

REVIEW

## Routine Early Coronary Angioplasty After Thrombolysis

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ABSTRACT

**KEY WORDS:** myocardial infarction,  
thrombolysis, reperfusion, coronary  
angioplasty

**ABBREVIATIONS**

PCI = percutaneous coronary intervention  
STEMI = ST-elevation myocardial  
infarction

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Over the recent years it has become abundantly clear that reperfusion by primary angioplasty in patients with ST-elevation myocardial infarction (STEMI) is the treatment of choice. For hospitals that lack facilities for percutaneous coronary intervention (PCI), on site thrombolysis remains their first option, or alternatively patients can be transferred to other institutions for PCI, if this can be accomplished within a tight time frame. For the latter strategy, an organized network of centers is needed to rapidly and safely transfer STEMI patients for primary PCI. Thus, although transferring STEMI patients for primary PCI appears to be a superior reperfusion strategy compared with on-site fibrinolysis at a no-PCI capable hospital, time delays associated with transferring patients for PCI in routine clinical practice remains a major drawback of the whole concept.

The tight time interval of 90-120 min needed to take full advantage of primary PCI, probably can be extended several hours, if an initial reperfusion treatment with thrombolysis is chosen, followed by routine angioplasty in the subsequent hours. This strategy, also referred as adjunctive PCI after thrombolysis in the literature, is easily differentiated from facilitated PCI, when a thrombolytic regimen is specifically used to maximize initial reperfusion rate and not in order to 'gain' time, and ischemia-driven PCI, when an intervention becomes mandatory after objective evidence of post-infarction ischemia. At least these are the convincing results from recent trials published over the last three years, such as TRANSFER-AMI, FAST-MI, GRACIA-2, WEST-MI, CARESS-AMI and NORDISTEMI.

When used early after the onset of symptoms, a pharmacoinvasive strategy that combines thrombolysis with a liberal use of PCI yields early and 1-year survival rates that are comparable to those of primary PCI. Finally, when analyzed according to the timing of PCI after thrombolysis, mortality tended to be lower with increasing time from thrombolysis when PCI was performed on a systematic basis, whereas it tended to increase with increasing time from thrombolysis when PCI was performed as a rescue procedure. Sufficient time course, probably >2-3 hours to 6-12 hours, which neutralizes the pre-hemorrhagic effect of thrombolysis and allows the antiplatelet agents to act, is the key point for a better outcome when thrombolysis is combined with early angioplasty. This appears to be a more effective and practical way to treat STEMI patients, at least for those hospitals, whereby immediate PCI is not available.

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**INTRODUCTION**


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In the middle of this decade the publication by Keeley et al.<sup>1</sup> of their comprehensive meta-analysis comparing intravenous thrombolytic treatment and angioplasty in ST elevation myocardial infarction (STEMI) convinced the vast majority of cardiologists that reperfusion by angioplasty should be the treatment of choice. Nevertheless, the fact that many hospitals lack facilities for percutaneous coronary intervention (PCI), and thus objective problems exist as how to organize in an appropriate time fashion the transport of such patients together with alternative therapies of combined pharmacoinvasive therapies, led to a relative delay in obtaining clear guidelines for the optimal treatment of STEMI. In the beginning of 2010, recent data determining the ideal time interval for intervention coupled with a variety of relative trial results (trial acronyms explained in [Table 1](#)), seem to clarify the chapter of STEMI

**TABLE 1.** List of trials' acronyms used in the text

1. AIR-PAMI: Air-Primary Angioplasty in Myocardial Infarction.
  2. ASSENT-4 PCI: Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention.
  3. CARESS-AMI: Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction
  4. DANAMI: Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction.
  5. FAST-AMI: French Registry on Acute ST-Elevation Myocardial Infarction.
  6. FINESSE: Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention.
  7. GRACIA: GRupo de Analisis de la Cardiopatía Isquémica Aguda.
  8. LIMi: Limburg Interventional Myocardial Infarction.
  9. NORDISTEMI: NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction.
  10. PRAGUE: PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis.
  11. TRANSFER-AMI: Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction.
  12. WEST: Which Early ST-elevation myocardial infarction Therapy.
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treatment better. Consequently, some reminders regarding the practice of transfer STEMI patients for subsequent angioplasty and the idea of pharmacoinvasive reperfusion before mechanical recanalization, in conjunction with the appropriate time interval to perform such strategies, are needed.

