

EDITORIAL

Acute Myocardial Infarction: Routine Early Angioplasty after Thrombolysis

Petros S. Dardas, MD, FESC

St Lukas Hospital, Thessaloniki,
Greece

KEY WORDS: acute myocardial infarction; reperfusion; thrombolysis; coronary angioplasty; coronary stenting

ABBREVIATIONS

ACC = American College of Cardiology
 AHA = American heart Association
 ASSENT = ASsessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (study)
 CABG = coronary artery bypass grafting
 CARESS-in-AMI = Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction (study)
 CK = creatine kinase
 ESC = European Society of Cardiology
 FAST-MI = French Registry on Acute ST-Elevation Myocardial Infarction (study)
 GRACIA = Grupo de Análisis de Cardiopatva Isquémica Aguda (study)
 NORDISTEMI = NORwegian study on DIstrict treatment of ST-elevation myocardial infarction (study)
 PCI = percutaneous coronary intervention
 SCAI = Society for Cardiovascular Angiography and Interventions
 SIAM III = Streptokinase in Acute Myocardial Infarction (study)
 STEMI = ST elevation myocardial infarction
 TIMI = thrombolysis in myocardial infarction
 TRANSFER AMI = Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (study)

Correspondence to:
 Petros Dardas, MD, St. Lukas Hospital,
 Thessaloniki, Greece; E-mail:
pdardas@otenet.gr

Manuscript received March 7, 2012;
 Accepted after revision March 24, 2012

ABSTRACT

Adjunctive percutaneous coronary intervention (PCI) performed between 2 and 24 hours after thrombolysis administered to a patient with an ST elevation myocardial infarction (STEMI) appears beneficial and safe. The rationale for routinely following fibrinolysis with PCI is that many patients have a persistent reduction in flow in the infarct-related artery; although fibrinolysis restores patency (TIMI grade 2 or 3) in 80% of infarct-related arteries, normalization of blood flow (TIMI grade 3) is seen in only 50 to 60% of arteries. Adjunctive PCI has been directly compared to a strategy of fibrinolysis and standard care (either PCI for a clinical indication or routine late PCI) in the TRANSFER AMI, GRACIA-1, NORDISTEMI, CARESS-in-AMI, and SIAM III trials, and found to have better outcomes. Based on these results, the 2010 European Society of Cardiology (ESC) guidelines recommend routine urgent PCI after successful fibrinolysis within 24 hours (class I recommendation, level of evidence A).

ADJUNCTIVE PCI IN ACUTE MYOCARDIAL INFARCTION

In contrast to the adverse effects seen with *facilitated* percutaneous coronary intervention (PCI) in the ASSENT-4 study, when catheterization was performed usually within 2 hours of fibrinolysis in patients with acute myocardial infarction, *adjunctive* PCI performed between 2 and 24 hours appears beneficial and safe. The rationale for following fibrinolysis with PCI is that many patients have a persistent reduction in flow in the infarct-related artery. Although fibrinolysis restores patency (TIMI grade 2 or 3) in 80% of infarct-related arteries, normalization of blood flow (TIMI grade 3) is seen in only 50 to 60% of arteries. As mentioned above, the clinical benefits of fibrinolytic therapy are seen only with the restoration of normal flow.^{1,2}

Evidence suggesting that the routine use of PCI after fibrinolysis is equivalent to PCI comes from the GRACIA-2 trial and the FAST-MI registry:

- **In the GRACIA-2** non-inferiority trial, patients were randomly assigned to full dose tenecteplase followed by stenting within 3 to 12 (mean of 4.6) hours of randomization or to primary stenting within 3 hours of randomization.³ Compared to primary PCI alone, the early routine post-fibrinolysis PCI group had a significantly higher frequency of complete epicardial and myocardial reperfusion (21% versus 6%), which was defined as TIMI 3 epicardial flow, TIMI 3 myocardial perfusion, and resolution of the initial sum of ST-segment elevation $\geq 70\%$. Both groups were

similar in terms of the extent of left ventricular myocardial damage (area under the CK and troponin curves and left ventricular ejection fraction at 6 weeks) and in terms of the 6-month composite incidence of death, reinfarction, stroke, or revascularization.

