Advances in Thrombolytic Therapy for Acute Myocardial Infarction

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There has been rapid proliferation of understanding and experience with thrombolytic therapy for acute myocardial infarction. Over the last few years, selective intracoronary infusion of lytic therapy has been replaced by intravenous administration because of the fundamental importance of time to reperfusion. Newer thrombolytic agents, such as tissue plasminogen activator (t-PA) and acylated streptokinase (APSAC), with properties distinct from streptokinase (SK) and urokinase, have been developed and have undergone extensive clinical trial evaluation. This review will focus primarily on the recent advances in thrombolytic therapy, with particular attention to efficacy, safety, and comparative aspects of the various agents currently or soon to be available.

Since the initial work with streptokinase (SK) more than 40 years ago by Tillett, Sherry, and colleagues,[1,2] there have been prodigious advances in the application of this form of therapy to patients. The major clinical focus of thrombolytic therapy has been acute myocardial infarction because of its high incidence, relatively small burden of fresh (minutes to hours) thrombus, ease of demonstrating clot dissolution, and fatal potential. Paralleling the development of fibrinolytic agents, several milestones in diagnosing and treating the patient with acute myocardial infarction have promoted the current rapid growth phase of clinical investigation. In chronologic order these include the postulate by Herrick in 1912 that coronary thrombosis was the inciting event of myocardial infarction,[3] direct infusion of SK into the infarct-related artery by Chazov and later Rentrop in the mid- and late 1970s,[4,5] and the angiographic demonstration of total occlusion of the coronary artery in nearly 90% of patients with fewer than 4 hours of symptoms by DeWood, with confirmation of thrombus at early coronary bypass surgery.[6] The large experience of DeWood and colleagues also served to demonstrate the safety of immediate coronary angiography and thus permitted the wide use of this procedure in the early hours of evolving myocardial infarction.

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THE FULL CIRCLE: INTRAVENOUS TO INTRACORONARY TO INTRAVENOUS THROMBOLYTIC THERAPY

The earliest application of thrombolytic therapy for acute myocardial infarction involved intravenously administered streptokinase (SK).[7] However, early clinical trials that used intravenous SK or urokinase did not show efficacy in terms of mortality reduction.[8,9] The disparity between previous findings and the current experience relates to the relatively late (up to 24 hours) administration and considerably lower doses of the fibrinolytic enzymes. Despite these shortcomings, pooled analysis of the intravenous studies of SK suggested a significant 20% reduction in mortality compared with placebo or conventional therapy.[10]

Intracoronary fibrinolytic therapy became popular in the early 1980s after Rentrop, Ganz, and others demonstrated the high efficacy of selective SK infusion for reperfusion of the occluded coronary artery.[11,12] In a major precedent for regulatory issues, (discussed subsequently) in 1982 the United States Food and Drug Administration (FDA) approved the use of intracoronary SK for acute myocardial infarction. The approval (and subsequent approval for urokinase) was based on the ability of intracoronary SK to restore patency of the occluded coronary artery without any data available at that time on ventricular function or mortality.

Two major randomized studies of intracoronary SK subsequently demonstrated salutary effects beyond the demonstration of reperfusion.[13,14] The

TABLE I

Summary of Modern Randomized Intravenous Streptokinase Trials

	Ref. No.	No. Patients	Mortality		P
A. Megatrials					
GISSI	35	11,806	↓ 19% (50% for Rx 0–1 hr)		<.001
ISIS-2	36	20,000	↓ 33% (0–4 hr)		<.001
			LV Function	Mortality	P
B. Intermediate trial					
ISAM	37	1741	↑	↓ 11%	NS
C. Smaller trials					
Western					
Washington	38	368	↑	↓ 35%	NS
New Zealand	39	175	↑	↓ 66%	.04

Modified with permission from Topol EJ: Clinical use of streptokinase and urokinase therapy for acute myocardial infarction. Heart Lung, *1987 (in press).*
LV = left ventricular.

Western Washington intracoronary SK trial demonstrated a striking 67% reduction of in-hospital mortality without improvement in ventricular function.[13] This seemingly paradoxical finding probably resulted from the relatively late time of reperfusion in the trial, with a mean time to SK initiation of 4.6 hours from symptom onset. Other randomized studies of intracoronary SK have similarly been unable to demonstrate improvement of ventricular function when therapy is delayed more than 3 hours from the symptom onset.[15–20] In contrast, the Dutch Inter-University randomized trial of intracoronary SK, with the adjunctive use of intravenous SK (43%) or coronary angioplasty (17%), showed both augmentation of ventricular function and reduction in mortality.[14,21] In this trial, patients received intracoronary SK at an earlier time—3.25 hours from the onset of symptoms. A smaller trial by Anderson et al., in which patients were treated relatively early, also demonstrated benefit of ventricular function.[22]

