# In-hospital and one-year outcomes of patients with high-risk acute myocardial infarction treated with thrombolysis or primary coronary angioplasty

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*Key words:*
**Angioplasty, primary; Myocardial infarction; Reperfusion; Thrombolytic therapy.**

*Background.* **The aim of this study was to observe the outcomes of high-risk patients with acute myocardial infarction treated with primary angioplasty and intravenous thrombolysis in a community setting.**

*Methods.* **A prospective study of the in-hospital and 12-month outcomes was conducted in 17 cardiology centers where primary angioplasty was available, and in 30 where it was not. Three thousand seventy-four patients in the first 12 hours of an evolving infarction were recruited; among these, 2227 patients who met one or more pre-defined criteria of increased risk were included in the study.**

*Results.* **Thrombolysis and primary angioplasty were respectively performed in 1090 and in 721 patients; 416 patients (18.7%) received no reperfusion treatment. The incidence of the primary combined in-hospital endpoint (death, non-fatal reinfarction and stroke) was similar in patients treated with thrombolysis (9.2%) and with primary angioplasty (10.7%) (odds ratio-OR 1.19, 95% confidence interval-CI 0.86-1.63, p = NS), and was higher (22.6%) in patients receiving no reperfusion treatment as compared to thrombolysis (OR 3.30, 95% CI 2.36-4.63, p < 0.0001). The occurrence of the 12-month endpoint (death, reinfarction, congestive heart failure and recurrent angina) was lower after primary angioplasty than after thrombolysis (26.8 vs 35.0%, OR 0.68, 95% CI 0.55-0.84, p = 0.0003), due to a lower incidence of angina. At multivariate analysis, older age, anterior infarction, Killip class > 1, high heart rate, and low systolic blood pressure on admission were all significantly associated with a higher incidence of both endpoints. The adjusted analysis confirmed that, despite similar in-hospital results after both reperfusion treatments, primary angioplasty was independently associated with better 1-year outcomes (relative risk 0.66, 95% CI 0.56-0.79, p < 0.0001).**

*Conclusions.* **In this observation in the community setting, a strategy of primary angioplasty in patients with high-risk myocardial infarction was not better than thrombolysis in terms of mortality or recurrent infarction, but was associated with less angina at 1 year.**

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## Introduction

The comparison of primary percutaneous transluminal coronary angioplasty (P-PTCA) and intravenous thrombolysis (TT) in the treatment of acute myocardial infarction (AMI) has been the object of several small randomized trials in recent years; a meta-analysis of the 2606 patients included in those trials has shown a significant 34% reduction (from 6.5 to 4.4%) in mortality at 30 days for patients treated with P-PTCA[1]. Evidence of benefit in higher-risk subgroups, however, is limited, comparative follow-up data are scarce, and several large registries[2-4], with the exception of the recently reported Maximal Individual Therapy in Acute Myocardial Infarction (MITRA)-Myocardial Infarction Registry (MIR) pooled data[5], have failed to document significantly better outcomes after P-PTCA as compared to TT. Some skepticism may remain, therefore, as to whether the results of those randomized trials can be transferred into clinical practice. This prospective study was designed to investigate the current use of P-PTCA and TT in the community setting, and to com-

pare the outcomes of patients with high-risk AMI receiving one of the above reperfusion treatments.

## Methods

**Study organization.** This study was a multicenter, prospective observational study jointly designed in 1998 by the Italian Association of Hospital Cardiologists (ANMCO) and the Italian Association of Interventional Cardiologists (GISE). Seventeen Italian cardiology centers which currently performed P-PTCA in AMI (type A centers), and 30 cardiology centers which did not (type B centers), participated in the study (see Appendix). To participate, each type A center was required to have performed at least 200 elective and 20 P-PTCA procedures in the 12 months preceding the start of the study; among type B centers, only sites with intensive care units dedicated to patients with acute coronary syndromes participated in the study.

**Study patients.** Patients presenting within 12 hours of the onset of symptoms (chest pain lasting ≥ 30 min, with ST-segment elevation of ≥ 0.1 or 0.2 mV in at least 2 peripheral or contiguous precordial leads, respectively) were recruited. Patients were considered at high risk if they had one or more of the following characteristics: female gender and age > 70 years, diabetes and age > 70 years, impaired left ventricular function (Killip class > 1) on admission, systolic blood pressure < 100 mmHg and heart rate > 100 b/min, large myocardial infarction (> 4 leads showing ST-segment deviation), previous Q-wave myocardial infarction in another electrocardiographic territory, contraindication to thrombolysis. Patients admitted to a participating site for rescue angioplasty after failed lysis were not included. The protocol was approved by the institutional review board of each hospital. All patients gave informed consent to their inclusion in the study.

**Treatment strategies.** Reperfusion strategies, including the use of stents and platelet glycoprotein IIb/IIIa antagonists during P-PTCA, and all other treatments were performed according to the local standards and to the judgment of the treating cardiologists.

