Management of STEMI in Low- and Middle-Income Countries

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ST-segment elevation in the setting of acute coronary syndrome suggests that the patient is at high risk for morbidity and mortality. These patients require not only early reperfusion (Figure 1) [1] but also full reperfusion (Figure 2) [2] when possible preferably by timely percutaneous coronary intervention (PCI), whereas non–ST-elevation myocardial infarction is generally approached by a less invasive and frequently delayed strategy. This white paper is focused on management of ST-segment elevation myocardial infarction (STEMI) in low- and middle-income countries (LMIC) where scarce resources, including paucity of trained medical personnel, lack of well-developed emergency medical services, access to resources, and other logistical challenges do not permit early PCI in the majority of patients unlike in high-income countries [3]. The treatment gap between high-income countries and LMIC is of concern because 80% of the cardiovascular mortality occurs in the latter; therefore, this white paper attempts to discuss challenges and strategies in the management of STEMI with the view of reducing morbidity and mortality.

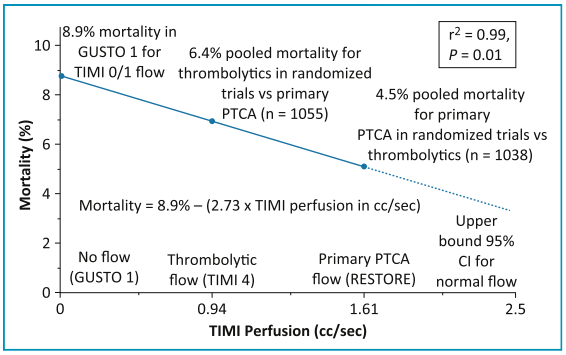

FIGURE 1. Relationship between coronary blood flow and mortality rate in patients with acute myocardial infarction. CI, confidence interval; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; PTCA, percutaneous transluminal coronary angioplasty; RESTORE, Randomized Efficacy Study of Tirofiban for Outcome and Restenosis; TIMI, Thrombolysis In Myocardial Infarction. Reproduced, with permission, from Gibson [1].

The authors report no relationships that could be construed as a conflict of interest.

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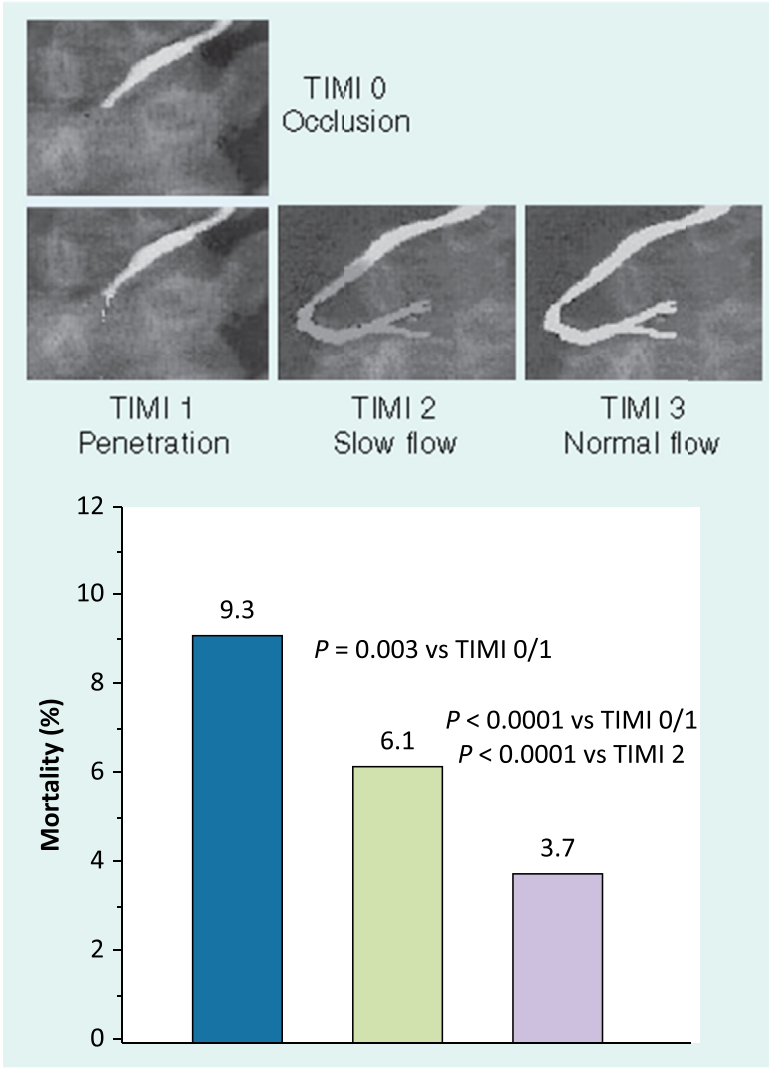


FIGURE 2. Correlation of TIMI (Thrombolysis In Myocardial Infarction) flow grade and mortality. A pooled analysis of data from 5,498 patients in several angiographic trials of reperfusion for ST-segment elevation myocardial infarction showed a gradient of mortality when the angiographic findings were stratified by TIMI flow grade. Patients with TIMI flow grade 0 or TIMI flow grade 1 had the highest rate of mortality; TIMI flow grade 2 was associated with an intermediate rate of mortality; and the lowest rate of mortality was observed in patients with TIMI flow grade 3. Reproduced, with permission, from Antman and Morrow [2].

HISTORY

The clinical syndrome accompanying acute MI was described by 2 Russian physicians, V.P. Obrastzov and N.D. Strazhesko, in 1910 [4], and then by James B. Herrick in 1912 [5]. Herrick cited a German translation of the Russian article, and he reported that "myocardial infarction was not an inescapable tocsin of doom, but that it was often survived, sometimes with little lasting damage" [6].

DEFINITION

Tables 1 and 2 present the classifications and definition of acute MI [7,8]. STEMI is a clinical condition that includes the following: 1) characteristic clinical features of myocardial ischemia; 2) persistent J-point ST-segment elevation in ≥2 contiguous leads (≥2 mm in men or ≥1.5 mm in women in leads V_2 and V_3 or ≥1 mm in other precordial or limb leads) in the absence of left bundle branch block (LBBB) or left ventricular (LV) hypertrophy; and 3) elevated biomarkers of myocardial cell death (cardiac troponin [cTn] is the preferred biomarker) [7].

In patients with transmural posterior injury, ST-segment depression may be observed in leads V_1 to V_4. Occasionally, very early in the pathogenesis of a STEMI, hyperacute T-wave changes may be seen on 12-lead electrocardiogram (ECG). Baselines ECG changes that might obscure a diagnosis of STEMI apart from LBBB and LV hypertrophy include paced rhythm, early repolarization, and Brugada syndrome. In those with baseline LBBB or right-paced ventricular rhythm, the activation of the LV occurs after the right ventricle (RV) and therefore there is delayed activation of the infarcted ventricle that is buried in the QRS complex. Thus, Q waves cannot be used to diagnose MI. Therefore, diagnosis of acute MI in those with LBBB depends on ST-segment changes in the same direction as the major QRS vector, including ST-segment depression of ≥1 mm in chest leads V_1, V_2, or V_3 or in inferior limb leads II, III, or aVF and elevation of ≥1 mm in lead V_5 or extremely discordant ST-segment deviation >5 mm. Limitations of the ECG include the fact that, often, it does not adequately detect involvement of the posterior, lateral, and apical walls of the LV. When the diagnosis of STEMI is suspected and the diagnosis cannot be confirmed by ECG due to confounding factors, transthoracic echocardiography may be helpful to detect focal wall motion abnormalities. Whenever there is a lingering doubt about the diagnosis of STEMI, coronary angiography should be considered for appropriate triage of the patient.

CLINICAL MANIFESTATIONS

History

Typically the chest pain in myocardial ischemia is in the sternal region and radiating to the left side of the chest and neck and down the medial side of the forearm and hand (Figure 3) [9]. Other areas where the pain can be felt are in the jaw, epigastrium, and back. When the pain is severe, it can be felt on the right side of chest and right arm as well. The quality of the pain is similar to angina pectoris but more severe and prolonged. It is perceived as crushing, squeezing, pressing, heavy, band-like, vise-like, strangling, constricting, aching, or even burning, but rarely as sharp

TABLE 1. Classification of acute MI dependent on third universal definition of MI

Type 1. Spontaneous MI
Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in 1 or more of the coronary arteries leading to the decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion nonobstructive or no CAD.
Type 2: MI secondary to an ischemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3. MI resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases when cardiac biomarkers were not collected.
Type 4a. MI related to PCI
MI associated with PCI is arbitrarily defined by elevation of cTn values $>5 \times$ 99th percentile ULN in patients with normal baseline values ($\leq$99th percentile ULN) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, 1 of the following are required: 1) symptoms suggestive of myocardial ischemia; 2) new ischemic ECG changes or new LBBB; 3) angiographic loss of patency of a major coronary artery or a side branch of persistent slow-or-no-flow or embolization; or 4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.
Type 4b. MI related to stent thrombosis
MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with $\geq$1 value above the 99th percentile ULN.
Type 5. MI related to CABG
MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values $>10 \times$ 99th percentile ULN in patients with normal baseline cTn values ($\leq$99th percentile ULN). In addition, 1 of the following are required: 1) new pathological Q waves or new LBBB; 2) angiographic documented new graft or new native coronary artery occlusion; or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

CABG, coronary artery bypass graft; CAD, coronary artery disease; cTn, cardiac troponin; ECG, electrocardiography; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; MI, myocardial infarction; PCI, percutaneous coronary intervention; ULN, upper limit of normal.
Adapted from Thygesen et al. [7].

pain or stabbing pain. Discomfort above the jaw or below the umbilicus is rarely seen in acute MI. Clenching of the fist during chest pain suggests myocardial ischemia (Figure 4) [10]. Accompanying symptoms include diaphoresis, nausea, vomiting, shortness of breath, weakness, restlessness, and apprehension. The discomfort of myocardial ischemia, compared with that of angina, can last for minutes to hours and is not relieved by rest or sublingual nitroglycerine. The onset can be related to exercise or emotional stress. In about 20% of the patients, acute MI is "silent" or painless or atypical in presentation, particularly in diabetics, women, and the elderly. The differential diagnosis of ischemic chest discomfort includes acute aortic dissection, reflux esophagitis, costochondritis, pleurisy, or pulmonary embolism.

Physical examination

There are no typical physical findings that are diagnostic or pathognomonic of acute MI and often the physical examination may be normal. Signs of sympathetic activity including tachycardia, hypertension, or both may accompany anterior wall MI, whereas signs of parasympathetic hyperactivity including bradycardia, hypotension, or both may accompany inferior wall MI. Fourth heart sound may be heard if carefully sought. The clinical examination should focus on determining the adequacy of vital signs and peripheral perfusion, on signs of heart failure and cardiogenic shock, and on signs of cardiac arrhythmias and mechanical complications (such as cardiac murmurs).

MANAGEMENT

Prehospital and initial management

More than one-half the mortality (Figures 5 and 6) [11] in acute MI occur within 1 h of onset of symptoms before the patient can reach the emergency department. And most of these deaths are due to ventricular fibrillation due to ischemia and can be reversed by prompt defibrillation. In addition, the first hour or the "golden hour" is the best opportunity (Figure 7) [12] to salvage myocardium by reperfusion. The total ischemic time (Figure 8) [13] is prolonged in LMIC. For example, the CREATE (Treatment and Outcomes of Acute Coronary Syndromes in India) registry [14] showed that the mean time delay from symptom onset to presentation to the hospital was 360 min in India. Therefore, there are considerable opportunities to reduce total ischemic time by implementing the following: 1) reduced patient delay; 2)

TABLE 2. Definition of acute MI

Definition of MI
Criteria for acute MI
The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any of the following criteria meets the diagnosis for MI:
• Detection of a rise and/or fall of cardiac biomarkers values (preferably cTn) with ≥1 value above the 99th percentile ULN and with ≥1 of the following:
◦ Symptoms of ischemia.
◦ New or presumed new significant ST-segment—T-wave (ST-T) changes or new LBBB.
◦ Development of pathological Q waves in the ECG.
◦ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
◦ Identification of an intracoronary thrombus by angiography or autopsy.
• Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
• PCI-related MI is arbitrarily defined by elevation of cTn values (>5 × 99th percentile ULN) in patients with normal baseline values (≤99th percentile ULN) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, 1 of the following are required:
◦ Symptoms suggestive of myocardial ischemia
◦ New ischemic changes
◦ Angiographic findings consistent with a procedural complication
◦ Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
• Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with ≥1 values >99th percentile ULN.
• CABG-related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 × 99th percentile ULN) in patients with normal baseline cTn values (≤99th percentile ULN). In addition, 1 of the following is required:
◦ New pathological Q waves or new LBBB
◦ Angiographic documented new graft or new native coronary artery occlusion
◦ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Abbreviations as in Table 1.
Adapted from Thygesen et al. [7].

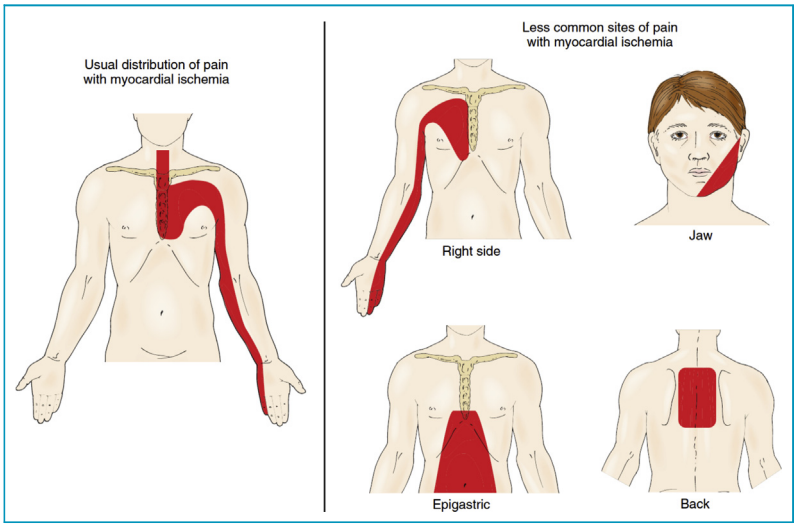


FIGURE 3. Pain patterns with myocardial ischemia. The usual distribution is referral to all or part of the sternal region, the left side of the chest, and the neck and down the ulnar side of the left forearm and hand. With severe ischemic pain, the right chest and right arm are often involved as well, although isolated involvement of these areas is rare. Other sites sometimes involved, either alone or together with other sites, are the jaw, epigastrium, and back. Reproduced, with permission, from Braunwald [9].

improvement of emergency medical system to deliver early therapy, particularly fibrinolysis; and 3) speedy transport to a medical facility to deliver fibrinolysis or PCI.

Patient delay. The greatest time lag to reperfusion is the patient's delay in seeking medical assistance (Figure 9) [15]. Given the lack of awareness of patients in LMIC countries [14,16,17], each direct encounter with an at-risk patient (e.g., diabetics, hypertensives, or patients with a history of angina) should be considered to be a teachable moment to increase awareness and regularly reinforced by mobile messaging systems. Patients should be encouraged to seek immediate medical attention when they have symptoms suggestive of acute coronary syndrome including chest pain, shortness of breath, or fatigue, particularly when accompanied by diaphoresis, lightheadedness, palpitations, or a sense of impending doom. They should be encouraged to properly use chewable aspirin and sublingual nitroglycerine when available and to call emergency services when such symptoms persists for >5 min [18].

Emergency medical systems. An important opportunity in LMIC is expanding the ability to perform pre-hospital ECG, delivering pre-hospital fibrinolysis [19], and developing a robust emergency medical system that comprises emergency dispatch, first response teams, and

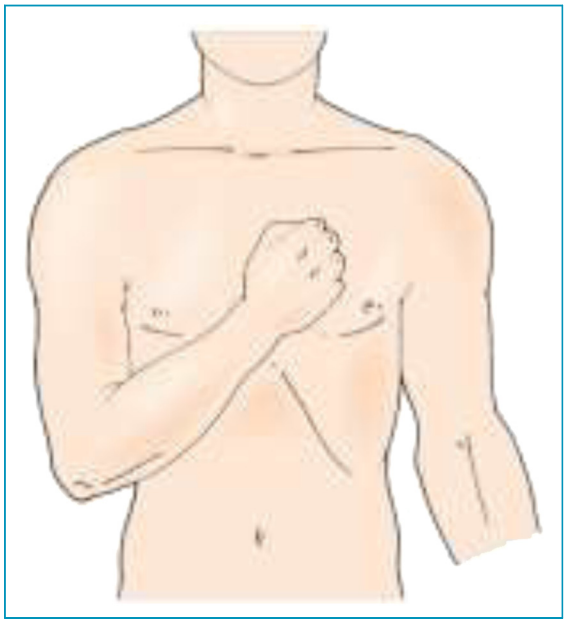


FIGURE 4. The Levine sign of acute myocardial ischemia. The clenched fist approximates the area of ischemic discomfort. Reproduced, with permission, from Braunwald [10].

ambulance response. Developing an ambulance service is a priority in most developing countries. This is important for rapid transfer of patients to appropriate hospitals and for interfacility transfer of patients in the pharmacoinvasive strategy. One of the recent success stories in India has been the development of an ambulance system that is equipped for the management of STEMI patients [20]. At present, it covers 372 million patients in 15 states and union territories and has over 3,500 ambulances making 4.5 trips per day with a cost per ambulance trip of INR

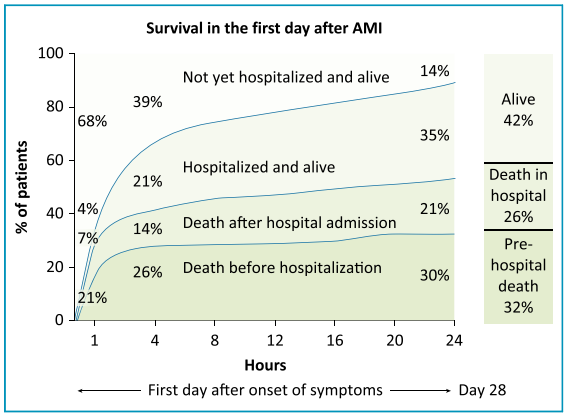


FIGURE 5. Survival in the first day after acute myocardial infarction. Reproduced with permission from Löwel H, Lewis M, Hörmann A. Prognostic significance of the pre-hospital phase in acute myocardial infarction: results of the Augsburg Myocardial Infarct Registry, 1985-1988 [in German]. Dtsch Med Wochenschr 1991;116:729-733.

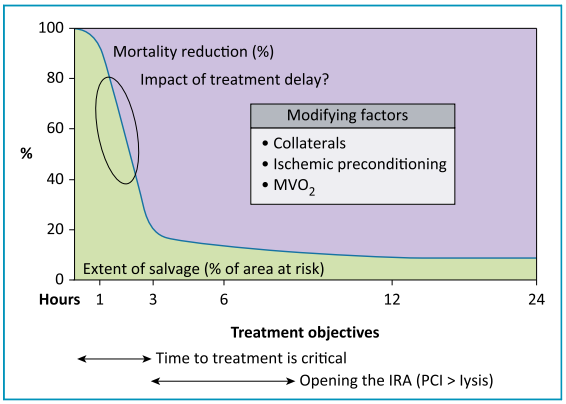


FIGURE 6. Relationship between mortality reduction and extent of salvage postulated relationship between duration of ischemia before reperfusion, extent of myocardial salvage, mortality reduction, and goals of therapy. IRA, infarct-related artery; MVO_2, myocardial oxygen consumption; PCI, percutaneous coronary intervention. Reprinted, with permission, from Opie and Gersh [11].

600 (~US$10). This is projected to reach 10,000 ambulances covering 1.3 billion individuals in the next few years. The pattern of use at present is predominantly focused on trauma and pregnancy but could easily include chest pain as an additional priority area. However, this would increase its use dramatically and strain the viability of its present free service. Consideration should be made to develop ambulance insurance through increased

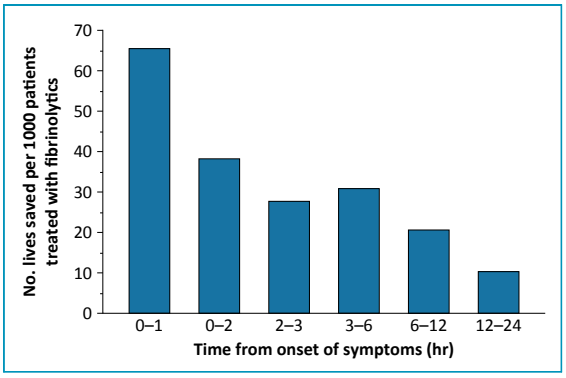


FIGURE 7. Importance of time to reperfusion in patients receiving fibrinolytic therapy for ST-segment elevation myocardial infarction. The data from 22 trials of fibrinolytic therapy were pooled and the findings stratified by the 6 time categories shown. The number of lives saved per 1,000 patients treated with fibrinolytics compared with placebo is greatest the earlier treatment is initiated after the onset of symptoms, and this decreases in a nonlinear fashion with incremental time delays. Because the lifesaving effect of fibrinolysis is maximal in the first hour from onset of symptoms, this has been referred to as the "golden hour" for pharmacologic reperfusion. Reproduced, with permission, from Boersma et al. [12].

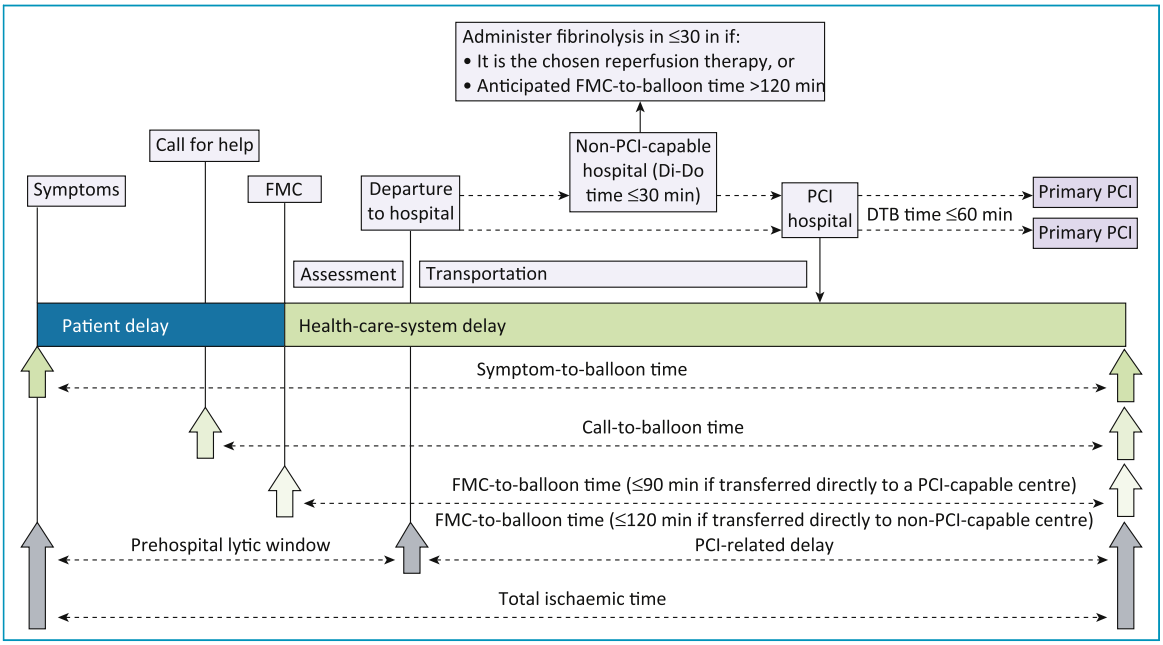


FIGURE 8. Important timeline metrics in management of ST-segment elevation myocardial infarction. Obstacles to reperfusion can be divided into delays related to patients and to the healthcare system. Percutaneous coronary intervention (PCI)-related delay is the extra time needed to do primary angioplasty rather than give on-scene pre-hospital thrombolysis. Delay can also occur if the nearest hospital is not PCI-capable. Depending on ST-segment elevation myocardial infarction network infrastructure, the non-PCI hospital is either bypassed or the patient is taken there before interhospital transfer to a primary-PCI center. In addition, a fibrinolytic agent can be given at the non-PCI-capable hospital. Delay intervals mandated by European and U.S. guidelines are superimposed [3,4]. Figure is not drawn to scale. Patient-related delays can vary substantially in length. DI-DO, door-in to door-out; DTB, door to balloon; FMC, first medical contact. Reproduced, with permission, from Gershlick et al. [13].

government support and restricting free service only to below-poverty-level families. This will help to expand the service and maintain its viability. With training of the paramedics, it should be possible to record a pre-hospital 12-lead ECG and deliver fibrinolysis or emergency medications in the ambulance depending on the strategy for an individual patient — primary PCI or pharmacoinvasive treatment. The same ambulance will also transport the

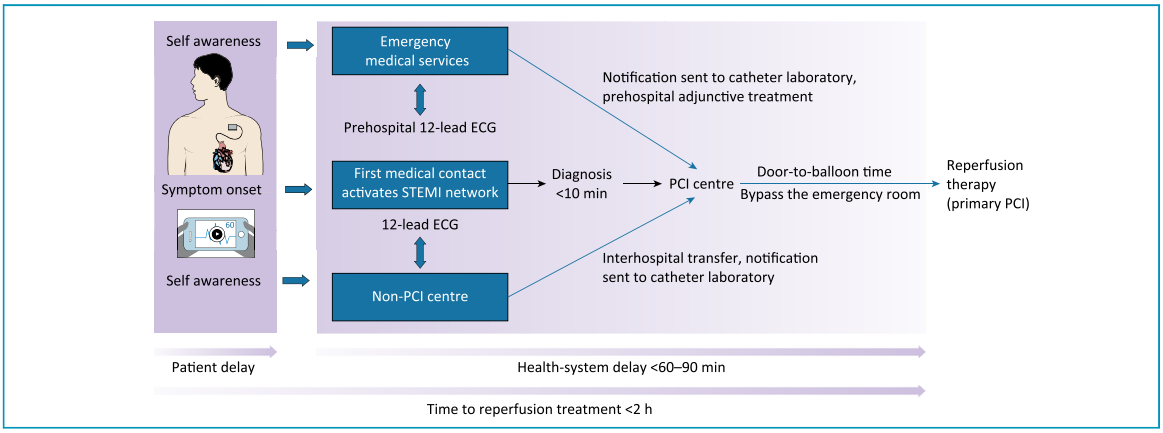


FIGURE 9. Patient-related and health-system delays in the ST-segment elevation myocardial infarction (STEMI) management continuum. There is a time-critical therapeutic window starting with symptom onset until reperfusion therapy for STEMI. Red arrows show where specific delays could potentially be reduced. Monitoring devices (either implantable or via a smartphone) could help to lessen patient delays. ECG, electrocardiogram; PCI, percutaneous coronary intervention. Reproduced, with permission, from Windecker et al. [15].

