Evaluation of Combination Thrombolytic Therapy and Timing of Cardiac Catheterization in Acute Myocardial Infarction

Results of Thrombolysis and Angioplasty in Myocardial Infarction—Phase 5 Randomized Trial

Robert M. Califf, MD; Eric J. Topol, MD; Richard S. Stack, MD; Stephen G. Ellis, MD; Barry S. George, MD; Dean J. Kereiakes, MD; Joseph K. Samaha, MD; Seth J. Worley, MD; Jeffrey L. Anderson, MD; Lynn Harrelson-Woodlief, MS; Thomas C. Wall, MD; Harry R. Phillips III, MD; Charles W. Abbottsmith, MD; Richard J. Candela, MD; William H. Flanagan, MD; Arthur A. Sasahara, MD; Susan J. Mantell, RN; and Kerry L. Lee, PhD; for the TAMI Study Group

Recent trials of myocardial reperfusion using single-agent thrombolytic therapy and sequential cardiac catheterization have supported a conservative approach to the patient with acute myocardial infarction. To evaluate combination thrombolytic therapy and the role of a previously untested strategy for the aggressive use of cardiac catheterization, we performed a multicenter clinical trial with a \(3 \times 2\) factorial design in which 575 patients were randomly allocated to one of three drug regimens—tissue-type plasminogen activator (t-PA) (\(n=191\)), urokinase (\(n=190\)), or both (\(n=194\)) — and one of two catheterization strategies—immediate catheterization with angioplasty for failed thrombolysis (\(n=287\)) or deferred predischarge catheterization on days 5–10 (\(n=288\)). Patients with contraindications to thrombolytic therapy, cardiogenic shock, or age of more than 75 years were excluded. Global left ventricular ejection fraction was well preserved and almost identical at predischarge catheterization (54%), regardless of the catheterization or thrombolytic strategy used (\(p=0.98\)). Combination thrombolytic therapy was associated with a less complicated clinical course, most clearly documented by a lower rate of reocclusion (2%) compared with urokinase (7%) and t-PA (12%) (\(p=0.04\)) and a lower rate of recurrent ischemia (25%) compared with urokinase (35%) and t-PA (31%). When a composite clinical end point (e.g., death, stroke, reinfarction, reocclusion, heart failure, or recurrent ischemia) was examined, combination thrombolytic therapy was associated with greater freedom from any adverse event (68%) compared with either single agent (urokinase, 55%; t-PA, 60%) (\(p=0.04\)) and with a less complicated clinical course when the composite clinical end points were ranked according to clinical severity (\(p=0.024\)). Early patency rates were greater with combination therapy, although predischarge patency rates after considering interventions to maintain patency were similar among drug regimens. No difference in bleeding complication rates was observed with any thrombolytic regimen. The aggressive catheterization strategy led to an overall early patency rate of 96% and a predischarge patency rate of 94% compared with a 90% predischarge patency in the conservative strategy (\(p=0.065\)). The aggressive strategy improved regional wall motion in the infarct region (–2.16 SDs/chord) compared with deferred catheterization (–2.49 SDs/chord) (\(p=0.004\)). More patients treated with the aggressive strategy were free from adverse outcomes (67% versus 55% in the conservative strategy, \(p=0.004\), and the clinical course was less complicated when the adverse outcomes were ranked according to severity (\(p=0.016\)). No significant increase in use of blood products resulted from the aggressive strategy. We conclude that combination thrombolytic therapy is effective for achieving early and sustained infarct artery patency and for reducing the incidence of in-hospital complications. The aggressive catheterization strategy may result in improved clinical outcomes, although further studies using noninvasive methods to detect lack of reperfusion and applying angiography in selected patients appear warranted. (Circulation 1991;83:1543–1556)
Despite the substantial survival benefit that intravenous thrombolytic therapy has achieved in clinical trials of acute myocardial infarction,\textsuperscript{1,2} the preferred pharmacological regimen and the role of cardiac catheterization after thrombolytic therapy continue to be debated.\textsuperscript{3} Previous studies have demonstrated that tissue-type plasminogen activator (t-PA), a relatively fibrin-specific agent, achieves a high early patency rate compared with the nonspecific agents streptokinase and urokinase,\textsuperscript{4–6} but these differences in patency rates diminish or disappear during the 24-hour period after treatment.\textsuperscript{7} This eventual equivalence in patency appears to result from higher reocclusion rates with t-PA\textsuperscript{8–10} in addition to late opening of arteries and lower reocclusion rates with nonspecific agents.\textsuperscript{10,11} Furthermore, differences observed in left ventricular function and clinical outcomes among the different types of agents have been much smaller in magnitude than the differences in early patency rates.\textsuperscript{12–16} We hypothesized that the combination of t-PA and urokinase would be a preferable thrombolytic regimen because of the high early patency rate achieved with t-PA and the low reocclusion rate associated with the addition of urokinase. In a pilot study, the combination of t-PA and urokinase resulted in a low reocclusion rate and a less complicated clinical course without an increase in bleeding.\textsuperscript{17} Regardless of which thrombolytic regimen is used, the maximum early infarct vessel patency rate appears to be approximately 75–85\%. The use of rescue angioplasty for vessels that fail to reperfuse can increase the patency rate to more than 95\%.\textsuperscript{18–22} Three randomized clinical trials examining the use of early angiography or angioplasty after treatment with t-PA concluded that immediate use of angioplasty did not confer an advantage with regard to the standard clinical endpoints or left ventricular function.\textsuperscript{18,23,24} Each of these trials used a strategy in which angioplasty was attempted in vessels that were patent early after thrombolytic therapy. No previous trial has evaluated a clinical strategy of early diagnostic catheterization with use of angioplasty only in patients with failure of early thrombolysis. The purpose of the present trial was to evaluate combination thrombolytic therapy versus monotherapy and an aggressive versus deferred cardiac catheterization strategy.

**METHODS**

**Patient Population**

The trial was conducted at seven regional cardiac referral centers in collaboration with 29 community hospitals (see “Appendix”). The protocol was approved by the institutional review boards at all participating sites. Enrollment began on April 8, 1988, and ended on May 25, 1989. Inclusion criteria were 1) symptoms compatible with acute myocardial infarction of 6 hours duration or less accompanied by an electrocardiogram with more than 1 mm (0.1 mV) ST segment elevation in two or more contiguous leads; 2) age of less than 76 years; 3) no contraindication to thrombolytic intervention, including prior stroke or other known intracranial disease, recent trauma or surgery, refractory hypertension, active bleeding, or prolonged (more than 10 minutes) cardiopulmonary resuscitation; 4) no prior coronary artery bypass graft surgery; 5) no prior Q wave infarction in the same distribution as the current infarction; and 6) absence of cardiogenic shock as defined by systolic blood pressure of less than 80 mm Hg with vasopressor requirement.

