Recombinant tissue-type plasminogen activator (rt-PA), streptokinase (SK), and anisoylated plasminogen-streptokinase activator complex (APSAC) have salutary effects on mortality when administered to patients with evolving acute myocardial infarction (MI). Studies suggest that intravenous rt-PA is more effective in reperfusing occluded infarct-related arteries than SK, and the results of ongoing studies directly comparing the influence of SK and rt-PA on mortality are awaited. The clinical role of agents such as APSAC, urokinase, and pro-urokinase, used alone or in combination, remains to be determined. It is evident that a variety of thrombolytic agents will be effective, and variables such as ease of administration, pharmacokinetics, fibrin specificity, effects on blood viscosity, and incidence of adverse effects need to be assessed to determine which agents are the most suitable for clinical use. There is an increased risk of bleeding at vascular puncture sites with all thrombolytic agents. Current indications for thrombolytic therapy include ischemic chest pain of at least 30 min duration that is unrelieved by nitroglycerin and is associated with ST-segment elevations of at least 0.1 mV in two contiguous electrocardiographic leads. Such therapy is usually reserved for patients less than 75 years old who are not at increased risk for bleeding and whose chest pain began less than 4-6 h prior to treatment. Trials are under way to determine whether patients with shorter pain duration, transient ST-segment changes (ie, unstable angina patients), chest pain associated with ST-segment depressions or T-wave inversions (ie, non-Q-wave infarction patients), or patients whose pain began more than 4 to 6 h earlier will benefit from early thrombolytic therapy. Other factors such as patient age, the likelihood of the diagnosis of MI, and the estimated risk of bleeding should also be considered. The findings of available major randomized trials indicate that early invasive procedures are generally unnecessary and that meticulous care must be exercised in the selection and management of patients subjected to thrombolytic therapy.

For more than 15 years therapies designed to limit the size of acute myocardial infarction (MI) have been tested in patients. It is well recognized that following MI, the mortality is directly related to the quantity of infarcted myocardium and the severity of ventricular dysfunction. Coronary arteriography in patients with acute MI has revealed that a thrombus occluding an atherosclerotic epicardial coronary artery is almost always present early in the course of Q-wave acute MI. This has led to a resurgence of interest in thrombolytic therapy, and it has now been established that thrombolysis, initiated early after coronary thrombosis, may restore coronary blood flow, reverse myocardial ischemia, reduce MI size, limit left ventricular (LV) dysfunction, and reduce mortality.

1. What are the common thrombolytic agents in clinical use and under investigation?

Streptokinase. (SK) itself is not a fibrinolytic agent. It combines with plasminogen to form an activator complex that combines with additional plasminogen and converts the latter into plasmin, which then lyses the fibrin in the thrombus. Since both circulating and fibrin-bound plasminogen are converted to plasmin, a systemic lytic state is produced. Streptokinase, a protein produced from ultrafiltrates of group C streptococci, may be antigenic. Consequently, allergic or anaphylactic reactions can occur in 1 percent of patients receiving short-term high-dose therapy. Previous streptococcal infection, and previous treatment with SK, can lead to the development of neutralizing antibodies. Streptokinase is also acted upon by plasmin inactivators; it has a plasma half-life of 10 to 18 min.

Tissue-type plasminogen activator. Tissue-type plasminogen activator (t-PA) is a naturally occurring protein, produced by endothelial cells, that has a much higher affinity for bound fibrin than for circulating plasminogen. Binding of t-PA to fibrin already in a thrombus causes local activation of plasminogen to plasmin. Although some free plasmin is released into the systemic circulation, a generalized lytic state is usually avoided. Recombinant t-PA (rt-PA) is produced in pharmacologic quantities by recombinant DNA technology. The plasma half-life of rt-PA is 5 to 10 min.

APSAC. In anisoylated plasminogen-streptokinase activator complex (APSAC), the active serine site is acylated, rendering it inert in serum. However, APSAC binds actively to fibrin because its lysine/fibrin binding sites are structurally and functionally separate from the catalytic center. Once bound, deacylation by hydrolysis commences, activation of APSAC

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occurs, and this continues in a controlled fashion. Thus, both the activation (deacylation) and the plasma clearance half-life of APSAC (70 min) are longer than those of SK, resulting in more sustained fibrinolytic activity. However, contrary to what was initially believed, APSAC is not fibrin specific.

