UTILIZATION OF EVIDENCE-BASED THERAPY FOR THE SECONDARY PREVENTION OF CORONARY ARTERY DISEASE: PREDICTORS AND IMPACT OF PHARMACIST-INITIATED INTERVENTIONS

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by

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DEDICATION

To the one whose feet Paradise rests on…..

My beloved mother …. For her prayers, unflagging love, and tremendous sacrifices which came with many difficulties and pains. She is always a constant source of inspiration and motivation in my life. I learned from her strength how to face life strappingly. Her support and love have pulled me throughout my difficult times.

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Yaman Walid Kassab

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My guidance depends totally on GOD; I have put my trust in Him. To Him I have totally submitted. (Huud – 88)

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And the last our praise is Alhamdulillah to the lord of the worlds

Yaman Walid Kassab

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4- **Kassab Y. W.**, Hassan Y. , Abd Aziz N. , AbdulRazzaq H. A. , AlKaf M. S., Ismail O. Assessment of the Secondary Prevention for Patients with Acute Coronary Syndrome in Penang General Hospital, Malaysia. *Proceeding of the 11th Asian Conference on Clinical Pharmacy ACCP*, June 24-27, 2011 Manila, Philippine.

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme Inhibitor
ACEP	American College of Emergency Physicians
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
AST	Aspartate Transaminase
BMI	Body Mass Index
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCU	Coronary Care Units
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
COPD	Chronic Obstructive Pulmonary Disease
CPGs	Clinical Practice Guidelines
CRC	Clinical Research Center
CRW	Cardiology Rehabilitation Ward
CVD	Cardiovascular Disease
DALYs	Disability-Adjusted Life Years
DAT	Dual Antiplatelet Therapy
DES	Drug-Eluting Stent
DM	Diabetes Mellitus

EBM	Evidence Based Medicine
EBT	Evidence Based Therapy
ECG	Electrocardiogram
GFR	Glomerular Filtration Rate
GP	Glycoprotein
HbA1c	Glycosylated Hemoglobin A1c
HDL	High-Density Lipoprotein
HPP	Hospital Pulau Penang
IHD	Ischemic Heart Disease
LBBB	Left-Bundle Branch Block
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LVD	Left Ventricular Disease
LVEF	Left Ventricular Ejection fraction
MI	Myocardial Infarction
MMAS	Morisky Medication Adherence Scale
MREC	Medical Research and Ethics Committee
NACB	National Academy of Clinical Biochemistry
NHAM	National Heart Association of Malaysia
NO	Nitrous Oxide
NSTEMI	Non ST segment Elevation Myocardial Infarction
NYHA	New York Heart Association
OMPN	Outpatient Medical Progress Notes
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
RAAS	Renin Angiotensin Aldosterone System
RCTs	Randomized Control Trials

RR	Relative Risk
RRR	Relative Risk Reduction
STEMI	ST segment Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TLC	Therapeutic Lifestyle Changes
UA	Unstable Angina
WHO	World Health Organization

UTILISASI PENGGUNAAN UBAT-UBATAN BERASASKAN BUKTI UNTUK PENCEGAHAN PENGULANGAN PENYAKIT ARTERI KORONARI: PERAMAL DAN IMPAK INTERVENSI OLEH AHLI FARMASI

ABSTRAK

Sejak beberapa dekad yang lalu, pencegahan pengulangan telah memainkan peranan yang semakin penting dalam pengurusan penyakit arteri koronari. Antara ubat-ubatan untuk pencegahan pengulangan jangka panjang adalah antiplatelet, penghalang-β, penghalang enzim angiotensin (ACEI) dan statin, yang telah terbukti amat berkesan dalam mengurangkan morbiditi dan mortaliti dalam kalangan pesakit koronari. Garis panduan perubatan di Malaysia menekankan penggunaan ubat-ubatan berasaskan bukti (evidence-based medicine, EBM) secara berterusan untuk rawatan jangka panjang selepas kejadian koronari akut (pencegahan pengulangan). Walaupun cadangan garis panduan telah diwujudkan, namun kajian melaporkan praktis EBM yang rendah pada pesakit sindrom koronari akut (acute coronary syndrome, ACS). Objektif utama kajian ini adalah untuk: (1) menentukan praktis EBM selepas kejadian koronari akut dan penggunaan berterusan dalam penjagaan pesakit luar, (2) menilai kesan intervensi yang dimulakan oleh ahli farmasi untuk meningkatkan penggunaan ubat pencegahan pengulangan semasa discaj (3) menilai kepatuhan pesakit terhadap EBM pada purata dua tahun selepas discaj, dan (4) menyiasat korelasi antara ketidakpatuhan pesakit dan peramal lain. Kajian ini menggunakan metodologi perbandingan intervensi dalam tiga fasa: pra-intervensi, intervensi, dan peringkat susulan. Dalam fasa pr-intervensi, audit retrospektif dijalankan dan suatu sampel rawak daripada rekod perubatan pesakit ACS yang dimasukkan ke Hospital Pulau

Pinang dalam tempoh Januari 2008 hingga Januari 2010 dipilih sebagai kumpulan kawalan. Fasa intervensi dijalankan dari Mac hingga September 2010. Dua orang ahli farmasi hospital, yang juga merupakan ahli dalam pasukan kardiologi memberikan perkhidmatan "ulasan ubat farmasi kolaboratif". Perkhidmatan yang disediakan sebaik mungkin melaksanakan semua intervensi dalam usaha meningkatkan kepatuhan kepada garis panduan bagi ACS. Ia terdiri daripada audit dan maklum balas. pengingat garis panduan diletakkan dalam rekod pesakit dan perbincangan dengan doktor pada setiap rondaan perubatan harian. Semasa fasa susulan, semua pesakit dalam kumpulan intervensi ditentukan dalam tempoh dua tahun untuk menyiasat preskripsi jangka panjang EBM dan kepatuhan pesakit terhadap terapi mereka. Sejumlah 380 orang pesakit telah dipilih secara rawak dengan 190 pesakit dalam setiap kumpulan. Pesakit dalam kedua-dua kumpulan dirawat oleh pasukan doktor yang sama dan dipadankan. Audit yang dijalankan dalam fasa pertama menunjukkan penggunaan EBM yang rendah. Kadar preskripsi discaj bagi gabungan EBM hanya 42.6%. Semasa fasa intervensi, sebanyak 72 intervensi telah dibuat oleh ahli farmasi, kes intervensi memulakan ubat adalah paling kerap (59.7%), inin diikuti dengan cadangan untuk menukar kepada ubat yang lain (23.6%) dan pengoptimuman dos ubat (16.6%). Daripada cadangan yang diutarakan, 65.3% diterima, 6.9% diubah suai, dan 27.8% ditolak. Majoriti intervensi yang diterima adalah dengan penghalang-β (38.46%) diikuti dengan ACEIs (28.8%) dan statin (21.15%). Intervensi secara signifikannya meningkatkan kadar preskripsi penghalang-β (daripada 75.8% kepada 84.2%), ACEIs (daripada 65.3% kepada 74.7%), dan statin (daripada 91.6% kepada 98.4%). Di samping itu, kemungkinan discaj dengan regimen daripada 4 kelas ubat-ubatan pencegahan pengulangan dalam kumpulan intervensi adalah 2.2 kali lebih tinggi daripada kumpulan kawalan. Berdasarkan kepatuhan ubat, dilaporkan bahawa majoriti

