ACUTE CORONARY SYNDROME IN YOUNG PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA AND FACTORS ASSOCIATED WITH ITS COMPLICATIONS

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LIST OF ABBREVIATIONS

ACEI	Angiotensin-Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
AOR	Adjusted Odds Ratio
BBB	Bundle Branch Block
BHF	British Heart Foundation
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Diseases
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
CK-MB	Creatine Kinase – Myocardial Band
CVD	Cardiovascular diseases
ECG	Electrocardiography
ENACT	European Network for Acute Coronary Treatment
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes
INCLEN	International Clinical Epidemiology Network
INTERHEART	International Heart
IQR	Interquartile Range
LMWH	Low-Molecular-Weight heparin
LV	Left Ventricular
MLogR	Multiple Logistic Regression

NCVD	National Cardiovascular Disease
NSTEMI	Non ST elevation Myocardial Infarction
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
ROC	Receiver Operation Characteristics
SD	Standard Deviation
SES	Socioeconomic Status
SLogR	Simple Logistic Regression
STEMI	ST Elevation Myocardial Infarction
TIA	Transient Ischaemic Attack
UA	Unstable Angina
UK	United Kingdom
US	United States
VF	Ventricular Fibrillation
VIF	Variance Inflation Factors
VT	Ventricular Tachycardia
WHO	World Health Organization

LIST OF SYMBOLS

<	Less than
>	More than
=	Equal to
≤	Less than and equal to
≥	More than and equal to
α	Alpha
β	Beta
%	Percentage
Δ	Precision

SINDROM KORONARI AKUT DI KALANGAN PESAKIT MUDA DI HOSPITAL UNIVERSITI SAINS MALAYSIA DAN FAKTOR-FAKTOR BERKAITAN DENGAN KOMPLIKASI

ABSTRAK

Penyakit vaskular koronari adalah punca utama mortaliti dan morbiditi di Malaysia. Pada tahun 2006, anggaran insiden sindrom koronari akut (SKA) di Malaysia adalah 141 per 100,000 penduduk dan kadar kematian pesakit di hospital adalah kira-kira 7%. Walaupun SKA berlaku kebanyakannya di kalangan pesakit yang tua, kira-kira 5 hingga 10% daripada kes-kes yang berlaku adalah pesakit muda yang berumur kurang daripada 45 tahun yang boleh mengakibatkan morbiditi yang tinggi dan menjejaskan kualiti hidup pada peringkat kehidupan yang paling produktif. Kajian ke atas SKA di kalangan pesakit muda di Malaysia adalah terhad dan hasil kajian ini diharap dapat digunapakai untuk rujukan dan penyelidikan untuk manfaat pesakit. Kajian ini bertujuan untuk mengenal pasti ciri-ciri, rawatan dan komplikasi SKA di kalangan pesakit muda yang berumur kurang daripada 45 tahun yang dimasukkan ke Hospital Universiti Sains Malaysia (HUSM) dan faktor-faktor yang berkaitan dengan komplikasi. Kajian ini merupakan tinjauan rekod retrospektif. Pesakit muda yang berumur kurang daripada 45 tahun yang disahkan menghidap SKA dan dimasukkan ke HUSM di antara 1 Januari 2002 hingga 31 Disember 2012 yang memenuhi kriteria penyertaan dan pengecualian telah dimasukkan ke dalam kajian ini. Maklumat data dikumpul dengan menggunakan senarai semak yang direka oleh penyelidik terdiri daripada sosiodemografi, sejarah perubatan, persembahan klinikal, penyiasatan makmal dan diagnosis, rawatan dan komplikasi. Logistik regresi mudah dan berganda telah digunakan untuk analisis data. Seramai 147 pesakit telah dimasukkan dalam kajian, dengan min

(sisihan piawai) umur 39.1 (4.97) tahun dan nisbah lelaki kepada perempuan adalah 3:1. Daripada semua pesakit, 64.6% telah disahkan sebagai angina tidak stabil, 15.6% sebagai tidak elevasi ST infaksi miokardium dan 19.7% elevasi ST infaksi miokardium. Faktor risiko yang paling kerap adalah dislipidemia (65.3%), diikuti oleh hipertensi (43.5%), sedang merokok (42.9%) dan penyakit jantung (29.9%). Kebanyakan pesakit dirawat dengan ubatan dengan 91.8% menerima aspirin dan statin, dan 86.4% menerima clopidogrel manakala streptokinase diberikan kepada 11.6%, heparin kepada 6.3% dan fondaparinux kepada 52.4%. Terdapat 73 pesakit (49.7%) mempunyai komplikasi SKA dengan komplikasi yang paling kerap ialah kegagalan fungsi jantung (35.4%) diikuti oleh aritmia (20.4%) dan paru-paru bengkak dan kejutan kardiogenik (kedua-duanya dalam 13.6%). Perokok [nisbah odd terselaras (NOT) 4.03; 95% julat keyakinan (JK) 1.33, 12.23; nilai p= 0.014], kencing manis [NOT 3.03; 95% JK 1.19, 7.71; nilai p= 0.020], dan rawatan farmakologi menggunakan fondaparinux [NOT 0.18; 95 % JK 0.08, 0.39, nilai p < 0,001] dan nitrat oral [NOT 0.18; 95% JK 0.08, 0.42; nilai p < 0.001] adalah faktor yang bererti untuk mendapat komplikasi SKA di kalangan pesakit muda yang dimasukkan di HUSM apabila pembolehubah lain dikawal. Kesimpulannya, terdapat prevalens yang tinggi bagi faktor risiko kardiovaskular, yang menunjukkan pentingnya program pencegahan primer. Kebanyakan pesakit dirawat dengan ubatan dan kegagalan fungsi jantung adalah komplikasi yang paling kerap berlaku. Status merokok dan kencing manis merupakan faktor risiko manakala rawatan farmakologi menggunakan fondaparinux dan oral nitrat merupakan faktor pelindung yang bererti untuk komplikasi SKA dikalangan pesakit muda yang dimasukkan ke HUSM.

