

CME CREDIT **EDUCATIONAL OBJECTIVE:** Readers will champion the establishment of community-wide protocols for emergency treatment of acute ST-segment elevation myocardial infarction

ELIAS B. HANNA, MD

Currently in the Department of Medicine, Cardiovascular Section, Louisiana State University, New Orleans; this article written while in the Department of Medicine, Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City

THOMAS A. HENNEBRY, MD

Department of Medicine, Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City

MAZEN S. ABU-FADEL, MD

Department of Medicine, Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City

Combined reperfusion strategies in ST-segment elevation MI: Rationale and current role

ABSTRACT

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for ST-elevation myocardial infarction (MI), but most patients do not arrive at a PCI facility within the recommended 90 minutes of first medical contact. If delay is expected, timely thrombolysis is recommended, followed by early transfer for PCI. The authors review the rationale behind three combined reperfusion strategies—facilitated PCI, pharmacoinvasive therapy, and rescue PCI—and data on their effectiveness.

KEY POINTS

When the expected door-to-balloon time is less than 90 minutes and the door-to-balloon time minus the door-to-needle time is less than 60 minutes, the preferred approach is PCI not preceded by thrombolysis.

Evidence suggests that routine early (but not immediate) PCI—ie, 2 to 6 hours after thrombolysis—is beneficial, particularly in patients with high-risk ST-elevation MI.

Hospitals and emergency services should participate in community-based and regional systems of care, with standardized protocols to ensure expeditious transfer and prompt reperfusion.

Prehospital thrombolysis followed by early transfer to a PCI facility as part of a community-based system of care may further improve outcomes of patients with very long transfer times.

EFFECTIVE AND RAPID REPERFUSION is crucial in patients with acute ST-segment elevation myocardial infarction (MI). The preferred strategy for reperfusion—when it can be performed in a timely fashion at an experienced facility—is primary percutaneous coronary intervention (PCI), which produces outcomes superior to those of pharmacologic thrombolysis.¹

See related editorial, page 567

Unfortunately, in the United States about half of patients present to hospitals that do not have PCI capability,² and in one analysis, 91% of transferred patients had a door-to-balloon time greater than the recommended 90 minutes, with a mean of 152 minutes.³ (In this case, the door-to-balloon time was the time that elapsed between entry into the first hospital and inflation of the PCI balloon at the second hospital.)

In situations such as these, a combined approach may be appropriate, with thrombolysis delivered by paramedics or at a local facility, followed by transfer to a PCI facility and performance of PCI within a few hours. However, this is feasible only if standardized community-based or regional protocols for prompt transfer and reperfusion are in place.

In this paper we discuss the rationale and the clinical data behind several approaches to combined reperfusion, as well as experiences with community-based care protocols.

doi:10.3949/ccjm.77a.10024

■ WITHIN 3 HOURS OF SYMPTOM ONSET, THROMBOLYSIS IS AS GOOD AS PCI

The PRAGUE-2 trial

In the randomized PRAGUE-2 trial,⁴ patients with ST-elevation MI who presented to a non-PCI facility had better outcomes if they were transferred promptly for PCI (median door-to-balloon time 97 minutes), as opposed to receiving local therapy with streptokinase. However, for patients presenting within 3 hours of symptom onset, the mortality rates were comparable with either strategy.⁴

See the glossary of clinical trial names, page 631

The CAPTIM trial

In the CAPTIM trial,⁵ patients who presented within 2 hours of symptom onset and who were randomized to receive prehospital thrombolysis had outcomes similar to those of patients treated with primary PCI, despite a short door-to-balloon time (82 minutes).

The Vienna STEMI Registry

In the Vienna STEMI Registry,⁶ the mortality rates with primary PCI and with thrombolysis were similar when patients presented within 2 hours of symptom onset. However, as the time from symptom onset increased, primary PCI appeared to offer an increasing survival benefit compared with thrombolysis.

Comments:

Thrombolysis is effective mostly in the first 2 to 3 hours, with some benefit up to 12 hours

Previous studies have shown that the sooner thrombolysis is given after symptom onset, the more effective it is. If it is given within an hour of symptom onset, the relative reduction in the mortality rate is 50% and the absolute reduction is 6.5% compared with no reperfusion therapy. If it is started in the second hour, the absolute reduction in the mortality rate drops to 4%, and a lesser benefit extends to patients presenting up to 12 hours after symptom onset.⁷ This time-dependent benefit is due to the fact that very early reperfusion of the occluded coronary artery may lead to full recovery of ischemic tissue and thus prevent necrosis. In addition, thrombolysis in the first

2 hours is highly efficacious in lysing a fresh thrombus.

These data support the current guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA), which state no preference for either thrombolytic therapy or PCI in ST-elevation MI if the presentation is less than 3 hours after symptom onset.⁸

Of note, in the CAPTIM trial and in the Vienna STEMI Registry, rescue PCI was available and was in fact used after thrombolysis in about 25% of patients, which might have contributed to the benefit of early thrombolysis.