pesakit mempunyai kepatuhan sama ada sederhana atau rendah sepanjang tempoh susulan dan hanya sebahagian kecil mempunyai kepatuhan yang tinggi. Tambahan pula, terdapat penurunan yang signifikan dalam skor "Morisky Medication Adherence Scale" (MMAS) merentasi tempoh tiga kali susulan berturut-turut. Pesakit lelaki dilaporkan mempunyai kepatuhan yang lebih tinggi berbanding dengan pesakit perempuan. Pesakit yang bekerja dilaporkan mempunyai kepatuhan lebih tinggi daripada yang tidak bekerja. Pesakit STEMI dilaporkan mempunyai kepatuhan tertinggi, diikuti oleh pesakit NSTEMI dan UA. Pesakit dengan pelbagai ko-morbiditi (≥ 3) atau pelbagai ubat-ubatan (≥ 5) dilaporkan mempunyai kepatuhan yang sangat rendah. Kesimpulannya, kajian ini menunjukkan bahawa intervensi yang dimulakan ahli farmasi secara signifikan meningkatkan kadar preskripsi discaj untuk terapi pencegahan pengulangan ACS. Kami juga merumuskan bahawa terdapat masalah ketidakpatuhan kepada ubat-ubatan dalam kalangan pesakit ACS di Malaysia. Tambahan pula, kajian ini menunjukkan bahawa pesakit yang terdiri daripada warga tua, tidak bekerja, pesakit dengan ubat-ubatan dan pelbagai komorbiditi adalah golongan yang paling memerlukan perhatian doktor untuk meningkatkan kepatuhan mereka terhadap regimen ubat.

UTILIZATION OF EVIDENCE-BASED THERAPY FOR THE SECONDARY PREVENTION OF CORONARY ARTERY DISEASE: PREDICTORS AND IMPACT OF PHARMACIST-INITIATED INTERVENTIONS

ABSTRACT

Over the past decades, secondary prevention has played a more and more important role in coronary artery disease management. Among the medications for long-term secondary prevention, antiplatelets, β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and statins were proven to be highly effective in reducing morbidity and mortality in coronary patients. Malaysian guidelines emphasize the continuous use of these evidence-based medications (EBMs) for long-term treatment after an acute coronary event. Despite the guideline recommendations, studies have reported an underuse of these EBMs in ACS patients. The main objectives of the current study were to: (1) quantify the prescription of EBMs at discharge following an acute coronary event and ongoing use in ambulatory care, (2) evaluate the impact of pharmacist-initiated interventions on improving the prescribing trend of secondary preventive therapies upon discharge, (3) evaluate patients' adherence to EBMs at an average of two years after discharge, and (4) investigate the relationship between patients' non-adherence and various predictors. This study adopted an interventional comparative methodology with three phases: pre-intervention, intervention, and follow-up phases. In the pre-intervention phase, a retrospective audit was conducted and a random sample of medical records pertaining to ACS patients admitted to Hospital Pulau Pinang during the period from January 2008 to January 2010 was chosen as the control group. The intervention phase was carried out from March to

September 2010. Two hospital pharmacists who were already apart of the cardiology team provided the "collaborative pharmacy medication review" service. The service implemented all possible interventions that might improve compliance with Malaysian guidelines for ACS. It consisted of audit and feedback, guideline reminders placed in patients' records, and discussion with every single prescriber during daily medical rounds. During the follow-up phase, all patients in the intervention group were followed up over a two year period to investigate the long term prescribing of EBMs as well as long term patients' adherence to their therapy. A total of 380 patients were randomly selected with 190 patients in each group. Patients in both groups were treated by the same team of physicians and matched.

The audit conducted in the first phase showed substantial underuse of these EBMs. The discharge prescription rate of combined EBMs was only 42.6%. During intervention phase, a total of 72 interventions were made by the pharmacists, of which drug initiation was most common (59.7%) followed by recommendations to change to another medication (23.6%) and optimization of medication dosing (16.6%). The prescribers accepted 65.3% of the recommendations as suggested and 6.9% with some modification and rejected 27.8% of the recommendations. Majority of accepted interventions were with β-blockers (38.46%) followed by those with ACEIs (28.8%) and statins (21.15%). The interventions significantly increase the prescription rates of β-blockers (from 75.8% to 84.2%), ACE-Is (from 65.3% to 74.7%), as well as statins (from 91.6% to 98.4%). In addition, the odds of being discharged on a regimen of 4 classes of secondary preventive medications in the intervention group were 2.2 times higher than the control group. Regarding medication adherence, majority of patients reported either medium or low adherence across the follow-up period with only small portion reported high adherence. Furthermore, there was a significant decrease in

MMAS scores across the three consecutive time periods. Male patients reported higher adherence than females. Employed patients reported higher adherence than unemployed. STEMI patients reported the highest adherent behavior, followed by NSTEMI and UA patients. Patients with multiple co-morbidities (≥ 3) or those who were prescribed multiple medications (≥ 5) reported significantly poorer adherence.