**Randomization**

After giving informed consent, patients were randomly assigned to both a thrombolytic regimen and a catheterization strategy. Randomization was accomplished by telephone contact with a cardiologist or nurse at the Thrombolyis and Angioplasty in Myocardial Infarction (TAMI) Coordinating Center. A permuted block, randomized design stratified only by regional center was used. Patients were assigned to receive intravenous urokinase, t-PA, or both. Simultaneously, they were assigned to either the aggressive cardiac catheterization strategy or the elective procedure (performed before discharge).

Urokinase (Abbokinase, Abbott Labs., Chicago) was given as a 1.5-million-unit intravenous bolus followed by a 1.5-million-unit infusion over 90 minutes.\textsuperscript{6} t-PA (Activase, Genentech, South San Francisco, Calif.) was given as 60 mg in the first hour, with 6 mg as a bolus, and a 20-mg infusion every hour for the next 2 hours for a total dose of 100 mg. The combined therapy arm consisted of 1.5 million units urokinase over 60 minutes with 1 mg/kg t-PA (10% given as a bolus and a maximum dose of 90 mg) over 60 minutes. Combined thrombolytic therapy was given simultaneously via two separate intravenous lines.\textsuperscript{17}

The aggressive catheterization strategy mandated an effort to obtain an angiogram of the infarct vessel as close as possible to, but not before, 90 minutes from initiation of thrombolytic therapy. If pharmacological thrombolysis had failed in this strategy, rescue

---

See p 1818

From the Division of Cardiology (R.M.C., R.S.S., L.H.-W., T.C.W., H.R.P. III, S.J.M., K.L.L.), Department of Medicine, and Division of Biometry, Department of Community and Family Medicine, Duke University Medical Center, Durham, N.C., Division of Cardiology (E.J.T., S.G.E.), Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Mich., Riverside Methodist Hospital (B.S.G., R.J.C.), Columbus, Ohio, The Christ Hospital (D.J.K., C.W.A.), Cincinnati, Ohio, Baptist Memorial Hospital (J.K.S., W.H.F.), Memphis Tenn., Lancaster General Hospital (S.J.W.), Lancaster, Pa., and LDS Hospital (J.L.A.), Salt Lake City, Utah.

Supported by Abbott Laboratories, Chicago, research grant HS-05635 from the Agency for Health Care Policy and Research, Rockville, Md., and research grant HL-36587 from the National Heart, Lung, and Blood Institute, Bethesda, Md.

Address for reprints: Robert M. Califf, MD, Duke University Medical Center, Box 31123, Durham, NC 27710.

Received June 4, 1990; revision accepted January 3, 1991.
angioplasty was attempted if the vessel was considered suitable by the investigator. Thus, rescue angioplasty was attempted if Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow was present at acute cardiac catheterization, the vessel was of adequate caliber, and no contraindications were present, including left mainstem stenosis in patients with left coronary infarct vessel location or lack of adequate identification of the culprit coronary artery in the setting of multiple vessel occlusion. If the vessel was patent, no coronary angioplasty was attempted unless clear evidence of severe ongoing ischemia was present. Most often, vascular access was obtained via the right femoral artery without central venous puncture unless angioplasty was performed, the patient was hemodynamically compromised requiring Swan-Ganz catheterization, or temporary transvenous pacing was needed. Only 5F or 6F Judkins catheters were used to perform angiography unless severe tortuosity of the peripheral arteries was present.

The deferred cardiac catheterization strategy required catheterization between 5 and 10 days after admission. Patients were eligible for urgent catheterization if one of the following events occurred: 1) symptoms compatible with myocardial ischemia lasting more than 20 minutes despite standard nitrate therapy and accompanied by either new ST segment changes or T wave changes on the electrocardiogram or by new hypotension, pulmonary edema, or holosystolic murmur; or 2) new pump failure manifested by sustained hypotension (systolic blood pressure of less than 90 mm Hg for 1 hour) or requirement for inotropic support for 1 hour without an obvious noncardiac cause.

To measure the primary end point of the trial, an effort was made to perform repeat catheterization before discharge on all patients, including those in the aggressive strategy group and those in the elective strategy group who required catheterization within 5 days.

In-Hospital Management

All patients were treated with 325 mg aspirin/day orally after entry into the trial, with the first dose given as soon as possible. Heparin was started at the end of the thrombolytic therapy infusion at a dose of 1,000 units/hr and maintained for at least 48 hours with the dose adjusted to maintain the activated partial thromboplastin time between 1.5-fold and twofold that of baseline. In the aggressive strategy, an additional 5,000 units heparin was given when vascular access was obtained; if rescue angioplasty was attempted, at least 2,000–5,000 more units/hr were given during the procedure. Prophylactic lidocaine was used in most patients with adjustment for liver disease, age, and heart failure. Nitrates and angiotensin converting enzyme inhibitors were used as clinically indicated. Patients were not given β-blockers unless indicated for hypertension, arrhythmia, or refractory symptoms of ischemia to avoid a confounding effect of β-blockers on left ventricular function.

Diltiazem was used in a dosage of 30–60 mg t.i.d. throughout the hospitalization.

Bleeding complications were observed carefully throughout the hospitalization. According to the consensus of the investigators, the protocol allowed transfusion with packed red blood cells only if the hematocrit decreased to 22% or less or if hemodynamic instability or recurrent ischemia not responsive to crystalloid infusion occurred with clinical evidence of significant blood loss.

Evaluation of Outcome

Patients were followed by study nurses throughout the hospitalization. Clinical events were recorded on case report forms and verified by independent study monitors who were without knowledge of the clinicians caring for the patients. The occurrence of any neurological deficit prompted a neurological consultation and a computed tomography scan, as dictated by protocol.

Neurological events were reviewed by an independent committee to classify the type of event. Reinfarction was diagnosed when a second elevation in cardiac enzymes occurred over the previous baseline or when a definitive clinical event occurred in the absence of enzymes. Repeat cardiac enzymes were obtained whenever a clinical event occurred suggesting severe recurrent ischemia. Congestive heart failure was recorded when one of the following events was documented: pulmonary edema on chest radiograph, rales more than bibasilar, or requirement for inotropic support. Recurrent ischemia was defined as symptoms compatible with myocardial ischemia for more than 20 minutes associated with new ST segment or T wave changes on the electrocardiogram or the need for emergency revascularization before the catheterization between day 5 and day 10.

