PERCUTANEOUS CORONARY INTERVENTION DURING INDEX ADMISSION VERSUS PHARMACO-INVASIVE STRATEGY FOR TREATMENT OF PATIENTS WITH ACUTE ST-ELEVATION MYOCARDIAL INFARCTION IN HOSPITAL USM ; A 5 YEARS EXPERIENCE

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LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
ADPI	Adenosine Diphosphate Inhibitors
BMI	Body Mass Index
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Diseases
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CK-MB	CK-Myocardial Band
cTnI	cardiac Troponin I
cTnT	cardiac Troponin T
DAPT	Dual Anti-Platelet Therapy
DBP	Diastolic Blood Pressure
DBT	Door to Balloon Time
DES	Drug Eluting Stent
DM	Diabetes Mellitus
DNT	Door to Needle Time
ECG	Electrocardiogram
ESC	European Society of Cardiology
FMC	First Medical Contact
GPIIb/IIIa	Glycoprotein IIb/IIIa
HTN	Hypertension
HUSM	Hospital Universiti Sains Malaysia
IHD	Ischemic Heart Diseases
IRA	Infarct Related Artery
LAD	left Anterior Descending
LBBB	Left Bandle Branch Block
LCX	Left Circumflex

LV	Left Ventricular
LVEF	LV Ejection Fraction
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MlogR	Multiple logistic Regression
NCVD	National Cardiovascular Database
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PPCI	Primary Percutaneous Coronary Intervention
RCA	Right Coronary Artery
ROC	Receiver Operating Characteristic
r-PA	reteplase
SBP	Systolic Blood Pressure
SD	Standard Deviation
SlogR	Simple logistic Regression
STEMI	ST-Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TNK	Tenecteplase

INTERVENSI KORONARI PERKUTANEUS SEMASA KEMASUKAN INDEK HOSPITAL BERBANDING DENGAN STRATEGI INVASIF FARMAKO BAGI RAWATAN PESAKIT DENGAN INFAKSI MIOKARDIUM ST-AKUT DI HOSPITAL USM ; PENGALAMAN 5 TAHUN

ABSTRAK

Strategi invasif farmako merupakan salah satu piawaian penjagaan pesakit dengan infarksi miokardial ST (STEMI), namun masa optimal mungkin tidak boleh dicapai kerana limitasi. Oleh sebab itu, kebanyakan pesakit menjalani intervensi koronari perkutaneus (PCI) pada waktu selepas kemasukan ke hospital indeks mereka.Walaubagaimanapun, hanya terdapat sedikit bukti yang wujud mengenai hasil strategi ini. Kajian ini bertujuan untuk membandingkan hasil klinikal PCI sewaktu kemasukan indeks dengan strategi invasif farmako terhadap pesakit yang mengalami STEMI. Kajian kohort retrospektif ini dijalankan di Hospital Universiti Sains Malaysia. Rekod perubatan pesakit STEMI yang dirawat secara PCI daripada Januari 2013 sehingga Mac 2018 diperolehi. Hasil klinikal kajian merupakan kadar Kejadian Kardiak Major yang Teruk (MACE) dan pendarahan utama pada hari ke-30 dan enam bulan selepas PCI. Analisis regresi logistik digunakan untuk menentukan faktor-faktor berkaitan dengan hasil MACE. Sejumlah 91 pesakit STEMI dianalisa. Dua puluh sembilan (31.9%) pesakit dirawat oleh strategi invasif farmako, dan enam puluh dua (68.1%) pesakit menjalani PCI sewaktu kemasukan indeks mereka. Pada hari ke-30 selepas PCI, kadar MACE dalam kumpulan invasif farmako dan PCI sewaktu kemasukan indeks adalah 10.7% berbanding dengan 10.3% (p=0.958). Kadar pada enam bulan adalah 8.3% berbanding 7.8% (p = 0.94). Kadar pendarahan utama pada 30 hari adalah satu (3.6%) berbanding tiada (p = 0.151) secara bandingan. Secara perbandingan, kadar pada enam bulan pertama seen hanyalah seorang (2.0%) untuk

kumpulan sewaktu kemasukan indeks. Keputusan analisis MLogR menunjukkan pembolehubah seperti jantina (nisbah ganjil Odd Ratio [OR]:10.9,95% selang keyakinan [CI]:1.35-87.80, p = 0.025), denyutan jantung (OR: 1.095, 95% CI: 1.031-1.164, p =0.003), dan sistolik BP (OR: 0.92, 95% CI: 0.87-0.97, p = 0.005) merupakan faktor signifikan yang dikaitkan dengan hasil MACE 30 hari selepas PCI. Pada enam pulan sejarah CAD sebelumnya (OR: 27.41, 95% CI: (1.97-380.21, p = 0.014), kadar denyut jantung (OR: 1.04, 95% CI: 1.02-1.14, p = 0.003), dan sistolik BP (OR: 0.93, 95% CI: 0.88- 0,98, p = 0.017) dikaitkan sekara signifikan dengan MACE. Kajian ini mencadangkan bahawa PCI ketika kemasukan indeks mungkin mempunyai hasil klinikal yang sama dengan strategi invasif farmako.

