Erratum

This article, which originally appeared on page 1792 of the June 1993 issue of Circulation, was mistakenly printed with figures from another article. The printer has agreed to reprint the article in its entirety.

Illusion of Reperfusion
Does Anyone Achieve Optimal Reperfusion During Acute Myocardial Infarction?

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Thrombolytic therapy significantly improves the natural history of acute myocardial infarction, but recent data suggest that current reperfusion strategies have yet to realize the maximum potential for reduction of mortality and salvage of ventricular function. Coronary patency rates as high as 85% assessed by angiography 90 minutes after initiation of treatment greatly overestimate the efficacy of thrombolytic regimens, as this conventional angiographic "snapshot" view does not satisfactorily reflect the dynamic processes of coronary artery recanalization and reocclusion or the adequacy of myocardial perfusion. In fact, only the unusual patient appears to achieve optimal reperfusion for acute myocardial infarction, with a substantial deterioration of benefit in many patients due to insufficiently early or rapid recanalization, incomplete patency with TIMI grade 2 flow or critical residual coronary stenoses, absence of myocardial tissue reflow despite epicardial artery patency, intermittent coronary patency, subsequent reocclusion, or reperfusion injury. Recently developed techniques to critically assess the quality of reperfusion, coupled with the introduction of novel pharmacological agents and an improved understanding of the roles and mechanisms of existing thrombolytic and adjunctive drugs, have provided the opportunity to overcome many of the present limitations of reperfusion therapy. Emerging strategies to achieve optimal reperfusion are directed at enhancement of the velocity and quality of thrombolysis, amelioration of the adverse effects of reperfusion, and use of alternative pathways to myocardial salvage. (Circulation. 1993;88:1361-1374.)

Key Words • thrombolysis • reocclusion • reperfusion • Clinical Progress Series

Thrombolytic therapy has been unequivocally demonstrated to markedly improve the natural history of acute myocardial infarction, with an approximate 30% reduction in mortality in randomized, controlled trials5-9 and more modest recovery of global or infarct-zone left ventricular function.5-9 In the decade since the introduction of thrombolytic agents for the management of infarction, substantial progress has been made in increasing acute patency rates,10,11 optimizing dosage regimens, recognizing the critical importance of coadministered antplatelet agents,2 and expanding patient selection criteria. These achievements, coupled with the seemingly paradoxical lack of apparent clinical benefit from more aggressive approaches with newer thrombolytic agents12,13 or routine, adjunctive mechanical infarct vessel revascularization,14-17 have led to a degree of complacency regarding the effectiveness of current myocardial reperfusion therapy.

Substantial recent data, however, suggest that thrombolytic strategies have yet to realize the maximum potential for reduction of mortality and salvage of ventricular function after acute myocardial infarction. Although an impressive proportion of patients are found to have "patent" infarct arteries after thrombolysis, this conventional assessment of efficacy in terms of an angiographic "snapshot" view does not satisfactorily reflect the dynamic processes of coronary arterial recanalization and reocclusion or the adequacy of myocardial perfusion. Newer technologies, such as contrast perfusion echocardiography and continuous 12-lead digital ECG, have enhanced detection of the stability and true extent of reperfusion. The purpose of this review is to provide a critical, contemporary evaluation of the efficacy of thrombolytic therapy, with consideration of each of the key components of "optimal reperfusion": rapid, complete, and sustained restoration of perfusion to the myocardium subserved by an infarct-related artery.

"Patency" Is Not Equal to "Reperfusion"

Contributing to the overly optimistic view of the effectiveness of current thrombolytic therapy is a tendency to equate the various terms used to describe the state of the infarct-related artery after administration of these agents. These terms, as strictly defined, are not interchangeable. "Patency" denotes the proportion of infarct arteries that are found to be unoccluded at the time of coronary angiography and consequently encompasses those vessels that were totally occluded at baseline, those that spontaneously achieved patency, and those that were acted on successfully by fibrinolytic agents. "Recanalization," a more rigorous measure than patency of the effectiveness of treatment, refers to
those infarct arteries that were demonstrated to be occluded at baseline and subsequently become patent with therapy, “Reflow” (for this discussion, at least) may be considered to represent the quality and briskness of blood flow in the epicardial artery beyond a patent stenosis. Finally, “reperfusion” may be seen as representing the ultimate goal and most pertinent end point of thrombolytic therapy; the reestablishment of tissue-level perfusion within the jeopardized myocardium. The dissociation that may exist between epicardial artery patency and myocardial tissue reperfusion has only recently become evident, and the exclusive angiographic end point addressed by nearly all previous clinical trials has been infarct vessel patency.

Restoration of Infarct Artery Patency

Although a few investigators have argued that the salutary effects of thrombolytic agents may result from mechanisms other than restoration of infarct artery patency,18 it is almost universally accepted that benefit with this form of therapy is linked to the establishment of an open artery. Failed recanalization after thrombolysis has been associated with higher rates of in-hospital mortality and morbidity and with minimal recovery of left ventricular function compared with outcome in patients in whom reperfusion is successful.19,20 Long-term prognosis also appears to be substantially improved among patients with an open artery compared with those who fail reperfusion therapy.21–25 Although a major caveat in interpreting these data has been the possibility that patients with successful restoration of patency may in some way represent a healthier cohort destined to have a better prognosis.

