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Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial

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Aims In patients with acute myocardial infarction and ST-segment elevation (STEMI), primary angioplasty is frequently not available or performed beyond the recommended time limit. We designed a non-inferiority, randomized, controlled study to evaluate whether lytic-based early routine angioplasty represents a reasonable reperfusion option for victims of STEMI irrespective of geographic or logistical barriers.

Methods and results A total of 212 STEMI patients were randomized to full tenecteplase followed by stenting within 3–12 h of randomization (early routine post-fibrinolysis angioplasty; 104 patients), or to undergo primary stenting with abciximab within 3 h of randomization (primary angioplasty; 108 patients). The primary endpoints were epicardial and myocardial reperfusion, and the extent of left ventricular myocardial damage, determined by means of the infarct size and 6-week left ventricular function. The secondary endpoints were the acute incidence of bleeding and the 6-month composite incidence of death, reinfarction, stroke, or revascularization. Early routine post-fibrinolysis angioplasty resulted in higher frequency (21 vs. 6%, $P = 0.003$) of complete epicardial and myocardial reperfusion (TIMI 3 epicardial flow and TIMI 3 myocardial perfusion and resolution of the initial sum of ST-segment elevation $\geq$70%) following angioplasty. Both groups were similar regarding infarct size (area under the curve of CK-MB: 4613 $\pm$ 3373 vs. 4649 $\pm$ 3632 μg/L/h, $P = 0.94$); 6-week left ventricular function (ejection fraction: 59.0 $\pm$ 11.6 vs. 56.2 $\pm$ 13.2%, $P = 0.11$; endsystolic volume index: 27.2 $\pm$ 12.8 vs. 29.7 $\pm$ 13.6, $P = 0.21$); major bleeding (1.9 vs. 2.8%, $P = 0.99$) and 6-month cumulative incidence of the clinical endpoint (10 vs. 12%, $P = 0.57$; relative risk: 0.80; 95% confidence interval: 0.37–1.74).

Conclusion Early routine post-fibrinolysis angioplasty safely results in better myocardial perfusion than primary angioplasty. Despite its later application, this approach seems to be equivalent to primary angioplasty in limiting infarct size and preserving left ventricular function.

Introduction

Early and complete reperfusion in the setting of acute myocardial infarction with ST-elevation (STEMI) is effective in limiting left ventricular damage and in improving clinical outcomes.[1] However, delays to presentation and treatment, and the limited efficacy of reperfusion therapies, are important obstacles in the attempt to achieve optimal reperfusion therapy.

Primary angioplasty is considered the gold standard of myocardial reperfusion when promptly performed by skilled teams.[2–5] However, as the efficacy of this therapy is time-dependent, logistical barriers and other constraints

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limit its use to no more than 20% of STEMI patients worldwide.[6–10] Moreover, although it has been documented that a door-to-balloon time exceeding 120 min is associated with a 41–62% increase in mortality, even in well-developed countries the vast majority of patients with STEMI who undergo primary angioplasty achieve mechanical reopening of the infarct-related artery beyond the established time limit from which left ventricular preservation and clinical benefit are less probable.[6–10] In contrast, intravenous thrombolysis is widely applicable, and in prior trials has been shown to unequivocally reduce mortality when given within 8–12 h of symptoms.[11] Furthermore, early administration of newer fibrin-specific thrombolytics is at least as effective as primary angioplasty, and can abort infarction and dramatically reduce mortality when given during the first 1–2 h of onset.[12,13] Consequently, immediate thrombolysis is now recommended as an alternative to primary angioplasty for patients in whom a door-to-balloon time longer than 90 min is expected.[14,15] Nevertheless, the utility of fibrinolytic drugs is limited by the risk of bleeding in some subgroups, suboptimal rates of reperfusion, particularly in the presence of 'older' thrombi, and a significant rate of reocclusion which has a powerful detrimental impact upon mortality.[16,17]

Recent studies have demonstrated that in the modern era of percutaneous coronary intervention, routine early post-fibrinolytic angiography and stenting may improve outcomes.[18–22] This approach combines the advantages of rapid and simple use of fibrinolysis for myocardial salvage with the advantages of stenting in achieving a normal stable flow; and could represent a reasonable alternative to primary angioplasty. However, the safety and efficacy of early post-fibrinolysis coronary intervention when compared with primary angioplasty is still unknown. Thus, we have carried out an open, non-inferiority, controlled, randomized trial in patients with STEMI to assess whether immediate fibrinolysis with tenecteplase followed by early cardiac catheterization and coronary stenting if indicated leads to a similar or greater degree of myocardial salvage and clinical outcomes than primary angioplasty; and therefore provides a wide time window for percutaneous intervention when the application of primary angioplasty within the optimal time limit is not possible.

Methods

Patient population

From July 2002 to March 2003, patients were enrolled from 15 Spanish and Portuguese hospitals, 10 of which had interventional facilities. Patients were enrolled if they were 18 years or older, had symptom onset within 12 h before randomization, had chest pain lasting more than 30 min, if they had ST-segment elevation of at least 0.1 mV in at least two limb leads, ST-segment elevation of at least 0.2 mV in two or more contiguous precordial leads, or left bundle-branch block or paced rhythm.

Exclusion criteria included contraindication to fibrinolysis; evidence of cardiac rupture; cardiogenic shock (systolic arterial pressure below 90 mmHg with no response to fluid administration or below 100 mmHg following vasoconstrictor medication administration in the absence of bradycardia); non-cardiac condition with a life expectancy of less than 12 months; aspirin, ticlopidine, clopidrogrel, or heparin contraindication; renal failure [indicated by a serum creatinine concentration above 2:5 mg/dL (221 μmol/L)]; history of neutropenia, thrombocytopenia, or hepatic dysfunction; inclusion in another clinical trial; previously known multivessel coronary artery disease not suitable for revascularization, major surgery pending in the following year, and peripheral vascular disease prohibiting catheterization.

Approval was obtained from Ethical Committees at both national and institutional level. An informational brochure was provided to each patient who met inclusion criteria and informed written consent was obtained from all patients. All patients were randomized to primary angioplasty or early routine post-fibrinolysis angioplasty using a central telephone system. The telephone randomization was done after informed consent was obtained and doctors who informed the patient rang for the allocation. Blocking was used to generate the random allocation sequence and to ensure close balance of the numbers in each group at any time during the trial. The block lengths were 4, 8 and successive 4 size blocks. Patients admitted to non-interventional hospitals were transported to the nearest interventional hospital and returned to the original hospital after angiography and revascularization were performed.

