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Reperfusion Therapy of Acute Myocardial Infarction

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IN 1979, DUCKERT reviewed the completed trials of intravenous (IV) thrombolytic therapy in acute myocardial infarction (MI) for this journal.[1] Duckert stated in his review, "It is fair to conclude that today the value of thrombolytic treatment of acute MI has not been established." Since this review, dramatic advances have been made in the understanding of pathogenesis of MI, knowledge of thrombolysis, advances in technology, and stratification of risk groups. With these advances in understanding and the completion of several large, prospective randomization clinical trials, a much clearer picture of the clinical use of reperfusion therapy of MI has evolved. In 1979, only prolonged IV infusion of thrombolytic agents had been studied; since then, numerous other reperfusion strategies, including coronary bypass, intracoronary streptokinase infusion, short-term high-dose IV infusion of thrombolytic agents, and coronary angioplasty (PTCA), have been used. For these reasons, a review of the current status of reperfusion therapy is timely. The rationale and experimental basis for using reperfusion therapy has been extensively reviewed elsewhere.[2-14] In an analysis of the clinical benefit of reperfusion therapy, three fundamental questions must be addressed. First, how does therapy alter the pathogenesis of acute MI? Second, does therapy salvage myocardium or, indirectly, does therapy preserve ventricular function? Finally, and most importantly, does therapy alter mortality? This review will examine these fundamental questions for each of the currently used reperfusion strategies. Before these questions can be addressed, an understanding of the natural history of thrombotic coronary occlusion, changes in ventricular function, and mortality must be examined.

NATURAL HISTORY OF CORONARY ARTERY OCCLUSION

Duckert stated in 1979 that "the theoretical basis for fibrinolytic therapy of acute infarction, at least to some investigators, is open to question."[1] This statement reflected the state of confusion that existed in the mid-1970s concerning the causal relationship between thrombus and transmural MI. Advances in clinicopathologic studies[15-18] have clarified the pathogenesis of MI, and it is now clear that thrombus plays an integral role in its onset. The trigger for thrombotic occlusion appears related to plaque fissure, plaque rupture, or intramural hemorrhage (Fig 1). With endothelial disruption, cholesterol, cholesterol esters, and collagen become exposed to platelets and other hematologic hemostatic constituents. These events typically occur in an area with high-grade atherosclerotic occlusion where diminished coronary blood flow is present. Although the exact trigger for the onset of acute occlusion is unknown, the observations of Mueller et al[15] on the diurnal variation in frequency of onset of MI provides an intriguing clue. Vasospasm,[19,20] possibly related to release of vasoconstrictor substances from the platelets, may play a role in further decreasing luminal diameter and blood flow. Thus, circadian

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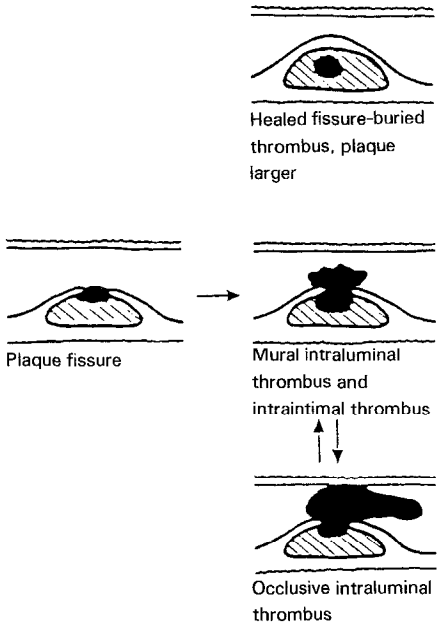

Fig 1. Plaque fissure may evolve to reseal or progress to subtotal or total coronary occlusion leading to unstable angina or myocardial infarction.

rhythm, stasis of blood flow, vasoconstriction, activation of platelets, and activation of the coagulation cascade combine to create a thrombotic occlusion.

The actual role of thrombotic occlusion was greatly debated in the late 1960s and 1970s.[21] In fact, the uncertainty concerning the role of thrombotic occlusion led to the uncertainty alluded to by Duckert concerning the value of thrombolytic therapy. If thrombus was merely a passive, secondary phenomenon that occurred in a highly stenosed segment of a coronary artery, the value of thrombolytic therapy in reestablishing blood flow would be limited. Histopathologic observations and postmortem angiography[18,22,23] greatly clarified the primary role of thrombotic occlusion. Ultimately, arteriography during acute MI established the clear role of thrombotic occlusion. Recently, coronary angioscopy[24] corroborated these arteriographic findings. The pioneering work of DeWood et al[25] established that coronary angiography could be safely performed early in acute MI, and that a high incidence of complete occlusion of the infarct-related artery existed.[26] Only a brief time elapsed from the demonstration of the presence of occluding thrombus to the pioneering work of Chazov et al[27] and Rentrop et al.[28] Rentrop et al demonstrated that occlusive thrombus could be penetrated with a guidewire,[29] then later that thrombus could be lysed with intracoronary streptokinase administration.[30] Several controlled trials of intracoronary streptokinase have now been completed. These trials allow further corroboration of the initial angiographic studies of DeWood et al.

CORONARY ANATOMY DURING TRANSLUMINAL INJURY

Before reviewing the angiographic findings, it must be emphasized that all intracoronary streptokinase reperfusion trials included patients with clearly defined symptom onset and with ST segment elevation, suggesting transmural injury by ECG criteria. The role of occlusive thrombus, the coronary anatomy, and initial ventricular function in patients with ST segment depression suggesting subendocardial injury or ischemia has not been fully defined.[31]

The incidence of total coronary occlusion varies with the duration of symptoms and use of IV heparin.[32-40] When arteriography is performed in patients with transmural injury within five hours of symptom onset, over 80% of the patients will have an occluded infarct-related artery (Fig 2). At six to 24 hours from onset of symptoms, 65% of the vessels remain occluded. Gibson et al[32] performed coronary angiography in 154 patients with Q-wave infarction, 11 ± three days after admission. Therapeutic anticoagulation was not used in this trial and 75% of the infarct arteries were occluded. In a long-term study, Pichard et al performed angiography on 39 patients 2 to 8 weeks after MI and found 80% of the infarct-related arteries to be totally occluded.[33] The New York University-Mount Sinai reperfusion study[34] and the Netherlands Interuniversity trial[35] treated control groups with continuous IV heparin. In the former study, only 23% of the infarct arteries were occluded at angiography ten to 14 days after admission. In the later study, 48% of the arteries were occluded in the recuperation phase. These studies demonstrate that a dynamic process of occlusion, spontaneous thrombolysis, and reocclusion commonly occurs during the first month after MI. Therapeutic anticoagulation enhances long-term patency. Without specific therapy, over 75% of the

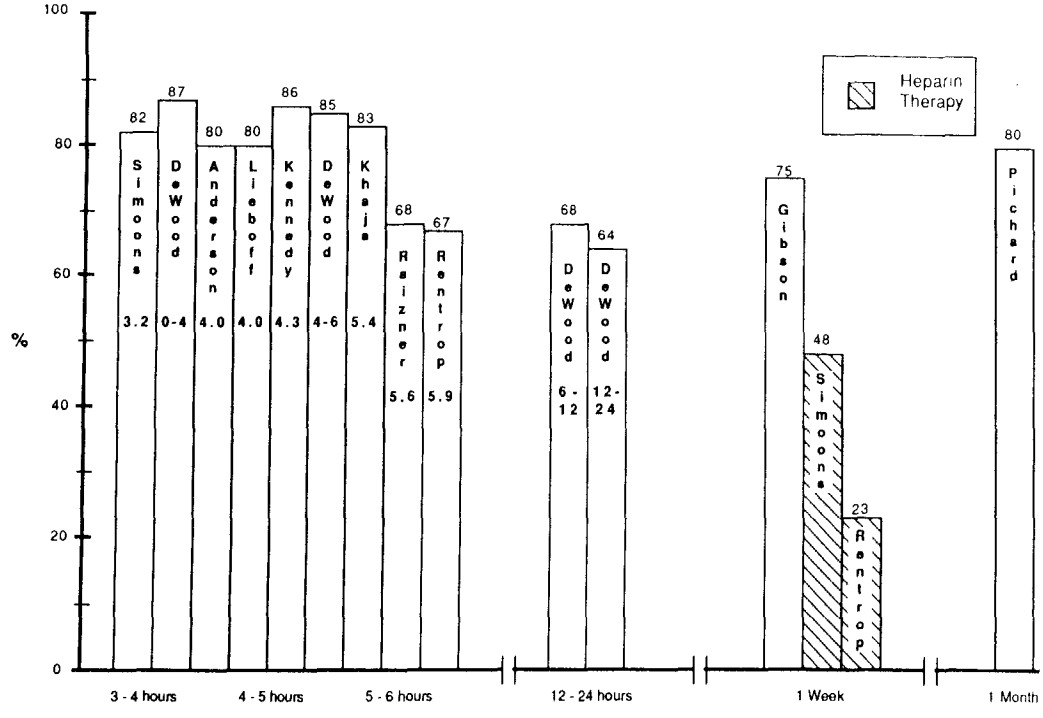

Fig 2. Prevalence of total coronary artery occlusion during MI. Time after symptom onset at which patients underwent angiography is depicted.[25,32-40]

infarct-related arteries will be occluded in the convalescence phase of acute MI. With this knowledge of the natural history of coronary occlusion, the acute and chronic results of reperfusion strategies can be more critically evaluated.

In addition to determining the prevalence of total occlusion, Stadius et al carefully characterized the coronary anatomy of the 250 patients enrolled in the Western Washington Intracoronary Streptokinase trial.[41] To be enrolled in this study, patients were required to have ST-segment elevation of 0.15 mV in two or more ECG leads and present within 12 hours of symptom onset. Coronary angiography was performed on an average of 4.1 hours after symptom onset. The infarct artery was the left anterior descending (LAD) (47%), right coronary artery (RCA) (45%), and circumflex (8%). In patients with LAD occlusion, 67.5% of the occlusions were in the proximal LAD and 30.7% of the occlusions were in the mid-LAD. In patients with RCA occlusion, 57.7% of the occlusions occurred proximally, 48.7% occurred in the midportion, and 3.6% occurred in the distal portion. Since ECG ST elevation was required for entry into this study, and the posterolateral surface is often not accompanied by these changes, only 8% of the patients had circumflex occlusion. Thus, coronary occlusion occurred in the proximal or midportion of the major epicardial branches in over 90% of the patients. A further important finding was that angiographic collaterals were much more common in RCA occlusions (58%) than in LAD occlusions (31%); $P < .05$. This finding may partially explain the following differences in clinical outcome between RCA and LAD occlusions.

NATURAL HISTORY OF CHANGES IN VENTRICULAR FUNCTION DURING MYOCARDIAL INFARCTION

With the knowledge that thrombotic coronary occlusion was present early in acute MI, a rationale for thrombolytic therapy existed. It was hoped that timely coronary reperfusion could interrupt the infarction and salvage myocardium. The most widely used parameter of myocardial salvage has been the change in global and

regional left ventricular wall motion. Despite the known limitations of ventricular imaging techniques in quantifying myocardial ischemia and infarction,[42] changes in systolic function are widely used. Changes in ventricular wall motion have been widely used because these measures are standardized, widely available, and have prognostic value.

In order to adequately assess the changes in ventricular function with reperfusion therapy, the changes occurring without this therapy must be examined. Wackers et al[43] examined the changes in radionuclide ejection fraction (EF) occurring during the first 24 hours of admission. Spontaneous changes in EF occurred in 19 of 34 patients with improvement in 11 patients and deterioration in eight. These investigators postulated that changes in sympathetic tone that occur early in acute MI might account for the early changes in ventricular function. Raizner et al[40] and Schreiber et al[44] measured serial global EF 24 hours after admission and predischarge in patients treated conventionally. No serial changes in mean global EF were found in either study. Similarly, Tamaki et al[45] found no change in serial global EF in 95 patients studied at 24 hours and day 10. Coromilas et al[46] reported in preliminary fashion serial radionuclide EF in 87 acute MI patients treated conservatively. No difference in EF occurred between days 1 and 3 and predischarge in this study. In contradistinction, regional wall motion has great variability between day 1 and day 10 post-MI. In the study of Tamaki et al, 30% of the severely hypokinetic segments changed (25% improved, 5% deteriorated). Improvement in at least one hypokinetic or akinetic segment was seen in 47% of these patients.

Shelbert et al[47] evaluated changes in ventricular function occurring after hospital discharge in 43 patients. Serial radionuclide ventriculograms were obtained within five days of admission and subsequently, 2 to 39 months (mean, 19.9 months) later. In this study, EF increased from 0.45 ± 0.02 to 0.49 ± 0.01 ($P < .01$). EF increased in 61%, decreased in 23%, and remained unchanged in only 16% of the patients.

The spontaneous variability of systolic ventricular function must be considered in the design and interpretation of reperfusion trials that use changes in ventricular function as an endpoint. This spontaneous variability may account for the conflicting results found in the early, noncontrolled reperfusion trials. Greatest variability in global and regional function occurs during the first 24 hours of admission, when hemodynamic changes, changes in sympathetic tone, and frequent administration of vasoactive agents occur. Least variability occurs in serial global EF measurements at 24 hours and predischarge. Even in this time interval, 25% of the dysynergic segments will spontaneously improve.

