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Clinical research

Effect of thrombolytic therapy on the risk of cardiac rupture and mortality in older patients with first acute myocardial infarction†

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Myocardial infarction;
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Elderly;
Thrombolysis;
Primary angioplasty

Aims To evaluate the effect of thrombolysis on mortality and its causes in older patients with acute myocardial infarction (AMI).
Methods and results An analysis of 706 consecutive patients ≥75 years old with a first AMI enrolled in the PPRIMM75 registry showed that although there were important differences in baseline characteristics among patients treated with thrombolysis, primary angioplasty (PA) and those who did not receive reperfusion therapy, 30 day mortality did not differ (29, 25, and 32%, respectively). The main cause of death in patients treated with thrombolysis was cardiac rupture (54%), whereas most of the other patients died in cardiogenic shock. Patients who received thrombolysis had a higher ($P < 0.0001$) incidence of free wall rupture (FWR) (17.1%) compared with those who did not receive reperfusion therapy (7.9%) or who underwent PA (4.9%). By multivariable analysis, patients treated with thrombolytic therapy (TT) showed an excess risk of FWR (OR, 3.62; 95% CI, 1.79–7.33), a hazard not observed in patients who underwent PA. When compared with patients who did not receive reperfusion therapy, the odds ratio of 30 day mortality was 1.07 (95% CI, 0.65–1.76) for patients treated with thrombolysis and 0.78 (95% CI, 0.45–1.34) for those who underwent PA. The figures for 24 month mortality were 0.78 (95% CI, 0.65–1.76) and 0.67 (95% CI, 0.28–0.81), respectively.
Conclusion Treatment of first AMI with TT increases the risk of FWR in very old patients, a risk not observed in patients treated with PA.

Introduction

At the present time, the role of thrombolytic therapy (TT) in elderly patients is an important unresolved question regarding reperfusion therapy for acute myocardial infarction (AMI). Intravenous thrombolysis reduces the short- and long-term mortality in patients younger than 75 years of age presenting with ST-segment elevation or left bundle branch block within 12 h of symptom onset.[1] In older patients, the evidence concerning the risk/benefit ratio of TT is less well established because the risk of related complications, particularly intracerebral haemorrhage, increases with age[2–5] and its efficacy may diminish.[6] Some studies have shown a survival advantage associated with the use of TT in patients ≥75 years of age with AMI,[7,8] but a number of observational studies have suggested an early mortality hazard,[9–11] with a long-term benefit in these patients.[10] The reasons for the possible initial hazard are currently unknown, but neither the increased risk of stroke nor the increased risk of severe haemorrhage explains it.[9]

We evaluated the effect of TT on short-term mortality and its causes in the cohort of patients enrolled in the Pronóstico del PRimer Infarto de Miocardio en Mayores de 75 Años (PPRIMM75) Registry, a database designed to assess the outcome and prognosis of first AMI in older patients admitted to a coronary care unit, based on extensive clinical data collection.[12–13] The outcomes were analysed according to the type of reperfusion therapy received by the patients.

Methods

Patients

The population consisted of all patients ≥75 years old admitted to the coronary care unit of Hospital General Universitario 'Gregorio Marañón' in Madrid, Spain, within 24 h from symptom onset with a definite diagnosis of first ST-segment elevation/left bundle branch block myocardial infarction between 1 October 1988 and 31 December 2000.

Variables

We abstracted variables related to baseline characteristics, infarct features, diagnostic procedures, treatment, and hospital course as