In conclusion this study has shown that pharmacist-initiated interventions can significantly increase the discharge prescription rates of ACS secondary preventive therapies. We also concluded that there is a problem of non-adherence to medications among patients with ACS in Malaysia. Furthermore, this study demonstrated that elderly, unemployed, patients with multiple medications and comorbidities were most in need for physicians' attention to improve their adherence to medication regimens.

CHAPTER 1

INTRODUCTION

1.1 Coronary Artery Disease: General Background

Cardiovascular disease (CVD) is recognized as a major global health problem. It affects every aspect of a patient's life, including quality of life, employment, and even causing premature death (Mathers & Loncar, 2006).

The term 'CVD' includes a wide variety of disorders, such as diseases of the heart muscle, the vascular system supplying the heart, the brain, and other vital organs. Although the term can include any disease that influences the cardiovascular system, in practice it usually refers to those involving atherosclerosis.

1.1.1 Global Disease Burden

CVD is the single most common cause of mortality worldwide and is expected to remain so for the next 20 years (Mathers & Loncar, 2006). The World Health Organization (WHO) estimates that 17.3 million people died from CVD in 2008, accounting for 30% of all global deaths, and projects that this number will rise to 23.6 million by 2030 (WHO, 2011).

Within CVD, coronary artery disease (CAD) is the most prevalent cardiac disorder. Due to its growing incidence across the world, CAD is considered an epidemic (WHO, 2009). It is estimated that 7.2 million people die from CAD annually, and this number is projected to increase to 11.1 million by 2020. Further, according to

the Global Burden of Disease estimates, CVD is responsible for 151 billion disability-adjusted life years (DALYs), representing 10% of the global disease burden, of which 62 billion is due to CAD (WHO, 2011).

1.1.2 Coronary Artery Disease in Malaysia

Malaysia is a multi-ethnic country with a population consisting of Malays, Chinese, Indians, and several other ethnicities. In 2010, the population of Malaysia was estimated at 28.3 million (Department of Statistics Malaysia, 2010).

Under the Ninth Malaysia Plan, CVD was documented as one of the top-eight diseases for priority research, as it recognized as becoming a major national health problem. Based on records of government hospital admissions and deaths, CAD has been the leading cause of admission and non-accidental death for the last 10 years (MOH-Malaysia, 2008).

In 2006, there were a total of 31,186 admissions to the 73 coronary care units in Malaysia, of which 12,534 admissions were due to acute coronary syndrome (ACS), a manifestation of CAD. The incidence of ACS admission in 2006 was therefore 47.1 per 100,000 population. Assuming half of all CAD patients first present with ACS and only half are admitted to the coronary care unit, with 1/3 dying before reaching hospital, a rough estimate of the incidence of CAD in Malaysia is 141 per 100,000 population (Wan Ahmad et al., 2011).

In 2004, a study on disease burden in Malaysia showed that CAD is the leading cause (9.8%) of disability-adjusted life years, accounting for 63% in men and 64% in women (WHO-Malaysia, 2009).

Further, Health Facts 2009 report showed that the leading causes of death in Ministry of Health hospitals were heart diseases and pulmonary circulation diseases (16.5%) (MOH-Malaysia, 2010). Additionally, the third-quarter 2010 Penang Statistical Report showed that CAD is the second main cause of mortality in Penang government hospitals, with 400 (14.8%) deaths attributed to this cause in 2009 (SERI, 2010).

1.2 Acute Coronary Syndrome (ACS)

1.2.1 Definition and Pathophysiology of ACS

The pathogenesis that underlies most clinical manifestations of CAD is now known to be a complex inflammatory process called coronary atherosclerosis (Libby & Theroux, 2005). This process is slow and insidious and usually starts early in life, although often not manifesting clinically until the age of 40 and beyond. The earliest and key event in the development of atherosclerosis is endothelial dysfunction (Sitia et al., 2010).

A number of factors, mechanical shear stresses, biochemical abnormalities, immunological factors, inflammation, age, male gender, obesity, and genetic alteration, directly contribute to the development and progression of endothelial "injury" or dysfunction and atherosclerosis (Falk, 2006).

The vascular endothelium, a selective lipoprotein-permeable barrier that separates the blood from vascular smooth muscle of the artery wall, is capable of a wide range of metabolic functions. It regulates anti-inflammatory, mitogenic, and contractile activities of the vessel wall, as well as the hemostatic process within the vessel lumen. Furthermore, the endothelium acts as a protective surface for the artery

wall, stimulates vascular smooth muscle relaxation, and inhibits thrombogenesis and atherosclerotic plaque formation (Bonetti, Lerman, & Lerman, 2003).

Impaired endothelial function increases permeability of the endothelium to low-density lipoprotein cholesterol (LDL-C) and inflammatory cells, and hence promotes their migration and infiltration in the sub-intimal vessel wall. This may lead to formation of fatty streaks in the coronary arteries and eventually to atherosclerotic plaques (Libby, 2001). Atheromatous plaques are mainly composed of: (1) connective tissue extracellular matrix, including collagen, proteoglycans, and fibronectin elastic fibers; (2) lipids, like crystalline cholesterol, cholesteryl esters, and phospholipids; (3) inflammatory cells such as monocyte-derived macrophages, T-lymphocytes; (4) smooth muscle cells; (5) thrombotic material with platelets and fibrin deposition; and (6) calcium deposits (Fuster, Moreno, Fayad, Corti, & Badimon, 2005).

Coronary plaques are constantly stressed by a variety of biochemical, mechanical and hemodynamic forces that may precipitate or "trigger" disruption or erosion of vulnerable plaques. Following plaque disruption, thrombogenic contents of the plaque are exposed to blood elements and trigger platelet aggregation, activation of the coagulation system, and ultimately thrombus formation (a clot) on the surface of the ruptured plaque. Such rapid coronary thrombosis may result in complete or partial occlusion, leading to clinical manifestation of ACS (Fuster et al., 2005).

ACS refers to a range of severe cardiac presentations which differ in degree, duration, and acuteness of coronary occlusion, and includes unstable angina (UA), non-ST-segment-elevation myocardial infarction (NSTEMI), and ST-segment-elevation myocardial infarction (STEMI).

1.2.2 Spectrum and Clinical Presentation of ACS

Although the term ACS is used collectively to describe UA, NSTEMI, and STEMI, the pathophysiology and clinical presentations of each differ, as do their treatments. The degree of coronary artery occlusion significantly correlates with presenting symptoms and with variations in electrocardiogram (ECG) findings and cardiac marker values. However, midline anterior chest discomfort continues to be the primary symptom of ACS.