ABSTRACT

Coronary vascular diseases are the main causes of mortality and morbidity in Malaysia. In year 2006, the estimated incidence of acute coronary syndrome (ACS) in Malaysia was 141 per 100,000 population, and the inpatient mortality rate was approximately 7%. Although ACS occurs mainly in older patients, about 5 to 10% of cases occur in young patients aged less than 45 years old causing considerable morbidity and affecting the quality of life in their most productive life. Studies on ACS in young patients in Malaysia are limited and thus the result of this study will hopefully applicable for further reference and research for the benefits of patients. This study was aimed to identify the characteristics, treatment and complications of ACS in young patients aged less than 45 years old admitted in Hospital Universiti Sains Malaysia (HUSM) and the factors associated with its complications. This study was a retrospective record review. Young patients aged less than 45 years old who diagnosed with ACS and admitted to HUSM between 1st of January 2002 to 31st of December 2012 who fulfilled the inclusion and exclusion criteria were included in the study. The data information were collected using a checklist performa designed by researcher consisted of socio-demography, medical history, clinical presentation, laboratory investigation and diagnosis, treatment and complications. Simple and Multiple logistic regressions were used for data analysis. A total of 147 patients were enrolled, with mean (standard deviation) age of 39.1 (4.97) years and male to female ratio of 3:1. Of total sample, 64.6% were diagnosed as unstable angina, 15.6% as non ST elevation myocardial infarction and 19.7% as ST elevation myocardial infarction. The most frequent risk factors of ACS were dyslipidaemia (65.3%), followed by hypertension (43.5%), current smoking (42.9%) and heart disease (29.9%). Most patients treated medically with 91.8% patients received aspirin and statin, and 86.4% received clopidogrel while streptokinase were

prescribed in 11.6% of patients, heparin in 46.3% and fondaparinux in 52.4%. There were 73 patients (49.7%) had complication(s) of ACS with the most common were heart failure, (35.4%) followed by arrhythmia (20.4%) and pulmonary oedema and cardiogenic shock (both 13.6%). Current smokers [adjusted odds ratio (AOR) 4.03; 95% confidence interval (CI): 1.33, 12.23; p value = 0.014], diabetic mellitus [AOR 3.03; 95% CI: 1.19, 7.71; p value = 0.020], and pharmacological treatments of fondaparinux [AOR 0.18; 95% CI: 0.08, 0.39; p value < 0.001] and oral nitrates [AOR 0.18; 95% CI: 0.08, 0.42; p value < 0.001] were the significant associated factors for complications of ACS in young patients admitted in HUSM when other variables were controlled. In conclusion, there was high prevalence of established cardiovascular risk factors in which indicating the importance of primary prevention. Most patients treated medically and heart failure was the most common complication. Smoking status and diabetes mellitus were the significant risk factors while pharmacological treatment of fondaparinux and oral nitrates were the significant protective factors for complications in ACS in young patients admitted in HUSM.

CHAPTER ONE

INTRODUCTION

1.1 Overview of Acute Coronary Syndrome (ACS)

Cardiovascular diseases (CVDs) are the number one cause of global death. In 2008, an estimated 17.3 million people died from CVD and an estimated 7.3 million were due to Coronary Artery Diseases (CAD). Projected almost 25 million people will die from CVD, mainly from heart disease and stroke by 2030 and remain the single leading cause of death (WHO, 2012). In the Euroheart Acute Coronary Syndrome (ACS) survey, 23% were less than 55 years old (Rosengren *et al.*, 2006). The Global Registry of Acute Coronary Events (GRACE) showed that 6.3% were patients less than 45 years old (Avezum *et al.*, 2005). CVDs are the main causes of mortality and morbidity in Malaysia. In 2006, the estimated incidence of ACS was 141 per 100,000 populations per year, and the inpatient mortality rate was approximately 7% (Ahmad *et al.*, 2011). In Thailand, 5.8% of patients with ACS are under the age of 45 years old and the risk factors in young patients differ from older group (Tungsubutra *et al.*, 2007).

ACS refers to a spectrum of clinical presentations ranging from unstable angina (UA) to non ST elevation myocardial infarction (NSTEMI) and to ST elevation myocardial infarction (STEMI). In terms of pathology, ACS arises from atherosclerotic plaque rupture with subsequent coronary thrombosis and/or spasm. The resulting coronary artery occlusion gives rise to intense myocardial ischaemia or even myocardial necrosis (Beltrame *et al.*, 2012).

ACS has higher prevalence in middle-aged and elderly patients; thus comparatively few studies have focused on the clinical presentation, treatment and outcome of ACS in young patients. ACS causes a significant morbidity, psychological effects, and financial

constraints for the person and the family when it occurs at a young age. There are differences of characteristics between young and older patients with ACS. Young patients with ACS commonly presented with chest pain but rarely heart failure (Schoenenberger *et al.*, 2011). Younger patients were more likely to have an STEMI (67.3%) than older group (Tungsubutra *et al.*, 2007).

The most important cardiovascular risk factors in ACS in young patients are smoking, family history of CAD, dyslipidaemia and obesity (Egred *et al.*, 2005; Tungsubutra *et al.*, 2007; Schoenenberger *et al.*, 2011). Smoking is an important cardiovascular risk factor that inversely related to age. The prevalence of smoking was from 70 to 90% among young ACS patients; and smoking was found up to 92% among young patients with reported atheromatous process (Egred *et al.*, 2005). Dyslipidaemia was also highly prevalence in young patients. A family history of CAD, considered as one of the most important risk factor. The patients with family history of CAD tend to have abnormal lipid profile especially hypertriglyceridaemia and low HDL, insulin resistance and obesity which strengthen the theory of common genetic linkage (Fox *et al.*, 2000; Egred *et al.*, 2005; Tungsubutra *et al.*, 2007).

