Impact of Different Reperfusion Modalities on Ventricular Function After Acute Myocardial Infarction

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Single-plane contrast ventriculography was performed on admission and before hospital discharge in more than 200 patients with acute myocardial infarction participating in a series of prospective clinical trials including intracoronary streptokinase, percutaneous transluminal coronary angioplasty (PTCA), intravenous tissue plasminogen activator (rt-PA) and thrombolysis (intravenous rt-PA or streptokinase) followed by PTCA. Both global ejection fraction (EF) and regional wall motion of the infarct zone were measured to assess serial changes. Patients treated with intracoronary streptokinase 3.6 ± 1.8 hours after symptom onset had no increase in EF (mean change 1 ± 6%, difference not significant [NS]), but patients treated with primary PTCA at 3.0 ± 1.2 hours did (mean improvement 8 ± 7%, p <0.001). Patients treated with sequential intravenous streptokinase and PTCA 2.6 ± 1.3 hours after symptom onset showed similar improvement in EF (mean change 6 ± 12%, p <0.002). Patients treated with rt-PA had no change in EF whether treated with rt-PA alone or rt-PA followed by immediate angioplasty (mean change −2 ± 8% and 0.5 ± 8%, p = NS, respectively). When angioplasty was used in patients with persistent occlusion after thrombolytic therapy, EF improved in those who had received intravenous streptokinase (mean change 10 ± 7%, p <0.002), but not those who had received rt-PA (+0.5%, p = NS). However, infarct zone regional wall motion improved in patients treated with intracoronary streptokinase (+0.59 ± 0.79 standard deviation/chord, p <0.05), primary PTCA (+1.32 ± 1.32, p <0.001), intravenous streptokinase and PTCA (+1.2 ± 1.2 standard deviation/chord, p <0.003), intravenous rt-PA alone (+0.43 ± 1.0, p = 0.002) or intravenous rt-PA and immediate PTCA (+0.37 ± 1.0, p = 0.0001).

Whereas serial improvement in EF appears to be limited to patients treated with primary PTCA or PTCA after intravenous streptokinase therapy, infarct zone regional wall motion improved regardless of the reperfusion method used. (Am J Cardiol 1988;61:45G-53G)

In the 1980s, the therapy of acute myocardial infarction has increasingly involved attempts to reperfuse the infarct zone, given the mounting evidence that timely reperfusion results in a lower mortality than conventional care.1,2 Although reperfusion itself may improve survival,3 the primary mechanism of decreasing mortality is presumed to be a reduction in infarct size.4 Reperfusion strategies have included various intracoronary5 and intravenous1 thrombolytic therapies, percutaneous transluminal coronary angioplasty (PTCA),6 coronary bypass7 and the combination of thrombolytic therapy and PTCA.6

The comparative efficacy of these strategies has been evaluated based on 3 primary endpoints: (1) coronary recanalization rates, (2) mortality reduction, and (3) limitation of infarction size. Whereas recanalization rates and mortality are easily evaluated, clinical quantification of infarct size has been difficult, relying on changes in systolic ventricular function with reperfusion. Although both contrast and radionuclide ventriculographic determination of global ejection fraction (EF) and regional wall motion have severe limitations in quantification of infarct size,6 they have gained widespread acceptance because of the ability to standardize values and to perform these studies in a sequential fashion in most patients. More important to their acceptance, however, is the fact that global ventricular function after reperfusion has important prognostic value.3,10

Since the inception of the coronary intervention program at the University of Michigan in 1981, we have attempted to systematically assess the impact of
different reperfusion modalities on changes in ventricular function after reperfusion therapy. The comparative recanalization rates of these treatment methods have been reported previously. This study will deal with the associated changes in ventricular function.

