A Pooled Analysis of Coronary Arterial Patency and Left Ventricular Function After Intravenous Thrombolysis for Acute Myocardial Infarction

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Individual studies of patency rates and left ventricular (LV) function after thrombolysis have generally been limited by small numbers of observations, wide confidence intervals, and limited numbers of time points. To obtain a more reliable estimate of patterns of patency and LV ejection fraction, a systematic overview of angiographic studies was performed after intravenous thrombolytic therapy. A total of 14,124 angiographic observations from 58 studies evaluating patency after no thrombolytic agent, streptokinase, standard dose tissue-type plasminogen activator (t-PA), accelerated dose t-PA, or anistreplase (anisoylated plasminogen streptokinase activator complex [APSAC]) were included. At 60 and 90 minutes, streptokinase had the lowest patency rates of 48% and 51%, respectively, standard dose t-PA and APSAC had similar intermediate rates of approximately 60% and 70%, and accelerated t-PA had the highest patency rates of 74% and 84%. By 2 to 3 hours and longer, the patency rates were similar for the various regimens. Reocclusion rates in studies including 1,172 patients randomized to t-PA versus a nonfibrin-specific agent were higher after t-PA (13.4% vs 8.0%, p = 0.002). Ten studies enrolling 4,088 patients treated with thrombolytic therapy versus control demonstrated a modest improvement in mean LV ejection fraction in the thrombolytic group at each of the times after thrombolytic therapy: hour 4, day 1, day 4, day 7 to 10, and day 10 to 28 after thrombolysis. By 4 days, mean ejection fraction was 53% versus 47% (thrombolytic vs control therapy, p <0.01); by 10 to 28 days it was 54.1% and 51.5%, respectively. In conclusion, this pooled analysis shows that accelerated t-PA resulted in higher 90-minute coronary arterial patency rates than other standard regimens, but that by 2 to 3 hours the rates were similar, and that reocclusion rates were higher after t-PA than nonfibrin-specific agents. Thrombolytic therapy resulted in only a small improvement in global LV function compared with results in the control group, which was fully apparent by 4 days after treatment.

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Reperfusion, sustained early patency, prevention of reocclusion, and preservation of left ventricular (LV) function are thought to be the basis for the beneficial effect of thrombolytic therapy in patients with acute myocardial infarction. Although many angiographic studies have assessed infarct artery patency and LV function in patients receiving thrombolytic therapy, the results of individual studies have generally been limited by wide confidence intervals because each study involved small numbers of patients. Moreover, individual angiographic studies have usually collected data at only 1 or 2 time points, failing to provide sequential information about infarct artery patency or LV function over time. This study provides a more reliable estimate of patterns of perfusion, reocclusion, and LV ejection fraction after frequently used intravenous thrombolytic regimens by pooling angiographic data from all available studies.

METHODS

Studies evaluating intravenous thrombolytic therapy with acute or follow-up angiography were identified by computer-aided search (Medline), careful review of reference lists of angiographic study reports, and related review articles, review of abstracts from the American Heart Association and American College of Cardiology meetings, and discussions with colleagues involved in this type of investigation. When different publications were found reporting data on the same group of patients, the more complete report was selected.

Studies that fulfilled the following criteria were included: ≥20 patients were enrolled, prospective design, and reporting of the total number of patients initially treated as well as the number who underwent angiography or ventriculography, or both. Publication of the studies that were included spanned the years 1984 to 1993. For the patency analysis, studies were included if they used intravenous streptokinase, standard dose tissue-type plasminogen activator (t-PA), accelerated dose t-PA, anistreplase (anisoylated plasminogen streptokinase activator complex [APSAC]), or no thrombolytic agent, and if they reported the number of patients who had patent infarct-related arteries and the mean time of angiography after initiation of treatment. Studies that used the following doses for each agent were included: streptokinase, >1.0 million U; standard t-PA, 0.75 to 1.5

mg/kg or 70 to 100 mg single chain and not meeting criteria for accelerated dosing; accelerated t-PA, >70 mg over 1 hour or 100 mg over 90 minutes, or both; or APSAC, 30 U over 2 to 5 minutes. For the analysis of reocclusion, studies were included that randomized patients to intravenous t-PA versus either streptokinase, APSAC, or urokinase, and reported early (approximately 90 minutes after initiation of thrombolytic therapy) and follow-up (≥24 hours after initiation of thrombolytic therapy) infarct-related artery patency. The largest single angiographic study after thrombolytic therapy, the Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) angiographic substudy,[1] had adequate power on its own to reliably determine patency rates and evaluate patency at serial time points after thrombolytic therapy, and thus was not included in this pooled analysis.

