


# Management of ST Elevation Myocardial Infarction (STEMI) in Different Settings

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## Abstract

### Keywords

- ▶ acute coronary syndrome
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ST-segment elevation myocardial infarction (STEMI) is a life-threatening condition that requires emergent, complex, well-coordinated treatment. Although the primary goal of treatment is simple to describe—reperfusion as quickly as possible—the management process is complicated and is affected by multiple factors including location, patient, and practitioner characteristics. Hence, this narrative review will discuss the recommended management and treatment strategies of STEMI in the circumstances.

ST-segment elevation myocardial infarction (STEMI) is a clinical syndrome defined by the presence of myocardial ischemic symptoms, electrocardiographic (ECG) findings of new ST-segment elevations in two continuous leads or new left bundle branch block, and subsequent detection of biomarkers indicative of myocardial injury.<sup>1</sup> It is estimated that the annual occurrence of all MIs are 605,000 new attacks and 200,000 recurrent attacks, with an estimated annual cost of \$12 billion to hospitals.<sup>2,3</sup> Fortunately, advances in the management of coronary heart disease have led to declining mortality rates.<sup>2</sup> Indeed, treatment of acute MI has progressed considerably over the past 100 years, from the early stages of bed rest and “expectant” management, development of tissue plasminogen activators and their use in fibrinolysis and myocardial reperfusion, to today’s current strategy with a variety of mechanical and pharmacologic modalities.<sup>4</sup> Given the scientific and technological advantages we now have, treatment strategies can be catered to better suit the patient and their presentation. The general framework for STEMI management has been outlined in **–Fig. 1.**

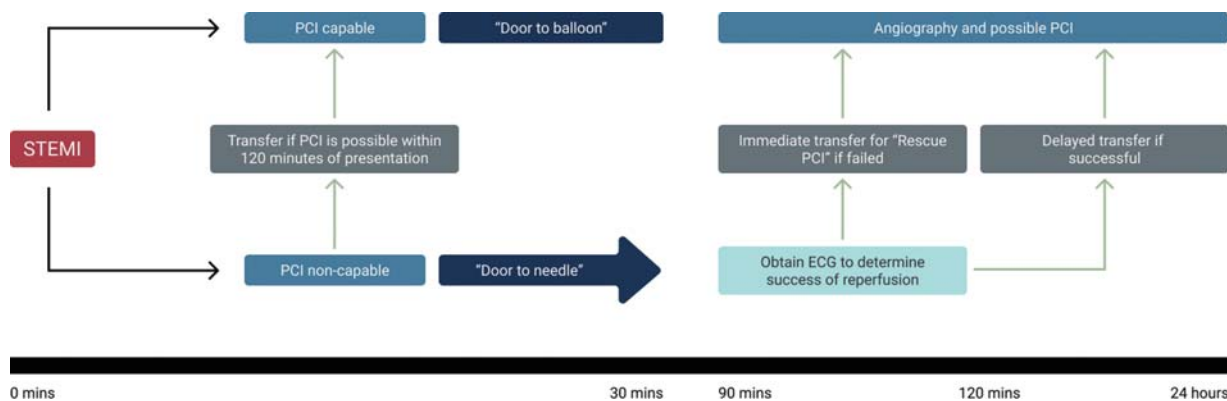
## Role for Prehospital Fibrinolysis

As mortality is high in STEMI patients with limited access to primary percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as a definite treatment, the concept of prehospital fibrinolysis was constituted. Despite the inferior benefit from in-hospital fibrinolysis compared with PCI, several studies however suggested non-inferior survival rates from prehospital fibrinolysis.<sup>5–7</sup> One meta-analysis demonstrated similar rates of all-cause mortality and cardiovascular (CV) mortality as well as decreased cardiogenic shock events at the expense of increased risk of hemorrhagic stroke.<sup>8</sup> In the US, this strategy has not been much adopted as of lack of clear benefit, particularly on hard endpoints<sup>9</sup> as well as deficiency of medical or paramedical training especially in rural areas.<sup>10</sup> In contrast, according to ESC guidelines,<sup>11</sup> prehospital fibrinolysis is recommended if trained medical or paramedical staff are able to interpret the ECG onsite or transmit the ECG to the hospital for definite reading, with the aim to administer within 10 minutes after STEMI is diagnosed.<sup>11</sup> With the advent of high-potency

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**Fig. 1** General ST-segment elevation myocardial infarction (STEMI) framework—Further triaging of STEMI patient.