PERCUTANEOUS CORONARY INTERVENTION DURING INDEX ADMISSION VERSUS PHARMACO-INVASIVE STRATEGY FOR TREATMENT OF PATIENTS WITH ACUTE ST-ELEVATION MYOCARDIAL INFARCTION IN HOSPITAL USM ; A 5 YEARS EXPERIENCE

ABSTRACT

The pharmaco-invasive strategy is one of the standards of care in patients with ST-elevation myocardial infarction (STEMI), but the optimal timing may not be achieved due to limitations. Thus a large number of patients underwent percutaneous coronary intervention (PCI) at a later timing during their index hospitalisation. However, little evidence is available on the outcome of this strategy. This study aimed to compare the clinical outcomes of PCI during index admission with a pharmaco-invasive strategy for patients with STEMI. This retrospective cohort study was conducted at Hospital Universiti Sains Malaysia (HUSM). Medical records of all STEMI patients who were treated by PCI from January 2013 to March 2018 were retrieved. The clinical outcomes of the study were the rate of Major Adverse Cardiac Event (MACE) and major bleeding at 30 days and six months post PCI. The multiple logistic regression analysis was used to determine the associated factors with MACE outcome. A total of 91 STEMI patients were analysed. Twenty-nine (21.9%) patients were treated by pharmaco-invasive strategy, and 62 (68.1%) patients underwent PCI during their index admission. At 30 days post PCI, the rate of MACE in the pharmaco-invasive and PCI during index admission groups were 10.7% vs 10.3% respectively ($p = 0.958$). The rates at six months were 8.3% vs.7.8% respectively ($p = 0.94$). The rates of major bleeding at 30 days was one (3.6%) and none ($p = 0.151$) . By contrast, the rate at six months was seen only in one (2.0%) for the PCI during index admission

group. The results of MLogR analysis showed that the variables of gender (odds ratio [OR]: 10.9, 95% confidence interval [CI]:1.35-87.80, p = 0.025), Heart rate (OR: 1.095, 95% CI: 1.031-1.164, p =0.003), and systolic BP (OR: 0.92, 95% CI: 0.87-0.97, p = 0.005) were a significant factors associated with MACE outcome at 30 days post PCI. At six months, the history of previous CAD (OR: 27.41, 95% CI: (1.97-380.21, p = 0.014), heart rate (OR: 1.04, 95% CI: 1.02-1.14, p = 0.003), and systolic BP (OR: 0.93, 95% CI: 0.88- 0,98, p = 0.017) were significantly associated with MACE. This study suggests that PCI during index admission may had similar clinical outcomes to a pharmaco-invasive strategy.

CHAPTER 1
INTRODUCTION

1.1 Background of the study

Acute Coronary Syndrome (ACS) is the critical complication of atherosclerotic coronary artery disease (CAD). It is divided into three main categories: ST-elevation myocardial infarction (STEMI), Non-STEMI, and unstable angina (Torres and Moayedi (2007). Around 25%-40% of all acute myocardial infarction (MI) constituted of STEMI (O'Gara *et al.*, 2013). It is still a major health problem, both in developed and developing countries. The principal treatment of patients with STEMI is reperfusion therapy which includes either pharmacological (by fibrinolysis) or mechanical by the coronary intervention (O'Gara *et al.*, 2013).

In patients with STEMI, the time to establish reperfusion is crucial because the time lost is equivalent to myocardium lost (Rathore *et al*., 2009). The ideal approach for the treatment of STEMI is early reperfusion (within the first 12 hours after symptoms onset) (O'Gara et al., 2013). Several studies had confirmed the strong association between the early reperfusion and improved clinical outcomes (Boden *et al.*, 2007). Reperfusion by fibrinolysis is still one of the main reperfusion strategies in many countries because of the cost and paucity of PCI capable centres (Mehta *et al.*, 2017). Fibrinolysis should be given within the first 3 hours of STEMI onset (O'Gara *et al.*, 2013).