For LV ejection fraction analysis, studies were included that randomized patients to intravenous thrombolytic therapy versus control therapy, and reported mean time to ventriculography, mean LV ejection fraction, standard deviation of ejection fraction, and number of patients included in the determination of mean ejection fraction.

Infarct-related artery patency analysis: Mean angiographic time points were pooled into 5 periods after the initiation of thrombolytic therapy: 1 hour (45 to 74 minutes), 90 minutes (75 to 104 minutes), 2 to 3 hours (105 to 195 minutes), 1 day (18 to 48 hours), and 3 to 21 days. For studies in which patients were not treated with thrombolytic therapy, the time interval was measured from initiation of placebo treatment or heparin. These time groupings were selected because the studies used angiographic end points clustered around them.

Reocclusion analysis: Reocclusion rate was calculated as the number of patients with an angiographically occluded infarct-related artery who had had a patent infarct-related artery at the end of a prior "90-minute" catheterization, divided by the total number of patients who had a patent artery at the 90-minute catheterization. The pooled reocclusion rate was calculated as the sum of the patients with reocclusion divided by the sum of the patients with originally patent infarct-related arteries.

Left ventricular ejection fraction analysis: For LV ejection fraction analysis, ventriculographic time points were pooled into 5 time periods: baseline (0 hours), 4 hours, 4 days, 7 to 10 days, and 10 to 28 days, at which time there was a clustering of ventriculographic deter-

TABLE I Patency Without Thrombolytic Therapy					
Study	Number of Patients	Time to Treatment (min)	Mean Cath. Time	Patency	95% CI
Baseline					
Anderson (1984)	23	168	0 min	9% (2/23)	
TIMI-I (1987)	289	285	0 min	20% (57/289)	
Timmis (1987)	40	186	0 min	28% (11/40)	
Pooled	352			20% (70/352)	16%–24%
1 hour					
Collen (1984)	14	284	45 min	7% (1/14)	
Topol (1987)	25	228	68 min	13% (3/23)	
Cribier (1986)	23	208	74 min	22% (5/23)	
Pooled	62			15% (9/60)	6%–24%
90 minute					
ECSG-1 (1985)	65	198	75–90 min	21% (13/62)	11%–31%
2–3 hour					
Guerci (1987)	66	192	2.5 hours	24% (15/62)	14%–35%
1 day					
TPAT (1989)	56	180	17 hours	29% (7/24)	
Durand (1987)	29	149	35 hours	13% (3/24)	
Pooled	85			21% (10/48)	9%–32%
3–21 day					
Bassand (1989)	119	188	4.1 days	36% (38/105)	
NHFA (1988)	71	195	5–7 days	41% (26/64)	
TPAT (1989)	56	180	10 days	59% (17/29)	
Kennedy (1988)	177	210	10 days	45% (47/105)	
ECSG-4 (1988)	366	168	10–21 days	78% (259/334)	
White (1987)	112	180	21 days	54% (50/92)	
O'Rourke (1988)	71	114	21 days	64% (40/63)	
Bassand (1987)	55	190	21 days	67% (31/46)	
Pooled	1,027			61% (508/838)	57%–64%

CI = confidence intervals; ECSG = European Cooperative Study Group for Recombinant Tissue-Type Plasminogen Activator in Acute Myocardial Infarction trial; Mean Cath. Time = mean time from initiation of treatment until coronary angiography; NHFA = National Heart Foundation of Australia study; Time to Treatment = time from symptom onset until initiation of thrombolytic or control treatment; TIMI = Thrombolysis in Myocardial Infarction trial; TPAT = Tissue Plasminogen Activator Toronto trial.

