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## Providing best practices for the management of ST-segment elevation myocardial infarction (STEMI): Pharmacoinvasive strategies

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### Abstract

Although primary PCI remains the preferred strategy for the treatment of STEMI, the lack of expanded PCI centers and prolonged transfer times have resulted in delayed reperfusion and thus increased mortality. A pharmacoinvasive strategy involving immediate fibrinolysis followed by transfer to a PCI center to perform angiography (and PCI of infarct-related arteries) within 2 and 24 hours after successful fibrinolysis offers immediate reperfusion and better outcomes in patients in whom primary PCI could not be achieved in a timely manner without an increase in bleeding complications. The article summarizes the evidence for this approach in terms of efficacy and safety.

**Keywords:** STEMI, fibrinolysis, PCI, Pharmaco-invasive strategy, reperfusion, mortality

### Introduction

Acute myocardial infarction (AMI) is defined as the presence of acute myocardial damage detected by abnormal cardiac biomarkers in the presence of acute myocardial ischemia <sup>[1]</sup>. It is useful to clinically differentiate patients with persistent chest discomfort (or other symptoms suggestive of ischemia) and ST-segment elevation in at least two adjacent leads, diagnosed as ST-elevation myocardial infarction (STEMI), who would benefit from early reperfusion therapy. The most comprehensive European STEMI registry in Sweden showed an incidence of STEMI of 58 per 100,000 per year in 2015 <sup>[2]</sup>.

Although mortality from STEMI has decreased recently due to increased use of early reperfusion, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention.

However, mortality remains significant. In-hospital mortality of unselected patients with STEMI in national registries of ESC countries varies between 4 and 12% <sup>[3]</sup>, with the reported one-year mortality among patients with STEMI in angiographic registries being approximately 10% <sup>[4, 5]</sup>.

The traditional approach to the treatment of STEMI involves either PCI, if possible in the time frame, or intravenous fibrinolysis. Primary PCI (immediate coronary angioplasty without prior thrombolysis) is the preferred reperfusion strategy in patients with STEMI within 12 hours of symptom onset, provided it can be performed within 120 minutes of first medical contact (FMC). However, lower mortality is observed only in centers with a high volume of PCI procedures performed by an experienced team that includes not only interventional cardiologists but also qualified support staff.

In large randomized clinical trials, primary PCI performed in large and experienced centers has been shown to reduce mortality, reinfarction, or stroke compared with fibrinolysis when treatment delays are similar <sup>[6-8]</sup>. However, in some cases it is not possible to offer primary PCI, whereas fibrinolysis can be given immediately. The maximum time delay in arranging primary PCI when fibrinolysis could be offered immediately, referred to as PCI-related delay, was set at 120 minutes <sup>[9]</sup>. Because primary PCI has been focused on treating patients with STEMI, many physicians feel powerless to decide on the best immediate treatment when faced with the threat of prolonged PCI-related delay in patients arriving at a non-PCI center. According to the survey, only about 20% of US hospitals have primary PCI services. However, an efficient ground and helicopter ambulance service was able to transport patients to PCI centers within the required time frame.

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A retrospective study of 97 STEMI patients transported to a PCI center by ground or helicopter ambulance found that door-to-PCI within 120 minutes accounted for 35.5% (11 of 31) of ground transport, 24.2% (16 of 31) of door-to-door PCI to PCI (16 dogs). 31). 66) Transportation by helicopter. Phillips M, Arthur AO, Chandwani R, Hatfield J, Brown B, Pog K, *et al.* Effectiveness of helicopter transport in patients undergoing primary percutaneous coronary intervention. *Air Med J.* May-June 2013; 32(3):144-52.

Confidence in the safety and efficacy of fibrinolysis has certainly been shaken in the modern era of PCI. A pharmacoinvasive strategy offers an alternative approach for patients ineligible for early primary PCI with comparable efficacy and safety.

### What is a pharmacologically invasive strategy

This includes administration of fibrinolysis immediately transported to a PCI center for angiography (and angioplasty if deemed appropriate) within 24 hours, regardless of whether fibrinolysis is successful or not. In the past, patients with STEMI were immediately transferred to angioplasty for fibrinolytic failure, a salvage approach to PCI. A UK randomized multicentre trial (RESCUE, 2005) of 427 STEMI patients who failed clot lysis found that event-free survival was significantly higher with acute PCI (84.6%, 95% CI 78.7-90).

