Thrombolytic Therapy in Acute Myocardial Infarction

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The salvage of myocardium in the setting of acute myocardial infarction has long been a goal of physicians involved in the care of patients with coronary artery disease. Understanding the role of thrombosis in the pathogenesis of acute myocardial infarction has led the way to an entirely new approach to the treatment of this entity. Thrombolytic therapy has now become a widely used form of treatment with encouraging results. Both intravenous and intracoronary administration of thrombolytic agents have been shown to promote recanalization of acutely occluded coronary arteries. Results of studies using the clot-specific agent, tissue plasminogen activator, intravenously have been most encouraging; successful reperfusion has been obtained in approximately 70% of patients treated. In addition, a recent large-scale trial has shown a reduction in morbidity and mortality with the early use of thrombolytic agents.

Ongoing trials should help delineate the precise role and timing of these agents as the initial form of therapy for acute myocardial infarction. Other issues that remain unresolved are the frequency of restenosis and the role of percutaneous transluminal coronary angioplasty in addition to thrombolytic therapy in the treatment of acute myocardial infarction.

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Coronary heart disease is the leading cause of death in the United States; over one-half million individuals die from it each year. Between 5 and 6 million Americans have chronic, symptomatic coronary artery disease. In 1983, over 680,000 individuals were hospitalized with myocardial infarction [1].

The medical management of myocardial infarction has evolved gradually over the past 30 years, from a strategy of permitting the heart to heal by putting the patient and the heart to rest to increasingly more active monitoring in coronary care units with aggressive treatment of identified abnormalities. It is uncommon for a patient with myocardial infarction to die of a primary rhythm disturbance in the acute phases of infarction [2]. Today, extensive myocardial injury is the most common cause of death and morbidity among patients hospitalized with acute myocardial infarction (AMI) [1]. Massive myocardial ischemia produces pump failure and serious ventricular arrhythmias [3]. Thus, short-term survival is intimately related to the size of myocardial infarction; loss of more than 40% of the left ventricular (LV) myocardium almost always results in death. The risk of death appears to decrease with decreasing infarct size.

Methods to reduce the extent and severity of myocardial damage have therefore been sought. Myocardial damage results from the disparity between oxygen demand and delivery in ischemic tissue. To limit infarct size, one can attempt to reduce myocardial oxygen demands or improve myocardial oxygen supply. Attempts to limit infarct size and improve early survival in AMI by pharmacologically decreasing myocardial oxygen demands have been disappointing [4–6]. Beta blockers have been shown to improve long-term survival when used prophylactically [7,8], and recent results from the MIAMI trial [9,10] have shown that, in a subgroup of patients with a high sympathetic activity, early administration of intravenous metoprolol tartrate had a significant effect on infarct size. Conclusive

findings documenting reduction of infarct size in humans are sporadic and inconsistent.

Intraaortic balloon pump counterpulsation (IABP) has also been used to decrease oxygen demands and improve myocardial perfusion. IABP has been shown to preserve myocardium in experimental animals when used immediately following coronary occlusion [11,12]. Reports of IABP in patients with anterior wall myocardial infarction without shock have shown prompt resolution of ST segment changes and preservation of R waves and LV function when instituted within the first six hours [13]. Despite encouraging case reports, IABP is an invasive technique, not without complications, and impractical for general use in AMI.

Reperfusion by early coronary artery bypass grafting (CABG) in AMI has been attempted. Myocardial salvage has been demonstrated with a significant improvement in LV function after CABG in AMI [14,15]. One retrospective study has shown both an in-hospital and long-term reduction in mortality in patients who underwent surgical revascularization within six hours of AMI [16]. Although acute revascularization by surgery may be efficacious, acute bypass grafting is impractical for widespread use, and other forms of reperfusing jeopardized myocardium are needed.

Role of Thrombosis in AMI

The role of coronary thrombosis in the pathogenesis of myocardial infarction has long been argued. Herrick [17] declared almost 75 years ago that the proper diagnosis for a patient with recent onset of acute prolonged chest pain was "coronary thrombosis" or "sudden obstruction of the coronary arteries." The theory of thrombosis as a cause of AMI was challenged in the 1950s when Branwood and Montgomery [18] suggested that thrombosis was a consequence of AMI rather than a cause. This was the prevailing thought in 1974 when Roberts [19] concluded that thrombosis was a result of reduced flow through an occluded vessel, and not the cause of AMI. Support for this theory came from autopsy studies showing patients who were dying from AMI who had severe coronary atherosclerosis without evidence of thrombosis [20]. Other evidence used to refute the role of thrombosis in AMI included (1) the increased incidence of thrombosis in patients with longer duration of symptoms before death from AMI, (2) the low incidence of coronary thrombosis in sudden death, (3) the absence of thrombosis in patients with nontransmural AMI, and (4) the high incidence of thrombosis in patients dying of cardiogenic shock [19,21]. This evidence was gained primarily from autopsy studies, and the role of thrombosis in the majority of patients who survived AMI remained unclear.

It became apparent that coronary arteriography in the early period of AMI would provide crucial information for defining the role of thrombosis in AMI. In 1979 Blanke and colleagues [22] reported on the changes in coronary morphology during the early stages of AMI. They described 13 of 18 patients who had total occlusion of the infarct-related coronary artery early in the AMI period. When these patients were studied at 55 ± 46 days after infarction, distal flow in the infarct-related artery was seen in 38% of patients whose artery had previously been totally occluded. All of these patients had residual lesions, and it was postulated that thrombosis superimposed on high-grade atherosclerotic vessels was the mechanism responsible for AMI.

Dewood and his colleagues [23] added evidence to this hypothesis when they reported on 517 patients with AMI who underwent coronary arteriography within 24 hours of the onset of symptoms. Of patients who were studied within the first 4 hours, 87% evidenced total coronary occlusion from coronary thrombi. The frequency of total occlusion decreased to 64% when patients were studied between 12 and 24 hours after the onset of symptoms. Because the incidence of coronary thrombosis decreased with time after the onset of symptoms it was unlikely that thrombosis was a result of AMI; rather, it appeared thrombosis was the cause. Current theory suggests that coronary artery thrombosis is critical in the pathogenesis of AMI and is the result of multiple factors including intimal defects from the rupture of an atherosclerotic plaque, platelet activation, and spasm [24–28].