**Methods**

**Patients:** Study 1: Between March 1981 and June 1982, 76 patients with suspected acute myocardial infarction were recruited for a randomized placebo-controlled clinical trial of intracoronary streptokinase administration. Inclusion criteria included admission to the hospital within 6 hours of symptom onset, ≥2 mm of ST-segment elevation in 2 or more involved electrocardiographic leads and absence of cardiogenic shock. Patients who had a contraindication to thrombolytic therapy or who were unable to give informed consent were excluded. Immediate cardiac catheterization was performed using either the Judkins or Sones technique. Left ventricular end-diastolic pressure was measured and contrast ventriculography was performed in the 30° right anterior oblique projection. After ventriculography, selective coronary angiography was performed in multiple projections. If complete coronary occlusion was present and unresponsive to intracoronary nitroglycerin, and if narrowing of the left main coronary artery greater than 70% was absent, patients were then randomized to receive either intracoronary streptokinase (total dose of 250,000 IU) or a dextrose solution. At the termination of infusion, arterial patency status was assessed and contrast ventriculography was repeated. A radionuclide ventriculogram was obtained within 72 hours (mean ± standard deviation [SD] 42 ± 27 hours), at 12 ± 4 days after admission and 5 ± 3 months after discharge. Analysis of left ventricular wall motion by contrast angiography was performed with standard catheterization laboratory computer and software (Electronics for Medicine, Honeywell). End-diastolic and end-systolic contours were traced and digitized with the computer light pen system, using only sinus beats not preceded by a premature beat. EF was calculated using the area-length method.

**Study II:** Between April 1, 1984 and October 31, 1984, 72 patients were enrolled in a 2-center randomized clinical trial of intracoronary streptokinase vs coronary angioplasty therapy, conducted at the University of Michigan Medical Center and William Beaumont Hospital, Royal Oak, Michigan. Inclusion criteria were as previously described, with the additional requirement that patients not have left main coronary stenosis of >60%, "left main coronary artery equivalent" disease, ≥70% stenosis of both proximal left anterior descending and proximal circumflex vessels), occlusion of a saphenous vein graft, or a distal occlusion of a tortuous circumflex artery judged not suitable for angioplasty. Fifty-six patients (78%) met these inclusion criteria, and were randomized to either immediate coronary angioplasty (29 patients) or intracoronary streptokinase infusion (27 patients). All patients received 5,000 U of heparin, and those patients undergoing angioplasty received an additional 5,000 U after randomization. They were maintained on an infusion of low molecular weight dextran (40 ml/min for 24 hours), and received aspirin (325 mg) and oral nifedipine (20 to 30 mg every 8 hours) in addition to a 24-hour infusion of nitroglycerin. Patients undergoing angioplasty also received verapamil (5 mg intravenously) before the procedure and intracoronary nitroglycerin (200 μg) immediately before angioplasty. Changes in ventricular function were assessed based on admission and predischARGE contrast left ventriculograms recorded in 46 of the 56 patients, and analyzed using the area-length method and the computer-assisted centerline chord method.

**Study III:** Between November 1, 1984 and September 21, 1985, 34 consecutive patients were treated with sequential high-dose intravenous streptokinase (1.5 million units) and emergency coronary angioplasty in a prospective nonrandomized clinical study. Clinical inclusion criteria were the same as the 2 previous randomized investigations. Heparin therapy consisted of 5,000 U administered intravenously at the start of catheterization, an additional 5,000 U administered before angioplasty, and a continuous infusion initiated when serum fibrinogen level was ≥100 mg/dl maintained until predischARGE angiography 7 to 10 days later.

**Study IV:** Between September 21, 1985 and January 31, 1986, a pilot, randomized, prospective clinical trial of immediate vs delayed coronary angioplasty was conducted after successful thrombolytic therapy using recombinant tissue-type plasminogen activator (rt-PA) as part of a 4-center trial of rt-PA sponsored by Genentech Inc. (South San Francisco, California). Patients were treated with an intravenous infusion of rt-PA at a dose of 1.25 mg/kg administered over 3 hours. At the University of Michigan, 50 patients were recruited, including 38 randomized to rt-PA infusion and 12 to placebo. The 38 patients treated with rt-PA underwent coronary angiography 2 hours after onset of infusion, which demonstrated an 84% patency rate of the infarct-related artery. Twenty-eight of these patients met predefined angiographic criteria and underwent a second randomization to either immediate or deferred PTCA. Contrast left ventricular angiography in the right anterior oblique projection was performed at the time of initial catheterization (before PTCA) and at the time of hospital discharge 7 to 10 days later, and were analyzed as previously described.

