

Pharmacological Therapy for ST-Segment Elevation Myocardial Infarction: A Review

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ABSTRACT

Coronary Heart Disease (CHD) is the cardiovascular disease due to plaque build-up in the coronary artery, reducing the blood flow to the heart. STEMI (ST-segment elevation myocardial infarction) is the CHD due to the ST-segment elevation in 12 and the cardiac marker elevation as Troponin I. The elevation is due to a blockage in the coronary artery, causing the blood perfusion and oxygen supply for the heart to decrease.

We searched the article on internet search engine, and scientific search engines including Scopus and PubMed and collected original articles including Randomized Clinical Trial [RCT], comparative, review article, prospective study, and a guideline about therapy pharmacology of STEMI from 1993 to 2019. The following keywords are used: "Guideline of STEMI", "STEMI" OR "streptokinase" OR "fibrinolytic" OR "Pharmacotherapy of STEMI" OR "PCI".

Conclusion: STEMI therapy management is discomfort management and reperfusion therapy. The reperfusion therapy is aimed to recover the myocardial blood flow, to heal the heart, and to reduce the mortality level. The primary coronary artery reperfusion can be administered with the primary percutaneous coronary intervention (PCI). PCI can open a blockage in the coronary artery and has a good effect on the short-term and long-term clinical results. Besides, it reduces the death risk, myocardial infarction, or repetitive stroke. Meanwhile, reperfusion using fibrinolytics is conducted when PCI is unavailable. Moreover, anticoagulant, antithrombotic, and vasodilators are supporting therapies for STEMI patients to reduce chest pain and prevent reinfarction.

Keywords: Coronary Heart Disease, STEMI, reperfusion, PCI, fibrinolytics

1. Introduction

Cardiovascular disease is the cause of 801,000 death cases in the United States of America (USA) [1]. The number continuously increases each year. The Sample Registration System (SRS) survey 2014 in Indonesia indicated that Coronary Heart Disease (CHD) contributed as the second main cause of death in all ages after stroke which was 12.9% [2]. Meanwhile, according to the data of Basic Health Research 2018, the highest rate of heart disease was in the North Kalimantan (2.2%), then Gorontalo, Yogyakarta, Jakarta, and Central Sulawesi [3].

The cardiovascular disease consists of Coronary Heart Disease (CHD), heart failure, ventricular arrhythmia, sudden cardiac death, rheumatic heart disease, abdominal artery aneurysm, periphery artery disease, and congenital heart disease [4]. The cause of CHD is the build-up of plaque in the coronary artery. The plaque is composed of fat, cholesterol, and calcium deposit built up in the coronary artery for years. The plaque thickens, narrowing and hardening the coronary artery (atherosclerosis) [5]. Atherosclerosis occurs due to chronic inflammation triggered by endothelial dysfunction in the blood vessel [6].

Narrowing due to atherosclerosis plaque can block the blood vessel and inhibit the blood flow to the heart. The

condition is called Acute Coronary Syndrome (ACS) [7]. The blockage inhibits the oxygen (O₂) supply to the myocardium, triggering the heart cell damage [4,8]. ACS includes Unstable Angina Pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [4].

ACS accompanied by the ST-segment elevation in the 12-lead electrocardiogram is known as STEMI. The symptom is the angina-pectoris-like pain in the left chest. In STEMI, the pain is more severe and longer (30 minutes or more). However, STEMI may occur without chest pain (20-25%) [9].

STEMI therapy management is to recover the myocardial blood flow, to save the heart, and to reduce the mortality level. Coronary artery reperfusion can be performed with a primary percutaneous coronary intervention (PCI) or fibrinolytics [10]. In line with the STEMI treatment development, supporting knowledge is required to succeed optimum tissue reperfusion. This review will discuss the therapies used in STEMI patients.

2. Stemi

STEMI is the product of prolonged total occlusion in an epicardial coronary vessel [11]. It is mainly due to broken

and eroded atherosclerosis plaque. When a plaque is ruptured, intravascular bleeding and thrombus formation will occur. The thrombus expands to the lumen and turns to be either occlusive or non-occlusive [10].