Fibrinolysis

The role of thrombosis in AMI having been demonstrated, attention was directed at perfecting pharmacological agents that could be used for thrombus dissolution. Thrombolytic therapy involves the dissolving of thrombi or emboli by digestion of their supporting fibrin framework. Thrombolytic drugs have been used in treating pulmonary emboli [29], deep venous thrombosis [30], and arterial emboli [31]. Each of these indications has a well-established yet somewhat limited application. The use of thrombolytic therapy for acute myocardial infarction has attained widespread application in the past six years.

Thrombolytic therapy involves the enhancement

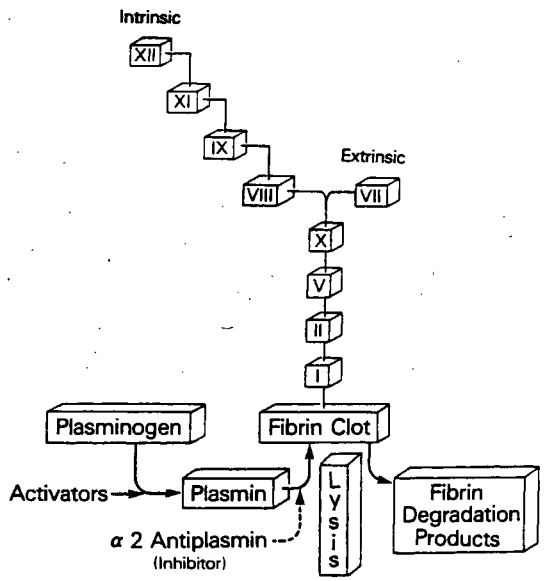

Fig 1. Normal fibrinolytic system for breakdown of thrombus.

of the body's own fibrinolytic system (Fig 1). In brief, the inactive proenzyme plasminogen is converted to the active enzyme plasmin, which lyses fresh fibrin clots, with generation of fibrin degradation products. Plasminogen is present in human plasma at a fairly constant concentration; however, because it is an acute phase reactant, levels will increase in certain conditions, such as surgery, trauma, infections, and AMIs [32]. Plasminogen is synthesized rapidly, and its concentration usually returns to normal within 24 hours after thrombolytic therapy is discontinued.

Plasmin, the active enzyme, is a nonspecific proteolytic enzyme that can digest fibrin, fibrinogen, prothrombin, and factors V and VIII. It is specific for dissolving fibrin clots within a thrombus. In the circulation, the large excess of plasmin inhibitor (alpha 2 antiplasmin) neutralizes the action of plasmin on other circulating proteins. Alpha 2 antiplasmin is also incorporated into the thrombi, providing clot stability. When plasmin levels in the circulation exceed that of the inhibitor, there is an increased risk of bleeding because of the depletion of clotting factors previously mentioned. Should hemorrhage occur during thrombolytic drug administration, fresh frozen plasma (4 units) or cryoprecipitate (4 units) should be administered intravenously with attention to the patient's volume status. Fibrinogen levels should be measured on an emergency basis.

Thrombolytic Agents

The three thrombolytic agents used in AMI are streptokinase, urokinase, and tissue plasminogen activator (t-PA) (Table 1). Other more recent agents include acylated-plasminogen-streptokinase activator complex, pro-urokinase and fibrin specific monoclonal antibodies. Thrombolytic agents are referred to as clot specific (t-PA) or nonclot specific (streptokinase, urokinase). Clot specificity refers to whether the drug activates only plasminogen at the site of a clot (specific) or whether it also activates circulating, nonclot bound plasminogen (nonspecific).

Streptokinase was discovered in 1933 by Tillett and Garner [33] when they found that a filtrate of beta hemolytic streptococci lysed a human plasma clot. Streptokinase indirectly activates plasminogen to plasmin by a proactivator-activator mechanism (Fig 2). When streptokinase is administered, it combines with plasminogen to form an activator complex. The streptokinase-plasminogen complex then activates the fibrinolytic mechanism by converting uncomplexed plasminogen to plasmin.

Table 1. Thrombolytic Agents

Characteristic	Streptokinase	Urokinase	Tissue Plasminogen Activator
Source	Bacterial culture	Renal cell culture	Recombinant DNA
Human-derived protein	No	Yes	Yes
Mode of plasminogen activation	Indirect	Direct	Direct, requires fibrin as a cofactor
Clot specific	No	No	Yes
Systemic lysis	Yes	Yes	No
Fibrinogen concentration	Decreased	Decreased	No change
Allergic reaction	Yes	No	None reported
Half-life	10–18 minutes	10–15 minutes	8–9 minutes
Cost	$42 per 250,000 U (usual dose, 1.5 mU)	$154 per 250,000 U (usual dose, 4.5 mU)	Unknown

DNA = deoxyribonucleic acid.

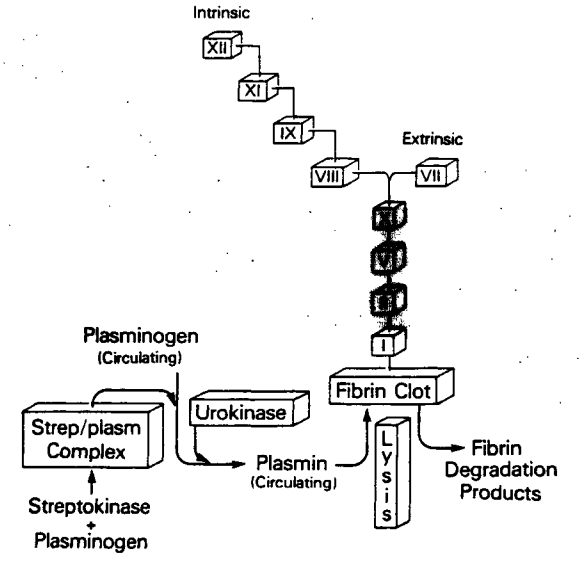

Fig 2. Site of action of streptokinase and urokinase.