During the first 24 hours after acute myocardial infarction, angiography reveals a patent infarct-related artery in only 9–29% of patients who have not been treated with reperfusion therapy.24–28 Thus, conventional angiographic assessment of the efficacy of various thrombolytic agents has focused on the establishment of infarct artery patency, typically at 90 minutes after initiation of therapy. By this criteria, early effective thrombolysis is achieved least frequently after treatment with intravenous streptokinase (43–64%29–31 or urokinase (53–66%32–34 and in nearly equal proportions of patients receiving tissue-type plasminogen activator (t-PA) in standard dosages (63–79%)35,36,37,29–34 or anistreplase (55–73%).36–41 Superior results have been obtained using accelerated dosing regimens of t-PA, with 90-minute patency rates ranging from 82% to 91% (mean, 85%) in five studies of a combined total of more than 500 patients.10,35,39,42–43

The “catch-up” phenomenon of infarct vessel patency with streptokinase and other nonfibrin-specific plasminogen activators renders angiographic differences between the thrombolytic agents less distinct after 2–3 hours, although at least 10–15% of patients will ultimately fail to achieve recanalization of the infarct-related artery, regardless of the thrombolytic regimen. The pathophysiological basis for the ineffectiveness of thrombolysis in some patients appears to be multifactorial. The relative proportions of platelet-rich and erythrocyte-rich zones in the occlusive thrombotic mass may be influenced by the depth of arterial plaque fissuring and wall injury,44–45 with platelet-rich thrombi exhibiting intrinsic resistance to clot lysis.46 Extrinsic luminal compression from plaque hemorrhage or extensive rupture, which has been referred to as “plaque disaster,”47 also may prevent pharmacological coronary revascularization on a mechanical basis. Beyond these differences in the constitution of the occlusive thrombus or underlying lesion, the antigenicity of streptokinase or anistreplase may limit the effectiveness of these agents,48 intrinsic fibrinolytic activity and that of plasminogen activator inhibitor–1 (PAI-1) vary among patients,49 and there appears to be substantial interindividual variability in fibrinogenolytic response to thrombolytic therapy.50 Finally, the currently available thrombolytic agents may be inadequately potent at maximal safe dosages and rates of administration.

Although patency rates appear to be acceptably high at 90 minutes after initiation of thrombolytic therapy, this parameter may not be an adequate reflection of optimal reperfusion. The clinical importance of rapidity of infarct artery recanalization remains a topic of considerable interest and controversy. The failure of large randomized trials to demonstrate clinical superiority of agents (t-PA and anistreplase) with greater rapidity of recanalization than streptokinase (although equivalent later patency rates) has led some to speculate that ultimate coronary patency, regardless of timing, may be the most important benefit of thrombolysis.51,52 Recent data from controlled trials of reperfusion therapy in late-entry patients, presenting from 6 to 24 hours after symptom onset, have confirmed a mortality reduction and left ventricular cavity remodeling effect as long as 12 hours after symptom onset.2,51,52 Importantly, the extent of benefit, such as the 27% relative mortality reduction by 35 days in the preliminary report of the LATE study,53 has been similar to that observed in trials of earlier treatment, suggesting that an open artery does confer an advantage at a time during which substantial diminution of myocardial necrosis would not be expected.53 Moreover, the mortality benefit from thrombolysis has been demonstrated to be disproportionately high in comparison to improvements in left ventricular function,54–56 a finding that supports the concept that mortality reduction is not necessarily linked to speed of reperfusion and salvage of myocardium.

Although it therefore seems apparent that a component of the clinical benefit derived from thrombolytic therapy is unrelated to the timing of recanalization, due perhaps to improved ventricular healing, remodeling, or electrophysiological stability,21–23 a rate-dependent effect clearly also exists. Patients randomized to streptokinase treatment within 3 hours of symptom onset in GISSI-11 and 4 hours in ISIS-25 experienced lower in-hospital mortality and greater risk reduction with thrombolysis than patients whose treatment was more delayed. In both of these large-scale trials, there was a 50% reduction in mortality for patients treated within the first hour of symptoms. Recent studies of prehospital thrombolysis also have supported the hypothesis that very early reperfusion therapy may result in dramatic reductions in death rates and infarct size. Mortality among patients in the Myocardial Infarction Triage and Intervention Project (MITI) in whom t-PA was administered within 70 minutes of symptom onset was only 1% compared with a 10% mortality (p<0.03) in patients treated after 70 minutes; infarct size (expressed as a percentage of the left ventricular mass) was 4.9% and 11.2% in the
two groups, respectively, in this preliminary report. Of striking importance, 40% of patients treated within the first hour in MITI subsequently had no thallium scintigraphic evidence of infarction. Similar benefit was evident in the European Myocardial Infarction Project (EMIP) prehospital trial, when anistreplase was administered within 1 hour of symptom onset. In the Israeli Study of Early Intervention in Myocardial Infarction, patients treated within 2 hours experienced no 60-day mortality, whereas the death rate among patients receiving rt-PA between 2–4 hours of symptom onset was 6.3% (p = 0.01). In a fourth study, global and regional left ventricular ejection fractions were found to be markedly improved by very early (<1.5 hours) treatment with streptokinase, in comparison to the lesser degree of myocardial salvage among patients undergoing thrombolysis between 1.5 and 4 hours.

It is also noteworthy that mortality rates in the control groups of patients enrolled during the first hour of symptoms in the large-scale thrombolytic trials were higher than for those patients treated after 6 hours (15.4% versus 13.9% in GISSI-1 and 13.4% versus 12.1% in ISIS-2 among patients presenting at <1 hour and >6 hours, respectively). Such early entry may have been prompted by more severe chest pain, pulmonary edema, or hemodynamic compromise and is a topic that warrants further clarification. It is conceivable, then, that patients presenting within the first hour of infarction are different from those presenting later, not only as a result of a shorter duration of ongoing myocardial necrosis and less mature thrombus at the arterial level but also prognostically. If this early-entry cohort of patients is at elevated baseline risk for mortality, the potential for risk reduction with thrombolysis may be expected to be greatest in this group.