TABLE 3. Killip-Kimball classification of heart failure

Class	Subclass	Characteristics	Mortality (1967)
I	A	No heart failure No rales or S_3	6%
II	B	Heart failure Rales (<50% lunges), S_3, and venous hypertension	17%
III	C	Severe heart failure: frank pulmonary edema Rales (>50% lungs)	38%
IV	D	Cardiogenic shock: signs include hypotension (systolic blood pressure ≤90 mm Hg) and evidence of peripheral vasoconstriction, such as oliguria, cyanosis, and diaphoresis Heart failure, often with pulmonary edema, has also been present in the majority of these patients	81%

Patients with higher Killip-Kimball class had more severe angiographic coronary artery disease, higher incidence of ventricular dysfunction, and larger myocardial infarctions.
Adapted from Killip et al. [35] and DeGeare et al. [36].

TABLE 4. GRACE risk score for ACS (0 to 258)

	Points
Age, yrs	
<40	0
40–49	18
50–59	36
60–69	55
70–79	73
≥80	91
Heart rate, beats/min	
<70	0
70–89	7
90–109	13
110–149	23
150–199	36
>200	46
Systolic blood pressure, mm Hg	
<80	63
80–99	58
100–119	47
120–139	37
140–159	26
160–199	11
>200	0
Creatinine, μmol/l	
0–34	2
35–70	5
71–105	8
106–140	11
141–176	14
177–353	23
≥354	31
Killip class	
I	0
II	21
III	43
IV	64
Other risk factors	
Cardiac arrest at admission	43
Elevated cardiac markers	15
St-segment deviation	30

ACS, acute coronary syndrome; GRACE, Global Registry for Acute Coronary Events.

patient to a "STEMI center" for further treatment, bypassing non-PCI hospitals on the way. These ambulances should be ideally equipped with oxygen, endotracheal tubes, suction apparatuses, battery-operated monitoring equipment, commonly used cardiovascular drugs, a DC defibrillator, and radiotelemetry systems to allow transmission of ECG signals to facilitate triage of STEMI patients. Telephone transmission of ECG data has been used for many years for monitoring pacemakers and arrhythmias. Analog transmission was used initially but with the availability of digital telephones, 12-lead ECG-transmission is now standard. ECG transmission has been assessed as reliable for ST-segment changes, infarct changes, atrial fibrillation, and T-wave changes [20]. STEMI INDIA has developed a "STEMI device," which is a handheld device with global positioning system and 2G/3G transmission capability [20]. These handheld devices are located in ambulances and with STEMI coordinators at each STEMI hospital. The device in the ambulance uses the global positioning system to locate the closest STEMI hospital and appropriate hub hospital. Data from this device are transmitted to the destination hospital and to the dedicated server at the STEMI coordinating center. The STEMI device can do an ECG at the point of first medical contact. The ECG recorded on the handheld device can be transmitted from the ambulance/spoke hospitals to the hub hospital and the STEMI coordinating center. The "on-call" cardiologist can read the ECG and confirm STEMI before the patient is administered pre-hospital fibrinolysis and is transported to a PCI hospital. A click of a button converts the device into a monitoring device. Systolic blood pressure (SBP), functional oxygen saturation, heart rate, and cardiac rhythm can be monitored during the transportation of the patient and the availability of age, heart rate, and SBP can permit early risk stratification of patients into high- and low-risk

TABLE 5. Risk corresponding to total points

	<96	96–112	113–133	>133
30-day death	3.1	5.3	5.9	11.2
12-month death	4.2	9.6	11.9	27.2

Values are percentages.

groups [21]. The device can be programmed to automatically transmit this data to the destination hospital. The device also has data entry capabilities protocols can be loaded on the handheld device. Patient data entry and access of the data record can occur continuously during patient care at any of the transfer sites. STEMI work flow process is integrated with specific management protocols and depends on the following: 1) location of patient; 2) location of closest STEMI hospital; and 3) patients clinical condition—fibrinolytic contraindications or cardiogenic shock. All this data is stored in the cloud and can be accessed for audit and research [20].

In high-income countries, about 30% of the eligible patients do not receive any form of reperfusion therapies and there is a failure to minimize delays in reperfusion because of inefficient systems of care [22] and logistical challenges. In Australia, only 40.2% of the population had access to timely PCI [23]. In LMIC, similar to the situation in remote areas of high-income countries, scarce resources and other important barriers [19] to expeditious delivery of PCI means that realistically PCI is generally not the best default option. Important constraints include long transport times from rural areas to PCI-capable hospitals resulting in significant loss of viable myocardium. Therefore, the door-in to door-out time may be the new metric that LMIC will need to focus on (Figure 8) [13]. However, optimizing the emergency medical system response or increasing primary PCI services resulted in marginal improvement in timely access (1.8% and 3.7%, respectively). Direct transport to PCI facilities and interhospital transfer for PCI improves timely access to PCI for 19.4% and 23.5% of the population, respectively. Moreover, any benefit of primary PCI when compared with onsite fibrinolysis was eliminated when the delay to primary PCI exceeded 120 min [24]. The number needed to treat increased from 23 to 250 when PCI-related delay increased from 60 min to >90 min. Factors that degraded the benefits of PCI are not only door-to-balloon and door-to-needle times but also patient characteristics—for example, the benefits of PCI were eliminated when the time to delivery was >40 min in young men with large anterior wall MI [25]. System delays, including pre-hospital system delay and door-to-balloon delay also associated with increased mortality—1 registry study with a medial follow-up period of 3.4 years showed that a system delay of 0 to 60 min corresponds to a mortality rate of 15.4%, which increased to 30.8% when the delay was 181 to 360 min [26]. When compared with fibrinolysis, shorter system delays of primary PCI was associated with reduced absolute mortality at 30-day and 8-year follow-up [27]. It is estimated that the outcomes for the 2 therapies tend to equalize as these delays move beyond 90 min when pre-hospital fibrinolysis can be delivered. In regional and remote Australia, pre-hospital fibrinolysis markedly improved access to timely

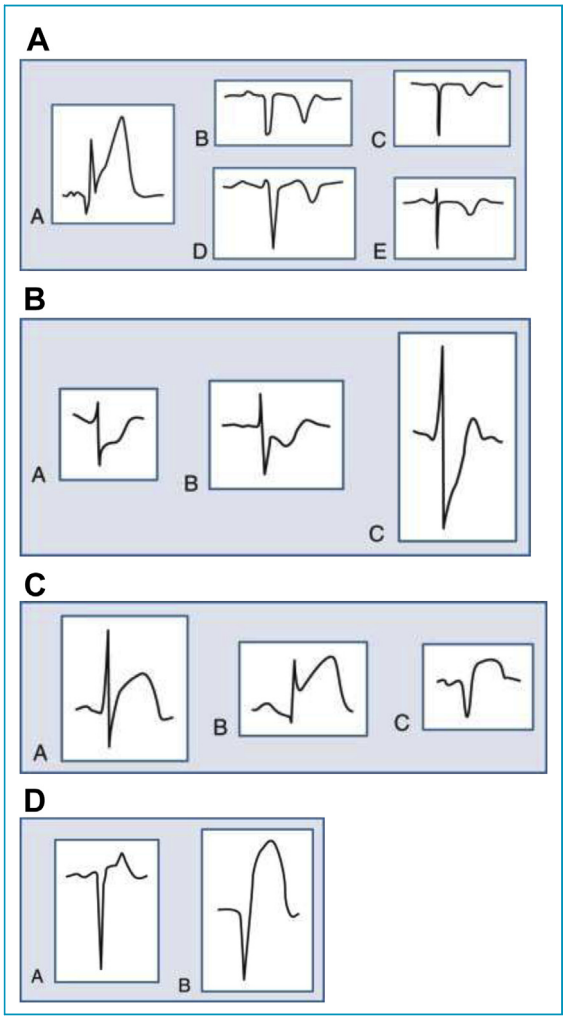


FIGURE 10. Electrocardiographic findings of acute myocardial infarction. (A) T-wave abnormalities of acute myocardial infarction: (a) prominent "hyperacute" T-wave; (b to e) T-wave inversions of non—ST-segment elevation myocardial infarction. (B) ST-segment depression: (a) flat; (b) down-sloping; (c) up-sloping. (C) ST-segment elevation: (a) convex ST-segment elevation; (b) obliquely straight ST-segment elevation; (c) convex ST-segment elevation. (D) Pathologic Q waves: (a) pathologic Q-wave of completed myocardial infarction; (b) simultaneous ST-segment elevation with pathologic Q-wave 2 h into the course of ST-segment elevation myocardial infarction. Reproduced, with permission, from Riordan and Brady [39].

reperfusion. The majority (93.2%) of the Australian population has timely access to reperfusion, mainly (53%) through fibrinolysis [23]. Fibrinolysis, therefore, seems to be the first-choice default reperfusion therapy in LMIC.

Pre-hospital fibrinolysis has been showed to be beneficial in randomized trials and a large meta-analysis demonstrated a 17% reduction in mortality. The CAPTIM (Comparison of Angioplasty and Pre-Hospital Thrombolysis in Acute Myocardial Infarction) study [28], which evaluated pre-hospital fibrinolysis plus rescue angioplasty against primary PCI reported that at 5-year follow-up patients given fibrinolysis within 2 h of STEMI had lower mortality rates (5.8%) than did primary PCI patients who had mortality rate of 11.1% [29]. Whereas patients treated with pre-hospital fibrinolysis after 2 h had a 5-year mortality rate of 14.5% compared with 14.4% for primary PCI [28,29]. The benefit of pre-hospital fibrinolysis has also been demonstrated by registry data [30–32].

However, fibrinolysis alone is not optimal. The REACT (Rapid Early Action for Coronary Treatment) trial found that recording an ECG 90 min after fibrinolytic therapy was delivered was an important determinant on whether rescue PCI is warranted [33]. The benefit of coronary angiography within 24 h of fibrinolytic therapy was also supported by the GRACIA-1 (Randomized Trial Comparing Stenting Within 24 Hours of Thrombolysis Versus Ischemia-Guided Approach to Thrombolysed Acute Myocardial Infarction With ST Elevation) study [34]. The CAPTIM study, which evaluated pre-hospital fibrinolysis plus rescue angioplasty against primary PCI, reported that at 5-year follow-up patients given fibrinolysis within 2 h of STEMI had lower mortality rates (5.8%) than did primary PCI patients who had mortality rate of 11.1% [29]. Whereas patients treated with pre-hospital fibrinolysis after 2 h had a 5-year mortality rate of 14.5% compared with 14.4% for primary PCI patients.

In-hospital management

The goals of management in the emergency department include early detection of STEMI and rapid deployment of resources to deliver reperfusion. In LMIC, there may be considerable delay in triaging a patient with chest pain due to the heavy load of patients in the general emergency department and the absence of dedicated chest pain centers. Whereas facilities may be akin to high-income countries in corporate hospitals and large public institutions in metro cities, the facilities even for thrombolysis may not be available in smaller towns and villages.

DIAGNOSIS AND RISK ASSESSMENT

Clinical examination

In a patient with suspected STEMI, the clinical examination including Killip class assessment [35,36] (Table 3) and the ECG should be performed and interpreted within 10 min of first medical contact (FMC). As cardiac arrhythmias are common in acute coronary syndromes, the patient should be attached to a bedside monitor and intravenous access should be obtained. History taking

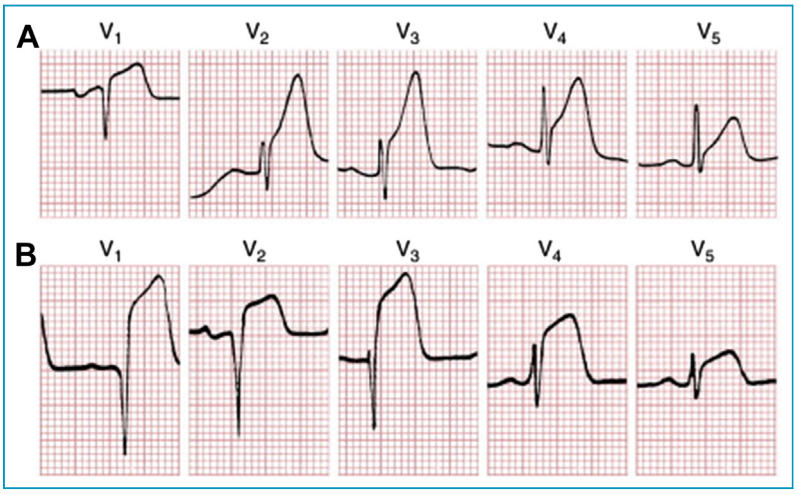


FIGURE 11. Chest leads from a patient with acute anterior ST-segment elevation myocardial infarction. (A) In the earliest phase of the infarction, tall, positive (hyperacute) T waves are seen in leads V_2 to V_5. (B) Several hours later, marked ST-segment elevation is present in the same leads (current of injury pattern), and abnormal Q waves are seen in leads in V_1 and V_2. Reproduced, with permission, from Goldberger [40].

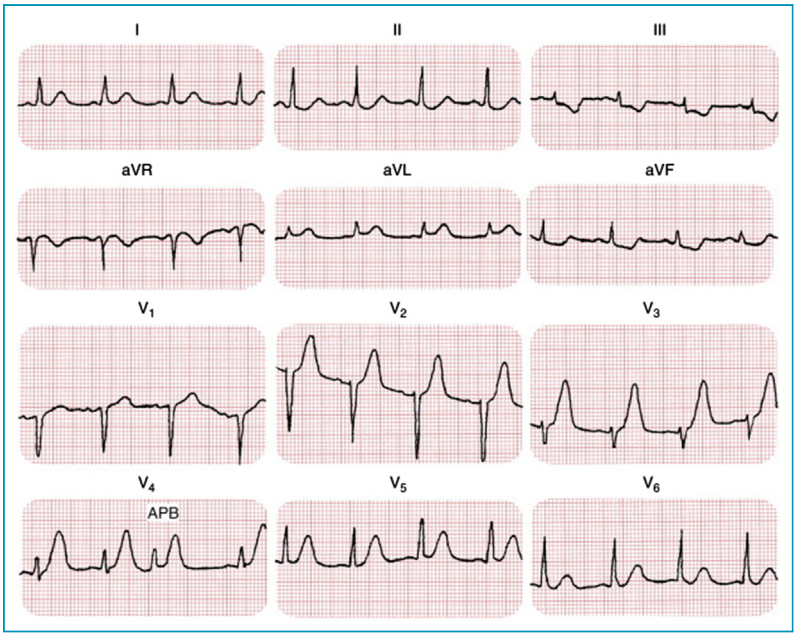


FIGURE 12. Hyperacute T waves with anterior ST-segment elevation myocardial infarction. This patient was complaining of severe chest pain. Notice the very tall (hyperacute) T waves in the chest leads. In addition, slight ST-segment elevations are present in lead aVL and reciprocal ST-segment depressions are seen in leads II, III, and aVF. Notice the atrial premature beat (APB) in lead V_4. Reproduced, with permission, from Goldberger [40].

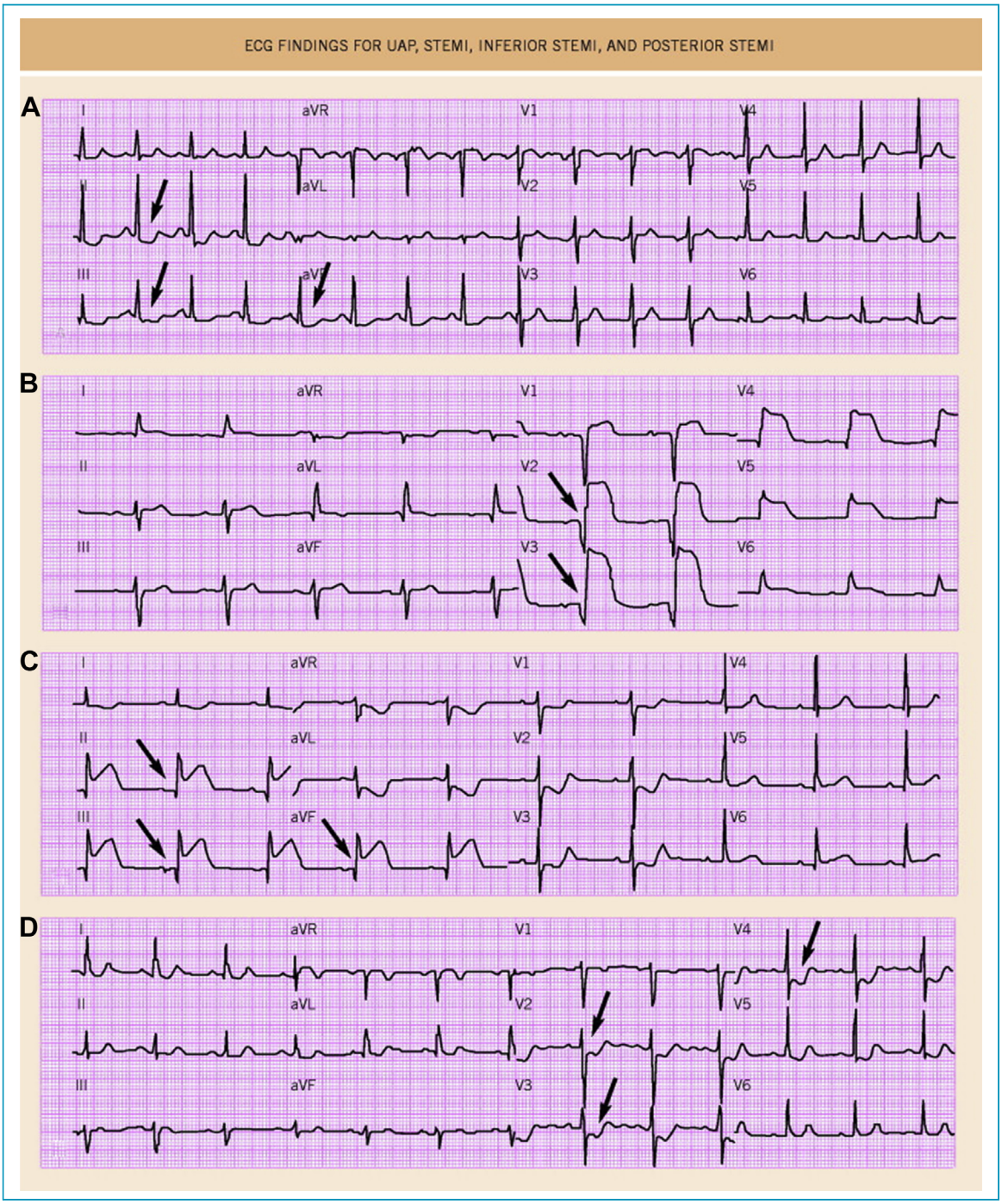


FIGURE 13. Electrocardiographic findings for unstable angina pectoris (UAP) and ST-segment elevation myocardial infarction (STEMI). (A) Unstable angina pectoris or non—STEMI. (B) Anterior STEMI suggesting occlusion of the proximal left anterior descending coronary artery. (C) Inferior STEMI. (D) Posterior STEMI. Reproduced, with permission, from Terkelsen [41].

includes assessment of coronary disease, cerebrovascular diseases, and risk factors that may interfere with initiation of fibrinolytic therapy including uncontrolled hypertension, history of previous intracranial hemorrhage, significant closed head or facial trauma within the past 3 months, bleeding risk, ischemic stroke, or signs and symptoms of stroke within the past 3 months.

Risk assessment on initial presentation

The important steps after establishing the diagnosis of STEMI are a rapid and accurate risk assessment and an effort to minimize the door-to-balloon time. Independent predictors of early mortality include age, heart rate, SBP, renal dysfunction, Killip class, previous infarction, diabetes mellitus, smoking status, time to reperfusion, cardiac arrest, anterior infarct location, and biomarker profile. Age, heart rate, SBP, and renal dysfunction are among the strongest independent prognostic variables with age and heart rate having a positive and SBP and renal dysfunction with inverse associations with risk of death. A popular risk stratification tool is the TIMI (Thrombolysis In Myocardial Infarction) risk score that was developed specifically for STEMI. The GRACE (Global Registry for Acute Coronary Events) score that includes renal dysfunction (Tables 4 and 5) has emerged as being among the best risk scores [37] because it can be applied to the entire spectrum of acute coronary syndromes (including non-STEMI) and it predicts both in-hospital and 6-month mortality. It is important that risk assessment is done not only at the time of diagnosis but also during hospitalization and at time of discharge. Realistically when STEMI patients who are at a remote location in LMIC need to undergo risk assessment, the risk index incorporating age, heart rate, and SBP is most likely to be useful in the rapid triage of patients [38].

ECG

ECG is an important tool in the evaluation of a patient with suspected MI. ST-segment elevation suggests coronary occlusion. The initial ECG is neither sensitive nor specific for MI. Therefore, to improve both the sensitivity and the specificity of the ECG, serial tracings must be obtained every 5 to 10 min or continuous 12-lead ST-segment monitoring must be done to detect development of ST-segment elevation to ensure early use of reperfusion therapies. ECG changes in STEMI evolve through 3 overlapping phases that include: 1) early hyperacute or acute phase; 2) evolved acute phase; and 3) chronic stabilized phase.

