THERAPY OF ACUTE MYOCARDIAL INFARCTION IN THE 1990s

L. David Hillis, M.D.

MEDICAL GRAND ROUNDS
UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER
DALLAS, TEXAS

MARCH 1, 1990

During the 1980s, the treatment of acute myocardial infarction changed dramatically. Thrombolytic therapy was introduced at the beginning of the decade, and over the next 10 years intravenously administered thrombolytic therapy was shown to be effective in (a) reestablishing antegrade flow in coronary arteries totally occluded by fresh thrombus, (b) improving left ventricular function in patients receiving it within 3 to 4 hours of the onset of chest pain, and (c) reducing mortality in those treated within 6 hours of the onset of pain. At the same time, substantial information was gathered concerning (a) the efficacy and safety of new, and hopefully better, thrombolytic agents, such as tissue plasminogen activator (tPA); (b) the utility of "adjuvant therapy" in conjunction with thrombolytic therapy, and (c) the optimal management of the patient with evolving myocardial infarction after a thrombolytic agent is given. My purpose today is twofold: first, to review the status of thrombolytic therapy as it stands at the end of the 1980s, reviewing what is known about its efficacy, safety, and limitations; and second, to discuss the potentially expanding role of thrombolytic therapy in the next decade. If preliminary data presently available give any indication of the future, one can predict -- with some confidence -- that thrombolytic therapy will be used much more widely in the year 2000 than it is in 1990.

WHO SHOULD RECEIVE THROMBOLYTIC THERAPY?

A. Type of Ischemic Event

1. 1980s: Those with Evolving Q wave Infarction: In the late 1970s and early 1980s, several pathologic and angiographic studies demonstrated that a totally occlusive coronary artery thrombus was present in > 90% of individuals with evolving Q wave myocardial infarction [1-6]. The thrombotic nature of these occlusions was supported by retrieval of thrombus during emergent coronary artery bypass surgery and by the characteristic angiographic appearance of retention of contrast material by an intraluminal filling defect [6]. Moreover, the incidence of total occlusion decreased with time to around 60% at 12 to 24 hours after the onset of infarction, presumably due to spontaneous lysis of thrombus, refuting the hypothesis that thrombosis occurred as a consequence of infarction (and not vice versa)

[5]. Subsequently, numerous angiographic studies confirmed the high incidence of total coronary occlusion in subjects with evolving Q wave infarction and showed that these occluded vessels often were recanalized with an intracoronary infusion of streptokinase [7-25].

2. 1990s: Those with Unstable Angina or Evolving Non Q Wave Infarction: In contradistinction to patients with evolving Q wave infarction, those with unstable angina at rest and evolving non Q wave infarction usually do not have pathologic or angiographic evidence of a totally occlusive coronary thrombus [1-4]. However, a number of studies have shown that a substantial percentage of these subjects have partially occlusive coronary thrombi that (a) are demonstrable angiographically (Table 1, below) and (b) are altered by the administration of a thrombolytic agent.

Table 1: Incidence of Partially Occlusive Coronary Thrombi in Patients with Unstable Angina at Rest

Authors	# patients studied	# patients with IC thrombi	%
Vetrovec et al [26]	12	11	92
Mandelkorn et al [27]	9	4	44
Capone et al [28]	44	23	52
Bresnahan et al [29]	67	24	36
Sherman et al [30]	10	7	70
Gold et al [31]	11	8	73
Gotoh et al [32]	37	21	57
TOTALS	190	98	52

As the data in Table 1 indicate, patients with unstable angina in whom coronary arteriography is performed in close temporal proximity to continued instability frequently have intracoronary thrombi, but most of these are not totally occlusive.

Similarly, the majority of subjects with evolving non Q wave myocardial infarction do not have a totally occlusive thrombus at the time of catheterization. DeWood et al [33]

performed coronary arteriography within 1 week of hospitalization in 341 patients with non Q wave infarction. Of those in whom angiography was accomplished within 24 hours of the onset of chest pain, a totally occlusive coronary thrombus was noted in only 26%. Mandelkorn et al [27] noted that only 2 of 8 patients with non Q wave infarction had a totally occlusive coronary thrombus, whereas the other 6 had partially occlusive thrombi. When these 8 patients were given an intracoronary infusion of streptokinase, distinct angiographic improvement occurred in 7.

There are few, if any, data dealing with the efficacy and safety of thrombolytic therapy in patients with unstable angina at rest and non Q wave myocardial infarction. Gold et al [31] randomized 23 patients with unstable angina at rest to receive placebo or intravenous tPA. Following therapy, unstable angina continued in 6 of the 11 placebo patients and in only 1 of the 12 who received tPA ($p < 0.05$). Subsequent coronary arteriography showed partially occlusive coronary thrombi in 8 of the 11 placebo patients and in 0 of the 11 tPA patients ($p < 0.05$). The recently initiated TIMI-3 study (of which we are a participating center) is designed to assess the efficacy and safety of intravenous tPA in patients with unstable angina at rest and non Q wave myocardial infarction. TIMI-3A is a randomized, double-blind, placebo-controlled trial to assess the efficacy of intravenous tPA on the perfusion characteristics of the ischemia-related coronary artery. It will enroll 300 patients from approximately 14 centers, with Parkland Hospital being 1 of them. TIMI-3B is a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of intravenous tPA as well as the efficacy and safety of an invasive or a conservative management strategy after drug has been administered. It will enroll approximately 2000 patients from > 40 centers. When TIMI-3A is completed (in 9 to 12 months), we will become a TIMI-3B center.

In short, in the 1980s, thrombolytic therapy was largely reserved for patients with evolving Q wave myocardial infarction, a group of subjects in whom intracoronary thrombus was of etiologic importance in the overwhelmingly majority. In the 1990s, thrombolytic therapy probably will be used frequently in patients with unstable angina at rest and evolving non Q wave infarction, since recently acquired data indicate that intracoronary thrombus is of pathophysiologic importance in a substantial percentage of these individuals. However, the overall

efficacy and safety of thrombolytic therapy in patients with these syndromes await confirmation in properly designed clinical trials, such as the TIMI-3 study described above.

B. Timing of Thrombolytic Therapy

1. 1980s: Those Who Can be Treated Within 4 to 6 Hours of the Onset of Chest Pain: In the late 1970s, studies in experimental animals showed that coronary reperfusion led to a reduction in infarct size only if it was accomplished within 3 to 4 hours of occlusion [34,35]. In patients with evolving Q wave infarction, the early administration of intravenous streptokinase or tPA was shown to improve left ventricular function in several placebo-controlled, randomized evaluations. For example, the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) Study Group [36] randomly assigned 1741 patients with evolving Q wave infarction to placebo or intravenous streptokinase, 1.5 million units over 60 minutes. All patients received therapy within 6 hours of the onset of chest pain, and 56% received it within 3 hours. Left ventricular function was assessed 3 to 4 weeks after infarction. As noted in Table 2 (page 6), the patients receiving streptokinase had a higher left ventricular ejection fraction than those receiving placebo. Similar data were reported by White et al [37] with intravenous streptokinase and by Guerci et al [38] with tPA. In both of the latter studies, all patients received thrombolytic therapy within 4 hours of the onset of chest pain. In contrast, little or no consistent improvement in global or regional left ventricular function occurs in patients in whom reperfusion is accomplished > 4 hours after the onset of pain [39-41]. In short, these carefully designed, placebo-controlled studies of intravenous thrombolytic therapy (streptokinase or tPA) [36-38] demonstrated that the early administration (usually < 4 hours) of a thrombolytic agent leads to a significant improvement in left ventricular function, whereas its later administration exerts no demonstrable influence.

