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Review on Current Trends in the Management of AcuteSTEMI

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Abstract: *The most severe form of Acute Coronary Syndrome is undoubtedly ST elevation myocardial infarction which requires immediate therapy. STEMI contributes approximately 25% to 40 % of Myocardial Infarction presentation. After completion of fibrinolysis, antithrombus agent such as low molecular weight heparin for instance enoxaparin, unfractionated heparin, reviparin or fondaparinux is given immediately for 48 hours. Prasugrel and ticagrelor are introduced recently and are more favoured for STEMI since STEMI is a highly pre-thrombic state where platelets are activated extensively. Early initiation of tirofiban together with clopidogrel, the clinical outcome in STEMI patients after primary Percutaneous Coronary Intervention had significantly improved. Tenecteplase is preferred over streptokinase due to its specific and fast onset which can achieve more rapid reperfusion of the occluded artery. A combined approach with antiplatelet and or anticoagulants with other lipid lowering agents and antihypertensive are warranted in the management of acute STEMI.*

Keywords:*Acute coronary syndrome; Myocardial infarction; Percutaneous coronary intervention; Antiplatelet; Fibrinolytic therapy.*

I. Introduction

Acute myocardial infarction (MI), also known as heart attack is associated with myocardial ischemia with significant evidence of myocardial injury or necrosis.[1]The third universal definition of MI introduced the term acute coronary syndrome (ACS) in concerned to patients with a suspicionof myocardial ischemia. ACS is further subdivided into ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA).[2]This article reviews on the current management and interventions focusing on STEMI. The most severe form of ACS is undoubtedly STEMI which requires immediate therapy.[3]In the last few decades, many advances have been made in the management plan of STEMI, with the aim of improving outcomein STEMI patients.

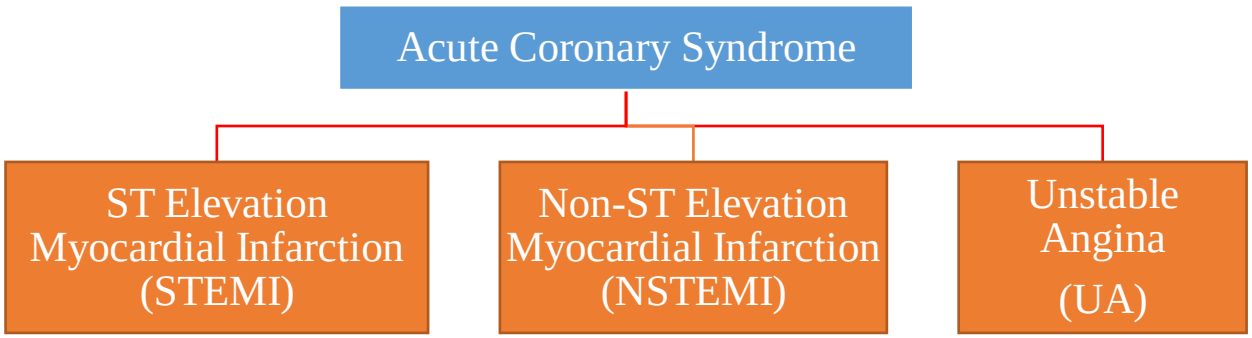

Figure 1:Classification of Acute Coronary Syndrome

II. Epidemiology

STEMI accounts for 30–45% within a 1.5 million hospitalizations for acute coronary syndrome annually in United States (US).In 2009, the number of patients with ACS discharged from hospitals of US were approximately 683 000.[4]Currently, STEMI contributes approximately 25% to 40 % of MI presentation.[5, 6, 7, 8]Figure 2 shows that the incidences of STEMI have decreased for the past decade, however, non-STEMI has shown an increasing trend.[4]