Study protocol and interventions

After providing informed consent, patients who satisfied the inclusion and exclusion criteria were randomly assigned to one of the two treatment groups: (i) early routine post-fibrinolysis angioplasty consisting of immediate fibrinolysis with tenecteplase followed by cardiac catheterization and coronary intervention if indicated within 3–12 h of randomization or (ii) primary angioplasty of the culprit artery under the protection of abciximab within 3 h of randomization. All patients received 200–500 mg of aspirin in the emergency room. Patients randomly assigned to early routine post-fibrinolysis angioplasty received tenecteplase over a period of 5 s based on bodyweight (30 mg if their bodyweight was less than 60 kg, 35 mg if it was 60–69 kg, 40 mg if it was 70–79 kg, 45 mg if it was 80–89 kg, and 50 mg if it was 90 kg or more), and an enoxaparin bolus of 30 mg followed by a subcutaneous dose of 1 mg/kg. Patients underwent catheterization within 3–12 h of randomization. The infarct-related artery was dilated if there was a total occlusion if the stenosis was greater than 50%, or if the TIMI flow grade (TFG) was less than 3. Stenting of culprit lesions were performed when they were morphologically suitable for stenting and when the procedure was expected to achieve an adequate result. To avoid thrombus compression and embolization, direct stenting was attempted when possible. When a large amount of myocardium was threatened by severe stenosis (>90% lumen reduction by visual estimation, located in a coronary segment with reference diameter larger than 2.75 mm), stenting of non-culprit lesions was performed. No additional low-molecular weight heparin was given if revascularization was successful. In this group, immediate rescue angioplasty was undertaken when both chest pain and ST-segment elevation persisted at 90 min following tenecteplase administration.

Patients randomly assigned to primary angioplasty received unfractionated heparin (to achieve an activated clotting time of 350–450 s during the invasive procedure) and abciximab, given as a bolus of 0.25 mg/kg of body weight, followed by a continuous infusion at a rate of 0.125 μg/kg/min (maximun 10 μg/min). Abciximab was administered in the emergency room, intensive cardiac unity, or catheterization laboratory before sheath insertion. No additional unfractionated or low molecular weight heparin was given if revascularization was successful. The Multi-link stent was used in both patient groups (Guidant CO.). Betablockers, angiotensin-converting-enzyme inhibitors, statins, and post-interventional antithrombotic therapy were administered to all patients, as outlined in the international guidelines.[14,15]

Study endpoints and definitions

The efficacy (primary) endpoint included the degree of epicardial and myocardial reperfusion after percutaneous coronary intervention,

infarct size assessment, and 6-week evolution of left ventricular function. Death, reinfarction, disabling stroke, or repeat ischaemia-driven coronary revascularization within 6 months after randomization constituted the clinical (secondary) endpoints. The key safety (secondary) endpoint was the incidence of major bleeding. Definitions provided were identical to those used in the previous GRACIA I trial.[22]

Epicardial and myocardial reperfusion

All angiograms were analysed at an independent angiographic core laboratory. The TFG and the TIMI myocardial perfusion grade (TMPG) were assessed by an experienced reader (C.M.G.) who developed the TMPG and was blinded to treatment assignment and clinical outcome. We used a cut-off point of 3 for both epicardial and myocardial grades as they have been shown strong predictors of outcome in patients with acute myocardial infarction.[23,24]

Additional assessment of myocardial perfusion was performed using ST-segment analysis. The amount of ST-segment elevation was measured manually 20 ms after the J-point, by a single observer blinded to treatment assignment and clinical outcome. The sum of ST-segment elevation was measured from leads I, aVL, and V1–V6 for anterior myocardial infarction and leads II, III, aVF, V5, and V6 for inferior myocardial infarction. The resolution of ST-segment elevation of the initial reperfusion strategy was stratified based on Schroder's method immediately after coronary revascularization in both groups.[25] Complete resolution was defined as resolution of the initial sum of ST-segment elevation $\geq$70%.

Finally, complete epicardial and myocardial reperfusion (full reperfusion) was defined as TFG 3 and TMPG 3 and resolution of the initial sum of ST-segment elevation $\geq$70% following angioplasty.

Infarct size assessment

CK-MB enzyme levels were measured at enrolment (baseline) and 6, 12, 18, 24, 30, 36, 42, and 48 h after enrolment. Infarct size was measured by the CK-MB area under the curve, calculated by the linear-trapezoidal method.[26] If the baseline or last value were missing, the corresponding value was set to zero. For missing values of intermediate time points, linear interpolation was used. Troponin T (cTnT) was also measured during enrolment (baseline) and 24, 48, 72, and 96 h after enrolment and area under the curve was calculated. All samples were analysed at a core laboratory. CK-MB mass and troponin T analyses were performed in serum on the Elecsys 2010 system (Roche Diagnostics, Mannheim, Germany) by an enzymochemiluminiscence assay methodology.

Evaluation of left ventricular function

Left ventriculograms were performed before percutaneous coronary intervention and at 6-weeks to assess changes in left ventricular size and function. Left ventriculography, in the 30° right anterior oblique projection, included the measurement of left ventricular volumes and ventricular ejection fraction(according to the area–length method), and the analysis of regional wall motion (according to the centreline method).[27,28] Regional wall motion indices were expressed as the mean chord motion score.

Statistical analysis

The number of patients included in the study was based on an estimate of the sample size needed to identify a statistical significant difference in the principal endpoints. For sample size calculation, we used two different variables: left ventricular volume (continuos variable) and final TIMI myocardial flow grade 3 (categorical variable). For the left ventricular volume,[29] we assumed a normal left ventricle endsystolic volume index of $39 \pm 7\ mL/m^2$, and we decided that the non-inferiory margin should be $7\ mL/m^2$ (18%). For a power of 80% in detecting a difference in the interval of non-inferiority less than 18% with a two-sided α value of 0.05, the minimum total number of patients was 172. For the TIMI myocardial flow grade 3,[30] we assumed a final TIMI myocardial flow grade 3 in 70% of the patients in the primary angioplasty group. For a power of 80% in detecting a difference in the interval of non-inferiority less than 18% with a two-sided α value of 0.05, the minimum total number of patients was 203. A total of 212 patients were finally included in the study. Such a sample provides a 80% power for detecting non-inferiority (a confidence internal limit of 18%) in the remaining primary endpoints considered. We performed both an intention-to-treat (ITT) analysis in all randomized patients ($n = 212$) for clinical efficacy and safety outcomes, and a per protocol (PP) analysis in patients with completed enzymatic/angiographic measurements ($n = 189$) for the primary endpoints.

Data were entered using double data entry and the accuracy of collected data was validated against medical records by an independent clinical research organization, Chiltern International (Spain, S.A.). Clinical and safety endpoints were reviewed and adjudicated by an independent events committee who were unaware of treatment assignment. The data are presented as mean and standard deviation, medians and their interquartile range (25th and 75th percentiles), or proportions. The non-inferiority between the two groups was assessed by means of 95% confidence intervals derived from a χ^2 test or Fisher's exact test for categorical data, and the non-parametric Wilcoxon rank-sum test for continuous data. Survival was analysed according to the Kaplan–Meier method. The relative risk of adverse events during the first 6 months after randomization was derived from proportional-hazards regression analysis. Differences in event-free survival were also assessed for significance by means of the log-rank test. All clinical events were reviewed and adjudicated by an independent events committee who were blinded to treatment assignment. A two-tailed *P*-value of less than 0.05 indicated statistical significance.

