Thrombolytic Therapy in Acute Myocardial Infarction: An Emergency Department Perspective

Bradford L. Walters

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Thrombolytic Therapy in Acute Myocardial Infarction: An Emergency Department Perspective

Bradford L. Walters, MD*

In the past several years there has been a revolution in the approach to acute myocardial infarction (MI) not unlike what happened in the treatment of bacterial infections with the advent of antibiotics. Physicians have been able to go from expectant management of complications to attacking the root cause of MI itself; thrombosis of a coronary artery. In the past, patients with chest pain were admitted to the coronary care unit (CCU) where the ultimate diagnosis was made over a period of time as various test results became available. Patients were watched for the development of complications such as arrhythmias or congestive heart failure. The role of the emergency physician was to identify those patients who required admission and to keep them alive until they could be transferred to the CCU. The majority of the responsibility for treating the patient fell to the admitting physician who, in most cases, was a cardiologist or internist.

The treatment of acute MI changed radically with the development of thrombolytic therapy in the 1980s, and the entire approach to acute MI continues to be revolutionized. With the ability to dissolve clots within the coronary artery came a need to initiate this treatment as rapidly as possible. Thus, the emergency physician has become a central figure for most patients with an acute MI who present to the emergency department. Time constraints made it impractical to wait for the cardiologist or internist to come in to treat the patient. Protocols were developed that allowed the emergency physician to assess the indications and contraindications for thrombolysis, to initiate treatment with such agents, and to begin treatment with adjunctive therapies without first consulting the admitting physician. It placed greater responsibilities upon the emergency physician as he or she was required to balance a myriad of factors and potential therapies that were not required in the prethrombolytic era. The various indications, absolute and relative contraindications, risk factors, interpretation of ECGs, and which adjunctive agents to use all must be addressed by the emergency physician in a short time. This article examines many of the issues confronting the emergency physician using thrombolytic agents to treat a patient with an acute MI.

Rationale for the Use of Thrombolytic Therapy

The use of thrombolytic agents for acute MI is not new. Initial work with streptokinase (SK) was reported in the late 1940s (1). However, whether coronary thrombosis was the cause or result of a MI was still in question in that era. While coronary artery thrombosis was postulated as the inciting event of an acute MI by Herrick (2) in 1912, not until 1980 did DeWood et al (3) demonstrate angiographically that 90% of patients within 4 hours of the onset of symptoms had obstruction of the infarct artery by a thrombus. In light of such findings, thrombolytic therapy was reconsidered with greater intensity. Additionally, DeWood et al (3) demonstrated the safety of coronary angiography in the early period of an acute MI, establishing the basis for assessing the effects of thrombolytic therapy in subsequent studies.

In the history of medicine no class of agent has been studied with the same intensity as the thrombolytic agents. Nor have so many patients been enrolled in such a short time in trials that are routinely international in scope. To provide optimal treatment, the emergency physician must be aware of the recommendations for thrombolysis, the studies that demonstrate specific applications, and the trials that have modified those applications.

The initial patients to receive thrombolytic therapy were those in whom the risk of complications was low. Patients were excluded if they had hypertension, a history of stroke, or were elderly. Typical inclusion and exclusion criteria for those initial trials are shown in Table 1; such criteria became the standard indications and contraindications for thrombolysis for many hospital protocols.

In many cases the exclusion criteria are subjective and imprecise. The exclusion of patients with a history of stroke is a good example. Is the risk of thrombolysis different for the patient who experienced a stroke 15 years previously compared to the one who had a stroke three months prior to the acute MI? How long after "major" surgery is it safe to administer a thrombolytic agent? Is there a difference in risk between a vigorous 80-year-old and a chronically ill 60-year-old patient? The treating physician must keep in mind that many of the exclusion and inclusion criteria were developed from studies whose primary goal was to select patients who had the lowest risk of complications. These are not necessarily the kinds of patients who present with an acute MI to the average emergency department. A major diffi-
The difficulty of providing thrombolytic therapy is to select patients likely to benefit from such treatment and to exclude those in whom the risk of a complication is excessive. The emergency physician must be aware of the "gray areas" because many patients do not fall neatly into inclusion and exclusion categories. Knowledge of these areas allows the physician to maximize the use of this powerful treatment for acute MI.

**Intracoronary Versus Intravenous Thrombolytic Therapy**

Initial studies of thrombolytic therapy involved the intravenous administration of SK (4). The first clinical trials did not show significant reductions in the most crucial parameter, mortality (5,6). These initial studies were flawed by use of low doses and late administration of SK. Subsequently, intracoronary administration of SK was demonstrated to be feasible and highly effective in reestablishing perfusion in a coronary artery occluded by thrombus if administered early after the onset of symptoms (7-9). In the Western Washington trial, a substantial reduction of in-hospital mortality was demonstrated using intracoronary SK (10). Patients treated early in the time course of symptoms (average of 4.6 hours) showed a 67% reduction in mortality (10). Other trials showed similar reductions in mortality using intracoronary thrombolytic agents (11-13). The importance of time is one of the most consistent findings; every study has shown that the sooner a patient is treated, the better the results. Despite the benefits of intracoronary thrombolytic agents, their administration presents formidable obstacles. First, only a small number of hospitals have the angiography facilities (19% as of 1986) (14). Second, substantial delays are incurred because of the time needed to call in personnel to the angiography suite, particularly during off hours. Finally, the intracoronary infusion of a thrombolytic is expensive.