Despite the potential for infarct vessel recanalization, recovery of ventricular function and mortality sparing, intracoronary administration of SK has lost favor. At this point, as far as a primary reperfusion strategy, it can almost be considered defunct. The reasons for the resurgence of interest in intravenous lytic therapy stem from several important considerations. First, intracoronary SK is quite impractical. In 1986, only a minority (19%) of U.S. hospitals were equipped with a cardiac catheterization laboratory.[23] Even in hospitals where cardiac catheterization is available, a 24-hour on-call arrangement is necessary, which is not only expensive but also leads to inherent delays during nonworking hours. It takes approximately 1.5 to 2 hours, on average, to achieve infarct artery recanalization in patients when therapy is primarily dependent on obtaining direct coronary access. Second, for intracoronary streptokinase to be effective, a systemic lytic state is a prerequisite.[24,25] Thus, the lower doses generally chosen for intracoronary compared with intravenous use do not offer the advantage of a diminished effect on the coagulation system. Third, a recent randomized trial of intracoronary SK versus direct coronary angioplasty demonstrate clear-cut advantages of mechanical therapy, once coronary access has been obtained, with regard to ventricular function and alleviation of the residual stenosis.[26] Also, several randomized trials of intracoronary versus intravenous SK underscore the advantage of simple, rapid initiation of therapy.[27–31] Finally, although the recanalization efficacy of intracoronary SK is relatively high (approximately 75%), newer, intravenously administered clot-selective agents such as tissue-plasminogen activator (t-PA) have achieved similar patency rates.[32–34] For all these considerations, future use of thrombolytic therapy for myocardial infarction will be by the intravenous rather than the intracoronary route.

MODERN TRIALS OF INTRAVENOUS STREPTOKINASE

In Table I, the major randomized trials of intravenous SK are summarized. All of these trials have used a 1.5 million unit SK dose given intravenously over 30 to 60 minutes. The two megatrials, GISSI and ISIS-2, collectively account for more than 30,000

TABLE II

Clinical Trials of IV t-PA in AMI Patients

Study	Year	Type of t-PA	No. of Patients	Dose	Efficacy (%)	Significant Bleeding %	Nadir Fibrinogen (% Baseline)
Collen et al.[32]	1984	DC	42	0.5–0.75 mg/kg	72	9	92
Williams et al.[33]	1985	DC	47	80 mg/3 hr	68	32	71
TIMI (phase I)[46]	1985	DC	143	80 mg/3 hr	66	6–10	67
Verstraete et al.[45]	1985	DC	64	0.75 mg/kg	70	8	76
Verstraete et al.[44]	1985	DC	64	0.75 mg/kg × 1.5 hr	61	2	52
Gold et al.[43]	1985	DC	29	0.4–0.75 mg/kg × 1–2 hr	83	NR	62
Topol et al.[34]	1987	SC	100	1.25 mg/kg × 3 hr	84	23	65
Topol et al.[48]	1987	SC	386	1.0 mg/kg × 1 hr then 15 mg/hr × 5 hr (total = 150)	75	32	47
TIMI (phase IE)[49]	1986	SC	258	90 mg/first hr, 60 mg over 4 hr	85*	NR	NR

* *Angiography at 18–48 hr.*
DC = double chain; NR = not reported; SC = single chain.
Modified with permission from Collen and Topol: Tissue-type plasminogen activator, in Topol EJ (ed): Acute Coronary Intervention. *New York, Alan R. Liss, 1987.*

randomized patients and demonstrate a 20% and 33% reduction in mortality, respectively.[35,36] Only the preliminary results of the placebo-controlled ISIS-2 trial are available thus far. The series consisted of approximately 4000 patients treated within 4 hours of symptom onset. Smaller trials that have also demonstrated salutary effects of IV SK include ISAM, the Western Washington, and the New Zealand studies. The ISAM trial sample size of 1741 patients was inadequate to detect an effect on mortality, but ventricular function was improved in the subset of patients (55% of total) who underwent ventricular function study. Also, CK-isoenzyme analysis showed a reduction of infarct size for the patients treated with SK compared with placebo.[37] The Western Washington trial of 368 patients did not demonstrate significant overall mortality or ventricular function benefit, but subgroup analysis demonstrated that patients with anterior infarction or those receiving SK within 3 hours derived significant recovery of ventricular function.[38] In contrast, the smaller New Zealand trial demonstrated significant overall beneficial ventricular function and increased survival effects.[39]

These five controlled studies of streptokinase did not incorporate early coronary angiography, so that the direct measure of efficacy—acute infarct vessel recanalization—was not detected. Of course, most of these studies would not have been possible if they required emergency coronary angiography. Other studies in which pretreatment or posttreatment angiography, or both, were performed demonstrated a relatively low, 50% efficacy for this agent given intravenously.[15,40–42] This discrepancy between relatively low recanalization efficacy and favorable clinical outcomes has led to the question of the actual mechanism of SK. This is discussed in "Nonthrombolytic and Rheologic Effects" and "Regulatory Issues."