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previously described.[12–13] Data were obtained directly from clinical records. Three groups were defined according to reperfusion strategy: (i) patients who received intravenous TT immediately after coronary care unit admission (TT), (ii) those who underwent percutaneous coronary intervention as the first reperfusion therapy (PA) and (iii) those who received no reperfusion therapy immediately after admission (no reperfusion). The type of treatment was individually decided by the physician in charge according to common clinical criteria. Mechanical complications comprised free wall rupture (FWR), interventricular septal rupture, and papillary muscle rupture. FWRs were classified as confirmed or suspected. Confirmed FWR was defined as the occurrence of electromechanical dissociation or severe and sudden haemodynamic compromise associated with at least one of the following: i) severe pericardial effusion (>1 cm) with intrapericardial echoes and criteria of cardiac tamponade by two-dimensional echocardiography,[14] (ii) haemopericardium by pericardiocentesis, and (iii) anatomical confirmation (surgical or post-mortem). Suspected FWR included cases of death due to electromechanical dissociation after a course free of signs of pump failure[15] but in whom none of the confirmation tests was available. The causes of in-hospital mortality were classified as due to cardiogenic shock or pump failure, mechanical complications (any cardiac rupture or electromechanical dissociation), and other causes. Deaths due to intracranial or systemic bleedings were individualized in the group of other causes of death. Thirty-day, 6 month, and 2 year mortality were assessed by hospital chart review and telephone calls for cases without death on re-admissions. Vital status at January 7, 2001 was obtained for patients enrolled during years 1988–97. For patients admitted during years 1998–2000, vital status was assessed in the same way at 24 months after index event. Finally, complete follow-up could be obtained for 694 patients at 30 days (98.2%), 690 at 6 months (97.6%), and 682 at 2 years (96.5%).

Statistical analysis

The comparisons between groups were performed with χ^2 and ANOVA tests. All P values were two tailed. When individual group to group comparisons were made, Bonferroni's correction was used. The independent contribution of reperfusion therapies to outcomes was assessed by multiple logistic regression analyses. For each analysis, a saturated model was created by the inclusion of all variables known or suspected to be associated with the outcome plus those found to be statistically associated in the study group, which were age, gender, Killip class, anterior location, reperfusion therapies, delay >6 h, β-blocker use within the first 24 h, and year of admission for FWR, and the same variables plus diabetes for mortality. Also, the interactions between reperfusion therapy and time delay and reperfusion therapy and gender were assessed as both variables have been previously associated with higher rates of death or FWR after TT.[9,10,16–18] Subsequently, a backwards stepwise system was used to remove the variables that did not have an independent association with the outcome, provided it did not change the coefficients of the target variables (reperfusion therapies). All analyses were performed with the SPSS version 11.0.1 software (SPSS Inc., 2001).

Results

The final data set contained 706 patients aged 75–96. Of those, 46% received reperfusion therapy: 23% intravenous thrombolysis (112 patients t-PA, 48 streptokinase, and four anistreplase) and 23% PA. There was a significant increase throughout the years of the study in the use of echocardiography, thrombolysis, and PA (all $P < 0.001$) but not in the incidence of mechanical complications or FWR (data not shown). As expected, several differences were found among treatment groups in baseline characteristics (*Table 1*) and in the use of diagnostic studies and concomitant pharmacological therapies (*Table 2*). During hospitalization, the groups showed a different incidence of most lethal complications: cardiogenic shock, already present on admission, and mechanical complications (*Table 2*). Also, there were differences in the cause of death. Although the majority of thrombolysis-treated patients died as a consequence of a mechanical complication, the largest part FWR, most deaths in the other two groups were due to cardiogenic shock.

Thrombolytic therapy and cardiac rupture

The incidence of mechanical complications during hospitalization by treatment group is shown in *Table 3*. FWR was diagnosed in 55 patients (7.8%), 50 of them (91%) died in hospital (*Table 3*). The best evidence of FWR was post-mortem confirmation in eight cases, surgical verification in 15, positive pericardiocentesis in 11, and clinical plus echocardiographic criteria in 21 cases. In other eight patients (1.1%), FWR was suspected after dying of electromechanical dissociation without previous haemodynamic deterioration but lacking other confirmation criteria.[15] Ruptures were classified as early (within 48 h of hospital admission) and late (>48 h). Early cases accounted for 63% of FWRs and 50% of suspected ruptures.