Results

Characteristics of the patients

A total of 212 patients were randomly assigned, 104 to early routine post-fibrinolysis angioplasty and 108 to primary angioplasty (*Figure 1*), of whom 89% (94 assigned to early routine post-fibrinolysis angioplasty and 95 to primary angioplasty) had analysable angiograms obtained as stipulated by the protocol (both initial and 6-week follow-up angiograms). Of the patients enrolled, nine died (4%) without undergoing the protocol angiography (three patients assigned to early routine post-fibrinolysis angioplasty and six to primary angioplasty). An additional 14 patients (7%) did not undergo the procedure for other reasons (refusal by the patient, a decision by the physician, clinical problems, incomplete data, or angiograms or ventriculograms which were un-analysable due to quality or technical problems). The frequency of missing data was similar between the two treatment groups. There were no differences in baseline characteristics between patients in the angiographic study and the overall population (*Table 1*). Clinical 6 month follow-up was available for all patients, thus analysis of clinical and safety endpoints was performed in all patients randomized.

Overall, baseline characteristics of the study population were similar to those of previous trials on primary angioplasty or fibrinolysis. Both groups had a similar time delay between onset of symptoms and randomization, but the time delay from randomization to percutaneous coronary intervention was significantly longer, as planned, in the

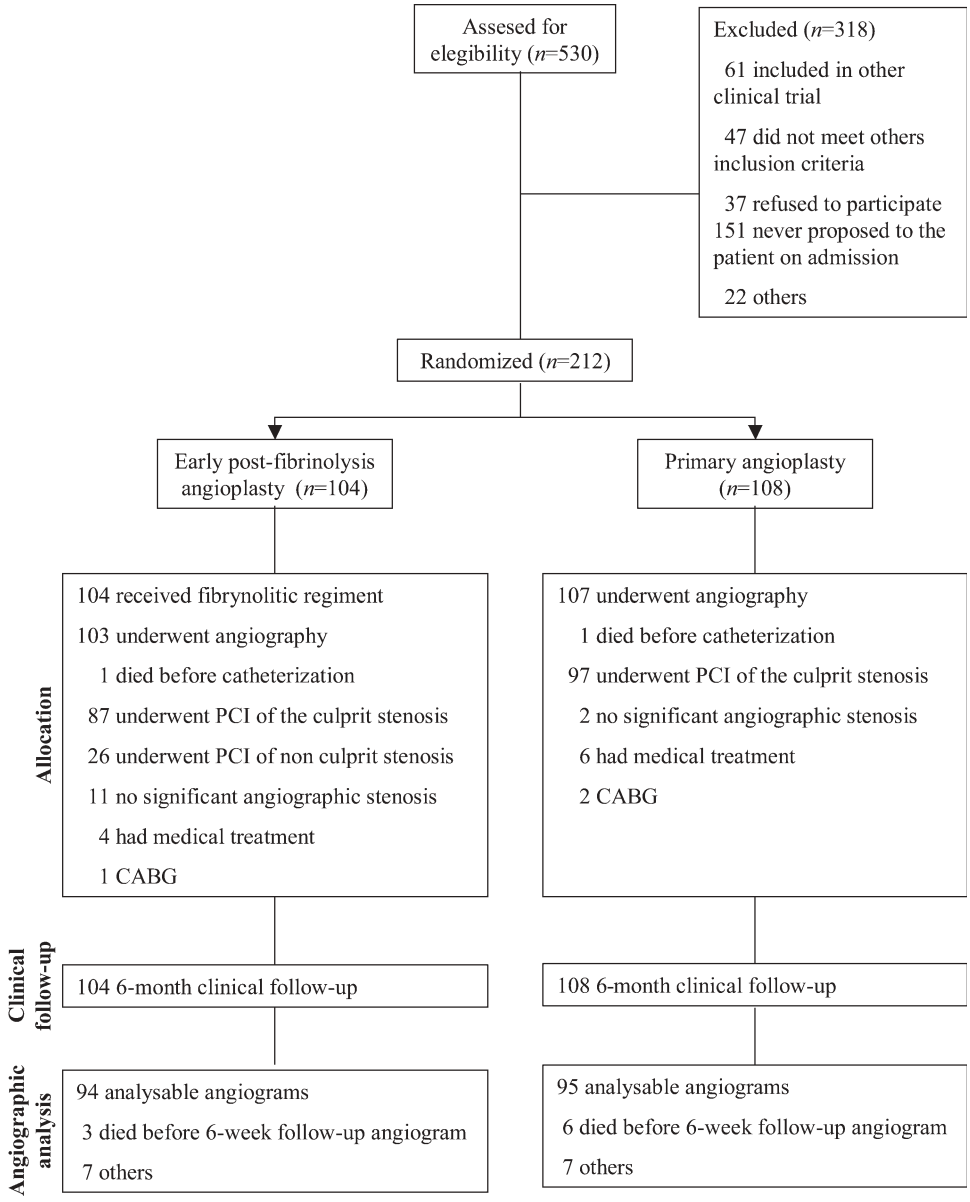

Figure 1 Flow chart.

early routine post-fibrinolysis angioplasty group. There were no differences in concomitant medications given during hospitalization, at discharge, or at the 6-month follow-up in either group. High proportions of patients received β-blockers (77%), angiotensin-converting-enzyme inhibitors (62%), statins (74%), aspirin (92%), and thienopyridines (91%). Abciximab was frequently given to patients who were assigned primary angioplasty (91%), of whom 82% received the drug in the catheterization laboratory before sheath insertion. Twenty-five percent of patients in the early routine post-fibrinolysis angioplasty group received abciximab at operator discretion following coronary angiography, depending upon angiographic evidence of thrombus or total occlusion. The angiographic profile of the patients is also depicted in *Table 1*. In comparison to the early routine post-fibrinolysis angioplasty group, patients undergoing primary angioplasty had a higher incidence of three vessel disease (3 vs. 14%, $P = 0.01$) and a lower rate of minimal residual coronary-artery stenosis (11 vs. 2%, $P = 0.008$).

Treatment interventions

Of the 104 patients randomized to early routine post-fibrinolysis angioplasty, 104 (100%) received the fibrinolytic regimen and 103 (99%) underwent delayed angiography. Angioplasty of the culprit lesion was attempted in 87 (84%) patients, stents were implanted in 84 (96%) of these patients, of whom 55% underwent direct stenting. Stenting of non-culprit lesions was performed in 26 (25%) of the patients who underwent catheterization. The lesion could be crossed and conventional balloon inflation was possible in all patients.