UROKINASE. Urokinase (UK) is a protein synthesized by epithelial tissue in humans. In contrast to SK, it can activate plasminogen directly, and it is nonantigenic. Urokinase can therefore be administered repeatedly to the same patient. Urokinase activates plasminogen equally well in the presence or absence of fibrin and has been isolated from urine and conditioned cell culture media in a single-chain form (single-chain urokinase plasminogen activator, or scu-PA, also known as pro-UK). This single-chain form is a true enzyme that activates a small quantity of plasminogen to plasmin. The plasmin generated then converts scu-PA to UK, which in turn activates plasminogen to plasmin. scu-PA has been produced by recombinant DNA techniques (rscu-PA) and, like rt-PA, is relatively fibrin specific; its half-life clearance from plasma is 3 to 6 min for 90 percent of the administered dose and 20 minutes for the remaining 10 percent.

2. Does IV thrombolytic therapy reduce the mortality of patients with evolving acute MI?

Three different thrombolytic agents have been shown to reduce the mortality of patients with suspected acute MI in major randomized trials (Fig 1). Intravenous SK was first used following acute MI in 1959; subsequently a number of clinical trials revealed a trend toward reduced mortality rates in patients treated with this agent. In many of the early trials thrombolytic therapy was instituted relatively late—12 to 24 h after the onset of chest pain. Several small studies demonstrated that high-dose (1.5 million U), brief IV administration of SK could be a safe, effective method of restoring coronary blood flow early in evolving infarction. In 1986 a classic randomized trial

![Graph showing mortality rates with different thrombolytic therapies](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21611/ on 06/26/2017)
of IV SK was reported by the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). In that study 11,806 patients were randomized within 12 h of the onset of infarction to receive 1.5 million U of IV SK or no thrombolytic treatment. At 21 days, overall hospital mortality was 10.7 percent in SK-treated patients vs 13.0 percent in controls; one year later the mortality was 17.2 percent vs 19.0 percent in the respective groups. It is a tribute to the GISSI investigators that 10.8 percent of the patients were randomized within 1 h of the onset of chest pain, and the results suggest that survival benefit was greatest in this subgroup. This important study showed conclusively that IV thrombolytic therapy administered to suitable patients in the early hours of evolving MI would confer a survival advantage.

In the Second International Study of Infarct Survival (ISIS-2), 17,187 patients entering 417 hospitals up to 24 h after the onset of symptoms of acute MI suspected from clinical findings alone (ECG changes at the time of entry were not a requirement) were randomly assigned to receive IV SK (1.5 million U), aspirin (160 mg/day for one month), placebo, or both therapies. The five-week vascular mortality was reduced in the SK group (9.2 percent) vs placebo (12.0 percent); in the aspirin group (9.4 percent) vs placebo (11.8 percent), and in patients treated with both therapies (5.2 percent) compared with patients receiving neither therapy (13.2 percent), representing odds reductions of 25 percent, 23 percent, and 42 percent, respectively (Fig 2). Life table estimates of one- and two-year survival also showed reduced mortalities for each of the treatment regimens compared with placebo (Fig 3).

In the Anglo-Scandinavian Study of Early Thrombolysis (ASSET), 13,318 patients admitted to 52 coronary care units with suspected MI were considered for inclusion in a double-blind study comparing rt-PA (100 mg) plus heparin with placebo plus heparin; 2,516 patients were randomly allocated to rt-PA and 2,495 to placebo. At one month the overall case fatality rates were 7.2 percent and 9.8 percent in the respective groups, a relative mortality reduction of 26 percent among patients treated with rt-PA. The European Cooperative Study Group for rt-PA (ECSG) also compared the effects of placebo and IV rt-PA on enzymatic infarct size, LV function, and clinical events in patients with acute MI who also received aspirin and heparin. Although the study was not designed as a mortality study, important reductions in early mortality rates were observed with rt-PA therapy. At 14 days and three months, the death rate among the rt-PA–treated patients was 2.8 percent and 5.1 percent, respectively, compared with 5.7 percent and 7.9 percent in the control group.