A number of mechanisms can explain the spontaneous improvement in EF. Ong et al[48] elegantly demonstrated that spontaneous improvement in wall motion may occur because of spontaneous recanalization of totally occluded vessels. Creatinine-Kinase Myocardial Band levels were measured serially in 34 patients with transmural ECG injury current. Patients who had early CK-MB release suggestive of spontaneous recanalization improved EF from 0.38 ± 0.09 to 0.48 ± 0.08 ($P < .001$). No improvement in EF occurred for patients with delayed CK-MB release. In an angiographically controlled study, Schwartz et al[49] found significant increases in EF in patients who presented with subtotal coronary occlusion or those with well-developed coronary collaterals. De Feyter et al[50] found that the spontaneous improvement in EF in patients with subtotal occlusion was equal to that achieved by streptokinase-induced coronary recanalization. Furthermore, Blanke et al[51] found that patients with subtotal coronary occlusion had a significantly higher initial EF than those with complete occlusion.

While spontaneous reperfusion, subtotal occlusion, and extensive angiographic collaterals allow for improved ventricular function, the presence of high-grade residual lesions may prevent improvement. Guerci et al[52] and Resenheck et al[53] performed angioplasty in patients with patent infarct arteries and a high-grade residual stenosis three days and 3 to 5 months post-MI, respectively. Exercise EF improved in the study of Guerci et al and rest EF improved in the study of Resenheck et al. Since angioplasty was performed late after symptom onset, myocardial salvage could not be the mechanism for improved ventricular function. Rather, these critical coronary lesions must prevent adequate return of

coronary blood flow to ischemic, but viable, myocardial segments.

Although spontaneous reperfusion may allow for improved ventricular function, Blanke et al[51] also found that those patients with persistent total occlusion and no collateral flow had 10.1% ± 7.5% decrease in absolute EF on serial contrast ventriculography. Rogers et al[54] confirmed that a significant decrease in EF occurs in patients with persistent total occlusion and no collateral flow.

A final major confounding influence on correlation between changes in ventricular function and salvage of myocardium is prolonged, postischemic "stunning" of the myocardium.[55] Experimental studies demonstrated that days or weeks[56,57] may be required for full return of myocardial function after reperfusion. Hinohara et al[58] and Erbel et al[59] demonstrated that further improvement in ventricular function occurs up to 3 to 9 months after hospital discharge in patients successfully reperfused by PTCA.

Recognition of the apparent prognostic value of these measures led to the impetus to determine ventricular function after MI. Schultze et al first demonstrated[60] that those patients with poor EF and complex ventricular ectopy were the highest-risk subgroup for sudden death in the year after recuperation from acute MI. Sanz et al[61] extended these observations to 259 consecutive patients undergoing cardiac catheterization 1 month after acute MI. Cox regression analysis of clinical and angiographic variables revealed that EF, the number of diseased vessels, and the presence of heart failure during admission were the only independent predictors of long-term survival. Patients with an EF of 0.50 or greater had a >95% probability of survival regardless of the extent of vessel disease. Patients with impaired ventricular function had a worse prognosis with worsening EF and with more extensive arteriographic vessel disease. Hugenholtz[62] demonstrated that a curvilinear relationship exists between EF and survival probability. Patients with an EF >45% have a <5% probability of death in the first year. Stadius et al[63] showed that impairment of ventricular function appears especially important in patients with anterior MI (Fig 3). The probability of 1-year mortality becomes >10% for patients with anterior MI when the EF value decreases below 45%. Patients with inferior MI do not reach a 10% probability of death until the EF decreases below 35%.

The widespread availability of radionuclide EF determination has allowed large numbers of patients to be studied and stratified according to risk. The Myocardial Infarction Limitation Infarct Size (MILIS) study group[64] and the Multicenter Post-Infarction research group[65] both found that radionuclide EF independently predicted survival in 533 and 781 patients followed in these two studies (Fig 4). Ahnve et al[66] followed 632 patients for at least 1 year. Patients with EFs >55% had a better than 90% survival probability. Survival probability worsened with worsening EF levels. In this study, an EF value of 0.45 optimally segregated low- and high-risk subgroups. Poor EF and complex ventricular arhythmias additionally predicted an increased risk of cardiac death in all three studies. These natural history studies demonstrate the importance of maintenance of ventricular function after acute MI in determining long-term surviv-

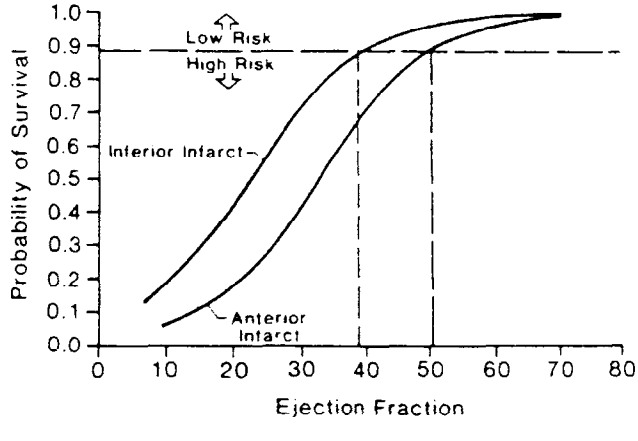

Fig 3. Probability of 1-year survival is calculated for patients with anterior and inferior MI in the Western Washington Intracoronary trial.[63]

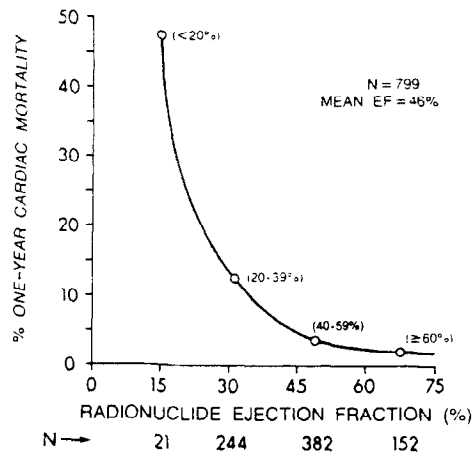

Fig 4. Probability of 1-year mortality is related to radionuclide EF. A curvilinear response exists in the multicenter postinfarction research study.[84]

al. To achieve a low risk for cardiac death, EF values >0.45 must be achieved. Patients with EF values >0.55 are at very low risk of cardiac death. These EF values should be remembered when assessing the clinical impact of reperfusion therapies.

It is apparent that patients with ECG evidence of transmural injury presenting within 12 hours of symptom onset are a heterogeneous group with respect to coronary anatomy and ventricular function. The large majority of these patients present with involvement of the proximal or mid-LAD or RCA. Spontaneous recanalization and subtotal coronary occlusion occur in up to 50% of the cases. A significant number of patients have well-developed coronary collaterals (most frequently in the RCA). Because of the presence of subtotal occlusion, spontaneous reperfusion, and collateral flow, improvement in ventricular function may occur naturally. The variable extent of collateral flow, occurrence of spontaneous reperfusion, and acute hemodynamic changes explain the great variability in ventricular function occurring within 24 hours of admission. Additionally, 30% of the patients may have spontaneous improvement during the hospital stay and up to 50% improve in chronic follow-up. The least variability occurs in serial measures of global systolic function obtained at 24 hours and predischarge. While spontaneous improvement in ventricular function is frequent, patients with persistent total occlusion and no collateral flow have a consistent and dramatic deterioration of global and regional function. Additionally, persistent severe coronary narrowing may prevent return of systolic function in reperfused, salvaged myocardial segments. Because of the great heterogeneity, small trials *must* have treatment groups carefully characterized by early and late angiography. Given the great variability of ventricular function occurring early after acute MI, the most sound analysis of ventricular function appears to be analysis of treatment effect on global or regional ventricular function in the convalescent phase. Because of the great spontaneous variability present in ventricular function, great caution and careful analysis of treatment groups must be used to assure that changes attributed to therapy would not have occurred by chance alone.

MORTALITY DURING MYOCARDIAL INFARCTION

Ultimately, the most important clinical question is not whether therapy can restore flow or improve function, but whether reperfusion therapy alters in-hospital and long-term survival. If survival is improved, then those reperfusion strategies that most effectively restore blood flow and improve ventricular function will be associated with the most effective improvement in survival.

Since patients with transmural MI are so heterogeneous with regard to infarct size and location, incidence of complete coronary occlusion, incidence of spontaneous reperfusion, and other medical conditions, it is not surprising that heterogeneous prognostic groups exist (Fig 5). It is mandatory that careful analysis of inclusion and exclusion criteria for thrombolytic trials be examined to assure that comparable control groups are present. As Yusuf et al[67] demonstrated, mortality rates varying from 6% to 36% occurred in the early IV thrombolytic trials and vary from 6% to 38% in the randomized intracoronary trials. Yusuf et al showed that if low-risk groups of patients are treated, enormous numbers of patients must be enrolled to demonstrate a modest, positive treatment effect.

In both design of future clinical investigation of reperfusion and in clinical patient care, it would therefore seem prudent to identify and treat patient subgroups of medium or high risk. A practical, useful method of identification of

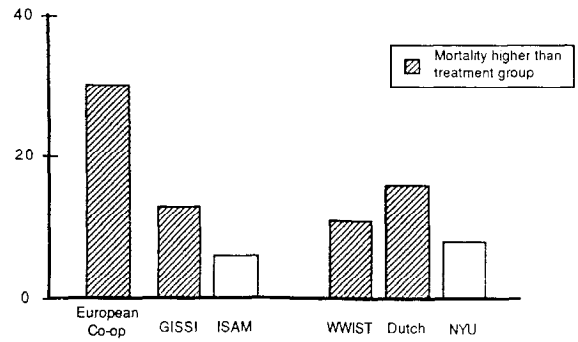

Fig 5. Control group mortality for the major published controlled IV and intracoronary streptokinase trials is presented.[34,35,38,75,126,141] WWIST, Western Washington Study; Dutch, Dutch Interuniversity Study; NYU, Mt. Sinai-New York University Study.

medium or high risk patients in the emergency ward is necessary. Physical examination and admission ECG allow rapid, early segregation of risk groups. Patients with anterior MI location are known to be at higher risk (Table 1). Patients with inferior MI and reciprocal anterior ST changes are also at increased risk.[68-71] Previous natural history studies[72,73] showed that a second MI involving a new myocardial distribution also adversely affects survival. Conversely, patients with isolated, first inferior MI have an excellent in-hospital and 1-year survival.

In addition to ECG MI location, physical examination allows segregation of low- and high-risk groups. Before the advent of thrombolytic or beta-adrenergic blockade therapy, Killip and Kimball demonstrated that risk groups with a hospital mortality of 6%, 17%, 38%, and 81% could be identified on the basis of admission physical examination.[74] In patients who are eligible for reperfusion therapy, the Gruppo Italiano per lo Studio Streptochinasi nell'Infarcto Miocardio (GISSI) trial confirms the prognostic value of stratification according to Killip Classification.[75] In this multicenter trial, mortality in the control group was 7.3%, 19.9%, 39.0%, and 70.1% for Killip Classification I to IV, respectively.

Table 1. Risk Stratification for Acute MI

	Mortality (%)
Low risk	
First, inferior MI	4-7
Killip class I	7.3
Medium risk	
Anterior MI	15-20
Killip class II	19.9
Inferior MI with reciprocal ST change	13
High risk	
Second MI	22
Age more than 75 years	35
Killip class III	39
Extreme risk	
Killip class IV (cardiogenic shock)	70

A third determinant of prognosis that is immediately available to clinicians is the patient's age. With advanced age, mortality dramatically increases with conservative care. Unfortunately, the morbidity and mortality of invasive procedures,[76] coronary bypass,[77] emergency PTCA,[78] and thrombolytic therapy[79] are also significantly higher. A major unanswered question is whether any reperfusion strategy will beneficially alter mortality in the aged.

These three simple, quickly available clinical parameters allow rapid segregation of risk groups. The highest risk occurs for patients in cardiogenic shock or pulmonary edema. Medium risk is present for patients with anterior MI, inferoposterior or inferolateral MI, second MI, and in the elderly. Patients with a first inferior MI who have no signs of heart failure are at low risk. If reperfusion is applied to low-risk groups, other endpoints apart from mortality must be examined, since it is unlikely that a decrease in mortality will occur.

THE THROMBOLYTIC AGENTS

Because reperfusion therapy first used thrombolytic agents, we will review the properties of the thrombolytic agents, with particular attention to new-generation enzymes with heightened efficacy. Streptokinase became available in the late 1950s,[80] but its use in acute MI was limited until the 1980s, when there was adequate angiographic documentation of coronary occlusion and thrombolysis. More recently, new clot-sensitive agents that can achieve similar efficacy as intracoronary streptokinase but allow rapid, simple, IV delivery became available (Fig 6).

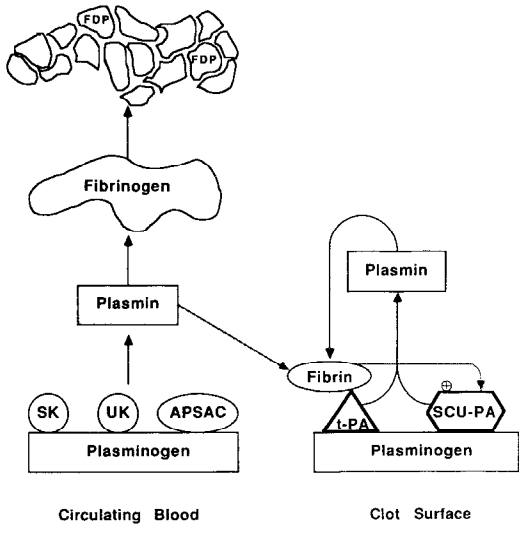

Fig 6. The mechanism for clot-specific thrombolytic agents is schematized. While systemic thrombolytic agents activate circulating plasmin, clot-specific agents only activate plasmin on the clot surface. SK; streptokinase.