The main symptom of STEMI is shortness of breath, nausea, vomiting, and unconsciousness. Similar to angina, pain is felt in the chest, throat, arm, epigastrium, or back. Nevertheless, the pain is more severe and longer. Most patients described it as oppressive pain in the chest [12]. The result of the electrocardiogram test indicates the ST-segment element in 12-lead and cardiac marker elevation as Troponin [9].

In STEMI, thrombus, emboli, atherosclerosis, or other conditions, which block the coronary artery, declining the blood perfusion, causing the oxygen supply for the heart to decrease. The formation of thrombus is initiated by the aggregation of platelet and fibrin strands which inhibit hemoglobin, reducing the oxygen supply. Thrombus build-up around the plaque will cover the coronary artery thoroughly [13].

The strategies in STEMI therapy management are to quickly recover the potency of full blockage in the coronary artery, to cut the ischemic time, and to reduce the infarction size [14,15]. The recommended therapy for tissue reperfusion is to use the primary percutaneous coronary intervention (PCI) or fibrinolytics [10]. Anticoagulant, antithrombotic, and vasodilator are the supporting therapies for STEMI patients to reduce chest pain and prevent reinfarction.

3. Management Therapy

a. Discomfort Management

To manage the discomfort due to chest pain, we can use nitrate. Glyceril trinitrate sublingual (GTN) of 300-500 µg is the first aid in an unstable angina condition or infarction-potential condition. Intravenous nitrate (GTN 0.6-1.2 mg/hour or isosorbide dinitrate 1-2 mg/hour) is effective to solve a failure in the left ventricle and reduce the repetitive or persistent ischemic pain [12]. Nitroglycerin sublingual is safe for most STEMI patients. It can increase the myocardial oxygen supply and widen the coronary vessel connected to infarction, hence reducing preload the needs of myocardial oxygen [15]

However, we must not perform a therapy using nitrate in patients with low systolic arterial pressure (<90 mmHg) or when the clinical symptoms of RV infarction appear (inferior infarction in the electrocardiogram, elevated jugular venous pressure, and hypotension). Nitrate must not be administered to patients who have used phosphodiesterase-5 inhibitor for erection dysfunction in the 24 hours prior as it can worsen the effect of nitrate hypotension. Meanwhile, the nitrate hypotension can be immediately reduced by the administration of intravenous atropine [15].

Besides nitrate, intravenous β-blocker; such as atenolol 5-10 is allowable to reduce the pain by reducing the needs of myocardial O₂ and reducing the short-term mortality and arrhythmia in patients after 12 hours of the symptom onset. It reduces the risk of the occurrence of ventricle fibrillation and reinfarction. However, it must not be administered to patients with heart failure and pulmonary edema, hypotension (systolic blood pressure < 105 mmHg) and bradycardia (heart pulse < 65/second) [12]. An oral β-blocker therapy should begin in the first 24 hours in patients with no contraindication [15]. The dihydropyridine calcium channel blockers (such as nifedipine or amlodipine) can be added if the patients feel persistent chest pain [12]

Morphine is an effective analgesic to reduce STEMI pain. The Cardiology Guideline in Europe and the USA recommends the use of morphine in ACS due to its analgesic effect. It reduces the sympathetic effect in the arteriolar and venous contraction, producing venous pooling which can reduce the cardiac output and arterial pressure [15]. However, some meta-analysis research concludes that morphine can reduce the antiplatelet effect of clopidogrel in the early onset of ACS symptoms, inhibiting the clopidogrel therapy effect [16].

b. Reperfusion Therapy

Reperfusion aims to fix the myocardial blood flow, saving myocardium, maintaining the function of the left ventricle, and reducing the mortality level. A successful reperfusion therapy greatly relies on the period passing between the symptom appearance and the therapy. Early reperfusion with a short period between “symptom-to-needle” and “door-to-needle” in patients with myocardial infarction is the main goal of reperfusion [17].