P2Y12 inhibitors and better medical care performance, it would be interesting if prehospital fibrinolysis in this era yielded equivalent or superior outcomes compared with more conventional strategies.

### Management of STEMI in a Non-PCI-capable Hospital

Despite advances in revascularization strategies and increases in the number of hospitals that offer PCI, circumstances remain where primary PCI is not available or there are significant delays in transfer. In the US, disparities in geographic, socioeconomic status, ethnicities and minority populations play an essential role in preventing full accessibility to PCI.<sup>12</sup> Understandably, delay in transfer to a PCI-capable facility is associated with a significantly increased risk of mortality.<sup>13</sup> To overcome these disparities and try to mitigate adverse outcomes, medical revascularization with fibrinolytic agents remains a necessary modality in the resource-limited setting.

Fibrinolytic therapy provides the most mortality benefit if it is given within 12 hours after symptom onset, with the largest absolute benefit if given less than 2 hours after the onset of symptoms.<sup>9,14–16</sup> Based on this evidence, both European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommended fibrinolytic therapy as initial management if PCI cannot be performed within 120 minutes of STEMI diagnosis in the absence of contraindications.<sup>10,11</sup>

► **Table 1** summarizes absolute and relative contraindication to pharmacological revascularization.

As ischemic time is a major component of infarct size, time-to-treatment has a significant impact on patient outcomes.<sup>17,18</sup> Based on the GUSTO trial, mortality rates rose significantly in accordance with time-to-needle. Similar results were shown by Berger et al, with 12.5%, 14.1%, and 19.9% mortality rates at 30, 30 to 90, and greater than 90-minute cutoff for time-to-needle.<sup>19,20</sup> Recently, these results were confirmed in the study by Mcnamara et al, showing higher odds of mortality if the treatment ensued within 30 to 45 minutes (1.17) and after 45 minutes (1.37), compared with treatment within 30 minutes.<sup>21</sup> Based on the findings from the STREAM trial, the ESC has set a goal of 10 minutes from STEMI diagnosis to treatment with fibrinolytics. The

names and dosages of recommended fibrinolytic agents has been summarized in ► **Table 2**.

An ECG should be obtained between 60 to 90 minutes following fibrinolytic therapy.<sup>22</sup> Established features of successful reperfusion are ST-segment resolution more than 50%, relief of chest pain, and the presence of a reperfusion arrhythmia. Should the ST segments fail to decrease by 50%, the patient should be taken for immediate angiography, commonly referred to as “rescue PCI.” This is supported by the REACT trial, where patients who failed fibrinolysis were randomized into the following three groups: rescue PCI, conservative care, and repeat fibrinolysis.<sup>23</sup> Patients in the “rescue PCI” group had better outcomes, driven by a decrease in reinfarction, without a clear mortality benefit. Similar results were also seen in the MERLIN trial, where patients who failed fibrinolysis were randomized into rescue PCI and conservative management.<sup>24</sup> Again, patients in the rescue PCI arm had a lower rate of composite end-point without a clear mortality benefit. Both ACC/AHA and ESC guidelines support the utilization of “rescue PCI” should a patient fail fibrinolytic therapy; however, AHA guidelines list a class IIa recommendation with “B” level of evidence, whereas ESC guidelines list this as a class I recommendation with “A” level of evidence.<sup>10,11</sup>

Should treatment with fibrinolytics be successful, both society guidelines still recommend transfer to a PCI-capable facility. Both the GRACIA and TRANSFER AMI studies showed improved outcomes in patients transferred for coronary angiography and revascularization following successful fibrinolysis.<sup>25,26</sup> Similar results have been shown in various other randomized control trials and meta-analyses. Despite the benefit of having multiple trials, the optimal time frame following fibrinolysis for coronary angiography and possible PCI has yet to be established. The median time frame for each trial differed as did the management strategies of oral and intravenous (IV) antiplatelets and fibrinolytics. Based on a composite of median time frames, both AHA and ESC guidelines recommend a 2- to 24-hour window following fibrinolytic therapy for angiography and possible PCI.