Two studies have examined the influence of APSAC on mortality in acute MI and were recently reported. The AIMS Trial Study Group performed a double-blind placebo-controlled trial of APSAC administered within 6 h of the onset of acute MI. An analysis of

![Figure 2. Cumulative vascular mortality rates during days 0 to 35 in the ISIS-2 study. Patients who entered hospitals up to 24 h after the onset of symptoms of acute MI were randomized to IV SK, aspirin (160 mg/day for one month), placebo, or both therapies. The five-week vascular mortality was reduced in patients receiving aspirin, SK, and both therapies, compared with the rate in patients given placebo. (From ISIS 2 Collaborative Group. Lancet 1995; 349:60. Reproduced by permission.)](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21611/)
mortality data was undertaken after 1,004 patients had been followed up for at least 30 days after randomization; 12.2 percent of 502 patients assigned to placebo had died within 30 days, compared with 6.4 percent of 502 patients assigned to APSAC (p = 0.0016). Because of this 47 percent reduction in 30-day mortality (95 percent confidence interval, 21 percent to 65 percent), patient entry into the trial was terminated. The estimated one-year mortality data showed a similar trend with a death rate of 19.4 percent in the placebo group compared with 10.8 percent in the APSAC-treated group. This favorable influence of APSAC on MI mortality was supported by a German multicenter trial which showed that APSAC administered to patients with acute MI of less than 4 h duration was associated with a reduced mortality within the first month (5.6 percent vs 12.6 percent) and less cardiogenic shock after 24 h (3.2 percent vs 9.5 percent) than was heparin therapy.13

Thus, three agents—rt-PA, SK, and APSAC—have been demonstrated to reduce mortality. The results of the important ongoing studies—the GISSI-2, which is comparing the effect of SK and rt-PA, and the ISIS-3, which is comparing the effect of SK, rt-PA, and APSAC on mortality—are awaited with interest. It is evident that a variety of agents will be effective thrombolytics. Variables such as ease of administration, pharmacokinetics, fibrin specificity, effects on blood viscosity, and risk profile need to be assessed to determine which agents are the most suitable for clinical use.

3. How do SK and t-PA compare in their ability to open occluded coronary arteries in clinical trials?

When assessing the results of trials with thrombolytic agents it is important to scrutinize critically the methodology and ascertain whether the end point studied is reperfusion of occluded coronary arteries (with occlusion of the infarct-related coronary artery being documented by angiography prior to therapy) or simply patency of coronary arteries, documented some time after the completion of therapy. (In the latter case, there is no proof of pretreatment occlusion.) Unless there is documentation of coronary artery occlusion at the commencement of therapy, it is impossible to know whether treatment groups are similar and whether documented differences in coronary arterial patency occur because (1) a proportion of the arteries were never occluded, (2) spontaneous endogenous lysis occurred, or (3) the therapy was effective. For these reasons, studies of reperfusion of documented coronary occlusion are the reference standard with which different agents should be compared. However, these studies are more difficult to carry out because pretreatment coronary arteriography delays the institution of therapy.

The first clinical trial that critically examined the differences between IV SK and rt-PA was the Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I.14 This trial was designed to compare the relative thrombolytic activity and side effects of IV t-PA and IV SK in patients with acute MI and angiographically documented, infarct-related total occlusion of the coronary artery. Streptokinase resulted in recanalization of totally occluded coronary arteries 90 min later in 32 percent of patients, whereas rt-PA resulted in recanalization over the same time period in 64 percent of patients. The mean time from onset of pain to drug

![Figure 3: Life-table estimates of 12- and 24-month survival in the ISIS-2 study. Patients who entered hospitals up to 24 h after the onset of symptoms of acute MI were randomized to IV SK, aspirin (160 mg/day for one month), placebo, or both therapies. The median follow-up represented is 15 months and the maximum follow-up is 34 months. The long-term follow suggests that mortality was reduced in patients receiving aspirin, SK, or both therapies compared with patients receiving placebo. (From ISIS 2 Collaborative Group. Lancet 1988; 2:349-60. Reproduced by permission.)](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21611/ on 06/26/2017)
infusion was 4 h, 47 min. It is important to emphasize that every patient entered into the trial had known coronary occlusion before treatment and that the primary end point of the study was recanalization of a totally occluded infarct-related artery (reperfusion) 90 min after the start of drug infusion. Thus, this randomized, double-blind, multicenter trial suggested that rt-PA was almost twice as effective as IV SK in opening occluded infarct-related coronary arteries (Fig 4). Since all patients underwent cardiac catheterization, hematoma formation at the cardiac catheterization access site was common, occurring in 43 percent of the rt-PA-treated group and 47 percent of the SK-treated group. Gastrointestinal tract bleeding was noted in 6 percent and 10 percent of the two groups, respectively. There were no clear-cut instances of fatal or central nervous system hemorrhages in either group.