UA and NSTEMI are considered closely related conditions in which the coronary artery stenosis is non-occlusive. The subgroup of UA / NSTEMI, which is also known as non-ST-segment-elevation (non-STE) ACS, defines the phase of symptomatic CAD which occurs after stable angina. Angina is considered unstable if it occurs for the first time, at rest, or accelerates in frequency or severity.

NSTEMI presentation is similar to that of UA, but differs in that ischemia is severe enough to cause sufficient myocardial damage, resulting in the release of detectable quantities of biochemical markers in the bloodstream from necrotic myocytes (Anderson et al., 2007; Bassand et al., 2007).

Chest pain associated with NSTEMI tends to be more persistent and more severe than that associated with UA. In both conditions, the frequency and intensity of pain may increase if not relieved by rest, nitroglycerin, or both, and may last longer than 15 minutes. Chest discomfort may radiate to the shoulder, down the left arm, to the back, or to the jaw. Other symptoms that may accompany chest discomfort include nausea, vomiting, diaphoresis, and shortness of breath. (Comeau, Jensen, & Burton, 2006).

In STEMI, which represents 30–45% of all ACS cases, there is myocardial necrosis following acute total coronary occlusion (Afolabi, Novaro, Pinski, Fromkin, & Bush, 2007). STEMI presentation is similar to that of UA/NSTEMI, but differs with persistent abnormalities on ECG (STE) and positive biomarkers such as troponin and creatine kinase–myocardial band (CK-MB) (Lloyd-Jones et al., 2010).

Many patients with myocardial infarction (MI) present with atypical symptoms, such as dyspnea, nausea, diaphoresis, syncope, or malaise. When these "atypical symptoms" are present without chest pain, they are known as "angina equivalents" (Anderson et al., 2011). Other patients may show no symptoms of MI (silent ischemia). A large, prospective, observational study of over 400,000 patients with confirmed MI showed that 33% did not have chest pain on presentation in hospital. Patients without pain tended to be older, diabetic, women, and those with prior heart failure (Canto et al., 2000). In another smaller study, only 53% of patients with MI had a chief complaint of chest pain. Shortness of breath was the complaint in 17%, cardiac arrest in 7%, and dizziness/weakness/syncope in 4% (Gupta, Tabas, & Kohn, 2002). Unfortunately, establishing diagnosis is more difficult in patients with atypical presentation, resulting in poorer outcomes. In addition, these patients are less likely to receive recommended therapies known to reduce the risk of mortality (i.e. aspirin, beta-blockers, heparin, thrombolysis, or primary angioplasty) (Dorsch et al., 2001). The second National Registry of Myocardial Infarction (NRMI-2) study in the United States showed that MI patients without chest pain had higher in-hospital mortality compared to those with chest pain (23% vs. 9%, respectively) (Canto et al., 2000).

1.2.3 Risk Factors for CAD

CAD is multifactorial in origin, giving rise to the risk-factor concept. Numerous epidemiological studies across the world have identified a large number of risk factors for CAD (Grundy et al., 2002). These risk factors can be classified into three broad categories: independent, predisposing, and conditional.

1.2.3.1 Independent Risk Factors

The presence of independent risk factors is of major importance in determining CAD occurrence and severity. The Framingham Heart Study showed that these risk factors are additive in their predictive value when combined. Accordingly, an individual's global risk for CAD can be estimated by summing the risk imparted by each of the independent risk factors. These include the following:

1.2.3.1 (a) Cigarette Smoking

The Framingham Heart Study was among the first to evaluate the relationship between cigarette smoking and CAD. It examined the level of association separately in men and women, the effect of smoking duration, and the impact of smoking cessation. This study identified cigarette smoking as one of the leading contributors to CAD (Carl, 1989).

The relationship between smoking and CAD risk is dose dependent and is observed among both men and women. Risk for CAD is increased by about 1.8 times in active smokers and by about 1.3 times in those exposed to passive or environmental smoke. In addition, heavy smoking (> 40 cigarettes per day) was found to almost double cardiovascular and overall mortality in those aged less than 65 years. Beyond

the age of 65, neither significant nor substantial gradients of risk could be demonstrated in either sex for cardiovascular morbidity (William, 1981).

The direct harmful effects of cigarette smoke to patients with angina include (1) rise in blood pressure and heart rate due to nicotine, which increases myocardial oxygen consumption, (2) impairment in oxygen delivery to the heart as a result of carboxyhemoglobin generation from carbon monoxide inhalation in smoke, (3) the negative inotropic effect of carboxyhemoglobin, (4) increased platelet stickiness and aggregation caused by carboxyhemoglobin, resulting in thrombotic tendencies, (5) lowered threshold for ventricular fibrillation during episodes of ischemia, owing to carboxyhemoglobin, and (6) impaired endothelial function (Freund, Belanger, D'Agostino, & Kannel, 1993; Ockene & Miller, 1997; William, 1981).

Observational studies estimate that quitting smoking decreases the risk of all-cause mortality among patients with CAD by almost 50%. Furthermore, approximately 40% of the increased risk is removed within 5 years of quitting, even though it takes several more years of non-smoking to reach the “normal” risk level for heart disease of those who have never smoked (Critchley & Capewell, 2003; O'Donnell & Elosua, 2008).

1.2.3.1 (b) Hypertension

The relationship between blood pressure and CAD incidence is examined in many observational cohort studies. The Global Burden of Disease study estimates that about 47% of all CAD is attributable to elevated blood pressure (Lawes, Hoorn, & Rodgers, 2008). In addition, epidemiological analyses show that higher risk for cardiovascular events and mortality begins at a blood pressure >115/75 mm Hg in the

general population, and doubles for every subsequent 20-mm Hg systolic or 10-mm Hg diastolic increase (Buse et al., 2007; Rosendorff et al., 2007).

