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Primary Angioplasty Versus Systemic Thrombolysis in Anterior Myocardial Infarction

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OBJECTIVES This study compares the efficacy of primary angioplasty and systemic thrombolysis with t-PA in reducing the in-hospital mortality of patients with anterior AMI.

BACKGROUND Controversy still exists about the relative benefit of primary angioplasty over thrombolysis as treatment for AMI.

METHODS Two-hundred and twenty patients with anterior AMI were randomly assigned in our institution to primary angioplasty (109 patients) or systemic thrombolysis with accelerated t-PA (111 patients) within the first five hours from the onset of symptoms.

RESULTS Baseline characteristics were similar in both groups. Primary angioplasty was independently associated with a lower in-hospital mortality (2.8% vs. 10.8%, $p = 0.02$, adjusted odds ratio 0.23, 95% confidence interval 0.06 to 0.85). During hospitalization, patients treated by angioplasty had a lower frequency of postinfarction angina or positive stress test (11.9% vs. 25.2%, $p = 0.01$) and less frequently underwent percutaneous or surgical revascularization after the initial treatment (22.0% vs. 47.7%, $p < 0.001$) than did patients treated by t-PA. At six month follow-up, patients treated by angioplasty had a lower cumulative rate of death (4.6% vs. 11.7%, $p = 0.05$) and revascularization (31.2% vs. 55.9%, $p < 0.001$) than those treated by t-PA.

CONCLUSIONS In centers with an experienced and readily available interventional team, primary angioplasty is superior to t-PA for the treatment of anterior AMI. (J Am Coll Cardiol 1999;33:605–11)
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Controversy still exists about the relative benefit of primary percutaneous transluminal coronary angioplasty (PTCA) over systemic thrombolysis for the treatment of acute myocardial infarction (AMI). Primary PTCA has shown clinical benefit over thrombolytic therapy in two randomized studies (1,2). In the GUSTO IIb study, the mortality of patients assigned to primary PTCA was not statistically different from patients assigned to tissue plasminogen activator (t-PA), although the patients treated by primary PTCA experienced a modest benefit in the combined endpoint of death, nonfatal reinfarction and disabling stroke (3). Recently, a metaanalysis of 10 randomized trials of primary PTCA versus thrombolysis in AMI that included 2,606 patients, demonstrated a significant reduction of mortality in patients treated by PTCA at the end of the study period (4).

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The size of the risk area of an occluded coronary artery is an important determinant of outcome in patients with AMI (5). Patients with anterior AMI have worse immediate and long-term prognosis than patients with nonanterior AMI, who normally have smaller risk areas (6–10). In addition, data from thrombolytic trials show that patients with large risk areas benefit most from reperfusion of the infarct related artery, whereas the benefit of thrombolysis in patients with small risk areas is usually modest (11). Therefore, if primary PTCA yields a more rapid and complete restoration of blood flow through the infarct related artery than does systemic thrombolysis, the benefit from PTCA should be more striking in patients with anterior AMI. On this basis, the purpose of our study was to determine whether primary PTCA is better than accelerated t-PA in reducing the in-hospital mortality of patients with anterior AMI.

METHODS

Patient selection. One-hundred and eighty-nine patients (86% of the study population) were enrolled in our own prospective randomized trial (12). The protocol of our trial

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
CABG	= coronary artery bypass graft surgery
CK-MB	= MB fraction of creatine kinase
LAD	= left anterior descending coronary artery
PTCA	= percutaneous transluminal coronary angioplasty
t-PA	= tissue plasminogen activator

stated that patients who arrived at the emergency department with suspected AMI were candidates for recruitment if chest pain had lasted between 30 min and 5 h without response to nitrates and the 12-lead electrocardiogram showed ST elevation of at least 0.2 mV in two or more contiguous precordial leads. Criteria for exclusion were contraindications to thrombolysis, left bundle branch block, age younger than 18 years and females of childbearing age. The remaining 31 patients (14% of the study population), who were also randomized and treated in our institution, belonged to a multicenter trial of primary PTCA versus accelerated t-PA in AMI (3). They were included in the present analysis because they exactly fulfilled all the inclusion criteria of our trial.