5%) repeated clot lysis (68.7%, 95% CI 61.1-76.4%) or conservative treatment (70.1%, 95% CI 62.5-77.7%)<sup>[10]</sup>. Similarly, after successful fibrinolysis (>50% resolution of ST-segment elevation, resolution of chest pain or typical reperfusion arrhythmias), some centers adopt a "watch-and-wait" strategy in which angiography is ordered only in case of recurrent ischemia. However, current data and guidelines clearly show that angiography is necessary within 2–24 hours after STEMI, not only in the presence of recurrent ischemia, but also after successful fibrinolysis. A pharmacologically invasive strategy proposes a new treatment that provides better outcomes for patients through the combination of two proven therapies.

This concept of combining intravenous fibrinolytics with early PCI is not new. An approach known as accelerated PCI is the administration of pre-planned PCI within 2 hours of fibrinolysis after administration of fibrinolysis. Several previous clinical studies have shown that this approach improves myocardial perfusion and thus improves clinical outcomes. However, this approach soon fell out of favor due to the high incidence of cardiac adverse events in randomized clinical trials. In the ASSENT-4 PCI study (2006). Randomized patients with STEMI to either primary PCI (n=838) or full dose tenecteplase (TNK) followed by PCI (n=829). The median time from symptom onset to randomization was 140 minutes in the TNK with PCI group compared to 135 minutes in the PCI alone group. PCI was performed in 91.1% of the primary PCI group and 87.1% of the TNK with PCI group (p=0.01), at a median of 104 minutes following TNK bolus administration. The trial was terminated early due to increased mortality in the facilitated PCI group. At 90 days, the primary endpoint of death, heart failure and shock was higher in the facilitated PCI group (19% vs. 13%, p=0.0055)<sup>[11]</sup>.

### Evidence behind the pharmaco-invasive strategy

**Randomized trials:** Several randomized trials have proven the efficacy and safety of the pharmaco-invasive approach.

TRANSFER-AMI trial (2009)<sup>[12]</sup>, performed at 52 sites in three provinces in Canada, randomized 1059 high-risk patients who had STEMI and received fibrinolysis at centers that did not have the facility to perform PCI. Patients were allocated either for immediate transfer for PCI within 6 hours of fibrinolysis or standard treatment (including rescue PCI if required). All patients received aspirin, clopidogrel, tenecteplase, and heparin. At 30 days, the primary endpoint (composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock) occurred in 11% of the routine early PCI group vs. 17.2% of patients assigned to the standard treatment (relative risk of early PCI 0.64, 95% CI 0.47-0.87, p=0.0040). Incidence of major bleeding was not significantly different. CARESS-IN-AMI trial (2008)<sup>[13]</sup> recruited 600 STEMI patients aged ≤75 years with one or more high-risk features (extensive STEMI, new onset LBBB, previous MI, Killip class >2, LVEF ≤35%) in hospitals in France, Italy and Poland. After initial treatment with aspirin, heparin, half-dose reteplase, and abciximab, patients were randomized to either immediate transfer to the nearest PCI center or management in the local hospital and transfer only in the presence of persistent ST elevation or clinical deterioration. The primary outcome (composite of death, reinfarction, or refractory ischemia) at 30 days occurred in 4.4% of the patients in the immediate PCI group compared to 10.7% in the standard care/rescue PCI group (hazard ratio 0.40, 95% CI 0.21-0.76, p=0.004). There was no difference in major bleeding (p=0.47) and risk of stroke (p=0.50). The NORDISTEMI trial (2010)<sup>[14]</sup> studied 266 STEMI patients living in rural areas in Norway where transfer delay for primary PCI was more than 90 minutes. All patients were treated with aspirin, clopidogrel, tenecteplase, and enoxaparin. Patients were randomized to immediate transfer for PCI or standard treatment and early transfer only if needed, to rescue PCI or clinical deterioration. Although the primary composite outcome of death, reinfarction, stroke, or new ischemia at 12 months was not statistically different (hazard ratio 0.72, 95% CI 0.44-1.18, p=0.19), the rate of death, reinfarction and stroke at 12 months was significantly reduced in the early invasive group compared with the conservative group (6% vs. 16%, hazard ratio 0.36, 95% CI 0.16-0.81, p=0.01). No significant differences in bleeding or infarct size were observed. The GRACIA-I trial (2004)<sup>[15]</sup> studied 500 thrombolysed STEMI patients in Spain and randomized to either early intervention within 24 hours of thrombolysis or an ischemia-guided approach. At 1 year, patients in the invasive group had a lower frequency of primary endpoint of death, reinfarction, or revascularization (risk ratio 0.44, 95% CI 0.28-0.70, p=0.0008). Index time in hospital was shorter in the invasive group with no differences in major bleeding or vascular complications. More recurrent ischemia was found in the conservative group. SIAM-III (2003)<sup>[16]</sup> study was a multicenter, randomized, prospective trial that compared 197 post-thrombolysis acute MI patients who were transferred for coronary angiography including stenting within 6 hours versus elective angiography after 2 weeks. Immediate stenting was associated with a significant reduction in the combined endpoint of ischemic events, death, reinfarction, and target lesion revascularization (25.65 vs. 50.6%, p=0.001) after six months. CAPITAL-AMI (2005)<sup>[17]</sup> randomized 170 high-risk STEMI patients in Canada to thrombolysis with tenecteplase alone versus thrombolysis followed by immediate angioplasty. At 6