Other clinical variables and definitions have been reported.17–19 As a summary measure of overall patient risk, a modified “TIMI not low-risk” classification was devised.20 Patients were classified as not low risk if they had at least one of the following characteristics: age of more than 70 years, anterior infarction, atrial flutter or fibrillation, systolic blood pressure of less than 100 mm Hg and sinus tachycardia (rate more than 100), rales more than half way up the back, pulmonary edema, or previous infarction.

Bleeding complications were classified in several ways, as previously described.27 Admission and nadir hematocrits were recorded as well as all blood product use during the hospitalization. Spontaneous or puncture-related bleeding sites were observed by study nurses throughout the hospital course. We used an index to characterize the extent of blood loss as proposed by Landefeld and colleagues—change in hematocrit from admission to nadir divided by 3 plus number of units of packed red blood cells transfused.

Angiographic Core Laboratory

All angiograms were reviewed by the Core Laboratory, University of Michigan, Ann Arbor, Mich.
Acute and predischarge coronary angiograms and left ventriculograms were analyzed by investigators blinded to treatment assignment. Parameters measured included TIMI grade on first injection, TIMI grade on first injection after 90 minutes, TIMI grade and visual luminal diameter narrowing on the “final diagnostic angiogram,” visual luminal diameter narrowing of non–infarct-related coronary artery segments, global left ventricular ejection fraction determined by the area–length method, and regional left ventricular function determined by the method described by Sheehan et al.

Statistical Analysis

Statistical analysis was performed at the TAMI Coordinating Center, Duke University Medical Center, Durham, N.C. The patient enrollment planned for the study was 450 patients with technically adequate 5–10-day ventriculograms with equal allocations to each of the six combinations of drug regimen and angiographic strategy. This sample size was required to detect an effect of either treatment strategy (drug or catheterization) of four ejection fraction points with an SD of 11 ejection fraction points, a power of more than 0.80, and an α of 0.05. Based on previous TAMI trials, a satisfactory ventriculographic acquisition rate of 80% was projected, requiring a total enrollment of 550–575 patients.

The primary hypothesis of the trial was that the combination drug therapy and aggressive catheterization strategy would lead to better global left ventricular function as measured by ejection fraction. Analysis of this hypothesis was performed using two-way analysis of variance with drug regimen, angiographic strategy, and their interactions as effects. The analysis strategy proceeded along the following stages. First, the treatment groups were compared for any overall differences with a 5 df test. If evidence for any differences was found, tests for treatment interactions were then performed. These tests assessed whether differences among drug regimens depended on which angiographic strategy was used and whether differences among angiographic strategies depended on which drug regimens were used. If no interactions were found, the drug effects and angiographic effects (the “main” effects of the strategies) were quantified and tested.

To reduce the risk of spurious findings, statistical testing using the strategy outlined above was limited to the primary hypothesis and five secondary hypotheses specified in the design of the trial. The major secondary hypothesis was that the combination of drug therapy and aggressive catheterization would reduce adverse clinical outcomes combined into a composite clinical end point. This end point assigned a ranking to the worst event for each patient during the initial hospitalization using the following ordered levels: death, stroke, reinfarction, recurrent ischemia or heart failure, and none of the above. The ranking was based on a survey of the participating investigators and has subsequently been verified in a large independent sample of cardiovascular specialists. Treatment effects with respect to the composite clinical end point were assessed using ordinal logistic regression and the analysis strategy outlined above. Supporting analysis based on a simple dichotomy of whether any of the above clinical end points occurred was performed using binary logistic regression analysis. Other secondary end points tested included regional left ventricular function (infarct and noninfarct zones), infarct artery patency, and bleeding event rates.

For continuous end points (ventricular function and bleeding index), two-way analysis of variance was used. For comparison of follow-up patency rates, binary logistic regression was used. Among patients randomized to the aggressive catheterization strategy, acute patency rates and reocclusion rates among the drug groups were compared using conventional χ² analysis. All end points (primary and secondary) were examined according to the principle of intention to treat. For descriptive presentation of the data, continuous baseline and outcome variables were summarized using the mean and SD, whereas discrete variables were described in percentages. A safety and data monitoring board met after 200 and 400 patients had been enrolled in the trial. The board remained blinded to treatment groups and examined the data for safety issues only. Formal interim statistical analyses were not performed, and left ventricular function data were not available to the data monitoring board.

Results

Baseline Characteristics

Baseline clinical and angiographic characteristics at the time of first catheterization of the patients categorized by thrombolytic treatment and catheterization strategy are presented in Tables 1 and 2, respectively. Although a balance was achieved with regard to baseline characteristics according to drug therapy, patients randomly assigned to receive aggressive cardiac catheterization had higher risk profiles with regard to a predominance of left anterior descending coronary artery involvement, presence of multiple-vessel coronary disease, and prevalence of patients with non–low-risk characteristics. Otherwise, the study population reflected a distribution of risk factors and baseline characteristics similar to that observed in previous trials of thrombolytic therapy for acute myocardial infarction.

Infarct Artery Patency

TIMI grade values for the various treatment strategies over time are displayed in Table 3 for patients randomized to receive aggressive catheterization. Patients treated with urokinase had lower patency rates at initial angiography, whereas the combination treatment resulted in the highest patency rates. As time elapsed, the patency rates became more similar in all three drug strategies, particularly with contrast
injections. The minimal luminal diameter in patients with patent arteries was greatest in the combination group. The use of rescue angioplasty increased the patency rate to more than 90% at the time of leaving the catheterization laboratory in all of the aggressive catheterization groups.

Predischarge infarct artery patency values are given in Table 4. At the time of hospital discharge, patency rates were higher in patients treated with early catheterization, although patency rates in all groups exceeded 85%. The high late patency in the delayed catheterization group resulted in part from the use of angiography and angioplasty in patients with occluded infarct-related arteries when ongoing ischemia or hemodynamic dysfunction was present.

