

**CORE CURRICULUM****Management of ST-segment-elevation myocardial infarction during the coronavirus disease 2019 (COVID-19) outbreak: Iranian “247” National Committee's position paper on primary percutaneous coronary intervention**

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**Abstract**

World Health Organization has designated coronavirus disease 2019 (COVID-19) as a pandemic. During the past several weeks, a considerable burden has been imposed on the Iranian's healthcare system. The present document reviewed the latest evidence and expert opinion regarding the management of ST-segment-elevation myocardial infarction during the outbreak of COVID-19 and outlines a practical algorithm for it.

## KEYWORDS

acute myocardial infarction/STEMI, percutaneous coronary intervention, thrombolytic therapy

## 1 | INTRODUCTION

The Iranian “247” primary percutaneous coronary intervention (PCI) Committee is a national scientific committee affiliated with the European Stent—save a life! Initiative with the primary objectives of enriching the scientific setting of primary PCI in Iran. In the past few weeks, Iran has faced a new viral acute respiratory disease, called coronavirus disease 2019 (COVID-19). The disease, which has been designated as a pandemic by the World Health Organization (WHO),<sup>1</sup> has already imposed a considerable burden on the country's healthcare system.<sup>2</sup>

The document presents the latest evidence and expert opinion regarding the management of ST-segment-elevation myocardial infarction (STEMI) during the outbreak of COVID-19 and similar scenarios and, outlines a practical algorithm for it.

## 2 | LATEST EVIDENCE REGARDING STEMI MANAGEMENT IN THE COVID-19 OUTBREAK

Regarding the preferred reperfusion strategy in STEMI during the COVID-19 outbreak, there is a paucity of data. No clinical trial has yet been performed, nor has any relevant official trial been registered in ClinicalTrials.gov or the WHO website. The available literature is also devoid of case series or cross-sectional studies concerning the best reperfusion strategy in the STEMI population during the COVID-19 outbreak.

Apropos STEMI management, thus far only the experiences of three scientific bodies namely the American College of Cardiology

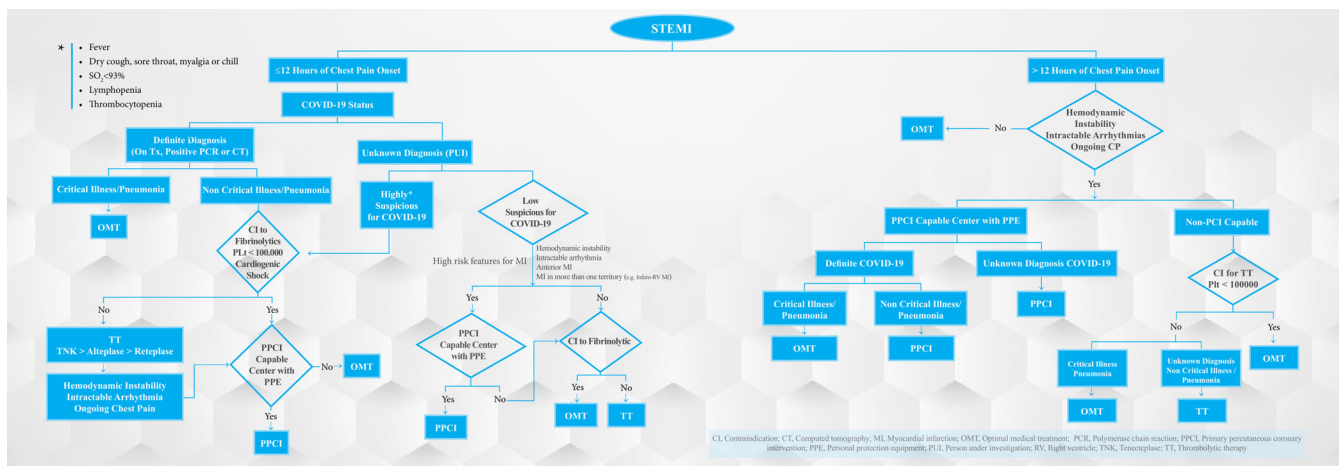
(ACC), the Society for Cardiovascular Angiography and Interventions (SCAI), and the European Society of Cardiology (ESC)<sup>3–6</sup> as well as Sichuan Provincial People's Hospital,<sup>7</sup> have been officially published. However, all these documents are based on expert opinion and not solid evidence.