**Outcome measures.** The primary study endpoints were: 1) the composite of death, non-fatal stroke and reinfarction during initial admission; 2) the composite of death, reinfarction, angina, and congestive heart failure during 1 year following enrolment. Recurrent myocardial infarction after inclusion in the study was defined as chest pain lasting ≥ 30 min accompanied by an increase in either creatine kinase or the creatine kinase-MB fraction at least 2 times the upper local limit of normal (or a new elevation in a downsloping plasma level curve) or electrocardiographic evidence of infarction. Angina was defined as typical chest pain associated with ischemic electrocardiographic changes during the initial hospital stay, or constituting the indication for new hospital admission after initial discharge. Congestive heart failure was defined as the occurrence of signs (Killip class 3 or 4) or symptoms (New York Heart Association class III or IV) of left ventricular failure during the initial hospital stay, or constituting the indication for new hospital admission after initial discharge. Stroke was defined as a new cerebral deficiency occurring after admission and lasting ≥ 24 hours. The door-to-balloon and door-to-needle times were defined as the intervals between hospital admission and the first balloon inflation or the start of intravenous lytic drug infusion respectively.

**Data collection and management.** All patients were observed during their initial hospital stay; a follow-up visit was planned at 12 months after discharge, and was replaced by a telephone interview when appropriate. In order to assess the consecutive recruitment of patients, after the end of the study all centers were required to provide an administrative summary of all the patients discharged during the study period with International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis codes 410.00 to 410.92. For non-recruited patients, information about both the cause for exclusion from the study and the in-hospital outcome was required.

**Statistical analyses.** Analyses were performed at the ANMCO Research Center. Descriptive statistics were used to describe the patient population, and the median or mean values were computed, as appropriate. Categorical values were compared using the $\chi^2$ test, or the Fisher exact test, as appropriate, and the odds ratio (OR) and 95% confidence interval (CI) were computed. Continuous variables were compared using the Student's t-test or analysis of variance. Logistic regression analysis was used to adjust for factors influencing the in-hospital outcome. The Cox regression model was used for the evaluation of factors independently associated with the 1-year outcome. To avoid potential bias, further adjusted analyses were performed excluding patients with contraindications to TT.

The following variables were studied in relation to the primary endpoints: a) continuous variables: age, systolic blood pressure, and heart rate on admission, b) dichotomous variables: gender, anterior as compared with non-anterior location of the infarct, Killip class on admission > 1 vs 1, time from symptom onset to admission (> 6 vs ≤ 6 hours), history of diabetes mellitus, history of hypertension, previous myocardial infarction, presence of other cardiovascular risk factors (1-2 vs none, and > 2 vs none, of the following: history of angina, of heart failure, of stroke, of peripheral vascular disease, of myocardial revascularization, dyslipidemia, family history of myocardial infarction), reperfusion treatment (P-PTCA vs TT, no reperfusion treat-

ment vs lysis), treatment with antiplatelet agents, with angiotensin-converting enzyme inhibitors, and with beta-blockers during the first 24 hours of admission. P values < 0.05 were considered statistically significant. All tests were performed using the SAS statistical package, version 8.0 (Cary, NC, USA).

## Results

**Recruitment.** Enrolment began in May 1998 and ended in June 1999, after 3074 patients had been recruited; of these, 2227 patients (72.4%) met the study criteria for high-risk AMI and constitute the study population.

**Patient characteristics.** The criteria for patient inclusion in the high-risk cohort are shown in table I; more than one criterion could be reported in the case report form, and ST-segment deviation in > 4 leads was present in the vast majority of patients. Reperfusion treatment was attempted by TT in 1090 patients, and by P-PTCA in 721 patients; in 416 patients (18.7%) no reperfusion treatment was attempted. As shown in table II, the baseline clinical characteristics of these three subsets of patients were different: those not submitted to reperfusion treatment were older, more often females, had a higher prevalence of diabetes mellitus, hypertension, previous myocardial infarction, congestive heart failure, peripheral vascular disease and stroke; in addition, a significantly greater proportion of patients without reperfusion treatment were admitted > 6 hours after symptom onset, were in Killip class > 1

**Table I.** Criteria for patient inclusion in the high-risk cohort (n = 2227).

| Criteria | % of patients with the criterion present |
|---|---|
| Female > 70 years | 17.8 |
| Diabetic patient > 70 years | 9.0 |
| Killip class > 1 on admission | 23.7 |
| SBP < 100 mmHg and HR > 100 b/min | 2.7 |
| ST-segment deviation in > 4 leads | 81.9 |
| Previous Q-wave MI | 11.4 |
| Contraindications to thrombolysis | 10.2 |

HR = heart rate; MI = myocardial infarction; SBP = systolic blood pressure.