From these data, which have led to the concept of a "golden first hour" during which initiation of thrombolytic therapy is most likely to result in mortality reduction and myocardial salvage (Figure 1), it may be inferred that a rapidity of infarct artery recanalization would also confer substantial benefit in terms of survival and preservation of ventricular function. Therefore, optimal reperfusion constitutes the establishment of angiographic patency as quickly as possible after administration of thrombolytic agents. Ideally, infarct artery recanalization would occur within 30 minutes or less of treatment, but such early angiographic data have been reported only infrequently. Patency rates at 60 minutes, however, are available from several angiographic studies (Table 1); thus, angiographic patency at 60 rather than 90 minutes after initiation of thrombolytic therapy should be considered the current benchmark toward optimal reperfusion. After therapy with streptokinase in one large study, the patency rate at 60 minutes was only 48%, whereas in patients treated with conventional doses of t-PA during three randomized trials, 45–62% (mean, 57%) of infarct arteries were open by 60 minutes. Accelerated dosage regimens of t-PA have been most efficacious, with a mean 60-minute patency rate of 72% (range, 65–76%) among 438 patients in four different reports. Thus, rapid restoration of infarct artery patency, the first criteria of optimal reperfusion, is achieved in fewer than three-fourths of patients treated with even the most aggressive current regimen of thrombolytic therapy for acute myocardial infarction.

**Obstacles to Optimal Reperfusion**

**Incomplete Coronary Patency**

Based on criteria proposed by the Thrombolysis in Myocardial Infarction (TIMI) study group, angiographic outcome after thrombolysis has been qualitatively classified according to the extent of radiographic contrast penetration beyond a coronary lesion: grade 0 (no flow), grade 1 (minimal penetration of contrast), grade 2 (delayed flow of contrast), or grade 3 ( brisk flow of contrast). By this scheme, arteries with TIMI grades 0 or 1 flow are regarded as occluded, whereas those exhibiting grades 2 or 3 flow typically have been considered "patent." Recent reports, however, challenge the previous conventional dogma that TIMI 2 and TIMI 3 flow are functionally equal with regard to effective infarct vessel recanalization. In an analysis of the TEAM-2 data comparing anistreplase with streptokinase, patients with TIMI 2 flow 90–240 minutes after thrombolysis had indexes of infarct size (enzymatic peaks, enzymatic times to peak, and evolution of summed ECG segments) comparable to those of patients with TIMI 0 or 1 flow but significantly inferior to indexes resulting from TIMI grade 3 perfusion. These investigators concluded that myocardial salvage with TIMI 2 flow was no better than in the presence of an occluded coronary artery. In a retrospective study of 907 patients in four multicenter German thrombolytic trials, in-hospital mortality was 7.1% and 6.6% among patients with early TIMI 0/1 and TIMI 2 flow, respectively (p = NS) but only 2.7% in those with TIMI 3 flow.
(p<0.01). During the combined Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) group experience of more than 1,200 patients,66 TIMI grade 2 flow after infarction was associated with significantly more frequent congestive heart failure and recurrent ischemia and with poorer global and regional left ventricular function than TIMI 3 flow; a trend toward less mortality with TIMI 3 flow also was noted in this preliminary analysis (10.1%, 6.1%, or 4.3% in patients with TIMI 0/1, 2, or 3 flow, respectively). Two groups of investigators64,65 have correlated TIMI 2 flow with an increased risk of reocclusion after coronary recanalization.

It is not clear whether TIMI 2 flow is a cause or marker of poorer prognosis after thrombolysis for acute infarction. Incomplete coronary patency may be inadequate to maintain myocardial viability, thus resulting in less myocardial salvage; alternatively, TIMI grade 2 distal blood flow after thrombolysis simply may be a consequence of extensive myocardial necrosis and edema and represent a "no-reflow" phenomenon. For whatever the reason, it is apparent that the attainment of TIMI 2 rather than TIMI 3 flow during acute myocardial infarction does not constitute optimal reperfusion. The relative frequencies of TIMI 2 and TIMI 3 flow among patients with "patent" coronary arteries have been remarkably consistent in different reports (Table 2). Among 370 patients in three randomized trials undergoing angiography 60 minutes after therapy with accelerated dosages of t-PA, 57% (range, 54–62%) and 17% (range, 15–19%) were found to have TIMI 3 and TIMI 2 flow, respectively.10,35,39 Thus, by the criteria of rapid and complete restoration of coronary patency, less than 60% of patients appear to achieve optimal reperfusion, even with accelerated thrombolysis.

The clinical importance of residual coronary stenosis after successful thrombolytic reperfusion also has been investigated recently. Leung and Lau66 reported that the presence of a severe, but subtotal, residual stenosis after anterior myocardial infarction was correlated with ventricular dilatation over the subsequent 6–12 months: end-diastolic and end-systolic volumes in 24 of 44 patients (55%) with coronary minimal luminal diameters of <1.5 mm were significantly greater than among those with ≥1.5-mm stenoses. Importantly, their results demonstrated that the degree of ventricular dilatation was related in a continuous manner to minimal lesion

### Table 1. Comparison of 60- and 90-Minute Patency Rates After Thrombolysis for Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Thrombolytic regimen</th>
<th>n</th>
<th>60-Minute patency (%)</th>
<th>90-Minute patency (%)</th>
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<tbody>
<tr>
<td>PRIMI30</td>
<td>Streptokinase</td>
<td>203</td>
<td>48</td>
<td>64</td>
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<tr>
<td>TAPS39</td>
<td>Anistreplase</td>
<td>210</td>
<td>60</td>
<td>70</td>
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<tr>
<td>RAAMI34</td>
<td>Standard t-PA</td>
<td>138</td>
<td>62</td>
<td>75</td>
</tr>
<tr>
<td>Smalling et al42</td>
<td>Standard t-PA</td>
<td>91</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>Topol et al24</td>
<td>Standard t-PA</td>
<td>75</td>
<td>57</td>
<td>69</td>
</tr>
<tr>
<td>RAAMI35</td>
<td>Accelerated t-PA</td>
<td>143</td>
<td>76</td>
<td>82</td>
</tr>
<tr>
<td>Smalling et al42</td>
<td>Accelerated t-PA</td>
<td>84</td>
<td>65</td>
<td>84</td>
</tr>
<tr>
<td>Neuhaus et al10</td>
<td>Accelerated t-PA</td>
<td>80</td>
<td>74</td>
<td>91</td>
</tr>
<tr>
<td>TAPS39</td>
<td>Accelerated t-PA</td>
<td>210</td>
<td>73</td>
<td>84</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td>61</td>
<td>75</td>
</tr>
</tbody>
</table>

**t-PA, tissue-type plasminogen activator.**

*95% Confidence interval.

