Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy

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CRD summary
The authors concluded that there was support for rescue percutaneous coronary intervention (PCI) and systematic and early PCI after fibrinolysis, but no support for fibrinolysis-facilitated PCI compared with primary PCI alone. Although the authors’ conclusion appears to follow from the results presented, the lack of an assessment of study quality makes it difficult to confidently assess the reliability of the conclusion.

Authors’ objectives
To evaluate the effects on death and reinfarction of three percutaneous coronary intervention (PCI) strategies conducted after fibrinolysis. The three strategies investigated were rescue PCI, systematic and early PCI and fibrinolysis-facilitated PCI.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched for studies published in the last 20 years; the search terms were reported. In addition, papers presented at major cardiac conferences and reference lists of studies and texts were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The duration of follow-up in the included studies ranged from hospital stay to 1 year.

Specific interventions included in the review
Studies eligible for inclusion were those that compared: rescue PCI (less than 12 hours after failed fibrinolysis) versus no PCI after failed fibrinolysis; systematic and early (within 24 hours) PCI, regardless of success of fibrinolysis, versus delayed and/or ischaemia-guided PCI; or fibrinolysis-facilitated PCI (with less than 6 hours delay between fibrinolysis and PCI) versus primary PCI alone. The studies could use any type of PCI and any type of fibrinolytic agent. Studies that compared delayed PCI with no PCI after fibrinolysis were excluded, as were those that compared combined-treatments facilitation with reduced doses of lytics plus full dose of glycoprotein inhibitors. Failed fibrinolysis was defined clinically as failure of ST-segment resolution with persistent chest pain, or angiographically as Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 to 1 within the infarct-related artery. The reviewers accepted the original study authors’ definitions of failed fibrinolysis and PCI delays.

The included studies were conducted during the ‘stent era’ (stenting rate greater than 25%) and the ‘balloon era’. In studies evaluating systematic and early angioplasty conducted in the ‘stent era’, aspirin and thienopyridines were given to more than 80% of patients receiving early PCI and glycoprotein IIb/IIIa receptor antagonists were given to between 10 and 30% of patients.

Participants included in the review
Studies in patients with ST-segment elevation myocardial infarction (STEMI) 12 hours or less from symptom onset were eligible for inclusion. The reviewers accepted the original authors’ definitions of STEMI. The mean age of the participants, where reported, ranged from 56 to 63 years. In all but one of the studies reporting information on gender, the majority of participants were male.

Outcomes assessed in the review
Studies that assessed death and reinfarction were eligible for inclusion. The primary review outcome was mortality. A combined end point of death or reinfarction was also used. The review also assessed major bleeding. The reviewers...
accepted the original authors’ definitions of outcomes and assessed outcomes at the longest end point reported.

**How were decisions on the relevance of primary studies made?**
Two reviewers independently selected the studies.

**Assessment of study quality**
The authors did not state that they assessed validity.

**Data extraction**
Two reviewers independently extracted the data on an intention-to-treat basis and resolved any disagreements through consensus. For each study, the numbers of patients with outcomes of interest were presented. Where required, the authors of primary studies were contacted for additional data.

**Methods of synthesis**

**How were the studies combined?**
The studies were grouped by intervention. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects method (Mantel-Haenszel).

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using the chi-squared statistic. Studies that compared systematic and early PCI versus delayed and/or ischaemia-guided PCI conducted during the 'stent era' and the 'balloon era' were analysed separately. Other differences between the studies were discussed.

**Results of the review**
Fifteen RCTs (n=5,106) were included.

Rescue PCI after failed fibrinolysis versus no PCI (5 RCTs, n=920).

At the longest follow-up, rescue PCI was associated with a non-statistically significant reduction in mortality compared with no PCI (OR 0.69, 95% CI: 0.41, 1.57, p=0.16), a significant reduction in the combined outcome of death or reinfarction (OR 0.60, 95% CI: 0.39, 0.92, p=0.019), and a significant increase in major bleeding (11.9% versus 1.3%, OR 9.05, 95% CI: 3.71, 22.06, p<0.001). Bleeding most commonly (82%) originated in the femoral sheath and no cases were fatal. No significant heterogeneity was found for any of these meta-analyses.

Systematic and early PCI versus delayed and/or ischaemia-guided PCI (6 RCTs, n=1,507).

Systematic and early PCI in the 'stent era' (3 RCTs) was associated with a non-statistically significant reduction in mortality (OR 0.56, 95% CI: 0.29, 1.07, p=0.07), a significant reduction in the combined outcome of death or reinfarction (7.5% versus 13.2%, OR 0.53, 95% CI: 0.33, 0.83, p=0.0067), and no significant increase in major bleeding (OR 1.18, 95% CI: 0.60, 2.30, p=0.64). In the 'balloon era', systematic and early PCI was associated with a non-statistically significant increase in mortality (5.5% versus 3.9%, OR 1.44, 95% CI: 0.69, 3.06, p=0.33) and the combined outcome of death or reinfarction (9.6% versus 5.7%, OR 1.76, 95% CI: 0.97, 3.21, p=0.06). No significant heterogeneity was found for any of these meta-analyses. Significant heterogeneity was found for the analysis of death and reinfarction when 'stent era' and 'balloon era' studies were combined.

Fibrinolysis-facilitated PCI versus primary PCI alone (4 RCTs, n=2,679).

Fibrinolysis-facilitated PCI was associated with a non-statistically significant increase in mortality (1.30, 95% CI: 0.92, 1.83, p=0.13) and a significant increase in reinfarction (5% versus 3%, OR 1.68, 95% CI: 1.12, 2.51, p=0.013). There was no significant difference between strategies in the risk of major bleeding (OR 1.23, 95% CI: 0.74, 2.05, p=0.42). No significant heterogeneity was found for any of these meta-analyses.
Authors' conclusions
There was support for rescue PCI and systematic and early PCI after fibrinolysis, but no support for fibrinolysis-facilitated PCI compared with primary PCI alone.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication bias. It was not clear whether any language restrictions had been applied, thus the potential for language bias could not be assessed. Only RCTs were included, but study validity was not assessed and so the results from these studies and any synthesis might not be reliable. Methods were used to minimise reviewer errors and bias at the study selection and data extraction stages of the review.

The studies were appropriately combined in meta-analyses, statistical heterogeneity was assessed, and differences between the studies were explored and discussed. Apart from the lack of an assessment of study validity, the review was well-conducted and clearly presented. Although the authors' conclusion appears to follow from the results presented, the absence of an assessment of study validity makes it difficult to confidently assess the reliability of the review.

Implications of the review for practice and research
Practice: The authors stated that all patients with failed fibrinolysis (persistent chest pain and/or lack of resolution of ST-segment elevation 60 to 90 minutes after starting administration) should proceed to catheterisation without delay; that systematic catheterisation with stent-PCI within 24 hours of thrombolysis improves outcomes compared with a noninvasive watchful waiting strategy; and that fibrinolysis cannot be recommended as a facilitating strategy for PCI. These findings suggest the need for a network organisation to provide rapid access to facilities for cardiac catheterisation. In addition, they stated that it appears reasonable to recommend immediate and systematic routine angiography in patients with large myocardial infarctions.

Research: The authors state the need for further research to evaluate the safety of rescue PCI for failed fibrinolysis and early (less than 24 hours) PCI, regardless of success of fibrinolysis, and to evaluate the benefits of concomitant treatment with glycoprotein IIb/IIIa inhibitors.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.