Apart from the SCAI statement,<sup>4</sup> the other documents have suggested systemic thrombolysis as the main therapeutic approach during the current situation. The focus of attention in the available recommendations is safety concerns. Nosocomial transmissions, if not worse than the case with (severe acute respiratory syndrome and Middle East respiratory syndrome, are a major problem allied to COVID-19.<sup>8,9</sup> The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly contagious, even from the asymptomatic population, with a large portion of nosocomial transmissions occurring through contacts between clinicians and visitors with no or mild symptoms of COVID-19.<sup>8</sup>

Very few catheterization laboratories (Cath labs) are equipped with negative ventilation systems and, consequently, the risk of transmission remains high with each encounter.<sup>5</sup> The success of the safety measures adopted is further compromised by limited access to personal protective equipment (PPE), staff exhaustion, and multiple re-exposures. Such safety concerns, along with the acceptable mortality benefit of the new generation of fibrinolytic agents, have placed thrombolytic therapy as a potential first choice on several occasions during the outbreak.

## 3 | PROPOSED ALGORITHM

The following points should be considered before the application of the protocol:



**FIGURE 1** Algorithm on the management of ST-segment-elevation myocardial infarction during COVID-19 [Color figure can be viewed at wileyonlinelibrary.com]

1. This is a consensus-based protocol, and the majority of its recommendations have been provided based on expert opinion.
2. It is strongly recommended that each and every "247" primary PCI-dedicated center continue registration of patients admitted with STEMI to the national database.
3. Due to the high transmission rate from asymptomatic patients, patient transport between centers regardless of the COVID-19 status should be restricted.<sup>2</sup>
4. Given the hitherto limited success of diagnostic modalities vis-à-vis COVID-19, patients can be characterized regarding their COVID-19 status as definite and indefinite. It is, therefore, prudent that patients with an indefinite diagnosis be treated with the highest safety measures because of the remarkable asymptomatic state and transmission rate of the disease during this epidemic.<sup>8</sup>
5. In cases with an indefinite COVID-19 diagnosis, highly suspicious patients (Figure 1) should be defined as those meeting one of the following criteria:
  - a. Fever.
  - b. Dry coughs, sore throat, myalgia, or chills.
  - c.  $SO_2 < 93\%$ .
  - d. Lymphopenia (less than 1,500 lymphocytes/ $\mu$ l).
  - e. Thrombocytopenia (less than 100,000 platelets/ $\mu$ l).
6. **Critical** patients with COVID-19 pneumonia (Figure 1) should be defined as those that meet one of the following three criteria: (1) respiratory failure, (2) septic shock, and (3) multiple organ failure. Patients with those criteria have a mortality rate of 49% and, consequently, supportive care should be the main strategy.<sup>8</sup>
7. In many occasion (Figure 1), thrombolytic therapy is the main reperfusion strategy in patients admitted less than 12 hr following the onset of chest pain. Our major concerns apropos the present recommendation are personal safety and nosocomial transmissions.
8. While primary PCI is considered the gold standard therapy in the management of primary PCI, the following statements strongly suggest that thrombolytic therapy may be a suitable substitute on special occasions:
  - a. During the first 3–6 hr from the symptom onset, thrombolytic therapy has gained comparable results with primary PCI.<sup>10,11</sup>
  - b. Delay in reperfusion therapy is widely acknowledged as a key determinant for poor survival.<sup>12</sup>
  - c. The emotional stress generated by the present outbreak, combined with the high burden imposed on healthcare systems, might significantly delay patient transfer to the Cath lab.<sup>13</sup>
9. During the outbreak, primary PCI should be permitted only in "247" primary PCI-dedicated centers in which appropriate PPE is adhered to (see below). It is vital that primary PCI be postponed and replaced by thrombolytic therapy, if PPE is not guaranteed.
10. When primary PCI is chosen as the main strategy, the following measures are strongly advised:
  - a. Due to considerable transmission from asymptomatic patients, standard PPE measures (see the safety section) should be undertaken for all patients regardless of their COVID-19 status. Those measures should be implemented before the transfer of patients to the Cath lab.
  - b. During the COVID-19 epidemic, patients should not be directly transferred to the Cath lab by emergency medical services bypassing the emergency department.
  - c. After PCI is accomplished, irrespective of the patient's COVID-19 status, complete disinfection procedures should be commenced in the Cath lab before the admission of a new patient.

