Acute Ischemic Heart Disease

An early invasive strategy versus ischemia-guided management after fibrinolytic therapy for ST-segment elevation myocardial infarction: A meta-analysis of contemporary randomized controlled trials

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Background Although the use of an early invasive strategy among patients with ST-segment elevation myocardial infarctions (STEMI) who are treated initially with fibrinolytic therapy is common, the safety and efficacy of this approach remains uncertain. We performed a meta-analysis to best estimate the benefits and harms of an early invasive strategy in STEMI patients treated initially with full-dose intravenous fibrinolytic therapy, as compared to a traditional strategy of ischemia-guided management.

Methods We included contemporary randomized controlled trials, defined a priori as those with >50% stent use during percutaneous coronary intervention (PCI). Outcomes extracted from the published results of eligible trials included all-cause mortality, reinfarction, stroke, and in-hospital major bleeding.

Results We identified 5 contemporary trials enrolling 1,235 patients who met our inclusion criteria. Of the patients randomized to an early invasive strategy, 86% underwent PCI with 87% receiving stents. Follow-up duration ranged from 30 days to 1 year. An early invasive strategy was associated with significant reductions in mortality (odds ratio [OR] 0.55, 95% CI 0.34-0.90) and reinfarction (OR 0.53, 95% CI 0.33-0.86) compared with ischemia-guided management. There were no significant differences in the risk of stroke (OR 1.31, 95% CI 0.42-4.10) or major bleeding (OR 1.41, 95% CI 0.74-2.69).

Conclusions An early invasive strategy after fibrinolytic therapy is associated with significant reductions in mortality and reinfarction. Our results suggest a potentially important role for this strategy in the management of STEMI patients but should be confirmed by large randomized trials. (Am Heart J 2008;156:564-572.e2)

The cornerstone of therapy for ST-segment elevation myocardial infarction (STEMI) is prompt reperfusion by either fibrinolytic therapy or primary percutaneous coronary intervention (PCI).1 Because of the limited availability of hospitals with cardiac catheterization laboratories, fibrinolytic therapy remains the most common form of reperfusion modality among patients with STEMI worldwide.1,2 Even after successfully achieving reperfusion with fibrinolytic therapy, patients with STEMI carry a substantial risk of death and recurrent myocardial infarction.3 It is unclear if an invasive strategy, with routine coronary angiography after fibrinolytic therapy is efficacious in comparison to a strategy of catheterization restricted to patients with clinical evidence of ischemia.

Randomized trials of balloon angioplasty that have evaluated an early invasive strategy in STEMI patients demonstrated an increased risk of adverse effects and a lack of benefit associated with routine cardiac catheterization and coronary revascularization after fibrinolytic therapy when compared with ischemia-guided
Extensively hand-searched to locate additional studies. We separately analyzed older studies of balloon angioplasty that compared an early invasive strategy with a routine early invasive strategy versus a traditional ischemia-guided management. As a result, an early invasive strategy after reperfusion with fibrinolytic therapy has a class IIb recommendation in the current American College of Cardiology/American Heart Association practice guidelines for PCI and STEMI, indicating conflicting evidence as to its usefulness or efficacy. However, given recent advances in modern catheter-based therapies including the use of intracoronary stents and adjunctive pharmacotherapy, it is debatable if the results of these older balloon angioplasty trials are applicable to contemporary interventional practice.

Despite the lack of guideline support for an early invasive strategy, there is significant enthusiasm to perform early cardiac catheterization after STEMI. In fact, observational data from the United States have shown that nearly 80% of STEMI patients who were treated with fibrinolytic therapy undergo cardiac catheterization during their initial hospitalization. This divergence of guideline recommendations and clinical practice has occurred despite the lack of any large multicenter trials demonstrating the safety and efficacy of this approach. Accordingly, we attempted to address this gap in knowledge by performing a meta-analysis to best estimate the potential risks and benefits associated with an early invasive strategy among STEMI patients who have been treated with fibrinolytic therapy, when compared to a traditional strategy of ischemia-guided therapy.