### Table 2. Grade 2 or 3 Coronary Flow After Thrombolysis for Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Thrombolytic regimen</th>
<th>Time to angiography (minutes)</th>
<th>TIMI 3 flow (%)</th>
<th>TIMI 2 flow (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAPS39</td>
<td>210</td>
<td>Accelerated t-PA</td>
<td>60</td>
<td>54</td>
<td>19</td>
</tr>
<tr>
<td>Neuhaus et al10</td>
<td>73</td>
<td>Accelerated t-PA</td>
<td>60</td>
<td>59</td>
<td>14</td>
</tr>
<tr>
<td>RAAMI35</td>
<td>87</td>
<td>Accelerated t-PA</td>
<td>60</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>RAAMI35</td>
<td>86</td>
<td>Standard t-PA</td>
<td>60</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>TAPS39</td>
<td>211</td>
<td>Anistreplase</td>
<td>60</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>TEAM-261</td>
<td>359</td>
<td>Anistreplase, streptokinase</td>
<td>90–240</td>
<td>56</td>
<td>16</td>
</tr>
<tr>
<td>Vogt52**</td>
<td>907</td>
<td>Accelerated t-PA, anistreplase, urokinase, r-PA</td>
<td>90</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
<td>57 (55–59)†</td>
<td>16 (15–17)†</td>
</tr>
</tbody>
</table>

**TIMI, Thrombolysis in Myocardial Infarction; t-PA, tissue-type plasminogen activator; r-PA, recombinant plasminogen activator.**

*Report is a composite of four different trials,10,33,39,89 two of which10,39 are included in this table.

†95% Confidence interval.
diameter. Another group has suggested that clinical outcome among patients with >50% stenoses after thrombolysis may be inferior to that in patients with low-grade residual narrowings,65 with an increased risk of recurrent ischemia, required revascularization, or death; these data were somewhat confounded, however, by the use of adjunctive angioplasty in 39% of patients in this study. Clearly, the prevalence of severe subtotal residual stenoses among different patient cohorts will vary according to the frequency with which coronary angioplasty is used in the period after myocardial infarction. Improved clinical outcome among patients treated with angioplasty rather than thrombolysis in preliminary reports of the randomized direct angioplasty trials67,68 also may have been related to less severe residual stenoses in the patients undergoing mechanical coronary recanalization.

**Inadequate Myocardial Perfusion Despite Coronary Patency**

The ultimate goal of optimal thrombolysis is salvage of jeopardized myocardium by restoration of perfusion at the tissue level. The recent development of myocar-dial contrast echocardiography, a technique in which microbubbles are injected into the coronary circulation and perfusion of the subserved myocardium is assessed by two-dimensional surface echocardiography, has allowed investigation of the microcirculatory changes in ischemic myocardium. In a provocative report, Ito et al69 described 39 patients with acute anterior myocardial infarction in whom recanalization was achieved by direct coronary angioplasty or thrombolysis. Contrast echocardiography demonstrated absence of myocardial reflow, despite a patent infarct artery, in 23% of these patients; patients without microcirculatory reflow had significantly less recovery of global or regional left ventricular function than did those in whom myocardial perfusion had been restored. The authors speculated that residual perfusion defects may be a consequence of extensive myocardial necrosis and microcirculatory damage. These data suggest that the epicardial coronary artery status as determined by angiography may be dissociated from the adequacy of myocardial tissue perfusion, and the absence of reperfusion in ≥20% of patients with acute infarction appears to portend poor functional recovery of jeopardized myocardium.

**Intermittent Coronary Patency**

Oscillatory reflow and occlusion after experimental coronary thrombosis and recanalization in animal models have been described70-72; this phenomenon appears to be due primarily to obstructive aggregation of platelets at a site of vascular endothelial disruption, followed by dislodgement and embolization (Figure 2A). Thrombin probably is an important mediator of platelet aggregation in this setting, as cyclical variations in coronary flow may be abolished, particularly during the early phase, by thrombin inhibition.72 Both thrombin and platelets are activated by thrombolytic agents.73,74 After successful thrombolytic therapy for acute myocardial infarction, intermittent coronary occlusion in 16–58% (mean, 34%) of patients can be demonstrated by serial angiography75,76 or inferred from continuous ECG monitoring76-78 (Figure 2B). In a small series by Kwon et al,78 recurrence of ST segment elevation on continuous ECG monitoring during the 12 hours after acute infarction was associated with a 27% rate of reocclusion by follow-up angiography compared with 0% reocclusion in the patients who did not exhibit recurrent ST segment elevation. Reocclusion occurred in all of the patients with intermittent patency by angiography as described by Grines et al.65 Lactate dehydrogenase (LDH) levels were significantly higher among the 34% of patients with a “highly variable ST vector magnitude” pattern on dynamic ST segment monitoring after t-PA treatment in the series by Dellborg et al,77 with a trend toward higher 1-year mortality as well (24% versus 9%, p=0.08). Thus, although the clinical significance of cyclical coronary flow after thrombolytic reperfusion remains to be clearly defined, this finding in nearly one third of patients may be associated with reduced myocardial salvage and poor long-term coronary patency.