Although pharmacologic revascularization remains a suitable option for patients presenting to a non-PCI-capable facility, especially when there is an anticipated delay of greater than 120 minutes to primary PCI, controversy and contraindications for fibrinolytic therapy should be considered.

**Table 1** Absolute and relative contraindication to direct fibrinolysis (adapted from ACC/AHA and ESC guidelines)<sup>11,59</sup>

Absolute contraindication	Relative contraindication
Any prior ICH	History of chronic, severe, poorly controlled hypertension
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)	Significant hypertension on presentation (SBP 180 mm Hg or DBP 110 mm Hg)
Known malignant intracranial neoplasm (primary or metastatic)	History of prior ischemic stroke 3 months
Ischemic stroke within 3 months	Dementia
Except acute ischemic stroke within 4.5 hour	Known intracranial pathology not covered in absolute contraindications
Suspected aortic dissection	Traumatic or prolonged (10 minutes) CPR
Active bleeding or bleeding diathesis (excluding menses)	Major surgery (3 weeks)
Significant closed-head or facial trauma within 3 months	Recent (within 2 to 4 weeks) internal bleeding
Intracranial or intraspinal surgery within 2 months	Noncompressible vascular punctures
Severe uncontrolled hypertension (unresponsive to emergency therapy)	Pregnancy
For streptokinase, prior treatment within the previous 6 months	Active peptic ulcer
	Oral anticoagulant therapy

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; DBP, diastolic blood pressure; ICH, intracranial hemorrhage; SBP, systolic blood pressure.

**Table 2** Recommended medications and doses for direct fibrinolysis (adapted from ACC/AHA and ESC guidelines)<sup>11,59</sup>

Medication	Dose	Fibrin specific	Note
Streptokinase	1.5 million U over 30–60 minute IV	No	Highly antigenic and contraindicated in previous exposure in 6 months
Retepase (rPA)	10 U IV bolus initially, followed by 10 U IV bolus 30 minute after	Yes	
Alteplase (tPA)	Bolus 15 mg IV, followed by infusion 0.75 mg/kg for 30 minute (up 50 mg) and, then 0.5 mg/kg for 60 minutes (up to 35 mg)	Yes	
Tenecteplase (TNK-tPA)	Single IV bolus with 30 mg for 60 kg; 35 mg for 60–69 kg; 40 mg for 70–79 kg; 45 mg for 80–89 kg; 50 mg for 90 kg.	Yes	

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology.

## Management of STEMI with Cardiogenic Shock

Cardiogenic shock in STEMI is highly associated with poor outcomes, with a mortality rate described between 50 to 80%.<sup>27–29</sup> Despite introduction of both inotropic agents and mechanical circulatory support, only timely revascularization has the strongest evidence to improve morbidity and mortality outcomes.<sup>30</sup> The benefit of early revascularization versus medical stabilization with fibrinolysis was seen in the SHOCK trial, which showed a mortality benefit by 6 months.<sup>31</sup> In the GUSTO-1 trial,<sup>32</sup> patients who received tissue plasminogen activator therapy were less likely to develop cardiogenic shock. However, there remains to be a lack of placebo-controlled trials comparing the use of fibrinolytics in cardiogenic shock. Current consensus statements recommend the use of fibrino-

lytics in cardiogenic shock associated with STEMI only when an early invasive approach cannot be achieved (Contemporary Management of Cardiogenic Shock).

## Management of STEMI with Fibrinolysis when the Diagnosis is in Doubt

It is not uncommon for practitioners to be confronted with STEMI mimickers, potentially resulting in misdiagnosis and mismanagement. Some reports have shown that between 2.3–2.6% of patients diagnosed with STEMI do not have evidence of coronary artery stenosis.<sup>33,34</sup> In such settings, fibrinolytic treatment would pose more harm rather than good, especially in the setting of STEMI imitators such as aortic dissection or subarachnoid hemorrhage. Exact and thorough clinical judgement should always be exercised to

ensure correct diagnosis, not always only following STEMI protocol, when ECG is shown.