TABLE II Intravenous Streptokinase Patency Studies (studies with ≥1.0 mU streptokinase)

Study	Number of Patients	Dose (mU/1 hour)	Time to Treatment	Mean Cath. Time	Patency	95% CI
1 hour						
PRIMI (1989)	203	1.5	140 min	61 min	48% (82/171)	
Cribier (1986)	21	1.5	115 min	74 min	52% (11/21)	
Pooled	224				48% (93/192)	41%–56%
90 minute						
ECSG-2 (1985)	65	1.0	156 min	75–90 min	55% (34/62)	
Stack (1988)	216	1.5	180 min	90 min	44% (95/216)	
TIMI-I (1987)	159	1.5	286 min	90 min	43% (63/146)	
Lopez-Sandon (1988)	25	1.5	<6 hours	90 min	60% (15/25)	
Hogg (1990)	63	1.5	209 min	90 min	53% (31/58)	
PRIMI (1989)	203	1.5	140 min	91 min	64% (124/194)	
Charbonnier (1989)	58	1.5	168 min	93 min	51% (27/53)	
Pooled	789				51% (389/754)	48%–55%
2–3 hour						
TEAM-2 (1991)	182	1.5	158 min	126 min	73% (129/176)	
Monnier (1987)	11	1.5	135 min	150 min	64% (7/11)	
Six (1990)	56	1.5	150 min	168 min	60% (32/53)	
Vogt (1988)	31	1.5	138 min	176 min	70% (21/30)	
Pooled	280				70% (189/270)	65%–75%
1 day						
PRIMI (1989)	203	1.5	140 min	14–36 hours	88% (160/181)	
Hogg (1990)	63	1.5	209 min	24 hours	88% (49/56)	
Lopez-Sandon (1988)	25	1.5	<6 hours	24 hours	75% (18/24)	
Durand (1987)	35	1.5	149 min	39 hours	82% (27/33)	
Ribeiro (1991)	50	1.2	180 min	48 hours	80% (40/50)	
Pooled	376				86% (294/344)	82%–89%
3–21 days						
PAIMS (1989)	85	1.5	127 min	4 days	77% (57/74)	
Kennedy (1988)	191	1.5	210 min	10 days	69% (89/130)	
Cherng (1992)	63	1.5	294 min	10–14 days	57% (16/28)	
Lopez-Sandon (1988)	25	1.5	<6 hours	15–21 days	90% (17/19)	
White (1987)	107	1.5	180 min	21 days	75% (74/99)	
White (1989)	135	1.5	150 min	21 days	75% (87/116)	
Bassand (1987)	52	1.5 mU/0.5 hour	210 min	21 days	68% (32/47)	
Pooled	658				73% (372/513)	70%–78%

PAIMS = Plasminogen Activator Italian Multicenter Study; PRIMI = Prourokinase in Myocardial Infarction trial; TEAM = Thrombolytic Trial of Eminase in Acute Myocardial Infarction; other abbreviations and explanations as in Table I.

minations. A "weighted average" for the ejection fraction was determined for the thrombolytic and the control groups by adding the multiples of the mean ejection fraction and sample size for each study and dividing by the total sample size. The difference between the mean ejection fractions at each time point was determined.

Statistical analysis: For each point estimate of patency, 95% confidence intervals were calculated. Because the time-patency curves for the different agents were generated from nonrandomized, distinct studies, formal statistical analyses for differences were not performed. The pooled rates of reocclusion were compared for statistical significance using a chi-square test. The difference between the thrombolytic-treated and control ejection fraction at each time point was tested with a Student's t test.

RESULTS

Infarct-related artery patency: Rates of infarct-related artery patency at various times after initiation of thrombolytic regimens are listed in Tables I to V. Figure 1 illustrates the pooled results of the 14,124 angiographic observations.[2–58] Early patency (60 and 90 minutes after

initiation of thrombolytic therapy) is lowest with streptokinase, similar for t-PA and APSAC, and higher for accelerated-dose t-PA. By 2 to 3 hours, there is little difference in patency among standard t-PA-, streptokinase, and APSAC-treated patients. By 1 day and beyond, the patency rates are similar for all 4 regimens. In fact, by 2 to 3 weeks after presentation, the difference in patency between those treated with thrombolysis and those not treated is less striking, with approximately 60% of control patients or heparin-treated patients exhibiting infarct-related artery patency.

The percentage of initially treated patients included in the patency determination declined over time, so that 90% to 95% of patients were included in the 90-minute time point and only 75% to 85% in the 3- to 21-day time point (Tables I to V).

