Identification and Management of Patients with Failed Thrombolysis after Acute Myocardial Infarction

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Clinical outcome after thrombolytic therapy for acute myocardial infarction is closely related to restoration of flow in the infarct-related artery. Because thrombolytic therapy does not achieve coronary artery patency in 15% to 50% of patients, the early identification and treatment of patients with failed thrombolysis may lead to improved clinical outcomes. Unfortunately, the noninvasive identification of patients with failed thrombolysis continues to be problematic. Reduction in chest pain, decrease in ST-segment elevation, and presence of arrhythmias, although suggestive of reperfusion, are not diagnostic. Biochemical markers may hold promise for improved early identification of failed thrombolysis. In the setting of failed thrombolysis, clinical outcome may be improved by "rescue" percutaneous transluminal coronary angioplasty (PTCA) of the infarct-related artery. Several studies suggest that successful rescue PTCA is associated with high technical success rates and improved clinical outcomes. However, these same studies also suggest that patients with failed rescue PTCA may have higher mortality rates than patients who are treated conservatively. On the basis of current data, if failed thrombolysis is suspected, rescue PTCA should be considered, particularly in patients with anterior myocardial infarction and early presentation. Further investigations are needed to study the role of adjunctive methods such as stenting, glycoprotein IIb/IIIa inhibition, and intra-aortic balloon counterpulsation in the setting of rescue PTCA. Because of the relative lack of prospective data in this area, additional studies are urgently needed to help improve the ability to identify and manage patients with failed thrombolysis after acute myocardial infarction.

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Clinical outcome after thrombolytic therapy for acute myocardial infarction is strongly associated with patency of the infarct-related artery (1–4). Unfortunately, thrombolytic therapy fails to achieve patency of the infarct-related artery in 15% to 50% of patients (1, 5–7). Percutaneous transluminal coronary angioplasty (PTCA) of persistently occluded infarct-related arteries (rescue PTCA) may improve outcome in patients with failed thrombolysis after acute myocardial infarction (8). This article reviews the current literature on the identification and management of patients with failed thrombolysis. Particular attention is paid to the noninvasive identification of reperfusion as well as the evidence for and against the use of rescue PTCA. Potential advances in the management of patients with failed thrombolysis are also reviewed.

Data were obtained from a search of the MEDLINE database (January 1984 to June 1999) to identify English-language articles related to the identification and management of patients with failed thrombolysis after acute myocardial infarction. Subject headings used were *thrombolytic therapy*, *angioplasty*, *myocardial infarction*, *myocardial reperfusion*, *intraaortic balloon counterpulsation*, *coronary stenting*, *glycoprotein IIb/IIIa inhibitors*, and *coronary artery bypass graft surgery* (CABG), and the textwords *rescue* and *salvage*. The bibliographies of identified articles were also evaluated for possible additional sources of information. Results from randomized trials were emphasized, but nonrandomized trials and case series were examined as well. Although every effort was made to identify all studies pertinent to this area, this review was not intended to be systematic or exhaustive in scope.

Relation between Patency of the Infarct-Related Artery and Mortality

Data from several trials have established the relation between the angiographic flow pattern in the infarct-related artery at 90 minutes after the initiation of thrombolytic therapy and subsequent mortality. The Thrombolysis in Myocardial Infarction (TIMI) Study Group defined a coronary perfusion grading system for use in the TIMI I trial that has

Table 1. Thrombolysis in Myocardial Infarction Flow and Mortality after Acute Myocardial Infarction*

Study (Reference)	Time to Angiography	Patients	Mortality		
			TIMI 0/1 Flow	TIMI 2 Flow	TIMI 3 Flow
		n	←—— % ——→		
Karagounis et al. [TEAM-2] (3)	90–240 min	359	10	7	5
Anderson et al. [TEAM-3] (10)	18–24 h	298	5	5	3
Vogt et al. (2)	90 min	907	7.1	6.6	2.7
Ross et al. [GUSTO] (1)	90 min	1167	8.9	7.4	4.4
Lincoff et al. [TAMI] (4)	90 min	1229	10.1	6.1	4.4
Pooled data (95% CI)		3960	8.9 (7.2–10.6)	6.7 (4.9–8.5)	3.8 (3.0–4.6)

* GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction; TEAM = Thrombolytic Trial of Eminase in Acute Myocardial Infarction; TIMI = Thrombolysis in Myocardial Infarction. Reprinted from *The American Journal of Cardiology*, Volume 75, Lincoff et al., copyright 1995, with permission from Excerpta Medica, Inc. (reference 4).