**TABLE 1** Fibrinolytic agent comparisons<sup>15</sup>

Fibrinolytic agent	Dose	Fibrin specificity <sup>a</sup>	Fibrinogen depletion	Antigenic	Patency rate (90-min TIMI 2 or 3 flow) (%)
Fibrin specific	--	--	--	--	--
Tenecteplase (TNK)	Single IV weight-based bolus <sup>b</sup>	++++	Minimal	No	85
Retepase (r-PA)	10 units +10 units IV bolus given 30 minute apart	++	Moderate	No	84
Alteplase (t-PA)	90-min weight-based infusion <sup>c</sup>	++	Mild	No	73–84
Nonfibrin specific	--	--	--	--	--
Streptokinase <sup>d</sup>	1.5 million units IV given over 30–60 min	No	Marked	Yes <sup>e</sup>	60–68

Abbreviations: r-PA, reteplase plasminogen activator; t-PA, tissue plasminogen activator.

<sup>a</sup>Strength of fibrin specificity: ++++ is stronger; ++ is less strong.

<sup>b</sup>Bolus of 30 mg for weight less than 60 kg, 35 mg for 60–69 kg, 40 mg for 70–79 kg, 45 mg for 80–89 kg, and 50 mg for 90 kg or greater.

<sup>c</sup>Bolus of 15 mg, infusion of 0.75 mg/kg for 30 min (maximum, 50 mg), then 0.5 mg/kg (maximum, 35 mg) over the next 60 min; the total dose not to exceed 100 mg.

<sup>d</sup>Streptokinase is no longer marketed in the United States but is available in other countries.

<sup>e</sup>Streptokinase is highly antigenic and absolutely contraindicated within 6 months of previous exposure because of the potential for serious allergic reaction.

**TABLE 2** Contraindications to fibrinolysis<sup>14,15</sup>

Absolute	Relative
Previous intracranial hemorrhage or stroke of unknown origin at any time	Transient ischemic attack in the preceding 6 months
Ischemic stroke in the preceding 6 months	Oral anticoagulant therapy
Central nervous system damage or neoplasms or arteriovenous malformation	Pregnancy or within 1-week postpartum
Recent major trauma/surgery/head injury (within the preceding 3 weeks)	Refractory hypertension (systolic pressure > 180 mmHg and/or diastolic pressure > 110 mmHg)
Gastrointestinal bleeding within the past month	Advanced liver disease
Known bleeding disorder (excluding menses)	Infective endocarditis
Aortic dissection	Active peptic ulcer
Noncompressible punctures in the past 24 hr (e.g., liver biopsy and lumbar puncture)	Prolonged or traumatic resuscitation