Reocclusion: All studies included in the reocclusion analysis used intravenous heparin in conjuction with thrombolytic therapy, with the traditional dose of a 5,000 U bolus and 1,000 U/hour infusion.

Rates of reocclusion in trials randomizing to t-PA versus the nonfibrin-specific agents streptokinase,[3] APSAC,[53] or urokinase[40,42,45] are listed in Table VI. Re-

TABLE III Intravenous Tissue-Type Plasminogen Activator (t-PA) Patency Studies (studies with 0.75 to 1.5 mg/kg or 70 to 100 mg t-PA)

Study	Number of Patients	Dose	Time to Treatment	Mean Cath. Time	Patency	95% CI
1 hour						
ECSG-5 (1988)	183	100 mg/3 hours	156 min	42 min	60% (108/180)	
Smalling (1990)	91	1.25 mg/kg/3 hours	228 min	56 min	45% (40/89)	
RAAMI (1992)	138	100 mg/3 hours	168 min	62 min	63% (54/86)	
Topol (1987)	75	1.25 mg/kg/3 hours	216 min	68 min	57% (40/70)	
Pooled	487				57% (242/425)	52%–61%
90 minute						
ECSG-2 (1985)	64	0.75 mg/kg/90 min	180 min	75–90 min	70% (43/61)	
TIMI-IIA (1988)	133	100 mg/6 hours	168 min	84 min	75% (98/131)	
TIMI-I (1987)	157	80 mg/3 hours	287 min	90 min	70% (100/143)	
RAAMI (1992)	138	100 mg/3 hours	168 min	90 min	77% (94/122)	
ECSG-1 (1985)	64	0.75 mg/kg/90 min	204 min	90 min	61% (38/62)	
TAMI-4 (1989)	50	100 mg/3 hours	243 min	90 min	52% (26/50)	
TAMI-5 (1991)	95	100 mg/3 hours	200 min	90 min	71% (67/95)	
Topol (1987)	75	1.25 mg/kg/3 hours	216 min	90 min	69% (49/71)	
Topol (1987)	142	1 mg/kg/hour	190 min	90 min	72% (102/142)	
Johns (1988)	68	1 mg/kg/90 min	180 min	90 min	76% (52/68)	
CRAFT (1991)	206	100 mg/3 hours	<6 hours	90 min	63% (126/199)	
Smalling (1990)	91	1.25 mg/kg/3 hours	228 min	90 min	70% (61/87)	
TAMI-3 (1989)	134	1.5 mg/kg/4 hours	168 min	92 min	79% (104/131)	
KAMIT (1991)	107	100 mg/3 hours	180 min	95 min	64% (65/102)	
GAUS (1988)	124	70 mg/90 min	<4 hours	97 min	69% (84/121)	
Pooled	1,648				70% (1,109/1,585)	68%–72%
2–3 hour						
Topol (1987)	75	1.25 mg/kg/3 hours	216 min	120 min	79% (59/75)	
Guerci (1987)	72	80/100 mg/3 hours	192 min	150 min	66% (44/67)	
Pooled	147				73% (103/142)	65%–80%
1 day						
GAUS (1988)	124	70 mg/90 min	<4 hours	24 hours	78% (82/105)	
TEAM-3 (1992)	164	100 mg	168 min	33 hours	86% (128/149)	
TIMI-IIA (1988)	128	100/150 mg/6 hours	174 min	33 hours	82% (93/114)	
TIMI-II (1989)	1,366	100 mg	156 min	33 hours	85% (1,040/1,229)	
Pooled	1,782				84% (1,343/1,597)	82%–86%
3–21 days						
ECSG-6 (1992)	652	100 mg/3 hours	170 min	3.4 days	79% (410/518)	
PAIMS (1989)	86	100 mg/3 hours	124 min	4.1 days	81% (63/78)	
Bassand (1989)	93	100 mg/3 hours	172 min	5.4 days	76% (64/84)	
NHFA (1988)	73	100 mg/3 hours	195 min	5–7 days	70% (43/61)	
TIMI-IIA (1988)	389	100/150 mg/6 hours	174 min	7–10 days	79% (240/303)	
Thompson (1991)	241	100 mg/3 hours	155 min	7–10 days	80% (157/196)	
GAUS (1988)	124	70 mg/3 hours	<4 hours	10 days	73% (63/86)	
Cherng (1992)	59	100 mg/3 hours	312 min	10–14 days	77% (23/30)	
Rapold (1989)	34	100 mg/3 hours	186 min	12.5 days	81% (25/31)	
ECSG-5 (1988)	367	100 mg/3 hours	156 min	15 days	87% (283/327)	
White (1989)	135	100 mg/3 hours	150 min	21 days	76% (94/124)	
O'Rourke (1988)	74	100 mg/3 hours	120 min	21 days	81% (55/68)	
Pooled	2,327				80% (1,520/1,906)	78%–81%