In young patients diagnosed with ACS, aspirin, beta-blockers, thrombolytic therapy and statins were all frequently prescribed. Unfractionated heparin was prescribed more often to the younger groups, whereas the rate of low-molecular-weight heparin (LMWH) usage remained relatively consistent among young and elder patients. Glycoprotein (GP) IIb/IIIa inhibitors were prescribed to nearly one-third of patients aged less than 45 years and their use decreased with advanced age. Angiotensin-converting enzyme inhibitors (ACEI) were prescribed more often in older patients (Avezum *et al.*, 2005).

Coronary angiography and percutaneous coronary intervention (PCI) were performed more frequently in young ACS patients. The mortality for ACS remains high particularly in

STEMI. Over 75% of STEMI patients received thrombolysis or proceeded to primary angioplasty. Patients who missed thrombolysis were twice likely to die than those who received. In a study of patients who underwent PCI, the prevalence revealed higher in young patients less than 40 years old as compared to older patients over 60 years old. PCI reduced mortality in NSTEMI and UA but not in STEMI (Chin *et al.*, 2008).

The cut off age of 45 years old had been used in most studies to define young patients with ACS and this same age also being used in this study (Avezum *et al.*, 2005; Egred *et al.*, 2005; Tungsubutra *et al.*, 2007). In the GRACE study that involved 24165 ACS patients in 102 hospitals in 14 countries in Europe, North and South America, Australia and New Zealand in which the impact of age on the management and outcome of ACS was evaluated and the patients were stratified into six categories; < 45 years, 45-54, 55-64, 65-74, 75-84 and $\geq$ 85 years. The youngest group was less than 45 years old (Avezum *et al.*, 2005). The Thai ACS registry, the patients were divided into three categories; < 45 years, 45-54 and > 54 years (Tungsubutra *et al.*, 2007). As conclusion, in this study the patients with age of less than 45 years old had been defined as young patients after considering of other studies globally and the neibourhood countries to facilitate this study for comparison and conclusion.

1.2 Rationale of the Study

Acute coronary syndrome (ACS) is a major health problem, with relatively high morbidity and mortality. The occurrence of ACS in young adults will lead to premature morbidity and mortality in the person's most productive years of life which also affect his or her family and working life. It may also affect not only physical but psychosocial of the patients.

Assessing the status of local setting by understanding the sociodemographic, clinical presentation and risk factors of ACS in young patients will provide local data that are

considerably useful in evaluating the effectiveness of management as well as preventive and control strategies and intervention for ACS. High prevalence of risk factors in ACS among younger age patients indicate that prevention should begin at early age. Studies on ACS in young patients in Malaysia are limited and thus the result of this study will be hopefully applicable for further reference and research for benefits of patients.

CHAPTER TWO

LITERATURE REVIEW

2.1 Acute Coronary Syndrome (ACS)

Acute coronary syndromes (ACS) encompass a spectrum of coronary artery diseases, ranging from unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). The term of ACS is useful because the initial presentation and early management of UA, NSTEMI and STEMI are frequently similar. The initial assessment requires a detailed history which include risk factor analysis, a physical examination, an electrocardiography (ECG) and measurement of serum cardiac marker (Achar *et al.*, 2005).

2.1.1 Unstable Angina (UA)

Angina is referred to any coronary heart disease syndrome resulting in myocardial ischaemia. The different coronary pathophysiological mechanisms may be responsible for the initiation of the myocardial ischaemia, including coronary artery spasm and microvascular dysfunction. Patients can present as exertional or rest angina, depending upon the underlying mechanism (Beltrame *et al.*, 2012). Table 2.1 shows the types of angina.

Table 2.1: Types of Angina. Adapted from British Heart Foundation: Coronary heart disease statistics 2010 (BHF, 2010)

Angina Syndrome	Clinical Features
Unstable Angina	1) Characterized by crescendo or rest angina 2) An acute coronary syndrome manifestation (may progress on to myocardial infarction) 3) Typically due to an unstable atherosclerotic plaque
Stable Angina	1) Characterized by exertional angina 2) Typically due to a stable but tight obstructive coronary artery
Prinzmetal Variant Angina	1) Characterized by rest or nocturnal angina 2) Typically due to coronary spasm
Decubitus Angina	1) Characterized by angina when lying down 2) Typically due to left ventricular dysfunction resulting in redistribution of pulmonary fluids and thus increased cardiac workload
Silent Ischaemia	1) Absence of angina in the presence of documented ischaemia 2) May occur with coronary artery or microvascular dysfunction
"Syndrome X"	1) Includes classical syndrome X, microvascular angina, coronary slow flow phenomenon 2) Characterized by prolonged episodes of exertional or rest angina 3) Typically due to coronary microvascular dysfunction

A patient presenting with UA may progress to NSTEMI or even STEMI. Unstable angina may be classified depending on the severity and clinical circumstances. UA and NSTEMI are heterogeneous disorders in which patients have widely varying risk which is important in management decision. Table 2.2 shows the classification of unstable angina.