TT was associated with a higher risk of early confirmed and confirmed/suspected FWR (*Table 3*). The incidence of FWR was not different in patients treated with PA compared with those who did not receive reperfusion therapy. Predictors of confirmed/suspected FWR are shown in *Figure 1*. In the whole group, the incidence of FWR in the patients who were admitted to the hospital within the first 6 h from symptom onset was 8% compared with 11.3% in those arriving later ($P = 0.17$). Among patients treated with thrombolysis, the incidence was higher in those admitted >6 h compared with those admitted earlier (33.3 vs. 15.1%, $P = 0.052$), but the interaction effect was not statistically significant in the multivariable analysis. There was a trend towards a higher incidence of FWR among patients treated with streptokinase or anistreplase compared with those who received t-PA (25 vs. 13.4%, $P = 0.066$). The independent effect of thrombolysis on the risk of FWR was calculated by multiple logistic regression analysis adjusting for age, gender, pulmonary congestion, anterior location, delay >6 h, β-blocker use within the first 24 h, and year of admission (*Figure 1*). After adjustment for confounding factors, TT emerged as the most powerful independent predictor of FWR. In contrast, PA did not influence the risk of FWR. When only confirmed ruptures were computed, the OR for TT was 4.55 (95% CI, 2.12–9.74).

Reperfusion therapy and mortality

Despite the marked differences in baseline characteristics, the crude in-hospital mortality did not significantly differ between the three treatment groups (*Table 2*). By multiple logistic regression analysis, thrombolysis did not show a significant effect on mortality compared with patients who did not receive reperfusion therapy (*Table 4*), but the individual risk estimates switched from a neutral or slightly deleterious effect at 30 days to a favorable trend at 6 and 24 months. Patients who underwent PA showed a trend for an improved

Table 1 Distribution of clinical variables of patients according to treatment group

	No reperfusion ($n = 378$)	Thrombolytic therapy ($n = 164$)	Primary angioplasty ($n = 164$)	*P*-value[a]
Age(years)[b]	80(77–84)	79(76–84)	78(76–83)	<0.0001
Female sex, *n* (%)	200(53)	82(50)	77(47)	0.43
Hypertension, *n* (%)	191(51)	80(49)	92(56)	0.37
Diabetes, *n* (%)	111(29)	42(26)	60(37)	0.08
Smoking, *n* (%)	73(19)	38(23)	39(24)	0.41
Previous angina, *n* (%)	96(26)	35(22)	37(23)	0.54
Killip Class, *n* (%)				0.001
I	254(67)	130(79)	105(64)	
II	57(15)	25(15)	24(15)	
III	32(9)	3(2)	13(8)	
IV	34(9)	6(4)	22(13)	
Anterior location, *n* (%)	131(35)	68(42)	93(57)	<0.0001
LVEF <0.31	67(21)	14(10)	40(26)	0.002
Time from symptom onset (hours)[b]	5(2–12)	3(2–4)	3(2–4.5)	0.47
Delay ≤6 h *n* (%)	212(56)	146(89)	143(87)	<0.0001

[a]*P* values for single comparison between the three groups.
[b]Median (25th–75th percentiles).

Table 2 Distribution of investigations, medical treatment, and outcomes during hospitalization according to treatment group

	No reperfusion ($n = 378$)	Thrombolytic therapy ($n = 164$)	Primary angioplasty ($n = 164$)	*P*-value[a]
Hospital investigations, *n* (%)				
Echocardiography	327(87)	155(95)	152(93)	0.007
Coronary angiography	66(18)	46(28)	164(100)	<0.0001
Medical treatment, *n* (%)				
Aspirin	320(85)	160(98)	148(90)	<0.0001
β-blockers	86(23)	70(43)	72(44)	<0.0001
Within first 24 h	45(12)	40(25)	40(24)	<0.0001
Intravenous nitroglycerin	254(69)	116(73)	105(64)	0.41
Heparin	254(70)	118(73)	162(99)	<0.0001
ACE-inhibitors	151(41)	82(50)	109(67)	<0.0001
Hospital outcomes, *n* (%)				
New onset cardiogenic shock	50(13.3)	12(7.3)	18(11.0)	0.09
Mechanical complications	35(9.3)	30(18.3)	9(5.5)	<0.0001
Stroke	9(2.4)	7(4.3)	9(5.5)	0.17
Death	122(32.3)	48(29.3)	41(25.0)	0.23
Cause of death, *n* (% of deaths)				<0.0001
Shock/pump failure	70(57)	14(29)	31(75)	
Mechanical complications	29(24)	26(54)	6(15)	
Other causes	23(19)	8(17)	4(10)	
Haemorrhagic	0	3(6.3)	0	

