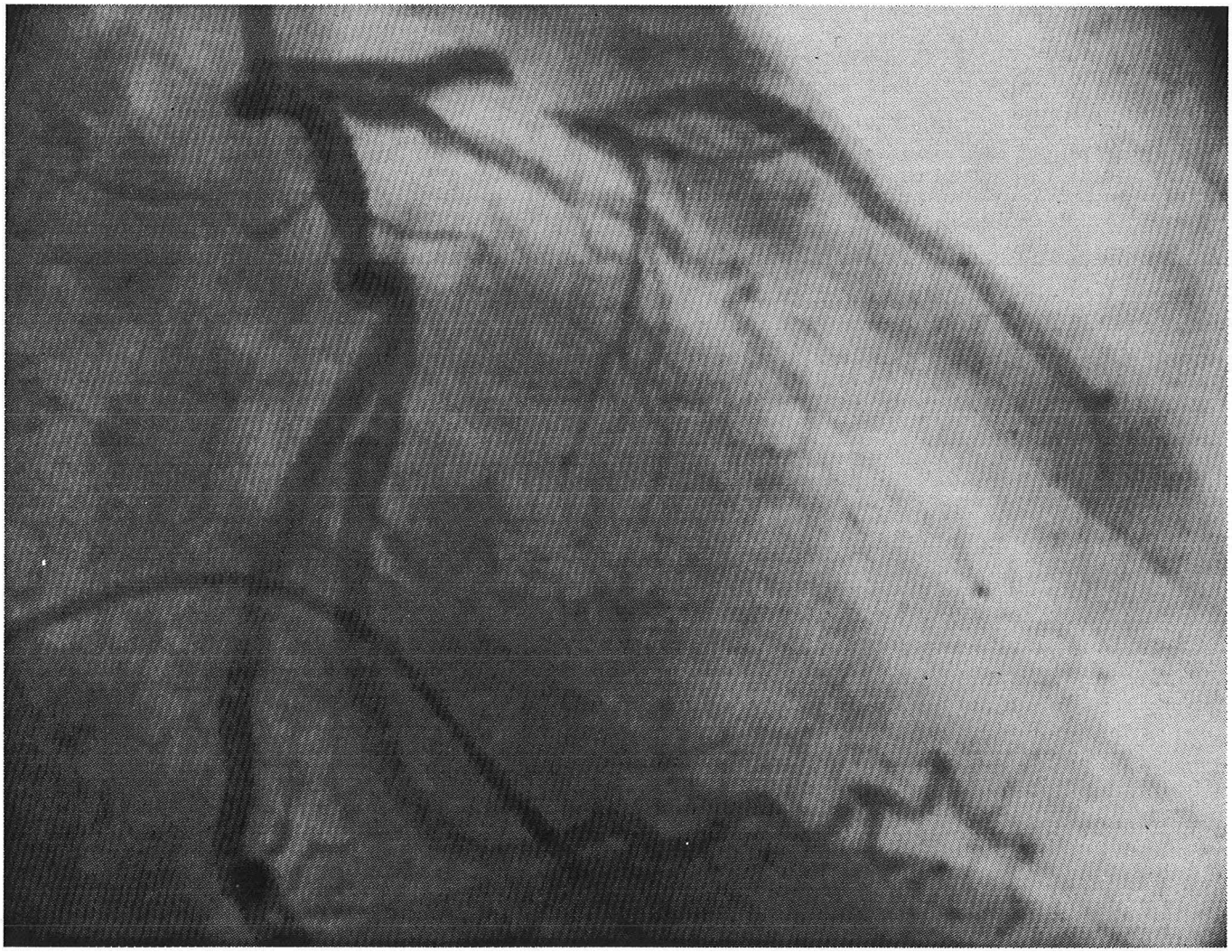
After GUSTO and PAMI:



Directions in Management of Acute Coronary Ischemia

Internal Medicine Grand Rounds

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Robert S. Meidell, M.D.

Almost exactly 5 years ago, I reviewed in this forum the clinical experience with thrombolytic therapy for acute myocardial infarction, largely as a prelude to a discussion of strategies, then under bench investigation, which offered promise to improve upon the successes of coronary reperfusion. In the interval, "standard" approaches to the management of patients early in the course of myocardial infarction have evolved. Some investigational strategies have transitioned from bench to clinical trial. Others have been abandoned. The mortality rates reported in clinical trials have fallen substantially, and the margins between treatment arms have contracted. The debates have changed, and in the process, the central issues have become more focused.

Enough has changed to warrant revisiting, at least in part, the topic of coronary reperfusion. My goals in so doing are: i) to describe our current clinical practice and review the data that provides a basis for that practice; ii) to update the list of promising investigational approaches that have moved to into clinical trial; iii) to refocus the "open questions" list; and iv) to review data from a large registry on the treatment of myocardial infarction in the United States, and discuss the implications of those findings with respect to the application of coronary reperfusion therapy in clinical practice.

Controlled Trials of Thrombolytic Therapy for Acute Myocardial Infarction

Between January 1984 and March 1991, six large prospective randomised trials comparing thrombolytic therapy to "conventional" management for patients presenting in the acute phase of myocardial infarction were performed and reported (GISSI 1986, ISAM 1986, AIMS 1988, ISIS-2 1988, Wilcox 1988, Rossi 1991). The design of these trials, GISSI-1, ISAM, AIMS, ISIS-2, ASSET and USIM, are summarized in Table I.

Table I: Prospective Randomised Placebo-Controlled Trials of Thrombolytic Therapy

Trial	GISSI-1	ISAM	AIMS	ISIS-2	ASSET	USIM
N	11,802	1,741	1,254	17,187	5,012	2,201
Agent	SK	SK	APSAC	SK	rt-PA (std)	UK (2 bolus
Control	Open	Placebo	Placebo	Placebo	Placebo	Open
ASA	No	iv bolus	No	Randomised	No	No
Heparin	No	titrated iv	titrated iv	No	iv	iv

In aggregate, these studies enrolled 39,197 patients, and clearly established an important survival advantage in patients receiving a thrombolytic agent for acute myocardial infarction. In their wake, however, a number of important questions remained unanswered:

- By what mechanism does thrombolytic therapy improve survival?
- Who benefits? With the exception of USIM, the original prospective trials had relatively loose inclusion criteria. Specifically, patients with

a variety of ECG findings (e.g. ST elevation, ST depression, bundle branch block, isolated T-wave inversion) were enrolled. Retrospective subgroup analysis suggested that benefit was limited principally to patients with ST segment elevation (or BBB). Similarly, the numbers of patients >65 years of age enrolled in any single trial were insufficient to establish definitive benefit in older persons.

- How long was the window of opportunity for thrombolytic therapy? Of the initial randomised trials, only GISSI-1 and ISIS-2 enrolled patients more than 6 hours after the onset of symptoms. In these trials, retrospective subgroup analysis suggested a benefit for "late" thrombolytic therapy, but the number of patients treated >12 hours after the onset of symptoms was insufficient to demonstrate a statistically significant benefit.

- Which agent? The original six prospective trials examined 4 different thrombolytic protocols - Streptokinase 1.5 MU administered over 1 hour, APSAC 30 U administered as a bolus, t-PA 100 mg over 3 hours using the TIMI IIb "standard" protocol, and urokinase 2 1MU boluses at a 1 hour interval. Each protocol produced a significant survival advantage over "conventional" therapy.

- What adjunctive therapy? In four of the original trials, no routine antiplatelet therapy was administered. In the ISIS-2 trial, administration of aspirin was associated with a significant reduction in mortality, and treatment with aspirin + SK resulted in a significantly lower mortality than either agent alone. Four of the six original trials employed routine intravenous heparin, but supplemental anticoagulation was not a randomised variable in any of these studies

- Is thrombolytic therapy or primary transluminal angioplasty the more effective approach to coronary reperfusion? Contemporary with clinical trials of thrombolytic therapy, a number of observational series of primary PTCA for acute myocardial infarction appeared, reporting very successful reperfusion rates and mortality rates comparable to those obtained in thrombolytic trials.

Since 1991, each of these questions has been addressed by additional clinical trials and/or by a retrospective analysis of data pooled from the 9 largest clinical trails of thrombolytic therapy published in 1994 by the Fibrinolytic Therapy Trialists (FTT) Collaborative Group (FTT 1994). This retrospective analysis was intended specifically to address the issue "who benefits?".

The Fibrinolytic Therapy Trialists

The FTT group reviewed the course of 58,600 patients enrolled in 9 parent trials, reanalyzing data from individual patients for selected information collected at enrollment, for deaths during days 0-35 and for major adverse events in hospital. The accumulated data was analyzed by intention-to-treat, using observed minus expected (O-E) and estimated "absolute difference" methodologies. The pooled data were examined for the effect of thrombolytic therapy in specific subgroups of patients, as follows:

- presenting ECG: BBB, ST elevation or depression or normal and by location of ischemic changes on ECG
- age <55, 55-65, 65-75 or >75
- gender
- systolic blood pressure <100, 100-149, 150-174 or >175
- heart rate <80, 80-99, >100
- prior infarct
- diabetes, and
- time from onset of symptoms to treatment

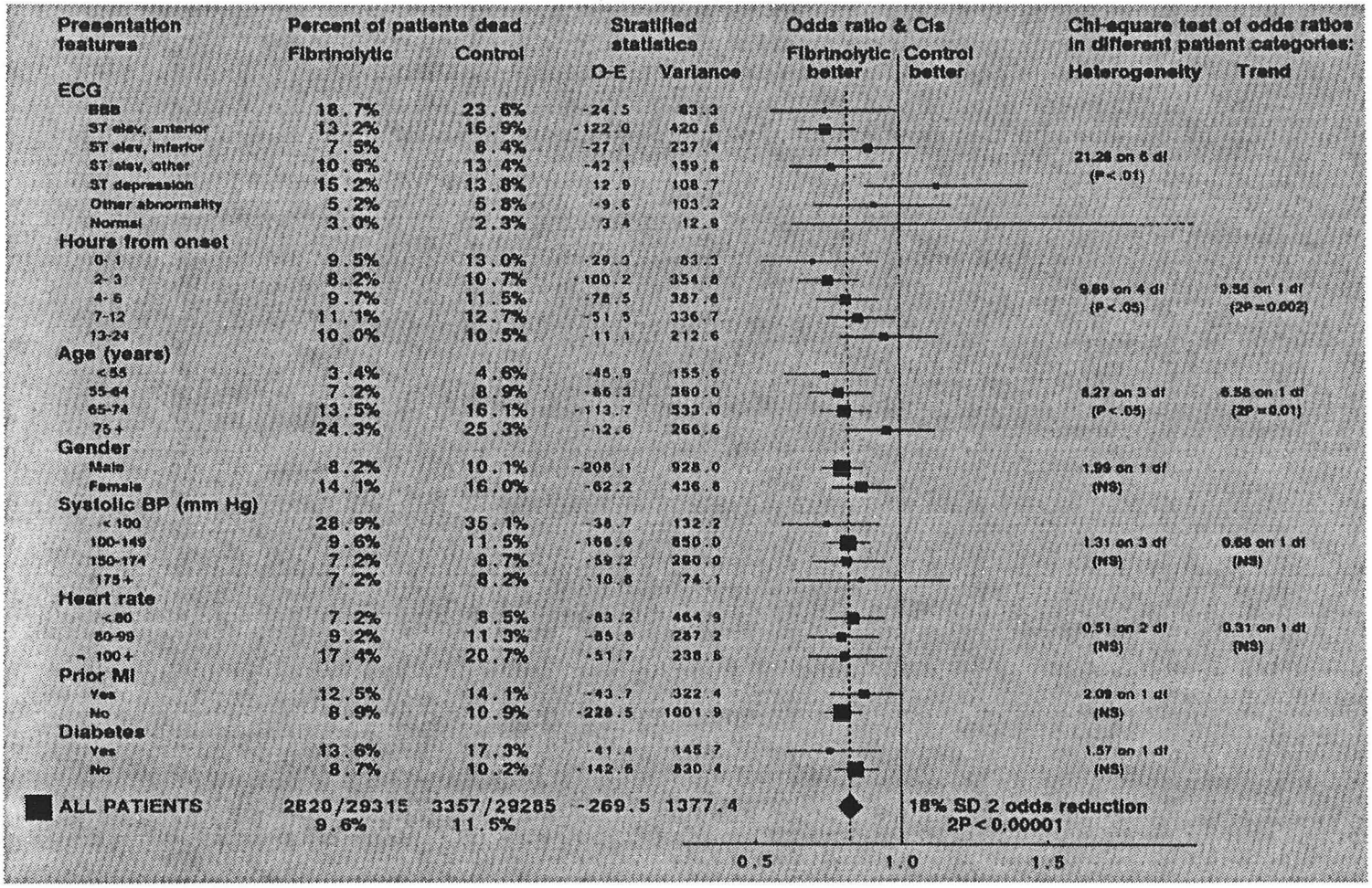

Figure 1: Analysis of the effect of thrombolytic therapy on 35 day survival in patient subgroups (FTT 1994)

The FTT subgroup analysis is shown in Figure 1. Clear survival benefit from thrombolytic therapy was observed in all subgroups with respect to diabetes, prior infarction, heart rate and gender. Mirroring the subgroup analysis from the ISIS-2 trial, the FTT analysis identified clear survival benefit in patients presenting with bundle branch block on the index electrocardiogram. Similarly, patients with ST segment elevation in anterior or lateral leads or in multiple distributions showed improved survival with thrombolytic therapy. Patients with inferior ST elevation showed a trend toward better survival, but the 95% confidence interval crossed unity. Patients with ST depression or a normal ECG showed no benefit (a trend toward worse 35 day mortality).