In the early phase, T waves increase in amplitude and widen over the area of injury—the so-called hyperacute pattern (Figures 10 to 12) [39,40]. ST segments evolve from concave to straightened to a convex upward pattern—so-called acute pattern (Figs. 10B to 10D). When the latter pattern merges with ST-T waves, it is described as a "tombstone" pattern (Figure 13) here [41]. ST-segment

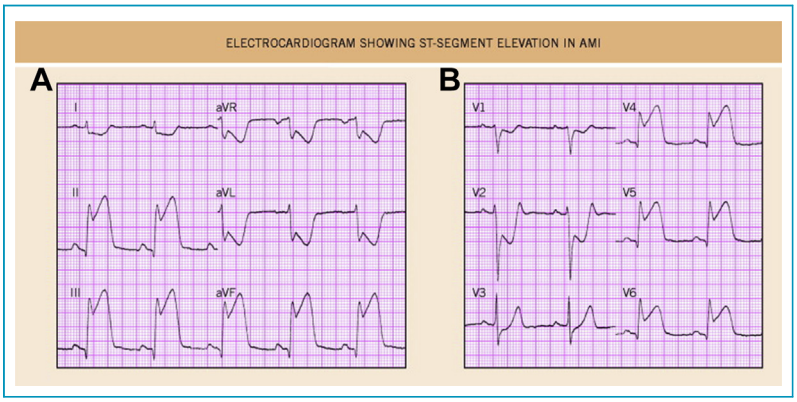


FIGURE 14. Electrocardiogram showing ST-segment elevation in acute myocardial infarction (AMI). There is a 9- to 10-mm ST-segment elevation in leads II, III, and aVF (A) but also ST-segment elevation in the apical leads V_4 to V_6 (B) and ST-segment depression in leads I, aVL, and V_1 to V_3. Note the positive terminal T-wave in V_1 to V_3, indicating extensive inferolateral infarction. Reprinted, with permission, from Crawford [42].

depression may occur in the leads opposite the ST-segment elevation and is referred to as a "reciprocal change" (Figure 14) [42]. The presence of reciprocal changes is associated with larger areas of myocardial injury and a worse prognosis, but it is also associated with greater benefits from achieving successful reperfusion. In the evolved acute phase, ST-segment elevation begins to revert, T waves in these leads become inverted, and pathologic Q waves or QS waves begin to develop. The Q or Q waves are >0.03 s in duration or have a depth of >30% of the R-wave amplitude or both. In the chronic phase, ST-segment elevation may resolve and is usually complete within 2 weeks of an inferior wall MI, but it is often longer with anterior wall MI. Symmetrical T-wave inversion can take weeks to months to revert or may persist indefinitely. Early reperfusion therapy tends to accelerate the reversion of ECG changes accompanying MI, and persistence of ST-segment elevation by >50% to 70% 1 to 2 h after fibrinolysis should prompt consideration for urgent coronary angiography and possibly "rescue angioplasty."

Age- and sex-dependent criteria for ST-segment elevation must be kept in mind while interpreting the ECG. Normal ST-segment elevation in leads V_2 and V_3 is <0.15 mV in women, <0.2 mV in men ≥40 years of age, and <0.25mV for men <40 years. The amount of ST-segment elevation required in other leads is ≥0.1 mV for both sexes. If the criteria for reperfusion requires an abnormality of >0.2 mm in these leads, then many women would be denied reperfusion [43]. In cases where there is ST-segment elevation only in 1 lead rather than the recommended 2 contiguous leads, then clinical judgment and serial recordings will be required to determine candidacy for reperfusion.

When there is ST-segment elevation in inferior limb leads (leads II, III, and aVF) it is desirable to obtain

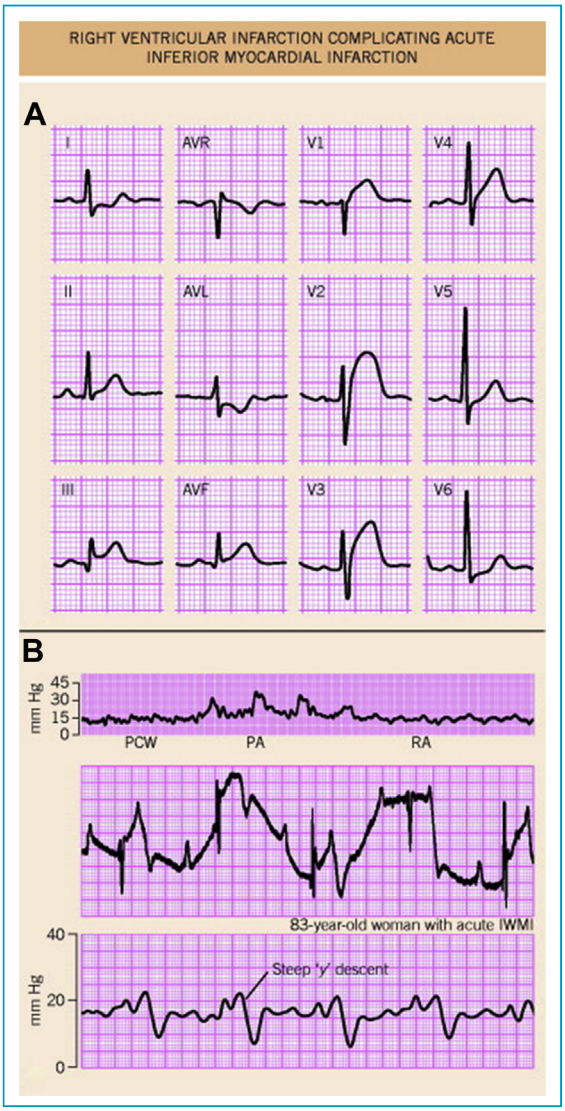


FIGURE 15. Findings in right ventricular infarction complicating an acute inferior myocardial infarction. (A) Electrocardiogram showing concomitant ST-segment elevation in V_1 through V_3 due to right ventricular involvement. (B) Hemodynamics showing an elevated right atrial (RA) pressure (with a steep y descent) and its equalization with the pulmonary wedge pressure (PCW), simulating the hemodynamic findings of cardiac tamponade. IWMI, inferior wall myocardial infarction; PA, pulmonary artery pressure. Modified from Geft et al. [44], Shah and Swan [45], and Cercek et al. [46].

right-sided precordial leads (V_3R and V_4R) to seek ST-segment elevation associated with RV infarction (Figures 15 and 16) [44–47]. Criteria for RV MI include ST-segment elevation >0.05 mV and >0.1 mV in men <30 years old [48]. One small study reported that the specificity and positive predictive value of ST-segment elevation in V_3R were 81% and 77%, respectively [49]. These increased to 100% when combined with ST-segment elevation in ≥1leads V_4R to V_7R. Another small study reported that the sensitivity of ST-segment elevation reached 100% in lead V_4R and decreased in leads V_1 to V_3; its specificity was highest (68.2%) in leads V_4R and V_3R, its negative predictive value was 100%, and its diagnostic efficiency was 80.6% [48]. The criterion of ST-segment elevation in lead V_4R being higher than that in leads V_1 to V_3 was less sensitive (78.6%) than ST-segment elevation in lead V_4R alone, but its specificity reached 100%, its positive predictive value was 100%, and its diagnostic efficiency 91.7%. Both these studies, however, were small studies.

Precordial ST-segment depression, especially when the terminal T-wave is positive (ST-elevation equivalent) (Figure 17) [50] in a patient presenting with acute coronary syndrome, suggests concomitant posterior STEMI with high specificity (92%) and should result in recording of the posterior ECG [51]. In about 50% of the patients with posterior infarction related to occlusion of the circumflex artery, ST-segment elevation is not seen in standard 12-lead ECG, therefore chest leads V_7, V_8, and V_9 should be recorded when there is ST-segment depression in chest leads V_1 to V_3 or when the ECG is nondiagnostic with symptoms of myocardial ischemia [52–54]. This is important because thrombolysis or PCI would be most beneficial in such patients in contrast to those without ST-segment elevation in posterior chest leads V_7 to V_9 (who present with anterior ischemia manifested by ST-segment depression in precordial anterior chest leads) where other antithrombotic therapies such as low molecular weight heparin or glycoprotein IIb/IIIa receptor inhibitors may be more appropriate. Overall, the cutoff point recommended for ST-segment elevation is 0.05 mV, and in men ≥40 years of age, it is 0.1 mV [55] in the posterior chest leads V_7 to V_9 to detect inferobasal STEMI.

The lead aVR is often overlooked in the interpretation because it lacks adjacent leads and is presumed to provide reciprocal information about the left lateral heart [56]. It is oriented in the opposite direction of the precordial leads V_4 and V_6 and limb leads I and II. Therefore, it gives an ECG report of not only the endocardial surface of the LV and apex, but also of the base of the interventricular septum, a region that is usually perfused by the septal branches of the proximal left anterior descending arteries (Figures 18 and 19) [56,57]. ST-segment elevation in lead aVR, greater than that in lead V_1, is an important marker of occlusions of the left main coronary artery or proximal pre-septal left anterior descending artery or multivessel disease artery [56,58,59]. In a study cohort of 15,000 patients, elevation of the ST segment in lead aVR within 6 h of presentation

was a poor prognostic factor with increased 30-day mortality [60].

Biphasic T waves or deeply inverted T waves (Figures 20 and 21) [61,62] in anterior precordial leads herald STEMI and are known as Wellens syndrome.

ECG changes can be used to localize the culprit coronary artery (Table 6 and Figures 18, 22 and 23) [63].

In patients with LBBB it is important to compare the current and previous ECG to determine whether the LBBB is new or old. In those with old LBBB, concordant ST-segment elevation suggests new MI [64]. Earlier studies suggested that ECG criteria for the diagnosis of MI were serial ECG changes (67% sensitivity), ST-segment elevation (54% sensitivity), abnormal Q waves (31% sensitivity), the sign of Cabrera (notching of 0.05 s in the ascending limb of the S wave in leads V_3 and V_4; 27% sensitivity), and initial positivity in lead V_1 and a Q wave in lead V_6 (20% sensitivity but 100% specificity for anteroseptal infarction) [65]. Subsequently, the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial investigators [66] found that 3 ECG criteria with independent values in the diagnosis of acute infarction in patients with LBBB were ST-segment elevation of $\geq$1 mm that was concordant with (in the same direction as) the QRS complex; ST-segment depression of $\geq$1 mm in lead V_1, V_2, or V_3; and ST-segment elevation of $\geq$5 mm that was discordant with (in the opposite direction from) the QRS complex (Figures 24 to 26) [39,67,68]. The low sensitivity of these criteria, however, limit their usefulness in the management of acute MI. Interpretation is not hampered in right bundle branch block, but the prognosis is poor. Therefore, the persistent ischemic symptoms in patients with bundle branch block merits prompt management.

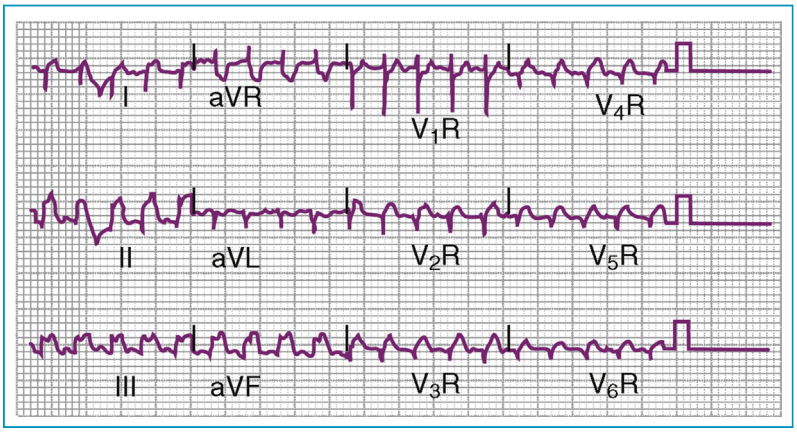


FIGURE 16. ST-segment elevations in right precordial leads. A case of right ventricular infarction in a 35-year-old heavy smoker who presented with 1 h of substernal chest pain. The 12-lead electrocardiogram showed an acute inferoposterior infarction. Right-sided leads V_4R to V_6R show ST-segment elevation, indicating right ventricular involvement. Reproduced, with permission, from Mani and Brown [47].

Ventricular pacing may also interfere with interpretation of ST-segment elevation (Figures 27 to 29) [64,67,69,70], and in such patients, coronary angiography should be considered in patients with active symptoms. In patients who are not pacemaker-dependent, reprogramming the pacemaker to allow evaluation of the native heart rhythm may be considered if it can be conducted without delay.

In some instances, ST-segment elevation may not occur despite total coronary occlusion including occluded

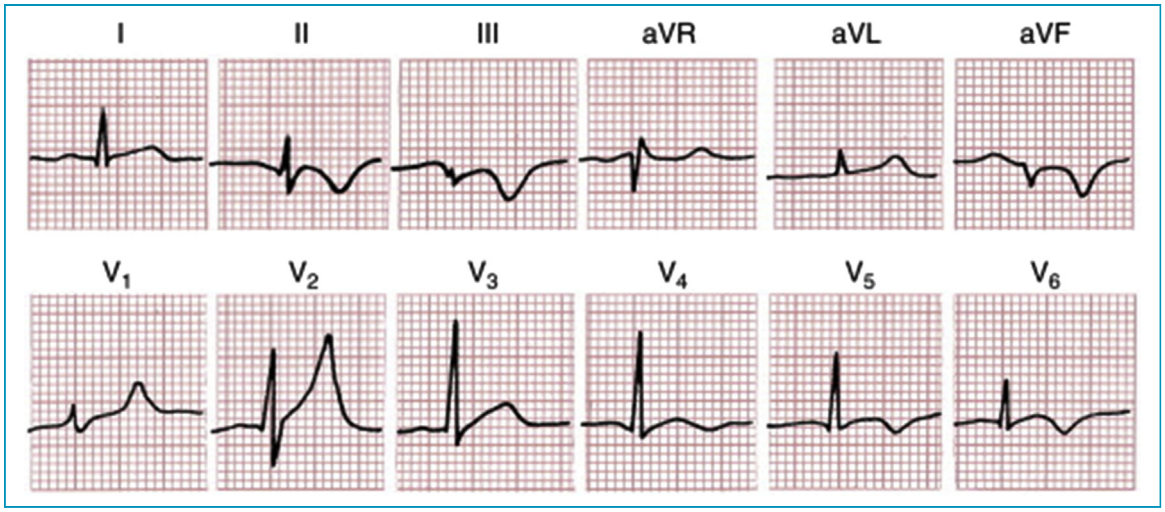


FIGURE 17. "Posterior" infarction. Notice the tall R waves in leads V_1 and V_2. This patient had a previous inferior infarction (Q waves in leads II, III, aVF) and probably a lateral infarction as well (T-wave inversions in leads V_4 to V_6). Notice also the reciprocally tall, positive T waves in anterior precordial leads V_1 and V_2. Reproduced, with permission, from Goldberger [50].

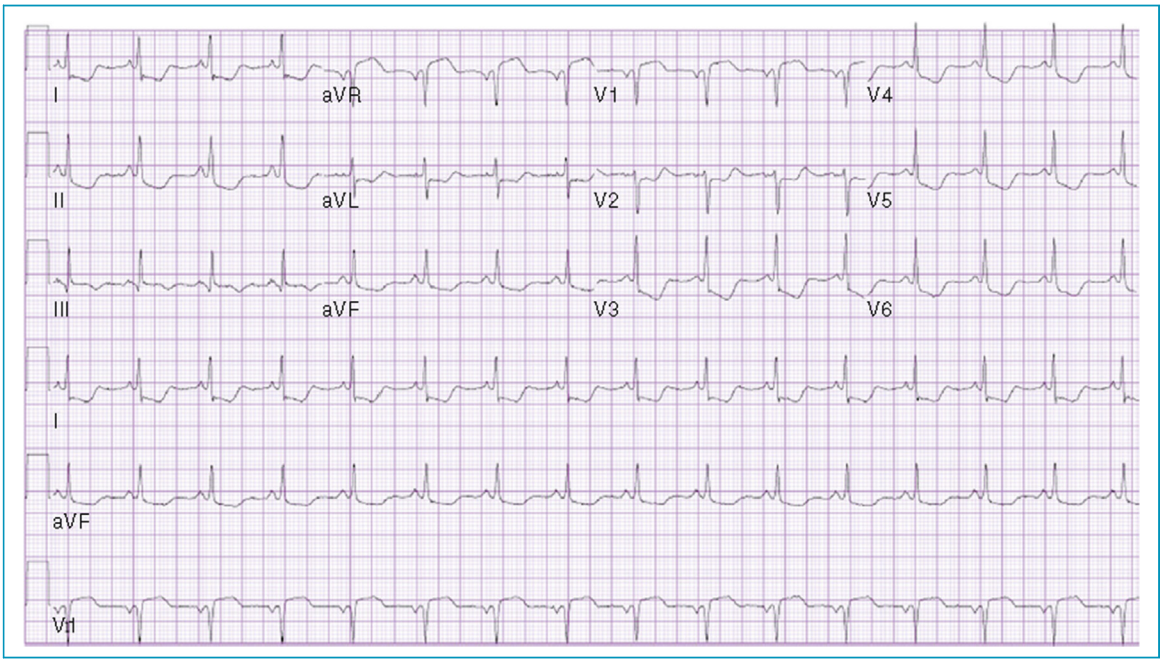


FIGURE 18. Left main coronary artery occlusion. Elevation in leads aVR and V_1 with global ST-segment depressions.

circumflex coronary artery [71,72], acute occlusion of a vein graft, or left main disease. Therefore, it is important to consider early coronary angiography in those with persistent ischemic symptoms despite the absence of ST-segment elevation.

Cardiac biomarkers

Cardiac biomarkers (Tables 7 and 8) [2,73,74] are the cornerstone for the diagnosis of acute MI in the new universal definition of MI [75,76]. In 1954, aspartate transferase (AST) was found to be elevated in acute MI [77] and was incorporated in the 1959 World Health Organization definition of MI [78]. Two of the 3 following criteria—1) symptoms of cardiac ischemia; 2) ischemic ECG changes; and 3) elevated biomarkers with AST as the biomarker of choice—composed the World Health Organization definition. With increasing use of AST, its limitations, particularly lack of specificity, became apparent. In 1960, it was reported that lactate dehydrogenase, an enzyme that catalyzes reversal oxidation of lactate to pyruvate, was found to be elevated in acute MI, but like AST it was nonspecific. In the same year, it was demonstrated that plasma creatine kinase (CK), an enzyme that catalyzes the transfer of high-energy phosphate from creatine phosphate to adenosine trisphosphate, was elevated in MI as well as in patients with skeletal muscle disease. CK was more

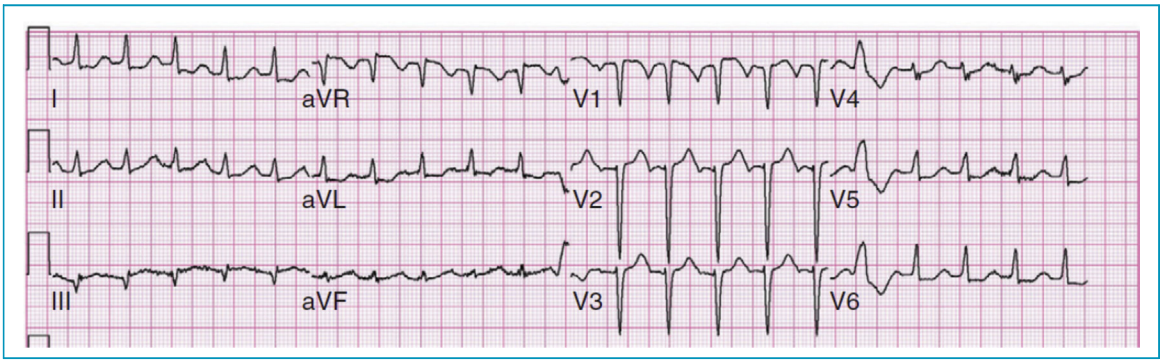


FIGURE 19. There is ST-segment elevation in leads aVR and V_1, which is consistent with ischemia (80% sensitive) of left main stem origin (i.e., the ST-segment elevation in aVR exceeds that of V_1). There is ST-segment depression in leads I, aVL, and V_5 to V_6. Reproduced, with permission, from Hutchison, and Rudakewich [57].

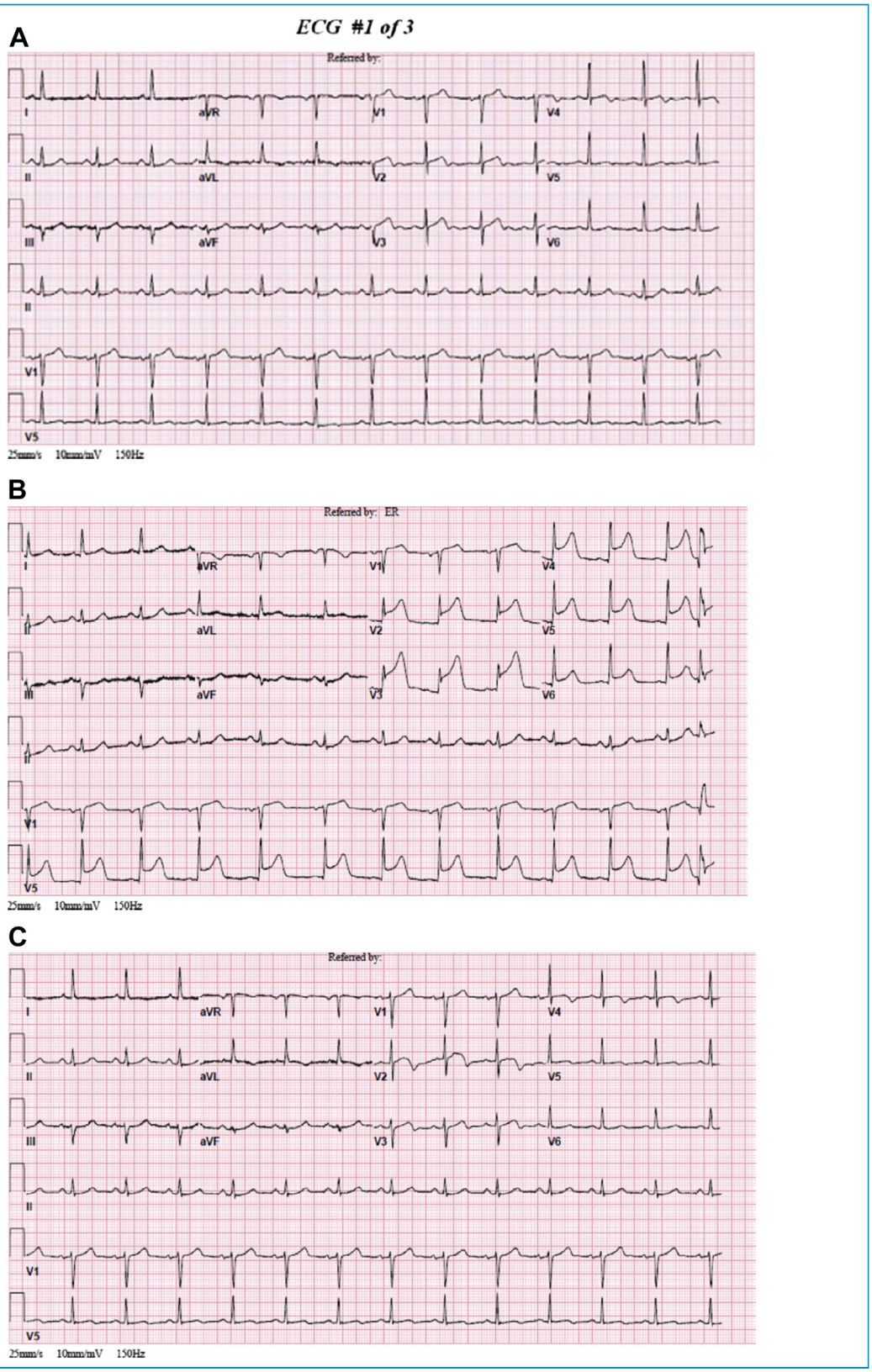


FIGURE 20. Electrocardiograms on arrival (A) and 25 (B) and 55 (C) min after emergency department presentation. Reproduced, with permission, from Donahue et al. [61].

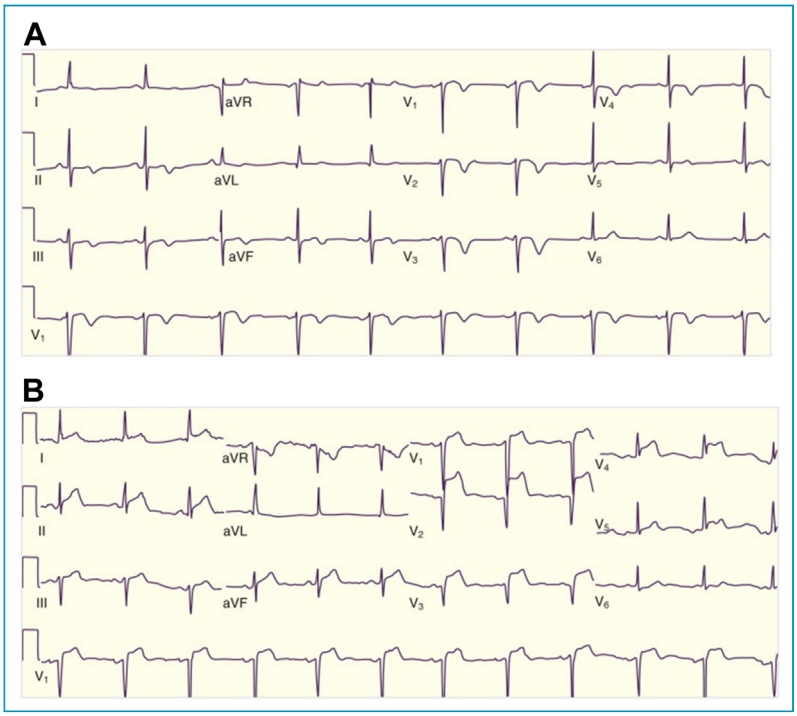


FIGURE 21. (A) 12-lead electrocardiogram in a woman with resolved chest pain. The deep symmetric precordial T-wave inversions represent Wellens syndrome. (B) ECG from the same patient obtained 30 min later with recurrent chest pain. Note the anterior ST-segment elevation is consistent with acute occlusion of the left anterior descending coronary artery. Reproduced, with permission, from Brown [62].

specific than AST or lactate dehydrogenase because its levels in the liver are low. In 1979, the World Health Organization definition was updated to include CK, AST, and lactate dehydrogenase [77,79–81]. Advances in electrophoresis helped identify CK isoenzymes, but these lacked sensitivity. Although advances in chromatography in 1974 and development of quantitative assays in the late 1970s improved the value of biomarkers, it is the development of immunoassays in the 1980s that allowed measurement of the creatine kinase–myocardial band (CK-MB) mass. However, the CK-MB mass is also found to be elevated in skeletal muscle damage, non-ischemic cardiac disease, and malignancies, which led to the development of troponin assays in the late 1980s [43,74,82,83].

