Diagnosis and Management of ST-segment elevation myocardial infarction: Review Article

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Abstract:

Disruption of intracoronary plaque with thrombus formation resulting in severe or total occlusion of the culprit coronary artery provides the pathophysiologic foundation for ST-segment elevation myocardial infarction (STEMI). Management of STEMI focuses on timely restoration of coronary blood flow along with antithrombotic therapies and secondary prevention strategies. The purpose of this review is to discuss the epidemiology, pathophysiology, and diagnosis of STEMI. In addition, the review will focus on guideline-directed therapy for these patients and review potential associated complications.

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Introduction:

Over the last 50 years, treatment of acute STEMI has been improved considerably. The widespread implementation of reperfusion (initially pharmacological and later mechanical) resulted in a magnificent reduction in the rates of in- hospital mortality from about 25% in the 1970s to 5% in the late 2010s. Mortality in real life, however, is higher than these figures shown in clinical trials. There is compelling evidence showing an association between the duration of ischaemia and mortality. This is the basis for timely reperfusion in STEMI. All actions should be made to reduce all components of the ischaemic time. Despite these advances, STEMI survivors are still at high risk of developing repetitive events, including reinfarctions, heart failure, and sudden death**(1).**

Etiology:

An ST-elevation myocardial infarction occurs from occlusion of one or more of the coronary arteries that supply the heart with blood. The cause of this abrupt disruption of blood flow is usually plaque rupture, erosion, fissuring or dissection of coronary arteries that results in an obstructing thrombus. The major risk factors for ST-elevation myocardial infarction are dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of coronary artery disease **(2)**.

Epidemiology:

Each year, an estimated more than 7 million people are diagnosed with acute coronary syndromes (ACS) worldwide. STEMI is caused by complete coronary artery occlusion and accounts for approximately 30% of ACS **(3)**. In 2013, 116,793 persons in the United States suffered a fatal MI with 57% occurring in men and 43% in women. The average age of incidence of a first MI is 65.1 for men and 72 for women. Approximately 38% of patients who present to the hospital with acute coronary syndrome have an ST-elevation myocardial infarction **(4)**.

Pathophysiology:

For an acute thrombotic coronary event to cause ST-segment elevation on a surface ECG, there needs to be a complete and persistent occlusion of blood flow. Coronary atherosclerosis and presence of high risk thin cap fibroatheroma (TCFA) can result in sudden onset plaque rupture. This results in changes in vascular endothelium resulting in cascade of platelet adhesion, activation and aggregation resulting in thrombosis formation **(5)**.

Coronary artery occlusion in animal models shows a "wave-front" of myocardial injury that spreads from the sub-endocardial myocardium to the sub-epicardial myocardium resulting in a transmural infarction that appears as an ST elevation on surface ECG. Myocardial damage occurs as soon as the blood flow is interrupted which makes timely management a necessity. Sudden onset acute ischaemia can result in severe micro-vascular dysfunction **(6)**.

Initial diagnosis and management:

Management of STEMI starts from the point of FMC, the time point when the patient is initially assessed by health care personnel who can obtain and interpret the ECG and deliver initial interventions (e.g. defibrillation). A working diagnosis of STEMI must be made first. This is usually based on symptoms consistent with myocardial ischaemia and signs (mainly ECG) **(7)**.

Table (1): The recommendation of initial diagnosis according to the European Society of Cardiology (ESC) guidelines **(7)**

Recommendations for initial diagnosis

Recommendations	Class[a]	Level[b]
ECG monitoring		
12-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min.[36,38]	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI.[44,45]	I	B
The use of additional posterior chest wall leads (V_7–V_9) in patients with high suspicion of posterior MI (circumflex occlusion) should be considered.[8,46–49]	IIa	B
The use of additional right precordial leads (V_3R and V_4R) in patients with inferior MI should be considered to identify concomitant RV infarction.[8,43]	IIa	B
Blood sampling		
Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment.[8]	I	C

ECG = electrocardiogram; FMC = first medical contact; MI = myocardial infarction; RV = right ventricle; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

Table (2): How to relief hypoxaemia and symptoms **(7)**

Relief of hypoxaemia and symptoms

Recommendations	Class[a]	Level[b]
Hypoxia		
Oxygen is indicated in patients with hypoxaemia (SaO_2 < 90% or PaO_2 < 60 mmHg).	I	C
Routine oxygen is not recommended in patients with SaO_2 ≥ 90%.[64–66]	III	B
Symptoms		
Titrated i.v. opioids should be considered to relieve pain.	IIa	C
A mild tranquillizer (usually a benzodiazepine) should be considered in very anxious patients.	IIa	C

i.v. = intravenous; PaO_2 = partial pressure of oxygen; SaO_2 = arterial oxygen saturation.
[a]Class of recommendation.
[b]Level of evidence.