**Reocclusion**

Although early and complete restoration of coronary patency may result in substantial salvage of myocardium during acute infarction, this initial benefit may be attenuated by subsequent occurrence of reocclusion. Experimental coronary reocclusion in animals negates the preservation of ventricular function achieved by reperfusion79; the clinical consequences of reocclusion in humans depend on the extent of initial salvage of jeopardized myocardium and the adequacy of collateral coronary flow. Among 91 patients with reocclusion documented angiographically 0.5–38 days after successful thrombolysis (with or without adjunctive angioplasty) in the TAMI trials,80 reocclusion was associated with a greater in-hospital mortality (11.0% versus 4.5%, p=0.001), less recovery of global or infarct-zone left ventricular function, and higher rates of pulmonary edema, hypotension, respiratory failure, and atrioven-tricular block than was sustained infarct artery patency. Although a few small series have suggested that the risk of reocclusion may be increased by the presence of intermittent coronary patency,81 TIMI 2 flow,82-84 or “complex morphology,”64 an analysis of 174 patients treated with t-PA demonstrated that the occurrence of reocclusion remains largely unpredictable; no relation was detected in this large series between recurrent ischemic events in 41 patients and the quantitative or morphological descriptors of the infarct-related artery assessed during acute coronary angiography.85 It is likely that thrombotic reocclusion is mediated primarily by the interaction of a number of hematological factors, including platelet activation, clot-bound thrombin, and the thrombogenicity of partially lysed clot.71,73,82,83 The reported incidences of reocclusion have varied widely, due in part to differences in treatment regimens (choice or combination of thrombolytic agents, dose and route of heparin therapy, treatment with aspirin) as well as to inconsistencies in methods of determination (rates of angiographic follow-up, inclusion or exclusion of patients who die or suffer reinfarction without angiography, and so on). In general, treatment with the fibrin-selective agent t-PA appears to be associated with higher rates of reocclusion than with the nonselective agents urokinase, streptokinase, or anistreplase.86-88,89 The role of adjunctive heparin therapy remains somewhat controversial, although three randomized trials
have demonstrated improved rates of sustained patency after administration of intravenous heparin with t-PA.\textsuperscript{84-86} The clinical reinfarction rate (a surrogate end point for reoclusion in the absence of angiographic followup) was nearly halved by treatment with aspirin in the ISIS-2 trial.\textsuperscript{2}

Because accelerated dosages of t-PA have been shown to produce the highest early infarct artery patency rates of all of the thrombolytic regimens, the incidence of reoclusion with this drug used in the most favorable manner is most pertinent to the consideration of optimal reperfusion. In five published studies in which t-PA was used in conjunction with both aspirin and intravenous heparin,\textsuperscript{10,26,33,34,39} the mean reoclusion rate among more than 500 patients was 13\% (range, 10--20\%). Combination of t-PA with a nonfibrin-selective thrombolytic agent holds promise as a means of reducing reoclusion after successful reperfusion; the reoclusion rate was 3\% among 102 patients in the KAMIT study of t-PA with streptokinase\textsuperscript{38} and ranged from 2\% to 9\% for the combination of t-PA and urokinase among 253 patients in three phases of the TAMI trials.\textsuperscript{34,43,87}

Further deterioration of infarct vessel patency occurs during the period after hospital discharge. Coronary angiography performed at 3 or 6 months after thrombolytic therapy during the TAMI-6 and the preliminary Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) trials demonstrated late reoclusion of 25--30\% of previously patent infarct-related arteries.\textsuperscript{51,88} The clinical significance of late reoclusion remains to be fully characterized.

**How Frequently Is Optimal Reperfusion Achieved?**

As defined by its key elements of rapid, complete, and sustained coronary recanalization with adequate myocardial tissue perfusion, "optimal reperfusion" is achieved in only a small subset of patients treated with thrombolytic agents. Figure 3 illustrates the diminishing proportion of patients in whom each of the critical criteria for optimal reperfusion is successively met. Although coronary patency may be achieved in 85\% of patients by 90 minutes after initiation of therapy with an accelerated regimen of t-PA, the rate of patency at 60 minutes, a more rigorous standard for rapid reperfusion, is substantially lower. Of patients with rapid recanaliza-
The magnitude of clinical benefit presently derived from thrombolytic therapy for acute infarction is consistent with the premise that only a minority of patients actually achieve optimal reperfusion. Mortality among treated patients remains substantial; among more than 50,000 patients receiving thrombolytic agents during the contemporary period of 1988–1991 in the GISSI-2 or ISIS-3 trials, the 35-day mortality rate was 10.1%. Reinfarction continues to occur in 3–4%, and congestive heart failure occurs in 10–15% of patients. Furthermore, except among patients in whom thrombolytic therapy is initiated very early in the course of infarction, salvage of left ventricular function has been only modest, with improvements in ejection fraction averaging only 2–3% with thrombolytic rather than placebo therapy. It therefore seems unlikely that clinical outcome after acute myocardial infarction can be further enhanced in any real manner without substantial improvements in the quality of reperfusion for the majority of treated patients.

### Emerging Strategies Toward More Optimal Reperfusion

Recently developed techniques to critically assess the quality of reperfusion in patients with acute infarction, coupled with the introduction of novel pharmacological agents and an improved understanding of the roles and mechanisms of existing thrombolytic and adjunctive drugs, have provided the opportunity to overcome many of the present limitations of reperfusion therapy. Progress may be made in each of three major fronts in the pursuit of optimal reperfusion: 1) enhancement of thrombolysis to rapidly attain brisk, true, and sustained reperfusion; 2) reduction in the incidence and severity of adverse effects of thrombolysis; and 3) use of alternative pathways to achieve myocardial salvage.