subsequently been used by many other investigators (9). According to this system, TIMI 0 flow represents complete coronary occlusion, TIMI 1 flow indicates some penetration of obstruction by the contrast but no perfusion of the distal coronary bed, TIMI 2 flow indicates perfusion of the entire coronary artery but with delayed flow, and TIMI 3 denotes full perfusion with normal flow. Lincoff and colleagues (4) reported the association between mortality rates and TIMI flow at 90 minutes in 1229 patients who had had myocardial infarction and participated in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials. A pooled analysis of similar data from other published trials was performed, and a consistent mortality gradient—improved survival with improved TIMI flow—is evident (1–4, 10) (**Table 1**). Given that thrombolysis achieves TIMI 3 flow in less than 60% of infarct-related arteries (1–3), these findings have been used to support the study of aggressive management strategies to improve coronary patency among patients with failed thrombolysis. Before exploring these management strategies, however, it is necessary to assess our ability to accurately identify patients with failed thrombolysis.

Identification of Failed Thrombolysis

The identification of patients with failed thrombolysis after acute myocardial infarction is problematic. Reduction in chest pain, decrease in ST-segment elevation, and presence of arrhythmias, although suggestive of reperfusion, are not diagnostic. Califf and colleagues (11), for example, studied 386 patients who underwent angiography 90 minutes after the initiation of treatment with tissue plasminogen activator (tPA) for acute myocardial infarction. These investigators found that 96% of patients who had complete resolution of ST-segment elevation had coronary patency but that ST-segment elevation completely resolved in only 6% of patients. Among patients with partial improvement in ST-segment elevation, 84% had coronary patency; however, these findings occurred in only 38% of patients. Unchanged ST-segment elevation was associated with a 63% patency rate, unchanged or worsened chest pain was associated with a 60% patency rate, and arrhythmias were not closely associated with coronary patency. Of patients with no ST-segment or symptom resolution, 56% were still found to have patent arteries at 90 minutes, demonstrating the difficulty of clinical determination of reperfusion. Other studies have documented varying correlations between electrocardiographic changes and reperfusion status (12–16). Results from one study even indicated that additional ST-segment elevation in the first hour after thrombolytic therapy may suggest reperfusion and a favorable outcome in patients with anterior infarctions (17).

In addition to symptoms and electrocardiographic changes, biochemical markers of reperfusion have also been examined. In a study of 38 patients with acute myocardial infarction who received various reperfusion therapies, Abe and coworkers (18) found that an increase in creatine kinase–MB fraction of 25 mU/mL or an increase in troponin T levels of 0.50 μg/mL 60 minutes after initiation of thrombolysis identified reperfusion with a sensitivity of 83% and a specificity of 100%. Stewart and associates (19) also studied creatine kinase–MB fraction and troponin T levels in 105 patients. These authors found that a fivefold increase in creatine kinase–MB fraction at 90 minutes had a sensitivity of 82% and a specificity of 66% for TIMI 3 flow; respective values associated with a fivefold increase in troponin T levels were 82% and 67% (19). In addition, several studies suggest that myoglobin may be a reliable marker of successful reperfusion, with sensitivities of 84% to 85%, specificities of 73% to 100%, and accuracies of 88% to 95% (19–21).

Although the use of biochemical markers to identify reperfusion is appealing, these markers have not proved to be as reliable in prospective testing. Laperche and colleagues (22), for the Prospective Evaluation of Reperfusion Markers (PERM) study group, examined a range of previously proposed curve slopes and thresholds of biochemical markers (myoglobin, troponin T, creatine kinase, creatine kinase–MB, and creatine kinase–MM) in 97 patients with acute myocardial infarction receiving thrombolytic therapy. These investigators found that the previously proposed diagnostic thresholds performed less well than in the original studies. Thus, the above studies demonstrate that the clinical identification of failed thrombolysis after acute myocardial infarction continues to be difficult.

Routine Angiography and Percutaneous Transluminal Coronary Angioplasty after Thrombolysis

Because of the difficulty in identifying patients with failed thrombolysis, one possible management strategy is the routine use of angiography and PTCA in all patients receiving thrombolytic therapy. Several early randomized trials studied this strategy. In the TAMI I trial, 197 patients with TIMI 2 or 3 flow of the infarct-related artery were randomly assigned to undergo immediate PTCA or elective PTCA at 7 to 10 days. No difference in mortality rates or left ventricular function was noted between these two strategies (23). The European Cooperative Study Group for recombinant tPA randomly assigned 367 patients who received tPA within 5 hours after acute myocardial infarction to one of two strategies: 1) coronary angiography and immediate PTCA or 2) conservative medical therapy. This trial was prematurely terminated after the investigators noted that 14-day mortality was 7% in the invasive therapy group and 3% in the conservative therapy group (24). In the TIMI II-A trial, 586 patients who received tPA within 4 hours of acute myocardial infarction were randomly assigned to one of three treatment strategies: 1) immediate angiography and PTCA if feasible, 2) angiography and PTCA delayed by 18 to 48 hours, or 3) angiography and PTCA only if ischemia recurred or was evident on predischarge stress testing (25). In this trial, rates of death, reinfarction, and rehospitalization were similar at 1 year among all three groups, and patients receiving the delayed invasive or conservative strategy had less need for blood transfusions or CABG than did patients receiving the immediate invasive strategy. Thus, early studies suggest that the routine use of immediate angiography and PTCA in all patients after thrombolytic therapy does not improve outcome. However, these studies did not specifically address the selective use of angiography and PTCA in the subset of patients with failed thrombolysis.