**Table II.** Clinical characteristics of the whole study population and of the high-risk cohort.

| | Total population (n=3074) | High-risk cohort (n=2227) | | | | |
|---|---|---|---|---|---|---|
| | | TT (n=1090) | P-PTCA (n=721) | No RT (n=416) | p | Total (n=2227) |
| Baseline characteristics | | | | | | |
| Female (%) | 23.5 | 26.8 | 22.1 | 40.1 | 0.001 | 27.8 |
| Age (years) | 64 ± 12 | 64 ± 12 | 63 ± 12 | 73 ± 12 | 0.001* | 65 ± 12 |
| > 70 years (%) | 30.6 | 32.1 | 27.9 | 60.1 | 0.001 | 36.0 |
| Previous angina (%) | 31.9 | 32.5 | 33.8 | 30.1 | 0.499 | 32.5 |
| Previous MI (%) | 15.5 | 15.9 | 17.5 | 25.0 | 0.001 | 18.1 |
| Previous PCI/CABG (%) | 5.7 | 4.9 | 7.9 | 5.1 | 0.063 | 5.9 |
| History of CHF (%) | 1.8 | 2.1 | 0.7 | 6.7 | 0.001 | 2.5 |
| History of stroke (%) | 3.6 | 2.4 | 2.5 | 12.5 | 0.001 | 4.3 |
| History of PVD (%) | 6.0 | 5.8 | 4.7 | 13.0 | 0.001 | 6.8 |
| History of dialysis (%) | 0.4 | 0.5 | – | 0.7 | 0.243 | 0.4 |
| History of hypertension (%) | 47.8 | 49.0 | 46.2 | 57.7 | 0.001 | 49.7 |
| History of DM (%) | 17.5 | 18.6 | 16.4 | 26.7 | 0.001 | 19.4 |
| Smoking habit (%) | 44.4 | 45.7 | 41.2 | 28.6 | 0.001 | 41.0 |
| Family history of MI (%) | 16.2 | 15.1 | 15.8 | 14.7 | 0.981 | 15.2 |
| Characteristics on admission | | | | | | |
| From symptom onset to admission (min) | 180 ± 160 | 152 ± 126 | 153 ± 124 | 224 ± 182 | 0.0001 | 178 ± 153 |
| Admitted > 6 hours after onset (%) | 9.8 | 6.9 | 7.5 | 20.9 | 0.001 | 9.7 |
| Killip class > 1 (%) | 17.2 | 18.9 | 25.1 | 33.9 | 0.001 | 23.7 |
| Killip class 3-4 (%) | 4.9 | 2.5 | 9.3 | 13.9 | 0.001 | 6.8 |
| HR > 100 b/min (%) | 8.7 | 7.3 | 9.7 | 18.8 | 0.001 | 10.2 |
| SBP < 100 mmHg (%) | 8.5 | 7.1 | 13.9 | 13.5 | 0.001 | 10.5 |
| Acute anterior MI (%) | 43.0 | 46.4 | 53.4 | 38.7 | 0.001 | 47.4 |
| Distribution by centers | | | | | | |
| Patients in type A centers | 1488 | 237 | 701 | 154 | – | 1092 |
| Patients in type B centers | 1586 | 853 | 20 | 262 | – | 1135 |

CABG = coronary artery bypass graft; CHF = congestive heart failure; DM = diabetes mellitus; HR = heart rate; MI = myocardial infarction; PCI = percutaneous coronary intervention; P-PTCA = primary percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; RT = reperfusion treatment; SBP = systolic blood pressure; TT = thrombolytic treatment. * no RT vs TT and no RT vs P-PTCA.

or had a heart rate > 100 b/min. The differences between patients treated with TT or P-PTCA were more limited, and the latter had a higher prevalence of advanced Killip class and hypotension or tachycardia on admission, and of anterior location of the infarction. A heart rate > 100 b/min and a systolic blood pressure < 100 mmHg were concomitantly present in 60 patients (2.7%): 32 were treated with P-PTCA, 8 with TT, and 20 without any reperfusion treatment. The distribution of patients receiving P-PTCA, TT and no reperfusion treatment by age classes and by the time intervals from the onset of symptoms are respectively detailed in table III and table IV; the use of reperfusion treatment decreased significantly across the three classes of increasing age and across the time intervals > 3 hours.

**Reperfusion treatment.** TT and P-PTCA were performed in 21.7 and 64.2% respectively of the 1092 patients admitted to type A centers, and in 75.2 and 1.7% respectively of the 1135 patients admitted to type B centers. It is of note that 20 patients admitted to type B centers had subsequent emergency transfer to other centers for P-PTCA. The number of patients without reperfusion treatment in type A centers was 154 (14.1%) vs 262 in type B centers (23.1%, $p < 0.001$). The median on-study number of P-PTCA procedures per month in type A centers was 3.6. In 701 patients admitted to type A centers P-PTCA was performed with a door-to-balloon time of 73 ± 114 min (median 50 min); this time interval was ≤ 60 min in 441 patients (62.9%). With regard to the patients submitted to P-PTCA, stents, intra-aortic balloon counterpulsation, and platelet glycoprotein IIb/IIIa antagonists were used in 85.4, 12.0 and 31.2% of cases respectively. P-PTCA was not performed in 391 patients admitted to type A centers; in 47 cases this decision was taken after emergency coronary angiography (due to a patent infarct-related artery or to an unfavorable lesion morphology); in the remaining 344 patients coronary angiography was not performed due to logistic constraints (131 cases), to the decision of the treating cardiologist (126 cases), to the patient's refusal or rapid unfavorable outcome (46 cases) or to other reasons (41 cases). Two hundred and thirty-three of these patients were treated with TT.