The issue became moot when trials using the intravenous route demonstrated a reduction in mortality equivalent to that achieved with intracoronary administration. Furthermore, intravenous administration of a thrombolytic agent could be achieved not only with greater ease and speed but also within the emergency department. The first two megatrials using intravenous SK (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico [GISSI-1] and the International Study of Intravenous Streptokinase [ISIS-2]) showed a mortality reduction equal to that in the intracoronary studies (15,16). Results of smaller trials were similar but the mortality reductions were not always statistically significant (17-19). Mortality reduction in these studies ranged from 11% to 66%. Tissue-plasminogen activator (t-PA) was shown to achieve patency rates equivalent to that achieved with intracoronary agents when administered up to 6 to 8 hours after the onset of symptoms (20-23) (Fig 1). Virtually all therapy is now given intravenously and treatment with these agents moved from the angiography suite to the emergency department.

Despite the ease with which intravenous thrombolytic agents can be given, a sizable proportion of MI patients are ineligible for this therapy using the inclusion criteria of the major trials. In many trials, patients who were at any risk for a complication were excluded. Moreover, the requirement to treat patients in the early stages of a MI eliminated an additional number of eligible patients. In the Thrombolysis in Myocardial Infarction (TIMI) trials, only 9% to 14% of patients with acute Mls met the inclusion criteria (24,25). Even liberalizing the inclusion criteria (e.g., by increasing the time frame of symptoms up to 6 hours) increases the percentage of patients eligible for treatment to only 25% (26-28). The major reason for excluding patients was that the duration of symptoms was too long; additional factors were age (over 75 years) and a nondiagnostic ECG (29). The Anglo-Scandinavian Study of Early Thrombolysis (ASSET) did not use any ECG criteria, and the GISSI trial included patients up to 12 hours from symptom onset. This increased the eligibility rates of patients presenting for treatment to 38% and 37%, re-
spective (15,30). It is important to realize that there is a high mortality rate in those patients who were excluded from these trials. In the TIMI-IIb trial, the in-hospital mortality for participating patients was 2.5% whereas mortality was 18% for those who were excluded because of some contraindication (25). These excluded patients represent a population that might derive significant benefit from thrombolysis (15,30,31). Despite the huge number of patients who have participated in various trials, the guidelines still are such that a majority of patients are excluded by some contraindication. If thrombolysis is to have a more substantial impact on the mortality of acute MI, issues of patient eligibility must be explored in the hope of including more patients.

The issue of determining a patient's eligibility for treatment has become a major responsibility of the emergency physician. Cooperation with admitting physicians (i.e., cardiologists and internists) has provided emergency physicians the freedom to make the initial decisions regarding thrombolytic therapy prior to contacting the admitting physician. While this allows for faster initiation of therapy, it has thrown greater responsibility on the emergency physician. The various criteria for thrombolytic therapy are in a state of flux. An intimate knowledge of this area will allow the emergency physician to provide this therapy with the least risk for subsequent complications.

Criteria for Thrombolytic Therapy

ECG criteria

Most trials of thrombolytic therapy required strict ECG evidence of infarction as a key inclusion criterion. Such acute changes assure a greater probability that the patient will actually be having a MI at the time of treatment. Typical ECG criteria are 1 to 2 mm of ST segment elevation in two contiguous leads. Some trials included the caveat that the ST segment elevation must persist after nitroglycerin administration, eliminating coronary artery spasm as an etiology of the acute MI. This ECG criterion has been relatively standard as an absolute indication for thrombolytic therapy. However, not all trials used ECG changes to screen patients for inclusion in the study. Both the ASSET and ISIS-2 trials based inclusion of patients purely on clinical and historical findings without requiring acute ECG changes. In these two trials, patients with chest pain and normal ECGs had a mortality rate that was low and minimal benefit was derived from thrombolytic treatment (30,32). In the GISSI-1 and ISIS-2 trials, patients with chest pain and only ST segment depression on their ECG also derived little benefit from treatment with thrombolytics. Contrary to the belief that patients with only depressed ST segments represent a low-risk group, this group proved to have a high mortality rate in both trials (16.3% and 20.5%, respectively) (15,29,32). Presently, acutely elevated ST segments is an absolute requirement before a patient can be considered for thrombolytic therapy.

The controversy of infarction location has also been an issue of thrombolytic therapy and ECG inclusion criteria. A number of studies have demonstrated that patients with inferior wall infarctions have a relatively low mortality rate. Pooled data from approximately 12,000 patients with inferior MIs treated with thrombolytic agents disclose a reduction in mortality from 8.7% in the control group to 6.8% in the treated group (29). While not as great a mortality reduction as that seen in anterior MIs, it is still significant. Exclusion based on location of the infarct does not seem justified.