Complementary investigations:

Blood sampling for serum markers is indicated in the acute phase but should not delay the reperfusion strategy. If in doubt regarding the possibility of acute evolving MI, emergency echocardiogram aids the provision of timely reperfusion therapy to these patients. If this is not available or if doubts persist after echocardiography, a primary PCI strategy is indicated. Use of CT should be confined to selected cases where acute aortic dissection or PE is suspected, but if STEMI diagnosis is likely, CT is not recommended **(7).**

Selection of reperfusion strategy: primary PCI versus fibrinolysis:

Table (3) shows 4 definitions of terms related to reperfusion therapy/ Figure 1 shows the reperfusion strategy recommended according to patient characteristics.

Table (3): Definitions of terms related to reperfusion therapy

Term	Definition
FMC	The time point when the patient is either initially assessed by a physician, paramedic, nurse or other trained EMS personnel who can obtain and interpret the ECG, and deliver initial interventions (e.g. defibrillation). FMC can be either in the prehospital setting or upon patient arrival at the hospital (e.g. emergency department)
STEMI diagnosis	The time at which the ECG of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or equivalent
Primary PCI	Emergent PCI with balloon, stent, or other approved device, performed on the IRA without previous fibrinolytic treatment
Primary PCI strategy	Emergent coronary angiography and PCI of the IRA if indicated
Rescue PCI	Emergent PCI performed as soon as possible in the case of failed fibrinolytic treatment
Routine early PCI strategy after fibrinolysis	Coronary angiography, with PCI of the IRA if indicated, performed between 2 and 24 hours after successful fibrinolysis
Pharmacoinvasive strategy	Fibrinolysis combined with rescue PCI (in case of failed fibrinolysis) or routine early PCI strategy (in case of successful fibrinolysis)

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ECG = electrocardiogram; EMS = emergency medical system; FMC = first medical contact; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Figure (1): Reperfusion strategies in IRA according to the time from symptom onset. In early presenters (i.e. those with STEMI diagnosis within 3 hours of symptom onset), a primary PCI

strategy is the reperfusion strategy of choice. If the anticipated time from STEMI diagnosis to PCI- mediated reperfusion is >120 minutes, then immediate fibrinolysis is indicated. After 3 hours (and up to 12 hours) of symptom onset, the later the patient presents, the more consideration should be given to a primary PCI strategy, as opposed to administering fibrinolytic therapy. In evolved STEMI (12– 48 hours after symptom onset), a routine primary PCI strategy (urgent angiography and subsequent PCI if indicated) should be considered in all patients. After 48 hours (recent STEMI), angiography should be performed, but routine PCI of a totally occluded IRA is not recommended. Regardless of the time from symptom onset, the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life- threatening arrhythmias is an indication for a primary PCI strategy. PCI, percutaneous coronary intervention; STEMI, STsegment elevation myocardial infarction **(7).**

There is ample evidence showing that, head- to- head, primary PCI is superior to fibrinolysis in reducing mortality, reinfarction, or stroke **(8).** However, in some circumstances, primary PCI is not an immediate option (e.g. patients diagnosed in the out- of- hospital setting) and fibrinolysis could be initiated instantly. The extent to which a PCI- related time delay diminishes the advantages of PCI over fibrinolysis has been widely debated. Despite the fact that no specifically designed study has addressed this issue and there are heterogenous data, there is consensus that a PCI- related time delay potentially mitigating the benefit of the mechanical intervention is 120 minutes **(7).**

