Strategies to Facilitate Primary Percutaneous Revascularization in Acute Myocardial Infarction

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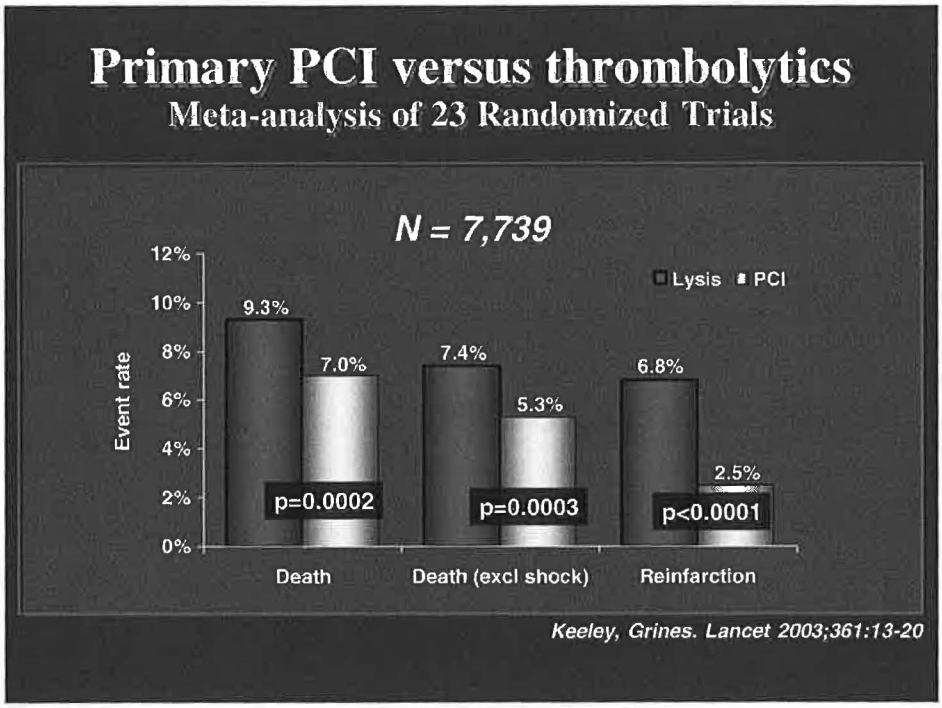
Disclosure: This presentation includes off label discussions on the use coronary revascularization and medical management of acute myocardial infarction.