Another area that can challenge the emergency physician relative to ECG interpretation involves those patients who have a left bundle branch block (LBBB). Interpretation of the ECG for ischemic changes is difficult in the presence of a LBBB. Results in this group of patients from the GISSI-1 trial showed little mortality difference between control and treated groups (8.6% versus 8.0%, respectively) (15). In contrast, in the ISIS-2 trial, patients with a LBBB had a mortality rate of 27.7% in the control group which decreased to 14% in the SK plus aspirin treatment group (32). In the absence of other contraindications, patients with chest pain consistent with MI and a LBBB should be considered for thrombolytic treatment even without acute ECG changes. However, patients who have chest pain but whose ECG is normal or shows only ST segment depression should be observed with serial ECGs and/or taken for emergency angiography.

Serum enzyme changes

The time constraints involved in treating patients with thrombolytic agents are such that the emergency physician cannot wait for most laboratory tests to be performed. However, those patients who do not qualify for treatment based on ECG criteria are frequently observed for a short time in the hope of seeing some change that will allow the diagnosis of acute MI. In a pilot study of patients with chest pain and nondiagnostic ECGs, serial creatine phosphokinase MB band (CPK-MB) assays were drawn to determine whether the pattern of rising enzyme levels correlated with having an acute MI. While an isolated total CPK or even CPK-MB assay may yield no significant information, repeated studies over a short time may reveal a trend that is sensitive and specific for infarction. In the pilot study a rising trend in CPK-MB was strongly correlated in those patients who were having an acute MI. In patients who have chest pain and nondiagnostic ECGs, serial CPK-MB testing may rapidly identify those who could benefit from thrombolysis (33).

Time to treatment

The time span between the onset of symptoms and the initiation of treatment with a thrombolytic agent has been a powerful predictor of success. In the first megatrial, GISSI-1, little benefit was found in patients first treated beyond 6 hours of the onset of symptoms (15). This observation correlates with the finding in animals that irreversible myocardial necrosis occurs within 6 hours after occlusion of a coronary artery (34). This 6-hour period has been accepted as the time limit in which patients must be treated with thrombolytic agents. However, the time of symptom duration can be difficult to determine accurately because few patients know precisely when their pain began. Minor chest pains may precede the pain for which the patient then seeks medical care. Patients may not note the time their pain began or may be poor historians. Accordingly, initiating or withholding thrombolytic therapy based on rigid time guidelines is
fraught with inaccuracy. The issue becomes even more confused by results of studies in which patients were treated late. Patients who survive the first 6 hours after a MI are still at high risk of dying and may benefit from thrombolysis (15,32,35). Combined data from several studies in which patients were treated up to 24 hours after the onset of symptoms show a significant reduction in mortality rates using intravenous SK (29).

In the 6- to 12-hour time frame, mortality was 13% in the control group compared to 11.6% in the treated cohort. When 12 to 24 hours elapsed between onset of symptoms and treatment, mortality was 11.8% in the control group versus 8.7% in the group given thrombolytic agents (29). These results were achieved despite the fact that SK is not particularly effective in lysing clots late in the course of coronary artery occlusion (36).

Thus, the decision whether to begin thrombolytic therapy is difficult when the time of onset of symptoms is uncertain. Emergency physicians have turned to other factors to help make this critical decision in those patients who present late. Ongoing chest pain, continued presence of acute changes on ECG, and lack of other contraindications to thrombolysis have been used to "justify" the use of thrombolytic agents in such patients.

A second important time factor that can impact patient outcome is that required to initiate thrombolytic therapy. Long delays in the emergency department can influence the success of thrombolysis. The TIMI-II trial patients who presented to the Hennepin County Medical Center in Milwaukee, WI, experienced substantial delays in the emergency department before treatment was initiated. The average time to complete required studies, interpret the results, place the intravenous lines, and obtain the thrombolytic agent from the pharmacy was approximately 90 minutes. It took even longer if the patient bypassed the emergency department and went directly to the CCU (37).

Expediting this process is an essential responsibility of the emergency physician. Many departments have established protocols in which patients suspected of myocardial ischemia are treated with the same team approach as trauma victims.

Bleeding risk

Some of the complications of thrombolytic therapy are bothersome and not life-threatening. They can usually be treated without interfering with the infusion of the thrombolytic agent. For example, the allergic reaction which can occur with SK will generally respond promptly to treatment with antihistamines and steroids. In most cases the infusion of SK need not be halted or may be stopped for a short time.

Bleeding that occurs subsequent to thrombolytic therapy is the most serious and a potentially fatal complication. Sometimes the bleeding is minor, such as oozing from a venipuncture or intravenous site. However, major bleeding can occur in the retroperitoneal space or intracranially causing a stroke. It is difficult to predict which patient may suffer a serious bleeding complication. Prolonged infusions of a thrombolytic agent and older age will increase the risk for bleeding (38,39). Other factors that increase the risk of hemorrhage are poorly understood, such as the excess bleeding found in hypertensive, thin, elderly women (40) whether or not they undergo an invasive procedure such as angiography (29).

