ABSTRACT
Acute ST-segment elevation myocardial infarction (MI) is caused by coronary plaque rupture/erosion and resultant thrombosis leading to an occluded epicardial infarct-related artery (IRA). Timely fibrinolytic therapy can re-establish coronary flow in this setting and salvage jeopardized myocardium. 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. Despite dramatic strides in the area of percutaneous intervention, thrombolysis remains the most utilized form of reperfusion treatment worldwide.

This review will focus on approved agents and the randomized trials that have led to their widespread utilization.

INTRODUCTION
Despite dramatic improvements in quality of care, acute myocardial infarction remains a leading public health concern. Mortality and left ventricular function are believed to be closely related to the extent of viable myocardium. Therefore, establishing rapid reperfusion of an occluded coronary artery is critical in minimizing morbidity and mortality.

Percutaneous coronary intervention (PCI) and thrombolysis are established reperfusion strategies. Although PCI is highly effective, a successful procedure requires advanced notification to shorten reperfusion time after onset of acute myocardial infarction symptoms. More importantly, PCI is available in only select institutions, whereas thrombolytic therapy is available to all. Therefore, these drugs play an essential role in treating acute myocardial infarction.

Since the introduction of streptokinase, major advances in thrombolytic therapy have taken place. Researchers expeditiously searched for an ideal agent with a rapid onset of action to establish patency, as well as an adequate half-life to facilitate rapid bolus administration and achieve optimum patency, maximum fibrin specificity, and minimum major bleeding. Before a discussion on old and new thrombolytic agents, detailed below is the pathophysiology of acute myocardial infarction.

Pathophysiology of Acute Myocardial Infarction
Most myocardial infarctions are a result of an occlusive thrombus that prevents coronary artery blood flow and adequate oxygen delivery to distal tissue, leading to myocardial cell death. The longer myocardium is deprived of oxygen, the greater the amount of cell loss. Damage often occupies the entire transmural thickness of the ventricular wall.

Unstable plaques of atherosclerotic coronary arteries commonly and unpredictably rupture, exposing the thrombogenic core, including collagen and other thrombogenic substances; thus begins a sequence of events encompassing thrombus formation. At the site of plaque rupture, platelets in close proximity adhere to exposed collagen by von Willebrand factor, forming a platelet blanket that lines the injured endothelium. Subsequently, release of various thrombogenic substances begins platelet activation. Thromboxane A2, formed from arachidonic acid in platelet membranes, adenosine diphosphate, and serotonin from dense granules, as well as circulating epinephrine and thrombin, induce conformational changes of the platelet receptor integrin glycoprotein (GP) Iib-IIIa. Endothelin released from exposed endothelial cells, together with a few of the mentioned and other thrombogenic substances, causes local vasoconstriction, thereby potentiating the thrombogenic environment.

Activated GP Iib-IIIa binds fibrinogen, forming interplatelet bridges, leading to platelet aggregation (Figure 1). These fibrinogen-platelet

Fig 1: After plaque rupture, transition from platelet adhesion to the vessel wall through platelet activation and aggregation with circulating fibrinogen. vWF = von Willebrand factor; GP = glycoprotein. (Adapted from Tsikouris JP et al, 1991)
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The coagulation cascade (Figure 2) begins as early as platelet adhesion to collagen. It is this system that generates fibrin, thereby forming an insoluble mesh surrounding the platelet plug and completing the coronary artery thrombus.

Reperfusion therapy with thrombolitics

The most common thrombolytic agents have been streptokinase (first generation thrombolytic agent) and alteplase (tissue type plasminogen activator, t-PA, second generation thrombolytic agent). In the meantime third generation thrombolytic agents have reached clinical practice. Many of them are derivatives of alteplase, the current gold standard for thrombolytic therapy in acute coronary syndromes with ST segment elevation. The most prominent among them are reteplase, tenecteplase, and lanoteplase.5

(See Appendix 1 for a comparative table )