All blood pressure subgroups had lower 35 day mortality with thrombolytic therapy, although for patients with initial systolic blood pressure >175, the confidence interval crossed unity. This appeared due, at least in part, to a progressive increase in the incidence of stroke following thrombolytic therapy with increasing blood pressure. A similar pattern was observed when the pooled data was examined for the effect of age. In all age groups, patients treated with thrombolytic therapy had lower than expected mortality, although in the oldest patients (>75 years) the confidence interval crossed unity, probably as a result of the small number of such patients analyzed. The absolute benefit to thrombolytic therapy was actually similar in patients < and >75 years of age.

Analysis of the benefit of thrombolytic therapy on 35 day mortality as a function of time from onset of symptoms to initiation of therapy revealed clear benefit for patients presenting within 12 hours. For the 13-24 hour interval, the confidence interval crossed unity. Unlike the situation for age, however, this reflected a decreasing absolute benefit of thrombolytic therapy with increasing time from onset of symptoms. Figure 2 illustrates the relationship between absolute reduction in mortality in lives/1000 patients as a function of delay to initiation of therapy. The regression line intersects the axis of net benefit between 18-24 hours.

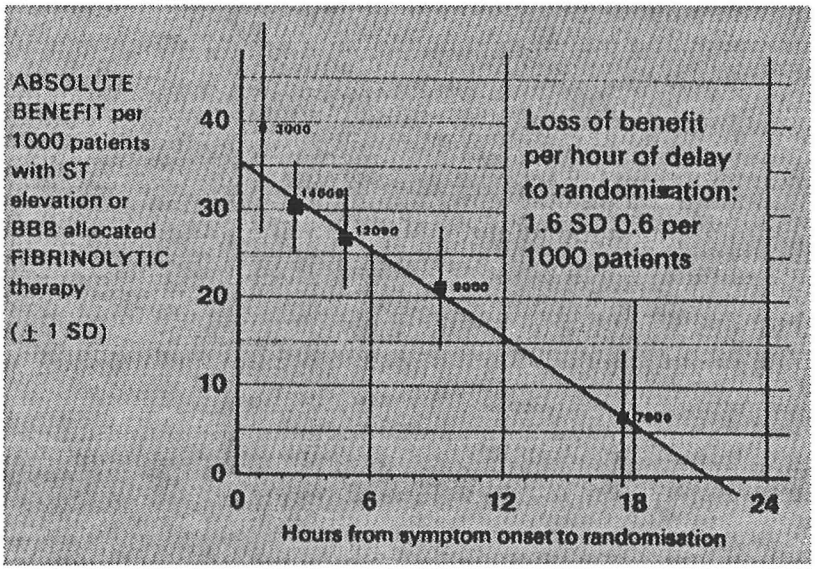

Figure 2: Effect of time to treatment on mortality (FTT 1994)

In summary, the FTT Collaborative Group analysis of the controlled prospective trials of thrombolytic therapy for acute myocardial infarction suggests that thrombolytic therapy improves survival in patients presenting

within 12-24 hours with suspected myocardial infarction and ST segment elevation or bundle branch block on an index electrocardiogram, irrespective of other clinical characteristics.

The Late Trials

Several of the early angiographic thrombolytic trials observed that the rate at which thrombolytic therapy succeeded in establishing reperfusion of the infarct-related artery was strongly related to the time from onset of symptoms to initiation of therapy. Of the six original randomised survival-endpoint trials of thrombolytic therapy for acute myocardial infarction, only GISSI-1 (17% of enrolled patients) and ISIS-2 (23% 6-12 hours, 14% >12 hours) included patients presenting more than 6 hours after the onset of symptoms. In both, analysis of the subgroup of patients presenting late produced a trend toward improved survival in patients receiving a thrombolytic agent which i) was substantially less than that observed in patients treated within 6 hours, and ii) did not achieve statistical significance.

Subsequent studies have addressed the issue of late thrombolytic therapy more directly. The TAMI-6 study examined 197 patients presenting within 6-24 hours from the onset of symptoms, randomising patients to t-PA (100 mg over 2 hours) or placebo, and examining the endpoints of infarct artery patency at 24 hours, ventricular function and left ventricular chamber size at 1 and 6 months. Treatment with t-PA resulted in a significant increase in patency of the infarct-related artery at 24 hours (65% vs 27%), and a reduction in LV chamber size at 6 months, although neither regional wall motion nor global left ventricular ejection fraction differed between the groups. This study demonstrated that infarct vessel reperfusion could be achieved in the majority of late-entry patients with thrombolytic therapy (or angioplasty), with a favorable effect on left ventricular remodeling.

In parallel, two survival-endpoint trials examined the efficacy of thrombolytic therapy in patients presenting more than 6 hours from the onset of symptoms. The EMERAS (**E**studio **M**ulticentrico **E**streptoquinasa **R**epublicas de **A**merica del **S**ur, 1993) trial randomised 2080 patients presenting 7-12 hours from symptom onset to either placebo or streptokinase 1.5 MU over 1 hour. There was a non-significant trend towards fewer deaths with SK (11.7% SK vs 13.2% control; 14+/-12% reduction, 95% CI: -33% to +12%) in patients treated within 7-12 hours. Little difference among the 1791 patients presenting after 12 hours was observed (11.4% SK vs 10.7% control. In the LATE (**L**ate **A**ssessment of **T**hrombolytic **E**fficacy, 1993) trial, 5711 patients with acute myocardial infarction were randomised to receive intravenous rt-PA (100 mg over 3 h) or placebo between 6-24 hours from symptom onset. Similarly wide confidence intervals were observed, also with a trend favoring thrombolytic therapy.

The best current synthesis of the efficacy of thrombolytic therapy in patients presenting late in the course of acute myocardial infarction is that

provided by the Fibrinolytic Therapy Trialists, which included the results of the EMERAS and LATE trials. Their analysis suggests that a delay between the onset of symptoms and initiation of therapy results in a loss of 1.5-2 lives/1000 patients/hour of delay, but that survival benefit remains to at least 12 hours, and perhaps to 18-24 hours. This data forms the basis of our current recommendation that eligible patients presenting within 12 hours should receive therapy directed at reestablishing antegrade blood flow in the infarct-related artery, and that such therapy should be considered in high risk patients presenting between 12-24 hours.

Comparison Trials of Thrombolytic Agents

ISIS-3, a prospective, randomised comparison trial of intravenous rt-PA, streptokinase or anistreplase for acute myocardial infarction with a primary endpoint of 35 day survival, disrupted the seemingly orderly development of therapeutic strategies directed at coronary reperfusion. Since TIMI-1 (and subsequently TAPS), it had been clearly established that treatment with rt-PA (and then accelerated dosing with rt-PA) resulted in more rapid restoration of antegrade blood flow in occluded coronary arteries than treatment with streptokinase (or APSAC). The absence of a difference in 35 day mortality in patients treated with these three agents called into question the "early open artery" hypothesis on which much of the effort directed at development of improved reperfusion strategies was based. Particularly in the United States, where many centers including our own had adopted "front-loaded" rt-PA as routine therapy for evolving Q-wave myocardial infarction, the ISIS-3 data was questioned, however. The protocol for administration of rt-PA in ISIS-3 was "standard", and adjunctive anti-thrombin therapy, when given, was subcutaneous rather than titrated intravenous heparin. Whether this protocol "biased" the study against the short-acting thrombolytic agent was debated.

In this setting, two prospective randomised trials of accelerated rt-PA with titrated systemic anticoagulation were undertaken. The smaller of these, the TIMI-4 trial, randomised 382 patients with evolving Q-wave myocardial infarction to therapy with front-loaded rt-PA, anistreplase or combination therapy with reduced doses of both agents (Cannon 1994). The primary end point was composite "unsatisfactory outcome" through hospital discharge. Patency of the infarct-related artery 60 minutes after the start of thrombolysis was significantly higher in rt-PA-treated patients (77.8% vs. 59.5% and 59.3%), and at 90 min, the incidence of TIMI grade 3 (normal) flow was also higher in rt-PA-treated patients (60.2% vs 42.9% and 44.8%). The incidence of unsatisfactory outcome was 41.3% for rt-PA compared with 49% for APSAC and 53.6% for the combination, and mortality at 6 weeks was lowest in the rt-PA-treated patients (2.2% vs. 8.8% and 7.2%). These findings supported the concept that more rapid reperfusion of the infarct-related artery is associated with an improved clinical outcome.

The **G**lobal **U**tilization of **S**treptokinase and **T**issue Plasminogen Activator for **O**ccluded Coronary Arteries (GUSTO) "megatrial" (Anonymous 1993) enrolled 41,021 patients from 1081 hospitals in 15 countries, randomising patients to one of 4 treatment strategies: i) streptokinase (1.5 MU) plus subcutaneous heparin [included as a standard for ISIS-3], ii) streptokinase plus titrated intravenous heparin, iii) accelerated rt-PA (15 mg bolus, .75 mg/kg or 50 mg over 30 min, .5 mg/kg or 35 mg over 60 min) plus titrated (aPTT 60-85s) intravenous heparin, or iv) combination thrombolytic therapy with reduced doses of rt-PA and streptokinase (1 mg/kg rt-PA over 60 min, 1 MU streptokinase over 60 min) plus titrated intravenous heparin. The primary endpoint of the trail was all-cause mortality at 30 days, although a number of secondary endpoints, and several stipulated subgroups (age >75, infarct location, time to presentation) were prospectively defined.

The primary endpoints of the GUSTO trial were published in early 1993. The mortality rates in the four treatment groups were: streptokinase/s.q. heparin 7.2%; SK/i.v. heparin 7.4%; accelerated rt-PA/i.v. heparin 6.3%, and combination thrombolytics/i.v. heparin 7.0%, representing a 14% reduction in mortality for accelerated t-PA vs the two streptokinase strategies (absolute mortality reduction 1%, $p = 0.001$). Rates of hemorrhagic stroke were 0.49%, 0.54%, 0.72% and 0.94%, respectively (a significant excess of hemorrhagic strokes for rt-PA and the combination strategy. The combined end point of death or disabling stroke was significantly lower in the rt-PA group (6.9% vs 7.8%).

More important than the primary endpoint megatrial was the companion angiographic substudy (Anonymous 1994), which was designed to test directly the "early open artery" hypothesis. The substudy involved 2431 patients evenly distributed among the GUSTO treatment arms, randomly assigned to coronary angiography at 90 minutes, 180 minutes, 24 hours, or 5 to 7 days after treatment. Angiography was repeated in the 90 minute group after 5 to 7 days. The 90 minute patency and TIMI grade 3 flow rates (summarized in Table II) for the 4 treatment arms were: rt-PA 81%/54%; sk-iv hep 60%/32%; sk-sq hep 54%/29%; combination 73%/38%. By 180 minutes, the patency rates were the same in the four treatment groups, and remained similar through 5-7 days. Reocclusion was infrequent in all four groups (4.9%-6.4%).

