Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis

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Aims

Multiple trials in patients with ST-segment elevation myocardial infarction (STEMI) compared early routine percutaneous coronary intervention (PCI) after successful fibrinolysis vs. standard therapy limiting PCI only to patients without evidence of reperfusion (rescue PCI). These trials suggest that all patients receiving fibrinolysis should receive mechanical revascularization within 24 h from initial hospitalization. However, individual trials could not demonstrate a significant reduction in ‘hard’ endpoints such as death and reinfarction. We performed a meta-analysis of randomized controlled trials to define the benefits of early PCI after fibrinolysis over standard therapy on clinical and safety endpoints in STEMI.

Methods and results

We identified seven eligible trials, enrolling a total of 2961 patients. No difference was found in the incidence of death at 30 days between the two strategies. Early PCI after successful fibrinolysis reduced the rate of reinfarction (OR: 0.55, 95% CI: 0.36–0.82; P = 0.003), the combined endpoint death/reinfarction (OR: 0.65, 95% CI: 0.49–0.88; P = 0.004) and recurrent ischaemia (OR: 0.25, 95% CI: 0.13–0.49; P < 0.001) at 30-day follow-up. These advantages were achieved without a significant increase in major bleeding (OR: 0.93, 95% CI: 0.67–1.34; P = 0.70) or stroke (OR: 0.63, 95% CI: 0.31–1.26; P = 0.21). The benefits of a routine invasive strategy over standard therapy were maintained at 6–12 months, with persistent significant reduction in the endpoints reinfarction (OR: 0.64, 95% CI: 0.40–0.98; P = 0.01) and combined death/reinfarction (OR: 0.71, 95% CI: 0.52–0.97; P = 0.03).

Conclusion

Early routine PCI after fibrinolysis in STEMI patients significantly reduced reinfarction and recurrent ischaemia at 1 month, with no significant increase in adverse bleeding events compared to standard therapy. Benefits of early PCI persist at 6–12 month follow-up.

Keywords

Early PCI • Fibrinolysis • Myocardial Infarction

Introduction

Primary percutaneous coronary intervention (PCI) is the gold-standard reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI), when this can be performed soon after symptom onset. Many STEMI patients, however, present to hospitals without capability of performing PCI or live in rural areas with a transfer time to hub centres too
Early PCI after fibrinolysis

long to undergo primary mechanical revascularization within the timelines recommended in the guidelines.2–3 The attempt to extend to these patients the benefits of mechanical revascularization using fibrinolysis followed by PCI has been hampered in the past by a higher frequency of both bleeding and ischaemic events after the intervention. Multiple trials have shown that STEMI patients treated with fibrinolysis should be routinely transferred to elective PCI within 24 h from initial hospitalization.4–10 An early invasive strategy after fibrinolytic therapy in STEMI patients achieves rapid stabilization of the culprit lesion in patients who may otherwise develop recurrent ischaemic events after an initially successful fibrinolysis. Moreover, it restores coronary flow in patients with a persistently occluded artery, who are not always easily identifiable based on symptoms and ST-segment changes. Despite the consistent results confirmed by two recent additional trials, the most recent ESC and ACC STEMI guidelines11,12 only provided a Class IIa recommendation for routine early PCI within 3–24 h after successful lytic therapy. This recommendation reflects the absence of a significant reduction in ‘hard’ endpoints such as death or reinfarction in any of the trials and the concern about an increased bleeding risk raised by previous trials using the different strategy of ‘facilitated’ PCI, designed to investigate the benefits of fibrinolysis before the primary mechanical revascularization in patients otherwise good candidates to primary PCI.13,14 The principal investigators of these randomized trials agreed to cooperate in a systematic meta-analysis comparing early routine PCI after fibrinolysis vs. standard therapy in STEMI patients, to define the benefits of routine invasive strategy after fibrinolysis on clinical and safety endpoints in STEMI.