Troponins are currently the preferred biomarker, but when they are not available the use of CK-MB (CKMB mass assay [not the activity assay]) is acceptable. It has been recommended that sex-specific cutoff values be used for CK-MB [84], and there should be a rise and/or fall with $\geq$1 value above the 99th percentile of the upper limit of normal. Similarly, for cardiac troponins I or T, there should be rise and/or fall with $\geq$1value above the 99th percentile of the upper limit of normal.

In many countries, troponin assays are not routinely available and CK-MB is used to diagnose acute MI. Creatinine kinase is an important enzyme in muscle metabolism and cellular energetics, where it serves as a temporary energy buffer and is involved in the transfer of energy from the mitochondria to the cytoplasm. It comprises mitochondrial and cytosolic forms. The cytosolic creatinine kinase exists as isoenzymes in dimers of 3 combinations of M (M = muscle form) and B (B = form) chains: MM, MB, and BB [85]. Levels of CK-MB usually rise above the normal range within 4 h after the onset of MI and therefore serial sampling over a 24-h period allows detection of MI (Figure 30) [75,86]. CK and CK-MB activity, however, lack early sensitivity as it takes at least 4 to 10 h from the onset of myocardial injury before blood levels of total CK and CK-MB activity begin to rise. Peak values occur within 24 h after the onset of acute MI and CK usually returns to baseline within 2 to 3 days. However, the specificity and sensitivity of the CK-MB assay is

TABLE 6. Localization of inferior wall MI and anterior MI

Inferior Wall MI—ST-Segment Elevation in Leads II, III, and aVF		
Right Coronary Artery		Circumflex Artery
ST-segment elevation in III > II		ST-segment elevation in II $\geq$ III
ST-segment depression >1 mm in I, aVL		ST-segment elevation in I, aVL, V_5 to V_6
ST-segment elevation in V_4R or V_1		ST-segment depression in V_4R
Anterior MI—ST-Segment Elevation in Leads V_1 to V_3		
Left Main Artery	Proximal Left Anterior Descending Artery	Distal Left Anterior Descending Artery
ST-segment elevation in aVR > V_1	ST-segment elevation in V_1 (>2.5 mm)	ST-segment elevation in II, III, aVF
Global ST-segment depressions	New right bundle branch block	
	ST-segment depression in II, III, aVF	

MI, myocardial infarction.
Adapted from Tung and Zimetbaum [63].

limited. In addition, the expression of CK-MB is not restricted to the myocardium and the false-positive results that are caused by analytical interferences. CK-MB has been found to be increased in a variety of clinical settings without myocardial damage, including release into blood due to skeletal muscle [87] damage (e.g., trauma, rhabdomyolysis, and various inflammatory and noninflammatory myopathies), pulmonary embolism, hypothyroidism, and asthma and release from uterus in the peripartum period. Moreover, some thyroid, prostatic, and lung cancers produce CK-MB, and CK-MB may also be increased when there is impaired clearance from blood (e.g., in hypothyroidism). Increased CK-MB is also frequently found in patients with azotemia but with no evidence of myocardial injury. The specificity of CK-MB can be enhanced when there is concomitant skeletal muscle damage by the calculation of the CK-MB/CK ratio. However, the CK-MB/CK ratio is not very sensitive. The limitation of this ratio is greatest when there is a greater extent of skeletal muscle injury, because larger quantities of CK-MM released will mask CK-MB of cardiac origin resulting in a decrease of the percentage of CK-MB [88,89]. Moreover, abnormally high relative indices in patients with normal total CK may not be valid. When the serum level of total CK is within the normal range, physicians should not draw any firm conclusions from the index as to whether patients have myocardial damage. The CK-MB biomarkers are more rapidly cleared than troponins and hence are more useful in detecting recurrent MI. The CK-MB assay is inexpensive and permits detection of reinfarction and therefore will continue to be used in LMIC countries. The troponin assays are probably most beneficial when the CK-MB assay is negative in the setting of ongoing ischemic symptoms with or without ischemic ECG changes.

In 2007, the World Heart Federation Task Force for Redefinition of Myocardial Infarction endorsed the use of cTn as the biomarker of choice for acute MI [90]. Troponin has three subunits: troponin C that bind to calcium ions; troponin T that binds to tropomyosin; and troponin I that binds to actin. Troponin is found in both cardiac and skeletal muscle but cTnI and cTnT isotypes have additional amino acid residues that allow them be identified, unlike TnC [91]. Troponin elevation and clearance depends on the infarct size (Figure 30). Generally, they are first detectable within 2 to 4 h after onset, are maximally sensitive at 8 to 12 h, peak at 10 to 24 h, and persist for 5 to 14 days. Their presence long after onset of MI allows them to be detected in patients presenting late (>1 to 2 days after acute MI), but they can obscure early diagnosis of a recurrent MI. Initial skepticism due to an increase in "positive" rate due to assay variability led to recommendations for only cutoff values with a coefficient of variation of <10% at the decision limit (99th percentile). This led to the development of high-sensitivity troponin assays to increase the analytical and consequently clinical sensitivity for detection of myocardial injury. These new assays will allow refined definition of the upper limit of normal and also will entail revisiting specificity as the upper 1% of the normal range [92]. cTn may be elevated in in non—acute coronary syndrome conditions such as demand ischemia (due to coronary spasm, coronary embolism, anemia, hypertension, arrhythmias, hypotension, or hypertension), myocarditis, Takotsubo syndrome, pulmonary embolism, sepsis, and renal failure. In renal failure, false-positive elevations are more likely to occur for cTnT than for cTnI, otherwise both these assays appear to be comparable. It is therefore important to interpret elevated cTn in the clinical context. Although

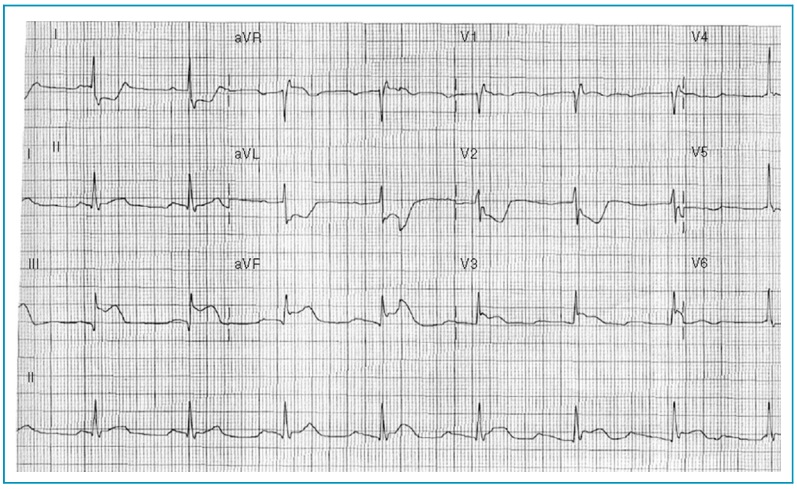


FIGURE 22. Inferior ST-segment elevation myocardial infarction. Elevation in lead III is greater than in lead II, and ST-segment depressions in leads I and aVL indicate the right coronary artery as the culprit vessel. Note the posterior injury current and the presence of complete heart block. Elevation in aVR suggests concomitant right ventricular infarction due to occlusion proximal to the right ventricular marginal branches.

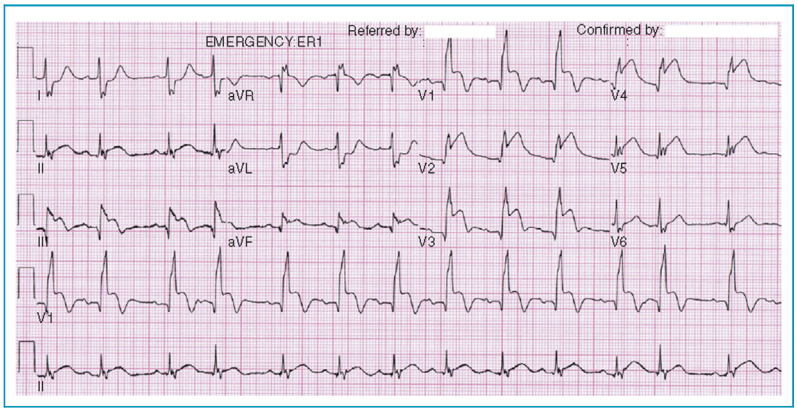


FIGURE 23. Anterior ST-segment elevation myocardial infarction. Occlusion of the proximal left anterior descending artery is indicated by the presence of diffuse precordial ST-segment elevations and right bundle branch block pattern. There is elevation in leads II, III, and aVF because the distal portion of the vessel wraps around the apex to supply the inferior wall.

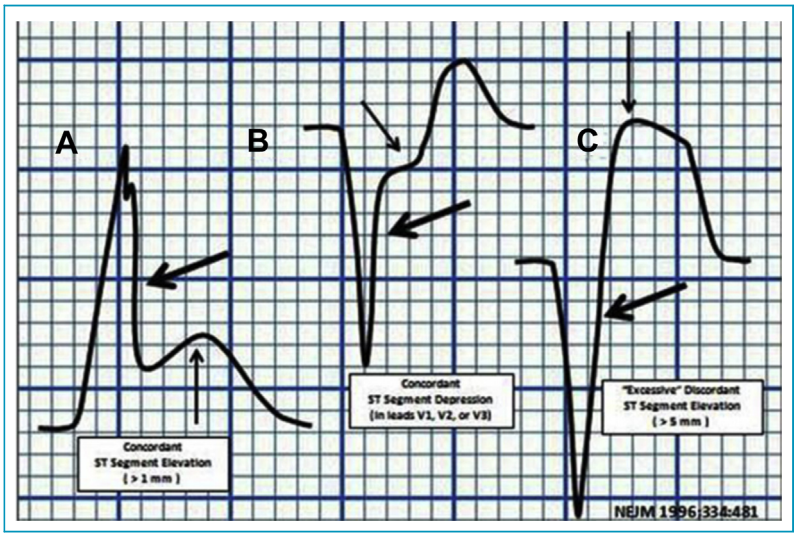
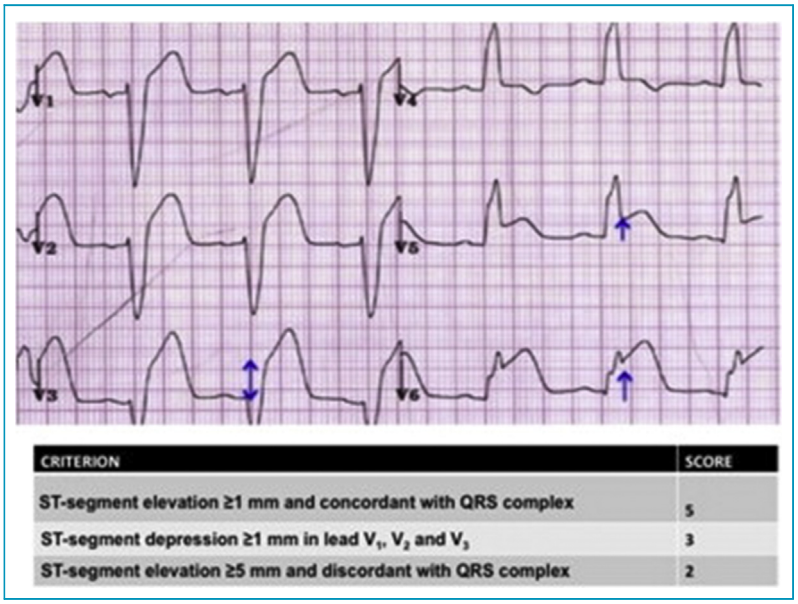


FIGURE 24. The presence of left bundle branch block and acute myocardial infarction: (A) concordant ST-segment elevation; (B) concordant ST-segment depression limited to leads V_1, V_2, and V_3; and (C) excessive discordant ST-segment >5 mm. Note that the relationship of the major, terminal portion of the QRS complex (thick arrow) and the initial portion of the ST segment (thin arrow) is the key determinant in the consideration of the these criteria [67].

cardiac biomarkers are useful in supporting the diagnosis of STEMI reperfusion should not be delayed in STEMI patients if results from laboratory examination are not immediately available.



CRITERION	SCORE
ST-segment elevation ≥1 mm and concordant with QRS complex	5
ST-segment depression ≥1 mm in lead V_1, V_2 and V_3	3
ST-segment elevation ≥5 mm and discordant with QRS complex	2

FIGURE 25. Sgarbossa criteria for diagnosing acute myocardial infarction in patients with left bundle branch block. Electrocardiogram shows discordant ST-segment elevation >5 mm in lead V_3 and concordant ST-segment elevation >1 mm in leads V_5 and V_6. Reproduced, with permission, from Kumar et al. [68].

Echocardiography

Echocardiography may be useful when a patient has severe ischemic symptoms (Figure 31) [93] but the regular 12-lead ECG does not manifest ST-segment elevation, instead the ECG shows changes such as hyperacute T waves (Figures 11 and 12) [40]. In such instances, echocardiography may reveal wall motion abnormalities due to ischemia—the sensitivity and specificity is >90%. However, lesser degrees of infarction may not lead to any changes, whereas older MI can cause similar abnormalities.

Coronary angiography

When coronary angiography is available, it should be considered in patients who do not meet criteria for acute MI despite suggestive symptoms. Using the radial artery to perform coronary angiography will minimize risk of peri-procedural hemorrhage and reduce length of stay [94].

THERAPY

The availability of effective treatments has successfully reduced fatality rates after cases of acute MI [95]. Therapies available include coronary reperfusion either with primary PCI or thrombolysis, and medical therapy in those not eligible for reperfusion.

General treatment measures

Supplemental oxygen. Supplemental oxygen should be administered in patients with arterial oxygen saturation <90% and to all uncomplicated patients for the first 6 h after presentation. There is scant data to support the routine use of oxygen in acute STEMI. A 3-fold higher risk of mortality associated with oxygen therapy (compared with room air) in acute MI was reported by a pooled Cochrane report of 3 clinical trials. It has been reported that oxygen can induce coronary vasoconstriction resulting in increased vascular resistance [96]. Therefore, oxygen should not be routinely administered for prolonged periods when arterial oxygen saturation is normal. It should also be administered cautiously in those with chronic obstructive pulmonary disease and carbon dioxide retention.

Sublingual nitroglycerin. Sublingual nitroglycerin should be administered to patients with ongoing chest discomfort as follows: 0.4 mg every 5 min for a total of 3 doses. Intravenous nitroglycerine should be initiated in those with continuing chest pain, hypertension, or management of pulmonary congestion. Nitrates should be avoided when SBP is <90 mm Hg or ≥30 mm Hg above baseline, in suspected RV infarction, severe bradycardia (<50 beats/min) or tachycardia (>100 beats/min).

Analgesia. The analgesic of choice for acute MI is morphine sulfate 2 to 4 mg administered intravenously with increments of 2 to 8 mg intravenously repeated at 5 to 15 min intervals.

Aspirin. The initial dose of aspirin at the start of STEMI treatment should be 162 to 325 mg chewable (nonenteric) aspirin with maintenance dose of 75 to 162 mg. Chewing the non-enteric-coated aspirin provides more rapid absorption through buccal than gastric mucosa. When aspirin is contraindicated or not tolerated due to allergy or dyspepsia, then clopidogrel monotherapy is an alternative. The first study to demonstrate the efficacy of aspirin in the setting of STEMI was the ISIS-2 (Second International Study of Infarct Survival). The study investigators reported that it conferred a 23% reduction in the odds of death versus placebo that was similar in magnitude in those subjects treated with fibrinolytic therapy alone. Incremental benefits were seen in those patients who received a combination of aspirin and fibrinolytic agents. In ISIS-2, the mortality reduction of aspirin was comparable when given within 4 h (25% mortality reduction), between 5 and 12 h (21% reduction), and between 13 and 24 h (21% reduction) [97]. The Antithrombotic Trialists' Collaboration reported that aspirin reduced the risk of nonfatal coronary events by 30% and vascular events by 15% [97]. Registry data showed that 30-day mortality was lower in Sweden than in the United Kingdom [98]. This report suggested that more 10,000 deaths at 30 days could have been prevented or delayed had U.K. providers done a better job of offering effective therapies, particularly primary PCI to treat STEMI and beta-blockers, to their patients.

Beta-blockers. Oral beta-blocker therapy should be initiated at FMC in the absence of contraindications such as reactive airways disease, PR interval >0.24 s or high degree atrioventricular (AV) block, cardiogenic shock, acute pulmonary edema, or low output state. Intravenous beta-blockers may be used only when there is significant hypertension (SBP >150 mm Hg).

Reperfusion

Coronary reperfusion therapy either in the form of PCI (angioplasty and stent insertion) or fibrinolysis (with agents such as streptokinase, reteplase, or tenecteplase) (Figures 32 to 35, Tables 9 and 10) should be administered as quickly as possible in all eligible acute STEMI patients [12,25,41,73,75,99]. Age, sex, or ethnicity should not be used to determine eligibility for reperfusion therapy. The choice of reperfusion therapy is determined by the following: 1) time from the onset of symptoms to initiation of reperfusion therapy; 2) risk of death after STEMI; 3) risk of bleeding; and 4) time for transportation to a skilled PCI center. In 1979, Reimer et al. [100] reported that the extent of myocardial necrosis and degree of reversibility was time-dependent (Figure 36). The results of the GISSI-1 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Acuto 1) trial [101,102] and the LATE (Late Assessment of Thrombolytic Efficacy Study) [103] confirmed the importance of early reperfusion. Every minute delay in reperfusion is associated with increased mortality. The 35-day mortality benefit associated with early therapy equates to 1.6 lives per 1,000 patients per hour of delay from symptom onset to treatment [12,15,100,104]. One study calculated that every delay of

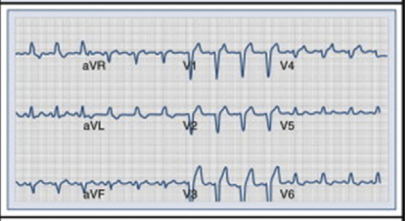
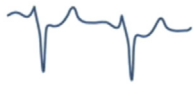
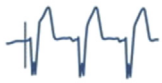
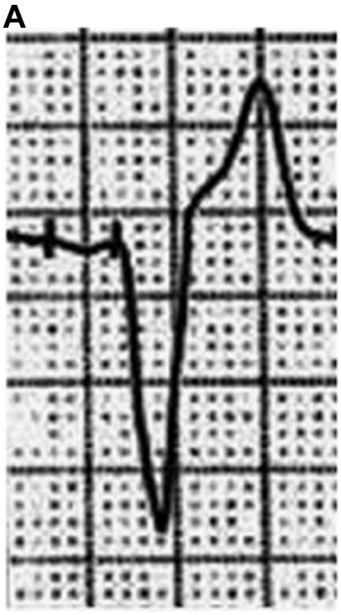
ECG finding	Comment	Example
New LBBB	New onset and with appropriate clinical correlation	
Concordant ST segment elevation	ST segment elevation >1 mm//concordant with QRS complex	
Concordant ST segment depression in leads V1, V2, and/or V3	ST segment depression >1 mm in leads V1, V2, or V3	
Discordant ST segment elevation	ST segment elevation >5 mm discordant with QRS complex	

FIGURE 26. Electrocardiographic (ECG) indications for reperfusion therapy in the left bundle branch block (LBBB) presentation. Reproduced, with permission, from Riordan and Brady [39].



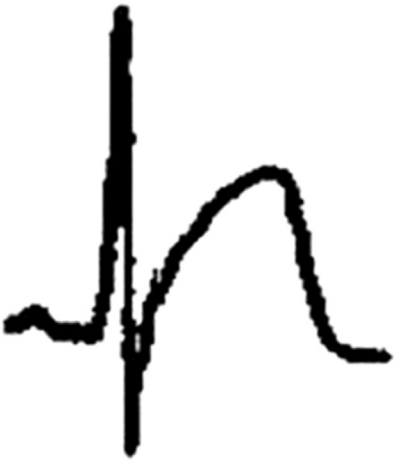


FIGURE 27. ST-segment elevation in the ventricular paced pattern (A) versus ST-segment elevation myocardial infarction (B) [67].

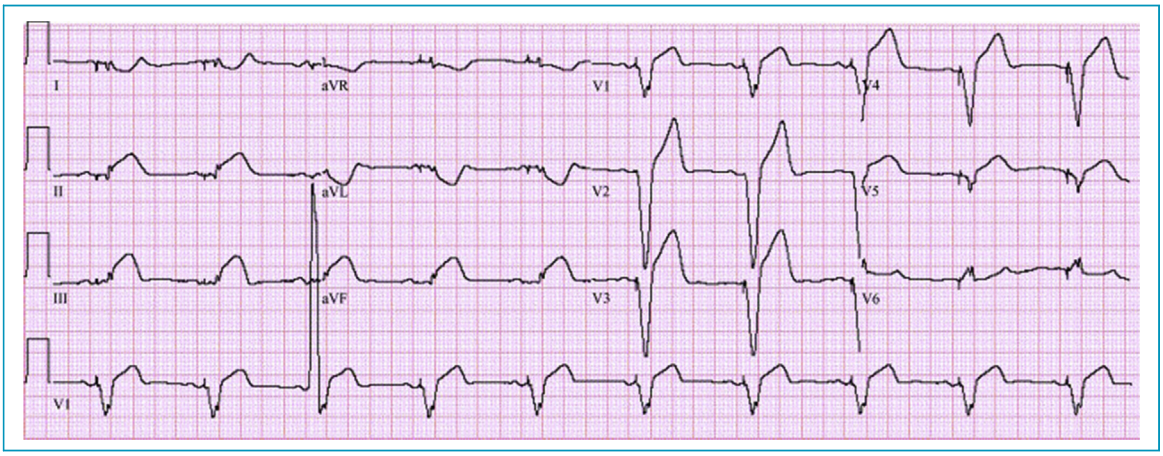


FIGURE 28. Right ventricular paced rhythm with acute myocardial infarction. Note concordant ST-segment elevation in leads II, III, and aVF and excessive, discordant ST-segment elevation in leads V_3 and V_4. Reproduced, with permission, from Brady et al. [69] and Cai et al. [64].