■ PRIMARY PCI MAY NOT BE SUPERIOR IF TRANSFER TIME IS LONG

Another time-related factor to consider is the PCI-related delay, ie, the theoretical difference between the expected time from first medical contact to balloon inflation (if the patient undergoes primary PCI) and the time from first medical contact to the start of thrombolytic therapy (if the patient undergoes primary thrombolysis).

A meta-analysis of 13 trials comparing PCI and thrombolysis showed that a PCI-related delay of more than 60 minutes might negate the potential advantage of primary PCI over immediate thrombolysis in terms of deaths.⁹

This observation has been further refined by data from the National Registry of Myocardial Infarction.¹⁰ In this analysis, patient factors, including age, duration of symptoms, and infarct location, significantly affected the point at which the PCI-related delay negated the survival advantage of primary PCI. The survival advantage of primary PCI was lost more rapidly—with a PCI-related delay as short as 40 minutes—in patients who presented sooner, were younger, or had anterior MI. Primary PCI maintained its survival advantage even with a PCI-related delay longer than 100 minutes in older patients or patients with nonanterior MI presenting more than 3 hours after symptom onset. Given that median door-to-balloon times in the United States may exceed 150 minutes when transfer is involved,³ primary PCI may be no better than primary thrombolysis in transferred patients who present early or who have large infarcts.

**ACC/AHA:
No preference
for either
thrombolytic
therapy or PCI
in ST-elevation
MI presenting
< 3 hours after
symptom onset**

Glossary of clinical trials discussed in this paper

ASSENT-4 PCI—Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention¹⁸

CAPTIM—Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction⁵

CARESS-in-AMI—Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction¹⁶

DANAMI-2—Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction³⁶

FINESSE—Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events¹⁹

PRAGUE-2—Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis⁴

REACT—Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis²⁰

SHOCK—Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock⁴¹

TRANSFER-AMI—Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction¹⁵

Although these results were derived from a post hoc analysis of a registry and the delay times reported were sometimes inaccurate, they suggest that both the PCI-related delay time and patient characteristics should be considered when selecting a reperfusion strategy. Thrombolytic therapy before and in conjunction with primary PCI was considered a potential solution to these concerns.

In addition, while the benefit of any reperfusion strategy depends on the time of presentation, the loss in benefit by later presentation is less pronounced with primary PCI than with thrombolysis, making thrombolysis less attractive in later presentations (> 3 hours).¹¹

Also, while thrombolytic therapy in patients older than 75 years was associated with a lower mortality rate compared with no therapy in a large Swedish registry,¹² this benefit was less striking than in younger patients. A meta-analysis of thrombolysis trials failed to show a similar benefit in patients over age 75 vs younger patients,¹³ whereas primary PCI remained effective and superior to thrombolysis in the elderly, with more absolute reduction in mortality rates in the elderly subgroup than with younger patients.¹⁴ This makes thrombolysis less attractive in the elderly, either as a stand-alone therapy or in conjunction with PCI. Studies of combined thrombolysis and PCI included very few patients over age 75.¹⁵⁻¹⁷

■ THREE COMBINATION REPERFUSION STRATEGIES

Three different combination reperfusion strategies for ST-elevation MI have been studied (FIGURE 1)^{15,16,18-20}:

Facilitated PCI is a strategy of thrombolysis immediately followed by PCI, with a planned door-to-balloon time of 90 to 120 minutes.

Pharmacoinvasive therapy means giving thrombolysis at a non-PCI facility and then promptly and systematically transferring the patient to a PCI facility, where PCI is performed 2 to 24 hours after the start of thrombolytic therapy, regardless of whether thrombolysis results in successful reperfusion.¹⁵ Thus, the time to PCI is longer than with facilitated PCI. Facilitated PCI addresses the value of pretreatment with thrombolytics or glycoprotein IIb/IIIa inhibitors in patients otherwise eligible for primary PCI, whereas pharmacoinvasive therapy addresses the value of routine early PCI after thrombolysis in patients who are not eligible for primary PCI.¹⁶

Rescue PCI refers to PCI that is performed urgently if thrombolysis fails, failure being defined as persistent hemodynamic or electrical instability, persistent ischemic symptoms, or failure to achieve at least a 50% to 70% resolution of the maximal ST-segment elevation 90 minutes after the infusion is started.