**Methods**

**Data sources**

Relevant published studies were identified through a computerized literature search of the Cochrane library, Embase, and Medline electronic databases from January 1950 to February 2007, using the key words angioplasty, stent, myocardial infarction, thrombolytic therapy, and fibrinolytic therapy (Figure 1). In addition, bibliographies of journal articles and relevant reviews were extensively hand-searched to locate additional studies.

**Study selection**

Two investigators (H.C.W., J.J.Y.) independently evaluated studies for possible inclusion, with any disagreements resolved by consensus. We included randomized controlled trials that enrolled patients with STEMI treated with full-dose intravenous fibrinolytic therapy and compared a routine early invasive strategy versus ischemia-guided management. Our primary analysis only included contemporary trials, which we defined a priori as those with >50% stent use during PCI. To gain perspective on potential differences in the safety and efficacy of an early invasive strategy in the pre-stent eras, we separately analyzed older studies of balloon angioplasty that compared an early invasive strategy with ischemia-guided management.

Importantly, we excluded any studies evaluating facilitated PCI because all patients who received fibrinolytic therapy in these trials had an invasive procedure as part of the study protocol. Study quality was evaluated based on the 5-point scale outlined by Jadad et al, with criteria for randomization with proper concealment of the allocation sequence, blinding of the patient and investigator to treatment allocation with description of the blinding method, and completeness of follow-up.

**Data extraction**

Clinical efficacy outcomes of interest included all-cause mortality and reinfarction, whereas safety outcomes of interest included stroke and in-hospital major bleeding. We accepted the original study definitions for all efficacy and safety outcomes (see Appendix A available online). Although the definitions of outcomes among the trials were not standardized, within each trial, the same criteria were applied equally to both the treatment and control groups. Follow-up periods ranged from 30 days to 1 year across the 5 trials. For studies with events reported at multiple time points, we used data from the longest follow-up period for our primary analysis.

**Statistical analysis**

A random effects model based on the DerSimonian and Laird method for combining results from the individual trials was used. Summary odds ratio (OR) and 95% CIs were calculated, as was summary absolute risk reduction and number needed to treat (NNT). We used a random effects model because of its more conservative summary estimate, which incorporates both within trial and between trial variance.

Heterogeneity between individual trials was evaluated using 2 methods. We calculated the Q-statistic to determine if statistical significant heterogeneity was present. In addition, we determine the $I^2$ index, which describes the proportion of variability due to heterogeneity between individual trials.

Sensitivity analyses were conducted to examine the robustness of the results by eliminating one study at a time from the analysis to determine if the pooled estimates were disproportionately influenced by a particular trial. As an additional sensitivity analysis, we also derived summary ORs using 30-day follow-up data from included studies.

Statistical significance was set as a $P$ value <.05. All statistical calculations were performed using comprehensive meta-analysis version 2 software (Biostat, Englewood, NJ).

**Results**

**Study selection**

The process of study selection and exclusion is outlined in Figure 1. We found 20 relevant articles of which we...
excluded 1 study that assessed only intracoronary fibrinolytic therapy \(^{10}\) and 1 study of combination half-dose fibrinolytic therapy with a glycoprotein GpIIb/IIIa receptor (Gp2b/3a) inhibitor. \(^{11}\) Of the remaining articles, there were 13 randomized trials of balloon angioplasty \(^{12-24}\) and 5 contemporary PCI trials. \(^{25-29}\) All of the contemporary trials with >50% stent use met our inclusion and exclusion criteria and constituted our primary analysis with 1,235 enrolled patients.