## Management of STEMI in PCI Capable Hospitals

In the absence of significant treatment delays, primary PCI remains the preferred treatment method for patients with STEMI. According to the largest meta-analysis<sup>35</sup> comparison between PCI and fibrinolysis, patients with PCI have high rates of thrombolysis in myocardial infarction (TIMI) 3 flow, lower rates of intracranial outcomes, shorter hospital stays, and overall lower rates of major adverse cardiovascular events.

In general, it is recommended to perform PCI in patients with STEMI within 12 hours of symptom onset. This is primarily based on previous observational studies which found lack of efficacy in reducing mortality, albeit with fibrinolysis.<sup>36,37</sup> It is however not uncommon for STEMI patients to present later than 12 hours, variably reported from 8 to 40%.<sup>38–40</sup> For patients with symptom onset greater than 12 hours, PCI may also be performed if there is clinical or electrocardiographic evidence of ongoing ischemia. In fact, Nepper-Christensen et al reported substantial myocardial salvage in STEMI patients with ongoing ischemic symptoms from 12 to 72 hours.<sup>41</sup> However for stable, asymptomatic patients with symptom onset longer than 48 to 72 hours, several studies have reported similar findings, which suggested minimal to no benefit in performing PCI compared with only medical therapy.<sup>42–44</sup> Based on these pieces of evidence, ESC guidelines recommend against PCI in asymptomatic patients who have signs of an occluded culprit artery > 48 hours after STEMI onset. Nevertheless, revascularization should still be considered in patients with ongoing symptoms or with unstable hemodynamics, as only stable patients were considered in the aforementioned studies.<sup>42–44</sup>

Antiplatelet therapy for patients undergoing primary PCI should include aspirin and a P2Y12 inhibitor. In the US, the preferred initial loading dose of aspirin is 325 mg, although

studies have suggested lower loading doses of aspirin may be as effective.<sup>45</sup> Following stent placement, 81 mg daily of aspirin has been established as an adequate maintenance dose, balancing the risks of ischemic events with bleeding.<sup>46</sup> P2Y12 antagonists inhibit the binding of adenosine diphosphate to the P2Y12 receptor and prevent platelet activation and aggregation. Of the current family of P2Y12 inhibitors, clopidogrel was initially shown to have improved outcomes in STEMI patients when added to aspirin therapy in the CLARITY-TIMI 28<sup>47</sup> and COMMIT/CCS-2 trials,<sup>48</sup> although in patients treated primarily with fibrinolysis. Clopidogrel's composition as a prodrug and the process of multiple enzymatic breakdowns before its activation led to the creation of faster acting P2Y12 inhibitors, prasugrel and ticagrelor. Prasugrel was studied against clopidogrel in TRITON-TIMI<sup>49</sup> and ticagrelor against clopidogrel in PLATO,<sup>50</sup> and both agents were shown to have decreased MACE when compared with clopidogrel. Recently, the only head-to-head comparison of prasugrel and ticagrelor was completed in the ISAR-REACT 5 trial.<sup>51</sup> Here, prasugrel and ticagrelor were compared in patients presenting with ACS, which consisted of approximately 41% STEMI. Patients who received prasugrel saw a 2.3% absolute risk reduction in the primary endpoint of MACE and, importantly, did so without a significant increase in risk of bleeding.<sup>51</sup> Although it is unlikely a trial of this nature would be repeated, more studies comparing the efficacy of prasugrel and ticagrelor would be welcomed, as the results of ISAR-REACT 5 were unexpected. Until more data are obtained, STEMI guidelines will likely follow suit with the most current ESC recommendations for either prasugrel or ticagrelor, followed by clopidogrel if these are not available or if contraindications exist.<sup>11</sup> The loading and maintenance doses of antiplatelet and anticoagulants used during primary PCI has been summarized in ► **Table 3**.