Appendix

Characteristics of Fibrinolytic Agents*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Source/Structure</th>
<th>Molecular Weight, kD</th>
<th>Mutation</th>
<th>Fibrin Specific Metabolism</th>
<th>Half-life, min</th>
<th>Mode of Action</th>
<th>Antigenic</th>
<th>Dosing</th>
<th>Other Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>Group A streptococci</td>
<td>47</td>
<td></td>
<td>Hepatic</td>
<td>18–23</td>
<td>Activator complex</td>
<td>Yes</td>
<td>1-h infusion</td>
<td></td>
</tr>
<tr>
<td>Alteplase, duteplase (tPA)</td>
<td>Recombinant, human</td>
<td>63–70</td>
<td>F, E, K, P domains</td>
<td>++</td>
<td>Hepatic</td>
<td>3–8</td>
<td>Direct</td>
<td>No</td>
<td>Bolus, 90-min infusion</td>
</tr>
<tr>
<td>Reteplase</td>
<td>Recombinant, human mutant tPA</td>
<td>39 Single-chain deletion</td>
<td>Lacks F, E, K1 domains; has K2, P domains</td>
<td></td>
<td>Renal</td>
<td>15–18</td>
<td>Direct</td>
<td>No</td>
<td>Double bolus</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>Recombinant plus mutation</td>
<td>39 Point substitutions</td>
<td></td>
<td>+++</td>
<td>Hepatic</td>
<td>18–20</td>
<td>Direct</td>
<td>No</td>
<td>Single bolus</td>
</tr>
</tbody>
</table>

*ISAM Intravenous Streptokinase in Acute Myocardial Infarction.

Appendix

Table 1: Placebo-Controlled Mortality Trials of Streptokinase*a,b

<table>
<thead>
<tr>
<th>Variables</th>
<th>GISSI-1</th>
<th>ISAMI</th>
<th>ISIS-2</th>
<th>EMERAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>11,806</td>
<td>1741</td>
<td>17,187</td>
<td>3568</td>
</tr>
<tr>
<td>Sites, No.</td>
<td>176</td>
<td>38</td>
<td>417</td>
<td>236</td>
</tr>
<tr>
<td>Dose/duration, h</td>
<td>1.5 MU/I</td>
<td>1.5 MU/I</td>
<td>1.5 MU/I</td>
<td>1.5 MU/I</td>
</tr>
<tr>
<td>Placebo blinding</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age criteria</td>
<td>All</td>
<td>&lt;75 y</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Symptom duration, h</td>
<td>&lt; 12</td>
<td>&lt; 6</td>
<td>&lt; 24</td>
<td>6–24</td>
</tr>
<tr>
<td>ECG criteria</td>
<td>ST or 2</td>
<td>ST 1</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Aspirin</td>
<td>+/-</td>
<td>Yes</td>
<td>Randomized</td>
<td>Yes</td>
</tr>
<tr>
<td>Heparin</td>
<td>+/-</td>
<td>IV</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Mortality follow-up, d</td>
<td>In-hospital</td>
<td>21</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

*a ISAM Intravenous Streptokinase in Acute Myocardial Infarction.
*b Adapted from Menon V Chest(2004)126 (3) suppl : S495-S575

Adapted from Menon V Chest(2004)126 (3) suppl : S495-S575
A serendipitous discovery by William Smith Tillett in 1933, followed by many years of work with his student Sol Sherry, laid a sound foundation for the use of streptokinase as a thrombolytic agent in the treatment of acute myocardial infarction. The drug found initial clinical application in combating fibrinous pleural exudates, hemothorax, and tuberculous meningitis. In 1958, Sherry and others started using streptokinase in patients with acute myocardial infarction and changed the focus of treatment from palliation to “cure.” Initial trials that used streptokinase infusion produced conflicting results. An innovative approach of intracoronary streptokinase infusion was initiated by Rentrop and colleagues in 1979. Subsequently, larger trials of intracoronary infusion achieved reperfusion rates ranging from 70% to 90%. The need for a meticulously planned and systematically executed randomized multicenter trial was fulfilled by the gruppo Italiano per la Sperimentazione della Streptochinasi nell’Infarto Miocardico (gISSI) trial in 1986, which not only validated streptokinase as an effective therapeutic method but also established a fixed protocol for its use in acute myocardial infarction. Currently, despite the wide use of tissue plasminogen activator in developed nations, streptokinase remains essential to the management of acute myocardial infarction in developing nations.