CLINICAL TRIALS OF TISSUE PLASMINOGEN ACTIVATOR

In contrast to the intravenous SK studies cited above, the experience with t-PA is considerably less in patient numbers but far greater with respect to angiographic characterization. In Table II, the published trials of IV t-PA are summarized. A two-chain preparation of t-PA (Genentech, San Francisco, CA) was used when the first patient received recombinant t-PA in February 1984. By late 1985, six clinical trials had been completed[32,33,43–46] with this preparation, and upscaling required a new production method (suspension culture), yielding a predominantly single-chain preparation. The dosing of t-PA is highly dependent on the preparation method, because the single-chain preparation has a 40% more rapid clearance.[34] The difference in pharmacokinetics is not actually related to the two-versus 1-chain characteristic but rather to other characteris-

tics of the production process.[47] All clinical trials performed since late 1985 have used the suspension-culture preparation.[34,48-51]

Several important results emerged from these t-PA trials. First, the remarkably high and consistent level of infarct vessel patency achieved of 70 to 75% has been demonstrated with IV t-PA even though the dose and preparation method varied. Second, initial studies suggested that reocclusion may be more problematic with t-PA,[33,43] but the use of a maintenance infusion (duration of therapy after the first-hour dose) for 3 to 6 hours reduced the rate of reocclusion to less than 12%.[43,48] The short half-life of the agent (<5 min) is particularly advantageous in the clinical setting of acute myocardial infarction. Once thrombolytic therapy has been initiated, the need may arise for emergency coronary bypass surgery or central venous access for temporary ventricular pacing. If significant peri-access or other bleeding occurs, the t-PA infusion can be stopped. Third, some fibrinogen and plasminogen breakdown clearly occurs with t-PA in such a way that this agent has relative but not absolute fibrin selectivity.[52-54] With the current dosing regimens, the fibrinogen nadir is approximately 30 to 50% of the baseline value, with only 10 to 12% exhibiting values of fibrinogen below 100 mg/dL.[53-55] Fourth, using pretreatment angiography, the Thrombolysis in Myocardial Infarction (TIMI) investigators demonstrated that a higher dose in the first hour does not increase the 90-minute patency rate but that it clearly speeds up the recanalization process.[51,55]

OTHER THROMBOLYTIC AGENTS: UROKINASE, APSAC, PROUROKINASE

Experience with IV urokinase to date has been relatively limited although Mathey demonstrated a 60% patency rate in a consecutive group of 50 patients,[56] and there are ongoing randomized comparative trials with t-PA and streptokinase. Cumulatively, more than 1000 patients have been treated with acylated streptokinase (APSAC),[57-63] but a recent multicenter randomized-comparative trial with pretreatment angiography demonstrated only a 44% recanalization frequency with APSAC 30 mg IV.[57] Both urokinase and APSAC can be given as a bolus and result in marked fibrinogen breakdown quite similar to that observed with SK. Like SK, APSAC is antigenic and, thus, will provoke a low incidence of allergic reactions(<5%) and has limited use for repeat dosing. Urokinase is a direct plasminogen activator without antigenicity or resistance. Prourokinase (scu-PA) is a naturally occurring human enzyme and is the single-chain precursor. To date, there is limited published experience with scu-PA, and no large trials have been completed. The small clinical experience suggests that scu-PA has an adequate (>50–60%) infarct vessel patency rate and the agent has a short half-life akin to t-PA.[64,65]

STREPTOKINASE VERSUS TISSUE PLASMINOGEN ACTIVATOR

To prevent the need for speculation, there have been two multicenter, randomized trials of IV SK compared with t-PA.[45,46] The results of these trials and related comparative information are shown in Table III. The TIMI phase 1 trial was devoted to establishing which of the two agents was better. Using a double-blind randomization, the TIMI Study Group showed there was a marked improvement of reperfusion rate with t-PA compared with SK. At seven serial observations during the first 90 minutes after onset of treatment, t-PA resulted in twice the reperfusion rate (90 minutes: 62% vs 31%, $P < .001$). The striking difference in efficacy is demonstrated in Figure 1 for either infarct vessels with TIMI grade 0 (no perfusion) or those with TIMI grade 1 (penetration without perfusion). These unanticipated, extreme differences in reperfusion frequency between the two agents resulted in premature termination of the trial.[46]