Most recently, we have tested the feasibility of a regionalized approach to interventional therapy of acute myocardial infarction. Patients who presented to W.A. Foote Memorial Hospital, Jackson, Michigan and South Macomb Hospital, Warren, Michigan, had rt-PA infusion initiated at the community hospital and were then immediately transported to the University of Michigan Medical Center for cardiac catheterization and coronary intervention. Topol et al. compared the reperfusion rates and changes in global and regional ventricular function in these patients to patients in whom rt-PA infusion was initiated on arrival at the University of Michigan, or patients in whom rt-PA was flown to the local community hospital and
infusion was initiated during helicopter transport. Catheterization procedures, coronary angiography, contrast ventriculography and pharmacologic therapy were the same as the previous rt-PA protocols.

Results

Intracoronary streptokinase therapy: The results of the initial randomized, placebo-controlled study of intracoronary streptokinase infusion have been reported by Khaja et al. Intracoronary streptokinase infusion (n = 20) or dextrose solution (n = 20) were administered 5.4 ± 1.9 hours after symptom onset, with coronary recanalization in 60% of streptokinase-treated patients. Contrast ventriculograms showed no change in either global EF or infarct zone regional wall motion. Only 3 of 19 patients treated with streptokinase and 3 of 20 treated with placebo had a global EF improvement of 5 percentage points or more (Fig. 1). To evaluate any later improvement in EF, radionuclide ventriculography was performed within 72 hours, at the time of hospital discharge and 3 months after discharge. Again, no differences were seen in the EF of the streptokinase-treated group compared with the placebo-treated control group (Fig. 2). Centerline-chord methodology for analysis of regional wall motion was not available at this time.

The next randomized clinical trial compared intracoronary streptokinase infusion to primary PTCA therapy. Twenty-three of 27 patients (85%) achieved anterograde recanalization with streptokinase at 4.8 ± 1.7 hours of symptom onset. EF was unchanged (48% initial, 49% predischarge), but infarct zone regional wall motion improved significantly (increased regional wall motion of 0.59 ± 0.79 SD/chord, p = 0.05).

Percutaneous transluminal coronary angioplasty: Twenty-nine other patients were randomized to primary PTCA in the aforementioned trial, with coronary recanalization in 24 of 29 patients (83%) at 4.1 ± 1.4 hours from symptom onset. Nineteen of these patients had adequate quality serial contrast ventriculograms on admission and hospital discharge, with an increase in global EF from 48 to 56% (mean improvement 8 ± 7%, p <0.001). When the serial changes in contrast EF were compared for the streptokinase- and angioplasty-treated groups (Fig. 3), 14 of 19 patients treated with angioplasty but only 4 of 20 patients treated with streptokinase had a ≥5% increase in EF. Greater improvement in infarct zone regional wall motion (1.32 ± 1.32 SD/chord) was also evident in the PTCA-treated group compared with the streptokinase-treated group (p <0.001).
Sequential intravenous streptokinase and percutaneous transluminal coronary angioplasty: Fung et al. reported on 34 patients treated with 1.5 million units of intravenous streptokinase followed by immediate catheterization and PTCA. When streptokinase infusion was initiated 2.6 hours after symptom onset, angiography documented a coronary patency rate of 62%. Coronary angioplasty was performed in 29 of 34 patients. Of the remaining 5 patients who did not have PTCA, the residual stenosis in the infarct-related artery was ≤50% at the time of immediate catheterization in 3, and lesions were located in the distal segments of small infarct-related arteries that were not judged suitable for PTCA in 2 patients, respectively. PTCA was successful in all 16 patients with subtotal coronary occlusion, and in 12 of 13 patients with persistent total occlusion despite thrombolytic therapy. Global EF improved from an initial EF of 53 ± 12% to 59 ± 13% (p < 0.002) at the time of hospital discharge (mean increase 6 ± 12%). Additionally, regional wall motion of the infarct segment improved from −2.7 ± 1.1 to −1.5 ± 1.7 SD/chord (p < 0.003) [mean change +1.2 ± 1.2 SD/chord]. When patients were subgrouped based on successful thrombolysis or unsuccessful thrombolysis, important differences in a change in ventricular function occurred (Fig. 4). Patients with successful thrombolysis tended to have a higher initial EF (56 ± 10% vs 49 ± 12%, p = 0.18), and more effectively preserved regional wall motion (−2.2 ± 1.0 vs −3.2 ± 1.0 SD/chord, p < 0.03) than patients with continued occlusion. No significant further improvement occurred in the patients who had successful thrombolytic therapy, with an EF of 58 ± 10% initially and 59 ± 10% at the time of hospital discharge (p = 0.19). However, there was a trend toward improvement in regional function of the infarct zone: −2.2 ± 1.0 to −1.2 ± 1.8 SD/chord (p = 0.06). In patients with continued occlusion after thrombolytic therapy, both global EF (49 ± 12% to 59 ± 12%, p < 0.002) and regional wall motion (−3.2 ± 1 to −1.9 ± 1.7 SD/chord, p < 0.002) increased significantly by the time of hospital discharge.