In 1986, the results of the Gruppo Italiano per lo Studio della Streptokinasi Nell' Infarto Miocardico (GISSI) study were published [42]. This multicenter unblinded trial from Italy compared mortality at 21 days in almost 12,000

Table 2: Effects of Intravenous Thrombolytic Therapy on Left Ventricular Function

Author	Drug/Dose	LVEF	Time from Pain to Drug
ISAM [36]	strep 1.5 mil u	PL 0.54 SK 0.57 p < 0.005	< 6 hours in all < 3 hours in 56%
White [37]	strep 1.5 mil u	PL 0.53 SK 0.59 p < 0.005	< 4 hours in all average, 3.0 hours
Guerci [38]	tPA 100 mg	PL 0.46 tPA 0.53 p < 0.02	< 4 hours in all average, 3.2 hours

patients with evolving Q wave infarction who received intravenous streptokinase (1.5 million units in 60 minutes)(n = 5860) or conventional therapy (n = 5852). Patients were enrolled in the study up to 12 hours after the onset of chest pain. Streptokinase induced a significant reduction (18%) in overall mortality (13.0% for those treated in a conventional manner, 10.7% for those given streptokinase; p = 0.002). Importantly, streptokinase reduced mortality only in those in whom therapy was initiated within 6 hours of the onset of pain; in fact, its beneficial influence was largely confined to those in whom the drug was begun within 3 hours (Table 3, below). A

Table 3: Results of the GISSI Trial

	Streptokinase n = 5860	Control n = 5852	p
Overall mortality	10.7%	13.0%	0.002
Time pain-to-drug			
< 3 hours	9.2%	12.0%	0.0005
3 to 6 hours	11.7%	14.1%	0.03
6 to 9 hours	12.6%	14.1%	NS
9 to 12 hours	15.8%	13.6%	NS

similar diminution in mortality with intravenous streptokinase was reported by White et al [37](12.9% for placebo, 2.5% for streptokinase; p = 0.012) and by the Second International Study of Infarct Survival (ISIS-2) [43](12% for placebo, 8% for streptokinase; p value not given) for patients in whom therapy was begun within 4 hours of the onset of chest pain.

In the early days of thrombolytic therapy, it was hypothesized that timely pharmacologic reperfusion of a totally occluded coronary artery would salvage jeopardized myocardium, leading, in stepwise fashion, to (a) improved left ventricular function and (b) diminished mortality. The above-mentioned studies demonstrated that intravenous thrombolytic therapy, indeed, accomplished these goals, provided that it was given soon (i.e., within 3, 4, or certainly 6 hours) after the onset of ischemic injury. The apparent necessity that thrombolytic therapy be given early -- and that it was not beneficial if given later than 6 hours after the onset of pain -- markedly limited the number of patients who were candidates, since a substantial fraction of subjects with evolving Q wave infarction do not seek or cannot reach medical assistance within this narrow time window.

2. <u>1990s: Those Who Can Be Treated Within 6 to 24 Hours of the Onset of Chest Pain, or Possibly Even Later</u>: Although the GISSI study showed that intravenous streptokinase improved survival only in those who received drug within 6 hours of the onset of chest pain, others suggested that reperfusion of the infarct-related coronary artery was beneficial even if it was accomplished > 6 hours after the onset of pain. Kennedy et al [9] showed that intracoronary streptokinase given > 6 hours after symptom onset improved survival without exerting a demonstrable effect on left ventricular function. Similarly, the Second International Study of Infarct Survival (ISIS-2) [44] demonstrated that intravenous streptokinase reduced mortality even when given 13 to 24 hours after the onset of pain. This apparent dissociation between the effects of a restoration of antegrade coronary flow on left ventricular function and survival raised the possibility that the pharmacologic restoration of antegrade flow may reduce mortality through a mechanism <u>independent</u> of its influence on left ventricular function, such as a diminution in electrical instability. In support of this hypothesis that "an open artery is always better than a closed one,"

preliminary studies suggested that successful coronary reperfusion in patients with acute myocardial infarction reduced the incidence of late potentials on signal averaged electrocardiography [45], inducible ventricular tachyarrhythmias, and sudden death [46,47].

In a series of analyses of the records of patients catheterized at Parkland over the past 12 years, Ricky Cigarroa, Rick Lange, and I have shown that residual antegrade flow in the infarct artery of patients with myocardial infarction profoundly improves long-term survival independent of its influence on left ventricular function. In our initial assessment [48], we identified all patients whom we had catheterized within 5 months of a myocardial infarction and who had disease of only the infarct-related coronary artery. Of the 208 patients who fulfilled these criteria, 68 had antegrade flow in the infarct artery (Group I), whereas the other 140 did not (Group II). Of the 68 with residual antegrade flow, 4 underwent coronary artery bypass surgery, and the other 64 were followed on long-term medical therapy. Of the 140 patients without residual antegrade flow in the infarct artery, 20 had bypass surgery, and 5 were lost to follow-up. Thus, we had information during long-term follow-up on medical therapy on (a) 64 patients with (Group I) and (b) 115 patients without (Group II) residual antegrade flow in the infarct artery.

As the data in Table 4 (page 9) indicate, the 64 Group I patients and the 115 Group II patients were similar in age, sex, risk factors for atherosclerotic cardiovascular disease, duration of follow-up, and -- most importantly -- left ventricular function. However, they differed dramatically in long-term survival: all 64 of those with residual antegrade flow in the infarct artery were alive at follow-up, whereas 21 (18%) of those without residual antegrade flow in the infarct artery had died. According to family members and medical records (when available), all 21 died suddenly, suggesting that they sustained an arrhythmic event.

Figure 1 (page 10) offers a pictoral display of these survival data.

Table 4: Comparison of Patients with and without Antegrade Flow in the Infarct Artery Following Myocardial Infarction

	Group I (n=64) Antegrade Flow	Group II (n=115) No Antegrade Flow
Age (years)	46 ± 9	47 ± 10
male	69%	77%
Risk factors for ASCVD		
hypertension	41%	49%
smoking	78%	82%
diabetes mellitus	25%	20%
Cholesterol > 270	13%	14%
Duration of follow-up (months)	46 ± 29	48 ± 28
LV ejection fraction	52 ± 14	52 ± 11
Mortality	0%	18% *

* $p < 0.001$ in comparison to Group I.

These data are taken from reference # 48.