CRAFT = Catheterization Rescue Angioplasty Following Thrombolysis trial; GAUS = German Activator Urokinase Study; KAMIT = Kentucky Acute Myocardial Infarction Trial; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction trial; RAAMI = Rapid Administration of Alteplase in Myocardial Infarction trial; other abbreviations and explanations as in Tables I and II.

occlusion occurred nearly twice as often with t-PA than with nonfibrin-specific thrombolytic agents (p = 0.002).

Left ventricular ejection fraction: Studies evaluating LV ejection fraction, by contrast or radionuclide angiography, after randomizing patients to thrombolytic therapy versus control groups are listed in Table VII.[9,10,12–17,59,60] The difference in ejection fraction between thrombolytic and control groups as a function of time after treatment is illustrated in Figure 2. Patients treated with thrombolysis had higher ejection fractions than control patients, although the absolute difference was only 3% at 10 to 28 days after treatment.

DISCUSSION

Infarct-related artery patency: This analysis confirms previous findings that early patency rates were higher with t-PA and APSAC than with streptokinase, and that the highest early rates of patency were with accelerated-dose t-PA. By 2 to 3 hours, the patency rates of streptokinase, standard dose t-PA, and APSAC were

TABLE IV Intravenous Accelerated Tissue-Type Plasminogen Activator Patency Studies (studies with ≥70 mg over 1 hour and/or 100 mg/90 min)

Study	Number of Patients	Dose	Time to Treatment	Mean Cath. Time	Patency	95% CI
1 hour						
Gemmell (1991)	33	70 mg/1 hour	208 min	49 min	77% (23/30)	
Smalling (1990)	84	1.2 mg/kg/60 min	216 min	56 min	65% (51/79)	
Neuhaus (1989)	80	100 mg/90 min	<6 hours	60 min	74% (54/73)	
TIMI-IIP (1987)	33	90 mg/60 min	180 min	60 min	82% (27/33)	
Purvis (1991)	60	70–100 mg/60 min	130 min	60 min	80% (35/44)	
TAPS (1992)	210	100 mg/90 min	162 min	61 min	73% (146/199)	
RAAMI (1991)	143	100 mg/90 min	162 min	61 min	76% (66/87)	
Pooled	643				74% (402/545)	70%–77%
90 minute						
Neuhaus (1989)	80	100 mg/90 min	<6 hours	90 min	91% (67/74)	
Smalling (1990)	84	1.2 mg/kg/60 min	216 min	90 min	84% (68/81)	
TAMI-7 (1992)	61	1.25 mg/kg/90 min	151 min	90 min	84% (51/61)	
Gemmell (1991)	33	70 mg/1 hour	208 min	90 min	87% (26/30)	
Purvis (1991)	60	70–100 mg/60 min	130 min	90 min	81% (48/59)	
RAAMI (1992)	143	100 mg/90 min	162 min	91 min	81% (104/128)	
TAPS (1992)	210	100 mg/90 min	162 min	91 min	84% (168/199)	
Pooled	671				84% (532/632)	82%–87%
1 day						
Neuhaus (1989)	80	100 mg/90 min	<6 hours	24 hours	92% (61/66)	
Gemmell (1991)	33	70 mg/1 hour	208 min	24 hours	83% (24/29)	
TAPS (1992)	210	100 mg/90 min	162 min	24–48 hours	85% (168/198)	
Pooled	323				86% (253/293)	82%–90%
3–21 days						
TAPS (1992)	210	100 mg/90 min	162 min	14–21 days	89% (157/177)	85%–94%

TAPS = Tissue Plasminogen Activator–Anisoylated Plasminogen Streptokinase Activator Complex Patency Study; other abbreviations and explanations as in Tables I to III.

similar, a finding that persisted at 24 hours and at 5 to 7 days. By 10 to 21 days, the patency rates even without thrombolytic treatment were surprisingly high—61% (95% confidence interval 57% to 64%). These findings are consistent with the GUSTO angiographic substudy results,[1] which found higher patency rates with accelerated t-PA than streptokinase at 90 minutes, but no significant difference in patency at 3 hours, 24 hours, or 7 days.

