# Thrombolysis in the age of Primary Percutaneous Coronary Intervention: Mini-Review and Meta-analysis of Early PCI

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**Abstract:**

**Objective:** Primary Percutaneous Coronary Intervention (PCI) is the treatment of choice for ST-segment Elevation Myocardial Infarction (STEMI) if performed within 90 minutes from first medical contact. However, primary PCI is only available for less than 25% of patients with STEMI. Early PCI or Pharmaco-invasive strategy has evolved from facilitated PCI but with more delayed timing from thrombolysis to PCI.

**Aim:** Assess the safety and effectiveness of Early PCI.

**Patients and Method:** We reviewed the data of the available therapy options for patients with STEMI. Then we performed a meta-analysis for all randomized controlled trials of early PCI versus standard therapy

**Results:** Five studies fulfilled our inclusion criteria. Our meta-analysis showed improved cardiovascular events with early PCI compared to standard therapy (odd ratio of 0.54; 95% Confidence interval 0.47-0.7, $p<0.001$). There were no significant bleeding complications when doing early PCI 4 to 24 hours after successful thrombolysis

**Conclusion:** Early PCI should be done to all STEMI patients within 24 hours after successful thrombolysis.

**Key words:** Pharmacoinvasive strategy, Early PCI, Acute myocardial infarction, Thrombolysis

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**Introduction:**

Treatment options of ST-segment elevation myocardial infarction (STEMI) include either primary percutaneous coronary intervention (PCI), thrombolytic therapy with the use of intravenous fibrinolysis, or combination of fibrinolysis followed by PCI. Primary PCI remains the treatment of choice when it can be performed rapidly (within 90 minutes) in centers facile with this process. [1] Fibrinolysis can be done either alone or followed by PCI as either rescue PCI, facilitated PCI or early (pharmaco-invasive) PCI. The role of PCI after successful fibrinolysis has been ill defined in the past with conflicting data. The term facilitated PCI is defined as immediate PCI after pharmacological therapy (either full dose fibrinolysis, or a combination of half dose fibrinolysis with platelet glycoprotein IIb/IIIa inhibitor). Early PCI or a pharmaco-invasive approach has been defined in recent trials as fibrinolysis in non-PCI centers followed by transfer to a PCI center for catheterization within 24 hours where primary PCI was not feasible; while rescue PCI is defined as PCI performed after failed fibrinolysis.

With the conceptual frame work: "time delay equals myocardium lost", the goal has been to achieve reperfusion as early as possible in each and all scenarios of STEMI understanding that for each 30-min delay in reperfusion may result in as much as an increase of 7.5% in 1-year mortality. [2-3] Although many previous studies have shown increased mortality if the delay for reperfusion was 2 hours or more, more contemporary studies have shown some delays even within the 90-minute window reflect an increase in 1-year mortality (each 30 minutes delay associated with 4% increase in one year mortality) particularly in elderly patients (≥65 years of age) [4]. Only 25% of patients with STEMI are treated by primary PCI in acute care hospitals in United States. [5] Only 4.2% of patients were treated within 90 minutes, and grew only to 15% when treated within 120 minutes. More recently the door-to-balloon (D2B) alliance, using the National Cardiovascular Data Registry (Cath PCI) Registry, has increased the percentage of patients who meet the contemporary guidelines for door-to balloon time of less than 90 minutes from 50% before 2005 to 76% in 2008. [6] However, the D2B alliance substantial effort has been performed in only those non-transfer patients who present to facilities capable of primary PCI. Those STEMI patients who present to non-PCI capable centers may thus still suffer from delayed door-to-balloon time, making fibrinolysis a more attractive and better up front option for many if not most STEMI patients who cannot be transferred to PCI facility in timely fashion. More than 1 hour PCI-related delay may negate the mortality benefit of PCI depending on the anatomic distribution of the myocardial infarction [7] and may in fact be shorter, 40-43 minutes, in anterior STEMI patient's less than 65 years of age. [8] Fibrinolysis is often associated with incomplete revascularization of the infarct-related artery where generally less than 60% of patients achieve Thrombolysis In Myocardial Infarction flow grade 3 (TIMI 3) with the potential increased risk of recurrent ischemia, reocclusion, or reinfarction following therapy. [9]

**Facilitated PCI versus Primary PCI**

It has been shown that primary PCI is superior to early PCI after successful fibrinolysis if the guidelines are met (Door to balloon time <90 minutes and PCI-related delay <60 minutes). The advantages of primary PCI were sustained during long-term follow-up and independent of factors like the type of fibrinolytic agent used. However, due to geographical and resources limitations, primary PCI is not feasible for most STEMI patients in the United States.