The survival data for patients after myocardial infarction with multivessel coronary artery disease are remarkably similar [49]. A total of 110 patients sustained a myocardial infarction, were subsequently catheterized, and were found to have disease of the infarct artery (with or without residual antegrade flow) as well as stenoses of 1 or both of the other coronary arteries. Of the 110, 35 had residual antegrade flow in the infarct artery, and the other 75 did not. The 2 groups were similar in age, sex, risk factors for atherosclerosis, and duration of follow-up, but -- as in those with disease of only the infarct artery -- they differed dramatically in long-term outlook. Of the 35 with residual antegrade flow, only 2 (6%) died of cardiac causes during long-term follow-up; in contrast, of the 75 without residual antegrade flow in the infarct artery, 24

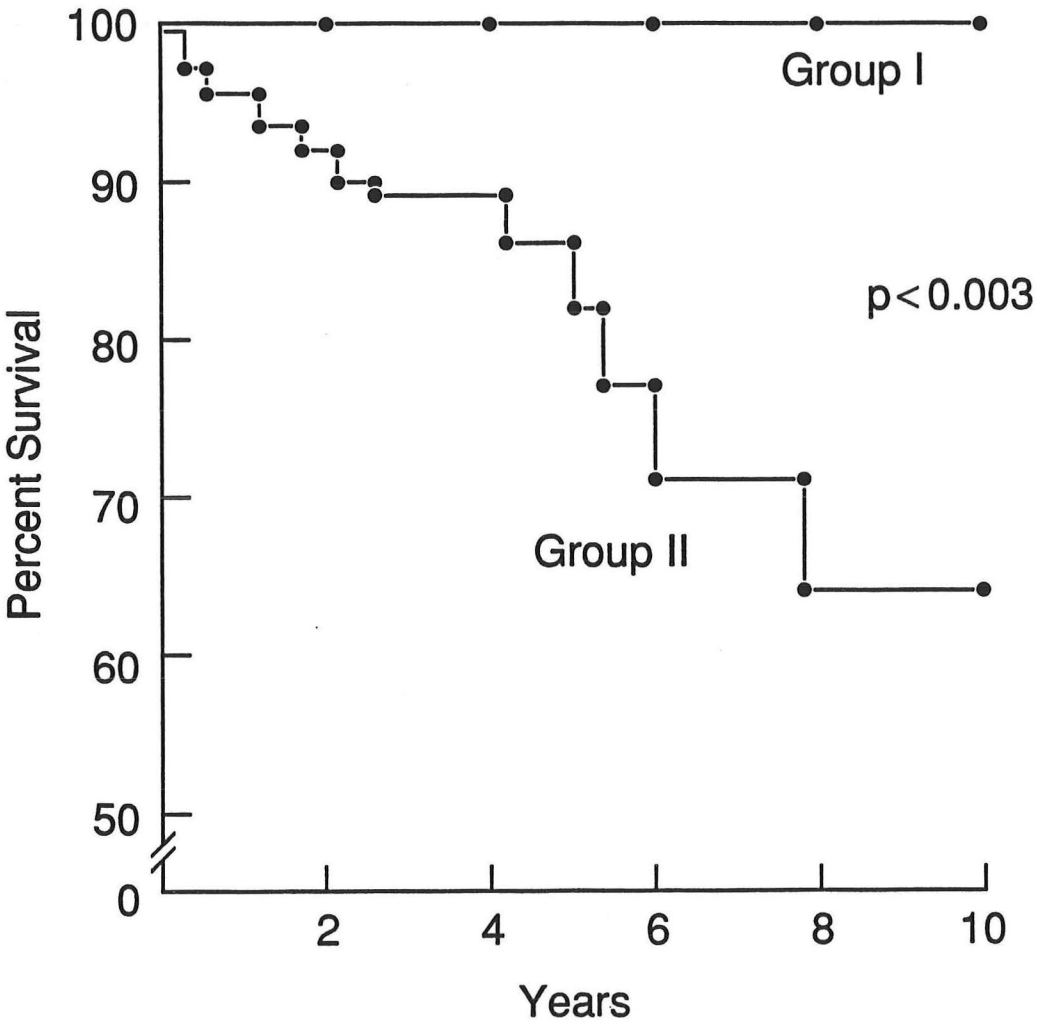

Figure 1: A life-table survivorship analysis for the two groups (Group I = antegrade flow in the infarct artery; Group II = no antegrade flow in the infarct artery). Over the 10 years of observation, Group I had a significantly better survival than Group II.

(32%) died of cardiac causes during a similar period of follow-up ($p = 0.017$ in comparison to those with residual antegrade flow).

From talking with family members and reviewing the medical records of the patients who died, it seemed that almost all the deaths were arrhythmic in origin. In an attempt to assess the propensity for electrical instability in patients after myocardial infarction with and without residual antegrade flow in the infarct artery, we performed signal averaged electrocardiography in 109 of the patients who comprised the study populations for the first 2 analyses [50]. Signal averaged electrocardiography allows the identification of low amplitude, high frequency signals (so-called late potentials) in the terminal portion of the QRS complex [51-53]. They are thought to be caused by slowed and asynchronous conduction through ischemic myocardium [54,55] or normal myocardium interspersed with fibrosis [53,56,57]. These late potentials are frequently detected in subjects with spontaneous or inducible ventricular tachycardia. In patients who have had myocardial infarction, they identify those at risk for subsequent arrhythmic events and sudden death [58-60].

Of the 109 subjects, 49 had residual antegrade flow in the infarct artery, and the other 60 did not. The groups were similar in age, sex, infarct artery, severity of coronary artery disease, and left ventricular function. However, only 4 (8%) of those with residual antegrade flow in the infarct artery had late potentials, whereas 24 (40%) of those without residual antegrade flow had them ($p < 0.001$).

In short, it appears that the presence or absence of residual antegrade perfusion of the infarct artery after myocardial infarction strikingly influences long-term survival, probably by reducing the propensity for an arrhythmic event. Furthermore, residual antegrade perfusion of the infarct artery exerts its salutary effect <u>independent of its influence on left ventricular function</u>. Thus, it is possible that the restoration of antegrade flow in the infarct artery -- pharmacologically or mechanically -- may be beneficial even if it is accomplished hours to days after the acute event. Thus, thrombolytic therapy may exert a beneficial effect even when given 12, 24, or even 36 hours after the onset of chest pain, and coronary angioplasty or bypass surgery may accomplish a similar goal if it is performed several days (or even weeks) after the event.

These possibilities await confirmation in properly designed prospective clinical trials.

C. Those without a Contraindication to Thrombolytic Therapy or Subsequent Anticoagulation As thrombolytic therapy has been given to large numbers of patients, we have learned that it is associated with complications in a small number. With any of the agents, the most frequent complication is bleeding. If concomitant arterial punctures are not performed, serious bleeding (requiring transfusion) is uncommon, and life-threatening hemorrhage occurs very rarely. In support of this, 5860 patients in the GISSI trial [42] received intravenous streptokinase without concomitant arterial puncture. Major bleeding occurred in only 19 (0.3%), and cerebrovascular events (ischemic or hemorrhagic) were noted in 10 (0.2%).

In contrast, the incidence of bleeding with streptokinase or tPA is substantial if arterial catheterization is performed within close temporal proximity to drug administration, and the risk of hemorrhage is similar with the 2 agents. In the TIMI report of Chesebro et al [61] in which patients were acutely catheterized and given intravenous streptokinase or tPA, bleeding, ecchymosis, or hematoma were noted in 66% of those receiving tPA and 67% of those receiving streptokinase. A major fall in hematocrit (> 15%) occurred in 15% and 16%, respectively, and a transfusion of $\geq$ 2 units of blood was required in 25% and 21%, respectively. No patient sustained an intracranial hemorrhage. Of all the patients who suffered a hemorrhagic episode (major or minor), the site of arterial puncture was the primary site of bleeding in 78% of those receiving tPA and 80% of those receiving streptokinase.

Table 5 (page 13) lists the absolute and relative contraindications to thrombolytic therapy. The administration of any thrombolytic agent to a patient with any of these contraindications is likely to be followed by a major hemorrhagic event. Thrombolytic therapy should be given to patients > 70 years of age with caution, since the incidence of hemorrhage is increased in the elderly [62].