This trial has been criticized for a number of reasons.[66,67] First, the patients were treated relatively late, at 4.8 hours, related to the requirement for pretreatment angiography. In retrospect, it became clear that SK was highly time dependent for achieving efficacy, so that administration more than 3 to 4 hours from the onset of symptoms resulted in extremely poor thrombolytic efficacy, approaching that seen with spontaneous recanalization.[6,41] In Figure 2, the results from TIMI graphically show time dependency of SK and lack of this characteristic for t-PA. However, superior thrombolytic efficacy was evident for t-PA versus SK even when the agents were administered fewer than 4 hours from symptom onset. Although a minority of patients (101 of 290, or 35%) treated in this trial were less than 4 hours from symptom onset, data from the European Cooperative trial, in which patients received t-PA at 2.6 hours from symptom onset (no pretreatment angiography), also demonstrated superior t-PA versus SK efficacy (70 vs 55%, respectively, $P = .054$) (Figure 3). Thus, t-PA has been unequivocally demonstrated to have improved thrombolytic efficacy over SK in two randomized trials over a broad time span (Figure 4). These findings account for the selection of t-PA as the agent of choice for future large-scale

TABLE III

Comparison of IV Streptokinase and Tissue Plasminogen Activator

	SK	t-PA
Dose	1.5 million unit	total 1.0–1.5 mg/kg, max 135 mg; first hour 0.75–1.0 mg/kg, max 90 mg
Infarct vessel patency	50%	70–75%
Time dependency	highly, <30% patency after 4 hr	no time dependency demonstrated
Reocclusion	unknown	10–15%
Hypotension	variable, severe in <5% patients	none
Half-life	alpha, 18 min; beta, 83 min	alpha, 4 min; beta, 30 min
Fibrinogen breakdown	severe	moderate
Serum viscosity	10–15% ↓	no significant change
Bleeding	common, peri-access; intracranial bleeding <0.5% in 20,000 patients	common, peri-access; intracranial bleeding <0.5% in 5000 patients
Allergic reactions	yes (fever, rash, anaphylactoid)	no
Repeat dosing	no; ↓ efficacy, ↑ allergic reactions	yes
Cost/dose	$200	$1500–2000*

** Projected cost, not FDA approved at time of report.*

trials in both the United States (TIMI) and European Cooperative Study groups.

Second, it has been argued that the dose of SK selected led to inherent bias.[66,67] The standard modern dose of 1.5 million units of SK was given in both trials, and all published experience with SK does not show a relationship between dose and recanalization rate.[28,29,40–42,68] Third, there was significant (33%) t-PA-induced fibrinogenolysis in TIMI, although nearly half that which was observed with SK.[69] Despite relative sparing of coagulation proteins, t-PA did not result in a reduction of bleeding complications in TIMI, which chiefly involved peri-access sites. Although the European Cooperative Study demonstrated less bleeding episodes or transfusion requirements for t-PA than SK,[45] the overall clinical trial bleeding complication rates with t-PA have not been significantly decreased compared with other lytic agents.

The reasons for this observation are multiple. A potent fibrinolytic enzyme, t-PA will lead to lysis of hemostatic plugs and noncoronary fibrin. Cardiac catheterization performed in the face of lytic therapy promotes the frequency and severity of peri-access hemorrhage. Adjunctive thromboprophylactic therapy with IV-administered heparin and antiplatelet agents further increases the likelihood of bleeding episodes.

Intracranial hemorrhage is the most serious and often catastrophic complication of fibrinolytic therapy. With IV-administered t-PA at a total dose of 150 mg, an increased incidence of 1.6% (approximately 16 of 1000 patients) was observed.[49,50,72] At doses up to 120 mg, however, the rate has been 0.4%. Intracranial bleeding appears to have a similarly low incidence with high-dose IV SK, with most reports citing less than 0.5%.[35,37,38] However, little is known about the pathophysiology of cerebrovascular bleeding induced by fibrinolytic therapy. The demographic risk factors that have thus far been associated with this event include female gender, advanced age, and long-standing or severe hypertension.[48] More data and understanding will be necessary before this dreaded complication can be avoided with any of the fibrinolytic enzymes.