Early trials of facilitated PCI after successful fibrinolysis in the pre-stent era failed to show clinical benefit for this combination strategy. [10-11] In both the Thrombolysis In Myocardial Infarction (TIMI-IIA) study and the European Cooperative study group (ECSG) studies showed potential harm in facilitated PCI as compared to thrombolysis alone, with a higher rate of bleeding (20% vs. 7.2%, $p<0.001$ and coronary artery bypass surgery (CABG) in the facilitated group (16.4% vs. 7.7%, $p=0.01$). Furthermore, The ECSG showed re-occlusion and re-infarction was increased in facilitated PCI presumably related to abrupt vessel closure secondary to a lack of stent use. With the advent of coronary stents there has been an increase in primary procedural success with reduction of abrupt closure, leading to recurrent ischemia or reinfarction, and the near elimination of the need for urgent CABG in

STEMI patients. [12] Additionally, improvements in procedural skills and better catheterization equipment including advancement in balloon technology, wire and stenting technology including drug-eluting stents as well as optimal use of antiplatelet and appropriate use of anticoagulation therapy including more recent direct thrombin inhibitors have afforded significant improvements in patient outcomes with STEMI.

Recent trials using current technology have also failed to show a clinical benefit of facilitated PCI. [13-14] The ASSENT-4 PCI (Assessment of the safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) and FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) trials are two large trials showing the definite superiority of primary PCI over facilitated PCI with potential harm of facilitated PCI. ASSENT-4 PCI was a randomized trial of 1667 STEMI patients to primary PCI versus tenecteplase-facilitated PCI. The primary endpoint (mortality, congestive heart failure or shock) at 90-day was 13% versus 19% in primary PCI versus facilitated PCI, respectively (relative risk 1.39, 95% CI 1.11-1.74; p=0.0045). The trial was terminated early due to higher in-hospital mortality in the facilitated PCI compared to primary PCI subjects. Interestingly however, there was significant impact in place of enrollment in ASSENT-4 trial; where the prehospital fibrinolysis group had the shortest pain-to-fibrinolytic delays (125 min) and the lowest 90-day mortality (3.1%) while the highest 90-day mortality was in the PCI capable hospital subject (8.4%) who was assigned to facilitated PCI (fibrinolysis to first balloon inflation was 92 min). [15]

The FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial [14] studied three strategies before primary PCI: combination abciximab plus half dose retaplase (828 patients) versus abciximab alone (818 patients) versus placebo prior to primary PCI (806 patients). At 90 days the primary outcome (mortality, cardiogenic shock, heart failure and ventricular fibrillation beyond 48 hours) were 9.8% in the combination facilitated PCI arm, 10.5% in the abciximab facilitated PCI arm, and 10.7% in the primary PCI alone arm, (p = 0.55). TIMI major or minor bleeding through discharge up to day 7 was higher in the combination facilitated PCI arm (14.5%) compared with either the abciximab facilitated PCI arm (10.1%; p = 0.008) or the primary PCI alone arm (6.9%; p < 0.001). Thus, using other modified strategies for facilitated PCI, i.e. using half dose fibrinolysis combined with platelet glycoprotein inhibitor or platelet glycoprotein inhibitor alone, failed to achieve the outcomes of primary PCI.

A meta-analysis by Keeley and colleagues [1] reviewing data from 23 randomized trials comparing primary angioplasty to intravenous fibrinolytic therapy, concluded that primary PCI is more effective in reducing mortality by two percent absolute risk reduction (odds ratio 1.38, 95% confidence interval1.01-1.87) in patients with STEMI compared to facilitated PCI. The findings favor primary PCI over facilitated PCI based on overall short-term mortality (7% vs. 9%, p=0.0002), nonfatal reinfarction (3% vs. 7%, p<0.0001), and stroke (1% vs. 2%, p=0.0004). In fact, this meta-analysis was driven mainly by the impact of ASSENT 4 which also led to the updated 2007 American College of Cardiology/American Heart Association STEMI guidelines to assign class III recommendation for a full-dose fibrinolysis facilitated PCI strategy.