Rescue Percutaneous Transluminal Coronary Angioplasty after Failed Thrombolysis

Only two randomized trials have specifically studied the use of rescue PTCA, but data from other trials, databases, and case series have also been analyzed in an attempt to study the possible benefit of this procedure (**Table 2**). Belenkie and colleagues (27) studied 28 patients with a persistently occluded infarct-related artery after thrombolytic therapy more than 3 hours after the onset of acute myocardial infarction; patients were randomly assigned to rescue PTCA ($n = 16$) or conservative treatment ($n = 12$). There was a nonsignificant trend for lower

Table 2. Reported Success Rates and Mortality in Studies of Rescue Percutaneous Transluminal Coronary Angioplasty*

Study (Reference)	Year	Patients Having Rescue PTCA	Controls†	Success Rate‡	Mortality among Patients Having Rescue PTCA	Mortality among Controls	*P* Value
		n		*n (%)*	*%*		
Califf et al. [TAMI 5] (26)	1991	52	17	43 (82.7)	NG	NG	NG
Belenkie et al. (27)§	1992	16	12	13 (81.3)	6.3	33.3	0.13
Ellis et al. (28)	1992	560	–	451 (80.5)	10.6	–	–
Steg et al. [CORAMI] (29)	1994	72	–	65 (90.3)	4.2	–	–
Ellis et al. [RESCUE] (30)§	1994	78	73	72 (92.3)	5.1	9.6	0.18
McKendall et al. [TIMI I/II database] (31)	1995	33	100	27 (81.8)	12.1	7.0	NS
Gibson et al. [TIMI 4] (32)	1997	58	37	52 (89.7)	12.1	10.8	NG
Ross et al. [GUSTO-1 angiographic substudy] (33)	1998	198	266	175 (88.4)	11.1	7.9	NG
Gruberg et al. (34)	1998	21	3	20 (95.2)	4.3	0.0	NG
Garot et al. (35)‖	1998	81	–	77 (95.1)	5.0	–	–
Juliard et al. (36)‖	1999	50	–	47 (94.0)	4.0	–	–

* CORAMI = Cohort of Rescue Angioplasty in Myocardial Infarction; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; NG = not given; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; RESCUE = Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction; TIMI = Thrombolysis in Myocardial Infarction.
† Controls were considered to be patients with TIMI 0 or 1 flow in infarct-related arteries who were managed conservatively.
‡ Successful rescue PTCA was defined in most series as restoration of TIMI 2 or 3 flow with less than 50% residual stenosis.
§ Randomized trial.
‖ Some overlap exists between the patients included in these two papers.

in-hospital mortality rates in the rescue PTCA group (6.3% compared with 33.3%; $P = 0.13$). The investigators concluded that although the number of randomly assigned patients was small, the trend toward lower mortality rates supports the hypothesis that rescue PTCA may be beneficial.

The Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints (RESCUE) study is the larger of the two trials that have specifically addressed rescue PTCA (30). The RESCUE study sample consisted of 151 patients with first anterior myocardial infarctions who were treated with thrombolytic therapy and were shown to have an occluded infarct-related artery (TIMI 0 or 1 flow) within 8 hours of pain onset. These patients were randomly assigned to undergo rescue PTCA ($n = 78$) or conservative medical management ($n = 73$). Ellis and coworkers (28) reported that recruitment of centers to participate in this trial was difficult because many investigators believed it would be unethical to withhold treatment in this setting. The RESCUE trial investigators reported a technical success rate of 92.3% (defined in most series as final TIMI flow grade of 2 or 3 and residual stenosis $< 50\%$), higher than that reported in previous series. Resting ejection fraction did not differ between groups at 30 days, although the exercise ejection fraction at 30 days was higher in the rescue PTCA group (43% in the rescue PTCA group compared with 38% in the conservative group; $P = 0.04$). There were also trends toward lower 30-day mortality (5.1% compared with 9.6%; $P = 0.18$) and less severe congestive heart failure (New York Heart Association functional class III or IV) (1.3% compared with 7.0%; $P = 0.11$) in the rescue PTCA group. A statistically significant benefit was reported in the rescue PTCA group for the combined outcome of death or severe congestive heart failure at 30 days (6.4% compared with 16.6%; $P = 0.05$).