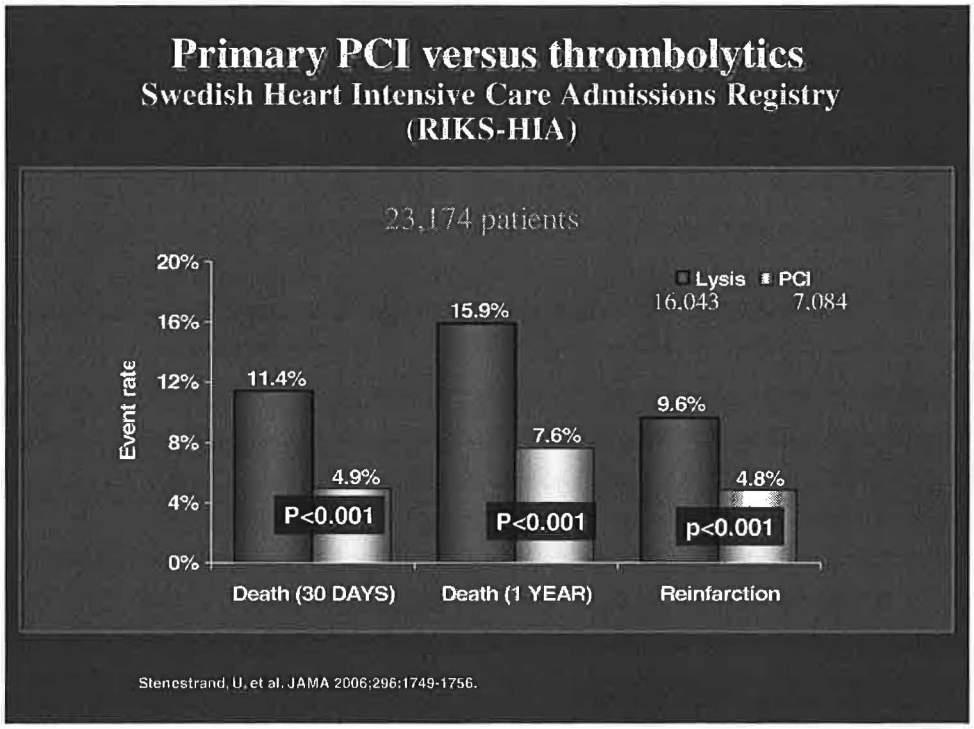
Introduction

Complete or near complete acute thrombosis of a major epicardial coronary artery manifesting by ST segment elevation myocardial infarction (STEMI) continues to account for nearly half of the 1.2 million cases of significant myocardial infarction in the United States each year (1). Reperfusion therapy by prompt administration of thrombolytic agents was established 2 decades ago, proved life saving and has remained the mainstay of therapy worldwide (2). Its use however has never been ideal due to the risk of severe hemorrhage and a loss of efficacy at reestablishing vessel patency as time elapses. It is estimated that <30% of patients with STEMI will ever be offered thrombolytics due to concerns about bleeding risk and the uncertainty about the risk to benefit ratio particularly when presentation is delayed or symptoms appear mild (3). Moreover among patients presenting within 12 hours of symptom onset and receiving thrombolytics appropriately, 25% do not clinically improve or achieve effective reperfusion (4). A major hemorrhagic complication occurs in 5-7%, and another 5% suffer recurrent thrombosis and infarction (7). Both hemorrhage and recurrent thrombosis are major predictors of mortality (5, 6).



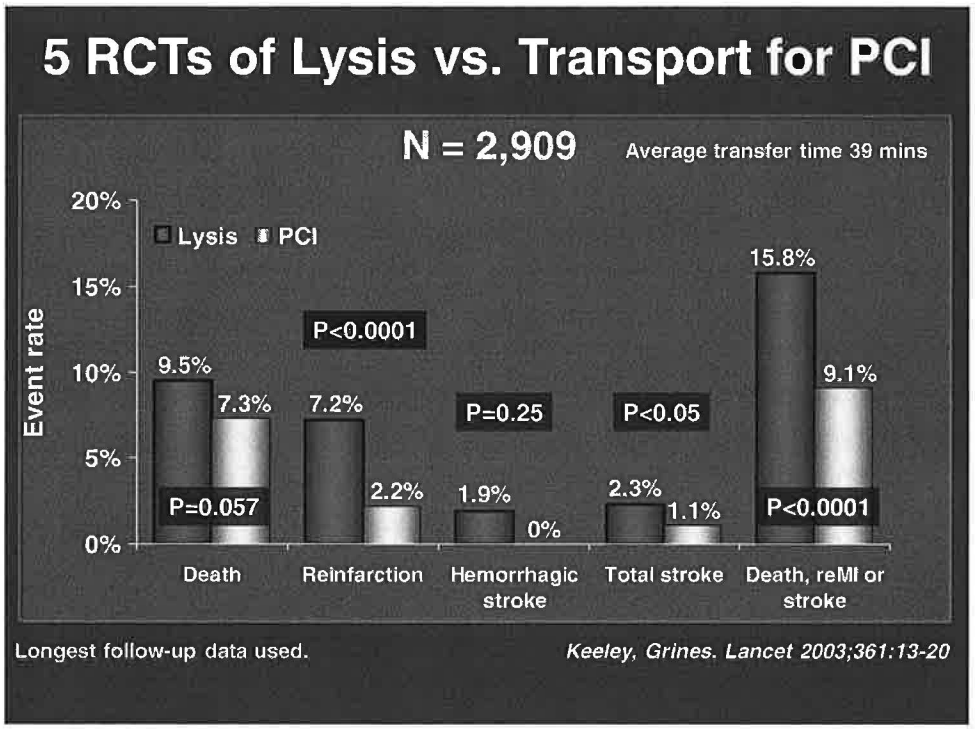
Primary percutaneous coronary intervention (PCI) defined as immediate coronary angiography and direct mechanical reperfusion of the infarct artery with angioplasty soon developed after limitations of thrombolytics were realized. It is now considered a much more effective method of reperfusion by its ability to establish reperfusion in >95% of patients compared with 75% after thrombolytics (7, 8). Normal coronary flow (TIMI 3