1.2.3.1 (c) Hypercholesterolemia

Hypercholesterolemia has long been recognized as a significant risk factor for CAD. The Framingham Heart Study, the Multiple Risk Factor Intervention Trial (MRFIT), and the Lipid Research Clinics Trial found a direct relation between levels of LDL-C (or total cholesterol) and the rate of new-onset CAD in both men and women who were initially free of CAD. The same relationship holds for recurrent coronary events in people with established CAD (Castelli, 1988; Gotto, 1997b; Rifkind, 1984). Furthermore, any LDL-C above 100 mg/dL appeared to be atherogenic (Grundy et al., 2002).

Strong epidemiological evidence implies benefit from lowering LDL-C. A recent meta-analysis of 14 randomised trials of statins with 90,056 participants showed that lowering LDL-C by 1 mmol/L reduces CVD events by 21% and total mortality by 12%, regardless of baseline risk (Cholesterol Treatment Trialists' Collaborators, 2005).

However, epidemiological studies have found high-density lipoprotein cholesterol (HDL-C) to be an independent predictor of cardiovascular risk. High levels of HDL-C are considered protective, whereas lower levels are associated with increased risk. Epidemiological data signify that a 1% reduction in HDL-C is associated with a 2–3% increase in CAD risk (Cooper et al., 2008; Nam, Kannel, & Dagostino, 2006).

1.2.3.1 (d) Diabetes

Diabetes is considered a powerful contributing factor in all forms of CVD. Epidemiological studies show that higher risk for cardiovascular events begins at glycosylated hemoglobin A1c (HbA1c) above 6.2%, the upper range of normal values, and each 1% rise in HbA1c is associated with a 15% and 18% increase in the relative risk of CVD among patients with type I and type II diabetes mellitus, respectively (Buse et al., 2007).

The increase in risk attributed to hyperglycemia per se is independent of the overweight/obesity and dyslipidemia usually noticed in patients with diabetes. Furthermore, the mortality rate in diabetic patients with established CAD is much higher than in non-diabetic patients (Grundy et al., 2002).

Glycemic control undoubtedly decreases the risk of macro-vascular complications in diabetic patients; nevertheless, currently there are no clinical trials on glycemic intervention showing clear-cut evidence that glucose lowering diminishes the risk of CVD (Buyken, von Eckardstein, Schulte, Cullen, & Assmann, 2007).

1.2.3.1 (e) Advancing Age

Risk for ischemic heart disease rises with advancing age in both men and women. The main reason for this is that age is a reflection of progressive accumulation of coronary atherosclerosis, which in turn reflects cumulative exposure to atherogenic risk factors (Grundy, 1999). Increased age-specific risk becomes most clinically significant in men in their mid-40s and in women around the age of menopause. At any given age, women are at lower risk for coronary disease than men. Risk in women lags behind that of men by approximately 10 to 15 years (Wilson et al., 1998).

1.2.3.2 Predisposing Risk Factors

Predisposing risk factors intensify the risk associated with causal (independent) risk factors (Grundy, Pasternak, Greenland, Smith, & Fuster, 1999). These risk factors are described in the following subsections.

1.2.3.2 (a) Obesity

Obesity has reached epidemic proportions globally. The WHO estimates that in 2008, more than 1.5 billion adults aged 20 years and above were overweight (BMI ≥ 25). Of these, over 200 million men and nearly 300 million women – approximately 10% of adults – were obese (BMI ≥ 30) (WHO, 2008).

Furthermore, overweight and obesity now rank as the fifth principal risk for mortality worldwide; annually more than 2.8 million adults die from complications associated with overweight and obesity. Moreover, 44% of the diabetes burden and 23% of CAD are attributable to overweight and obesity (WHO, 2009).

Obesity was classified by the American Heart Association (AHA) as a major, modifiable risk factor for CVD. Risk is particularly raised when obesity has a predominant abdominal fat distribution (Grundy et al., 2002). Abdominal obesity is defined by a waist circumference greater than 102 cm in men or 88 cm in women.

Obesity, especially abdominal obesity, raises blood pressure and total cholesterol levels, lowers HDL-C levels, and even increases the risk of type II diabetes (Hubert, Feinleib, McNamara, & Castelli, 1983). In addition, some studies show that abdominal obesity is related to endothelial dysfunction, a marker of CAD (Carr & Brunzell, 2004; Wessel et al., 2004).

1.2.3.2 (b) Physical Inactivity

Physical inactivity is also defined by the AHA as a major, modifiable risk factor. Many studies, including the Framingham Heart Study, show that physical inactivity increases the risk for CAD (Grundy et al., 1999); furthermore, some studies estimate the increase in CAD risk to be about 1.5 times (Lloyd-Jones et al., 2010).

1.2.3.2 (c) Family History of Premature CAD

A positive family history of premature CAD is a major risk factor for CAD. Relative risk for CAD in first-degree relatives (parent, sibling, or offspring) has been reported in several studies to be from 2 to 12 times that of the general population (Grundy et al., 2002). Risk rises with the number of affected first-degree relatives and at earlier ages of onset in the probands. Among first-degree relatives, it seems that siblings of probands have the greatest relative risk (Pohjola-Sintonen, Rissanen, Liskola, & Luomanmaki, 1998).

1.2.3.3 Conditional Risk Factors

Conditional risk factors are associated with higher risk for CAD, even though their causative and independent contributions to CAD remain to be documented (Grundy et al., 1999). These factors are described in the following subsections.

1.2.3.3 (a) Homocysteine

Homocysteine is a sulfur-containing amino acid derived from conversion of methionine to cysteine (Kardesoglu, Uz, Isilak, & Cebeci, 2010). Elevated levels of homocysteine most likely result from deficiencies in some B vitamins and several rare hereditary diseases, or they can be drug-induced (Ntaios, Savopoulos, Grekas, &

Hatzitolios, 2009). Evidence has accumulated to support the concept that elevated plasma homocysteine is a strong predictor for the incidence of and mortality from atherosclerosis, CVD, and ischemic stroke, and this graded association is noted to be independent of other traditional risk factors (Bostom et al., 1999; Tanne et al., 2003).

Elevation of serum homocysteine is associated with higher risk for CAD. The mechanism underlying the relation between homocysteine and CAD is not yet fully understood, even though patients with severe hereditary forms of hyper-homocysteinemia have premature vascular damage and atherosclerosis (Giles, Croft, Greenlund, Ford, & Kittner, 2000).