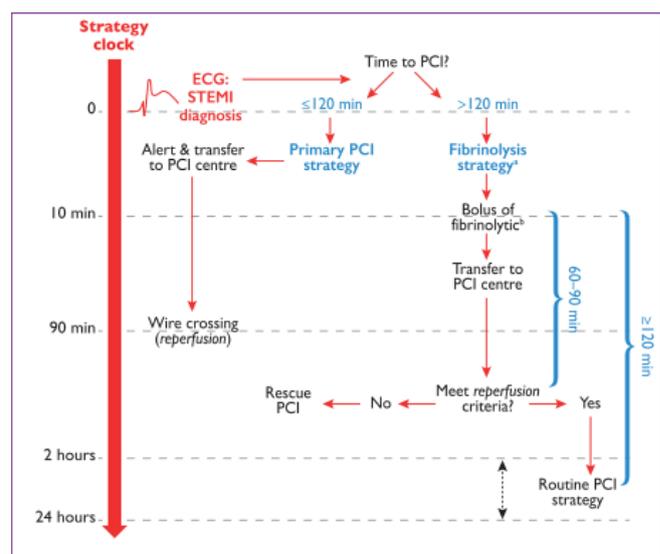


Figure 1 Reperfusion Therapy Strategy [15]

The reperfusion therapy recommended by the American Heart Association (AHA) and *Perhimpunan Dokter Spesialis Kardiovaskuler Indonesia* (PERKI) is the percutaneous coronary intervention (PCI) and fibrinolytics [14,18]. If the patients are positive STEMI based on the result of the electrocardiogram test, PCI should be conducted if the symptoms appear for ≤ 120 seconds. If they appear for > 120 seconds, the “door-to-needle” reperfusion strategy using fibrinolytics should be used. The reperfusion criteria should be checked 60-90 minutes after the fibrinolytics administration (Figure 1) [15]. The key factor in STEMI treatment is the ischemic time, or when the symptoms appear until the reperfusion therapy. The longer the artery is exposed to occlusion, the wider the ischemic wave which extends from endocardium to epicardium so an immediate reperfusion act must be made [19].

1) PCI (Percutaneous Coronary Intervention)

Primary PCI is the reperfusion strategy recommended for STEMI patients applied within 12 hours of the symptom onset and 120 minutes of STEMI diagnosis. Research suggests evidence that the mortality rate is lower in patients who take the primary PCI. An immediate primary PCI will result in a lower mortality rate [20].

Primary PCI gives advantages to patients demonstrating contraindication to fibrinolytic therapy. The combination of primary PCI, glycoprotein IIb/IIIa receptor antagonist, and intracoronary stent implantation will give the best result [15]. Besides, it is more effective than fibrinolytics in opening a blockage in the coronary artery. Also, it has a good effect on the clinical result, either in the short or long term and can minimize the death risk, myocardial infarction, or repetitive stroke [16].

Primary PCI is more recommended for undoubted diagnosis than fibrinolytics. It is allowable for patients with cardiogenic shock, elevated bleeding risk, and 2-3 hours of the symptom onset. It is recommended when plaque is very mature and almost impossible to be lysed by fibrinolytics [12]. Nevertheless, the PCI implementation is limited as the health workers implementing must acquire special skills, not to mention it is very expensive. As a result, PCI is only available in few hospitals [15].

2) Fibrinolytic Therapy

Fibrinolytic therapy is the required reperfusion strategy in STEMI therapy when primary PCI cannot be punctually conducted. Fibrinolytic administration can prevent 30 early deaths per 1000 patients treated within six hours after the symptom onset. The therapy should be given in 12 hours of symptom onset if primary PCI is unlikely to be conducted within 120 minutes of STEMI diagnosis and when there is no contraindication. It is ideally given within 30 minutes after the symptom onset [14].