Besides bleeding complications, the major concern after successful thrombolysis is for sustained patency of the infarct vessel. Because serial acute and follow-up angiography has not been performed in any large-scale trial with IV SK, the true incidence of reocclusion is completely unknown. Smaller studies of IV SK have reported a wide range of reocclusion from 5 to 30%.[40–42,45,46] The TAMI trial defined the angiographic reocclusion rate with t-PA with the use of acute coronary angiography in 386 patients and follow-up at 1 week in 95% of surviving

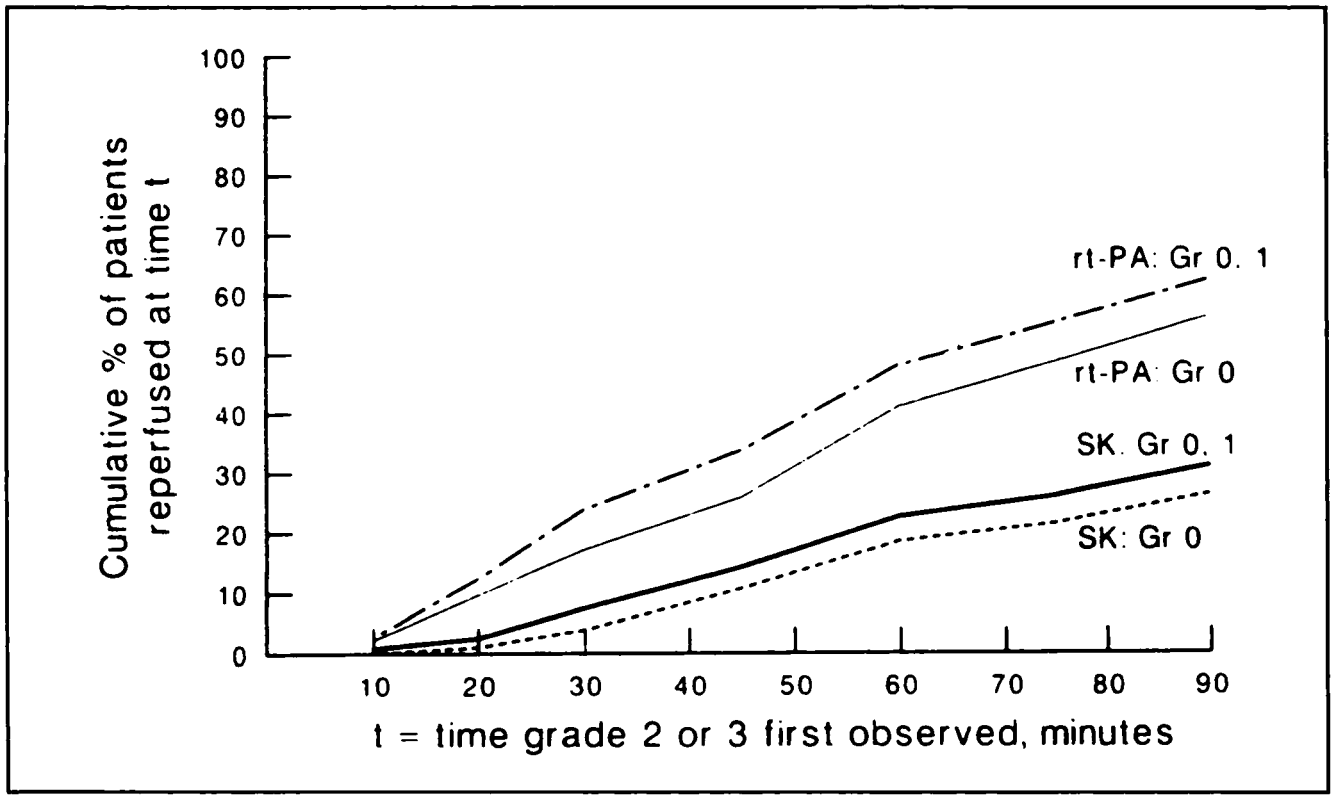

Figure 1. Coronary thrombolytic efficacy of tissue plasminogen activator (t-PA) versus streptokinase (SK). At seven serial time intervals of angiographic observation up to 90 minutes after the start of therapy, t-PA elicited reperfusion twice as often. (Reprinted with permission. Cheseboro et al: Circulation 1987;76:142–154.)

patients. For those patients with a significant residual stenosis who did not undergo angioplasty, the incidence of reocclusion was 13% (total t-PA dose = 150 mg/6–8 hr).[48]

LEFT VENTRICULAR FUNCTION AND MORTALITY

Two recent randomized, double-blind, placebo-controlled trials of t-PA have demonstrated significant left ventricular improvement. Both the Johns Hopkins and Australian trials were just completed, but preliminary data are quite similar and support a seven- to eight-point global ejection-fraction advantage for patients receiving t-PA compared with placebo.[70–72] There has not yet been a large enough randomized, prospective trial of t-PA compared with placebo or other reperfusion strategies to evaluate mortality effects.