### Enhanced Thrombolysis

Among the most important accomplishments in the development of reperfusion therapy has been recognition of the profound benefit of very early administration of thrombolytic agents. As illustrated in Figure 1, several studies have demonstrated that mortality may be reduced by more than 50% during the golden first hour after symptom onset,\(^{1,2,57-59}\) whereas mortality advantage drops sharply thereafter to a virtual plateau for the remainder of the 6–12-hour window of proven benefit. It appears, in fact, that very early initiation of therapy results in a more marked improvement in clinical outcome than all other modifications of thrombolytic regimens or adjunctive interventions combined. However, only a small minority of patients with acute infarction actually receive very early therapy. During the GISSI-1, GISSI-2, and ISIS-2 experiences with more than 40,000 patients between 1984 and 1989,\(^{1,2,12}\) only 10.8% were treated within 1 hour of symptom onset; even more disappointing is that only 3% of 14,000 patients entered into the ongoing Global Utilization of Streptokinase or t-PA for Occluded Coronary Arteries (GUSTO) trial have been treated within 60 minutes. Although a component of the time delay between symptom onset and administration of thrombolytic therapy may be unavoidable, the currently dismal performance record in this regard may be improved by enhanced efforts toward public education and rapid triage of patients presenting

### FIGURE 3. Anticipated diminishing proportion of patients successively meeting each of the criteria for optimal reperfusion after treatment for acute myocardial infarction with an accelerated regimen of tissue-type plasminogen activator. Although individual outcomes are treated as independent in this schematic, there probably is some degree of interaction between outcomes, such as TIMI grade 2 flow and reoclusion, although the magnitude of such interactions has not been defined. To the extent that this figure fails to account for these interactions between outcomes, the attrition in optimal reperfusion is exaggerated. The adverse effects of critical residual stenosis, relatively late administration of thrombolytic therapy, and reperfusion injury are not included in this diagram as well; to the extent that these factors limit effective reperfusion, this figure underestimates the attenuation of thrombolytic benefit.

<table>
<thead>
<tr>
<th>Status</th>
<th>Proportion</th>
</tr>
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<tbody>
<tr>
<td>90-minute Patency</td>
<td>85%</td>
</tr>
<tr>
<td>60-minute Patency</td>
<td>75%</td>
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<tr>
<td>TIMI Grade 3 Flow</td>
<td>57%</td>
</tr>
<tr>
<td>No Myocardial Perfusion</td>
<td>(23%)</td>
</tr>
<tr>
<td>Intermittent Patency</td>
<td>(34%)</td>
</tr>
<tr>
<td>Reooclusion</td>
<td>(13%)</td>
</tr>
</tbody>
</table>

The following table illustrates the anticipated diminishing proportion of patients successively meeting each of the criteria for optimal reperfusion after treatment for acute myocardial infarction with an accelerated regimen of tissue-type plasminogen activator. Although individual outcomes are treated as independent in this schematic, there probably is some degree of interaction between outcomes, such as TIMI grade 2 flow and reoclusion, although the magnitude of such interactions has not been defined. To the extent that this figure fails to account for these interactions between outcomes, the attrition in optimal reperfusion is exaggerated. The adverse effects of critical residual stenosis, relatively late administration of thrombolytic therapy, and reperfusion injury are not included in this diagram as well; to the extent that these factors limit effective reperfusion, this figure underestimates the attenuation of thrombolytic benefit.

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with chest pain to prompt initiation of reperfusion therapy (including prehospital thrombolysis in some settings).^{37,59}

Currently under investigation are several approaches to improving the efficacy of reperfusion therapy through optimization of dosing, timing, or selection of thrombolytic agents. The potency standard by which new regimens are assessed now is the accelerated administration of t-PA, originally proposed by Neuhaus et al.,^{10,59} with or without adjustment of dosage for weight.^{45} Although further intensification of "front-loaded" thrombolytic dosing has been examined by the TAMI study group, rates of infarct artery patency obtained by more rapid infusion of t-PA actually were lower than those with the Neuhaus et al regimen.^{43} Increase of total t-PA dose beyond 100 mg has led to an excessive incidence of intracranial hemorrhage (2.1–2.4%) in other studies.^{16,62} It thus appears that the ceiling of rapid acute patency with t-PA monotherapy may have been reached, with additional increments in recanalization rates achieved only at the expense of substantially greater risk of serious hemorrhagic complications. More encouraging preliminary data have associated a reduced incidence of reocclusion with the combination of fibrin-selective and nonselective thrombolytic agents,^{34,36,43,67} although the speed or extent of acute arterial recanalization does not appear to be influenced by combination therapy. The large-scale randomized GUSTO trial is examining the clinical impact of accelerated and combined thrombolytic regimens.

Novel plasminogen activators have been developed that appear to exhibit increased fibrin affinity, fibrin specificity, or serum half-lives. Recombinant plasminogen activator (r-PA), a t-PA deletion mutant with enhanced fibrinolytic activity and extended half-life, has been initially evaluated in 143 patients in the GRECO study,^{89} with very early 30-minute patency rates ranging from 66% to 73% in the preliminary report of this dose-escalation trial. Vampire bat salivary plasminogen activator (bat-PA) exhibits increased fibrin selectivity and potency by virtue of its requirement for fibrin as a cofactor, potentially leading to improved thrombolytic activity without increased bleeding risk.^{90}

A number of new platelet antagonists have been developed as potential adjuncts to thrombolytic reperfusion. A growing body of evidence, summarized in a recent review by Coller,^{91} suggests that platelets exert a major adverse influence on the efficacy of thrombolytic therapy by increasing the resistance of clot to fibrinolysis, delaying reperfusion, and facilitating cyclical flow and reocclusion. In animal models, cyclical flow variations and reocclusion after thrombolysis can be abolished by thromboxane A2 antagonists.^{71} Aspirin, an inhibitor of thromboxane A2 production via cyclo-oxygenase blockade, was shown in the ISIS-2 trial to substantially diminish mortality and reinfarction rates in patients with acute myocardial infarction, an effect that was additive to that of streptokinase.^{2} Multiple mechanisms of platelet activation that are independent of the thromboxane pathway exist, however, thus limiting the effectiveness of thromboxane antagonism by aspirin or other drugs in preventing rethrombosis.^{89} The most promising new antiplatelet agents under investigation are those directed against the GPIIb/IIIa receptor, the final common pathway leading to platelet aggregation. Blockade of this membrane receptor by the potent monoclonal antibody 7E3 has been shown to accelerate coronary artery recanalization with t-PA, prevent reocclusion, and decrease infarct size in animal models.^{79,94} Murine 7E3 administered with t-PA was well tolerated while producing profound platelet inhibition in a preliminary report of a dose-escalation trial of 60 patients with acute myocardial infarction;^{83} chimeric 7E3 also has been safely used during a pilot study in patients undergoing elective coronary angioplasty. Several other antagonists of the GPIIb/IIIa receptor, which competitively bind the common recognition site to the tripeptide sequence arginine-glycine-aspartate, also have been isolated or synthesized; as with the 7E3 antibody, these antagonists have been demonstrated in animal studies to effectively increase the speed of coronary thrombolysis and limit reocclusion.^{96,97} Integrelin and MK-852, oligopeptide GPIIb/IIIa inhibitors of this class, are under clinical investigation in patients with unstable angina.

