EVOLVING CONCEPTS IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION, 1988

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OUTLINE

Over the past 5-10 years, the treatment of acute myocardial infarction has changed dramatically. In the late 1970s and early 1980s, several important observations were made concerning the pathogenesis, course, and possible therapy of infarction. First, numerous pathologic and angiographic studies demonstrated that an occlusive coronary artery thrombus is present in the vast majority ($\geq$ 90%) of individuals with acute transmural myocardial infarction [1-6]. Second, rapid lysis of an intracoronary thrombus, with resultant reperfusion, can be achieved in most patients following the intracoronary or intravenous administration of streptokinase, urokinase, or tissue plasminogen activator [7]. Third, studies in experimental animals showed that prompt reperfusion after temporary coronary artery occlusion salvages jeopardized myocardium and reduces infarct size [8-12]. By 1985, it was clear that thrombolytic therapy could be given to patients with acute myocardial infarction and that clot lysis could be achieved in the majority.

Until 1-2 years ago, however, the most important questions regarding thrombolytic therapy were unanswered. As of March, 1988, many-- but not all-- have been clarified. Our discussion today will address the following questions:

a. What are the pertinent characteristics of the 3 presently available thrombolytic agents?

b. When administered intravenously, what effect do these agents have on left ventricular function and mortality?

c. What are the risks of intravenous thrombolytic therapy?

d. After clot lysis has been achieved, what therapeutic modalities, if any, should be employed?

After we have reviewed the available data and have attempted to answer these questions, I shall offer a suggested therapeutic approach to the typical patient with acute myocardial infarction.

PHARMACOLOGY OF AVAILABLE THROMBOLYTIC AGENTS

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-plasminogen complex acts to convert plasminogen to plasmin [13]. Initially, the plasmin that becomes available combines with circulating alpha-2-antiplasmin. Eventually, however, all available alpha-2-antiplasmin is consumed, so that free plasmin appears in the circulation. Plasmin is a serine protease which degrades fibrin, fibrinogen, and clotting factors V, VIII, and XIII. Therefore, it produces a systemic lytic state that persists

until these clotting factors and fibrinogen are resynthesized.

Streptokinase is a foreign protein. Low titers of anti-streptokinase antibodies are ubiquitous in the general population. Resistance to its fibrinolytic effects may occur if high titers of antistreptokinase antibodies are present (due to previous streptokinase administration or recent streptococcal infection). An occasional patient with marked streptokinase resistance is reported [14].

Since streptokinase leads to the degradation of plasminogen (its own cofactor), massive doses may not produce more of a fibrinolytic effect than more modest doses. In fact, there is no consistent relationship between the dose of streptokinase and the degree of fibrinolytic activity once a systemic lytic state is achieved.

In patients with acute myocardial infarction, streptokinase may be administered directly into the involved coronary artery [15-18], but this involves ready access to a catheterization laboratory and its attendant personnel. When streptokinase is given intravenously, a dose of 750,000-1,500,000 units is infused over 30 to 60 minutes. This dose produces a systemic lytic state, with a precipitous fall in circulating levels of plasminogen and fibrinogen as well as a concomitant increase in fibrin degradation products. The data displayed in Table 1 are representative of the influence of a large intravenous dose of streptokinase (1,500,000 units given over 60 minutes)[19].

Table 1: Coagulation Results from 30 patients following 1.5 million units of intravenous streptokinase

Variable	Before Streptokinase	1-3 hrs after Streptokinase	Hospital Discharge
Plasminogen (%)	97 ± 22	15 ± 8*	107 ± 35
Fibrinogen (mg/dl)	342 ± 98	161 ± 85*	638 ± 280*
FDPs (μg/ml)	21 ± 80	283 ± 168*	1 ± 4

All data are mean ± 1 standard deviation. * $p < 0.01$ in comparison to baseline. FDP = fibrinogen degradation product.

B. Urokinase Urokinase differs from streptokinase in several ways [13]. (a)It *directly* activates plasminogen to plasmin. (b)Since it is nonantigenic, it is better tolerated than streptokinase and has a lower incidence of resistance. (c)Although it induces a

systemic lytic state, it appears to deplete plasminogen less than streptokinase [20]. (d)It is several times more expensive than streptokinase; for this reason, it has usually been used only in patients who are likely to have high titers of anti-streptokinase antibodies.

