

# Management Strategies for ST-Elevation Myocardial Infarction in the Emergency Department

*Shereif H. Rezkalla, MD; Mubashir Ahmed, MD*

## ABSTRACT

Review of existing evidence supports that percutaneous coronary intervention (PCI) is superior to thrombolytic therapy in patients with acute myocardial infarction. If, however, a dedicated intervention team is not available onsite, transfer to another facility should be considered if reperfusion could be achieved within 90 minutes. If that goal cannot be achieved within 120 minutes, thrombolytic therapy should be administered with a planned transfer to a facility with PCI capability. In patients with cardiogenic shock or recurrence of anginal chest pain, PCI should be immediately considered. The value of administering full or modified dose thrombolytic therapy and then transferring for immediate PCI has not been demonstrated yet. Development of dedicated protocols for management of ST-elevation myocardial infarction developed by a community-based emergency medical service, emergency department, and cardiovascular service is highly recommended.

## INTRODUCTION

At the dawn of the last century, the majority of patients who died of sudden cardiac death were found to have coronary artery occlusion at autopsy. The occlusion was found to be secondary to a thrombus, thus the term coronary thrombosis was born. In the late 1940s, the syndrome of acute myocardial infarction was diagnosed clinically.<sup>1,2</sup> Shortly thereafter, it sparked interest in the medical community since it was associated with significant mortality.<sup>3</sup> Treatment was mainly symptomatic until the discovery of anticoagulants<sup>4</sup> and, later on, thrombolytic therapy.<sup>5</sup>

**Author Affiliations:** Marshfield Clinic, Marshfield, Wis (Rezkalla) University of Madison School of Medicine and Public Health, Madison, Wis (Rezkalla); University of Wisconsin Medical School, Milwaukee Clinical Campus, Milwaukee, Wis (Ahmed).

**Corresponding Author:** Shereif Rezkalla, MD, Director of Cardiovascular Research, Department of Cardiology, Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449; phone 715.387.5845; fax 715.389.3808; e-mail rezkalla.shereif@marshfieldclinic.org.

With the emergence of acute angioplasty and stenting in acute coronary syndromes, it soon became established as a superior alternative to thrombolytic therapy. If a patient with acute myocardial infarction presents to a hospital with experienced, high-volume operators, acute intervention will result in higher patency rates, fewer complications, and thus a better outcome.<sup>6-8</sup> The majority of hospitals, however, do not have a cardiac catheterization laboratory, and thrombolytic therapy is the accepted modality in this situation. If, however, access to a hospital with an experienced catheterization laboratory is available, a decision will need to be made regarding which strategy is superior: administration of an immediate thrombolytic therapy or transfer to a nearby facility for percutaneous coronary intervention (PCI). This review will attempt to answer this challenging question.

### *Time to Reperfusion*

It is well accepted that a more rapid and complete restoration of blood flow to the infarction zone is associated with better left ventricular performance and a better patient outcome.<sup>5</sup> It is intuitive, then, to conclude that if a patient presents with an acute myocardial infarction to a non-PCI capable hospital, it is better to give an immediate thrombolytic agent rather than transfer the patient to a qualified catheterization laboratory for primary intervention. Unfortunately, the answer is not that simple.

The success rate of thrombolytic therapy in all patients, particularly in high-risk populations, is less than expected.<sup>9,10</sup> Only patients who achieve thrombolysis in myocardial infarction (TIMI)-III flow (normal flow) following thrombolytic therapy will achieve a good outcome.<sup>11</sup> In the published trials, the best thrombolytic regimen achieves TIMI-III flow in only 54% of patients.<sup>12</sup> Even patients with successful reperfusion need to maintain that. If reocclusion or recurrent ischemia develops, adverse outcomes are to be expected.<sup>13</sup> The effectiveness of reperfusion was marked only in

patients with a very short onset to reperfusion, with 63% in the group of patients <2 hours, but then the effectiveness progressively decreases with every hour that passes. This is reflected in a mortality rate of 5.5% in patients receiving thrombolytic therapy within 2 hours, yet it nearly doubles at 4 or more hours.<sup>14</sup> When all these factors are balanced with the delay that is inherent in transferring such patients for primary intervention, it seems that only randomized studies may accurately clarify these issues.

Development of regional strategies complemented by regional cardiac registries will help establish the best plan for various local communities. When a patient presents to the emergency department with a myocardial infarction, should the patient be given thrombolytic therapy or transferred for primary intervention? Is there a role for facilitated angioplasty? We will review the published randomized trials that explored these challenges.