Assessment of patency at later time points may be affected by patient dropout. By 1 day after treatment, typically only 85% to 90% of patients originally enrolled in a study will have analyzable angiographic data, and

at later times only about 80% (data contained in Tables I to V). Because the patients who withdraw are more unstable or may have died, and because such patients are more likely to have occluded infarct-related arteries than the surviving patients,[61] the reported patency rates may overestimate the true rate.

Reocclusion: In assessing reocclusion, comparison of agents between different nonrandomized studies should be regarded with caution because of the lack of a common definition of reocclusion. For this analysis, reocclusion was defined as angiographically documented occlusion of the infarct artery that had been patent either
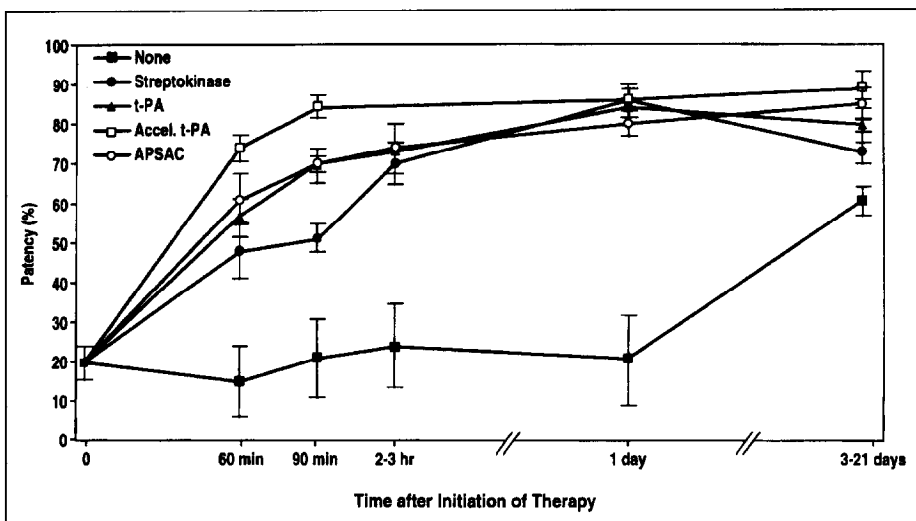

FIGURE 1. Pooled angiographic patency rates, with 95% confidence intervals, over time after no thrombolytic agent, streptokinase, conventional dose tissue-type plasminogen activator (t-PA), accelerated (Accel.) dose t-PA, and anisoylated plasminogen streptokinase activator complex (APSAC). Rates include 14,124 angiographic observations.

TABLE V Intravenous Anisoylated Plasminogen Streptokinase Activator Complex (APSAC) Patency Studies

Study	Number of Patients	Dose	Time to Treatment	Mean Cath. Time	Patency	95% CI
1 hour						
TAPS (1992)	210	30 U	150 min	60 min	60% (123/204)	
Kasper (1986)	50	30 U	151 min	64 min	64% (32/50)	
Pooled	260				61% (155/254)	55%–67%
90 minute						
TAPS (1992)	210	30 U	150 min	90 min	70% (142/202)	
Lopez-Sendon (1988)	22	30 U	<6 hours	90 min	86% (19/22)	
Hogg (1990)	65	30 U	199 min	90 min	53% (32/60)	
Charbonnier (1989)	58	30 U	162 min	95 min	70% (38/54)	
Relik-van Wely (1991)	156	30 U	106 min	96 min	73% (106/145)	
Pooled	511				70% (337/483)	66%–74%
2–3 hours						
TEAM-2 (1991)	188	30 U	159 min	2.1 hours	72% (132/183)	
Vogt (1988)	30	30 U	142 min	2.6 hours	77% (23/30)	
Monnier (1987)	14	30 U	141 min	2.7 hours	93% (13/14)	
Pooled	232				74% (168/227)	68%–80%
1 day						
Hogg (1990)	65	30 U	199 min	24 hours	81% (47/58)	
Lopez-Sendon (1988)	22	30 U	<6 hours	24 hours	91% (20/22)	
TEAM-3 (1992)	161	30 U	156 min	30 hours	89% (133/149)	
TAPS (1992)	210	30 U	150 min	24–48 hours	93% (183/196)	
SWIFT (1991)	397	30 U	180 min	48 hours	68% (255/373)	
Pooled	855				80% (638/798)	77%–83%
3–21 days						
Bassand (1989)	112	30 U	187 min	3.9 days	77% (82/106)	
TAPS (1992)	210	30 U	150 min	14–21 days	90% (157/174)	
Lopez-Sendon (1988)	22	30 U	<6 hours	15–21 days	81% (17/21)	
Pooled	344				85% (256/301)	81%–89%