Streptokinase

To date, the largest experience with any agent has been with streptokinase. In two recent European randomized trials, over 7,000 patients were treated with 1.5 million units of streptokinase compared with placebo or conventional treatment.[75,81] In these large trials, angiography was not performed. In a pooled analysis of most of the smaller clinical trials of IV streptokinase with angiographic patency data, 50% efficacy was shown.[82] Despite the very high dose of streptokinase used, this disappointing rate of infarct vessel recanalization may be attributed to the lack of clot-specificity of streptokinase. Streptokinase binds indiscriminately to circulating plasminogen or clot-bound plasminogen. As a result, there is systemic activation of the hemostatic system components with consumption of plasminogen, fibrinogenopenia, and high titers of fibrinogen degradation products (Fig 6). In most patients, this results in low levels of fibrinogen, usually <50 mg/dL. However, in the majority of patients, the fibrinogenolysis is well tolerated, and significant bleeding episodes are uncommon. The frequency of serious bleeding episodes, including intracranial hemorrhage, in the large GISSI trial was 0.03%.[75]

The systemic lytic effect of streptokinase may have other potential advantages or disadvantages. Previous studies with intracoronary streptokinase demonstrated that a systemic lytic effect after streptokinase is required for maximum patency to be achieved.[83,84] After infarct vessel patency is established, the prolonged state of fibrinogen breakdown may promote sustained patency. However, this point remains theoretical because reocclusion appears to occur in the 12% to 25% of patients after reperfusion with streptokinase.[85-87] In turn, high levels of fibrinogen degradation products (FDP), affect platelet function by inhibiting aggregation.[88] While this factor may also promote infarct vessel patency, the combination of critically low clotting proteins and platelet dysfunction may increase the hazard of bleeding after surgical procedures. In the setting of acute MI, patients may require coronary artery bypass surgery and the risk of significant bleeding after streptokinase may be appreciable.[89]

Because streptokinase is derived from beta-hemolytic streptococci, the body recognizes this enzyme as a foreign protein. The incidence of allergic reactions is, however, relatively low, and <5% in most reported series[90,91] consisting of fever, drug rash, and anaphylactoid reactions in decreasing order of frequency. Resistance is likely in patients treated with a second dose of streptokinase and may even be seen with primary treatment, particularly in patients with very high levels of antistreptococcal antibody (ASO) titers.

A major untoward side effect of high-dose IV streptokinase therapy is hypotension, which may be a significant problem in patients with baseline hemodynamic compromise. The incidence of hypotension ranges from 2% to 15% in reported series.[90-92] Lew et al required the use of vasopressors, particularly norepinephrine, in nearly 15% of the patients[92] treated with IV streptokinase.

Overall, streptokinase is moderately effective but has no clot selectivity, and has the worse side effect profile among the agents available. Its cost, however, is the least, and is approximately $150 to $200 for 1.5 million units.

Urokinase

The naturally occurring enzyme urokinase has several advantages over streptokinase. However, its use has been limited by the cost of this agent, which is approximately $1,500 to $2,000 for 2 to

3 million units. Clinical trials with IV urokinase have shown that its efficacy may be better than streptokinase (60% to 65%), but the experience is limited and a randomized trial of streptokinase *v* urokinase has not yet been completed. A recent urokinase *v* tissue plasminogen activator trial demonstrated a high (>65%) patency for IV urokinase at a dose of 3 million units.[93]

At equimolar doses of urokinase and streptokinase, slightly less systemic activation of fibrinogen does occur. However, at the large doses of 2 to 3 million units of urokinase currently used, severe fibrinogenopenia occurs with values of fibrinogen <10% to 20% of baseline present after therapy.[94] Compared with streptokinase, little or no hypotension, allergic reactions, primary or secondary resistance have been found after urokinase therapy. Urokinase can be administered as a bolus without an apparent change in efficacy or increased toxicity.[93,94] Recently, in vivo synergism with tissue-type plasminogen activator and urokinase was suggested.[95] This synergistic effect was not seen with urokinase and its parent molecule pro-urokinase.[95]

Tissue Plasminogen Activator

Tissue plasminogen activator (rt-PA) was first administered to a patient in 1981[96]; at that time, the material was derived from a melanoma cell line. With recombinant DNA techniques, the genetic expression and cloning of rt-PA became possible and the first patients were treated in early 1984.[97] Since the initial use of rt-PA for acute MI, there were over 5,000 patients treated with two different preparations. The first form of t-PA that was available was a two-chain preparation with a half-life of approximately four to five minutes.[98] More recently, the predominant single-chain preparation was used and the half-life was reduced approximately 40%. Due to the difference in clearance, the effective doses for the two preparations varied, but their overall efficacy was similar—70% to 75%.[98] Since the single-chain form will be commercially available, suggested doses will refer to this preparation.

The IV dose of rt-PA that has proved effective ranges from 60 mg to 100 mg over the first hour. A total dose of 100 mg IV over three hours is now the FDA-approved dose. The work of Topol et al[99] suggests that a dose adjusted by weight may reduce fibrinogen breakdown and bleeding complications.[99] A dose of 1 mg/kg over the first hour, with 10% of this dose administered as a bolus was used in previous trials.[100] After the first hour, a prolonged low-dose maintenance of rt-PA (10 mg/hr to 20 mg/hr for four to eight hours) appears to reduce the incidence of reocclusion, lessens the residual stenosis as detected by quantitative angiography, and is not associated with further hemostatic breakdown.[101]

Several theoretical advantages are present for rt-PA therapy compared with streptokinase. First, as the physiologic mediator of fibrin dissolution, rt-PA is an efficient enzyme that circulates naturally in very small quantities (2 ng/mL to 15 ng/mL). This enzyme requires the presence of the plasminogen-fibrin complex for avid binding to occur, rendering t-PA clot selective. However, if too much rt-PA is present, circulating plasmin may be formed and, in turn, break down fibrinogen. Thus, rt-PA offers relative clot selectivity, a predominantly dose-dependent phenomenon.[88,89] Despite the use of low doses in patients, however, there may be significant depletion of fibrinogen that resembles the systemic lytic state associated with streptokinase and urokinase. The relative clot selectivity accounts for, in part, the heightened thrombolytic efficacy of rt-PA compared with streptokinase as determined in two randomized trials.[102,103]

Second, owing to the enzyme's short half-life, an infusion of rt-PA may be discontinued in the event of untoward bleeding. This might allow for more simple and rapid management of a bleeding complication, as compared with other thrombolytic agents (eg, streptokinase and urokinase) that have a long half-life. Third, like urokinase, rt-PA is a natural human enzyme, and no resistance or allergic phenomena have been observed.

The bleeding complications that occur after rt-PA differ from those compared with streptokinase or urokinase. Chiefly, bleeding after rt-PA is usually due to fibrinolysis and is more likely to occur acutely. Bleeding at peri-access sites, gingival mucosa, or even gastrointestinal sites may occur soon (within one hour) after onset of therapy. On the other hand, bleeding after the nonselective agents is due to fibrinogenolysis and is slightly more apt to occur several hours or even days after therapy is initiated. It is very difficult to define accurately the risk of bleeding attributable to thrombolytic therapy alone, because

patients often receive concomittant anticoagulation and antiplatelet therapy.

A rapid-acting, low molecular weight inhibitor to rt-PA is present in humans and at increased concentration in patients with coronary artery disease and hypertriglyceridemia.[104,105] The exact physiologic role of the inhibitor is not known, but its activity is markedly reduced by activated protein C.[104]

Recently, synergism of rt-PA with pro-urokinase and t-PA with urokinase was shown in the rabbit jugular vein model[95] and in patients with acute coronary thrombolysis.[106] This property may allow for small (eg 10 mg) quantities of each of two thrombolytic agents to be used with similar efficacy as expected with a single agent at high doses. Synergism may enable high clot selectivity, less material to be required in order to achieve thrombolysis, and perhaps increased efficacy. Now that rt-PA has been sequenced and cloned, there is potential for controlled changes in the molecule such that modified, hybrid rt-PA enzymes with different clot selectivity, half-life, and related properties can be produced.

Pro-Urokinase

Like rt-PA, pro-urokinase, ie, single-chain urokinase plasminogen activator (scu-PA), is a naturally occurring human enzyme that can be produced from renal-cell carcinoma cell culture or via genetic engineering techniques. Pro-urokinase is the precursor to urokinase, but unlike the latter, the single-chain form has fibrin selectivity. Under conditions when no fibrin is present, there is circulating inhibitor to scu-PA. The properties of this inhibitor are not yet fully defined. When fibrin is present, the inhibitor is inactivated, thus rendering scu-PA clot selective. The relative extent of clot selectivity of scu-PA is similar to that of t-PA; at higher doses there is less fibrin specificity.[107-111]

In addition to having allergic potential, (scu-PA) has a short half-life. Dosing appears to be very similar to rt-PA, as described above. Thrombolytic efficacy has been demonstrated to be in the 65% to 75% range, but larger, completed studies are not available, and there is considerably less experience with this agent compared with rt-PA. The scu-PA enzyme has the potential to heighten clot-selective thrombolysis by virtue of its synergistic effect with rt-PA.[95,106]

Acylated Streptokinase

The acylated derivative of streptokinase (APSAC) has several properties that differ from the parent compound. This preparation can be given as a bolus over two to four minutes, and unlike streptokinase, it has a less significant hypotensive effect. APSAC has a long duration of action, and the allergic effects appear to be reduced compared with streptokinase.[112-114] The thrombolytic efficacy of 30 mg of APSAC, the currently used dose, is quite similar to that of intracoronary streptokinase as demonstrated by a large, multicenter trial.[115] As with streptokinase, there does not appear to be any clot selectivity associated with APSAC.[116] This property may account for a decreased thrombolytic efficacy compared with that of rt-PA but as yet, no randomized study exists to compare these two new agents.

Over the past few years, new clot-selective and derivative preparations have become available. Although the efficacy of these IV thrombolytic agents is greater compared with the first-generation agents, there is likely to be further progress in the refinement of thrombolytic therapy. Synergism with clot-selective enzymes and new modifications of the rt-PA molecule provide exciting potential.

CLINICAL TRIALS OF THROMBOLYTIC THERAPY

Intracoronary Streptokinase Administration

After Rentrops' pioneering investigations,[34] numerous small, nonrandomized clinical trials of intracoronary streptokinase were conducted.[117-123] These studies were flawed in design but demonstrated that intracoronary streptokinase could be safely administered within the first six hours of acute MI. In 1985, Simoons et al[35] reported the last prospective randomized trial of intracoronary streptokinase infusion. In total, seven major prospective randomized clinical trials of intracoronary streptokinase administration were published.[34-40]

In the first angiographically controlled study, Khaja et al determined[39] that intracoronary streptokinase infusion was significantly more effective than placebo in achieving coronary recanalization. Reported recanalization rates have varied for intracoronary infusion, and range from 60% to 90%.[82] In review of the randomized

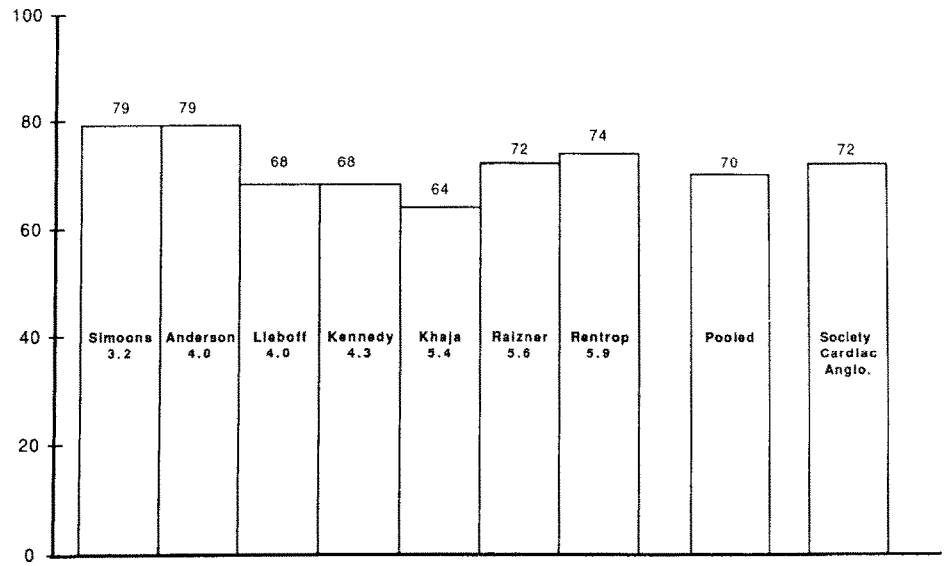

Fig 7. Efficacy of intracoronary streptokinase administration. Angiographically documented reperfusion rates for the randomized intracoronary streptokinase trial are presented. Pooled reperfusion rate is similar to that for the Society of Cardiac Angiography study.[117]

trials, it is apparent that efficacy is related to time of onset of infusion (Fig 7). In the two clinical trials in which therapy was initiated within four hours of symptom onset, reperfusion rates of 70% were achieved. Those studies with therapy initiated between four and 4.5 hours had the lowest recanalization rates. At this time, the fibrin clot presumably is more refractory to thrombolytic therapy. Later, some element of endogenous thrombolysis occurs and reperfusion rates again slightly improve. Overall, a reperfusion rate of 70% was achieved in pooling the results of the seven clinical trials. This reperfusion rate is comparable to that reported in the large registry of the Society of Cardiac Angiography.[117]

While intracoronary streptokinase conclusively reestablished antegrade blood flow, conflicting results were found concerning changes in ventricular function after therapy. A time dependency for efficacy in improvement of global or regional left ventricular (LV) function occurs (Fig 8). As these randomized clinical trials demonstrate, patients treated conventionally have no change in serial global EF measured acutely and prior to hospital discharge. Two of seven studies found a significant increase in EF in streptokinase-treated patients. These studies had the highest reperfusion rates and shortest time to initiation of therapy. Patients treated after four hours of symptom onset had no change in global EF with therapy. The lack of improved global LV function does not preclude the possibility that survival may be improved with successful therapy. Based on review of these randomized clinical trials, it is apparent that intracoronary streptokinase will result in improved global LV function when treatment is initiated early after symptom onset. However, therapy initiated four or more hours after symptom onset is unlikely to result in improved global LV function.

