European Heart Journal (2011) **32**, 51–60
doi:10.1093/eurheartj/ehq375

Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) randomized trial and pooled analysis with previous studies

Héctor Bueno[1]*, Amadeo Betriu[2], Magda Heras[2], Joaquín J. Alonso[3], Angel Cequier[4], Eulogio J. García[5], José L. López-Sendón[6], Carlos Macaya[5], and Rosana Hernández-Antolín[5], on behalf of the TRIANA Investigators†

[1]Departments of Cardiology, Hospital General Universitario Gregorio Marañón, Dr Esquerdo, 46, 28007 Madrid,Spain; [2]Departments of Cardiology, Hospital Clínic, Barcelona,Spain; [3]Departments of Cardiology, Hospital de Fuenlabrada, Fuenlabrada, Spain; [4]Departments of Cardiology, Hospital Bellvitge, Hospitalet de Llobregat, Barcelona, Spain; [5]Departments of Cardiology, Hospital Clínico San Carlos, Madrid, Spain; and [6]Departments of Cardiology, Hospital Universitario La Paz, Madrid, Spain

Received 24 May 2010; revised 7 July 2010; accepted 23 July 2010; online publish-ahead-of-print 22 October 2010

Aims To compare primary percutaneous coronary intervention (pPCI) and fibrinolysis in very old patients with ST-segment elevation myocardial infarction (STEMI), in whom head-to-head comparisons between both strategies are scarce.

Methods and results Patients ≥75 years old with STEMI <6 h were randomized to pPCI or fibrinolysis. The primary endpoint was a composite of all-cause mortality, re-infarction, or disabling stroke at 30 days. The trial was prematurely stopped due to slow recruitment after enroling 266 patients (134 allocated to pPCI and 132 to fibrinolysis). Both groups were well balanced in baseline characteristics. Mean age was 81 years. The primary endpoint was reached in 25 patients in the pPCI group (18.9%) and 34 (25.4%) in the fibrinolysis arm [odds ratio (OR), 0.69; 95% confidence interval (CI) 0.38–1.23; $P = 0.21$]. Similarly, non-significant reductions were found in death (13.6 vs. 17.2%, $P = 0.43$), re-infarction (5.3 vs. 8.2%, $P = 0.35$), or disabling stroke (0.8 vs. 3.0%, $P = 0.18$). Recurrent ischaemia was less common in pPCI-treated patients (0.8 vs. 9.7%, $P < 0.001$). No differences were found in major bleeds. A pooled analysis with the two previous reperfusion trials performed in older patients showed an advantage of pPCI over fibrinolysis in reducing death, re-infarction, or stroke at 30 days (OR, 0.64; 95% CI 0.45–0.91).

Conclusion Primary PCI seems to be the best reperfusion therapy for STEMI even for the oldest patients. Early contemporary fibrinolytic therapy may be a safe alternative to pPCI in the elderly when this is not available.
Clinicaltrials.gov # NCT00257309.

Keywords Acute myocardial infarction • Elderly • Primary angioplasty • Fibrinolysis • Randomized controlled trial

* Corresponding author. Tel: +34 91 5868293, Fax: +34 91 5868 276, Email: hecbueno@jet.es

† For complete list of investigators see Appendix 1.

Introduction

Primary percutaneous coronary intervention (pPCI) is currently the treatment of choice for patients presenting with ST-segment elevation myocardial infarction (STEMI). Fibrinolysis is a valuable alternative when mechanical reperfusion is not available in a timely fashion. However, the value of these therapies in very old patients, the fastest growing population group, is not well established because elderly patients have been either excluded or rarely enroled in reperfusion clinical trials.[1–4] In fact, only two small randomized trials comparing pPCI and fibrinolysis in the elderly have been performed, with discordant results.[5–7]

We undertook the TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) trial to compare the efficacy and safety of pPCI and fibrinolysis in very old STEMI patients. We hypothesized that mechanical reperfusion was superior to fibrinolysis to reduce the incidence of death, re-infarction, and disabling stroke at 30 days.

Methods

TRIANA was a randomized multicentre, open-label clinical trial, which included patients ≥75 years of age presenting with STEMI within the first 6 h after symptom onset at one of the participating centres (23 Spanish hospitals, all of them with cath lab facilities and an active primary angioplasty programme), who were eligible for fibrinolytic therapy and capable of providing informed consent prior to randomization. ST-segment elevation myocardial infarction was defined by the presence of chest pain lasting at least 20 min not responding to nitrates, plus one of the following: ST-segment elevation ≥2 mm in two or more electrocardiographic precordial leads or ST-elevation ≥1 mm in two or more frontal leads, or left bundle branch block. Exclusion criteria included any documented contraindication to the use of fibrinolytics according to the current European Society of Cardiology guidelines,[8] presence of cardiogenic shock at the time of randomization, an estimated door-to-balloon time >120 min; STEMI suspected as being caused by stent thrombosis, chronic renal failure (creatinine >2.5 mg/dL), expected life expectancy <12 months, or participation in another clinical trial within 30 days prior to randomization. The study protocol was approved by all institutional Ethics Committees.

Immediately after STEMI was diagnosed and inclusion/exclusion criteria confirmed, a written informed consent was obtained for each patient (an oral consent was accepted provided there was written consent of a witness related to the patient and independent from the study and enroling institution if the patient was unable to sign it). Consenting patients were randomized through a central telephone system, and allocated to the selected strategy.

Fibrinolysis group

Immediately after randomization, a weight-adjusted single intravenous dose of tenecteplase (TNK) was given ranging from 30 mg in patients <60 kg to 50 mg in those weighting ≥90 kg. Simultaneously, a 60 units/kg bolus of unfractionated heparin was administered up to a maximum of 4000 units followed by an infusion of 12 units/kg/h (up to a maximum of 1000 units/h) with an initial adjustment to maintain an activated partial thromboplastin time 1.5–2 times the upper normal limit. Based on the results of the COMMIT trial,[9] clopidogrel 75 mg daily without loading dose was added since January 2007. An electrocardiogram (ECG) was routinely performed 90 min after lytic administration, and urgent coronary angiography indicated if there were no signs of coronary reperfusion. The use of glycoprotein IIb/IIIa inhibitors was discouraged if rescue PCI was needed. After reperfusion, the use of coronary angiography was recommended only when there was evidence of spontaneous or induced recurrent myocardial ischaemia.