Of the 16 patients who underwent angiography but did not undergo angioplasty, 11 had no significant angiographic stenosis. Among the remaining five patients, four were recommended for medical treatment because of coronary artery disease that was unsuitable for percutaneous coronary intervention or coronary bypass surgery revascularization. One patient underwent predischarge coronary artery bypass surgery due to multi-vessel coronary disease unsuitable for

Table 1 Baseline, time intervals to treatment, and angiographic characteristics

Early routine	Post-fibrinolysis angioplasty ($n = 104$)	Primary angioplasty ($n = 108$)	*P*-value
Baseline characteristic			
Age (year)	62.5 ± 12.6	64.3 ± 12.9	
Median	61	67.5	0.281
Interquartile range	53–72.75	55.25–74.0	
Male sex, *n* (%)	83 (79.8)	89 (82.4)	0.629
Hypertension, *n* (%)	43 (41.3)	43 (39.8)	0.820
Diabetes, *n* (%)	24 (23.1)	30 (27.8)	0.432
Current smoking, *n* (%)	52 (50.0)	49 (45.4)	0.500
Cholesterol, (>5.5 mmol/L), *n* (%)	35 (33.7)	42 (38.9)	0.428
Family history, *n* (%)	17 (16.3)	19 (17.6)	0.809
Previous myocardial infarction, *n* (%)	4 (3.8)	12 (11.1)	0.082
Previous angina, *n* (%)	16 (15.4)	26 (24.1)	0.113
Previous angioplasty, *n* (%)	2 (1.9)	9 (8.3)	0.073
Heart rates (beats/minutes)	77.2 ± 18.1	73.3 ± 17.6	
Median	73	70	0.105
Interquartile range	64–90	60–83	
Systolic blood pressure (mm Hg)	135.2 ± 20.5	134.2 ± 21.6	0.730
Medical treatment			
Aspirin, *n* (%)	93 (89.4)	98 (90.7)	0.927
Beta-blockers, *n* (%)	10 (9.6)	14 (13.0)	0.442
ACE-inhibitors, *n* (%)	10 (9.6)	5 (4.6)	0.251
Calcium antagonists, *n* (%)	4 (3.8)	4 (3.7)	0.999
Time from symptoms to treatment			
Interval from onset of symptoms to randomization	3.3 ± 2.2	3.2 ± 1.9	
Median	3.0	3.0	0.839
Interquartile range	2.0–4.0	2.0–4.0	
Interval from randomization to angiography	5.9 ± 3.2	1.1 ± 0.5	
Median	4.6	1	<0.001
Interquartile range	3.4–8.1	0.7–1.4	
Angiographic features	($n = 103$)	($n = 107$)	
Infarct related artery location			0.089
Left anterior descending, *n* (%)	47 (45.6)	51 (47.7)	
Left circumflex, *n* (%)	15 (14.6)	6 (5.6)	
RCA, *n* (%)	41 (39.8)	50 (46.7)	
Number of vessels disease			0.003
Non-stenotic vessels, *n* (%)	11 (10.7)	2 (1.9)	
Single-vessel disease, *n* (%)	57 (55.3)	60 (56.1)	
Double-vessel disease, *n* (%)	32 (31.1)	30 (28.0)	
Triple-vessel disease, *n* (%)	3 (2.9)	15 (14.0)	
Degree of stenosis, % of diameter	59.3 ± 23.4	84.6 ± 23.4	<0.001
Evidence or thombus, *n* (%)	69 (67.0)	97 (90.7)	<0.001

Data on initial angiographic features were missing for two patients who died before catheterization could be performed (one in the early post-fibrinolysis angioplasty group and one in the primary angioplasty group).

stenting. At 90 min, 46% of patients did not have ECG signs of reperfusion although nearly half of them referred pain relief. In this group, stent angioplasty was performed before the recommended catheterization time window (3–12 h) in three patients with persistent chest pain and ST-segment elevation.

Among the 108 patients randomly assigned to primary angioplasty, 107 patients (99%) underwent immediate angiography. Angioplasty of the culprit lesion was attempted in 97 patients (91%), stents were implanted in 95 (98%) of these patients, of whom 6% underwent direct stenting. The lesion could be crossed and conventional balloon inflation was possible in all patients. Of the 10 patients who underwent angiography but did not undergo angioplasty, two had no significant angiographic stenosis. Among the remaining eight patients, medical treatment was considered to be the best initial strategy for six patients due to coronary artery disease unsuitable for percutaneous or coronary bypass surgery revascularization; and two patients underwent coronary surgery due to multi-vessel disease and at least moderate mitral regurgitation. An additional patient initially considered not suitable for percutaneous or coronary bypass surgery revascularization underwent urgent surgery in the immediate follow-up due to ventricular septal defect.

Epicardial and myocardial perfusion

Sixty-seven percent of patients treated with early routine post-fibrinolysis angioplasty had TIMI 3 flow in the infarct-related artery at initial angiography compared with 14% in the primary angioplasty group ($P < 0.001$). Despite these differences, the rate of post-procedural TIMI 3 flow

Table 2 Angiographic characteristics of both epicardial and myocardial perfusion

Variable	Early routine post-fibrinolysis angioplasty ($n = 94$), *n* (%)	Primary angioplasty ($n = 95$), *n* (%)	95% confidence interval
At baseline			
Infarct related artery TIMI grade			
0	10 (10.6)	63 (66.3)	
1	2 (2.1)	5 (5.3)	
2	19 (20.2)	14 (14.7)	
3	63 (67.0)	13 (13.7)	(41.6–65.1)
TIMI myocardial perfusion grade			
0	15 (16.0)	57 (60.0)	
1	27 (28.7)	22 (23.2)	
2	0	0	
3	52 (55.3)	16 (16.8)	(25.9–51.0)
After the procedure			
Infarct related artery TIMI grade			
0	1 (1.1)	3 (3.2)	
1	0	0	
2	11 (11.7)	12 (12.6)	
3	82 (87.2)	80 (84.2)	(−6.9–13.0)
TIMI myocardial perfusion grade			
0	8 (8.5)	13 (13.7)	
1	39 (41.5)	58 (61.0)	
2	0	0	
3	47 (50.0)	24 (25.3)	(11.4–38.1)
At 6-week follow-up			
Infarct related artery TIMI grade			
0	0	3 (3.2)	
1	0	2 (2.1)	
2	3 (3.2)	2 (2.1)	
3	91 (96.8)	88 (92.6)	(−2.2–10.5)
TIMI myocardial perfusion grade			
0	4 (4.2)	12 (12.6)	
1	12 (12.8)	16 (16.8)	
2	0	0	
3	78 (83.0)	67 (70.6)	(0.5–24.4)

Only patients with analysable angiograms (both baseline and at 6-week follow-up) are included.

was high in both groups (87 vs. 84%, $P = 0.55$). The rate was even higher in the two groups at the 6-week follow-up (97 and 93%, $P = 0.33$) (*Table 2*). Only one patient in each group with post-procedural TIMI 3 flow presented a TIMI flow <3 (angiographic reoclussion) in the 6-week follow-up angiogram.

On initial angiography, 55% of patients treated with early routine post-fibrinolysis angioplasty had a TIMI myocardial perfusion grade of 3 compared with 17% in the primary angioplasty group ($P < 0.001$). In contrast to the epicardial TFGs, the post-procedural and 6-week TMPG 3 rate were also higher in the early routine post-fibrinolysis angioplasty group (50 vs. 25%, $P < 0.001$ and 83 vs. 71%, $P = 0.04$; respectively. *Table 2*).

Although no significant difference in ST-resolution at 1 and 3 h after randomization was observed between groups, compared with patients in the primary angioplasty group, the rate of complete ST-resolution after coronary revascularization in patients with early routine post-fibrinolysis angioplasty was significantly higher (43 vs. 61%, $P = 0.02$). Full reperfusion (TFG 3, TMPG 3, and complete ST-elevation resolution) following angioplasty was more common in the post-fibrinolysis angioplasty group than in the primary angioplasty group ($P = 0.003$) (*Figure 2*).