Table 5: Contraindications to Thrombolytic Therapy

Absolute

a. Active internal bleeding
b. Recent (< 2 months) cerebrovascular accident or neurosurgical procedure
c. Recent (< 10 days) major surgery, organ biopsy, or puncture of a noncompressible vessel
d. Recent serious gastrointestinal bleeding
e. Recent serious trauma, including prolonged CPR

Relative

a. Severe hypertension (systolic pressure > 200, diastolic pressure > 110)
b. Recent minor trauma, including brief CPR
c. Hemostatic defect
d. Severe hepatic or renal disease
e. Age > 70 years [62]
f. Diabetic hemorrhagic retinopathy

WHICH THROMBOLYTIC AGENT SHOULD BE GIVEN?

A. Streptokinase Streptokinase has no direct enzymatic activity of its own. In circulating plasma, it combines with free and fibrin-bound plasminogen; the resultant streptokinase-fibrinogen complex acts to convert plasminogen to plasmin [63]. Initially, the plasmin that becomes available combines with circulating alpha-2 antiplasmin. Eventually, all available alpha-2 antiplasmin is consumed, and free plasmin appears in the circulation. Plasmin is a serine protease that degrades fibrin, fibrinogen, and clotting factors V, VIII, and XIII. Therefore, it produces a systemic fibrinolytic state that persists until these clotting factors and fibrinogen are resynthesized.

Streptokinase is a foreign protein. Low titers of antistreptokinase antibodies are ubiquitous in the general population. Resistance to its fibrinolytic effects may occur if high titers of antistreptokinase antibodies are

present because of previous streptokinase administration or recent streptococcal infection. An occasional patient with marked streptokinase resistance is reported [64].

When streptokinase is given intravenously, a dose of 750,000 to 1,500,000 units is infused in 30 to 60 minutes. A more rapid infusion usually causes hypotension. This dose produces a systemic fibrinolytic state [65], with a precipitous fall in circulating levels of plasminogen and fibrinogen, as well as a concomitant increase in fibrinogen degradation products.

After its intravenous administration, streptokinase successfully induces thrombolysis in 30 to 60% of patients with evolving myocardial infarction, with an average of about 40%. Its efficacy in causing clot lysis is dependent on the elapsed time from onset of pain (and presumably clot formation) to drug administration. Thus, its efficacy in inducing coronary reperfusion is as high as 55 to 60% when it is given to patients < 3 to 4 hours after the onset of pain; conversely, its efficacy in restoring antegrade coronary flow falls to 30 to 35% when it is given to patients 6 to 8 hours after the onset of pain [61,66-68] (Table 6, page 16).

B. Anisoylated plasminogen streptokinase activator complex (APSAC) The anisoylated derivative of streptokinase is a "second generation" thrombolytic agent with certain advantages over streptokinase. First, the compound is activated only by deacylation and, therefore, can be given as a bolus. Second, unlike the streptokinase-plasminogen activator complex, which is subject to degradation by plasma inhibitors and plasmin antiactivators, the acyl form results in greater persistence of fibrinolytic activity and somewhat greater thrombolytic potency than equivalent doses of streptokinase [69]. The typical dose of intravenous APSAC is 30 mg or 30 units given in 2 to 5 minutes. With this dose, intravenous APSAC induces coronary reperfusion in 50 to 55% of patients [70,71] (Table 6, page 16).

At the same time, APSAC has certain drawbacks. Similar to streptokinase, it is immunogenic, so that an occasional patient with antibodies to streptokinase has an allergic reaction to APSAC. It is prepared via heated human plasma, which introduces the remote potential of transmission of a viral component. When APSAC becomes available for general use in this country, it is anticipated that its cost will be similar to that of urokinase and tPA.

C. Urokinase Urokinase differs from streptokinase in several ways. It directly activates plasminogen to form plasmin. Since it is nonantigenic, it is better tolerated than streptokinase and has a lower incidence of resistance. Although it induces a systemic fibrinolytic state, it appears to deplete fibrinogen less than streptokinase [11]. It is several times more expensive than streptokinase. For this reason, it usually has been used only in patients who are likely to have high titers of antistreptokinase antibodies.

In most therapeutic trials of urokinase, a loading dose of 2500 to 4500 CTA units/kg is given over 15 to 60 minutes, followed by the same dose per hour for 12 to 24 hours. With this dose, a mild depletion of plasminogen and fibrinogen is noted, with marked fibrinolytic activity in circulating plasma. Higher doses reduce plasminogen and fibrinogen levels to a similar extent as streptokinase [72].

D. Tissue plasminogen activator Both streptokinase and urokinase convert circulating plasminogen to plasmin, producing a systemic fibrinolytic state. Tissue plasminogen activator (tPA) is said to be "clot selective." After its intravenous administration, it is avidly bound to the plasminogen and fibrin within the interstices of a thrombus. Its affinity for circulating (free) plasminogen is low (1/500 of its affinity for plasminogen-fibrin within an existing clot). As a result of these relative affinities, tPA produces "local" thrombolysis without causing a systemic fibrinolytic state. It produces a modest decline in systemic fibrinogen and plasminogen concentrations, as well as a mild increase in fibrinogen degradation products. These changes in plasminogen, fibrinogen, and fibrinogen degradation products appear to be related to the amount of tPA administered [73] but are not as marked as those noted following streptokinase.

Tissue plasminogen activator is nonantigenic and causes no adverse reactions with rapid intravenous administration. Repeated administration is possible without producing an antibody response. It has a brief duration of action [74], so that its thrombolytic effect can be "turned off" quickly if bleeding occurs or invasive procedures (i.e., coronary arteriography or bypass surgery) are required.

1. 1980s Mode of Administration: From the time of its first use in patients with myocardial infarction until

the end of the decade, a number of dosage regimens of tPA were evaluated, ranging from as little as 0.4 to 0.5 mg/kg to as much as 150 mg total dose. In phase II of the TIMI study [75], it became clear that the 150 mg dose was associated with an unacceptably high incidence (1.6%) of intracranial hemorrhagic events, so that the total dose was reduced to 100 mg. This standard dose -- 100 mg given over 3 hours, with 60 mg in the first hour and 20 mg in each of the next 2 -- was shown to induce coronary thrombolysis in 60 to 75% of patients [38,61,76-80], a higher percentage than that reported with intravenous streptokinase (Table 6).

2. 1990s Mode of Administration: Table 6 provides a summary of studies which have angiographically assessed the incidence of coronary reperfusion following the intravenous administration of streptokinase, tPA, and APSAC.

Table 6: Reperfusion rates with intravenous thrombolytic therapy

Author	Time from Pain to Drug (Hours)	Reperfusion n	Reperfusion %
Streptokinase			
Neuhaus [66]	3.4	24/40	60
Spann [67]	3.5	21/43	49
Chesebro [61]	4.7	37/119	31
Hillis [68]	4.5	11/34	32
TOTALS		93/236	39
Tissue Plasminogen Activator			
Collen [79]	4.7	25/33	76
Williams [76]	4.8	25/37	68
Gold [80]	3.0	24/29	83
Chesebro [61]	4.5	70/113	62
TOTALS		144/212	68
APSAC			
Bonnier [70]	2.5	23/36	64
Anderson [71]	3.4	59/115	51
TOTALS		82/151	54

As noted, streptokinase (1.5 million units in 60 minutes) induced reperfusion in 30 to 60%, with an average of only 39%; APSAC induced reperfusion in an average of 54%; and tPA was successful in establishing reperfusion in an average of 68%. This 68% incidence of coronary thrombolysis was obtained with 100 to 150 mg, given in 3 to 6 hours.