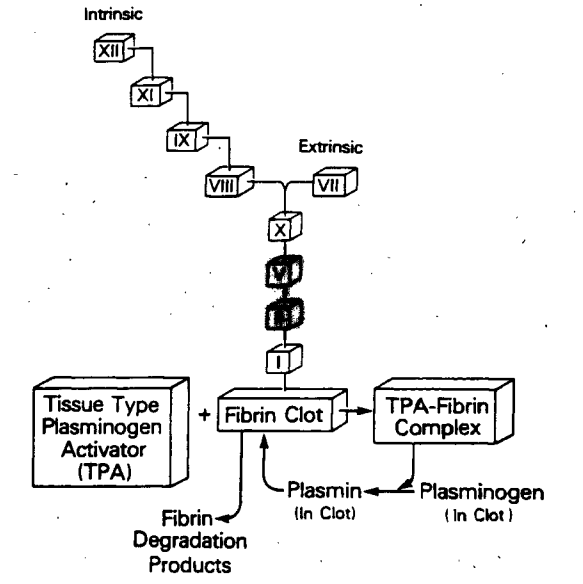

Fig 3. Site of action of tissue-type plasminogen activator.

Streptokinase is antigenic because it is a foreign protein, and most patients have circulatory anti-streptokinase antibodies with levels that depend on the nature of previous streptococcal infections. When streptokinase therapy is started, antibody-antigen complexes may be formed, which may affect the efficacy of treatment.

In addition to the risk of bleeding, adverse effects of streptokinase include temperature elevation, mild allergic reactions (urticaria, flushing), occasional nausea, vomiting, headaches, and hypotension. Anaphylaxis is rare. Streptokinase may be stored at room temperature, is relatively inexpensive, and has been the most extensively evaluated agent to date.

Urokinase was isolated from human urine by Macfarlane and Pillings [34] in 1946 and named in 1952 [35]. A product of human cells, urokinase is not antigenic to humans and does not react with neutralizing antibodies as does streptokinase. Urokinase has the advantage of having a short half-life. Urokinase is a direct activator, and is capable of initiating fibrinolysis without forming an activator complex (see Fig 2). Urokinase is difficult to produce in large quantities and thus is very expensive. Urokinase, like streptokinase, produces large amounts of fibrin and fibrinogen degradation products, which act as circulatory anticoagulants.

Several naturally occurring clot-selective plasminogen activators that do not induce systemic fibrinolysis (a systemic lytic state) are now being investigated. Tissue-type plasminogen activator is a naturally occurring serine protease found in endothelial cells that has a much higher affinity for fibrin than for circulating plasminogen. Only after tissue-type plasminogen activator is bound to fibrin does local conversion of plasminogen to plasmin and local clot dissolution take place (Fig 3).

Tissue-type plasminogen activator was originally isolated and purified from a human melanoma cell line [36,37]. Recently, biologically active tissue-type plasminogen activator has been cloned and expressed from the deoxyribonucleic acid (DNA) activator gene in *Escherichia coli* [38]. It has biologic properties similar to that obtained from the melanoma cell line. The successful cloning and expression of the human t-PA gene has facilitated synthesis of sufficient quantities of recombinant tissue type plasminogen activator (rt-PA) for more widespread clinical investigation. Therapeutic levels of t-PA can be achieved consistently with short-term infusions of appropriately selected doses without inducing a systemic lytic state, which predisposes to bleeding [39]. In an animal model [40], rt-PA permitted rapid and predictable coronary thrombolysis without systemic fibrinolysis when the drug was given intravenously. It appears that rt-PA results in a progressive fibrinolysis and does not induce spontaneous thrombolysis or movement, dislodgement, or embolization of clot.

Pro-urokinase is a precursor of urokinase, first identified in tissue culture media [41] and later purified from several sources [42]. Although the mechanism of action of pro-urokinase remains to be established, it appears that it can induce more clot-selective thrombolysis in animal preparations than urokinase [43] and does not induce a systemic fibrinolytic state in animals [44]. Clinical trials with pro-urokinase are planned to commence in early 1986.

An acylated streptokinase-plasminogen complex has been developed that demonstrates fibrinolytic efficacy with reduced systemic effect on coagulation variables in animal experiments [45,46]. The inactivated human plasminogen-streptokinase complex is activated by deacylation after binding to fibrin, thus causing less systemic fibrinolysis. These agents are protected from inactivation by circulating alpha 2 antiplasmin but still bind to fibrin, whereupon the acyl group is removed nonenzymatically. This produces localized fibrin-bound plasmin. Deacylation tends to be slow, and the onset of thrombolysis may be delayed. Preliminary human trials are encouraging [47].

Timing of Reperfusion and Myocardial Salvage

Although effective thrombolytic agents were available, the critical question regarding the timing of reperfusion needed to be examined. Reimer and Jennings' [48] canine studies demonstrated that timely reperfusion of an occluded artery can reduce infarct size. With increasing duration of occlusion, myocyte death propagates from the subendocardium to the subepicardium. Reperfusion carried out 40 minutes after coronary ligation in dogs will salvage 60 to 70% of the myocardium at risk, whereas reperfusion carried out three hours after occlusion will reduce infarct size by only 10 to 20% [48–50]. Other studies have shown myocardial salvage at periods up to six hours after experimental coronary occlusion [51,52]. In humans, the relationship of duration of occlusion and myocardial necrosis is less well defined. Unlike the canine model, well-developed collaterals to the infarct zone exist in some patients and may provide some perfusion of the myocardium at risk despite acute coronary occlusion [53]. Given the experimental evidence of the potential reversibility of ischemic injury with early reperfusion, clinical trials of thrombolytic therapy in AMI were attempted.

Intracoronary Streptokinase

Thrombolytic therapy has been used in an attempt to achieve reperfusion in the setting of AMI for many years. The initial use of thrombolytic therapy involved intracoronary administration of streptokinase to localize the thrombolytic agent to the site of thrombosis. Reugsegger and associates [54] as early as 1959 were successful in lysing thrombi in dogs by intracoronary administration of thrombolysin. In 1976 Chazov and co-workers [55] reported the first successful use of intracoronary streptokinase in patients with AMI. To our knowledge, the first clinical trial demonstrating successful recanalization of thrombosed coronary arteries in a large number of patients was reported by Rentrop and colleagues [56] in 1979. This led the way for numerous other clinical investigations using intracoronary streptokinase (ICSK) in AMI.