30 min was associated with a relative risk for 1-year mortality of 1.075 (95% confidence interval: 1.008 to 1.15, p = 0.041)—that is, roughly 8% excess annual mortality for every 30-min delay [105]. In addition, the degree of flow is also important, resulting in the development of the TIMI flow grade (Figure 2) [106]. Mortality is lower among patients with TIMI flow grade 2 or 3, compared with TIMI flow grade 0 to 1, was achieved

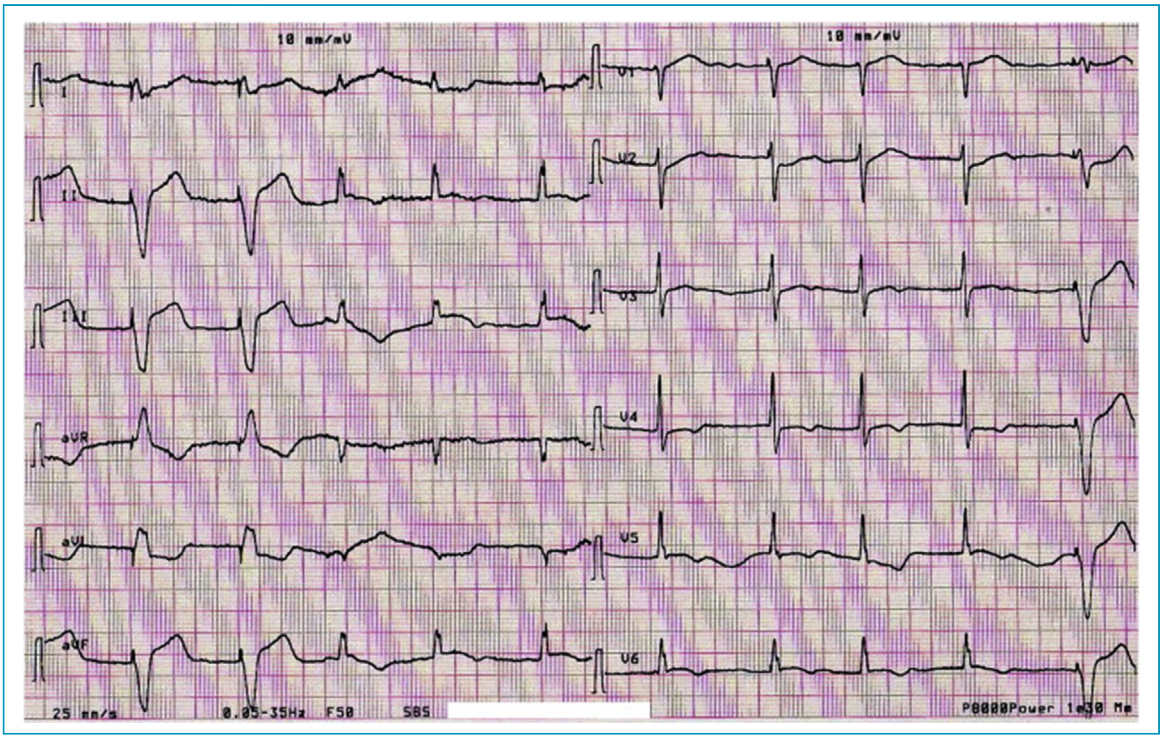


FIGURE 29. The electrocardiogram showed atrial fibrillation with non-paced complexes ST-segment elevation on lead III aVF and ST-segment depression on lead I avL (on the last 2 complexes of these leads); mild ST-segment elevation on lead II (on the last 2 complexes of this lead) and lead V_6 (except on the last complex of this lead); T negative on leads II and III aVF (on the last 3 complexes of these leads), V_4, V_5, and V_6 (except on the last complex of these leads). Paced ventricular complexes were also shown. Reproduced, with permission, from Patanè [70].

TABLE 7. Biomarkers for evaluation of patients with STEMI

Biomarker	Molecular Weight (Da)	Range of Time to Initial Elevation (h)	Mean Time to Peak Elevations (Nonreperfused)	Time to Return to Normal Range
Frequently used in clinical practice				
CK-MB*	86,000	3–12	24 h	48–72 h
cTnI†	23,500	3–12	24 h	5–10 days
cTnT	33,000	3–12	12 h to 2 days	5–14 days
Infrequently used in clinical practice				
Myoglobin	17,800	1–4	6–7 h	24 h
CK-MB tissue isoform	86,000	2–6	18 h	Unknown
CK-MM tissue isoform	86,000	1–6	12 h	38 h

cTnI, cardiac troponin I; cTnT, cardiac troponin T; CK-MB, creatine kinase-MB; CK-MM, creatine kinase-MM; STEMI, ST-segment elevation myocardial infarction.

*Increased sensitivity can be achieved with sampling every 6 or 8 h.

†Multiple assays are available for clinical use; clinicians should be familiar with the cutoff value used in their institution.

Modified from Antman et al. [2,73].

within 90 min after acute STEMI [107]. Therefore, the goal of reperfusion is not only early reperfusion but also restoration of normal flow (Figures 1 and 2). The ability of Swedish doctors to deliver reperfusion to 73% of patients within the recommended time of 90 min from first diagnostic ECG (with a mean delay from the first diagnostic ECG to PCI of 60 min when fibrinolysis was used in selected remote areas) [108] is currently considered a model for all countries to strive for. The OAT (Occluded Artery Trial) trial investigators [109] found that there is no indication to open an occluded vessel outside the therapeutic window in an asymptomatic patient following STEMI, which makes it important that the total ischemic time is minimized for each and every patient.

Coronary angiography and follow-on PCI. Coronary angiography followed by PCI should be recommended, as follows: 1) to patients presenting with acute STEMI presenting within 12 h of the onset of symptoms and when primary PCI can be delivered within 120 min; 2) to patients with acute STEMI with ongoing symptoms of active myocardial ischemia presenting >12 hours after the onset of symptoms; 3) to patients with acute STEMI and cardiogenic shock presenting within 36 h (preferably12 h) of the onset of symptoms of STEMI; 4) to patients who have ongoing symptoms of myocardial ischemia after fibrinolysis; 5) to all patients who have residual or persistent STEMI elevation 60 to 90 min after administration of fibrinolysis; and 6) to clinically stable patients during the same hospital admission after successful fibrinolysis. The level of consciousness after cardiac arrest caused by suspected acute STEMI, age, sex, or ethnicity should not be used to determine eligibility for coronary angiography and follow-on PCI if indicated. PCI is the preferred reperfusion option to fibrinolysis because it restores TIMI flow grade 3 in 70% to 90% of the patients

TABLE 8. Summary of cardiac biomarkers

Biomarker	Performance in Diagnosis	Performance in Prognosis
Necrosis		
cTn	Highly sensitive and specific for myocardial necrosis. Current gold standard biochemical criterion for AMI.	Highly predictive of adverse cardiac events including death, further ischemia, and need for revascularization. Treatments instigated in response to cTn results improve outcomes.
AST	First biochemical marker of AMI but lacks specificity. No longer used for this purpose.	No data.
CK/CK-MB	Second line biomarker for the diagnosis of AMI, but not as sensitive or specific as cTn.	Not consistently predictive of future events.
LDH	Lacks specificity. No longer used for this purpose.	No data.
Myoglobin	Marker of AMI early after symptom onset, lacks specificity.	Predictive of mortality. No data to suggest myoglobin-guided treatment influences outcomes.

AMI, acute myocardial infarction; AST, aspartate transferase; CK, creatine kinase; CK-MB, creatine kinase–myocardial band; cTn, cardiac troponin; LDH, low-density lipoprotein.

Adapted from Aldous [74].

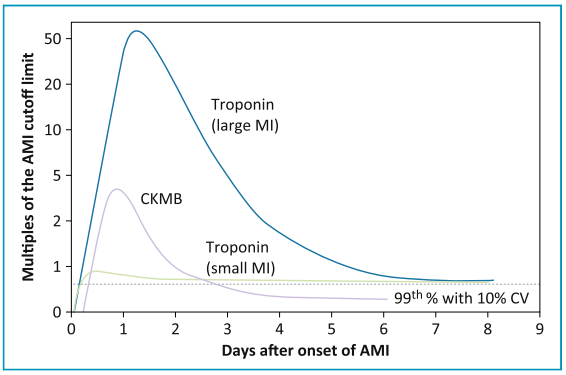


FIGURE 30. Time course of the appearance of various markers in the blood after acute myocardial infarction (AMI) [75]. Shown are the time concentrations/activity curves for troponin after large and small infarctions, and creatine kinase—myocardial band (CK-MB). Note that with cardiac troponin some patients have a second peak in addition. CV, coefficient of variation.

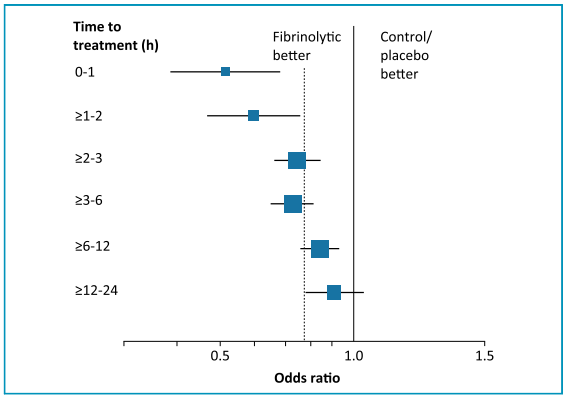


FIGURE 32. Advantages of early reperfusion therapy [12]. Proportional effect of fibrinolytic therapy on 35-day mortality according to treatment delay. Odds ratios, plotted with 95% confidence intervals on a log scale, are significantly different over the 6 groups (Breslow-Day test, p = 0.001). Areas of black squares are proportional to the amount of statistical information.

with lower risk of intracranial bleeding risk. Coronary angiography is recommended and PCI is certainly the preferred option in high-risk patients, even when the initial strategy is fibrinolytic therapy: for example, Killip class 2 or higher, cardiogenic shock, cardiac failure, extensive ST-segment elevation, new LBBB, hemodynamic or electrical instability, or inferior wall MI with LV ejection fraction ≤0.35. STEMI patients at significant (≥4%) risk of intracranial hemorrhage should be treated with PCI rather than fibrinolytic therapy. PCI should not be performed in a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise, and nonculprit vessels should be treated by staged procedure preferably during index admission; nor should it be performed in asymptomatic patients >12 h after the onset of STEMI (if they are electrically and hemodynamically stable).

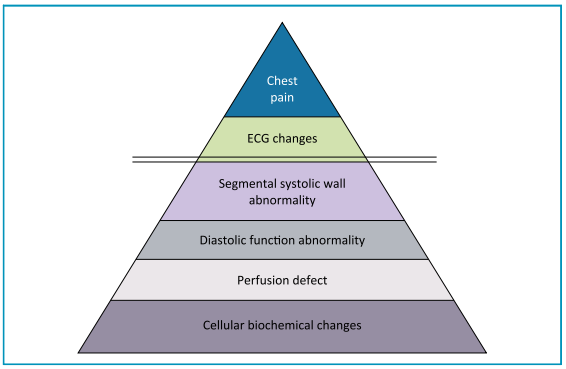


FIGURE 31. The sequence of events during myocardial ischemia. Given this sequence of events, echocardiography represents a unique and sensitive tool for early detection of myocardial ischemia, particularly by its ability to identify regional wall motion abnormalities. ECG, electrocardiogram. Reproduced, with permission, from Diaz et al. [93].

When PCI is the reperfusion strategy of first choice, instead of fibrinolysis, it is known as primary PCI. When reperfusion fails to occur with fibrinolysis, a rescue PCI is performed to open the infarct vessel. Primary PCI results in better outcomes than fibrinolysis (Figure 37) [110], and provides immediate assessment of coronary anatomy and hemodynamic data. It establishes TIMI flow grade 3 in 70% to 90% of the patients, nearly eliminates risk of intracranial hemorrhage, and is preferable in high-risk patients such as those with severe heart failure, cardiogenic shock, or hemodynamic or electrical instability [73]. It also allows early hospital discharge [111], and rapid identification of patients who will not benefit from reperfusion therapy, including those patients who spontaneously reperfuse the infarct-related coronary artery, those with coronary vasospasm, or those with aortic dissection involving the ostia of the coronary arteries. The limitations of primary PCI include the following: 1) 7% risk of major bleeding typically at the access site of the femoral arteries [110]; 2) vascular complications requiring surgical repair in about 0.4% to 2% of the patients [112,113]; and 3) 0.5% to 13% risk of acute renal failure [112]. The latter is dependent on pre-existing renal dysfunction, the age of the patient, volume status of the patient, and the quantity of contrast material used during PCI. Some have thought the meta-analysis comparing PCI and fibrinolysis does not tell the whole story because the postulated benefit of PCI was

confined to patients receiving in-hospital fibrinolysis. In addition, when patients with cardiogenic shock were omitted from the analysis and the comparison was just made with tissue plasminogen activator as opposed to all fibrinolytic drugs such as streptokinase and urokinase, then the outcomes with PCI and fibrinolysis were comparable [114] (Figures 34 and 38)

Fibrinolysis. Fibrinolysis (Table 11) [104] has shown to reduce short-term mortality by 18% overall and as much as 25% in patients with STEMI or new LBBB (Figures 32 and 39) [12,117]. The benefit of fibrinolysis has been observed in patients treated with fibrinolysis as late as 6 to 12 h from the onset of ischemic symptoms but the most dramatic effects are in those who are given the drug <2 h after symptoms (Figure 39) [117]. The short-term survival benefit observed with fibrinolysis is maintained over 1- and 10-year follow-up [43]. Reduction in reinfarctions after fibrinolysis has been observed due the development of better antiplatelet and antithrombotic therapies [118]. Fibrinolysis is the preferred option when PCI therapy cannot be delivered in a timely fashion. When the difference in delivery between primary PCI and fibrinolysis is >60 min, outcomes are similar. One analysis of 21 trials showed as the PCI-related time delay increased, the absolute mortality reduction favoring primary PCI at 4 to 6 weeks versus fibrinolysis decreased (0.94% decrease per additional 10-min delay, p = 0.006) (Figure 40) [119]. Therefore, fibrinolysis should be recommended to acute STEMI patients presenting within 12 h of onset of symptoms when primary PCI cannot be delivered within 120 min (during which time fibrinolysis can be given). Pre-hospital fibrinolysis therapy should be administered if primary PCI will be delayed by >120 min from FMC or >60 min from the time of administration of fibrinolysis. Fibrinolytic therapy should not be administered to asymptomatic patients whose initial symptoms of STEMI began >24 h earlier nor to patients whose 12-lead ECG shows only ST-segment depression except in the case of true posterior MI. In LMIC, fibrinolysis remains the treatment of choice for reperfusion because of the lack of availability of PCI. Reperfusion achieved in the first hour after onset of symptoms is associated with the most reduction in mortality—the so-called golden hour of reperfusion [12]. There is a 50% reduction in mortality when reperfusion by fibrinolytic agent is administered within 60 to 90 min [120]. In the MITI (Myocardial Infarction Triage and Intervention) trial [121], thrombolytic therapy with alteplase started within 70 min of symptoms reduced early mortality from 8.7% to 1.2% when compared with a longer delay of 180 min. An analysis of 58,000 patients in fibrinolytic trials reported that mortality was reduced by 25% in patients randomized to fibrinolysis between 2 to 3 h after symptom onset and 18% in those randomized between 4 and 6 h [117]. Even patients randomized between 7 to 12 h had a 14% reduction in mortality. Although a range of fibrinolytic

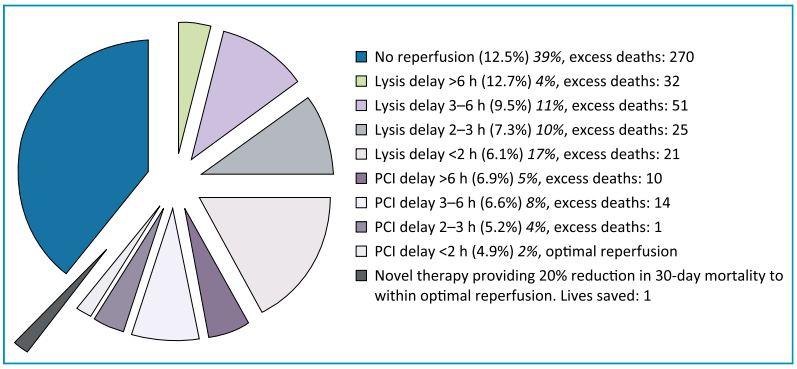


FIGURE 33. Missed opportunities in reperfusion for ST-segment elevation myocardial infarction. (Reproduced with permission from White HD, Chew DP. Acute myocardial infarction. Lancet 2008;372:570—84 [43].) Estimates of the proportion of all ST-segment elevation myocardial infarction patients receiving either fibrinolysis or catheter-based reperfusion (italics) at various degrees of delay, combined with literature-based estimates of mortality observed with the reperfusion modality and associated delay (parentheses). Excess deaths estimated by multiplying the excess mortality rate above primary percutaneous coronary intervention (PCI) undertaken within 2 h of onset of symptoms by the proportion of patients at risk in a cohort of 10,000 patients presenting with ST-segment elevation myocardial infarction (Boersma E, for the Primary Coronary Angioplasty vs. Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J 2006;27:779—88 [99], and Eagle KA, Goodman SG, Avezum A, et al., for the GRACE Investigators. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet 2002;359:373—7 [126].).

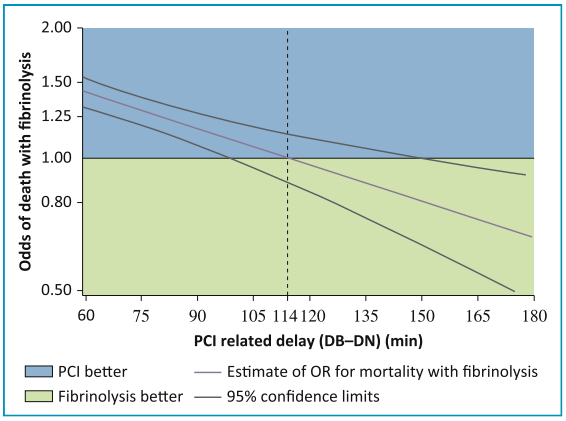


FIGURE 34. Time to percutaneous coronary intervention (PCI) versus fibrinolysis in ST-segment elevation myocardial infarction. (Reproduced with permission from White HD, Chew DP. Acute myocardial infarction. Lancet 2008;372:570—84 [43].) Increasing delay in initiating catheter-based reperfusion mitigates the incremental benefits of primary PCI over fibrinolysis. PCI-related delay = door to balloon time (DB) − door to needle time (DN). Adapted, with permission, from Pinto et al. [25] and Jaffe et al. [75].

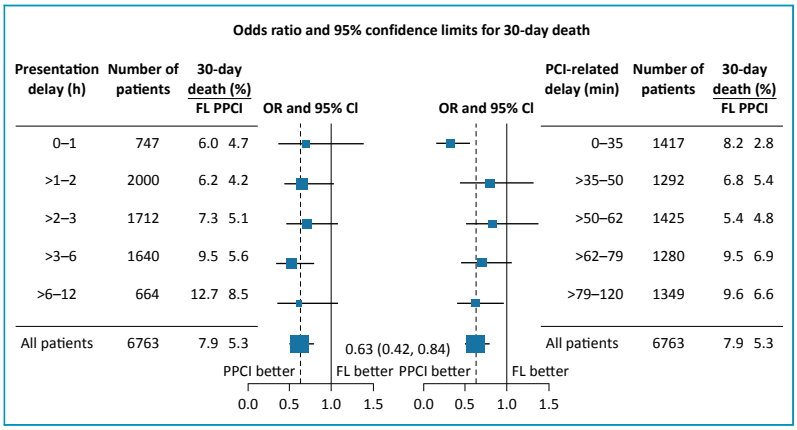


FIGURE 35. Odds ratios (OR) and 95% confidence limits (CI) for 30-day death in patients randomized to primary percutaneous coronary intervention (PPCI) compared with fibrinolysis (FL) according to presentation delay and extra delay used to perform PPCI instead of fibrinolysis (PCI-related delay). Reproduced, with permission, from Boersma [98] and Terkelsen [41].

agents are available in LMIC, streptokinase remains the most commonly used agent because of cost [122]. Limits of fibrinolysis include the following: 1) intracranial hemorrhage resulting in death or disabling stroke in 0.6% to 1.4% of patients, particularly in the elderly (Figure 41) [2,110,117,123–127]; 2) failed reperfusion of the infarct-related artery in 15%; 3) restoration of normal coronary blood flow in only 50% [128], resulting in reduced myocardial salvage and reduced survival [129]; and 4) reocclusion of the infarct-related artery occurs in 30% of the patients, resulting in reinfarction within the subsequent 3 months [130].

Pharmacoinvasive strategy. Pharmacoinvasive strategy could be useful when primary PCI cannot be done within 2 h of FMC, or if fibrinolysis can be given >60 min earlier than can primary PCI, irrespective of whether the patient is located in a rural or urban area. It involves pre-hospital fibrinolysis plus planned angiography (at 6 to 24 h in hemodynamically stable patients) as rescue angioplasty for failed fibrinolysis has now been shown to be equivalent (by results of the STREAM [Strategic Reperfusion Early After Myocardial Infarction] trial [131]) or better (by results of the CAPTIM trial [28,29]) to primary PCI in patients who present early. The CAPTIM trial [120] and PRAGUE-2 (Primary Angioplasty in Patients Transported from Community Hospitals to Specialized PTCA Units with or without Emergency Thrombolysis-2) trials [132] suggested that in earlier presenting patients (within 2 h) had similar or lower mortality with fibrinolysis than with primary PCI. A recent pilot study from India [133] reported that pharmacoinvasive strategy can be implemented in STEMI patients who are not selected for primary PCI, and the findings suggested that outcomes may be similar to PCI at the end of 1 year; larger studies are needed to confirm these findings.

TABLE 9. Assessment of reperfusion options for STEMI patients.

Step 1. Assess time and risk.
- Time since onset of symptoms
- Risk of STEMI
- Risk of fibrinolysis
- Time require for transport to a skilled PCI laboratory

Step 2. Determine whether fibrinolysis or invasive strategy is preferred.
- If presentation is <3 h and there is no delay to an invasive strategy, there is no preference for either strategy.

Fibrinolysis is generally preferred if:
- Early presentation (≤3 h from symptom onset and delay to invasive strategy)
- Invasive strategy is not an option:
  - Catheterization laboratory occupied or not available
  - Vascular access difficulties
  - Lack of access to a skilled PCI laboratory*†
- Delay to invasive strategy:
  - Prolonged transport
  - Door-to-balloon − door-to-needle >1 h‡§
  - Medical contact-to-balloon or door-to-balloon is >90 min

An invasive strategy is generally preferred if:
- Skilled PCI laboratory is available with surgical backup
- Skilled PCI laboratory is available, defined by:†‡
  - Medical contact-to-balloon or door-to-balloon is <90 min
  - Door-to-balloon − door-to-needle <1 h
- High risk from STEMI
  - Cardiogenic shock
  - Killip class ≥3
- Contraindications to fibrinolysis, including increased risk of bleeding and ICH
- Late presentation
  - Symptom onset was >3 h earlier
- Diagnosis of STEMI is in doubt

ICH, intracranial hemorrhage; other abbreviations as in Tables 2 and 7

*Operator experience exceeds 75 primary PCI cases per year.
†Team experience exceeds 36 primary PCI cases per year.
‡Applies to fibrin-specific agents.
§This calculation implies that the estimated delay to the implementation of the invasive strategy is >1 h versus immediate initiation of fibrinolytic therapy.
Adapted from Antman et al. [73].

TABLE 10. Contraindications and cautions for fibrinolytic use in STEMI

Absolute contraindications
- Any previous intracranial hemorrhage
- Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months except acute ischemic stroke within 3 h
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3 months

Relative contraindications
- History of chronic severe poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
- History of previous ischemic stroke >3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (>10 min) CPR or major surgery (<3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase, anistreplase: previous exposure (>5 days earlier) or previous allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; INR, international normalized ration; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

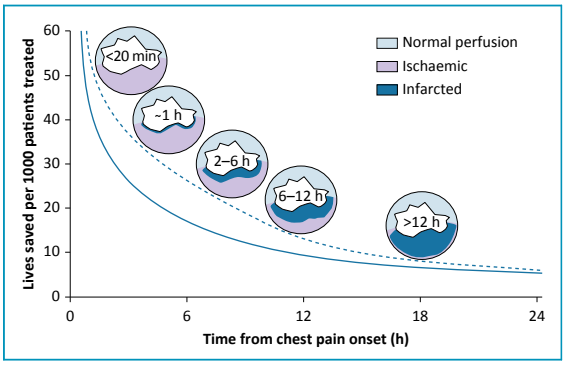


FIGURE 36. Relation between time to reperfusion and benefit accrued [15]. Heart cross sections show the left ventricle at increasing durations of epicardial coronary artery occlusion. This idea of progressive necrosis is modeled on experimental data [100]. The benefit of reperfusion in terms of lives saved at 35 days (solid line) is time-dependent and modeled on benefit seen in patients randomized to fibrinolysis versus placebo [12]. In the first hour after symptom onset, reperfusion significantly reduces mortality. During the first 2 to 3 h, potential benefits are large and time to treatment is critical. The shorter the time, the greater the benefit. Later, on the "flat" part of the curve, time is less of a factor possibly because of progressive infarction shown in the heart cross sections and the priority is to open the infarct-related artery; in this setting, a mechanical approach is preferable. The relation between an effective cardioprotective intervention and reperfusion is depicted by the dotted line. These relationships might be modified by other factors such as myocardial oxygen uptake, collaterals, and preconditioning [104].

Medical therapy

Medical therapy should be recommended in patients with acute STEMI who are not eligible for reperfusion (e.g., those with excessive bleeding risk, those patients in whom coronary angiography reveals no hemodynamically significant coronary lesions, or those presenting too late to benefit from reperfusion therapy). STEMI patients should be admitted to a unit where critical care is being provided. They can be transferred to a step-down unit in 12 to 24 h if stable.