Tissue plasminogen activator therapy: Coronary recanalization was documented angiographically in 32 of 38 patients (84%) treated with rt-PA (1.25 mg/kg) over 3 hours. Thirteen patients were randomized to rt-PA infusion alone, initiated 4.1 ± 1.1 hours after symptom onset with estimated reperfusion at 5.4 ± 1.4 hours. The EF in this group was 52 ± 12% initially and

![Figure 3](image3.png)

**FIGURE 3.** Changes in serial ejection fraction were determined from analyses of serial contrast ventriculograms obtained before therapy and before hospital discharge. The mean ± standard error of the mean are shown. SK = streptokinase; PTCA = percutaneous transluminal coronary angioplasty.

![Figure 4](image4.png)

**FIGURE 4.** Left ventricular ejection fraction (LVEF) on initial angiography early (E) and 10 days after therapy, A, patients with initially unsuccessful thrombolytic therapy; B, patients with initial successful thrombolytic therapy; C, patients with widely patent infarct-related arteries at the time of initial catheterization. L = late.
Infarct Regional Wall Motion

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Left Ventricular Global Function

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p = NS

50% ± 11% at discharge (mean change -2.11 ± 8%, difference not significant [NS]). Regional wall motion was -2.62 ± 1.41 SD/chord initially and -2.86 ± 1.23 SD/chord (p = NS). Fifteen patients were treated with immediate angioplasty after successful rt-PA infusion. In these patients, global EF was 53 ± 11% at entry and 53 ± 13% at discharge (p = NS), but regional wall motion improved significantly from -2.94 ± 0.82 to -2.11 ± 1.45 SD/chord (mean change 0.83 ± 0.094, p < 0.007). Two of 15 patients treated with rt-PA and PTCA vs 2 of 13 patients treated by rt-PA alone had a ≥5% increase in global EF (Fig. 5).

Community hospital administration of intravenous tissue plasminogen activator: To further decrease the interval from symptom onset to thrombolytic therapy, we attempted to institute a program permitting administration of rt-PA in community hospitals rather than having patients flown by helicopter to our referral center before initiation of therapy. Using this strategy, the duration of symptoms before drug administration could be decreased, from 3.8 ± 1.2 to 2.1 ± 0.8 hours. Early drug administration appeared to yield more effective preservation of ventricular function, since patients treated at the community hospital had an initial EF of 54% ± 8% compared with 50% ± 9% (p < 0.01) in patients in whom therapy was initiated at our referral center. This preservation of ventricular function tended to persist until hospital discharge, with patients treated in the community hospital having an EF of 55% ± 9% compared with 52% ± 10% (p = 0.08) for those treated at the referral center.

Discussion

Preservation of ventricular function after reperfusion plays a dominant role in determining survival after hospital discharge. Our serial experience using different reperfusion strategies and agents has provided data regarding the effect of these treatment modalities on left ventricular function. Single-plane, right anterior oblique contrast ventriculography was performed at initial catheterization and (except for Study 1) at the time of hospital discharge, allowing nonrandomized comparison among groups. Because these studies involve small numbers of patients treated with different initial success rates, subsequent reocclusion rates and adjunctive therapies, such comparisons must be made cautiously.

Our 2 randomized trials of intracoronary streptokinase administration demonstrated no improvement in global ventricular function. Analysis of 7 randomized
trials published to date (Fig. 6) reveals that efficacy is time-dependent, with significant improvement in EF confined to the studies of Anderson et al. and Simoons et al., in which the time to initiation of streptokinase therapy was shortest. Because intracoronary streptokinase infusion imposes an obligatory time delay of 1 to 2 hours from presentation to the initiation of drug therapy, it is unlikely that most patients could be treated within this 4-hour time window. Lack of improvement in global EF, however, does not preclude a significant improvement in regional ventricular function, as was seen in our second trial of intracoronary streptokinase despite the prolonged duration of symptoms. Whether this observed improvement in regional wall motion imparts a survival advantage is unknown.