Randomization and treatment groups. Eligible patients were given 300 mg of aspirin intravenously unless there was a known allergy. They were taken to the coronary care unit and were informed about the protocol which had been approved of by the hospital institutional review board. An informed consent was obtained for being included in the trial. Enrolled patients were randomly allocated to primary PTCA (group A) or systemic thrombolysis (group B).

Patients randomly assigned to primary PTCA were immediately taken to the cardiac catheterization laboratory. In our center there is a continuous availability of a coronary interventional team. A bolus of 10,000 I.U. of heparin was administered and small additional boluses if necessary to achieve an activated clotting time longer than 350 s. The procedure was started with a right coronary angiography first in order to assess this artery and the status of the collateral circulation to the left anterior descending artery (LAD) (13). Primary PTCA was performed using conventional catheter-balloon technique. Stents were used only for suboptimal balloon PTCA results or flow-limiting dissections. An intraaortic balloon pump was inserted in patients with hemodynamic instability or in patients with large infarctions when TIMI flow in the LAD was lower than grade 2 at the end of the procedure. Left ventriculography was not performed during this procedure. Femoral sheaths were removed 4 to 8 h after the procedure when the activated partial-thromboplastin time was lower than 60 s. Once the sheaths were withdrawn, heparin was restarted and the dose adjusted aiming for a partial-thromboplastin time twice the control value during 48 h.

Patients randomly assigned to thrombolysis received single-chain tissue plasminogen activator (t-PA, alteplase) as a front-loaded regimen starting with a 15 mg intravenous bolus, followed by an infusion of 0.75 mg/kg over 30 min (maximum 50 mg) and then, 0.50 mg/kg over 60 min (maximum 35 mg). An intravenous bolus of heparin (5,000 I.U.) was administered simultaneously with alteplase and was followed by a continuous perfusion of heparin, initially at 1,000 I.U./h and later adjusted to achieve a partial-thromboplastin time twice the control value.

Adjunctive pharmacologic therapy followed the standards of the coronary care unit. Heparin was administered in patients from both treatment groups for at least 48 h. The indication of anticoagulation after this period was individualized to each patient independently of the treatment group assigned.

Angiographic evaluation. In patients from group A, the number of diseased vessels (diameter narrowing 50% or more), the level of LAD occlusion and the TIMI flow in the LAD at the baseline diagnostic coronary angiography are reported. The occlusion of the LAD was considered proximal if located before the first well-developed septal branch, distal if located after the third diagonal branch and mid if located between these limits. The primary PTCA procedure was considered successful when the TIMI flow in the LAD at the end of the procedure was grade 2 or 3 and the residual stenosis was less than 50 percent. Patients from group B did not undergo an early coronary catheterization following thrombolysis unless clinically indicated.

The protocol of our trial encouraged the performance of a routine predischarge cardiac catheterization with coronary angiography and left ventriculography for patients from both treatment groups to assess the patency and residual stenosis of the LAD and the left ventricular ejection fraction (LVEF). However, the indication of revascularization was established on clinical bases.

Clinical course. The primary objective of this study was to examine in-hospital death. Secondary objectives were to examine the occurrence of nonfatal reinfarction, postinfarction ischemia and the need for revascularization procedure after the initial treatment (primary PTCA or t-PA). Reinfarction was defined as the recurrence of ischemic chest pain of at least 30 min duration with ST segment elevation of a minimum of 0.1 mV over the previous ST segment in two contiguous leads and an enzyme profile consistent with the diagnosis. Postinfarction angina was defined as the recurrence of ischemic chest pain with electrocardiographic changes without fulfilling criteria for reinfarction. Postinfarction ischemia was defined as the presence of spontaneous postinfarction angina and/or positive stress test before discharge. Independently of the treatment group assigned, severe ischemic symptoms that persisted or recurred despite optimal pharmacologic therapy were treated by emergency coronary angiography and revascularization. The in-hospital and sixth month follow-up cumulative rates of death,

Table 1. Baseline Characteristics of the Patients

	Group A n = 109	Group B n = 111
Age, years: *median (25th–75th percentiles)*	63 (53–71)	60 (53–74)
Male	91 (84%)	89 (80%)
Smokers	67 (62%)	78 (70%)
Hypercholesterolemia*	23 (21%)	37 (33%)
Hypertension	35 (32%)	43 (39%)
Diabetes Mellitus	13 (12%)	19 (17%)
Previous myocardial infarction	14 (13%)	14 (13%)
Killip class at admission:		
Class I	99 (91%)	100 (90%)
Class II	6 (5%)	6 (5%)
Class III	2 (2%)	1 (1%)
Class IV	2 (2%)	4 (4%)

Differences were not statistically significant for any comparison, except for hypercholesterolemia (*p = 0.04).

nonfatal reinfarction, postinfarction ischemia and revascularization were analyzed. The sixth month follow-up was accomplished by personal interview or by telephone call if the personal interview was not feasible.