Antiplatelet agents

Aspirin. The initial dose of aspirin at the start of STEMI treatment should be 162 to 325 mg chewable (nonenteric) aspirin with maintenance dose of 75 to 162 mg (Figure 42) [134]. When aspirin is contraindicated or not tolerated due to allergy or dyspepsia, clopidogrel monotherapy is an alternative. The first study to demonstrate the efficacy of aspirin in the setting of STEMI was ISIS-2 [97]. The study investigators reported that it conferred an overall 23% reduction in the odds of death versus placebo that was similar in magnitude in those subjects treated with fibrinolytic therapy alone. Incremental benefits were seen in those patients who received combination of aspirin and fibrinolytic agents. The Antithrombotic Trailists' Collaboration reported that aspirin reduced the risk of nonfatal coronary events by 30% and vascular events by 15% [97]. Low-dose aspirin (75 to 162 mg) should be recommended to all patients after an acute MI and continued indefinitely.

$P2Y_{12}$ antagonists/thienopyridines. Clopidogrel, prasugrel, or ticagrelor in combination with 81 mg aspirin should be recommended for up to 12 months in those who received a drug-eluting stent, for ≥1month, and possibly continuing for 12 months, in those who have received a bare-metal stent or not received a stent or for those who received medical management (Figures 43 and 44) [2,135,136]. The CLARITY-TIMI 28 (Clopidogrel as

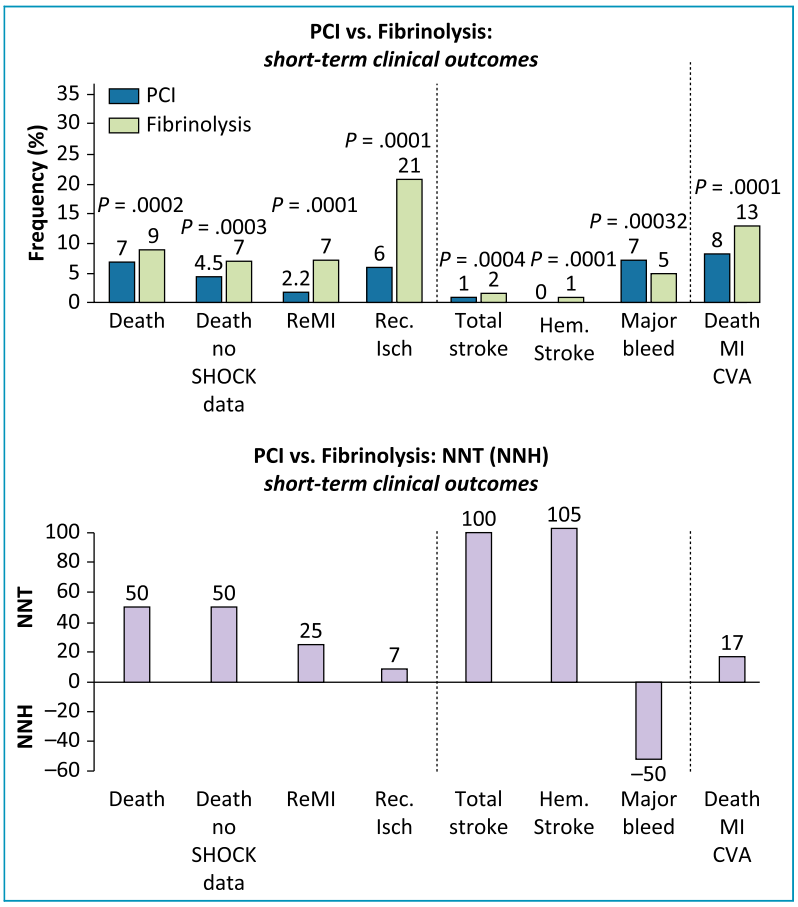


FIGURE 37. Percutaneous coronary intervention (PCI) versus fibrinolysis for ST-segment elevation myocardial infarction. The short-term (4 to 6 weeks) outcomes for the various endpoints shown are plotted for patients with ST-segment elevation myocardial infarction randomized to PCI or fibrinolysis for reperfusion in 23 trials (N = 7,739). Based on the frequency of events for each endpoint in the 2 treatment groups, the number needed to treat (NNT) or number needed to harm (NNH) is shown for the short-term (bottom left) and long-term (bottom right) outcomes. The magnitude of the treatment differences for death, nonfatal reinfarction, and stroke vary depending on whether PCI is compared with streptokinase or a fibrin-specific lytic. For example, when primary PCI is compared with alteplase and the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial is excluded, the mortality rate is 5.5% versus 6.7% (odds ratio: 0.81; 95% confidence interval: 0.64 to 1.03, p = 0.081). CVA, cerebrovascular accident; Hem, hemorrhagic; MI, myocardial infarction; Rec Isch, recurrent ischemia; ReMI, recurrent myocardial infarction. Modified from Keeley et al. [111].

Adjunctive Reperfusion Therapy Trial) found that in patients treated with fibrinolysis and aspirin, the addition of clopidogrel (300-mg loading dose and 75 mg daily) reduced major events by 20% [137] with the same rates of major bleeding and intracranial hemorrhage in both groups. In those undergoing nonurgent PCI, adding clopidogrel almost halved the incidence of major events [137]. Clopidogrel (75 mg without loading dose) reduced all-cause mortality by 7% in the 45,852-patient COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction) study of STEMI [136] without any increase in overall bleeding, including in patients >70 years old (Figures 44 and 45) [2,136,138].

Clopidogrel 75 mg daily should be added to aspirin for STEMI patients treated with fibrinolytic therapy or when no reperfusion therapy is administered and in such instances treatment should continue for at least 14 days. A loading dose of a thienopyridine is recommended for STEMI patients when PCI is being considered. Recommended regimens include 1 of the following:

- Clopidogrel 300 to 600 mg should be administered as early as possible before or at the time of primary or nonprimary PCI.
- Prasugrel 60 mg should be administered as early as possible for primary PCI.
- Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor $P2Y_{12}$, provides faster, greater, and more consistent $P2Y_{12}$ inhibition than does clopidogrel. The loading dose is 180 mg and this followed by a dose of 90 mg twice daily [139].

For nonprimary PCI STEMI patients, the recommendations are as follows:

- If fibrinolytic therapy and clopidogrel have been administered, then clopidogrel should be continued as the thienopyridine of choice.
- If fibrinolytic therapy has been administered without thienopyridine, then a loading dose of 300 to 600 mg of clopidogrel should be administered as the thienopyridine of choice.
- If fibrinolytic therapy has not been administered, then a loading dose of 300 to 600 mg of clopidogrel should be administered. However, if PCI is planned or the coronary anatomy is known, then a loading dose of 60 mg of prasugrel should be administered promptly, no later than 1 h after the PCI.
- Prasugrel is not recommended in STEMI patients for whom a PCI is planned who have a previous history of stroke or transient ischemic attack.

The duration of $P2Y_{12}$ antagonist/thienopyridine therapy recommendations are as follows:

- Clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be recommended for ≥12 months in STEMI patients receiving a bare-metal stent or a drug-eluting stent.
- In patients with first-generation drug-eluting stents, consideration should be given to recommending therapy beyond 15 months; however, for newer drug-eluting stents, the trend in recent trials is to administer therapy for periods <12 months.

- Therapy should be discontinued if the risk of morbidity due to bleeding outweighs the benefits of therapy.
- When coronary artery bypass graft (CABG) is planned, it is recommended that clopidogrel should be discontinued for ≥5 days and ≥7 days for those receiving prasugrel.

Anticoagulant therapy. The benefits of administering anticoagulant therapy in STEMI patients include reducing the incidence of deep vein thrombosis, pulmonary embolism, ventricular thrombus formation, and cerebral embolism. In addition, it assists in the establishment and maintenance of patency of the infarct-related artery. Anticoagulants that have been demonstrated to be efficacious in STEMI patients undergoing fibrinolysis include unfractionated heparin (UFH), fondaparinux (provided serum creatinine <3.0 mg/dl), and enoxaparin (provided serum creatinine level <2.5 mg/dl). Patients who receive fibrinolytic therapy should receive anticoagulants for a minimum of 48 h and preferably for the duration of index hospitalization, up to 8 days when receiving either enoxaparin or fondaparinux medications; whereas for UFH, it is limited to 48 h to limit the possibility of heparin-induced thrombocytopenia. In those undergoing PCI, UFH can be continued but before administering additional boluses, it is important take into account the administration of glycoprotein IIb/IIIa inhibitors. UFH dose during PCI includes a starting bolus dose of ≤50 U/kg, and then the dose is titrated to achieve a target activated clotting time of below 200 s.

In patients who had received enoxaparin subcutaneously at least 8 to 10 h prior to PCI, an additional intravenous dose can be administered. Fondaparinux should not be used as sole anticoagulant therapy to support PCI because of the risk of thrombosis of the cardiac catheter.

UFH is beneficial in STEMI—for every 1,000 patients treated with UFH compared with aspirin alone, there are 5 fewer deaths ($p = 0.03$) and 3 fewer recurrent infarctions ($p = 0.04$) at the expense of 3 more major bleeds ($p = 0.001$) [140]. Other benefits of UFH include possibly maintaining the patency of the infarct-related artery and possibly reducing the burden of LV thrombus. Therefore, it is considered prudent to administer heparin after thrombolysis for ≥48 h with a goal of maintaining activated partial thromboplastin time (aPTT) at 1.5× to 2× the control time. Marked prolongation of aPTT (>90 to 100 s), particularly in women, elderly patients, and low-body weight individuals is associated with a greater burden of bleeding, particularly intracranial hemorrhage. Frequent monitoring of aPTT particularly in the first 12 h is recommended. aPTT however may be higher following fibrinolysis particularly after administration of streptokinase making it difficult to assess the coagulation status.

Low molecular weight heparins are comparable to heparin in ensuring early (60 to 90 min) reperfusion of the infarct artery [140], but they appear to be better in reducing the rates of reocclusion of the infarct artery, reinfarction, and recurrent ischemic events [141].

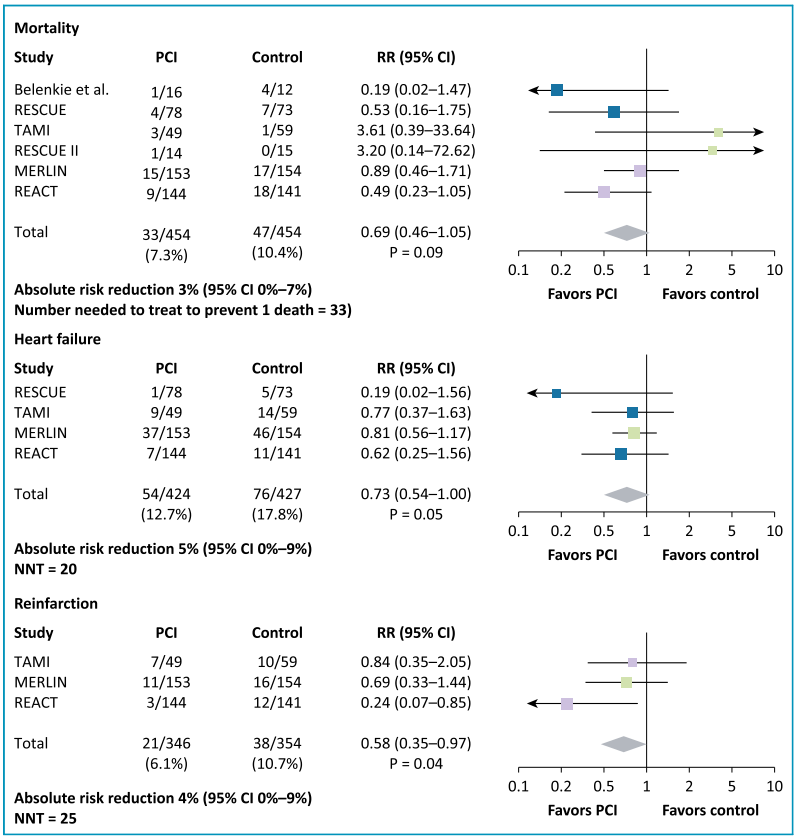


FIGURE 38. Meta-analysis of studies comparing rescue PCI with medical therapy (including repeat thrombolysis) for failed thrombolysis. PCI seems to be superior. RR, relative risk; other abbreviations as in Figures 6, 35 and 37. Data from Wijeysundera et al. [115] and Gogo et al. [116].

TABLE 11. Characteristics of fibrinolytic agents

	Streptokinase	Alteplase (tPA)	Reteplase	Tenecteplase
Fibrin selective	No	Yes	Yes	Yes > tPA
Plasminogen binding	Indirect	Direct	Direct	Direct
Duration of infusion, min	60	90	10 + 10	5–10 s
Half-life, min	23	<5	13–16	20
Fibrinogen breakdown	4+	1–2+	Not known	> tPA
Early heparin	Probably yes	Yes	Yes	Yes
Hypotension	Yes	No	No	No
Allergic reactions	Yes	No	No	No
TIMI flow grade 3, 90 min	32%	45%–54%	60%	≈ tPA
TIMI flow grade 2 to 3 at				
90 min	53%	81%–88%	83%	No data
2–3 h	70%–73%	73%–80%	No data	No data
24 h	81%–88%	78%–89%	No data	No data

TIMI, Thrombolysis In Myocardial Infarction; tPA, tissue plasminogen activator.
Adapted from Opie and Gersh [104].

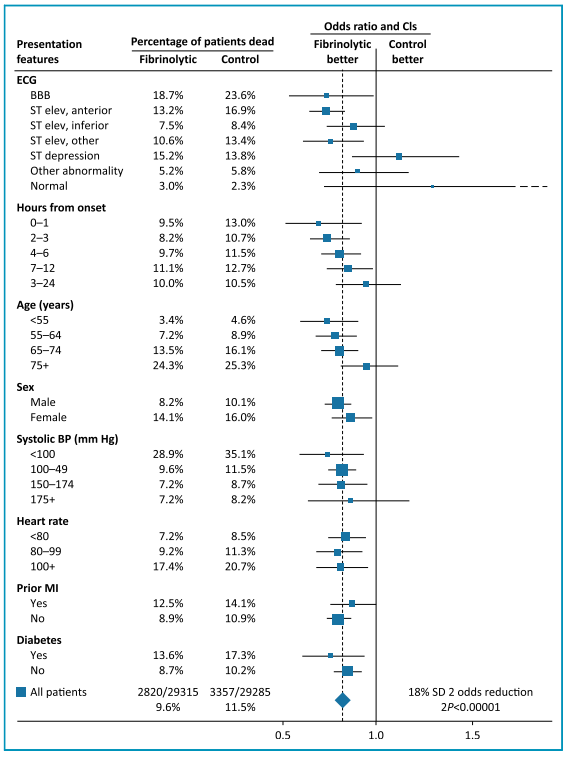


FIGURE 39. Mortality differences during days 0 to 35 subdivided by presentation features in a collaborative overview of results from 9 trials of thrombolytic therapy. The absolute mortality rates are shown for fibrinolytic and control groups in the center portion of the figure for each of the clinical features at presentation listed on the left side of the figure. The ratio of the odds of death in the fibrinolytic group to that in the control group is shown for each subdivision (squares), along with its 99% confidence interval (horizontal line). The summary odds ratio at the bottom of the figure corresponds to an 18% proportional reduction in 35-day mortality and is highly statistically significant. This translates to a reduction of 18 deaths per 1,000 patients treated with thrombolytic agents. BBB, bundle branch block; BP, blood pressure; other abbreviations as in Figures 1, 9, and 30. Reproduced, with permission, from Fibrinolytic Therapy Trialists' Collaborative Group [117].

Direct thrombin inhibitors, such as hirudin, reduce the incidence of recurrent MI by 25% to 30% when compared with use of heparin in patients receiving fibrinolysis, but they do not reduce mortality and results in high rates of major bleeds [142]. Whereas, in patients undergoing PCI, when administered for short duration, bivalirudin, when compared with heparin and glycoprotein IIb/IIIa inhibitors, was associated not only with a significant reduction in mortality at 30 days and at 1 year, but also with 40% reduction of major bleeding [143]. However, the HEAT-PPCI (Unfractionated Heparin Versus Bivalrudin in Primary Percutaneous Coronary Intervention) single-center study [144]

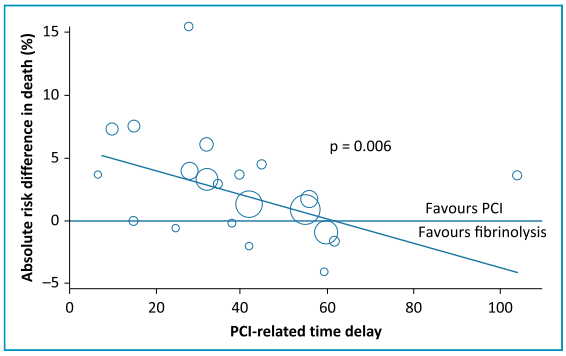


FIGURE 40. Absolute risk reduction in 4- to 6-week mortality rates with primary percutaneous coronary intervention (PCI) as a function of PCI-related time delay. Circle size reflects the sample size of the individual study. The solid line represents the weighted meta-regression. Values $>$ 0 favor PCI and values $<$ 0 favor fibrinolysis. Reprinted with permission from Nallamothu et al. [119].

suggested that UFH was superior to bivalirudin. Whether bivalirudin is superior to heparin monotherapy must await the results of the multicenter 6,800-patient MATRIX trial, which is expected to complete recruitment by the end of 2014.

Beta-blockers. Beta-blockers should be initiated as soon as possible after acute STEMI in hemodynamically stable patients and the dose should be up-titrated to the maximum tolerated or target dose (Figure 45) [138]. They should be continued indefinitely in those with LV systolic dysfunction and for $\geq$12 months after STEMI in those without LV systolic dysfunction or heart failure. Patients with contraindications for beta-blockers in the first 24 h of STEMI should be re-evaluated for candidacy. Recently reported data from the OBTAIN (Optimal Beta-blocker Therapy After Myocardial Infarction) registry, which included >7,000 acute MI patients, suggested that patients discharged on roughly 25% of target beta-blocker dose had a significantly lower mortality than those discharged on higher or lower doses (presented at the American College of Cardiology Annual Scientific Session, March 29-31, 2014, Washington, DC.).

ACE inhibitors. Angiotensin-converting enzyme (ACE) inhibitors should be initiated in STEMI patients and continued indefinitely when LV systolic dysfunction persists (Figure 46) [145]. The dose should be up-titrated at short intervals of 12 to 24 h, and up-titration should be completed within 4 to 6 weeks after discharge. In patients intolerant to ACE inhibitors, angiotensin-receptor blockers should be considered when there are signs of heart failure on chest x-ray or LV ejection fraction is <40%. Renal function, particularly blood urea nitrogen and serum creatinine, serum electrolytes, and blood pressure should be checked before starting therapy, monitored until treated with a stable dose, and then monitored at least once a year. More frequent

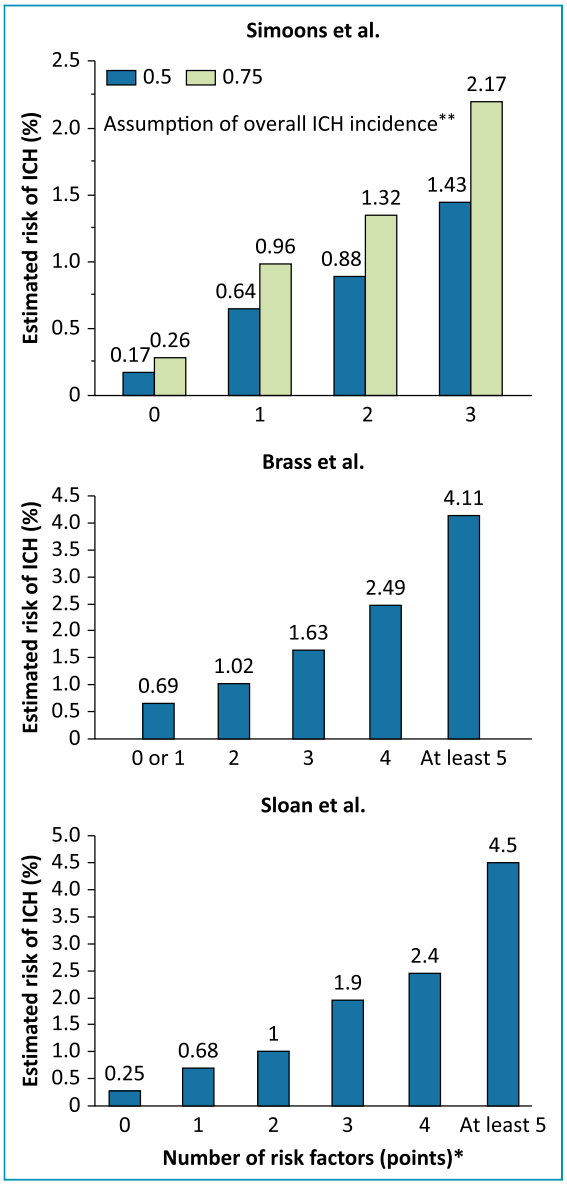


FIGURE 41. Estimation of risk of intracranial hemorrhage (ICH) with fibrinolysis [2]. The number of risk factors is the sum of the points based on criteria established in the studies shown. *Although the exact risk factors varied among the studies, common risk factors across all the studies included increased age, low body weight, and hypertension on admission. **If the overall incidence of ICH is assumed to be 0.75%, patients without risk factors who receive streptokinase have a 0.26% probability of ICH. The risk is 0.96%, 1.32%, and 2.17% in patients with 1, 2, or 3 risk factors, respectively. Data from Simoons et al. [123]; Brass et al. [124]; and Sloan et al. [125]. Modified from Keeley et al. [110].

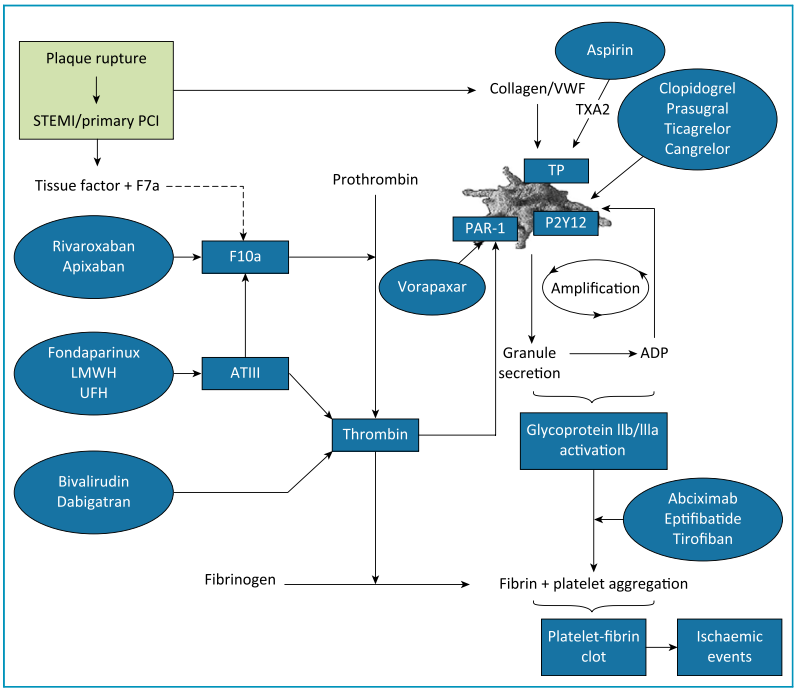


FIGURE 42. Platelet activation, adhesion, and aggregation cascade, and targets for antithrombotic drug therapy to support primary PCI [134]. De novo plaque rupture can lead to STEMI. Exposure of the subendothelial matrix and subsequent release of vasoactive factors enable platelet activation and release of important secondary agonists, thromboxane A2 (TXA2) and adenosine diphosphate (ADP). Through autocrine and paracrine mechanisms, these locally generated secondary agonists have an essential role in the sustained activation of glycoprotein IIb/IIIa receptors and stable platelet aggregation. Plaque rupture also results in tissue factor exposure that binds to activated factor VII (F7a) to form a complex that activates factor X (F10) to F10a. Initial formation of small amounts of thrombin results in perpetuation of the coagulation process on the surface of activated platelets, where large amounts of thrombin are generated. Thrombin finally catalyzes the conversion of soluble fibrinogen to insoluble strands of fibrin, thereby initiating clot formation. ATIII, antithrombin III; LMWH, low-molecular-weight heparin; PAR-1, coagulation factor II (thrombin) receptor; P2Y12, purinergic receptor P2Y, G-protein coupled, 12; TP, thromboxane A2 receptor; UFH, unfractionated heparin; VWF, von Willebrand factor; other abbreviations as in Figures 6 and 9.

monitoring should be considered if there is intercurrent dehydration, deteriorating renal function, or development of hyperkalemia.