The placebo-controlled IV SK studies that have addressed left ventricular function are those of ISAM, Western Washington and New Zealand.[37–39] In ISAM, only a subset of patients were studied, but patients receiving SK had an increased global ejection fraction. Subgroup analysis of the Western Washington trial demonstrated improvement of left ventricular function in patients with anterior infarction. Despite the relatively small size of the New Zealand trial, mortality was reduced and global ejection fraction was increased in the SK-treated patients. As discussed earlier, the GISSI and ISIS-2 megatrials convincingly demonstrated the survival advantage conferred by early administration of SK compared with conventional or placebo therapy, respectively.[35,36]

NONTHROMBOLYTIC AND RHEOLOGIC EFFECTS

Recently, the U.S. FDA Cardiorenal Advisory Committee pointed out the disproportionate effects of IV SK on infarct vessel recanalization compared with mortality reduction.[72] With SK thrombolytic efficacy of approximately 50% and acute-phase mortality

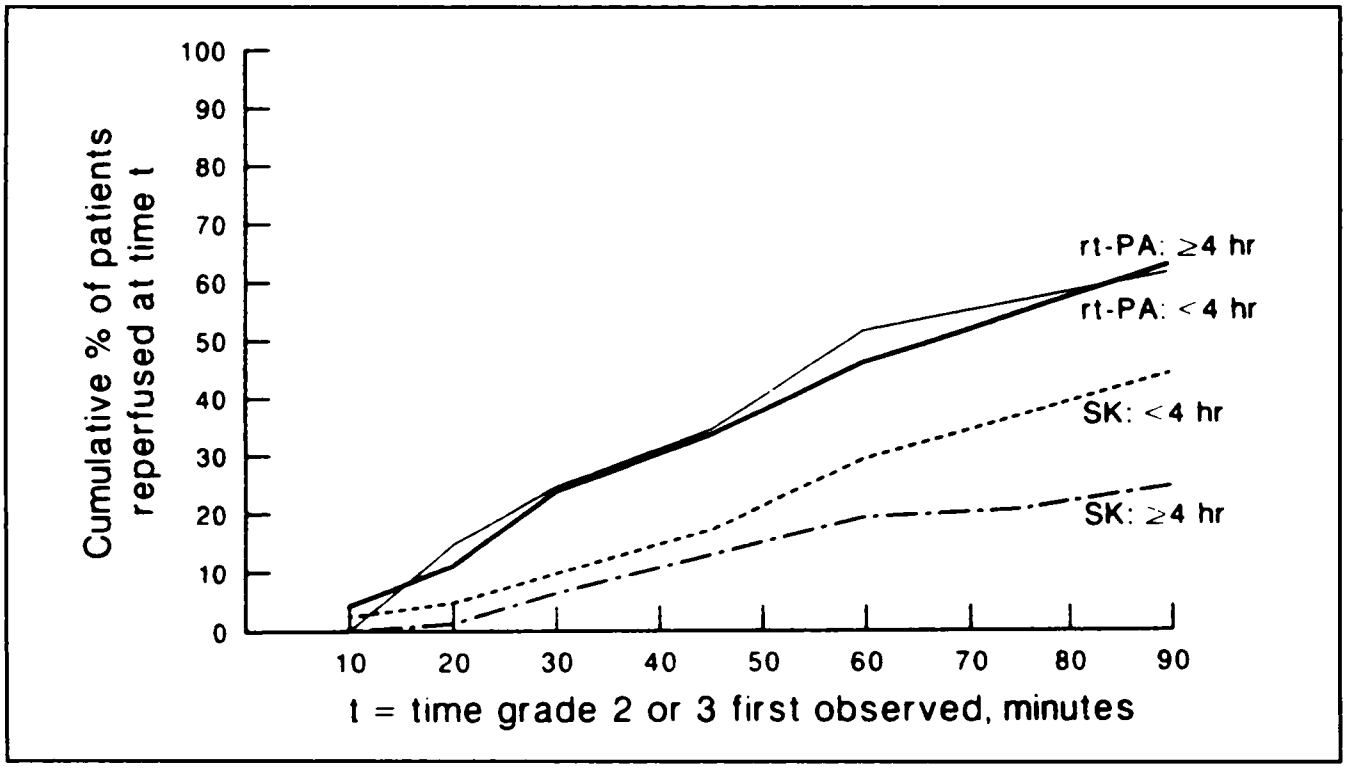

Figure 2. Difference of lytic efficacy of tissue plasminogen activator (t-PA) versus streptokinase (SK) over time. No significant difference was noted for patients treated less than or more than 4 hours from symptom onset with t-PA compared with substantially less efficacy for SK after 4 hours. (Reprinted with permission, Cheseboro et al: Circulation 1987;76:142–154.

substantial reduction of 20 to 33%,[15,35,36] the committee members suggested that the nonthrombolytic actions of IV SK may be operational. Of the various actions of SK, blood pressure reduction, viscosity reduction, and attendant rheologic alterations, antiplatelet effects, and free oxygen radical scavenging properties are potentially beneficial in the setting of myocardial reperfusion. However, none of these properties has been adequately evaluated in prospective, clinical trials.