Infarct size

The median (interquartile range) number of CK-MB samples for patients alive through 48 h was similar between the early routine post-fibrinolysis treatment group and the primary angioplasty group. Seven or more CK-MB samples were collected from 95% of early routine post-fibrinolysis patients and 94% of primary angioplasty patients. The number of deaths within 48 and 96 h (two early routine post-fibrinolysis and four primary) and therefore the number of patients with imputed infarct size, was similar between groups. As with CK-MB, there was no difference in the number of troponin T samples among the two treatments groups.

There was no significant difference in infarct size between the two groups: CK-MB area under the curve for early routine post-fibrinolysis angioplasty 4613 $\pm$ 3373 vs. primary angioplasty 4649 $\pm$ 3632 ng/mL/h, $P = 0.94$; cTnT area under the curve for post-fibrinolysis angioplasty 246 $\pm$ 157 vs. primary angioplasty 271 $\pm$ 111 ng/mL/h, $P = 0.41$.

Baseline CK-MB and cTnT levels did not differ markedly between the two groups: post-fibrinolysis angioplasty, 20 $\pm$ 45 vs. primary, 23 $\pm$ 42 ng/mL, $P = 0.64$ for CK-MB; post-fibrinolysis angioplasty, 0.22 $\pm$ 0.63 vs. primary, 0.56 $\pm$ 1.55 ng/mL, $P = 0.09$ for cTnT. Similar results were

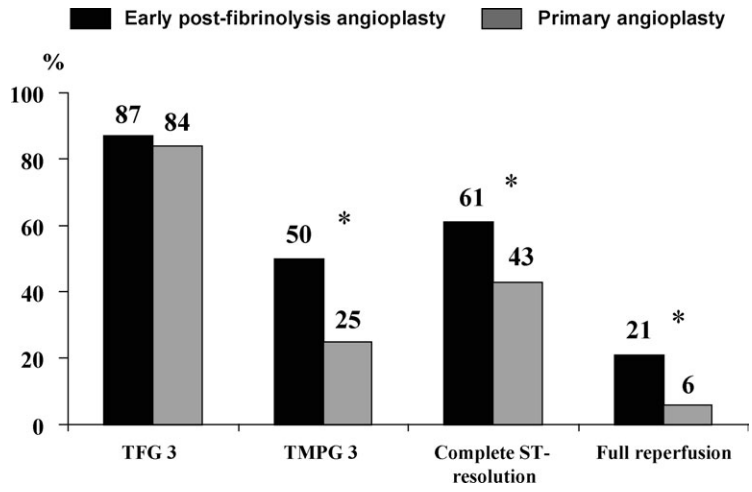

Figure 2 Prevalence of TFG 3, TIMI myocardial perfusion grade 3, complete ST-resolution, and full reperfusion after coronary intervention in the post-fibrinolysis angioplasty group compared with the primary angioplasty group. Full reperfusion denotes the prevalence of patients who achieved TFG 3, TIMI myocardial perfusion grade 3, and complete ST-resolution following percutaneous coronary intervention. *$P < 0.01$.

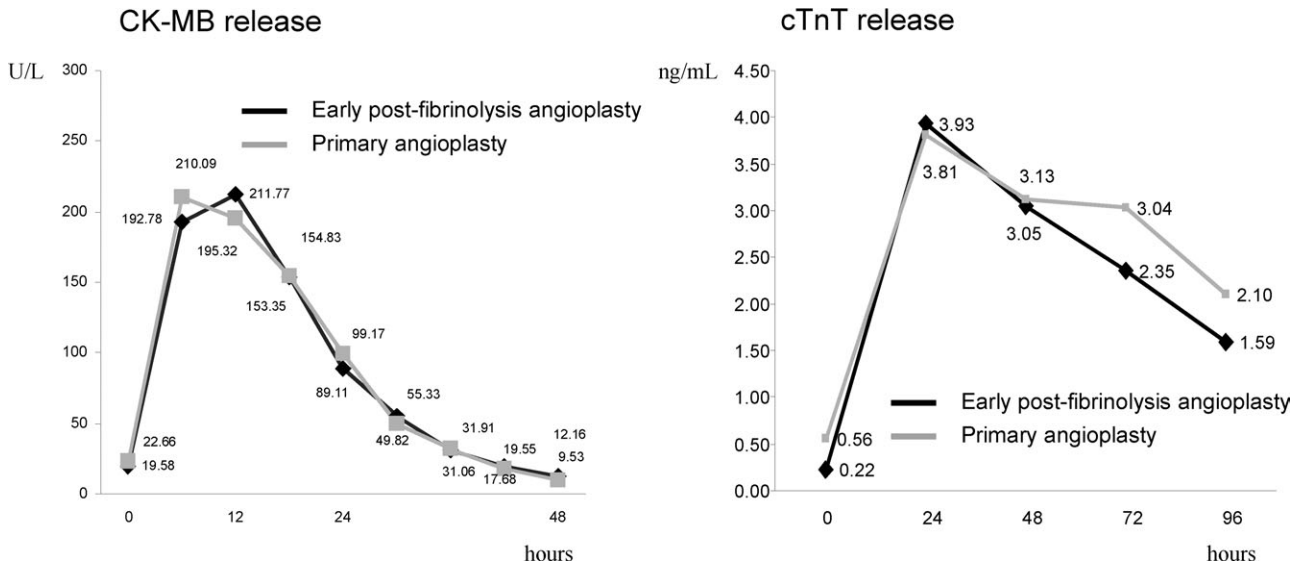

Figure 3 Comparative chronological release, represented by the area under the curve, of CK-MB and cTnT in the post-thrombolysis and the primary angioplasty groups. There were no differences between groups.

found for peak CK-MB and cTnT levels between the two groups: post-fibrinolysis, 262 $\pm$ 188 vs. primary, 267 $\pm$ 213, $P = 0.86$ for CK-MB; facilitated, 4.4 $\pm$ 2.7 vs. primary, 4.2 $\pm$ 3.4, $P = 0.75$ for cTnT ng/mL (*Figure 3*).

Left ventricular function

Among the 189 patients assigned to angiographic evaluation at the 6-week follow-up, baseline, and 6-week, indexes of ventricular function were similar among both groups (*Table 3*). At 6-weeks, a significant increase in the left ventricular ejection fraction was observed in each of the two groups compared with baseline.

Safety and efficacy

Three patients in the early routine post-fibrinolysis angioplasty group (3%) and five patients in the primary group (5%) died during the first 30 days following randomization. There was one case of non-fatal reinfarction among patients in the early routine post-fibrinolysis angioplasty group and one case among patients in the primary angioplasty group. Three patients in the post-fibrinolysis angioplasty group and three patients in the primary angioplasty group required coronary revascularization. The composite endpoint of death, reinfarction, disabling stroke, or revascularization at 30 days was reached in six patients in the early routine post-fibrinolysis angioplasty group (6%) and in eight patients in the primary angioplasty group (7%). There was no significant difference in major bleeding rate among the groups; two patients (2%) in the post-fibrinolysis angioplasty group experienced major bleeding, with one episode of intracranial haemorrhage, and three patients (3%) in the primary angioplasty group.