Effect of Intracoronary Therapy on Mortality

Finally, the most fundamental question must be addressed. Does intracoronary streptokinase result in improved survival? As Yusuf et al have demonstrated,[67] each randomized intracoronary streptokinase trial lacks sufficient power to demonstrate conclusively a survival advantage. When the intracoronary trials are pooled (Fig 9), a trend toward mortality reduction is apparent. Only two clinical trials, the Western Washington trial[38] and Netherlands Interuniversity trial[35] randomized over 100 patients in each treatment group (Table 2). In the Netherlands trial, 1-year survival was 91% in the thrombolysis group (n = 269) compared to 84% for the control (n = 264) $P = .01$. In the Western Washington trial,

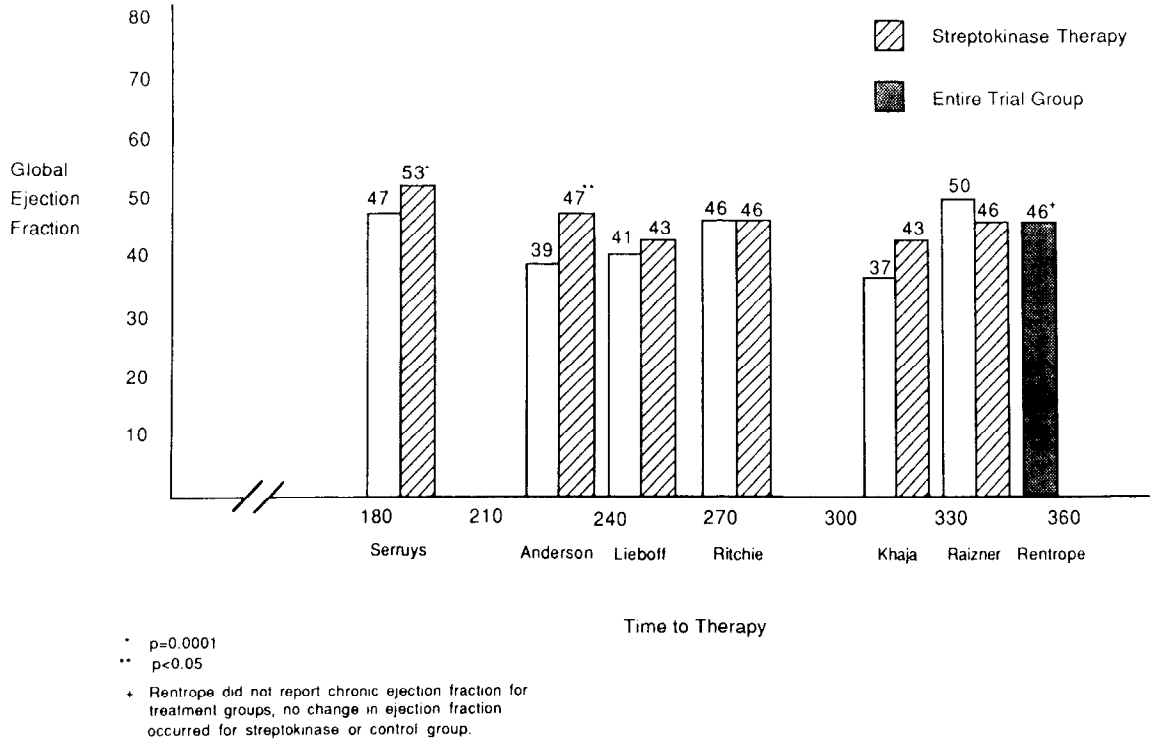

Fig 8. Impact of intracoronary streptokinase on chronic global EF (randomized trials). Impact of streptokinase therapy is related to time to onset of infusion.[34,36,37,39,40,124,179] Rentrop[34] did not report chronic EF for treatment groups. No changes in EF occurred for streptokinase-treated patients or placebo-treated patients.

1-month mortality was reduced from 11.2% for 116 control patients to 3.7% for 134 streptokinase-treated patients. The beneficial impact of streptokinase therapy was lost at 1-year follow-up. One-year survival was 92% compared to 85% for streptokinase and control groups, respectively. Again, because of the relatively small sample size, a real mortality reduction at 1 year may have been missed. Apart from differences in sample size, a further major difference in therapy of patients after thrombolysis in these two trials merits observation. In the Western Washington trial, 28% of the patients treated with thrombolytic therapy underwent revascularization with PTCA or bypass in the year after therapy. In the Netherlands trial, 46 patients in the thrombolysis group underwent immediate PTCA after successful thrombolysis and 62 underwent elective PTCA or bypass after discharge. In total, 108 out of 269 (40%) of the patients in this trial underwent revascularization after thrombolytic therapy. The differences in revascularization may explain the differences in 1-year mortality present in these two trials, since in the Western Washington trial, late mortality was highest in patients with anterior MI who had partial reperfusion.

A second major difference in these trials was the time to initiation of therapy. The Western Washington trial was strictly an intracoronary infusion study with therapy started a mean of 4.3 hours after symptom onset. In the Netherlands trial, intracoronary therapy was initiated 3.2 hours after symptom onset in the first 152 patients. In the last 117 patients, IV streptokinase was administered prior to catheterization. Overall, in the later trial the median time from symptom onset to hospital admission was 1.5 hours. In spite of these differences in trial design, overall 30-day mortality was similar at 6.3% for the Netherlands trial and 7.2% for the Western Washington trial. Mortality in the control group was also similar at 12% and 11.2%, respectively. Thirty-day mortality was 3.7% in the Western Washington thrombolysis group and 5.9% in the Netherlands thrombolysis group. Despite the earlier time of presentation and significant improvement in global EF for the Netherlands

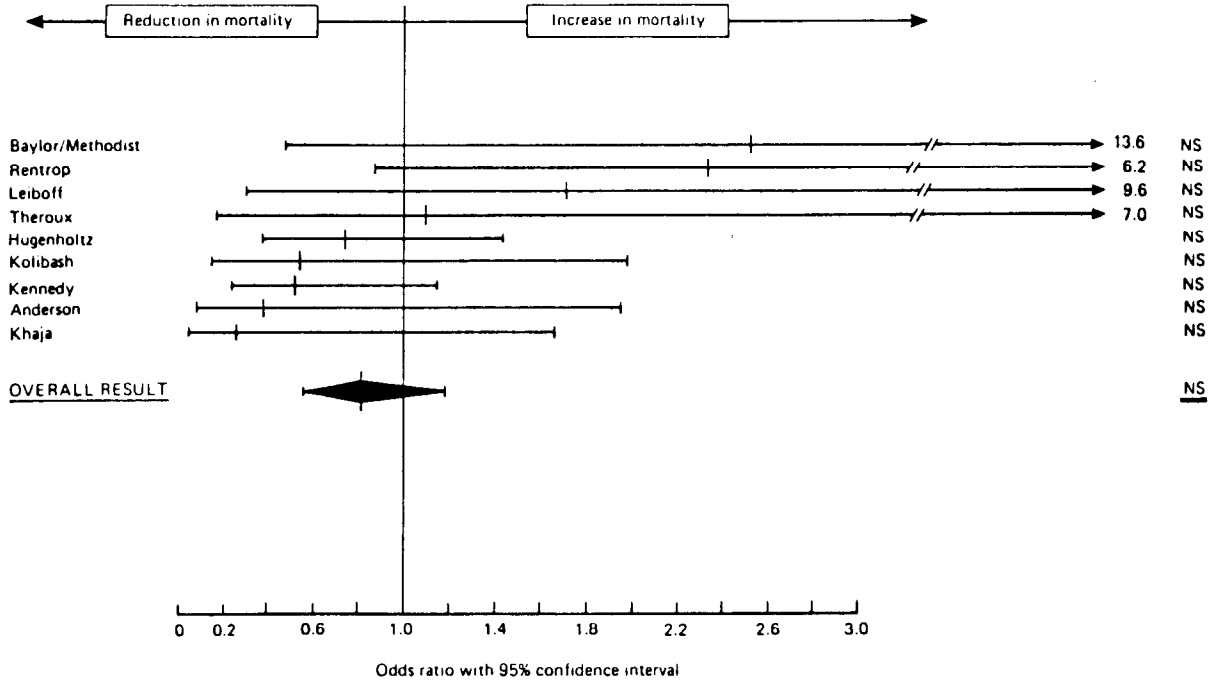

Fig 9. Odds ratio for mortality reduction is presented for the intracoronary streptokinase trials.[67] Values to the left of 1.0 represent a decreased mortality compared to control. The pooled results suggest a mortality reduction, because of the relatively small sample size, the 95% confidence interval crosses 1.0. The Netherlands study was not included in this analysis.

trial, the 30-day mortality was similar for both studies. These findings suggest that myocardial reperfusion has a beneficial prognostic impact on 30-day survival independent of improvement in global ventricular function or limitation of tomographic thallium infarct size.[124] Late survival may be contingent on completeness of revascularization after intracoronary streptokinase therapy.

In summary, intracoronary streptokinase results in reperfusion rates of approximately 70%, with efficacy somewhat contingent upon the time of initiation of therapy. Global ventricular function can be improved with very early therapy. A significant reduction in mortality occurs with therapy. This mortality reduction may be independent of the extent of myocardial salvage or improved global LV function. To enhance late survival, further revascularization may be required, especially in patients with anterior MI and partial reperfusion.

IV Streptokinase Therapy

From Fletcher's first use of IV streptokinase therapy in 1959[125] to the European Cooperative Study Group trial in 1979[126] prolonged IV infusion of streptokinase was the standard method of administration. A great deal of the early controversy concerning the efficacy of IV streptokinase related to a lack of consensus concerning the role of thrombotic coronary occlusion and the efficacy of streptokinase in inducing coronary

Table 2. Comparison of Western Washington and Netherlands Interuniversity Trials

Trial	M	T	C	Symptom Duration*	Reperfusion Rate (%)	Early PTCA (%)	Late PTCA (%)	30-Day Mortality (%)		1-Year Mortality (%)	
								T	C	T	C
Netherlands	533	269	264	3.2	79	17	23	5.9	12	9	16
Western Washington	250	134	116	4.0	68	—	28	3.7	11.2	8	15

Abbreviations: M, mortality; T, thrombolysis group; C, control group.

*Time to angiography.[35,38]

thrombolysis. The widespread use of early cardiac catheterization during acute MI allowed for documentation of the efficacy of IV streptokinase. Schroeder's pioneering work demonstrated that 52% of the patients treated with a 30-minute infusion of 500,000 units of streptokinase had angiographically documented immediate coronary thrombolysis.[127] A plethora of studies of reperfusion rates varying from 31%[128] to 96%[129] have been reported. Rogers et al[130] demonstrated that a dose-response relation exists since only one of ten patients treated with 500,000 units had documented reperfusion, while seven of 16 patients treated with 1-million units did so ($P < .005$). Currently, most IV regimens consist of a 1-million to 1.5 million-unit infusion over 45 minutes to one hour; higher doses are under investigation.