ACE: Angiotensin converting enzyme.
[a]*P*-values for single comparison between the three groups.

survival at each time interval when compared with patients who did not receive reperfusion therapy. When time to treatment was taken into consideration in an exploratory mode, a clinically relevant difference in the effect of TT compared with the other options was observed (*Figure 2*). When patients who received TT arrived within first 6 h from symptom onset, they showed lower mortality rates compared with the others. In contrast, those who were treated behind 6 h showed a trend to higher mortality. By multiple logistic regression analyses, the interaction TT × delay >6 h (excluding patients who received PA) was marginally significant ($P = 0.05$). However, the interaction was not statistically significant when reperfusion therapy was introduced in the model as a single variable.

Discussion

In our study, we observed a more than a three-fold increase in the risk of FWR within the first 48 h of treatment in older patients treated with thrombolysis compared with those who did not receive reperfusion therapy, a disadvantage not found in patients who underwent PA. The increase in the incidence of FWR is the most likely cause of the lack of benefit on early mortality associated with thrombolysis

Table 3 In-hospital incidence of cardiac rupture in the treatment groups

	No reperfusion ($n = 378$)	Thrombolytic therapy ($n = 164$)	Primary angioplasty ($n = 164$)	P-value[a]
Confirmed FWR, n (%)	21(5.6)	27(16.5)	7(4.3)	<0.0001
≤48 h	12(3.2)	21(12.8)	2(1.2)	<0.0001
>48 h	9(2.4)	6(3.7)	5(3.0)	0.70
Suspected FWR, n (%)	6(1.6)	1(0.6)	1(0.6)	0.47
≤48 h	3(0.8)	1(0.6)	0	0.53
>48 h	3(0.8)	0	1(0.6)	0.53
Confirmed + suspected FWR, n (%)	27(7.1)	28(17.1)	8(4.9)	<0.0001
≤48 h	15(4.0)	22(13.4)	2(1.2)	<0.0001
>48 h	12(3.2)	6(3.7)	6(3.7)	0.94
Interventricular septal rupture, n (%)	10(2.6)	2(1.2)	0	0.08
Papillary muscle rupture, n (%)	4(1.1)	1(0.6)	2(1.2)	0.84

[a] P-values for single comparison between the three groups.

observed in our population. Conversely, patients treated with PA did not show an increase in the risk of FWR.

Thrombolytic therapy and FWR risk

The incidence of FWR found in our study is higher than previously reported.[17–21] That difference is mostly explained by the inclusion criteria. The PPRIMM75 Registry consisted exclusively of patients ≥75 years old with a first AMI and enrolled a high proportion of women. Moreover, non-ST-segment elevation MIs were excluded. We expect this group to have a much higher than average risk of FWR.[17,18,20–22] We specifically sought to study this population, and therefore, our results are not comparable to those obtained in less selected populations. When our results are compared with those obtained in similar populations, the divergence is less. Maggioni *et al.*[22] reported in 2117 patients >70 years old treated with TT, a 25% incidence of electromechanical dissociation among those who died during hospitalization (a less specific surrogate of cardiac rupture), a 86% rate of cardiac rupture among autopsies performed, and a 31.9% in-hospital mortality rate in octogenarians. Actually, the real problem concerning cardiac rupture after AMI is underdiagnosis, not overdiagnosis. The fact that FWR has been a subject of research in our CCU and the high rate of echocardiographic studies performed at our institution are likely causes of the high rate of FWR diagnosis found.