Recent data suggest that the incidence of reperfusion following intravenous tPA is markedly increased if the drug is given more rapidly, with a sizable portion infused over the first 30 minutes. Neuhaus et al [81] administered such a "front-loaded" regimen of tPA to 80 patients with evolving myocardial infarction. Specifically, these authors gave tPA in the following manner: 15 mg as a bolus, 50 mg infused over 30 minutes, and 35 mg infused over the following 60 minutes (total, 100 mg in 90 minutes). At the end of the infusion, 91% of the patients had angiographic evidence of reperfusion. Similar data (angiographic evidence of reperfusion in 27 of 28 patients to whom such a "front-loaded" regimen of tPA was given) have been reported by Williams et al [82].

In the 1990s, we will learn how best to give tPA, and we will have the opportunity to use agents that are more effective than tPA at inducing thrombolysis. It is not inappropriate to foresee the day when coronary thrombolysis will be achieved in almost every patient to whom a thrombolytic agent is given, even 12 to 36 hours after the onset of the event.

In summary, tissue plasminogen activator offers several advantages in comparison to other agents that are currently available (streptokinase, urokinase, and APSAC). Most importantly, it induces thrombolysis in substantially more patients than the other agents. In addition, it is nonantigenic, and, therefore, one is not concerned about an allergic reaction. At the same time, <u>tPA is very good at lysing clots</u>; as a result, hemorrhagic complications occur with its administration in the same way (and with the same frequency) that they occur with any thrombolytic agent.

SHOULD "ADJUVANT THERAPY" BE ADMINISTERED?

The administration of other agents in conjunction with thrombolytic therapy has been advocated as a means of (a) further reducing the extent of myocardial ischemic injury and/or (b) slowing the time course of ischemic injury, so that reperfusion exerts a maximal beneficial influence. Studies in experimental animals have suggested that beta-adrenergic blockade may augment the salvage of myocardium induced by reperfusion [83]. In the TIMI II trial [75], 1390 of the 3262 patients given tPA also were treated with metoprolol, either immediate (15 mg intravenously at the time of tPA administration, followed by oral maintenance therapy)(n = 696) or deferred (oral maintenance therapy begun on hospital day 6)(n = 694). Although immediate beta-blockade was well tolerated, it did not affect mortality or left ventricular ejection fraction, but it did lower the incidence of nonfatal reinfarction and recurrent ischemic events during hospitalization (Table 7, below). It appeared to be particularly beneficial in 2 subgroups: those treated within 2 hours of the onset of symptoms and those at low-risk (by initial risk assesment).

Table 7: Clinical events in patients receiving immediate or deferred metoprolol therapy

	Immediate n = 696	Deferred n = 694	p
Within the first 6 days			
death	2.4%	2.4%	NS
reinfarction	2.3%	4.5%	0.06
nonfatal reinfarction	2.3%	4.5%	0.02
recurrent ischemia	15.4%	21.2%	0.005
Within the first 42 days			
death	3.7%	3.6%	NS
reinfarction	4.3%	6.3%	0.09
nonfatal reinfarction	3.9%	6.1%	0.06
recurrent ischemia	31.2%	33.9%	NS

AFTER CLOT LYSIS HAS BEEN ACHIEVED, HOW SHOULD THE PATIENT BE MANAGED?

A. Role of Immediate Catheterization and Angioplasty

Advocates of immediate catheterization and angioplasty after thrombolytic therapy hoped that such a strategy would allow one to (a) open vessels in patients in whom thrombolytic therapy had been unsuccessful (i.e., those whose infarct arteries were still occluded) and (b) reduce the residual stenosis in patients in whom thrombolytic therapy had been successful. In turn, this management strategy would improve coronary perfusion, limit infarct size, preserve left ventricular function, and reduce the incidence of recurrent ischemic events. In practice, however, the results of such an aggressive strategy have been disappointing. Three large, randomized trials have compared the efficacy and safety of immediate catheterization and angioplasty to those of delayed catheterization and angioplasty routinely [78,84] or only if required by a recurrence of symptoms [85] (Table 8,page 20). In all 3 studies, tissue plasminogen activator was given. As the data in Table 8 indicate, immediate catheterization and angioplasty following thrombolytic therapy offered no demonstrable benefit as regards left ventricular function and short-term mortality when compared to delayed catheterization and angioplasty [78,84] or a completely noninvasive management strategy [85]. Furthermore, immediate catheterization and angioplasty were associated with an increased incidence of hemorrhagic complications, emergent coronary artery bypass surgery, and death. Although all 3 trials used tPA, similar data have been reported when immediate catheterization and angioplasty were utilized following intravenous streptokinase [86].

B. Role of Routine Revascularization Before Discharge

The question of whether routine catheterization and angioplasty are beneficial before hospital discharge in patients who have received thrombolytic therapy has been addressed by 2 large randomized trials. In the TIMI IIB trial [75], 3262 patients were treated with intravenous tPA and then randomly assigned to an invasive management strategy (catheterization and angioplasty, if coronary anatomy was suitable, 18 to 48 hours after tPA) or a conservative one (catheterization and angioplasty only for those with recurrent angina or a positive submaximal exercise test). In comparison to the conservative management strategy, the invasive one did not cause an improvement in left ventricular function or a reduction in

Table 8: Trials Assessing the Advantages and Disadvantages of Immediate Catheterization and Angioplasty Following Thrombolytic Therapy

	TAMI [78]		ECSG [85]		TIMI IIA [84]	
	Immed	7-10 d	Immed	None	Immed	18-48 h
Predischarge LVEF (%)	53	56	51	51	50	49
In-hospital mortality (%)	4	1	7	3*	7	6
Success rate of PTCA (%)	85	94	90	-	84	93
Recurrent infarction (%)	-	-	4	7	7	4
Emergent surgery (%)	7	2	-	-	4	2
Transfusion (%)	22	18	10	4	20	7*
Complications (%)	-	-	-	-	12	4*

Immed = immediate

* $p < 0.05$ in comparison to immediate.

the incidence of reinfarction or death (Table 9, page 21). In fact, adverse clinical events (emergent coronary artery bypass surgery, intracranial hemorrhage, non-fatal reinfarction, or death) occurred more frequently in those treated aggressively (13.0% versus 10.6%, $p = 0.04$). The SWIFT (Should We Intervene Following Thrombolysis) study [87] reached remarkably similar conclusions. These investigators treated 800 patients with anisoylated plasminogen streptokinase activator complex (APSAC), after which each was randomly assigned to (a) routine delayed catheterization and angioplasty or (b) careful observation, with catheterization and angioplasty only for those with

recurrent angina. The groups were similar in left ventricular function (measured 3 months after infarction) and survival (Table 9, below).

Table 9: Trials of thrombolysis followed by routine catheterization and revascularization in myocardial infarction

	TIMI IIB [75]		SWIFT [87]	
	Conserv n=1626	Invasive n=1636	Conserv n=403	Invasive n=397
Lytic agent	tPA		APSAC	
Duration of follow-up	42 days		90 days	
Reinfarction	5.8%	6.4%	9.7%	13.9%
Mortality	4.7%	5.2%	3.2%	4.8%
Mortality at 1 year [81]	7.6%	7.0%	-	-

The incidence of reinfarction and mortality is similar for each management strategy.

Both these trials provide powerful support for a conservative management strategy for patients with myocardial infarction who have received thrombolytic therapy. According to this scheme, the patient who has been given thrombolytic therapy undergoes catheterization and angioplasty only for recurrent angina or a performance on exercise testing suggestive of ischemia. If neither occurs, the patient is discharged from the hospital on low-dose aspirin and is observed closely during rehabilitation.