### RANDOMIZED TRIALS FOR TRANSFER

One of the first studies to address whether transfer for primary intervention was superior to thrombolytic therapy on site was a trial by Vermeer et al.<sup>15</sup> The 224 patients with acute myocardial infarction were randomized to 1 of 3 arms: thrombolytic therapy with alteplase in the non-PCI capable hospital, thrombolytic therapy followed by transfer for rescue intervention if needed, or transfer for primary balloon angioplasty. The treatment was started within 10 minutes in the thrombolytic group, while angiography was started 85 minutes after randomization. Despite this significant delay, patients randomized to primary intervention showed a trend to improved outcomes, although the study was not powered to yield statistically significant results. The patients had an ambulance transport time that ranged between 20-30 minutes with no transfer-related complication. Soon to follow was the “Primary Angioplasty in acute myocardial infarction patients from General community hospitals transported for percutaneous transluminal coronary angioplasty Units versus Emergency thrombolysis” (PRAGUE<sup>16</sup> and PRAGUE-2<sup>17</sup>) studies from Europe, and the “Angioplasty in Myocardial Infarction” (Air PAMI) study<sup>18</sup> from the United States. All showed similar trends in benefit in the group that was transferred for primary intervention. In the “DANish trial in Acute Myocardial Infarction-2”<sup>19,20</sup> (DANAMI-2) study, Andersen et al randomized 1572 patients with acute myocardial infarction to thrombolytic therapy with intravenous alteplase or transfer for primary intervention, mainly including placement of coronary stents. The median distance of transfer was 29

miles (range: 2-88 miles). Despite an hour delay at the start of intervention as compared with more immediate administration of the thrombolytic therapy, better outcomes were observed in patients in the intervention group relative to the combination endpoint of reinfarction, disabling stroke, and death, where a 40% reduction was observed in the primary intervention arm ( $P=.002$ ). One controlled study from France did not show a clear benefit from transfer for intervention;<sup>21</sup> however, in this particular study, a 26% crossover rate of the patients in the thrombolytic arm to the rescue angioplasty arm was observed.

Unfortunately, the transfer time in the United States (and probably in real life practice outside organized trials) is much longer. In the National Registry of Myocardial Infarction data, the median door-to-balloon time was 180 minutes.<sup>22</sup> An organized effort at each individual hospital needs to be done to significantly shorten this time. Since the majority of the studies were not powered to achieve significance for targeted endpoint analysis, Dalby et al conducted a meta-analysis for 6 published randomized studies.<sup>23</sup> A statistically significant benefit was noted for endpoints including reinfarction and stroke in the transfer-for-primary-intervention group, accompanied by an observed trend for the reduced mortality endpoint.

### *Lessons Learned from Randomized Trials for Transfer*

In general, evidence supports that when a patient presents with acute myocardial infarction to a non-PCI capable hospital, transfer to a hospital with a dedicated interventional team is superior to thrombolytic therapy, provided that intervention can be accomplished in a timely manner. A goal of door-to-balloon time should be about 90 minutes or less. Transport and primary intervention remains the treatment of choice irrespective of whether the choice of thrombolytic therapy was a streptokinase, alteplase, or tissue plasminogen activator.

The transfer distance varied between the studies with up to 88 miles in the DANAMI-2 study, yet no transfer-related complications or mortality were reported. These observations remained true whether transfer occurred by ambulance or by air (Air PAMI). Thus, it appears safe to transfer patients with acute myocardial infarction provided qualified advanced life support trained personnel are supervising the transfer. Outcomes in patients transferred for intervention did not vary with the nature of the myocardial infarction and remained true whether only anterior myocardial infarction, high-risk myocardial infarction, or all myocardial infarction were considered.

It is important that patients with shock are stabilized prior to intervention. This is true also when a patient with myocardial infarction is transferred from the hospital to the catheterization laboratory. Additionally, in preparation for primary intervention, acidosis needs to be corrected, ionotropes started for hypotension, and intubation started in those patients with respiratory arrest. Pharmacological treatment prior to transfer in most studies were similar and included aspirin, beta-blockers, and a bolus of unfractionated heparin without a heparin drip. Intravenous administration of IIb/IIIa was occasionally used per the discretion of the referring physician. No ticlopidine or Plavix was given prior to transfer.