Of the 13 balloon angioplasty trials, we included 4 trials enrolling 5,018 patients who compared an early invasive strategy versus ischemia-guided management for our secondary analysis. Of the excluded studies, 3 trials that had a factorial design and did not directly compare an invasive strategy with ischemia-guided management among patients treated with fibrinolytic therapy \(^{18,21,23}\); 3 trials compared a routine early invasive strategy with a routine delayed invasive strategy \(^{12,16,22}\); and 3 trials compared a routine delayed invasive strategy (PCI at day 5 to 6 weeks) with ischemia-guided management. \(^{15,17,24}\)

All included studies in both the primary and secondary analysis had a Jadad score of 3, with appropriate randomization and complete follow-up of patients.

Contemporary trials with stents

**Study design.** Table I summarizes the study designs of the 5 contemporary PCI trials (see Appendix B available online). Of the 1,235 patients included in these trials, 530 (43%) presented with an anterior STEMI. Streptokinase was used in one trial, \(^{29}\) with the remaining studies using fibrin-specific fibrinolytic agents.

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**Table I**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Number of Patients</th>
<th>Median Follow-Up (months)</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>1,235</td>
<td>12</td>
<td>Primary Endpoint</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>5,018</td>
<td>12</td>
<td>Primary Endpoint</td>
</tr>
<tr>
<td>Contemporary</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1**

**Process of study selection for routine early invasive strategy versus ischemia-guided management.**

- **Medline, Embase, Cochrane Library 1950-2007:**
  - **search terms:** angioplasty, stent, myocardial infarction, fibrinolysis, thrombolytic therapy
  - **restricted to:** human AND randomized controlled trial
  - 4 meta-analysis identified and bibliographies hand-searched

- 222 citations

- 20 articles evaluated

- **EXCLUDED:**
  - 1 randomized trial involved intra-coronary fibrinolytic therapy
  - 1 randomized trial involved combination of Gp2b/3a inhibitor and half-dose fibrinolytic therapy

- **5 CONTEMPORARY PCI TRIALS WITH STENTS**
  - 5 trials met inclusion/exclusion criteria

- **13 BALLOON ANGIOPLASTY TRIALS**
  - 4 trials met inclusion/exclusion criteria
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>No. of patients enrolled</th>
<th>Follow-up duration</th>
<th>Mean age (y)</th>
<th>Females (%)</th>
<th>Stent use (%)</th>
<th>Adjunctive medication for PCI †</th>
<th>Median time from fibrinolytic to PCI in early invasive arm</th>
<th>Indications for inhospital angiogram in ischemia-guided arm</th>
<th>% of patients in ischemia guided arm with inhospital angiogram (and rescue PCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contemporary trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WEST 25</td>
<td>2006</td>
<td>204</td>
<td>30 d</td>
<td>58</td>
<td>20</td>
<td>97</td>
<td>Aspirin Clopidogrel Enoxaparin Gp2b3a (48%)</td>
<td>295 min</td>
<td>Standard of care</td>
<td>58 (14)</td>
</tr>
<tr>
<td>CAPITAL AMI 27</td>
<td>2005</td>
<td>170</td>
<td>6 m</td>
<td>58</td>
<td>25</td>
<td>89</td>
<td>Aspirin Clopidogrel Heparin Gp2b3a (14%)</td>
<td>90 min</td>
<td>Persistent chest pain and ST elevation 90 min after lytic; deteriorating hemodynamic status; recurrent ischemia</td>
<td>67 (9)</td>
</tr>
<tr>
<td>GRACIA-1 26</td>
<td>2004</td>
<td>499</td>
<td>12 m</td>
<td>60</td>
<td>14</td>
<td>80</td>
<td>Aspirin Ticlopidine Heparin Gp2b3a (32%)</td>
<td>17.6 h</td>
<td>Recurrent ischemia with ECG changes; hypotension; ventricular tachycardia; positive stress test with HR &lt;100/min or &lt;5 METS</td>
<td>21 (NA)</td>
</tr>
<tr>
<td>SIAM III 28</td>
<td>2002</td>
<td>163</td>
<td>6 m</td>
<td>63</td>
<td>12</td>
<td>100</td>
<td>Aspirin Clopidogrel Heparin Gp2b3a (10%)</td>
<td>210 min</td>
<td>Ongoing ischemia</td>
<td>24 (11)</td>
</tr>
<tr>
<td>PRAGUE 29,30</td>
<td>2000</td>
<td>199</td>
<td>12 m</td>
<td>61</td>
<td>30</td>
<td>79</td>
<td>Lysine salicylate Ticlopidine Fraxiparin</td>
<td>60 min</td>
<td>Post-MI angina, failed fibrinolysis, reinfarction</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Balloon angioplasty trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWIFT 14</td>
<td>1991</td>
<td>397</td>
<td>12 m</td>
<td>55</td>
<td>18</td>
<td>0</td>
<td>Heparin</td>
<td>Within 48 h</td>
<td>Recurrent chest pain/post-MI angina/positive stress test</td>
<td>13 (NA)</td>
</tr>
<tr>
<td>Rogers et al 19</td>
<td>1990</td>
<td>586</td>
<td>12 m</td>
<td>57</td>
<td>16</td>
<td>0</td>
<td>Aspirin (22%) Heparin</td>
<td>32 h</td>
<td>Refractory ischemia refractory to medical therapy</td>
<td>18 (NA)</td>
</tr>
<tr>
<td>TMI-II 13</td>
<td>1989</td>
<td>3262</td>
<td>42 d</td>
<td>56</td>
<td>18</td>
<td>0</td>
<td>Aspirin (10%) Heparin</td>
<td>32.5 h</td>
<td>Recurrent chest pain despite medical therapy/positive stress test</td>
<td>33 (NA)</td>
</tr>
<tr>
<td>Simoons et al 20</td>
<td>1988</td>
<td>367</td>
<td>3 m</td>
<td>56</td>
<td>12</td>
<td>0</td>
<td>Aspirin Heparin</td>
<td>42 min</td>
<td>NA</td>
<td>6 (NA)</td>
</tr>
</tbody>
</table>