The use of rescue angioplasty in the aggressive arm as a treatment strategy allowed specific evaluation of the impact of this procedure on patency. Of 69 patients with occluded vessels at acute catheterization, 52 underwent rescue angioplasty, two immediately received emergency coronary artery bypass graft surgery, and 15 were treated conservatively because of anatomy unsuitable for angioplasty or insufficient myocardium at risk to merit the procedure in the judgment of the clinician. The median time to rescue angioplasty from symptom onset was

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. Baseline Catheterization Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

| t-PA, tissue-type plasminogen activator. |
| t-PA, tissue-type plasminogen activator. |
Final diagnostic angiogram (%)  
<table>
<thead>
<tr>
<th>TIMI grade 0 (%)</th>
<th>TIMI grade 1 (%)</th>
<th>TIMI grade 2 (%)</th>
<th>TIMI grade 3 (%)</th>
<th>TIMI grade 2 or 3* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>12</td>
<td>18</td>
<td>53</td>
<td>71</td>
</tr>
</tbody>
</table>

Final diagnostic angiogram (%)  
<table>
<thead>
<tr>
<th>TIMI grade 0 (%)</th>
<th>TIMI grade 1 (%)</th>
<th>TIMI grade 2 (%)</th>
<th>TIMI grade 3 (%)</th>
<th>TIMI grade 2 or 3† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>10</td>
<td>18</td>
<td>58</td>
<td>76</td>
</tr>
</tbody>
</table>

Reocclusion (n) (%)‡  
<table>
<thead>
<tr>
<th>t-PA (%)</th>
<th>Urokinase (%)</th>
<th>Combination (%)</th>
<th>Catheterization strategy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (11)</td>
<td>6 (7)</td>
<td>2 (2)</td>
<td></td>
</tr>
</tbody>
</table>

MINIMAL LUMINAL DIAMETER (mm)  
<table>
<thead>
<tr>
<th>t-PA</th>
<th>Urokinase</th>
<th>Combination</th>
<th>Catheterization strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72±0.47</td>
<td>0.61±0.54</td>
<td>0.77±0.59</td>
<td></td>
</tr>
</tbody>
</table>

LEGEND  
* p=0.135 (2 df) for any overall differences.  
† p=0.349 (2 df) for any overall differences.  
‡ p=0.04 (2 df) for any overall differences.

331 minutes (range, 192–606 minutes). The procedure was successful (50% or less residual stenosis) in 43 patients and established patency with more than 50% residual stenosis in three patients. In six patients, the artery remained occluded despite attempted angioplasty. Reocclusion occurred before hospital discharge in six of the patients with patency at the end of the initial rescue procedure. None of the patients treated with combination therapy undergoing successful rescue angioplasty experienced reocclusion during the hospital course.

**Left Ventricular Function**

As displayed in Table 5, the majority of patients had well-preserved left ventricular function. No significant differences were evident with regard to global left ventricular function for any treatment strategy (p=0.98). No differences in infarct zone regional function were found among drug strategies.

**TABLE 3.  Patency Rates—Aggressive Catheterization Strategy**

<table>
<thead>
<tr>
<th></th>
<th>t-PA (n=95)</th>
<th>Urokinase (n=95)</th>
<th>Combination (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 90° angiogram (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI grade 0</td>
<td>17</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>TIMI grade 1</td>
<td>12</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>TIMI grade 2</td>
<td>18</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>TIMI grade 3</td>
<td>53</td>
<td>38</td>
<td>59</td>
</tr>
<tr>
<td>TIMI grade 2 or 3*</td>
<td>71</td>
<td>62</td>
<td>76</td>
</tr>
</tbody>
</table>

**Clinical Outcomes**

With regard to frequently reported clinical outcomes, a trend in favor of combination therapy was observed for each end point (Table 6). Mortality and reinfarction rates were low in all groups. The major differences in outcome for pharmacological treatments were the lower rates of recurrent ischemia and reocclusion in patients treated with combination therapy.

When the composite clinical end point (e.g., death, stroke, reinfarction, heart failure, or recurrent ischemia) using the ordinal scale was evaluated, definitive evidence of an overall difference was found (p=0.013). Patients treated with the combination therapy (p=0.024) and aggressive catheterization (p=0.016) had a lower rate of events compared with those of patients receiving other drug and catheterization regimens, respectively. The highest rate of freedom from any event was observed in the group treated with both combination therapy and aggressive catheterization (72%), whereas the lowest rate of freedom from any event was observed in the group treated with urokinase without aggressive catheterization (46%). No treatment interactions were observed. When the same results were analyzed with any clinical event as the end point (without ranking them according to severity), the tests for overall effect (p=0.009), drug effect (p=0.04), and catheterization effect (p=0.003) all remained significant.

**Bleeding Complications**

The frequency and severity of bleeding complications were similar for all three drug regimens when surgical patients were excluded, except for the slightly higher rate of intracranial bleeding with monotherapy (Table 7). One of the episodes of intracranial hemorrhage with t-PA was unusual in that it occurred 13 days after treatment, while the patient was receiving heparin. The transfusion rates of the acute catheterization strategy were similar to those of the deferred catheterization approach. Similar results occurred when all patients were included. As evidenced by the lower nadir hematocrits in the acute catheterization approach, this small difference probably resulted from the strategy of avoiding transfusion unless necessary.

**Discussion**

These findings point to the promise of pharmacological approaches for stabilization of the ruptured atherosclerotic plaque and to the potential for specifically targeted mechanical approaches to augment the beneficial effects of thrombolytic therapy. Overall, with regard to the hospital course, the patients...
treated with combination thrombolytic therapy and aggressive cardiac catheterization did better in a broad spectrum of outcome measures than patients receiving the other strategies. The combination approach to thrombolytic therapy achieved both rapid and sustained coronary artery patency. The use of acute catheterization as a triage procedure with angioplasty only for occluded infarct arteries resulted in improved infarct zone regional left ventricular function \( (p=0.004) \) and a lower rate of combined negative end points \( (p=0.016) \) during the hospitalization. If a noninvasive method of detecting reperfusion can be achieved, this trial demonstrates that a strategy of selective intervention in patients with persistently occluded infarct arteries holds substantial promise to reduce negative clinical outcomes and improve regional left ventricular function.