In addition to a dose-response relationship, a clear temporal relationship for efficacy of reperfusion is present (Fig 10). A major methodologic difference that obscured comparisons of reperfusion rates in many trials was the lack of systematic baseline angiography before the initiation of therapy. Proponents of baseline angiography favored documentation of coronary occlusion before the initiation of therapy.[138] Others felt that baseline angiography delayed the initiation of therapy and decreased its efficacy.[133] Comparisons of trials with and without baseline angiography suggests that reperfusion rates were lower in patients in which posttreatment angiograms were performed. After four hours of symptom onset, less than 50% of the vessels were recanalized. Up to 77% of vessels may be recanalized with therapy administered within three hours of symptom onset. Since very early initiation of therapy appears crucial, both for decreasing mortality[75] and preservation of ventricular function,[139] future trial designs should incorporate early IV therapy followed by immediate posttreatment angiography to document reperfusion. With this trial design, a reperfusion rate approaching 60% for IV streptokinase therapy is expected, and other thrombolytic agents must be compared with this standard. It must be recog-

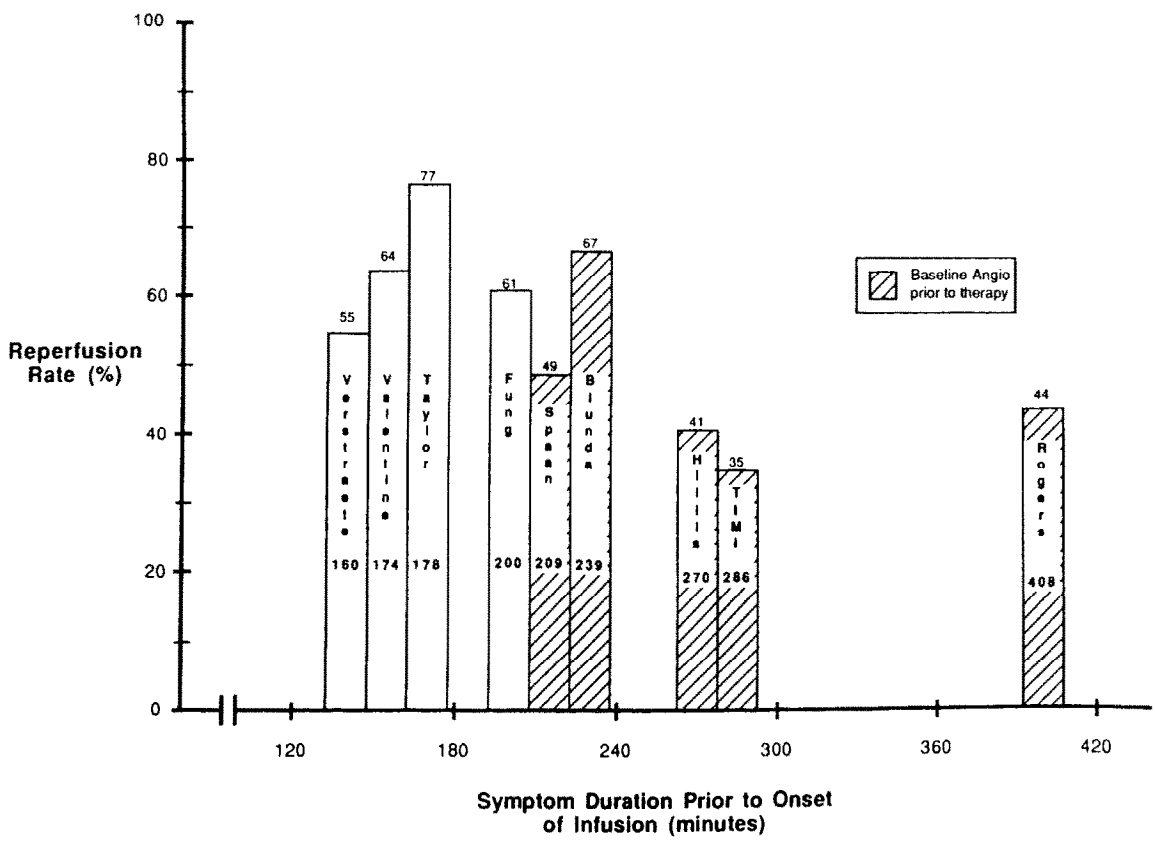

Fig 10. Effect of symptom duration on efficacy of IV streptokinase. The angiographically documented reperfusion rates for the published IV trials using immediate angiography are presented.[102,130-137]

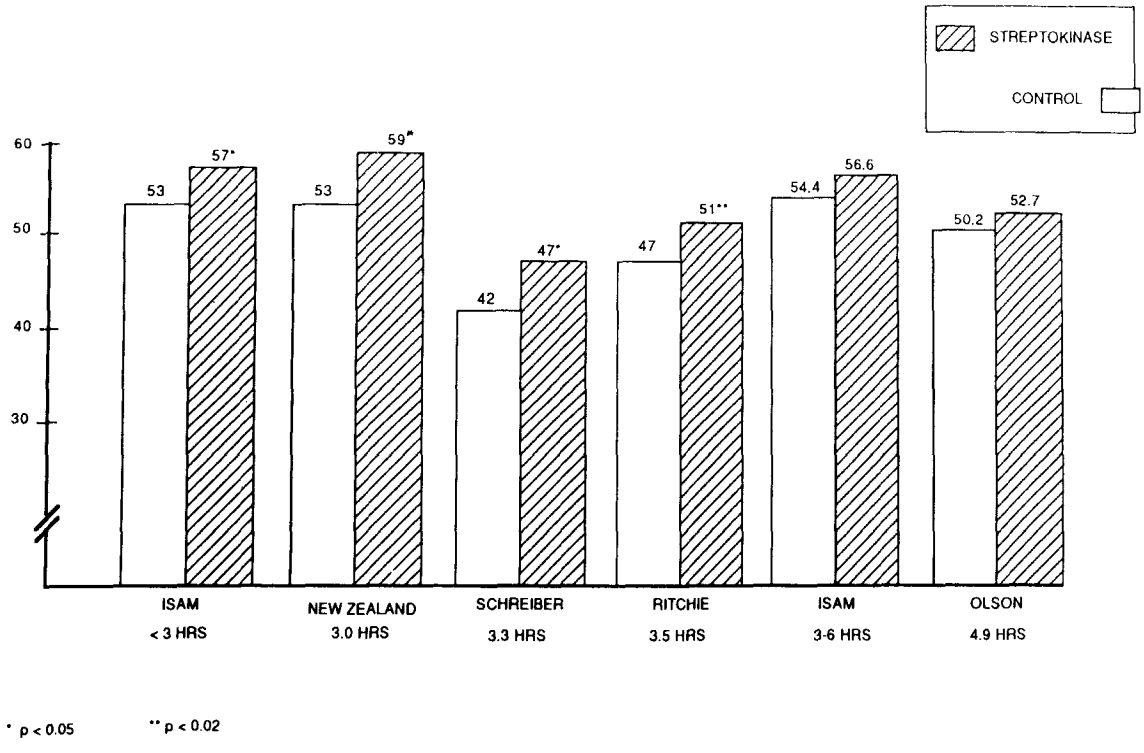

Fig 11. Impact of IV streptokinase on chronic global EF (randomized trials). Effect of IV streptokinase on chronic EF is compared to the time of onset of therapy.[44,124,141-143]

nized, however, that up to 20% of the patients treated will have subtotal coronary occlusion prior to therapy. The clinical impact of thrombolytic therapy in this subset of patients was not addressed.

The published studies comparing IV to intracoronary streptokinase administration have been reviewed by Lo.[140] The pooled reperfusion rates were 73% for IV and 72% for intracoronary therapy. Methodologic problems exist with all these studies except for that of Rogers et al.[130] This study randomized 51 patients who had documented coronary occlusion to IV or intracoronary therapy. Intracoronary therapy was significantly more effective than IV therapy. Patients were treated later than 5.5 hours after symptom onset in this trial. Review of angiographically documented reperfusion studies (Figs 6 and 9) suggests that within three hours of symptom onset, reperfusion rates are comparable (with intracoronary therapy slightly superior). After three hours, intracoronary therapy is clearly more effective in achieving arterial recanalization.

Five prospective placebo-controlled randomized trials analyzed the impact of IV streptokinase therapy on chronic global ventricular function (Fig 11). The largest of these trials, Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) enrolled 1,741 patients presenting within six hours of acute MI.[141] Fifty-five percent of the patients treated with streptokinase had therapy initiated within three hours of symptom onset. Patients treated within three hours had a significantly higher EF compared with the heparinized control groups. No difference between treated and control group was present for patients treated three to six hours after symptom onset. In a smaller placebo-controlled trial, Schreiber et al studied 38 patients who were randomized within 3.3 hours of symptom onset.[44] Serial radionuclide ventriculography demonstrated improvement only in the streptokinase-treated patients. Olson et al[142] treated 52 patients with streptokinase or placebo at 4.9 hours after symptom onset. No change in global EF measured seven to ten days later occurred in either group. Recently, two other large, randomized, placebo-controlled trials of IV streptokinase have been reported. The New Zealand study[143] found improved global EF (53 ± 13.5 *v* $59 \pm 10.5\%$ $P < .005$) for patients with their first

infarct who were treated with streptokinase. The Western Washington Intravenous trial[144] reported that the radionuclide EF is significantly higher (50.8 *v* 46.6, $P < 0.02$) for patients treated with streptokinase compared to placebo. Patients were treated 3.5 ± 1.4 hours from symptom onset in this 367-patient multicenter study.

Analysis of these randomized studies confirms that a time dependency for improvement in ventricular function exists (Fig 11). Patients treated within four hours of symptom onset are likely to improve global LV function compared with placebo. Of interest, enzymatic estimates of reperfusion (early peak CK-MB) were 74%, 79%, and 44% for the Schroeder, Schreiber, and Olson studies, respectively. The Schreiber and Olson studies were too small to analyze the effect of therapy in the subgroups with anterior or inferior MI. The ISAM trial and the New Zealand study have subdivided patients based on MI location and found improvement in global ventricular function for both anterior and inferior MI groups. The Western Washington trial also analyzed patient subgroups and found that patients with anterior MI and those treated within three hours of symptom onset are most likely to improve global ventricular function.

In summary, extensive data demonstrate that a time dependency is present both for coronary recanalization and improved global ventricular function with IV streptokinase therapy. Patients treated within three hours of symptom onset are most likely to have coronary recanalization and improved ventricular function. Further studies are required to more extensively analyze changes in regional wall motion, ventricular response to exercise, and to identify subgroups most likely to benefit from therapy.

Effect of IV Therapy on Mortality

IV streptokinase trials attempting to demonstrate improved survival have been conducted since the mid 1960s. To date, over 20,000

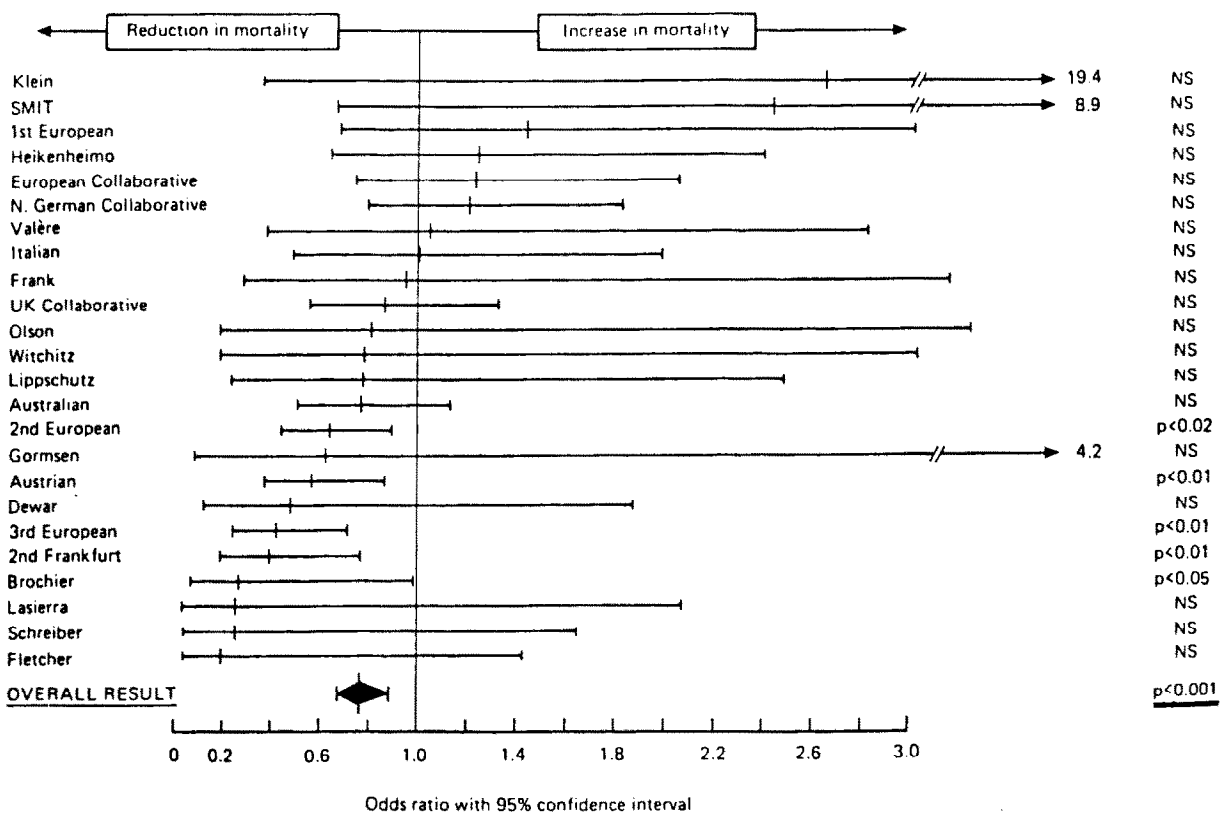

Fig 12. The odds ratio of the pooled controlled trials of streptokinase is present.[67] The 95% confidence interval remains to the left of 1, suggesting an unequivocal mortality reduction. The GISSI Study, ISAM Study, and ISIS II trial were not completed at the time of this analysis.

patients have been enrolled in published placebo controlled trials. Because of this voluminous experience, definitive conclusions regarding efficacy of therapy can now be made. Yusuf et al[67] has pooled all prolonged infusion trials and demonstrated that a 22% risk reduction occurs with streptokinase therapy (Fig 12). Because of the large number of patients treated, this mortality reduction achieved great statistical power. Of interest, in Yusuf's analysis a time dependency for mortality reduction did not seem to exist. In the largest, most recent prolonged infusion trial (The European Cooperative Study), mortality was reduced from 30.6% to 15.6% ($P < .01$) at six months.[126] This mortality reduction occurred although streptokinase infusion began a mean of eight hours after symptom onset. While the exact mechanism for mortality reduction in these early trials in unknown, it is unlikely that a beneficial reduction of MI size occurred. Mortality reduction may be related to delayed reperfusion in these trials. Since brief, high-dose infusion protocols are most frequently used now, the findings from earlier studies may not be applicable.

Fortunately, two large, randomized, brief, high-dose IV trials have been reported. The multicenter GISSI trial[75] randomized 11,806 patients and found a significant reduction in mortality for patients treated within six hours of symptom onset. The German multicenter ISAM trial[141] randomized 1,746 patients and found no reduction in mortality. The similarities and differences in these studies must be examined to draw conclusions concerning brief, high-dose IV therapy (Table 3).