In contradistinction to intracoronary streptokinase, primary PTCA was associated with a significant improvement in global ventricular function. Our findings have subsequently been corroborated by Rothbaum et al., who demonstrated that patients with anterior myocardial infarction achieved a 13 ± 12% increase and patients with inferior myocardial infarction a 10 ± 12% absolute increase in global EF after primary PTCA. Although primary angioplasty therapy provides high rates of coronary recanalization and effective preservation of global ventricular function, it entails an obligatory time delay of 1 to 1½ hours from patient presentation to reperfusion, and requires highly sophisticated personnel and resources. Thus, it is unlikely that angioplasty therapy will be widely applied as a primary reperfusion modality. On the other hand, while initial intravenous thrombolytic therapy allows earlier reperfusion than angioplasty alone, it carries a significant risk of cerebral hemorrhage (0.4 to 1.4%) or extensive intramural hemorrhage of the infarct artery or the associated myocardial zone. For these reasons, a randomized clinical trial comparing sequential intravenous thrombolytic therapy and angioplasty to primary angioplasty alone should be conducted in the subset of patients who can be treated within 3 hours of symptom onset.

Our experience with intravenous rt-PA alone has provided conflicting results. The pilot study showed no improvement in regional wall motion in patients treated solely with rt-PA, whereas the subsequent Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial showed significant improvement in regional function in patients treated with rt-PA alone (Fig. 7).

Similar conflicting data exist for rt-PA therapy followed by immediate angioplasty. The initial pilot study suggested that immediate angioplasty was essential for myocardial salvage, since only patients treated with angioplasty had improvement in regional ventricular function. In the TAMI study, however, equal improvement in regional function occurred whether patients were treated with immediate or deferred PTCA. This may be explained by 2 major differences in trial design between the pilot study and TAMI study: (1) Patients in the pilot study were treated 3.8 hours after symptom onset, whereas those in the TAMI study were treated 2.9 hours after symptom onset; and (2) the pilot study used a short duration of rt-PA infusion and lower mean dose than that used in the TAMI trial. Thus, earlier and more prolonged rt-PA infusion in the TAMI trial may have minimized coronary reocclusion and allowed better preservation of ventricular function without resorting to immediate PTCA.

**FIGURE 6.** The impact of intracoronary streptokinase on ventricular function at the time of discharge is depicted. Patients treated in the Andersen study and the Serruys study had an improvement in global ventricular function. In both of these studies patients were treated within 4 hours of symptom onset. *p = 0.0001; **p < 0.05; + = Rentrop did not report chronic ejection fraction for treatment groups; no change in ejection fraction occurred in streptokinase or control group.
We have now had the opportunity to study extensively the changes in ventricular function after intravenous rt-PA in the TAMI study based on the 266 of 386 patients (69%) treated 2.9 ± 1.1 hours after symptom onset who underwent serial, paired contrast ventriculography of suitable quality for analysis. Linear regression analysis revealed that relief of chest pain before catheterization, baseline EF less than 55%, presence of Thrombolysis in Myocardial Infarction Trial flow grade II or III and lack of coronary reocclusion were independently associated with improved global ventricular function. The findings of the TAMI trial are relevant to our earlier experience with sequential intravenous streptokinase therapy and immediate PTCA as reported by Fung et al. Although regional wall motion was significantly improved after successful thrombolytic therapy (either intravenous streptokinase or intravenous rt-PA), the major differences between these 2 treatment strategies resided in patients in whom thrombolytic therapy had failed. Because 36% of the patients in the TAMI study in whom thrombolytic therapy was unsuccessful and reperfusion was achieved by angioplasty had documented coronary reocclusion, the impact of PTCA meditated-reperfusion was negated. On the other hand, patients treated with PTCA in whom streptokinase therapy was unsuccessful had a 9% point increase in global EF and a significant improvement in regional wall motion. These findings have been corroborated by Stack et al. Although intravenous streptokinase resulted in only a 40% reperfusion rate, the addition of angioplasty lead to an increase in a global EF from 44 to 49% at the time of hospital discharge (p <0.0001) in the Stack study. The beneficial impact of a systemic thrombolytic agent in patients undergoing “salvage” PTCA has been further investigated by Stack et al. This group examined 58 patients who underwent PTCA after unsuccessful thrombolytic therapy with rt-PA compared with 24 patients who underwent PTCA after unsuccessful therapy with rt-PA and urokinase (0.5 to 2.0 million units). Coronary reocclusion rates decreased dramatically (from 31 to 5%) by the addition of urokinase. More important, no change in global or regional ventricular function was evident among patients treated with rt-PA alone, whereas a 6% increase in global EF and a 0.36 SD/chord increase in regional wall motion (p <0.004) occurred among patients treated with both rt-PA and urokinase. These findings suggest that the addition of a systemic thrombolytic drug significantly decreases coronary reocclusion and enhances myocardial salvage when PTCA is performed after unsuccessful intravenous thrombolytic therapy. A compelling argument can thus be made for a formal, prospective, randomized clinical investigation of sequential intravenous thrombolytic therapy with clot-selective vs systemic thrombolytic drugs and sequential angioplasty.