The most feared bleeding complication and that most frequently associated with a morbid outcome is intracranial bleeding (ICB). In a study of 154 cases of spontaneous ICB (not associated with thrombolytic therapy), 54% of the patients were hypertensive on presentation, 45% gave a history of hypertension, and 46% were elderly. A total of 27% had a prior cerebral event such as a stroke or intracranial tumor. However, 41% of the patients who suffered ICB had no obvious risk factor for ICB (41).

Patients who are elderly or hypertensive or have a history of stroke or intracranial tumor are considered at high risk for ICB and are excluded from thrombolytic protocols. In the Thrombolysis and Angioplasty in Myocardial Infarction study, 0.7% of the patients suffered ICB. The investigators could identify at least one risk factor in each of these patients. However, 80% of patients who did not have ICB also had one such "risk" factor. In fact, the authors were unable to identify patients with a high potential for ICB based on age, aspirin use, hypertension, or prior cerebrovascular accident (42). Thus, while hypertension and advanced age do increase the risk for ICB in patients undergoing thrombolysis, the event is difficult to predict in a specific patient.

All thrombolytic agents seem to be associated with a similar rate of ICB (Table 2). SK, t-PA, and anisoylated plasminogen streptokinase activator complex (APSAC) given intravenously have a rate of ICB of 0.4% to 0.5% (39,43,44). This complication rate was found with a t-PA dose of 100 mg. In the TIMI-IIb study, a dosage of 150 mg was associated with a rate of ICB of 1.9%. In view of this result, 100 mg of t-PA is the most commonly used dose (39). Newer regimens have been proposed using weight-dosing and front-loading protocols in addition to combinations with other agents. Initial studies have demonstrated no increase in ICB, raising the possibility that t-PA therapy can be safely administered in a regimen that may maximize coronary artery patency (45-48).
Table 2
Comparison of the Thrombolytic Agents*

<table>
<thead>
<tr>
<th></th>
<th>SK</th>
<th>t-PA</th>
<th>APSAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1.5 million units</td>
<td>100 mg x 3 hrs</td>
<td>30 units</td>
</tr>
<tr>
<td>Patency</td>
<td>50%</td>
<td>70% to 75%</td>
<td>50% to 55%</td>
</tr>
<tr>
<td>Time-dependent</td>
<td>4 hours</td>
<td>Little demonstrated</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Severe in &lt; 5% of patients</td>
<td>Rare</td>
<td>Like SK</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 minutes</td>
<td>5 minutes</td>
<td>90 minutes</td>
</tr>
<tr>
<td>Fibrinogen depletion</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>ICB</td>
<td>&lt; 0.5%</td>
<td>&lt; 0.5%</td>
<td>&lt; 0.5%</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Repeat dosing</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>$264</td>
<td>$2,200</td>
<td>$2,375</td>
</tr>
</tbody>
</table>

SK = streptokinase, t-PA = tissue-plasminogen activator, APSAC = anisoylated plasminogen streptokinase activator complex, ICB = intracranial bleeding.

Hypertension

Hypertension is an important consideration in patients undergoing thrombolytic therapy because of the increased risk for ICB. Hospital protocols for the use of thrombolytic agents have absolute and relative contraindications based on blood pressure. However, it is not clear what actually constitutes an unacceptable level of hypertension (Table 1). The important question of whether hypertensive patients whose blood pressure is controlled in the emergency department can be treated safely with thrombolytic agents has not been studied adequately.

The causes of hypertension are multifactorial with anxiety and pain playing a significant role. Hypertension due to pain and/or anxiety often cannot be distinguished readily from chronic hypertension. However, such situational causes of hypertension should respond to medications that control pain and anxiety (e.g., nitrates and narcotics). Persistent hypertension may require the use of antihypertensive agents such as nifedipine, parenteral nitroglycerin, or nitroprusside. Careful titration of antihypertensive therapy is important because inducing hypotension could worsen myocardial ischemia. When acceptable blood pressure levels are achieved in patients, many emergency physicians will commence thrombolytic therapy. Justification for this policy is found in the ISIS-2 study in which 1,141 patients whose initial systolic blood pressure was over 175 mm Hg were entered into the study. The treatment group mortality was less than that of the control group, 5.7% versus 8.7%, respectively (32). Thus, in hypertensive patients without other contraindications to thrombolysis, whose blood pressure can be controlled adequately in the emergency department, thrombolytic therapy offers improved mortality.