In total, TT was performed in 1090 patients, namely in 237 patients in A centers, and 853 patients in B centers. Patients in A vs B centers were more often over 70 years of age (39.2 vs 30.1%, $p = 0.007$), and had a history of hypertension (60.8 vs 45.7%, $p = 0.004$). All other baseline characteristics were similar.

Overall, TT was performed with a mean door-to-needle time of 42 ± 50 min (median 30 min); the time from admission to treatment was thus significantly shorter for TT than for P-PTCA ($p < 0.001$). Alteplase, streptokinase and other lytic drugs were used in 77.5, 17.3 and 5.2% of patients respectively.

Of the 2227 patients considered in the analysis, 227 (10.2%) had a contraindication to receive TT. The main reasons for exclusion from TT were absolute clinical contraindications (active bleeding, recent trauma or major surgery, and recent traumatic cardiopulmonary resuscitation).

Patients with contraindications to TT were older and had a more unfavorable clinical profile. Diabetes, previous myocardial infarction, stroke and peripheral vascular disease were significantly more frequent in these patients than in those without contraindications. At study entry, blood pressure was significantly lower, and the heart rate as well as the Killip class were significantly higher.

As expected, this more severe clinical profile was associated with a poor outcome: the in-hospital mortality was 17.2% for patients with contraindications to TT vs 9.5% for those without contraindications ($p = 0.0003$).

With regard to the reperfusion treatment, 57 (25.1%) of the 227 patients with contraindications were treated with P-PTCA (55 in type A centers and 2 in type

**Table III.** The distribution of patients receiving primary percutaneous transluminal coronary angioplasty (P-PTCA), thrombolytic treatment (TT) and no reperfusion treatment (RT) by age classes in the high-risk cohort (n = 2227).

| | < 55 years | 55-75 years | > 75 years |
|---|---|---|---|
| TT | 250 (54.58%) | 652 (50.58%) | 188 (39.17%) |
| P-PTCA | 181 (39.52%) | 433 (33.59%) | 107 (22.29%) |
| No RT | 27 (5.90%) | 204 (15.83%) | 185 (38.54%) |
| Total | 458 | 1289 | 480 |

$p < 0.0001$ ($\chi^2$).

**Table IV.** The distribution of patients receiving primary percutaneous transluminal coronary angioplasty (P-PTCA), thrombolytic treatment (TT) and no reperfusion treatment (RT) by time intervals from the onset of symptoms in the high-risk cohort (n = 2227).

| | < 1 hour | 1-3 hours | 3-6 hours | 6-12 hours |
|---|---|---|---|---|
| TT | 273 (51.61%) | 538 (51.69%) | 204 (46.26%) | 75 (34.72%) |
| P-PTCA | 184 (34.78%) | 339 (32.56%) | 144 (32.65%) | 54 (25%) |
| No RT | 72 (13.61%) | 164 (15.75%) | 93 (21.09%) | 87 (40.28%) |
| Total | 529 | 1041 | 441 | 216 |

$p < 0.0001$ ($\chi^2$).

B centers), while 170 (74.9%) did not receive any reperfusion therapy (55 patients in type A centers and 115 in type B centers).

Non-primary angioplasty during the initial 2 days after hospital admission was performed in 37 (3.39%) out of 1090 patients treated with TT.

**Concomitant drug regimens.** The adjunctive treatments administered during the initial hospital stay are shown in table V. As compared to patients treated with TT, those treated with P-PTCA received both beta-blockers and angiotensin-converting enzyme inhibitors less often during their hospital stay, and the former drugs remained substantially underprescribed at discharge in patients undergoing P-PTCA. A lower use of aspirin and other antiplatelet agents was also apparent in patients receiving no reperfusion treatment.