At 6 months, the incidence of death, reinfarction, stroke (no cases of stroke were observed during follow-up), or

revascularization was 10% in the early routine post-fibrinolysis angioplasty group compared with 12% in the primary angioplasty group, (relative risk, 0.80; 95% confidence interval, 0.37–1.74) (*Figure 4*). The clinical and safety endpoints and individual components are shown in *Table 4*.

Finally, the increment in the primary and secondary endpoints were also analysed in several subgroups. These results are given in *Figure 5* and show the increment in the endsystolic volume index and clinical findings among the subgroups.

Table 3 Left ventricular function evolution

Variable	Early routine post-fibrinolysis angioplasty ($n = 94$)	Primary angioplasty ($n = 95$)	95% confidence interval
Ejection fraction			
At baseline	53.5 ± 11.1	53.5 ± 12.8	(−3.38, 3.45)
At 6-week follow-up	59.0 ± 11.6	56.2 ± 13.2	(−0.69, 6.39)
Increment	5.5 ± 11.1	2.7 ± 10.8	(−0.32, 5.93)
ESVI (mL/m^2)			
At baseline	28.4 ± 10.3	28.1 ± 10.1	(−2.64, 3.19)
At 6-week follow-up	27.2 ± 12.8	29.7 ± 13.6	(−6.24, 1.28)
Increment	−1.22 ± 10.38	1.53 ± 9.39	(−5.58, 0.07)
Wall motion (SD/chord)			
At baseline	−1.44 ± 0.52	−1.59 ± 0.47	(0.01, 0.29)
At 6-week follow-up	−0.91 ± 0.69	−1.13 ± 0.67	(0.03, 0.42)
Increment	0.53 ± 0.60	0.46 ± 0.54	(−0.09, 0.24)
Abnormal chords (no.)			
At baseline	31.4 ± 18.7	35.6 ± 17.2	(−9.41, 0.85)
At 6-week follow-up	18.3 ± 17.3	22.8 ± 21.7	(−10.14, 1.07)
Increment	−13.1 ± 17.9	−12.8 ± 19.1	(−5.54, 5.03)

Discussion

The main finding of our trial is that, in patients with STEMI, the strategy of performing routine stent-angioplasty within 3–12 h of fibrinolysis is safe and equivalent to primary stenting in preserving myocardial function. Of note, this strategy seems to produce better and earlier myocardial perfusion than primary angioplasty, as demonstrated by the presence of higher rate ST-segment normalization immediately after coronary revascularization and better angiographic reperfusion parameters in this group. To the best of our knowledge, this is the first evidence that the application of a combined lytic-based pharmacological and mechanical reperfusion approach to acute myocardial infarction is feasible and could safely allow a wide time window for the definitive repair of the infarct-related artery. If these findings are confirmed in large-scale clinical trials, the combination of immediate thrombolysis and routine early coronary stenting could extend the benefits of early coronary intervention to the entire population with acute myocardial infarction, irrespective of geographical and logistical barriers.

The present study included patients with STEMI who were randomized to early planned coronary intervention after fibrinolysis or primary agioplasty with the participation of 10 tertiary centres and 5 community hospitals. Although the usefulness of lytic-based facilitated angioplasty has been addressed in the ASSENT-4 trial, the BRAVE trial, both studies are conceptually and methodologically different from our trial.[31,32] In the ASSENT-4 trial, 1667 patients with STEMI were randomized to primary stent-angioplasty or the same intervention after the administration of full dose of tenecteplase. In this trial, primary and facilitated patients had to receive intervention within an identical short delay: 1–3 h from randomization. Importantly, unfractionated heparin was used in both groups, clopidogrel was optional, and IIb/IIIa inhibitors were forbidden in the facilitated group. The trial has stopped enrolment after a planned interim analysis showed higher 30-day mortality in the facilitated group. Interestingly, this difference was not associated to more bleeding, but to a higher incidence of

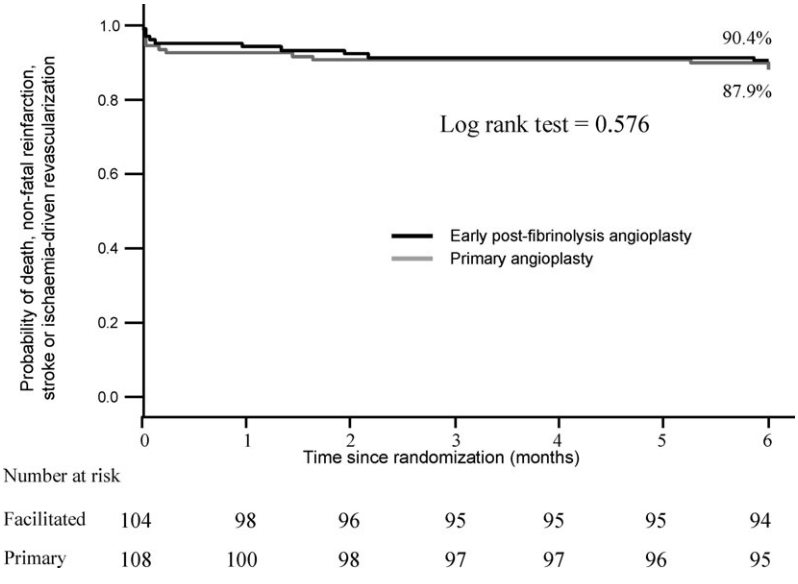

Figure 4 Cumulative incidence of the clinical endpoint of death, non-fatal recurrent myocardial infarction, stroke, or ischaemia-guided revascularization.

reocclusion-related events; suggesting a prothrombotic effect of fibrinolysis combined with too early vascular intervention, which was insufficiently prevented by the adjunctive antithrombotic regimen.[31] Similarly, the BRAVE trial compared primary vs. facilitated stent-angioplasty performed with similar delay (2.1 and 2.0 h from the start of study drug to angiography, respectively), but unlike in the ASSENT-4 and in our trial, in this study, the facilitated group underwent intervention after receiving a combination of half dose of reteplase plus abciximab instead of a full dose of lytic. Although such a combination produced a higher percentage of pre-intervention TIMI 3 and seemed to prevent reocclusion, these benefits did not result in smaller infarct size or better outcome, and a trend towards a higher incidence of bleeding in the facilitated group was found.[32] The main difference between the studies mentioned earlier and our trial is conceptual. We assumed that primary angioplasty is superior to facilitated angioplasty when the intervention is performed with a similar delay. Therefore, although all the participating hospitals were able to provide primary angioplasty within the recommended time, in our trial, post-fibrinolysis intervention delay was established with two specific aims: (a) to avoid the side-effects of post-fibrinolysis intervention performed too early after the administration of full dose of lytics and (b) to assess the usefulness of this strategy in the worst scenario, when long delays due to logistical reasons are inevitable. Thus, by protocol post-fibrinolysis intervention had to be performed within 3–12 h of the administration of tenecteplase. In addition, in order to prevent reocclusion associated to early mechanical manipulation of the culprit artery, all patients received clopidogrel and enoxaparin was used instead of unfractionated heparin.[33,34] As a result and unlike in the ASSENT-4, primary and post-fibrinolysis stenting had a low and identical incidence of ischaemic events and 6-week angiographic reocclusion. It is also important that in spite of the longer intervention delay, post-fibrinolysis intervention resulted in an equivalent