Table II: Infarct artery status by treatment in the GUSTO trail

	SK + SQH	SK + IVH	t-PA + IVH	Combination
Patency: 90 min	54	6 0	81	73
180 min	73	74	76	85
24 hour	77	80	86	94
5-7 days	72	84	84	80
TIMI 3 flow: 90 min	29	32	54	38
180 min	35	41	43	53
5-7 days	51	58	58	55

Table III summarizes the relationship between treatment and left ventricular function.

Table III: Relation between treatment and LV function (Holmes 1995)

	SK + SQH	SK + IVH	t-PA + IVH	Combination
LVEF (90 min)	58 +/- 15	57 +/- 15	59 +/- 15	58 +/- 15
Regional Wall Motion (% preserved)	18	19	29	21

While global ejection fraction did not differ between patients in the 4 treatment arms, therapy with rt-PA was associated with a significant preservation of regional wall motion, and a reduction in the extent of left ventricular myocardium demonstrating abnormal wall motion.

Probably the most important finding of the GUSTO trial was not the relationship between treatment and outcome, but rather the relationship between the early restoration of normal antegrade blood flow in the infarct-related artery and clinical outcome. Patients, irrespective of treatment, with TIMI grade 3 flow at 90 minutes had both better post-infarction left ventricular function and a significantly lower 30 day mortality (4.4% vs 8.9%) than patients with TIMI grades 0 or 1 flow. From the relationship between TIMI flow grade and mortality in the angiographic substudy, the GUSTO investigators developed a model for predicting mortality rate differences in the main GUSTO trial (Simes 1995) predicated on the assumption that any differences in treatment effects on 30-day mortality were mediated through differences in 90-minute patency for the four treatments. Predicted/observed 30-day mortality rates for the four treatments were SK/s.q hep 7.46%/7.28%; SK/i.v. hep 7.26%/7.39%; rt-PA 6.31%/6.37%, and combination 6.98%/6.96%, with the correlation between predicted and observed results 0.97 and R^2=0.92. Subsequent analysis of early mortality rates (first 24 hours after initiation of therapy) demonstrated that this flow-grade related differences in mortality rate appeared as early as 24 hours from initiation of treatment (Kleiman 1994). The close relation between the predicted and observed 30-day mortality rates supported the conceptual basis of thrombolytic therapy - that early and complete restoration of infarct artery perfusion represents the essential goal of myocardial reperfusion therapy.

Figure 3 summarizes the findings of GUSTO with regard to 30 day mortality in the prespecified subgroups of age < or > 75, anterior or other infarct location, an time from onset of symptoms to therapy. Clear benefit for treatment with rt-PA was observed in patients < 75 years of age, patients with anterior infarction, and patients treated within 4 hours of the onset of symptoms. For patients falling outside of these groups, the odds ratio favored treatment with rt-PA, but the 95% confidence intervals crossed unity.

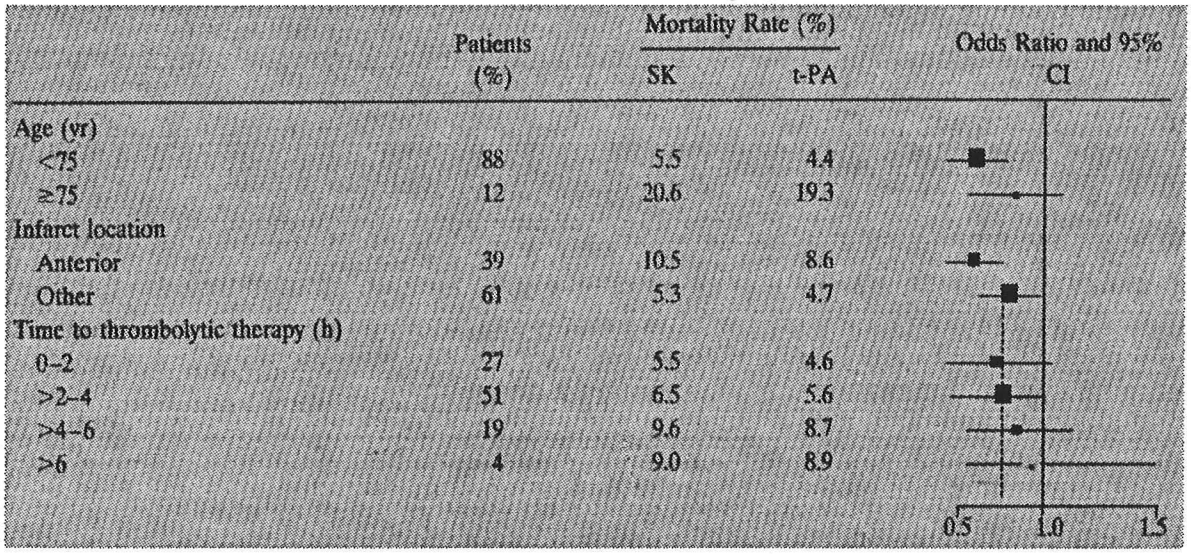

Figure 3: Subgroup analysis in the GUSTO trial (Holmes 1995).

The effect of time to treatment on differential mortality in the treatment arms has been the subject of some discussion. A progressive reduction in the mortality differences between the treatment arms with increasing delay in administration of a thrombolytic agent was observed. The number of patients treated late was small (~4%), and definitive conclusions are difficult, but the data suggest that, like the benefit of thrombolytic therapy itself, the marginal benefit of rt-PA over alternative agents diminishes with time.

For patients > 75, at least part of the decrement in benefit associated with rt-PA therapy resulted from an excess incidence of hemorrhagic stroke, which was more marked in the older population than in the study population as a whole (2.08% vs 1.23%). Recently, an analysis of strokes complicating thrombolytic therapy in the GUSTO trial has been published (Gore 1995). Overall, stroke was more common (1.64% vs 1.19%) in patients treated with rt-PA, and virtually all of this difference was the result of an increase in the rate of hemorrhagic stroke (0.88% vs 0.46%). In addition to age, risk factors for stroke were low body weight, hypertension and prior cerebrovascular disease.

Thrombolytic Therapy for Unstable Angina and Non-Q Wave MI

The Fibrinolytic Therapy Trialists analysis supported the use of fibrinolytic agents in virtually all subgroups analyzed with one exception, the subgroup of patients presenting with ST segment depression on the index electrocardiogram. Pooled data from these trials suggested a trend toward a less favorable survival outcome in patients treated with a thrombolytic agent. The issue of thrombolytic therapy in patients with unstable angina and non-Q infarction has been addressed more directly, however, in several specific prospective, randomised clinical trials.

A number of small trials have reported discouraging results for thrombolytic therapy in patients with either unstable angina or acute non-Q wave myocardial infarction. The UNASEM trial (Bar 1992, 1994) randomised 159 patients presenting with a typical history of unstable angina, no prior myocardial infarction, and ECG abnormalities indicative of ischemia to anistreplase or placebo. All patients underwent baseline and 12-28 hour post-therapy angiography. While a significantly greater decrease in mean diameter stenosis between the first and second angiogram was observed in the anistreplase group (11% vs 3%, $p = 0.008$) as a result of reopening of occluded vessels, no beneficial clinical effects were found and bleeding complications were significantly greater in patients who received thrombolytic therapy (21 vs 7). In a retrospective analysis, the angiographic appearance of a thrombus did not predict a subgroup of patients benefiting from thrombolytic therapy. Schreiber and colleagues (1992) reported a randomised trial of 149 patients with unstable angina randomised to urokinase plus heparin, urokinase plus aspirin or heparin alone. The primary endpoint was 96 hour clinical status. No significant differences between the groups were observed for the incidence of intractable angina, and a trend toward fewer infarctions in the heparin group was observed. The trial, planned for 600 patients, was terminated prematurely. Freeman et al (1992) reported similarly disappointing results in a series of 70 patients with unstable angina treated with heparin and aspirin and randomised to either rt-PA or placebo. They observed no difference in the incidence of cardiac events, and both larger mean resting thallium perfusion defect and longer total duration of ST segment depression on Holter monitoring, despite a lower incidence of thrombus on repeat coronary angiography. In contrast, Sansa and colleagues (1991) reported that patients with unstable angina randomised to heparin or urokinase demonstrate similar degrees of angiographic improvement between index and 8 day coronary angiograms. White et al (1995) have more recently reported a series of 112 patients randomised to conventional therapy with or without streptokinase within 6 hours of presentation with unstable chest pain and 1 mm ST segment depression on an index electrocardiogram. The frequency of a combined end point of death, myocardial infarction, early angiography, and a positive exercise test was 82% with streptokinase and 75% with placebo.

More positive effects from thrombolytic therapy in unstable angina/non-Q infarction have also been reported, although less commonly. The TRIC study reported more favorable results in 205 men with unstable angina or non-Q infarction treated with aspirin, heparin and a β-blocker and randomised to placebo or rt-PA infusion. The combined incidence of infarction, refractory angina or inducible ischemia on exercise testing was lower in patients receiving t-PA at discharge (53% vs 70%) and 1 month later (61% vs 80%), although the frequency of revascularization procedures was not different. Romero and colleagues (1995) have recently reported a trial in 67 patients of prolonged (3 day) administration of a low-dose infusion of rt-PA in comparison with standard therapy (including aspirin and heparin) for unstable angina. The incidence infarction (2.7% vs 12.9%) and emergency revascularization (0% vs 25%), and the number of ischemic episodes (103 vs 237) were reduced in patients randomised to low-dose thrombolytic therapy, with no significant bleeding complications.

Recently, the results of the TIMI-IIIb trial (Anonymous 1994), a large (n=1473) prospective, randomised trial of thrombolytic therapy and early revascularization in patients with unstable angina/NQMI have been reported. This trial was a 2X2 factorial design, comparing i) t-PA vs placebo as initial therapy and ii) early coronary arteriography followed by revascularization when the anatomy was suitable vs coronary arteriography followed by revascularization if initial medical therapy failed. All patients were treated with bed rest, anti-ischemic medications, aspirin, and heparin. Death, myocardial infarction, or failure of initial therapy at 6 weeks occurred in 54.2% of the t-PA-treated 55.5% of placebo-treated patients. Both new myocardial infarction (7.4% vs 4.9%) and intracranial hemorrhage (4 vs 0) were more common in t-PA-treated patients.

The second comparison in the TIMI-IIIb trail addressed the role of early angiography and revascularization in the same patient population. The end point for the comparison (death, myocardial infarction, or an unsatisfactory symptom-limited ETT at 6 weeks) occurred in 18.1% of patients assigned to the conservative and 16.2% of patients assigned to the early invasive strategy (p = NS). The early invasive strategy was associated with a lower average length of initial hospitalization and incidence of rehospitalization within 6 weeks.

The role of thrombolytic therapy as an adjunct to transluminal angioplasty for unstable angina was addressed by the recently reported TAUSA (Thrombolysis and Angioplasty in Unstable Angina) trial (Ambrose 1994). In this trial, 469 patients were randomised to placebo or one of two doses (250- or 500,000 U) of urokinase (with aspirin and heparin) administered at the time of PTCA for unstable angina. Urokinase therapy did not reduce the incidence of thrombus, and increased the incidence of abrupt closure (10.2% vs 4.3%), an effect that was greater at the higher urokinase dose. Adverse clinical events were twice as common in patients receiving urokinase.

In aggregate, the available clinical data appear to confirm the suggestion of the Fibrinolytic Trialists retrospective analysis, that thrombolytic agents do not favorably influence the acute clinical course of patients presenting with unstable ischemic syndromes and ST segment depression on an electrocardiogram, nor does thrombolytic therapy improve post-hospital prognosis. Early (routine) angiography/revascularization may shorten hospital stay, but does not clearly improve clinical outcome over a strategy that reserves intervention for patients failing initial medical therapy. Finally, adjunctive use of a fibrinolytic agent in the setting of PTCA for unstable ischemia appears to increase the incidence of acute vessel closure and myocardial infarction over that seen with angioplasty alone.