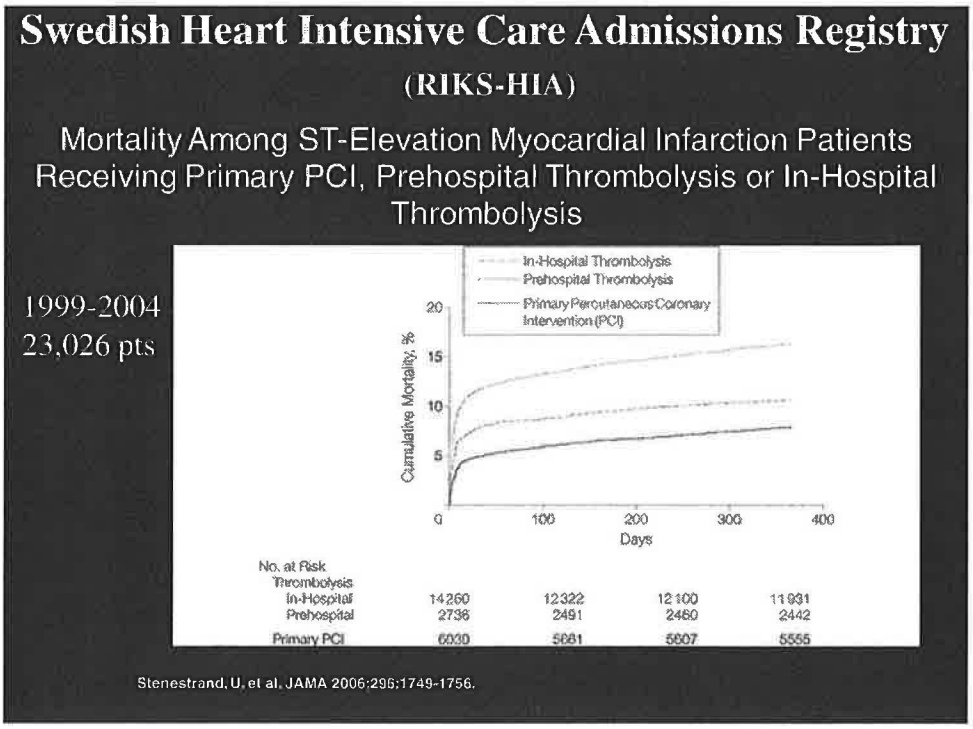
flow) as well as resolution of ST elevation, indicators of effective reperfusion and optimal prognosis, is achieved in 90% of patients with primary PCI compared to 65% of patients receiving thrombolytics (7, 8). The advantages of primary PCI have now been confirmed in multiple clinical trials and meta-analyses comparing rapid primary PCI to thrombolytics over the course of 10 years. In a detailed analysis involving 7739 patients, Keeley and colleagues showed significant reductions in mortality, recurrent infarction, stroke, and bleeding complications (9). Mortality in patients without shock was reduced from 7% to 5% and the results persisted at 1 year. These findings have been widely embraced by clinicians and hospitals, are endorsed by professional scientific societies, and are now included in ACC/AHA guideline recommendations (10). The use of primary PCI for reperfusion has risen rapidly in the US and worldwide and for the first time more patients in the US, more patients may receive primary PCI as reperfusion for acute myocardial infarction. Significant challenges however have emerged in how to deliver this therapy which is labor intensive, resource intensive and associated with inherent delay. It has been suggested that in the real world the challenges of offering primary PCI to most patients may be too great as most US hospitals are not capable of primary PCI (11, 12). This article re-examines the data supporting primary PCI, the effects of delay for primary PCI, strategies to expand and expedite primary PCI, and medical interventions that may facilitate the success of primary PCI.



Timing of reperfusion and outcomes with primary PCI versus thrombolytics

The efficacy of thrombolytic therapy is without doubt time dependent with the largest mortality benefits seen during the first 1-2 hours after symptom onset and essentially no further benefit seen beyond 12 hours (2). The latter has been confirmed in clinical trials and correlated with decreasing effectiveness at restoring vessel patency as thrombotic burden becomes large and organized, and microvascular damage and tissue edema ensues which impairs further blood transit through the infarcted myocardium (13, 14). Primary angioplasty on the other hand is effective in reestablishing coronary flow well beyond 12 hours and effectiveness continues to exceed 90% even at 24 hours. Whether presenting very early (<2hrs) or within the more common time frame of 2-12 hours, primary PCI is more successful at myocardial salvage and clinical outcomes are superior when compared to thrombolytics (15, 16,17). While a steep drop off in number of lives saves is seen for thrombolytics after the first 3 hours, such gradient has not seen with primary PCI (18). For patients arriving after 3 hours of symptoms, primary PCI is therefore highly recommended over thrombolytics when it can be offered. In fact a clinical trial of late primary PCI (12-48 hours beyond symptom onset) improved myocardial salvage and clinical outcomes over conservative care, a group that has consistently shown no response to thrombolytics. In this study infarct size and recurrent infarction were significantly reduced (19). Therefore among patients who are poor candidates for thrombolytics due to very late presentation, late primary PCI is appearing to be a preferred strategy. Some have argued that if the patient presents to a facility without primary PCI, thrombolytics should be administered due to safety and logistical concerns about transferring such patients. However multiple studies now confirm that if the patient can be transferred rapidly to a PCI capable facility, outcomes are better. In a separate meta-analysis of randomized trials, involving 2909 patients, recurrent infarction, stroke and mortality were reduced in the group transferred for primary PCI (9). Finally others have argued that if thrombolytics can be given prior to hospital arrival, it should be advocated because of its effectiveness when given very early against the obligatory delay in delivering primary PCI. However, even in this cohort of patients, bleeding, stroke and reinfarction has been reduced with primary PCI and a strong trend toward lower mortality was seen (20). In the Swedish RIKS-HIA registry involving 26,205 pts with STEMI, primary PCI was superior to pre-hospital or in-hospital thrombolysis and the advantage of primary PCI was seen at all reperfusion time frames from <60 min to several hours (17). Moreover the mortality with thrombolytic reperfusion at 2 hours only barely exceeded primary PCI at the 6^{th} -7^{th} hour. Investigators have also tested whether primary PCI would remain advantageous in less busy or non-PCI hospitals. The available data continues to support superiority of this strategy over thrombolytics (21, 22).