The association between TT and risk of FWR in younger patients has been a controversial issue.[23–28] Although the effect of late thrombolysis on FWR has been debated,[16,23] now there is agreement that early thrombolysis reduces the absolute incidence of cardiac rupture. However, some studies have suggested that TT may increase the risk of FWR in patients of advanced age,[17,22] particularly older women,[17,23] or in patients with infarcts of anterior location.[29] This is the first report to provide convincing evidence that this is in fact the case. The risk is higher in these subgroups particularly when treatment is initiated beyond 6 h from symptom onset. The reasons by which the risk of FWR increases after TT in elderly patients deserve further investigation.

Should thrombolysis be avoided in the oldest patients?

The patients who received TT were at the lowest expected death risk according to admission characteristics. Although a better outcome would have been anticipated only considering the selection bias, we found no difference in 30 day mortality compared with the other patients. The study is underpowered to obtain definite conclusions, but our results are compatible with a lack of benefit of TT on early mortality in this population. Previous investigators have described an early mortality hazard associated with TT in older patients,[9–11] but no explanation for this effect have been provided yet. Thieman *et al.* found in an investigation on 7864 medicare patients >64 years old that TT was associated with a 38% increase in 30 day adjusted mortality risk when compared with no reperfusion, caused by an excess in the number of deaths within the first 2 days, which occurred only in patients >75 years old. This risk was higher in female patients and in patients with anterior infarcts treated behind the first 6 h. Neither systemic bleeding nor intracerebral haemorrhage explained the adverse outcome.[9] Our finding of an increased risk of FWR in the first 48 h in women and patients with anterior infarctions, particularly when are treated later, provide a comprehensive explanation for all these findings. Conversely, our results suggest that the use of TT may be associated with a long-term survival advantage as others have previously shown.[8,10]

In our study, the patients who were treated with PA showed a significantly lower incidence of FWR than those treated with TT. This difference may be explained by the reduction in the risk of cardiac rupture associated with the use of PA as suggested by others,[30,31] by a true increase in the risk of FWR caused by TT, as the marked increase in the incidence of FWR in patients treated with thrombolysis compared with those who did not receive reperfusion