In STEMI patients without persistent symptoms 12– 48 hours after symptom onset, a small (n = 350) randomized study showed improved myocardial salvage and 4- year survival in patients treated with primary PCI, compared with those on conservative treatment alone. Thus, in these patients, primary PCI should be considered. However, in stable patients with persistent occlusion of infarct-related arteries (IRAs) 3– 28 days after MI, the large **(n = 2150)** Occluded Artery Trial revealed no clinical benefit from routine coronary intervention with medical management, beyond that from medical management alone. A meta- analysis of trials, testing whether late recanalization of an occluded infarct artery is beneficial, showed no benefit of reperfusion. Therefore, routine PCI of an occluded IRA in asymptomatic patients >48 hours after symptoms onset is not indicated. Patients presenting with transient ST- segment elevation (angina and ST- segment elevation whose ECG completely normalizes and symptoms disappear) have a high probability of having a coronary spasm (with or without MI). In these patients, early coronary angiography within 24 hours is recommended **(7).**

A recent clinical trial enrolled patients with transient ST- segment elevation and randomized them into immediate versus delayed (24- hour) angiography. Infarct size and clinical outcomes were not different between groups **(9).**

Figure 2 shows the maximum target times according to the reperfusion strategy (primary PCI).

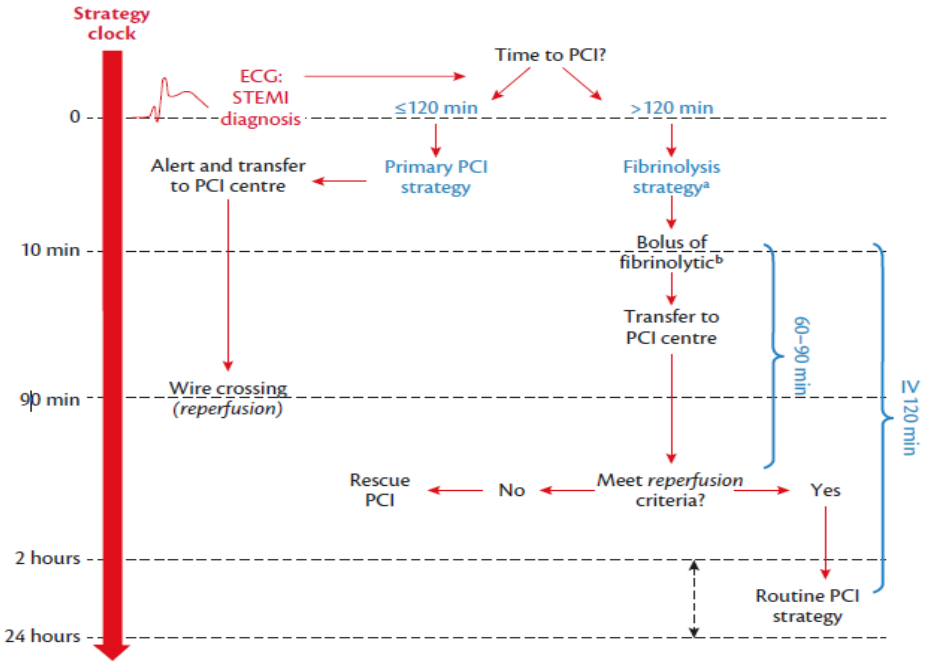

Figure (2): Maximum target times according to reperfusion strategy selection in patients presenting via EMS or in a non- PCI centre. STEMI diagnosis is time zero for the strategy clock. Target times from STEMI diagnosis represent the maximum time to do specific interventions. a If fibrinolysis is contraindicated, direct for primary PCI strategy, regardless of the time to PCI. b10 minutes is the maximum target delay time from STEMI diagnosis to fibrinolytic bolus administration; however, it should be given as soon as possible after STEMI diagnosis (after ruling out contraindications). ECG, electrocardiogram; PCI, percutaneous coronary intervention; STEMI, ST- segment elevation myocardial infarction **(7).**

Primary PCI:

Primary PCI is defined as an urgent coronary angioplasty (with or without stenting) performed in the context of STEMI. Fibrinolytic therapy is not used in primary PCI. Primary PCI is the preferred therapeutic option when it can be performed expeditiously by an experienced team, including interventional cardiologists and skilled supporting staff. Lower mortality rates among patients undergoing primary PCI are observed in centres with a high volume of PCI procedures **(10).**

Primary PCI is effective in securing and maintaining coronary artery patency and avoids some of the bleeding risks of fibrinolysis. Randomized clinical trials comparing timely performed primary PCI with in- hospital fibrinolytic therapy in high- volume, experienced centres have shown more effective restoration of patency, less reocclusion, improved residual LV function, and, most importantly, a better clinical outcome with primary PCI **(11).**

Procedural aspects of primary PCI:

Table (4): The procedural aspects of the primary percutaneous coronary intervention strategy**(7)**.