**TRANSFERRING STEMI PATIENTS FOR PRIMARY PCI**

The concept of transferring patients with STEMI for primary PCI was supported by a number of trials. In the largest experience of transfer for primary PCI, the Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2), 1,572 patients with STEMI were randomly assigned to on-site accelerated tissue plasminogen activator or primary PCI at 24 hospitals in Denmark.<sup>2</sup> Patients who were randomized to primary PCI at referral centers were transferred to one of 5 invasive centers, provided that the transfer would likely take up to 3 hours. The DANAMI-2 trial was stopped early because of an approximately 40% lower incidence of the primary end point of recurrent myocardial infarction, disabling stroke, or death at 30 days with primary PCI compared with fibrinolysis (8.5% vs. 14.2%;  $p=0.002$ ). This initial experience has shown that an organized network of centers could rapidly and safely transfer STEMI patients for primary PCI.

In the PRAGUE study (PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis), the safety and feasibility of interhospital transfer of patients with STEMI in the Czech Republic was evaluated.<sup>3</sup> Patients were randomly assigned to three groups: group A received intravenous streptokinase; group B received streptokinase with immediate transfer to an invasive center for subsequent PCI; and group C was transported to an invasive center without receiving fibrinolytic therapy. Transfer was tolerated well, with rare nonfatal complications and no deaths. The primary composite end point (reinfarction, stroke, or death at 30 days) was reduced across groups A, B, and C (23%, 15%, and 8%, respectively;  $p < 0.02$ ). The following PRAGUE-2 trial<sup>4</sup> randomized 850 STEMI patients from community hospitals in the Czech Republic to on-site fibrinolysis with streptokinase or transfer to invasive centers for primary PCI. There was a modest trend toward reduction in the primary end point of 30-day mortality with primary PCI versus streptokinase (6.8% vs. 10.0%;  $p < 0.12$ ). Analysis of a prespecified subgroup of patients who presented within 3 hours of symptom onset showed no mortality benefit with transfer for PCI (7.3% vs. 7.4%), whereas patients who presented within 3 to 12 hours of symptom onset had a significant reduction in mortality (6.0% vs. 15.3%;  $p < 0.02$ ). Therefore, the PRAGUE-2 results confirm the feasibility of transferring STEMI patients for primary PCI, but also suggest that transfer for primary PCI may primarily benefit patients who do not present soon after

symptom onset. In the AIR-PAMI trial,<sup>5</sup> patients transferred for primary PCI had a non-significant lower risk of reinfarction, disabling stroke, or death at 30 days (8.4% vs. 13.6%; p=0.33).

Recently published meta-analyses<sup>6,7</sup> of results from fibrinolysis versus primary PCI trials, included data from 5 trials (DANAMI-2, PRAGUE-1 and -2, AIR-PAMI, and the Limburg Intervention/MI trial) that compared on-site fibrinolysis with immediate transfer for primary PCI. Combined data from these trials showed that transfer for primary PCI was associated with a significant decrease in the composite end point of nonfatal myocardial infarction, stroke, or death compared with fibrinolysis (Table 2). These cumulative results underscore the concept that transferring STEMI patients for primary PCI appears to be a superior reperfusion strategy compared with on-site fibrinolysis at a no-PCI capable hospital, but time delays associated with transferring patients for PCI in routine clinical practice may be a major drawback of the whole concept.