A large number of randomized and nonrandomized trials of ICSK have been reported. In general, patients who are selected to receive thrombolytic therapy are seen with persistent ST-segment elevation despite sublingual nitroglycerin. Persistent ST elevation, coupled with typical chest pain, has proved to be a reliable predictor of AMI [16]. Patients with atypical symptoms and nonspecific ST changes are excluded, as are those with contraindications to thrombolytic therapy. These include recent prolonged CPR, recent cerebral vascular accident, recent surgery, or active peptic ulcer disease.

Patients are generally admitted through the emergency ward or transferred from a facility without cardiac catheterization capabilities. Routine AMI care, including attempts at pain control and prophylactic lidocaine, are begun. Patients are frequently given parenteral steroids and antihistamines in an attempt to minimize allergic reactions. Immediate cardiac catheterization is performed including coronary cineangiography and left ventriculography. The infarct-related artery is visualized, and intravenous nitroglycerin is infused directly into the affected coronary artery in an attempt to rule out reversible spasm as the cause of AMI. If reperfusion is established, no further thrombolytic therapy is attempted. In most patients vasodilators will not restore antegrade flow, and streptokinase is then infused into the coronary artery. Although doses vary, a bolus of 10,000 to 30,000 units is used, followed by a continuous infusion of 2,000 to 5,000 units per minute. The infusion is continued until antegrade flow is observed or a total dose of 150,000 to 500,000 units is achieved. The infarct-related artery is periodically reopacified (approximately every 15 minutes) via selective coronary injection. In addition to angiographic evidence of reperfusion, the new onset of arrhythmias, rapid resolution of ST-segment elevations, and relief of chest pain often accompany successful thrombolysis [56–62]. A rapid early peak of MB (muscle/brain hybrid) creatine kinase in 8 to 15 hours, compared with 18 to 24 hours in conventionally treated patients, may also be observed with recanalization [60]. When clinical signs of reperfusion are noted, angiography is repeated to document restoration of antegrade flow. Successful thrombolysis usually takes approximately 30 minutes; the average dose is 65,000 units [63,64]. The rate of early rethrombosis may be extremely high [59]; therefore, ICSK infusion is continued for 60 minutes. Most medical centers then place patients

on full-dose intravenous heparin therapy and continue routine AMI care in the coronary care unit.

Efficacy of Intracoronary Streptokinase

Randomized trials have demonstrated ICSK to be significantly more effective than placebo in restoring coronary artery flow in AMI [65]. ICSK has been shown to produce thrombolysis in approximately 75% of cases of completely obstructed coronary arteries. Table 2 shows the recanalization rates in nine studies using ICSK [58,59,65–71].

Most trials of ICSK have used a protocol that treats patients within four hours after the onset of symptoms [66–68]. This is based on experimental and clinical studies that suggest four hours is the maximum time for myocardial salvage in AMI [72,73]. Other studies failed to show a relationship between initiation of thrombolytic therapy and successful reperfusion. Smalling and associates [74] reported similar rates of reperfusion in patients treated at 3 hours (70%), 6 to 12 hours (73%), and 12 to 18 hours (69%) after the onset of symptoms.

Effect of Intracoronary Streptokinase on Myocardial Salvage and Left Ventricular Function

Although ICSK has repeatedly been shown to be highly successful in establishing antegrade flow in an obstructed coronary artery, the effect of this reperfusion on the salvage of myocardium remains unclear. Definitive quantitative measurements of infarct size have been difficult to obtain. Blanke and co-workers [75] using QRS mapping protocols showed that the sum of the R-wave amplitudes in the precordial leads (V1–V6) was significantly higher in ICSK-treated patients with AMI when compared with controls. Studies using thallium 201 perfusion-imaging techniques demonstrated successful reperfusion of ischemic myocardium after ICSK therapy [76,77].

The effect of ICSK on LV function has been variable. Anderson and associates [66], in a randomized trial of ICSK, showed that ventricular function, as assessed by ejection fraction (EF) and echocardiographic wall motion index, was significantly better in patients treated with streptokinase than in controls. In contrast, Khaja and co-workers [65], and Lieboff and associates [68] in randomized trials failed to show improvement in global EF in patients treated with streptokinase, although both these trials had a relatively low rate of successful reperfusion. The Western Washington trial [69] also failed to demonstrate improvement in LV function despite a short-term reduction in mortality in patients treated with streptokinase.

Despite numerous trials, there is no consensus regarding the effect of ICSK on LV function (Table 3). Difficulty in showing improved LV function may be a result of a number of factors. Unpredictable changes in LVEF have been shown to occur within the first 24 hours after an AMI [77]. These spontaneous changes in LV function in the peri-infarct period will tend to confound results regarding the effect of therapy. Because it may remain normal in AMI, global ejection fraction may be an inappropriate index of LV function because of compensatory hyperkinesis in noninfarcted regions of myocardium. Regional wall motion analysis may, therefore, better reflect the effect of therapy on myocardial salvage. A computer analysis of segmental wall mo-

Table 2. Dosage and Recanalization Rates with Intracoronary Streptokinase

Study	Time from Symptom Onset to Treatment (hrs)	Streptokinase Dose		Recanalization Rate (%)
		Infusion (U)	Total Dose (U)	
Mathey et al [58]	< 3.0	2,000/min	Not given	73
Ganz et al [59]	< 3.0	2–4,000/min	200–400,000	**94**
Khaja et al [65]	5.4 ± 1.9	15,000/2 min (bolus)	250,000	**60**
Anderson et al [66]	4.0 ± 0.75	5,000/min	5,000 until reperfusion then 3,000 for 30–60 min	75
Serruys et al [67]	< 4.0	4,000/min	250,000	**83**
Lieboff et al [68]	< 4.0	2–4,000/min	240,000	**68**
Kennedy et al [69]	4.6 ± 3	4,000/min	286,000 ± 77,800	**68**
Rentrop et al [70]	< 6.1 ± 3.0	2,000/min	180–240,000	74
Rentrop et al [71]	Not given	1–2,000/min	128,000 ± 36,000 (maximum dose, 220,000)	85

Table 3. Effect of Intracoronary Streptokinase (ICSK) on Left Ventricular Ejection Fraction (EF)

Study	No. of Patients		Time from Symptom to Infusion	Rate Recanalization (%)	Change (%) in EF	
	ICSK	Control			ICSK	Control
Khaja et al [65]	20	20	5.40 ± 1.90	60	3	2
Anderson et al [66]	24	26	4.00 ± 0.75	75	3.9 ± 4.6	−3.0 ± 8.4[a]
Lieboff et al [68]	20	17	<4.03	68	−2.8	−0.8
Kennedy et al [69]	134	116	4.6 ± 3	68	1.0	0
Rentrop et al [70]	23	24	6.0 ± 3	74	2.1 ± 1.1	−1.4 ±9.5

[a] $p < .001$.

tion has demonstrated that early successful reperfusion by ICSK improves regional contractility of jeopardized myocardial regions [78].