Procedural aspects of the primary percutaneous coronary intervention strategy

Recommendations	Class[a]	Level[b]
IRA strategy		
Primary PCI of the IRA is indicated.[114,116,139,140]	I	A
New coronary angiography with PCI if indicated is recommended in patients with symptoms or signs of recurrent or remaining ischaemia after primary PCI.	I	C
IRA technique		
Stenting is recommended (over balloon angioplasty) for primary PCI.[146,147]	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.[148–151,178,179]	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.[143–145,180]	I	A
Routine use of thrombus aspiration is not recommended.[157,159]	III	A
Routine use of deferred stenting is not recommended.[153–155]	III	B
Non-IRA strategy		
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.[167–173]	IIa	A
Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock.	IIa	C
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C

CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

Arterial access route during primary PCI:

The Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) trial recruited 8400 MI patients who were randomly allocated to transradial or transfemoral access **(12)**. The radial access site was associated with lower risks of access site bleeding, vascular complications, need for transfusion, and a lower 30-day mortality. At 1 year follow- up, MACEs did not differ between patients assigned to radial, compared with, femoral access, but net adverse clinical events were fewer with radial access**(13).**

Primary PCI technique:

Stenting is the technique of choice during primary PCI. DES reduce the risk of repeated target vessel revascularization, compared with BMS, in STEMI **(14).** A meta-analysis of randomized trials of newer-generation DES even showed improved safety, with a lower risk of stent thrombosis and cardiac mortality, compared with BMS **(15).**

In the clinical Evaluation of the Xience- V stent in Acute Myocardial INfArcTION (EXAMINATION) trial **(n = 1500)**, use of everolimus- eluting stents in patients with STEMI was associated with lower risks of target vessel revascularization and stent thrombosis, and with a 5- year reduction in all- cause mortality, compared with BMS **(16).**

In the Norwegian Coronary Stent Trial (NORSTENT) trial, 9000 patients undergoing PCI (26% with STEMI) were randomized to DES or BMS. There were no differences in incidence of the primary endpoint (composite of death from any cause or non- fatal spontaneous MI) after a median follow- up of 5 years, but DES were associated with lower rates of definite stent thrombosis and repeat revascularizations **(17)**.

Delaying stenting in primary PCI is not recommended in STEMI since in the DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction (DANAMI 3) trial, **(n = 1200)**, deferred stenting had no effect on the primary clinical outcome (composite of all- cause mortality, nonfatal MI, or ischaemia-driven revascularization of non-IRA lesions) over a median follow-up of 42 months **(18).**

Routine thrombus aspiration is not recommended in STEMI since two large RCTs showed no benefit on clinical outcomes of the routine aspiration strategy overall or in any subgroup of patients indicating high thrombotic risk. A safety concern emerged in one of these trials, with an increase in risk of stroke **(19).**

Table (5): Procedural aspects of the primary percutaneous coronary intervention strategy **(7)**

Procedural aspects of the primary percutaneous coronary intervention strategy

Recommendations	Class[a]	Level[b]
IRA strategy		
Primary PCI of the IRA is indicated.[114,116,139,140]	I	A
New coronary angiography with PCI if indicated is recommended in patients with symptoms or signs of recurrent or remaining ischaemia after primary PCI.	I	C
IRA technique		
Stenting is recommended (over balloon angioplasty) for primary PCI.[146,147]	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.[148–151,178,179]	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.[143–145,180]	I	A
Routine use of thrombus aspiration is not recommended.[157,159]	III	A
Routine use of deferred stenting is not recommended.[153–155]	III	B
Non-IRA strategy		
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.[167–173]	IIa	A
Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock.	IIa	C
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C

CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

Management in stable STEMI patients:

Multivessel disease is common in patients with STEMI. Evidence supporting immediate (preventive) revascularization of additional significant coronary stenoses was lacking until recently. One small study published in 2010 allocated 214 STEMI patients with multivessel disease to three arms: IRA angioplasty only, simultaneous treatment of non- IRA lesions, and staged revascularization of the non- IRA. At a mean follow- up of 2.5 years, patients allocated to IRA angioplasty only had more MACEs than those treated with other strategies **(20).**

More recently, four larger randomized clinical trials have compared PCI of the IRA only versus complete revascularization: Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial (n = 450) **(21)**; Complete Versus Lesion- Only Primary PCI trial (CvLPRIT) trial (n = 300) **(22);** Third DANish Study of Optimal Acute Treatment of Patients With STEMI: PRImary PCI in MULTIvessel Disease (DANAMI- 3– PRIMULTI) trial (n = 600) **(23)**; and Compare- Acute trial (n = 900) **(24).**

Design of trials in terms of timing of non- IRA PCI (immediate or staged) and indication for non- IRA PCI (angiography- or FFR- guided) was heterogenous, making it difficult to draw definite conclusion on these issues. In terms of clinical benefits, results of these trials are, however, homogenous; primary outcome (composite of different endpoints) was significantly reduced in the complete revascularization group in all four trials. Total mortality was not statistically different in any of the four trials. Repeat revascularization was significantly reduced in all trials but CvLPRIT. Recent meta- analyses have shown that complete revascularization reduces the incidence of hard endpoints **(25).**

Revascularization of non- IRA lesions should be considered in stable STEMI patients with multivessel disease before hospital discharge. In the absence of a face- to- face clinical trial, the optimal timing of revascularization (immediate versus staged) cannot be ascertained, albeit immediate non- IRA PCI in selected cases might be the best strategy.

Management in STEMI patients in shock:

Up to 80% of STEMI patients presenting in shock have multivessel disease. Despite the fact that there was controversy, the consensus from observational and non- randomized studies was that multivessel PCI during the index procedure was beneficial in STEMI patients presenting in shock **(26).**

The only randomized clinical trial prospectively testing the benefits of multivessel PCI in this population is the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT- SHOCK) trial **(27).**

In this contemporaneous trial, 700 MI patients in shock (62% with STEMI) with multivessel disease were randomized to IRA- only PCI during the index procedure (18% of these patients underwent staged non- IRA PCI) or multivessel PCI during the index procedure. At 1 month, all- cause mortality was significantly higher in the ‘multivessel PCI during the index

procedure' group (51.5% versus 43.3%). Results were consistent across prespecified subgroups, including presence/ absence of chronic total occlusion of the non- IRA. The crossover rate was not high. At 1- year follow- up, mortality did not differ significantly between the two groups [50.0% and 56.9%, RR 0.88 (0.76– 1.01)]. However, the rates of repeat revascularization were significantly higher in the IRA- only PCI group than in the multivessel PCI group (32.3% versus 9.4%, respectively), as were the rates of rehospitalization for heart failure (5.2% versus 1.2%, respectively) **(28).**

From these data, the recommendation for STEMI patients with multivessel disease presenting in shock is to perform IRA- only PCI during the index procedure. Later on, when the patient is stable, staged non- IRA PCI before hospital discharge seems a reasonable approach.

Rescue PCI:

Rescue PCI is defined as PCI performed on a coronary artery which remains occluded despite prior fibrinolytic therapy. Compared to a conservative strategy, rescue PCI is associated with improved clinical outcomes (less heart failure and reinfarction and a trend towards lower all- cause mortality) at the cost of an increased risk of stroke and bleeding complications. Therefore, rescue PCI is indicated when ST- segment resolution is <50% within 90 minutes of thrombolytic administration **(29).**

Adjunctive antithrombotic treatments:

Patients undergoing primary PCI should receive a parenteral anticoagulant and DAPT, a combination of aspirin and a P2Y12 inhibitor, in all cases. Routine GPIIb/ IIIa inhibitors have not been consistently associated with a clinical benefit and thus are left for bailout in cases of high thrombus burden upon the decision of the interventional cardiologist.