Statistical analysis. All analyses adhered to the intention to primary treatment principle. Differences in means between both groups were analyzed with the Student *t*-test for unpaired observations. For comparisons of proportions between groups, the Chi-square test was used, except in cases whose expected values were less than 5 in which case we used the Fisher exact test. Multivariate analysis for mortality was performed by multiple logistic regression. Odds ratios were expressed together with 95% confidence intervals. All results were analyzed using a two-sided significance level of 0.05, but all p values <0.20 are reported. Data analyses were performed by using the statistical software SPSS 7.5 for Windows 95, from SPSS Inc., 1996.

RESULTS

Study population. Two-hundred and twenty patients with anterior wall AMI less than five hours from the onset of symptoms were randomized in our institution from July 1991 to May 1996. One-hundred and nine patients were assigned to primary PTCA (group A) and 111 patients were assigned to thrombolysis with t-PA (group B). In this period, 632 patients with anterior AMI were admitted to our coronary care unit. Among these, 67 patients who were admitted in the first five hours of evolution were referred for primary PTCA without having been enrolled in the trial because of having exclusion criteria, patient's refusal or physician's preference.

The baseline clinical characteristics of the two groups are summarized in Table 1. The median elapsed time between the onset of symptoms and hospital admission was 120 min in both groups (25th and 75th percentiles = 85–180 min in group A and 80–175 min in group B, p = NS).

In-hospital therapy. Of the 109 patients randomly assigned to primary PTCA, 1 patient (1%) had a normal coronary angiogram, 66 patients (60%) had single-vessel disease, 25 patients (23%) had double-vessel disease and the other 17 (16%) had triple-vessel disease. The level of LAD occlusion was located in the proximal segment in 40 patients (37%), in the mid segment in 64 patients (59%) and in the distal segment in 4 patients (4%). The baseline TIMI flow in the LAD was grade 0 in 87 patients (80%), grade 1 in 7 patients (6%), grade 2 in 11 patients (10%) and grade 3 in 4 patients (4%). Of the 94 patients with an occluded LAD (TIMI flow grades 0 or 1), 31 patients (33%) had collateral circulation to the LAD.

One-hundred and seven patients from group A (98%) underwent primary PTCA of the LAD. One patient had a coronary anatomy unsuitable for PTCA and was treated by coronary artery bypass grafting (CABG). The other patient had a normal coronary angiogram at baseline in spite of the infarction being confirmed by electrocardiogram and enzyme profile. The median elapsed time from the onset of symptoms to the first balloon inflation was 197 min (25th and 75th percentiles = 150–250 min). The median length of time from the onset of symptoms to the end of the primary PTCA procedure was 225 min (25th and 75th percentiles = 180–295 min). Fourteen patients (13%) received 21 stents because of a suboptimal balloon PTCA result or dissection. In the majority of patients, PTCA was attempted only to the infarct related artery, but in 3 cases additional PTCA to another vessel was performed due to persistent hemodynamic instability. None of the patients assigned to PTCA had previously received systemic thrombolysis. The PTCA procedure was successful in 101 patients (94.4%) and TIMI grade 3 flow at the end of the procedure was obtained in 73 patients (68.2%). No patient underwent emergency CABG because of complications during the PTCA. Four patients from group A underwent CABG in the first 72 h after primary PTCA because of extensive coronary artery disease unfavorable for further percutaneous revascularization.

All patients from group B received systemic thrombolysis with t-PA. The median elapsed time from the onset of symptoms to the start of the t-PA infusion was 150 min (25th and 75th percentiles = 105–215 min).

Significant differences between groups A and B were not found in the administration of aspirin (98% of patients in both groups), early intravenous betablockers (16% vs. 21%, p = NS), oral betablockers (48% vs. 53%, respectively, p = NS), angiotensin-converting-enzyme inhibitors (45% vs. 51%, p = NS) and oral anticoagulants (15% vs. 10%, p = NS) during hospitalization.