**FACILITATED PCI**

Stone et al<sup>8</sup> observed that independently of the TIMI

flow after a direct PCI in STEMI, the most important factor consists of how this flow stands before the beginning of PCI, as patients arriving with a TIMI III flow have a better prognosis than those arriving with TIMI 0, I, II flow, even if all of them have a TIMI III flow after the procedure. This observation generated the term «facilitated PCI» some years ago in order to describe the practice of an almost immediate PCI in STEMI, just preceded by some help from a fibrinolytic drug. This combination approach to a pharmacoinvasive recanalization has the rationale to reap the benefits and avoid the disadvantages of each method. It is well known that time to recanalization which generally favours thrombolysis and adequacy of restoration of perfusion that generally favours PCI were found to be pivotal determinants of a favourable outcome with either approach.

Compared with standard thrombolysis, which achieves TIMI 3 flow rates of 50% at 60 min and 60% at 90 min, primary angioplasty takes longer to perform, reducing the early benefit, but achieves greater TIMI 3 flow rates by 90 min. Because pharmacologic intervention can be initiated immediately, it is a promising initial step. Because PCI offers more complete recanalization, it may be a particularly

**TABLE 2.** Occurrence of composite primary endpoint in different studies of Transfer-PCI, facilitated-PCI and thrombolysis followed by routine angioplasty.

TRANSFER PCI					
STUDY	PCI included in initial treatment	PCI not included in initial treatment	P	Favours	
(DANAMI-2) <sup>2</sup>	8.5%	14.2%	p=0.002	PCI	
(PRAGUE-1) <sup>3</sup>	8%	23%	p<0.02	PCI	
(PRAGUE-2) <sup>4</sup> -All	6.8%	10.0%	p < 0.12	PCI	
(PRAGUE-2) <sup>4</sup> <3h	7.3%	7.4%	p=NS	NS	
(PRAGUE-2) <sup>4</sup> >3h	6.0%	15.3%	p < 0.02	PCI	
AIR-PAMI <sup>5</sup>	8.4%	13.6%	p=0.33	PCI	
FACILITATED PCI					
STUDY	Primary PCI	Facilitated PCI	P	Favours	
ASSENT-4 PCI <sup>9</sup>	13%	19%	p=0.0045	Primary PCI	
FINESSE <sup>10</sup>	10.7%	9.8%	p=0.55	NS	
THROMBOLYSIS FOLLOWED BY ROUTINE ANGIOPLASTY					
STUDY	Routine PCI post thrombolysis	Rescue/Delayed PCI	P	Favours	
TRANSFER-AMI <sup>13</sup>	11.0%	17.2%	p=0.004	Routine PCI	
CARESS <sup>16</sup>	4.4%	10.7%	p=0.004	Routine PCI	
NORDISTEMI <sup>18</sup>	6.0%	16.0%	p=0.01	Routine PCI	
STUDY	Routine PCI post thrombolysis	Primary PCI	P	Favours	
FAST-MI registry <sup>14</sup>	4.3%	5.0%	p=NS	NS	
GRACIA-2 <sup>17</sup>	10%	12%	p=0.57	NS	

welcome subsequent step. Although results of previous studies of routine early PCI after fibrinolytic therapy also demonstrate no convincing clinical benefit of facilitated PCI over standard PCI, their negative conclusions were attributed to the non-use of stents, low-profile guiding catheters, steerable wires, and smaller-sized sheaths, and before platelet glycoprotein IIb/IIIa inhibitors and thienopyridines became available. However, recent results from 2 major clinical trials were also disappointing.<sup>9,10</sup> In the ASSENT-4 PCI trial<sup>9</sup> (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention), 1,619 patients with STEMI of less than 6-hour duration were randomised to standard PCI (n=838) or PCI preceded by administration of full-dose tenecteplase (n=829). All patients received aspirin and a bolus, without an infusion, of unfractionated heparin. The median time from bolus tenecteplase to first balloon inflation was 104 min. The study was terminated early, because the primary end-point (a combination of death, or congestive heart failure or cardiogenic shock) was noted in 19% (151 of 810) of patients assigned facilitated PCI versus 13% (110 of 819) of those randomised to primary PCI (relative risk 1.39, 95% CI 1.11–1.74; p=0.0045).