Overwhelming evidence from many studies has shown that mechanical reperfusion is more superior compared to fibrinolytic therapy. Hence it becomes the reperfusion strategy of choice for acute STEMI (Nielsen *et al.*, 2010). Primary Percutaneous Coronary Intervention (PPCI) is a class I reperfusion strategy for the treatment of patients with STEMI (Van de Werf *et al.*, 2006). It is defined as an

emergent percutaneous catheter intervention in the setting of STEMI, without previous fibrinolytic treatment (Members *et al.*, 2012). It is an ideal reperfusion strategy but may be unavailable in many centres; thus, the pharmaco-invasive strategy is an alternative option (Rashid *et al.*, 2016).

Pharmaco-invasive strategy is defined as the administration of fibrinolytic therapy followed by performing angiography and percutaneous coronary intervention (PCI) within 3–24 h after initiation of fibrinolytic therapy (O'Gara *et al.*, 2013). It is one of the standards of care in patients with STEMI (Ibanez et al., 2017), but the optimal timing may not be achieved due to some limitations. Hence a considerable number of patients underwent PCI at a later time during their index hospitalisation (Fan *et al.*, 2015). For that, the implementation of PCI more than 24 hours after STEMI is a common approach (Yazici *et al.*, 2009).

Many studies have reported that the late PCI had favourable clinical outcomes as compared to conservative treatment (Yousef *et al.*, 2002). The open-artery hypothesis postulates that the late opening of a totally occluded artery after STEMI onset was associated with beneficial clinical outcomes (Abbate *et al.*, 2003). The possible mechanism that might explain these benefits is the presence of residual antegrade blood flow, and a large amount of myocardium still viable, even late post-STEMI (Schömig *et al.*, 2005).

Major Adverse Cardiac Events (MACE) is a composite endpoint of clinical events that indicates the efficacy and safety outcomes. These events consist of all-cause mortality (including cardiac death), stroke, recurrent MI, re-hospitalization due to heart failure, or repeated coronary revascularization (Kip *et al.*, 2008). MACE are significantly associated with morbidity and mortality in patients with CAD who

underwent PCI. The early recognition and treatment of associated risk factors with MACE outcome are essential to decrease the mortality rate (Tsai *et al.*, 2017).

Bleeding is a well-known complication after PCI procedure as multiple antithrombotic drugs are commonly used. The major type is reported in $\leq 6\%$ of patients (Subherwal et al., 2012).

1.2 Problem statement

CAD is the leading cause of death worldwide (World Health Organization, 2017). In Malaysia, it is on the top of five causes of mortality (World Health Organization, 2015). The rate of mortality after acute MI is consistent between 8 and 10 % from 2006 until 2012 (Wan Ahmad WA, 2013). The early revascularization by pharmaco-invasive or PPCI remain a major obstacle in certain centres, especially in developing countries, and many STEMI patients worldwide might have missed it (Eagle *et al.*, 2002). Therefore, the delayed PCI has become the third option. However, the evidence for the benefits and timing of this strategy still requires further studies (Zheng *et al.*, 2017). Locally in this country, fibrinolytic therapy is accounted for 81% of the reperfusion therapy. It has been the major reperfusion strategy for STEMI patients who were presented to non-PCI capable centres. The PPCI was accessible only for 16.4% of STEMI patients at PCI-capable centres (W.A Wan Ahmad, 2017).

1.3 Justification of the study

There is a large controversy in the literature about the benefits of delayed PCI for latecomer STEMI patients. Locally, the hospitalization of STEMI patients usually takes 5-7 days and therefore, the revascularization during this time should have an impact on the patients' outcomes. A large percentage (33.4%) of STEMI patients underwent PCI during their index admission (Ahmad, 2015). However, the outcome and timing of this strategy are not clearly defined. Furthermore, very few studies are available on the types of reperfusion therapy (Seong and John, 2016). Thus this study aimed to compare the efficacy and safety of PCI during index admission with a pharmaco-invasive strategy for the treatment of patients with acute STEMI.

1.4 Objectives of the study

1.4.1 General objective

To compare the efficacy and safety of PCI during index admission versus pharmaco-invasive strategy for the treatment of patients with acute STEMI.

1.4.2 Specific objectives

1- To determine the association between the types of PCI strategies with outcome of MACE in patients with STEMI.

2- To determine the association between the types of PCI strategies with the outcome of major bleeding in patients with STEMI.

1.5 Research questions

Is PCI during index admission as effective as a pharmaco-invasive strategy in reducing the rate of MACE in patients with acute STEMI ?

Is PCI during index admission as safe as a pharmaco-invasive strategy in reducing the numbers of major bleeding as a complication ?

1.6 Study hypothesis

PCI during index admission is effective and safe as a pharmaco-invasive strategy in the treatment of STEMI patients.

