absolute risk reductions associated with fibrinolytic administration were quite favorable.

Infarct Size and Site
The extent of myocardial injury appears to be more relevant than the site in determining in-hospital mortality and efficacy of thrombolytic therapy. In the GISSI Trial, SK significantly reduced mortality only in anterior and multiple site infarcts. There was a progressive increase in the mortality rate based on infarct size (6.5% in small infarcts to 9.6% in the modest, 14.3% in large and 21.7% in extensive).

Effect of Fibrinolytic Therapy on Mortality
Early intravenous fibrinolysis undoubtedly improves survival in patients with STEMI. Mortality varies considerably, depending on the patients included for study and the adjunctive therapies used. As previously mentioned, the benefit of fibrinolytic therapy appears to be the greatest when agents are administered as early as possible, with the most dramatic results obtained when the drug is given less than 2 hours after symptoms begin. Fibrinolytic therapy trialists collaboration group indicated an 18% reduction in short-term mortality with thrombolytics but as much as a 25% reduction in mortality for the subset patients with ST-segment elevation or bundle branch block. Two trials, Late Assessment of Thrombolytic Efficacy (LATE) and Estudio Multicéntrico Estreptoquinasa Republicas de América del Sur (EMERAS), provide evidence that a mortality reduction may still be observed in patients treated with thrombolytic agents between 6 hours and 12 hours from the onset of ischemic symptoms.

Choice of Agent
The clinicians must weigh the risk of mortality and the risk of ICH when confronting a fibrinolytic-eligible patient with STEMI. Constraints are placed on physicians by the health care system in which they practice. In patients, presenting within 4 hours of symptom onset, the speed of reperfusion of the infarct vessel is of paramount importance and a high-intensity fibrinolytic regimen such as accelerated t-PA is the preferred treatment, except in those for whom the risk of death is low (e.g. a young patient with a small inferior myocardial infarction (MI)] and the risk of ICH is increased (e.g. acute hypertension), in whom SK and accelerated t-PA are approximately equivalent choices. For those, presenting between 4 hours and 12 hours after the onset of chest discomfort, the speed of reperfusion of the infarct vessel is of lesser importance, and SK and accelerated t-PA are therefore generally equivalent options, given the difference in costs. Of note, for those presenting between 4 hours and 12 hours from symptom onset with a low-mortality risk but an increased risk of ICH (e.g. older patients with inferior MI, systolic pressure > 100 mm Hg and heart rate < 100 beats/minutes), SK is probably preferable to t-PA because of cost considerations if fibrinolytic therapy is prescribed at all in such patients.

In those patients considered as appropriate candidates for fibrinolysis and for whom t-PA would have been selected as the agent of choice in the past, clinicians should now consider as using a bolus fibrinolytic such as rPA or TNK. The rationale for this recommendation is that bolus fibrinolysis has the advantage of ease of administration, a lower chance of medication errors (and the associated increase in mortality when such medication errors occur) and less noncerebral bleeding, and also offers the potential for prehospital treatment.

Intracoronary Thrombolytic Therapy
Rentrop first reported IC administration of SK in the management of patients with AMI. The efficacy of IC fibrinolytic therapy was studied among patients undergoing primary PCI. In a study by Sezer, IC SK (250 KU of IC SK over 3 minutes) was associated with significantly better coronary flow reserve compared to the control group 2 days following the procedure. However, this did not translate into improvements in left ventricular size and function at 6 months. Intracoronary TNK is a safe, well-tolerated and effective treatment for the management of thrombotic complications in high-risk complex PCI. Kelly and coworkers demonstrated that TNK-supported PCI significantly improved the no-reflow phenomenon among high-risk PCI patients.

Recommendations
For the patients with STEMI, as per American College of Cardiology (ACC)/American Heart Association (AHA) guidelines fibrinolysis is preferred if patients present early (≤ 3 hours from symptoms onset), invasive strategy is not an option, or delay to invasive strategy is expected (prolonged transport, door to balloon—door to needle time more than 1 hour or medical contact to balloon or door to balloon > 90 minutes). Moreover, for those presenting to non-PCI centers, it is reasonable for high-risk patients who receive fibrinolytic therapy as primary reperfusion therapy to be transferred as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy (Class Ia recommendation, Level of Evidence: B).

Conclusion
In the setting of STEMI, fibrinolysis continues to be an option for reperfusion in non-PCI centers and in patients presenting early (< 3 hours) where delay to invasive strategy is expected. The evolution of thrombolytic drugs over the last 2 decades has seen transition from first generation (SK, urokinase) to fibrin-specific, nonantigenic, second (alteplase, t-PA) and third generation thrombolytics (rPA, TNK) with longer half lives, resistance to PAI-1, better 90 minutes timing of thrombolytic treatment and cost effectiveness in a given health care system. Future research might see development of optimal thrombolytic strategy with ability of maximal reperfusion and with minimal bleeding and reocclusion complications.

References
among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. BMJ. 1998;316:1337-43.