months, the incidence of primary endpoints (death, reinfarction, recurrent unstable ischemia, stroke) was lower in the tenecteplase-facilitated angioplasty group (11.6% vs. 24.4%,  $p=0.04$ ). This difference was largely driven by a reduction in the rate of recurrent unstable ischemia (8.1% vs. 20.7%,  $p=0.03$ ). There was no difference in major bleeding (8.1% vs. 7.1%,  $p=1.0$ ). STREAM trial (2013) evaluated a strategy of fibrinolysis and coronary angiography within 6 to 24 hours compared with primary PCI among patients with STEMI who were unable to undergo primary PCI within 1 hour. Primary endpoint included all-cause death, myocardial infarction, shock or congestive heart failure at 30 days. 1,892 STEMI patients were randomised to fibrinolysis and coronary angiography (944) versus primary PCI (948). After 21% of participants were enrolled, the protocol was amended to reduce the dose of tenecteplase by 50% for patients aged 75 years or more. Coronary angiography was performed within 6 to 24 hours unless rescue PCI was required. Median time between symptom onset and reperfusion was 100 minutes in the fibrinolysis group versus 178 minutes in the primary PCI group ( $p<0.001$ ). Primary endpoint occurred in 12.4% of the fibrinolysis group versus 14.3% of the primary PCI group ( $p=0.21$ ) at 30 days. There was no difference in individual endpoints of all-cause mortality, reinfarction or congestive heart failure. However, fibrinolysis was associated with an increase in intracranial haemorrhage. After the protocol amendment that halved the dose of tenecteplase among patients  $\geq 75$  years, there was no longer a significant difference in intracranial bleed. Even at 1 year, there was no difference in the incidence of all-cause death (6.7% vs. 5.9%,  $p=0.52$ ) and cardiovascular death (4.0% vs. 4.1%,  $p=0.93$ ) in fibrinolysis versus primary PCI groups respectively.

Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y *et al.* Fibrinolysis or Primary PCI in

ST-Segment Elevation Myocardial Infarction. *N Engl J Med* 2013;368:1379-1387.

Table 1 summarizes the randomized controlled trials comparing the pharmaco-invasive strategy versus primary angioplasty.

**Meta-analyses**

Two large meta-analyses have addressed this issue and provided encouraging results in favour of the pharmaco-invasive strategy. Borgia *et al.* (2010) [18] performed a meta-analysis of seven randomized trials involving 2961 patients to define the benefits of early PCI within 24 h after successful fibrinolysis over standard therapy on clinical and safety endpoints in STEMI. 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 ischemia (OR 0.25, 95% CI 0.13-0.49,  $p<0.001$ ) at 30-day follow-up. This was 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,  $p=0.21$ ). These benefits persisted at 6-12 months. Similarly, D’Souza *et al.* (2011) [19] meta-analyzed eight randomized trials involving 3195 patients to study the advantage of routine early PCI over standard ischemia-guided PCI following fibrinolysis. The combined endpoint of 30-day mortality, reinfarction, and ischemia was reached in 7.3% of patients in the routine early PCI group vs. 13.5% in the ischemia-guided PCI group following lysis (OR 0.47, 95% CI 0.32-0.68,  $p<0.0001$ ) favouring routine early PCI, driven by significant reduction in both reinfarction (OR 0.62, 95% CI 0.42-0.90,  $p<0.011$ ) and ischemia (OR 0.21, 95% CI 0.10-0.47,  $p<0.001$ ). There was no significant difference in 30-day mortality or major bleeding.