**Baseline Characteristics**

By chance, a higher proportion of patients randomized to the aggressive strategy was high risk based on clinical characteristics devised by the TIMI trial\(^{26} \) and based on angiographic findings. Coincidentally, the patients randomized to the aggressive strategy in TIMI \(^{23} \) and the European Cooperative Study\(^{24} \) also were higher-risk patients at baseline. Patients at high risk because of old age, cardiogenic shock, or prior coronary artery bypass graft surgery were excluded from the trial. Thus, the results cannot be extrapolated to all patients with acute myocardial infarction but must be confined to patients meeting the entry criteria.\(^{32-34} \)

**Early Patency**

The trends in early patency rates in the present trial reflect the findings expected based on previous studies.\(^{4,7,8} \) Regimens including t-PA can be expected to achieve higher early patency rates compared with monotherapy with nonspecific fibrinolytic agents. The more rapid infusion of t-PA in the first hour in the combination group may explain the trend toward higher early TIMI grades with this regimen.\(^{35} \) Some recent studies have found an excellent overall result with “front-loaded” t-PA,\(^{36,37} \) raising the issue of whether the observed benefit of the combination therapy was a result of the t-PA regimen instead of the addition of urokinase. The combination therapy, however, did not surpass the patency rates observed with t-PA alone at 90 minutes. Despite the impressive effect of the combination therapy on the breakdown of hemostatic proteins,\(^{17} \) the regimen did not improve on the previous “ceiling” of \( 70-80\% \) in early patency rates. The mechanism for resistance to early patency in \( 20-30\% \) of patients remains elusive, although recent information suggests that complex plaque architecture with intraplaque hemorrhage may account for failure to reperfuse,\(^{38} \) a cause that would not respond to more powerful thrombolytic therapy. Other possible causes of failure to reperfuse include platelet-rich thrombi,\(^{39} \) inadequate drug delivery resulting from flow patterns, and resistance resulting from inhibitors of the plasminogen activators.

**Reocclusion**

The mechanism by which the combination prevented reocclusion remains speculative, although this outcome is consistent with our previous findings from the TAMI 2 pilot study.\(^{16} \) Overall, the reocclusion rate in the TAMI studies of 601 patients with t-PA monotherapy is \( 13.5\% \) (95% confidence limits, 10.8% and 16.2%) compared with 6.8% (95% confidence limits, 3.0% and 10.5%) in 176 patients receiving urokinase monotherapy and 6.3% (95% confidence limits, 2.8% and 9.8%) in 189 patients receiving combination therapy. Several mechanisms may be operative. First, our previous research has demon-

---

**TABLE 5. Left Ventricular Function**

<table>
<thead>
<tr>
<th>Follow-up ejection fraction*</th>
<th>t-PA</th>
<th>Urokinase</th>
<th>Combination</th>
<th>Catheterization strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive catheterization</td>
<td>54±13</td>
<td>55±11</td>
<td>54±12</td>
<td>54±12</td>
</tr>
<tr>
<td>Elective catheterization</td>
<td>54±12</td>
<td>54±10</td>
<td>53±11</td>
<td>54±11</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>54±12</td>
<td>54±11</td>
<td>54±12</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up infarct zone (SDs/chord)†

<table>
<thead>
<tr>
<th>Follow-up infarct zone (SDs/chord)†</th>
<th>t-PA</th>
<th>Urokinase</th>
<th>Combination</th>
<th>Catheterization strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive catheterization</td>
<td>-2.02±1.13†</td>
<td>-2.37±1.09</td>
<td>-2.09±1.38</td>
<td>-2.16±1.21§</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>-2.44±1.21</td>
<td>-2.63±1.19</td>
<td>-2.40±1.10</td>
<td>-2.49±1.16</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>-2.23±1.19</td>
<td>-2.50±1.14</td>
<td>-2.26±1.24</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up noninfarct zone (SDs/chord)‡

<table>
<thead>
<tr>
<th>Follow-up noninfarct zone (SDs/chord)‡</th>
<th>t-PA</th>
<th>Urokinase</th>
<th>Combination</th>
<th>Catheterization strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive catheterization</td>
<td>0.13±1.36</td>
<td>0.30±1.48</td>
<td>0.12±1.33</td>
<td>0.19±1.39</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>0.06±1.41</td>
<td>0.25±1.05</td>
<td>0.33±1.41</td>
<td>0.22±1.31</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>0.09±1.38</td>
<td>0.28±1.28</td>
<td>0.24±1.37</td>
<td></td>
</tr>
</tbody>
</table>

\( t-PA, \text{ tissue-type plasminogen activator.} \)

\( *p=0.98 \) for overall effect (5 df).

\( †p=0.02 \) for overall effect (5 df).

\( §p=0.78 \) for overall effect (5 df).

\( §p=0.004 \) for effect of catheterization strategy.

\( p=0.11 \) for effect of thrombolytic strategy.
strated that the production of fibrin(ogen) degradation products is associated with a reduction in reocclusion rates in patients treated with t-PA.40 Basic experiments have demonstrated that fibrin(ogen) degradation products serve as receptor blockers, occupying the platelet glycoprotein IIb/IIIa receptor and thereby inhibiting platelet aggregation.41 Second, the combination produced the beneficial effect of rapidly achieving a wide lumen with the combined fibrinolytic effect, thereby leading to better flow characteristics and less continuing clot formation. The results of this randomized trial are bolstered by previous investigations by our group17 and Verstraete (Juliard et al42) demonstrating a low reocclusion rate with this particular combination and by the almost identical findings of Grines and colleagues43,44 using t-PA and streptokinase in combination. The low reocclusion rates observed in all groups may have been aided by the routine use of aspirin,45 intravenous heparin,46,47 and possibly nitrates and calcium channel blockers.

**Left Ventricular Function**

The results with regard to left ventricular function confirm those of previous studies demonstrating the absence of major differences in global left ventricular function despite differing early patency rates. Randomized trials comparing t-PA with streptokinase13-16,48 and urokinase6 have failed to demonstrate differences in global left ventricular function despite consistently higher acute reperfusion rates with fibrin-specific therapy. Collectively, these trials raise the important issue of whether resting left ventricular function is an adequate end point with which to compare the clinical efficacies of reperfusion strategies.31,49 Many recent studies have demonstrated the possibility that the mortality reduction resulting from reperfusion occurs to a great extent because of factors other than left ventricular function as currently measured.2,50 These potential mechanisms include more salutary infarct healing with favorable remodeling of the ventricle, scaffolding of the ventricle, and reducing the risk of sudden death resulting from a favorable influence on electrophysiological properties of the myocardium.