The maximum benefit from transfer occurs when transfer was accomplished in about an hour. Benefit was demonstrated when the first balloon inflation was begun up to 2 hours after initial diagnosis. No sufficient data are available beyond 2 hours. The sooner the intervention can be established, the greater the benefit. In the "Global Utilization of Streptokinase and Tissue-plasminogen activator for Occluded coronary arteries" (Gusto IIb) study, which compared thrombolytic therapy to direct coronary intervention, mortality in the angioplasty group correlated with how soon the first balloon inflation was accomplished.<sup>24</sup> Patients who had their first balloon inflation in 1 hour or less from enrollment had a mortality rate of 1%, while those who had their balloon inflation done  $\geq 91$  minutes later had a 6.4% mortality rate. In the DANAMI trial, the ambulance crew that brought the patient to the community hospitals waited at the emergency department to transfer the patient to the angioplasty center if the patient was randomized to transfer. In several studies, protocols incorporated direct admission to hospitals with a catheterization laboratory so patients bypassed the second emergency department. These study design configurations emphasize the necessity for each angioplasty center to develop a specific protocol for care of such patients where the major goal is shortening the time to first balloon inflation. Further, a protocol for community-based transfer needs to be in place to expedite patient transfers. Patients may need to be transferred, preferentially to angioplasty centers, if acute myocardial infarction is suspected.<sup>25</sup>

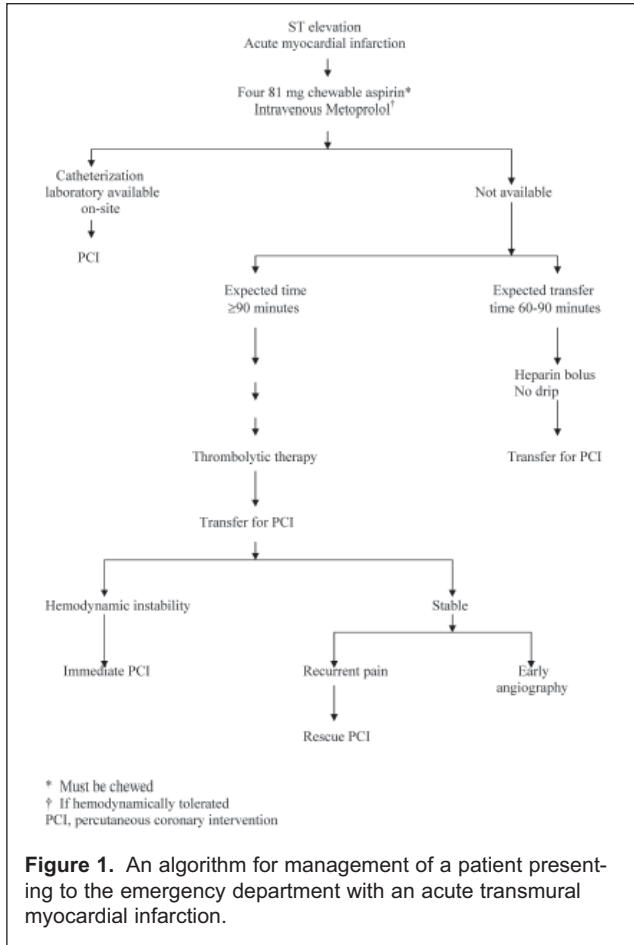
### FACILITATED ANGIOPLASTY

Physicians encountering a delay in intervention in a qualified catheterization laboratory of more than 1-2 hours for patients experiencing an acute myocardial infarction<sup>20</sup> must consider whether or not initiation of

thrombolytic therapy is warranted. Administration of thrombolytic therapy (full or modified dose) and referral of the patient for immediate angioplasty or stenting is known as facilitated angioplasty. The hypothesis supporting this strategy is to enhance the probability of achieving an early open vessel in a subset of patients, thus improving left ventricular function, and then performing primary intervention to assure a successful opening in almost all patients with no significant coronary stenosis.

Whereas early intervention refers to performing the procedure within 24 hours, rescue intervention refers to performing the procedure only if chest pain or reinfarction occurs.<sup>26</sup> Califf et al randomized 575 patients with acute myocardial infarction to immediate catheterization or deferred pre-discharge angiography. Those who had the immediate catheterization (where immediate was defined as catheterization within 3-10 hours) had improved clinical outcome compared to patients with delayed intervention.<sup>27</sup> In a similar study, Fernandez-Aviles et al randomized 500 patients with ST elevation myocardial infarction who received tissue-plasminogen activator prior to immediate or ischemia-guided angiograms. Better outcomes were observed in the group who underwent immediate angiography. However, the time elapsed prior to the angiogram and intervention, where appropriate, was up to 24 hours with the mean time to angiography being 19.6 hours from the onset of symptoms.<sup>28</sup> In patients with myocardial infarction complicated by a cardiogenic shock, immediate angiography is clearly recommended since there is a mortality benefit at 6 months.<sup>29</sup>