A PCI-related delay > 60 minutes may negate the potential advantage of primary PCI over immediate thrombolysis

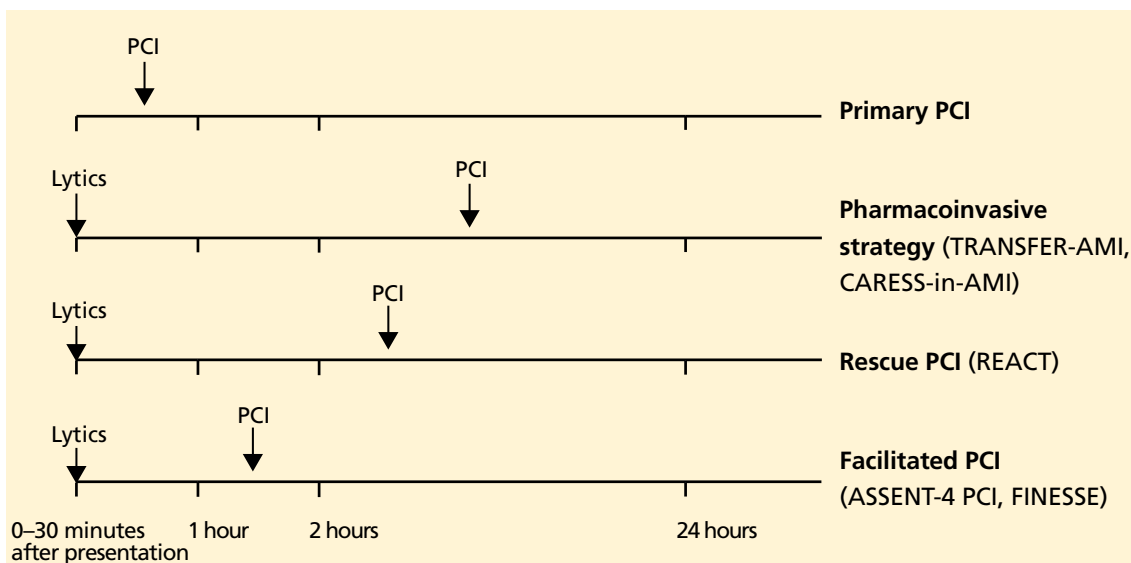


FIGURE 1. The timing of percutaneous coronary intervention (PCI) in relation to thrombolysis in the pharmacoinvasive strategy, rescue PCI strategy, and facilitated PCI strategy, with the respective clinical trials that addressed and defined these strategies. (See the glossary on page 631 for complete names of studies.)

Thrombolysis is a less attractive option in the elderly, either as stand-alone therapy or in conjunction with PCI

FACILITATED PCI: NEGATIVE RESULTS IN CLINICAL TRIALS

ASSENT-4 PCI trial

In the ASSENT-4 PCI trial,¹⁸ patients receiving full thrombolytic therapy before PCI had a higher rate of in-hospital death, bleeding, and cardiovascular events at 90 days than patients treated with primary PCI.

This trial recruited patients arriving at hospitals with or without PCI capability. The door-to-balloon time was about 110 minutes in both groups, which might not have been prolonged enough to show a benefit from a timely addition of thrombolysis. In addition, antiplatelet therapy was limited in these patients: glycoprotein IIb/IIIa inhibitors were not given, and clopidogrel (Plavix) was not appropriately preloaded, and this might have offset the potential benefit of early PCI. In fact, data suggest that platelet activation and aggregation are heightened after thrombolysis,²¹⁻²³ and that glycoprotein IIb/IIIa antagonists can inhibit these effects.²³

The FINESSE trial

In the FINESSE trial,¹⁹ patients were randomized to undergo primary PCI, to undergo PCI

facilitated (ie, preceded) by abciximab (ReoPro), or to undergo PCI facilitated by half-dose reteplase (Retavase) and full-dose abciximab. Despite a median door-to-balloon time of 132 minutes, the three strategies were associated with similar rates of death, heart failure, or ischemic outcome at 90 days. Even though the dosage of heparin was weight-adjusted, more major bleeding events occurred with the facilitated strategies.

Comments: Some subgroups may still benefit from facilitated PCI

The results of ASSENT-4 PCI and FINESSE led to the conclusion that PCI facilitated by full-dose thrombolysis should be avoided, and called into question the value of PCI facilitation using glycoprotein IIb/IIIa inhibitors with or without half-dose thrombolytic therapy.

However, subgroup analyses of these trials identified some subgroups that may benefit from a facilitated strategy. In ASSENT-4 PCI, 45% of patients were enrolled at PCI hospitals with a minimal PCI-related delay time. These patients had the worst outcome with the facilitated strategy. In contrast, patients who had a short time from pain onset to thrombolysis (2 to 3 hours) and who were given prehos-

pital thrombolysis had a trend toward better outcomes with facilitated PCI.²⁴ And in FINESSE, 60% of patients were enrolled at centers with PCI capability. Analysis of a small subgroup of patients with a Thrombolysis in Myocardial Infarction study (TIMI) risk score of 3 or greater presenting to non-PCI hospitals within 4 hours of symptom onset suggested a potential reduction of ischemic events with the facilitated strategy in these patients.²⁵

Thus, for patients seen in the first 2 to 3 hours after symptom onset, immediate thrombolysis is recommended if PCI will likely be delayed, with or without plans for subsequent early PCI. “Time is muscle,” especially during the first 3 hours.