We hypothesized that the aggressive catheterization strategy would lead to improved infarct zone function because rescue angioplasty would achieve patency in arteries refractory to opening with throm-

**Table 6. Clinical Events**

<table>
<thead>
<tr>
<th></th>
<th>t-PA (%)</th>
<th>Urokinase (%)</th>
<th>Combination (%)</th>
<th>Catheterization strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Reinfarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
<td>14</td>
<td>16</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>16</td>
<td>17</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent ischemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
<td>28</td>
<td>25</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>34</td>
<td>44</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>31</td>
<td>35</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td><strong>Any of above events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
<td>37</td>
<td>36</td>
<td>28</td>
<td>33†</td>
</tr>
<tr>
<td>Deferred catheterization</td>
<td>44</td>
<td>54</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>Drug strategy</td>
<td>40</td>
<td>45</td>
<td>32‡</td>
<td></td>
</tr>
</tbody>
</table>

*p=0.009 for overall differences by binary logistic regression and p=0.013 by ordinal logistic regression (5 df).  
†p=0.005 for catheterization strategy by binary logistic regression and p=0.016 by ordinal logistic regression (1 df).  
‡p=0.04 for drug strategy by binary logistic regression and p=0.024 by ordinal logistic regression (2 df).
bolytic therapy. Previous studies have demonstrated that measurement of global left ventricular function may underestimate the impact of reperfusion strategies on tissue within the area of myocardium undergoing infarction. The zone of myocardium remote from the infarction frequently becomes hypercontractile during the acute phase. This compensation tends to diminish differences in overall ejection fraction measurements.51,52 The differences in regional function between the catheterization strategies represent a substantial biological effect, despite the lack of difference in global left ventricular function. However, the clinical significance of regional infarct zone function has not been clearly demonstrated.

**Clinical Outcomes**

The clinical courses of patients given combination thrombolytic therapy were more benign than those of patients treated with other strategies. The risks of recurrent ischemia, reocclusion, and intracranial hemorrhage were lowest in patients treated with the combination. When the composite clinical end point was used, an uncomplicated hospital course was substantially more frequent with the combination (p<0.024), particularly when patients also had an acute catheterization.

Interpretation of the clinical end point when considering early catheterization must be tempered with judgment regarding the degree to which early catheterization of all patients should be regarded as a negative feature of the aggressive catheterization strategy. In essence, in our analysis the need for emergency or urgent catheterization beyond the first several hours of the infarction is counted as a negative end point in both groups. On the other hand, the acute catheterization used in all patients in the aggressive strategy is not counted as a negative end point with the composite end point. Furthermore, the in-hospital mortality rate was higher, although not significantly, in the aggressive group, like in all previous trials.18,23,24 In all of these trials, however, the difference has narrowed53 or reversed54,55 in follow-up. The major positive impact of the aggressive strategy was in reducing the incidence of severe recurrent ischemia mandating further intervention. The relative value of avoiding these events during the hospital course compared with undergoing immediate catheterization must be balanced when applying these therapeutic strategies to clinical practice.

The composite clinical end point was developed to provide a sensitive measure of differential clinical benefits in trials not primarily designed to assess mortality differences. The ordinal scale was developed by a consensus process of the investigators without knowledge of the trial results. The ranking of death, stroke, and reinfarction was unanimous among the investigators. Although for this trial, the composite end point remains statistically significantly different for drug and catheterization strategies (p<0.05) regardless of whether the ordinal scale is used, we prefer the ordinal ranking because it conforms to standard clinical thinking by assigning greater importance to more serious end points.

**Bleeding**

Bleeding complication rates were similar in the present trial regardless of the thrombolytic regimen used, confirming our previous pilot study results that the combination of t-PA and urokinase is not associated with a higher rate of bleeding compared with

<table>
<thead>
<tr>
<th>TABLE 7. Hemorrhagic Complications of Non–Coronary Artery Bypass Graft Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Intracranial bleeding (%)</strong></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
</tr>
<tr>
<td>Deferred catheterization</td>
</tr>
<tr>
<td>Drug strategy</td>
</tr>
<tr>
<td><strong>Units transfused (n)</strong></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
</tr>
<tr>
<td>Deferred catheterization</td>
</tr>
<tr>
<td>Drug strategy</td>
</tr>
<tr>
<td><strong>Nadir hematocrit</strong></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
</tr>
<tr>
<td>Deferred catheterization</td>
</tr>
<tr>
<td>Drug strategy</td>
</tr>
<tr>
<td><strong>Bleeding index</strong></td>
</tr>
<tr>
<td>Aggressive catheterization</td>
</tr>
<tr>
<td>Deferred catheterization</td>
</tr>
<tr>
<td>Drug strategy</td>
</tr>
</tbody>
</table>

* t-PA, tissue-type plasminogen activator.

*Bleeding index=units transfused+(change in hematocrit/3).
monotherapy.17 The high intracranial bleeding rate with t-PA and urokinase monotherapy is of concern, but the sample size is far too small to reliably estimate the true rate. Experience with more than 5,000 patients treated with the same dosage regimen of t-PA used in the present study has demonstrated an intracranial hemorrhage rate of only 0.5%.8,5 Similar results have been reported for urokinase.

A surprising finding of the present study was that the transfusion rates were not higher after acute catheterization compared with the deferred strategy. This finding apparently resulted from the strict criteria for transfusion established in the protocol by consensus of the investigators. The guidelines were developed in view of previous results from the TAMI and TIMI trials27,56,57 showing a potentially excessive rate of transfusion in patients receiving acute catheterization with no evidence of benefit. The bleeding index confirms that more bleeding (presumably peri-access) occurred in the acute catheterization group but that clinically significant bleeding was rare.

Limitations

Because of logistical issues, neither the drug nor the catheterization strategy could be blinded. In an effort to minimize the effect of this problem, criteria for clinical decision making were objectively specified in the study protocol, and careful monitoring for bias occurred throughout the trial. The sample size of this trial was designed to assess differences in left ventricular function (four ejection fraction points) at a time when the effects of earlier and sustained patency on global left ventricular function were considered to be more profound. Recent data suggest that the effects of thrombolytic therapy on left ventricular function measurements are dissociated from their effects on clinical outcomes.31,49 For this reason, left ventricular systolic function measures will probably not be acceptable as the only primary end points for future trials and alternative clinical outcome measures such as the composite clinical end point used in the present trial will be required. Furthermore, the techniques of intravascular intervention are continuing to evolve, so current clinical trials should be regarded as benchmarks in an evolving effort to achieve and sustain infarct artery patency while minimizing risk, whether mechanically or pharmacologically. Finally, sample size limits the extent to which important end points such as death, reinfarction, and stroke can be evaluated.