Primary percutaneous coronary intervention group

Patients were transferred to the cath lab as soon as possible. Both coronary arteries were visualized; left ventriculography was not performed routinely. Coronary angioplasty was performed at the investigator's discretion using any approved techniques and devices. Only the culprit vessel was targeted for pPCI. At the beginning of the procedure, a bolus of 60 units/kg of unfractionated heparin (with a maximum of 4000 units) was administered. Patients who received a stent were treated with clopidogrel, 300 mg loading dose given immediately before implantation, and 75 mg daily with a variable duration according to the type of stent. Use of glycoprotein IIb/IIIa inhibitors was discretionary. Concomitant medication such as aspirin, β-blockers, angiotensin-converting enzyme-inhibitors, statins, or others were given according to the guidelines.

The primary endpoint of the study was the incidence of the combination of all-cause mortality, re-infarction, or disabling stroke at 30 days after randomization. Secondary endpoints were the incidences of major bleeding, recurrent ischaemia requiring urgent catheterization, all-cause mortality, and cause of death at 30 days, and time elapsed until presentation of any component of the composite endpoint at 12 months.

Event adjudication and operational definitions

All major events were centrally adjudicated by an independent expert committee (Appendix 1) blinded to the treatment received by the patients, using standardized definitions (Appendix 2).

Statistical analysis

Continuous variables are summarized using medians and 25th–75th percentiles unless otherwise indicated; discrete variables are represented as frequencies and percentages. χ^2 tests were used for comparisons between proportions with calculations of odds ratios (ORs)

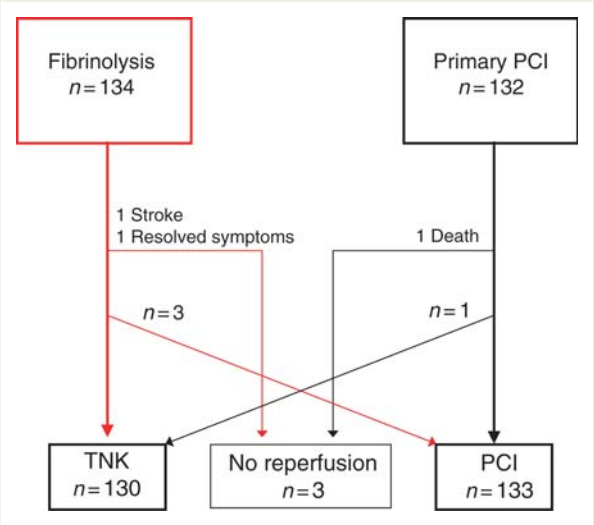

Figure 1 Chart flow of management in patients randomized to the TRIANA study. PCI, percutaneous coronary intervention.

Table 1 Baseline clinical characteristics

	Primary PCI (n = 132)	Fibrinolysis (n = 134)
Baseline characteristics		
Age, years (mean ± SD)	81.2 ± 4.6	81 ± 4.3
Male gender, *n* (%)	74 (56.1)	76 (56.7)
Weight, kg (mean ± SD)	70.3 ± 11	69 ± 10.5
Height, cm (mean ± SD)	162.5 ± 7.8	161.8 ± 8.4
Risk factors, *n* (%)		
Hypertension	78 (59.1)	91 (67.9)
Dyslipidaemia	36 (27.3)	56 (41.8)
Diabetes mellitus	45 (34.1)	35 (26.1)
Treatment with insulin	14 (10.6)	12 (9)
Current smokers	20 (15.2)	15 (11.2)
Previous cardiovascular disease, *n* (%)		
Previous myocardial infarction	10 (7.6)	12 (9)
Unstable angina	12 (9.1)	23 (17.2)
Chronic stable angina	18 (13.6)	14 (10.4)
Previous PCI	5 (3.8)	7 (5.2)
Previous CABG	1 (0.8)	2 (1.5)
Heart failure	1 (0.8)	2 (1.5)
Peripheral artery disease	12 (9.1)	14 (10.4)
Admission characteristics		
Systolic blood pressure, mmHg (mean ± SD)	132.3 ± 23.1	136.1 ± 24.8
Heart rate, b.p.m. (mean ± SD)	73.4 ± 18	75.5 ± 17.9
Killip class, *n* (%)		
1	108 (81.8)	113 (84.3)
2	20 (15.2)	15 (11.2)
3	4 (3)	4 (3)
ECG presentation, *n* (%)		
Anterior location	64 (48.5)	56 (41.8)
Left bundle branch block	3 (2.3)	3 (2.2)
TIMI risk score (mean ± SD)	5.7 ± 1.7	5.6 ± 1.5
Creatinine, mg/dL (mean ± SD)	1.13 ± 0.34	1.09 ± 0.36

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIMI, thrombolysis in myocardial infarction.

and exact 95% confidence intervals (CIs). When the number of expected cases was less than five, Fisher's exact test was used. The Student's *t*-test or the Mann–Whitney *U*-test was used to compare continuous values. Survival curves were calculated by the Kaplan–Meier product-limit method. Adjusted survival analysis was performed by fitting Cox proportional hazards models. Because of the small sample size, this was not used as a multivariate model but enabled us to calculate hazard ratios, which may be interpreted as risk ratios, with 95% CIs. All endpoints underwent intention-to-treat analysis with *P*-values < 0.05 considered significant.