In most therapeutic trials of urokinase, a loading dose of 2500-4500 CTA units/kg is given over 15-60 minutes, followed by the same dose per hour for 12-24 hours. With this dose, a mild depletion of plasminogen and fibrinogen is noted, with marked fibrinolytic activity in circulating plasma. Higher doses reduce the plasminogen and fibrinogen levels to a similar extent as streptokinase [21].

C. Tissue Plasminogen Activator Both streptokinase and urokinase convert circulating plasminogen to plasmin, producing a systemic fibrinolytic state (and, therefore, increasing the risk of hemorrhage). Recent efforts have centered on the development of so-called "clot-selective" thrombolytic agents, which produce local fibrinolysis without marked systemic effects. In November, 1987, the Food and Drug Administration approved recombinant tissue plasminogen activator (r-tPA) for general use. After its intravenous administration, r-tPA is avidly bound to the plasminogen and fibrin within the interstices of a thrombus. Its affinity for circulating (free) plasminogen is very low (1/500th of its affinity for plasminogen-fibrin within an existing clot). As a result of these relative affinities, r-tPA produces thrombolysis without causing a systemic fibrinolytic state. To be sure, as Table 2 demonstrates, r-tPA induces 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 r-tPA that is administered [22]. However, the observed changes are not as marked as those noted following streptokinase (shown in Table 1).

Aside from the fact that r-tPA produces "local" fibrinolysis without a systemic fibrinolytic state, r-tPA is nonantigenic and causes no adverse reactions with rapid intravenous administration. Repeated administration is possible without producing an antibody response. It has a very brief duration of action [23], so that its thrombolytic effect can be "turned off" quickly if bleeding occurs or invasive procedures (i.e., coronary angioplasty or bypass surgery) are required.

The recommended dose of intravenous r-tPA is 100 mg total, given in the following way: 6 mg over the first 1 minute, followed

Table 2: Coagulation results from patients following intravenous r-tPA (from reference # 22)

	before r-tPA	3 hours after r-tPA
80 mg r-tPA		
plasminogen (%)	96 ± 15	59 ± 19*
fibrinogen (mg/dl)	325 ± 80	314 ± 62
FDPs (μg/ml)	2 ± 6	47 ± 115*
100 mg r-tPA		
plasminogen (%)	99 ± 18	51 ± 17*
fibrinogen (mg/dl)	349 ± 85	319 ± 86*
FDPs (μg/ml)	8 ± 46	104 ± 188*
150 mg r-tPA		
plasminogen (%)	99 ± 21	41 ± 16*
fibrinogen (mg/dl)	310 ± 91	230 ± 70*
FDPs (μg/ml)	6 ± 19	132 ± 202*

All data are mean ± 1 standard deviation. * $p < 0.01$ in comparison to baseline. FDP = fibrin degradation product.

by 54 mg for the remainder of the first hour (total dose during hour # 1 = 60 mg); 20 mg each during hours # 2 and 3. r-tPA is presently very expensive: a 100 mg dose costs about $2000 (in contrast to 1.5 million units of streptokinase, which costs about $150).

EFFECTS OF THROMBOLYTIC THERAPY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

A. Reestablishment of Antegrade Blood Flow

1. Intracoronary Streptokinase/Urokinase Numerous authors have administered streptokinase directly into the occluded coronary artery in patients with transmural myocardial infarction. The data from these studies are displayed in Table 3 (page 7). As these data demonstrate, intracoronary streptokinase restores antegrade flow in 71% of occluded arteries, and the average time from initiation of therapy to restoration of flow is 30 minutes. The data for urokinase (given intracoronary) are similar.

Although the overall reperfusion rate with intracoronary streptokinase is 71%, successful thrombolysis is slightly more likely in those to whom the drug is administered early after the onset of chest pain. According to Kennedy et al [38], those

given intracoronary streptokinase within 6 hours of pain had a reperfusion rate of 75%, whereas those given the drug beyond 6 hours had a reperfusion rate of only 58%.