Several studies have looked at the clinical efficacy of APSAC. To compare the efficacy of APSAC and SK on reperfusion, 240 patients with acute MI (and documented coronary occlusion) were randomly allocated to early treatment with either IV APSAC (30 U in 2 to 4 min) or intracoronary SK (160,000 U over 60 min) in addition to heparin therapy. Reperfusion was evaluated angiographically over 90 min. Rates of reperfusion for the two treatment regimens were 51 percent after IV APSAC and 60 percent after intracoronary SK. The success of IV therapy depended on the time to treatment: 60 percent of APSAC patients treated within 4 h exhibited reperfusion, compared with 33 percent of those treated after 4 h. APSAC given as a rapid injection was generally well tolerated, although the reduction in blood pressure at 2 to 4 min was greater after APSAC than after SK. Bleeding events were more frequent after APSAC but occurred primarily at the site of catheter insertion, and no intracranial bleeding was noted.

In a multicenter study of pro-UK designed to test its effect on reperfusion of completely occluded coronary arteries and to examine its fibrin specificity, 40 patients with acute MI were administered pro-UK IV. Reperfusion of the occluded coronary arteries occurred in 51 percent of the patients. The relative fibrin specificity of pro-UK was confirmed, with fibrinogen levels falling only 10 percent from baseline, while α₂-antiplasmin levels decreased to 39 percent and plasminogen levels decreased to 64 percent of initial values. Fibrinogen degradation products increased 63 percent, and the fibrin-specific D-dimer increased 8.7-fold. Thus, pro-UK is a moderately effective, relatively clot-selective coronary thrombolytic agent.

These studies suggest that IV rt-PA is more effective at reperfusing occluded infarct-related arteries than SK (see Fig 4), and that there is an increased risk of bleeding at vascular puncture sites with all the thrombolytic agents in use. It is important to remember that studies of coronary artery "patency" after lytic therapy will generally report that a greater percentage of patients have "open" arteries during follow-up because only about 80 percent of patients have coronary artery occlusions at the outset. If coronary arteriography is performed later in the natural history of acute MI, there is a greater likelihood of spontaneous clot lysis by endogenous physiologic mechanisms. The clinical role of agents such as APSAC, UK, or pro-UK, used alone or in combination, remains to be defined.

4. What are the current indications for thrombolytic therapy in patients with myocardial ischemia or infarction?

Current indications for thrombolytic therapy include ischemic chest pain of 30 min duration that is unrelieved by nitroglycerin and is associated with ST-segment elevations of at least 0.1 mV in two contiguous leads. Such therapy is usually reserved for patients less than 75 years old who are not at increased risk for bleeding and whose chest pains began less than 4 to 6 h before treatment. Trials are under way to determine whether patients with shorter duration of pain and transient ST-segment changes (ie, unstable angina) or patients with chest pain associated with persistent ST-segment depressions or T-wave inversions (ie, non-Q-wave infarction) will benefit from early thrombolytic therapy. To select suitable candidates at low risk of bleeding from thrombolytic therapy, it is critical that physicians share fully with nurses and paramedical personnel the responsibility for interpreting the history and ECG changes in patients with suspected MI. Obviously, physicians must attempt to diagnose accurately and withhold thrombolytic therapy from pa-

![Figure 4](image-url)
tients with aortic dissection, pericarditis, early repolarization ECG changes, and noncardiac chest discomfort. Emergency room physicians especially must be skilled in making these assessments and initiating thrombolytic therapy.