■ PHARMACOINVASIVE STRATEGY: GOOD RESULTS IN HIGH-RISK PATIENTS

A number of randomized studies during the last 10 years have examined the value of a pharmacoinvasive strategy (TABLE 1).^{15,16,26–29}

The TRANSFER-AMI trial

The TRANSFER-AMI trial¹⁵ randomized 1,059 patients with high-risk ST-elevation MI (ie, anterior or high-risk inferior) at non-PCI centers to undergo either pharmacoinvasive care, ie, full-dose tenecteplase (TNKase) with immediate transfer for PCI or standard care, ie, tenecteplase with transfer for rescue PCI if the patient had persistent ST-segment elevation, chest pain, or hemodynamic instability.¹⁵ The goal was to perform PCI within 6 hours of thrombolysis, and the median time to PCI was 3.9 hours (range 2–6 hours). In the standard-care group, 35% of patients needed to be transferred for rescue PCI. Unlike in the ASSENT-4 trial, over 80% of patients received aggressive antiplatelet therapy with both 300 mg of clopidogrel and glycoprotein IIb/IIIa inhibitors.

The rate of cardiovascular events at 30 days was significantly lower with pharmacoinvasive therapy than with standard care and rescue PCI (11% vs 17%, $P = .004$). This difference was driven by lower rates of recurrent ischemia, reinfarction, and heart failure.

The CARESS-in-AMI study

The CARESS-in-AMI study¹⁶ found a similar improvement in ischemic outcomes in 600 pa-

tients with high-risk ST-elevation MI arriving at non-PCI centers if they had received pharmacoinvasive therapy. Patients received half-dose reteplase and abciximab and were randomized either to be immediately transferred for PCI (median time to PCI 2.25 hours) or to be transferred only if they had persistent ST-segment elevation or clinical deterioration.¹⁶ The event rate was low with pharmacoinvasive therapy, comparable to that achieved in primary PCI trials.

Interestingly, no significant increase was seen in the risk of major and minor bleeding in these two trials despite the use of a femoral approach for PCI in over 80% of the cases; this is probably due to the delays between thrombolytic administration and PCI and to the use of a highly fibrin-specific thrombolytic agent and adjusted-dose heparin.

Meta-analysis of pharmacoinvasive trials

A meta-analysis²⁹ of studies of systematic early PCI (mainly with stenting) within 24 hours of thrombolysis showed a reduction in the rates of mortality and reinfarction with this strategy, without an increase in the risk of major or intracranial bleeding.³⁰ In contrast to the results of the trials of facilitated PCI, a pharmacoinvasive strategy improved outcomes in these trials because the delay between thrombolysis and PCI was more than 2 hours, ie, long enough to prevent bleeding complications, and because most patients randomized in these trials presented within 2 to 3 hours of symptom onset, when the time to reperfusion is critical. After 3 hours, the PCI-mediated myocardial salvage is less time-dependent. Moreover, trials of pharmacoinvasive strategy used aggressive antiplatelet therapy with clopidogrel and glycoprotein IIb/IIIa inhibitors.

Comment:

Pharmacoinvasive strategy in the guidelines

These results and those of the subgroup analysis from the FINESSE trial suggest that patients with high-risk ST-elevation MI treated at non-PCI hospitals have better outcomes without an increase in major bleeding events when given thrombolysis and then immediately transferred for routine PCI, rather than being transferred only if reperfusion fails.

Hence, the 2009 update of the ACC/AHA

After thrombolysis, 40% of patients do not achieve TIMI grade 3 flow

guidelines³¹ gives a class IIa recommendation for transferring patients with anterior ST-elevation MI or high-risk inferior ST-elevation MI treated with thrombolysis to a PCI-capable facility where PCI is performed as part of a pharmacoinvasive or rescue strategy soon after thrombolysis.

This strategy has been particularly studied in patients younger than 75 years presenting with high-risk types of ST-elevation MI early (< 3 hours) after symptom onset. If not at high risk, the patient may be transferred to a PCI facility after receiving thrombolysis or observed in the initial facility (class IIb recommendation). Consideration should be given to starting anticoagulant and antiplatelet therapy before and during transfer—ie, 300 mg of clopidogrel before transfer for PCI and glycoprotein IIb/IIIa inhibitor therapy during PCI.

The European Society of Cardiology (ESC) guidelines³² recommend early routine angiography 3 to 24 hours after successful thrombolysis. This time window was selected to avoid PCI during the prothrombotic period in the first few hours after thrombolysis and to minimize the risk of reocclusion with PCI delays of more than 24 hours (class IIa recommendation).

Larger randomized trials are still needed to establish whether the pharmacoinvasive strategy confers a survival benefit, to determine its usefulness in low-risk inferior or lateral ST-elevation MI, and to further refine the time window when PCI is both safe and beneficial after thrombolysis.³³

■ RESCUE PCI REDUCES MORTALITY RATES

Rescue PCI is the most accepted form of thrombolysis-PCI combination.