Age

Most early trials of thrombolytic agents restricted their use to younger patients. The age of 75 years was the usual upper limit for treated patients. Data regarding the risk of bleeding, particularly ICB, seemed to support such caution. However, this elderly group frequently presents to the emergency department with acute MI. People older than 65 years comprise the fastest growing population group in the United States. In 1987 this age group comprised 12% of the population and is expected to rise to 20% by the year 2030. The fastest growing segment of this elderly group, those over 85 years old, represents a pool of patients in whom thrombolysis can offer substantial benefits (49). The mortality rate for acute MI and the incidence of associated complications such as congestive heart failure and left ventricular failure are higher in the older age groups (50-55). In several of the trials that included patients older than 75 years, higher mortality and increased incidence of hemorrhagic complications were seen in the older patients (56,57). However, not all studies report more frequent complications in elderly patients. In GISSI-1, the group of 592 patients over age 70 had no greater incidence of bleeding complications relative to younger patients (15). Whatever the risk of thrombolysis, the elderly age group showed significant mortality benefit from treatment (Fig 2). In the ISIS-2 trial, patients older than 70 years in the control group had the highest mortality rates of the entire study (21.6% to 23.8%). This same group obtained a substantial benefit from treatment with reductions in mortality ranging from 15.7% to 33.6% (32). Pooled data from five large trials (Intravenous Streptokinase in Acute Myocardial Infarction study, GISSI-1, ISIS-2, ASSET, and the APSAC Intervention Mortality Study) revealed that the mortality rate for elderly patients was 22.1% in the control groups which was reduced to 17.9% in the treated groups (P < 0.0001) (Fig 2). The conclusion that strict chronologic age should not be used as an absolute contraindication to thrombolytic therapy seems justified.

Recent Megatrials

Within the past year some of the concepts and controversies regarding thrombolytic therapy have been addressed in two ambitious trials. The GISSI-2 and ISIS-3 megatrials attempted to address the controversy over which agent is better, SK or t-PA. Both trials were large and included the use of aspirin and heparin as adjunctive agents. In addition, both trials liberalized inclusion criteria in order to enroll older patients and those with longer time intervals from the onset of symptoms. In the ISIS-3 trial, one arm of the protocol looked at atypical presentations including patients who did not have acute ECG changes.

Before the results of these trials can be evaluated, it is important to note the mortality rates established by preceding trials. Pooled data from 25 major trials show a mortality rate of 11.8% in the control group (n = 18,679), 9.4% in the SK treatment group (n = 16,824), and 5.6% in the t-PA treatment group (n = 16,824). Pooled data from five large trials (Intravenous Streptokinase in Acute Myocardial Infarction study, GISSI-1, ISIS-2, ASSET, and the APSAC Intervention Mortality Study) revealed that the mortality rate for elderly patients was 22.1% in the control groups which was reduced to 17.9% in the treated groups (P < 0.0001) (Fig 2). The conclusion that strict chronologic age should not be used as an absolute contraindication to thrombolytic therapy seems justified.
A second randomization divided patients into the heparin and placebo-heparin groups. Patients in the heparin group received 12,500 units subcutaneously starting 12 hours after administration of the thrombolytic agent. All patients received aspirin and those who qualified were given beta-blockers. No statistical difference in mortality was seen between SK or t-PA (8.5% and 8.9%, respectively). There was also no mortality difference between the heparin and placebo-heparin groups. Both agents were associated with an equal number of complications and strokes (59-61).

The ISIS-3 trial compared SK, APSAC (antistreptase), and t-PA (duteplase) in a randomized protocol. This study included 46,092 patients from 20 countries who were divided into the “certain” and “uncertain” groups in terms of the indications for thrombolysis. The “certain” group presented within 6 hours with typical chest pain accompanied by an ECG showing acute changes. These patients were randomized first to receive one of the three thrombolytic agents and then into the heparin or placebo-heparin group. The heparin was given as in GISSI-2, 12,500 units subcutaneously, but was started 4 hours after the thrombolytic agent. The “uncertain” group included patients with typical chest pain who presented beyond 6 hours after the onset of symptoms and/or did not have acute ECG findings. Patients in this group were first randomized into a no thrombolytic/aspirin only/placebo group and a thrombolytic group. The thrombolytic group was then randomized to receive one of the three agents as done in the “certain” group. The primary endpoint of this trial was mortality at five weeks.

The results of ISIS-3 have yet to be published but some of the findings have been presented at conferences in the United States (Table 3). The mortality rates were not statistically different among the three thrombolytic agents with or without heparin. Available subgroup analysis revealed no mortality difference among the three agents in patients presenting within 6 hours of symptoms and who had ST segment elevation on ECG (the “certain” group). Except for allergic reactions (more frequent with SK and APSAC as expected), the side effects were similar for all agents. Complications were infrequent, demonstrating the safety of thrombolysis even when patients outside traditional parameters are included. One unexpected finding was the higher rate of ICB for t-PA compared to SK and APSAC (Table 3). The mortality rates were not statistically different among the three agents for SK), and 2) t-PA produces far less fibrin split products. However, in two studies of the effect of heparin and t-PA on coronary artery patency, results were significantly better when intravenous heparin was given immediately after the t-PA infusion (62,63).