Methods

Study research

A comprehensive literature search on MEDLINE and Cochrane Library electronic database was conducted to identify all published randomized controlled trials performed after 1999 comparing early PCI, performed within 24 h from fibrin-specific lytic therapy, to the standard strategy in STEMI patients presenting in non-PCI centres. The search was performed for the following keywords: ‘early PCI’, ‘immediate PCI’, ‘thrombolysis’, ‘fibrinolysis’, ‘PCI’, ‘angioplasty’, ‘invasive strategy post-thrombolysis’, ‘early PCI post-thrombolysis’ and was restricted to English language and peer-reviewed journals. Reference lists of identified studies were reviewed to ensure that potential eligible trials were not excluded from the search. Two investigators independently evaluated studies for possible inclusion (C.D.M.,F.B.). We excluded studies that utilized non fibrin-specific agents, studies on facilitated angioplasty, and balloon-PTCA trials. Trials included were those designed to investigate the benefits and feasibility of a routine invasive strategy with immediate transfer for early PCI after successful fibrinolysis in patients in whom primary PCI is not readily available, and therefore trials on facilitated PCI were excluded. The methodological quality of each trial was assessed based on the method of randomization and evidence of masked outcome assessments, according to the 5-point scale by Jadad et al.15

Data extraction

Clinical endpoints of interest included all-cause death, reinfarction, combined death/reinfarction, recurrent ischaemia, and revascularization at 30 days and longer follow-up. Safety outcome included major bleeding and stroke at 30 days. Endpoint definitions for each trial are reported in Appendix A. Definition differences were resolved by consensus between all co-authors of this paper, who are also lead investigators of the individual trials. Clinical and safety endpoints were extracted from the published manuscripts by two investigators (K.D., F.B.) and confirmed by the main investigators of each selected trial.

Endpoint and definition differences

Clinical endpoints were separately analysed at 30-days and 6–12 month follow-up, to critically assess the benefit of the early PCI strategy compared with standard therapy at short and longer follow-up after STEMI. Both clinical (death, reinfarction, the combined endpoint death/reinfarction, recurrent ischaemia, revascularization) and safety endpoints (major bleeding and stroke) were assessed at 30 days, whereas only clinical endpoints were assessed at 6–12 months. The WEST trial was excluded for the 6–12 month analysis because of the lack of data beyond the first month from recruitment.

All-cause death was reported in all trials, which also used similar definitions of reinfarction (see Appendix A). The definition of recurrent ischaemia and the classification of major bleeding present greater differences. In four trials, the definitions for recurrent ischaemic events were limited to the reappearance of electrocardiographic changes,6,8,10,11 while in the other trials new arrhythmias10 or anginal symptoms were also considered.7,15 In the GRACIA-1 trial, recurrent ischaemia included positive pre-discharge stress-test test. The principal investigator of this last trial (F.F.A.) kindly provided a list of patients with positive pre-discharge stress test and we were able to overrule the initial attribution to the recurrent ischaemia group if this was the only reason.

Major bleeding definitions followed the TIMI classification in four trials.6–8 In the NORDISTEMI trial, major bleeding was reported according to the GUSTO classification, but the principal investigator (S.H.) kindly provided these data according to the TIMI classification, so that we were able to enter them in this format. In the other trials, major bleeding was reported using different classifications, which were, however, very similar to the TIMI classification and were used as such.9,10 Revascularization definitions were reported in only three trials.5,7,9

Statistical analysis

Data from each trial were entered on an intention-to-treat basis. Summary odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random effects model, incorporating between and within-study variance.16 When statistical significance was reached, the number of patients needed to be treated to avoid one event (NNT = 1/(absolute risk difference)) and its 95% CI (Newcombe-Wilson method) were calculated. When the number of events was 0, a 0.5 correction factor was added to each number for calculation of the odds ratio and its variance. Heterogeneity between individual trials was evaluated using the Q-statistic and the I² index.17 The latter was calculated by applying the formula $I^2 = [(Q - df)/Q] \times 100$, where $Q$ is the statistic $\chi^2$ square, and $df$ its degrees of freedom. A $I^2$ index value greater than 50% was considered as indicative of large heterogeneity. Publication bias was assessed by funnel plots [precision (inverse of SE) vs. log odds ratio] and Egger’s regression test.18 Sensitivity analyses were conducted to examine the robustness of the results by eliminating one study at a time from the analysis, to determine whether the pooled estimates were disproportionately influenced by a particular trial. Weighted random effect meta-regression was performed to explore the relationship between...
the profile risk of STEMI patients enrolled in each trial and the effect of early PCI on the clinical endpoints of reinfarction and death/reinfarction, as previously reported.19 Statistical significance was set at a P-value <0.05 and all tests performed were two-sided. The statistical calculations were performed using Review Manager 5.0 and R version 2.9.2 statistical software. The study was performed in accordance with the Quality of Reporting of Meta-analysis (QUORUM) guidelines.20