Table 2.2: Classification of Unstable Angina. Adapted from (Hamm and Braunwald, 2000)

	Clinical Circumstances:		
	A Develops in presence of Extracardiac Condition That Intensifies Myocardial Ischaemia (Secondary UA)	B Develops in Absence of Extracardiac Condition (Primary UA)	C Develops Within 2 weeks of AMI (Post-infarction UA)
Severity:			
I- New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II- Angina at rest within past month but not within preceding 48h (angina at rest, subacute)	IIA	IIB	IIC
II-Angina at rest within 48h (angina at rest, acute)	IIIA	IIIB-Tneg IIIB-Tpos	IIIC

2.1.2 Non ST Elevation Myocardial Infarction (NSTEMI) and ST Elevation Myocardial Infarction (STEMI)

Acute myocardial infarction (AMI) can be defined based on clinical, ECG, biochemical, and pathological characteristics (Van de Werf *et al.*, 2008). Clinically, AMI has been sub-classified on the basis of the presenting ECG as either Non-ST-elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI). The immediate clinical management differs so that it is important to differentiate these two forms of AMI. In NSTEMI, it does not require immediate intervention although early invasive therapy (at least within days) is preferred. In contrast with STEMI, immediate coronary reperfusion strategies

(either percutaneous coronary interventions or thrombolysis) on arrival to hospital are important in order to reduce the mortality (Beltrame *et al.*, 2012). Table 2.3 shows the revised definition of myocardial infarction.

Table 2.3: Revised Definition of Myocardial Infarction. Adapted from (Thygesen *et al.*, 2007)

Criteria for acute, evolving or recent Myocardial Infarction
Either one of the following satisfies the diagnosis for acute, evolving or recent Myocardial Infarction: 1. Typical rise and / or fall in cardiac biomarkers (preferably troponin) with at least one of the following: - Ischaemia symptoms - Development of pathological Q waves in ECG - Electrocardiographic changes indicative of ischaemia (ST- segment elevation or depression) - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality 2. Pathologic findings of an acute myocardial infarction
Criteria for healing or healed Myocardial Infarction
Either one of the following satisfies the diagnosis for healing or healed Myocardial Infarction: 1. 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 2. Pathological findings of a healed or healing myocardial infarction

2.2 Burden of ACS

The ACS are common causes of emergency hospital admission and major burden on health care resources in industrial countries (Fox *et al.*, 2000). The World Health Organization (WHO) estimates CVD caused almost 32% of all deaths in women and 27% in men in 2004. In 2008, CAD is the most common cause of CVD deaths accounting for 7.25 million deaths/year, or 12.8% of all deaths worldwide. In many middle and high income countries, CAD is the single leading cause of death (WHO, 2012). In the United Kingdom (UK) in 2008, CAD was responsible for about one in five male deaths and one in eight female deaths; a total of 88,000 CAD deaths (15% of total deaths) (BHF, 2010). Similarly in the United States (US) in 2005, CAD was responsible for one of every five deaths, accounting for 445,687 deaths (18% of total deaths) (Lloyd-Jones *et al.*, 2009). In Australia in 2006, CAD accounted for 22,983 deaths (17% of all deaths) and once more was the most common condition responsible for Australian (AIHW, 2010).

Trend of an increasing rate of CAD mortality noted in some developing countries. Developing countries contribute a major share to the global burden of cardiovascular disease. AMI remains one of the leading causes of death in the developing world as well as in the developed world (Abdallah *et al.*, 2006). The WHO estimates that 60% of the global burden of CAD occurs in the developing countries. Although mortality estimates are difficult to obtain in some of these countries, broad assessments of overall CVD epidemiology report rising CVD mortality in urban China, Malaysia, Korea and Taiwan. In China, CVD mortality increased as a proportion of total deaths from 12.8% in 1957 to 35.8% in 1990 (Khor, 2001). The trend might be due to rapid urbanization, socioeconomic and health changes, together with an increase in life expectancy (Beltrame *et al.*, 2012).

Based upon self-reported AMI in a UK national survey, the prevalence of AMI was reported as approximately 4.1% of men and 1.7% of women in 2006 (BHF, 2010). The

prevalence is age-dependent, extending from 1% of men less than 45 years of age to 17% of those more than 75 years old. Similarly, in the US, based upon national survey data available from the American Heart Association, the prevalence of AMI was 3.6% in 2006 (Lloyd-Jones *et al.*, 2009). The prevalence was slightly higher in African American males (5.1%) compared with Caucasian males (4.9%) but lower in African American (2.2%) females compared with their Caucasian counterparts (3%). The prevalence of AMI was greater in the elderly compared with those less than 50 years of age as similar with UK population. In contrast, in developing countries such as South Asian countries (India, Pakistan, Bangladesh, Sri Lanka, and Nepal), the highest prevalence of AMI is seen in those younger than 40 years of age, whereas it is less marked in those older than 60 years (Joshi *et al.*, 2007).

CVD remains an important cause of death in Malaysia accounting for 20-25% of all deaths in government hospitals from 2000- 2005. Following an AMI, the mortality rate was about 20% in 2004. This high rate could have been due to late presentation and diagnosis, leading to delayed treatment. Occasionally the diagnosis could have been missed. In 2006, the estimated incidence of coronary disease in Malaysia was 141 per 100 000 populations. The in-patient mortality rate is approximately 7% (CPG, 2007a; Ahmad *et al.*, 2011).

Table 2.4: 10 Principles Cause of Death in Ministry of Health Malaysia (MOH) Hospitals, 2007.