Adjunctive therapy with thrombin inhibitors may attenuate thrombin-mediated platelet activation and recurrent thrombosis during fibrinolytic therapy.^{72,74,98} Heparin diminishes the incidence of reocclusion when administered in high doses after thrombolysis with t-PA,^{84–86} but it has been ineffective in accelerating or enhancing acute infarct artery patency.^{37} The anticoagulant potency of this thrombin inhibitor appears to be modest, due in part to the dependence of heparin on antithrombin-III and its inability to act on thrombin bound to fibrin clot.^{63} Hirudin, a peptide derived from the saliva of medicinal leeches that selectively binds to the fibrinogen recognition and catalytic sites of thrombin, holds promise as a powerful adjunct to thrombolysis. In experimental animal studies, recombinant hirudin is more active than heparin in preventing thrombus formation, inhibiting clot-bound and circulating thrombin, and blocking platelet activation.^{99,100} Adjunctive treatment of acute myocardial infarction with hirudin is under evaluation in the ongoing TIMI V and VI trials. Other synthetic thrombin inhibitors have been shown in early animal experiments to be effective in diminishing vascular thrombosis, including PPACK,^{101} an irreversible catalytic site alkyler, and argatroban, a competitive antagonist.^{102} In addition, selective inhibition of factor Xa, a central component of both the intrinsic and extrinsic coagulation cascades, has resulted in dramatic acceleration of thrombolytic reperfusion and prevention of reocclusion in an animal model.^{92}

The key role played by both platelets and thrombin in antagonizing the action of fibrinolytic drugs provides rationale for combination adjunctive therapy with antiplatelet and antithrombin agents. The incremental value of heparin added to thrombolytic and aspirin therapy was examined in the GISSI-2 and ISIS-3 randomized trials,^{12,13} with no significant difference in 35-day mortality observed after heparin treatment. Extrapolation of these results is limited, however, by the predominantly subcutaneous route of heparin administration and lack of anticoagulation monitoring used in these studies; infarct artery patency, particularly with t-PA, has been correlated with the intensity of heparin anticoagulation.^{103} The potential clinical benefits of intravenous heparin therapy combined with aspirin and t-PA or streptokinase is under investigation in the
randomized GUSTO trial. Direct thrombin inhibition and platelet fibrinogen receptor blockade using a combination of low doses of hirudin and integrin, respectively, have produced an additive effect in preventing reocclusion after thrombolysis in an animal model in one preliminary report.104

Improved coronary patency by the use of adjunctive medications may be accompanied by a higher bleeding risk. Aspirin coadministered with thrombolytic agents appears to be safe; addition of aspirin to streptokinase in the randomized ISIS-2 study did not result in an increase in the rate of major or intracranial hemorrhage,2 and the elevated incidence of intracranial hemorrhage with aspirin and t-PA in the TIMI-II trial has been attributed to the high dose (150 mg) of t-PA.105 Excess bleeding risk resulting from the addition of heparin to thrombolytic therapy has not been evaluated systematically in large randomized studies without concomitant aspirin use. Combination adjunctive therapy with aspirin and heparin appears to entail a slightly elevated hemorrhagic risk. The combined results of GISSI-212 and ISIS-32 demonstrated a small but significantly increased incidence of cerebral hemorrhage and major noncerebral bleeds with the addition of heparin to the thrombolytic/aspirin regimen (particularly with streptokinase), although the overall incidence of stroke was not affected by heparin treatment. The safety of novel antiplatelet and antithrombin agents in conjunction with thrombolytic therapy is being examined.

The role of adjunctive mechanical revascularization by coronary angioplasty during thrombolysis for acute myocardial infarction remains controversial. Major randomized trials have shown unequivocally that immediate percutaneous transluminal coronary angioplasty (PTCA) confers no clinical benefit after successful thrombolysis.14,15,17 Similarly, a strategy of routine PTCA on the first or second day after thrombolysis has been shown to be inferior to one of deferred PTCA or "watchful waiting."16,106 Performance of angioplasty to restore coronary patency in the setting of failed reperfusion, however, commonly is performed, and a randomized controlled study to evaluate the efficacy of this "rescue" strategy is under way.107 Moreover, early (within 90 minutes) percutaneous revascularization for recurrent ischemia after successful thrombolysis has been demonstrated to diminish in-hospital mortality in a retrospective analysis.108 The role of coronary angioplasty in patients with incomplete (TIMI 2) reperfusion or intermittent patency has not been examined.

Selective application of coronary angioplasty or other adjunctive strategies to patients with suboptimal reperfusion after thrombolysis will be critically dependent on the ability to rapidly and noninvasively assess the adequacy of myocardial perfusion. During a prospective study of 144 patients treated with thrombolytic therapy,109 the status of infarct artery patency was predicted correctly using continuous 12-lead ST segment recovery analysis in all except 20 patients; notably, TIMI 2 flow or collateralized occlusions were present in 13 of the 20 patients in whom predicted patency was incorrect in this preliminary report. Encouraging results by these and other investigators77,78 suggest that continuous ECG ST segment monitoring may prove to be a reliable real-time technique of identifying infarct artery patency and allow specific therapies to be targeted to patients who have not achieved optimal reperfusion.