Conclusions

In concert with other studies, the TAMI 5 trial supports the concept that fibrin specificity leads to more rapid achievement of patency of the infarct artery, but over time patency rates will “catch up” after treatment with a nonspecific agent. Agents without fibrin specificity produce a slower rate of infarct artery patency but lead to similar predischarge left ventricular function. The lack of an increase in bleeding complications for combination therapy is noteworthy and is probably related to the briefer duration of t-PA therapy.43,58,59 These results provide substantial evidence that a combination of a fibrin-specific agent to achieve patency as quickly as possible concurrent with a nonspecific agent to prevent reocclusion will lead to the best clinical outcomes. Whether the effect of urokinase in this combination can be equalled by streptokinase43,44 or a potent antiplatelet60 or antithrombin agent61 remains to be seen.

The overview of catheterization strategies reveals a mixture of differences and similarities among our study and previous randomized trials. Cardiac catheterization was associated with a statistically insignificant increase in the risk of early death but, when performed in the acute phase, led to a substantially lower incidence of subsequent recurrent ischemia. Importantly, the present study and other studies evaluating emergency cardiac catheterization in patients with acute myocardial infarction have not had sufficient power to evaluate mortality differences. The 20% improvement in regional infarct zone function suggests that the aggressive strategy preserves myocardium, although the prognostic significance of regional function improvement without improvement in global function remains uncertain.

In contrast to recent trials26,62 using different strategies, results of the present study underscore the potential value of a more aggressive posture toward patients with evolving myocardial infarction, with regard to both combination thrombolytic therapy and acute-phase cardiac catheterization. The improved in-hospital outcomes after the acute phase of the infarction with the more aggressive strategy must be weighed against the cost and logistical issues involved with this strategy and the possible increase in early mortality when individual treatment decisions are made. Furthermore, these results do not pertain to the sizable proportion of patients who were excluded from this trial, many of whom have poor prognoses33,34 and may benefit from early catheterization. Perhaps more important, the positive findings point to the possibility for even more effective solutions to the goal of establishing early infarct vessel patency and maintaining long-term patency. Pharmacological approaches can stabilize the disrupted atherosclerotic plaque, thus substantially reducing the risk of reocclusion and recurrent ischemia. If noninvasive methods of detecting reperfusion can be developed,63,64 mechanical techniques in the most appropriate pharmacological environment can be targeted to specific patients who will benefit because the acute catheterization strategy used in the present study was primarily oriented toward the use of rescue angioplasty to open infarct arteries that had failed to reperfuse.

Acknowledgments

The authors wish to thank Cynthia Day and Stephanie Williams for preparation of the manuscript and Dr. Joseph C. Greenfield Jr. and Dr. Bertram Pitt for their support and guidance throughout this trial. Most important, we wish to thank the many physicians and
nurses in community hospitals who volunteered time and effort to make this trial possible.

Appendix

TAMI 5 Study Group
Duke University Medical Center, Durham, N.C.

Robert M. Califf, MD (Principal Investigator); Thomas Wall, MD; Richard Stack, MD; Harry Phillips III, MD; Robert H. Peter, MD; Ken Morris, MD; Victor Behar, MD; Y. Kong, MD; Thomas Bashore, MD; Peter Quigley, MD; James Bengtson, MD; Michael Honan, MD (former); Christopher O'Connor, MD; Robert Bauman, MD; Susan Mantell, RN (former); Eric Berrios, RN; Linda Sneed, RN (former); Cynthia Flanagan, RN; and Margaret Liu, RN.

Collaborating centers. Alamanse County and Alamance Memorial Hospitals, Burlington, N.C.: James Strickland, MD; Javed Masoud, MD; Gene Griner, MD; Michael DiMeo, MD; William Wilcockson, MD; Stuart Schneider, MD; Donald Pathman, MD; and Paul Mele, MD. Franklin Regional Medical Center, Louisburg, N.C.: Paul Kile, MD. Granville Medical Center, Oxford, N.C.: John Anderson, MD; David Whitcomb, MD; and Stephen Ertischek, MD. Maria Parham Hospital, Henderson, N.C.: Depak Pasi, MD, and J. Franklin Mills, MD. The Memorial Hospital, Danville, Va.: Syed Ahmed, MD; Steven Davis, MD; Stuart Smith, MD; and Phillip Levin, MD. Onslow Memorial Hospital, Jacksonville, N.C.: Andre Tse, MD, and Edgardo Bianchi, MD. Person County Memorial Hospital, Roxboro, N.C.: Mark Zawodniak, MD; Thomas Long, MD; and Wayne Bierbaum, MD. Randolph Hospital, Inc., Asheboro, N.C.: Milkiat Dhatt, MD, and Shiv Harsh, MD. Richmond Memorial Hospital, Rockingham, N.C.: Michael Hennigan, MD; Moosa Hajaishiekh, MD; John Vetter, MD; John Flannery, MD; and Daniel Hall, MD. Southeastern General Hospital, Lumberton, N.C.: John Hoekstra, MD; G.M. Devine, MD; C.R. Beasley, MD; S.B. Hegde, MD; E.B. Knight, MD; H.N. Lee, MD; S.N. Naik, MD; and D.L. Richardson, MD. Wilson Memorial Hospital Inc., Wilson, N.C.: James Whitaker, MD; John Lund, MD; and Mitchell Hardison, MD.

University of Michigan Medical Center, Ann Arbor, Mich.

Eric J. Topol, MD (Coprincipal Investigator); Stephen Ellis, MD; Elizabeth Nabel, MD; Eric Bates, MD; Steven Werns, MD; Joseph Walton, MD; Eva Kline, RN; Laura Gorman, RN; and Barbara Schumaker, HRA.

Collaborating center. W.A. Foote Memorial Hospital, Jackson, Mich.: John Maino II, MD (former); Gregory Baumann, MD; Constance Doyle, MD; Mary Anne Mangelson, MD; Patricia Lamb, MD; Sid Shah, MD; Nathan Sherman, MD; Douglas Salyards, MD; Nathan Kander, MD; Kevin Kelly, MD; Tama Martini, MD; Rajesh Shah, MD; and Ronald Wainz, MD.

Riverside Methodist Hospital, Columbus, Ohio

Barry S. George, MD; Richard Candela, MD; Ronald Frazier, MD (former); Joseph Mayo, MD (former); Ramona Masek, RN; and Ann Pickel, RN. Collaborating center. Hardin Memorial Hospital, Kenton, Ohio: Murlidhar Deshmukh, MD; Adarsh Sharma, MD; and Chung Chang, MD.