- d. If possible, resuscitation should be performed outside the Cath lab (see the resuscitation section).
  - e. Radial access should be the dominant approach by virtue of its safer access management.
  - f. Culprit vessel-only PCI should be the main strategy.
  - g. Hemodynamic instability and intractable arrhythmia should be defined per the latest ESC recommendation.<sup>14</sup>
11. In patients with STEMI, the fibrinolytic agent of choice is tenecteplase according to the ESC and ACC guidelines due to its superior efficacy in terms of the patency rate (90 min of TIMI flow Grade 2 or 3) (Table 1), unless the patient has the contraindications shown in Table 2.<sup>14-16</sup> Nonetheless, another factor that should be considered is the difference between fibrinolytics in terms of bleeding. As patients with COVID-19 could be at higher risk of bleeding, in particular in severe cases, the fibrinolytic with the least potential of bleeding should be applied.<sup>17-19</sup> Fortunately, tenecteplase appears to be the superior agent because of its association with less fibrin depletion. In light of the higher success rate of tenecteplase, it can be recommended as the agent of choice.<sup>14-16</sup> In elderly patients (older than 75 years old), a half dose of tenecteplase is recommended.<sup>14</sup> Consequently, the suggested fibrinolytics of choice in patients with COVID-19 can be described as follows: tenecteplase > alteplase > reteplase. Streptokinase is not recommended owing to the association between its use and the high risk of bleeding and the low success rate. Nevertheless, if there is no alternative, streptokinase can be used provided that the risks and benefits associated with its application be taken into consideration. Unfractionated heparin (UFH) can be initiated 3 hr after its infusion completion with the conventional bolus and the maintenance dose if the activated partial thromboplastin time is less than 50 ms.
- For fibrin-specific agents including alteplase, reteplase, and tenecteplase, UFH can be administered concomitantly before the end of fibrinolytic therapy with an intravenous (IV) bolus dose of 60 U/kg (maximum 4,000 U), followed by an infusion of 12 U/kg/hr (maximum 1,000 U), adjusted to maintain the activated partial thromboplastin time at 1.5 to 2.0 times control for between 24 and 48 hr (Class I, LOE: C). (The ESC 2017 guideline mentions 24 hr.)<sup>14,15</sup> Enoxaparin can also be drawn upon as an adjuvant anticoagulant. If the patient is aged 75 years or younger, 15 min after a bolus of 30 mg, enoxaparin (1 mg/kg) is administered subcutaneously twice daily (maximum 100 mg per dose for the first two doses). Enoxaparin should be administered preferably for the duration of the index hospitalization. For those older than 75 years old, 0.75 mg/kg of enoxaparin can be administered subcutaneously twice daily (maximum 75 mg for the first two doses) without a bolus dose.<sup>14,15</sup> Both ACC and ESC guidelines strongly support enoxaparin (compared with UFH) as the preferred parenteral anticoagulant with fibrinolysis (Class I, LOE: A).<sup>14,15</sup> Enoxaparin is also preferred to UFH for anticoagulation extending beyond 48 hr.<sup>14,15</sup> Still, if the patient is at high risk of bleeding due to COVID-19, UFH would be a better option because of the availability of protamine as a reversal agent.
12. Bleeding complication management: According to the ESC guideline regarding the management of acute coronary syndrome in patients with thrombocytopenia, a complete blood count before lytic therapy is recommended since the administration of thrombolytic agents is contraindicated in patients with a platelet count of below 100,000/mcL.<sup>20</sup> This protocol can be implemented in those with higher suspicion of COVID-19, defined as the presence of associated symptoms or a PaO<sub>2</sub> level of less than 93%.<sup>17</sup> Patients infected with COVID-19 and coagulopathy are at higher risk of mortality. Coagulopathy is defined as a 3-s extension of the prothrombin time or a 5-s extension of the activated partial thromboplastin time. When there is bleeding, the following treatment measures should be attempted within 48 hr of the administration of fibrinolytic drugs<sup>21</sup>:
- a. Stop the infusion of fibrinolytics and other antithrombotic drugs.
  - b. Administer 12 ml/kg of fresh frozen plasma.
  - c. Administer 1 g of intravenous tranexamic acid three times a day.
  - d. When faced with fibrinogen depletion, administer cryoprecipitates or fibrinogen concentrates.
  - e. It is advisable that the fibrinogen level be measured before the administration of fibrinolytics. Protamine can also be used for the management of bleeding with UFH/enoxaparin. Platelet transfusion should generally be avoided except for those undergoing neurosurgical interventions.<sup>22</sup>
13. Given the hitherto limited success of diagnostic modalities vis-à-vis COVID-19, patients can be characterized regarding their COVID-19 status as definite and indefinite. It is, therefore, prudent that patients with an indefinite diagnosis be treated with the highest safety measures because of the remarkable asymptomatic state and transmission rate of the disease during this epidemic.<sup>8</sup>