**In-hospital outcomes.** The in-hospital mortality was 7.7% in the total population (3074 patients), and 10.2% in the high-risk cohort; the in-hospital outcome of the latter is shown in table VI. The incidence of the composite in-hospital endpoint of death, reinfarction and stroke was 12.2% in the whole high-risk cohort; it was similar in patients treated with TT (9.2%) and in those treated with P-PTCA (10.7%, OR 1.19, 95% CI 0.86-1.63, p = 0.26), while it was significantly higher in patients receiving no reperfusion treatment (22.6%, OR 3.30, 95% CI 2.36-4.63, p < 0.0001). The total in-hospital mortality after P-PTCA and TT was 8.5 and 7.2% respectively. Since patients treated with P-PTCA presented with more severe clinical conditions, the mortality trend appeared to be reversed at adjusted analysis (logistic regression model) (OR 0.76, 95% CI 0.50-1.16 for P-PTCA vs TT), although the difference remained statistically not significant. Each component of the primary endpoint was similar in these treatment subgroups, except for the mortality that was significantly higher in patients without reperfusion treatment. Post-infarction angina was significantly less frequent after P-PTCA than after TT (3.7 vs 16.9%), as was the rate of elective revascularization procedures performed 24 hours after the onset of symptoms (6.3 vs 10.5%). Analysis, by type of center (A vs B), of the 1090 patients treated with TT showed a similar incidence of the primary endpoint (10.1 vs 8.9%): adjusted analysis showed OR 0.88, 95% CI 0.51-1.53. The length of hospital stay was shorter in patients treated with P-PTCA than in those treated with TT (9 ± 6 vs 11 ± 6 days). Logistic regression analysis (Table VII) showed that advanced age, a lower systolic blood pressure, a higher heart rate and an advanced Killip class on admission, an anterior site of infarction and a history of hypertension were all significantly associated with the occurrence of the primary in-hospital endpoint, while the type of reperfusion treatment was not. The adjusted model, in which patients with contraindications to TT were excluded, showed similar results: the type of reperfusion

**Table V.** Drug treatment in the high-risk cohort (n = 2227) during the initial hospital admission.

| | Initial 24 hours | | | | 24 hours to discharge | | | | Prescribed at discharge | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TT | P-PTCA | No RT | p | TT | P-PTCA | No RT | p | TT | P-PTCA | No RT | p |
| Beta-blockers | 41.7 | 24.1 | 26.0 | 0.001 | 58.0 | 34.8 | 32.9 | 0.001 | 56.9 | 38.2 | 39.8 | 0.001 |
| Antiplatelets | 90.6 | 94.9 | 76.7 | 0.001 | 89.5 | 92.0 | 71.6 | 0.001 | 93.2 | 96.1 | 82.9 | 0.001 |
| Heparin-AC | 89.4 | 88.2 | 79.8 | 0.001 | 76.2 | 68.9 | 63.7 | 0.001 | 33.4 | 8.3 | 29.7 | 0.001 |
| Nitrates | 78.4 | 50.8 | 83.7 | 0.001 | 73.6 | 42.7 | 76.9 | 0.001 | 70.6 | 37.0 | 78.6 | 0.001 |
| Statins | 3.2 | 3.5 | 1.4 | NS | 17.2 | 16.9 | 8.2 | 0.001 | 23.5 | 23.6 | 12.8 | 0.001 |
| ACE-inhibitors/ARB | 34.3 | 24.6 | 33.2 | 0.001 | 69.8 | 62.1 | 57.2 | 0.001 | 71.8 | 67.7 | 64.8 | 0.032 |

Values are percentage of patients. AC = anticoagulants; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; P-PTCA = primary percutaneous transluminal coronary angioplasty; RT = reperfusion treatment; TT = thrombolytic treatment.

**Table VI.** In-hospital and 1-year cumulative events in the high-risk cohort by reperfusion treatment.

| | TT (n=1090) | P-PTCA (n=721) | No RT (n=416) | p | Total (n=2227) |
|---|---|---|---|---|---|
| Components of in-hospital endpoint (%) | | | | | |
| Death | 7.2 | 8.5 | 21.4 | | 10.2 |
| Reinfarction | 1.5 | 1.7 | 1.0 | | 1.4 |
| Stroke | 0.5 | 0.5 | 0.2 | | 0.5 |
| Combined primary in-hospital endpoint | 9.2 | 10.7 | 22.6 | 0.26* | 12.2 |
| OR (95% CI) | 1 | 1.19 (0.86-1.63) | 3.30 (2.36-4.63) | < 0.0001** | |
| 1-year outcomes* (%) | | | | | |
| No. patients available/ eligible for follow-up | 950/1012 (93.9%) | 635/660 (96.2%) | 310/327 (94.8%) | | 1895/1999 (94.8%) |
| Death | 12.9 | 13.0 | 32.9 | | 16.7 |
| Reinfarction | 3.4 | 1.8 | 2.6 | | 2.7 |
| Angina§ | 14.2 | 7.1 | 10.1 | | 11.1 |
| Congestive heart failure§ | 4.5 | 4.9 | 5.1 | | 4.7 |
| Combined primary 1-year endpoint | 35.0 | 26.8 | 50.7 | | 35.2 |
| OR (95% CI) | 1 | 0.68 (0.55-0.84) | 1.92 (1.52-2.41) | 0.0003* < 0.0001** | |

CI = confidence interval; OR = odds ratio; P-PTCA = primary percutaneous transluminal coronary angioplasty; RT = reperfusion treatment; TT = thrombolytic treatment. * P-PTCA vs TT; ** no RT vs TT; § see definitions in the methods section. A hierarchical method was used: the rate of reinfarction was calculated only in survivors; the rate of angina in the patients still alive and without reinfarction at 1 year; the rate of congestive heart failure in the patients still alive and without reinfarction and angina at 1 year.

