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Clinical Experience With Primary Percutaneous Transluminal Coronary Angioplasty Compared With Alteplase (Recombinant Tissue-Type Plasminogen Activator) in Patients With Acute Myocardial Infarction

A Report From the Second National Registry of Myocardial Infarction (NRMI-2)

ALAN J. TIEFENBRUNN, MD, FACC, NISHA C. CHANDRA, MD, FACC,*
WILLIAM J. FRENCH, MD, FACC,† JOEL M. GORE, MD, FACC,‡ WILLIAM J. ROGERS, MD, FACC§

Saint Louis, Missouri; Baltimore, Maryland; Torrance, California; Worcester, Massachusetts; and Birmingham, Alabama

Objectives. **We sought to compare outcomes after primary percutaneous transluminal coronary angioplasty (PTCA) or thrombolytic therapy for acute myocardial infarction (MI).**

Background. **Primary PTCA and thrombolytic therapy are alternative means of achieving reperfusion in patients with acute MI. The Second National Registry of Myocardial Infarction (NRMI-2) offers an opportunity to study the clinical experience with these modalities in a large patient group.**

Methods. **Data from NRMI-2 were reviewed.**

Results. **From June 1, 1994 through October 31, 1995, 4,939 nontransfer patients underwent primary PTCA within 12 h of symptom onset, and 24,705 patients received alteplase (recombinant tissue-type plasminogen activator [rt-PA]). When lytic-ineligible patients and patients presenting in cardiogenic shock were excluded, baseline characteristics were similar. The median time from presentation to initiation of rt-PA in the thrombolytic group was 42 min; the median time to first balloon inflation in the primary PTCA group was 111 min ($p < 0.0001$). In-hospital mortality was higher in patients in shock after rt-PA than after PTCA (52% vs. 32%, $p < 0.0001$). In-hospital mortality was the same in lytic-eligible patients not in shock: 5.4% after rt-PA and 5.2% after PTCA. The stroke rate was higher after lytic therapy (1.6% vs. 0.7% after PTCA, $p < 0.0001$), but the combined end point of death and nonfatal stroke was not significantly different between the two groups (6.2% after rt-PA and 5.6% after PTCA). There was no difference in the rate of reinfarction (2.9% after rt-PA and 2.5% after PTCA).**

Conclusions. **These findings suggest that in lytic-eligible patients not in shock, PTCA and rt-PA are comparable alternative methods of reperfusion when analyzed in terms of in-hospital mortality, mortality plus nonfatal stroke and reinfarction.**

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Percutaneous transluminal coronary angioplasty (PTCA) and intravenous administration of plasminogen activators are alternative approaches to achieving coronary artery reperfusion in patients with evolving myocardial infarction (MI). The status of primary PTCA has been detailed in recent reviews (1,2). Small, controlled studies comparing primary PTCA with thrombolytic therapy in patients suitable for either treatment have yielded conflicting results, but have suggested a survival advantage for patients undergoing PTCA, especially in patients with anterior infarctions (3–7). The merits of primary PTCA relative to thrombolytic therapy, without the constraints of a controlled study, are still being elucidated.

The National Registry of Myocardial Infarction (NRMI) is an ongoing observational data base of patients presenting with acute MI (8). The purpose of this study was to describe the experience with primary PTCA compared with alteplase (recombinant tissue-type plasminogen activator [rt-PA]) in NRMI-2.

Methods

NRMI-2. The Second National Registry of Myocardial Infarction is an ongoing voluntary observational phase IV (postmarketing) study sponsored by Genentech, Inc. Individual patient data on presenting characteristics, demographic data, procedures, medications and outcomes are collected at

From the Washington University School of Medicine, Saint Louis, Missouri; *Johns Hopkins Bayview Medical Center, Baltimore, Maryland; †Harbor University of California Los Angeles Medical Center, Torrance, California; ‡University of Massachusetts School of Medicine, Worcester, Massachusetts; and §University of Alabama Medical Center, Birmingham, Alabama. The National Registry of Myocardial Infarction is supported by a grant from Genentech, Inc., South San Francisco, California.

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Address for correspondence: Dr. Alan J. Tiefenbrunn, Washington University School of Medicine, Cardiovascular Division, 660 South Euclid Avenue, Box 8086, St. Louis, Missouri 63110. E-mail: atiefenbrun@imgate.wustl.edu.