- **In the FAST-MI registry** of 1714 real-world ST-elevation myocardial infarction (STEMI) patients treated with primary PCI, fibrinolysis followed by PCI, or no reperfusion, there was no significant difference with regard to in-hospital (4.3% versus 5%) or one year mortality (6% versus 8%) between the two reperfusion groups.⁴

Adjunctive PCI has been directly compared to a strategy of fibrinolysis and standard care (either PCI for a clinical indication or routine late PCI) in the TRANSFER AMI, GRACIA-1, NORDISTEMI, CARESS-in-AMI, and SIAM III trials.⁵⁻⁹ Although each trial had a different study design, and therefore addressed slightly different patient populations, a strategy of adjunctive PCI (between 2 and 6 hours after fibrinolysis) had better outcomes than a strategy of standard care. The first three of these trials represent the best available evidence.

TRANSFER AMI trial – In the TRANSFER AMI trial, 1059 high-risk STEMI patients, who presented to a non-PCI hospital and were treated with fibrinolytic therapy (tenecteplase) within 2 hours of the onset of chest pain, were randomly assigned to either urgent transfer for cardiac catheterization (PCI within 6 hours) or to standard care.⁵ High risk was defined as ST-segment elevation ≥ 2 mm in two anterior leads or ST-segment elevation ≥ 1 mm in two inferior leads plus at least one of the following: systolic blood pressure of < 100 mmHg, heart rate > 100 beats/min, Killip class II or III, ST-segment depression ≥ 2 mm in the anterior leads, or ST-segment elevation ≥ 1 mm in right-sided lead V4 (V4R). Standard care was defined as transfer for rescue and/or urgent PCI or for routine catheterization after 24 hours.

The mean time to catheterization after fibrinolysis was 3 hours in the urgent transfer group and 33 hours in the standard care group. At 30 days, the primary composite end-point (death, reinfarction, heart failure, severe recurrent ischemia or shock) occurred significantly less often in the urgent transfer group (11% versus 17.2%; odds ratio-OR 0.64, 95% confidence intervals-CI 0.47-0.87). Most of the benefit was attributable to a reduction in reinfarction or recurrent ischemia. The bleeding rates were similar in the two groups.

NORDISTEMI trial – In the NORDISTEMI trial, 266 low to high risk patients with STEMI, with expected transfer delays of more than 90 minutes, were treated with fibrinolytic therapy and then randomly assigned to a strategy of either immediate transfer for angiography/possible PCI or ischemia-guided treatment in local hospitals.⁹ In the invasive and conservative groups, PCI was performed in 89% and 71% and at a median time of 163 minutes and 3 days respectively.

The primary end point of death, reinfarction, stroke, or new ischemia at one year did not differ between the invasive

and conservative groups (20.9% versus 27.3%, hazard ratio [HR] 0.72; 95% CI 0.44-1.18 respectively). However, the secondary end point of death, reinfarction, or stroke at one year was significantly lower in the invasive arm (6% versus 15.9%, HR 0.36; 95% CI 0.16-0.81).

GRACIA-1 trial – In the GRACIA-1 trial, 500 patients with an acute STEMI were treated with full dose fibrinolytic therapy and then randomly assigned to either angiography and PCI if indicated or ischemia-driven cardiac catheterization in less than 24 hours (mean 17 hours) followed by PCI with stenting or coronary artery bypass grafting (CABG), if appropriate.⁶ The primary end-point was death, myocardial infarction, or ischemia-driven revascularization.

At one year, interventional therapy was associated with a significant reduction in the incidence of the primary end-point (23% versus 51%) and a trend toward a reduction in the incidence of death or myocardial infarction (17% versus 29%). Interventional therapy was also associated with significantly shorter hospitalization (7 versus 11 days) and no increase in bleeding.

**ADJUNCTIVE OR EARLY ELECTIVE PCI
– MAJOR SOCIETY GUIDELINES**

Major society guidelines have come to varying conclusions about the value of angiography followed, if the anatomy is suitable, by adjunctive or early elective PCI:

The 2005 ESC guidelines concluded that the evidence supported routine coronary angiography after successful fibrinolysis.¹⁰

The 2007 ACC/AHA focused update on STEMI and the 2007 ACC/AHA/SCAI focused update for PCI came to the following conclusions:

- Coronary angiography and, if appropriate, PCI after fibrinolysis was recommended in patients with recurrent myocardial infarction, moderate to severe spontaneous or provokable ischemia during recovery, or cardiogenic shock or hemodynamic instability.¹¹⁻¹³
- PCI was thought reasonable in patients with a left ventricular ejection fraction $\leq 40\%$, serious ventricular arrhythmias, or clinical heart failure during the acute episode even though subsequent evaluation shows a left ventricular ejection fraction $> 40\%$.¹¹⁻¹³
- PCI of a hemodynamically significant stenosis in a patient infarct artery greater than 24 hours after STEMI was thought reasonable.
- PCI of a totally occluded artery greater than 24 hours after STEMI in patients who had one or two vessel disease, were hemodynamically and electrically stable, and had no evidence of severe ischemia was not recommended.