CHAPTER 2
LITERATURE REVIEW

2.1 Epidemiology of coronary artery diseases

CAD is one of the leading causes of death worldwide. It caused 17.9 million deaths in 2016, signifying 31% of all global deaths. The majority of deaths were reported in the middle - and low - income countries (World Health Organization, 2017). By 2030, it is expected to cause >23.6 million deaths (Benjamin *et al.,* 2018). The ischemic heart disease (IHD) related deaths are increased by 41.7% from 1990 to 2013 (Bloom *et al.,* 2012). It made 43.8% of all cardiovascular deaths In the United State (Benjamin *et al.,* 2018). In Malaysia, IHD is the leading cause of death and accounted for 13.9 % of all death causes (Department of Statistics 2018).

2.2 Pathophysiology of coronary artery diseases

The most common underlying cause of CAD is atherosclerosis (Libby, 2001). Atherosclerosis defined as chronic multifocal immune-mediated inflammatory disease associated with the formation of a fibroproliferative plaque of medium and large size arteries (Dotter and Judkins, 1989). The pathophysiological mechanisms leading to CAD development include endothelial dysfunction, inflammation, vasospasm and obstructive thrombus formation (AP, 2008; Ross, 1986)

The endothelium is a single layer lining the arteries and forms a unique barrier between blood and thrombogenic subendothelial tissues. It mediates the process of growth, hemostasis, and inflammation throughout the circulatory system. Endothelial dysfunction is the first step in developing atherosclerotic plaque (Kitta *et al.*, 2009)

The early component lesion of atherosclerotic plaque is a fatty streak which is a localized collection of macrophages and fat inside the intimal layer of arteries. This is

followed by the formation of the fibrous cup which composed of lipids, blood proteins, and inflammatory cells. The devastating complication of atherosclerotic plaque is a heart attack and stroke, which is mainly caused by obstructive thrombi. These thrombi are developed as a consequence of plaque rupture, which forms 80% of coronary artery thrombosis in men and 60% in women (Falk, 2006). The stages of atherosclerotic plaque formation are shown in Figure 2.1.

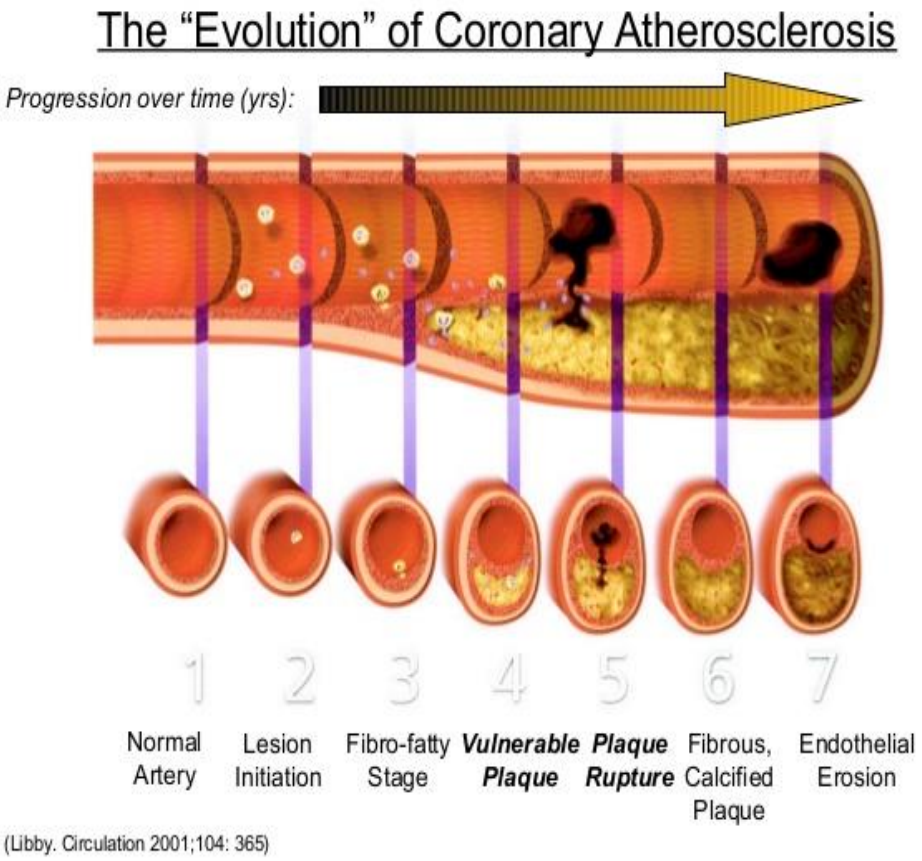

Figure 2.1 Stages of coronary atherosclerotic plaque formation. Adopted from (Libby, 2001).