Diseases	Percentage (%)
1. Heart Diseases and Diseases of Pulmonary Circulation	16.49
2. Septicaemia	13.38
3. Malignant Neoplasms	11.28
4. Cerebrovascular Diseases	8.50
5. Pneumonia	7.43
6. Accidents	5.20
7. Diseases of the Digestive Systems	4.86
8. Certain Conditions Originating in the Perinatal Period	4.11
9. Nepthritis, Nephrotic Syndrome and Nephrosis	4.09
10. Ill-define Conditions	2.55

Source: Health Informatic Centre, Planning and Development Division, MOH, 2007

2.3 Burden of ACS in Young Patients

Coronary heart disease (CHD) represents the leading cause of death in adults not only in western world but also worldwide. CHD may be manifest as myocardial infarction which is lethal and can be present as sudden death. Although myocardial infarction occurs mainly in older patients, however, 5 to 10% of cases occur in younger patients less than 45 years of age. If it occurs in young age, the disease causes a significant morbidity, psychological effects and financial constraints for the person and the family. The protective effect that offered by young age has been slowly taken away by the increased prevalence of risk factors for CHD in adolescents such as smoking, obesity and lack of activity. This will result in an increase disease burden in the near furture (Egred *et al.*, 2005).

Although ACS in younger patients are generally associated with favorable prognosis, the personal and societal burden of premature coronary disease is substantial (Tungsubutra *et al.*, 2007). The young patient is of particular interest considering the years of potential life lost (Schoenenberger *et al.*, 2011).

2.4 History and Clinical Presentation of ACS

Symptoms of ACS include chest pain, referred pain, nausea, vomiting, dyspnea, diaphoresis, and lightheadedness. Pain may be referred to the arm, jaw, neck, back, or even abdomen. Pain in which radiating to the shoulder, left arm, or both arms increases the likelihood of ACS (Goodacre *et al.*, 2002).

Typical angina is described as substernal pain, occurs on exertion, and is relieved with rest. Patients with all three of these features have a greater likelihood of having ACS than patients with none, one, or even two of these features. However, some patients may present without chest pain or atypical symptoms and these do not necessarily rule out ACS. However,

a combination of atypical symptoms improves identification of low-risk patients (Achar *et al.*, 2005).

The physical examination in patients with ACS is usually normal. Ominous physical findings include a new mitral regurgitation murmur, hypotension, pulmonary crackles, a new third heart sound (S3 gallop), and new jugular venous distention. Chest-wall tenderness reduces the likelihood of ACS (Goodacre *et al.*, 2002).

2.5 ECG Changes in ACS

The ECG provides information that assists in stratifying the patient's risk of having ACS, establishing the diagnosis, and determining the treatment strategy. Accuracy of diagnosis is enhanced when the ECG is obtained in a patient with ongoing chest pain (Achar *et al.*, 2005).

ECG changes of ST-segment elevation greater in lead III than in lead II with ST-segment depression of more than 1mm in lead I, lead aVL or both showed involvement of right coronary artery. In left circumflex coronary artery involvement, the findings in ECG will be ST segment elevation in lead I, aVL, V5 and V6 and ST-segment depression in lead V1, V2 and V3. ST-segment elevation in leads V1, V2 and V3 with right bundle branch block and Q wave or both showed that proximal left anterior descending artery is infarcted. In proximal left anterior descending artery involvement, ECG changes will be ST-segment elevation in leads V1, V2 and V3 with ST-segment depression of more than 1mm in leads II, III and aVF while in distal left anterior descending artery involvement, there will be changes of ST-segment elevation in leads V1, V2 and V3 with ST-segment depression of $\leq$ 1mm or ST-segment elevation in leads II, III and aVF (Zimetbaum and Josephson, 2003).

2.6 Biochemical Markers in ACS

Creatine kinase (CK) is an enzyme that is not only found in striated muscle of the heart but also found in striated muscle and tissues of the brain, kidney, lung, and gastrointestinal tract. It is widely available marker but has low sensitivity and specificity for cardiac damage. Because it also can be found in other organ, CK levels may be elevated in a number of noncardiac conditions, including trauma, seizures, renal insufficiency, hyperthermia, and hyperthyroidism (Karras and Kane, 2001). A serum CK level may be used as a screening test to determine the need for more specific testing. The serum CK level rises within three to eight hours after myocardial injury, peaks by 12 to 24 hours, and returns to baseline within three to four days. Although CK commonly was measured serially, at the time of hospital admission and six to 12 hours after admission, this marker largely has been replaced by cardiac troponins and creatine kinase – myocardial band (CK-MB). CK-MB is much more cardiac specific than CK alone, and is useful for the early diagnosis of acute myocardial infarction (Braunwald *et al.*, 2002).

CK-MB typically is detectable 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. The CK-MB mass assay is more sensitive than the CK-MB activity assay. Like the CK level, the peak CK-MB level does not predict infarct size; however, it can be used to detect early reinfarction. Serial CK-MB levels commonly are obtained at admission to the emergency department and are repeated in six to 12 hours, depending on the assay that is used (Braunwald *et al.*, 2002).

Troponins (T, I, C) are found in striated and cardiac muscle. Because the cardiac and skeletal muscle isoforms of troponin T and I differ, they are known as the “cardiac troponins.” They are the preferred markers for the diagnosis of myocardial injury. Troponin T and I generally have similar sensitivity and specificity for the detection of myocardial injury. Unlike troponin I levels, troponin T levels may be elevated in patients with renal disease,

polymyositis, or dermatomyositis. The cardiac troponins typically are measured at emergency department admission and repeated in six to 12 hours. Patients with a normal CK-MB level but elevated troponin levels are considered to have sustained minor myocardial damage or microinfarction, whereas patients with elevations of both CK-MB and troponins are considered to have had AMI. The cardiac troponins may remain elevated up to two weeks after symptom onset, which makes them useful as late markers of recent AMI (Braunwald *et al.*, 2002; Achar *et al.*, 2005).