The efficacy of streptokinase with regard to mortality evaluated in four large, placebo-controlled trials is represented in Table 1. The Fibrinolytic Therapy Trialists’ Collaborative Group combined trials investigating streptokinase for treatment of acute MI in a metaanalysis. The authors observed an overall benefit among patients with ST-segment elevation or bundle-branch block irrespective of age, sex, BP, heart rate, or prior MI, or diabetic status. Furthermore, the treatment benefit was greater the earlier treatment was initiated. For patients treated within 6 h, the absolute reduction in mortality was 30 lives saved per 1,000 patients treated; for patients treated within the first 7 to 12 h after symptom onset, it was 20 lives saved per 1,000 treated. Consistent across these trials, the treatment benefit observed in the first 21 to 42 days was maintained up to 1 year. For patients treated between 13 h and 18 h after symptom onset, there was an uncertain trend toward mortality reduction of approximately 10 lives saved per 1,000 treated. Fibrinolytic therapy was associated with approximately four extra strokes per 1,000 patients treated, most of which occurred within 2 days. About 50% were associated with an early death, and so were already accounted for in the overall mortality reduction. Of the remaining patients with stroke, 25% were moderately or severely disabled and the other 25% were not. The metaanalysis thus suggested a treatment benefit for most patients who present with acute MI within 12 h of symptom onset.

Tissue plasminogen activator

All available fibrin-specific thrombolytic agents have the same general mechanism of fibrinolysis. They have the property of fibrin-enhanced conversion of plasminogen to plasmin. When introduced into systemic circulation at pharmacologic concentrations, alteplase (rt-PA), reteplase (r-PA), and tenecteplase (TNK) preferentially bind to fibrin in a thrombus and catalyze cleavage of entrapped plasminogen to plasmin. This begins local fibrinolysis with limited systemic proteolysis. These agents differ from the prototype streptokinase (nonfibrin-specific) in that they enzymatically cleave plasminogen to plasmin, whereas streptokinase causes an indirect conformational change in the plasminogen molecule, which then acts as plasmin.

Alteplase

Alteplase (recombinant tissue-type plasminogen activator) stimulates the fibrinolysis of blood clots by converting plasminogen to plasmin. The efficacy of intravenous alteplase in the early treatment of patients with acute myocardial infarction has been unequivocally proven, and results from the GUSTO trial indicate a significant advantage in 30-day survival for alteplase in an accelerated dosage regimen (< or = 100mg infused over 90 minutes rather than 3 hours) over streptokinase. The advantage of the accelerated alteplase dosage regimen seems to be maintained for at least 1 year. The role of heparin as adjunctive therapy to thrombolysis remains to be fully defined but heparin administration appears to be more important in conjunction with alteplase than with streptokinase. Ideally, patients should receive alteplase as soon as possible after the onset of symptoms of acute myocardial infarction and, while therapy is most beneficial when administered early, survival is improved when the drug is administered up to 12 hours after symptom onset. The accelerated regimen of alteplase...
used in the GUSTO trial demonstrated a survival advantage in patients \(< \text{or} \leq 75\) as well as those \(> 75\) years of age which was at least as great as that seen with streptokinase. Similarly, alteplase reduces mortality in patients with both anterior and inferior infarctions; however, those with anterior wall infarctions show an improved outcome over those with inferior infarcts. On the basis of pharmacoeconomic analysis of GUSTO data, the accelerated alteplase regimen cost an estimated additional \$US32,678\ per year of life saved compared with a conventional streptokinase regimen. Cumulative 1-year costs were greater in patients who received the accelerated alteplase regimen but survival was significantly greater than in patients who received streptokinase. No difference in quality of life was evident in patients who received either treatment.