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
ECG = electrocardiogram, electrocardiographic
LBBB = left bundle branch block
MI = myocardial infarction
NRMI = National Registry of Myocardial Infarction
PTCA = percutaneous transluminal coronary angioplasty
rt-PA = recombinant tissue-type plasminogen activator
STE = ST segment elevation
TIMI = Thrombolysis in Myocardial Infarction

participating hospitals in 50 states. Details of data collection and quality control for NRMI have been published (8).

Definitions. Only patients with acute MI, documented according to local hospital criteria, usually by electrocardiography, serial cardiac enzymes or angiography, are included in NRMI-2. "Transfer" patients are those who are initially admitted to the hospital or evaluated at another institution before being transferred to the index registry hospital. Treatment time for patients receiving intravenous thrombolytic therapy is defined as the time that the lytic bolus or infusion is initiated. Treatment time for patients undergoing primary PTCA is defined as the time of first balloon inflation. Concomitant medications are recorded separately as those ordered within 24 h of hospital admission or at discharge. Invasive procedures, major clinical events and adverse outcomes are recorded if they occurred at any time during the initial hospital stay. Strokes are recorded as hemorrhagic, thromboembolic or thromboembolic with hemorrhagic conversion. Major bleeding is defined as bleeding other than intracranial that resulted in substantial hemodynamic compromise. "Not low risk" patients are defined using criteria modified from the Thrombolysis In Myocardial Infarction (TIMI) phase II trial (9), with ST segment elevation (STE) and one or more of the following: age $\geq$70 years, previous MI, first blood pressure $<$100 mm Hg *and* pulse rate $>$100 beats/min, heart failure (Killip class II, III or IV) at presentation or anterior infarct location.

Patient selection. Patients who were not transferred from another institution and who received reperfusion therapy within 12 h of symptom onset were evaluated. Only patients actually undergoing primary PTCA were included; there was no analysis of patients taken to the catheterization laboratory during the course of evolving MI in whom PTCA was not performed. Only data from patients receiving thrombolytic therapy with alteplase (rt-PA) were analyzed to ensure a uniform treatment regimen. Data analysis was limited to patients with a minimal 48-h hospital stay (or death).

Statistical methods. Patients receiving rt-PA were compared with lytic-eligible patients undergoing primary PTCA in terms of descriptive statistics summarizing the following sets of variables: demographic data, medical history, baseline clinical characteristics, mortality, stroke incidence, subsequent events, subsequent procedures and time to event variables (onset to presentation, presentation to treatment and onset to treatment). Categoric variables were described using frequencies and percentages, whereas continuous variables were described using the mean and median values (25th, 75th percentiles).

Equality between the rt-PA and PTCA treatment groups for frequencies of categoric variables was tested by chi-square analysis. Differences among continuous variables were assessed by the *t* test for mean values and by the nonparametric sign test for median values. The effect of treatment modality (rt-PA vs. PTCA) on mortality was assessed after adjustment for potential confounding factors in a multiple logistic regression model, with death or survival as the binary outcome or dependent variable.

The logistic regression analysis yielded an odds ratio for each of the descriptors, providing a measure of association between each of these variables and mortality after adjusting for the effects of the other variables in the model. Ninety-five percent confidence intervals for the odds ratio were used to identify descriptors with odds ratios significantly different from 1, thus indicating a significant effect on mortality due to these variables.

Areas under the receiver operating curve were calculated to assess the discriminatory power of each logistic model. The C statistic was 0.79 for these models, indicating satisfactory specificity as well as sensitivity.

Results

Patients. The data for this report are drawn from patients enrolled in NRMI-2 from June 1, 1994 through October 31, 1995. The total number of patients enrolled was 172,742. Of these, 35,887 (20.8%) were transfer patients. Of the nontransfer patients, 89,565 (65.5%) had no initial reperfusion strategy.