The REACT trial

The REACT trial²⁰ showed that rescue PCI performed at a mean of 4.5 hours after failed thrombolysis reduces the rate of adverse cardiovascular events by more than 50% at 6 to 12 months and reduces the 5-year mortality rate by more than 50% compared with conservative management.²⁰ As in the pharmacoinvasive strategy, aggressive antiplatelet regimens were used in the REACT trial.

A meta-analysis of rescue PCI trials

A meta-analysis of rescue PCI trials³⁴ confirmed these results, showing a reduction in heart failure and reinfarction and a trend toward a lower mortality rate with rescue PCI.³⁴ After thrombolysis, 40% of patients do not achieve grade 3 TIMI flow, which explains why in modern clinical trials 30% of patients treated with thrombolysis require rescue PCI.^{5,15,16,35}

For patients with high-risk ST-elevation MI, current ACC/AHA guidelines assign a class IIa recommendation to rescue PCI.³¹

■ WHEN PATIENTS WITH ST-ELEVATION MI PRESENT TO A NON-PCI HOSPITAL

Transfer for primary PCI vs thrombolysis at the non-PCI hospital

The DANAMI-2 trial³⁶ found that immediate transfer for PCI was superior to on-site thrombolytic therapy, as measured by a reduction in the rate of ischemic events (composite of death, myocardial infarction, or stroke at 30 days): 8.5% vs 14.2% ($P < .001$). There were no deaths during transfer.³

The PRAGUE-2 trial⁴ showed similar results for patients presenting 3 to 12 hours after symptom onset (30-day mortality rate 6% with immediate transfer vs 15.3% with on-site thrombolysis, $P < .002$), whereas patients presenting within 3 hours of symptom onset had a similar mortality rate with either therapy.⁴

Comment. These trials showed that transfer for primary PCI is superior to thrombolytic therapy when performed in a timely fashion. However, they were done in countries with established transfer networks and short distances between community hospitals and PCI centers, with a PCI-related delay of only 44 minutes and a door-to-balloon time of 90 minutes despite transfer. The large-scale application of this prompt transfer policy is not practical in most regions in the United States. Thus, a strategy of local thrombolysis followed by routine early transfer for routine or rescue PCI seems warranted when the door-to-balloon time or the PCI-related delay time is expected to be too long.

All patients with cardiogenic shock should be revascularized on an emergency basis

Experiences with community-based systems of care and prehospital thrombolysis

In Minnesota, Henry et al³⁷ developed a PCI-based treatment system and an integrated transfer program for ST-elevation MI involving 30 hospitals within 210 miles of the Minneapolis Heart Institute. Participating hospitals were divided into two zones: zone 1 hospitals were within 60 miles, and zone 2 facilities were between 60 and 210 miles from the Heart Institute. Zone 2 patients received half-dose tenecteplase (if thrombolytic therapy was not contraindicated) in anticipation of a lengthy transfer time.

The median door-to-balloon time for zone 1 patients was 95 minutes (interquartile range 82 and 116 minutes) and for zone 2 patients 120 minutes (interquartile range 100 and 145 minutes). The diagnosis of ST-elevation MI was made by the emergency department physician, who activated the system with a phone call. The patient was then directly transferred to the catheterization laboratory, most often by helicopter.

The in-hospital death rate for patients who presented to the PCI center and for patients in zones 1 and 2 was similarly low (about 5%).³⁷

In France, the FAST-MI registry,¹⁷ which collected outcome data for different reperfusion strategies, found that thrombolysis yielded in-hospital and midterm results that were comparable to those of primary PCI. Of note, thrombolysis was started early after symptom onset (about 2 hours), and was started in the ambulance in two-thirds of cases. Nearly all patients underwent a pharmacoinvasive strategy that combined thrombolysis with coronary angiography and PCI within 24 hours of symptom onset. These findings suggest that timely thrombolysis followed by semiurgent transfer for PCI is an alternative to primary PCI for patients presenting to hospitals with no PCI capability, and that this alternative offers similar benefit to that of primary PCI.

Five centers in the United States have reported their experience with half-dose thrombolysis in the prehospital setting (in the field or during transfer) or at a non-PCI hospital, followed by prompt transfer to a PCI facility. In this registry of almost 3,000 patients,³⁸ patients treated with thrombolysis had better outcomes than patients directly transferred

for primary PCI, with a significantly lower 30-day mortality rate (3.8% vs from 6.4%), and no increase in bleeding.^{38,39} The mean door-to-balloon time was long (168 minutes in the primary PCI group and 196 minutes in the thrombolysis-PCI group), which might explain the benefit achieved with prompt thrombolysis.