2.2.1 The concept of vulnerable atherosclerotic plaques

Atherosclerotic plaques of coronary arteries are structurally and biologically heterogeneous. It is composed of a lipid-rich core and covered by a fibrous cap. The majority of these plaques are still quiescent during the lifetime. A few numbers become complicated by rupture and formation of obstructive thrombi. Thus, these thrombogenic plaques are called vulnerable or high-risk plaques (Schaar *et al.*, 2004).

Vulnerable plaque is considered as high-risk plaque, predisposing to rupture, if characterized by one of the following features: an active inflammatory process, thin fibrous cap, large lipid content, surface fissuring, endothelial erosions with platelet activation and/or calcified nodules. In this ruptured plaque, the structural defects usually occurred in the fibrous cap leading to exploration of lipid-rich core to blood and enhancing formation of thrombi (Guyton, 2001).

Plaque size is not correlated with plaque vulnerability to rupture (Varnava, 2002). A lot of coronary plaques are not visible by angiography and carry a high thrombogenic risk after rupture (Tedgui and Mallat, 2001). Figure 2.2 shows the different types of vulnerable plaques.

ACS usually developed due to the sudden rupture of the plaque fibrous cap. This rupture is triggered by some factors like extreme physical activity, emotional distress, sexual activity, cocaine use, and acute infection (Servoss, 2002). Myocardial infarction occurred due to irreversible complete coronary artery occlusion which begins to develop 15-20 minutes after severe ischemia (Reimer and Jennings, 1979).

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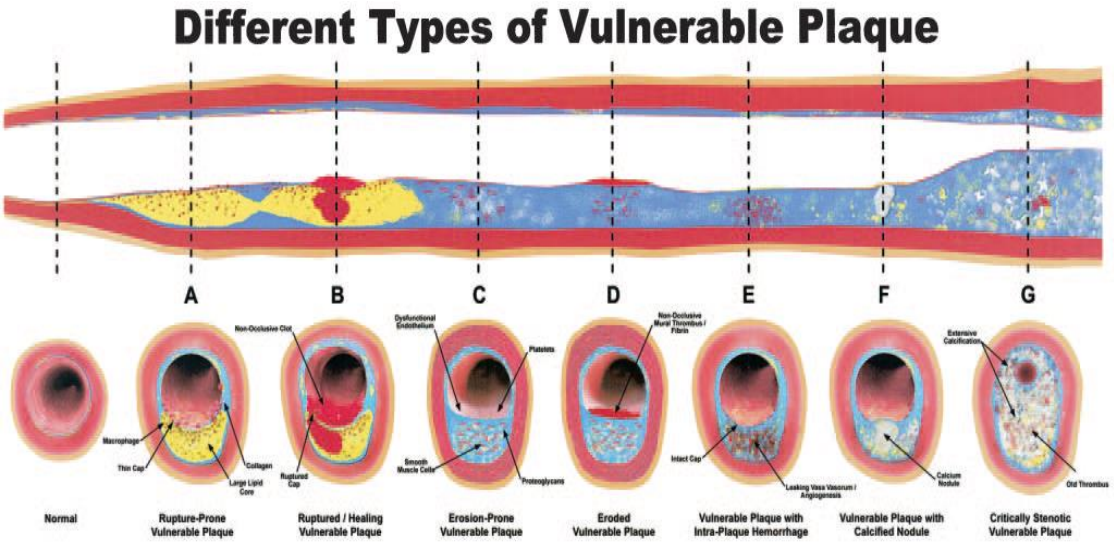

Figure 2.2 Types of vulnerable plaques

A: Rupture-prone plaque which characterized by large lipid core and thin fibrous cap, **B**: Ruptured plaque with subocclusive thrombus and early organization, **C**: Erosion-prone plaque with proteoglycan matrix, **D**: Eroded plaque with subocclusive thrombus, **E**: Intraplaque hemorrhage, **F**: Calcific nodule bulging into the vessel lumen, **G**: Chronically stenotic plaque with severe calcification. Adopted from (Naghavi *et al.*, 2003).

2.2.2 Risk factors for atherosclerotic coronary artery diseases

Several factors are contributed to the development of atherosclerotic CAD. These usually divided into two main categories: a) modifiable risk factors which mainly include Hypertension (HTN), hypercholesterolemia, Diabetes Mellitus (DM), obesity, and smoking. It accounted for more than 50% of risk factors associated with cardiovascular mortality (Patel *et al.*, 2015) b) non-modifiable factors include age, male gender, and family history of CAD (Wilson *et al.*, 1998)**.**

2.3 Acute coronary syndrome

ACS is a clinical syndrome resulting from an acute onset of myocardial ischemia or infarction. This syndrome mainly includes three clinical entities: STEMI (30%), non-STEMI (25%), or unstable angina (38%) (Torres and Moayedi, 2007). The term ACS is used because the initial presentation and early management of these entities are similar (Achar *et al*., 2005). Figure 2.3 shows the different presentation of ACS.