In the FINESSE trial<sup>10</sup> (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) a total of 2,453 patients with STEMI who presented 6 hours or less after the onset of symptoms to receive combination-facilitated PCI, abciximab facilitated PCI, or primary PCI. The mean thrombolysis bolus-to-balloon time was 90 min. The primary end point was the composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization. The primary end point occurred in 9.8%, 10.5%, and 10.7% of the patients in the combination-facilitated PCI group, abciximab-facilitated PCI group and primary-PCI group, respectively (P = 0.55); 90-day mortality rates were 5.2%, 5.5% and 4.5%, respectively (P = 0.49). Overall, there was a graded increase in the rates of bleeding, intracranial hemorrhage and transfusions in the PCI-facilitated groups. In all three treatment groups combined, the rate of death was associated with the extent of bleeding (18.2% with TIMI major bleeding, 6.1% with TIMI minor bleeding, and 2.6% with little or no bleeding; P<0.001). According to author's conclusions, neither facilitation of PCI with reteplase plus abciximab, nor facilitation with abciximab alone significantly improved the clinical outcomes, as compared with abciximab given at the time of PCI, in patients with STEMI.

The final damnation of facilitated PCI was signed again by Keeley et al.<sup>11</sup> By identifying 17 trials of patients with STEMI assigned to facilitated (n=2,237) or primary (n=2,267) PCI, they report that the facilitated approach resulted in a greater than two-fold increase in the number of patients with initial TIMI grade 3 flow, compared with the primary approach

(832 patients [37%] vs 342 [15%], odds ratio 3.18, 95% CI 2.22–4.55); however, final rates did not differ (1706 [89%] vs 1803 [88%]; 1.19, 0.86–1.64). Significantly more patients assigned to the facilitated approach than those assigned to the primary approach died (106 [5%] vs 78 [3%]; 1.38, 1.01–1.87), had higher non-fatal reinfarction rates (74 [3%] vs 41 [2%]; 1.71, 1.16–2.51), and had higher urgent target vessel revascularisation rates (66 [4%] vs 21 [1%]; 2.39, 1.23–4.66). The increased rates of adverse events seen with the facilitated approach were mainly seen in thrombolytic-therapy-based regimens. Facilitated intervention was associated with higher rates of major bleeding than primary intervention (159 [7%] vs 108 [5%]; 1.51, 1.10–2.08). Hemorrhagic stroke and total stroke rates were higher in thrombolytic-therapy-containing facilitated regimens than in primary intervention (hemorrhagic stroke 15 [0.7%] vs two [0.1%], p=0.0014; total stroke 24 [1.1%] vs six [0.3%], p=0.0008). Thus, nowadays, facilitated PCI offers no benefit over primary PCI in STEMI treatment and facilitated interventions with thrombolytic-based regimens should be avoided (Table 1).

#### **THROMBOLYSIS FOLLOWED BY ROUTINE ANGIOPLASTY**

The time to treatment with primary PCI is an important determinant of the clinical outcome among STEMI patients. Observations by Pinto et al<sup>12</sup> made upon time delays in STEMI-related PCI are well known and they established a mean delay of 114 minutes not to be exceeded, in order to obtain a better therapeutic result with primary PCI, rather than pharmacologic reperfusion with thrombolysis. But this time interval probably seems to become longer if an additional 1-2 hours delay is added and probably more (but not exceeding 24 hours in total), if an initial reperfusion treatment with thrombolysis is chosen, followed by routine angioplasty in the subsequent hours. At least these are the convincing results from recent trials, such as TRANSFER-AMI, FAST-MI, GRACIA-2, WEST-MI, CARESS-AMI, NORDSTEMI, all published over the last three years and summarized in Table 2.