Table 2 Reperfusion-related variables

	Primary PCI (n = 132)	Fibrinolysis (n = 134)	*P*-value
Times, minutes (median, 25th–75th percentiles)			
Symptom onset to randomization	180 (135–255)	180 (135–263)	0.991
Symptom onset to balloon or needle	245 (191–310)	195 (150–270)	<0.0001
Randomization to balloon or needle	59 (35–75)	10 (5–15)	<0.0001
Door-to-balloon or needle	99 (73–133)	52 (32–69)	0.002
Start of reperfusion ≤120 min, *n* (%)	5 (3.8)	18 (13.4)	<0.0001
Fibrinolysis, *n* (%)	1 (0.8)	129 (96.3)	
Tenecteplase dose (mg, mean ± SD)	—	37 ± 5	
Effective reperfusion, *n* (%)	—	99 (73.9)	
Rescue PCI, *n* (%)	—	20 (14.9)	
Primary PCI, *n* (%)	130 (98.5)	3 (2.2)	
Baseline results			
Infarct-related artery, *n* (%)			
Left main	1 (0.8)	—	
Left anterior descending	56 (42.4)	—	
Circumflex	18 (13.6)	—	
Right coronary	49 (37.1)	—	
Other/unknown	8 (6.1)	—	
Infarct-related artery stenosis, % (mean ± SD)	96.4 ± 11.6	—	
Infarct-related artery TIMI flow, *n* (%)			
0	84 (63.6)	—	
1	16 (12.1)	—	
2	14 (10.6)	—	
3	11 (8.3)	—	
Not available	7 (5.3)		
Final results			
Infarct-related artery residual stenosis, % (mean ± SD)	10.6 ± 25	—	
Infarct-related artery TIMI flow, *n* (%)	—		
0	7 (5.3)	—	
1	2 (1.5)	—	
2	13 (9.8)	—	
3	103 (78)	—	
Not available	7 (5.3)		

PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

The sample size was estimated on the basis of the results of the TRIANA pilot registry,[10] with the following assumptions: 21.7% incidence of the primary endpoint in the fibrinolysis group and 12.9% in the pPCI group. At alpha-level 5% and beta-level 20%, with an expected 1% loss to follow-up rate, the sample size needed to show differences was calculated in 570 patients.

Pooled analysis

Additionally, we conducted a quantitative analysis combining our results with those of previous reperfusion trials performed in older patients by calculating ORs and 95% CIs for each trial. A χ^2 analysis was used to assess heterogeneity. Because the latter was not significant, a fixed effects model was used. An overall OR with 95% CI was calculated, with studies weighted according to the Mantel–Haenszel method using a Review Manager® 4.2.7 software.

Results

Since March 2005, 266 patients with STEMI were randomized, 132 to pPCI and 134 to fibrinolysis. The study flowchart is shown in *Figure 1*. The study was interrupted due to slow recruitment in December 2007. Baseline characteristics were well balanced between groups except for dyslipidaemia (*Table 1*). Age ranged from 75 to 94 years.

Table 2 shows the information related to reperfusion therapies. Tenecteplase was administered in a median of 10 min after randomization and achieved a clinically successful reperfusion in 74% of patients. Rescue PCI was performed in 15% of cases. Among patients who underwent pPCI, baseline thrombolysis in myocardial infarction (TIMI) flow 0–1 was present in 78% of the available studies. A TIMI 3 flow was achieved after the procedure in 82.4% of the patients who underwent pPCI. Glycoprotein IIb/IIIa antagonists were used during reperfusion in 65 patients (49.6%), coronary stents in 111 (84%), and intra-aortic ballon pump in 6 (4.5%).

In-hospital management is shown in *Table 3*. More patients in the pPCI arm received clopidogrel, heparin, and nitroglycerine. Coronary angiography was performed in 40% of the patients after fibrinolysis, 15% on an urgent basis, and non-primary PCI was performed in 37%.

The primary endpoint (30-day death, re-infarction, or disabling stroke) was achieved in 18.9% of the patients treated with pPCI when compared with 25.4% of the patients treated with fibrinolysis (OR, 0.69; 95% CI 0.38–1.23). The incidence of each of the components of the primary endpoint and other outcomes is shown in *Table 4*. Although not statistically significant, all-cause mortality, re-infarction, and stroke were directionally lower with pPCI. Importantly, there were only four strokes in the fibrinolysis group, all of them originally ischaemic. There were no significant

Table 3 In-hospital management

	Primary PCI (n = 132)	Fibrinolysis (n = 134)	P-value
Medical treatment, *n* (%)			
Aspirin	127 (96.2)	130 (97)	0.73
Clopidogrel	121 (91.7)	84 (62.7)	<0.0001
Unfractionated heparin	117 (90.0)	122 (91.0)	0.77
Dose during reperfusion (UI, mean ± SD)	5134 ± 1672	3852 ± 726	<0.0001
Low-molecular-weight heparin	7 (5.4)	9 (6.7)	0.65
Intravenous nitroglycerine	66 (50)	91 (67.9)	0.004
Oral β-blockers	101 (76.5)	102 (76.1)	0.85
Angiotensin-converting enzyme inhibitor	108 (81.8)	115 (85.8)	0.44
Diuretics	66 (50)	60 (44.8)	0.36
Inotropic agents	26 (19.7)	22 (16.4)	0.47
Statins	118 (89.4)	117 (87.3)	0.46
Procedures, *n* (%)			
Echocardiography	117 (88.6)	124 (92.5)	0.27
Pre-discharge LVEF			0.17
>50%	47 (35.6)	61 (45.5)	
>40–50%	30 (22.7)	28 (20.9)	
30–40%	27 (20.5)	14 (10.4)	
<30%	15 (11.4)	12 (9)	
Unknown	9 (6.8)	10 (7.5)	
Non-invasive testing	6 (4.5)	26 (19.4)	<0.0001
Positive test	0 (0)	11 (42.3)	<0.0001
Coronary angiography	19 (14.4)	54 (40.3)	<0.0001
Non-primary PCI	16 (12.1)	49 (36.6)	<0.0001
Coronary artery bypass grafting	2 (1.5)	0 (0)	0.25
Hospital stay, days (median, 25th–75th percentiles)	9 (6–13)	9 (7–13)	0.78

PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction.