The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction emphasized the use of troponins as critical markers of the presence of myocardial necrosis (Antman *et al.*, 2000). Although troponins are accurate in identifying myocardial necrosis, the latter is not always secondary to atherosclerotic coronary artery disease. Therefore, in establishing the diagnosis of NSTEMI, cardiac troponins should be used in conjunction with appropriate clinical features and electrocardiographic changes. Myocardial injury of diverse origins (e.g., myocarditis, trauma, or cardioversion) may cause necrosis and release of troponins. Although these may be considered instances of NSTEMI, they should be distinguished on clinical grounds from the more common form of NSTEMI secondary to coronary atherosclerosis (Braunwald *et al.*, 2002).

2.7 Risk Factors of ACS

2.7.1 Sociodemographic Characteristics

The Global Registry of Acute Coronary Events (GRACE) reported that the mean age of AMI patients in developing countries ranges from 55 to 65 years, which is lower than in the developed world (65 to 68 years) (Fox *et al.*, 2000; Abdallah *et al.*, 2006). The European Network for Acute Coronary Treatment (ENACT) study showed that the mean age of unstable angina was 65.2 years and myocardial infarction was 63.8 years and overall, 30% of patients from the study were female (Fox *et al.*, 2000). In young population, 5.8% patients were less than 45 years old and the youngest patient in the study was 22.8 years old as reported from the Thai ACS registry (Tungsubutra *et al.*, 2007). In Malaysia, from National Cardiovascular Disease Database (NCVD)-ACS Registry, the mean (standard deviation (SD)) age for all subjects was 59 (12) years which was significantly younger than that of GRACE and other ACS registries. And for STEMI, NSTEMI and UA patients, mean age were 56, 62 and 60 years respectively. Male to female ratio was 3:1. The highest incidence of ACS for men was in 50–60 year age group and for women in 70–80 years group. The proportion of Malay, Chinese, Indian and other races contributed 49%, 23%, 23% and 5% respectively (Ahmad *et al.*, 2011). CAD is the leading cause of mortality for both adult males and females alike worldwide. Although the initial manifestation of CAD is delayed in females by about ten years compared to males, there is not an abrupt increase in CAD mortality rates for females immediately following menopause but a progressive increase over subsequent years (Beltrame *et al.*, 2012).

Socioeconomic status (SES) indicators, including education, income and occupation, are associated with CAD risk factors, morbidity, and mortality. Patients with less education, lower income, and blue-collar occupations are associated with increased rates of CAD and increased risk of CAD mortality. Correspondingly, lower SES groups also have the least

favourable lifestyle characteristics, including obesity, smoking, high cholesterol, hypertension, and lack of physical activity. The British Heart Foundation (BHF) reports a clear gradient in CAD mortality across low to high SES group. The inequality is more striking in females than males, with the CAD death rate being five times higher in female blue-collar workers compared to females in professional occupations (Beltrame *et al.*, 2012).

2.7.2 Clinical Presentation

The symptoms of UA/NSTEMI may be indistinguishable from that of STEMI. Chest pain is the presenting symptom in most patients. Chest pain was the most frequent symptoms during hospital admission in young patients with 9 of 10 patients having chest pain (Schoenenberger *et al.*, 2011). Chest pain or discomfort is usually retrosternal, central or in the left chest and may radiate to the jaw or down the upper limb. It may be crushing, pressing or burning in nature and the severity of the pain is variable. A significant number of patients, especially women, diabetics and the elderly, presented with atypical symptoms. These include; dyspnoea without any history of chest pains, unexplained sweating, nausea and vomiting, syncope and presyncope, fatigue and epigastric discomfort. In patients with these presentation(s) and with a prior history of CAD, a family history of premature CVD, diabetes and other cardiovascular risk factors, the index of suspicion of ACS should be high. Prior history of diabetes and renal disease will influence management (CPG, 2011).

Dyspnea and sign of heart failure were less common in younger patients. The Killip classification is a system used in individuals with an ACS, for risk stratification. Patients were classified into four classes during physical examination. Patients in Class I demonstrated no evidence of heart failure. Patients in Class II had findings consistent with mild to moderate heart failure; patients in Class III demonstrated overt pulmonary edema and

patients in Class IV were in cardiogenic shock. Only few young patients (5.7%) presented with Killip class II or higher (Schoenenberger *et al.*, 2011). The proportion presenting presenting with heart failure (Killip class 3-4) increased markedly with age (Rosengren *et al.*, 2006). In NCVD-ACS, 76% of STEMI patients were in class I and II, 9% were in class III and IV (Ahmad *et al.*, 2011). Table 2.4 showed the clinical and haemodynamic subsets of AMI. The 30-day mortality was only 7% in Killip Class I and markedly increased to 70% in Killip Class IV (CPG, 2007a). Presence of left ventricular failure (hypotension, respiratory crackles or S3 gallop) and arrhythmias carry a poor prognosis. Carotid bruits or peripheral vascular disease indicates extensive atherosclerosis and a higher likelihood of concomitant CAD. Table 2.4 shows the clinical and haemodynamic subsets in AMI.

Table 2.5: Clinical and Haemodynamic Subsets in AMI. Adapted from (CPG, 2007a)

Killip's Classification	**Clinical Features**	**Approximate proportion of patients with AMI (%)**	**30 day - Mortality (%)**
I	No signs of LV failure	71.0	7
II	S3 gallop, bibasal crackles	23.0	20
III	Acute pulmonary oedema	3.7	39
IV	Cardiogenic shock	2.3	70

For type of ACS, younger patients frequently presented with STEMI (73.1%) (Schoenenberger *et al.*, 2011). Similarly in Thai registry, younger patients were likely to have an STEMI, 67.3% (Tungsubutra *et al.*, 2007).