The incidence of major haemorrhage associated with alteplase therapy appears to be similar to that seen with other fibrinolytic agents, increasing with increasing dose; however, the risk of stroke, particularly haemorrhagic stroke, is higher with alteplase than with streptokinase. Thus, alteplase has become firmly established as a first-line option in the management of acute myocardial infarction. On the basis of accumulated evidence, the greatest risk reduction with alteplase therapy may be in certain high risk groups, such as those with anterior infarcts, selected elderly patients and those who present late after symptom onset.

**Reteplase**

Reteplase (recombinant plasminogen activator, r-PA) is a single chain deletion mutant of alteplase that is expressed in Escherichia coli and, therefore, is expressed as an unglycosylated protein (table 2, figs 4 and 5). Reteplase includes 355 amino acids with a total molecular weight of 39 kDa. The molecule consists of kringle 2 and the protease domain of the alteplase molecule. Because of the deletion of the fibronectin finger region, the binding of reteplase to fibrin is significantly reduced in comparison with that of alteplase. Although kringle 2 (known to stimulate protease in the presence of fibrin) is part of the reteplase molecule, reteplase is stimulated in the presence of fibrin to a lower extent than alteplase, suggesting that the fibronectin finger is involved in the stimulation of the protease as well. Reteplase, in comparison with alteplase, is characterised by reduced fibrin selectivity. In the absence of fibrin, reteplase and alteplase do not differ with respect to their activity as plasminogen activators, nor do they differ with respect to their inhibition by the plasminogen activator inhibitor type 1 (PAI-1). The elimination of reteplase from the circulating plasma predominantly occurs in the liver. Because of the deletion of the fibronectin finger region, the epidermal growth factor domain and kringle 1, as well as the carbohydrate side chains, the hepatic elimination of the molecule is reduced.

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**Table 2: Alteplase: structure of the molecule and function of its components**

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibronectin finger</td>
<td>Binding to fibrin</td>
</tr>
<tr>
<td>Epidermal growth factor domain</td>
<td>Elimination by hepatocytes</td>
</tr>
<tr>
<td>Kringle 1</td>
<td>Elimination by liver endothelial cells</td>
</tr>
<tr>
<td>Kringle 2</td>
<td>Stimulation of protease by fibrin</td>
</tr>
<tr>
<td>Protease domain</td>
<td>Splitting of plasminogen</td>
</tr>
<tr>
<td>Carbohydrate side chain</td>
<td>Elimination from plasma</td>
</tr>
</tbody>
</table>

Reteplase, tenecteplase, and lanoteplase are derivatives of alteplase, components of which have been deleted or changed.

PAI-1, plasminogen activator inhibitor type 1.
Consequently, plasma half life is increased to 14–18 minutes (versus 3–4 minutes with alteplase). This allows reteplase to be administered as bolus (versus as an initial bolus followed by an infusion, as with alteplase). Since early recurrences of the infarct related coronary artery had been observed with the single bolus administration, it was replaced by a double bolus one. The best results have been obtained with a double bolus of 10 U each 30 minutes apart in the case of an acute myocardial infarction. Reteplase has been approved for the thrombolytic treatment of acute myocardial infarction. In clinical trials, reteplase in comparison with alteplase is equal in efficacy and superior in its application as a double bolus that also facilitates prehospital initiation of reperfusion therapy.

Reteplase has been approved for the thrombolytic treatment of acute myocardial infarction. In the RAPID I (recombinant plasminogen activator angiographic phase II international dose finding study) trial reteplase was superior to alteplase (administered over three hours) with respect to patency of the infarct related coronary artery. With reteplase patency was reached earlier and more frequently than with alteplase. This was confirmed in the RAPID II (reteplase vs alteplase patency investigation during myocardial infarction) trial where alteplase was administered in the accelerated regimen (over 1.5 hours). However, in the GUSTO (global use of strategies to open occluded coronary arteries) III trial mortality after 30 days did not differ between patients treated with reteplase and those treated with alteplase. This discrepancy may be explained by more frequent patent infarct related vessels that reoccluded more often, leading to the same net benefit. In summary, reteplase in comparison with alteplase is equal in efficacy and superior in its application as a double bolus that also facilitates prehospital initiation of reperfusion therapy.