Table 4 Thirty-day and one-year outcomes

	Primary PCI ($n = 132$)	Fibrinolysis ($n = 134$)	OR (95%CI), pPCI vs. lysis	*P*-value
30-day outcomes, *n* (%)				
Primary endpoint (death, re-infarction, disabling stroke)	25 (18.9)	34 (25.4)	0.69 (0.38–1.23)	0.21
All-cause mortality	18 (13.6)	23 (17.2)	0.76 (0.39–1.49)	0.43
Cause of death, *n* (% of deaths)				0.36
Pump failure	4 (22)	5 (22)		
Mechanical complication or EMD	5 (28)	11 (48)		
Other	9 (50)	7 (30)		
Re-infarction	7 (5.3)	11 (8.2)	0.63 (0.24–1.67)	0.34
<24 h	2 (1.5)	6 (4.5)	0.33 (0.07–1.66)	0.28
>24 h	5 (3.8)	5 (3.7)	1.02 (0.29–0.36)	0.98
Stroke	1 (0.8)	4 (3)	0.16 (0.02–1.37)	0.37
Ischaemic stroke	1 (0.8)	4 (3)	0.16 (0.02–1.37)	0.37
Haemorrhagic stroke	0	0[a]		
Disabling stroke	1 (0.8)	4 (3)	0.16 (0.02–1.37)	0.37
New heart failure	14 (10.6)	15 (11.2)	0.94 (0.43–2.04)	0.88
Shock	13 (9.8)	7 (5.2)	1.98 (0.77–5.14)	0.15
Recurrent ischaemia	1 (0.8)	13 (9.7)	0.07 (0.01–0.55)	0.001
Mechanical complications	4 (3.0)	10 (7.5)	0.49 (0.16–1.48)	0.17
Major haemorrhage	5 (3.8)	6 (4.5)	0.84 (0.25–2.82)	0.78
Transfusion	7 (5.3)	4 (3)	1.82 (0.52–6.37)	0.38
Major haemorrhage or transfusion	12 (9.1)	9 (6.7)	1.39 (0.56–3.41)	0.47
Acute renal failure	8 (6.1)	10 (7.5)	0.79 (0.30–2.08)	0.64
One-year outcomes (cumulative)				
Death, re-infarction, or disabling stroke	36 (27.3)	43 (32.1)	0.79 (0.47–1.34)	0.39
All-cause mortality	28 (21.2)	31 (23.1)	0.90 (0.50–1.60)	0.71
Cardiac	18 (13.6)	23 (17.2)		
Non-cardiac	5 (3.8)	7 (5.2)		
Unknown	5 (3.8)	1 (0.7)		
Re-infarction	11 (8.3)	14 (10.4)	0.78 (0.34–1.59)	0.56
Stroke	1 (0.8)	5 (3.8)	0.20 (0.02–1.71)	0.37
Heart failure	19 (14.4)	20 (14.9)	0.96 (0.49–1.89)	0.90
Recurrent ischaemia	1 (0.8)	16 (11.9)	0.06 (0.01–0.43)	<0.001
Major haemorrhage	8 (6.1)	7 (5.2)	1.17 (0.41–3.33)	0.77
Urgent rehospitalization				
n (% of hospital survivors)	34 (29.3)	29 (26.1)	1.27 (0.72–2.24)	0.59
Cardiac	19 (16.5)	16 (14.4)		
Non-cardiac	17 (14.8)	13 (11.7)		

PCI, percutaneous coronary intervention; EMD, electromechanical dissociation.
[a]One patient developed an ischaemic stroke after a coronary angiography on the seventh day of evolution, which converted to haemorrhagic stroke on the following day leading to death.

differences in other complications such as major haemorrhage, blood transfusion, or renal failure. Primary PCI greatly reduced recurrent ischaemia needing urgent coronary angiography at 30 days. The outcomes for the composite endpoint and for mortality at 1 year are shown in *Figure 2*.

The efficacy of pPCI vs. fibrinolysis on the primary endpoint according to different pre-defined subgroups is shown in *Figure 3*. Only 23 patients received reperfusion within the first 2 h from symptom onset, 18 with fibrinolysis, and 5 with pPCI. No deaths occurred in these patients at 30 days compared with 16.7% in those treated later ($P = 0.03$). They also showed a lower incidence of the primary endpoint (4.3 vs. 23.8%, $P = 0.03$), but the numerical difference in event rates in favour of pPCI over fibrinolysis remained unchanged.

The results of our study were pooled with those of the two previous randomized trials comparing fibrinolysis and pPCI in older

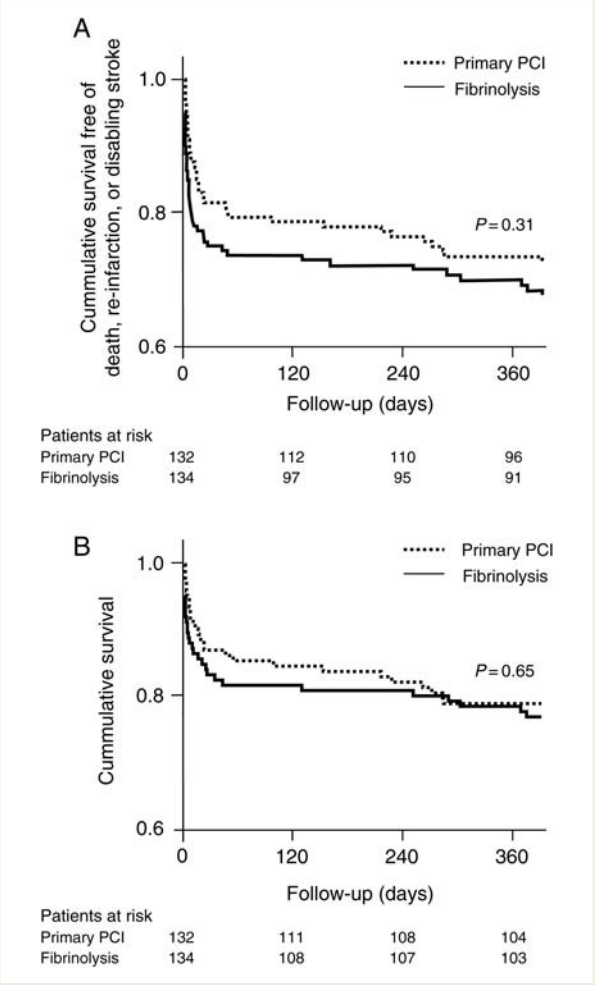

Figure 2 One-year Kaplan–Meier survival curves free of death, re-infarction, or disabling stroke (primary endpoint) (*A*) or all-cause mortality (*B*). PCI, percutaneous coronary intervention.