CARDIOGENIC SHOCK

Patients presenting with left ventricular cardiogenic shock derive a large mortality benefit from revascularization, whether they are transferred or directly admitted to a PCI center.⁴⁰ Moreover, in the SHOCK registry, patients with predominant right ventricular cardiogenic shock had an in-hospital mortality rate similar to that of patients with predominant left ventricular cardiogenic shock, and revascularization (PCI or surgical revascularization) was associated with a strikingly lower mortality rate in both groups.⁴¹

Thus, all patients with left or right cardiogenic shock should be revascularized on an emergency basis, either surgically or percutaneously.

While trials of pharmacoinvasive therapy excluded patients with cardiogenic shock,^{15,16} thrombolytic therapy was associated with improved outcomes in the drug-therapy group of the SHOCK trial and in hypotensive patients randomized in the early thrombolysis trials.¹³ Thus, the ACC/AHA guidelines recommend thrombolytic therapy before transfer if a patient presents in shock within 3 to 6 hours of onset of the MI and delays in transport and intervention are anticipated.⁸

PUTTING IT ALL TOGETHER: MANAGEMENT STRATEGIES

Taking into account the importance of time to presentation, the PCI-related delay time, and patient and MI characteristics, as well as whether a regional transfer system is in place (as in Minnesota), we suggest an algorithmic approach to the management of ST-elevation MI at a non-PCI facility (FIGURE 2).

If an effective transfer system is in place, primary PCI not preceded by thrombolytic therapy or glycoprotein IIb/IIIa inhibitor therapy

Every community should develop a coordinated transfer strategy between non-PCI and PCI hospitals

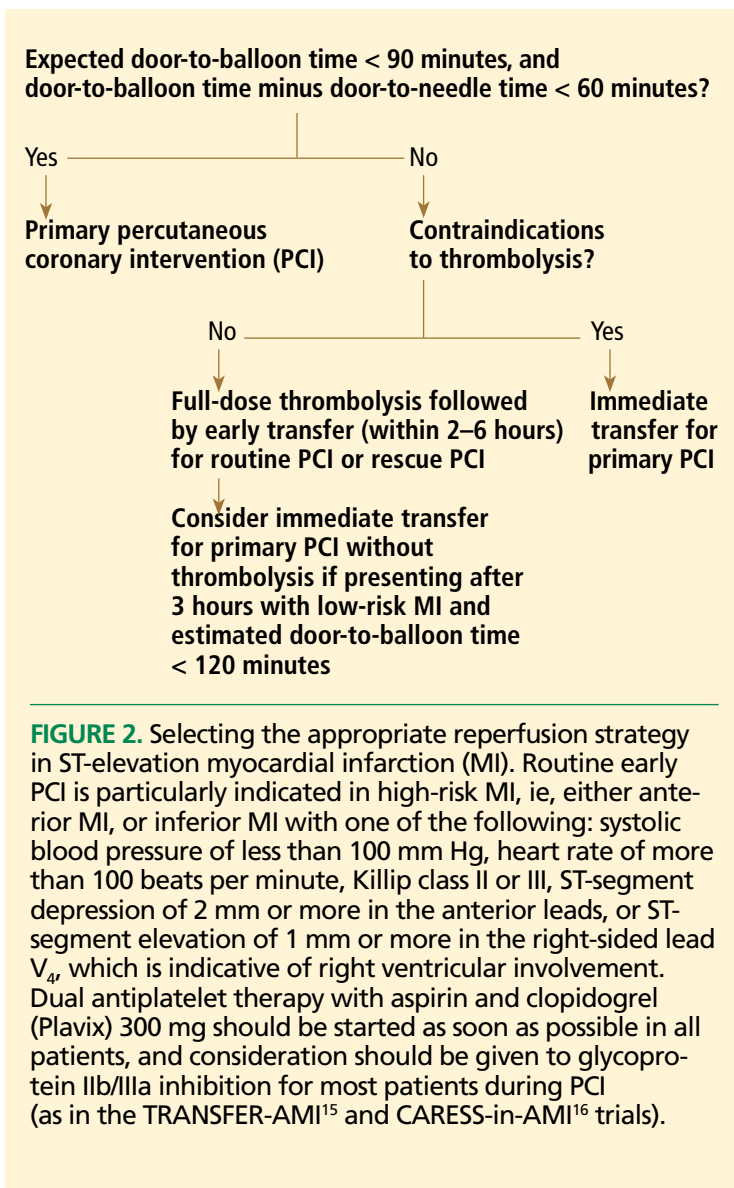


FIGURE 2. Selecting the appropriate reperfusion strategy in ST-elevation myocardial infarction (MI). Routine early PCI is particularly indicated in high-risk MI, ie, either anterior MI, or inferior MI with one of the following: systolic blood pressure of less than 100 mm Hg, heart rate of more than 100 beats per minute, Killip class II or III, ST-segment depression of 2 mm or more in the anterior leads, or ST-segment elevation of 1 mm or more in the right-sided lead V_4r , which is indicative of right ventricular involvement. Dual antiplatelet therapy with aspirin and clopidogrel (Plavix) 300 mg should be started as soon as possible in all patients, and consideration should be given to glycoprotein IIb/IIIa inhibition for most patients during PCI (as in the TRANSFER-AMI¹⁵ and CARESS-in-AMI¹⁶ trials).

is the preferred approach, according to ACC/AHA and ESC guidelines.^{31,32} Giving thrombolytics immediately before PCI is harmful and thus should be avoided when the expected door-to-balloon time is 90 minutes or less.