Treatment was administered within 12 h of symptom onset with either an intravenous thrombolytic agent or primary PTCA in 38,787 patients (28.3% of the nontransfer group). Of these, 3,940 (10.2%) were treated with streptokinase or anistreplase, 29,908 (77.1%) were treated with alteplase (rt-PA) and 4,939 (12.7%) underwent primary PTCA. Of the patients who had PTCA, 4,052 (82%) were identified as having no contraindication to thrombolytic therapy ("lytic-eligible" patients). Of those receiving rt-PA, 24,705 (82.6%) had the required minimal 48-h follow-up. In addition, 7,998 patients were treated after 12 h of symptom onset (or complete data on treatment times were not available), 357 underwent immediate surgical revascularization and 148 were treated with an intracoronary thrombolytic agent. The 4,052 lytic-eligible patients who had PTCA and the 24,705 patients who had rt-PA with minimal 48-h follow-up form the primary comparison groups for this report.

Presenting characteristics. The presenting characteristics of the lytic-eligible patients undergoing primary PTCA are compared with those of the patients receiving alteplase (Table 1). The thrombolytic-treated patients were more likely to be women, had a higher incidence of diabetes and were more likely to be current smokers. Although fewer of the thrombolytic-treated patients had anterior wall MI, there was

Table 1. Characteristics on Admission of Patients Receiving Alteplase Compared With Lytic-Eligible Patients Undergoing Primary Percutaneous Transluminal Coronary Angioplasty

	rt-PA (n = 24,705)	PTCA (n = 4,052)	p Value
Mean age (yr)	61.1%	60.5%	0.01
≥75 yr old	15.1%	15.6%	NS
Male	70.1%	72.5%	0.002
Previous MI	18.0%	18.8%	NS
Previous stroke	2.9%	2.5%	NS
Previous CABG	6.5%	7.3%	NS
Previous PTCA	6.8%	13.0%	0.0001
Diabetes	18.4%	17.1%	0.05
Hypertension	42.4%	41.7%	NS
Previous CHF	3.5%	3.5%	NS
Current smoker	38.9%	35.8%	0.0001
Anterior MI	35.7%	39.1%	0.0001
Not low risk	55.0%	51.2%	0.0001
Killip class II	9.5%	9.0%	NS
Killip class III	2.3%	2.3%	NS
Killip class IV (shock)	1.3%	4.2%	0.0001
STE or LBBB on 1st ECG	87.6%	76.2%	0.0001

Data presented are percent of patients. CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; ECG = electrocardiogram; LBBB = left bundle branch block; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; rt-PA = recombinant tissue-type plasminogen activator; STE = ST segment elevation.

a higher percentage of these patients in the "not low risk" category. Significantly more of the patients in the PTCA group had previous PTCA. There were three times as many patients in the PTCA group who had cardiogenic shock at presentation. More patients in the PTCA group did not have STE or left bundle branch block (LBBB) on their presenting electrocardiograms (ECGs).

Patients receiving alteplase. An accelerated dose regimen, defined for this analysis as infusion completed within 100 min, was prescribed in 92% of the patients receiving alteplase. Of patients in the rt-PA group, therapy with oral aspirin was reported in 92%, intravenous heparin in 97% and intravenous beta-blockers in 28%.

Patients undergoing PTCA. Lytic-ineligible patients were older (64.1 vs. 60.5 years), had a higher incidence of previous stroke (14.4% vs. 2.5%) and were more likely to be >75 years old (24.9% vs. 15.6%) and women (37.3% vs. 27.5%) compared with lytic-eligible patients (all $p < 0.0001$). The in-hospital mortality rate for lytic-ineligible patients in the PTCA group was much higher than that for lytic-eligible patients in the PTCA group (13.6% vs. 6.2% for all patients, 12.5% vs. 5.2% for those not presenting with cardiogenic shock, both $p < 0.001$).

Of the patients in the PTCA group, aspirin use was recorded in 86%, intravenous heparin in 95% and intravenous beta-blocker in 16%.

Treatment intervals. The median duration of symptoms before hospital presentation was 1.5 h for both groups (Table 2). The median time to initiation of rt-PA ("door to drug" time) was 42 min, with 72% of patients receiving rt-PA within 1 h and 91% within 2 h. The median time to balloon inflation for lytic-eligible patients in the PTCA group was 111 min. Ten percent of these patients were treated within 1 h, and approximately two-thirds between 1 and 3 h after hospital arrival.