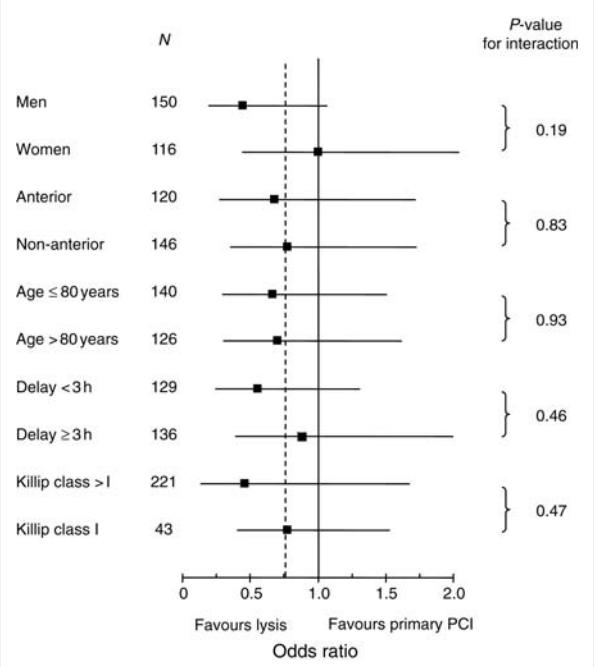

Figure 3 Odds ratio for efficacy of primary angioplasty compared with fibrinolysis according to different pre-defined subgroups. PCI, percutaneous coronary intervention.

patients.[5–7] Differences in baseline characteristics, designs, and results are shown in Appendix 3. The overall risk of death, re-infarction, or disabling stroke was substantially lower for patients allocated to pPCI compared with those treated with fibrinolysis (14.9 vs. 21.5%; OR, 0.64; 95% CI 0.45–0.91; $P = 0.013$). The pooled rate of death showed a similar trend in favour of pPCI, but the difference was not statistically significant (*Figure 4*).

Discussion

We conducted a randomized trial comparing pPCI and fibrinolysis in a series of very old patients with STEMI. Unfortunately, the study had to be prematurely interrupted due to the slow recruitment rate and the impossibility to reach the target population. However, the study results are meaningful and may be clinically useful when combined with previous evidence.

Effects of reperfusion in the elderly

The use of fibrinolysis for the treatment of STEMI in the elderly has been controversial from the beginning. A first meta-analysis found that its effect on mortality was not superior to placebo in patients >75 years old.[11] A later reassessment of the same data including only properly selected patients indicated that the benefit in the oldest patients was actually greater than that for younger patients.[12] Finally, some observational studies suggested that fibrinolysis could be deleterious in very old patients with STEMI,[13,14] whereas only patients treated with pPCI showed better 30-day survival compared with those who did not receive reperfusion therapy.[15]

To date, only two randomized studies have specifically addressed the issue of pPCI vs. fibrinolysis in the elderly. In the Zwolle[5] study, the 46 patients allocated to pPCI showed a lower 2-year mortality rate compared with those treated with streptokinase (15 vs. 32%, $P = 0.04$). The larger, yet unpublished, Senior PAMI trial,[6,7] which randomized 481 patients >70 years old failed to document differences between pPCI and fibrinolysis in the primary outcome (30-day mortality or stroke) or in mortality (Appendix 3). Moreover, a *post-hoc* analysis showed a non-significant trend towards a higher mortality rate in patients >80 years old allocated to pPCI (19 vs. 16%).[7] With this in mind, the present study was undertaken to further define the role of these strategies in a contemporary clinical setting with updated antithrombotic ancillary therapies.

Clinical outcomes

In this trial, pPCI was associated with a non-significant reduction in the composite endpoint of death, recurrent infarction, and disabling stroke after 30 days, with a similar direction in the estimates of the effect on each of the three individual components of the