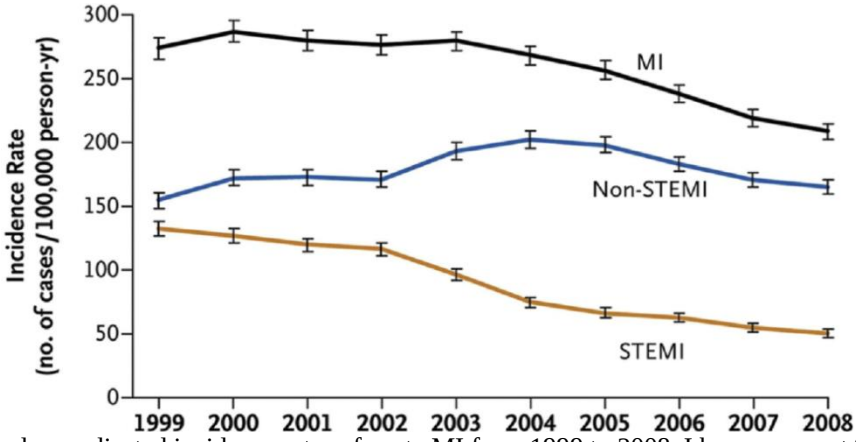

Figure 2: Age- and sex-adjusted incidence rates of acute MI from 1999 to 2008. I bars represent 95% confidence intervals. MI indicates myocardial infarction; STEMI, ST-elevation myocardial infarction.[4]

Approximately 30% of STEMI patients are women; female is strongly associated with failure to receive reperfusion therapy despite the absence of contraindications and were generally presented later after symptom appears. In-hospital, mortality from STEMI declined steadily from 1997 to 2006, except in men aged <55 years.Besides, diabetes mellitus is associated with higher short- and long-term mortality after STEMI due to greater risk of myocardial tissue perfusion impairment after restoration of epicardial coronary flow. [4]

III. Aetiology and Pathophysiology

The inciting event of acute STEMI is due to the rupture of atherosclerotic plaque which exposes the subendothelium and thrombogenic lipid to the circulating blood. This leads to the activation of platelet and clotting factor where platelets immediately attach and aggregate causing thrombus formation.[10, 11, 12]Development of arterial thrombus causes blockage or interruption of coronary blood flow to myocardium.When more than 75% of fixed coronary arteries are blocked, it can limit the oxygen and nutrient supply to myocardium which will then precipitate to MI or STEMI.[9, 13]

Situations that can increase the myocardial metabolic demand of oxygen include excessive physical activity, severe hypertension such as hypertrophic obstructive cardiomyopathy and abnormal valve stenosis. Abnormal valve stenosis lowers the cardiac output and decreases the mean aortic pressure where this pressure is important for coronary perfusion.[9, 13]Other modifiable factors like sedentary lifestyle, smoking, diabetes mellitus, hypertriglyceridemia, dyslipidaemia and obesity may worsen the condition by increasing the risk of atherosclerosis and myocardial infarction.[14]

IV. Management of Acute STEMI

When a patient suspected with acute STEMI is admitted to emergency department, a quick assessment must be done to ensure the suitability of the patient for undergoing reperfusion therapy by either primary Percutaneous Coronary Intervention (PCI) or fibrinolytic therapy.[15,16]For high risk patients and those contraindicated to fibrinolysis, primary PCI is recommended and the recommended door-to-balloon (DTB) time and door-to-needle time (DTN) are shown in Figure 3.[16, 17, 18]Treatment in delayed primary PCI or fibrinolytic therapy are associated with higher mortality rate but this relationship is more critical in patient who undergoing fibrinolytic therapy.[19]

Figure 3: Recommendation time for DTB and DTN time. DTB time is from the arrival to hospital to the balloon inflation time while DTN time is from the arrival to hospital to the fibrinolysis therapy time. [16, 17, 18]

In current era, primary PCI is the preferred reperfusion therapy because studies have shown that mortality rate and incidence of MI or death are lower in patients who undergoing PCI.[17, 18, 20-23] However, there are still some variations in the clinical practice from country to country. This is because primary PCI therapy is not availablein some hospitals in developing countries.[17]Before starting of reperfusion therapy (DNT or DTB) on patient diagnosed with STEMI, few initial management can be done as shown in the Figure 4.