Table 2. Time to Treatment Intervals for Lytic-Eligible Patients

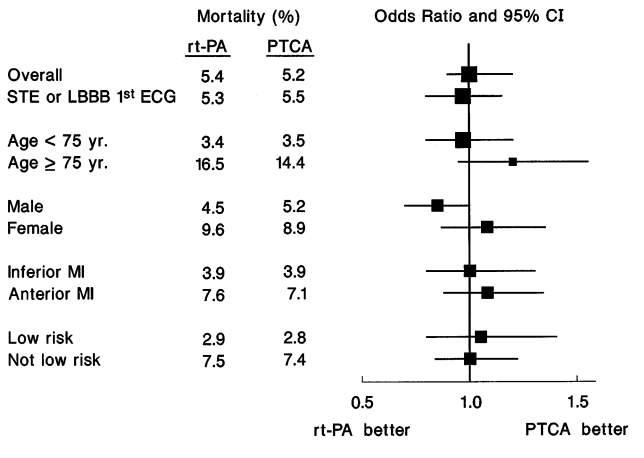
	rt-PA (n = 24,705)	PTCA (n = 4,052)	p Value
Onset–presentation (min)	90 (55,160)	89 (55,165)	NS
Presentation–treatment (min)	42 (28, 67)	111 (81,159)	0.0001
Onset–treatment (min)	145 (95, 230)	216 (152, 329)	0.0001
Onset–treatment <4 h (%)	76.5	56.9	0.0001

Data presented are median (25th, 75th percentiles). Abbreviations as in Table 1.

Outcomes. *Mortality.* In-hospital mortality for lytic-eligible patients not presenting in cardiogenic shock is presented in Figure 1. The overall in-hospital mortality rate for these two groups of patients was similar—5.4% after rt-PA and 5.2% after PTCA. (At this mortality level, the sample size provides a 73% probability of detecting a difference in absolute mortality of 1%.) For patients who presented with STE or LBBB on their first ECG, in-hospital mortality was again similar—5.3% after rt-PA and 5.5% after PTCA. Unadjusted in-hospital mortality for patients grouped by age, gender, infarct location and risk stratification did not identify a significant advantage of either treatment modality for any subgroup.

Multiple logistic regression analysis was performed to assess variables that might be predictive of increased mortality. These variables included age (<75 vs. ≥75 years), gender, infarct location (anterior vs. inferior), previous MI, previous stroke, STE or LBBB on first ECG, Killip class, previous PTCA, history of coronary artery bypass graft surgery (CABG), time to treatment (<4 h vs. ≥4 h) and treatment modality (rt-PA vs. PTCA). Variables independently predictive of increased mortality risk were Killip class 2 or 3, age ≥75 years, previous stroke, female gender, treatment interval >4 h

Figure 1. Odds ratios and 95% confidence intervals (CI) for reduction in mortality in lytic-eligible patients not in shock treated with rt-PA compared with PTCA.



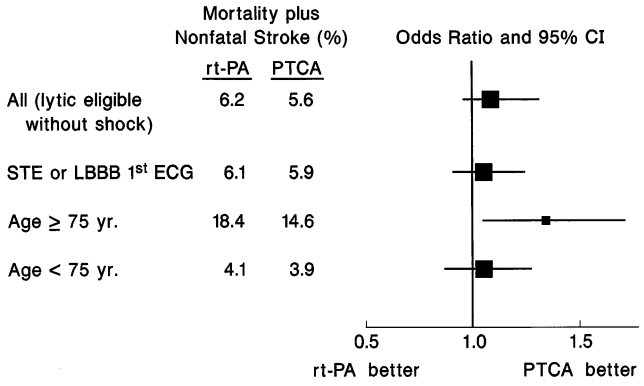


Figure 2. Odds ratios and 95% confidence intervals (CI) for reduction in the combined end point of in-hospital mortality plus nonfatal stroke in patients treated with rt-PA compared with PTCA.

from symptom onset and anterior infarct location. Treatment modality was not an independent predictor of mortality.

For patients presenting in cardiogenic shock, mortality was very high in both groups of patients, but was significantly higher in those patients receiving rt-PA compared with PTCA (52.3% vs. 32.4%, $p < 0.0001$).