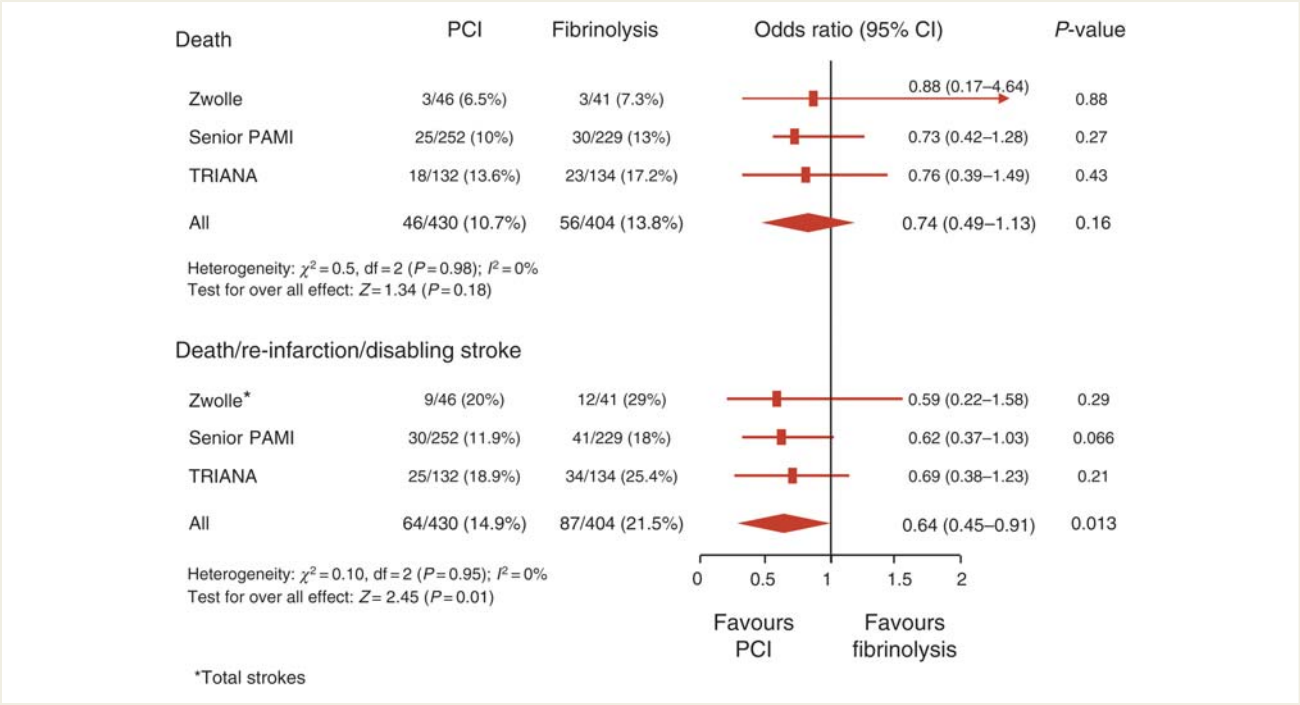

Figure 4 Odd-ratios for mortality and the combined endpoint in the three randomized trials comparing primary percutaneous coronary intervention and fibrinolysis performed in very old patients with ST-segment elevation myocardial infarction. PCI, percutaneous coronary intervention.

primary endpoint. Interestingly, pPCI was associated with a very substantial reduction in recurrent ischaemia, which remained significant throughout the follow-up. Although generally regarded as a soft endpoint, recurrent ischaemia was precisely defined in the present study as that requiring catheterization, and was externally adjudicated. It is remarkable that the small proportion of patients who underwent reperfusion within the first 2 h from symptom onset achieved excellent clinical results.

The cost of fibrinolysis in terms of bleeding was low. Only four strokes occurred in this treatment arm and none of them were originally haemorrhagic. In addition, no differences in major bleeding or transfusion need between the two treatments could be demonstrated. Careful dosing and monitoring of antithrombotic and anticoagulant medications, including TNK, aspirin, clopidogrel, and heparin, probably accounted for it.

In keeping with contemporary practice, use of stents in this trial was higher (84%) than in representative studies (51% in the Zwolle series[5]). In spite of that, TIMI 3 grade flow in TRIANA was comparatively lower (83% of those attempted vs. 90%). These differences might be due to either a more globally representative outcome in the present study, to the fact that even in angiographic core laboratories determinations of TIMI flow are often discrepant, or both.

Overall perspective after TRIANA

The observations using data from all prospective randomized trials performed in very old patients with STEMI provide good evidence that pPCI improves outcomes in this setting. Although the need for a large community-based multicentre confirmation trial still remains desirable, successful enrollment for such a study appears—as in previous attempts—very unlikely since most clinicians are strongly convinced of the superiority of pPCI.[4]

Study limitations

The study was halted prematurely before the planned enrollment could be met. This decision was taken by the executive committee owing to slow recruitment. As a result, the study is underpowered to properly test the primary endpoint. We used restrictive entry criteria, particularly concerning high blood pressure and prior history of stroke. This translated into a reduction in the number of potential candidates and a more selected population, but major concern about safety, particularly increased bleeding risk, dictated this policy. Also, the population enroled was quite fit, with a low prevalence of heart failure in the past and on admission, which may reduce the extrapolability of the results to broader populations. The present study was unblinded as comparisons between angioplasty and pharmacologic reperfusion therapy are by nature, and thus, suboptimal. However, patient treatments were blinded to the event adjudication committee. Better outcomes could have been obtained in both arms if faster reperfusion had been achieved, and current recommended co-adjuvant therapies, such as abciximab or higher clopidogrel loading doses had been more frequently used in patients undergoing pPCI. However, that was not standard care in 2004 when the study was designed. Finally, rescue PCI, a procedure that could influence outcome, was only performed in 15% of the patients receiving fibrinolytic treatment, a rate probably low for today standards in

younger people. As a reference, although the number of rescue PCIs performed in the Zwolle trial[5] and in Senior PAMI[7] was not stated, in the latter 37% of patients underwent in-hospital repeated catheterization, a proportion comparable with that in TRIANA.

Conclusions

Our results complement previous work suggesting that pPCI may offer clinical advantage over fibrinolytic therapy as manifested by the trends towards improvements in the combined endpoint of death, re-infarction, and stroke at 30 days in the oldest patients. In addition, we have observed that mechanical reperfusion encompasses a significant reduction in adjudicated recurrent ischaemia. Thus, pPCI seems to be the reperfusion strategy of choice also in very old patients presenting with STEMI. Since state-of-the-art fibrinolysis appears to be safe, it may be considered a valuable alternative when pPCI is not available, particularly when initiated early.

Acknowledgements

We appreciate Dr Mónica Massotti's contribution to the development of the pooled analysis.

Funding

The TRIANA study was an initiative of the Working Group on Ischaemic Heart Disease and the Working Group on Interventional Cardiology of the Spanish Society of Cardiology, and was funded by the Fondo de Investigaciones Sanitarias del Instituto Carlos III (grant # PI042122), the Spanish Society of Cardiology, and additional support through unrestricted grants from sanofi-aventis, Boston Scientific, Guidant, Johnson & Johnson, and Medtronic. Funding to pay the Open Access publication charges for this article was provided by the Working Group on Ischaemic Heart Disease, and the Working Group on Interventional Cardiology of the Spanish Society of Cardiology.