An important distinction to be noted is that these trials examined facilitated PCI and not early PCI. The real-world option may therefore be early PCI rather than facilitated PCI in the current era of primary PCI compared to fibrinolysis alone. This strategy could afford the benefit of mechanical reperfusion-especially in those considered high risk or with high risk features (i.e. anterior myocardial infarction, shock etc.) or when primary PCI is not feasible for those patients not in proximity to a primary PCI center or when transfer times becomes long (>90 min).

## Early PCI after successful fibrinolysis versus Fibrinolysis

### Meta-analysis

We conducted our own meta-analysis, comparing early PCI versus standard fibrinolysis therapy. The early studies during the pre-stent era showed increased risk of bleeding with early PCI with no clinical benefit compared to fibrinolysis alone. Further, there have been three previous meta-analyses conducted mainly to assess the safety of facilitated PCI rather than early PCI. [16-18]

**Methods:**

We included randomized controlled trials using MEDLINE search in English language from 1990 to March 2011. We have used the key words of ST segment elevation myocardial infarction, Percutaneous Coronary Intervention, early Percutaneous Coronary Intervention, pharmaco-invasive strategy, facilitated percutaneous coronary intervention and thrombolysis. The inclusion criteria was randomized controlled trial of early invasive strategy (Early PCI, Pharmaco-invasive) compared to standard therapy after fibrinolysis when primary PCI was not feasible. We found five randomized trials that fit this criteria and include: SIAM III (Southwest German Interventional Study in Acute Myocardial Infarction), [19] GRACIA I (Routine invasive strategy within 24 hours of thrombolysis versus ischemia-guided conservative approach for acute myocardial infarction with ST-segment elevation), [20] CARESS-in-AMI (Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction), [21] TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction), [22] and NORDISTEMI (Norwegian study on District treatment of ST-Elevation Myocardial Infarction) [23] as summarized in Table 1. In order to maintain clinical homogeneity in our meta-analysis, we excluded other trials such as PRAGUE (Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis) [24] and WEST (Which Early ST-elevation myocardial infarction Therapy) [25] because they were primarily facilitated PCI trials and the former two trials compared facilitated PCI versus primary PCI. However in all included trials early transfer with catheterization within 24 hours of presentation did occur.

Statistical analysis was performed using the Review Manager 5. Odds ratio (OR) and 95% confidence intervals (CIs) were used as summary statistics. The pooled OR was calculated by using a random-effect model to be more conservative despite of insignificant clinical and statistical heterogeneity. Between study heterogeneity was analyzed by means of $I2 = [(Q - df)/Q] 100\%$, where Q is the $\chi 2$ statistic and df is its degrees of freedom.

**Findings and Discussion:**

Figure 1, shows the forest plot summarizing our meta-analysis early PCI associated with improved cardiovascular events with odd ratio of 0.54 (95% Confidence interval 0.47-0.7, $p<0.001$) with no significant bleeding complications as seen in figure 2. There is minimal clinical heterogeneity and insignificant statistical heterogeneity ($I2= 12.6\%$, $p=0.33$) among the five randomized control trials.

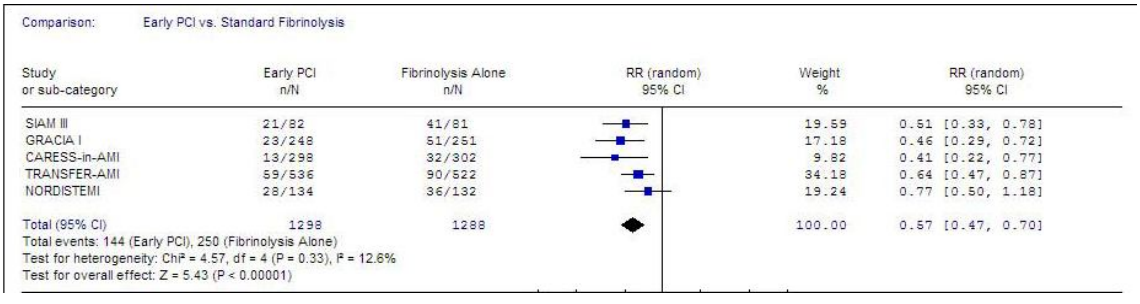


**Fig. (1). Forest plot of the included randomized controlled trials for early PCI versus standard thrombolysis therapy**