When comparing these two studies, three major differences apart from sample size are apparent. First, the GISSI trial enrolled patients up to 12 hours from symptom onset while the ISAM trial only enrolled patients up to six hours from symptom onset. Second, the control group mortality was almost doubled in the GISSI trial (13% *v* 7.1%). Since control group mortality was identical for anterior and inferior MIs in these studies, the preponderance of inferior MIs enrolled in the ISAM trial may have diluted the potential benefit of thrombolytic therapy. Finally, the control patients in the ISAM trial were heparinized while the GISSI control patients were not. Since heparin therapy alone can induce reperfusion chronically in up to 50% of the infarct arteries, this drug may alter mortality itself. An unexplicable finding is the apparently higher mortality for streptokinase treated patients with anterior MI in the ISAM trial (20% *v* 17% for control). Since 80% of all GISSI coronary care units (CCUs) participated in the GISSI trial, it is likely that this study was more representative of all patients presenting during the early phase of acute MI. Because of the low control-group mortality in the ISAM trial, no survival advantage could be demonstrated.

The large number of patients treated in the GISSI trial allows for analysis of subgroups of patients, Table 4. The most striking mortality reduction occurred in patients treated within one

Table 4. GISSI Study Subgroup Analysis

Decreased Mortality	No Decreased Mortality
Anterior MI, multiple location MI	Inferior MI
First MI	Second MI
Age <65	Age >65
Symptoms <6 hours	Symptoms >6 hours
Men and women	
Killip class I and class II	Killip class III and class IV

Table 3. Randomized High-Dose IV Streptokinase Trials

Study	No. of Patients	Symptom Duration (h)	Mortality (%)		Anterior (%)		Inferior (%)	
			T	C	T	C	T	C
GISSI[75]	11,806	12	10.7	13.0*	14.5†	18.4	6.8	7.2
ISAM[141]	1,741	6	6.3	7.1	20.1	17.4	4.0	4.6
New Zealand[143]	219	4	3.7	12.5	—	—	—	—
ISIS II[81]	4,000	4	8	12‡	—	—	—	—
Western Washington[144]	367	6	6.3	9.6	10.4	22.4§	4.0	1.8

Abbreviations: T, treated patients; C, controls.

*$P < .0005$.

†$P < .001$.

‡Reported as "proof beyond reasonable doubt."

§P .05.

hour of symptom onset. In this subgroup, a 47% mortality reduction occurred (15.4% to 8.2%, $P = .0001$). Mortality reduction occurred for both males and females. Only patients under age 65 benefited from therapy. Patients with inferior or lateral MI had no mortality reduction, while those with anterior or multiple location MI did. Patients with first MI had mortality reduced while those with previous MI did not. Finally, patients with Killip Class I or II had reduced mortality while those with Class III or IV did not. In the GISSI trial, patients most likely to benefit from IV therapy were those age 65 or less, with anterior MI, without signs of heart failure who present within six hours of symptom onset of their first infarction.

A third final, major IV trial is currently being conducted. The ISIS-II trial is designed to enroll 20,000 patients in groups treated zero to four hours, four to 12 hours, and 12 to 24 hours after symptom onset. The policy board has reported that a significant mortality reduction already is present in patients treated zero to four hours.[81] A 33% mortality reduction from 12% to 8% was achieved in this subgroup. Surprisingly, despite this mortality reduction, the investigators plan to continue to enroll patients until the 20,000-patient sample size is achieved.

In summary, brief, high-dose IV streptokinase therapy is clearly beneficial when therapy is initiated early. An *unequivocal* mortality reduction is achieved with therapy initiated within six hours of symptom onset. Coronary reperfusion is most likely with therapy initiated within three hours of symptom onset. Improved ventricular function is also more likely to occur with therapy initiated within three hours of symptom onset. These studies demonstrate the urgent time dependency for clinical efficacy. Future trials must employ strategies in which therapy is instituted as soon as possible including home or ambulance institution of infusion. The prolonged infusion trials suggest that mortality may be reduced independent of myocardial salvage. Future studies must determine whether delayed reperfusion independently imparts a survival advantage.

CLINICAL TRIALS OF RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR

Van de Werf et al[144] first reported that purified recombinant tissue plasminogen activator (rt-PA) obtained from the Bowes melanoma line recanalized six of seven patients with total coronary occlusion. Two randomized, placebo-controlled, angiographic studies studied the efficacy of double-chain rt-PA in achieving arterial recanalization. Colleen et al[95] first demonstrated that rt-PA recanalized 75% of the patients with occluded coronary arteries in a 50-patient, multicenter study. Patients were treated with a one-hour IV infusion of 0.5 mg/kg rt-PA. Pretreatment angiography was required in this trial. For this reason, therapy was instituted at 4 ± 1 hours after symptom onset.

Verstraete et al[145] also studied the efficacy of rt-PA in achieving coronary recanalization compared to placebo control. Patients were randomly treated with IV heparin and a 0.75 mg/kg infusion of rt-PA or heparin plus placebo control. In this study, baseline, pretreatment angiography was not performed. Most patients were treated within four hours of symptom onset. Coronary recanalization was achieved in 61% of rt-PA treated patients compared to 21% of placebo control ($P < .001$). A fall in fibrinogen level to $52\% \pm 29\%$ of pretreatment value occurred in patients treated with rt-PA. No major bleeding complications occurred in this study. Only one patient required a blood transfusion. These studies thus conclusively demonstrated the efficacy of IV rt-PA as a thrombolytic agent.

As discussed earlier, the major advantage of rt-PA over previously available nonselective agents is the increased efficacy in achieving coronary recanalization. Two large published studies have addressed this issue. The National Heart Lung and Blood Institute (NHLBI) sponsored Thrombolysis in Myocardial Infarction (TIMI) trial prospectively compared IV rt-PA with IV streptokinase.[138,146] In this study, 47 patients were initially treated with a 90-minute infusion of double-chain rt-PA after baseline angiography. Coronary recanalization occurred in 25 of 37 (68%) of the patients with initial complete coronary occlusion. One third of the patients with reperfusion achieved by rt-PA reoccluded before hospital discharge. The TIMI study group subsequently performed a randomized clinical trial in patients presenting within seven hours of symptom onset.[102] Patients were treated with 1.5 million units of IV streptokinase or a three-hour rt-PA infusion. Therapy was initiated a mean of 4.6 hours after symptom

onset. Reperfusion was achieved in 60% of the rt-PA-treated patients compared to 40% of the streptokinase-treated patients ($P < .001$). Although initial reperfusion rates were higher for rt-PA, at hospital discharge an equal percentage of patients had patent infarct arteries.[147] Coronary arteriography was repeated in 109 of 143 rt-PA patients and 98 of 147 streptokinase patients. TIMI Grade II or III flow was present in 79 of 109 rt-PA patients (72%) compared with 72 of 98 streptokinase-treated patients (73%) P = NS.

The European Cooperative Study Group[103] also studied the comparative efficacy of rt-PA and streptokinase. Patients were treated with 0.75 mg/kg rt-PA over 90 minutes or 1.5 million units of streptokinase over one hour. At initial angiography (posttreatment), 70% of the rt-PA-treated patients had patent vessels compared to 55% of the patients treated with streptokinase ($P = .054$). Fibrinogen levels were markedly lower for patients treated with streptokinase, and fibrin degradation products were significantly higher.

With advances in recombinant DNA technology, a new predominantly single-chain rt-PA preparation has been developed. This agent will be available for widespread clinical application. In a placebo-controlled trial, Topol et al have studied the thrombolytic efficacy of single-chain t-PA.[98] One hundred patients were treated with a three-hour infusion of rt-PA or placebo in a blinded random fashion. Angiography performed at 60 minutes demonstrated that 57% of the rt-PA-treated patients had patent arteries compared to 13% of the placebo-control patients ($P < .001$). At this point, therapy was unblinded. Drug infusion continued and angiography performed at 90 and 120 minutes demonstrated further increased coronary reperfusion with 69%, then 79% of the infarct arteries achieving angiographic patency with t-PA therapy.

These reperfusion rates are higher than those achieved by IV streptokinase in the studies in which the two agents were compared.[102,103] Importantly, the time dependency present for efficacy of IV streptokinase therapy does not appear to exist for rt-PA (Fig 13). Although early coronary reperfusion is higher, final arterial patency may not be different. Ganz et al[129] have reported that 63 of 66 patients (95%) of the patients treated with high-dose IV streptokinase had patent infarct arteries when delayed catheterization was performed before hospital dis-

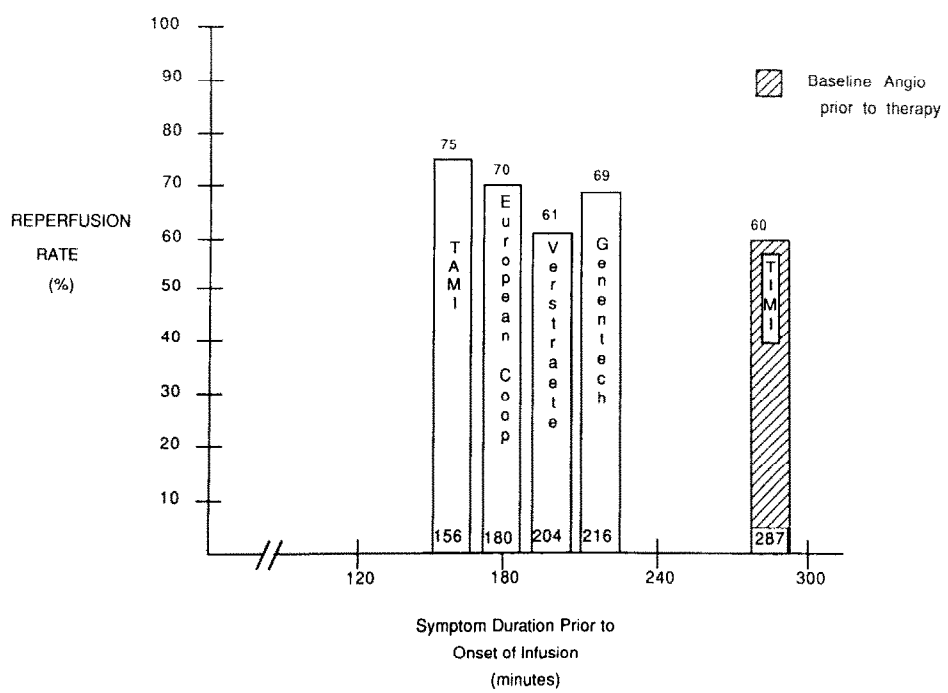

Fig 13. Efficacy of IV tPA therapy. Reperfusion rates for the angiographically documented rt-PA trials are compared to the time at which treatment was initiated.[98,100,103,138,145]

charge. Since all other studies using early angiography found much lower reperfusion rates with streptokinase, one could postulate that significantly delayed reperfusion occurred in the Ganz et al study. Current treatment regimens employing rt-PA include a prolonged infusion of this agent. Delayed reperfusion may also occur with rt-PA therapy. In the run-in phase of the TIMI II Study,[148] 196 patients underwent catheterization 32 hours after the start of rt-PA infusion. TIMI grade II or III perfusion was present in 87% of the patients. Whether delayed reperfusion is of clinical benefit has not been determined. Since myocardial salvage has been shown to be critically time dependent, reperfusion strategies yielding the highest, earliest levels of reperfusion have greatest efficacy in salvaging myocardium.

The impact of IV rt-PA therapy on ventricular function has not yet been subjected to extensive analysis. Topol et al first examined the impact of rt-PA therapy on regional wall motion in a blinded, semiqualitative study of serial echocardiography.[149] Echocardiography was performed before rt-PA therapy, at 24 hours and 10 days after therapy. A marked improvement in regional wall motion occurred for patients treated with sequential rt-PA and PTCA, but no change occurred for myocardial segments reperfused by rt-PA alone or those segments not reperfused.

The effect of IV rt-PA therapy alone on ventricular function was addressed by the NHLBI-sponsored TIMI Study reported by Sheehan et al[150] and the multicenter Thrombolysis Angioplasty Myocardial Infarction TAMI Study reported in preliminary fashion by O'Neill et al.[151] During the TIMI Study 290 patients were randomized to IV rt-PA or IV streptokinase therapy. Serial contrast ventriculograms were analyzed in 145 patients (77 rt-PA and 68 streptokinase treated). No serial improvement in global EF occurred for either subgroup. Final EF was 49.9% ± 9.4% and 49.1% ± 11.7%, $P = .85$ for rt-PA and streptokinase patients, respectively. Regional wall motion significantly improved for both subgroups. Regional wall motion was identical predischarge (−2.6% ± 1.0% *v* 2.6% ± 1.0%, $P = .99$). Thus, despite the higher early recanalization rates achieved by rt-PA, equivalent improvement in ventricular function occurred for both agents.

Subgroup analysis revealed that significant improvement in global EF occurred for patients with subtotal coronary occlusion at the time of initial angiography and those with persistently patent vessels at the time of repeat catheterization. These authors further describe an interesting subgroup of patients who achieved delayed reperfusion. In 29 patients, angiography at the termination of thrombolytic therapy demonstrated an occluded vessel, whereas angiography at repeat catheterization found recanalization had occurred. No change in EF or regional wall motion occurred.

In the TAMI Study, 386 patients were treated with IV rt-PA.[100] Serial contrast ventriculography was performed in 266 of 359 surviving patients. Detailed linear regression analysis was performed to determine factors associated with improved global or regional wall motion.[151] As reported by Topol et al,[100] a significant improvement in regional wall motion occurred for successfully reperfused patients who were candidates for immediate PTCA. No change in serial EF occurred. Ventricular function was significantly better at the time of hospital discharge if thrombolytic therapy was initially successful. Interestingly, in this study only those patients undergoing emergency coronary bypass surgery had improvement in global EF.