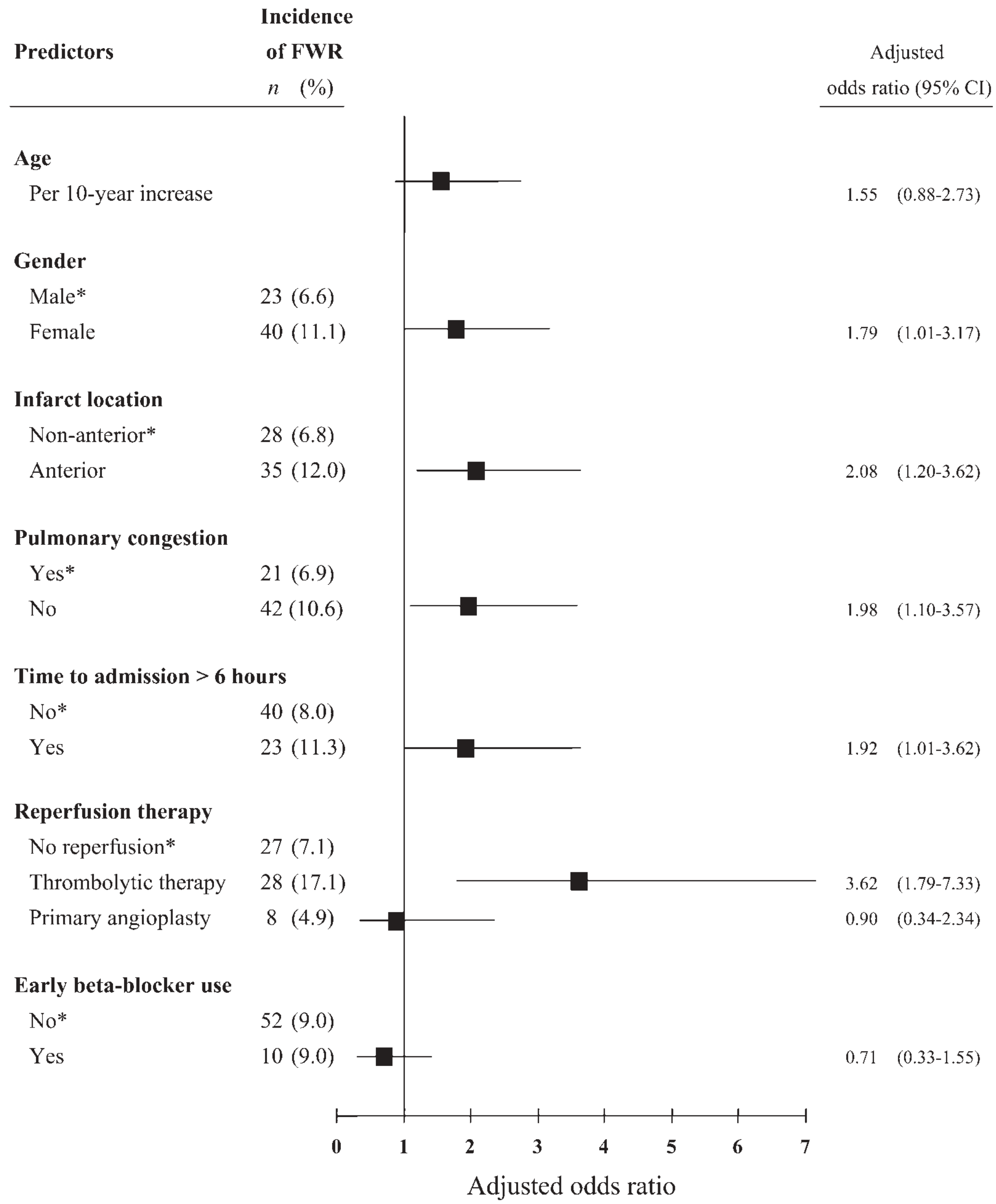

Figure 1 Predictors of confirmed/suspected FWR by multiple logistic regression analysis. The model was adjusted for age, gender, Killip class, infarct location, delay >6 h, type of reperfusion therapy, β-blocker use within 24 h of admission, and year of admission. Asterisks denote the reference variables.

therapy suggests, or by both. Although PA may be the treatment of choice for elderly patients with AMI they should not be denied TT, particularly in the first 6 h from symptom onset. However, an individualized risk/benefit assessment is needed in older patients who arrive after 6 h from symptom onset and for whom no other reperfusion therapy is available, particularly in women and anterior infarcts.

The early use of β-blockers (within first 24 h) was associated with a favourable trend on survival but opposite to that previously reported,[32] no benefit in reducing FWR neither in the whole population nor in patients treated with TT was found. However, because of the disappointingly low rate of its use in our population, a protective effect cannot be ruled out.

Our study has several issues to consider. The mode of treatment was not allocated randomly but on the basis of the physician's choice. Therefore, unmeasured baseline differences may explain part of the differences in mortality between treatment groups. Although only half of the patients had anatomical confirmation of the rupture, our study is based on a very careful definition of cardiac rupture, using diagnostic criteria that give an overall specificity >95%. Of the 55 cases defined as confirmed FWR, 23 had anatomic confirmation (specificity 100%), 11 presented with sudden cardiac tamponade treated with pericardiocentesis in which blood was extracted from the pericardium (specificity ~100%), and 21 developed electromechanical dissociation associated with cardiac tamponade with

Table 4 Independent predictors of 30 day, 6 month, and 24 month mortality by multiple logistic regression analysis