Rapid primary PCI: The importance of Door-to-Balloon (D2B) time

Despite the apparent benefits of primary PCI in most settings, delay in administration of this intervention has a clinical impact (18, 23-26). Those patients arriving early continue to experience better outcomes compared to those arriving hours after the onset of

symptoms, and mortality rises as door-to-balloon (D2B) interval increases, a reflection of the time elapsed from hospital arrival to reperfusion in the cardiac catheterization laboratory (CCL). In the cohort of 29,222 pts from the National Registry of Myocardial Infarction, mortality was 3.0%, 4.2%, 5.7%, and 7.4%, for door-to-balloon intervals of <90 min, 90-120 min, 120-150 min, and >150 min (26). This finding appears most important in the high risk patients (elderly, anterior infarcts) as well as those presenting early (26, 27). While some of the clinical characteristics accounting for longer door-to-balloon times may be independently associated with increased mortality, the association of increasing mortality remained after adjusting for these risk factors. At present only 40% of patients in the US achieve a D2B time of <90 min and <75% are treated within 120 min. In STEMI patients that require inter hospital transfer to a PCI center, <5% achieve a D2B time of < 90 min (28, 29). Factors associated with longer D2B times include older age, atypical symptoms, inconclusive ECG, complex history, female sex, non-white race, less experience with primary PCI, presentation after hours, and the need for transfer (30, 31). Considerable effort is been implemented to ensure the majority of patients are treated within 90 minutes and is now regarded by Joint commission and other accrediting bodies as a key quality initiative. Rapid transfer for PCI and early activation of the CCL has been one of the most important advances in improving door-to-balloon intervals and the best results have been seen in hospitals with emergency departments and cardiac catheterization laboratories committed to rapid primary PCI 24 hours a day and 7 days a week (32, 33).

Characteristics Associated with Poor Door-to-Balloon times

Characteristic	Incremental D2B time, min	P value
No chest pain at presentation	+17.9	0.001
Diabetes	+8.2	0.004
Prior CABG	+17.4	<0.001
Symptom onset > 2 hrs	+13-30	<0.001
Non diagnostic ECG	+8-40	<0.001
Arrival after hours	+13-16	<0.001
Arrival at urban teaching hospital	+23.9	<0.001

Nallamothou et al ,*Circulation*, 2005;111:761-767

The emergency department in expediting primary PCI

Emergency department personnel have become invaluable in improving access to primary PCI. In previous years the decision to proceed to primary PCI was made by an on call cardiologist after reviewing the history and confirming the ECG by visual inspection. Not uncommonly direct patient examination and consultation would often follow before a decision is made to proceed with primary PCI. An interventional cardiologist would then need to be notified and then the rest of the CCL team notified. This created significant delay and D2B times of 90 min were hardly achievable especially after hours. Several improvements have been advocated and tested with good results. First, the diagnosis of STEMI should be made by the emergency department (ED) physician at first contact from a rapid history and ECG assessment. Training in recognizing symptoms of cardiac ischemia and ECG interpretation is therefore essential. Suitability for treatment with primary PCI can be rapidly determined, treatment recommendation made, and then the entire CCL team activated by a single centralized paging system. This activation notifies the laboratory and on call physicians, nurses and technicians and ideally involves a text message briefly describing the patient at hand and location. ED staff can then immediately proceed with completing evaluation and preparing the patient for transport to the CCL rather than waiting to further discuss the case with a cardiologist. Such a sequence can be duplicated outside the ED, such as in the clinic or office setting. Safe but rapid transport should be emphasized and in the clinically stable patient, any time consuming and potentially traumatic procedures should be avoided. Vascular access should be limited to peripheral intravenous lines and urethral catheters avoided. Added benefits are seen when a dedicated group of hospital staff either in the ED or elsewhere respond to the activation and are involved in preparation and transport of the patient and of the CCL to receive the patient. Recently Bradley and et al. reported data from a cross-sectional study of 365 acute care hospitals providing PCI (34, 35). The investigators found 6 core practices associated with reduced D2B times, and included: 1) The ED staff activating the CCL directly; 2) a single central paging system; 3) pre-hospital activation while a patient is in route; 4) CCL team arrival within 20-30 min; 5) immediate availability of a cardiologist; and 6) prompt and real-time feedback between the CCL and ED.

