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

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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 enrolling 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.

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

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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 enrolled in reperfusion clinical trials. In fact, only two small randomized trials comparing pPCI and fibrinolysis in the elderly have been performed, with discordant results.

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, 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 enrolling institution if the patient was unable to sign it). Consentining 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, 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. χ² tests were used for comparisons between proportions with calculations of odds ratios (ORs).
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.
The sample size was estimated on the basis of the results of the TRIANA pilot registry, 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 $\chi^2$ 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 3  In-hospital management

| Medical treatment, $n$ (%)                                      | Primary PCI ($n = 132$) | Fibrinolysis ($n = 134$) | $P$-value |
|----------------------------------------------------------------|--------------------------|--------------------------|-----------|
| 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.
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

| 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 (8.5)               | 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 (0.29–3.36)          | 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*                    |                           | 0.37   |
| 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.

*aOne 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 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. 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. Finally, some observational studies suggested that fibrinolysis could be deleterious in very old patients with STEMI, whereas only patients treated with pPCI showed better 30-day survival compared with those who did not receive reperfusion therapy.

To date, only two randomized studies have specifically addressed the issue of pPCI vs. fibrinolysis in the elderly. In the Zwolle 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, 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%). 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
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). 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.

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 enrolled 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\(^3\) 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.

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**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, Amadeu Betriu, Ángel 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), Ángel Chahorrro, Ramón López-Palop, Alex Sionis, Fernando Arós.

**Participating centres, number of patients enrolled, and principal investigators:**

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- Hospital Virgen de la Macarena, Sevilla (3): Rafael Ruiz, Rafael Hidalgo;
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- 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 increased 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 | 2000–2005 |
| Study years | 1996–1999 | 2000–2005 | 2005–2007 |
| Patients enrolled, 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 Netherlands) | Multicentre international | 23 hospitals in Spain |
| Lytic agent | SK 100% | SK 38%; TNK/tPA/rPA 62% | TNK 100% |
| Antiplatelet therapy | Aspirin i.v. 450 mg | Aspirin 300 mg, clopidogrel 75 mg q.d. × 28 days | 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, (P25–P75); 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 (%) | 61; pPCI: 48 | 60; pPCI: 58 | 56; pPCI: 57 |
| Diabetes (%) | 17; pPCI: 24 | 20; pPCI: 25 | 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.

*Since December 2006.*
### Table A2  Comparison of trials results

| Endpoints                      | de Boer   | Senior PAMI | TRIANA  |
|--------------------------------|-----------|-------------|---------|
| **Primary endpointa (%)**     | 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**                       | 11b       | 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) |

*aSee definition in Table 1; pPCI, primary percutaneous coronary intervention.

*bNon-cerebral bleeding.

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