Results

Trial search results

The electronic database search process (Figure 1) identified 546 citations, of which 513 were excluded because they did not meet the inclusion criteria. Among the 33 remaining trials, 26 were excluded because they were trials of facilitated13,14,21–25 or rescue PCI,16–17 used balloon angioplasty or non fibrin-specific lytic therapy.22–26 Seven randomized controlled trials met the inclusion criteria and were eligible for the study.4–10 The WEST trial10 compared three treatment groups (standard therapy, early PCI and primary PCI), but could be included due to detailed extensive reporting of data on early PCI vs. standard therapy in the manuscript.

Trial characteristics

Trial characteristics are summarized in Table 1. A total of 2961 patients were enrolled, of whom 1471 patients were randomized to standard STEMI therapy and 1490 patients to a routine invasive strategy with early PCI within 24 h after successful fibrinolysis. Follow-up ranged from 30 days to 1 year. The fibrinolytic agent used was tenecteplase in four trials,4–6,10 accelerated alteplase in GRACIA-1, half-dose reteplase with full-dose abciximab in the CARESS-IN-AMI trial, and full-dose reteplase in the SIAM-III trial.

In most trials, randomization and fibrinolysis were performed during first hospitalization in a non-PCI capable centre. In the WEST10 and NORDISTEMI5 trials, nearly 50% of randomized patients received pre-hospital fibrinolysis directly in the ambulance and were transferred to a PCI centre. In the GRACIA-1 trial,9 76% of patients received fibrinolysis and PCI in the same hospital. Reported time-window intervals from symptom onset to lytic therapy were similar across the selected trials, whereas time from administration of fibrinolysis to early PCI ranged from 84 min6 to 16.7 h9 (Figure 2).

In all included trials, over 80% of patients underwent PCI after angiography in the early PCI arm (mean 87.5%) because of residual diameter stenosis >50–70% in the culprit vessel or suboptimal TIMI flow (<3). PCI after fibrinolysis was performed by femoral...
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Inclusion criteria</th>
<th>Lytic agent (type)</th>
<th>Strategy</th>
<th>Symptoms to lytic therapy (min)</th>
<th>Lytic therapy to early PCI (min)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARESS-IN-AMI (2008)</td>
<td>High-risk STEMI patients presenting ≤ 12 h from symptom onset.</td>
<td>r-PA (half dose)$^\text{a}$</td>
<td>Standard therapy (301 patients) (rescue PCI in 31%) Immediate PCI after lysis (299 patients) (PCI in 86%)</td>
<td>165$^\text{b}$</td>
<td>—</td>
<td>Combined death, reinfarction and recurrent ischaemia at 30 days.</td>
</tr>
<tr>
<td>GRACIA-1 (2004)</td>
<td>STEMI patients presenting ≤ 12 h from symptoms onset.</td>
<td>Alteplase (accelerated dose)</td>
<td>Standard therapy (251 patients) (rescue PCI in 12%) Early PCI &lt; 6–24 h from lysis (248 patients) (PCI in 80%)</td>
<td>187</td>
<td>—</td>
<td>Combined death, reinfarction, ischaemic-induced revascularization at 12 months.</td>
</tr>
<tr>
<td>CAPITAL-AMI (2005)</td>
<td>High-risk STEMI patients presenting ≤ 6 h from symptom onset.</td>
<td>TNK</td>
<td>Standard therapy (84 patients) (rescue PCI in 9.5%) Early PCI &lt; 3 h from lysis (86 patients) (PCI in 89%)</td>
<td>120$^\text{b}$</td>
<td>—</td>
<td>Combined death, reinfarction, ischaemic events or stroke at 6 months.</td>
</tr>
<tr>
<td>SIAM-III (2003)</td>
<td>STEMI patients presenting ≤ 12 h from symptom onset.</td>
<td>r-PA</td>
<td>Standard therapy (81 patients) (rescue PCI in 12%) Early PCI &lt; 6 h from lysis (82 patients) (PCI in 100%)</td>
<td>216</td>
<td>—</td>
<td>Combined death, reinfarction, recurrent ischaemia, target lesion revascularization at 6 months.</td>
</tr>
<tr>
<td>TRANSFER-AMI (2009)</td>
<td>High-risk STEMI patients presenting ≤ 12 h from symptom onset.</td>
<td>TNK</td>
<td>Standard therapy (522 patients) (rescue PCI in 25%) Early PCI &lt; 6 h from lysis (537 patients) (PCI in 85%)</td>
<td>115$^\text{b}$</td>
<td>—</td>
<td>Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock at 30 days.</td>
</tr>
<tr>
<td>WEST (2006)$^\text{e}$</td>
<td>STEMI patients presenting ≤ 6 h from symptom onset.</td>
<td>TNK</td>
<td>Standard therapy (100 patients) (rescue PCI in 14%) Early PCI &lt; 24 h from lysis (104 patients) (PCI in 86%)</td>
<td>113$^\text{b}$</td>
<td>295$^\text{b}$</td>
<td>Combined death, reinfarction, recurrent ischaemia, new CHF, cardiogenic shock, and major ventricular arrhythmia at 30 days.</td>
</tr>
<tr>
<td>NORDISTEMI (2010)</td>
<td>STEMI patients presenting ≤ 6 h from symptom onset.</td>
<td>TNK</td>
<td>Standard therapy (132 patients) (rescue PCI in 27%) Immediate PCI after lysis (134 patients) (PCI in 86%)</td>
<td>126$^\text{b}$</td>
<td>163$^\text{b}$</td>
<td>Combined death, reinfarction, recurrent ischaemia, or stroke at 12 months.</td>
</tr>
</tbody>
</table>