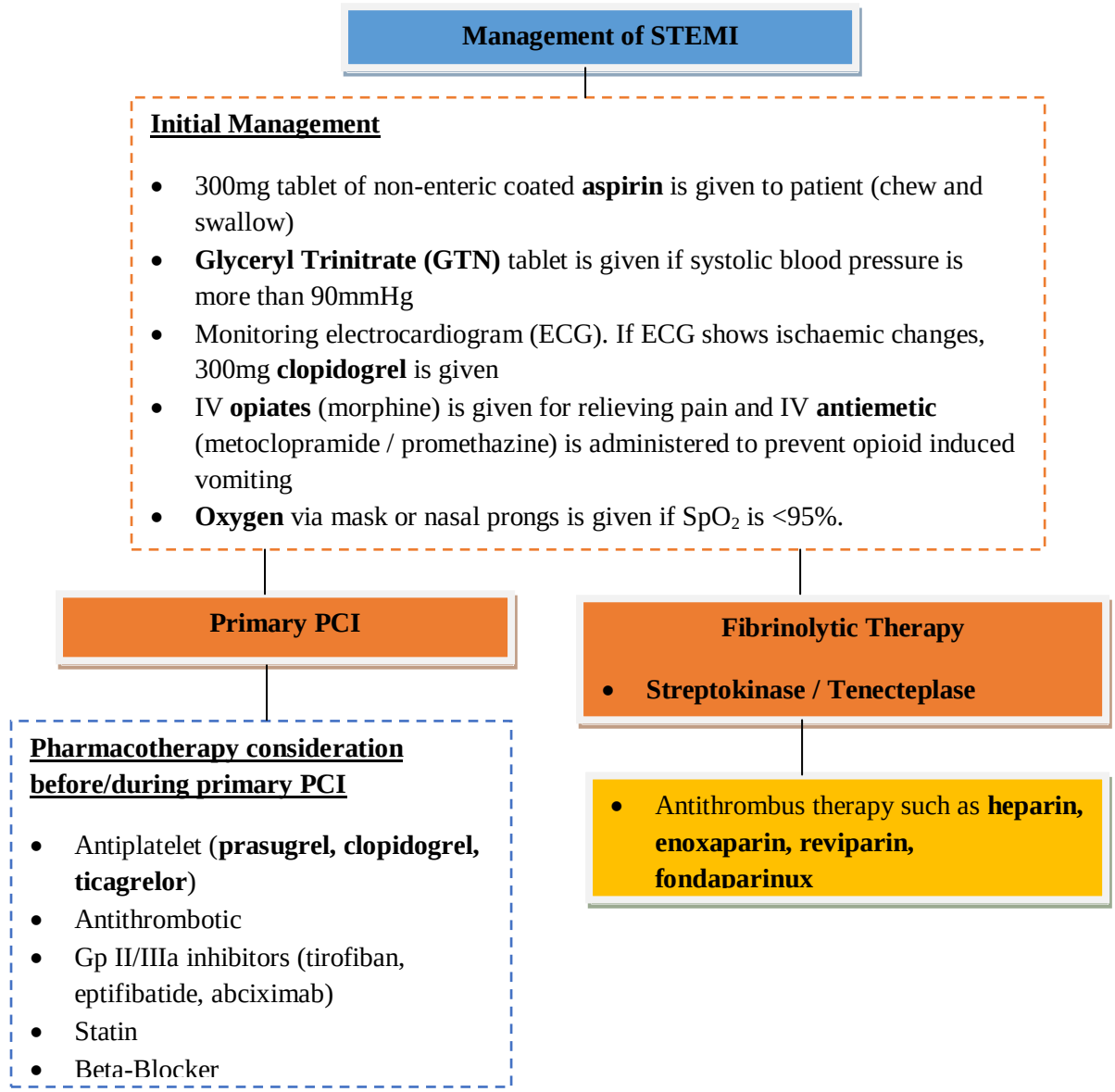

Figure 4: Management of STEMI[16]