In addition to the two randomized trials that have specifically addressed rescue PTCA, investigators have examined the results of several other studies in which non–randomly assigned subgroups of patients underwent rescue PTCA. In the TAMI 5 trial, 575 patients with acute myocardial infarction were randomly assigned in a 3×2 factorial design (26). Patients were assigned to one of three thrombolytic strategies (tPA alone, urokinase alone, or both) and to one of two catheterization strategies: 1) an aggressive strategy in which angiography was performed at 90 minutes and rescue PTCA was attempted only for TIMI 0 or 1 flow in the infarct-related artery ($n = 287$) or 2) a conservative strategy in which predischarge angiography was done at 5 to 10 days after admission ($n = 288$). In-hospital event rates were low, but freedom from a composite end point of adverse outcomes (death, stroke, reinfarction, reocclusion, heart failure, or recurrent ischemia) favored the aggressive strategy (67% of patients in the aggressive group had none of these events compared with 55% of patients in the conservative group; $P = 0.004$). However, the major effect of the aggressive strategy was reduction of the incidence of severe recurrent ischemia (25% compared with 35%); mortality rates were similar. Furthermore, only 69 patients in the aggressive treatment group had TIMI 0 or 1 flow, and only 52 of these patients actually underwent rescue PTCA. Thus, this study did not directly address the issue of rescue PTCA.

Not all studies examining the use of rescue PTCA have reported positive results. The TIMI 4 investigators studied outcomes in the subgroup of patients who underwent rescue PTCA among a total of 402 patients randomly assigned to receive one of three thrombolytic strategies (tPA, anistreplase, or both) (32). Patients found to have TIMI 0 or 1 flow in infarct-related arteries at 90 minutes were assigned to rescue PTCA ($n = 58$) or conservative management ($n = 37$) in a nonrandomized manner at the discretion of the operator. Although patients undergoing rescue PTCA had improved TIMI flow immediately after the procedure, by 18 to 36 hours the rates of TIMI 2 or 3 flow did not differ between patients undergoing rescue PTCA and those undergoing conservative treatment (80% compared with 71%; $P > 0.05$). In addition, no mortality benefit was noted, and both groups had a 35% incidence of a combined adverse outcome of death, severe congestive heart failure, shock, recurrent myocardial infarction, or ejection fraction less than 40%.

In addition to the above studies, several case series and nonrandomized studies have examined rescue PTCA (28, 29, 31, 33–36) (**Table 2**). The case series suggest that technical success rates are improving with rescue PTCA. Despite improving success rates, however, there is a trend for higher mortality rates among patients undergoing rescue PTCA compared with patients who did not undergo rescue PTCA (31–34). These results are most likely due to selection bias, with sicker patients having undergone rescue PTCA and more stable patients having received conservative therapy. In contrast to these nonrandomized studies, the results of the two randomized trials suggest that rescue PTCA may improve outcome, particularly in patients presenting within 8 hours of symptom onset with an anterior myocardial infarction (27, 30).

Several limitations of the studies that examined rescue PTCA should be noted. First, most studies accepted TIMI 2 flow and TIMI 3 flow as indicators of successful thrombolysis. In the studies of rescue PTCA performed to date, rescue PTCA was done only in patients with TIMI 0 or 1 flow and was not done in those with TIMI 2 or 3 flow. However, mortality rates associated with TIMI 2 and TIMI 3 flow are not equivalent (**Table 1**), and attempting rescue PTCA of infarct-related arteries with TIMI 2 flow may also improve outcome. For this reason, previous studies may have underestimated the numbers of patients who might benefit from rescue PTCA. The RESCUE II trial is enrolling patients to examine this issue (37), and the results of this trial may increase the number of patients who may be eligible for rescue PTCA.

A second limitation is that rescue PTCA has been examined only in a small number of patients in a small number of studies. The RESCUE trial, for example, examined only 151 patients, and the composite end point of death and severe congestive heart failure barely achieved statistical significance. A larger study may have shown a statistically stronger benefit in favor of rescue PTCA in this presumably higher-risk subset of patients with anterior myocardial infarctions. However, given the paucity of patients randomly assigned in trials of rescue PTCA, it is difficult to make firm recommendations about which patients might benefit from this therapy.

Finally, the few studies that examined rescue PTCA were performed before the common use of adjunctive therapies, such as stenting and glycoprotein IIb/IIIa inhibition. In addition, previous studies may have underused intra-aortic balloon counterpulsation. Thus, they may have underestimated the potential benefit of rescue PTCA.