2.7.3 Smoking

According to the INTERHEART study, smoking was the most important risk factor for AMI globally (Abdallah *et al.*, 2006). From ‘‘The Atlas of Heart Disease and Stroke” by WHO, the prevalence of smoking among ACS patients were 12% and it was one of the contribution of the classical CAD risk factors to the overall burden of disease in developing countries (WHO, 2012). While in ENACT study showed smoking among UA was 35% while among MI was 46% (Fox *et al.*, 2000). The prevalence of smoking has been shown to be increasingly prevalence in young adults and adolescents reaching up to 9% (Egred *et al.*, 2005). Smoking was the most prevalent cardiovascular risk factors in young patients with 3 of 4 young patients being current smoker (Schoenenberger *et al.*, 2011). This was similar finding in Thailand when 66% of patients age less than 45 years were smokers (Tungsubutra *et al.*, 2007). Considering smoking habit, 33% of entire cohort and 50% of STEMI population were active smokers and 24% of entire cohort was ex-smokers were found from NCVD-ACS Registry (Ahmad *et al.*, 2011).

2.7.4 Dyslipidaemia

The INTERHEART Study revealed that hypercholesterolemia (high ApoB/ApoA levels) is a significant risk factor for AMI in Southeast Asia (Yusuf *et al.*, 2004). The ENACT study showed that dyslipidaemia among UA was 31% while among MI was 20% (Fox *et al.*, 2000). There were 55.9% subjects in the NCVD-ACS registry diagnosed with dyslipidaemia, while 43.6% from GRACE registry (Ahmad *et al.*, 2011).

2.7.5 Diabetes mellitus

The ENACT study showed diabetes mellitus among UA was 23% while among MI was 19% (Fox *et al.,* 2000). The Malaysia NCVD-ACS registry showed that 55% of ACS had underlying diabetes mellitus (Ahmad *et al.,* 2011).

2.7.6 Hypertension

The ENACT study showed that hypertension among UA was 51% while in MI was 41% (Fox *et al.,* 2000). Hypertension was the most prevalent cardiovascular risk factor, present in 72.6% subjects in the Malaysia NCVD-ACS registry, higher as compared to 57.8% from the GRACE study (Ahmad *et al.,* 2011).

2.7.7 Obesity

In other hand, obesity also has emerged as a major risk factor for CAD in the recent years. In the developing world, it was estimated that one third of the population were obese. The risk of developing CAD in obese patients was estimated to be about three times more than in those with normal body weight (Abdallah *et al.,* 2006). Obesity is a growing concern among young adults and children and it has increased by threefold in the UK in the past two decades. Insulin resistance, which by itself is a marker for CHD, has been found among 24% of school children in USA. Metabolic syndrome and insulin resistance were found in two thirds of young people with MI (Egred *et al.,* 2005)

2.7.8 Family History of CAD

Younger patients have a higher prevalence of a positive family history. In the Thai Registry, 23.6% of patients had family history of coronary (Tungsubutra *et al.*, 2007) while in the Malaysia NCVD-ACS registry, 19.7% had a positive family history (Ahmad *et al.*, 2011).

2.8 Management of ACS

2.8.1 Pharmacology

The primary modality for opening up occluded arteries in AMI remains thrombolysis in developing as well as developed countries. Many developing countries are not able to provide enough cardiac catheterization laboratories to support programs for primary angioplasty as a primary modality of treatment for AMI. This is the reason for the use of thrombolytic therapy as a mainstay of treatment for STEMI in these countries and it is higher than what is reported in developed countries (Abdallah *et al.*, 2006).

In the ENACT study, a high proportion of AMI patients received thrombolytic therapy; 51% by initial diagnosis (upon arrival in hospital) and 43% by final diagnosis (during admission with complete investigations). Most patients received aspirin (96%), nitrates (80%) and some form of heparin (90%). There was wide variation in the use of calcium antagonists, beta-blockers, low-molecular–weight heparin and glycoprotein IIb/ III1 inhibitors. Overall use of low molecular weight heparin was 34% in AMI. (Fox *et al.*, 2000).

In Malaysia, 70% received fibrinolytic therapy among STEMI patients. Reasons for not receiving fibrinolytic therapy included primary percutaneous coronary intervention (PCI) in 8%, presentation after more than 12 hours in 13%, contraindications to streptokinase in 5%, the remaining 3% included missing data and refusal to treatment. Streptokinase was

solely used as fibrinolytic agent. Aspirin and statins were prescribed in more than 90%, beta blocker in 66%, clopidogrel in 59%, ACE-I in 58% and LMWH in 51% and GP receptor inhibitor in 4% of all patients. Prescription rate for LMWH in NSTEMI and UA patients were 68% and 64% respectively (Ahmad *et al.*, 2011).

Patients less than 45 years old were likely to received aspirin, thienopyridine, GP IIb/ IIIa antagonist, beta blocker and statins, whereas they were less likely to received nitrates and calcium channel blocker. Young patients with STEMI tended to received fibrinolytic therapy (Tungsubutra *et al.*, 2007). Younger patients seem to tolerate the thrombolytic agents better with a good ST segment resolution in the ECG (Egred *et al.*, 2005)

2.8.2 Surgical Intervention

From the ENACT study, 41% of UA patients underwent coronary angiography and 23% of UA patients underwent percutaneous coronary intervention (PCI). For AMI patients, 33% of patients underwent angiography and 23% underwent PCI (Fox *et al.*, 2000).

In Malaysia, based on NCVD-ACS registry, coronary angiography was performed in 35% of all patients during the hospital admission and out of those who had angiography, 46% had PCI. Among those who had PCI, 56% belonged to STEMI, 30% belonged to NSTEMI and 14% belonged to UA group. Coronary Artery Bypass Graft Surgery (CABG) was performed only in 0.02%. Majority of NSTEMI and UA patients were treated medically while PCI was done in 14% and 9% respectively (Ahmad *et al.*, 2011).