By report of the manufacturers, systolic blood pressure reduction with IV SK is modest, averaging only 5 to 7 mm Hg.[72] Clearly, this minimal diminution of blood pressure would not be associated with a significant afterload reduction. Furthermore, acute-phase reduction of blood pressure in myocardial infarction has not been demonstrated to limit infarct size or decrease mortality in patients.[73]

Blood viscosity reduction with SK also appears to be mild, averaging 10 to 17% in two reported studies.[74,75] In a small comparative study, IV SK resulted in a significant (60%) fibrinogen reduction and only a 10% decline in blood viscosity, whereas t-PA low-

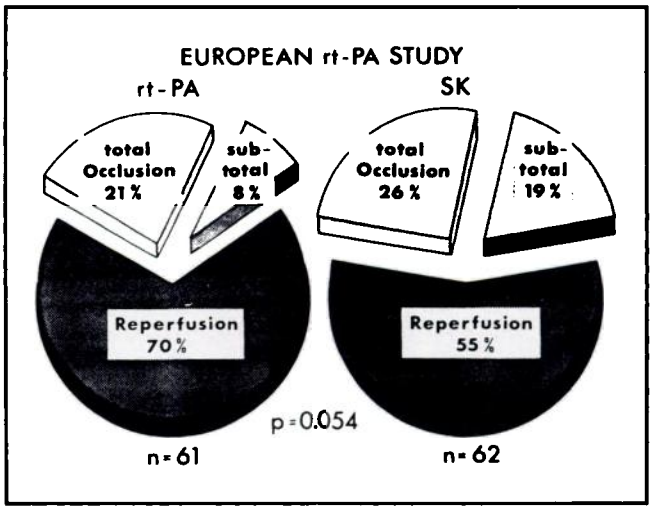

Figure 3. Difference of infarct vessel patency for tissue plasminogen activator (t-PA) versus streptokinase (SK) at 90 minutes of therapy in the randomized European Cooperative Study. Patients received SK at a median of 2.6 hours from symptom onset. (Reprinted with permission. Erbel R: The European Cooperative Trials in Acute Myocardial Infarction, in. Topol EJ (ed): Acute Coronary Intervention, New York, Alan R. Liss, 1987.)

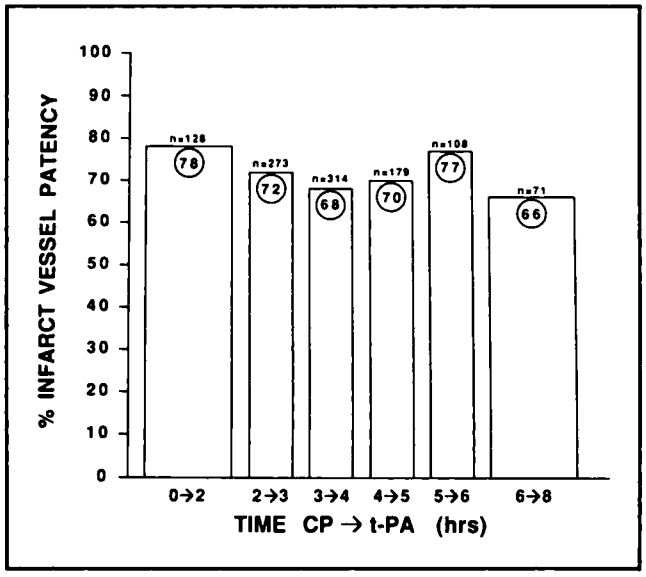

Figure 4. Consistent efficacy of tissue plasminogen activator (t-PA) over a broad time window. In a total of 1073 patients treated with IV t-PA between 20 minutes and 8 hours from symptom onset, a high level of infarct vessel patency at 90 minutes was achieved. (Data presented at FDA Cardiorenal Advisory Committee, May 29, 1987, Bethesda, MD. On file, Genentech, Inc., San Francisco, CA).

ered plasma fibrinogen by 20% and blood viscosity by 6%. Red blood cell deformity was not differently affected by SK versus t-PA.[75] Although reduction in viscosity is correlated with improved microcirculatory blood flow and decline in total peripheral resistance,[74-76] the modest changes of blood or plasma viscosity demonstrated with SK may not be substantial enough to significantly alter clinical outcome. With scant data currently available, the viscosity and rheologic effects of fibrinolytic agents certainly require further investigation.