Technical Success Rates and Potential Complications of Rescue Percutaneous Transluminal Coronary Angioplasty

Success rates of rescue PTCA in early series were approximately 80%, but more recent studies report rates ranging from 88% to 95% (**Table 2**). These results suggest an improving trend in the technical success rates of rescue PTCA. It has been suggested that success rates in rescue PTCA may be affected by the type of thrombolytic agent used. A meta-analysis of early studies suggested better success and lower reocclusion rates when rescue PTCA followed thrombolysis with non–fibrin-specific agents, such as streptokinase and urokinase (28). However, this finding was not supported by an analysis of patients who underwent rescue PTCA in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO)-1 angiographic substudy; similar success and reocclusion rates were seen among each thrombolytic strategy used (streptokinase alone, tPA alone, or both) (33). Thus, the data from the GUSTO-1 trial suggest that success is not affected by the type of thrombolytic agent used.

Decreasing complication rates associated with rescue PTCA are also being reported. In the TIMI II-A trial, transfusion requirements were much higher in the group that had immediate invasive PTCA than in the conservative therapy group (13.8% compared with 2.0%; $P < 0.001$) (25). The Streptokinase Angioplasty Myocardial Infarction trial studied 122 patients with myocardial infarction who were randomly assigned to receive streptokinase or placebo before immediate PTCA (38). A significantly greater transfusion requirement was reported in the group that received thrombolysis before PTCA (39% compared with 8%; $P < 0.001$), as was a greater need for CABG (10.3% compared with 1.6%; $P = 0.03$). More recent trials have not shown these higher complication rates, perhaps partially because less intensive anticoagulation regimens were used. In the TAMI 5 trial (26), no significant increase in the use of blood products was noted between the aggressive and conservative strategies, and the GUSTO-1 angiographic substudy (33) showed no excessive bleeding and a low rate (1%) of emergency CABG among the patients undergoing rescue PTCA.

A disturbing trend in almost all series is mortality rates greater than 30% among patients in whom attempts at rescue PTCA failed (27, 31–33, 39, 40). These rates are substantially higher than the 7% to 11% mortality rates seen in patients with occluded infarct-related arteries who are treated conservatively (2, 30, 32). It has been hypothesized that the stress of PTCA itself, anemia due to blood loss, or contrast-induced negative inotropic effects and hypotension may contribute to this increased mortality (39). Trauma that results from attempted PTCA and prevents delayed spontaneous reperfusion has also been proposed as a contributing factor (39). However, it has been noted that patients who die after unsuccessful rescue PTCA often have poor prognoses before the procedure. In the GUSTO-1 angiographic substudy, for example, 5 of the 7 patients who died after failure of rescue PTCA had been in cardiogenic shock (33). In an analysis of TAMI study patients in whom rescue PTCA failed, 7 of the 9 patients who died after failure of rescue PTCA had developed cardiogenic shock before or during angiography (39). Thus, failed rescue PTCA itself may not be responsible for the high mortality rates observed. These patients were probably sicker and had poorer prognoses to begin with.

Rescue Percutaneous Transluminal Coronary Angioplasty Combined with Other Treatments

Because rescue PTCA has been examined in a small number of studies, use of adjunctive methods in this setting has largely been governed by inference from studies of primary PTCA. Until recently, for example, acute myocardial infarction was considered a contraindication to the use of coronary stenting because of the risk for stent thrombosis. However, improved clinical outcomes have recently been reported with primary stenting (as opposed to primary PTCA without stenting) in several small trials (41–45). The Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial (45), for example, randomly assigned 150 patients to undergo primary PTCA or to primary PTCA with stenting. In this study, the stented group had a significantly lower rate of the composite primary end point of death, reinfarction, or need for revascularization (9% compared with 28%; P = 0.003). The Primary Angioplasty in Myocardial Infarction (PAMI) Stent Pilot trial (46) studied the feasibility of routine primary stenting in 240 patients with acute myocardial infarction. The investigators reported a 98% success rate and an in-hospital mortality rate of only 0.8%. These results support the feasibility, safety, and possible superiority of PTCA with stenting in the setting of acute myocardial infarction.

Although stenting during primary PTCA is becoming increasingly common, the role of stenting in rescue PTCA is still unclear. Little research on this question has been reported in the literature. Rodriguez and colleagues (47) reported the results of stenting in 30 patients with acute myocardial infarction, including 13 who underwent rescue PTCA. Stent deployment was successful in all 13 patients, and the only in-hospital death occurred in 1 of the patients having rescue PTCA who was in cardiogenic shock. Himbert and coworkers (48) reported the outcome of bailout coronary stenting in 50 patients with acute myocardial infarction, including 9 patients undergoing rescue PTCA. Stenting was performed successfully in 49 patients, and only 1 patient had acute closure. Thus, the few data available suggest that stenting is feasible in the setting of rescue PTCA. However, additional studies in this area are clearly indicated.