Early initiation of therapy may be the key to reduction in infarct size. Davies and co-workers [79] recently showed that ICSK therapy begun in a selected subset of patients within two hours of onset of symptoms may prevent infarction in over 50% of cases. Sheehan and associates [80] also showed significant myocardial salvage and improved regional wall motion in patients with successful reperfusion treated within two hours after onset of symptoms.

Mortality

The results of randomized trials of ICSK have been equivocal regarding the effect of thrombolytic treatment on mortality. Three of the trials [65,66,68], each involving between 40 and 50 patients, could not demonstrate a significant difference in survival between successfully reperfused patients and controls. The Western Washington randomized trial [69] involved 250 patients and found a three-fold reduction in mortality at 90 days in the ICSK-treated group. At one year follow-up, [81] there was a significant improvement in mortality when adjustments were made for EF and infarct location. Patients who had successful reperfusion had a mortality of 2.5% at one year compared with a mortality of 16.6% in either patients with partial reperfusion or controls.

When the data from nine randomized trials of ICSK were pooled and analyzed [82], a 20% reduction in mortalilty was obtained, although this was not believed to be statistically significant given the small sample size and relatively low incidence of mortality in AMI. In a recent report, Simoons and colleagues [83], in their trial involving 533 patients, found a significant reduction in mortality in patients treated with thrombolytic therapy within four hours of onset of symptoms. Mortality was reduced at both 28 days and one-year follow-up.

Failure to demonstrate conclusively a difference in mortality in ICSK trials may be due to inadequate sample size, because less than 1,500 patients have been randomized in the previously discussed trials. Future trials involving several thousand patients will be needed to estimate reliably the effect of ICSK on mortality.

It is likely that certain subgroups of patients with AMI will benefit preferentially from thrombolytic therapy. Infarct location has been shown to effect the outcome from thrombolytic intervention. Smalling and colleagues [84] showed a significantly greater reduction in mortality in patients with anterior wall AMI treated with ICSK compared with patients with inferior wall AMI. Ramos and coworkers [85] also failed to show a significant effect of ICSK on survival of patients with inferior MI within the first 15 months, even when angioplasty or revascularization surgery was added to therapy.

Complications of ICSK

Despite localization of streptokinase to the site of thrombosis with ICSK, activation of the fibrolytic system is achieved, resulting in a systemic lytic state [86]. Hemorrhagic complications are, therefore, the most common untoward consequence of thrombolytic therapy. Hemorrhagic infarction confined to myocellular necrosis has been described in patients who died after treatment with ICSK [87], although it is unlikely that there is an adverse effect on outcome of infarction in streptokinase-treated survivors of AMI. Hemorrhagic complications are generally confined to local hematoma formation at the site of arterial and venipuncture sites [88]. Isolated case reports of gastrointestinal, retroperitoneal, mediastinal [89], and intracranial [90] hemorrhages have been described. It has been estimated that bleeding complications requiring transfusion occur in 1.3% of ICSK-treated patients [91]. Proper patient selection can help prevent more serious hemorrhagic complications.

Reperfusion-associated arrhythmias are a com-

mon complication of thrombolytic therapy, occurring in up to 80% of patients treated with ICSK [92]. Frequent premature ventricular contractions and accelerated idioventricular rhythms are the most common arrhythmias associated with successful reperfusion [92]. Arrhythmias are often a marker of recanalization and rarely cause morbidity or mortality. Case reports of fatal cardiogenic shock secondary to coronary artery embolization of clot dislodged during catheter manipulation have been described [93], although this complication appears to be extremely rare.

Intravenous Streptokinase

The use of an intravenously administered thrombolytic agent has many potential advantages over intracoronary thrombolysis. Intravenous therapy requires minimally trained personnel or minimally specialized facilities. Therapy can be carried out in hospitals without cardiac catheterization laboratories and can be initiated immediately after the onset of symptoms. The additional cost of intravenous therapy over conventional treatment is minimal.

Numerous randomized trials of intravenous streptokinase (IVSK) in AMI have been reported since 1960. Unfortunately, many of these trials have had faulty protocol design, improper patient selection, and inappropriate data collection [88]. Yusef and colleagues [82] recently reviewed the design structure of 20 randomized trials of IVSK [94–115]. Most of these studies have used a low-dose protocol with a loading dose of 0.25 million units, followed by a prolonged infusion over 12 to 24 hours [99–109,112,113,115]. The time between onset of symptoms and treatment has been variable; therapy was usually initiated less than six hours after onset of symptoms; in three trials [94–97], however, patients were treated more than 24 hours after onset of symptoms. The recanalization rates in most of these trials were not systematically studied, making interpretation difficult.

More recent trials have used a high-dose short-term infusion of IVSK. When successful thrombolysis is determined using indirect parameters, without baseline angiography, recanalization rates of 73 to 96% have been reported [86,110,115–118]. Studies using baseline angiography (Table 4) show a range of 10 to 62% for successful recanalization with high-dose IVSK (86,119–122].

A recent report from the Thrombolysis in Myocardial Infarction (TIMI) trial [123] showed a reperfusion rate of 41% when high-dose (1.5 million units) streptokinase was given to patients with AMI and total coronary occlusion. Therapy was initiated an average of 4.5 hours after the onset of symptoms.

Table 4. Recanalization Rates with Intravenous Streptokinase

Study	Streptokinase Dose (U)	Recanalization Rate (%)
Schroeder et al [86]	500,000	52
Rogers et al [119]	1 million	44
Saltups et al [120]	500,000	30
Alderman et al [121]	725,000	62
Spann et al [122]	1.5 million	48
Thrombolysis in Myocardial Infarction study group [123]	1.5 million	41

Sustained reperfusion was seen in only 30% of patients. Spann and co-workers [122] also noted that their initial rate of successful reperfusion was 49%, but sustained recanalization was seen in only 35% of patients.