Modification of Adverse Effects of Thrombolysis: The Early Hazard

Mortality data derived from several large, placebo-controlled trials of thrombolytic therapy have demonstrated the phenomenon of "early hazard." During the first 24 hours after therapy, patients receiving thrombolytic agents are at higher risk for death than are placebo-treated controls (Figure 4).52,110 although subsequent survival benefit from thrombolytic treatment translates into an overall net improvement in mortality. Importantly, a collaborative analysis of seven major randomized, controlled thrombolytic trials suggested that the early hazard may not be present in patients receiving thrombolytic therapy within 3 hours of symptom onset, whereas a progressive increase in the magnitude of early hazard was linked to increasing intervals between symptom onset and treatment thereafter; in contrast, subsequent (day 2 and later) benefit derived from thrombolysis was not a function of time to treatment.111 This finding clearly implicates the early hazard as a critical determinant of the diminished net mortality benefit among patients in whom thrombolytic therapy is initiated more than 1–2 hours after onset of infarction (Figure 1). Thus, interventions aimed at amelioration of the early hazard may substantially diminish the overall mortality associated with myocardial infarction.

It remains unclear why thrombolysis produces a deleterious effect on clinical outcome during the first 24 hours; bleeding complications, for example, do not appear responsible, as predominant causes of mortality in these patients include heart failure, electromechani-
cal dissociation, and ventricular rupture.\textsuperscript{110,112} The potential role of cardiac tamponade early after thrombolysis, as reported by Renkin et al, deserves further study.\textsuperscript{113} It is possible, although speculative, that myocardial hemorrhage or extension of myocardial necrosis induced by reperfusion injury plays a role in the pathogenesis of early hazard.\textsuperscript{114} In addition, recurrent ischemia due to early reocclusion or intermittent patency may, in the setting of reperfusion injury after successful thrombolysis, produce a degree of myocardial necrosis equal to that caused by complete failure of infarct vessel recanalization. Although microvascular injury and endothelial dysfunction have been demonstrated in animal models of ischemia and reperfusion, leading to the no-reflow phenomenon, myocardial hemorrhage, and diminished myocardial salvage,\textsuperscript{115–118} the clinical importance of reperfusion injury after thrombolysis remains controversial. In experimental models, superoxide dismutase and catalase,\textsuperscript{119} N-acetylcysteine,\textsuperscript{119} adenosine,\textsuperscript{120} and perfuorochemicals\textsuperscript{121} have limited reperfusion injury through neutralization of oxygen free radicals or inhibition of neutrophil function, but benefit in humans has yet to be shown with these agents. During a randomized controlled trial in which superoxide dismutase was administered intravenously to patients undergoing primary or rescue coronary angioplasty for acute myocardial infarction, treatment with superoxide dismutase offered no benefit over placebo with regard to improvement in ventricular function, although the incidence of reperfusion arrhythmias was reduced.\textsuperscript{122} In a preliminary report of another randomized trial by the TAMI group, adjunctive therapy with the perfuorochemical Fluosol-DA in patients receiving t-PA for acute infarction also failed to produce a measurable improvement in global or regional ventricular function.\textsuperscript{122} Delineation of the role of reperfusion injury in the early hazard of thrombolysis in humans may now be possible using myocardial contrast perfusion or cardiac magnetic resonance imaging or must await demonstration of clinical benefit by pharmacological interventions that have previously limited reperfusion injury in experimental models.

**Alternative Pathways of Myocardial Salvage**

A recent study from Japan has suggested that substantial myocardial salvage during acute infarction is not necessarily dependent on restoration of infarct vessel patency. Yanagisawa-Miwa et al\textsuperscript{124} administered a single intracoronary bolus of human recombinant basic fibroblast growth factor (bFGF) or placebo to dogs after experimental occlusion of the left anterior descending coronary artery; angiographic and pathological examination 30 days later demonstrated a fourfold decrease in infarct size and a doubling of left ventricular ejection fraction among bFGF-treated animals compared with controls, despite persistent occlusion of the infarct-related artery. Myocardial salvage was attributed to the angiogenic action of bFGF, which stimulated growth of collateral arterioles and capillaries from the adjacent circumflex coronary artery to ischemic myocardium in the distribution of the occluded vessel. This provocative report provides the first preliminary evidence that salvage of myocardium may be accomplished by mechanisms other than epicardial artery recanalization, raising the prospect of an entirely new class of adjunctive pharmacological interventions for acute myocardial infarction.

**Conclusions**

With the state-of-the-art thrombolytic therapy in 1993, only the unusual patient achieves the elusive goal of optimal reperfusion for acute myocardial infarction. “Illusion” is defined by the American Heritage Dictionary as the “…state or condition of being deceived by erroneous perceptions or beliefs,” and an “illusion of reperfusion” has indeed been created by the imperfect barometer of the static 90-minute angiographic view of coronary patency. In fact, clinical and experimental data clearly demonstrate a sobering deterioration of benefit derived from coronary recanalization that is not early, not rapid, with incomplete reflow, with critical residual stenoses, unaccompanied by tissue-level reperfusion, diminished by cyclical patenty or frank reocclusion, or possibly negated by reperfusion injury. The “open vessel” hypothesis that prognosis is improved by restoration of infarct artery patency has not and cannot truly be tested until optimal reperfusion becomes a practical reality.

An appreciation of the limitations of current thrombolytic strategies, coupled with the development of novel pharmacological agents and of new techniques for assessing the adequacy of myocardial perfusion, has created a window of opportunity to enhance the quality of reperfusion therapy for acute myocardial infarction. Although various combinations of thrombolytic and adjunctive agents may be targeted to the specific barriers to optimal reperfusion, the pathogenesis and cause-and-effect relations among poor myocardial salvage and the phenomena of intermittent patency, TIMI 2 flow, and no-reflow also must be explored. Rather than complacency with current treatment regimens and approaches, expectations for clinical benefit from reperfusion therapy should be upgraded. By the end of this second decade of thrombolytic therapy, mortality for eligible patients with acute myocardial infarction may once again be halved if the inadequacies of present methodologies can be surmounted.

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Illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction?
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