CONCLUDING REMARKS

During the decade of the 1990s, we are likely to use thrombolytic therapy much more often than in the past. First, we shall administer these agents to patients with unstable angina at rest and evolving non Q wave myocardial infarction, since partially occlusive coronary thrombi are the cause of clinical instability in most of these patients. Second, we shall give thrombolytic therapy to patients with evolving Q wave infarction even though chest pain began many hours before therapy is initiated, since the establishment of antegrade coronary flow improves survival independent of its influence on left ventricular function. Third, we shall administer tissue plasminogen activator, or even better agents, in a manner that will induce thrombolysis in almost all patients.

Ten to twenty years ago, the mortality from acute myocardial infarction in all large trials was 15 to 20%. In the TIMI II trial, the mortality during the first year after infarction was only 7%. We are entering an era in which patients with myocardial infarction who reach the hospital seldom die of the infarction.

REFERENCES

1. Buja LM, Willerson JT. Clinicopathologic correlates of acute ischemic heart disease syndromes. Am J Cardiol 1981; 47:343-356.

2. Davies MJ, Fulton WFM, Robertson WB. The relation of coronary thrombosis to ischemic myocardial necrosis. J Pathol 1979; 172:99-110.

3. Davies MJ, Woolf N, Robertson WB. Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi. Br Heart J 1976; 38:659-664.

4. Freifeld AG, Schuster EH, Bulkley BH. Nontransmural versus transmural myocardial infarction. A morphologic study. Am J Med 1983; 75:423-432.

5. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980; 303:897-902.

6. Terrosu P, Ibba GV, Contini GM, Franceschino V. Angiographic features of the coronary arteries during intracoronary thrombolysis. Br Heart J 1984; 52:154-163.

7. Khaja F, Walton JA Jr, Brymer JF, Lo E, Osterberger L, O'Neill WW, Colfer HT, Weiss R, Lee T, Kurian T, Goldberg AD, Pitt B, Goldstein S. Intracoronary fibrinolytic therapy in acute myocardial infarction. Report of a prospective randomized trial. N Engl J Med 1983; 308:1305-1311.

8. Anderson JL, Marshall HW, Bray BE, Lutz JR, Frederick PR, Yanowitz FG, Datz FL, Klausner SC, Hagan AD. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N Engl J Med 1983; 308:1312-1318.

9. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1983; 309:1477-1482.

10. Leiboff RH, Katz RJ, Wasserman AG, Bren GB, Schwartz H, Varghese PJ, Ross AM. A randomized, angiographically controlled trial of intracoronary streptokinase in acute myocardial infarction. Am J Cardiol 1984; 53:404-407.

11. Tennant SN, Dixon J, Venable TC, Page HL Jr, Roach A, Kaiser AB, Frederiksen R, Tacogue L, Kaplan P, Babu NS, Anderson EE, Wooten E, Jennings HS III, Breinig J, Campbell WB. Intracoronary thrombolysis in patients with acute myocardial infarction: Comparison of the efficacy of urokinase with streptokinase. Circulation 1984; 69:756-760.

12. Rogers WJ, Mantle JA, Hood WP Jr, Baxley WA, Whitlow PL, Reeves RC, Soto B. Prospective randomized trial of intravenous and intracoronary streptokinase in acute myocardial infarction. Circulation 1983; 68:1051-1061.

13. Rentrop KP, Feit F, Blanke H, Stecy P, Schneider R, Rey M, Horowitz S, Goldman M, Karsch K, Meilman H, Cohen M, Siegel S, Sanger S, Slater J, Gorlin R, Fox A, Fagerstrom R, Calhoun WF. Effects of intracoronary streptokinase and intracoronary nitroglycerin infusion on coronary angiographic patterns and mortality in patients with acute myocardial infarction. N Engl J Med 1984; 311:1457-1463.

14. Raizner AE, Tortoledo FA, Verani MS, Van Reet RE, Young JB, Rickman FD, Cashion WR, Samuels DA, Pratt CM, Attar M, Rubin HS, Lewis JM, Klein MS, Roberts R. Intracoronary thrombolytic therapy in acute myocardial infarction: A prospective, randomized, controlled trial. Am J Cardiol 1985; 55:301-308.

15. Blunda M, Meister SG, Schechter JA, Pickering NJ, Wolf NM. Intravenous versus intracoronary streptokinase for acute transmural myocardial infarction. Cathet Cardiovasc Diagn 1984; 10:319-327.

16. Anderson JL, Marshall HW, Askins JC, Lutz JR, Sorensen SG, Monlove RL, Yanowitz FG, Hagan AD. A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction. Circulation 1984; 70:606-618.

17. DeCoster PM, Melin JA, Detry JMR, Brasseur LA, Beckers C, Col J. Coronary artery reperfusion in acute myocardial infarction: Assessment by pre- and postintervention thallium-201 myocardial perfusion imaging. Am J Cardiol 1985; 55:889-895.

18. Valentine RP, Pitts DE, Brooks-Brunn JA, Williams JG, Van Hove E, Schmidt PE. Intravenous versus intracoronary streptokinase in acute myocardial infarction. Am J Cardiol 1985; 55:309-312.

19. Taylor GJ, Mikell FL, Moses HW, Dove JT, Batchelder JE, Thull A, Hansen S, Wellons HA Jr, Schneider JA. Intravenous versus intracoronary streptokinase therapy for acute myocardial infarction in community hospitals. Am J Cardiol 1984; 54:256-260.

20. Cribier A, Berland J, Champoud O, Moore N, Behar P, Letac B. Intracoronary thrombolysis in evolving myocardial infarction. Br Heart J 1983; 50:401-410.

21. Ganz W, Geft I, Maddahi J, Berman D, Charuzi Y, Shah PK, Swan HJC. Nonsurgical reperfusion in evolving myocardial infarction. J Am Coll Cardiol 1983; 1:1247-1253.

22. Alderman EL, Jutzy KR, Berte LE, Miller RG, Friedman JP, Creger WP, Eliastam M. Randomized comparison of intravenous versus intracoronary streptokinase for myocardial infarction. Am J Cardiol 1984; 54:14-19.

23. Cowley MJ, Hastillo A, Vetrovec GW, Fisher LM, Garrett R, Hess ML. Fibrinolytic effects of intracoronary streptokinase administration in patients with acute myocardial infarction and coronary insufficiency. Circulation 1983; 67:1031-1038.

24. Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. Circulation 1981; 63:307-317.

25. Smalling RW, Fuenter F, Matthews MW, Freund GC, Hicks CH, Reduto LA, Walker WE, Sterling RP, Gould KL. Sustained improvement in left ventricular function and mortality by intracoronary streptokinase administration during evolving myocardial infarction. Circulation 1983; 68:131-138.

26. Vetrovec GW, Leinbach RC, Gold HK, Cowley MJ. Intracoronary thrombolysis in syndromes of unstable ischemia: Angiographic and clinical results. Am Heart J 1982; 104:946-952.

27. Mandelkorn JB, Wolf NM, Singh S, Shechter JA, Kersh RI, Rodgers DM, Workman MB, Bentivoglio LG, LaPorte SM, Meister SG. Intracoronary thrombus in nontransmural myocardial infarction and in unstable angina pectoris. Am J Cardiol 1983; 52:1-6.

28. Capone G, Wolf NM, Meyer B, Meister SG. Frequency of intracoronary filling defects by angiography in angina pectoris at rest. Am J Cardiol 1985; 56:403-406.