The discrepancy between rates of reperfusion using pretreatment angiography and delayed angiographic assessment may be due to the fact that early angiography may underestimate recanalization rates. This would be the case if thrombolysis were to occur after the early period, when angiography is being performed. The converse is true: In the absence of baseline angiography, recanalization rates may be overestimated because patients with incomplete occlusion, estimated to be as many as 33% [70], will erroneously appear to have recanalized when noninvasive tests are used. In contrast, patients with incomplete occlusion are usually excluded from most acute angiography studies. There is an inherent delay in initiating therapy when pretreatment angiography is performed. It is possible that early infusion of IVSK may achieve higher rates of successful thrombolysis secondary to more rapid initiation of therapy. In support of this theory, Simoons and associates [83] performed acute angiography in patients treated with IVSK less than four hours after the onset of symptoms. They reported that the infarct-related coronary artery was occluded in 59% of patients treated with early IVSK compared with 82% of nontreated patients. Koren and colleagues [124] recently reported a study involving early treatment of IVSK via mobile care units. Treatment was begun an average of 1.7 ± 0.8 hours from the onset of symptoms. They reported that 81% of patients had patency of their infarct-related vessel when evaluated by angiography four to nine days after admission.

The definition of reperfusion also varied between studies. This variation in the criteria used for recanalization and differences in sample size may also contribute to the wide variation in success rates for reperfusion and patient outcome in the

various studies. The TIMI trial used strict criteria for reperfusion. The infarct-related vessel was assigned a numerical grade after thrombolytic therapy; "0" represented no perfusion, "1," penetration without perfusion, "2," partial perfusion, and "3," complete perfusion. This system allowed a more uniform analysis of results from the various centers participating in the trial.

Effect of IVSK on Myocardial Salvage and LV Function

There is only limited, conflicting data from controlled randomized trials of the effect of IVSK on LV function. Anderson and associates [117] found no significant improvement in LV function in patients treated with either ICSK or IVSK. A number of nonrandomized studies have reported a reduction in infarct size or improved LV function secondary to IVSK [58,59,125]. Spann and colleagues [122] reported a reduction in early ventricular dysfunction after sustained reperfusion with IVSK. A recent report [124] described a group of patients treated less than 1.5 hours after the onset of symptoms who had higher global LVEFs and regional EFs than patients treated between 1.5 and 4 hours after onset of symptoms.

Mortality and IVSK

The effect of IVSK therapy on mortality has been examined in a number of trials, although results have been inconclusive. A recent review found that only 5 of 21 randomized trials of IVSK [82] achieved significance with respect to mortality [98,108,109, 112, 113]. Nine studies showed insignificant favorable trends with the use of IVSK [94,95,100,101, 103,105,107,110,111], and 7 studies showed slightly insignificant negative effects [96,97,99,102,103, 114,115]. When the data from all the trials were pooled and analyzed [82], it appears that thrombolytic therapy produced a significant (22 ± 5%, $p < .001$) reduction in odds of death and an even larger reduction in the odds of reinfarction. Whether thrombolytic therapy was begun less than 6 hours or 12 to 24 hours after symptoms did not affect the reduction in mortality. After comparing trials in which thrombolytic therapy was or was not followed by anticoagulants it was concluded that the reduction in mortality is independent of subsequent anticoagulation.

Results of a recent large-scale Italian study [126] showed a significant reduction in mortality with the use of IVSK. This multicenter trial, conducted between June 1984, and June 1985, enrolled over 12,000 patients in an unblinded trial comparing IVSK with routine care. End points were mortality at three weeks, six months, and one year. Eligibility included patients with AMI who presented within 12 hours from the onset of symptoms. Overall mortality was 10.63% (623/5,863) in streptokinase-treated patients versus 12.99% (760/5,850) in patients who received routine care. This was a significant reduction in mortality ($p < .05$). Patients who were treated within one hour of the onset of symptoms had an 8.1% (47/580) mortality versus 15.3% (90/590) in controls. Heparin was used in 17% of patients, although there was no consistent approach to anticoagulation. Early reinfarction rates were independent of the use of anticoagulants. Major bleeding, requiring transfusion, occurred in only 0.3% of treated patients. This is the first large-scale study to document the efficacy of IVSK in the treatment of AMI. The study gains its significance from the large number of patients enrolled.

Although definitive conclusions regarding the effect of IVSK on mortality cannot be reached at this time, an examination of the overall data available strongly suggests a substantial benefit from this form of therapy. Results of other ongoing large-scale trials should further aid in delineating the effects of IVSK as a therapeutic intervention in AMI.

Complications of IVSK

The complications of IVSK appear similar to those of ICSK [118,119]. Complications associated with IVSK are primarily related to bleeding. The incidence of bleeding using a high-dose short-term infusion has varied from 0 to 21% [86,116–119,121]. Minor bleeding may in fact be an indication of effective treatment, because the intent of thrombolytic therapy is to dissolve thrombi and prevent their reformation. The potential for major bleeding episodes has been a deterrent for the more widespread use of thrombolytic agents. When Yusef and co-workers [82] reviewed 14 intravenous (IV) thrombolytic trials, which reported bleeding complications, there was a 10% excess of minor skin bleeding in treated versus control patients. There was a 0.8% excess in gastrointestinal (GI) bleeding, a 2.3% excess in genitourinary bleeding, and a small 0.3% excess of strokes in patients treated with IVSK compared with controls. Treatment was stopped because of bleeding in 1.9% of streptokinase-treated patients versus 0.5% of controls. No

patient was reported to have had a fatal hemorrhage in any of these trials. In one study [126] involving over 5,000 patients randomized to IVSK, minor bleeding was seen in 3.7% of patients. Major bleeding requiring transfusion occurred in only 0.3% of patients.

Rapid IVSK infusion has been associated with a significant decrease in blood pressure in a number of studies [116,121,127,128]. In most patients the hypotension is transient and easily managed by slowing or stopping the infusion, placing the patient in Trendelenburg's position, or administering dopamine. Data suggests that the risk of hypotension is related to the extent of damage to the myocardium, and that reductions in blood pressure may be avoided by limiting the rate of infusion of IVSK [128].