In the TRANSFER-AMI trial<sup>13</sup> (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction), 1,059 high-risk patients who had a STEMI and who were receiving fibrinolytic therapy at centers that did not have the capability of performing PCI, were randomized to either standard treatment (including rescue PCI, if required, or delayed angiography) or a strategy of immediate transfer to another hospital and PCI within 6 hours after fibrinolysis. All patients received aspirin, tenecteplase, and heparin or enoxaparin; concomitant clopidogrel was recommended. The primary end point was the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days. PCI was performed in 67,4% of the patients assigned to standard treatment a median of 21.9 hours after randomiza-

tion and in 84.9% of the patients assigned to routine early PCI a median of 3.9 hours after administration of tenecteplase. At 30 days, the primary end point occurred in 11.0% of the patients who were assigned to routine early PCI and in 17.2% of the patients assigned to standard treatment (relative risk with early PCI, 0.64; 95% confidence interval, 0.47 to 0.87;  $p = 0.004$ ). There were no significant differences between the groups in the incidence of major bleeding.

Interestingly, the same findings described in the TRANSFER-AMI were available almost one year ago from the FAST-MI registry<sup>14</sup> (French Registry on Acute ST-Elevation Myocardial Infarction), which rather than a trial, is a report of daily practice of STEMI treatment in France. The purpose of the study was to assess contemporary outcomes in STEMI patients, with specific emphasis on comparing a pharmacoinvasive strategy (thrombolysis followed by routine angiography) with primary PCI. Of the thrombolysis group 96% underwent subsequent angiography, with 84% undergoing PCI (58% within 24 hours of receiving thrombolysis). In the thrombolysis cohort the mean time interval from lysis to PCI was 290 minutes and in the primary PCI group 300 min. In-hospital mortality was 5.0% in patients with primary PCI and 4.3% in those with thrombolysis. One-year survival was 94% for thrombolysis and 93% for primary PCI. Thus, when used early after the onset of symptoms, a pharmacoinvasive strategy that combines thrombolysis with a liberal use of PCI yields early and 1-year survival rates that are comparable to those of primary PCI. Finally, when analyzed according to the timing of PCI after thrombolysis (according to quartiles of time delay from thrombolysis to PCI), 30-day mortality was 4.1% in the first and second quartiles (time from lysis to PCI=220 minutes) versus 3.6% in the third and fourth quartiles; mortality tended to be lower with increasing time from thrombolysis when PCI was performed on a systematic basis, whereas it tended to increase with increasing time from thrombolysis when PCI was performed as a rescue procedure.

The results of WEST and GRACIA-2 trials are also in the same wavelength, as the WEST (Which Early ST-elevation myocardial infarction Therapy) trial<sup>15</sup> showed that thrombolytic therapy followed by systematic PCI within 24 hours yielded results comparable to those of primary PCI. More recently in the GRACIA-2 trial<sup>16</sup> (GRupo de Analisis de la Cardiopatía Isquémica Aguda) a total of 212 STEMI patients were randomized to full tenecteplase followed by stenting within 3–12 hours of randomization (early routine post-fibrinolysis angioplasty; 104 patients), or to undergo primary stenting with abciximab within 3 hours of randomization (primary angioplasty; 108 patients). The primary endpoints were epicardial and myocardial reperfusion, and the extent of left ventricular myocardial damage, determined by means of the infarct size and 6-week left ventricular function. Early routine post-fibrinolysis angioplasty resulted in higher frequency (21 vs. 6%,  $P=0.003$ ) of complete epicardial and

myocardial reperfusion (TIMI 3 epicardial flow and TIMI3 myocardial perfusion and resolution of the initial sum of ST-segment elevation >70%) following angioplasty. Both groups were similar regarding infarct size (area under the curve of CK-MB:  $4613 \pm 3373$  vs  $4649 \pm 3632$  mg/L/h,  $P=0.94$ ); 6-week left ventricular function (ejection fraction:  $59.0 \pm 11.6$  vs.  $56.2 \pm 13.2\%$ ,  $P=0.11$ ; end-systolic volume index:  $27.2 \pm 12.8$  vs.  $29.7 \pm 13.6$ ,  $P=0.21$ ); major bleeding (1.9 vs. 2.8%,  $P=0.99$ ) and 6-month cumulative incidence of the primary endpoint (10% vs. 12%,  $P=0.57$ ; relative risk: 0.80; 95% confidence interval: 0.37–1.74).