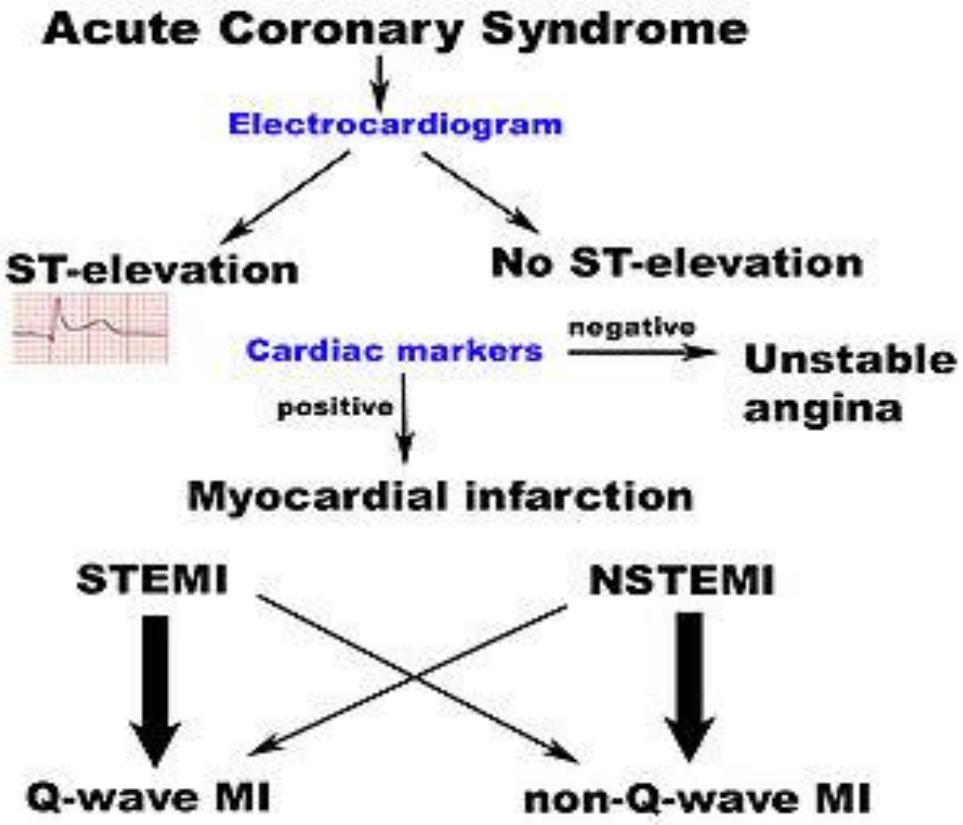

Figure 2.3 The different presentation of ACS. Adopted from (Alpert *et al*., 2000).

Acute MI is a clinical term used when there is evidence of myocardial injury and clinical evidence of myocardial ischemia. Acute myocardial injury defined as an elevation of cardiac troponins above the upper limits of normal. Clinical evidence of myocardial ischemia is indicated by the presence of ischemic symptoms and electrocardiographic (ECG) changes consistent with ischemia (Thygesen *et al.*, 2018). Based on the underlying causes acute MI is classified into five main categories as shown in Table 2.1.

Table 2.1 Universal classification of myocardial infarction. Adopted from (Thygesen K *et al.*, 2012).

Myocardial Infarction subtypes	Etiology
Type 1: Spontaneous MI	Related to atherosclerotic plaque rupture in one or more of the coronary arteries.
Type 2: MI secondary to an ischemic imbalance	Secondary to non CAD causes e.g., anemia, respiratory failure, hypotension.
Type 3: MI resulting in death when biomarker values are unavailable	Cardiac death with clinical evidence of myocardial ischemia but death occurring before obtaining of blood samples and before raising of cardiac enzymes.
Type 4a: MI related to PCI	MI associated with PCI.
Type 4b: MI related to stent thrombosis	MI associated with stent thrombosis.
Type 5: MI related to Coronary Artery Bypass Grafting	MI associated with CABG.