Table 4 Cardiovascular events and bleeding complications

Outcome	Early routine post-fibrinolysis angioplasty ($n = 104$)	Primary angioplasty ($n = 108$)	95% confidence interval
Cardiovascular event			
Death, *n* (%)	3 (2.9)	6 (5.6)	(−0.08, 0.03)
Non-fatal reinfarction, *n* (%)	1 (1.0)	1 (0.9)	(−0.02, 0.03)
Disabling stroke, *n* (%)	1 (1.0)	0	(−0.01, 0.03)
Ischaemia-driven revascularization, *n* (%)	7 (6.7)	7 (6.5)	(−0.06, 0.07)
Any of the previous cardiovascular events, *n* (%)	10 (9.6)	13 (12.0)	(−0.11, 0.06)
Bleeding complication			
Any bleeding, *n* (%)	11 (10.6)	8 (7.4)	(−0.04, 0.11)
Major bleeding[a], *n* (%)	2 (1.9)	3 (2.8)	(−0.05, 0.03)
Re-admission, *n* (%)	11 (10.6)	10 (9.3)	(−0.07, 0.09)
Index hospitalization (days)	3.6 ± 2.6	4.3 ± 3.0	(−1.43, 0.09)

[a]One episode of intracranial haemorrhage in the fibrinolysis-facilitated group. This was also computed as disabling stroke.

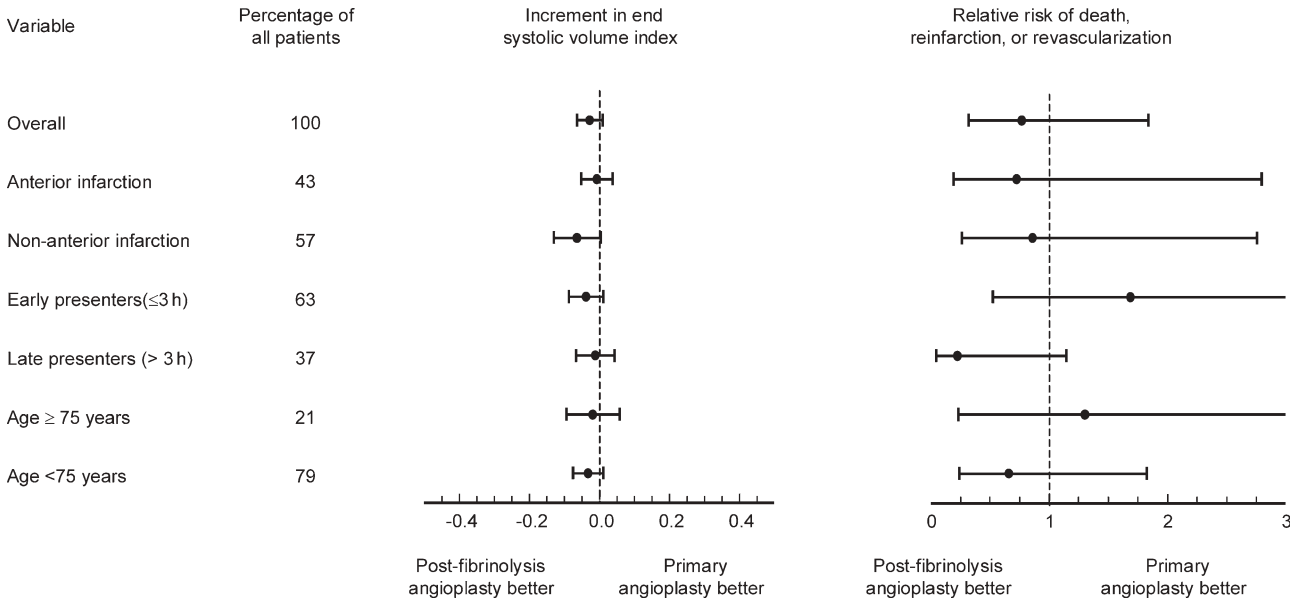

Figure 5 Increment in endsystolic volume index and the relative risk of death, reinfarction, or revascularization at 6 months in the early routine post-fibrinolysis group when compared with the primary angioplasty group, according to various characteristics. Horizontal bars indicate the 95% confidence intervals.

infarct size and ventricular outcome when compared with primary stent-angioplasty under abciximab protection. Concordantly, both groups of patients had a similar clinical evolution. Finally, although our study was not powered to detect differences with respect to haemorrhagic complications, we observed a low incidence of major bleeding, which was similar in both groups and not different from that observed after the isolated use of lytics,[35] or in primary angioplasty performed with IIb/IIIa inhibitors;[36] and seems to be lower than that reported in studies which combined lytics and IIb/IIIa inhibitors before intervention in the infarct-related artery.[32,35,37]

Therefore, our findings suggest that the time window between fibrinolysis and angioplasty can be safely widened up to 6 h after first medical contact. These results are similar to the recently published WEST trial which, in a small sample size, showed that a pre-hospital fibrinolytic regimen rapidly delivered, coupled with a strategy of regimented rescue and routine coronary intervention within 24 h of initial treatment, may not be clinically different from timely expert percutaneous coronary intervention.[38] Thus our study and the WEST study may also provide the basis for further large-scale trials based on clinical endpoints to definitely assess the potential role of post-fibrinolysis angioplasty in the management of patients with STEMI admitted in hospitals without cardiac catheterization facilities. This basis is reliable, as we have used sensitive and practical techniques to assess the amount of muscular and microvascular myocardial damage, which have been identified as the most reliable surrogates in prediction survival after myocardial infarction. First, we have consistently found no differences between post-fibrinolysis and primary patients with regard to infarct size, left ventricular volumes and ejection fraction, which have been shown to be the most powerful predictors of survival after acute myocardial infarction as they are significantly related to prognosis; changes in these measurements reflect changes in mortality and both the direction and the magnitude of change in these parameters cause a proportional change in survival.[29,39] Furthermore, the facilitated group showed a trend towards better left ventricular outcome, particularly in terms of left ventricular endsystolic volume, the most powerful independent predictor of long-term mortality after infarction. Secondly, we have compared the impact of the two strategies on both epicardial flow and myocardial perfusion, which have also been identified as strong predictors of post-infarction left ventricular evolution and clinical outcome,[40,41] leading to the modern paradigm according to which the concept of 'time is muscle' should be expanded to include myocyte and microvascular reperfusion.[1,42] In our study, post-fibrinolysis angioplasty patients underwent coronary angiography much later than primary patients and therefore some of them could have achieved spontaneous recovery of culprit artery flow. However, this mechanism does not justify the magnitude of the observed difference (pre-interventional TIMI 3 flow: 67 and 14% in post-fibrinolysis and primary patients, respectively), which demonstrates that previous fibrinolysis produces better pre-intervention epicardial perfusion than primary angioplasty performed under IIb/IIIa inhibitors; as previously reported by others.[19,32] In addition, we observed that post-fibrinolysis angioplasty patients had better pre-intervention and post-intervention myocardial perfusion, documenting that the benefit of the fibrinolytic-based approach depends mainly on the open microvascular hypothesis. Concordantly, in our study patients allocated to post-fibrinolysis intervention showed a lower thrombotic burden than primary patients, with fewer culprit vessels showing significant stenosis, less severe narrowing in the infarct-related lesion, and fewer lesions with direct evidence of thrombus. Altogether, these data are in concordance with the trend towards better evolution of left ventricular parameters observed in the post-fibrinolysis angioplasty group and suggest that the facilitation with fibrinolysis 'stops the clock', allowing patients to be transferred for definitive mechanical repair.