STEMI, ST-elevation myocardial infarction; TNK, tenecteplase; r-PA, reteplase; CHF, congestive heart failure.

$^\text{a}$Plus abciximab of 0.25 mg/kg/bolus followed by 0.125 μg/kg/min infusion for 24 h.

$^\text{b}$Expressed as median. Other times as average.

$^\text{c}$Calculated as (time from symptom onset to early PCI) − (time from symptom onset to lytic therapy).

$^\text{d}$Includes 29 patients referred to rescue PCI.

$^\text{e}$Includes also one arm randomized to primary PCI.
artery access in the vast majority of patients in all studies, with the exception of the NORDISTEMI trial in which a radial approach was used in 83% of patients. All trials used a dual antiplatelet regime, with aspirin and clopidogrel for at least 1 month after PCI. Anticoagulation therapy during STEMI consisted of unfractionated heparin in four trials, predominantly enoxaparin in two trials, or an approximate equal mix of both. Abciximab was used in early PCI was administered in <50% of patients in five trials (23.6% of patients, from 9.8 to 48%), while it was administered in 83% of patients in the TRANSFER-AMI trial and in all patients in the CARESS-IN-AMI trial.

The rate of rescue PCI in the standard therapy group was higher in the three more recent trials (27.4%) compared with the four older studies (12%). Indications for rescue PCI included persistent chest pain, <50% resolution in ST-segment elevation and hemodynamic instability of 90 min from initiation of fibrinolysis in all studies, with the exception of the NORDISTEMI trial in which the pre-defined time limit was 60 min from lytic therapy. A planned strategy of coronary angiography and possible PCI in the standard therapy arm during initial hospitalization or in the first week after STEMI was applied in two trials.

Cumulative meta-analysis

Clinical endpoints at 30 days

There were 56 deaths (3.8%) in the standard conservative group and 49 deaths (3.3%) in the early invasive group, without significant differences between the two strategies (OR: 0.87; 95% CI: 0.59–1.30; P = 0.51; Figure 3A). Early PCI after fibrinolysis was associated with a significant reduction in reinfection (2.6 vs. 4.7%; OR: 0.55, 95% CI: 0.36–0.82; P = 0.003; NNT 48, 95% CI: 29–138; Figure 3A), the combined endpoint of death/reinfarction (5.6 vs. 8.3%; OR: 0.65, 95% CI: 0.49–0.88; P = 0.004; NNT 37, 95% CI: 22–113; Figure 3B) and recurrent ischaemia (1.9 vs. 7.1%; OR: 0.25, 95% CI: 0.13–0.49; P < 0.001; NNT 19, 95% CI: 15–27; Figure 3B) compared with standard therapy.