CAPITAL AMI, Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis alone in Acute Myocardial Infarction study; Gp2b/3a, glycoprotein IIb/IIIa receptor inhibitors; GRACIA-1, Grupo de Analisis de el Cardiopatia Isquemica Aguda trial; NA, Data not available; PRAGUE, Primary Angioplasty in patients transferred from general community hospitals to specialized percutaneous transluminal coronary angioplasty units with or without emergency thrombolysis trial; SIAM III, Southwest German Interventional Study in Acute Myocardial Infarction study; SWIFT, Should We Intervene Following Thrombolysis Trial; TMI, Thrombolysis in Myocardial Infarction trial; WEST, Which early ST-Elevation myocardial infarction therapy trial.

†Adjunctive medication used in all patients unless when % of use given.
Of the 620 patients randomized to an early invasive strategy, 7 patients received coronary artery bypass grafting (1.1%) and 531 patients (86%) underwent PCI, with stent use ranging from 79% to 100%. Reported median time delays from fibrinolytic administration to PCI in these patients ranged from 68 minutes to 16.7 hours (weighted average time of 8.4 hours); 45% of patients required transfer to an interventional facility after fibrinolytic administration.

The indications for inhospital angiography in the ischemia-guided arm are shown in Table I. The percentage of patients randomized to ischemia-guided management who underwent inhospital angiography ranged from 14% to 67%, with a median delay ranging from 23 hours to 3.1 days after fibrinolytic administration (weighted mean delay of 47 hours). Only 38 patients in the ischemia-guided arm underwent rescue PCI for failed reperfusion.