	30 days		6 months		24 months	
	OR	95%CI	OR	95% CI	OR	95% CI
Age[a]	1.42	1.17–1.72	1.42	1.17–1.72	1.47	1.22–1.78
Female sex	1.70	1.17–2.46	1.59	1.11–2.30	1.51	1.06–2.15
Diabetes	1.10	0.75–1.62	1.20	0.82–1.76	1.41	0.97–2.06
Killip Class >I	4.31	2.96–6.27	5.00	3.44–7.29	4.97	3.39–7.30
Anterior location	1.28	0.88–1.85	1.40	0.97–2.02	1.42	0.99–2.03
Time to admission >6 h	1.14	0.75–1.73	1.24	0.82–1.88	1.12	0.74–1.68
Early BB treatment[b]	0.59	0.34–1.04	0.50	0.29–0.88	0.48	0.28–0.81
Thrombolysis[c]	1.07	0.65–1.76	0.86	0.52–1.40	0.78	0.48–1.26
Primary angioplasty[c]	0.78	0.45–1.34	0.73	0.29–0.88	0.67	0.28–0.81

OR, odds ratio; CI, confidence interval.
[a]Effect per 5 year intervals.
[b]β-blocker treatment within first 24 h from hospital admission.
[c]Effect compared to no reperfusion therapy.

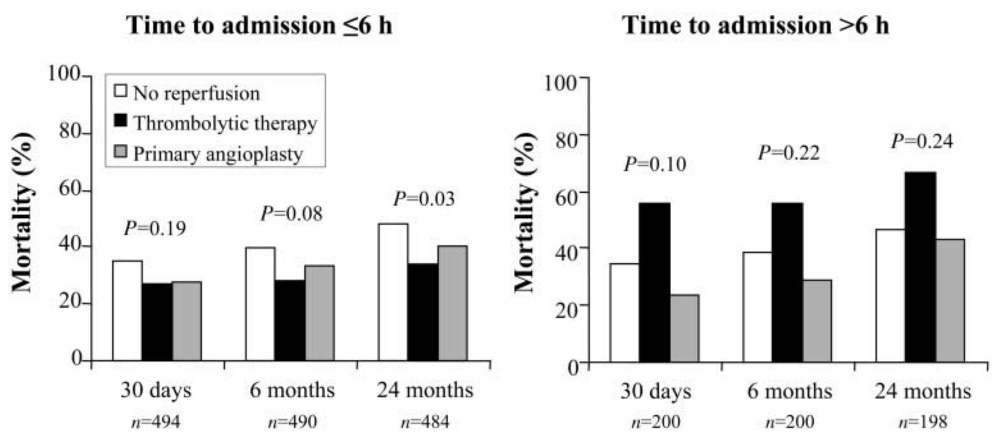

Figure 2 Mortality rates at 30 days, 6 months, and 24 months according to the type of reperfusion therapy received and the time to admission. *P*-values for single three-group comparisons at each time point.

intrapericardial echoes demonstrated by two-dimensional echocardiography (specificity 99.8%).[12] Calculating these values, in the worst of cases, we could have failed one diagnosis out of 55. Even if that were true, it would not have modified the conclusions drawn from our results, given the strength of the association. The cases defined as suspected FWR may have a lower specificity according to the diagnostic criteria used, which has been reported as high as 95%.[15] We decided to analyse confirmed and suspected FWR together because (i) it is the most conservative estimate of the impact of TT on FWR incidence (the association with confirmed FWR is even greater) and (ii) it mitigates potential diagnostic bias (echocardiographic studies performed more frequently in the TT group). The bias that the lower use of echocardiography and reperfusion therapies formed the first years of the study may produce on the results was controlled by the inclusion of the year of admission in the regression models. The study is underpowered to draw conclusions on important issues raised by our results, particularly the effect of thrombolysis in mortality, and the real impact of some interactions such as those related to time to treatment or type of lytic agent. Finally, the results have been obtained exclusively in first-time myocardial infarctions. Whether this effect applies to subsequent episodes needs further investigation.

Conclusions

In elderly patients, treatment of first AMI with TT increases the risk of FWR, an effect that may attenuate its early benefit, particularly when treatment is started after the first 6 h from symptom onset and especially in women and in infarcts of anterior location. This risk is not observed in patients treated with PA. Research on the optimal time and type of reperfusion therapy in older patients is urgently needed.

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