In-hospital course. Two patients from group A who had the LAD occluded at the basal angiography and one patient from group B developed a peak serum level of the MB fraction of creatine kinase (CK-MB) less than twice the upper limit of normality. In the remaining patients, a typical

Table 2. In-Hospital Clinical Events

	Group A n = 109	Group B n = 111	p Value
Major adverse events:			
Death	3 (2.8%)	12 (10.8%)	0.02
Non-fatal reinfarction	4 (3.7%)	6 (5.5%)	NS
Stroke	0	3 (2.7%)	0.08
Death, reinfarction or stroke	7 (6.4%)	20 (17%)	0.01
Free-wall rupture*	4 (3.7%)	9 (8.1%)	0.16
Minor adverse events:			
Bleeding requiring transfusion	3 (2.8%)	4 (3.6%)	NS
Post-infarction angina	9 (8.3%)	16 (14.4%)	0.15
Post-infarction ischemia†	13 (11.9%)	28 (25.2%)	0.01
New revascularization procedure:	24 (22.0%)	53 (47.7%)	< 0.001
PTCA to the LAD‡	17 (15.6%)	39 (35.1%)	0.001
CABG§	7 (6.4%)	14 (12.6%)	0.12

*All free-wall ruptures were proved at autopsy or operation; †Defined as post-infarction angina or positive stress test; ‡In-hospital PTCA of the LAD after the initial treatment (PTCA or t-PA); §In-hospital CABG after the initial treatment; CABG = Coronary artery bypass graft surgery; LAD = Left anterior descending coronary artery; PTCA = Percutaneous transluminal coronary angioplasty.

enzyme profile consistent with the diagnosis of AMI was observed. Table 2 summarizes the adverse clinical events of patients from both treatment groups that occurred during hospitalization. Mortality was lower in group A (3 patients from group A [2.8%] vs. 12 patients from group B [10.8%], p = 0.02). In group A the causes of death were cardiogenic shock (1 patient) and free-wall rupture (2 patients). In group B they were cardiogenic shock (5 patients), free-wall rupture (5 patients), hemorragic stroke (1 patient) and coronary perforation with cardiac tamponade complicating a PTCA procedure performed due to a reinfarction (1 patient). The independent effect of primary PTCA on the reduction of the in-hospital mortality was confirmed after adjustment for age, sex, hypercholesterolemia, diabetes and previous infarction (adjusted odds ratio 0.23, 95% confidence interval 0.06 to 0.85, p = 0.02). Additionally, age (odds ratio per year of increase 1.06, 95% confidence interval 1.01 to 1.11, p = 0.03) and diabetes mellitus (odds ratio 3.8, 95% confidence interval 1.2 to 12.1, p = 0.03) were also independently associated with in-hospital mortality by stepwise multiple logistic regression.

There were no differences in the occurrence of nonfatal reinfarction in either group. There were three strokes (two embolic and one hemorragic stroke) and all of them were in group B. Group A had a lower frequency of post-infarction ischemia than group B (11.9% vs. 25.2%, p = 0.01).

Predischarge cardiac catheterization. Seventy-three patients from group A (67%) and 77 patients from group B (69%) underwent a predischarge cardiac catheterization including coronary angiography and left ventriculography. The angiographic findings of these patients are summarized in Table 3. Group A showed a better TIMI flow in the LAD and a lower diameter stenosis. The left ventricular ejection fraction was similar in both groups. The proportion of patients who underwent PTCA of the LAD (excluding primary PTCA procedures) was significantly lower in group A than in group B (17 patients [15.6%] vs. 39 [35.1%], p = 0.001). Group A also had a tendency to undergo CABG less frequently than group B (7 patients [6.4%] vs. 14 [12.6%], p = 0.12). The median length of hospitalization was 15 days in each group (25th and 75th percentiles = 11–20 days in group A and 12–19 days in group B, p = NS).