**Death**

<table>
<thead>
<tr>
<th>Study name</th>
<th>OR (95% CI)</th>
<th>Invasive</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEST</td>
<td>0.23 (0.03 - 2.12)</td>
<td>1/104</td>
<td>4/100</td>
</tr>
<tr>
<td>CAPITAL AMI</td>
<td>0.98 (0.19 - 4.97)</td>
<td>3/86</td>
<td>3/84</td>
</tr>
<tr>
<td>GRACIA 1</td>
<td>0.55 (0.24 - 1.27)</td>
<td>9/248</td>
<td>16/251</td>
</tr>
<tr>
<td>SIAM 3</td>
<td>0.41 (0.12 - 1.39)</td>
<td>4/82</td>
<td>9/81</td>
</tr>
<tr>
<td>PRAGUE 1</td>
<td>0.61 (0.28 - 1.35)</td>
<td>12/100</td>
<td>18/99</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>0.55 (0.34 - 0.90)</strong></td>
<td><strong>29/620</strong></td>
<td><strong>50/615</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q-value 1.35 df 4 (p 0.85) $I^2$ 0

**Reinfarction**

<table>
<thead>
<tr>
<th>Study name</th>
<th>OR (95% CI)</th>
<th>Invasive</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEST</td>
<td>0.62 (0.21 - 1.81)</td>
<td>6/104</td>
<td>9/100</td>
</tr>
<tr>
<td>CAPITAL AMI</td>
<td>0.37 (0.12 - 1.10)</td>
<td>5/86</td>
<td>12/84</td>
</tr>
<tr>
<td>GRACIA 1</td>
<td>0.59 (0.25 - 1.38)</td>
<td>9/248</td>
<td>15/251</td>
</tr>
<tr>
<td>SIAM 3</td>
<td>0.99 (0.14 - 7.18)</td>
<td>2/82</td>
<td>2/81</td>
</tr>
<tr>
<td>PRAGUE 1</td>
<td>0.46 (0.17 - 1.29)</td>
<td>6/100</td>
<td>12/99</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>0.53 (0.33 - 0.86)</strong></td>
<td><strong>28/620</strong></td>
<td><strong>50/615</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q-value 1.01 df 4 (p 0.91) $I^2$ 0

**Mortality and reinfarction.** There were 29 deaths (4.7%) in the early invasive arm and 50 deaths (8.1%) in the ischemia-guided management arm. A routine early invasive strategy was associated with a significant reduction in all-cause mortality (absolute risk reduction of 2.8% with NNT of 36, summary OR 0.55, 95% CI 0.34-0.90; $P = .02$), when compared with ischemia-guided management (Figure 2).

Similarly, an early invasive strategy was associated with a significant reduction in reinfarction (absolute risk reduction of 2.7% with NNT of 37, summary OR 0.53, 95% CI 0.33-0.86, $P = .01$) when compared with ischemia-guided management, with a reinfarction rate of 4.5% in the early invasive arm (28 events) versus 8.1% in the ischemia-guided management arm (50 events) (Figure 2).

**Safety outcomes.** For safety outcomes, the incidence of stroke was relatively uncommon in both groups with only 7 cases (1.1%) in the early invasive arm and 5 (0.8%) in the ischemia-guided arm. There was no significant difference in the risk of stroke (summary OR 1.31, 95% CI 0.42-4.10, $P = .64$) between the early invasive or ischemia-guided groups (Figure 3).

For inhospital major bleeding, there was no significant difference between the early invasive and ischemia-guided groups (summary OR 1.41, 95% CI 0.74-2.70, $P = .30$), with 29 cases in the early invasive group (4.6%) compared with 17 in the ischemia-guided group (2.8%) (Figure 3).

**Sensitivity analysis and heterogeneity.** Sensitivity analyses showed that results for both all-cause mortality
and reinfarction were not disproportionately influenced by any of the 5 trials included in the meta-analysis. Using only 30-day outcomes showed consistent benefits associated with an early invasive strategy for both mortality (summary OR 0.70, 95% CI 0.41-1.20) and reinfarction (summary OR 0.59, 95% CI 0.34-1.10). There was no statistically significant heterogeneity detected in the analysis of any of the efficacy or safety outcomes.

Balloon angioplasty trials

The study designs of the 4 balloon angioplasty trials that compared a routine early invasive strategy versus ischemia-guided management are shown in Table 1.13,14,19,20 Tissue-type plasminogen activator was used in all trials except the Should We Intervene Following Thrombolysis Trial (SWIFT) that used anistreplase.14 We analyzed these older studies to provide a comparison and highlight any differences between contemporary PCI after STEMI and balloon angioplasty during the prestent era.