Table 3: Reperfusion rates after intracoronary streptokinase

Author (ref #)	Reperfusion rate		Time from onset of pain to Drug
Rogers [24]	19/25	76%	6.5 hours
Rentrop [25]	32/43	74%	5.9
Tennant [20]	20/35	57%	5.7
Raizner [26]	8/16	50%	5.6
Khaja [15]	12/20	60%	5.4
Kennedy [17]	73/108	68%	4.6
Blunda [27]	8/13	62%	4.4
Anderson [28]	18/21	86%	4.3
DeCoster [29]	18/21	86%	4.1
Anderson [16]	15/20	75%	4.0
Leiboff [18]	15/22	68%	4.0
Valentine [30]	50/85	59%	4.0
Taylor [31]	44/63	70%	3.6
Cribier [32]	39/61	64%	3.6
Ganz [33]	64/74	86%	3.4
Alderman [34]	11/15	73%	3.3
Cowley [35]	16/18	89%	
Rentrop [36]	17/20	85%	
Smalling [37]	73/100	73%	
OVERALL	552/780	71%	

2. Intravenous Streptokinase Although it is clear that intracoronary streptokinase or urokinase can quickly achieve thrombolysis in most patients with acute transmural myocardial infarction, this therapeutic approach has obvious disadvantages. First, cardiac catheterization must be performed, and, therefore, there is an obligatory delay between patient presentation to the Emergency Room and initiation of therapy. Even in the centers most experienced in this approach, this delay is 45-120 minutes. Second, most patients with myocardial infarction do not have immediate access to a facility that can deliver intracoronary therapy at any hour of the day or night. For these reasons, the rapid *intravenous* administration of an effective thrombolytic agent would permit earlier and more widespread use of this therapeutic modality in patients with acute infarction.

A number of published studies have utilized acute coronary arteriography before and during intravenous streptokinase to assess the rate of reperfusion; the results of these reports are displayed

in Table 4. As these data indicate, reperfusion was achieved with intravenous streptokinase in 129 of 304 patients (42%). Antegrade coronary flow was restored an average of 45 minutes after therapy was begun. The rate of reperfusion with intravenous streptokinase appears to be highly dependent on the elapsed time from onset of chest pain to initiation of therapy. In the 3 studies in which this average time was > 4 hours [7,19,24], reperfusion was accomplished in only 59 of 175 patients (34%). In contrast, in the 5 trials in which this average time was ≤ 4 hours [27,34,39-41], reperfusion was achieved in 70 of 129 patients (54%).

Table 4: Reperfusion rates after intravenous streptokinase

Author (ref #)	Reperfusion rate		Time from onset of pain to Drug
Rogers [24]	8/26	31%	6.8 hours
TIMI [7]	40/115	35%	4.8
Hillis [19]	11/34	32%	4.5
Blunda [27]	6/12	50%	4.0
Schroeder [39]	11/21	52%	3.8
Spann [40]	21/43	49%	3.5
Neuhaus [41]	24/40	60%	3.4
Alderman [34]	8/13	62%	3.4
OVERALL	129/304	42%	

3. Intravenous Tissue Plasminogen Activator The TIMI investigators performed emergent coronary arteriography both before and during the intravenous infusion of r-tPA, 80 mg over 3 hours. As the data in Table 5 (page 9) demonstrate, r-tPA induced reperfusion in 63% of these patients. In a direct comparison with intravenous streptokinase, r-tPA induced reperfusion in 62%, whereas streptokinase did so in only 35% ($p < 0.01$)[43]. In several subsequent studies, r-tPA was initiated in the Emergency Room, and coronary arteriography was performed soon thereafter (within 1-3 hours, while the r-tPA infusion was still running). In these reports, r-tPA induced reperfusion in 66-75% (average, 73% of patients)(Table 5).

As noted previously, the recommended dose of r-tPA is 100 mg, given over 3 hours (60 mg during hour # 1, 20 mg each during hours # 2 and 3). A larger dose (i.e., 150 mg) has been associated with an unacceptably high incidence of intracranial bleeding; as a result, the total dose should not exceed 100 mg.

In summary, a reperfusion rate of about 70% is achieved with *intracoronary* streptokinase and *intravenous* r-tPA, and the reperfusion

Table 5: Reperfusion rates after intravenous r-tPA

Author (ref #)	Reperfusion rate		Time from onset of pain to Drug
A. Pre- and post-treatment coronary arteriography			
Williams [42](TIMI)	25/37	68%	4.8 hours
Chesebro [43](TIMI)	70/113	62%	4.7 hours
OVERALL	95/150	63%	
B. Post-treatment (1-3 hours after r-tPA) coronary arteriography			
Verstraete [44]	43/61	70%	3.0
Topol [45]	288/386	75%	2.9
Guerci [46]	44/67	66%	3.2
OVERALL	375/514	73%	

rate may be as high as 75% when the time from onset of chest pain to initiation of therapy is < 4 hours. In contradistinction, *intravenous* streptokinase achieves reperfusion in only 42% of all patients and in only 54% of those in whom the elapsed time from pain to therapy is < 4 hours. In the studies in which *intravenous* r-tPA and *intravenous* streptokinase have been directly compared [43,44], the reperfusion rate with r-tPA has been significantly greater than with streptokinase.