Table (6): Periprocedural and post-procedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention **(7)**

Periprocedural and post-procedural antithrombotic therapy[a] in patients undergoing primary percutaneous coronary intervention

Recommendations	Class[b]	Level[c]
Antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.[186,187]	I	A
Aspirin (oral or i.v. if unable to swallow) is recommended as soon as possible for all patients without contraindications.[213,214]	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.[192–194]	IIb	A
Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin i.v. should be considered.[200–202]	IIa	A
Routine use of bivalirudin should be considered.[209,215]	IIa	A
Fondaparinux is not recommended for primary PCI.[199]	III	B

GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.
[a]Dose regimens are specified in *Table 6*.
[b]Class of recommendation.
[c]Level of evidence.

Anticoagulation:

Anticoagulant options for primary PCI include UFH as the default strategy, with enoxaparin as an alternative in some cases. Bivalirudin may be considered, but its use is mostly restricted to patients with heparin- induced thrombocytopenia. Use of fondaparinux in the context of primary PCI was associated with potential harm in the Organization for the Assessment of Strategies for Ischemic Syndromes 6 (OASIS 6) trial and is not therefore recommended **(30).**

Heparins:

There have been no placebo- controlled trials evaluating UFH in primary PCI, but there is a large body of experience with this agent. UFH is the anticoagulant of choice during primary PCI. Dosage should follow standard recommendations for PCI (i.e. initial bolus of 70– 100 U/ kg). Enoxaparin [0.5 mg/ kg IV, followed by subcutaneous (SC) treatment] was compared with UFH in one randomized, open- label trial [the Acute Myocardial Infarction Treated with primary angioplasty and intravenous enoxaparin Or unfractionated heparin to Lower ischemic and bleeding events at short- and Long- term follow- up (ATOLL) trial, 900 STEMI patients].The primary composite endpoint of 30- day death, MI, procedural failure, or major bleeding was not significantly reduced by enoxaparin, but there were reductions in the composite main secondary endpoint of death, recurrent MI or ACS, or urgent revascularization. Importantly, there was no indication of increased bleeding from use of enoxaparin **(31).**

In the perprotocol analysis of the ATOLL trial (<87% of the study population), IV enoxaparin was superior to UFH in reducing the primary endpoint, ischaemic endpoints, mortality, and major bleedings. Based on these considerations and on the substantial clinical experience with enoxaparin in other PCI settings, enoxaparin is a valid alternative to UFH during primary PCI **(32).**

Bivalirudin:

There have been several trials comparing bivalirudin with UHF (with or without GPIIb/ IIIa), with mixed results **(33).** The Bivalirudin versus Heparin in ST- Segment and Non– ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence- based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial (VALIDATE-SWEDEHEART) enrolled 6000 MI patients (3000 with STEMI) undergoing PCI under potent P2Y12 inhibitors without GPIIb/ IIIa to bivalirudin or heparin during the index procedure. The rate of the combined endpoint of all- cause death, MI, or major bleeding was not different among groups **(34)**. Despite the fact that bivalirudin may be considered as an alternative to UFH during primary PCI, its main indication during primary PCI is for patients with HIT **(35)**.

Antiplatelet therapy:

DAPT (aspirin plus P2Y12 inhibitor) is the standard of care for STEMI patients for the year following the event. Aspirin should be given orally (PO) (preferably 150– 300 mg), including chewing, or IV (150 mg) after STEMI diagnosis. There is limited evidence in regard to when the P2Y12 inhibitor should be initiated in STEMI patients. The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial is the only randomized study testing the safety and efficacy of different timings of P2Y12 inhibitor initiation in STEMI. In this trial, patients were randomized to receive ticagrelor either during transfer to a primary PCI centre or immediately before angiography **(36).**

Table (7): Doses of antiplatelet and anticoagulant co-therapies in patients undergoing primary percutaneous coronary intervention or not reperfused **(7)**