5. How long after the onset of pain of presumed MI should one consider initiating thrombolytic therapy?

The results of the GISSI-1 study suggested that survival benefit appeared greatest in patients given SK in the early hours after the onset of chest pain. The hypothesis that thrombolytic therapy might confer a survival advantage if administered more than 6 h after the onset of the pain of presumed acute MI was generated by an overview of previous trials and led to the design of the ISIS-2. In this study, 17,187 patients entering hospitals up to 24 h after the onset of symptoms of suspected acute MI (ECG changes at the time of entry were not a requirement) were randomly allocated to treatment with IV SK (1.5 million U), aspirin (160 mg/day for one month), placebo, or both therapies. The five-week reductions in vascular mortality for patients receiving therapy 13 to 24 h after pain onset were 21 percent with SK or aspirin treatment and 38 percent with combined aspirin and SK treatment, compared with reductions for patients receiving therapy from 0 to 4 h of 35 percent for SK, 25 percent for ASA, and 53 percent for SK + ASA. The entry criteria for ISIS-2 allowed a heterogeneous group of patients with presumed ischemic cardiac pain in the previous 24 h to receive active treatment. Although the ISIS-2 Collaborative Group indicated that late thrombolytic therapy was associated with a salutary effect in patients with symptoms (but not necessarily ECG changes) of suspected acute MI, there is no agreement at this time as to whether thrombolytic therapy should be administered between 6 and 24 h after the onset of chest pain in acute MI. This important question is being addressed in several ongoing clinical trials.

6. What are the contraindications to thrombolytic therapy in patients with suspected acute MI?

The major contraindications for thrombolytic therapy are conditions in which the risk of bleeding is increased. In particular, any history of a cerebrovascular accident, intracranial or intraspinal disease, or clouded consciousness is regarded as an absolute contraindication to thrombolytic therapy. A history of a bleeding diathesis, recent acute internal hemorrhage, major surgery or trauma within ten days, traumatic cardiopulmonary resuscitation, a recent arterial or venous puncture in a noncompressible site, or uncontrolled hypertension is also a contraindication for thrombolytic therapy.

7. What are the complications of thrombolytic therapy?

In the TIMI trial (phase I), all patients underwent pretreatment coronary angiography, i.e., arterial punctures and placement of monitoring lines, and were treated with either IV rt-PA or SK. The frequency of major and minor hemorrhagic events (33 percent in the rt-PA group and 31 percent in the SK group) and of associated transfusions (22 percent and 20 percent) were comparable in the two groups. More than 70 percent of the bleeding episodes in each group occurred at catheterization or vascular puncture sites. In the TIMI-IIA study where immediate vs delayed (18 to 48 h after the onset of chest pain) catheterization and PTCA were performed following thrombolytic therapy, immediate cardiac catheterization and/or PTCA was associated with a higher complication rate (including new coronary artery occlusion, arrhythmia, hypotension, pulmonary edema, cardiac arrest, and anaphylaxis) than the same procedure performed at 18 to 48 h (12.4 percent vs 4.0 percent). The risk of transfusion of more than one unit of blood (in patients not requiring coronary artery bypass graft surgery) was 11.3 percent in the immediate catheterization group vs 3.1 percent in the delayed catheterization group. The risk of intracranial hemorrhage was 0.5 percent in both groups. A principal hazard of early angiography was bleeding at the catheterization puncture site.

In the ISIS-2 study, in which patients were given 1.5 million U of SK IV over a one-hour period, the risk of bleeding requiring a transfusion was 0.5 percent, vs 0.2 percent for control patients, and the risk of cerebral hemorrhage was 0.1 percent, vs no cerebral hemorrhage in control patients. All the cerebral hemorrhages occurred on the day of randomization or the following day. Of the seven patients in whom this complication was reported, six died and there was one severe disability. Interestingly, although SK therapy was associated with an excess of early stroke, there were fewer strokes in this patient group later in the hospital course, so that the overall risk of stroke was similar to that of the placebo group. In patients receiving aspirin therapy alone, there was no significant excess of cerebral hemorrhage, and bleeding requiring transfusion was reported with similar frequency in both placebo- and aspirin-treated groups. In patients treated with both SK and aspirin, there was a 0.3 percent excess of "major bleeding" when compared with patients receiving no active treatment. Overall, the combination of SK and aspirin was associated with 0.5 percent fewer strokes than in patients receiving neither therapy. In general, patients in the ISIS-2 study were not heavily invaded with monitoring lines or arterial punctures, and cardiac catheterization was infrequent.
In the TIMI-II trial, intracranial hemorrhage (documented by computed tomography) occurred in 1.9 percent of 582 patients who received 150 mg of rt-PA and in 0.5 percent of 2,952 patients treated with 100 mg of rt-PA.