A random effects meta-analysis of the balloon angioplasty trials showed that a routine early invasive strategy was not associated with any difference in mortality (summary OR 1.14, 95% CI 0.81-1.61, P = .46) or reinfarction (summary OR 1.02, 95% CI 0.80-1.31, P = .85) when compared with ischemia-guided management. An early invasive strategy was associated with a significant increase in major bleeding (15.5%) in comparison with ischemia-guided management (12.4%) (summary OR 1.35, 95% CI 1.13-1.61, P = .001). There was no difference in stroke between the 2 groups (summary OR 1.06, 95% CI 0.57-2.03, P = .83).

Discussion

In this systematic review of contemporary treatment strategies among STEMI patients treated with fibrinolytic therapy, we found that an early invasive strategy was associated with significant reductions in the risk of death and reinfarction, as compared to a strategy of ischemia-guided management. Furthermore, we did not find a significantly increased risk of stroke or major bleeding associated with an early invasive strategy; however, given that the CIs around these safety estimates were relatively wide, potentially important risks remain plausible. Further studies are needed to confirm these findings and to evaluate the longer-term outcomes associated with this strategy.

Current practice guidelines recommend that cardiac catheterization be limited to STEMI patients who have
recurrent chest pain, left ventricular dysfunction, or abnormal noninvasive assessment after successful reperfusion with fibrinolytic therapy. These cautions against routine cardiac catheterization are because of results from older randomized trials. For example, the largest trial in the balloon angioplasty era, Thrombolysis in Myocardial Infarction II (TIMI II) study showed increased bleeding associated with an early invasive approach, with little benefit in reducing death or myocardial infarction. However, these older trials were conducted in an era where STEMI patients were only treated with periprocedural aspirin and heparin, without adjunctive therapy such as thienopyridines or Gp2b/3a inhibitors; furthermore, coronary interventions were limited to balloon angioplasty without coronary stents. As a result, complications when compared to contemporary standards were significantly more frequent; in the TIMI trial, 7.7% of patients had total occlusion of the infarcted related artery and 4.4% had recurrent myocardial infarction after the initial angioplasty. Thus, it is unclear if the results from these older trials are relevant in today’s contemporary interventional practice.

The results of our meta-analysis that focused on contemporary trials diverged substantially from older balloon angioplasty studies. In our secondary analysis of balloon angioplasty trials, we did not find any benefit in mortality or reinfarction associated with early angiography in the present era, consistent with earlier studies. In contrast, we found an early invasive strategy with contemporary PCI reduced the relative risk of death and myocardial infarction by almost half compared with an ischemia-guided strategy. These estimates for mortality and reinfarction were robust across additional sensitivity analyses. Although we cannot exactly identify the reasons for the discrepancy, the use of adjunctive pharmacotherapies such as thienopyridines, appropriate dosages of heparin, and the use of Gp2b/3a inhibitors likely played an important role in addition to the use of stents.

Results from our study should be distinguished from studies of facilitated PCI. Facilitated PCI is defined as pharmacologic reperfusion treatment administered before primary PCI to bridge the time delay between first contact and mechanical reperfusion. In trials of facilitated PCI, patients randomized to facilitated and primary PCI had similar door-to-balloon times and all patients underwent protocol-mandated cardiac catheterization. In that setting, studies have not shown any additional benefit of facilitated PCI, but an increased risk of stroke and bleeding when compared to primary PCI. Trials included in our study had an average delay of 8.4 hours between fibrinolytic administration and cardiac catheterization, with a range from 68 minutes to 16.7 hours. Under these conditions, we found that an early invasive approach after fibrinolytic therapy was beneficial when compared to an ischemia-guided approach; however, it remains unclear as to the optimal timing of coronary angiography after fibrinolytic therapy.