B. Left Ventricular Function Numerous uncontrolled studies [18,26,30,47-50], almost all of which have used intracoronary streptokinase, have reported that global and/or regional left ventricular function is improved with coronary reperfusion. However, only recently has *intravenous* therapy with streptokinase or r-tPA been shown to improve global left ventricular function in placebo-controlled, randomized evaluations. The I.S.A.M. Study Group randomly assigned 1741 patients with acute myocardial infarction to placebo or intravenous streptokinase (1.5 million units over 60 minutes)[51]. All patients received therapy within 6 hours of chest pain, and 56% received it within 3 hours. Three to 4 weeks later, left ventriculography was performed. As noted in Table 6 (page 10), the patients who received streptokinase had a left ventricular ejection fraction of 0.57, whereas those who received placebo had an ejection fraction of 0.54 ($p < 0.005$).

Similar data concerning the salutary influence of intravenous streptokinase on left ventricular performance have been reported by White et al [52](Table 6). These authors blindly and randomly assigned 219 consecutive patients with acute myocardial infarction to placebo

Table 6: Effects of intravenous thrombolytic therapy on left ventricular function

Author (ref #)	Drug/Dose	LV ejection fraction	Time pain to drug
I.S.A.M. [51]	streptokinase 1.5 million u	streptokinase 0.57 placebo 0.54 $p < 0.005$	< 6 hours in all < 3 hours in 56%
White [52]	streptokinase 1.5 million u	streptokinase 0.59 placebo 0.53 $p < 0.005$	3.0 hours
Guerci [46]	r-tPA, 100 mg	r-tPA 0.53 placebo 0.46 $p < 0.02$	3.2 hours

or intravenous streptokinase, 1.5 million units over 30 minutes. In all patients the elapsed time from onset of chest pain to initiation of therapy was < 4 hours. At 21 days, left ventriculography was performed, from which left ventricular ejection fraction was calculated. The patients who received streptokinase had an average ejection fraction of 0.59, whereas the placebo group had an average ejection fraction of only 0.53 ($p < 0.005$).

Intravenous r-tPA, 80-100 mg infused over 3 hours, has been shown to exert a beneficial effect on left ventricular function. Guerci et al [46] randomly assigned 72 patients with acute myocardial infarction to r-tPA therapy and 66 to placebo. In all patients the elapsed time from onset of pain to initiation of therapy was < 4 hours. On the 10th hospital day, left ventriculography was performed, revealing an average left ventricular ejection fraction of 0.53 in the r-tPA group and 0.46 in the placebo group ($p < 0.02$)(Table 6). Of those treated with placebo, congestive heart failure over the days following infarction was noted in 33%, whereas it occurred in only 14% of those receiving r-tPA ($p < 0.01$).

In short, these 3 carefully designed, placebo-controlled studies of intravenous thrombolytic therapy (streptokinase or r-tPA) clearly demonstrate that the *early administration* (usually < 4 hours) of a thrombolytic agent leads to a significant improvement in left ventricular function. In all probability, the later administration of streptokinase or r-tPA would not induce a substantial improvement in left ventricular ejection fraction.

C. Mortality Although several uncontrolled reports have suggested that successfully reperfused patients (with intracoronary streptokinase) have a lower mortality than those who do not reperfuse [37,38,53,57], the 6 controlled trials [15-18,25,26] which have assessed the influence of intracoronary streptokinase on mortality have consistently failed to demonstrate a beneficial effect (Table 7).

Table 7: Effect of intracoronary streptokinase on mortality

Author (ref #)	mortality rate streptokinase	placebo	p value
Anderson [16]	1/24	4/26	NS
Raizner [26]	4/29	2/35	NS
Rentrop [25]	13/62	6/61	NS
Khaja [15]	1/20	4/20	NS
Leiboff [18]	4/22	2/18	NS
Kennedy [17]	11/134	17/116	NS
OVERALL	34/291	35/276	
	11.7%	12.7%	

For these 6 studies, the average elapsed time from onset of chest pain to initiation of therapy was 4.8 hours. In the opinion of many, this delay may have prevented streptokinase from exerting a beneficial effect.