Strategies facilitating primary PCI 365 acute care hospitals

Strategy	D2B time saved (min)	P value
Cath lab and team activated by ED	8.2	0.01
Full activation by a single central page	13.2	<0.01
EMS transmission of pre hospital ECG	23.2	<0.01
Cardiac lab staff expected within 20-30 min	19	<0.01
Feedback provided to all participants	8.6	<0.01

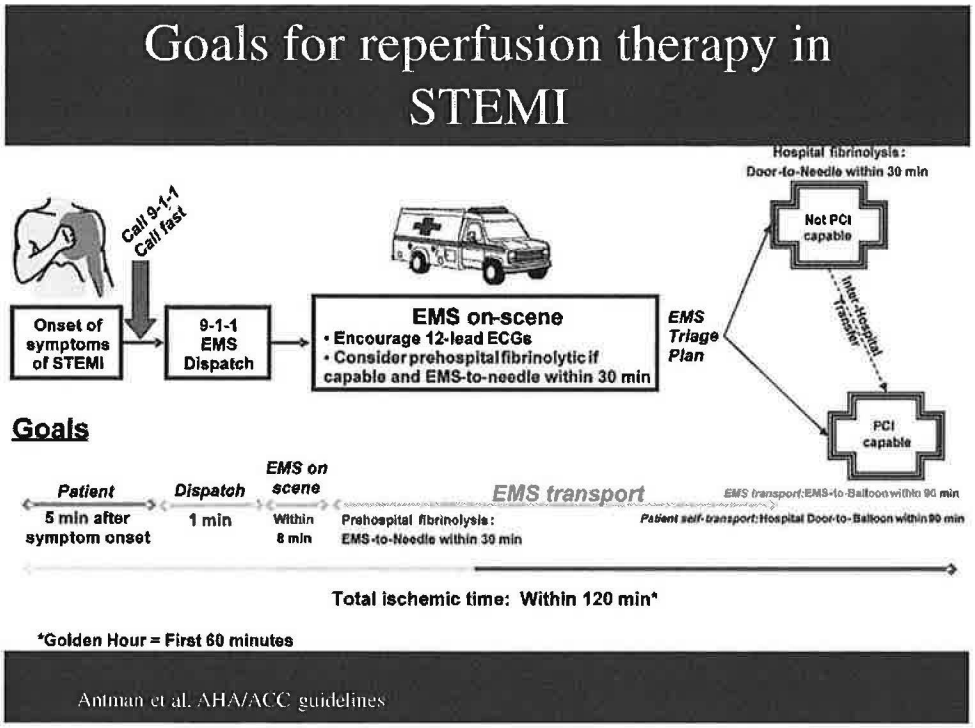
Number of strategies adopted	D2B time (min)
0	110
1	100
2	88
3-4	82

Bradley et al. N Engl J Med 2006;355:2308-2320.

Inter-hospital transfer programs in expanding primary PCI

Transfer for primary angioplasty had long been reserved for patients who had clear contradictions to thrombolytics or who failed initial reperfusion with thrombolytics and remained symptomatic. Transfer was considered risky and too complicated to offer the majority of patients. Moreover available data suggested an acceptable D2B time could not be achieved and the advantage of primary PCI over thrombolytics would be lost. A number of centers have now demonstrated that with well orchestrated protocols in place, patients can be rapidly assessed at an initial presenting hospital and then rapidly transferred to a PCI center for intervention. Successful programs have formed committed relationships with outlying or rural hospitals that would allow receipt of STEMI patients at all times and activate the CCL team ahead of arrival. Transportation may be via ground or air ambulance but must be expeditious in order to accomplish a treatment delay of less than 60 min. Ambulance availability and ability to transmit obtained ECGs therefore important. At the Minneapolis Heart Institute, a region-wide transfer program has been established involving 31 community non-PCI hospitals as far out as 210 miles. For patients transferred from distances <60 miles, the median D2B time is 95 minutes, and 120 minutes for transfers from >60 miles (36). Physicians and investigators at the Mayo Clinic and St. Mary's hospital have established a similar transfer program involving 28 hospitals up to 150 miles away. Patients with STEMI and symptoms for > 3 hours are routinely transferred. In their recent analysis of 105 consecutive transfer patients, the median D2B time was 105 min with 12% achieving D2B

time of <90 minutes (37). Finally, in North Carolina, a state-wide program involving 10 PCI centers and 55 non PCI centers also have reported a highly successful program (39). Following interventions such as state-wide educational campaigns, early CCL activation, and improved transport systems, D2B time for transferred patients fell from 165 min to 128 min, and 13% of such patients achieve D2B times < 90 min compared to 4 % previously.