The Christ Hospital, Cincinnati, Ohio

Dean J. Kereiakes, MD; Charles W. Abbottsmith, MD; Linda Anderson, RN; Linda Martin, RN; Nancy Higby, RN; Richard Sieving, MD; Wendy Howard, RN; and David Lauston, RN.

Collaborating centers. Bethesda North Hospital, Cincinnati, Ohio: Pete Caples, MD, and Theodore Waller, MD. Fort Hamilton–Hughes Hospital and Mercy Hospital of Hamilton, Hamilton, Ohio: James Scott Jr., MD; George Manitsas, MD; Kenneth Wehr, MD; and Richard Willis, MD. Middletown Regional Hospital, Middletown, Ohio: Walter Roehl Jr., MD. Our Lady of Mercy Hospital–Anderson, Cincinnati, Ohio: Eli Roth, MD; Michael Smith, MD; and David Drake, MD.

Baptist Memorial Hospital, Memphis, Tenn.

Joseph K. Samaha, MD; William H. Flanagan, MD; Bruce Wilson, MD; Frank McGrew, MD; Beate Griffin, RN; Veronica Condon, RN; Betty Ehemann, RN; Leighann White, RN; Marc Crupie, MD (former); William Falvey, MD; Fenwick Chappell, MD (former); Linda Yates, MD; James Hannifin, MD; Marsha Dean, RN; Carolyn Maroney, RN; and Barbara Wells, RN.

Collaborating centers. Baptist Memorial Hospital–Tipton, Covington, Tenn.: Jesse Cannon, MD; George Chambers, MD; Sam Broffitt, MD; Barrett Matthews, MD; John Douglas Clark, MD (former); and Edward Ritch Davis, MD. Baptist Memorial Hospital–Forrest City, Forrest City, Ark.: Frank Schwartz, MD. Baptist Memorial Hospital–Lauderdale, Ripley, Tenn.: Joe Hunt, MD; Arden J. Butler, MD; William H. Tucker, MD; B.G. Robbins, MD; and S.M. Fann, MD. Baptist Memorial Hospital–Union City, Union City, Tenn.: Halbert Dodd II, MD; R. Paul Hill, MD; and Laurence Jones, MD. Greenwood Leflore Hospital, Greenwood, Miss.: Jeff Moses, MD, and Timothy Reynolds, MD. Missouri Delta Medical Center, Sikeston, Mo.: David Pfefferkorn, MD; Michael Chouinard, MD; Jennifer R. Swiney, MD; William C. Shell, MD; Jim Heath, MD; Michael E. Critchlow, MD; and Brad J. Angelos, MD. Northwest Mississippi Regional Medical Center, Clarksdale, Miss.: Timothy H. Lamb, DO; Travis Wayne Yates, DO; Andrea Lee Smith, MD; G.D. Berryhill Jr., MD; and William Bobo, MD. Union County General Hospital, New Albany, Miss.: Thomas F. Barkley, MD, and Thomas A. Shands, MD.
Lancaster General Hospital, Lancaster, Pa.

Seth J. Worley, MD; J.H. Gault, MD; R.D. Gentzler, MD; I.D. Smith, MD; J.P. Slovak, MD; E.W. Supple, MD; Sherry Lane, RN; Deborah Leed, RN (former); and Deborah Ramsey, RN.

LDS Hospital, Salt Lake City, Utah

Jeffrey L. Anderson, MD; Labros Karagounis, MD; and Steve Ipsen, RN.

Collaborating centers. St. Mark’s Hospital, Salt Lake City, Utah, and Cottonwood Hospital, Murray, Utah: J. Joseph Perry, MD; Keith L. Ritchie, MD; and David C. Boorman, MD. Utah Valley Regional Medical Center, Provo, Utah: Charles F. Dahl, MD; John K. Frischknecht, MD; Ronald W. Asay, MD; and Douglas R. Smith, MD.

TAMI Coordinating Center, Duke University Medical Center, Durham, N.C.

Lynn Harrelson-Woodlief, MS; Sharon Karnash, BS; Lynne Aronson, BS (former); Kristina Sigmon, MS; Grace Wilson, BS; Joy Miller, RN; Tammy Allen, RN; Kerry Lee, PhD; Jane Boswick, MPH (former); and Robert Califf, MD.

Angiography Core Laboratory–University of Michigan Medical Center

Darrell Debowey, MD; John Kunkel, BS; Peter Thomasma, BS; and Eric Topol, MD.

MUGA Core Laboratory–University of Michigan Medical Center

Markus Schwaiger, MD; Keith Aaronson, MD (former); and Sheila Squicciarini, BS, RT(N).

ECG Core Laboratory–Duke University Medical Center

Galen Wagner, MD, and Peter Clemmensen, MD (former).

Pharmacy Core Laboratory–Duke University Medical Center

Laura Stewart, RPh, and Tom Burrus, RPh.

Hematology Core Laboratory–University of Vermont

David Stump, MD (former); Dagnija Thornton, BS; and Elizabeth Macy, BS (former).

Economics and Quality of Life Substudies–Duke University Medical Center

Daniel Mark, MD, and James Melton, MHA.

Data and Safety Monitoring Board

Joseph C. Greenfield, MD; Joseph Loscalzo, MD; Daniel Mark, MD; Mark Hlatky, MD (former); David Pryor, MD; Arthur Sasahara, MD; James Lancaster, PhD; Kerry Lee, PhD; Lynn Harrelson-Woodlief, MS; Lynne Aronson, BS (former); and Sharon Karnash, BS.

References

2. Braunwald E: Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: Should the paradigm be expanded? Circulation 1989; 79:441–444
16. The International Study/GISSI 2 Study Group: In-hospital mortality and clinical course of 20,891 patients with suspected...


**KEY WORDS**  
- thrombolysis  
- acute myocardial infarction  
- angioplasty  
- clinical trials
Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction. Results of thrombolysis and angioplasty in myocardial infarction--phase 5 randomized trial. TAMI Study Group.
R M Califf, E J Topol, R S Stack, S G Ellis, B S George, D J Kereiakes, J K Samaha, S J Worley, J L Anderson and L Harrelson-Woodlief

Circulation. 1991;83:1543-1556
doi: 10.1161/01.CIR.83.5.1543

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/83/5/1543

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/