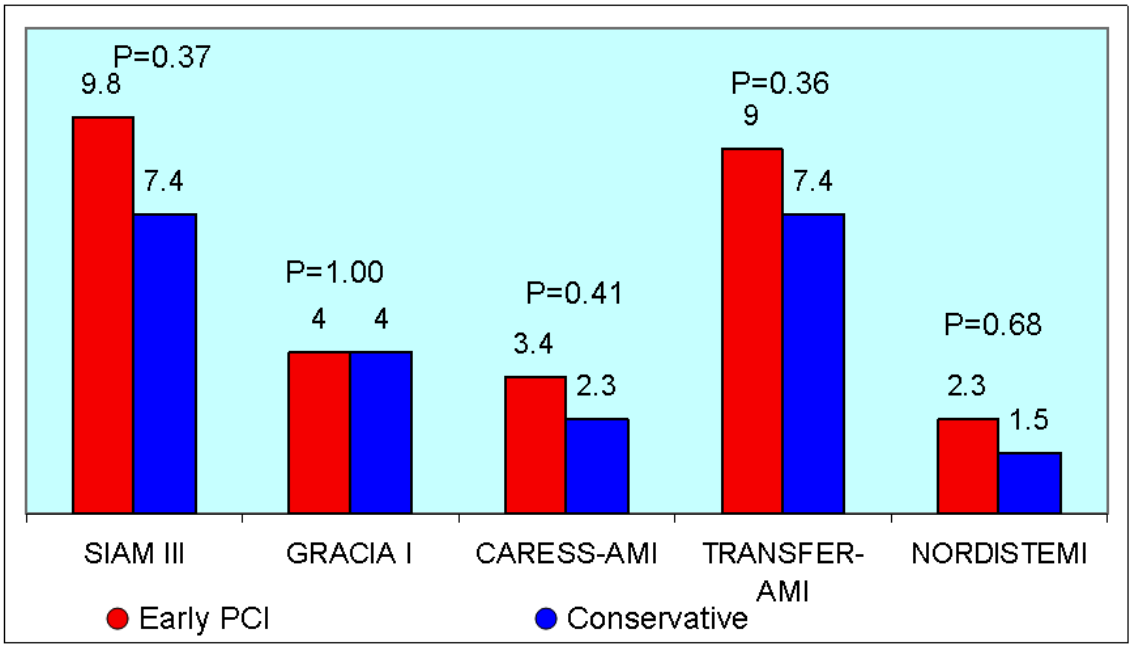


**Fig. (2). Major bleeding outcomes in Early PCI versus standard thrombolysis therapy**

This meta-analysis confirms the effectiveness of early PCI after successful fibrinolysis when primary PCI was not feasible. All of the included five trials required transfer to PCI capable centers while primary PCI was not feasible. It is worth noting that GRACIA 1 conducted in 15 out of 22 participating sites were PCI-capable centers, but all early PCI were performed 6 hours after fibrinolysis.

In SIAM-III as depicted in table 1 showed significant improvement in the primary outcomes in early PCI. It also showed no difference in major bleeding between the two groups (7.4% fibrinolysis alone versus 9.8% early PCI, p=0.400), see figure 1. Clopidogrel was used in this trial if the patient received a stent, for total duration of 4 weeks. Theinopyridine in GRACIA 1 was also only mandated if patient was allocated to early PCI. GARCIA 1 study showed as seen in table 1, a 1-year improvement in death, re-infarction, revascularization from (9% in early PCI versus 21% in fibrinolysis alone, p=0.0008) which is driven mainly by a lower revascularization rate in the intervention arm (12% versus 4%, RR 0.30, p=0.001), with a trend of reduced rate of death and re-infarction as well as no difference in major bleeding (1.6% in each group) or vascular complications. The overall mortality in GRACIA-1 was as low as 2% at 30 days. The cause of such low mortality rate in this trial might be attributed to the exclusion of patients with cardiogenic shock, PCI performed within 6-24 hours after fibrinolysis (median time from fibrinolysis to first balloon inflation was 16.7 hours, which may reduces bleeding complications), high TIMI flow 3 (81%) before PCI and 27% of patients received abciximab.