Emergency medical services in expediting primary PCI

Another significant advancement gaining support is to allow ambulance personal perform, interpret and relay results of an ECG prior to hospital arrival in patients with suspected STEMI. This may allow direct transfer of the patient to a hospital capable of performing primary PCI bypassing nearer hospitals without that capability. Moreover the cardiac catheterization laboratory team may be activated even while on route substantially reducing the D2B time. This is particularly important after hours where it may take 20-30 min for CCL personnel to arrive the hospital and another 20-30 minutes to prepare to receive the patient. For patients in remote locations where the ambulance transport time may require 45 min to 1 hour such a strategy may reduce overall time to reperfusion. In a city-wide program (40), Le May and colleagues out of Ontario Canada successfully trained paramedics in ECG interpretation and allowed them to transport patients directly to a PCI facility based on their impression. STEMI was confirmed in >90% of cases and compared to patients who were transported to the

administered with thrombolytics, then primary PCI may be performed after some delay. This is particularly important when primary PCI cannot be performed upfront because of delay exceeding one hour or the lack of vascular access. This was recently studied in the Transfer AMI Trial where following thrombolytics at non PCI hospitals, patient were administered clopidogrel and then randomized to routine PCI or standard care. Outcomes, particularly recurrent ischemia and infarction were significantly improved (47). Finally for patients with failed thrombolytics manifesting by persistent, early recurrent ischemia or cardiogenic shock, rescue PCI is beneficial and highly recommended regardless of time after thrombolytic administration (48).

Antiplatelet and antithrombin agents

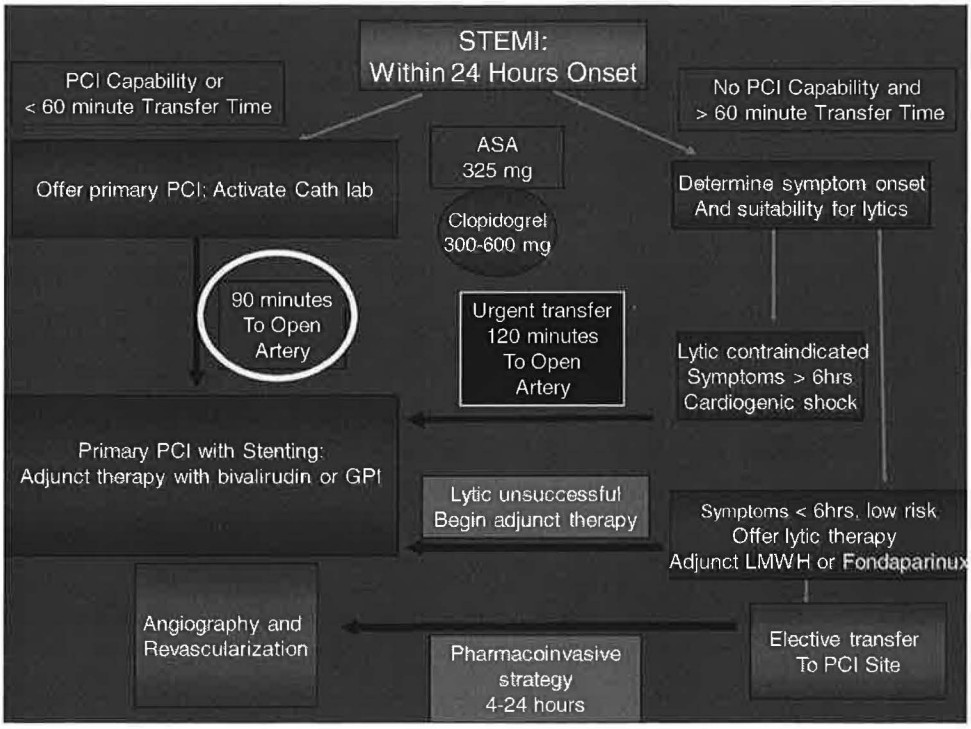
Glycoprotein (GP) IIb/IIIa antagonists are potent intravenous platelet inhibitors and block fibrinogen related cross-linking of individual platelets, the final step in platelet aggregation. Their antithrombotic effects are sufficient to establish vessel patency in up 20% of patients and reduce thrombus burden ahead of primary PCI. Several studies have now confirmed reduced risk of recurrent infarction and improved acute angiographic outcomes. In a meta-analysis of such studies, de Luca has shown that compared to placebo, severe recurrent infarction is reduced from 1.9% to 1% and mortality from 3.4% to 2.4% (49). The data therefore support GPIIb/IIIa inhibitors over placebo as adjunct in primary PCI.