Total angiographic observations: 14,124 (some patients had more than 1 angiogram).
SWIFT = Should We Intervene Following Thrombolysis trial; other abbreviations and explanations as in Tables I to IV.

initially or after an intervention on a 90-minute angiogram. Because patients who had patent infarct-related arteries at initial angiography and then died or had reinfarction without follow-up angiography are not included as reoccluded, the reocclusion rates reported likely underestimate the true rates.

This analysis included only studies in which patients were randomized between t-PA and a nonfibrin-specific agent (either streptokinase, APSAC, or urokinase),

which results in a more pronounced systemic fibrinolytic state that theoretically reduces the risk of reocclusion. Despite the use of intravenous heparin, which improves infarct-related artery patency after t-PA,[47,62] t-PA was associated with a substantially higher rate of reocclusion than the nonfibrin-specific agents. The reocclusion results are in contrast to the GUSTO angiographic substudy results,[1] where the rate of reocclusion was low with both accelerated t-PA and streptokinase. In the

FIGURE 2. Difference in left ventricular ejection fraction (EF) between thrombolytic-treated and control patients versus time after thrombolytic treatment. Data are from randomized trials of thrombolytic therapy versus control, and are pooled at the serial time points. Data include 3,066 ventriculographic observations.
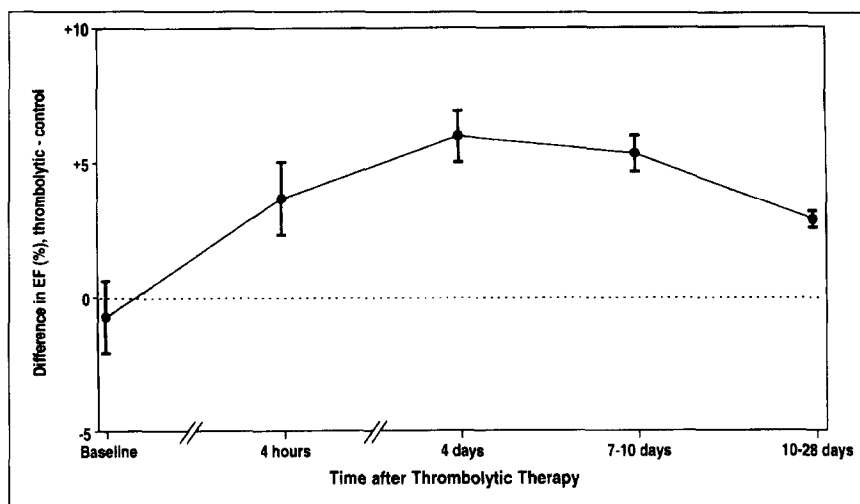
TABLE VI Reocclusion Rates (defined as angiographic reocclusion among patients who had patent infarct-related arteries at early catheterization) After Tissue Plasminogen Activator Versus Streptokinase, (SK) Anisoylated Plasminogen Streptokinase Activator Complex (APSAC), or Urokinase (UK)

Study	Timing of Catheterization		Thrombolytic Agent	
	Early Cath.	Late Cath.	t-PA	SK, APSAC or UK
TIMI-I (1987)	90 min	Predischarge	20% (17/86)	9% (4/44) (SK)
TAPS (1992)	90 min	24–48 hours	10% (18/179)	2.4% (4/168) (APSAC)
GAUS (1988)	90 min	24 hours	15% (13/88)	6.5% (5/77) (UK)
CRAFT (1991)	90 min	7–10 days	14% (26/180)	15% (25/170) (UK)
TAMI-5 (1991)	90 min	5–10 days	11% (10/94)	6% (6/97) (UK)
Pooled			13.4% (84/627) (95% CI: 11%–16%)	8.0% (44/556) (95% CI: 3%–10%)

Abbreviations as in Tables I to V.