The use of platelet glycoprotein IIb/IIIa inhibition has also been proposed as a means of improving outcomes among patients undergoing rescue PTCA. Lefkovits and colleagues (49) reported results among 66 patients who underwent primary (n = 44) or rescue (n = 22) PTCA in the Evaluation of c7E3 (abciximab) to Prevent Ischemic Complications (EPIC) trial. Outcomes among the patients undergoing rescue PTCA were not analyzed separately because the outcomes in both groups were similar. The investigators reported a significant reduction in the primary composite end point (death, reinfarction, emergency CABG, or repeated emergency angiography) among patients in the abciximab bolus and infusion group compared with patients in the placebo group at both 30 days (4.5% compared with 26.1%; P = 0.06) and 6 months (4.5% compared with 47.8%; P = 0.002). These results provide initial evidence for the use of glycoprotein IIb/IIIa inhibition during PTCA for acute myocardial infarction and perhaps for rescue PTCA as well.

Nevertheless, because few data are available in this area, the use of glycoprotein IIb/IIIa inhibition in the setting of rescue PTCA should be approached with caution. All patients undergoing rescue PTCA have received full-dose thrombolytic therapy; thus, the addition of glycoprotein IIb/IIIa inhibitors may lead to major bleeding complications. In Lefkovits and colleagues' series, for example, 9 of the 13 major bleeding episodes occurred in patients who underwent rescue PTCA, all of whom had received thrombolytic therapy within the previous 12 hours (49). Furthermore, current trials are examining whether the combination of thrombolytic therapy and glycoprotein IIb/IIIa inhibition in the setting of acute myocardial infarction will lead to improved patency rates and thus decrease the need for rescue PTCA. Clearly, we have little information on the use of glycoprotein IIb/IIIa inhibition in the setting of rescue PTCA; additional studies in this area are needed.

The use of intra-aortic balloon counterpulsation has also been suggested for improving outcome in rescue PTCA. Nonrandomized studies have indicated that intra-aortic balloon counterpulsation may decrease reocclusion (50, 51) and improve left ventricular function (51) after reperfusion therapy in acute myocardial infarction. However, the results from randomized trials have been conflicting. The Randomized IABP Study Group randomly assigned 182 patients sent for emergency cardiac catheterization within 24 hours of acute myocardial infarction, including 51 patients undergoing rescue PTCA, to the use of intra-aortic balloon counterpulsation or standard care (52). The investigators reported a significantly lower rate of a composite end point of death, stroke, reinfarction, emergency PTCA or CABG, or recurrent ischemia in the intra-aortic balloon group (13% compared with 24%; P = 0.04). In contrast, the PAMI-II investigators randomly assigned 437 high-risk patients who underwent primary PTCA to undergo intra-aortic balloon counterpulsation or traditional care and showed no benefit in clinical outcomes (53). The intra-aortic balloon counterpulsation strategy, in comparison with standard therapy, did not reduce the rate of infarct-related reocclusion (6.7% compared with 5.5%; $P > 0.2$), reinfarction (6.2% compared with 8.0%; $P > 0.2$), or in-hospital death (4.3% compared with 3.1%; $P > 0.2$) and was associated with a higher incidence of stroke (2.4% compared with 0.0%; $P = 0.03$). In addition, use of intra-aortic balloon counterpulsation did not result in enhanced myocardial recovery; no difference was found in resting and exercise left ventricular ejection fractions measured 6 weeks after discharge.

Only one study specifically addressed the use of intra-aortic balloon counterpulsation in the setting of rescue PTCA. Ishihara and associates (54) nonrandomly assigned the first 20 consecutive patients with anterior myocardial infarctions who underwent rescue PTCA to standard care and the next 40 similar patients to the use of intra-aortic balloon counterpulsation (54). The patients treated with intra-aortic balloon counterpulsation had significantly decreased reocclusion rates (2.5% compared with 25.0%; $P < 0.05$), better evolution in predischarge mean ejection fraction (6.8–percentage point increase compared with 2.0–percentage point decrease; $P < 0.05$), and a nonsignificant trend toward decreased mortality (5.0% compared with 20.0%; P value not significant). These results suggest that intra-aortic balloon counterpulsation may be helpful in patients undergoing rescue PTCA. Nevertheless, the negative results of the PAMI II investigators suggest that further studies are warranted.

Surgical Intervention and Medical Management

Alternative strategies for the management of patients with failed thrombolysis include surgical intervention and medical therapy alone. Some studies have documented the feasibility of emergency CABG in the setting of acute myocardial infarction (55–57). Emergency CABG performed within 6 hours of the onset of symptoms may improve outcomes, as demonstrated by DeWood and colleagues (57) in their analysis of 440 patients undergoing emergency CABG for acute transmural myocardial infarction in the prethrombolytic era. Significantly lower in-hospital mortality rates (3.8% compared with 8.0%; $P = 0.05$) and 10-year mortality rates (8.2% compared with 21.0%; $P < 0.01$) were noted in the group undergoing early CABG.