#### 14. Safety concerns:

- a. The PPE protocol provides a guide for the management of the Cath lab rooms and staff so as to guarantee appropriate treatment standards via the application of all infection prevention and control measures during the management of suspected, likely, or confirmed cases of viral infection.<sup>23</sup>
  - b. All patients transferred to the Cath lab should wear nonfiltered facemasks, if they can tolerate them.
  - c. The number of personnel entering the Cath lab area should be restricted.
  - d. If feasible, specialized negative pressure ventilation in the Cath lab is recommended.
  - e. An isolation room immediately next to the Cath lab should be provided for the personnel to wear or remove their PPE.
  - f. A path should be clearly designated for patients exiting the Cath lab.
  - g. A checklist should be placed in the Cath lab in order to check the availability of the following items:
    - i. Surgical masks.
    - ii. N95 or filtering face piece (FFP2 and FFP3) masks.
    - iii. Disposable gowns.
    - iv. Disposable shoe covers or surgical plastic boots (if possible).
    - v. Gloves (two pairs for each person).
    - vi. Protective goggles/visor/face shield.
    - vii. Any disposable water-repellent gown if there is a risk of important splashes of organic material.
  - h. All actions regarding PPE should be properly registered.
  - i. All unnecessary devices should be removed from specific Cath labs and only disposable items should be kept in the room.
  - j. Upon the termination of each procedure, the disinfecting team should discharge their duties completely, rendering minutes and even hours of delay between two procedures inevitable. This further underscores the significance of postponing elective angiography and devoting the Cath lab to necessary interventions.
- 15 Antithrombotic regimen during the COVID-19 outbreak: Concerning P2Y12 inhibitors of choice, clopidogrel is recommended for fibrinolytic therapy candidates. In patients candidated for primary PCI, ticagrelor can be the recommended agent. However, in patients with a definite diagnosis of COVID-19 on treatment with lopinavir/ritonavir, ticagrelor is not recommended due to interaction and high risk of bleeding. Prasugrel is not associated with significant interactions, but it predisposes patients to bleeding. As these patients are at higher risk of bleeding, in particular in severe cases, clopidogrel can again be introduced as the preferred agent. It should be noted that clopidogrel also has significant interactions with lopinavir/ritonavir, which may reduce its conversion to active metabolites.
- 16 The following points should be considered with regard to optimal medical therapy:
- a. In regard to statins, atorvastatin and rosuvastatin need to be dose-adjusted in patients on lopinavir/ritonavir. The maximum recommended dose for these agents is 20 and 10 mg, respectively. This dose modification is due to the high risk of toxicity associated with these agents when used concomitantly with lopinavir/ritonavir.
  - b. Concerning beta-blockers, the monitoring of the heart rate and blood pressure is highly recommended. This strategy is more pronounced for those with similar pathways of metabolism. Therefore, metoprolol, carvedilol, and bisoprolol, which are used based on the guidelines in this population, should be administered while concomitantly monitoring the pulse and blood pressure.<sup>24</sup>
  - c. Regarding angiotensin-converting enzymes/angiotensin-receptor blockers (ACEIs/ARBs), despite the conflicting data pertaining to the potential benefit or harm associated with these agents, it is recommended that they be prescribed and continued in this population. The reason behind this statement is the proven beneficial cardiovascular effects of ACEIs/ARBs in patients with acute coronary syndrome.
- 17 The following points should be considered during the resuscitation and management of patients with STEMI<sup>25</sup>:
- a. Full aerosol-generating procedure (AGP) PPE should be worn by all members of the resuscitation/emergency team before entering the room. Staff members require a gown, goggles, gloves, and an FFP3 mask before starting chest compressions.
  - b. Sets of AGP PPE should be on the resuscitation trolley (or where the resuscitation equipment is stored) to be readily available at all times.
  - c. No chest compressions or airway procedures such as those detailed below should be undertaken without full AGP PPE.
  - d. Airway interventions should be carried out by experienced individuals.
  - e. Compression-only cardiopulmonary resuscitation (CPR) should be commenced and the patient's cardiac arrest rhythm should be monitored as soon as possible.
  - f. Mouth-to-mouth ventilation and pocket mask use should be avoided.
  - g. If the patient is already receiving supplemental oxygen therapy through a facemask, the mask should be left on the patient's face during chest compressions as this may limit aerosol spread. Otherwise, a facemask should be placed on the patient's face.
  - h. The number of staff in the room (if a single room) should be minimized.
  - i. All equipment used during CPR should be disposed of or cleaned.

## 4 | CONCLUSION

The present document, in compliance with the available evidence and clinical judgment, seeks to provide a practical protocol for the

management of STEMI. Indubitably, all the aforementioned recommendations are subject to change given the fluidity of the COVID-19 epidemic status.

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