In an *in vitro* study comparing antiplatelet effects of SK urokinase, and t-PA, the most substantial inhibitory action was demonstrated for t-PA, related to platelet-fibrin binding.[77] With higher levels of fibrinogen degradation products (FDP) generated by SK compared with t-PA, it is also possible that there may be more disaggregation with the former agent.[78] The actual platelet function *in vivo* effects in humans for the various fibrinolytic agents have not been adequately differentiated to date.

The free oxygen radical scavenging property of SK has been characterized as modest,[79] and the importance of this effect in myocardial reperfusion is a controversial subject.[80,81] Limitation of reperfusion injury by free radical scavengers has not been demonstrated in humans although this is the focus of current clinical trials.[82] With SK weak scavenging effect, it is unlikely to be of clinical significance. Recently, t-PA was suggested to have a direct myocardial function salutary effect in the experimental feline model,[83,84] but again no clinical data exists to confirm or rebut this observation.

In summary, there are multiple modest nonthrombolytic effects of SK, which have not been well characterized. Moreover, none of the effects have been correlated with favorable clinical outcome or improvement in ventricular function.

REGULATORY ISSUES

The FDA advisory panel decision to recommend approvability status for IV SK but not t-PA led to considerable controversy.[72,85-89] As the data for the two agents were carefully scrutinized, it became apparent that the strengths and weakness for each were diametrically opposed. On the one hand, little data were available for the recanalization efficacy of IV SK but the GISSI, ISIS-2 megatrials and pooled analyses confirmed mortality reduction with this agent.[35,36,90] For t-PA, considerable evidence for high thrombolytic efficacy was presented, but lacking was a large-scale placebo-controlled trial for mortality effects. For both agents, data on improvement of left ventricular function was presented but not accepted as conclusive for the panel. Also, there was discussion regarding the different doses of t-PA used in the trials (ranging from 90–150 mg total IV dose of the single-chain preparation) and a completely inaccurate account of the incidence of intracranial bleeding.[72] The latter unfortunately casted doubt and concern over t-PA as a safe fibrinolytic agent.

Since this meeting, data from two placebo-controlled studies of t-PA which substantially show left ventricular functional recovery, have become available.[70,71] The availability of these data to the FDA may ultimately lead to approval of t-PA in upcoming months. However, an important issue has been raised by the panel's decision. Should a fibrinolytic agent require proven mortality or ventricular function benefit before it can be approved for use in myocardial infarction?

In 1982, when the FDA approved intracoronary SK, the answer was clearly no. No data were available to confer more than coronary thrombolytic efficacy for this reperfusion strategy. Has the field so changed in 5 years? Is coronary thrombolysis dissociated from clinical outcomes and ventricular function?

From clinical experience and the data currently available, it is clear that the major effect of all fibrinolytic agents in this setting is to lyse intraluminal thrombus and restore blood flow through the af-

fected coronary artery. Recanalization may be of "cosmetic" benefit only when therapy is instituted too late or when myonecrosis is already complete. As long as fibrinolytic therapy is administered early and judiciously, there will be definite overall improvement in ventricular function and reduction in mortality. Denial of this principle violates the fundamental pathophysiology of acute myocardial infarction. Provided that safety of a fibrinolytic agent is confirmed, correction of the underlying occlusive clot disorder by lysis *must* be a desirable end point in the patient with myocardium at jeopardy. The dilemma for future regulatory boards will be in the definition of efficacy of a fibrinolytic agent. In a rapidly proliferating field of many new agents and manufacturers, this will undoubtedly lead to difficulties. If the effects of one fibrinolytic agent have correlation between thrombolytic and clinical efficacy, will this be adequate for all future enzymes? This question is currently unsettled. The efficacy threshold may be debated for many classes of drugs. For example, should all hypertensive agents document survival and stroke-avoidance benefit beyond effective lowering of blood pressure? Obviously, this is not the case. However, the analogy to fibrinolytic therapy is apparent.

FUTURE OF THROMBOLYTIC THERAPY

The last 5 years may be considered the rapid growth phase of understanding and experience with thrombolytic therapy for acute myocardial infarction. Concurrently, three new agents (t-PA, APSAC, prourokinase) have been developed for clinical use, and further biochemical modifications of these agents and combination therapies are being explored.[91-95] The ultimate goals of rapid, 100% coronary thrombolytic efficacy, zero reocclusion, and absence of bleeding are highly unlikely to be achieved. There is no doubt, however, that considerable investigation will follow to approximate more closely these important objectives. In planning future clinical trials and eventual clinical release of fibrinolytic agents, regulatory agencies will have to develop rational and consistent guidelines for the definition of efficacy.

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