The proportion of patients undergoing a coronary angiography decreased with age (Rosengren *et al.*, 2006). From the Thai registry, coronary angiography and PCI were performed more frequently in patients aged less than 45 years old. Young patients with STEMI tended to received primary PCI (Tungsubutra *et al.*, 2007). PCI in older patients were

associated with procedural complications such as myocardial infarction rate of 5%, urgent coronary artery bypass grafting (CABG) of 1% and mortality of 1%. The success rate of percutaneous procedures was higher in younger patients approaching 93%. CABG carries a better success rate in younger patients. Survival rate were found to be 92% at five years and 86% in 10 years respectively in patients less than 40 years, compared with 75% and 58% for patients over 65 years old (Egred *et al.*, 2005).

Young patients showed less diffuse atherosclerotic lesions as compared to patients of the older group: in young patients, 75% showed one-vessel CAD and 23.2% two- or three-vessel CAD. The proportion of young patients with normal coronary arteries was 1.8%. (Schoenenberger *et al.*, 2011).

2.9 Complications of ACS

In-hospital complications of AMI patients has steadily decline over the last several decade to less than 10% (Rogers *et al.*, 2000). This remarkable achievement is due to the development of rapid pharmacologic and mechanical reperfusion and adjunctive pharmacotherapy. The development of rapid cardiac referral networks and coronary care units also contributed to the decline. Despite of medical advances, AMI remains a life threatening illness and physician should always be aware of possible complications. Likewise, newer therapies for ACS such as PCI have come increasingly complex and inherently carry their own risk of complications (Pattanayak and Gelfand, 2009).

IHD was the predominant cause of congestive heart failure (CHF), accounting for 49.5% (Chong *et al.*, 2003). Patients aged less than 45 years old had the lowest incidence of heart failure as the incidence increased with increasing age (Tungsubutra *et al.*, 2007). Heart failure increasingly with age in which 10.2% in men and 11.3% in women of young patients

(Rosengren *et al.*, 2006). Pulmonary oedema was reported about 2.3% in men and 4.2% in women of young patients with ACS (Rosengren *et al.*, 2006).

Bradycardia and heart block following an ACS typically occur either because of exaggerated vagal tone, or due to the ischemia/infarction of the actual conduction tissue. Sinus bradycardia and varying degrees of AV block are often seen in inferior and posterior MI due to increased vagal tone. On the other hand, in anterior MI conduction disturbances are caused by necrosis of the bundle of His and its branches. Sinus bradycardia and AV block may be observed in the early period of an inferior myocardial infarction. These vagally mediated bradycardias are often transient, and initially tend to respond to anticholinergic action of atropine. In the 24 to 72 hours following symptom onset, AV conduction delay may be caused by tissue edema (in addition to vagal tone) and is therefore less responsive to atropine. Second-degree heart block can occur either at the level of the AV node or below the node at the level of the His bundle (Pattanayak and Gelfand, 2009).

Atrial fibrillation is a common arrhythmia during and immediately following STEMI, occurring about 5–10% of the time. This is because many of the risk factors for STEMI, such as hypertension, obesity, and diabetes, are also the substrate for atrial fibrillation. Furthermore, the high catecholamine state and elevation of left atrial pressure in STEMI act as triggers for atrial fibrillation. An important consideration in atrial fibrillation is that rapid heart rates can increase myocardial ischemia and decrease cardiac output, thereby making early cardioversion a possible option (Pattanayak and Gelfand, 2009). Atrial fibrillation occurred in few of the youngest patients, 2.7% (Rosengren *et al.*, 2006).

Ventricular tachyarrhythmias occurring during and early following acute MI are the leading cause of death in ACS prior to hospital presentation. Sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) complicate 10% of STEMI and 2.5% of NSTEMI presentation, with the majority occurring in the first 48 hours (Pattanayak and

Gelfand, 2009). Patients with sustained VT are frequently symptomatic as consequence of both from hemodynamic effects of AV dissociation and from inefficient left ventricular (LV) contraction, and therefore immediate therapy with synchronized cardioversion is required. Patients with well-tolerated sustained VT may be treated pharmacologically. Many deaths occur in the very first hours after STEMI due to ventricular fibrillation (VF) (Van de Werf *et al.*, 2008).

Cardiogenic shock due to pump failure remains the most common cause of in-hospital complications with patients diagnosed with ACS. Data from the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO)-IIb trial suggest that cardiogenic shock complicates approximately 4% of acute STEMI and 2.5% of NSTEMI cases (Holmes Jr *et al.*, 1999). Overall about 2% of ACS patients are in shock upon hospital presentation. Despite primary reperfusion and adjunctive medical therapy, cardiogenic shock can develop in some patients in the hospital. As ACS therapy advanced in the last 10 years, the rate of in-hospital cardiogenic shock fell by approximately 75% (from 10.6% to 2.7%) (Jeger *et al.*, 2008). The etiology of shock usually progressive infarction of the LV. The cardiogenic shock was increasingly with age in which 3% of young men and 4.7% of young women patients had shock during their hospital admission (Rosengren *et al.*, 2006).

Recurrent ischaemia and reinfarction increased only slightly with age in men and not all in women. In young patients, men had 10.6% and women had 13.6% of recurrent ischaemia and for reinfarction, men had 1.3% and women had 2.5% (Rosengren *et al.*, 2006).

In-hospital mortality was lower in the younger group, 7.4% compared to elder group of more than 54 years old, 14.1% (Tungsubutra *et al.*, 2007). Outcome was excellent in young patients, only 1.5% died during the hospitalization in Switzerland (Schoenenberger *et al.*, 2011). Overall, the in-hospital death increased from 1% among patients less than 55 years to 17% in patients more than 85 years (Rosengren *et al.*, 2006). By NCVD-ACS registry, the