To assess the safety of an early invasive strategy, we evaluated postprocedural bleeding because it has been demonstrated to be an important predictor of adverse outcomes after PCI. This is especially relevant in the setting of a postfibrinolytic state and the additional antplatelet and antithrombin agents necessary during PCI. We did not observe an overall increased risk of bleeding associated with an early invasive strategy compared with ischemia-guided management. Nonetheless, our estimate had relatively wide CIs leading us to believe that an increased risk of bleeding with a routine early invasive strategy remains plausible.

In addition, we did not find an increased risk of stroke among patients who were randomized to an early invasive strategy after STEMI fibrinolytic therapy. Similar to the estimates of bleeding, we cannot exclude the potential risk of stroke associated with an early invasive strategy as these estimates are based on relatively few events (7 cases [1.1%] in the invasive group and 5 cases [0.8%] in the ischemia-guided group). To place these estimates in context, recent meta-analyses have shown that the risk of stroke associated with facilitated PCI was 1.1%, compared with 0.3% for primary PCI, 3.4% for rescue PCI, and 2% for fibrinolytic therapy.

Several limitations of our study merit consideration. First, given the dramatic advances in interventional cardiologic studies, we chose to evaluate contemporary trials rather than including all available evidence on an early invasive strategy in STEMI. These contemporary trials were defined as those in which >50% of patients who underwent PCI received a stent. Although this may appear arbitrary, in fact approximately 87% of the patients in our trials received a stent during PCI. Other definitions to classify contemporary practice, such as the use of a different stent use threshold or another marker of contemporary practice (such as the date of publication), would have included the same set of trials. Second, many trials had relatively low rates of rescue PCI likely reflecting strong evidence to support the benefit of rescue PCI has only emerged recently. Therefore, our results may be overestimating the true benefit of an invasive strategy if all patients who failed fibrinolysis received rescue PCI. Finally, despite the lack of statistical heterogeneity, the designs of these trials were varied for number of treatment arms and the delay from fibrinolytic therapy to coronary angiography. As such, the results of this meta-analysis should be considered hypothesis generating rather than conclusive.

In summary, our meta-analysis suggests that a routine early invasive strategy is associated with improved clinical outcomes for STEMI patients after fibrinolytic therapy, in comparison to ischemia-guided management. These results should be confirmed by ongoing large multicenter randomized controlled trials before routine implementation.
References