Two notable differences between SK and t-PA are 1) the shorter half-life of t-PA (approximately 5 minutes compared to 20 minutes for SK), and 2) t-PA produces far less fibrin split products. The longer half-life of SK, along with the greater quantity of fibrin split products, produces a more sustained systemic lytic state than that produced by t-PA (Table 2). Therefore, therapy with t-PA might prove to be more sensitive to the anticoagulant effect of immediate intravenous heparin in order to maintain a longer lytic state. Delayed administration of subcutaneous heparin may have influenced the results of t-PA more than that of SK in the GISSI-2 and ISIS-3 trials. Pooled data from a number of studies confirm that mortality is lower in patients who receive intravenous heparin than in those who do not. In 34,581 patients from five different trials (GISSI-1 and -2, ISIS-2, the Heparin-Aspirin Reperfusion Trial (HART), and the Studio sulla Calci-parina nell’Angina e nella Trombosi Ventricolare nell’Infarto [SCATI] trial) who received either t-PA or SK without heparin, the combined mortality rate was 9.3% (15,32,59,60,62,64). The 9,298 patients from 15 different trials (ASSET, the European Cooperative Study Group trials I-V, HART, ISIS-2, National Heart Foundation of Australia Coronary Thrombolysis Group, New Zealand I-II, SCATI, TIMI-II pilot-IIb) who received intravenous heparin after either SK or t-PA had a pooled mortality rate of only 5.5% (30,32,39,62,64-74). Along the same lines,
a summary of the ISIS-2 data by Topol (75) revealed the following mortality rates: SK + aspirin = 9.6%; SK + aspirin + subcutaneous heparin = 7.6%; SK + aspirin + intravenous heparin = 6.4%. The group receiving intravenous heparin again had the lowest mortality rate (75).

Adjunctive Agents and Thrombolytic Therapy

Aspirin

In various studies, a number of adjunctive agents combined with thrombolytic therapy have been found to be extremely beneficial. Several enhance the lytic state created by the thrombolytic agent and others have been found to have mortality benefits. Generally, the emergency physician initiates the administration of these adjunctive agents.

The simplest to use and one of the most effective adjunctive agents is aspirin. Its antiplatelet effect reduces the reinfarction rate and augments the improvement in mortality achieved by thrombolysis. In the ISIS-2 trial, the beneficial effect of aspirin was equal to that of intravenous SK alone in terms of reduced mortality. There was further reduction in mortality when aspirin was combined with SK (32). Since that study, aspirin has been a part of virtually all trials of thrombolytic agents including those reporting the lowest mortality rates yet (39,70). In a study of 100 patients with anterior acute MI treated with a thrombolytic and heparin, the incidence of reinfarction was significantly lower in the group receiving aspirin (76).

The amount of aspirin administered has varied in different trials. Doses between 80 to 325 mg/day have been used and most protocols call for the first dose to be given in the emergency department. It is recommended that the first dose be chewed to promote faster absorption. The American College of Cardiology/American Heart Association currently suggests a dose of 160 mg/day beginning immediately in patients undergoing thrombolysis (77).

Heparin

Heparin is the second adjunctive agent to consider. Its use, benefits, risks, and routes of administration are controversial. Current practice in the United States is to administer heparin intravenously with or just after the thrombolytic agent. Frequent monitoring of the anticoagulation status is important to assure that therapeutic levels are achieved rapidly. The goal of heparin therapy is to prevent reoclusion of the coronary artery once thrombolysis has been successful. The optimal regimen has yet to be determined. The TIMI-1 trial proposed a 5,000 U bolus of heparin given immediately after infusion of the thrombolytic agent. Thereafter, an infusion of 1,000 U/hr should be adjusted to maintain an activated partial thromboplastin time 1.5 to 2.0 times greater than control. This regimen has become standard in most thrombolytic protocols employing intravenous heparin (36). However, other regimens of heparin administration have been advocated, notably in the GISSI-2 and ISIS-3 trials in which heparin was given subcutaneously some time after the thrombolytic agent had been infused. Concerns over this delay in heparin administration and the lack of anticoagulation monitoring have been discussed. The HART trial (62) and Bleich et al (63) suggest a synergistic effect between heparin and t-PA. There are also data to support the concept that heparin is an important adjunctive agent with SK (75). In the SCATI trial, patients receiving SK were given a bolus of intravenous heparin followed by subcutaneous heparin. The heparin group had significantly lower mortality (4.6%) compared to the control nonheparin group (8.8%) (64). Subcutaneous, unmonitored heparin has not been used extensively in the United States and intravenous heparin has been widely accepted.

Percutaneous transluminal coronary angioplasty

One adjunctive treatment to thrombolysis which seemed promising initially has been found not only to be ineffective in lowering mortality but actually to increase complications. It seems logical that to open up an area of stenosis caused by an atherosclerotic plaque in a coronary artery would help prevent reocclusion and subsequent ischemia. Coronary thrombosis commonly occurs in the narrowed artery lumen where the plaque also acts as a nidus of thrombosis. In a number of studies percutaneous transluminal coronary angioplasty (PTCA) was performed soon after thrombolysis, aiming to open up any stenotic areas in the infarct artery. In the TIMI-IIa and -IIb trials, patients who underwent early PTCA had no lower mortality than those treated conservatively with delayed angiography and highly selective angioplasty. In addition, complications such as bleeding requiring transfusion were more common in the early PTCA group (39,68,74,78,79). Early angiography with PTCA offers no mortality benefit and increases complications. The need for angioplasty in an otherwise stable patient is low.