Despite the earlier time to initiation of therapy in the TAMI Study (2.9 hours) *v* 4.9 hours in the TIMI Study and the frequent use of immediate PTCA in the TAMI Study, no differences in serial EF occurred. Significant improvement in regional wall motion occurred from both studies. Since neither study had a placebo control, the true impact of rt-PA on ventricular function is difficult to assess.

The final major clinical question of whether rt-PA therapy reduces mortality remains unanswered. The NHLBI sponsored TIMI Study was initially designed to determine whether IV thrombolytic therapy improves survival. With publication of the GISSI Study the TIMI investigators felt it was not ethical to withhold thrombolytic therapy. The TAMI investigators concurred with this decision. For this reason, no large placebo-controlled trials with mortality reduction as a primary endpoint have been conducted with rt-PA. Since streptokinase and rt-PA are entirely different agents with differing hemodynamic effects, differing antiplatelet effects, and

differing biologic half-lives, extrapolating the mortality results from streptokinase therapy to rt-PA therapy may not be appropriate. In the future, the comparative efficacy of rt-PA and streptokinase on mortality reduction will be tested in the ISIS-III trial.

In summary, rt-PA is an extremely promising thrombolytic agent. Its major advantage over nonselective agents is its enhanced thrombolytic efficacy. The efficacy of rt-PA compares favorably to intracoronary streptokinase and is more effective than IV streptokinase. The time dependency for efficacy is less striking for rt-PA than for streptokinase. Initial studies demonstrated that a major risk of reocclusion (up to 30%) existed after rt-PA-induced reperfusion. The prolonged infusion protocols currently used have decreased reocclusion rates to less than 15%. Although immediate reperfusion rates are higher with rt-PA than with streptokinase, final arterial patency may not be different. Therapy initiated within three hours of symptom onset will result in improved regional wall motion. No studies have shown improved global ventricular function with rt-PA alone. The impact of this therapy on mortality has not been addressed.

CORONARY ANGIOPLASTY THERAPY OF MYOCARDIAL INFARCTION

Mechanical coronary artery recanalization has been attempted since the earliest experience with cardiac catheterization during MI. Oliva first demonstrated that coronary recanalization could be achieved with contrast injections and intracoronary nitroglycerin.[19] Rentrop's first experience with guidewire coronary recanalization was so impressive that he was stimulated to pursue this therapy during acute MI.[28] Early studies[122] suggested that higher rates of coronary recanalization could be achieved by subselective streptokinase administration. It is possible that some element of mechanical recanalization explained these early positive results. With the advent of balloon angioplasty technology,[152] only a short period elapsed before PTCA was attempted during acute MI. Since initial catheters and balloon tips were inflexible and rigid, the initial use of angioplasty occurred in patients with subtotal coronary occlusion after streptokinase therapy.[153,154] Hartzler et al[155] and Meyer et al[156] demonstrated that angioplasty could be safely and effectively performed after streptokinase in the first two large, published clinical series.

The use of angioplasty in acute MI initially occurred to correct two major deficiencies in intracoronary streptokinase therapy. These deficiencies were the prevalence of severe residual stenosis after therapy and the lack of improved ventricular function with reperfusion. Subsequently, a number of investigators have studied the efficacy of angioplasty alone in achieving arterial recanalization[157-161] (Fig 14). Because of the inherent time delay involved in patient transport and angiography, most patients were previously treated after three hours of symptom onset. Despite the delayed time to initiation of therapy, angioplasty consistently resulted in arterial patency rates above 80%. Thus, this therapy is superior to IV thrombolytic therapy in achieving arterial recanalization. Efficacy of therapy does not appear to be time dependent.

The impact of angioplasty on improvement in ventricular function has not been adequately

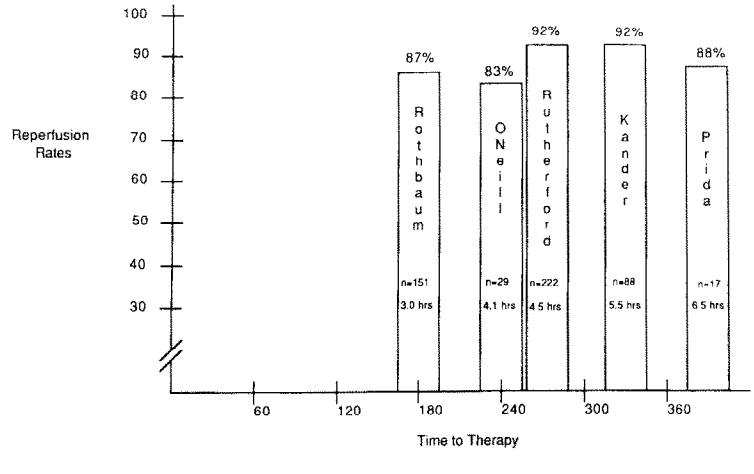

Fig 14. Arterial patency after primary angioplasty therapy. Reperfusion rates for primary PTCA therapy are compared to the time at which PTCA was performed after symptom onset.[157-161]

addressed. O'Neill et al[158] found that angioplasty resulted in a 7% increase in global EF while patients treated with intracoronary streptokinase alone had no serial change in global EF. Similarly, Rothbaum et al[157] prospectively treated 151 patients with PTCA as the sole reperfusion agent. Patients were treated a mean of three ± one hours from symptom onset. A striking increase in EF occurred in this uncontrolled study. Patients with anterior MI had an EF increase of 13% ± 12% ($P < .001$) and those with inferior MI increased 10% ± 12% ($P < .001$). Similarly, Hartzler reported a 16% increase in global EF for 27 patients treated 3.3 hours from symptom onset.[155] Again, this study was uncontrolled. Although all these studies lack true control groups, the striking changes in global EF that occurred in the O'Neill, Hartzler, and Rothbaum studies are impressive when compared to the results reported for thrombolytic therapy.

Because of the enormous manpower and laboratory requirements, it is unlikely that a randomized study of sufficient sample size will ever test the value of PTCA therapy alone in improving survival. Future clinical trials will most likely address the issue of the role of PTCA in improving survival after thrombolytic therapy. Although it is unlikely that PTCA will be found to improve survival for all MI patients, certain high-risk subgroups may benefit. Patients with cardiogenic shock complicating acute MI are an extraordinarily high-risk subgroup. This group represents 12% of all patients with acute MI. A hospital mortality of 85% exists[75] with current therapy. Lee et al reviewed the University of Michigan experience with cardiogenic shock.[162] In this study, 83 patients with rigidly defined criteria for cardiogenic shock were treated between 1975 and 1985. A reduction in mortality from 83% to 50% occurred for the 24 patients treated with PTCA therapy compared to the conventionally treated patients. Other small clinical series have examined the impact of PTCA on mortality.[163-165] Overall, for the 74 reported cases, a 49% survival occurred. Since other therapeutic strategies including intraaortic balloon counterpulsation,[166] coronary bypass,[167] and thrombolytic therapy[75] have not altered survival, PTCA is an extremely promising therapy for this high-risk subgroup.

Another major subgroup that may benefit from PTCA includes those patients failing thrombolytic therapy. In a preliminary report, Califf et al[168] demonstrated the clinical utility of angioplasty after failed thrombolytic therapy. The TAMI Study treated 386 patients with transmural MI with IV rt-PA. Patients underwent catheterization within 90 minutes of onset of infusion. At angiography, 96 of 386 patients (25%) had failed thrombolytic therapy. Ten of these patients had small infarcts and were treated conservatively; all did well. Angioplasty was attempted by 86 patients and resulted in reperfusion in 89% of the patients, with a mortality rate of 8%. Mortality for the 9 patients who failed both thrombolytic therapy and angioplasty was 44%. Although uncontrolled, these findings suggest that prognosis can be improved by angioplasty-induced reperfusion after failed thrombolytic therapy.

In summary, the role of PTCA as primary therapy of acute MI has not been adequately defined. Early studies suggest that PTCA is superior to IV thrombolytic therapy and at least equivalent to intracoronary therapy[158] in achieving coronary recanalization. The O'Neill et al[158] and Erbel et al[59] studies suggest that PTCA is superior to intracoronary streptokinase in improving ventricular function. These findings must be corroborated by future studies. Angioplasty has not been shown to improve survival except in patients with cardiogenic shock. Because of logistic and manpower constraints, it is unlikely that this therapy will be widely applied as a sole reperfusion treatment modality. The question as to whether a patient who is seen in a center with the capability of PTCA (within three hours of symptom onset) would best be treated by IV thrombolytic therapy alone or PTCA alone must await further study.

CLINICAL STUDIES OF COMBINATION THROMBOLYTIC AND ANGIOPLASTY THERAPY

RECANALIZATION RATES

Meyer et al[153] first described the use of PTCA in MI in a 72-year-old female who developed cardiogenic shock 31 hours after successful intracoronary streptokinase therapy of a right coronary artery occlusion. PTCA of a subtotal RCA occlusion successfully reversed the shock syndrome. Other brief case reports soon

followed.[169,170] These early studies all used PTCA after streptokinase therapy.

Meyer et al first reported a large clinical series using PTCA after streptokinase therapy.[156] In this study 64 patients were treated with intracoronary streptokinase infusion. After angiography, 21 patients were deemed suitable for PTCA; it was successful in 17 of 21 patients. Patients were selected based on the presence of high-grade residual stenosis. Patients failing thrombolytic therapy were not treated. Hartzler subsequently extended the use of PTCA to patients failing thrombolytic therapy.[155] The combination of thrombolytic agents and PTCA has provided high rates of coronary recanalization. Kitazume et al[171] achieved recanalization in 90% (20 of 22) of patients combining intracoronary urokinase and PTCA. Prida et al[161] successfully recanalized 18 of 22 (82%) of the patients treated with streptokinase and PTCA. Holmes et al also achieved successful recanalization in 23 of 29 (79%) of the patients treated with streptokinase and PTCA.[172] These early reports were retrospective reviews of a clinical experience. Fung et al[134] first prospectively evaluated sequential IV streptokinase followed by immediate PTCA. Thirty-four consecutive patients were treated with 1.5 million units of IV streptokinase 2.6 hours after symptom onset. Cardiac catheterization was immediately performed and PTCA was attempted on all suitable patients. PTCA was attempted on all 13 patients who failed lytic therapy with 12 of 13 having successful recanalization. PTCA was attempted in 16 of 18 patients with post-streptokinase therapy high-grade obstructive lesions, and was successful in all 16. Three patients had less than 50% residual stenosis at initial angiography. On discharge from the laboratory, this approach resulted in a recanalization rate of 97%.

Combination therapy with PTCA and tissue plasminogen activator is now the focus of intense clinical investigation. Topol et al[173] reported a pilot experience with PTCA and rt-PA. In this study, 38 patients were treated with a three-hour infusion of rt-PA. Catheterization revealed recanalization in 32 of 38 (84%) of patients two hours after the onset of rt-PA infusion. PTCA was attempted in all six rt-PA failures with successful reperfusion occurring in five of six patients. Thus, 37 of 38 patients (97%) left the catheterization laboratory with patent coronary arteries. Based on this promising early experience with combination rt-PA and PTCA, the multicenter TAMI Study prospectively treated 386 patients with IV rt-PA. PTCA was used in patients failing lytic therapy or those randomized to PTCA after successful thrombolysis (Fig 15). Angiography at 90 minutes demonstrated recanalization in 288 (75%) of the patients. PTCA was performed in 86 of 96 patients with failed thrombolysis and was successful in 79 of 86 (92%) of the patients. Thus, 358 of 384 (93%) of the patients were discharged from the laboratory with patent vessels. However, this study has pointed out the risk of immediate PTCA since 7% of the patients undergoing PTCA after successful rt-PA therapy required urgent bypass due to coronary dissection or rethrombosis.

A major deficiency of the combination of rt-PA and PTCA is the inability of this combination to prevent coronary reocclusion. Gold et al[169] first suggested that PTCA could decrease reocclusion after streptokinase therapy. One of the major aims of the TAMI Study was to prospectively test the value of immediate *v* elective PTCA in preventing coronary reocclusion after rt-PA therapy. Reocclusion occurred in 11% of the 99 patients treated with immediate PTCA and 13% of the patients with elective PTCA. Thus, after successful rt-PA therapy (6-hour

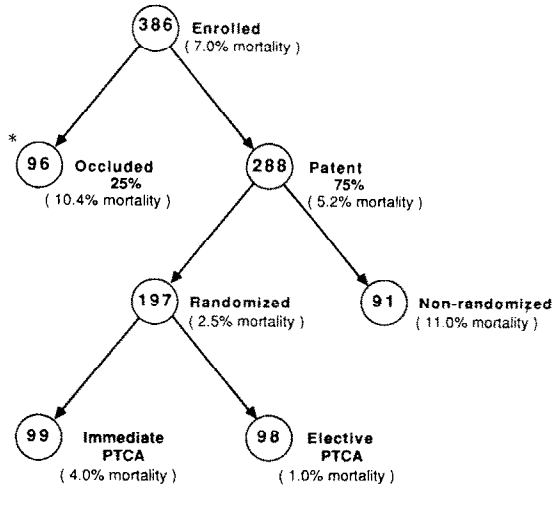

Fig. 15. TAMI trial design. Patient triage for the TAMI Study is presented. At 90-minute angiography, 75% of the patients had patent vessels. After "salvage PTCA," 94% of the patients had patent vessels. Two patients did not undergo initial angiography.*

infusion) no decrease in reocclusion occurred with immediate PTCA. The reocclusion rates after "salvage" PTCA in patients failing thrombolytic therapy were even more disappointing. In the TAMI Study, 96 patients failed thrombolytic therapy. PTCA was attempted in 86 patients and successful in 79. At recatheterization 1 week later 29% of this subgroup had coronary reocclusion.