**Table VII.** Primary endpoint adjusted analysis in high-risk patients (n = 2227).

| Variable | In-hospital primary endpoint (n=271) | | | 1-year primary endpoint (n=785) | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p | RR | 95% CI | p |
| Age (continuous) | 1.07 | 1.05-1.08 | < 0.0001 | 1.03 | 1.02-1.03 | < 0.0001 |
| Female gender | 1.12 | 0.80-1.55 | 0.5105 | 1.24 | 1.05-1.46 | 0.0098 |
| History of DM | 1.15 | 0.80-1.63 | 0.4529 | 1.08 | 0.91-1.28 | 0.3651 |
| History of hypertension | 1.44 | 1.07-1.95 | 0.0179 | 1.08 | 0.93-1.25 | 0.3155 |
| Previous MI | 1.44 | 1.00-2.06 | 0.0484 | 1.43 | 1.20-1.70 | < 0.0001 |
| Risk factors (2 vs none) | 0.92 | 0.64-1.33 | 0.6639 | 1.14 | 0.94-1.38 | 0.1861 |
| Risk factors (> 2 vs none) | 0.88 | 0.53-1.46 | 0.6253 | 1.49 | 1.16-1.90 | 0.0015 |
| HR on admission (continuous) | 1.01 | 1.00-1.02 | 0.0083 | 1.01 | 1.00-1.01 | 0.0001 |
| SBP on admission (continuous) | 0.98 | 0.98-0.99 | < 0.0001 | 0.99 | 0.99-1.00 | < 0.0001 |
| Killip class (> 1 vs 1) on admission | 3.04 | 2.23-4.15 | < 0.0001 | 2.03 | 1.74-2.38 | < 0.0001 |
| Acute anterior vs non-anterior MI on admission | 1.41 | 1.04-1.92 | 0.0270 | 1.23 | 1.06-1.43 | 0.0053 |
| Time from symptom onset | 1.39 | 0.89-2.16 | 0.1462 | 1.18 | 0.95-1.48 | 0.1372 |
| P-PTCA vs TT | 0.87 | 0.60-1.27 | 0.4774 | 0.66 | 0.56-0.79 | < 0.0001 |
| No RT vs TT | 1.06 | 0.72-1.56 | 0.7747 | 1.02 | 0.84-1.23 | 0.8766 |

CI = confidence interval; DM = diabetes mellitus; HR = heart rate; MI = myocardial infarction; OR = odds ratio; P-PTCA = primary percutaneous transluminal coronary angioplasty; RR = relative risk; RT = reperfusion treatment; SBP = systolic blood pressure; TT = thrombolytic treatment.

treatment was not independently associated with the in-hospital primary endpoint (P-PTCA vs TT: OR 0.87, 95% CI 0.60-1.27, p = 0.4774).

**One-year outcomes.** Follow-up data (Table VI) were available for 1895 high-risk patients (94.8%) out of 1999 discharged alive. The baseline characteristics of the 104 patients whose follow-up data were unavailable did not differ significantly from those of the patients who completed the 12-month observation. After discharge, patients with initial TT underwent myocardial revascularization more often than those with P-PTCA (26.3 vs 14.1%, p < 0.001). At 1 year, the incidence of the composite endpoint (death, reinfarction, angina and heart failure) was 35.2% in the whole high-risk cohort; it was 35.0% in patients treated with TT, 26.8% in those

treated with P-PTCA (OR 0.68, 95% CI 0.55-0.84, p = 0.0003) and 50.7% in patients not receiving any reperfusion treatment (OR 1.92, 95% CI 1.52-2.41, p < 0.0001). Figure 1 shows the Kaplan-Meier curves of the 1-year primary endpoint. The curves diverged very early after study entry, without any apparent further divarication throughout the study.

Angina was the only component of the 1-year primary endpoint showing a significantly lower incidence in patients treated with P-PTCA than in those treated with TT.

The Cox regression model (Table VII) showed that older age, female gender, previous infarction, presence of > 2 additional cardiovascular risk factors, lower systolic blood pressure, higher heart rate, and advanced Killip class on admission, and an anterior site of infarction were all significantly associated with the primary composite 1-year endpoint, as was reperfusion treatment with P-PTCA vs TT (relative risk 0.66, 95% CI 0.56-0.79, p < 0.0001). The adjusted model, in which patients with contraindications to TT were excluded, confirmed this result (relative risk 0.64, 95% CI 0.54-0.78, p < 0.0001).

**Administrative data verification.** A complete administrative summary of all patients discharged or deceased during the study enrolment period with codes consistent with AMI was provided by 14/17 (82%) of type A centers and by 26/30 (87%) of type B centers; it showed that, overall, 58.4% of all patients with the index codes had been recruited in the former and 41.3% in the latter, and that the most frequent cause for patient exclusion was the absence of ST-segment elevation in 23 and 32% of cases respectively; the total in-hospital mortality for patients not recruited was 13.0 and 8.9% respectively, as compared with 10.0 and 7.4% for those recruited in the study.