All hospitals (whether or not they offer PCI) and regional emergency medical services should participate in a community-based system of care for ST-elevation MI, with protocols for expeditious transfer as defined and coordinated by the American Heart Association initiative “Mission: Lifeline.” In addition, a system of field triage and direct transport to the catheterization laboratory of a PCI facility

after field activation significantly reduces door-to-balloon times and improves outcomes.⁴²

If such a system is not in place, then a pharmacoinvasive strategy seems best: ie, local full-dose thrombolysis (if not contraindicated) followed by transfer to a PCI facility and routine performance of PCI 2 to 6 hours after thrombolysis—in conjunction with aggressive early dual oral antiplatelet therapy and “downstream” glycoprotein IIb/IIIa inhibition. This approach is associated with outcomes similar to those of primary PCI.^{15–17,37}

Prehospital thrombolysis delivered by paramedics and followed by early transfer to a PCI facility has been associated with further reduction in mortality rates compared with in-hospital thrombolysis (as in the Swedish registry⁴³), and a reduction in death rate comparable to that of primary PCI in patients presenting early. This is an adequate strategy in regions where such a system can be established.^{5,17,38,43,44}

Patients presenting more than 3 to 4 hours after symptom onset, older patients, and patients with lower-risk MI or a higher risk of bleeding may still be suited for primary PCI even when the door-to-balloon time is 90 to 120 minutes, as stated by the European guidelines,³² or when the PCI-related delay time is as long as 100 minutes.¹⁰ On the other hand, while the ACC/AHA guidelines recognize that in these patients the mortality advantage of primary PCI vs thrombolytic therapy is maintained with more prolonged door-to-balloon times, they nevertheless state that the focus should be on developing systems of care to increase the number of patients with access to primary PCI in less than 90 minutes rather than extending the acceptable window for door-to-balloon time.

In conclusion, for patients presenting with ST-elevation MI who cannot undergo timely primary PCI, the best approach seems to be prehospital thrombolysis delivered by paramedics or local thrombolysis at the non-PCI hospital followed by transferring the patient and performing PCI within a few hours. This is especially important in patients with high-risk ST-elevation MI who present early after symptom onset, when the extent of myocardial necrosis associated with delayed primary PCI is largest.

In addition, every community should develop a coordinated transfer strategy between non-PCI and PCI hospitals. ■

REFERENCES

- 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.
- Waters RE 2nd, Singh KP, Roe MT, et al. Rationale and strategies for implementing community-based transfer protocols for primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004; 43:2153–2159.
- Chakrabarti A, Krumholz HM, Wang Y, Rumsfeld JS, Nallamothu BK; National Cardiovascular Data Registry. Time-to-reperfusion in patients undergoing interhospital transfer for primary percutaneous coronary intervention in the U.S: an analysis of 2005 and 2006 data from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2008; 51:2442–2443.
- Widimský P, Budesínský T, Voráč D, et al; 'PRAGUE' Study Group Investigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. *Eur Heart J* 2003; 24:94–104.
- Steg PG, Bonnefoy E, Chabaud S, et al; Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) Investigators. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 2003; 108:2851–2856.
- Kalla K, Christ G, Karnik R, et al; Vienna STEMI Registry Group. 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.
- Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348:771–775.
- Antman EM, Anbe DT, Armstrong PW, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Canadian Cardiovascular Society. 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 (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110:e82–e292.
- Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol* 2003; 92:824–826.
- 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.
- Boersma E; Primary Coronary Angioplasty vs Thrombolysis Group. 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.
- Stenestrand U, Wallentin L; Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). Fibrinolytic therapy in patients 75 years and older with ST-segment-elevation myocardial infarction: one-year follow-up of a large prospective cohort. *Arch Intern Med* 2003; 163:965–971.
- 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. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994; 343:311–322.
- Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993; 328:673–679.
- Cantor WJ, Fitchett D, Borggundvaag B, et al; TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009; 360:2705–2718.
- 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; 371:559–568.
- 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.
- 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.
- Ellis SG, Tendera M, de Belder MA, et al; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008; 358:2205–2217.
- Carver A, Rafelt S, Gershlick AH, Fairbrother KL, Hughes S, Wilcox R; REACT Investigators. Longer-term follow-up of patients recruited to the REACT (Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis) trial. *J Am Coll Cardiol* 2009; 54:118–126.
- Rasmanis G, Vesterqvist O, Gréen K, Edhag O, Henriksson P. Evidence of increased platelet activation after thrombolysis in patients with acute myocardial infarction. *Br Heart J* 1992; 68:374–376.
- Gurbel PA, Serebruany VL, Shustov AR, et al. Effects of reteplase and alteplase on platelet aggregation and major receptor expression during the first 24 hours of acute myocardial infarction treatment. GUSTO-III Investigators. *Global Use of Strategies to Open Occluded Coronary Arteries. J Am Coll Cardiol* 1998; 31:1466–1473.
- Coulter SA, Cannon CP, Ault KA, et al. High levels of platelet inhibition with abciximab despite heightened platelet activation and aggregation during thrombolysis for acute myocardial infarction: results from TIMI (thrombolysis in myocardial infarction) 14. *Circulation* 2000; 101:2690–2695.
- Ross AM, Huber K, Zeymer U, et al. The impact of place of enrollment and delay to reperfusion on 90-day post-infarction mortality in the ASSENT-4 PCI trial: assessment of the safety and efficacy of a new treatment strategy with percutaneous coronary intervention. *JACC Cardiovasc Interv* 2009; 2:925–930.
- Herrmann HC, Lu J, Brodie BR, et al; FINESSE Investigators. Benefit of facilitated percutaneous coronary intervention in high-risk ST-segment elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention hospitals. *JACC Cardiovasc Interv* 2009; 2:917–924.
- 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.
- Fernandez-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; 364:1045–1053.
- Le May MR, Wells GA, Labina M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). *J Am Coll Cardiol* 2005; 46:417–424.
- 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.
- Wijeyesundera HC, You JJ, Nallamothu BK, Krumholz HM, Cantor WJ, Ko DT. An early invasive strategy versus ischemia-guided management after fibrinolytic therapy for ST-segment elevation myocardial infarction.