IVSK Versus ICSK

Nine studies dealt specifically with the comparison of IVSK and ICSK in the treatment of AMI [117–119,121,127,129–133]. Five of these studies were prospective randomized trials [117,119,121,130, 131]. Reperfusion rates and doses are shown in Table 5. Most studies showed insignificant differences in rates of reperfusion between ICSK and IVSK. Pooled data [134] showed a recanalization rate of 73% for IVSK and 72% for ICSK. Angiography was performed prior to and during therapy with IVSK in only four of these studies [119,121, 129,131]. Studies involving pretreatment angiography showed a combined reperfusion rate of 51% for IVSK. As previously mentioned, it is possible that successful reperfusion was overestimated in studies that did not involve pretreatment angiography.

Table 5. Recanalization Rate: Intracoronary Versus Intravenous Streptokinase

Study	Pretreatment Angiography in IVSK	Recanalization Rate (%) IC	IV
Anderson et al [66]	No	76	73
Taylor et al [118]	Yes	77	75
Rogers et al [119]	Yes	76	44[a]
Alderman et al [121]	Yes	73	62
Blunda et al [129]	Yes	85	67
Rogers et al [130]	No	64	86
Saltups et al [131]	Yes	81	31[b]

[a] $p < .005$.
[b] $p < .01$.
IC = intracoronary; IV = intravenous; IVSK = intravenous streptokinase.

Studies comparing the efficacy of IVSK versus ICSK had small sample sizes, and data regarding the effect of therapy on LV function has been variable. Taylor and associates [118] found no significant differences in early angiographic assessment of LV function or late assessment by radionuclide ventriculography in patients treated with either ICSK or IVSK. Other studies [127,132] also failed to show improvement in EF with streptokinase therapy regardless of route of administration. Rogers and colleagues [130] showed that EF in 62% of IVSK-treated patients improved, whereas only 23% of ICSK-treated patients improved over baseline. Anderson and associates [117] reported a modest but significant improvement in wall motion at 10 days in both groups of patients treated with thrombolysis. However, the small number of subjects and the low incidence of mortality in AMI do not allow definitive conclusions.

Major bleeding complications appear to be similar in trials of IVSK versus ICSK [118,119,121,127, 129,130]. Minor femoral hematomas occurred in 9% of IVSK patients versus 1.6% of ICSK patients in the study by Taylor and co-workers [118]. Anderson and colleagues [117] also reported that minor bleeding occurred in 18.5% of IVSK-treated patients versus 4.3% of the ICSK-treated group. In contrast, a higher incidence of femoral hematomas was present in ICSK-treated patients in the study by Rogers and associates [119].

No definitive conclusions can be drawn regarding the superiority of IVSK versus ICSK therapy in AMI. ICSK most likely has a higher early angiographic rate of reperfusion, although beneficial effects on LV function and mortality have not been conclusively demonstrated. Despite more localized administration with ICSK, hemorrhagic complications resulting from a systemic lytic state appear equal with IV administration.

Acylated Streptokinase

Acylation of the active center of streptokinase yields a compound that may exhibit potent fibrinolytic activity without inducing a systemic fibrinolytic state [45,135,136]. Clinical experience in AMI has been limited. Reperfusion rates approaching 90% have been reported with intravenous use of this acylated compound [47,137–139]. Large-scale trials with the p-anisoyl derivative BRL 26921 are now ongoing and should aid in determining the efficacy of this new apparently clot-specific agent.

Urokinase in AMI

Urokinase, a nonclot–specific thrombolytic agent, has undergone only limited clinical testing in AMI. There is only limited experience with intracoronary infusion of urokinase. Recanalization rates of 62 to 94% have been described [140–142]. Five randomized trials using urokinase in AMI have been reported. A European collaborative study [143] of 341 patients with AMI found a significantly faster regression of electrocardiographic changes in urokinase-treated patients when compared with controls. There was no difference in mortality or functional class at one year between urokinase and placebo. An infusion over an 18-hour period produced a systemic fibrolytic state in all patients. A review of three other small trials of IV urokinase [144–146] revealed that overall mortality was not improved, although lack of effect may be secondary to the small number of patients. A recent report [147] using acute coronary angiography showed that early treatment with IV urokinase produced reperfusion in 60% of patients. Wall motion was improved in all patients who had successful thrombolysis within two hours of the onset of symptoms. Urokinase is difficult to purify from urine, and the cell culture–derived material is extremely expensive to produce. Although urokinase may be an effective thrombolytic agent, its prohibitive cost has limited its use in clinical trials.

Tissue-Type Plasminogen Activator

Results from experimental studies of tissue-type plasminogen activator (t-PA) in animals [40] were promising and suggested that this new clot-specific agent had potential for treating patients with AMI [148]. Van de Werf and colleagues [149], in 1984, published what is perhaps the first study of rt-PA in patients. IV administration of 20,000 to 40,000 units/min rt-PA was used for a 30- to 60-minute period. Successful coronary thrombolysis, confirmed by angiography, was found in 6 of 7 patients with evolving AMI.

Stimulated by this initial report, a multicenter, blinded randomized trial of rt-PA was begun in a larger number of patients [150]. Intravenous infusion of 0.5 mg/kg of rt-PA over 60 minutes, or the same dose followed by 0.25 mg/kg for an additional 60 minutes, resulted in thrombolysis and recanalization in 75% of patients. In addition, there was no production of a clinically significant systemic lytic state. A recent European cooperative trial [151] was designed to compare rt-PA with IVSK in a blinded randomized fashion. Results in 129 patients showed patency of infarct-related artery was 70% for rt-PA–treated patients compared with 55% in patients treated with 1.5 million units of IVSK. Hospital mortality was identical in both groups, although episodes of bleeding complications were less in the rt-PA–treated patients.

To evaluate further the role of IV thrombolytic therapy in AMI, the National Heart, Lung and Blood Institute sponsored TIMI, a large, ongoing randomized controlled multicenter trial [152]. Phase I of this trial was designed to examine the relative thrombolytic activity and side effects of IV rt-PA and IVSK in patients with AMI. A double-blind, multicenter randomized comparison of 60 mg of rt-PA with 1.5 million units of IVSK was performed in 310 patients who were seen less than seven hours after the onset of acute symptoms and with angiographically documented total occlusion of the infarct-related artery. Arteriography was performed before drug administration. Reperfusion occurred in 60% of patients given rt-PA compared with 35% of IVSK-treated patients. Bleeding complications were similar for both patient groups, and no major unexpected side effects or toxicity were noted. It was concluded that rt-PA successfully recanalizes coronary arteries at a rate similar to that of ICSK without the inconvenience, risk, cost, or delay associated with acute cardiac catheterization. The results of the TIMI trial with respect to such end points as mortality, infarct size, and LV function have yet to be reported.