Tenecteplase

Tenecteplase is also called the TNK-mutant of alteplase. The molecule does not constitute a deletion mutant of alteplase (as reteplase does). Instead, it consists of the alteplase molecule with the exception of three point mutations (Fig. 6). At position 103 of the polypeptide the aminoacid threonine has been replaced by asparagine leading to a new glycosylation site. The carbohydrate chain that is linked to this site enlarges the molecule, thereby reducing its elimination and prolonging its plasma half life. At position 117 asparagine has been replaced by glutamine. By the exchange of this amino acid the carbohydrate side chain that facilitates hepatic elimination has been removed. Hence, plasma half life is further prolonged. Finally, at position 296–299 the amino acids lysine, histidine, arginine, and arginine have been replaced by four amino acids alanine. Consequently, the inhibition by PAI-1 is reduced 80 times in comparison with alteplase. The amino acids that were replaced at the three positions are called T, N, and K according to the one letter code for amino acids, which leads to the expression TNK-mutant. Since the molecule is expressed in CHO (Chinese hamster ovary) cells, it is expressed with carbohydrate side chains linked to the glycosylation sites of the polypeptide.

The relatively long plasma half life of tenecteplase (approximately
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The ACC recommendations for the use of these agents are as follows:

- For patients with ischemic symptoms characteristic of acute MI of < 12 h in duration, and ST elevation or left bundle-branch block (of unknown duration) on ECG, administration of any approved fibrinolytic agent (Grade 1A).
- Use of streptokinase, anistreplase, alteplase, reteplase, or tenecteplase (all Grade 1A).
- For patients with symptom duration < 6 h, the administration of alteplase or tenecteplase over streptokinase (Grade 1A).
- For patients with known allergy or sensitivity to streptokinase, alteplase, reteplase, or tenecteplase (Grade 1A).
- For patients with recurrent acute MI, clinician should not use repeat administration of streptokinase (Grade 2C).
- For patients with ischemic symptoms characteristic of acute MI of < 12 h in duration and 12-lead ECG findings consistent with a true posterior MI, fibrinolytic therapy (Grade 2C).
- For high-risk patients with ongoing symptoms characteristic of acute MI or hemodynamic compromise and duration of 12 to 24 h who have ST elevation or left bundle-branch block, administration of IV fibrinolytic therapy (Grade 2B).
- In health-care settings where prehospital administration of fibrinolytic therapy is feasible and primary angioplasty is not available, prehospital administration of fibrinolytic therapy only (Grade 1A).
- For patients with acute MI who are candidates for fibrinolytic therapy, administration within 30 minutes of arrival to the hospital.

In the trials the most critical adverse event was bleeding. Intracranial hemorrhage occurred at a rate less than 1% with r-PA, rt-PA, and TNK, with higher frequency in patients older than 75 years. It should be noted that in GUSTO-I streptokinase caused less ICh than rt-PA in patients 75 years of age and older. As discussed, other noncerebral major bleeding complications requiring blood transfusions occurred at a similar rate with r-PA and rt-PA, and according to ASSENT-2 was significantly less with TNK.

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Adverse Effects

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No other adverse events have been reported. Unlike streptokinase, rechallenge with fibrin-specific agents does not produce an antigenic response.

Due to the life-threatening nature of bleeding complications, numerous contraindications and warnings are attached to these agents. Contraindications for r-PA, rt-PA, and TNK include active internal bleeding; intracranial or intraspinal surgery or trauma within 2 or fewer months; intracranial neoplasm, arteriovenous malformation, or aneurysm; bleeding diathesis; and severe uncontrolled hypertension. Conditions that may increase the risk of bleeding (warnings) are recent major surgery (< 10 days), cerebrovascular disease, recent (< 10 days) gastrointestinal or genitourinary bleeding, recent (< 10 days) trauma, hypertension (> 180 mm Hg systolic, > 110 mm Hg diastolic), acute pericarditis, subacute bacterial endocarditis, hemostatic defects secondary to severe hepatic or renal disease, significant liver dysfunction, pregnancy, retinopathy, current therapy with oral anticoagulants (warfarin), and septic thrombophlebitis. Although advanced age (> 75 yrs) increases the risk of bleeding, these patients still experience significant benefit from therapy.