Safety endpoints at 30 days

No differences were observed in the incidence of stroke and major bleeding between the two strategies (Figure 4). Stroke was relatively uncommon in both groups, with only 11 (0.7%) events in the early invasive group and 19 (1.3%) in the standard group (OR: 0.63, 95% CI: 0.31–1.26; P = 0.21). The incidence of major bleeding was 4.9% in the early PCI group and 5% in the standard therapy group (OR: 0.93, 96% CI: 0.67–1.31; P = 0.70).

Clinical endpoints at 6–12 months

There was no difference in mortality at 6–12 months between the two treatment strategies (4.8 vs. 5.4%; OR: 0.88, 95% CI: 0.62–1.25; P = 0.48; Figure 5). A routine early invasive strategy after fibrinolysis was associated with a significant reduction in reinfarction (3.9 vs. 6%; OR: 0.64, 95% CI: 0.40–0.98; P = 0.03; NNT 46, 95% CI: 26–187; Figure 5) and the combined endpoint of death/reinfarction (8.6 vs. 11.2%; OR: 0.71, 95% CI: 0.52–0.97; P = 0.03; NNT 37, 95% CI: 20–206; Figure 5) at 6–12 month follow-up compared with standard therapy.

Baseline risk and the benefit of early PCI

Meta-regression analysis was applied to explore the relationship between the baseline risk of the STEMI population in each trial and the benefit of early PCI on reduction of the endpoints reinfarction and death/reinfarction at 30 days. The baseline risk of the STEMI population was defined as the rate of events in the standard group of each trial and, and it was plotted in a weight-adjusted linear-function with its log odds ratio. The regression analysis showed a trend toward a reduction of reinfarction and death/reinfarction in higher risk STEMI patients (Figure 6).

Sensitivity analysis

Sensitivity analysis confirmed the robustness of results on clinical and safety endpoints at 30 days. Results on reinfection and death/reinfarction at 6–12 months were strongly influenced by the pooled analysis. However, they did not vary after excluding the CARESS-IN-AMI trial, the only study using a combo-therapy with abciximab and hald-dose fibrinolysis in both treatment groups, and the SIAM-III trial, which presented the higher rate of delayed PCI in the standard group (100%) between the trials.

Results with high heterogeneity

Revascularization at 30 days and 6–12 months and recurrent ischaemic events at 6–12 months (Supplementary data, Figure S1) presented a high degree of heterogeneity (I² > 50%). Random effects analysis showed that patients were more likely to receive revascularization at 6–12 month follow-up but not at 30 days. No significant difference in recurrent ischaemic events at 6–12 months was also found. The high degree of heterogeneity and the skewed distribution of the trials in the funnel plots indicate that these results present high risk of publication bias and therefore cannot be considered conclusive.

Discussion

This meta-analysis demonstrates that routine early referral for PCI after fibrinolysis in patients for whom primary PCI is not readily available leads to a significant reduction in reinfection, recurrent ischaemia, and the combined endpoint of death/reinfarction, during the first month after STEMI. Early PCI strategy after successful fibrinolysis does not reduce mortality at 30 days compared with the early invasive strategy but reduces the risk of reinfarction and death/reinfarction.
Figure 3  Clinical endpoints at 30 days. Odds ratios and 95% confidence intervals for (A) death and reinfarction and for (B) combined death/reinfarction and recurrent ischaemia between early PCI and standard therapy. Size of data markers indicates the weight of each trial. There is no difference in incidence of fatal events between the two strategies. Early PCI after successful fibrinolysis provides clear benefits on reduction of the rates of reinfarction, combined endpoint death/reinfarction and recurrent ischaemia at 30-day follow-up compared with standard therapy.
a conventional ischaemia-driven approach. The benefits of early routine PCI after fibrinolysis occur in the absence of an increased risk of adverse events (stroke or major bleeding) and persist at longer follow-up (6–12 months). These results support the routine implementation of an early invasive strategy after successful fibrinolysis in this population, with a trend towards a further reduction of reinfarction and death/reinfarction in higher risk STEMI patients.