## Appendix A. End point definitions

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Reinfarction</th>
<th>Major bleeding</th>
<th>Stroke</th>
</tr>
</thead>
</table>
| **WEST**<sup>25</sup> | 1. In the first 18 h after randomization, recurrent signs and symptoms of ischemia at rest accompanied by new or recurrent ST-segment elevations 0.1 mV in at least 2 contiguous leads lasting >30 min  
2. After 18 h, new Q waves (by Minnesota Code Criteria) in ≥2 leads and/or enzyme evidence of reinfarction: reevaluation of creatine kinase-MB (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 reelevated to ≥2 times the upper limit of normal and increased by 25% or be reelevated to 200 U/mL over the previous value. If reevaluated to <2 times the upper limit of normal, the total CK must exceed the upper limit of normal by 50% and exceed the previous value by 2-fold or be reelevated to 200 U/mL  
3. Reinfarction after PCI, CK >3 times the upper limit of normal and >50% the previous value and/or new Q waves (Minnesota Code) in ≥2 contiguous leads  
4. Reinfarction after coronary artery bypass graft surgery, CK >5 times the upper limit of normal and >50% above the previous value and/or new Q waves (Minnesota Code) in ≥2 contiguous leads                                                                 | Major bleeding—bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or cardiopulmonary resuscitation to maintain a sufficient cardiac output | Not defined                                  |
| **CAPITAL AMI**<sup>27</sup> | Recurrent ischemic symptoms at rest lasting >30 min and accompanied by the following:  
1. new or recurrent ST-segment elevation of >1 mm in any contiguous lead,  
2. new left bundle branch block, or  
3. reelevation in serum CK level to greater than twice the upper limit of normal and >50% above the lowest level measured after the infarction | TIMI criteria                                                                                                           | Focal neurologic deficit, compatible with damage in the territory of a major cerebral artery with signs or symptoms persisting for >24 h |
| **GRACIA-1**<sup>26</sup> | Typical chest pain lasting >30 min with a new increment of CK-MB isoenzyme with or without new electrocardiogram abnormalities  
CK criteria  
1. if within 48 h of infarction, positive when it appeared during descendent phase of isoenzyme curve of initial infarction and >150% of last measurement,  
2. if was >48 h after the initial infarction, positive if 3x normal value,  
3. if within 48 h of angioplasty or surgery, then at least 5x normal value | Not defined                                                                                                           | Not defined                                  |
| **SIAM III**<sup>28</sup> | ≥2 of the following:  
1. chest pain lasting for >30 min,  
2. new significant ST-elevation, or  
3. rise in the serum CK level to >3x the upper limit of normal | Need for transfusion, bleeding requiring surgical intervention, bleeding documented by computed tomography or ultrasound, intracerebral, ocular, retroperitoneal, abdominal, intestinal, urogenital, or a decrease in hemoglobin level >4g within 72 h of intervention | Not defined                                  |
| **PRAGUE**<sup>29,30</sup> | Subsequent recurrent symptoms of myocardial infarction combined with a more than double increase in CK-MB fraction or new electrocardiogram changes | Not defined                                                                                                           | New neurologic deficit lasting >24 h        |
## Appendix B. Inclusion and exclusion criteria of trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Time of randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEST^{25}</td>
<td>Male or nonpregnant females &gt;18 y with symptoms presumed secondary to STEMI lasting ≥20 min accompanied by electrocardiogram evidence of high risk (total ST deviation &lt;4 mm)</td>
<td>Primary PCI available within 1 h</td>
<td>Before fibrinolytic administration</td>
</tr>
<tr>
<td>CAPITAL AMI^{27}</td>
<td>&lt;6 h of chest discomfort lasting &gt;30 min duration and having ≥1 mm ST-segment elevation in ≥2 contiguous leads or left bundle branch block with high-risk features*</td>
<td>Active bleeding, history of stroke or central nervous system damage, major surgery, or trauma within 3 mo, uncontrolled hypertension, prolonged cardiopulmonary resuscitation, warfarin treatment, prior coronary artery bypass graft, PCI within 6 m, shock, pregnancy, Gp2b3a within 7 d, or heparin within 6 h</td>
<td>Before fibrinolytic administration</td>
</tr>
<tr>
<td>CAPITAL AMI^{27}</td>
<td>Patients &gt;18 y old with STEMI and received fibrinolytic agent within 12 h of pain onset</td>
<td>Shock, pregnancy, warfarin, active bleeding, major surgery within 2 wk</td>
<td>6 h after fibrinolytic administration</td>
</tr>
<tr>
<td>SIAM III^{28}</td>
<td>Age &gt;18 y with symptoms of STEMI for &lt;12 h and diagnostic electrocardiogram, eligible for fibrinolysis Culprit artery &gt;2.5 mm with diameter stenosis of &gt;70% and TIMI flow &lt;grade 3</td>
<td>Renal failure requiring dialysis</td>
<td>During fibrinolytic administration</td>
</tr>
<tr>
<td>PRAGUE^{29,30}</td>
<td>STEMI &lt;6 h after onset of symptoms</td>
<td>Contraindication to fibrinolysis, absence of femoral pulsation</td>
<td>Before fibrinolytic administration</td>
</tr>
</tbody>
</table>

*High-risk features defined as (1) anterior infarction with ST-segment elevation >2 mm in each of 2 contiguous precordial leads; (2) extensive nonanterior infarction, ≥8 leads with >1 mm ST-segment elevation or depression or both, or the sum of ST-segment elevation >20 mm; (3) Killip class 3; or (4) systolic blood pressure >100 mm Hg.