Dosage and Administration

Both r-PA and TNK are administered as rapid bolus infusions. Two

Table 3: Dosing in Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient Weight (kg)</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-PA</td>
<td>≤ 60</td>
<td>0.6 U + 1.0 U</td>
</tr>
<tr>
<td>rt-PA</td>
<td>60-69.9</td>
<td>1.0 U + 1.0 U</td>
</tr>
<tr>
<td></td>
<td>70-79.9</td>
<td>1.5 U + 1.0 U</td>
</tr>
<tr>
<td></td>
<td>&gt; 80</td>
<td>2.0 U + 1.0 U</td>
</tr>
<tr>
<td>TNK</td>
<td>≤ 60</td>
<td>0.6 mg</td>
</tr>
<tr>
<td></td>
<td>60-69.9</td>
<td>0.8 mg</td>
</tr>
<tr>
<td></td>
<td>70-79.9</td>
<td>1.0 mg</td>
</tr>
<tr>
<td></td>
<td>&gt; 80</td>
<td>1.2 mg</td>
</tr>
</tbody>
</table>

a All drugs are administered intravenously.
b Bolus doses are administered 30 minutes apart and over 2 minutes.
c Bolus dose is administered over 5-10 seconds.
rapid bolus doses separated by 30 minutes of r-PA are required for all patients; TNK is administered as a single bolus over 5-10 seconds based on weight. On the other hand, rt-PA is administered as a front-loaded bolus-infusion regimen. Once acute myocardial infarction is diagnosed appropriately by ECG, expeditious administration (preferably within 6 hours of symptom onset, as in survival trials) of all thrombolytic agents is recommended so that rapid reperfusion is established (Table 3).

Dosage adjustment of r-PA, rt-PA, and TNK based on significant renal or hepatic dysfunction or increasing age is not officially recommended, primarily due to lack of investigation of these issues. However, with approximately 100% hepatic metabolism, it is unlikely that rt-PA or TNK requires dosage adjustments based on renal dysfunction alone. Due to warnings discussed earlier, rt-PA and TNK should be administered to patients with hepatic or renal dysfunction with extreme caution. As discussed, r-PA has hepatic and renal elimination and therefore should be given with caution when elimination is compromised. Although elderly patients are at increased risk for bleeding, they do obtain significant benefit from the drugs and should be considered candidates for recommended dosages until proven otherwise.1

Unfractionated heparin and aspirin should be administered in conjunction with these drugs. Published guidelines of the American College of Cardiology-American Heart Association recommended a lower dosage of heparin in patients receiving fibrin-specific thrombolytics: bolus of 60 U/kg (maximum 4000 U) and initial infusion of 12 U/kg/hour (maximum 1000 U/hr).1

Adjuvante therapy

In the past decade, attention has focused on improving the potency, efficacy, and administrative ease of fibrinolytic agents. A therapeutic ceiling of reperfusion success was recognized and has led to the testing of newer adjuvantive therapies like GP IIb/IIIa inhibitors (Tirofiban, eptifibatide and abciximab) and LMWHRoxaparin and dalteparin) in this clinical setting. The current endeavor is to synergistically combine the merits of fibrinolysis and percutaneous intervention into a seamless reperfusion strategy.

The ACC recommends the use of adjuvantive treatment with antithrombotic agents in patients receiving fibrinolysis for acute myocardial infarction.

CONCLUSIONS

The initial description of a prolonged infusion of streptokinase for patients with acute MI appeared in 1958. Several smaller studies followed, but no definitive benefit was discernable. A metaanalysis of these early studies, however, suggested a significant mortality benefit. This coupled with angiographic observations of reperfusion among patients receiving intracoronary streptokinase ushered in the modern era of reperfusion therapy for acute MI. 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. Use of tissue plasminogen activators and the role of adjuvantive medications was clarified, and the limitations and complications of therapy have become apparent.

REFERENCES

7. Menon V et al. Thrombolysis and adjuvantive therapy in acute myocardial infarction Chest 2004;126;549S-575S