MI: Myocardial Infarction, CAD: Coronary Artery Diseases, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Grafting

2.3.1 Evaluation of acute coronary syndrome

The cardinal symptom of MI is chest pain. The common associated symptoms are shortness of breath, diaphoresis (sweating), nausea, and/or vomiting. Female and diabetic patients may not experience chest pain or may be presented with atypical manifestation like palpitations, anxiety, and a feeling of being acutely ill (Kar-mun and Schneider, 2009). When a patient presented with suspected acute MI, a brief history, physical examination, an ECG tracing, and cardiac enzyme should be obtained within 10 minutes of the patient arrival to the hospital (Antman *et al.*, 2004). Unstable angina is characterised by normal levels of cardiac biomarkers, and with/without ECG changes. NSTEMI is characterised by positive myocardial biomarkers and ECG changes, in the form of ST-segment depression or prominent T-wave inversion but without persistent ST-segment elevation. STEMI is characterised by persistent ST-segment elevation or new left bundle branch block on ECG tracing and elevated levels of cardiac biomarkers (Anderson *et al.*, 2007). Figure 2.4 shows the diagnostic criteria for MI.

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

Figure 2.4 Global criteria for myocardial infarction diagnosis. Adopted from (Abbate *et al.*, 2008).

2.3.2 Management of acute coronary syndrome

The main objective of treatment in acute coronary syndrome, apart from symptom relief, is the disruption of myocardial ischemia by the restoration of coronary blood flow. Also, the reduction in risk of heart failure and arrhythmia which usually developed secondary to myocardial ischemia. Another an important objective, in the treatment of ACS, is the prevention of recurrent thromboembolic events (Anderson *et al.*, 2007).

2.3.2(a) Medical treatment of acute coronary syndrome

For patients with suspected ACS, the initial treatment should be included 162-325 mg of aspirin, oxygen if needed, nitroglycerin, heparin, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, and morphine for pain control if indicated (Yang EH, 2008).

2.3.2(b) Revascularization of acute coronary syndrome

In addition to medical therapy, the further reperfusion by the known revascularization strategies is needed to relieve symptoms, improve and prolong life. These strategies are including either pharmacological by the administration of fibrinolytic therapy or mechanical by PCI implementation (Anderson *et al.*, 2007).

2.4 ST-Elevation Myocardial Infarction (STEMI)

STEMI is a clinical syndrome characterized by the presence of myocardial ischemic symptoms and associated with persistent electrocardiographic ST-segment elevation and/or subsequent raising of the cardiac enzymes (Thygesen *et al*., 2012).

2.4.1 Epidemiology of STEMI

Around 25%-40% of all acute MI are constituted of STEMI. It remains a major health problem (O'Gara *et al.*, 2013). According to European STEMI registry, the incidence rate of STEMI is 58 per 100000 per year in 2015 (Ibanez *et al*., 2017). In Malaysia, it consisted of 46.1% of the ACS presentation (W.A Wan Ahmad, 2017).

2.4.2 Diagnosis of STEMI

Diagnosis of patients with STEMI should be started with the first medical contact (Ibanez *et al.*, 2017). STEMI usually diagnosed by the presence of at least two of the following three criteria: a history of persistent chest pain, ST-segment elevation or new left bundle branch block (LBBB) changes on ECG tracing, and rise and/or fall of the serum cardiac biomarkers (de Torbal *et al.*, 2006).

2.4.2(a) ECG criteria of STEMI

ECG tracing must be acquired and interpreted as soon as possible in all STEMI patients to enable the early diagnosis and triage (Ibanez *et al*., 2017). It considered a vital part of STEMI diagnosis. The serial ECG recordings are recommended as it can provide critical information, especially if the initial ECG is not diagnostic. As well, it is a helpful tool for determination of reperfusion success and occurrence of re-occlusion.

In addition, the ECG tracing can provide information on the locations of STEMI (Thygesen *et al.*, 2018). These different locations are shown in Table 2.2.

The ECG criteria depend on the changes of the electrical currents of the heart (measured in millivolts). The ECG standard calibration is 10 mm/mV. So, 0.1mV equals 1mm square on the vertical axis. The criteria of ST-segment elevation (measured at the J-point) that underlying the acute ongoing coronary occlusion is at least two contiguous leads with ST-segment elevation $\geq$ 2.5mm in men < 40 years, $\geq$ 2mm in men $\geq$ 40 years, or $\geq$1.5mm in women in leads V2–V3 and/or $\geq$ 1mm in the other leads [in the absence of LV hypertrophy or LBBB)] (Thygesen K *et al.*, 2012).

Table 2.2 Different STEMI locations on ECG tracing. Adopted from (Bonow RO, 2012)

STEMI Location	Leads	ECG findings
Anteroseptal	V1 – V3	ST elevation, Q wave
Extensive anterior	V1 – V6	ST elevation, Q wave
Posterior	V7 – V8	ST elevation, Q wave
	V1 – V2	ST depression, Tall R
Anterolateral	I, AVL, V5 – V6	ST elevation, Q wave
Inferior	II, III, AVF	ST elevation, Q wave
Right Ventricular (RV)	V4R	ST elevation

2.4.2(b) Cardiac enzymes in STEMI

Creatine Kinase (CK), CK-Myocardial Band (CKMB) and cardiac Troponins T and I (cTnT and cTnI) are commonly used biomarkers for the diagnosis of myonecrosis. cTnT and cTnI are the preferred biomarkers for acute STEMI diagnosis. If a cTn assay is not available, the best alternative is CK-MB which is measured by a mass assay (Thygesen *et al.,* 2018). If the clinical presentation is compatible with myocardial ischemia, a dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals usually indicates MI (Thygesen *et al.,* 2012).