Doses of antiplatelet and parenteral anticoagulant co-therapies in primary PCI	
Antiplatelet therapies	
Aspirin	Loading dose of 150–300 mg orally or of 75–250 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day In patients with body weight ≤60 kg, a maintenance dose of 5 mg/day is recommended Prasugrel is contra-indicated in patients with previous stroke. In patients ≥ 75 years, prasugrel is generally not recommended, but a dose of 5 mg/day should be used if treatment is deemed necessary
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg *b.i.d.*
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 hours
Eptifibatide	Double bolus of 180 µg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for up to 18 hours
Tirofiban	25 µg/kg over 3 min i.v., followed by a maintenance infusion of 0.15 µg/kg/min for up to 18 hours
Parenteral anticoagulant therapies	
UFH	70–100 IU/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned 50–70 IU/kg i.v. bolus with GP IIb/IIIa inhibitors
Enoxaparin	0.5 mg/kg i.v. bolus
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/hour for up to 4 hours after the procedure
Doses of antiplatelet and parenteral anticoagulant therapies in patients not receiving reperfusion therapy	
Antiplatelet therapies	
Aspirin	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day orally
Parenteral anticoagulant therapies	
UFH	Same dose as with fibrinolytic therapy (see Table 7)
Enoxaparin	Same dose as with fibrinolytic therapy (see Table 7)
Fondaparinux	Same dose as with fibrinolytic therapy (see Table 7)

b.i.d. = twice a day; GP = glycoprotein; i.v. = intravenous; IU = international units; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

Fibrinolytic agents:

Streptokinase was the first fibrinolytic agent available. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) and International Study of Infarct Survival demonstrating a 23% reduction in 30- day mortality among patients randomized to streptokinase, compared to those on control therapy **(37).**

Fibrinolysis with this agent was also associated with a small, but significant, excess of ICH (0.4% versus 0.1%). Today, a fibrin- specific agent should be preferred. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trialan accelerated infusion of the fibrin- specific agent tPA alteplase with concomitant IV heparin resulted in ten fewer deaths per 1000 patients treated, when compared to streptokinase at the cost of three additional strokes. Single- bolus weight- adjusted tenecteplase (TNK- tPA) is equivalent to accelerated tPA with respect to 30- day mortality and is associated with a

significantly lower rate of non- cerebral bleeding and less need for blood transfusion. A recent meta- analysis showed that there are significant differences between various fibrinolytic regimens. TNK- tPA and tPA with an accelerated infusion regime should be considered over streptokinase and a non- accelerated infusion of tPA **(38).**

Hazards of fibrinolysis:

Fibrinolytic therapy is associated with a small, but significant, excess of strokes, largely attributable to cerebral haemorrhage, appearing on the first days after treatment. Advanced age, lower weight, female gender, prior cerebrovascular disease, and hypertension on admission are significant predictors of ICH [52]. In the most recent STREAM trial, the initial excess in ICH (1% incidence) was reduced to 0.5% after protocol amendment to reduce the dose of tenecteplase by 50% in patients >75 years. Major non- cerebral bleeds can occur in 4– 13% of patients **(39)**. Contraindications to fibrinolytic therapy are shown in table 8.

Table (8): Contraindications for fibrinolysis **(39).**

ABSOLUTE	**RELATIVE**
➢ Previous ICH or stroke of unknown origin at any time ➢ Ischaemic stroke in the preceding 6 months ➢ Central nervous system neoplasms or arteriovenousmalformation ➢ Recent major trauma/ surgery/ head injury (within the preceding month) ➢ Known bleeding disorder (excluding menses) ➢ Aortic dissection ➢ Non- compressible punctures in the past 24 hours (e.g. liver biopsy, lumbar puncture)	➢ Transient ischaemic attack in the preceding 6 months ➢ Oral anticoagulant therapy ➢ Pregnancy or within 1 week postpartum ➢ Refractory hypertension (SBP >180 mmHg and/ or DBP >110 mmHg) ➢ Advanced liver disease ➢ Infective endocarditis ➢ Active peptic ulcer ➢ Prolonged or traumatic resuscitation

Routine angiography after fibrinolytic therapy:

If there is evidence of persistent occlusion, reocclusion, or reinfarction with recurrence of ST-segment elevation after fibrinolysis, immediate angiography and rescue PCI are indicated. In this setting, re- administration of fibrinolysis has not been shown to be beneficial. Even if it is likely that fibrinolysis was successful, a strategy of routine early angiography is recommended if there are no contraindications. Several randomized trials and contemporary meta- analyses have shown that early routine angiography with subsequent PCI (if indicated) after fibrinolysis reduced the rates of reinfarction and recurrent ischaemia. Routine angiography should be performed 2– 24 hours after successful fibrinolysis **(40).**

Acute complications of ST- segment elevation myocardial infarction:

Pump failure:

Heart failure during the acute phase of STEMI is associated with poor short- and long-term prognosis. Echocardiography is the key diagnostic tool and should be performed to assess the extent of myocardial dysfunction and possible complications such as MR and VSD. Patients with pulmonary congestion and SaO2 of <90% require O2 therapy, with a target of 95%, and may require periodic blood gas control. In severe heart failure and shock (Killip III/ IV), CPAP or intubation with ventilatory support may be required. Inotropic agents may be of value in severely hypotensive patients.