Conflict of interest: H.B. reports having received consulting fees from Almirall, Astra-Zeneca, Bayer, BMS, and sanofi-aventis, and research grants from BMS, and Pfizer. A.B., M.H., J.J.A., A.C., E.J.G., J.L.L-S., C.M., and R.H-A. declare they have no potential conflict of interest that might constitute an embarrassment to any of the authors if it were not to be declared and were to emerge after publication, including shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product.

Appendix 1

Study organization

Steering Committee: Héctor Bueno (chair), Rosana Hernández-Antolín (co-chair), Joaquín J. Alonso, Amadeo Betriu, Angel Cequier, Eulogio J. García, Magda Heras, José L. López-Sendón, Carlos Macaya.

Data Safety and Monitoring Board: José Azpitarte (chair).

Adjudication Committee: Ginés Sanz (chair), Angel Chamorro, Ramón López-Palop, Alex Sionis, Fernando Arós.

Participating centres, number of patients enroled, and principal investigators:

- Hospital General Universitario Gregorio Marañón, Madrid (30): Eulogio García-Fernández, Rafael Rubio;
- Hospital 12 de Octubre, Madrid (29): Felipe Hernández, Juan Carlos Tascón;
- Hospital Virgen de la Salud, Toledo (23): José Moreu;
- Hospital Clínic de Barcelona (20): Amadeu Betriu, Magda Heras;
- Hospital Clínico San Carlos, Madrid (19): Rosana Hernández-Antolín, Antonio Fernández-Ortiz;
- Hospital Central de Asturias, Oviedo (19): César Morís, Ignacio Sánchez de Posada;
- Hospital Bellvitge, Barcelona (18): Ángel Cequier, Enrique Esplugas;
- Hospital Universitario Virgen de las Nieves, Granada (17): Rafael Melgares;
- Hospital Universitario de Canarias, Las Palmas (15): Francisco Bosa, Martín Jesús García-González;
- Hospital de Navarra, Pamplona (15): Román Lezáun, José Ramón Carmona;
- Hospital Juan Canalejo, A Coruña (14): José Manuel Vázquez, Alfonso Castro-Beiras;
- Hospital Santa Creu i Sant Pau, Barcelona (8): Joan García Picart, José Domínguez de Rozas;
- Hospital Juan Ramón Jiménez, Huelva (8): José Díaz Fernández;
- Complejo Hospitalario de León (4): Felipe Fernández Vázquez, Norberto Alonso;
- Hospital Marqués de Valdecilla, Santander (4): José Javier Zueco, José María San José;
- Hospital Clínico Universitario de Valladolid (4): Alberto San Román, Carolina Hernández;
- Hospital Virgen de la Victoria, Málaga (4): José María Hernández García, Ángel García Alcántara;
- Hospital Universitario Son Dureta, Palma de Mallorca (3): Armando Bethencourt, Miquel Fiol;
- Hospital Cruces, Bilbao (3): Xabier Mancisidor, Xabier Mancisidor;
- Hospital Virgen de la Macarena, Sevilla (3): Rafael Ruiz, Rafael Hidalgo;
- Hospital Universitario La Paz, Madrid (3); Nicolás Sobrino, Isidoro González Maqueda;
- Hospital Txagorritxu, Vitoria (2): Alfonso Torres, Fernando Arós;
- Hospital Universitario de Santiago de Compostela (1): Antonio Amaro, Michel Jaquet.

Appendix 2

Study operational definitions

All events were evaluated by an *ad hoc* independent committee of experts, including three cardiologists and one neurologist, who were blinded to the treatment received by the patient. The following operative definitions were used for outcome adjudication.

Death: death of any cause that occurred since randomization until the end of follow-up. Information was obtained from clinical records or any other reliable source. The causes of death at 30 days were classified in three groups: shock or heart (pump) failure, mechanical complications or electromechanical dissociation, and other causes (including bleeding).

*Re-infarction***:** it was defined according to the time of occurrence. Within first 24 h after randomization, re-infarction was defined as the recurrence of symptoms of myocardial ischaemia with

ST-segment elevation >0.1 mV in at least two or more adjacent leads for at least 30 min. After the first 24 h, troponin re-elevation or increase of creatine kinase-MB levels or appearance of new Q-waves in two or more leads were also requested.

Disabling stroke: presence of new permanent focal or generalized neurologic symptoms affecting the normal life of a patient, associated to abnormal findings (ischaemic or haemorrhagic lesions) in a computed tomography or magnetic resonance imaging.

Heart failure: presence of new symptoms or signs suggesting heart failure (dyspnoea, orthopnoea, third sound, or rales on pulmonary auscultation associated with signs of pulmonary congestion in a chest X-ray) after the first 24 h.

Recurrent ischaemia: cardiac catheterization indicated for angina with ST-segment shift or T-wave inversion, provided that re-infarction criteria were not fulfilled.

Shock: presence of persistent hypotension (systolic blood pressure <90 mmHg with no response to volume load) associated with signs of low cardiac output, regardless of its cause.

Mechanical complication: clinical evidence of rupture of the free ventricular wall or the interventricular septum, or severe mitral regurgitation secondary to total or partial rupture of a papillary muscle, confirmed by any diagnostic technique.

Major bleeding: cerebral haemorrhage or any other bleeding associated with a haemoglobin drop ≥5 g/dL, or an absolute haematocrit drop ≥15%.

The time from admission to the initiation of therapy was calculated as the time to the start of the lytic infusion or the first balloon inflation.