CARESS-in-AMI and TRANSFER-AMI enrolled only high-risk patients with slight difference in their definitions, see table 2. Clopidogrel was only given in case of PCI and stenting in CARESS-in-AMI but mandatory in all patients in TRANSFER-AMI. CARESS-in-AMI was the only trial in early PCI using half dose fibrinolysis with IIb/IIIa inhibitors, which showed a significant clinical benefit for early PCI in expense of more major bleeding (2.3% fibrinolysis alone vs.3.4% early PCI, p=0.47) as shown in table 1 and figure 1

**Table (1). Early PCI randomized control trials when primary PCI was not feasible and their respective primary outcomes**

| Study | Patients No. | Study population: STEMI patients | Medications | lysis to PCI | Primary Outcomes (Fibrinolysis vs early PCI) |
|---|---|---|---|---|---|
| SIAM-III | 110 | fibrinolysis randomized to PCI within 6 hr vs. after 2 weeks | Retaplase<br>ASA<br>UFH | 3.7 hr | 6 Months death, reinfarction, ischemic events, or target lesion revascularization<br>(5.6 vs. 25.6%, p=0.001) |
| GRACIA-1 | 500 | fibrinolysis randomized to PCI within 24 hr vs, ischemia guided PCI | Alteplase<br>ASA<br>UFH<br>Theinopyridine if stent used | 16.7 hr | 1 year death, reinfarction,or revascularization<br>(21% vs. 9%, p=0.008) |
| CARESS-in-AMI | 600 | High risk STEMI patients treated with retaplase or half dose retaplase if randomized to immediate transfer for PCI | Retaplase<br>Abciximab<br>ASA<br>Theinopyridine if stent used | 2.3 hr | 30 day death, reinfarction, and refractory ischemia<br>(10.7% vs. 4.4%, p=0.005) |
| TRANSFER-AMI ( | 1059 | High risk STEMI patients treated with fibrinolysis randomized to PCI within 6 hours or standard therapy | TNK<br>ASA<br>Antithrombin<br>Clopidogrel<br>IIb/IIIa inhibitors | 3.9 hr | 30 day death, reinfarction, recurrent ischemia, new onset worsening heart failure and cardiogenic shock<br>(17.2% vs. 11%, p=0.0013) |
| NORDISTEMI | 266 | fibrinolysis and randomized to immediate transfer for PCI or standard therapy | TNK<br>ASA<br>Antithrombin<br>Clopidogrel | 2.7 hr | 1 year death, reinfarction, stroke or new ischemia<br>(27% vs. 21%, p=0.19)<br>Secondary outcome was 1 year death, reinfarction or stroke (16% vs 6%, p=0.01) |

**Table (2). High risk STEMI definition in CARESS-in-AMI and TRANSFER-AMI**

| Trial | High risk STEMI definition |
|---|---|
| CARESS-in-AMI | Anterior MI alone with ≥2 mm of ST elevation in ≥2 leads Inferior MI with: (At least one)<br>• Extensive ST-segment elevation<br>• New-onset left bundle-branch block<br>• Previous MI<br>• Killip class >2, or<br>• Left ventricular ejection fraction ≤35% |
| TRANSFER-AMI | Anterior STEMI<br>Inferior STEMI with: (At least one)<br>• systolic blood pressure < 100 mm Hg<br>• Heart rate > 100 beats per minute<br>• Killip class II or III<br>• ST-segment depression of 2 mm or more in the anterior leads<br>• ST-segment elevation of 1 mm or more in right-sided lead V4 (V4R) |

TRANSFER-AMI was the largest early PCI trial; in which coronary angiogram was performed in 98.5% (85% had PCI) of patients randomized to the early PCI group and 88.7% (67.4% had PCI) of patients randomized to standard medical treatment group. Interestingly, glycoprotein IIb/IIIa inhibitors use was high in this trial (81.2% and 83.6% in standard-therapy and early PCI groups, respectively). TRANSFER-AMI and NORDISTEMI are the only two trials mandating the use of clopidogrel to all patients. The clinical benefits of early PCI were driven mainly by the reduction of ischemia except in NORDISTEMI. Despite the primary endpoint in NORDISTEMI was not statistically significant, the predefined secondary endpoints (12 month composite of death, reinfarction, or stroke) was significantly reduced in the early PCI group compared with the conservative group (6% vs. 16%, hazard ratio: 0.36, 95% confidence interval: 0.16 to 0.81, p= 0.01) with no significant differences in bleeding or infarct size were observed. The modest benefit of early PCI in NORDISTEMI might be related to the soft definition of ischemia (defined as angina beyond 12 hours of randomization) with no requirement for ECG changes or enzyme rise, inclusion of lower risk population in contrast to TRANSFER-AMI and CARESS-in-AMI, and more than half of the patients received prehospital fibrinolysis which might translate to improved clinical outcomes of standard therapy group.