Combination Antithrombotic Therapy

The role of aspirin in the setting of acute myocardial infarction was established in the ISIS-2 trial. The HART and GUSTO trials established an important role for titrated intravenous heparin as an adjunct to thrombolytic therapy in patients with evolving Q-wave myocardial infarction. Similarly, both aspirin and heparin are of documented efficacy in the short term management of patients with unstable coronary ischemia. Until recently, however, no data existed on the relative efficacy of these commonly used agents, nor was it clear whether the beneficial effects of these agents were additive. In the last several years, a number of prospective trials have addressed these issues.

Theroux and colleagues (1993) randomised 484 patients presenting with unstable angina to therapy with aspirin (325 mg bid) or heparin (5000-U intravenous bolus followed by a perfusion titrated to the aPTT). In hospital myocardial infarction occurred in 0.8% of patients randomised to heparin and 3.7% treated with aspirin ($p = .035$). The same authors, however, have observed a significant incidence of early (within 96 hours of hospital discharge) recurrent unstable ischemia (14/107) in patients treated with heparin alone. A significantly lower rate of recurrent ischemia was observed in patients discharged after treatment with aspirin or a combination of aspirin and heparin (Theroux 1992).

The **A**ntithrombotic **T**herapy in **A**cute **C**oronary **S**yndromes (ATACS) trial (Cohen 1994) randomised 214 pateints with resting chest pain and ST segment depression on an index electrocardiogram to either aspirin (162.5 mg daily) or a combination of aspirin and titrated intravenous heparin followed by titrated coumadin, beginning within 12 hours of presentation and continuing for 12 weeks. Primary end points were recurrent angina with ECG changes, myocardial infarction, and/or death. Analysis by intention to treat of primary events at 12 weeks revealed a significant reduction in total ischemic events in the combination group versus aspirin alone (10.5% versus 27%, $P = .004$), at the expense of a slight increase in bleeding complications.

Less favorable results have been reported by Holdright et al (1994), who randomised 285 patients presenting with unstable angina to therapy with aspirin

(150 mg/d) or aspirin plus titrated intravenous heparin in addition to "standard" antianginal therapy with long-acting nitrates, β-blocker and diltiazem. The study endpoints were the frequency and duration of ischemia assessed by ST segment monitoring, and the incidence of combined in-hospital myocardial infarction and death. The authors observed no significant differences between the two treatment arms in the number of patients with transient myocardial ischemia, the number of episodes of ischemia or the total duration of transient ischemia. In addition, the incidence of in-hospital myocardial infarction or death was similar in both groups. This latter study appears to conflict with an emerging consensus that heparin therapy is associated with incremental benefit when added to aspirin and "standard" antianginal therapy in the setting of unstable coronary ischemia.

Comparative Trials of Thrombolysis and Primary Transluminal Angioplasty

On 11 March 1993, the New England Journal of Medicine published three prospective, randomised trials comparing thrombolytic therapy to percutaneous transluminal angioplasty as primary therapy for acute myocardial infarction.

The **P**rimary **A**ngioplasty in **M**yocardial **I**nfarction (PAMI; Grimes 1993) study examined 395 patients enrolled within 12 hours of the onset of chest pain meeting TIMI IIb ECG criteria for evolving Q-wave myocardial infarction. All patients were treated with 325 mg aspirin, intravenous nitroglycerin, a 10,000 U bolus of intravenous heparin and continuous infusion heparin to maintain the aPTT 1.5-2.0 X control. Patients were then randomised to one of two treatment strategies. One group (200 patients) received 100 mg rt-PA (using the FDA approved standard protocol) followed by medical management following the "conservative" arm of the TIMI IIb trial. The second group (195 patients) underwent immediate diagnostic catheterization, and if a suitable culprit lesion was identified, immediate transluminal angioplasty. The primary endpoint of the study was the incidence of death or non-fatal in-hospital reinfarction. In addition, left ventricular ejection fraction (by radionucleide ventriculography) was examined 24 h after presentation, exercise testing was performed prior to hospital discharge, and rest and exercise radionucleide ventriculography was performed six weeks after discharge.

The protocol permitted "unscheduled catheterization" with or without "rescue angioplasty" for those patients randomised to thrombolytic therapy for failure of chest pain to resolve within 120 minutes of initiation of therapy or recurrent ischemia (chest pain with ECG changes or clinical deterioration). Of the 200 patients initially assigned to thrombolytic therapy, 126 (63%) underwent unscheduled catheterization, and 72 (36%) underwent unscheduled PTCA (14 for failure of thrombolysis, 35 for recurrent unstable ischemia, and 15 for an abnormal pre-discharge ETT). Of patients randomised to immediate catheterization and angioplasty, 20 patients were excluded by virtue of

unsuitable (LMCA, 3 vessel CAD with high-risk culprit lesion morphology, small infarct-related vessel, patent infarct related artery with residual stenosis <70%) anatomy. The remaining 175 patients underwent PTCA of the infarct-related artery. Primary angiographic success (patent infarct-related artery with residual stenosis <50%) was achieved in 170/175 patients undergoing angioplasty.

Time from randomization to treatment was less in patients treated with rt-PA (32 vs 60 min), but as not all patients underwent catheterization, time to reperfusion was not determined.

The principal observations from the PAMI trial, shown on an intention-to-treat basis, are presented in Figure 4. With respect to the primary endpoint, the combined incidence of death and non-fatal reinfarction was 12% in the rt-PA group and 5.1% in the group randomised to primary angioplasty (p=0.02). In

Event	PTCA Group (N = 195)		t-PA Group (N = 200)		P Value
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	
Reinfarction	5	2.6 (0.4–4.8)	13	6.5 (3.1–9.9)	0.06
Death					
Overall	5	2.6 (0.4–4.8)	13	6.5 (3.1–9.9)	0.06
Low risk†	3	3.1 (0–6.6)	2	2.2 (0–5.2)	0.69
Not low risk†	2	2.0 (0–4.7)	11	10.4 (4.6–16.2)	0.01
Nonfatal reinfarction or death	10	5.1 (2.1–8.1)	24	12.0 (7.5–16.5)	0.02

Figure 4: Primary endpoints in the PAMI trial (Grines 1993).

patients classified as "not low risk" (age >70, anterior infarction, heart rate >100), PTCA was associated with a lower in-hospital mortality (2.0 vs. 10.4%, p=0.01). The incidence of recurrent ischemia (5.1 vs 23.5%), abnormal pre-discharge ETT (3.0 vs 23%) and recurrent chest pain without ECG changes (4 vs 11%) were all lower in patients randomised to primary angioplasty. Left ventricular ejection fractions at 24 hours and 6 weeks did not differ in the two groups (0.51 vs 0.53).

The mortality rate in the thrombolytic therapy group (6.5%) in the PAMI trial has been criticized as somewhat higher than rates from other recent trials. A breakdown of the mortality is therefore of interest. Of 13 deaths, 7 occurred in patients >70 years of age. 9 deaths occurred in patients suffering recurrent ischemic events, 2 after attempted rescue PTCA. 4 patients died as a result of intracranial hemorrhage. Notably, all of the difference in mortality between the trail arms occurred in patients classified as "not low risk", and could be

accounted for by lower rates of recurrent ischemia and intracranial hemorrhage in patients randomised to primary angioplasty. A subsequent retrospective analysis of mortality in the PAMI trial (Stone 1995) demonstrated that the only variables independently related to in-hospital death or nonfatal reinfarction were advanced age and treatment by t-PA versus angioplasty. The reduction in in-hospital death or reinfarction with angioplasty versus t-PA was particularly marked in patients >/= 65 years of age, and the beneficial effect of angioplasty was maintained at 6-month follow-up (8.2% vs. 17.0%, p = 0.02).

Much of the beneficial effect of angioplasty on mortality appears to be related to the observed differences in the rate of recurrent ischemic events (Stone 1995). In the PAMI trial, recurrent ischemia occurred in 56 patients (28.0%) after rt-PA but in only 20 patients (10.3%) after coronary angioplasty (p < 0.0001), and by multivariate analysis, angioplasty was the strongest predictor of freedom from recurrent ischemia. Interestingly, the incidence of recurrent ischemia was similar in the two treatment arms within the first 48 hours, but after day 2 recurrent ischemia occurred in only 1.1% of patients who received primary angioplasty compared with 13.5% who received rt-PA.

The Zwolle (Netherlands) trial (Zilstra 1993) randomised 142 patients presenting within 6 hours of the onset of symptoms (or 12 hours with ongoing symptoms) and otherwise meeting TIMI IIb entry criteria. All patients received 300 mg aspirin intravenously, intravenous nitroglycerin sufficient to maintain systolic blood pressure at least 110 mmHg and intravenous heparin to an aPTT of 2-3 X control. 72 patients were treated with streptokinase, 1.5 MU over 1 hour. The remaining 70 patients underwent immediate catheterization. In 65/70 patients, anatomy suitable for transluminal angioplasty was identified (2 excluded for a patent infarct-related artery, 3 for multivessel disease requiring emergent coronary bypass surgery). Primary angiographic success (TIMI grade 2 or 3 flow and a residual stenosis <50%) was achieved in 64/65 patients undergoing PTCA. Time from randomization to therapy was 30 min in the SK group, and 61 min in those treated with primary angioplasty.

The primary endpoints of the Zwolle trial were recurrent ischemia prior to hospital discharge, left ventricular ejection fraction (radionucleide ventriculography prior to discharge) and late patency of the infarct-related artery (angiography at varying times after hospital discharge). Additionally, stable patients underwent stress testing prior to hospital discharge.

The primary endpoints of the trial are summarized in Figure 5. Recurrent infarction/ischemia was more common (38 vs 9%), and left ventricular ejection fraction was lower (45 vs 51%) in patients treated with streptokinase. Late catheterization demonstrated patency of the infarct-related artery in 68% of patients treated with streptokinase, and 91% of patients following primary angioplasty. In addition, residual stenosis of the infarct-related artery was more severe (76% vs 36%) in SK-treated patients at the time of late angiography. Trends (not achieving significance) toward a higher incidence of death, stroke,

bleeding and heart failure were observed in patients treated with thrombolytic therapy. 42% of streptokinase-treated vs 14% of PTCA-treated patients required an additional revascularization procedure (PTCA or CABG). Notably, data were not analyzed separately for patients in differing "risk" categories. It is therefore unknown whether, like the PAMI trial, the differences favoring primary angioplasty derived principally from effects in those at greatest clinical risk. Subsequent extension of this study to a population of 301 patients (de Boer 1994a) demonstrated in-hospital mortality rates of 7% vs 2% in the streptokinase and angioplasty groups, respectively ($p = 0.024$). Similarly, recurrent infarction (10% vs 1%) was lower in the angioplasty group, and pre-discharge ejection fraction was improved (44 +/- 11% vs 50 +/- 11%). The better residual left ventricular function in patients managed with primary angioplasty correlated with a smaller myocardial injury as assessed by enzyme release (de Boer 1994b). The observed differences were more pronounced in patients with anterior infarction, and in patients presenting within 2 hours after onset of symptoms.

The Mayo Clinic trial (Gibbons 1993) of immediate angioplasty for myocardial infarction was designed to test the hypothesis that immediate angioplasty would result in greater myocardial salvage than thrombolytic therapy. The study enrolled 108 patients with chest pain of between 30 minutes and 12 hours duration and either ST elevation or ST depression on an index ECG. All patients were treated with 162 mg aspirin and intravenous heparin to an aPTT of 2-2.5 X control. 56 patients were randomised to treatment with duteplase (two-chain rt-PA) by a "standard" protocol, of whom 51 were treated (5 excluded for prolonged resuscitation or uncontrolled hypertension). 47 patients were randomised to immediate transluminal angioplasty, of whom 45 underwent the procedure (2 excluded for widely patent infarct-related artery). Primary angiographic success (normal antegrade flow and residual stenosis <50%) was achieved in 42/45. Median times from presentation to treatment were 232 and 277 minutes for patients in the thrombolytic and PTCA groups, respectively. Of patients assigned to thrombolytic therapy, 36% underwent a revascularization procedure during the index hospital admission for recurrent ischemia.