The TAMI study group completed a pilot study of the combination of rt-PA and urokinase.[174] This study was conducted to determine whether these agents had synergistic effects and whether coronary reocclusion could be lessened by a systemic fibrinolytic state. One hundred and forty six patients were treated with increasing doses of both agents. Recanalization rates were documented with immediate angiography. Group 1 received 25 mg rt-PA and .5 megaunits urokinase. Group II received 25 mg rt-PA and 2 megaunit urokinase. Group III received 1 mg/kg t-PA and .5 megaunit urokinase. Group IV received 1 mg/kg of rt-PA and 1 megaunit of urokinase. Group V received 1 mg/kg t-PA and 2 megaunits of urokinase. Recanalization rates of 36%, 37%, 71%, 72%, and 75% were achieved. These recanalization rates are no higher than those achieved by rt-PA above. Significantly, however, reocclusion rates were only 4%.

IMPACT OF COMBINATION STRATEGIES ON VENTRICULAR FUNCTION

Fung et al evaluated the impact of streptokinase and PTCA therapy on ventricular function.[134] Ventricular function was evaluated using single-plane contrast ventriculography performed immediately and prior to hospital discharge. Ejection fraction and centerline-chord wall motion were assessed. Ejection fraction increased from 53% ± 12% to 59% ± 13% ($P < .002$) and wall motion of the infarct artery increased from −2.7 ± 1.1 to −1.5 ± 1.7 SD units/chord ($P < .003$). Improvement in function primarily occurred in patients who initially failed streptokinase therapy (Fig 16). Patients achieving streptokinase-mediated coronary recanalization had no improvement in EF after PTCA. Since a high level of baseline EF (56% ± 10%) was present in this subgroup on admission, there was little room for subsequent improvement in function.

To determine whether immediate PTCA was required for improved ventricular function after rt-PA administration, a small randomized pilot study was conducted at the University of Michigan.[173] In this clinical trial, 38 patients were treated with 1.25 mg/kg of single-chain rt-PA over three hours. Therapy was initiated 3.8 ± 1.1 hours after symptom onset. After two hours of infusion, 84% of the infarcted arteries were patent. Patients with a residual stenosis >50% were randomized to early *v* delayed PTCA. Contrast ventriculography was performed preintervention and 7 to 10 days post-MI. Global EF was unchanged for either group. Regional wall motion was significantly improved for patients undergoing immediate PTCA, however, but unchanged for those undergoing delayed PTCA (Fig 17). Therefore, this pilot study suggested that sequential rt-PA and PTCA were required to achieve improved ventricular function.

To corroborate these findings and determine the role and timing of PTCA, the TAMI study group was organized.[100] This four-institution

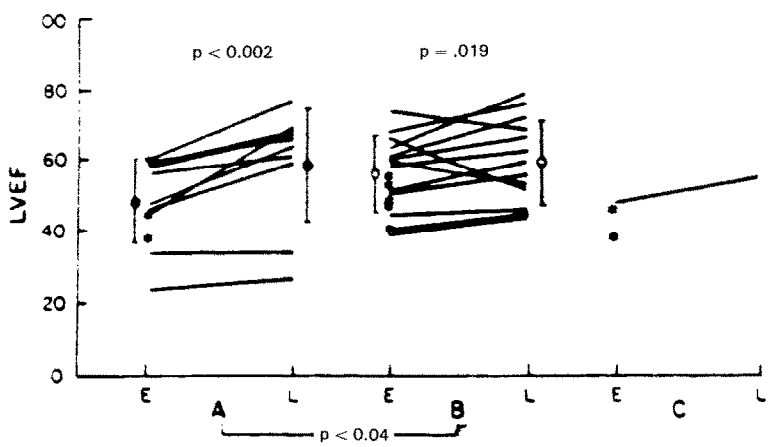

Fig 16. Left ventricular angiography initially and predischarge in patients is presented.[134] Patients' subgroups include Group A (failed thrombolytic therapy), Group B (successful thrombolytic therapy), and Group C (residual stenosis less than 50% at initial angiography). E = initial study; L = predischarge study.

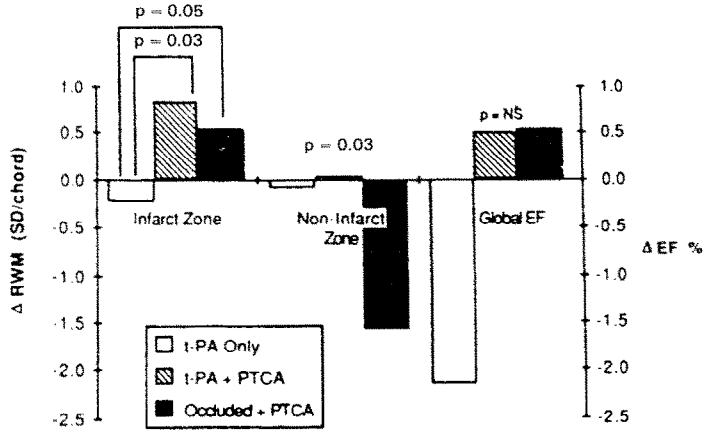

Fig 17. Serial changes in global and regional wall motion for patients are presented.[173] Patients undergoing PTCA had improved regional wall motion regardless of status of arterial recanalization prior to PTCA. No improvement in regional motion occurred for patients treated with rt-PA alone. No improvement in global function occurred for any group.

study enrolled 386 patients presenting within four hours of symptom onset. Patients were treated with a total dose of 150 mg single-chain rt-PA. After 90 minutes of drug infusion, 75% of infarct-related arteries were patent. Furthermore, 198 patients were found to have patent vessels that were technically suitable for PTCA. Patients were randomly allocated to immediate or delayed PTCA. Contrast ventriculograms were performed pre-PTCA and at hospital discharge. No change in global EF occurred for either group. Regional wall motion assessed by the centerline-chord method was significantly improved for both groups. However, no differences in changes in ventricular function were observed upon comparison of the two groups (Fig 18).

In comparing these two studies, there are two differences in trial design that might explain the discrepant findings concerning ventricular function. First, in the pilot study all patients were transported to the University of Michigan prior to the onset of therapy. In the TAMI Study, thrombolytic therapy was usually started in the emergency ward. As a result, therapy was instituted 3.8 hours after symptom onset in the pilot study and 2.9 hours after symptom onset in the TAMI Study. Earlier initiation of therapy allowed for improved regional function even in patients treated with rt-PA alone. Second, a five-hour maintenance infusion was used in the TAMI trial, but not in the pilot study. Gold et al[101] showed that prolonged rt-PA infusion significantly lowers the risk of coronary reocclusion. Brown et al[175] demonstrated that significant ongoing thrombolysis occurs after initial angiographic patency is achieved by thrombolytic therapy. Thus, the prolonged infusion decreases reocclusion and enhances ongoing thrombolysis. This therapy thereby allows improved ventricular function to occur even when thrombolytic therapy alone is used.

The discordant findings comparing the impact of streptokinase and PTCA *v* rt-PA and PTCA on ventricular function merit further analysis. After arterial patency is achieved by either rt-PA

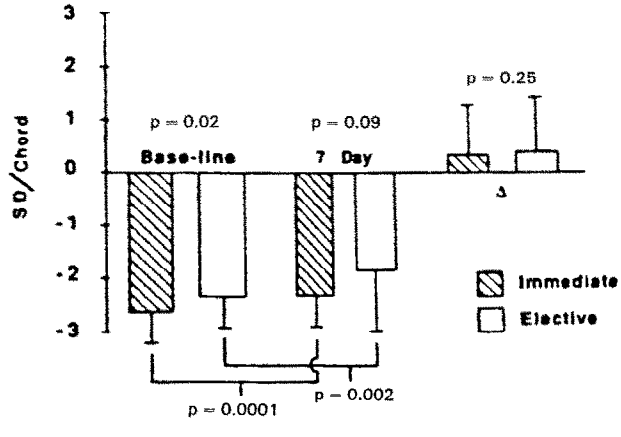

Fig 18. Sequential regional wall motion for patients in the TAMI Study[100] who were randomized to immediate or deferred PTCA is presented. EF did not improve for either group. Regional wall motion improved significantly whether PTCA was used immediately or later.

or streptokinase, EF is not further improved by the addition of PTCA. Patients failing streptokinase do however have a major improvement in EF. In the Fung study,[134] EF increased from 49% ± 12% to 59% ± 12%, $P < .002$ for patients achieving PTCA-mediated reperfusion after failed IV streptokinase therapy. In contrast to these findings, median global EF was initially 52% and was 51% 1 week later in the 65 patients treated in the TAMI Study with salvage PTCA after unsuccessful rt-PA therapy.[151] Since 30% of this later group had reocclusion, it is not surprising that there was no overall increase in global EF.

MORTALITY AFTER COMBINATION THERAPY

The impact of combination therapy on mortality can be only indirectly addressed by the TAMI Study. In this study a 7% hospital mortality occurred. Mortality was higher in patients failing rt-PA therapy (10.4% *v* 5.2%). Mortality was especially high (55%) in patients failing both rt-PA and PTCA therapy. Since this study excluded patients in cardiogenic shock and had no placebo control, definitive statements regarding mortality reduction could not be made. Califf has now reported an 8-month follow-up of this patient cohort.[176] A strikingly low 2% mortality occurred. These findings suggest that aggressive revascularization may dramatically decrease post-MI mortality. Again without a true control group, definitive statements regarding long-term mortality cannot be made from the TAMI Study.

In summary, the combination of IV thrombolytic therapy and immediate PTCA has great promise as a reperfusion strategy. A substantially higher rate of recanalization is achieved than that by thrombolytic agents alone. Early initiation of thrombolytic therapy is useful in achieving prompt reperfusion. Reperfusion can be documented by immediate catheterization, and recanalization can be mechanically accomplished if thrombolytic therapy has failed. Since reocclusion and further myocardial salvage is not enhanced by PTCA after successful thrombolysis, the need for PTCA in these patients is less compelling. Ultimately, the impact of these combination strategies on mortality will be addressed by the NHLBI-sponsored TIMI trial and the European Cooperative Study.[177]

SUMMARY OF REPERFUSION STRATEGIES

Recanalization Rates

Intracoronary streptokinase administration was the first well-documented method of achieving coronary recanalization. Recanalization rates of 70% to 80% are expected with some time dependency present. Intravenous streptokinase achieves recanalization in up to 65% of the patients. A much more critical time dependency for efficacy is present. After six hours of symptom duration, the recanalization rate of 30% to 40% is identical to that spontaneously occurring. Although the optimal dose of rt-PA has not been defined, recanalization rates of 70% to 75% are expected with doses of rt-PA ranging from 100-150 mg. There does not appear to be a temporal relation to efficacy for this agent. Mechanical recanalization with PTCA appears more effective than thrombolytic approaches because recanalization rates of 90% or more are achieved. Coronary reocclusion remains a problem that has been resolved in part by prolonged rt-PA infusion protocols or by the use of systemic thrombolytic agents in combination with early PTCA. Depending on the recanalization protocol used, recurrent ischemia and reocclusion will occur in 10% to 30% of the patients. These events mandate that patients be closely observed and treated in centers where definitive revascularization is available.

Changes in Ventricular Function

Thrombolytic therapy with IV or intracoronary streptokinase will improve global ventricular function when therapy is initiated within three to four hours of symptom onset. Primary angioplasty is more effective in improving ventricular function than intracoronary streptokinase. The efficacy of PTCA alone compared to early IV streptokinase alone, or streptokinase in combination with PTCA has not been tested. To date, an improvement in global ventricular function for rt-PA therapy alone or in combination with PTCA has not been demonstrated. The efficacy of rt-PA compared to placebo is currently under study in Australia and at The Johns Hopkins University. Although IV rt-PA resulted in higher rates of coronary recanalization than IV streptokinase in the TIMI Study, the improvement in ventricular function was identi-

cal for the two treatment groups. Combination therapy with IV streptokinase and PTCA may result in improved EF, whereas combination rt-PA and PTCA does not. These two strategies must be formally compared in future trials. Comparison of the impact of various thrombolytic agents on ventricular function is essential, since myocardial salvage may be multifactorial and not related solely to recanalization rates.

Impact on Mortality

The most compelling data for improved survival are related to IV streptokinase therapy. Patients most likely to benefit include those under age 65, with anterior MI, with the first MI and with Killip class I or II. Unfortunately, patients at highest risk (Killip class III or IV or those with second MI) do not appear to benefit from this therapy.

Intracoronary streptokinase also appears to improve survival, especially if complete reperfusion is achieved. Long-term survival may be contingent on complete recanalization. Arterial patency independently appears to improve survival irrespective of the degree of residual ventricular dysfunction. Arterial patency also predicts improved survival after primary PTCA[160] or after rt-PA and PTCA therapy.[175] Mortality is most likely decreased in patients of medium or high clinical risk. Patients at low risk do not have mortality reduced by myocardial reperfusion. In the future, accurate noninvasive methods of assessing myocardium at risk and detecting coronary recanalization are required. Until then, cardiac catheterization offers significant diagnostic information and potentially is an avenue for mechanical recanalization with PTCA. These invasive procedures will have the most compelling indication in patients with medium or high clinical risk.

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