The goal of the therapy is a quick recovery from the potential of a fully blocked coronary artery. The use of fibrinolytics is proven effective to reduce the mortality rate by 25-50%. The highest effectiveness will be acquired if fibrinolytics are administered less than 2 hours after the symptom onset [14,15]. However, the effectiveness declines if fibrinolytics are given to patients with more than 12 hours of symptom onset. Within those hours, the plaque has been formed and mature, making it difficult to be lysed [12].

According to Global Utilisation of Streptokinase and T-PA for Occluded coronary arteries-1 (GUSTO-1), the success rate of fibrinolytics is 50-60% (20). Other research conveys that the success rate is 59% [22]. Furthermore, the meta-analysis research explains that fibrinolytics can decline the mortality rate [23].

Fibrinolytics are divided into a non-fibrin-specific agent and fibrin-specific agent. The non-fibrin-specific agents are streptokinase and urokinase; while the specific ones are alteplase, tenecteplase, and reteplase [17,24]. The fibrinolytics recommended for STEMI by PERKI are streptokinase, alteplase, and tenecteplase [18].

Streptokinase is a non-fibrin-specific agent belonging to the streptococcus group which is β -hemolytic group-C streptococci. Streptokinase combines with circulated plasminogen to form an activator complex which produces plasmin and breaks thrombus [24,25]. The dose of streptokinase infused is 1.5 million IU in 100 mL of saline solution for 30-60 minutes [18].

Alteplase is a natural enzyme (specific plasminogen) produced with recombinant DNA technology using human tissue culture. Alteplase is “clot selective”. With fibrin, it can form a bond in the clot surface and activate plasminogen bound to fibrin. Plasmin is formed from the plasminogen in which the fibrin molecule breaks into plasmin and soluble clumps. The initial dose of alteplase recommended by PERKI is 15 mg in a bolus. A slow intravenous infusion is subsequently given with the dose of 0.75 mg/KgBB (max. 50 mg) for 30 minutes and 0.5 mg/KgBB (max. 35 mg) for 60 minutes. The dosage regimentation is due to a very brief half-life of alteplase. A systemic anticoagulant is given before alteplase to manage reocclusion [18,24].

Fibrinolytics gives a good advantage with an evidence-A level if given to patients with 30 minutes of symptom onset. However, it demonstrates a side effect which is bleeding. Several conditions are contradicted to fibrinolytics; such as hemorrhagic stroke, ischemic stroke within the last six months, operative trauma or severe head trauma in the last three months, and gastrointestinal bleeding in the last one month. The conditions are because fibrinolytics can increase bleeding risk [18].

c. Other Therapies

These therapies are therapies used to support reperfusion therapy and to maintain the condition of a blood vessel after the reperfusion therapy [9].

1) Antithrombotic Agent

The first goal of antiplatelet and anti-thrombin agent treatment is to build and strengthen the condition of the artery after reperfusion therapy. The second goal is to reduce the potential of thrombus or thrombosis formation in the vein. Aspirin, a standard antiplatelet agent for STEMI patients, indicates the use of therapy based on Antiplatelet Trialists. Aspirin reduces the mortality rate by 27%. P2Y₁₂ ADP receptor antagonist prevents thrombocyte aggregation and activation. P2Y₁₂ inhibitors; such as clopidogrel given to patients taking the fibrinolytic therapy are proven effective to prevent infarct artery reocclusion in patients with successful reperfusion therapy. Glycoprotein IIb/IIIa inhibitor is used to prevent thrombotic complications in STEMI patients taking PCI [26]. Clopidogrel in aspirin is in the evidence A level [18].

The standard anti-thrombin agent used is unfractionated heparin (UFH). When the agent is added to aspirin therapy and non-fibrin specific fibrinolytic agents; such as streptokinase, it declines the mortality rate. Intravenous UFH helps maintain the artery condition after reperfusion when given to the aspirin regimen and relatively fibrin-specific fibrinolytic agents (tPA, rPA, or TNK). The initial UFH dose recommended in bolus is 60 U/kg (max. 4,000 U). After the dosage, UFH of 12 U/kg is hourly infused (max. 1000 U/hour). Besides UFH, other anticoagulants which can be used are low-molecular-weight heparin (LMWH), fondaparinux, or bivalirudin. LMWH is more effective due to its higher bioavailability since it is administered subcutaneously and greater anti-Xa:IIa activity [18].