Patients underwent ^{99m}Tc-sestamibi imaging on presentation and 6-14 days after presentation. Radionucleide ventriculography was performed prior to hospital discharge. In addition to primary endpoints, mortality, recurrent ischemic events and estimated hospital charges were analysed.

The principal observations of this study are summarized in Figure 5. No differences in final infarct size or the extent of myocardial salvage as assessed by isonitrile imaging were observed between treatment groups. While no risk stratification data were presented, no treatment-related differences were observed in patients with either anterior or non-anterior infarctions. There were also no significant differences in secondary endpoints, including death (0 vs 1), recurrent infarction (2 vs 0), CABG (8 vs 2) and post-infarction left ventricular ejection fraction (0.50 vs 0.53) [all values rt-PA vs PTCA]. Estimated costs for

the two treatment strategies favored primary angioplasty ($16,811 vs $21,400) largely as a result of shorter hospital confinement (7.7 vs 10.6 days), although the difference failed to achieve statistical significance.

An important consideration in the decision to manage a patient presenting early in the course of myocardial infarction with thrombolytic therapy or primary angioplasty is the time required to "administer" the chosen therapy. Ribeiro and colleagues (1993) analyzed time to treatment in 100 consecutive patients presenting to a single center within 6 hours of the onset of symptoms. They reported that time to treatment was significantly delayed in the angioplasty group (238 +/- 112 vs. 179 +/- 98 min, p = 0.005), although no differences in 48-h infarct-related artery patency or left ventricular ejection fraction were observed (patency 74% vs. 80%; ejection fraction 59 +/- 13% vs. 57 +/- 13%; angioplasty vs. streptokinase, p = NS for both).

Time to treatment, however, is probably the wrong measure by which to judge alternative therapeutic strategies. From the early experience in the TIMI and TAMI trials, it is well established that the time from initiation of thrombolytic therapy to effective arterial reperfusion is significant (frequently >60 minutes). Berger and colleagues (1994) have reported an analysis of the Mayo Clinic trial data for time to reperfusion in those patients assigned to primary angioplasty. In these 48 patients, the mean time from randomization to arrival in the laboratory was 45 minutes; it took a mean of 6 additional minutes for arterial access to be obtained, and a mean of 27 additional minutes to achieve reperfusion (mean total time randomization to reperfusion 78 minutes, reperfusion rates at 50, 80 and 110 minutes 12%, 54% and 83%). The authors compared these rates to those observed in the TIMI-1 trial for patients treated with rt-PA (24%, 57% and 71%, respectively). This analysis, however, may not reflect current practice either, as the protocol for administration of rt-PA in the TIMI-1 trial ("standard") is associated with lower early reperfusion rates than the GUSTO "accelerated" protocol.

In the context of the global changes in medical practice being driven by economic considerations, the cost of alternative therapeutic strategies has become a central consideration. While the costs experienced in any "trial" predict poorly the subsequent experience in routine clinical application, some analyses of the costs associated with thrombolytic and primary angioplasty therapy for acute myocardial infarction have been reported. The PAMI investigators (Mark 1995) have reported economic data from the primary angioplasty registry. Baseline and follow-up medical costs and counts of resources consumed were collected from enrollment to 6-month follow-up. The total mean hospital cost (not charge) was $13,113, with mean physician fees of $5,694. During the follow-up period, repeat coronary angiography was performed in 21% of patients, whereas 13% had repeat angioplasty and 3% bypass surgery. Mean hospital follow-up costs were $3,174, with mean physician

fees of $1,443 (Total index admission costs $18,807, 6 month costs $23,424). Comparative cost data from the Mayo Clinic trial have been reported (Reeder 1994), showing no significant difference in cost between the two initial treatment strategies. Smaller observational studies have reported similar observations, with the higher initial procedural costs of primary angioplasty offset by i) a higher incidence of recurrent ischemic events in patients receiving thrombolytic therapy requiring a greater number of "late" procedures, and ii) a trend toward shorter hospital stay in patients undergoing primary angioplasty (Mark 1991).

Novel Plasminogen Activators

Even with the most successful current thrombolytic regimens, coronary reperfusion is achieved in only ~80-85% of patients with acute myocardial infarction, and normal (TIMI grade 3) antegrade coronary blood flow 90 minutes after initiation of therapy is achieved in slightly more than half. In addition, thrombotic reocclusion of the infarct related artery occurs in 5-15% of patients. First generation (native) plasminogen activators have several properties that may contribute to the incidence of primary and/or secondary failure of thrombolysis. Streptokinase and (two chain) urokinase exhibit no fibrin specificity, and thus do not target fibrinolytic activity to a thrombus. Urokinase and tissue plasminogen activator are subject to specific and rapid inactivation in plasma by plasma serpins (serine protease inhibitors), most importantly, plasminogen activator inhibitor-1. T-PA is rapidly cleared from the circulation by receptor-mediated uptake by the liver.

The structure and function of these proteins, and of other, novel plasminogen activators have been investigated for a number of years in an effort to develop more efficacious therapeutic agents. Reviews of these efforts have been published (Gerard 1989). Recently, the first of the second generation plasminogen activators have entered clinical trials.

Variant u-PA

While two-chain (mature) urokinase is a non-selective plasminogen activator, generation of urokinase from its single chain proenzyme form is catalyzed by plasmin, and occurs preferentially on a fibrin surface. Thus, in theory, prourokinase could function as a fibrin-selective thrombolytic agent. Recently, Weaver and colleagues (1994) have reported a phase-I clinical trial of recombinant glycosylated prourokinase in patients with acute myocardial infarction. Aspirin (325 mg), intravenous heparin and prourokinase (60- or 80-mg monotherapy or 60 mg "primed" with a preceding bolus dose of 250,000 IU of recombinant urokinase) were administered to 128 patients. Coronary angiography was performed at 60 and 90 min and 24 hours. The coronary artery patency rate at 90 min was similar for all three regimens, averaging 73%, and TIMI grade 3 flow rates averaged 52%. These rates are close to those observed

for accelerated rt-PA in the GUSTO trial. Reocclusion was infrequent (1.4%), and relative fibrin specificity was observed at all doses studied.

Variants of t-PA

Efforts to reengineer t-PA have focused on i) extending the half-life by eliminating or blocking the epidermal growth factor domain of the heavy chain and eliminating glycosylation sites responsible for hepatic receptor-mediated clearance, and ii) mutagenesis of the catalytic chain of the enzyme to render it resistant to inhibition by PAI-1.

Studies performed at this institution identified several years ago identified the structural basis for the interaction of t-PA and PAI-1. Deletion of a loop of residues in the light chain of t-PA, or mutagenesis of the enzyme to alter positively charged residues in this loop to neutral or acidic residues rendered the enzyme resistant to serpin inhibition. Subsequently, Shohet et al (1994) demonstrated that serpin-resistant variants of t-PA were more effective in lysing platelet-rich clots. Plans for phase-1 clinical trials of a variant t-PA based on the principals of this work are planned.

Extended half-life variants of t-PA are somewhat farther in the developmental pathway. In 1993, Tebbe and colleagues (1993) reported initial efficacy studies with BM 06.022, a non-glycosylated variant of human t-PA that can be administered as a bolus. These investigators administered two boluses (10 MU, the 5 MU 30 min later) to 50 patients with acute myocardial infarction, and assessed infarct artery patency. At 90 minutes following the first bolus, the infarct artery was patent in 39 of 50 patients. The subsequent German Recombinant Plasminogen Activator Study (Neuhaus 1994) examined the efficacy of single bolus reteplase (BM 06.022) in 142 patients in a dose-escalation study. At doses of 10 MU and 15 MU, patency rates at 90 minutes were 66% and 75%, respectively. Very early reocclusion was common, however, (17% and 13%), while late reocclusion (between 90 min and hospital discharge) occurred in 7% and 5%. Two bleeding complications requiring transfusion or surgical intervention and one nonfatal intracranial hemorrhage were encountered. Eight patients had a reinfarction, and five patients died, all of cardiac causes. The primary success rates observed in these early trials appear comparable, but not superior to those achieved with current thrombolytic protocols.

The RAPID trial (Smalling 1995) randomised 606 patients with acute myocardial infarction to one of four treatment arms: i) tPA 100 mg over 3 hours, ii) r(eteplase)-PA as a 15-MU single bolus, iii) r-PA as a 10-MU bolus followed by 5 MU 30 minutes later, or iv) r-PA as a 10-MU bolus followed by 10 MU 30 minutes later. Coronary arteriography was performed at 30, 60, and 90 minutes and at hospital discharge. The 10 + 10-MU r-PA group achieved better 90-minute (63% vs 49%) and 5- to 14-day TIMI 3 flow (88% vs 71%) than the t-PA group. Global ejection fraction (53 vs 49%) and regional wall motion in the 10 + 10-MU r-PA group were superior to those of the t-PA group at hospital

discharge. The 15-MU and 10 + 5-MU r-PA patency and left ventricular function results were similar to those of the t-PA and inferior to those of the 10 + 10-MU r-PA group. Bleeding complications were similar in all groups. Whether, however, the results achieved with reteplase would compare favorably with those obtained with accelerated rt-PA has not been examined.

Staphlokinase

Staphlokinase is a 136 amino-acid single chain protein produced by strains of S. aureus. While the capacity of staphlokinase to promote fibrinolysis has been long recognized, only recently has it been demonstrated that staphlokinase forms a 1:1 stoichiometric complex with plasmin(ogen), forming a potent plasminogen activator (Collen 1993). Staphlokinase possesses an important theoretical advantage as a potential therapeutic plasminogen activator. While other plasminogen activators are subject to inactivation by inhibitors which accumulate in proximity to forming thrombi, neutralization of the plasmin-staphlokinase complex by alpha 2-antiplasmin results in dissociation of functionally active staphlokinase from the complex and its recycling to other plasminogen molecules. This dissociation-recycling process may explain the high fibrinolytic potency of STAR in plasma (in the presence of high concentrations of alpha 2-antiplasmin; Silence 1993).

In animal studies, recombinant staphlokinase demonstrates potent thrombolytic effects. Recently, the STAR Trial Group has reported a randomised trial of STAR (10 or 20 mg i.v.) vs accelerated rt-PA for acute myocardial infarction. One hundred patients presenting within 6 hours of the onset of symptoms and with ST segment elevation on ECG were randomly assigned to treatment with one of the thrombolytic agents plus titrated iv heparin and oral aspirin. The primary endpoint was patency of the infarct artery at 90 minutes. TIMI grade 3 flow was observed in 50% and 74% (10/20mg respectively) of STAR patients vs 58% of those receiving rt-PA. No systemic fibrinogen breakdown was observed in STAR-treated patients. There were no hemorrhagic complications. Patients receiving STAR did develop neutralizing antibody titers following therapy.

Antiplatelet Strategies

Since the observations in the ISIS-2 trial that aspirin therapy dramatically reduces mortality in patients with acute myocardial infarction, and that the effects of aspirin are additive to those of a thrombolytic agent, antiplatelet therapy for myocardial infarction has become standard. Despite the routine use of aspirin, significant rates of both primary failure and secondary reocclusion following thrombolytic therapy remain. This has stimulated efforts to develop more effective antiplatelet strategies.

Platelet Glycoprotein IIb/IIIa Receptor Blockade

The central role of the platelet integrin, glycoprotein IIb/IIIa, in platelet aggregation is illustrated schematically in Figure 5. GpIIb/IIIa binds with high affinity the tripeptide motif arginine-glycine-aspartic acid (RGD), a sequence present in fibronectin, vitronectin, thrombospondin, fibrinogen and von Willebrand factor. Because the latter two proteins are multivalent, they form cross-bridges linking platelets into aggregates. Genetic deficiency of this mechanism (Glanzmann's Thrombasthenia) results in mucocutaneous bleeding and an essentially infinite prolongation of template bleeding time, but rarely results in life-threatening hemorrhage. This suggested that blockade of the platelet GpIIb/IIIa receptor might be an effective and safe anti-thrombotic strategy.