## Discussion

**Representativeness of real-world patients.** Administrative verification showed that in the MISTRAL study patients were consecutively enrolled and that they were representative of the population of patients with ST-elevation AMI being admitted to community centers in current clinical practice, as described in other recent databases[5].

**Use of reperfusion treatments.** Underuse of reperfusion therapy is a recurrent finding in studies evaluating the management of patients with AMI. In the MISTRAL study the proportion of patients (including those with contraindications to lysis) who were left without reperfusion treatment was 18.7%, while it was 24% among lytic-eligible patients admitted within 6 hours of symptom onset in the Second National Registry of Myocardial Infarction (NRMI-2)[3], and it was even higher (36.8%) among lytic-eligible patients admitted within 12 hours in the German registry[5]. P-PTCA was performed in 64.2% of our patients in centers with P-PTCA facilities. A more marked underuse of mechanical reperfusion (42% of all lytic-eligible patients within 12 hours of onset) at sites performing P-PTCA was apparent in the German registry[5].

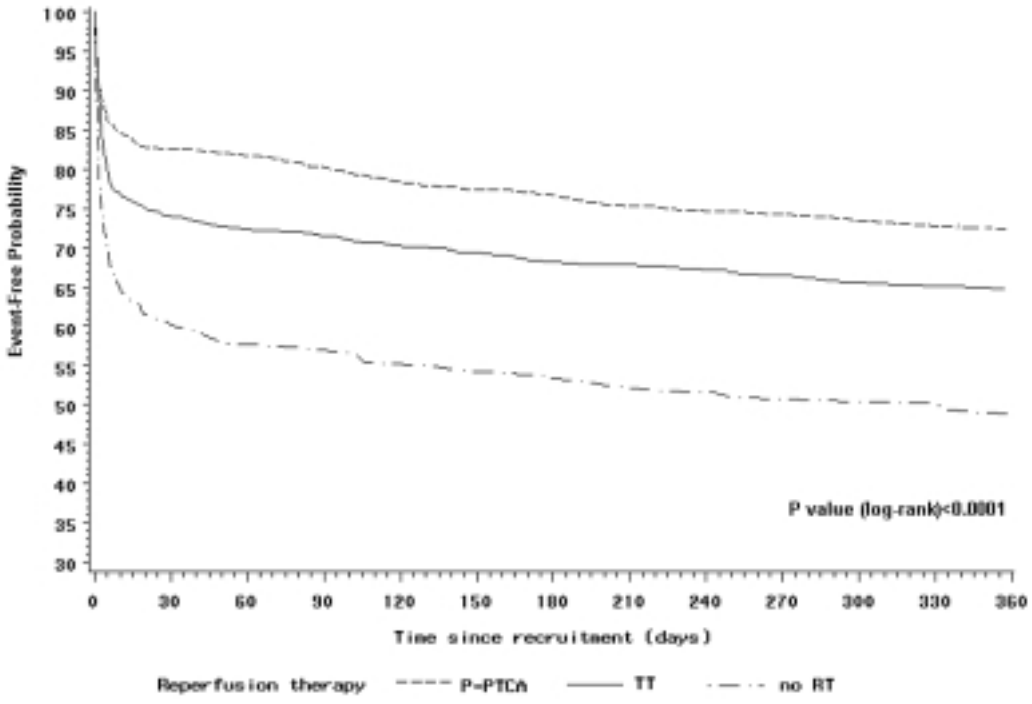


**Figure 1.** *Kaplan-Meier curves for the 1-year primary endpoint (composite endpoint of death, reinfarction, angina and heart failure). P-PTCA = primary percutaneous transluminal coronary angioplasty; RT = reperfusion treatment; TT = thrombolytic treatment.*

**Quality of reperfusion treatment.** An increase in the door-to-balloon time for P-PTCA has been shown to be associated with an increased short-term mortality[6,7]; although both patient- and hospital-related factors may contribute to delaying P-PTCA[8], the time from admission to intracoronary balloon inflation may be a useful marker of the quality of care for these patients[6,9]. The door-to-balloon time in our study was 73 ± 114 min (median 50 min), and it was ≤ 60 min in 63% of patients; this compares favorably with a mean time of 1.7 ± 1.2 hours in the Myocardial Infarction Triage and Intervention (MITI) registry 1988-1994[2], with the median time of 111 min in NRMI-2 1994-1998 where only 10% of lytic-eligible patients underwent P-PTCA within 60 min of admission[3] and with the median time of 70 min in the German registry, where however 18% of patients treated with P-PTCA had been transferred from other hospitals[5].

The door-to-needle time for TT may also be a marker of the quality of care, and an upper limit of 30 min has become a recommended standard in the United States[9]. The door-to-needle time for all patients receiving TT in our study (mean 42 ± 50 min, median 30 min) was shorter than in the MITI registry (mean 1 ± 1 hour)[2] and NRMI-2 (median 42 min)[3], and it was similar to that of the German registry[5].