Appendix 3

Randomized controlled trials comparing primary percutaneous intervention vs. fibrinolysis in older patients with ST-segment elevation myocardial infarction

Table A1 Comparison of trials designs and baseline characteristics

	de Boer	Senior PAMI	TRIANA
Age limit (years)	>75	≥70	≥75
Time limit	<6 h (6–24 h, if continuing ischaemia)	<12 h	<6 h
Study years	1996–1999	2000–2005	2005–2007
Patients enroled, *n* (lytics/pPCI)	87 (41/46)	481 (229/252)	266 (134/132)
Primary endpoint (all incidence at 30 days)	Death, re-infarction, or stroke	Death or disabling stroke	Death, re-infarction, or disabling stroke
Participant hospitals	Single centre (Zwolle, the Netherland)	Multicentre international	23 hospitals in Spain
Lytic agent	SK 100%	SK 38%; TNK/tPA/rPA 62%	TNK 100%
Antiplatelet therapy lysis arm	Aspirin i.v. 450 mg	N/A	Aspirin 300 mg, clopidogrel 75 mg q.d. × 28 days[a]
Antiplatelet therapy pPCI arm	Aspirin i.v. 450 mg ticlopidine 250 mg b.i.d. × 2 weeks[a]	N/A	Aspirin 300 mg, clopidogrel 300 mg + 75 mg q.d.
Anticoagulation	UFH (for aPTT 2–3)	N/A	UFH 60 units/kg (maximum 4000 U)
Glycoprotein IIb/IIIa inhibitors for pPCI	Not used	N/A	Abciximab (49.6%)
Stents during pPCI	51%	N/A	84%
Door to reperfusion, minutes (mean ± SD)	Lytics: 31 ± 15; pPCI: 59 ± 19	Lytics: 62; pPCI: 82	Lytics: 59 ± 40; pPCI: 107 ± 47
Age, years median, (P_{25}–P_{75}); range	Lytics: 81 (78–84); 75 (N/A); pPCI: 80 (77–84); 75 (N/A)	Lytics: 77 (N/A); 70–101; pPCI: 78 (N/A); 70–99	Lytics: 80 (78–84); 75–94; pPCI: 80 (78–84); 75–94
Male gender (%)	Lytics: 61; pPCI: 48	Lytics: 60; pPCI: 58	Lytics: 56; pPCI: 57
Diabetes (%)	Lytics: 17; pPCI: 24	Lytics: 20; pPCI: 25	Lytics: 34; pPCI: 26
Anterior location (%)	50	45	45
Killip >II (%)	Lytics: 10; pPCI: 13	N/A	Lytics: 3; pPCI: 3

N/A, not available; pPCI, primary percutaneous coronary intervention.
[a]Since December 2006.

Table A2 Comparison of trials results

		de Boer	Senior PAMI	TRIANA
Endpoints				
Primary endpoint[a] (%)	Lytics	29	13	25.4
	pPCI	9	11.3	18.9
Mortality (%)	Lytics	22	13	17.2
	pPCI	7	10	13.6
Re-infarction (%)	Lytics	15	5.4	8.2
	pPCI	2	1.6	5.3
Stroke (%)	Lytics	7	N/A	3
	pPCI	2	N/A	0.8
Disabling stroke (%)	Lytics	N/A	2.2	3.0
	pPCI	N/A	0.8	0.8
Major bleeding (%)	Lytics	7	N/A	4.5
	pPCI	11[b]	N/A	3.8
Risk/odds ratios lysis vs. pPCI				
Primary endpoint		RR 4.3 (1.2–20)	N/A	OR 1.46 (0.81–2.61)
Mortality		RR 4.0 (0.9–24.6)	N/A	OR 1.31 (0.67–2.56)
Re-infarction		N/A	N/A	OR 1.60 (0.60–4.25)
Disabling stroke		N/A	N/A	OR 4.03 (0.44–36.5)

[a]See definition in Table 1; pPCI, primary percutaneous coronary intervention.
[b]Non-cerebral bleeding.

References

1. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *JAMA* 1992;**268**:1417–1422.
2. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA* 2001;**286**:708–713.
3. Krumholz HM, Gross CP, Peterson ED, Barron HV, Radford MJ, Parsons LS, Every NR. Is there evidence of implicit exclusion criteria for elderly subjects in randomized trials? Evidence from the GUSTO-1 study. *Am Heart J* 2003;**146**: 839–847.
4. Alexander KP, Newby LK, Armstrong PW, Cannon CP, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM, Ohman EM. American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation* 2007; **115**:2570–2589.
5. de Boer MJ, Ottervanger JP, vaṅt Hof AWJ, Hoornethe A, Suryapranata H, Zijlstra F, on behalf of the Zwolle Myocardial Infarction Study Group. Reperfusion therapy in elderly patients with acute myocardial infarction. A randomized comparison of primary angioplasty and thrombolytic therapy. *J Am Coll Cardiol* 2002;**39**:1723–1728.
6. Senior PAMI. Primary angioplasty versus thrombolytic therapy for acute myocardial infarction in the elderly. http://www.clinicaltrial.gov/ct2/show/NCT00136929. (14 May 2010).
7. Senior PAMI. Primary PCI not better than lytic therapy in elderly patients. http://www.theheart.org/article/581549.do. (14 May 2010).
8. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, Julian D, Lengyel M, Neumann FJ, Ruzyllo W, Thygesen C, Underwood SR, Vahanian A, Verheugt FW, Wijns W. Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;**24**:28–66.
9. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**:1607–1621.
10. Bardají A, Bueno H, Fernández-Ortiz A, Cequier A, Auge JM, Heras M. Características clínicas, tratamiento y evolución del infarto agudo de miocardio en ancianos tratados médicamente. Resultados del registro TRIANA 2. *Rev Esp Cardiol* 2005;**58**:351–358.
11. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311–322.
12. White HD. Thrombolytic therapy in the elderly. *Lancet* 2000;**356**:2028–2030.
13. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation* 2000;**101**:2239–2246.
14. Soumerai SB, McLaughlin TJ, Ross-Degnan D, Christiansen CL, Gurwitz JH. Effectiveness of thrombolytic therapy for acute myocardial infarction in the elderly: cause for concern in the old-old. *Arch Intern Med* 2002;**162**:561–568.
15. Berger AK, Radford MJ, Wang Y, Krumholz HM. Thrombolytic therapy in older patients. *J Am Coll Cardiol* 2000;**36**:366–374.