Very recently, the results of the Combined Abciximab REteplase Stent Study (CARESS) trial<sup>17</sup> confirmed that a policy of systematic PCI after thrombolysis was superior to a policy of PCI restricted to cases needing rescue based on symptoms and lack of resolution of ST elevation. In this trial the primary outcome (a composite of death, reinfarction, or refractory ischemia at 30 days, occurred in 13 patients (4.4%) in the immediate PCI group compared with 32 (10.7%) in the standard care/rescue PCI group (hazard ratio 0.40; 95% CI 0.21–0.76, log rank  $p=0.004$ ) and the time interval between thrombolysis and PCI was 135 minutes. In the NORDSTEMI trial<sup>18</sup> (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction), a total of 266 patients with acute STEMI with more than 90-min transfer delays to PCI were treated with tenecteplase, aspirin, enoxaparin, and clopidogrel and randomized to immediate transfer for PCI or to standard management in the local hospitals with early transfer, only if indicated for rescue or driven-ischemia PCI. The median time from fibrinolysis to PCI was 163 min (2.7 hours) in the early invasive group and the composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive compared with the conservative group (6% vs. 16%, hazard ratio: 0.36, 95% confidence interval: 0.16 to 0.81,  $p=0.01$ ).

Putting the puzzle together of time window appropriate and necessary with pharmacologic reperfusion with thrombolysis, what we observe is that in facilitated PCI trials when by protocol an immediate angioplasty was performed, the mean time was 104 min in ASSENT-4 and 90 min in FINESSE after thrombolysis. On the other hand, in trials when “early” angioplasty was performed later on after initial thrombolysis, either by protocol (3–12 hours in GRACIA-2) or by logistic reasons (2.7 hours in NORDSTEMI, 3.9 hours in TRANSFER-AMI, 4.8 hours in FAST-MI), results were better, even if the same thrombolytic treatment as in the PCI facilitated trials was used. It is obvious the longer delay between fibrinolysis and PCI may also reduce the risk of bleeding resulting in an increased efficacy of a such a strategy. Fibrinolysis is associated with increased platelet activation and aggregation, which can be counteracted with potent antiplatelet therapy. The prothrombotic state that exists after administration of fibrinolysis, may be amplified when coronary stenting is per-

formed within hours after fibrinolysis. Thus, a potent adjunctive antithrombotic treatment is needed, although the adjunct antithrombotic therapy may impact on the risk of ischemic and hemorrhagic complications when PCI is performed (very) early after fibrinolysis. Finally, the specific time course (probably more than 2-3 hours up to 6-12 hours) which neutralizes the pre-hemorrhagic effect of thrombolysis and allows the antiplatelet effects of old and new potent drugs (clopidogrel, prasugrel) to act is the key point for a better outcome when thrombolysis is combined with early angioplasty.

In **conclusion**, almost three decades after initiation of intravenous thrombolysis and/or angioplasty as treatment of STEMI, the interaction of time appropriateness and availability to apply interventional techniques, in the context of an evolving atherothrombotic process, in conjunction with better knowledge of the pathophysiology of the fibrinolytic properties, elucidated and clarified the whole spectrum of therapeutic interventions. Terms as facilitated, rescue, delayed or elective PCI after myocardial infarction make no more sense and the glossary of current therapeutic choices became shorter and simpler, as the key word is actually reperfusion and as such it should be obtained, either by primary PCI or thrombolysis followed by routine angioplasty (adjunctive PCI) as the more effective ways to treat STEMI patients.

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