Taken together, the findings of these major randomized trials emphasize the need to avoid invasive procedures and to exercise meticulous care in the selection and management of patients subjected to thrombolytic therapy.

8. Are the salutary effects of thrombolytic therapy due solely to infarct size reduction?

It had been widely assumed that reductions in mortality associated with thrombolytic therapy of acute MI were directly related to myocardial salvage and lesser degrees of myocardial dysfunction among patients treated with thrombolytic therapy. Indeed, a number of trials in the thrombolytic era have suggested that patients receiving lytic therapy develop less LV dysfunction in the territory of a patent infarct-related artery. However, mortality reduction is not always accompanied by easily detectable improvements in LV function. Although this phenomenon may be due in part to the relatively well-preserved initial LV function in acute MI trial patients, a discordant relationship between improved mortality and improved LV function nevertheless appears to exist. For example, in the Western Washington Trial, patients were treated with placebo or intracoronary SK and had an average of 5 h after the onset of symptoms. The majority of actively treated patients had successful reperfusion of the infarct-related artery, but this was not associated with improvement in global or regional LV function or infarct size measured two months after the acute event. Interestingly, at the time of these measurements, patients who had received thrombolytic therapy had a lower mortality than those who did not. Patency of the infarct-related coronary artery proved to be an important independent predictor of survival. In patients with Q-wave MI who have spontaneous reperfusion of the infarct-related artery (as a result of normal, intrinsic thrombolytic mechanisms that would not be responsible for very early reperfusion and, therefore, for tissue salvage) and who have never received thrombolytic therapy, LV function is more likely to be preserved than in patients in whom the infarct-related artery remains occluded. Clinical observations also suggest that patients treated with thrombolytic therapy within 3 or 4 h of acute MI and whose infarct-related artery remains occluded 90 min later have a relatively high subsequent mortality. It is possible that an open infarct-related artery may have a beneficial effect in addition to and unrelated to salvage of myocardium which reduces remodeling of infarcted myocardium and total ventricular dilatation. It is also possible that an open infarct-related artery may contribute to electrical stability and the development of collateral vessels.

Thus, it appears that an open infarct-related artery confers an advantage to patients with acute MI that is independent of any measured changes in LV function. The reasons for this putative beneficial effect are the subject of ongoing studies.

9. What is the role of percutaneous transluminal coronary angioplasty (PTCA) in patients with acute MI?

Because a significant underlying atherosclerotic plaque appears to be the nidus for thrombus formation in a preponderant fraction of patients with Q-wave MI, the problem of maintaining coronary flow following thrombolysis has generated intense interest. With the proliferation of laboratories in which coronary angioplasty is performed, the role of primary PTCA compared with thrombolytic therapy in patients with acute MI has been questioned. In one study such patients were prospectively randomized to receive either SK (n = 27) or PTCA (n = 29). Remarkably, the time to recanalization was 4.1 vs 4.8 h, and the success rate—85 percent and 83 percent—was similar in both groups. However, PTCA was more effective in reducing residual stenosis and improving ventricular function. The same investigators have also reported that the incidence of postinfarct angina and reinfarction was reduced in patients treated with t-PA followed by PTCA (two of 15), compared with the incidence in patients treated with t-PA alone (seven of 13).

Because of the expertise, expense, and complex logistics required to perform PTCA rapidly in patients with acute MI, and because of uncertainty as to whether immediate or deferred angioplasty would be beneficial in patients with evolving acute MI, the TIMI investigators designed protocols to assess the role of PTCA in patients who had been treated with IV rt-PA, heparin, and aspirin early in the course of acute MI.

In the TIMI-IIIA study, all patients were treated with IV rt-PA within 4 h of the onset of acute MI. PTCA of the infarct-related artery was attempted in 72 percent of the 195 patients assigned to immediate PTCA (within 2 h of the start of the rt-PA infusion) and adequate dilation was achieved in 84 percent. PTCA was attempted in 55 percent of the 194 patients assigned to deferred PTCA (18 to 48 h after the onset of acute MI), and in 90 percent of the attempts, improvement occurred.