Statins. All patients (including diabetics) with vascular disease would benefit from statin therapy (probably high-intensity statins) based on a meta-analysis of 90,056 subjects irrespective of their initial lipid profile [146]. The study investigators estimated that for every 40 mg/dl (1.0 mmol/l) decrease in low-density lipoprotein cholesterol, the 5-year relative risk for major coronary events is reduced

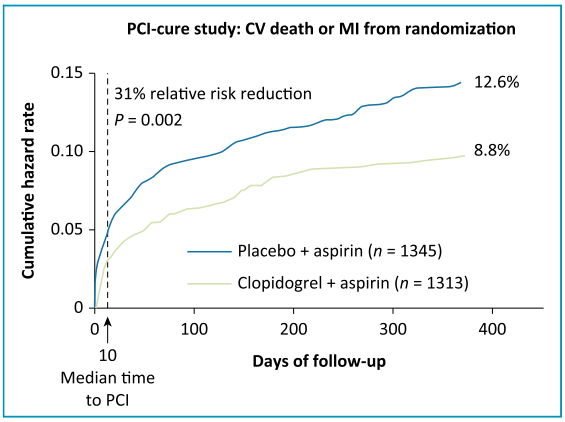


FIGURE 43. PCI-CURE (Effects of Pretreatment With Clopidogrel and Aspirin Followed by Long-Term Therapy in Patients Undergoing Percutaneous Coronary Intervention): Composite of MI or cardiovascular death from randomization to end of follow-up in PCI patients with acute coronary syndrome. Abbreviations as in Figures 3, 6, and 30. Reproduced, with permission, from Mehta et al. [135].

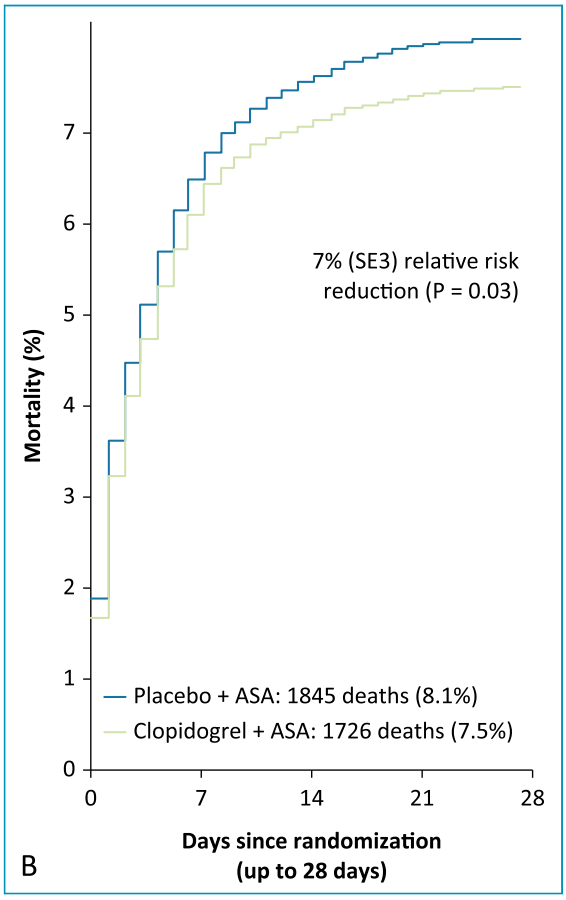


FIGURE 44. Impact of addition of clopidogrel to aspirin (ASA) in ST-segment elevation myocardial infarction patients [2]. Effect of the addition of clopidogrel on in-hospital mortality after ST-segment elevation myocardial infarction is shown. These time-to-event curves show a 0.6% reduction in mortality in the group receiving clopidogrel plus aspirin (n = 22,961) compared with placebo plus aspirin (n = 22,891) in the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction) trial. Modified from Chen et al. [136].

by one-fifth (Figure 47) [146]. Although the absolute risk reduction is dependent on the initial risk, they estimated that over a 5-year period statin therapy might reduce the overall risk of major cardiovascular events by one-third.

Nitroglycerin. Intravenous nitroglycerine is indicated in the first 48 h after STEMI for persistent angina, hypertension, or heart failure. However, the decision to administer oral, topical, or intravenous nitrate should not preclude mortality-reducing therapies such as beta-blockers or ACE inhibitors. Nitrates should be avoided when SBP is <90 mm Hg or ≥30 mm Hg above baseline or in cases of suspected RV infarction, severe bradycardia (<50 beats/min), or tachycardia (>100 beats/min).

Aldosterone receptor blockers. STEMI patients with symptoms of heart failure and LV systolic dysfunction therapy should be started within 3 to 14 days after acute MI, preferably after initiation of ACE-inhibitor or angiotensin-receptor blocker therapy. Monitoring of serum electrolytes and renal function should be considered before initiating therapy, and after 48 h, 1 and 4 weeks, and at 3 months, and quarterly thereafter; and after 1 week of dose up-titration. Aldosterone-receptor antagonists should be avoided when there is significant renal dysfunction, that is, serum creatinine ≥2.5 mg/dl in men and ≥2.0 mg/dl in women, or when serum potassium is ≥5 mEq/l, particularly when patient is already receiving ACE-inhibitor therapy.

COMPLICATIONS

Important complications of MI include recurrent chest pain, RV infarction, heart failure, pulmonary edema (Figure 48), free wall rupture, rupture of interventricular septum, rupture of a papillary muscle, cardiogenic shock, LV aneurysm, cardiac arrhythmias, pericardial effusion or pericarditis, venous thrombosis, and pulmonary embolism [39].

Recurrent chest pain suggests recurrent ischemia or possibly pericarditis. Recurrent ischemia requires optimization of medical therapy with beta-blockers and nitrates. Patients with persistent symptoms despite intensification of medical therapy may require repeat PCI and evaluation for CABG. Patients with recurrent STEMI may need to be treated with re-administration of tissue plasminogen activator or a glycoprotein IIb/IIIa inhibitor together with intravenous nitroglycerine, beta-blockade, and heparin. Streptokinase should not be administered because it

induces neutralizing antibodies. PCI is preferred when available. Acute pericarditis typically occurs 2 to 4 days after a massive transmural infarction. Rarely hemorrhagic effusion with tamponade can develop. Anticoagulation, therefore, should be withdrawn if pericardial effusion increases. Pericarditis developing 2 to 4 weeks after MI suggests immune-mediated Dressler syndrome. The incidence of this syndrome has substantially decreased in the modern early reperfusion era. High-dose aspirin therapy (650 mg enteric-coated every 4 to 6 h) is recommended for pericarditis. Colchicine and nonsteroidal anti-inflammatory drugs may be used for pericarditis not responding to aspirin. However, nonsteroidal anti-inflammatory drugs should not be administered for protracted periods due to the risk of myocardial scar thinning and infarct expansion and due to their effect on platelet function. In refractory cases of pericarditis, corticosteroids may be considered.

Heart failure and cardiogenic shock

There are several distinct patterns of hemodynamic changes that occur after acute MI and each requires a specific approach to diagnosis, monitoring, and therapy (Figures 49 to 51 and Table 12) [147–149]. Cardiogenic shock is a severe form of LV failure characterized by marked hypotension (SBP <80 mm Hg) and reduction in cardiac index (<1.8 l/min/m^2) despite high LV filling pressure (pulmonary capillary wedge pressures >18 mm Hg). It suggests >40% of LV contractile function is impaired and is associated with a mortality rate >70% to 80% despite aggressive medical therapy. When cardiogenic shock is not quickly reversed by pharmacological and inotropic support, then intra-aortic balloon counterpulsation (IABP) should be considered. Other options are emergency PCI or CABG. Beta-blockers and calcium channel blockers should not be administered in this low-output state.

IABP involves introduction of the deflated balloon catheter into the femoral artery and is advanced into the aorta (Figures 52 and 53) [46,57]. The ECG triggers inflation of the balloon during early diastole, resulting in augmentation of coronary blood flow. The deflation of the balloon during early systole reduces LV afterload. IABP does not improve mortality but allows stabilization of the patient for PCI or CABG. It is indicated for mechanical complications of acute MI such as acute mitral regurgitation and acute ventricular septal defect, refractory post-MI ischemia, or recurrent intractable ventricular tachycardia or fibrillation. Its use in cardiogenic shock treated with primary angioplasty is limited. It should be avoided with severe aortic regurgitation or severe peripheral vascular disease.

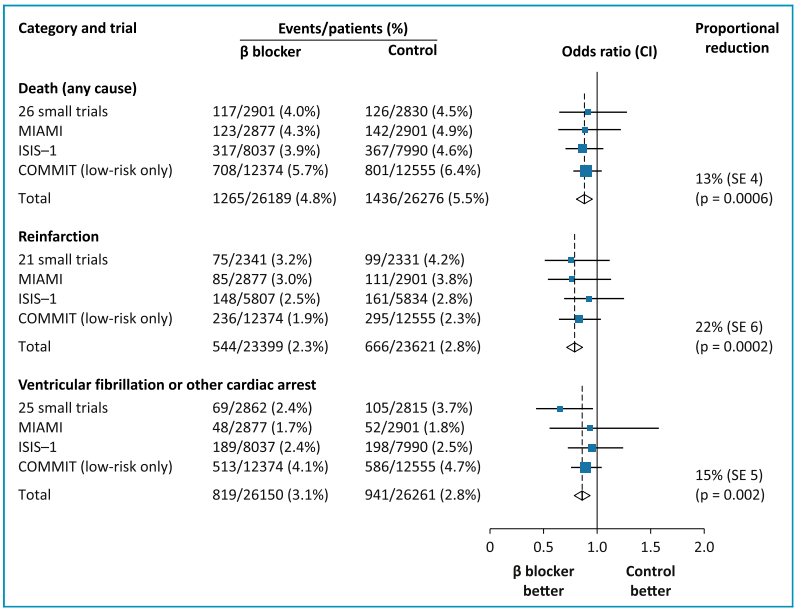


FIGURE 45. Meta-analysis of effects of intravenous and then oral beta-blocker therapy on death, reinfarction, and cardiac arrest during the scheduled treatment periods in 26 small randomized trials, MIAMI (Metoprolol in Acute Myocardial Infarction), ISIS-1 (First International Study of Infarct Survival), and the low-risk subset of COMMIT. For COMMIT, data are included only for patients who presented with systolic blood pressure >105 mm Hg, heart rate >65 beats/min, and Killip class I (as in MIAMI). Five small trials included in the ISIS-1 report did not have any data on reinfarction. In the ISIS-1 trial, data on reinfarction in hospital were available for the last three-quarters of the study, involving 11,641 patients. Odds ratios in each (squares with area proportional to number of events) comparing outcome in patients allocated beta-blockers to that in patients allocated control drugs, along with 95% confidence interval (horizontal line). Overall odds ratios and 95% confidence intervals are indicated by diamonds. Abbreviations as in Figures 1 and 44. Reproduced, with permission, from Chen et al. [138].

RV infarction should be kept in mind in all patients with inferior wall STEMI, particularly when there are impaired hemodynamics (Figure 54) [150] and the presence of Kussmaul sign (jugular venous distension on inspiration) (Table 13) [47]. Right-sided precordial leads, particularly V_4R, should be recorded in the first 24 h after onset of symptoms to detect ST-segment elevation, and an echocardiogram should be performed to detect RV dilation and dysfunction. Management includes early reperfusion, correction of accompanying bradycardia, and restoration of AV synchrony by temporary AV sequential pacing. Intravenous fluids may need to be administered to optimize RV pre-load (i.e., target PCWP is >17 mm Hg) and inotropic support may be required when fluid challenge alone is not adequate. Cardioversion should be used

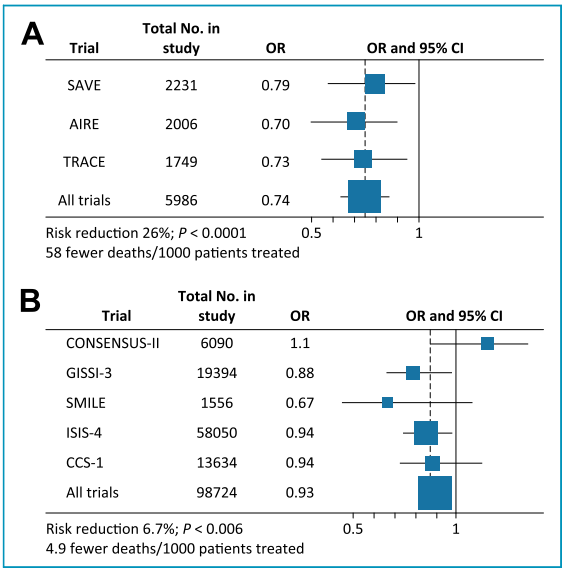


FIGURE 46. Effect of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction—results from the long-term (top) and short-term (bottom) trials. AIRE, Acute Infarction Ramipril Efficacy Study; CCS-1, Chinese Cardiac Study; CONSENSUS II, The Effects of the Early Administration of Enalapril on Mortality in Patients With Acute Myocardial Infarction: Results of the Cooperative New Scandinavian Enalapril Survival Study II; GISSI-3, Effects of Lisinopril and Transdermal Glycerol Trinitrate Singly and Together on 6-Week Mortality and Ventricular Function After AMI; ISIS-4, Fourth International Study of Infarct Survival; SAVE, Survival and Ventricular Enlargement Trial; SMILE, The Effects of the Angiotensin-Converting-Enzyme Inhibitor Zofenopril on Mortality and Morbidity After Anterior Myocardial Infarction; TRACE, The Trandolapril Cardiac Evaluation Study; other abbreviations as in Figures 1 and 34. Reproduced, with permission, from Gornik and O'Gara [145].

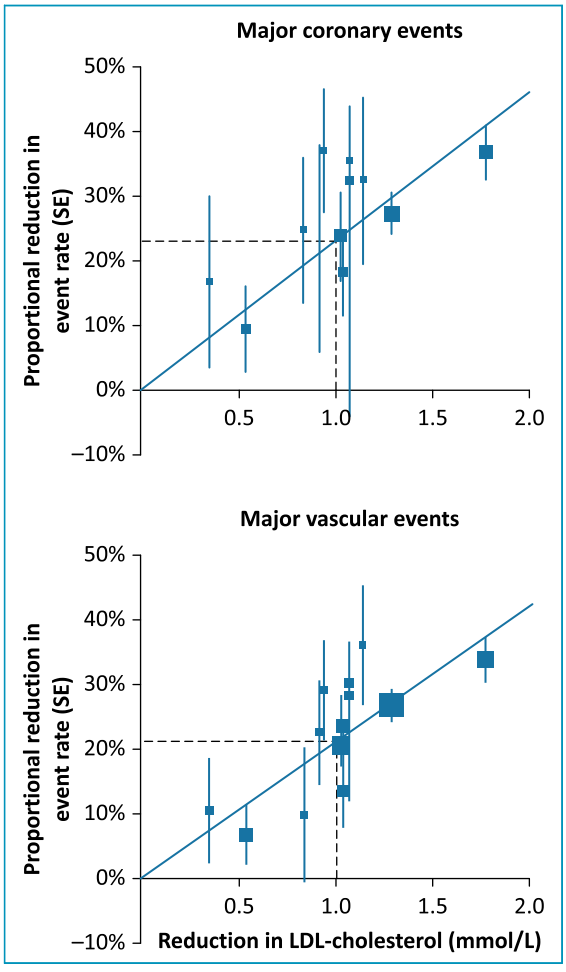


FIGURE 47. Relation between proportional reduction in incidence of major coronary events and major vascular events and mean absolute low-density lipoprotein (LDL) cholesterol reduction at 1 year. Reproduced, with permission, from Baigent et al. [146].

to restore normal sinus rhythm in atrial fibrillation, which occurs in about one-third of the patients with RV infarction, because it can result in severe hemodynamic compromise.

Mechanical causes of low-output state or heart failure include mitral regurgitation, ventricular septal defect (Figure 55) [93], and rupture of the LV free wall (Figure 56) [151]. Such patients should be referred for cardiac surgery for emergent surgical repair, and during surgery, CABG should be undertaken at the same time if technically feasible.

Acute mitral regurgitation usually results from rupture or dysfunction of a papillary muscle. Total rupture results in death in 75% of the patients within 24 h. Intravenous nitroprusside is used to reduce pre-load and inotropic support with dobutamine and/or dopamine is often required. IABP is used to stabilize the patient prior to emergent surgical repair. Surgery is associated with a high mortality rate of 25% to 50%, but, when compared with medical therapy alone, surgery results in better survival and functional outcome.

Ventricular septal defect is most likely to occur in patients who receive fibrinolysis, in elderly patients, and those with hypertension (Figure 55) [93]. All septal defects should be repaired if the patient is an appropriate surgical candidate based on age and comorbidities. Prior

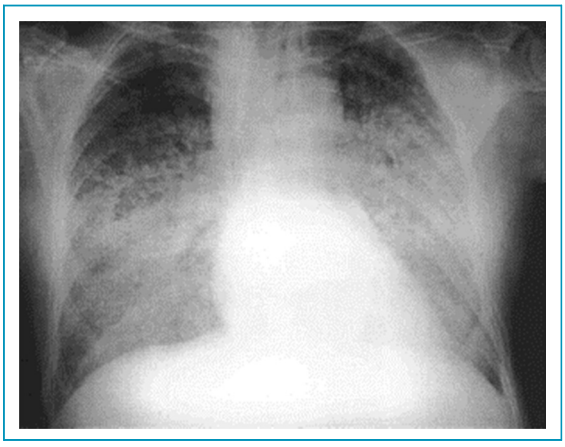


FIGURE 48. Chest radiograph showing cardiomegaly and pulmonary edema in an acute myocardial infarction patient with cardiogenic shock and multivessel coronary artery disease. Reproduced, with permission, from Riordan and Brady [39].

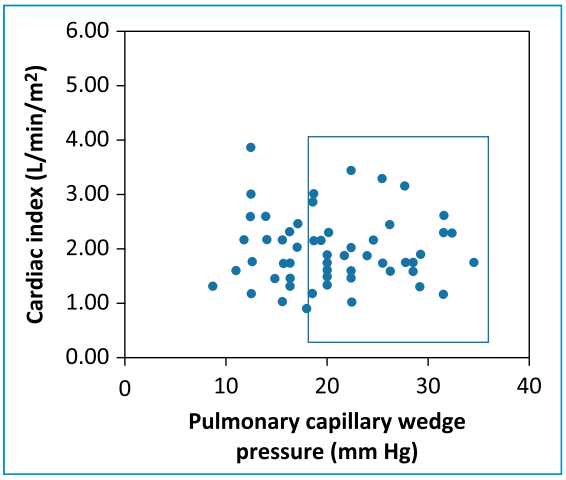


FIGURE 50. In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) registry, the clinically established category of isolated hypoperfusion cases (n = 61) according to presence or absence of rales or pulmonary congestion revealed, compared with hemodynamic parameters, how difficult it is to establish the presence of pulmonary congestion in shock cases. At least one-half of the isolated hypoperfusion (no pulmonary congestion) cases had frankly high pulmonary capillary wedge pressures. Reproduced, with permission, from Menon et al. [148].

to surgery, intravenous nitroprusside, intravenous dobutamine, and IABP are often required to stabilize the patient.

LV aneurysm tends to develop after large anterior wall MI (Figures 57 to 59) [40,46,93,151]. Aneurysmectomy and CABG are required if there is refractory heart failure, ventricular tachycardia, or embolization despite optimal medical therapy and PCI. This complication is less commonly observed in the reperfusion era of treatment.

Rupture of LV free wall results in acute cardiac tamponade with sudden death. In a small minority of patients, localized containment or "resealing" results in LV "pseudoaneurysm." In such instances, medical stabilization with inotropic support and IABP may be required before emergency surgical repair.

Tachyarrhythmias complicating acute STEMI include atrial flutter and atrial fibrillation, and ventricular tachycardia and ventricular fibrillation.

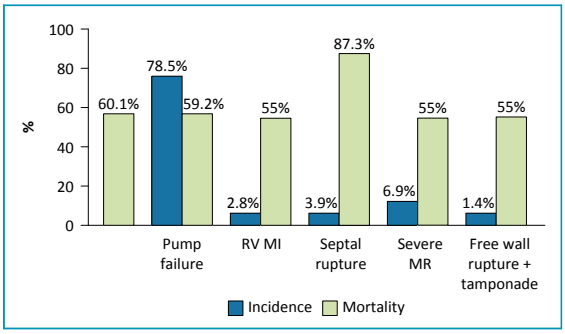


FIGURE 49. The large majority (78.5%) of SHOCK registry cases were left ventricular pump failure. Right ventricular (RV) infarction and "mechanical complications" accounted for the remainder. MR, mitral regurgitation; other abbreviations as in Figures 30 and 37. Reproduced, with permission, from Hochman et al. [147].

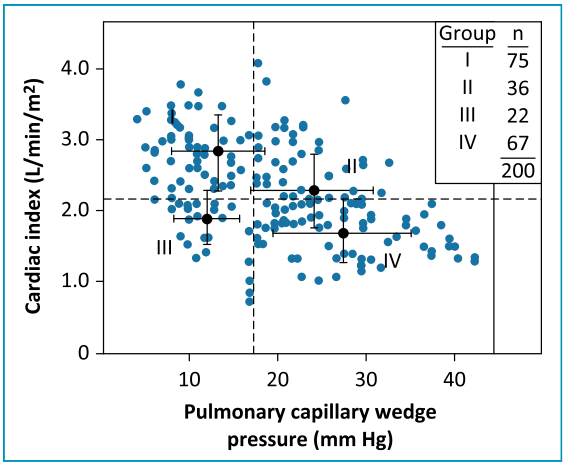


FIGURE 51. Hemodynamic subsets, derived from 200 cases of myocardial infarction. Abbreviations as in Figures 30 and 49. Reproduced, with permission, from Forrester et al. [149].

TABLE 12. Forrester classification of heart failure

Class		Hemodynamic Subsets PCWP	CI	Mortality	Clinical Subsets Mortality	PCWP	CI
I		<18	>2.2	3%	11%	12 ± 7	2.7 ± 0.05
II	Pulmonary congestion	>18	>2.2	9%	11%	23 ± 5	2.3 ± 0.4
III	Peripheral hypoperfusion	<18	<2.2	23%	18%	12 ± 5	1.9 ± 0.4
IV	Pulmonary congestion and peripheral hypoperfusion	>18	<2.2	51%	60%	27 ± 8	1.6 ± 0.6

CI, cardiac index; PCWP, pulmonary capillary wedge pressure.
Adapted from Forrester et al. [149].

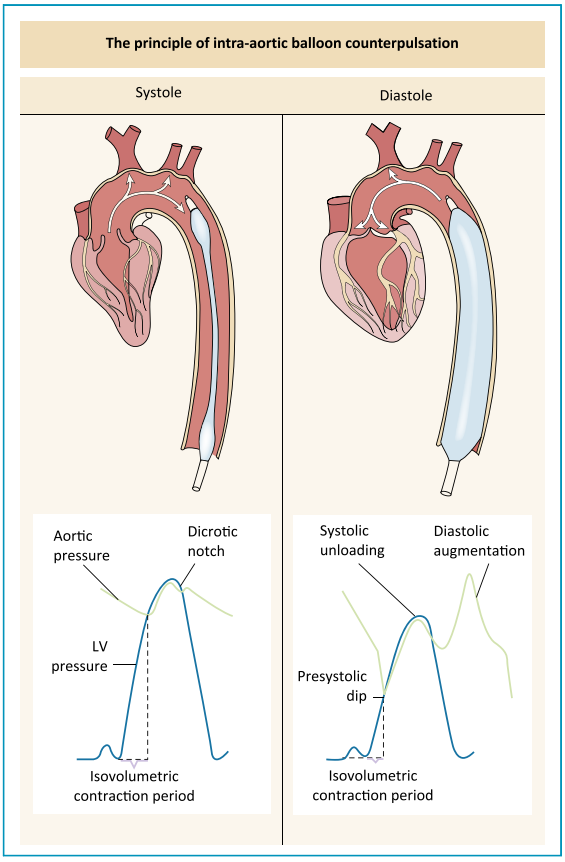


FIGURE 52. The principle of intra-aortic balloon pump. Initiation of balloon inflation is timed to the arterial dicrotic notch, producing an augmentation in proximal aortic diastolic pressure. Deflation of the balloon is timed to begin just before the onset of the next ventricular systole, which produces the systolic unloading effect (presystolic dip). LV, left ventricular. Reproduced, with permission, from Cercek and Shah [46].