1.2.3.3 (b) Elevated Lipoprotein (a)

Lipoprotein (a) (LP (a)), is an LDL-like particle in which apolipoprotein B-100 is covalently bound to glycoprotein apoprotein (a). Apoprotein (a) has a similar structure to plasminogen but does not have its enzymatic action. Therefore, it can inhibit fibrinolysis by binding to the catalytic complex of plasminogen, tissue plasminogen activator, and fibrin, leading to thrombosis (Marcovina & Koschinsky, 2003).

Several studies establish a significant correlation between serum lipoprotein (a) levels and CAD risk (Grundy et al., 1999). A meta-analysis of 27 prospective studies supports the proposition that elevated LP (a) levels have a significant and independent predictive power for CAD risk (Danesh, Collins, & Peto, 2000). In addition, concomitant elevations of LP (a) and LDL-C are reported to have synergy in rising risk in both men and women with dyslipidemia (Grundy et al., 2002).

1.2.3.3 (c) C-Reactive Protein (CRP)

A wealth of evidence now supports the role of chronic inflammatory process in the development and progression of atherosclerosis (St-Pierre et al., 2005). Inflammatory processes may contribute to plaque instability and thrombosis, thus increasing the risk of ACS (Drakopoulou et al., 2009). Several studies suggest that inflammatory markers, such as C-reactive protein (CRP), have predictive value for future coronary events (Fichtlscherer, Heeschen, & Zeiher, 2004).

CRP is an acute-phase plasma protein synthesized by the liver and has been demonstrated to reflect the degree of coronary inflammation and provide unique information unrelated to biomarkers of myocyte necrosis and hemodynamic stress in patients with ACS. High-sensitivity test appears to be the preferred method for measurement of CRP; plasma high-sensitivity C-reactive protein concentrations greater than 3 mg/L appear to be an independent predictor of risk for developing ACS in patients without known CAD (Drakopoulou et al., 2009).

1.2.3.4 Prevalence Rates of CAD Risk Factors in Malaysia

In 2008, a non-communicable diseases survey was conducted to provide surveillance baseline information to assess the extent of non-communicable disease risk factors in Malaysia. The survey gathered a wide range of data on the socio-demographic status and non-communicable disease risk factors of people aged between 25 and 64 years. The following prevalence rates were found: 34.7% had elevated blood pressure; 10.5% had high blood glucose; 53.5% had raised cholesterol levels; 44.2% were overweight; 14.0% were obese; 48.6% had abdominal obesity; 21.5% were current smokers; 60.5% were physically inactive; 12.2% consumed

alcohol; and 18.1%, 29.7%, 28.4%, 13.8% and 7.0%, had one, two, three, four and more than four non-communicable disease risk factors, respectively (WHO-Malaysia, 2011).

1.2.4 Diagnosis of Acute Coronary Syndrome

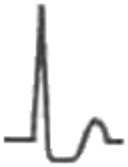
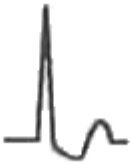
Differentiating ACS from non-cardiac chest pain is the main diagnostic challenge. Initial assessment requires a detailed case history (including risk factor analysis), physical examination, an ECG, and cardiac markers measurement (cardiac troponin in particular). Therapeutic decision making is based on this approach.

1.2.4.1 Electrocardiogram

ECG is an important and central tool to evaluate a patient with suspected ACS. Clear evidence exists to support the association between a delay in management and death in STEMI (Weaver et al., 1993). Therefore, a 12-lead ECG should be performed rapidly on all patients with a presentation consistent with ACS. According to the AHA/ACC guidelines for patients with chest pain, an initial screening ECG should be done and interpreted within 10 minutes of arrival at an emergency department (Kushner et al., 2009). The main ECG findings indicative of myocardial ischemia or infarction are STE, ST-segment depression, and T-wave inversion (Table 1.1).

Sub-endocardial ischemia results in ST-segment depressions and/or T-wave flattening or inversions, while severe transient transmural ischemia can result in STEs (Amsterdam, Diercks, & Kirk, 2009). Existing Q waves are not indicative of acute ischemia but do strongly suggest prior MI and the existence of underlying CAD (Anderson et al., 2007).

Table 1.1. Common Transient ECG Abnormalities in ACS

Normal	Sub-endocardial ischemia			Transmural Ischemia
	 ST depression (Horizontal)	 ST depression (Down sloping)	 T wave inversion	 ST elevation

(Anderson et al., 2007).

Unfortunately, ECG is a fairly specific but relatively insensitive test for the presence of myocardial ischemia; this could be attributable to the fact that some parts of the heart are more "electrically silent" than others, hence myocardial ischemia may not be detected on a surface ECG. In spite of the prognostic value of the initial ECG, a normal or non-specific ECG does not entirely exclude the possibility of ACS. Slater and colleagues evaluated 775 consecutive patients with symptoms suggestive of ACS; 107 had normal ECG and 73 had minimal changes. Of these patients, 10% with a normal ECG had acute MI, and 6% with minimal changes developed acute MI (Slater et al., 1987).

Even when non-diagnostic, ECG offers important risk-stratification information. For example, patients with confirmed MI but normal ECG have only 50% of the in-hospital mortality rate of patients with diagnostic tracings (Anderson et al., 2007). STEMI diagnosis depends upon the presence of characteristic ECG findings:

- New-onset STE higher than or equal to 1 mm (≥ 0.1 mV) in at least two contiguous leads
- Appearance of presumably new left bundle branch block (LBBB)

Diagnosis of UA/NSTEMI depends on the presence of particular ECG features, as following:

- ST-segment depression greater than 0.5 mm (> 0.05 mV)
- Symmetrical T-wave inversion greater than 0.2 mV in precordial leads.

1.2.4.2 Biochemical Cardiac Markers

Along with clinical features and ECG, cardiac biomarker measurements are now considered a cornerstone in the assessment of patients suspected of ACS. Actually, a class I recommendation from the guidelines of the National Academy of Clinical Biochemistry (NACB) reads as follows: "Biomarkers of myocardial necrosis should be measured in all patients who present with symptoms consistent with acute coronary syndromes" (Morrow et al., 2007).

Biochemical markers provide a noninvasive means of determining whether MI has occurred; they also provide important prognostic information. When ischemia gives way to infarction, there is a loss of integrity of the myocardial cell membrane. A series of macromolecules are in turn released into the systemic circulation. Of these, the optimal biological marker for MI would be the one: highly specific to myocardium, rapidly released, and sufficiently persistent in the circulation to allow detection (Morrow et al., 2007).