29. Bresnahan DR, Davis JL, Holmes DR Jr, Smith HC. Angiographic occurrence and clinical correlates of intraluminal coronary artery thrombus: Role of unstable angina. J Am Coll Cardiol 1985; 6:285-289.

30. Sherman CT, Litvack F, Grundfest W, Lee M, Hickey A, Chaux A, Kass R, Blanche C, Matloff J, Morgenstern L, Ganz W, Swan HJC, Forrester J. Coronary angioscopy in patients with unstable angina pectoris. N Engl J Med 1986; 315:913-919.

31. Gold HK, Johns JA, Leinbach RC, Yasuda T, Grossbard E, Zusman R, Collen D. A randomized, blinded, placebo -controlled trial of recombinant human tissue-type plasminogen activator in patients with unstable angina pectoris. Circulation 1987; 75:1192-1199.

32. Gotoh K, Minamino T, Katoh O, Hamano Y, Fukui S, Hori M, Kusuoka H, Mishima M, Inoue M, Kamada T. The role of intracoronary thrombus in unstable angina: Angiographic assessment and thrombolytic therapy during ongoing anginal attacks. Circulation 1988; 77:526-534.

33. DeWood MA, Stifter WF, Simpson CS, Spores J, Eugster GS, Judge TP, Hinnen ML. Coronary arteriographic findings soon after non-Q-wave myocardial infarction. N Engl J Med 1986; 315:417-423.

34. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wave front phenomenon of ischemic cell death. I. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977; 56:786-794.

35. Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979; 40:633-640.

36. ISAM Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.). Mortality, morbidity, and infarct size at 21 days. N Engl J Med 1986; 314:1465-1471.

37. White HD, Norris RM, Brown MA, Takayama M, Maslowski A, Bass NM, Ormiston JA, Whitlock T. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987; 317:850-855.

38. Guerci AD, Gerstenblith G, Brinker JA, Chandra NC, Gottlieb SO, Bahr RD, Weiss JL, Shapiro EP, Flaherty JT, Bush DE, Chew PH, Gottlieb SH, Halperin HR, Ouyang P, Walford GD, Bell WR, Fatterpaker AK, Llewellyn M, Topol EJ, Healy B, Siu CO, Becker LC, Weisfeldt ML. A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. N Engl J Med 1987; 317:1613-1618.

39. Schwarz F, Schuler G, Katus H, Hofmann M, Manthey J, Tillmanns H, Mehmel HC, Kubler W. Intracoronary thrombolysis in acute myocardial infarction: Duration of ischemia as a major determinant of late results after recanalization. Am J Cardiol 1982; 50:933-937.

40. Mathey DG, Schofer J, Sheehan FH, Becher H, Tilsner V, Dodge HT. Intravenous urokinase in acute myocardial infarction. Am J Cardiol 1985; 55:878-882.

41. Sheehan FH, Mathey DG, Schofer J, Dodge HT, Bolson EL. Factors that determine recovery of left ventricular function after thrombolysis in patients with acute myocardial infarction. Circulation 1985; 71:1121-1128.

42. Gruppo Italiano per lo Studio della Streptokinasi Nell' Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; 1:397-401.

43. ISIS Steering Committee. Intravenous streptokinase given within 0-4 hours of onset of myocardial infarction reduced mortality in ISIS-2. Lancet 1987; 1:502.

44. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349-360.

45. Gang ES, Lew AS, Hong M, Wang FZ, Siebert CA, Peter T. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. N Engl J Med 1989; 321:712-716.

46. Kersschot IE, Brugada P, Ramentol M, Zehender M, Waldecker B, Stevenson WG, Geibel A, de Zwaan C, Wellens HJJ. Effects of early reperfusion in acute myocardial infarction on arrhythmias induced by programmed stimulation: A prospective, randomized study. J Am Coll Cardiol 1986; 7:1234-1242.

47. Sager PT, Perlmutter RA, Rosenfeld LE, McPherson CA, Wackers FJT, Batsford WP. Electrophysiologic effects of thrombolytic therapy in patients with a transmural anterior myocardial infarction complicated by left ventricular aneurysm formation. J Am Coll Cardiol 1988; 12:19-24.

48. Cigarroa RG, Lange RA, Hillis LD. Prognosis after acute myocardial infarction in patients with and without residual anterograde coronary blood flow. Am J Cardiol 1989; 64:155-160.

49. Lange RA, Cigarroa RG, Hillis LD. Influence of residual antegrade coronary blood flow on survival after myocardial infarction in patients with multivessel coronary artery disease. Coronary Artery Disease 1990; 1:1-5.

50. Lange RA, Cigarroa RG, Wells PJ, Kremers MS, Hillis LD. Influence of antegrade flow in the infarct artery on the incidence of late potentials after acute myocardial infarction. Am J Cardiol 1990; 65:in press.

51. Berbari EJ, Scherlag BJ, Hope RR, Lazzara R. Recording from the body surface of arrhythmogenic ventricular activity during the ST segment. Am J Cardiol 1978; 41:697-702.

52. Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. Circulation 1981; 235-242.

53. Winters SL, Stewart D, Targonski A, Gomes JA. Role of signal-averaging of the surface QRS complex in selecting patients with nonsustained ventricular tachycardia and high grade ventricular arrhythmias for programmed ventricular stimulation. J Am Coll Cardiol 1988; 12:1481-1487.

54. Simson MB, Unterecker WJ, Spielman SR, Horowitz LN, Marcus NH, Falcone RA, Harken AH, Josephson ME. Relation between late potentials on the body surface and directly recorded fragmented electrograms in patients with ventricular tachycardia. Am J Cardiol 1983; 51:105-112.

55. El-Sherif N, Scherlag BJ, Lazzara R. Electrode catheter recordings during malignant ventricular arrhythmia following experimental acute myocardial ischemia. Evidence for re-entry due to conduction delay and block in ischemic myocardium. Circulation 1975; 51:1003-1014.

56. Gardner PI, Ursel PC, Fenoglio JJ, Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation 1985; 72:596-611.

57. Breithardt G, Borggrefe M. Pathophysiologic mechanisms and clinical significance of ventricular late potentials. Eur Heart J 1986; 7:364-385.

58. McGuire M, Kuchar D, Ganis J, Sammel N, Thorburn C. Natural history of late potentials in the first ten days after acute myocardial infarction and relation to early ventricular arrhythmias. Am J Cardiol 1988; 61:1187-1190.

59. Gomes JA, Mehra R, Barreca P, El-Sherif N, Hariman R, Holtzman R. Quantitative analysis of the high frequency components of the signal-averaged QRS complex in patients with acute myocardial infarction: A prospective study. Circulation 1985; 72:105-111.

60. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: Natural history and prognostic significance. Circulation 1986; 74:1280-1289.

61. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis LD, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis in Myocardial Infarction (TIMI) trial, phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987; 76:142-154.

62. Chaitman BR, Thompson B, Wittry MD, Stump D, Hamilton WP, Hillis LD, Dwyer JG, Solomon RE, Knatterud GL, and TIMI investigators. The use of tissue-type plasminogen activator for acute myocardial infarction in the elderly: Results from Thrombolysis in Myocardial Infarction phase I, open label studies, and the Thrombolysis in Myocardial Infarction phase II pilot study. J Am Coll Cardiol 1989; 14:1159-1165.

63. Marder VJ. Pharmacology of thrombolytic agents. Implications for therapy of coronary artery thrombosis. Circulation 1983; 68 (Suppl I):2-5.