In 1986, the results of the so-called GISSI study were published [58]. This multicenter unblinded trial from Italy compared mortality at 21 days in almost 12,000 patients with acute myocardial infarction who received intravenous streptokinase (1.5 million units over 60 minutes) (n = 5860) or placebo (n = 5852). Patients were enrolled in the study and received streptokinase or placebo up to 12 hours after the onset of chest pain. As the data in Table 8 (page 12) indicate, streptokinase induced a significant reduction (18%) in overall mortality (10.7% for streptokinase, 13.0% for placebo; p = 0.002). Importantly, however, as the data in the Table demonstrate, streptokinase reduced mortality only in those in whom therapy was initiated within 6 hours of the onset of pain, and its beneficial influence was largely confined to those in whom the drug was begun within 3 hours. In fact, those individuals who were treated with streptokinase within 3 hours of chest pain enjoyed a 23% reduction in mortality. A similar diminution in mortality with intravenous streptokinase has been reported by White et al [52](2.5% with streptokinase, 12.9% with placebo; p = 0.012) as well as the Second International Study of Infarct Survival (so-called ISIS-2)(8% with streptokinase, 12% with

Table 8: Results of the GISSI trial [58]

	Streptokinase (n=5860)	Control (n=5852)	p
Overall Mortality (21 days)	10.7%	13.0%	0.002
Time pain-drug (hours)			
≤ 3	9.2%	12.0%	0.0005
3-6	11.7%	14.1%	0.03
6-9	12.6%	14.1%	NS
9-12	15.8%	13.6%	NS
Site of Infarction			
anterior	14.5%	18.4%	0.0006
inferior	6.8%	7.2%	NS
lateral	10.0%	8.4%	NS
multiple location	9.0%	13.9%	0.002

placebo; p value not given)[59]. In both of these studies, all patients received therapy within 4 hours of the onset of chest pain.

The data from the GISSI study (displayed above in Table 8) demonstrate that intravenous streptokinase did not exert an effect on mortality in patients with inferior or lateral infarctions, whereas it did so in those whose infarctions were anterior or multiple in location. For the most part, anterior infarctions are generally large, whereas inferior infarctions are usually small, and lateral infarctions are intermediate in size. As a result, inferior (small) infarctions are associated with a low mortality regardless of therapy (7.2% with placebo, 6.8% with streptokinase). In contrast, those with anterior (large) infarctions who served as controls had an 18.4% mortality, which fell to 14.5% with streptokinase ($p = 0.006$). In short, the beneficial influence of any therapy on mortality is difficult to demonstrate if the mortality with placebo is low, but it is substantially easier if the mortality with placebo is high.

No report has compared the influence of r-tPA and placebo on mortality in patients with acute myocardial infarction. Relatively small studies (in comparison, at least, to the huge GISSI data base) have demonstrated that intravenous r-tPA and intravenous streptokinase are associated with a similar mortality at 21 days after infarction (4% for r-tPA, 5% for streptokinase)[43]. Since r-tPA exerts a beneficial influence on left ventricular function similar in magnitude to that of streptokinase [46,51,52], it is assumed that r-tPA-- like streptokinase-- reduces mortality in patients with acute myocardial infarction.

D. Complications With streptokinase or r-tPA, 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 [58] 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 r-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 [43] in which patients were acutely catheterized and given intravenous streptokinase or r-tPA, bleeding, ecchymosis, or hematoma were noted in 66% of those receiving r-tPA and 67% of those receiving streptokinase; a major fall in hematocrit (> 15%) occurred in 15% and 16%, respectively; and a transfusion of 2 or more 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 r-tPA and 80% of those receiving streptokinase.

In Table 9 are listed the absolute and relative contraindications to thrombolytic therapy (streptokinase, urokinase, or r-tPA). The administration of either agent to a patient with any of these

Table 9: Contraindications to thrombolytic therapy

ABSOLUTE
Active internal bleeding
Recent (< 2 months) cerebrovascular accident or neurosurgical procedure
Recent (< 10 days) major surgery, organ biopsy, or previous puncture of noncompressible vessel
Recent serious GI bleeding
Recent serious trauma, including prolonged CPR
RELATIVE
Severe arterial hypertension (systolic BP > 200 mm Hg, diastolic BP > 110 mm Hg)
Recent minor trauma, including brief CPR
Hemostatic defects; severe hepatic or renal disease
Age > 65 years
Diabetic hemorrhagic retinopathy

contraindications is likely to be followed by a major hemorrhagic event. Thrombolytic therapy should be given to patients > 65 years of age

with caution, since the incidence of hemorrhage is increased in the elderly.