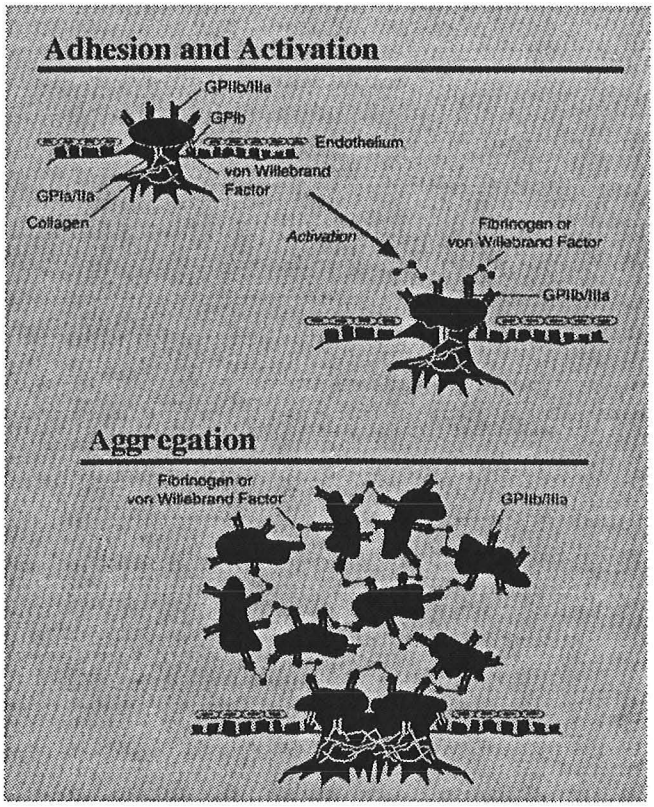

Figure 5: Function of GpIIb/IIIa (Coller 1994).

Abciximab

In the early 1980's, Dr. Barry Coller at Mount Sinai described the isolation of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa complex, and demonstrated that an $F(ab')_2$ derivative of this antibody could essentially completely abolish platelet aggregation in a canine model (Coller, 1985). Numerous studies in animal models of vascular thrombosis supported the potential utility of the antibody as an antithrombotic agent (reviewed in Coller 1995), and since 1992 a commercial version of a chimeric mouse/human $F(ab')_2$ anti-GpIIb/IIIa (generic name: abciximab) has been under clinical investigation.

The EPIC study (1994) randomised 2099 patients undergoing "high risk" (severe unstable angina, evolving myocardial infarction or high-risk morphologic characteristics) coronary angioplasty or atherectomy to standard therapy with or without abciximab (bolus, infusion or both). The primary end point was the combined incidence of death, nonfatal myocardial infarction, unplanned surgical revascularization, unplanned repeat percutaneous procedure, unplanned implantation of a coronary stent, or insertion of an intraaortic balloon pump for

refractory ischemia. Supplementing standard therapy with bolus and infusion of abciximab resulted in a 35 percent reduction in the rate of the primary end point (12.8 vs. 8.3%), at the expense of a 14% increase in the incidence of bleeding complications. Six month follow-up on patients in the EPIC study has been reported (Topol 1994), demonstrating a sustained (26%) reduction in repeat target vessel revascularization (16.5% vs 22.3%; p = 0.007).

The European Cooperative Study Group (Simoons 1994) examined the efficacy of abciximab as adjunctive therapy in patients presenting with unstable angina. 60 patients with unstable pattern chest pain and reversible ECG changes despite conventional medical therapy were randomised to c7E3 Fab or placebo for 24 hours after an index coronary angiogram. Anti-GpIIb/IIIa therapy was associated with a reduced incidence of recurrent ischemia (9 vs 16) and major events (death, infarction, urgent revascularization: 1 vs 12), and a higher incidence of improved TIMI grade flow in the culprit vessel (6 vs 1) in comparison to a placebo control group.

Recently, the results of the TAMI-8 pilot study, examining the efficacy of abciximab as an adjunct for thrombolytic therapy of acute myocardial infarction have been reported (Kleiman 1993). In this open, dose-escalation study, 60 patients receiving rt-PA and c7E3Fab were compared to 10 patients receiving a conventional thrombolytic regimen. Significant bleeding occurred in 25% of treated patients. Coronary angiography demonstrated a higher rate of patency of the infarct related artery in abciximab-treated patients (92 vs 56%). Results of an expanded, clinical-endpoint trail are anticipated.

Integrilin

In 1989, a tetrapeptide, RGDY, was shown to competitively inhibit binding of RGD-containing proteins to the platelet GpIIb/IIIa receptor in vitro, and to prevent thrombotic occlusion after balloon injury in a canine femoral artery model (Haskel 1989). This observation spurred the development of a cyclic RGD-containing heptapeptide, integrilin, as a potential anti-thrombotic agent.

The IMPACT study examined the efficacy of integrilin in 150 patients undergoing elective percutaneous coronary intervention. Patients were randomised to placebo or either 4 or 12 hours of integrilin infusion, and followed for the occurrence of myocardial infarction, stent implantation, repeat urgent/emergency revascularization or death. Integrilin administration resulted in a mean 86% inhibition of platelet aggregation. There was a trend toward reduction in end-point events from 12.2% (placebo) to 9.6% (4h) or 4.1% (12h) which did not achieve statistical significance. Major bleeding occurred in 8%, 8%, and 2% of patients, respectively.

The results of IMPACT-II, a prospective placebo-controlled study of 4010 patients undergoing elective or urgent PTCA randomised to the same three treatment arms (all patients treated with aspirin and heparin) have been presented at the European Society of Cardiology meetings. The combined endoint of death, infarction or urgent recurrent revascularization was reduced at

24 hours by integrilin therapy (placebo 9.3%, low dose 6.8%, high dose 7.0%). Reportedly, major bleeding events were not more common in treated patients. An angiographic substudy in which 617 patients underwent repeat angiography at 6 months was reported to show no apparent effect on luminal diameter or the incidence of restenosis, however.

Modification of Prostanoid Metabolism

The important effects of aspirin as an adjunct in thrombolytic therapy for acute myocardial infarction imply an important role for thromboxane A2 in mediating stable coronary occlusion. Aspirin antagonizes TxA2 production, but may simultaneously block endothelial production of prostacyclin. In animal models, both prostacyclin analogs and more specific inhibitors of thromboxane synthesis and/or receptor binding have shown promising effects in models of acute vascular occlusion. Clinical experience with these agents as adjuncts in the setting of unstable myocardial ischemia or infarction is limited, however.

Prostacyclin analogs

Prostacyclin and its stable analog iloprost inhibit platelet aggregation to multiple agonists, exerting effects beyond those of aspirin. Experiments in animals, however, have suggested that iloprost can interfere with t-PA mediated thrombolysis by accelerating clearance of t-PA from plasma. Kerins and colleagues (Kerins 1992) examined the kinetics of t-PA clearance in 12 patients receiving t-PA for acute myocardial infarction, however, and noted that neither elimination kinetics nor plasma protein binding of t-PA was altered by iloprost. Clinical studies to determine whether iloprost might be efficacious as an adjunct in the setting of thrombolysis, however, are not yet available.

Ridogrel

Aspirin, by nonselectively blocking cyclooxygenase both in platelets and in endothelial cells, not only inhibits the thromboxane A2 pathway of platelet activation but at the same time also the generation of vasodilating and platelet-inhibitory prostanoids, such as prostacyclin, by the endothelial cells. Ridogrel, by inhibiting thromboxane A2 synthase and blocking the thromboxane A2/prostaglandin endoperoxide receptors, is a more potent antiplatelet agent than aspirin and might offer an advantage over aspirin as an adjunct to thrombolysis. The **R**idogrel versus **A**spirin **P**atency **T**rial (RAPT) randomised 907 patients with acute myocardial infarction treated with streptokinase (1.5 MU) to either aspirin or ridogrel (Anonymous 1994). The primary end point was coronary patency (TIMI flow grades 2 and 3) at predischarge angiography. Angiographic patency (72.2% vs 75.5%), the frequency of clinical markers of reperfusion, and the incidence of major clinical events were similar in ridogrel and aspirin groups. In post hoc analysis, a lower incidence of new ischemic events (reinfarction, recurrent angina, ischemic stroke) was observed with ridogrel (13% vs 19%), while no difference in bleeding complications was

observed. The authors concluded that, while ridogrel did not appear superior to aspirin in enhancing the fibrinolytic efficacy, it may be more effective in preventing new ischemic events.

Thrombin Inhibitors

In addition to catalyzing the proteolytic cleavage of fibrinogen to fibrin, thrombin plays a central regulatory role in the coagulation cascade by i) catalyzing the activation of factors V and VIII thereby amplifying coagulation, ii) activating factor XIII, which cross-links fibrin monomers thereby stabilizing nascent thrombi, and iii) functioning as a potent agonist of platelet activation.

As a thrombin inhibitor, heparin suffers from several important limitations:

i) as an indirect inhibitor, the biological activity of heparin varies with the availability of antithrombin III, producing substantial variation in anticoagulant efficacy;
ii) the heparin-antithrombin III complex is inactive on thrombin bound to a clot;
iii) heparin does not antagonize the "mediator" activity of thrombin in platelet activation;
iv) heparin is inactivated by platelet factor 4 and heparinase(s) released from activated platelets, and
v) heparin-antithrombin III inhibits existing thrombin, but does not prevent generation of new thrombin by the prothrombinase complex.

The extent to which one or more of these factors may contribute to the incidence of primary failure of thrombolytic therapy, may underlie the failure of heparin to prevent early reocclusion in roughly 20% of patients with primarily successful reperfusion, or may limit the efficacy of heparin in preventing thrombotic occlusion in the settings of unstable angina or transluminal revascularization is unknown. These "failures", however, have stimulated the development of new antithrombotics that overcome one or more of the mechanistic limitations of heparin.

Characteristics of emerging thrombin inhibitors are most readily visualized in the context of at least a schematic representation of the structure and function of thrombin (Figure 6, Lefkovitz 1994). Four distinct "sites" on the thrombin molecule, a fibrin binding site, a substrate recognition site, the catalytic site and the heparin binding site, are of interest. Binding of fibrinogen to thrombin occurs at both the substrate recognition (anion-binding exosite) and catalytic sites. Binding of thrombin to the platelet surface (and thus platelet activation by thrombin) is apparently mediated by the catalytic site alone. Heparin binds to thrombin at a distinct site. Binding of thrombin to fibrin via the fibrin-binding site presumably induces a conformation change in the thrombin molecule rendering the heparin-binding site unavailable.