Enoxaparin can more significantly reduce the composite endpoint of non-fatal reinfarction/death and urgent revascularization than UFH in STEMI patients taking fibrinolytics. Despite its highly potential bleeding effect, enoxaparin is more effective and safer than UFH. In patients with anterior infarction location, severe left ventricular dysfunction, heart failure, embolism history, mural thrombus based on the 2-dimensional electrocardiogram result, or atrial fibrillation, the elevation of lung or systemic thromboembolism risks can happen. If the condition occurs, patients can be given an anti-thrombin therapy (LMWH or UFH) followed with warfarin therapy when being treated at a hospital for at least three months [26].

2) β -blocker

The use of β -blocker in STEMI patients gives an advantage in an acute administration and as the secondary prevention after infarction. Intravenous β -blocker can repair the needs of myocardial oxygen, reduce pain, reduce the infarction size, and reduce the ventricular arrhythmia. In patients taking fibrinolytics, β -blocker does not reduce the mortality rate but reduces the repetitive ischemic incident and reinfarction. In conclusion, β -blocker is indeed useful for STEMI patients but is not for the contradicted [26].

3) Inhibition of the Renin-angiotensin Aldosterone System

Inhibitor angiotensin-converting enzyme (ACEI) can reduce the mortality rate after STEMI and is more effective when used with aspirin and β -blocker. The effectiveness is more obvious in patients with a high risk. Short-term use of ACE inhibitor is not selective for all STEMI patients with stable hemodynamics; such as patients with a systolic blood pressure >100 mmHg. It is due to the reduction of ventricular remodeling after infarction with the reduction of congestive heart failure risk. The risk of repetitive infarction is lower in patients taking ACE inhibitors after infarction [26].

Angiotensin receptor blockers (ARBs) should be given to STEMI patients who are intolerant-ACE inhibitor and shows clinical signs or has a radiographic diagnosis of heart failure. The long-term aldosterone blockage must be prescribed for STEMI patients without significant kidney dysfunction in which the creatinine level is ≥ 2.5 mg/dL in males and ≥ 2.0 mg/dL in females. ARBs can be administered to hyperkalemic patients (potassium level ≥ 5.0 mEq/L) who have taken an ACE-inhibitor therapy, patients with left ventricular ejection fraction $\leq 40\%$, and patients with heart failure or diabetes mellitus. Multidrug regimen to inhibit the aldosterone renin-angiotensin system is proven effective to reduce cardiovascular mortality and sudden heart failure after STEMI. Nevertheless, a thorough exploration of it is not yet conducted [26].

4) Nitrate

The advantageous effect of nitroglycerin in the ventricular remodeling and ischemic process causes intravenous nitroglycerin is frequently used with the initial dose and until 200 $\mu\text{g}/\text{minute}$ when the hemodynamic stability can be managed for the first 24-48 hours after infarction. However, the use of regular intravenous nitroglycerin is less effective than a beta-adrenoceptor and ACE inhibitor. Some uses of nitroglycerin (glyceryl trinitrate or GTN) are direct vasodilatation from the coronary artery in the area with plaque, venous dilatation, reducing preload. Vasodilation with afterload reduction can reduce the needs of myocardial oxygen [27].

Nitroglycerin is for constant pain and as a vasodilator in patients with infarction related to the left ventricular disorder or hypertension. Nitrate is reportedly useful as in STEMI; there may be reduced ventricular filling pressure, wall tension, heart performance. Besides, it has an antiplatelet effect. Meanwhile, a long-term/regular nitrate is proven ineffective for STEMI patients, so nitrate is recommended to be given within the first 48 hours [28].

4. Conclusion

In the therapy management for STEMI patients, the therapy mainly recommended by AHA and PERKI is the

reperfusion therapy which is PCI. However, when PCI is impossible, the recommended reperfusion therapy is fibrinolytic therapy.

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