As noted above, the risk of a bleeding complication is similar with intravenous streptokinase and r-tPA, since both agents are effective at lysing recently formed thrombi. However, the half-life of r-tPA is extremely short (< 10-15 minutes), so that its thrombolytic influence is rapidly terminated once the infusion is discontinued. In contrast, the systemic fibrinolytic state produced by a large bolus of intravenous streptokinase is difficult to reverse, and 12-24 hours are usually required for adequate regeneration of plasminogen, fibrinogen, and clotting factors V, VIII, and XIII.

E. Reocclusion In most patients with acute myocardial infarction, a significant stenosis in the infarct-related artery is present at the site of thrombus formation. Despite meticulous anticoagulation with intravenous heparin followed by oral aspirin +/- dipyridamole, reocclusion of the infarct-related artery occurs in 10-35% of patients before hospital discharge [43]. In most of these, reocclusion is due to recurrent thrombus formation. Any beneficial effect of successful reperfusion on left ventricular function and mortality is negated by reocclusion.

Two factors appear to be associated with an increased risk of reocclusion. First, both Harrison et al [60] and Serruys et al [61] have demonstrated that the severity of residual stenosis is directly related to the propensity for reocclusion. In the Iowa study [60], rethrombosis occurred in 7 of 13 patients (54%) with a minimal cross-sectional area < 0.4 mm^2 and in 0 of 11 with a cross-sectional area > 0.4 mm^2. Second, inadequate or interrupted anticoagulation is associated with an increased chance of reocclusion.

As yet, there is no consensus as to the most effective management of a high-grade residual stenosis in the infarct-related artery. On the one hand, some investigators argue that the chance of reocclusion is low with aggressive anticoagulation [33], and they point out that the severity of residual stenosis consistently decreases between the acute angiogram and hospital discharge [32,60]. This change is presumably due to continued lysis of thrombus, resolution of coronary vasospasm, and/or remodeling of a ruptured atherosclerotic plaque.

On the other hand, other investigators argue that the risk of reocclusion with a high-grade residual stenosis is sufficiently high to warrant mechanical revascularization with coronary angioplasty or bypass surgery. It is hoped that these procedures will diminish

the risk of reocclusion, thereby improving left ventricular function and life expectancy. In 2 recent reports [45,46], intravenous r-tPA was given to patients with acute myocardial infarction and was followed by catheterization and angioplasty (if feasible) of the infarct-related artery. In a placebo-controlled comparison, Guerci et al [46] demonstrated (a)that r-tPA (given an average of 3.2 hours after the onset of chest pain) leads to an improvement in left ventricular function and (b)that elective coronary angioplasty (performed on the third hospital day) reduces the incidence of recurrent ischemic events and improves left ventricular function during submaximal exercise. Topol et al [45] showed that immediate angioplasty after r-tPA offers no clear advantage over a more delayed procedure (7-10 days after infarction).

The current phase of the TIMI study is designed to assess the efficacy and safety of delayed (18-48 hour) angioplasty in patients who have received r-tPA. All patients with acute myocardial infarction who can receive r-tPA (100 mg) within 4 hours of the onset of chest pain and who have no contraindications are given the study drug and are randomly assigned to (a)no catheterization or (b)catheterization 18-48 hours later, with angioplasty of the infarct-related artery (if anatomically appropriate). It is hoped that the results of this study will offer insight into the need for mechanical intervention once thrombolytic therapy is given.

A SUGGESTED APPROACH TO THE PATIENT WITH ACUTE MYOCARDIAL INFARCTION

A. Who should receive thrombolytic therapy?

1. Those with electrocardiographic evidence of evolving *transmural* ("Q wave") myocardial infarction. As mentioned on page 3, numerous pathologic and angiographic studies [1-6] have demonstrated that an occlusive coronary artery thrombus is present in most ($\geq$ 90%) individuals with acute transmural infarction. In contrast, the role of coronary thrombosis in *nontransmural* ("non-Q-wave") myocardial infarction is less certain. In these patients, pathologic [1-4] and angiographic [62] studies have shown thrombotic coronary occlusion in < 50% of patients. Angiographically, some patients with nontransmural infarction appear to have partial thrombotic coronary artery occlusion, but the importance of this finding is unknown. At present, therefore, the exact role of thrombolytic therapy in patients with nontransmural myocardial infarction is uncertain.