Based on compelling evidence, cardiac troponins are the markers that most closely meet these criteria, and hence have become fundamental to diagnosis of MI, and are used for guidance of therapy and intervention for patients presenting with signs and symptoms of ACS. They are useful in detecting MI in patients presenting with atypical histories and non-diagnostic ECGs. Troponin testing also provides valuable

information in terms of risk-stratifying patients with ACS. There appears to be a clear link between the quantity of troponin measured and subsequent risk of death (Antman et al., 1996).

Troponin complex has three structural regulatory proteins, troponin T, troponin I, and troponin C. Troponin C isoforms exist in both smooth and cardiac muscle and therefore lack sufficient cardiac specificity for clinical use (Thygesen, Alpert, & White, 2007).

Troponins appear in circulation after onset of complete coronary occlusion subsequent to myocardial necrosis, so several hours usually pass before release and detection in the bloodstream. While troponins I and T appear in the blood within 4 to 6 hours after necrosis; troponin I levels stay elevated for 4 to 7 days, whereas troponin T levels remain raised for 10 to 14 days. A critically essential factor when using cardiac troponins is timing of blood sample collection. Current recommendations from American College of Emergency Physicians (ACEP) state that measurement is to be done upon admission, followed by serial sampling based on the clinical circumstances. For most patients, this includes sampling at hospital admission and again 6–9 hours later. This helps to confirm or exclude the diagnosis and may be useful in estimating infarct size (Fesmire et al., 2006). Guidance is that a maximal concentration of cardiac troponins exceeding the decision limit (99^{th} percentile of values for reference control group) at least once within the first 24 hours after the acute event is sufficient to indicate myocardial necrosis consistent with MI (Morrow et al., 2007; Thygesen, Alpert, White, et al., 2007).

Before the era of troponin, CK-MB isoenzyme assay was considered the gold standard marker for MI diagnosis. CK-MB performs less well than the cardiac troponins in terms of both sensitivity and specificity for MI. Case reports show that histologically proven MI is present in patients presenting with ACS who have normal levels of CK-MB but elevated troponins (Pettijohn et al., 1997). Recent guidelines indicate that CK-MB "mass" measurements are the next best choice when cardiac troponin is not available (Morrow et al., 2007).

CK-MB also begins rising in the six-hour range but returns to normal values at approximately 48 hours post-MI (Fesmire et al., 2006). As a result, if a patient is admitted with raised troponin and CK-MB serum levels and several days later experiences recurrent chest pain, troponin would be less sensitive to detecting new myocardial injury, since it would still be raised. Therefore, CK-MB measurements can be useful to indicate early reinfarction (Antman et al., 2000).

Similarly to troponins, the diagnostic limit for CK-MB is set as the 99th percentile in a sex-specific reference control group. Taking into account the lower tissue specificity as compared with troponin, it is suggested that two consecutive measurements of CK-MB exceeding this decision limit be considered sufficient biochemical indication of MI (Morrow et al., 2007).

Elevation of CK-MB level is directly correlated to mortality and risk of adverse outcomes in patients with non-STE ACS, and the increased risk starts with CK-MB levels just above normal (Zimmerman et al., 1999).

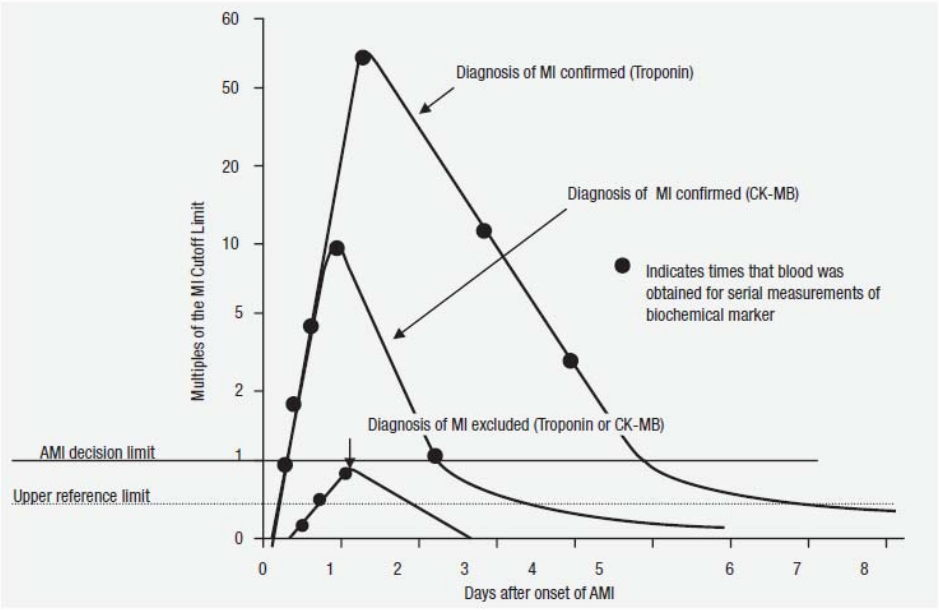


Figure 1.1. Biochemical markers in suspected acute coronary syndrome
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1.2.4.3 Risk Stratification of ACS Patients

Estimated risk of mortality or short-term adverse outcomes, based on clinical characteristics, is challenging and imprecise. Over the last 10 years, the importance of early risk stratification has been universally acknowledged in practice guidelines, with a current AHA/ACC class 1A recommendation for risk stratification in the setting of non-STE ACSs (Anderson et al., 2007; Ranasinghe et al., 2011).

Risk assessment is needed to guide triage and direct management strategy for patients with ACS (Anderson et al., 2011; Ranasinghe et al., 2011). Even in the setting of STEMI, where initial therapeutic options are well-established, patient risk characteristics have an influence on early therapeutic decision making (Morrow et al., 2000).

Risk stratification in ACS patients not presenting with STE is more complicated, because in-hospital outcomes for this group differs, with reported mortality rates of 0–12%, reinfarction of 0–3%, and recurrent severe ischemia of 5–20% (Steg et al., 2002).