Fibrinolytic Therapy

Studies have shown that fibrinolytic therapy is able to reduce mortality rate up to 50% and stop the infarct of STEMI when it is given within 2 hours from the time of symptoms onset.[24-27]

Streptokinase or Tenecteplase

Choices of fibrinolytics are streptokinase or tenecteplase. However, tenecteplase (TNK) is widely used in clinical practice nowadays especially in elderly with hypertension, diabetes, hyperlipidaemia or even for smokers.[28]

The coronary flow with TNK is better than streptokinase as its fibrin activity is more specific and selective as well as it gives a faster onset of action with a longer half-life by a single bolus infusion. This is also supported by coronarography which shows the rate of blood flow is 42.6% greater in patients with TNK group in comparison with streptokinase. Moreover, TNK is more resistant to plasminogen activator inhibitor-1 (PAI-1) as compared to alteplase and reteplase.According to the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT) 2 study, TNK reduced the major bleeding and mortality rate in STEMI patients with delayed treatment of PCI.[29]

V. Antithrombus Therapy

After completion of fibrinolysis, antithrombus agent such as low molecular weight heparin (LMWH) for instanceenoxaparin, unfractionated heparin (UFH), reviparin or fondaparinux is given immediately for 48 hours. [16]

Enoxaparin and Heparin

In a study conducted by Elliott M. Antman et al, enoxaparin, a LMWH was compared with UFH as an adjunctive therapy with fibrinolysis in patients with STEMI. Studies have revealed that enoxaparin shows a more reliable anticoagulation level without the need of therapeutic monitoring. Less mortality rate, emergency revascularization and re-infraction occurred in enoxaparin group. However, there was increased bleeding episode in STEMI patients treated with enoxaparin group.[30] Besides, a randomized controlled study from non-ST Elevation Acute Coronary Syndrome (NSTEACS) showed that MI rate and death was lower in the 49 000 patients with enoxaparin in ACSpatients as compared with UFH.[31]

Besides, Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 trial from the American Heart Association (AHA) demonstrated that LMWH was associated with lower risk of occluded artery infraction and recurrent stroke. Moreover, the trial also found that STEMI patients whom received enoxaparin have a lower rate of death or recurrent MI regardless the age and gender of patients as well as the location and symptoms onset of STEMI.[32]

However, this was opposed by the an International Randomized study comparing IV enoxaparin to IV UFH in primary PCI (ATOLLor acute STEMI treated with primary angioplasty and IV enoxaparin or UFH to lower ischemic and bleeding events at short- and long-term follow-up) trial which had shown that there was no difference in incidence of death and major bleeding between LMWH and UFH. However, enoxaparin resulted in a significantly reduced rate of the recurrent MI as the main secondary endpoint in STEMI patients.[33]Other choices of antithrombus agents are reviparin and fondaparinux.

Reviparin

Reviparin is a LMWH which significantly reduced mortality and re-infarctionat 30 days with lower rate of recurrent ischemiain patients with STEMI presenting within 12 hours of symptom onset. Despite an increase in life threatening bleeding, the overall benefits of reviparin still outweighs its risks.[34]

Fondaparinux

Fondaparinuxessentiallyreduced the 30-day mortality and re-infarction without increasing bleeding and strokes, particularly in patients who were not undergoing primary PCI as shown in Organization for Assessment of Strategies for Ischemic Syndromes (OASIS) 6 Randomized Trial for patients with acute STEMI. Moreover, both efficacy and safety were homogeneousin patients who received or did not receive UFH. This proves that fondaparinux is safe to be used in patients whom previously received UFH.[35] However, fondaparinux was associated with an increase in catheter-related thrombus and coronary angiographic complication.[36]

Pharmacotherapy Consideration Before/During Primary PCI

Different classes of drugs can be given before undergoing primary PCI or during primary PCI. Theclass of drugs are as below:

Antiplatelet

Clopidogrel has been used broadly in clinical practice. However, it may not be the ideal agent as it exhibits slow, weak and variable platelet inhibition action. Recently, the novel drugs, P2Y12 inhibitors such as prasugrel and ticagrelor are introduced and are more favoured for STEMI since STEMI is a highly pre-thrombic state where platelets are activated extensively.[37]

Prasugrel compared with Clopidogrel

According to the Journal of Cardiovascular Interventions, prasugrel was proven to achieve a better and faster platelet inhibition while compared with clopidogrel in healthy individuals.Approximately 60% of STEMI patients scheduled for pre-PCI with a loading dose of 600 mg clopidogrel failed to achieve sufficient platelet inhibition effect even after 4 hours.[38] Besides, the platelet activity after 2 hours and 5 days of prasugreladministration was also lower thanclopidogrel.[39]Prasugrel also resulted in reduction of the primary and secondary end point of death, cardiovascular disease and recurrent MI. Although it was demonstrated with increased risk of bleeding, prasugrel is still in favour in clinical practice.[29] It is concluded that prasugrel was associated with improved efficacy and similar safety compared with clopidogrel in patients undergoing primary PCI.[40, 41] Hence, prasugrelis preferable overclopidogrel in primary PCI setting.[38]

Ticagrelor compared with Clopidogrel

Ticagrelor provides more consistent inhibition of platelet aggregation, cardiovascular risk, death, MI and thrombosis than clopidogrel. It also contributes toimprovement in survival rate. According toPlatelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor exhibited similar rates of total major bleeding compared with clopidogrel that became statistically significant beginning 30 days after randomization.[42] Fatal events were not common and occurred at a similar frequency between the clopidogrel and ticagrelor in the trial. However, ticagrelor was associated with a higher rate of stroke and side effects such as bradycardia and dyspnoea compared to clopidogrel. After 30 days on treatment, net clinical benefit favoured ticagrelor.[42, 43]

Prasugrel compared with Ticagrelor

In a study published in the Journal of the American College, prasugrel showed to be non-inferior compared with ticagrelor in terms of residual platelet reactivity 2 hours after the loading dose inSTEMI patients undergoing primary PCI.[44] Moreover, based on studies published in the American Heart Journal on the performances of ticagrelor with prasugrel, 360mg ticagrelor was not success to achieve a faster and platelet inhibition as compared with the standard 60mg prasugrel loading dose after administration of 12 hours.Prasugrel demonstrated a decreased risk of stent thrombosis than ticagrelor whereas ticagrelor was associated with a reduced risk of any major bleeding compared with prasugrel.[45, 46]Moreover, 360mg of ticagrelor has optimum platelet reactivity after administration of 2 hours and 60mg whileprasugrel achieved antiplatelet inhibition with reduced risk of thrombosis after the administration of 12 hours. There wasno significant difference in rates of overall death and stroke between them.

VI. Glycoprotein IIb/IIIaInhibitors

Tirofiban, Eptifibatide and Abciximab

According to OngoingTirofibanIn Myocardial infarction Evaluation (On-TIME) 2 trial, early and pre-hospital administration of high bolus dose (HBD) tirofiban showed a promising result in ST-segment resolution, both before and after primary PCI. It is believed that the improvement in myocardial reperfusion by HBD tirofiban resulted in mortality reduction. Through early initiation of tirofiban together with clopidogrel, the clinical outcome in STEMI patients after primary PCI had significantly improved.[47]

In addition, several studies have been conducted to compare the effectiveness of small molecules glycoprotein IIb/IIIa inhibitors (smGPIs) such as tirofiban and eptifibatide with abciximab. The smGPIs have different specificity and binding characteristic from abciximab.[48] Data in a meta-analysis demonstrated that smGPIs (tirofiban or/and eptifibatide) were equivalent to abciximab in achieving clinical outcome in STEMI patients.[48, 49]Both smGPIs and abciximab wereable to achieve same rate of initial Thrombolysis In Myocardial Infarction (TIMI) flow and cumulative ST-segment resolution in primary PCI. However, tirofiban group was associated with lower risk of thrombocytopenia compared to abciximab.[48]Moreover, same safety and efficacy effects can be achieved with the lower cost eptifibatide.[49]