As we have matured in our understanding of reperfusion therapy, the critical role that early therapy plays in myocardial salvage has become apparent. Koren et al. demonstrated that very early administration of thrombolytic therapy results in effective preservation of global ventricular function, since only patients with intravenous streptokinase therapy within 90 minutes of symptom onset had significant increase in EF. Our experience with community hospital administration of rt-PA also suggest good initial ventricular function in patients treated less than 2 hours after symptom onset. These findings provide further impetus for establishing reperfusion protocols for emergency room physicians, and perhaps even paramedics, to administer these agents as soon as possible after myocardial infarction has been diagnosed.

**Conclusions**

In 1979, Rentrop et al. demonstrated that nonsurgical coronary recanalization could be achieved during the evolutionary stages of acute myocardial infarction. Although coronary recanalization could be
achieved, the clinical benefit of this therapy remained unproved until the completion of the GISSP and Netherlands Intermuniversity studies, both of which showed evident clinical benefit of thrombolytic reperfusion on survival. Major questions, however, still exist about optimal reperfusion therapy. In assessing the clinical use of these reperfusion strategies, their impact on mortality, coronary recanalization rates and preservation of ventricular function must be compared. Our own experience suggests that intracoronary thrombolytic therapy is outdated. Although primary angioplasty therapy is an effective reperfusion strategy associated with high recanalization rates and effective preservation of ventricular function, logistic constraints of time delay and intense manpower requirements make it applicable to only a small number of cases. Intravenous thrombolytic therapy would be more applicable and is likely to become standard care for acute myocardial infarction. Our experience suggests that further augmentation of ventricular function does not occur with immediate PTCA in patients in whom thrombolytic therapy is successful. Significant clinical benefit can still be derived, however, in patients in whom thrombolytic therapy has been unsuccessful, especially when a systemic thrombolytic agent (streptokinase or urokinase) is added. Because our clinical criteria are currently inadequate to predict reperfusion status noninvasively,27 our current reperfusion strategy involves very early administration of thrombolytic therapy to suitable patients followed by immediate catheterization to document arterial recanalization. In patients with unsuccessful thrombolytic reperfusion, immediate angioplasty is applied. When this strategy is undertaken then more than 90% of patients leave the catheterization laboratory with a patent infarct-related artery. Patients in whom thrombolytic reperfusion is unsuccessful still derive significant myocardial salvage from PTCA-mediated reperfusion. The requirement that all patients with acute myocardial infarction who received thrombolytic therapy undergo immediate cardiac catheterization carries adverse logistic and financial consequences. A more effective strategy would be to stratify patients according to risk. Patients with extensive areas of jeopardized myocardium (anterolateral myocardial infarction or cardiogenic shock) are at highest clinical risk, and are most likely to benefit from this aggressive reperfusion strategy. Patients at lower risk could be treated with intravenous thrombolytic therapy alone, delaying catheterization and PTCA of an appropriate subgroup until the most desirable interval after thrombolytic therapy.

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