COMBINED REPERFUSION

- dial infarction: a meta-analysis of contemporary randomized controlled trials. *Am Heart J* 2008; 156:564–572, 572.e1–e2.
31. **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 American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2009; 54:2205–2241.
 32. **Van de Werf F, Bax J, Betriu A, et al.** Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29:2909–2945.
 33. **Mukherjee D, Moliterno DJ.** The timely coupling of mechanical revascularization following thrombolysis for myocardial infarction. *Cardiology* 2007; 107:337–339.
 34. **Wijeyesundera HC, Vijayaraghavan R, Nallamotheu BK, et al.** Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2007; 49:422–430.
 35. **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.
 36. **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.
 37. **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.
 38. **Denktas AE, Athar H, Henry TD, et al.** Reduced-dose fibrinolytic acceleration of ST-segment elevation myocardial infarction treatment coupled with urgent percutaneous coronary intervention compared to primary percutaneous coronary intervention alone results of the AMICO (Alliance for Myocardial Infarction Care Optimization) Registry. *JACC Cardiovasc Interv* 2008; 1:504–510.
 39. **Smalling RW.** Ischemic time: the new gold standard for ST-segment elevation myocardial infarction care. *J Am Coll Cardiol* 2009; 54:2154–2156.
 40. **Hochman JS, Sleeper LA, White HD, et al; SHOCK Investigators.** Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001; 285:190–192.
 41. **Jacobs AK, Leopold JA, Bates E, et al.** Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. *J Am Coll Cardiol* 2003; 41:1273–1279.
 42. **Pedersen SH, Galatius S, Hansen PR, et al.** Field triage reduces treatment delay and improves long-term clinical outcome in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 2009; 54:2296–2302.
 43. **Björklund E, Stenestrand U, Lindbäck J, Svensson L, Wallentin L, Lindahl B.** Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. *Eur Heart J* 2006; 27:1146–1152.
 44. **The European Myocardial Infarction Project Group.** Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993; 329:383–389.

ADDRESS: Elias B. Hanna, MD, Department of Medicine, Section of Cardiology, Louisiana State University, Room 323, Box T4M-2, 1542 Tulane Avenue, New Orleans, LA 70112; e-mail ehanna10@yahoo.com.



Digestive Disease Institute Week

September 28 – October 1, 2010
InterContinental Hotel and Bank of
America Conference Center
Cleveland, Ohio

**International Summit on
Fibrosis in Intestinal
Inflammation: Mechanisms and
Biological Therapies**

September 28 – 29, 2010

**46th Annual
Gastroenterology Update
2nd Annual
Hepatic-Pancreatic-Biliary Course**

September 30 – October 1, 2010

**7th Annual
Laparoscopic Colorectal
Surgery Course**

September 28 – 29, 2010

**31st Annual
Turnbull
Symposium**

September 30 – October 1, 2010

These activities have been approved for
AMA PRA Category 1 Credit™.

**REGISTER ONLINE AT:
www.cfcme.org/Digestive10**