For abciximab, comparison was done between the intracoronary (IC) and intravenous (IV) bolus administration during primary PCI. According to Cardiology Journal, a remarkable reduction of >50% in mortality, target vessel restenosis (TVR) and MI incidencewas observed with IC route.[50]Besides, in the randomised Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV versus IC in ST-Elevation Myocardial Infarction (LIPSIAbciximab-STEMI) trial, it was shown that IC route of administration provided some favourable outcomes after 6 months such as reduction in infarct size, significant recovery of left ventricular function and most importantly lowering in major adverse cardiovascular event.[51]

Statins

Low-density lipoprotein-cholesterol (LDL-C) is a well-known risk factor for development and progression of coronary artery disease. A trial comparing statin-pre-treated and statin-naive patients with STEMI undergoing PCI with low admission LDL-C levels (< 70 mg/dl) reported statin pre-treatment were associated with lower in-hospital and long-term mortality and less frequent heart failure incidence compared to statin-naïve groups.[52]Statintherapy also benefits STEMI patients by its early antiplatelet effect, which seems to be independent of its cholesterol lowering effect. This effect occurs in addition to effect of contemporary antiplatelet therapy which includes aspirin and clopidogrel.[53]

Beta-Blocker

The evidence of beta-blocker use as secondary MI prevention and for peri-operative is recommended by the American Heart Association unless there are contraindications. According to studies conducted, beta blocker given after successful primary PCI can lower mortality rate and sudden cardiac death by 1.5% compared with non-beta blocker group who are more likely to experience life-threatening arrhythmias.[54,55]Moreover, benefits of beta-blockers can be extended to primary PCI pre-proceduralIV beta-blocker as the patients showed

greater degree of left ventricular ejection fraction (LVEF) recovery in addition to reduction in30-day mortality.However, new onset of congestive heart failure was slightly more frequent and no survival benefit with pre-procedural beta-blockers was observed in patients receiving beta-blockers at home.[56]

VII. Summary and Conclusion

Primary PCI is superior to fibrinolytic therapy as a reperfusion therapy as the mortality rate and myocardial infarction or death is lower in primary PCI.[17-18, 20, 21-23] However, in Malaysia, majority of the hospitals are using fibrinolytic therapy rather than primary PCI as the main reperfusion therapy.[16]

For fibrinolytic therapy, tenecteplase is preferred over streptokinase due to its specific and fast onset which can achieve more rapid reperfusion of the occluded artery.[28, 29]Tenecteplase is often given as a single bolus dose.[57, 58]After fibrinolytictherapy, enoxaparin is given immediately. Enoxaparin is preferred as it causesless mortality and MI rate. UFH, reviparin and fondaparinux are other choices of antithrombus therapy. However, fondaparinux is not recommended as the sole anticoagulant during PCI because it increases the risk of catheter thrombosis.[36]

In order to achieve a good outcome, some pharmacotherapies are considered before undergoing primary PCI or during primary PCI in order to obtain a good epicardial flow as well as optimum reperfusion of the myocardial microvasculature.[59, 60] These therapy involve antiplatelet, antithrombotic, glycoprotein IIb/IIIa inhibitor, beta blocker and statin.

Studies have shown that antiplatelet therapy of prasugrel achieved more antiplatelet inhibition in comparison with ticagrelor and clopidogrel.[39, 45, 46, 61]Besides, prasugrel reduces death and recurrent MI. Although prasugrel demonstrated an increased risk of bleeding,prasugrel is still in favour in clinical practice.[29]

Besides that, high loading or re-loading dose of statins have been shown to be beneficial in preventing peri-procedural MI in ACS patients undergoing PCI while pre-procedural IV beta-blocker during primary PCI have showed greater LVEF recovery of patient and reduce rate of 30-day mortality.[56, 62-65]

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