**Table 1:** Summary of randomized controlled trials comparing the pharmaco-invasive strategy vs. primary angioplasty

Study (year)	Sample	Inclusion criteria	Strategy	Symptoms to lysis (min, median)	Lysis to early PCI (min, median)	Primary endpoint	Results
CARESS-IN-AMI (2008)	600	High-risk STEMI <12 hours from symptom onset, post-lysis.	Group 1: Immediate transfer for PCI. Group 2: Standard therapy (including rescue PCI).	163	125	30-day death, reinfarction, recurrent ischemia.	Primary outcome 4.4% (group 1) vs. 10.7% (group 2) (HR 0.40; 95% CI 0.21-0.76, $p=0.004$ ). Major bleeding 3.4% vs. 2.3 ( $p=0.47$ ). Strokes 0.7% vs. 1.3% ( $p=0.50$ ).
GRACIA-I (2004)	500	STEMI <12 hours from symptom onset, post-lysis.	Group 1: Immediate transfer for PCI <24 hours. Group 2: Standard therapy (including rescue PCI).	184	1002	12-month death, reinfarction, revascularization.	Primary outcome 9% (group 1) vs. 21% (group 2) (RR 0.44, $p=0.0008$ ), driven by lower revascularization rate in the intervention arm (4% vs. 12%, RR 0.30, $p=0.001$ ). No difference in the rate of major bleeding during the index hospitalization by treatment group (1.6% in each group).

CAPITAL-AMI (2005)	170	High-risk STEMI <12 hours from symptom onset, post-lysis.	Group 1: Immediate transfer for PCI <3 hours. Group 2: Standard therapy (including rescue PCI).	120	84	6-month death, re-infarction, ischemic events or stroke.	Primary outcome 11.6% (group 1) vs. 24.4% (group 2) (p=0.04), driven by a reduction in the rate of recurrent unstable ischemia (20.7% vs. 8.1%, p=0.03). No significant differences were observed in the rates of death/stroke or major bleeding.
SIAM-III (2003)	163	STEMI <12 hours from symptom onset, post-lysis.	Group 1: Immediate transfer for PCI <6 hours. Group 2: Standard therapy (including rescue PCI).	204	210	6-month death, re-infarction, recurrent ischemia, target lesion revascularization.	Primary outcome 25.6% (group 1) vs. 50.6% (group 2) (p=0.001), driven by the reduction in ischemic events (4.9% vs. 28.4%, p=0.01). No difference in major bleeding (9.8% vs. 7.4%, p=0.4). EF improved in group 1 both at two-weeks (56.7% vs. 52.5%, p=0.037) and six months (61.5% vs. 56.4%, p=0.018).
TRANSFER-AMI (2009)	1059	High-risk STEMI <12 hours from symptom onset, post-lysis.	Group 1: Immediate transfer for PCI <6 hours. Group 2: Standard therapy (including rescue PCI).	114	234	30-day death, re-infarction, recurrent ischemia, new CHF, cardiogenic shock	Primary outcome 11.0% (group 1) vs. 17.2% (group 2) (RR 0.64; 95% confidence interval, 0.47 to 0.87; P=0.004). No significant differences between the groups in the incidence of major bleeding.
WEST (2006)	304	STEMI <6 hours from symptom onset.	Group 1: TNK and usual care. Group 2: TNK, followed by angiography <24 hours (including rescue PCI). Group 3: Primary PCI	122	295	30-day death, re-infarction, recurrent ischemia, new CHF, cardiogenic shock, major ventricular arrhythmias.	Primary outcome 25% (Group 1), 24% (Group 2), and 23% (Group 3). Higher death and recurrent MI in Group 1 vs. Group 3 (13.0 vs. 4.0%, p=0.021), no difference between Group 2 (6.7%, p=0.378) and 3.
NORDISTEMI (2010)	266	STEMI <6 hours from symptom onset, post-lysis.	Group 1: Immediate transfer for PCI. Group 2: Standard therapy (including rescue PCI)	121	163	12-month death, re-infarction, recurrent ischemia, stroke.	Primary outcome 21% in the early invasive group compared with 27% in the conservative group (HR: 0.72, 95% confidence interval: 0.44 to 1.18, p = 0.19). No significant differences in bleeding. No difference in infarct size were observed.
STREAM (2013)	1892	STEMI <6 hours from symptom onset, unable to undergo PCI within 1 hour.	Group 1: PPCI. Group 2: lysis (followed by PCI).	100	178 (symptoms to PPCI)	30-day death, re-infarction, CCF, shock.	Primary outcome 12.4% of the fibrinolysis group versus 14.3% of the primary PCI group (p = 0.21). Intracranial hemorrhage after protocol amendment: 0.5% vs. 0.3% (p = 0.45), major non-intracranial bleeding: 6.5% vs. 4.8% (p = 0.11). No difference in mortality at 1 year.
GRACIA II (2007)	212	STEMI <12 hours from	Group 1: PPCI within 3 hours.	195	66 (randomization to	6-week epicardial/myocardial	Early routine post-lysis angioplasty resulted in