Two previous meta-analyses also provided results in favour of an early revascularization therapy after lysis, but with some important differences from the current meta-analysis. Collet et al. compared trials performed in the ‘pre-stent’ and ‘post-stent era’. However at the time of their meta-analysis, only three modern ‘post-stent era’ trials were available. Wijeysundera et al. reported a benefit from early routine invasive strategy, including a reduction in death and reinfarction, but this meta-analysis was not restricted to trials employing fibrin-specific lytic agents and did not include the recent CARESS-IN-AMI, TRANSFER-AMI and NORDISTEMI trials.

The results of our meta-analysis suggest that the current conservative approach after fibrinolysis in patients for whom PCI is not readily available, i.e. ischaemia-guided strategy (waiting for reperfusion to occur after fibrinolysis and referring patients to rescue PCI thereafter) is not as beneficial as early referral to PCI. Since there is a growing network of 24/7 PCI centres worldwide, transfer to a PCI centre should not be delayed, to avoid the risk of an extension of myocardial damage in case the patient does not respond to fibrinolysis or has recurrent ischaemic events. With the exception of the GRACIA-1 trial, all other trials in the meta-analysis offered a short time from lysis to PCI, around or below the minimum time of 3 h after lysis currently recommended by the AHA/ACC and ESC guidelines. None of the patients randomized in these trials received fibrinolysis as a preparation to primary angioplasty (facilitated PCI). Patients did not qualify for primary PCI because the expected transfer time exceeded the 90 min, which was the time limit for primary PCI at the time these trials were conducted. Furthermore, unlike trials of facilitated PCI in which the comparison arm is primary PCI, in all trials included in this meta-analysis the comparison is a conservative strategy using PCI as rescue treatment or beyond 24 h. These are important differences that qualify these trials as proposers of a pharmacoinvasive strategy radically different compared with the classical ‘facilitated approach’.

**Limitations**

The main limitation, common to many cumulative meta-analyses, is the difference in endpoint definitions and the variability of strategy between trials, e.g. treatment after fibrinolysis in the standard therapy group. To address this concern, this meta-analysis was
performed applying a random effects model approach, which assumes that variables have a multivariate normal distribution and patients are considered to be a random sample from a wider study population. This approach allows the between-trial variability in the estimates of treatment difference to be accounted for in the overall estimate and its standard error. Moreover this meta-analysis included only randomized controlled trials, to avoid the unavoidable bias in selection criteria of observational studies enrolling STEMI patients. A recent meta-analysis of randomized and observational trials comparing primary PCI and fibrinolysis showed partially discordant results in the two types of studies. The authors, as investigators of the selected trials, could provide sufficient information to achieve a more homogeneous classification for the endpoints with the greatest differences in definitions (major bleeding, recurrent ischaemia).

As this was a cumulative meta-analysis, data on optimal timing of early PCI after fibrinolysis or on selected subgroups could not be provided. A patient-level analysis of these trials has been designed by the authors of this manuscript (clinicaltrials.gov registration NCT 01014182) with the main goal to identify the optimal timing for early PCI after fibrinolysis and the subgroups more likely to benefit. Still, additional prospective trials with broader inclusion criteria and of larger size might be necessary to address these questions.

**Figure 5** Clinical endpoints at 6–12 months. Odds ratios and 95% confidence interval for death, reinfarction, and combined death/reinfarction between early PCI and standard therapy. Size of data markers indicates the weight of each trial. Benefits observed after early PCI on reduction of reinfarction and combined endpoint death/reinfarction are maintained in longer follow-up.
Conclusions

In patients with STEMI who cannot be offered primary PCI, the gold-standard reperfusion therapy within 90–120 min from symptom presentation, a routine invasive strategy applied early after fibrinolysis is associated with a significant reduction of reinfarction and recurrent ischaemia in the first month after STEMI. The benefit of early PCI after fibrinolysis is not associated with a significant increase in bleeding events compared with standard therapy and persists at 6–12 month follow-up. These findings call for a change in the current conservative attitude to wait the response to treatment in patients receiving fibrinolysis, and prompt the organization of an appropriate network for rapid transfer to PCI centres also of those patients who for logistic reasons cannot undergo primary angioplasty.

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Appendix A: Inclusion criteria for STEMI patients and endpoint definitions in selected trials
Inclusion criteria

**CARESS-IN-AMI**
High-risk STEMI patients admitted to a spoke centre within 12 h from onset of symptoms, with cumulative ST-segment elevation of more than 15 mm, new onset LBBB, previous myocardial infarction, Killip class of two or more, or left ventricular ejection fraction \( \leq 35\% \) or less.