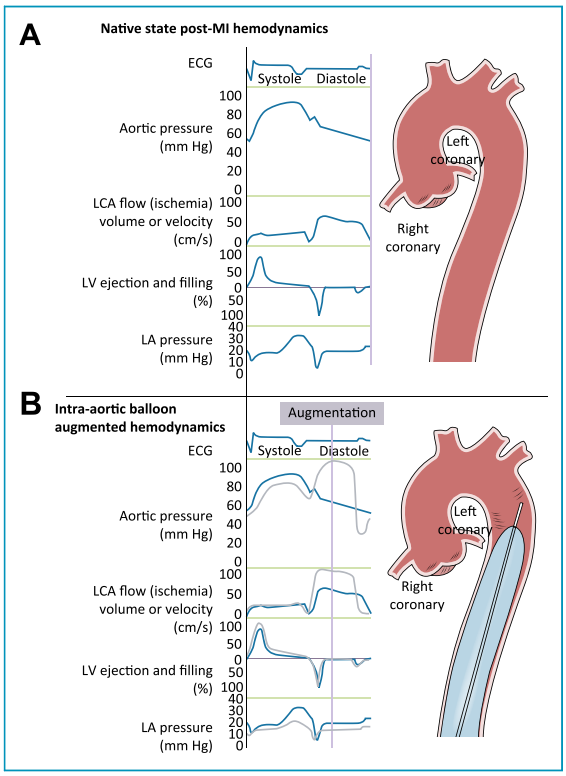


FIGURE 53. (A) Cardiogenic shock native state hemodynamics. The mean, systolic, and diastolic arterial blood pressures are low—60% of usual. Left coronary artery (LCA) flow is reduced because of the lowered perfusion pressure (aortic diastolic pressure — [elevated] left ventricular diastolic pressure). Left coronary flow, though, is diastole predominant because the perfusion pressure is positive only in diastole. Left ventricular ejection is an early systolic phenomenon, and left ventricular filling is predominantly an early diastolic occurrence because of the elevated left atrial pressure. Left atrial (LA) pressure is elevated, and the waveform is revealing of the overload of the left atrium—a V-wave occurs. (B) Intra-aortic balloon-augmented hemodynamics. Intra-aortic balloon inflation at the dicrotic notch increases intra-aortic volume and pressure. With deflation, late diastolic pressure falls beneath the native level, such that the next systolic ejection occurs against an initially lower pressure—"assisting" ejection. This lessening of afterload to the left ventricle results in a 10% to 15% increase in ejection and a lowering of ventricular volumes and pressure. Consequently, left atrial pressure is reduced. Abbreviations as in Figures 9, 30, and 52. Reproduced, with permission, from Hutchison and Rudakewich [57].

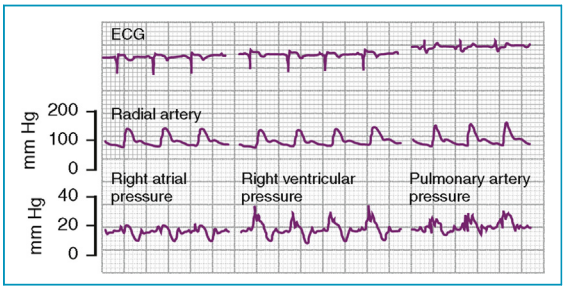


FIGURE 54. Hemodynamic tracings in right ventricular infarction. Noncompliant pattern of right ventricular infarction, with elevated right atrial pressure, a deep y descent in the atrial tracing, dip and plateau diastolic pattern in the right ventricle, and relatively low pulmonary artery pressure. ECG, electrocardiogram. Reproduced, with permission, from Lorrell et al. [150].

Atrial fibrillation occurs in about 10% to 15% of patients after MI, usually within the first 24 h. The incidence of atrial flutter and other supraventricular arrhythmias is lower. Risk factors include older age, larger infarct size, heart failure, atrial infarction, and pericarditis. Patients with atrial fibrillation will require therapy for rate control, anticoagulant therapy, and consideration for cardioversion. Systemic embolization may occur in the first day, so it is important to start anticoagulation early in atrial fibrillation.

Primary ventricular fibrillation can result in mortality within the first 24 h, and its incidence is 3% to 5% within the first 4 h and then it declines rapidly over the next 24 to 48 h. Management of ventricular tachycardia and ventricular fibrillation is per advanced cardiac life support protocols including electric cardioversion. Prophylactic lidocaine reduces primary ventricular fibrillation but does not reduce, and may even increase, mortality and hence is not recommended. Refractory arrhythmias, such as persistent polymorphic ventricular tachycardia, require pharmacological therapies to reduce cardiovascular ischemia and myocardial oxygen demand. These include beta-blockade, IABP, emergent PCI or CABG, extracorporeal membrane oxygenation, and optimization of serum potassium and magnesium levels. For slower stable ventricular tachycardia, intravenous amiodarone or lidocaine may be given for 6 to 24 h.

Accelerated idioventricular rhythm (60 to 100 beats/min) frequently occurs within the first 12 h and is usually benign. It often heralds the onset of reperfusion with fibrinolytic therapy. Usually antiarrhythmic therapy is not indicated unless it is compromising hemodynamics.

Bradyarrhythmias and conduction delays complicating STEMI are managed depending on the type of STEMI,

TABLE 13. Hemodynamic findings in cases of RV infarction

Elevated right atrial pressure (>10 mm Hg)
Right atrial pressure/pulmonary wedge pressure ratio >0.8
Noncompliant jugular venous pattern (prominent y descent)
Dip and plateau RV diastolic pressure pattern
Depressed and delayed (often bifid) RV systolic pressure
Decreased cardiac output
Hypotension

RV, right ventricular.
Adapted from Mani and Brown [47].

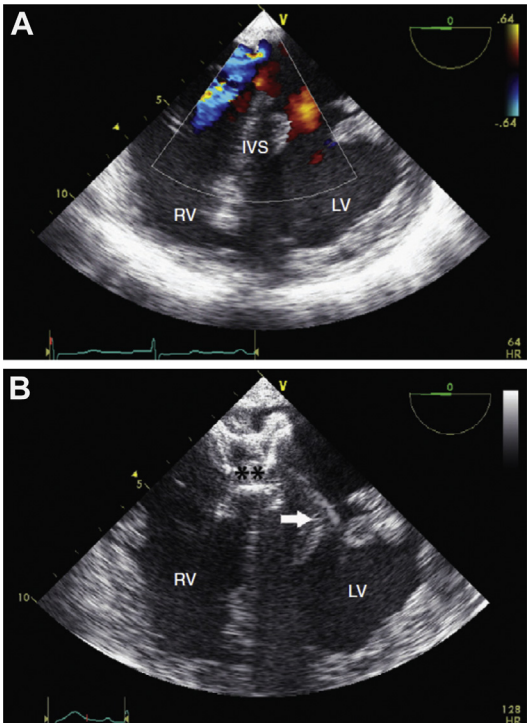


FIGURE 55. Three days after an acute inferior myocardial infarction, clinical deterioration and a new systolic murmur were observed in this patient. (A) Transesophageal transgastric view at 0° with color Doppler showed a shunt from the left to the right ventricle, typical of a ventricular septal defect. (B) Transesophageal echocardiography guidance of percutaneous closure of this ventricular septal defect. ** indicates Amplatzer device. IVS, interventricular septum; other abbreviations as in Figures 49 and 52. Reproduced, with permission, from Diaz et al. [93].

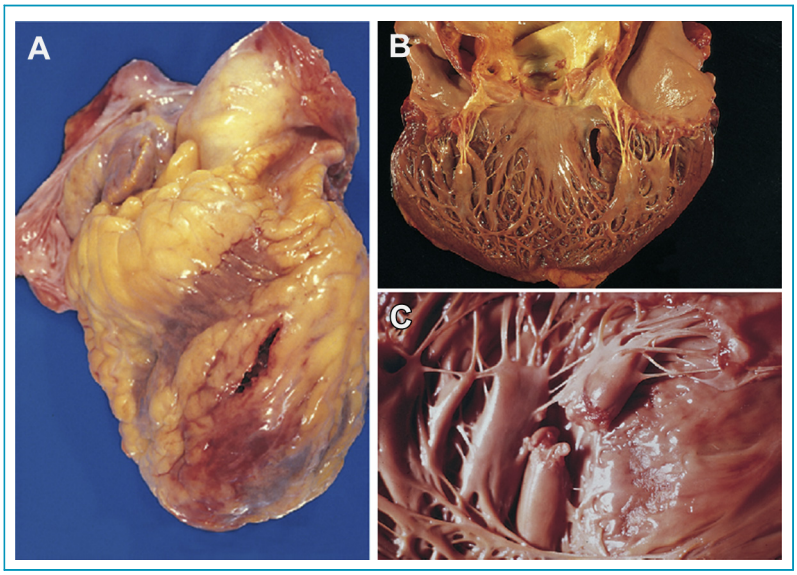


FIGURE 56. Cardiac rupture syndromes complicating ST-segment elevation myocardial infarction. (A) Anterior myocardial rupture in an acute infarct. (B) Rupture of the ventricular septum. (C) Complete rupture of a necrotic papillary muscle. Reproduced, with permission, from Schoen [151].

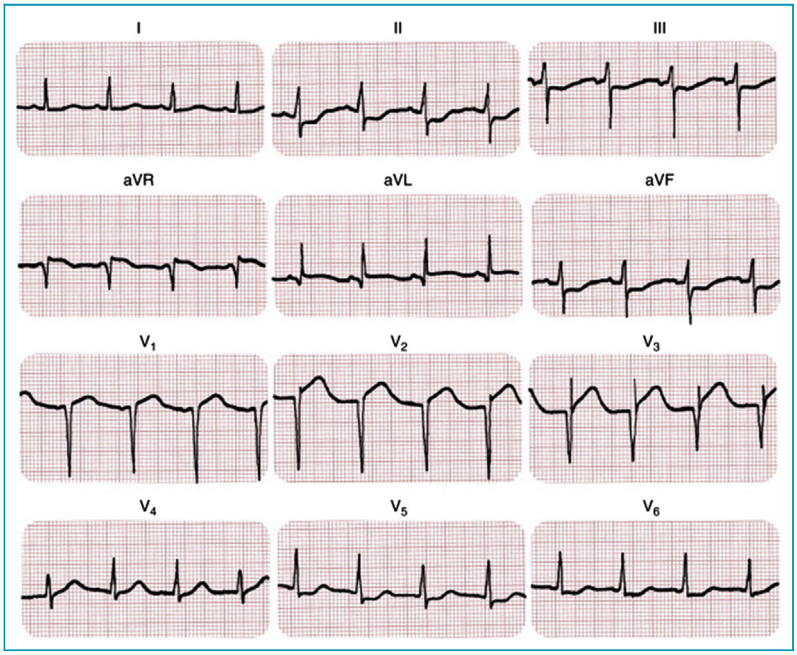


FIGURE 57. Anterior wall aneurysm. The patient had a myocardial infarction several months before this electrocardiogram was taken. Notice the prominent Q waves in leads V_1 to V_3 and aVL, the persistent ST elevations in these leads, and the reciprocal ST segment depressions in the inferior leads (II, III, and aVF). The persistence of ST-segment elevations more than 2 to 3 weeks after an infarction suggests the presence of a ventricular aneurysm. Reproduced, with permission, from Goldberger [40].

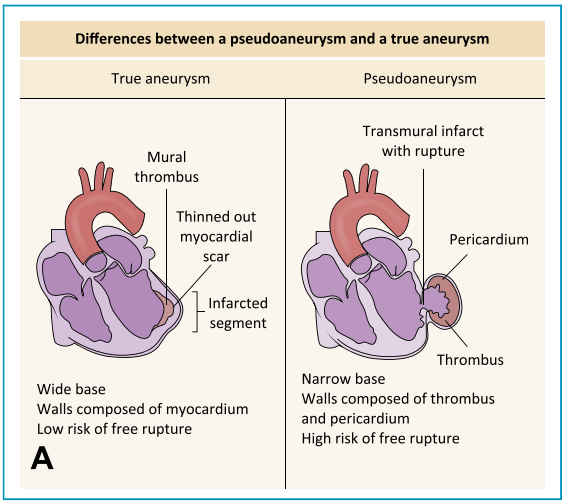


FIGURE 58. Pseudoaneurysm and true aneurysm. (A) The features of a true ventricular aneurysm compared with those of a false ventricular aneurysm. Cercek and Shah [46].

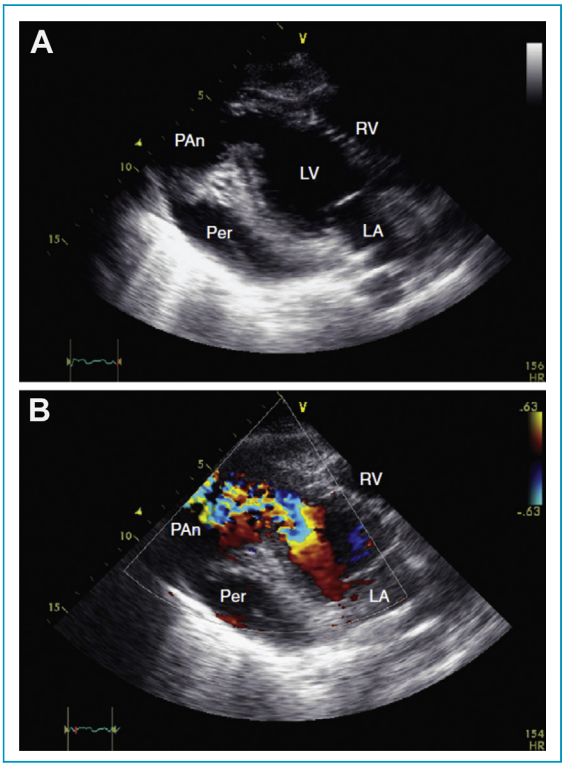


FIGURE 59. (A) Apical long-axis view, slightly off-axis, shows abrupt discontinuity of the distal inferolateral wall, resulting in a communication between the LV and a large cavity that appears to be a pseudoaneurysm. The "aneurysmal" cavity was pulsatile during real-time imaging. (B) On color Doppler, flow is seen from the LV toward the pseudoaneurysmal cavity (arrow). PAn, pseudoaneurysm; Per, pericardial effusion; other abbreviations as in Figures 49, 52, and 53. Reproduced, with permission, from Diaz et al. [93].

TABLE 14. Permanent pacing for bradycardia or conduction blocks associated with STEMI infarction

Class I
1. Permanent ventricular pacing is indicated for persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or third-degree AV block within or below the His-Purkinje system after STEMI (level of evidence: B).
2. Permanent ventricular pacing is indicated for transient advanced second-degree or third-degree infranodal AV block and associated bundle branch block. If the site of the block is uncertain, an electrophysiologic study may be necessary (level of evidence: B).
3. Permanent ventricular pacing is indicated for persistent and symptomatic second-degree or third-degree AV block (level of evidence: C).
Class IIb
1. Permanent ventricular pacing may be considered for persistent second-degree or third-degree AV block at the AV node level (level of evidence: B).
Class III
1. Permanent ventricular pacing is not recommended for transient AV block in the absence of intraventricular conduction defects (level of evidence: B).
2. Permanent ventricular pacing is not recommended for transient AV block in the presence of isolated left anterior fascicular block (level of evidence: B).
3. Permanent ventricular pacing is not recommended for persistent first-degree AV block in the presence of bundle branch block that is old or of indeterminate age (level of evidence: B).
4. Permanent ventricular pacing is not recommended for persistent first-degree AV block in the presence of bundle branch block that is old or of indeterminate age (level of evidence: B)
Sinus Node Dysfunction After STEMI
Class I
1. Symptomatic sinus bradycardia, sinus pauses >3 s, or sinus bradycardia with heart rate <40 beats/min and assisted hypotension or signs of systemic hemodynamic compromise should be treated with an intravenous bolus of atropine, 0.6 to 1 mg. If bradycardia is persistent and maximal (2 mg) doses or atropine have been used, transcutaneous or transvenous (preferably atrial) temporary pacing should be instituted (level of evidence: C).

AV, atrioventricular; STEMI, ST-segment elevation myocardial infarction.
Adapted from Antman et al. [152].

severity of bradycardia and location of the heart block. Sinus bradycardia occurs in 30% to 40% of patients with acute inferior wall MI. It is particularly common in the first hour of acute MI and following recanalization of the right coronary artery. Typically, the AV block is vagally mediated and therefore anticholinergic therapy (atropine 0.5 to 1.5 mg intravenously) is indicated in symptomatic sinus bradycardia—heart rate <50 beats/min associated with hypotension, ischemia, or escape ventricular arrhythmia. It is also indicated in ventricular asystole. Atropine is not indicated and can even worsen infranodal AV block accompanying anterior MI. Other therapeutic options for bradycardia include observation, temporary venous pacing, and transcutaneous pads with standby pacing. Permanent pacing is indicated in second-degree AV block of the His-Purkinje conducting system with bilateral bundle branch

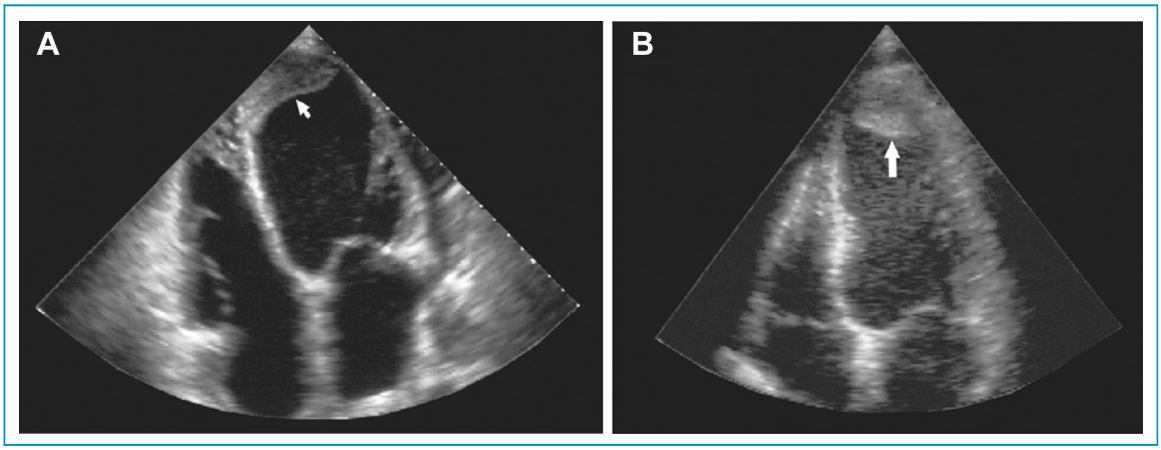


FIGURE 60. Left ventricular thrombi in the apical 4-chamber view from 2 different patients. An organized and nonmobile thrombus is detected in the first patient (arrow in A), and a mobile thrombus (arrow in B) is seen in the second patient in a region of akinesia and apical aneurysm. The latter patient suffered a stroke within hours of this echocardiographic examination. Reproduced, with permission, from Diaz et al. [93].

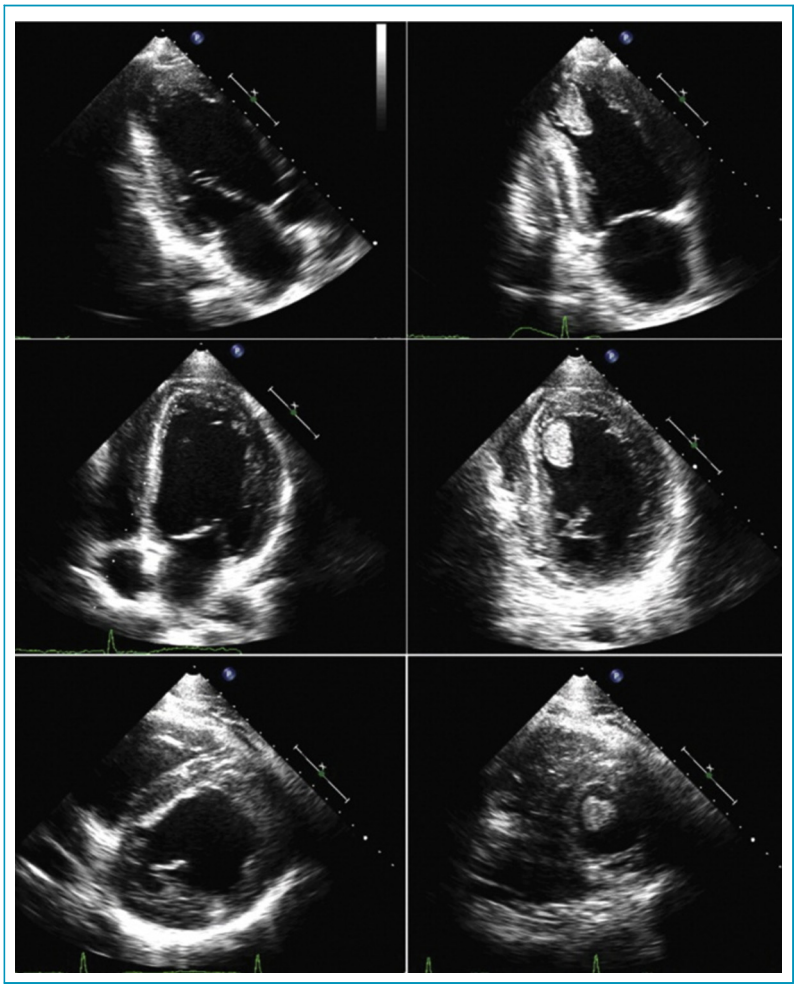


FIGURE 61. Transthoracic echocardiography reveals a large and protruding apical thrombus. The images on the left are obtained along a plane in which the thrombus does not fall. The images on the right have been optimized to view the thrombus. The thrombus resides in an inferior apical aneurysm; given the tendency of apical views to foreshorten the apex, the area of disease is less apparent on standard views. Reproduced, with permission, from Hutchison and Rudakewich [57].

block or third-degree AV block within or below the His-Purkinje conducting system, transient advanced second- or third-degree infranodal AV block, or associated bundle-branch block (Table 14) [152]. Permanent pacing is not indicated in transient AV blocks in the absence of intraventricular blocks.

LV thrombus may be seen in transmural anterior wall MI (Figures 60 and 61) [57,93]. These patients will require heparin initially followed by oral anticoagulants until serial echocardiograms have shown that the thrombus has resolved.

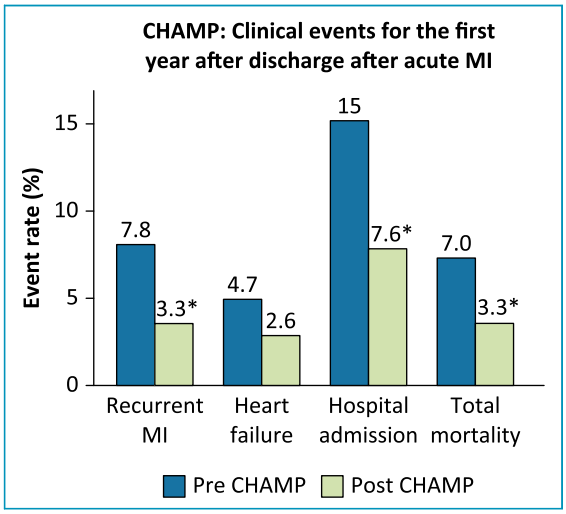


FIGURE 62. CHAMP (Cardiac Hospitalization Atherosclerosis Management Program): clinical events for the first year after discharge after acute myocardial infarction (MI). Modified from Fonarow et al. [153] and Hass and Smith [154].

OUT-OF-HOSPITAL MANAGEMENT

Secondary prevention

Lifestyle changes that should be recommended to patients include tobacco cessation, weight management, moderation of alcohol consumption, and regular physical activity (Figure 62) [153,154]. Tobacco cessation including smokeless tobacco should be encouraged. A small percentage of patients will be able to make a clean break, whereas others may need 2 or 3 attempts to give up tobacco. Alcohol consumption should be limited to no more than 21 units of alcohol per week for men, or 14 units per week for women and to avoid binge drinking (i.e., no more than 3 alcoholic drinks in 1 to 2 h). Patients should be encouraged to be physically active for at least 30 to 40 min a day to the point that they get slightly breathless. The patients should start at a level that is comfortable and the duration and intensity of activity should be increased in a gradual and stepwise manner. Patients should be encouraged to achieve a body mass index between 18.5 to 25 kg/m^2. The weight loss could be gradual and a realistic target is about 2 to 4 pounds a month. In diabetic patients, the goal for glycosylated hemoglobin C is <7%.

STEMI is a manifestation of the continuum of coronary artery disease. Every caregiver must recognize that secondary prevention should be aggressively promoted, including cardiac rehabilitation. The goal of therapy in STEMI is to ensure that this translates into many decades of productive life for the patient.

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