Three classes of direct thrombin inhibitors have been identified. Hirudin, a 65 amino acid protein initially isolated from the leech *Hirudo medicinalis*, binds to thrombin via both the substrate recognition and catalytic sites. Hirulog is a synthetic analog of hirudin which mimics its interaction with thrombin. Hirugen, a synthetic 12 amino acid peptide corresponding to the C-terminal residues of hirudin, binds to the substrate recognition site on the thrombin molecule. Finally, small molecular analogs of the fibrinogen cleavage site which bind specifically to the catalytic site of thrombin have been developed. PPACK is a tripeptide-chloromethylketone analog of fibrinopeptide A which irreversably inactivates thrombin by alkylating the active site histidine residue. Argatroban is an arginine analog which functions as a competitive inhibitor of fibrinogen binding to the catalytic site. With the exception of Hirugen, which demonstrates relatively weak

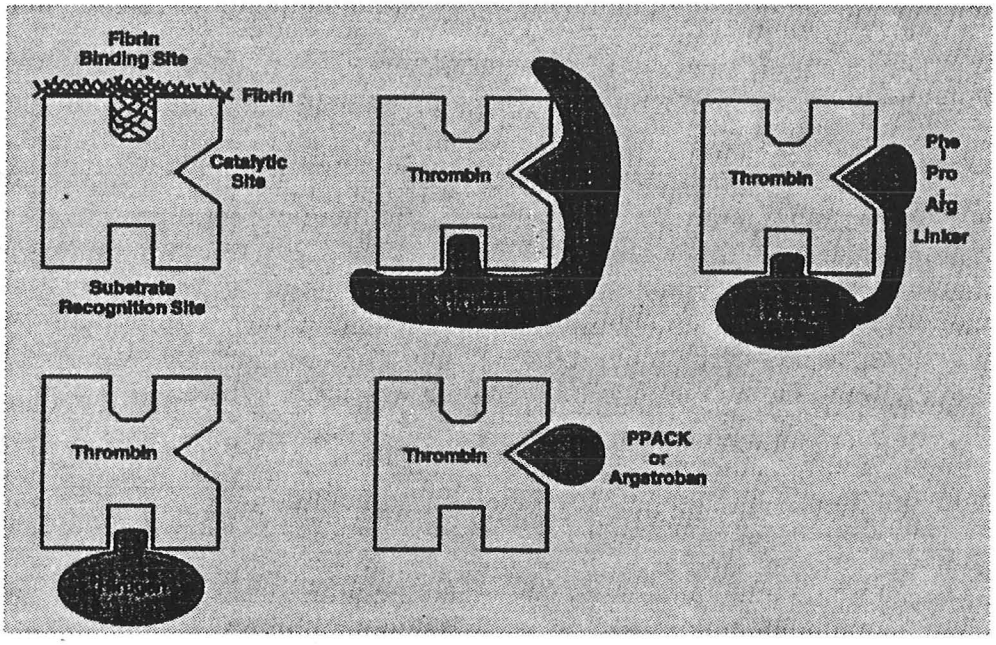

Figure 6: Schematic representation of thrombin inhibitors (Lefkowitz 1994).

antithrombin activity, each of these agents is in some stage of clinical evaluation as an anticoagulant following transluminal angioplasty or atherectomy, as an alternative to heparin for unstable angina, and/or as an adjunct for thrombolytic therapy.

Hirudin

van den Bos and colleagues (van den Bos 1993) compared hirudin to heparin in 113 patients with stable angina undergoing PTCA, monitoring clinical events, ST segment deviation on ECG and repeat coronary angiography at 24 hours. Myocardial infarction and/or emergency coronary bypass surgery occurred in 1.4% of hirudin-treated and 10.3% of heparin-treated patients. ST segment displacement occurred in 4% and 11%, and normal perfusion in the instrumented vessel was observed in 100% and 91%, respectively. Puncture

site bleeding was encountered in 4 hirudin patients. A similar favorable effect of hirudin on early post-angioplasty outcome has now been reported from the HELVETICA trial (Serruys 1995), a prospective comparison of heparin and either intravenous or subcutaneous hirudin for 72 hours following angioplasty in 1141 patients with unstable angina. Administration of hirudin was associated with a significant reduction in early cardiac events (11.0% vs 7.9% and 5.6% in the respective groups). No difference in the rate of clinical events at 6 months (primary endpoint), or in the luminal diameter of the instrumented vessel at 6 months were observed, however.

Topol and colleagues (Topol 1994) treated 166 patients presenting with unstable angina (rest ischemic pain, abnormal ECG, and >/= 60% stenosis of a culprit vessel) with heparin or hirudin on a dose-escalating protocol. Hirudin treatment (overall) was associated with a better average luminal diameter and % stenosis at 72-120 hours.

The TIMI-5 trial (Cannon 1994) randomised 246 patients with evolving Q-wave myocardial infarction to accelerated t-PA with either heparin or hirudin. Patency of the infarct-related artery at 90 minutes (64.8% vs 57.1%) and 24 hours (97.8% vs 89.2%), reocclusion rate (1.6% vs 6.7%) and the rate of death or recurrent myocardial infarction (6.8% vs 16.7%) were all favorably associated with hirudin therapy with no observed difference in the rate of hemorrhagic complications. The potential of hirudin as an adjunct to streptokinase therapy was examined in the TIMI-6 trial (Lee 1995), in which 193 patients with acute myocardial infarction were randomised to hirudin (3 escalating doses [bolus/infusion] .15/.05, .3/.1 or .6/.2 mg/mgh^{-1}) versus heparin in conjunction with streptokinase (1.5 MU) and aspirin (325 mg/day). The incidence of major hemorrhage was similar between the heparin group (5.6%) and any of the hirudin dose groups (5.5%, 6.5%, and 5.6%). At hospital discharge the occurrence of death, nonfatal reinfarction, congestive heart failure, or cardiogenic shock was greater in patients receiving the lowest dose of hirudin (21.6%) or heparin (18.3%) than in those receiving the higher doses of hirudin (9.7% and 11.4%), although these differences did not achieve statistical significance.

Based on these phase II trials, three large prospective trials of recombinant hirudin for acute myocardial infarction and/or unstable angina were initiated. The TIMI 9A trial (Antman 1994) randomised patients to a modified weight-adjusted heparin regimen vs hirudin (bolus of 0.6 mg/kg followed by a fixed-dose 96-hour infusion of 0.2 mg/kg per hour) as adjunctive therapy for acute myocardial infarction. Enrollment was suspended after 757 patients, however, because rates of hemorrhage in both treatment arms were higher than expected (rates for hirudin vs heparin: intracranial hemorrhage 1.7% vs 1.9%; major spontaneous hemorrhage elsewhere 7.0% vs 3.0%; major hemorrhage at instrumented sites 5.2% in both groups). As a result, the TIMI 9B study was redesigned with reduced anticoagulant doses (hirudin bolus 0.1 mg/kg and

infusion 0.1 mg/kg per hour/ heparin 1000 U/h without weight adjustment), titrated to a target aPTT of 55 to 85 seconds.

The GUSTO IIa trial (Anonymous 1994), randomising patients presenting with acute myocardial ischemia (infarction or unstable angina) to therapy with either heparin or hirudin [dose: 0.6 mg/0.2 mgh^{-1}] (in patients with evolving Q-wave infarction as an adjunct to thrombolysis) was similarly suspended for excessive hemorrhagic complications. The incidence of hemorrhagic stroke tended to be higher for patients receiving hirudin (t-PA and heparin 0.9%; t-PA and hirudin 1.7%; streptokinase and heparin 2.7%; streptokinase and hirudin 3.2%), and these rates were substantially higher than those observed in patients receiving thrombolytic therapy and heparin in the GUSTO I trial (0.7%). Risk of hemorrhagic stroke correlated with a higher aPTT.

The **H**irudin for **I**mprovement of **T**hrombolysis (HIT III) study (Neuhaus 1994) randomised patients presenting within 6 hours of the onset of acute myocardial infarction to accelerated rt-PA with aspirin and either heparin or hirudin [dose 0.4 mg/0.15 mgh^{-1}]. After enrollment of 302 patients, the trial was stopped after an increased rate of intracranial bleeding was observed in the hirudin group (5/148 vs 0/154). Increases in overall stroke rate (3.4% vs 1.3%) and death (13/148 vs 6/154) were also observed in patients receiving hirudin.

Hirulog

Dose ranging studies with hirulog, a 20 amino acid hirudin analog carrying substrate recognition and catalytic site binding domains linked by a polyglycine tract, have demonstrated predictable, dose-related prolongation of the aPTT which correlates well with plasma hirulog concentrations (Cannon 1993). A similar dose-related prolongation of aPTT has been reported in a phase I dose-ranging study of hirulog as an intraprocedural anticoagulant during transluminal angioplasty (Topol 1993). In this study, high dose (bolus 0.45-0.55 mg/kg, infusion 1.8-2.2 mg/kg/h) hirulog was associated with a lower rate of abrupt vessel closure (3.9% vs 11.3%) than lower dose therapy. In a dose ranging study of hirulog as therapy for unstable angina, Lidon and colleagues (Lidon 1993) reported that escalating doses of hirulog were progressively effective, and that at 1 mg/kg/h, 20/21 patients demonstrated clinical stabilization without bleeding complications.

The Hirulog Angioplasty Study (Bittl 1995) randomised 4098 patients undergoing angioplasty for unstable or postinfarction angina to either heparin or hirulog immediately before angioplasty. The primary endpoint was the combined in-hospital incidence of death, myocardial infarction, abrupt vessel closure, or rapid clinical deterioration of cardiac origin. Hirulog did not significantly reduce the incidence of the primary end point (11.4% vs. 12.2%), but did result in a lower incidence of bleeding (3.8% vs. 9.8%). In the subgroup of patients with post-infarction angina, hirulog reduced the risk of immediate ischemic complications, but this difference was no longer apparent at six month follow-up.

The TIMI-7 trial (Fuchs 1995) randomised 410 patients with unstable angina to therapy with aspirin plus one of four doses of hirulog (infusions of 0.02, 0.25, 0.5 or 1.0 mg/kg/h). The primary end point was the combined incidence of death, nonfatal MI or recurrent pain at rest with ECG changes by 72 hours, and did not differ between treatment groups. The incidence of death or nonfatal MI through hospital discharge was significantly lower in patients treated with >/= 0.25 mg/kg/hr (3.2% vs 10.0%). Only 0.5% of patients experienced major hemorrhagic complications.

The efficacy of hirulog as adjunctive therapy to streptokinase in patients with acute myocardial infarction was examined by Theroux and colleagues (Theroux 1995). 68 patients underwent index coronary angiography, and received streptokinase (1.5 mU) and aspirin. Patients were randomised to heparin, low-sustained (0.5 mg/kg/h X 12h then 0.1 mg/kg/h) or high (1 mg/kg/h X 12h) dose hirulog. Angiographic patency of the culprit coronary artery lesion was assessed 90 and 120 minutes, and again after 4 +/- 2 days. Patency rates at 90 minutes were 46%, 96% and 79%, respectively. TIMI grade 3 flow was observed in 31%, 85% and 61% of patients in the 3 treatment groups.

Argatroban

The catalytic site directed arginine analog argatroban exerts apparently complex effects on coagulation, demonstrating reversible inhibition of the catalytic activity of thrombin and of factor Xa, and inhibiting thrombin generation in human plasma following activation of either the intrinsic or extrinsic pathways (Callas 1995). In pilot studies, argatroban has been reported to inhibit thrombus formation following administration to patients undergoing transluminal coronary angioplasty (Suzuki 1995). Gold and colleagues (Gold 1993) have reported on a series of 43 patients treated with continuous infusion argatroban (0.5-5.0 µg/kg/min X 24 hours) for unstable angina pectoris. Argatroban infusion resulted in a dose-related increase in aPTT, but no bleeding time prolongation or spontaneous bleeding. Symptomatic myocardial ischemia did not occur during therapy. The authors observed a high (9/43) incidence of recurrent rest angina associated with an increase in thrombin-antithrombin III complexes and fibrinopeptide A levels within 24 hours after argatroban was discontinued, however. Whether this reflects a "rebound" hypercoagulable state following administration of the direct thrombin inhibitor or simply a re-emergence of the underlying unstable ischemic syndrome has been debated (Willerson 1993).

Low MW Heparin

Low molecular weight fractions of heparin demonstrate anti-Xa and anti-thrombin activity with relatively little prolongation of the aPTT. In animal experiments, LMW heparin fractions have been demonstrated to inhibit vascular thrombosis in a variety of models without producing an important bleeding tendency.

Limited clinical data is available with respect to the potential utility of LMW heparin in the treatment of ischemic heart disease. Gurfinkel and colleagues (1995) have reported a prospective, randomised trial of aspirin, aspirin plus intravenous heparin or aspirin plus subcutaneous Nadroparin, a LMW heparin preparation, in patients with unstable angina presenting within 6 hours of rest pain. LMW heparin therapy was associated with significant reductions in the rates of recurrent angina, non-fatal myocardial infarction and urgent revascularization in comparison to the control groups, suggesting that treatment with aspirin plus a high dose of low molecular weight heparin during the acute phase of unstable angina may be significantly better than conventional therapy. No studies of LMW heparin as an adjunct to thrombolytic therapy for acute myocardial infarction are yet available.