**GRACIA1**
STEMI patients with chest pain lasting between 30 min and 12 h, not responding to nitroglycerin, with ST-segment elevation \( \geq 1 \) mm in two or more contiguous leads, or with LBBB or with paced rhythm.

Reinfarction

Recurrent symptoms or signs of MI lasting more than 30 min with new Q-wave or ST-T segment changes or new-onset LBBB and recurrent significant rise of cardiac enzyme levels. The increase in CK-MB level was considered significant when it occurred after at least a 25% decrease in CK-MB from a prior peak level and was \( \geq 2 \) times the upper limit of normal (ULN) in the absence of coronary interventions, \( \geq 3 \) times above the ULN after PCI or \( \geq 5 \) times above the ULN after bypass grafting.

Re-ischaemia

Recurrent chest pain with ST-segment deviation or definite T-wave inversion occurring more than 12 h after randomisation persisting for at least 10 min despite nitrates, beta blockers or calcium channel blockers and not fulfilling the diagnosis of myocardial reinfarction.

Intracranial bleeding (haemorrhagic stroke) and extracranial major bleeding at 30 days, including retroperitoneal or intracranial bleeds, bleeds requiring blood transfusion, or with a haemoglobin decrease of 50 g/L or more. Bleeds were also classified according to the TIMI criteria as major (intracranial, overt bleeding with a decrease of haemoglobin \( >5 \) g or haematocrit \( >15\% \)) and minor (spontaneous gross haematuria or haematemesis with a decrease of haemoglobin \( >30 \) g/L but with \( <15\% \) decrease of haematocrit). Stroke not reported.

Adverse events

Myocardial ischaemia was defined as spontaneous (at rest) or stress-induced recurrence of typical angina pectoris (or anginal equivalent) that had to coincide with new ECG abnormalities, or abnormal stress test.

Major bleeding or vascular complication was defined as any complication causing death, need for surgery or transfusion, or extended time in hospital. Minor bleeding not reported. Stroke not reported.
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Reinfarction</th>
<th>Re-ischaemia</th>
<th>Adverse events</th>
</tr>
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<tbody>
<tr>
<td><strong>SIAM-III</strong></td>
<td>Patients presenting with symptoms of MI present for &lt; 12 h and having, on the basis of 12-lead electrocardiography, ST-segment elevation of at least 1 mm in two or more limb leads, ST-segment elevation of at least 2 mm in the precordial leads, or new LBBB.</td>
<td>Two or more of the following criteria: chest pain lasting for more than 30 min; a new significant ST-elevation; and a rise in the serum creatine kinase level to &gt; 3 × the upper normal limit.</td>
<td>Ischemic events included unplanned hospitalization and/or unplanned angiography due to post-infarction angina, recurrent angina pectoris lasting for more than 15 min despite the administration of nitrates or being accompanied by ECG changes, pulmonary edema, or hypotension.</td>
</tr>
<tr>
<td><strong>CAPITALAMI</strong></td>
<td>High-risk STEMI patients presenting &lt; 6 h of the onset of chest discomfort of &gt; 30 min duration and having &gt; 1 mm ST-segment elevation in two or more contiguous leads or left bundle branch block on a 12-lead electrocardiogram were eligible if they had one of the following high-risk criteria: (i) anterior infarction with ST-segment elevation &gt; 2 mm in each of two contiguous precordial leads; (ii) extensive non-anterior infarction: eight or more leads with &gt; 1 mm ST-segment elevation or depression or both, or the sum of ST-segment elevation &gt; 20 mm; (iii) Killip class 3; or (iv) systolic blood pressure &lt; 100 mm Hg.</td>
<td>Reinfarction was defined as recurrent ischaemic symptoms at rest lasting &gt; 30 min and accompanied by: (i) new or recurrent ST-segment elevation of &gt; 1 mm in any contiguous leads; (ii) new left bundle branch block; or (iii) re-elevation in serum creatine kinase level to greater than twice the upper limit of normal and ≥ 50% above the lowest level measured after infarction. If reinfarction occurred within 18 h, enzyme criteria were not used.</td>
<td>Recurrent unstable ischaemia was defined as recurrent symptoms of ischaemia at rest associated with new ST-segment or T-wave changes, hypotension, or pulmonary edema.</td>
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<td><strong>TRANSFERAMI</strong></td>
<td>High-risk STEMI patients were eligible if they presented within 12 h of symptom onset with chest pain more than 30 min in duration and ST-segment elevation of 2 mm or more in the anterior leads or 1 mm or more in the inferior leads. In addition, inferior STEMI patients were required to have one of the following: systolic blood pressure lower than 100 mmHg; heart rate of higher than 100 beats/min; Killip class II or III; 2 mm or more of ST-segment depression in the anterior leads; or 1 mm or more of ST-segment elevation in the right-sided lead position V4, indicative of right ventricular involvement.</td>
<td>During the first 18 h after enrolment, reinfarction was diagnosed on the basis of recurrent ST-segment elevation and recurrent chest pain lasting at least 30 min. After 18 h, the diagnosis of reinfarction required that there be an elevation in the MB fraction of creatine kinase to higher than the upper limit of the normal range (more than three times the upper limit of normal after PCI and more than five times the upper limit of normal after coronary-artery bypass surgery) or new Q waves.</td>
<td>Recurrent ischemia was defined as chest pain lasting 5 minutes or longer associated with ST-segment or T-wave changes.</td>
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WEST