Whereas these studies, as well as others,<sup>15,30</sup> support a strategy of aggressive therapy with early angiography that is superior to delayed angiography or ischemia guided strategy, they do not address the impact of facilitated angiography in patients receiving thrombolytic therapy prior to direct transfer to catheterization laboratory in a tertiary referral center. The intellectual reasoning for the facilitated immediate intervention is simply to achieve very early reperfusion, thus preserving left ventricular function. Ross et al randomized 606 patients with ST elevation myocardial infarction to an intravenous 50 mg bolus of recombinant tissue-type plasminogen activator or placebo, followed by immediate angiography and revascularization as needed. However, no difference in the ejection fraction (58%) was observed between the two study arms.<sup>31</sup> In a smaller study by Kurihara et al, ejection fraction was also similar between facilitated and direct intervention.<sup>32</sup> A plethora of studies cast a significant doubt about the value of fa-



cilitated angioplasty. Many do not see any benefit.<sup>33-36</sup> Some suggest it does not lead to better left ventricular function.<sup>37,38</sup> Other studies showed an increase in complication rate in facilitated intervention, including more bleeding complications, higher transfusion rate, and a trend toward increased mortality.<sup>39-41</sup> Furthermore, another study was terminated prematurely because of concerns about the safety of facilitated angioplasty.<sup>42</sup> Recently, the primary versus tenecteplase-facilitated PCI in patients with ST-segment elevation myocardial infarction trial was reported.<sup>43</sup> The study included 1667 patients randomized to primary PCI or facilitated PCI. A higher in-hospital mortality rate was noted in the facilitated arm ( $P=.01$ ). Although the study was designed to enroll 4000 patients, it was terminated prematurely by the data and safety monitoring board in light of the higher mortality rate noted in the facilitated PCI arm.

What if immediate intervention is not a protocol mandated procedure, but was left to the clinical judgment of the managing cardiologist? Berger et al reviewed 2200 patients who presented with acute myocardial infarction and hemodynamic instability presenting

as cardiogenic shock as part of the Gusto-1 trial. The revascularization was not protocol mandated but was performed only at the discretion of the cardiologist. The patients who received revascularization experienced a 38%, 30-day mortality rate versus a 61%, 30-day mortality rate in the conservative group ( $P=.0001$ ).<sup>44</sup> Thus, when angiography was complemented by individual clinical judgment, the benefit of facilitated intervention was apparent. Other studies also suggested the value of individual clinical judgment in selecting the appropriate acute myocardial infarction patient for a revascularization procedure.<sup>45</sup>

Most studies did not show a benefit from facilitated angioplasty. One reason is that the expected benefit from thrombolytic therapy is limited to approximately 50% of patients who achieve TIMI-III flow. Full dose thrombolytic therapy increases bleeding complications, including serious events such as intracerebral bleeding. There is also strong evidence that thrombolytic therapy may cause platelet activation<sup>46</sup> or intraplaque hemorrhages,<sup>47</sup> both of which have an untoward effect on coronary intervention. Thus, studies exploring the use of lower-dose thrombolytic therapy or the combination therapy with IIb/IIIa platelet receptor inhibitors in a large-scale randomized trial may be warranted in assessing the relative value of facilitated angioplasty. The long awaited “Facilitated Intervention with Enhanced reperfusion Speed to Stop Events” (FINESSE) trial may provide some additional valuable insights.<sup>48</sup> At this time, the available data do not support routine use of facilitated angioplasty. The official guidelines of the American College of Cardiology and the American Heart Association state that facilitated PCI might be performed in higher-risk patients when bleeding risk is low.<sup>49</sup>

**CONCLUSION**

When a patient with an acute myocardial infarction presents to the emergency department, the best strategy is to attempt PCI if an experienced team is immediately available. If transfer to an experienced catheterization laboratory can be arranged within 60 to 90 minutes with the expected first balloon inflation occurring at 90 minutes or less from presentation to the initial emergency department, direct intervention still is the preferred strategy. If a catheterization laboratory is not immediately available, thrombolytic therapy should be administered with a planned early angiography and intervention if needed. A delay of about 24 hours will decrease the bleeding complications and should be encouraged unless there is hemodynamic instability. No supportive data exist to recommend immediate (facilitated) PCI, and it

should not be routinely performed. Since some existing evidence suggests that facilitated PCI may be associated with increased adverse outcomes, all efforts should focus on a rapid transit time from onset of symptoms to PCI. Standardized protocols for expedited transfer for PCI need to be developed for community emergency medical systems.<sup>50</sup> A suggested algorithm is depicted in Figure 1.

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