Beta-blockers

Although not directly synergistic with thrombolytic agents, beta-blockers are considered to be important adjunctive agents in patients with acute MI. Beta-adrenergic blockade reduces the oxygen demand of the myocardium and has been found to improve the prognosis of patients in studies not involving thrombolytics (80). In the TIMI-IIIb trial, metoprolol was given intravenously to patients who had no contraindications to beta-blockade (Table 4). The dose was 15 mg given intravenously (in three 5 mg doses over 15 minutes) followed by oral metoprolol. This use of beta-blockers reduced the incidence of recurrent, nonfatal infarction and lowered mortality in comparison to those given oral beta-blockers starting six days after thrombolysis (39). In the absence of any contraindications, patients undergoing thrombolysis should receive beta-blockers in an effort to reduce mortality further.

Choice of Thrombolytic Agent and Dosing Regimen

No aspect of thrombolytic therapy engenders as much controversy as does the choice of agent. Currently there are three drugs in clinical use: SK, t-PA, and APSAC (Table 2). Urokinase has been used both alone and in combination with other thrombolytics but is not commonly used clinically. Each thrombolytic agent has a slightly different physiologic profile which the emergency physician must keep in mind.
SK is the agent which has been in use the longest and with which we have the greatest clinical and experimental experience. Derived from bacteria, it is a foreign protein and has allergenic and antigenic potential. In studies of arterial patency, SK had a significantly lower rate compared to t-PA (36). However, data from the GISSI-2 and ISIS-3 trials have not shown that higher patency rates influence mortality as both SK and t-PA were similar in that respect (59,60). A nonclot-specific agent, SK acts on plasminogen throughout the body. Levels of fibrinogen fall precipitously and levels of fibrin split products rise (Table 2). These effects, along with the relatively long half-life of SK, prolong a sustained generalized lytic state. SK seems to produce a modestly higher incidence of hypotension and serious bleeding requiring transfusion compared to t-PA (59,60). The incidence of allergic reactions is low and generally responds to treatment with antihistamines and/or steroids. Many physicians no longer pretreat patients for allergy as was once advocated with SK. However, the antigenic potential of SK is significant in that patients develop antibodies to SK and the agent cannot be readministered at a later date (Table 2). In virtually all trials the current dose of SK is 1.5 million units infused over 60 minutes.

t-PA is a drug derived from a recombinant DNA process. It is clot-specific in that its thrombolytic activity increases significantly in the presence of a thrombus, creating a lytic environment only in that area. It was thought that this characteristic would lead to fewer systemic bleeding complications because the t-PA would be active only in the area of a coronary thrombus. However, physiologic clots are present throughout the body and t-PA creates a generalized lytic state as these clots are lysed along with the pathologic ones. Because t-PA is a human product, there is no allergic or antigenic potential. Therefore, it can be readministered at a later date without risk of antibody reaction. Therapy with t-PA produces a lower rate of serious bleeding compared to SK, but the ICB rate is similar (Table 2).

Of all the agents, t-PA is the most potent in terms of arterial patency rates and is not as time-dependent as SK. The efficacy of t-PA in terms of restoring patency of the infarct vessel is relatively uniform over at least 8 hours from onset of the symptoms (36,65,67) (Fig 1). SK is far more time-dependent and the patency rate tends to diminish three hours after occlusion (62). However, this difference has not resulted in a demonstrable decrease in mortality rate. The dose of t-PA, unlike SK, has been altered in an attempt to increase the coronary patency. Both front-loading and weight-dosing t-PA regimens which seem to increase patency have been proposed and are being used in several studies (47,48). However, at this time the most common dose of t-PA is 100 mg infused over three hours. The TIMI protocol called for a bolus of 6 to 10 mg followed by an infusion of 50 to 54 mg over the next 60 minutes for a total of 60 mg in the first hour. The last 40 mg was given in the next two hours at 20 mg/hr (57,74). This regimen does not produce the high ICB rate seen with the 150 mg dose. Urokinase has been combined with t-PA, but the two agents did not act synergistically and no increase in patency was seen. Therefore, this combination has not been used clinically to any extent (81).

Of all thrombolytic agents, APSAC has the most limited clinical and experimental use. Compared to the vast experience with SK and the considerable experience with t-PA, only a minimum of patients have been studied with APSAC (43,82-85). This agent is a form of SK. The molecule incorporates an anisoyl site which must be metabolized before APSAC becomes active SK. It is more clot-specific than SK but not to the degree of t-PA. APSAC has the longest half-life of all the thrombolytic agents (83) (Table 2). Its administration does not require an infusion and can be given simply as a 30 unit bolus over two to five minutes. This property may be important in the prehospital setting or when establishing several intravenous lines is difficult. As a derivative of SK, APSAC carries an allergic potential. The patient will also develop antibodies which precludes its use at a future date.