Stroke. The incidence of stroke was higher in patients treated with rt-PA, owing to higher rates of intracranial bleeding. The total stroke rate was 1.6% after rt-PA compared with 0.7% after PTCA, with intracranial bleed rates of 1.0% and 0.1%, respectively (all $p < 0.0001$). The incidence of the combined end point of death and nonfatal stroke was not significantly different between the two treatment modalities for the groups as a whole, for those presenting with STE or LBBB on their first ECG or for those <75 years old (Fig. 2). However, for patients ≥75 years old, the combined end point was significantly higher in the rt-PA group than in the PTCA group (18.4% vs. 14.6%, $p < 0.03$), owing primarily to the high rate of intracranial bleeding (2.5%) observed in the older patients treated with rt-PA.

Subsequent events. For patients not presenting in cardiogenic shock, the incidence of recurrent ischemia was significantly higher in patients receiving rt-PA than in those lytic-eligible patients undergoing PTCA (14.6% vs. 9.8%, $p < 0.001$). However, the incidence of recurrent MI was not significantly different (2.9% vs. 2.5%). The incidence of late congestive heart failure was identical at 10.6%. Fewer patients in the rt-PA group than in the PTCA group developed late cardiogenic shock (3.4% vs. 7.7%, $p < 0.001$). The incidence of major bleeding was lower in the rt-PA–treated patients than in the PTCA-treated patients (3.2% vs. 4.0%, $p < 0.01$).

Subsequent procedures. Of the patients not presenting in cardiogenic shock, 3.5% of rt-PA–treated patients underwent rescue PTCA. An additional 18.6% of the rt-PA–treated patients underwent elective PTCA and 7.3% underwent elective CABG. Immediate CABG was performed in 2.5% of the patients undergoing PTCA, and an elective bypass procedure was performed in 6.5% of the patients in the PTCA group. A second PTCA procedure was performed in 15.5% of the patients in the primary PTCA group. Subsequent revascularization may be underestimated owing to late transfer of patients for elective CABG or PTCA. Intraaortic balloons were placed in 20.8% of the patients undergoing PTCA who were not in shock, whereas intraaortic balloon counterpulsation was done in only 3.4% of the patients in the rt-PA group ($p < 0.0001$).

Patients excluded because of early transfer. Of the total group of patients receiving rt-PA, 17.4% were transferred within 48 h of admission (only 2.4% of patients undergoing primary PTCA were transferred). Comparison of the presenting characteristics of lytic-treated patients who were transferred early with those of patients remaining in the hospital suggests that the transfer patients were not at increased risk of death or stroke. The proportion of patients classified as "not low risk" in the transfer group was identical to that in the group remaining in the hospital (55%). Other prognostic variables were more favorable for the transfer patients. These patients were younger (58.5 vs. 61.1 years), with a lower proportion >75 years (9.6% vs. 15.1%), were less likely to be women (26.8% vs. 29.9%), were more likely to present in Killip class I (89.1% vs. 87.0%) (all $p < 0.001$) and had a lower incidence of previous stroke (2.3% vs. 2.9%, $p < 0.03$). In a subset of 13,298 patients treated with rt-PA at PTCA-capable hospitals, only 5.3% were transferred within 48 h, and the mortality rate for those remaining in the hospital was the same as that for the rt-PA–treated patients from all hospitals (5.4%).

Discussion

The NRMI-2 data are unique in that they reflect recent "real-world" clinical experience with a large number of patients treated at institutions across the United States. Some of the patients selected for primary PTCA included those with a contraindication to thrombolytic therapy, those with hemodynamic instability and those in whom there was diagnostic uncertainty. However, the major cohort of patients having primary PTCA is remarkably similar, in terms of demographic data, presenting characteristics and baseline risk, to that group treated with lytic therapy.

Comparison with PAMI, GUSTO-I, MITI and GUSTO-IIb. The in-hospital mortality rate of 5.4% for patients treated with rt-PA is consistent with that recorded in other trials of rt-PA combined with oral aspirin and intravenous heparin (9,10). The in-hospital mortality rate in this study is lower than the 6.5% in-hospital mortality rate reported for the rt-PA–treated patients in the Primary Angioplasty in Myocardial Infarction (PAMI) trial (3). However, patients in PAMI were treated later (mean time 3.8 vs. 2.4 h) and did not receive an accelerated rt-PA regimen.