Several clinical risk-stratification scoring systems are now widely available, based on initial medical history, ECG, and laboratory tests which can predict mortality or recurrent cardiac events in patients with ACS. The most commonly used scoring systems include platelet glycoprotein IIb/IIIa in UA: Receptor Suppression Using Integrilin Therapy (PURSUIT) (Boersma et al., 2000), Fast Revascularization during Instability in Coronary Artery Disease (FRISC) (Lagerqvist et al., 2005), Thrombolysis in Myocardial Infarction (TIMI) (Antman et al., 2000; Morrow et al., 2000), and Global Registry of Acute Cardiac Events (GRACE) risk scores (Granger et al., 2003). All these scoring systems were obtained from randomised controlled trial populations, except the GRACE registry, which was derived from an international "real life" observational registry.

1.2.4.3 (a) TIMI Risk Score for UA/NSTEMI

Antman et al. designed a 7-point risk score validated as being a useful prognostic tool to predict risk of developing an adverse cardiac outcome (mortality, new or recurrent infarction, or severe recurrent ischemia needing revascularization) through 14 days of presentation for patients with non-STE ACS (Antman et al., 2000; Pollack, Sites, Shofer, Sease, & Hollander, 2006).

TIMI risk score was originated from the TIMI IIB trial database and has been validated in several other trials of UA/NSTEMI (Chase et al., 2006). The score composes of seven predictor variables, each worth 1 point. Thus, scores may range between zero and seven. In accordance with this score, patients are stratified into high-risk (5–7 points), medium-risk (3–4 points), or low-risk (0–2 points) categories (see Table 1.2). Studies show that rates of adverse events increase significantly as TIMI risk score increases. Risks ranged from 2–5% with a score of 0/1, to more than 30–

40% for a score of 6/7 (Owen & Diercks, 2009). Furthermore, TIMI risk score seems to be predictive of increasing benefit from certain therapies as risk rises (Antman et al., 2000; Cannon et al., 2001).

Table1.2. TIMI risk score for UA / NSTEMI

Variables	Points
• Age ≥ 65	1 point
• At least 3 risk factors for CAD (dyslipidemia, HPT, DM, premature cardiovascular disease family history status)	1 point
• Known CAD (Myocardial infarction history, documented CAD > 50% stenosis)	1 point
• ST- segment deviation ≥ 0.5mm on ECG at presentation	1 point
• At least 2 anginal events in last 24 hours	1 point
• Use of anti-platelet agent (ASA) in last 7 days	1 point
• Elevated serum cardiac enzymes/markers	1 point
Total	**0 – 7**

(Antman et al., 2000).

1.2.4.3 (b) TIMI Risk Score for STEMI

Morrow et al. developed a clinical risk score validated as a simple bedside integer score that may be applied to assess short-term mortality risk within 30 days of presentation for patients with STEMI (Morrow et al., 2000; Morrow et al., 2001).

TIMI risk score for STEMI was derived from the InTIMI II trial database and is based on eight clinical risk indicators routinely available at hospital presentation. The total score for each patient is the summation of the points for each risk indicator present (range 0–14) (Morrow et al., 2001).

Studies find that risks of all-cause mortality at 30 days increase significantly as TIMI risk score increases. Risks ranged from 0.8–4.4% with a score of 0/3, to 35.9% for a score of more than 10 (Morrow et al., 2001).

Table 1.3. TIMI risk score for STEMI

Variables	Points
• Age ≥ 75	3 points
• Age 65 to 74	2 points
• Diabetes *OR* Hypertension *OR* history of angina (onset more than 2 weeks ago) *OR* New onset angina (Less than 2 weeks)	1 points
• Systolic BP <100 mmHg	3 points
• Heart Rate > 100 beat per minute	2 points
• Killip II-IV	2 points
• Weight < 67 kg	1 points
• Anterior STE (Leads V_1 to V_4) *OR* Left Bundle Branch block (BBB)	1 points
• Time to Treatment > 4 hours	1 points
Total	**0 – 14**

(Morrow et al., 2001).

1.2.5 Complications of Acute Coronary Syndrome

Patients with a history of ACS are particularly susceptible to developing a wide range of complications. They have a risk of more than 20% of heart failure, myocardial reinfarction, stroke, and death within 5 years (Pattanayak & Gelfand, 2009). Other complications include cardiogenic shock, valvular dysfunction, ventricular and atrial arrhythmias, bradycardia, heart block, and venous thromboembolism (Fox et al., 2006; Spinler & Denus, 2011). In fact, around 60% of mortality from ACS occurs in patients with prior cardiac events (Vermeer & Bajorek, 2008).

1.2.6 Management of Acute Coronary Syndrome

Once a patient presents to hospital and is diagnosed with ACS, management serves two purposes: reducing the burden of disability and mortality after the attack, and minimizing risk of a recurrent ischemic event, referred to as secondary prevention. Acute treatment of ACS involves (1) immediate relief of ischemic chest discomfort during the acute attack, (2) early revascularization of the culprit coronary artery to

prevent infarct expansion (in case of acute MI) or total occlusion and MI (in case of UA), and (3) prevention of death, coronary artery reocclussion, or other complications.

In the past 20 years, the management of ACS has advanced and undergone numerous changes. Pharmacotherapy of ACS has evolved to include combinations of anti-ischemic therapy, fibrinolytics, and antithrombotics. In addition, pharmaco-therapy has incorporated with reperfusion therapy and restoration of blood supply to the infarct-related artery through interventional techniques such as percutaneous coronary intervention (PCI) and/or coronary artery bypass graft surgery (CABG) (Spinler & Denus, 2011).

1.2.6.1 Anti-ischemic Therapy

Anti-ischemic treatments primarily address the demand side of the myocardial ischemia equation. Treatments commonly used currently include oxygen, nitrates, morphine, β-blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors (ACEI). These treatments are described in greater detail in the following subsections.

1.2.6.1 (a) Oxygen

Oxygen administration is frequently recommended in international guidelines for all patients with suspected myocardial ischemia; nonetheless, there is controversy about its safety and efficacy. A systematic review, including non-randomised studies, does not confirm that supplemental oxygen decreases acute myocardial ischemia; in fact, some evidence suggests it may actually aggravate ischemia (Nicholson, 2004). The ACC recommendations suggest administering oxygen only to those patients with a peripheral oxygen saturation of less than 90%, although this cut-off is apparently