The cost of thrombolytic agents is a growing concern, and there are major differences between the various agents. At Henry Ford Hospital, charges for the three agents are currently $164 for SK, $2,200 for t-PA, and $1,700 for APSAC (86). With increasing pressure to control the cost of medical care, this issue can be a deciding factor in the choice of agent. Moreover, to date no study has shown definitively that one agent is superior to any other. The impact of GISSI-2 and ISIS-3 is limited because these trials varied from the usual heparin protocols used in the United States. Accordingly, the decision as to which agent to use should be based on which agent is most readily available in the emergency department as well as which agent the physician is most familiar.

### Global Utilization of SK and t-PA for Occluded Coronary Arteries

Future studies may answer the question of the relative advantages of SK, t-PA, or APSAC. Currently the Global Utilization of Streptokinase and rt-PA for Occluded Coronary Arteries (GUSTO) trial holds such promise. This megatrial will involve centers in the United States and abroad in a comparison study of SK, t-PA, and SK combined with t-PA. All patients will receive...
intravenous heparin and aspirin at standard doses. By using the front-loaded, weight-adjusted, Neuhaus t-PA regimen, GUSTO will attempt to maximize vessel patency and aggressively test the "open-artery" theory. In addition, this trial will examine the question of sustaining early patency by the use of intravenous heparin and aspirin. An interesting part of this trial will be the arm which combines SK and t-PA seeking to capitalize on the early patency power of t-PA with the more sustained lytic effect of SK. This trial, which is currently in progress, may answer many of the questions left open by the GISSI-2 and ISIS-3 trials.

**Summary**

The use of thrombolytic agents allows the emergency physician to attack the primary etiology of an acute MI; occlusion of a coronary artery by a thrombus. This treatment has had a major impact on mortality and morbidity of acute MI. However, thrombolysis has its complications, some of them serious, and the risks of therapy must be balanced against the benefits. The complication of greatest concern is ICB which is fatal in the majority of cases. All thrombolytics currently in clinical use have similar ICB rates. While some differences in other complications exist between the thrombolytics, they are too small a factor to influence the choice of a thrombolytic agent. Currently, only a minority of acute MI patients are being treated with thrombolytic agents. There are a variety of reasons for this fact, but the main problem is that patients are excluded by criteria derived from the experimental trials which established the efficacy of thrombolytic therapy. Because these studies eliminated the higher risk patients, the benefits were maximized and the complications minimized. Strict application of the inclusion and exclusion criteria established by such studies is too conservative and may eliminate many patients who can benefit from thrombolytic therapy. Two such examples are the criteria for age and time from onset of symptoms. As more trials include older patients, it has become clear that this group can derive considerable benefit from thrombolysis despite a higher rate of complications. The maximum 6-hour time limit from onset of symptoms to initiation of treatment was established by the GISSI-1 trial and has been continued in many other studies. However, those trials which treated patients outside of this early period do demonstrate a benefit for late thrombolysis. Although a short interval to treatment is considered the most powerful predictor of success, reliable assessment of this key parameter depends on the accuracy of the patient's history. Holding to a rigid time frame may exclude patients who would otherwise benefit from treatment. A crucial function of the emergency physician is to assess all historical factors in order to decide whether an individual patient is a suitable candidate for treatment.

The interpretation of the ECG has great importance because concrete evidence of myocardial ischemia is necessary before deciding whether to use a thrombolytic agent. Interpretation of ECGs which fall outside the classic criteria of 1 to 2 mm of ST segment elevation in two consecutive leads becomes difficult in terms of whether they represent true myocardial ischemia. In patients with typical chest pain and a LBBB, which may mask ischemic changes, the use of thrombolytics has shown some benefit and is justified. No significant reduction in mortality has been shown in those patients with chest pain whose ECGs show only ST segment depression.

To administer thrombolytic therapy successfully, physicians must be familiar with the three agents currently in use. The use of front-loaded, weight-adjusted regimens of t-PA is becoming more popular and its impact on mortality may become more evident as results of new trials, such as GUSTO, are reported. APSAC may offer an advantage in being able to be given as a single bolus. SK is the agent which has been in use the longest and is the least expensive. The choice of agent can be difficult and unfortunately is clouded by cost issues as well as by medical ones. The economics of treating MI is a complex issue. Acute MI occurs frequently and huge expenses are incurred in its treatment. There are large differences in the cost of the various agents but thus far no study has clearly shown that any single agent is superior to any other. Furthermore, no study has clearly shown that superior patency rates lead to lower mortality rates. More relevant than pure economic issues, the treating physician must be familiar with a readily available agent in order to administer it in an efficient manner to the patient presenting to the emergency department with an acute MI. Despite its difficulties and regardless of the agents used (APSAC, t-PA, or SK), thrombolytic therapy is the most important intervention in improving survival in acute MI patients.

**References**


75. Topol EJ. Controversies in cardiology. Presented at the 40th Annual Scientific Session of the American College of Cardiology, March 6, 1991, Atlanta, GA.