64. Lew AS, Neer T, Rodriguez L, Geft IL, Shah PK, Ganz W. Clinical failure of streptokinase due to an unsuspected high titer of antistreptokinase antibody. J Am Coll Cardiol 1984; 4:183-185.

65. Gottlich CM, Cooper B, Schumacher JR, Hillis LD. Do different doses of intravenous streptokinase alter the frequency of coronary reperfusion in acute myocardial infarction? Am J Cardiol 1988; 62:843-846.

66. Neuhaus KL, Tebbe U, Sauer G, Kreuzer H, Kostering H. High dose intravenous streptokinase in acute myocardial infarction. Clin Cardiol 1983; 6:426-430.

67. Spann JF, Sherry S, Carabello BA, Denenberg BS, Mann RH, McCann WD, Gault JH, Gentzler RD, Belber AD, Maurer AH, Cooper EM. Coronary thrombolysis by intravenous streptokinase in acute myocardial infarction: Acute and follow-up studies. Am J Cardiol 1984; 53:655-661.

68. Hillis LD, Borer J, Braunwald E, Chesebro JH, Cohen LS, Dalen J, Dodge HT, Francis CK, Knatterud G, Ludbrook P, Markis JE, Mueller H, Desvigne-Nickens P, Passamani ER, Powers ER, Rao AK, Roberts R, Roberts WC, Ross A, Ryan TJ, Sobel BE, Williams DO, Zaret BL, and co-investigators. High-dose intravenous streptokinase for acute myocardial infarction: Preliminary results of a multicenter trial. J Am Coll Cardiol 1985; 6:957-962.

69. Marder VJ, Rothbard RL, Fitzpatrick PG, Francis CW. Rapid lysis of coronary artery thrombi with anisoylated plasminogen:streptokinase activator complex. Ann Intern Med 1986; 104:304-310.

70. Bonnier HJRM, Visser RF, Klomps HC, Hoffmann HJML, and the Dutch Invasive Reperfusion Study Group. Comparison of intravenous anisoylated plasminogen streptokinase activator complex and intracoronary streptokinase in acute myocardial infarction. Am J Cardiol 1988; 62:25-30.

71. Anderson JL, Rothbard RL, Hackworthy RA, Sorensen SG, Fitzpatrick PG, Dahl CF, Hagan AD, Browne KF, Symkoviak GP, Menlove RL, Barry WH, Eckerson HW, Marder VJ for the APSAC Multicenter Investigators. Multicenter reperfusion trial of intravenous anisoylated plasminogen streptokinase activator complex (APSAC) in acute myocardial infarction: Controlled comparison with intracoronary streptokinase. J Am Coll Cardiol 1988; 11:1153-1163.

72. Verstraete M, Collen D. Pharmacology of thrombolytic drugs. J Am Coll Cardiol 1986; 8:33B-40B.

73. Mueller HS, Rao AK, Forman SA, and TIMI investigators. Thrombolysis in myocardial infarction (TIMI): Comparative studies of coronary reperfusion and systemic fibrinogenolysis with two forms of recombinant tissue-type plasminogen activator. J Am Coll Cardiol 1987; 10:479-490.

74. Tiefenbrunn AJ, Robison AK, Kurnik PB, Ludbrook PA, Sobel BE. Clinical pharmacology in patients with evolving myocardial infarction of tissue-type plasminogen activator produced by recombinant DNA technology. Circulation 1985; 71:110-116.

75. TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial. N Engl J Med 1989; 320:618-627.

76. Williams DO, Borer J, Braunwald E, Chesebro JH, Cohen LS, Dalen J, Dodge HT, Francis CK, Knatterud G, Ludbrook P, Markis JE, Mueller H, Desvigne-Nickens P, Passamani ER, Powers ER, Rao AK, Roberts R, Ross A, Ryan TJ, Sobel BE, Winniford M, Zaret B, and coinvestigators. Intravenous recombinant tissue-type plasminogen activator in patients with acute myocardial infarction: A report from the NHLBI thrombolysis in myocardial infarction trial. Circulation 1986; 73:338-346.

77. Verstraete M, Bory M, Collen D, Erbel R, Lennane RJ, Mathey D, Michels HR, Schartl M, Uebis R, Bernard R, Brower RW, deBono DP, Huhmann W, Lubsen J, Meyer J, Rutsch W, Schmidt W, von Essen R. Randomized trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Report from the European Cooperative Study Group for recombinant tissue-type plasminogen activator. Lancet 1985; 1:842-847.

78. Topol EJ, Califf RM, George BS, Kereiakes DJ, Abbottsmith CW, Candela RJ, Lee KL, Pitt B, Stack RS, O'Neill WW, and the Thrombolysis and Angioplasty in Myocardial Infarction Study Group. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987; 317:581-588.

79. Collen D, Topol EJ, Tiefenbrunn AJ, Gold HK, Weisfeldt ML, Sobel BE, Leinbach RC, Brinker JA, Ludbrook PA, Yasuda I, Bulkley BH, Robison AK, Hutter AM, Bell WR, Spadaro JJ, Khaw BA, Grossbard EB. Coronary thrombolysis with recombinant human tissue-type plasminogen activator: A prospective, randomized, placebo-controlled trial. Circulation 1984; 70:1012-1017.

80. Gold HK, Leinbach RC, Garabedian HD, Yasuda T, Johns JA, Grossbard EB, Palacios I, Collen D. Acute coronary reocclusion after thrombolysis with recombinant human tissue-type plasminogen activator: Prevention by a maintenance infusion. Circulation 1986; 73:347-352.

81. Neuhaus KL, Feuerer W, Jeep-Tebbe S, Niederer W, Vogt A, Tebbe U. Improved thrombolysis with a modified dose regimen of recombinant tissue-type plasminogen activator. J Am Coll Cardiol 1989; 14:1566-1569.

82. Williams DO. Personal communication.

83. Hammerman H, Kloner RA, Briggs LL, Braunwald E. Enhancement of salvage of reperfused myocardium by early beta-adrenergic blockade (timolol). J Am Coll Cardiol 1984; 3:1438-1443.

84. TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI IIA results. JAMA 1988; 260:2849-2858.

85. Simoons ML, Arnold AER, Betriu A, de Bono DP, Col J, Dougherty FC, von Essen R, Lambertz H, Lubsen J, Meier B, Michel PL, Raynaud P, Rutsch W, Sanz GA, Schmidt W, Serruys PW, Thery C, Uebis R, Vahanian A, van de Werf F, Willems GM, Wood D, Verstraete M, for the European Cooperative Study Group for recombinant tissue-type plasminogen activator (rtPA). Thrombolysis with tissue plasminogen activator in acute myocardial infarction: No additional benefit for immediate percutaneous coronary angioplasty. Lancet 1988; 1:197-203.

86. Stack RS, O'Connor CM, Mark DB, Hinohara T, Phillips HR, Lee MM, Ramirez NM, O'Callaghan WG, Simonton CA, Carlson EB, Morris KG, Behar VS, Kong Y, Peter RH, Califf RM. Coronary perfusion during acute myocardial infarction with a combined therapy of coronary angioplasty and high-dose intravenous streptokinase. Circulation 1988; 77:151-161.

87. de Bono DP, Pocock SJ, for the SWIFT Investigators Group. The SWIFT study of intervention versus conservative management after anistreplase thrombolysis. Circulation 1989; 80 (Suppl II):418 (abstract).