Sixth month follow-up. The clinical status was assessed at the sixth month postinfarction in 190 of the 201 patients eligible for follow-up, 99 patients from group A and 91 patients from group B. The proportion of missing patients at the sixth month postinfarction was 5% in group A and 6% in group B. After discharge, there were no differences in the occurrence of death (two patients from group A [2.0%] vs. one patient from group B [1.1%], p = NS), nor nonfatal

Table 3. Pre-Discharge Cardiac Catheterization

	Group A n = 73	Group B n = 77	p Value
Level of LAD acute occlusion*:			NS
Proximal segment	28 (38.3%)	24 (38.1%)	
Mid-segment	44 (60.2%)	36 (57.1%)	
Distal segment	1 (1.5%)	3 (4.8%)	
TIMI flow in the LAD:			< 0.001
Grade 0	2 (2.7%)	14 (18.2%)	
Grade 1	0	5 (6.5%)	
Grade 2	7 (9.6%)	15 (19.5%)	
Grade 3	64 (87.7%)	43 (55.8%)	
LAD stenosis, %†	31 (20–40)	70 (50–90)	< 0.001
LVEF, %†	48 (40–60)	47 (39–60)	NS

*The level of LAD acute occlusion could not be determined in 14 patients from group B; †LVEF and LAD stenosis are presented as median and the 25th and 75th percentiles; LAD = Left anterior descending coronary artery; LVEF = Left ventricular ejection fraction; TIMI = Thrombolysis in Myocardial Infarction (trial).

Table 4. Cumulative Sixth Month Adverse Clinical Events*

	Group A	Group B	p Value
Death	5 (4.6%)	13 (11.7%)	0.05
Nonfatal reinfarction	6 (5.5%)	8 (7.2%)	NS
Revascularization†	34 (31.2%)	62 (55.9%)	< 0.001

*The in-hospital events are included in these figures. †PTCA or CABG in the first 6 months after the initial treatment. Abbreviations as in Table 2.

reinfarction (two patients from group A [2.0%] vs. one patient from group B [1.1%], p = NS). Unstable angina appeared in five patients from group A and in nine patients from group B (5.1% vs. 9.9%, p = NS). Percutaneous luminal coronary angioplasty was performed on 11 patients from group A and 13 patients from group B (11.2% vs. 14.4%, p = NS). One patient from group A and three patients from group B underwent CABG (1% vs. 3.3%, p = NS). The cumulative incidence of death, nonfatal reinfarction and percutaneous or surgical revascularization at the sixth month postinfarction are presented in Table 4.

DISCUSSION

Our study includes patients with anterior AMI admitted to our hospital within five hours from the onset of symptoms and randomly assigned to primary PTCA or systemic thrombolysis with accelerated t-PA. Patients treated by primary PTCA experienced a reduction in mortality, recurrent ischemia and need for revascularization of the infarct related artery during the hospital stay. At the six-month follow up, post discharge adverse events were infrequent and similar in both groups. The reduction of in-hospital mortality observed in patients treated by primary PTCA was maintained at six months and the cumulative incidence of percutaneous or surgical revascularization was also significantly lower in the PTCA group. Therefore, in a hospital committed to mechanical reperfusion, primary PTCA of the infarct related artery in patients with anterior AMI offers an immediate clinical advantage over systemic thrombolysis with t-PA which is maintained at midterm follow-up.

Our results apply to a strategy based on initial treatment with either primary PTCA or t-PA and subsequent additional revascularization when clinically appropriate. Patients from both groups were treated by emergency coronary angiography and revascularization for episodes of severe ischemic symptoms that persisted or recurred despite optimal pharmacologic therapy. Less severe postinfarction ischemia was treated by elective coronary revascularization during the same hospitalization when indicated. Because a substantial amount of patients from both groups underwent coronary revascularization for recurrent ischemia during hospitalization, this study represents a comparison of two strategies, rather than a study of the use of primary PTCA versus thrombolysis alone.

Randomized studies do not ensure the control of potential confounding variables if the size of the study groups is not large enough. Small differences in the distribution of these variables may result in confusion if they are strongly associated with the response object of the study. Therefore, we used a multiple logistic regression analysis to confirm the independent effect of primary PTCA on the reduction of in-hospital mortality. After adjustment for age, sex, hypercholesterolemia, diabetes and previous infarction, primary PTCA treatment remained an inverse independent predictor of in-hospital death.