CK-MB starts to rise in the serum four to six hours after the onset of ischemia, peaks in 12 to 24 hours and normalizes in two to three days. CK-MB levels usually requested at the emergency department and repeated in 6 to 12 hours, depending on the assay that is used. CK-MB assessment is helpful in the diagnosis of reinfarction (Alpert *et al.,* 2000).

Troponins become detectable in the blood within 3-4 hours after MI onset and raising to peak within 6 hours. It is not helpful in the diagnosis of reinfarction because it is still elevated until 10-14 days post-MI (Thygesen *et al.*, 2018).

2.4.3 Complications of STEMI

Patient with STEMI diagnosis has significant morbidity and mortality (Thygesen *et al.,* 2018). In spite of medical advances, acute myocardial infarction remains a life threatening disease and sometimes associated with fatal complications.Therefore, a physician should always be aware of these sequales. STEMI complications are either direct outcome of a disease or adverse effects of therapies (Pattanayak and Gelfand, 2009)

Acute complications of STEMI include arrhythmias, sudden cardiac death, cardiogenic shock, congestive heart failure, re-infarction, fibrinous pericarditis, cardiac free-wall rupture, mural thrombus, and distal embolization (Burke and Virmani, 2008).

Arrhythmias are common early complications of STEMI and carry a high risk for sudden cardiac death especially, the ventricular type (Gorenek *et al.,* 2014). The early and complete revascularization reduces the risks of ventricular arrhythmias and cardiovascular death (Ibanez *et al.,* 2017).

Cardiogenic shock is referred to as case of persistent hypotension (SBP <90mmHg) with signs of hypoperfusion. It complicates 6–10% of all STEMI cases and still the leading cause of death. It is accounted for more than 50% of in-hospital mortality (McManus *et al.,* 2011). The onset of shock after STEMI event is usually variable. It does not often happen before admission; in the majority of cases it develops within the first 24 h (McManus *et al.,* 2011).

The long-term complications commonly include heart failure and left ventricular (LV) systolic dysfunction (Weir *et al.,* 2006). LV dysfunction is the most frequent consequence of STEMI. It is still a powerful independent predictor of mortality (Ibanez *et al.,* 2017). The early and successful myocardial reperfusion associated with significant improvement in ventricular function (Ibanez *et al.,* 2017).

2.4.4 Treatment of STEMI

STEMI patients are usually presented with persistent chest pain and should be evaluated promptly at the time of presentation. If ACS is the leading diagnosis, the initial assessment must include ECG recording and preliminary interventions. These include: airway, breathing, circulation assessment, taking a brief history and examination, giving oxygen if indicated, relieving the chest pain, and giving aspirin as bolus dose 325mg (Reeder *et al.*, 2016). After this initial assessment, the early coronary reperfusion should be carried out as early as possible. It is considered the gold standard in the management of STEMI patients (Ibanez *et al.*, 2017).

2.4.5 Reperfusion strategies in STEMI

Reperfusion therapy is the cornerstone for the treatment of acute STEMI patients (O'Gara *et al.*, 2012). Implementation of reperfusion strategies as early as after STEMI onset are aimed to diminish the total ischemic time (the time from symptoms onset to giving reperfusion), preserve myocardium viability, optimize myocardial salvage, and reduce mortality (Anderson *et al.*, 1996). Timely and complete restoration of blood flow for the culprit artery is an extremely beneficial approach. It reduces the infarct size, preserves the LV function, and improves the rate of survival (Braunwald, 1993).

2.4.5(a) Time delay

Implementation of reperfusion therapy in a timely manner is the key issue in the management of STEMI patients (Neumann *et al.*, 2018). Several important time intervals should be considered. These represent the total ischemic time and include: a) Time from arterial occlusion to symptom onset. b) Time from symptom onset to the

First Medical Contact (FMC). c) Time from the FMC to the introducing of reperfusion strategies (Door to Balloon Time (DBT) or Door to Needle Time (DNT). There is a strong impact of time delay on the mortality especially for those who were presented with cardiogenic shock (Neumann *et al.*, 2018). Studies conducted in Malaysia have shown that the delay in STEMI management was associated with a high mortality rate (CPG, 2014). Figure 2.4 shows the components of total ischaemic time and delays of initial management.