There were no significant differences in the rates of major bleeding or transfusion as shown in figure 1 across all early PCI trials. In TRANSFER-AMI, using severe GUSTO bleeding definition, the rate was 1.5% in standard therapy versus 1.1% in early PCI group, p=0.55). Low bleeding rates may have been reduced in this trial because of the use of smaller sheath size, earlier sheath removal, radial access (used in 17% of cases), the administration of lower doses of anticoagulants, and the elimination of post procedural heparin infusions.

**Optimal Timing for Early PCI**

In the light of CARESS-in-AMI and TRANSFER AMI, ACC/AHA focus STEMI guidelines update in 2009 stated "it is reasonable for high-risk patients who receive fibrinolytic therapy as primary reperfusion therapy at a non–PCI-capable facility to be transferred as soon as possible to a PCI-capable facility where PCI can be performed either when clinically needed or as a pharmaco-invasive strategy. Consideration should be given to initiating a preparatory antithrombotic (anticoagulant and antiplatelet) regimen before and during patient transfer to the catheterization laboratory (Class IIa, Level of evidence: B).

The timing for early PCI is still unclear. Obviously, the timing of early PCI is later than facilitated PCI based on previous trials which has been associated with no clinical benefit and potential harm compared with primary PCI as seen in ASSENT4 and FINESSE trials. The time between fibrinolysis and PCI was short in these two trials (90 to 104 min).

Thus, the optimal time for early PCI may potentially be between 2-24 hours. Figure 3 shows the median time from fibrinolysis to early PCI. As per TRANSFER-AMI, the suggested timing may be best between 4 to 24 hours from successful fibrinolysis. Additionally, waiting beyond 24 hours may be harmful due to the potential risk of re-occlusion may result in recurrent ischemia and/or reinfarction. Therefore, based on these trials and our meta-analysis we suggest that early PCI or pharmaco-invasive strategy for most patients who present with STEMI without the up-front option for primary PCI (within 90 minutes) to be the preferred method of revascularization. The optimal timing from fibrinolysis to PCI remains ill defined though likely would be over 4 hours but less than 24 hours as suggested in previous studies.

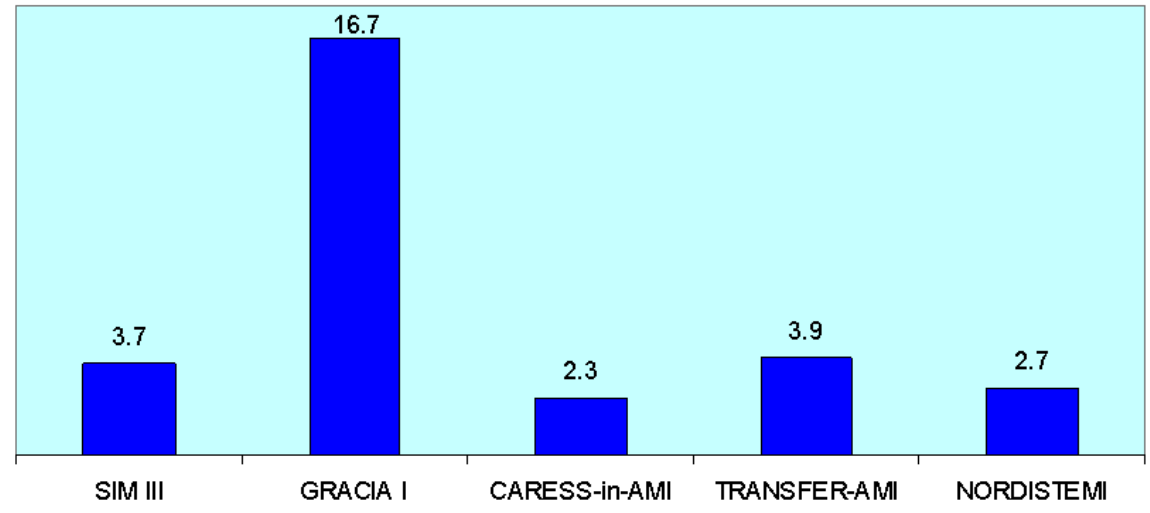


**Fig. (3). Median time of thrombolysis to early PCI (hours)**

## Conclusion

Our meta-analysis supports the paradigm for the STEMI system of care to include transferring especially high-risk STEMI patients (i.e. all anterior STEMI and inferior STEMI with high risk features) for early PCI after successful fibrinolysis, probably within 4-24 hours after fibrinolysis, who present to facilities that are not capable to perform primary PCI.

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