		symptom onset.	Group 2: lysis followed by early PCI within 12 hours.		angiography in group 1)	reperfusion, LV damage (infarct size, LV function).	higher frequency (21 vs. 6%, P = 0.003) of complete epicardial and myocardial reperfusion. Both groups were similar regarding infarct size (P=0.94); 6-week left ventricular function (ejection fraction P=0.11; end-systolic volume index P=0.21; major bleeding (P=0.99) and 6-month cumulative incidence of the clinical endpoint (10 vs. 12%, P = 0.57; relative risk: 0.80; 95% confidence interval: 0.37-1.74).
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STEMI, ST-Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; PPCI: Primary Percutaneous Coronary Intervention; TNK, Tenecteplase; HR, Hazard ratio; CI, Confidence Interval; RR, Relative Risk.

**Optimal timing of PCI after fibrinolytic therapy**

Since failed trials of facilitated PCI showed evidence of increased bleeding, concerns have been raised about what is the optimal time for angiography after successful fibrinolysis.

ASSENT-4 trial (2006) that involved a strategy of facilitated PCI showed increased mortality at 90 days where PCI was performed after a median 1.7 hours post-lysis. Subsequent trials favouring pharmaco-invasive strategy showed improved outcomes when median fibrinolysis to angiography times were 4.5 hours in WEST trial (2006), 4.6 hours in GRACIA-2 trial (2007), 3.5 hours in CARESS-IN-AMI trial (2012) and 8.1 hours in STREAM trial (2013).

Dimopoulos K, Dudek D, Piscione F *et al.* Timing of events in STEMI patients treated with immediate PCI or standard medical therapy: implications on optimisation of treatment from the CARESS-IN-AMI trial. *Int J Cardiol*, 154 (2012), pp. 275-281.

Danchin *et al* demonstrated that 30-day mortality in patients treated with fibrinolysis followed by PCI (the pharmaco-invasive strategy) was 5.2% when PCI done ≤128 min, 2.6% when PCI done 129-220 min, and lowest 1.5% when PCI done >220 min after fibrinolysis. Danchin N, Coste P, Ferrieres J *et al.* Comparison of thrombolysis followed by broad use of PCI with primary PCI for STEMI. *Circulation*, 118 (2008), pp. 268-276.

Based on the above-mentioned data, the European Society of Cardiology and the American Heart Association recommend performing angiography after fibrinolysis between 2-24 hours and 3-24 hours respectively.

**Place in guidelines**

The 2017 European Society of Cardiology (ESC) Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [20] have given a Class IA recommendation for performing angiography and PCI of the infarct-related artery, of indicated, between 2 and 24 h after successful fibrinolysis. The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction [21] has recommended to

perform angioplasty of the infarct-related artery after successful fibrinolysis between 3 and 24 hours with Class IIA recommendation.

**Conclusion**

Although primary PCI remains the preferred strategy to treat STEMI, the lack of widespread PCI centers and prolonged transfer times from non-PCI to PCI centers has led to delayed reperfusion resulting in increased mortality. Recent evidence has suggested that STEMI patients presenting to non-PCI centers can safely undergo fibrinolysis upon presentation followed by transfer to PCI center for angiography between 2 to 24 hours. This strategy provides immediate reperfusion, has comparable beneficial effects on outcomes versus primary PCI and not associated with increase in bleeding.

**Conflict of Interest**

The authors declare no conflict of interest, financial or otherwise.

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None.

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