STEMI patients in whom reperfusion therapy (primary PCI, fibrinolysis or transfer for rescue PCI) was feasible within 3 h of randomization were enrolled. STEMI lasting at least 20 min accompanied by ECG evidence of high risk. These included: ≥ 2 mm of ST elevation in two or more contiguous precordial leads or limb leads; or ≥ 1 mm ST elevation in two or more limb leads coupled with ≥ 1 mm ST depression in two or more contiguous precordial leads (total ST deviation of 4 mm) or presumed new left LBBB.

In the first 18 h after randomization: recurrent signs and symptoms of ischaemia at rest accompanied by new or recurrent ST-segment elevations of ≥ 0.1 mV in at least two contiguous leads lasting ≥ 30 min. After 18 h: new Q-waves in two or more leads and/or enzyme evidence of re-infarction: re-evaluation of CK-MB or troponin to above the upper limit of normal and increased by > 50% over the previous value. The total CK must either be re-elevated to two times or more the upper limit of normal and increased by > 50% or be re-elevated to > 200 U/mL over the previous value. If re-evaluated to less than two times the upper limit of normal, the total CK must exceed the upper limit of normal by > 50% and exceed the previous value by two-fold or be re-elevated to > 200 U/mL. Reinfarction after PTCA (with or without stenting): CK greater than three times the upper limit of normal and 50% greater than the previous value and/or new Q-waves (Minnesota Code) in two or more contiguous leads. Reinfarction after CABG surgery: CK greater than five times the upper limit of normal and > 50% greater than the previous value and/or new Q-waves (Minnesota Code) in two or more contiguous leads.

NORDISTEMI

STEMI patients with symptoms of myocardial infarction present for > 6 h and ECG indicative of an acute STEMI (≥ 2 mm ST-segment elevation in two contiguous precordial leads or > 1 mm ST-segment elevation in two contiguous extremity leads or new left bundle branch block), with expected time delay from first medical contact to PCI > 90 min.

Reinfarction in the first 18 h was defined as recurrent symptoms of ischaemia at rest accompanied by new ST-segment elevation of ≥ 0.1 mV in at least two contiguous leads, lasting > 30 min. After 18 h, the definition was: new Q waves in two or more leads, or new increase in concentrations of creatine kinase-MB or troponins above the upper limit of normal (> 3X upper limit of normal after PCI and > 5X upper limit of normal after coronary artery bypass graft), and > 50% higher than the previous value.

Symptoms of ischaemia with ST deviation or definite T-wave inversion persisting for at least 10 min despite medical management while in hospital.

New myocardial ischaemia was defined as unstable angina (chest pain at rest suspicious for coronary disease with or without ECG changes), recurrent angina Grades II–IV (Canadian Cardiovascular Society classification) or severe arrhythmias (ventricular tachycardia/ventricular fibrillation) that appeared more than 12 h after randomization.

Major bleeding: bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or CPR to maintain a sufficient cardiac output. Stroke: not reported.

Stroke was defined as a new focal, neurological deficit of vascular origin lasting more than 24 h. Bleeding complications were classified according to the GUSTO classification.