Thienopyridines have been studied extensively in acute myocardial infarction managed with thrombolytics and have been associated with an improvement in clinical outcomes including total mortality (50, 51). Since their use is indicated following PCI, it is reasonable to initiate therapy ahead of primary PCI. A clopidogrel dose of 600mg is needed to achieve adequate platelet inhibition in this setting although the level of inhibition remains significantly less compared with GPIIb/IIIa inhibitors. Nevertheless at this level, the addition of GP IIb/IIIa to a background of 600mg clopidogrel did not offer any additional clinical benefit in a recent study. Clopidogrel can therefore be used to obviate the need for GPIIb/IIIa inhibitors if bleeding risk is a significant concern (52). A new oral thienopyridine, prasugrel is in investigation and achieves better levels of platelet inhibition and at a faster rate compared to clopidogrel (53).

Unfractionated heparin remains the most commonly used antithrombin however it is ineffective at promoting recanalization of the infarct vessel ahead of primary PCI. The direct thrombin inhibitor bivalirudin has recently been compared against heparin and GPIIb/IIIa inhibitors in STEMI and outcomes appear better, primarily due to a reduction in bleeding complications (54). Bivalirudin therefore appears to be an attractive alternative to GPIIb/IIIa inhibitors particularly in patients at risk for bleeding.

Conclusions

Primary PCI when it can be offered is superior to thrombolytic therapy for reperfusion in STEMI. While the best outcomes are seen when primary PCI can be delivered rapidly, outcomes remain better than thrombolytic therapy even when transfer to a different facility is required or reperfusion would be delayed by as long as an hour. Systems of care that empower the ED and EMS in decision making, and transfer programs between PCI and non PCI hospitals can be easily implemented to increase the availability and rapidity of primary PCI to more patients (55-58). Even when thrombolytic therapy is administered, a strategy of delayed PCI appears beneficial for most patients. Antiplatelet agents and direct thrombin inhibitors such as bivalirudin enhance the outcomes of primary PCI and can be initiated ahead of intervention.



References

1. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897-902.
2. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311-322.
3. Grzybowski M, Clements EA, Parsons L, et al. Mortality benefit of immediate revascularization of acute ST-segment elevation myocardial infarction in patients with contraindications to thrombolytic therapy: a propensity analysis. JAMA 2003;290:1891-1898.
4. Lincoff AM, Topol EJ. Illusion of reperfusion: does anyone achieve optimal reperfusion during acute myocardial infarction? Circulation 1993;88:1361-1374.
5. Gibson CM, Karha J, Murphy SA, et al. Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the Thrombolysis in Myocardial Infarction trials. J Am Coll Cardiol 2003;42:7-16.
6. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. *J Am Coll Cardiol.* 2007; 49: 1362–1368.
7. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-1622.
8. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957-966.
9. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
10. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused update of the ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:210-247.
11. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation 2006;114:2019-2025
12. McNamara RL, Herrin J, Bradley EH, et al. Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. J Am Coll Cardiol 2006;47:45-51
13. EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de Américas del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet.* 1993;342:767-772.
14. The LATE Investigators. Assessment of thrombolytic efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet.* 1993;342:759-766.

15. Andersen HR, Nielsen TT, Rasmussen K, ET AL. DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med.* 2003; 349: 733–742.
16. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J 2006;27:779-788.
17. Stenestrand U, Lindbäck J, Wallentin L. Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. JAMA 2006;296:1749-1756.
18. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941-2947.
19. Schomig A, Mehilli J, Antoniucci D, et al. Beyond 12 Hours Reperfusion AlternatiVe Evaluation (BRAVE-2) Trial Investigators. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. *JAMA.* 2005; 293: 2865–2872.
20. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet 2002;360:825-829.
21. Aversano T, Aversano LT, Passamani E, et al. Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. JAMA 2002;287:1943-1951.
22. Wharton TP, Grines LL, Turco MA, et al. Primary angioplasty in acute myocardial infarction at hospitals with no surgery on-site (the PAMI-No SOS study) versus transfer to surgical centers for primary angioplasty. J Am Coll Cardiol 2004;43:1943-1950.
23. De Luca G, Suryapranata H, Ottervanger JP, et al. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation.* 2004;109:1223-1225.
24. Brodie BR, Stone GW, Cox DA, et al. Impact of treatment delays on outcomes of primary percutaneous coronary intervention for acute myocardial infarction: analysis from the CADILLAC trial. Am Heart J 2006;151:1231-1238.
25. Berger PB, Ellis SG, Holmes DR Jr, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. Circulation 1999;100:14-20.
26. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006;47:2180-2186.
27. Brodie BR, Hansen C, Stuckey TD, et al. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. *J Am Coll Cardiol.* 2006; 47: 289–295
28. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary

intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. Circulation 2005;111:761-767.
29. McNamara RL, Herrin J, Bradley EH, et al. Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. J Am Coll Cardiol 2006;47:45-51.
30. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation 2006;114:2019-2025.
31. Magid DJ, Wang Y, Herrin J, et al. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. JAMA 2005;294:803-812
32. Canto JG, Every NR, Magid DJ, et al. The volume of primary angioplasty procedures and survival after acute myocardial infarction. N Engl J Med 2000;342:1573-1580.
33. Magid, D. J., Calonge, B. N., Rumsfeld, J. S., et al. Relation Between Hospital Primary Angioplasty Volume and Mortality for Patients With Acute MI Treated With Primary Angioplasty vs Thrombolytic Therapy. *JAMA* 284: 3131-3138
34. Bradley EH, Curry LA, Webster TR, et al. Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. Circulation 2006;113:1079-1085.
35. Nallamothu BK, Bradley EH, Krumholtz HM. Time to treatment in primary percutaneous coronary intervention. N Engl J Med 2007;357:1631-1638.
36. Henry TD, Sharkey SW, Burke MN, et al. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. *Circulation*. 2007; 116: 721–728.
37. Ting HH, Rihal CS, Gersh BJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI protocol. Circulation 2007;116:729-736.
38. Aguire FV et al. Rural Interhospital Transfer of ST-Elevation Myocardial Infarction Patients for Percutaneous Coronary Revascularization. Circulation. 2008;117:1145-1152.)
39. Jollis JG, Roettig ML, Aluko AO, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. JAMA 2007;298:2371-2380.
40. Le May, M. R., So, D. Y., Dionne, R., et al. A Citywide Protocol for Primary PCI in ST-Segment Elevation Myocardial Infarction. *NEJM* 358: 231-240
41. Kalla K, Christ G, Karnik R, et al. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). Circulation 2006;113:2398-2405
42. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med 2006;355:2395-2407.
43. Abbate, A., Biondi-Zoccai, G. G.L., Appleton, D. L., et al. Survival and Cardiac Remodeling Benefits in Patients Undergoing Late Percutaneous Coronary Intervention of the Infarct-Related Artery: Evidence From a Meta-Analysis of Randomized Controlled Trials. *J Am Coll Cardiol* 51: 956-964
44. GW Stone, D Cox and E Garcia *et al.*, Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute

myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials, *Circulation* 104 (2001), pp. 636–641.
45. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet 2006;367:569-578.
46. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. Lancet 2006;367:579-588.
47. Cantor WJ. American College of Cardiology 2008 Scientifc Sessions. Presented March 30, 2008; Chicago, IL.
48. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 2005;353:2758-2768.
49. De Luca, G., Suryapranata, H., Stone, G. W., et al. Abciximab as Adjunctive Therapy to Reperfusion in Acute ST-Segment Elevation Myocardial Infarction: A Meta-analysis of Randomized Trials. *JAMA* 293: 1759-1765.
50. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-1189.
51. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005; 366: 1607–1621.
52. Mehilli J. et al. American College of Cardiology 2008 Scientifc Sessions. Presented March 30, 2008; Chicago, IL.
53. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-2015.
54. Stone GW et al. Horizons AMI. In press. Presented TCT 2007.
55. Canto JG, Zalenski RJ, Ornato JP, et al. Use of emergency medical services in acute myocardial infarction and subsequent quality of care: observations from the National Registry of Myocardial Infarction 2. Circulation 2002;106:3018-3023.
56. Nallamothu BK, Bates ER, Wang Y, Bradley EH, Krumholz HM. Driving times and distances to hospitals with percutaneous coronary intervention in the United States: implications for prehospital triage of patients with ST-elevation myocardial infarction. Circulation 2006;113:1189-1195
57. Granger CB, Henry TD, Bates WER, et al. Development of systems of care for ST-elevation myocardial infarction patients: the primary percutaneous coronary intervention (ST-elevation myocardial infarction-receiving) hospital perspective. *Circulation.* 2007; 116: e55–e59
58. Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. Circulation 2007;116:217-230.