Apart from the use of surrogate endpoints already mentioned, some important limitations must be admitted regarding the interpretation of our results. First, as a comparison between strategies involving different invasive procedures and time windows, our study was necessarily an open-labelled trial. However, bias is unlikely to have occurred because both the core-lab assessment of the perfusion or ventricular endpoints and the adjudication of the clinical adverse events were performed by experts blinded to the assigned treatment. Secondly, we must acknowledge that the study is underpowered for clinical events and safety and a larger clinical outcome study for confirmation of our results is mandatory. Thirdly, both the International Conference on Harmonization (ICH E9, Food and Drug Administration, DHHS, 1998), as the Committee on Proprietary Medical Products Points-to Consider (Committee on Proprietary Medical Products Points-to Consider. Points to consider on switching between superiority and non-inferiority. CPMP, 2000) specifically states: '...similar conclusions from both the ITT and PP are required in a non-inferiority trial'. This approach makes sense, as the ITT tends to give an (although, perhaps not ideal) estimate of the overall effect that the experimental treatment will have on the population, since not all people taking the experimental product in the population will take it for the full course as prescribed. The PP results estimate the overall effect of the full course of experimental treatment. Both sets of results are important and should be considered when assessing if the study objective is met. We performed both a ITT ($n = 212$) analysis for clinical efficacy and safety outcomes (*Table 3*) and PP ($n = 189$) analysis for the main primary haemodynamic outcomes (*Table 2*). Finally and very importantly, this trial did not properly address the issue of rescue angioplasty for failed fibrinolysis, as it was designed before recent findings documenting the importance of early resolution of ST-segment elevation as an independent guide for the indication rescue angioplasty.[43]

Despite these limitations, our findings seem to be relevant, as they suggest that the strategy of performing stenting hours after intravenous fibrinolysis is applicable to the entire population with acute myocardial infarction, and could represent a good alternative for the still high proportion of victims of this condition for whom primary angioplasty is not available or requires an excessive delay. Therefore, the GRACIA-2 trial could be considered as a base for further studies aimed at assessing the efficacy of combined pharmaco-mechanical reperfusion strategies widely applicable in the earliest phase of ST-elevation acute myocardial infarction.

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Conflict of interest: none declared.

Appendix

The participants in the GRACIA-2 study were as follows: Operations Committee—F.F.-A. (principal investigator), J.J.A., P.L.S.; Steering Committee—F.F.-A., P.L.S., J.J.A., G.P., C.M.G., A.C.-B., J. Sanchis, P. Abreu; Data Coordinating Center (Instituto de Ciencias del Corazón, Valladolid, Spain)—I. Gómez, P. Mota; Clinical Events Committee—J. Torres (chair), J.A. San Román, L. de la Fuente; TIMI Angiographic Core Laboratory (Brigham and Women's Hospital, Boston, MA, USA)—M.G. (director); Electrocardiographic (ECG) Core Laboratory (Hospital do Meixoeiro, Vigo, Spain)—J. Goicolea (director); Biomarker Core Laboratory (Instituto de Ciencias del Corazón, Valladolid, Spain)—A. Revilla, R. Gallardo, P. Mota; Clinical Centers (listed in order of number of patients enrolled): Instituto de Ciencias del Corazón, Valladolid, Spain: F.F.-A., P.L.S., J.J.A., G.P., C.H., R.Sanz, B. Ramos, F. Gimeno, J.M. Durán, J. Bermejo; Hospital Río Hortega, Valladolid, Spain: J. Blanco, J.J. Sanz; Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain: J.A.B., J.M.H., M.F. Jiménez-Navarro; Hospital Río Carrión, Palencia, Spain: J.L.-M.; Hospital Virgen del Rocio, Sevilla, Spain: L. Díaz de la Llera; Complejo Hospitalario de León, Spain: F. Fernández-Vazquez, A. Pérez de Prado; Hospital Virgen de la Salud, Toledo, Spain: J. Moreu, L. Rodríguez-Padial; Hospital Clínico San Carlos, Madrid, Spain: R.A.H., C. Macaya, F. Alfonso; Hospital Juan Canalejo, A Coruña, Spain: A.C.-B., N. Vazquez; Hospital do Meixoeiro, Vigo, Spain: J. Goicolea, R. Ruiz; Hospital Fernando Fonseca, Amadora, Portugal; P. Abreu; Hospital Clínico Universitario,Valencia, Spain: J. Sanchis, V. Bodí, F.J. Chorro; Hospital Miguel Servet, Zaragoza, Spain: I. Calvo, C. Alonso; Hospital Rafael Méndez, Lorca, Spain: S. Nicolás; Hospital Los Arcos, Santiago de la Ribera, Spain: F. Martínez. Centers with interventional facilities: Instituto de Ciencias del Corazón, Valladolid, Spain; Hospital Clínico Virgen de la Victoria, Málaga, Spain; Hospital Virgen del Rocío, Sevilla, Spain; Complejo Hospitalario de León, Spain; Hospital Virgen de la Salud, Toledo, Spain; Hospital Clínico San Carlos, Madrid, Spain; Hospital Juan Canalejo, A Coruña, Spain; Hospital do Meixoeiro, Vigo, Spain; Hospital Clínico Universitario, Valencia, Spain; Hospital Miguel Servet de Zaragoza. Centers without interventional facilities: Hospital Río Hortega, Valladolid, Spain; Hospital Río Carrión, Palencia, Spain; Hospital Fernando Fonseca, Amadora, Portugal; Hospital Rafael Méndez, Lorca, Spain; Hospital Los Arcos, Santiago de la Ribera, Spain.

Contributions

F.F.-A. conceived the study, designed the protocol, obtained the funding, and supervised the analysis of the results. J.J.A. and P.L.S. actively helped to the conception of the study and the design of the protocol, were responsible for statistical analysis, supervised the recruitment of patients and their follow-up, and analysed the results. A.C.-B. contributed to obtain the funding, oversaw the study, and acted as guarantor for the report. J.B., R.G., J.A.-B., and J.L.-M. participated in design, data management, and analysis of the study. G.P., F.F.-V., J.M., R.A. H., and C.M.G. participated in the design of the interventional protocol and in the analysis of data. F.F.-A. wrote the report in collaboration with P.L.S., C.M.G., and the other authors.

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