2. Those with evidence of large or small transmural infarction. As the data from the GISSI trial [58] indicate, intravenous streptokinase

exerted a beneficial influence on mortality in patients whose infarctions were anterior or multiple in location, whereas there was no difference in mortality between streptokinase-treated and control in those with inferior or lateral infarctions (Table 8, page 12). Clearly, therefore, intravenous thrombolytic therapy should be given to patients with electrocardiographic or hemodynamic evidence of anterior and/or large infarction.

Should the patient with an apparently small transmural infarction (inferior or lateral) receive thrombolytic therapy? In my opinion, the answer is "yes." White et al [52] demonstrated that intravenous streptokinase induced an improvement in left ventricular function in comparison to placebo (Table 6, page 10), *and this improvement in ventricular function was true for those with anterior (left ventricular ejection fraction, 0.57 with streptokinase, 0.49 with placebo; $p < 0.05$) and inferior (ejection fraction, 0.60 with streptokinase, 0.55 with placebo; $p < 0.05$) infarctions.*

3. Those who can receive thrombolytic therapy within 4 hours of the onset of chest pain. Almost all the studies that have shown that intravenous streptokinase or r-tPA improves left ventricular function and/or mortality have given the drug within 4 hours of the onset of chest pain (Table 6, page 10 and Table 8, page 12). Furthermore, the data from the GISSI trial (Table 8, page 12) demonstrate that most of the beneficial effect of streptokinase on mortality is confined to those patients who received the drug within 3 hours.

4. Those without a contraindication to thrombolytic therapy and anticoagulation.

B. Which thrombolytic agent should be given? r-tPA offers several advantages in comparison to streptokinase. First, intravenous r-tPA is roughly twice as effective as intravenous streptokinase in reestablishing antegrade blood flow in an occluded coronary artery [43]. Second, r-tPA is relatively "clot-selective," producing local thrombolysis without a substantial systemic fibrinolytic effect. Its effects on circulating concentrations of plasminogen and fibrinogen are not nearly as marked as those of streptokinase (Table 1, page 4 and Table 2, page 6). Third, r-tPA is nonantigenic, whereas the administration of streptokinase is occasionally associated with an allergic reaction and rarely with full-blown anaphylactic shock. Of the 5860 patients given streptokinase in the GISSI trial [58], allergic reactions occurred in 99 (1.6%), and anaphylactic shock was noted in 7 (0.1%). In addition, the rapid intravenous administration of streptokinase sometimes causes transient hypotension (96 of 5860, 1.6%) or shivering and fever (21 of 5860, 0.4%). These events have not been reported in association with r-tPA. Since r-tPA

is nonantigenic, it can be administered repeatedly without producing an antibody response. Fourth, r-tPA has a very brief duration of action [23], theoretically allowing its thrombolytic effect to be "turned off" if bleeding occurs or invasive procedures (i.e., angiography and angioplasty) are required.

At present, the major disadvantage of r-tPA in comparison to streptokinase is cost-- a 100 mg dose of r-tPA costs about $2000, whereas 1.5 million units of streptokinase is only about $150. Despite this marked difference in cost, r-tPA offers several distinct and important advantages. *In my opinion, therefore, r-tPA is the thrombolytic "drug of choice."*

C. How should the patient be managed after he or she has received intravenous thrombolytic therapy? After a 3 hour intravenous infusion of r-tPA is initiated, the patient should be started *immediately* on full-dose intravenous heparin, beginning at 1000 units/hour and adjusting the dose to maintain the activated partial thromboplastin time (PTT) at 2-3 times control. *Adequate heparinization is crucial in order to minimize the chance of reocclusion.* Heparin therapy is continued for 2-5 days, at which time low dose (i.e., 325 mg/day) aspirin is begun and continued long-term (for several months).

Should all patients who have received thrombolytic therapy be electively catheterized (2-4 days after thrombolytic therapy) and undergo angioplasty of the infarct-related artery (if anatomically feasible)? At present, the answer to this question is unknown but should be available within the next 6-12 months.

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