Although stenting the culprit lesion causing the STEMI is the clear goal of primary PCI, the management of multivessel disease with STEMI has remained controversial. Multivessel disease is seen in approximately 50% of patient's presenting

**Table 3** Recommended medications and doses for STEMI treatment (adapted from ACC/AHA and ESC guidelines)<sup>11,59</sup>

Medications	Loading dose	Maintenance dose	Note
Aspirin	162–324 mg	81 mg OD	
Clopidogrel	600 mg	75 mg OD	
Ticagrelor	180 mg	90 mg BID	
Prasugrel	60 mg	10 mg OD	
Enoxaparin	n/a	1 mg/kg SC twice a day	0.75 mg/kg BID in > 75 YO 1 mg/kg OD in eGFR 15–30
UFH	70–100 IU/kg	12–15 IU/kg/hr	50–70 IU/kg if concomitant abciximab
Fondaparinux	n/a	n/a	Not recommended as a single agent for primary PCI
Bivalirudin	0.75 mcg/kg	1.75 mcg/kg/hr	1.4 mcg/kg/hr (eGFR 30–60)
Abciximab	0.25 mcg/kg	0.125 mcg/kg/min	
Eptifibatide	180 mcg/kg	2 mcg/kg/min	1 mcg/kg/min if eGFR < 50 maximum use up to 18 hours
Tiroiban	25 mcg/kg	0.15 mcg/kg/min	0.075 mcg/kg/min

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

with STEMI.<sup>52</sup> Previously, PCI of the nonculprit or noninfarct artery during STEMI was discouraged, as it was thought to cause harm.<sup>10</sup> Led by advances in PCI technique and technology, a series of randomized control trials emerged, which reevaluated the management of multivessel disease in STEMI. The PRAMI, CvLPRIT, DANAMI-3 PRIMULTI, and Compare-Acute trials randomized patients presenting with STEMI to PCI of the culprit lesion only or PCI of all significant lesions.<sup>53–56</sup> The study design of each trial varied between how the significance of nonculprit lesions were determined: angiographically or by fractional flow reserve; and when PCI of the nonculprit lesions were performed: during the index STEMI procedure, staged, or both. Nonetheless each of these trials showed significant improvement in primary outcomes of MACE in their complete revascularization arms, mostly driven by decreases in the need for repeat revascularization. Interestingly, none of the trials were able to show an isolated benefit for mortality or nonfatal MI, although trends toward mortality benefits were seen in one meta-analysis<sup>57</sup>. Recently, however, the COMPLETE trial, which separated STEMI patients into culprit lesion PCI only or staged PCI of nonculprit lesions, was able to show significant reductions in cardiovascular death and MI, which were attributed to the stronger statistical power of this study compared with its predecessors.<sup>58</sup> Based on the above findings, the AHA modified their recommendations in the 2015 focused update<sup>59</sup> from class III to class IIb, and the ESC provides a class IIa recommendation for multivessel disease PCI.<sup>11</sup>

### Stenting in Primary PCI

The first interventional treatment for coronary artery disease (CAD) was percutaneous balloon angioplasty by Dr. Gruentzig in 1977.<sup>60</sup> Despite superior benefits over thrombolysis, post-procedural patency for balloon angioplasty was not impressive, with high restenosis rates up to 30 to 50%, often requiring reintervention.<sup>35,61–64</sup> Since the introduction of stenting technology, coronary stenting has been the preferred treatment method during primary PCI.<sup>65–67</sup> Multiple meta-analyses have shown the benefits of coronary stenting when compared with balloon angioplasty, with lower risks of reinfarction and target vessel revascularization.<sup>68,69</sup> However, the safety and benefits of drug eluting versus bare metal stents in STEMI continues to be debated. The EXAMINATION<sup>70</sup> and COMFORTABLE AMI<sup>71</sup> trials both showed a decrease in target lesion reinfarction and target lesion revascularization after 1 year in patients who received 2nd generation drug-eluting stents. Importantly, both trials showed a reduction in major adverse cardiovascular events after 5 years in the drug-eluting stent arms without an increase in definite very late stent thrombosis.<sup>70,71</sup> Therefore, The ACC/AHA guidelines give a Class IA recommendation for either bare metal or drug-eluting stents.<sup>72</sup> On the contrary, ESC guidelines designate a Class IA recommendation for drug-eluting over bare metal stents, based on the lower risks of subacute and late stent thrombosis in comparison with bare metal stents.<sup>73,74</sup>

Nevertheless, the risk of drug-eluting stent thrombosis is significant, especially with early DAPT discontinuation.<sup>75–77</sup>

Thus, bare metal stents should still be considered over drug-eluting stents in situations where patient compliance is in question, there is an elevated bleeding risk, or there is an anticipated surgery within the upcoming year.