Cardiogenic shock:

CS is defined as persistent hypotension (systolic blood pressure ≤90 mmHg) with signs of hypoperfusion. It complicates 6– 10% of all cases of STEMI and remains a leading cause of death, with in- hospital mortality rates approaching 50% **(41).**

Haemodynamically, it is characterized by cardiac index ≤2.2 L/ min/ m2, wedge pressure ≥18 mmHg, and diuresis usually <20 mL/ hour. Shock is also considered to be present if IV inotropes and/ or mechanical support are needed to maintain a systolic blood pressure of >90 mmHg. LV function and associated mechanical complications should be evaluated urgently by 2D Doppler echocardiography. The first step in the treatment of patients with CS is to identify the mechanism and to correct any reversible cause (hypovolaemia, drug- induced hypotension, or arrhythmias) or alternatively to initiate treatment of potential specific causes such as mechanical complications or tamponade. Management of CS in STEMI patients includes immediate reperfusion and haemodynamic stabilization with medical therapy or mechanical circulatory support. IV inotropic agents or vasopressors are usually required to maintain a systolic blood pressure of ≥90 mmHg and to increase the cardiac output and renal perfusion. Dobutamine is the initial therapy for patients with predominantly low cardiac output, while noradrenaline is preferred over dopamine in patients with CS **(42).**

IABP counterpulsation does not improve outcomes in patients with STEMI and CS without mechanical complications **(43)**. Therefore, routine IABP counterpulsation is not recommended but may be considered for haemodynamic support in selected patients. Mechanical LVADs have been used in patients not responding to standard therapy, including inotropes, fluids, and IABP, but evidence regarding their benefits is limited **(44).**

Therefore, short- term mechanical circulatory support may be considered to stabilize patients and preserve organ perfusion (oxygenation) as a bridge to recovery of myocardial function, cardiac transplantation, or even LVAD destination therapy on an individual basis **(45).**

Mitral regurgitation:

MR is common and occurs usually after 2– 7 days. There are four mechanisms of acute MR in this setting: mitral valve annulus dilatation due to LV dilatation; papillary muscle dysfunction usually due to inferior MI; concomitant LA infarction; and rupture of the trunk or tip

of the papillary muscle. In most patients, acute MR is secondary to papillary muscle dysfunction, rather than rupture. Most patients with acute MR should be operated early because they may deteriorate suddenly. CS and pulmonary oedema with severe MR require emergency surgery. Most patients need IABP placement during preparation for coronary angiography and surgery**(46)**.

Arrhythmias and conduction disturbances:

Life- threatening arrhythmias, such as VT, VF, and complete AV block, may be the first manifestation of ischaemia and require immediate correction. VF occurring early after STEMI (≤48 hours) has only been associated with increased in- hospital (but not longterm) mortality. Use of prophylactic β- blockers in the setting of STEMI reduces the incidence of VF. AF complicates 10– 20% of STEMIs where it is associated with higher stroke rates and inhospital mortality **(47).**

Pericarditis:

Pericarditis associated with STEMI may cause chest pain that can be easily misinterpreted as recurrent infarction or post- infarction angina. However, contrary to these entities, pericarditis- induced pain is usually of a sharp nature and related to posture and respiration. It is often accompanied by a pericardial rub. Antiinflammatory therapy is recommended in post-STEMI pericarditis to hasten symptom remission and reduce recurrences. Aspirin is recommended as the first- choice anti- inflammatory therapy post- STEMI. Colchicine is recommended as the first- line therapy as an adjunct to aspirin/ non- steroidal anti- inflammatory drugs (NSAIDs) therapy (3 months) and is also recommended for the recurrent forms (6 months)**(48)**.

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