TABLE VII Randomized Trials of Intravenous Thrombolytic Agents Versus Control Evaluating Left Ventricular Ejection Fraction*

Study	Time to Treatment	Time to EF	Method	Agent	LV Ejection Fraction (%)				EF/Total (no.)
					Active	SD	Control	SD	
Evaluation at baseline									
Guerci (1987)	3.2 hours	0	R	t-PA	49.5	1.8†	50.2	2†	126/138 (91%)
Evaluation at hour 4									
TPAT (1989)	3.0 hours	3.8 hours	R	t-PA	49.1	1.6†	45.4	1.9†	106/115 (92%)
Evaluation on day 4									
Bassand (1989)	3.1 hours	4 days	C	APSAC	53	13	47	12	211/231 (91%)
Evaluation on days 7–10									
NHFA (1988)	3.3 hours	7 days	C	t-PA	57.7	15.7	51.7	15.1	103/144
TPAT (1989)	3.0 hours	9 days	R	t-PA	53.6	1.6†	47.8	2.2†	104/115
Kennedy (1988)	3.5 hours	10 days	C	SK	54.3	12.2	50.7	12.6	170/368
Guerci (1987)	3.2 hours	10 days	R	t-PA	53.2	2.0†	46.4	2.0†	117/138
Pooled					54.5		49.2		494/765 (65%)
Evaluation on days 10–28									
ECSG-4 (1988)	2.9 hours	10–22 days	C	SK	50.7	10.9	48.5	11.3	565/721
Meinertz (1988)	2.8 hours	14–21 days	C	APSAC	57	13	58	13	256/313
Bassand (1989)	3.1 hours	19 days	R	APSAC	43	12	39	12	179/231
O'Rourke (1988)	1.9 hours	21 days	C	t-PA	61	13	54	14	126/145
White (1987)	3 hours	21 days	C	SK	59	10.5	53	13.5	155/172
ISAM (1986)	<6 hours	3–4 weeks	C	SK	56.8	0.7†	53.9	0.7†	848/1,741
Pooled					54.1		51.5		2,129/3,323 (64%)

*A total of 3,066 ventriculographic observations are included.
†Standard error.
C = contrast ventriculography; EF/Total = number of patients who were included for determination of ejection fraction/number of patients enrolled in the study; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction trial; Method = method of determination of ejection fraction; R = radionuclide ventriculography; Time to EF = time until the determination of left ventricular ejection fraction; other abbreviations as in Tables I to VI.

GUSTO trial, the heparin dose and adjustment scheme were more aggressive, with a target activated partial thromboplastin time of ≥2 times control.

Left ventricular ejection fraction: Studies evaluating LV ejection fraction after intravenous streptokinase, t-PA, or APSAC versus control or conventional treatment have found a modest improvement in treated patients (Table VII). Contrary to theoretical evidence that myocardial function may not fully recover for several days or weeks after a severe ischemic insult,[63] this analysis showed no further improvement in LV ejection fraction after day 4 evaluation in patients treated with thrombolytic therapy (Figure 2). This finding is consistent with an analysis of patients in the Thrombolysis and Angioplasty in Myocardial Infarction trials who underwent serial angiography after thrombolytic therapy.[64] In contrast, patients not given thrombolytic therapy showed a late improvement in LV ejection fraction. This may be related to further reocclusion in treated patients and

spontaneous reperfusion of initially collateralized zones in untreated patients.[65]

Studies using ejection fraction as an end point have been limited by a high proportion of missing values due to the typical 5% to 10% early mortality and additional 15% to 30% technically inadequate or unobtained studies. Because patients with missing values are those who have died and those who are sicker, a group with poor LV function, such studies generally overestimate true ventricular function.[66] When patients with poor LV function who might otherwise have died are saved by thrombolytic therapy, factoring in their low ejection fractions decreases the ejection fraction in the thrombolytic-treated groups.

This pooled analysis, by incorporating all available data from studies that are individually too small to give stable estimates of angiographic end points, provides a context in which to interpret future angiographic reperfusion studies.

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