No differences were observed between the two PTCA groups for LV ejection fraction measured before hospital discharge (50 percent and 49 percent, respectively). However, immediate catheterization/PTCA was associated with an increased frequency of bleeding.
and the need for coronary artery bypass surgery. Thus, immediate performance of coronary arteriography and PTCA provided no advantage over delaying these procedures for 18 to 48 h and in fact was associated with increased morbid events and the need for surgical revascularization.

These findings are consistent with those of two other major studies. In the Thrombolysis and Angioplasty in Myocardial Infarction study (TAMI), all patients underwent coronary angiography immediately after receiving rt-PA, and those with an open infarct-related artery considered suitable for PTCA were randomly assigned to immediate PTCA or elective PTCA. Despite the differences in design, the results in the immediate PTCA group were similar to those observed in the immediate PTCA group in the TIMI-IIA study. A European study compared an invasive strategy (angiography and PTCA) with a noninvasive strategy following thrombolysis with rt-PA. PTCA was attempted in 93 percent of 180 patients assigned to the invasive strategy; the mortality in this group was significantly higher than in patients treated noninvasively (7 percent vs 3 percent). Neither of these studies showed a difference in ventricular function between immediate and delayed PTCA, but in both studies patients who underwent immediate PTCA were more likely to require emergency coronary artery bypass graft surgery and/or to experience reocclusion or recurrent ischemic events than patients who underwent the procedures later.

A further comparison of invasive and conservative strategies after treatment with IV t-PA in acute MI was reported by the TIMI-II investigators. In this study, 3,262 patients received rt-PA within 4 h of the onset of chest pain thought to be caused by acute MI and were randomly assigned to either routine coronary arteriography and PTCA (when the anatomy was suitable), performed 18 to 48 h after trial entry, or to no angiography or PTCA unless symptoms or evidence of uncontrolled spontaneous or provokable ischemia developed. The primary end point of the study was survival free of recurrent infarction at six weeks. In this study, 1,636 patients were assigned to the invasive strategy and 1,626 patients to conservative treatment. Reinfarction or death within 42 days, the primary end point, occurred in 10.9 percent of the group assigned to the invasive strategy and in 9.7 percent (no significant difference) of those assigned to the conservative strategy (Fig 5). There were no significant differences between the two groups in the ejection fraction at rest or during exercise, either at hospital discharge or six weeks after randomization. Intracranial hemorrhage occurred in 1.9 percent of the 582 patients who received 150 mg of rt-PA and in 0.5 percent of the 2,952 patients who received 100 mg of rt-PA.

Thus, in patients with acute MI who were treated with rt-PA and heparin followed by aspirin, an invasive strategy of coronary arteriography 18 to 48 h after the onset of symptoms, followed by prophylactic PTCA, offered no advantage in terms of reduction in mortality or reinfarction compared with a more conservative strategy in which these procedures were undertaken only in patients with recurrent ischemia. This latter strategy was also less complex and less costly.

![Figure 5](image-url)
10. Do any clinical signs predict coronary reperfusion after thrombolytic therapy?

Successful coronary reperfusion can be manifested clinically by sudden relief of chest pain, resolution of ST-segment elevations on the ECG, or arrhythmias (usually accelerated idioventricular rhythm or frequent ventricular premature beats). A rapid early peak of MB-CK release may also be detected. However, these signs are not accurate predictors of the perfusion status of the coronary arteries after lytic therapy. One study has suggested that abrupt ECG repolarization changes are strongly predictive of an open infarct-related artery a few days later. Based on angiographic indices of patency of occluded coronary arteries, neither resolution of pain nor resolution of ST-segment changes on serial ECGs accurately predicts perfusion status.

11. What is the role of antithrombotic therapy after thrombolysis?

The incidence of rethrombosis after successful clot lysis may be as high as 15 percent to 20 percent, and many centers use heparin and/or aspirin following thrombolytic therapy to prevent reocclusion. Of interest, neither agent was used routinely in the GISSI trial, in which IV SK administered in the early hours of evolving MI conferred a survival advantage. In ISIS-2, aspirin alone (160 mg/day) or in combination with SK reduced five-week vascular mortality in patients with suspected MI. Although the influence of heparin and aspirin on the incidence of coronary reocclusion after thrombolytic therapy is not established, both agents are commonly used.

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