Percutaneous Transluminal Coronary Angioplasty with Thrombolytic Therapy

Thrombolytic therapy for patients with AMI is associated with several major unresolved problems. First, up to 40% of occluded coronary arteries may not open by lytic therapy [58,63,65,66,71,76,153–157]. Second, reinfarction or reocclusion occurs in up to 20% of patients in whom reperfusion was initially successful [65,153,157–159] (Table 6). Le-

Table 6. Reocclusion after Successful Thrombolysis

Study	Treatment	Reocclusion Rate
Merx et al [157]	ICSK + heparin	20/129 (15%)
Gold et al [158]	ICSK + heparin or ASA	11/40 (28%)
Harrison et al [153]	ICSK + heparin	7/24 (29%)
Ferguson et al [159]	ICSK + heparin	7/34 (21%)

ICSK = intracoronary streptokinase; ASA = acetylsalicylic acid.

Table 7. Thrombolytic Therapy and Percutaneous Transluminal Angioplasty in Acute Myocardial Infarction

Study	Treatment	Successful Angioplasty	Mortality
Meyer et al [162]	ICSK, then PTCA	17/21 (81%)	1/21 (4.7%)
Hartzler et al [161]	ICSK and PTCA alone or in combination	48/76 (63%)	6/76 (7.7%)
Gold et al [160]	ICSK, then PTCA	22/28 (79%)	0/28 (0%)
Papapietro et al [163]	ICSK, then PTCA	13/18 (72%)	1/18 (5.6%)
Holmes et al [164]	ICSK and PTCA alone or in combination	43/55 (78%)	5/66 (8%)

ICSK = Intracoronary streptokinase; PTCA = percutaneous transluminal coronary angioplasty.

sions with high-grade stenosis after thrombolysis (a cross-sectional luminal area of less than 0.4 mm^2 or greater than 60% stenosis) are at a higher risk for reocclusion. Third, subsequent revascularization is often necessary because of severe residual stenosis and a persistently unstable clinical course. Therefore, methods of treatment for achieving and maintaining reperfusion continue to evolve.

Percutaneous transluminal coronary angioplasty (PTCA) theoretically provides important advantages for selected individuals receiving thrombolytic therapy. The theoretical benefits include reopening of occluded arteries when thrombolytic therapy has failed and, most important, reducing the severe stenosis that frequently persists after thrombolysis. The use of angioplasty during AMI has potential disadvantages. One concern is that trauma to the vessel wall during angioplasty may rupture plaques, expose vessel wall elements, and propagate thrombi.

PTCA has now been applied successfully in patients with AMI [160–164]. Gold and associates [160] reported on patients treated with PTCA immediately following ICSK. Sixteen of 28 patients had no reflow with ICSK, and angioplasty was successful in reestablishing flow in 11 of these. The other 12 patients had severe residual stenosis ranging from 60 to 95% after streptokinase. PTCA significantly reduced the residual stenosis in 11 of 12 patients. There was a 20% reduction in luminal stenosis following angioplasty. There were no deaths in this study (Table 7).

Papapietro and colleagues [163] reported on 18 patients who underwent PTCA after thrombolytic therapy. Eleven patients had severe residual stenosis after successful thrombolysis, and PTCA was successful in 9 of these. Seven patients had unsuccessful thrombolysis with persistent total coronary occlusions. Angioplasty successfully opened four vessels. Coronary obstruction decreased from 91 to 27% in the 13 patients undergoing successful PTCA. There was only 1 in-hospital death among the 18 patients. Thus, PTCA appears to be safe and successful in the immediate postreperfusion period. In addition, PTCA is very effective in reducing the degree of residual stenosis after streptokinase. A reduction in luminal stenosis would be expected to decrease ischemic events because of restenosis or reocclusion. Schwarz and co-workers [165] reported reinfarction in 10 of 42 patients treated with streptokinase alone; however, reinfarction did not occur in 28 patients treated with streptokinase and PTCA.

Significant limitations exist in performing PTCA in patients with AMI. In many individuals, the coronary anatomy is not suitable for PTCA [160,162]. Also, the procedure may be unsuccessful in many patients [160,161] and is associated with a significant risk of dissection in this setting. In addition, there has been a high incidence of reocclusion and restenosis [160,161]. In summary, PTCA is a relatively safe procedure in the periinfarct period. It produces beneficial changes in coronary anatomy, but its applicability is limited and it is associated with a significant incidence of late complications.

Given the potential for safe and effective dissolution of thrombotic occlusions of the infarct-related artery, residual stenosis presents a secondary problem: reocclusion. A high-grade residual stenosis is likely to occlude. The high incidence of reocclusion in the open-label TIMI phase [166] underscores the need to evaluate whether mechanical revascularization by PTCA protects the thrombolysis-mediated patency of the infarct-related coronary artery. The major objective of TIMI phase II, a randomized, multicenter (30 clinical units) trial, is assessment of the role of thrombolytic therapy and PTCA in AMI.

Conclusions

The potential of limiting infarct size, preserving LV function, and decreasing morbidity and mortality related to AMI make thrombolytic therapy an exciting prospect [167]. Early treatment with thrombolytic therapy will restore infarct-related vessel patency in the majority of patients (ICSK equivalent to

IV rt-PA, both superior to IVSK). The early use of IV rt-PA would appear to be the most practical, quickest, and safest approach to reperfusion in most patients with AMI.

However, the role of thrombolytic therapy depends on more than the ability to reopen thrombosed infarct-related arteries. Whether such therapy will salvage myocardium, limit infarct size, preserve LV function, and significantly reduce morbidity and mortality (both short and long term) has yet to be established. In addition, whether thrombolytic therapy alone will be sufficient or whether additional invasive therapy will be needed is not known. Thrombolytic therapy for AMI is indicated in centers that are capable of dealing with its complications and have facilities for performing mechanical interventions that are frequently needed shortly after thrombolytic therapy. Support for ongoing trials is needed to determine the place of thrombolytic therapy in clinical practice.

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