### Management of STEMI during the COVID-19 Pandemic

In December of 2019, a novel RNA Coronavirus was found to be causing a highly contagious viral pneumonia. This virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its resultant infection was named Coronavirus disease 2019 (COVID-19). As the infection spread worldwide in the spring of 2020, medical operations were severely affected, including management strategies for patients presenting with STEMI. Many centers worldwide reported a decrease in STEMI presentations combined with an increase in door to balloon times.<sup>78–80</sup> These changes were thought to be due to patient's reluctance to present to a hospital and delays in care related to increased triage time, COVID testing, and more complex catheterization laboratory protocols. These delays in presentation and treatment led to increased rates of in-hospital mortality.<sup>79,80</sup> Both the AHA/ACC and ESC released statements regarding the management of MI during the COVID-19 pandemic.<sup>81,82</sup> Fibrinolysis has been suggested as an alternative to PCI to reduce potential exposure to cardiac catheterization laboratory staff, but as PCI will eventually be needed in most cases, both statements list primary PCI as the preferred treatment method in patients presenting to PCI-capable hospitals.

### Management of STEMI with Active or High Risk of Bleeding

Bleeding is a well-known complication of any acute coronary syndrome (ACS), including STEMI, and can independently increase the risk of stroke, recurrent MI, or death.<sup>10</sup> There are several components of STEMI management which can be adjusted to minimize the risk of bleeding. Fibrinolysis should be avoided if there is concern for significant bleeding (– **Table 1** for absolute and relative contraindications). If fibrinolysis is pursued, tenecteplase appears to have a safer bleeding risk profile when compared with alteplase, owed in part to tenecteplase's weight-based dosing. In a double-blind, randomized trial, patients who received tenecteplase had fewer noncerebral bleeding complications and less need for blood transfusion.<sup>83</sup> Should PCI be performed, radial access should be considered when feasible. In the RIVAL trial, radial access did not significantly reduce the rate of major bleeding when compared with femoral access in STEMI patients, although radial access did have lower rates of vascular complications, namely, large hematomas and pseudoaneurysms requiring repair.<sup>84</sup> In regard to anticoagulation during PCI, the benefits of decreased major bleeding with bivalirudin when compared with heparin plus a GIIb/IIIa inhibitor were described in the HORIZONS-AMI trial<sup>85</sup> and have been confirmed with meta-analysis.<sup>86</sup> Finally, stent selection should be guided by the patients bleeding risk, with bare metal stents favored over drug-eluting stents in patients with high-bleeding risk.

## Management of STEMI with Cardiac Arrest

Sudden cardiac arrest is one of the most devastating clinical presentations to the hospital as the survival rate rarely exceeds 10%.<sup>87</sup> Importantly, the most common reason for sudden cardiac arrest is CAD, accounting for up to 80% of presentations.<sup>88</sup> Thus, medical practitioners should be vigilant to screen for ACS, regardless of underlying conditions and demographics.

It is however still unclear whether immediate cardiac catheterization laboratory activation for unconscious patients with STEMI who survived sudden cardiac death is superior to delayed activation. Despite similar ECG morphologies, there are still many conditions mimicking true STEMI.<sup>33,34</sup> For this reason, thoughtful decision-making should be discussed among care providers and with patients or their decision-makers, as not all patients would benefit from the invasive measures. On the other hand, sudden cardiac arrest survivors with good neurologic recovery and clear ST-segment elevations should be treated with immediate angiography and PCI if lesions are amenable, which is supported by one study, showing up to 85% of acute thrombotic coronary occlusion.<sup>89</sup>

## Summary and Conclusions

The different circumstances of each STEMI patient should be taken into consideration before catheterization laboratory activation. As with most complex diseases, an individualized treatment plan is required for every patient, and as technological and pharmacologic advancements continue, treatment strategies should continue to become more specialized.

### Conflict of Interest

None declared.

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