Miscellaneous Adjunctive Therapeutic Interventions

Rescue angioplasty

One of the principal limitations of thrombolytic therapy is the rate of primary failure, i.e. the rate at which intravenous thrombolytic therapy fails to achieve early infarct artery patency. In theory, angioplasty could be employed to establish reperfusion in patients failing primary thrombolytic therapy. Observations from the TIMI-II and TAMI-1 (aggregate 54 patients) trials suggested that transluminal angioplasty could be performed successfully (~85-90%) in this population. Recently, Ellis and colleagues (Ellis 1994) reported the results of a prospective trial of rescue angioplasty vs conservative management in patients with acute anterior wall myocardial infarction, with the primary endpoints of left ventricular function and clinical outcome (death, heart failure or ventricular tachycardia) at 30 days. The trial randomised 151 patients treated with a thrombolytic agent for anterior infarction and demonstrated to have an angiographically occluded infarct-related artery within 8 hours of symptoms to either aspirin, heparin and coronary vasodilators (conservative therapy) or to immediate angioplasty. Rescue angioplasty was successful in 72/78 patients. Resting 30-day ejection fraction was 40 +/- 11% in the angioplasty group and 39 +/- 12% in the conservative group, although exercise ejection fraction was slightly better in angioplasty patients. The incidence of adverse clinical outcomes (death: 5% vs 10%; severe heart failure: 1% vs 7%) favored rescue angioplasty, although only the combined endpoint of death or heart failure achieved statistical significance. Additional trials of rescue angioplasty are in progress, although a practical strategy for clinical application is not yet apparent.

In a retrospective analysis of the TAIM-1 through -4 data, Topol and colleagues (1989) reported that no clinical indicators could reliably discriminate patients with patent and occluded infarct-related arteries following thrombolytic therapy, an observation widely upheld by subsequent experience. Similarly, no currently available non-invasive techniques permit reliable identification of patients who might benefit from rescue angioplasty. Routine catheterization of

patients following thrombolytic therapy is associated with a substantial risk of significant bleeding (~25% in the TIMI-1 trial). In view of the suggestion from the Rescue trial that patients at high risk (anterior infarction) might benefit from rescue angioplasty, Drs. Landau, Hundley and colleagues at U.T. Southwestern have been conducting a study to determine whether urgent gated cardiac magnetic resonance imaging can identify patients with a persistently occluded left anterior descending coronary artery.

Coronary Bypass Surgery

While non-elective coronary bypass surgery has been performed early after myocardial infarction relatively commonly, only recently have data concerning efficacy and outcome in patients following thrombolytic therapy become available. Retrospective review of patients enrolled in the TAMI-1, -3 and -5 trials (Kereiakes 1991) revealed that 303 (22%) of 1387 consecutive patients required urgent (19.3%) or emergent (2.6%) coronary bypass grafting. Indications included failed angioplasty (12%); left main or equivalent coronary disease (9%); complex or multivessel coronary disease (62%); recurrent postinfarction angina (13%); and refractory pump dysfunction, mitral regurgitation, ventricular septal rupture or abnormal predischarge functional test (1% each). The course and outcome for these patients was relatively reassuring. Although patients having bypass surgery were older, and had more extensive coronary disease, worse ventricular function, and more comorbid conditions than the overall population of patients enrolled in these studies, they did not have a higher incidence of death, either in hospital (7% vs 6%) or at long-term follow-up of survivors (7% vs 6%), and demonstrated greater recovery of left ventricular function (3.4% vs 0.16%) than nonsurgical patients. The latter observation, while encouraging, is certainly biased by the high incidence in the surgical group of patients with ongoing or recurrent ischemia.

Similar data have been reported from the TIMI-II trial (Gersh 1995), in which 390/3339 patients required early CABG. Perioperative mortality rates were strongly correlated with the timing of surgery (16.7% within 24 hours of presentation vs 3.9% for surgery >24 hours after presentation), in part reflecting emergency intervention in patients with mechanical complications, failed PTCA or shock. Among the 322 perioperative survivors, the 1-year mortality rate after discharge was only 2.2% and 1.9%, respectively, in the two groups. These data are reassuring with regard to the prognosis of patients requiring surgical revascularization after thrombolysis, in particular, for recurrent unstable ischemia.

IABP

Intra-aortic balloon counterpulsation is effective in the temporary management of unstable ischemia and refractory heart failure. The use of IABP as an adjunct to coronary reperfusion therapy has been examined retrospectively from data collected on 810 consecutive patients enrolled in the

TAMI trials (Ohman 1991). 85 of these 810 patients were treated with IABP, and as expected, had a high incidence of anterior infarction (62%), multivessel CAD (67%), TIMI grade 0 or 1 flow (44%) and depressed ejection fraction (mean 40%). This high risk population had a very high in-hospital mortality rate (32% vs 4% overall in the TAMI population), but showed no reinfarction or reocclusion of the infarct-related artery during treatment with the IABP as assessed by repeat angiography.

On the basis of these observational results, suggesting that IABP may have a specific role after thrombolytic therapy in treating patients at high risk for reocclusion or hemodynamic deterioration, a prospective trial of IABP following primary angioplasty for acute myocardial infarction was undertaken (Ohman 1994). A total of 182 patients undergoing primary angioplasty for infarction were randomised to conventional management or IABP. Repeat cardiac catheterization was performed at a median of 5 days after randomization. Rates of severe bleeding (2% vs 1%) and vascular repair or thrombectomy (5% vs 2%) were similar. Patients randomised to aortic counterpulsation had significantly less reocclusion of the infarct-related artery (8% vs 21%, $p < .03$), suggesting that careful use of aortic counterpulsation can prevent reocclusion of the infarct-related artery in patients undergoing acute cardiac catheterization during myocardial infarction.

Fluisol

Experimental studies in animals have suggested that salvage of ischemic but viable myocardium by coronary reperfusion may be limited by reperfusion injury, and several experimental studies have suggested that the perfluorochemical Fluisol can ameliorate this process. An observational report on 26 patients (Forman 1991) had suggested similar beneficial effects on salvage of ischemic myocardium and post-infarction ventricular function in man. The TAMI-9 study (Wall 1994) examined the potential of intravenous Fluisol as an adjunct to rt-PA in 430 patients with acute myocardial infarction, with primary endpoints of global ejection fraction, regional wall motion, infarct size measured by tomographic thallium imaging, and a composite clinical outcome measure. No significant difference in ejection fraction (52% vs 51%l) or regional wall motion was demonstrated, nor was there a significant difference in thallium infarct size. Rates of death and stroke were no different. Patients who received Fluosol experienced less recurrent ischemia, but more transient congestive heart failure and pulmonary edema. Overall, no beneficial effect on ventricular salvage or function, or clinical outcome could be demonstrated.

Superoxide Dismutase

One candidate mechanism for reperfusion injury is the generation of a burst of oxygen free radicals after reperfusion of acutely ischemic myocardium. Experimental studies in animals have suggested that administration of free radical scavengers, in particular superoxide dismutase, can block reperfusion

injury. Flaherty and colleagues (Flaherty 1994) have reported a randomised clinical trial of intravenous r-SOD begun before percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction. This study randomised 120 patients to either placebo or r-SOD, and examined left ventricular function at hospital discharge and 4-6 weeks later. Both r-SOD and placebo-treated patients showed improvement in global and regional left ventricular function after successful reperfusion, and no additional improvement was observed in the patients treated with r-SOD.

Clinical Application: the National Registry of Myocardial Infarction

Since 1990, demographic, procedural and outcome data from patients presenting to 1073 hospitals in the United States have been collected and compiled in the National Registry of Myocardial Infarction. Through 1993, 240,989 patients have been enrolled from 14.4% of all U.S. hospitals (Rogers 1994). Parkland Memorial Hospital has participated in this registry since 1992. Large urban, teaching and academic hospitals are somewhat overrepresented, but the size of the registry alone makes it the best current source of information on the routine clinical management of patients presenting to U.S. hospitals with acute myocardial infarction. Two observations from the registry are important in the context of this discussion. Table IV presents data on the fraction of patients in selected subgroups treated with a thrombolytic agent.

Table IV: National Registry Data (Rogers 1994)

ECG Findings	% of Patients Treated with Thrombolytic Agent or PTCA
Anterior ST elevation	42.6%
Inferior ST elevation	49.0%
Lateral ST elevation	39.6%
ST depression	4.2%
Other	32.4%

As shown, even in groups for which the benefit of thrombolytic therapy is clear (ST segment elevation) and those at "high risk" (anterior Q-wave infarction), a minority of patients receive thrombolytic therapy. While this might have reflected agressive use of primary angioplasty, only 3.1% of the patients not receiving thrombolytic therapy underwent an alternative reperfusion procedure. The majority of patients received no therapy (except aspirin) directed at reestablishing perfusion of the infarct related artery (only 73% received aspirin). The two most common reasons for this were "physician preference" (tabulated when no other reason could be identified), and patient age (rates of reperfusion therapy fell progressively for patients >50 years of age). Extrapolating from the FTT "absolute benefit data" and these registry numbers, this pattern of therapy predicts an absolute excess mortality between 50-75 lives/1000 patients, almost

10-times the difference between alternative thrombolytic strategies in the GUSTO trial.

Secondly, Figure 7 shows the effect on mortality in registry patients of the time from the onse of symptoms to treatment. Median time from onset of symptoms to presentation in registry patients was 2.2 hours. Mean "door to drug" time was an additional 99 minutes (median 57 minutes). These times have not improved significantly over the 4 year span of the registry. Mean "door to drug" times as little as 22 minutes have been reported in some clinical trials. The FTT review suggests an excess mortality of ~2 lives/1000 patients/hour of delay.

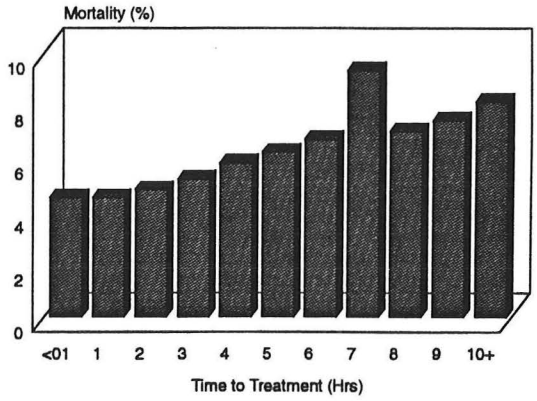

Figure 7: Effect of time to treatment on mortality (Rogers 1994).

Summary

Over the 5 years since I last reviewed the use of fibrinolytic therapy for acute myocardial infarction, "standard" therapy has evolved. The characteristics of patients for whom therapy directed at restoring antegrade flow in the infarct related artery is associated with a significant reduction in mortality are now relatively well defined. Even more importantly, the goal of reperfusion therapy - the rapid restoration of normal flow in the infarct artery - is now clear. Comparison of alternative strategies to achieve this goal, while still debated, appear to favor more aggressive (accelerated rt-PA, primary angioplasty) approaches, at least in "high risk" patients presenting early in the course of evolving myocardial infarction. A number of investigational strategies have progressed to clinical trials, and in some cases, the early results are comparable (although not yet clearly superior) to the best current strategies.

The summary above presents the data members of the Cardiology Division have considered in formulating our current recommendations for the management of patients with acute myocardial infarction. At Parkland, the use of accelrated rt-PA with oral aspirin and titrated intravenous heparin is a "standard" approach in patients lacking an important contraindication, and primary angioplasty is considered for patients at "high risk" when the projected time to intervention is not > 1-1.5 hours, or when a thrombolytic agent is contraindicated. While specifics of our "standard" approaches can be debated, we succeed in treating a high fraction of eligible patients.

The differences between treatment arms in more recent clinical trials are narrowing, in part reflecting the success of " current standard" therapy in

reducing mortality in the control group. The arguments are now over "benefit" of a few lives/1000. In contrast, the pattern of broad clinical practice in the United States continues to lag the established standard. Approximately 75% of patients get some therapy of proven benefit, and fewer than half of eligible patients appear to receive lytic (or interventional) therapy. The estimated "cost" of this pattern of practice is measured in tens of lives/1000 patients. Delays in initiation of therapy also appear common and costly. If the extensive clinical data on reperfusion therapy for myocardial infarction support one consensus recommendation, it is treat, treat with something, and do so quickly.

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