The institutional volume of P-PTCA cases has also been shown to influence the in-hospital mortality of patients with AMI[10,11] and, together with the door-to-balloon time, it is considered as a marker of the quality of care. The median value of 3.6 on-study procedures per month by type A centers in MISTRAL lies in the upper caseload tertile of NRMI-2[6] and in the middle caseload tertile of the pooled NRMI-2 and 3 databases[10], and is probably higher than the median value in the MITRA-MIR study where 1327 patients were treated with mechanical reperfusion at 50 participating sites with P-PTCA facilities over about 2 years[5]. It may be of interest that in 1999 (i.e. the year when patient recruitment in MISTRAL ended), a median of 75 P-PTCA procedures were performed in the 17 type A centers participating in the study, with only 1 center reporting < 40[12].

**Patient outcomes.** The criteria used for the inclusion of patients in the MISTRAL study resulted in a study cohort with a moderately increased in-hospital mortality (10.2%), as compared to the total population (7.7%). Patients treated with P-PTCA in our study tended to have a moderately worse risk profile on admission and to receive less intensive adjunctive treatment than those treated with thrombolysis. Although the in-hospital mortality after both P-PTCA and TT in our study (8.5 and 7.2% respectively) was higher than in the MITI registry (5.5 and 5.6%)[2] and NRMI-2 (5.2 and 5.4%)[3], our data on the comparative acute outcome of either reperfusion treatment are consistent with those of previous studies. In contrast with these previous studies, a 10.6% in-hospital mortality was reported for the whole population of unselected patients receiving reperfusion treatment within 12 hours in the recently published German registry[5]. The baseline patient characteristics in that study were, overall, strikingly similar to those of the MISTRAL patients, except for a lower incidence of heart failure on admission. A lower in-hospital mortality after P-PTCA as compared to TT (6.4 vs 11.3%, OR 0.54, 95% CI 0.43-0.67) was observed in the German study[5], and was confirmed after adjustment for some confounding variables; interestingly, although the overall prevalence of adverse risk factors appeared to be rather well balanced between the two treatment groups in that study, heart failure on admission was less frequent in the P-PTCA group – while the reverse was true in MISTRAL. The MITRA-MIR study showed that patients treated later than 2 hours from symptom onset benefited more from P-PTCA. The lack of superiority of P-PTCA vs TT in MISTRAL could be due to the fact that 89.2% of the patients were treated within the first 2 hours of the onset of symptoms. The use of beta-blockers and angiotensin-converting enzyme inhibitors during the first 48 hours of admission in the MITRA-MIR study was also significantly higher in the P-PTCA group, while the opposite was observed in MISTRAL. A comparison of the results of these two observational studies should, therefore, be made with caution.

The in-hospital outcomes of the MISTRAL patients treated with P-PTCA and with TT were similar. Adjusted analysis confirmed this finding, and also showed that old age, low systolic blood pressure, high Killip class, elevated heart rate on admission, and anterior infarction were all predictors for an acute outcome – which is consistent with data from previous registries[2,3,5] and from large trials with TT[13]. At 1 year, initial treatment with P-PTCA, as compared to TT, was associated with a significantly lower incidence of the primary composite endpoint; this was due to a substantially lower incidence of severe angina, all other components of the composite endpoint being similar.

The lack of reperfusion treatment in the MISTRAL patients, as in other reports[14], was associated with worse baseline clinical characteristics and a more severe clinical picture at presentation; drug treatment during hospitalization was also less intensive in these patients than in those with initial reperfusion therapy. The in-hospital outcome of patients not receiving reperfusion treatment was as poor in MISTRAL (21.4% mortality, 22.6% combined primary endpoint) as it was in MITRA-MIR (20.4 and 23.6%, respectively)[5], and at 1-year follow-up one third of those patients had died.

**Conclusions.** In this nationwide prospective non-randomized observational study in the community setting, P-PTCA was performed in a timely fashion at centers where this reperfusion technique was available, but was used in a relatively limited number of patients. In the

study population, P-PTCA resulted in a lower incidence of the pre-specified composite 12-month outcome measure than TT. The advantage of P-PTCA over TT, however, was limited to a lower incidence of angina over 1 year. Despite logistical constraints to the widespread use of P-PTCA, experience with this reperfusion strategy is rapidly increasing in many centers of the National Health System in our country. Recent randomized studies[15] have shown that emergency transfer for P-PTCA instead of local treatment with TT may be beneficial in patients with AMI. Although this strategy was used in only 20 of our patients, it is recognized that it might be especially advantageous in high-risk patients such as those included in this study. New observations in the community setting may therefore be warranted. Further clinical investigations and more intensive management, both early during hospitalization and after discharge, are especially required for patients currently left without any reperfusion treatment since their short- and long-term outcomes remain very poor; emergency transfer to a center with an established P-PTCA program may be a valuable option for these patients.

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## Appendix

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*Data Management and Statistical Analyses*

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