The 2009 ACC/AHA focused update on STEMI gave a weak recommendation for the transfer of high risk patients who

received fibrinolytic therapy from hospitals not capable of PCI as part of a pharmacoinvasive strategy.¹² They also considered it reasonable to use the same approach for low-risk patients.

According to the 2010 ESC guidelines, routine urgent PCI is indicated after successful fibrinolysis (resolved chest pain/discomfort and ST-segment elevation) within 24 hours (class I recommendation, level of evidence A). In the case of successful fibrinolysis, patients are referred within 24 hours for angiography and revascularization as required.^{14,15}

We generally agree with the ESC guidelines, which support routine coronary angiography after fibrinolysis in most patients, even in the absence of ischemia at rest or after stress, arrhythmias, left ventricular dysfunction, or heart failure.¹⁰ Patients with important co-morbidities or a strong preference to not undergo coronary angiography may be candidates for medical therapy.

SUMMARY AND RECOMMENDATIONS

In stable STEMI patients who have received fibrinolysis, the following recommendations exist:

- Due to the possibility of reocclusion after apparently successful fibrinolysis, immediate transfer of all patients who have received fibrinolytic therapy (including those who appear to be at low risk), either in a non-PCI hospital or in an ambulance, to a PCI capable hospital is recommended.
- It is NOT recommended to perform planned PCI within the first two hours. This is known as facilitated PCI, and is associated with worse outcomes.
- For patients with high-risk features, including but not limited to anterior myocardial infarction, Killip class ≥ 2 , inferior infarction with evidence of right ventricular involvement, systolic blood pressure of < 100 mmHg, heart rate > 100 beats/min, immediate (any time after 2 hours) diagnostic angiography and PCI if needed, as opposed to a strategy of PCI only for an indication such as clinical instability or inducible ischemia is recommended.
- For patients **not at high risk**, routine coronary angiography and PCI if indicated as opposed to a strategy of coronary angiography (with PCI if indicated) only for an indication such as clinical instability or inducible ischemia is recommended. Although the optimal timing of routine angiography and possible PCI for such patients has not been determined, it should be performed within 6 to 24 hours. However, catheterization for indication only is a reasonable strategy for patients at low risk who have a preference to not undergo routine coronary angiography.

REFERENCES

1. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investi-

gators. *N Engl J Med* 1993; 329:673-682.

2. Ross AM, Coyne KS, Moreyra E, et al. Extended mortality benefit of early postinfarction reperfusion. GUSTO-I Angiographic Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. *Circulation* 1998;97:1549-1556.
3. Fernández-Avilés F, Alonso JJ, Peña G, et al, GRACIA-2 (Grupo de Análisis de Cardiopatía Isquémica Aguda) Investigators. Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial. *Eur Heart J* 2007;28:949-960.
4. Danchin N, Coste P, Ferrières J, et al, FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the french registry on acute ST-elevation myocardial infarction (FAST-MI). *Circulation* 2008;118:268-276.
5. Cantor WJ, Fitchett D, Borgundvaag B, et al, TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009;360:2705-2718.
6. Fernández-Avilés F, Alonso JJ, Castro-Beiras A, et al, GRACIA (Grupo de Análisis de la Cardiopatía Isquémica Aguda) Group. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004;364(9439):1045-1053.
7. Di Mario C, Dudek D, Piscione F, et al, CARESS-in-AMI (Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction) Investigators. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 2008;371(9612):559-568.
8. Scheller B, Hennen B, Hammer B, et al, SIAM III Study Group. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 2003;42:634-641.
9. Böhmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). *J Am Coll Cardiol* 2010; 55:102-110.
10. Silber S, Albertsson P, Avilés FF, et al, Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;26:804-847.
11. Antman, EM, Hand, M, Armstrong, PW, et al. 2007 focused update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report

ROUTINE PCI AFTER THROMBOLYSIS

- of the ACC/AHA Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2008; 51:210-247.
12. Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the ACC Foundation/AHA Task Force on Practice Guidelines. *J Am Coll Cardiol* 2009;54:2205-2241.
 13. Writing Committee Members, Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the ACC Foundation/AHA Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011;124:e574-651. Epub 2011 Nov 7.
 14. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. *Eur Heart J* 2010; 31: 2501–2555.
 15. Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009;360:2705–2718.