For most patients with failed thrombolysis, however, the high risk for bleeding complications associated with emergency CABG (55, 58) makes this strategy unattractive. Nevertheless, for selected patients, this approach may be beneficial. One example would be a patient with failed thrombolysis who is found to have high-grade left main coronary artery stenosis and a freshly occluded proximal left anterior descending coronary artery. Because of the size and location of the myocardial infarction and the fact that the left main lesion makes rescue PTCA a high-risk procedure, this patient might benefit from emergency CABG. Another situation would be one in which the patient is in cardiogenic shock but rescue PTCA is technically not possible. However, given the additional risk for bleeding in the setting of failed thrombolysis, emergency CABG should be reserved for selected high-risk patients.

Another possible management strategy is medical therapy alone. If the patient is hemodynamically stable with a small myocardial infarction, medical therapy alone is likely to yield a good clinical outcome. Treatment should include such agents as heparin, aspirin, β-blockers, nitrates, and angiotensin-converting enzyme inhibitors. For patients with hemodynamic instability or large-territory myocardial infarctions, the use of glycoprotein IIb/IIIa inhibition should be considered to enhance the likelihood of spontaneous reperfusion, and intra-aortic balloon counterpulsation should be considered to increase coronary perfusion pressure. Finally, a second attempt at thrombolytic therapy should be considered. Mounsey and colleagues (59) randomly assigned 37 patients who had acute myocardial infarction with less that 25% reduction in ST-segment elevation 90 minutes after streptokinase treatment to either tPA (100 mg delivered over a 3-hour period) or placebo. The group receiving rescue thrombolysis with tPA was found to have higher left ventricular ejection fractions (44% compared with 34%; $P = 0.04$). Although only small numbers of patients have received this treatment (59, 60), the repeated use of thrombolytic therapy may be useful in some instances.

Conclusion

Clinical outcomes among patients with acute myocardial infarction have been shown to be closely related to TIMI flow in the infarct-related artery. Because thrombolytic therapy does not achieve coronary artery patency in 15% to 50% of patients, the early identification and treatment of patients with failed thrombolysis may lead to improved clinical outcomes. Unfortunately, symptoms and electrocardiographic changes are only imprecise indicators of whether thrombolytic therapy has been successful. In contrast, biochemical markers hold promise for improved early identification of patients with failed thrombolysis. To date, the benefits of rescue PTCA have not been clearly established, and the available data suggest that failed rescue PTCA may be associated with higher mortality rates than conservative therapy is. Nevertheless, there was a trend toward improved outcomes in the two randomized trials of rescue PTCA. For this reason, if failure of thrombolysis is suspected, immediate angiography and res-