The incidence of intracranial bleeding after rt-PA in this study is somewhat higher than that observed in the Global Use of Strategies To Open occluded arteries (GUSTO) trial (10,11). This is partly explained by the higher proportion of patients >75 years old treated in NRMI-2 (15.6% vs. 12%). However, even those <75 years old had an intracranial bleed

rate of 0.7%, compared with 0.52% reported in GUSTO. This difference may relate to patient selection; in particular, it is observed that only 0.7% of patients in GUSTO had a previous stroke (11), but 2.9% of patients treated with rt-PA in this study had a history of stroke.

Lytic-eligible patients who were not in shock and who underwent primary PTCA had an in-hospital mortality rate of 5.2%, comparable to that of patients receiving rt-PA. This is twice the in-hospital mortality rate (2.6%) observed for the overall group of patients undergoing PTCA in the PAMI trial (3). Contrary to the results of PAMI, subgroup analysis did not reveal a high risk group that clearly fared better in terms of mortality after PTCA. However, death plus nonfatal stroke occurred less frequently after PTCA in patients >75 years old. The mortality advantage of PTCA over thrombolytic therapy was confined to patients ≥65 years old in the PAMI trial (12). The rate of recurrent MI after PTCA in this study is nearly identical to the 2.6% rate observed in the PAMI trial (3), but in contrast to the PAMI results, is not significantly different from the 2.9% rate of reinfarction observed after thrombolysis.

The in-hospital mortality rate for 1,050 patients with STE undergoing primary PTCA in the Myocardial Infarction Triage and Intervention (MITI) Registry was 5.5%, identical to the 5.5% observed in these patients in NRMI-2 (13). MITI Registry patients undergoing PTCA had baseline characteristics similar to those of 2,095 patients receiving thrombolytic therapy, and there was no significant difference in mortality at hospital discharge or at 1-year follow-up (13). Compared with MITI, NRMI-2 data are more recent and national in scope and represent a larger number of patients.

Data in this study are also comparable to the results of the randomized GUSTO-IIb substudy comparing 573 patients treated with rt-PA with 565 patients undergoing primary PTCA. Seven-day mortality in GUSTO-IIb was similar to the in-hospital mortality observed in NRMI-2 and did not differ by treatment modality (14).

Study limitations. This was an analysis of an observational data base, not a randomized, controlled trial. Observed similarities or differences in outcomes may be related to differences in patient selection and baseline characteristics rather than to treatment effects. However, after the exclusion of patients in cardiogenic shock and those identified as ineligible for lytic therapy, the remaining patients referred for either primary PTCA or alteplase therapy appear to be at very similar baseline risk.

Incomplete follow-up of patients enrolled in NRMI-2 is a potential problem, because data on patients transferred to another institution are not consistently available and mortality could be underestimated. This is of particular concern for lytic-treated patients, because a disproportionate number are transferred early. A 48-h minimal follow-up period was selected because the majority of deaths (10), reinfarctions (15) and intracranial bleeding episodes (11) occur during this period.

Conclusions. These data indicate that within NRMI-2, treatment is initiated significantly later for patients undergoing primary PTCA than for those treated with alteplase (rt-PA). The mortality in patients in shock is very high, but is lower in patients receiving primary PTCA than in those receiving lytic therapy. In the absence of shock or a contraindication to lytic therapy, baseline characteristics, in-hospital mortality and reinfarction rates were similar whether patients received rt-PA or underwent PTCA. Unadjusted mortality was the same in various patient groups defined by age, infarct location, gender and risk category. Although more intracranial bleeding was observed in patients receiving rt-PA, the incidence of the combined end point of mortality and nonfatal stroke was also not significantly different between the rt-PA–treated patients and PTCA-treated patients, except in those >75 years old.

These results suggest that primary PTCA may be the preferred treatment for certain subgroups of patients, including those with a contraindication to lytic therapy, those with hemodynamic instability and those at increased risk of intracranial bleeding, such as the elderly. However, in lytic-eligible patients not in shock, PTCA and rt-PA are comparable, alternative means of reperfusion when analyzed in terms of in-hospital mortality, mortality plus nonfatal stroke and reinfarction.

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