In some previously published studies, patients with anterior AMI seemed to obtain an additional benefit from direct PTCA over thrombolysis (14–17), but none of them was specifically designed to study the outcome of patients with anterior AMI in this setting. We chose to undertake this study in only one center trying to offer a more uniform treatment in each group, particularly with respect to the primary PTCA procedure whose efficacy largely relies on the experience of the center (18). The angiographic success rate of primary PTCA in the present study was 94%. The success rate of PTCA in this study was similar to other randomized trials (1–3,19) and some observational series (20–23). Whether or not the reduction in mortality observed in the present study could be accomplished in hospitals with less experience or less commitment to primary PTCA remains to be seen. The absence of added benefit of primary PTCA over systemic thrombolysis in patients with anterior AMI observed in the Gusto IIb trial (24) might reflect the relatively small experience in primary PTCA of some participating centers.

Some concern has been raised about the time delay linked to primary angioplasty (20). The median elapsed time from the onset of symptoms to the hospital admission was 120 min in both groups. The median length of time from the onset of symptoms to the initiation of treatment was 197 min in group A (first balloon inflation) and 150 min in group B (start of the t-PA infusion). Estimations of the time to reperfusion could not be reliably determined in both groups. In group A, the median elapsed time from the onset of symptoms to the end of the primary PTCA procedure was 225 min, although the time to the end of the primary PTCA procedure overestimates the time to the restoration of flow to the infarct related artery. In group B, patients did not undergo early coronary angiography following thrombolysis. Since previous studies have shown that patency rates higher than 80% do not occur before 90 min of the start of front-loaded t-PA (25–27), the longer time that was necessary to start the primary PTCA procedure may have been compensated for a more rapid restoration of blood flow once the treatment started.

In previous trials (1,3,19) patients treated by primary PTCA had a shorter length of hospitalization than patients treated by thrombolysis. In our study, the hospital stay was similarly long in both groups. This was due to the fact that our study protocol stated that stress tests should not be

performed before the ninth day postinfarction, as well as encouraged the performance of a routine predischarge cardiac catheterization for patients from both treatment groups to assess the status of the infarct related artery and the LVEF. The infarct related artery was more frequently patent and the diameter stenosis was smaller in patients treated by primary PTCA. As in some previous trials (1,19), the LVEF was similar in survivors from both groups.

Limitations of the study. The study protocol did not call for a baseline assessment of the left ventricular ejection fraction, but indirect data such as the equal prevalence of previous myocardial infarction, the similar distribution in Killip class and the random assignment of the two groups suggest that it was probably similar in both groups. The proportion of patients who were in cardiogenic shock or clinical heart failure on admission was lower than the expected which explains in part the low overall mortality of our study population. The difficulty in obtaining an informed consent from the sickest patients, the urgency to treat them and the physician's preference for using primary PTCA for patients in cardiogenic shock or heart failure may explain the low proportion of these patients who were enrolled in this trial, as occurred in earlier randomized studies (28). Additionally, the exclusion from this trial of patients ineligible for thrombolysis, who frequently have a high risk clinical profile (29,30), may have contributed to the low overall mortality. Thus, the 2.8% in-hospital mortality rate of the primary PTCA arm of this trial contrasts with the 16.4% mortality of the whole anterior AMI population treated by primary PTCA within 6 h of symptoms in our center in a similar period, who had a 16% prevalence of shock at admission and frequently had contraindications to thrombolytics (13).

The proportion of patients receiving early intravenous beta-adrenergic blocking agents was low in both treatment groups which might explain in part the high rate of free-wall rupture observed in our study. Previous thrombolytic trials have demonstrated the beneficial effect of early intravenous betablockade on the reduction of myocardial rupture.

This study had a long inclusion period and there have been advances in the treatment of AMI, especially in interventional practice, since this study first began. Although no thrombolytic regimen has been clinically proven to be superior to front-loaded t-PA, new promising thrombolytics and combinations of these with glycoprotein IIb/IIIa receptor antagonists or antithrombin agents are being evaluated. On the other hand, the wider use of stents and the greater experience in primary PTCA procedures, the improvement in the PTCA catheter technology and the use of adjunctive pharmacological therapy like glycoprotein IIb/IIIa antagonists might improve the result of PTCA in patients with AMI. However, while no pharmacological regimen shows a significant clinical superiority over front-loaded t-PA, primary PTCA may be considered as the best therapeutic choice for the treatment of anterior wall AMI in centers with an experienced and readily available interventional team.

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