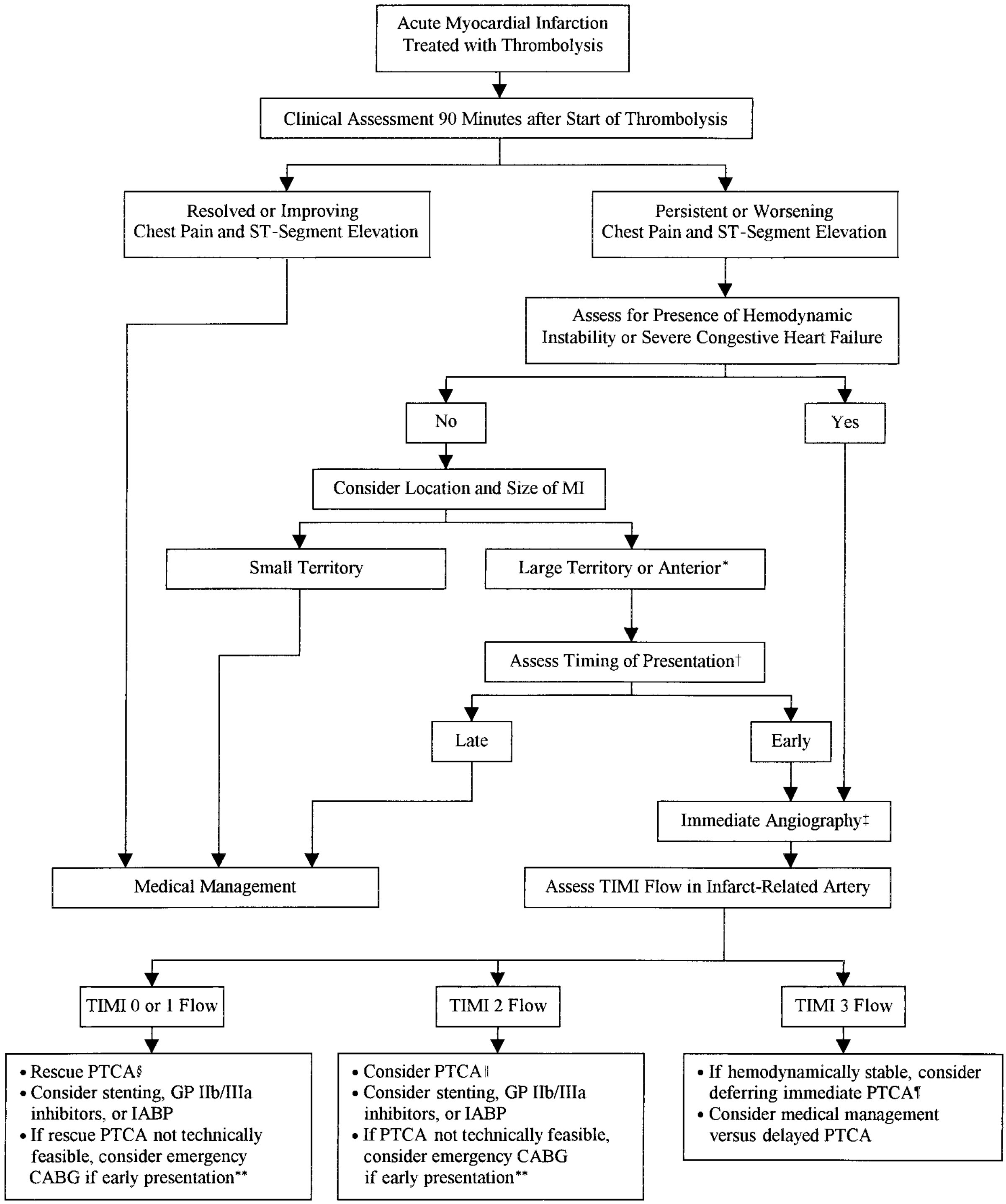

Figure. Approach to the patient with failed thrombolysis. Symptoms and electrocardiographic signs are poorly diagnostic of coronary artery patency and lead to an underestimate of the proportion of patients whose vessels have reperfused. Biochemical markers may increase the ability to identify failed thrombolysis but are not yet ready for routine clinical use. Patients with acute myocardial infarction (*MI*) and suspected failed thrombolysis should be considered for immediate angiography and possible rescue percutaneous transluminal coronary angioplasty (*PTCA*). Factors to be considered include hemodynamic instability, presence of severe congestive heart failure, size and location of the myocardial infarction, and timing of presentation. Only two randomized clinical trials have directly examined the use of rescue PTCA. The following footnotes indicate the evidence in support of aspects of the figure. *Data from the Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints (RESCUE) trial suggest that patients with anterior myocardial infarction and failed thrombolysis may benefit from rescue PTCA (30). †Patients in the RESCUE trial were randomly assigned within 8 hours of chest pain onset (30). ‡If access to a cardiac catheterization laboratory is not possible, repeated thrombolysis should be considered (59, 60). §To date, two randomized trials (27, 30) suggest clinical benefit of PTCA of infarct-related arteries with Thrombolysis in Myocardial Infarction (*TIMI*) 0 or 1 flow. ‖Few data are available concerning the possible benefits of immediate PTCA of infarct-related arteries with TIMI 2 flow. The ongoing RESCUE II trial will help answer this question. ¶The Thrombolysis and Angioplasty in Myocardial Infarction 1 trial suggests that clinical outcomes do not improve with immediate compared with delayed PTCA after successful thrombolysis. There was a trend toward a higher rate of emergency coronary artery bypass grafting (*CABG*) precipitated by acute vessel occlusion in patients undergoing immediate PTCA (23). **For patients with acute transmural myocardial infarction, DeWood and colleagues (57) found that early emergency CABG (within 6 hours of symptom onset) improved short- and long-term mortality compared with late surgery (performed more than 6 hours after symptom onset). However, this study was performed in the prethrombolytic era, and the additional bleeding risks posed by full-dose thrombolytics suggest that this therapy should be reserved for selected groups of high-risk patients. GP = glycoprotein; IABP = intra-aortic balloon counterpulsation.

cue PTCA should be considered; a suggested clinical approach is summarized in the **Figure**. Recent studies suggest that success rates and outcomes of rescue PTCA are improving, but additional studies are necessary before the final role of this therapy can be determined. The RESCUE II trial will address the issue of rescue PTCA in the setting of TIMI 2 flow and will provide much-needed guidance about the types of patients who should undergo rescue PTCA. Adjunctive methods, such as stenting, glycoprotein IIb/IIIa inhibition, and intra-aortic balloon counterpulsation, also need to be assessed in the setting of rescue PTCA. Because of the large number of patients who do not achieve coronary patency with thrombolytic therapy and the relative lack of prospective data in this area, additional studies are urgently needed to improve our ability to identify and manage patients with failed thrombolysis after acute myocardial infarction.

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