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Systolic blood pressure on admission, clinical characteristics and mortality in patients hospitalised for acute coronary syndrome at Charlotte Maxeke Johannesburg Academic Hospital

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.0 INTRODUCTION

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).[1-3] Unstable angina and non-ST-segment elevation myocardial infarction (MI) account for about 2.5 million hospital admissions worldwide.[2]

Atherothrombosis, defined as ischaemic heart disease and cerebrovascular disease, is the leading cause of death worldwide, exceeding deaths from AIDS, cancer or infectious disease.[4] In-hospital death and re-infarction affects 5% to 10% of patients with UA or myocardial infarction.[2] Despite optimal treatment, death or rehospitalisation due to ACS occurs in another 5 to 10% of patients in the month after an acute episode.[2] In the United Kingdom, it is estimated that there are about 120,000 hospital admissions due to non-ST elevation ACS.[4] In a published report, about 1.1 million Americans will have a new or recurrent coronary event every year, and approximately 2.2 million hospitalisations for ACS occur every year.[4]

According to World Health Organisation (WHO), ischaemic heart disease has been identified as the leading cause of death in all regions of the world, except in the African region.[5] However, current data suggests that ischaemic heart disease (IHD) is the eighth most common cause of death in the region.[6,7] This may be related to change in lifestyle, increased industrialisation and urbanisation within developing countries. Increasing industrialisation and urbanisation, while raising living standards and increasing lifespan for many, is also accompanied by changes that bring about emergence of risk factors for coronary heart

disease. Identification of prognostic risk factors in patients with ACS has been advocated especially during early hours of admission. Risk has been regarded an important "driver" of management decisions and accurate yet simple methods of risk assessment are important for patient care.[2]

Careful evaluation and identification of patients at risk is recommended in order to institute appropriate therapy for such patients. The risk evaluation of patients with ACS is a continuous process that involves integration of non-invasive and invasive data at presentation and whilst in hospital. Several longitudinal studies have shown that increased age, sex, diabetes, high creatinine level, cardiac arrest during presentation, increased heart rate, and lower systolic blood pressure (SBP) at admission are associated with higher in-hospital mortality among patients with ACS.[8-12]

The aim of this work is to further evaluate the prognostic significance of SBP levels on hospital admission among patients presenting with ACS at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

1.1 BACKGROUND

The term ACS could have been described as far back as 2600 BC when Egyptian papyrus scrolls recorded that patients with acute chest pain were at high risk of death.[4] Acute coronary syndrome has evolved as a useful operational term to refer to any constellation of clinical symptoms that are compatible with acute myocardial ischemia (Fig. 1).[2] This encompasses MI (ST-segment elevation and depression, Q-wave and non-Q-wave) and UA. The term is now widely accepted because it reflects the reality that at first contact with the patient, only chest pain at rest or on minimal exertion might be present and no definite diagnosis is established. It is also consistent with the common pathophysiological mechanism believed to

be responsible for most cases of unstable angina and myocardial infarction, with and without ST-segment elevation.[2]

ACS is therefore divided into two large groups, based on the presence or absence of ST-segment elevation. If ST-segment elevation is present, the development of a myocardial infarction seems likely and is termed ST-segment elevation myocardial infarction (STEMI). In the absence of ST elevation, biochemical markers are required for further categorisation. If concentrations of cardiac enzymes or troponins rise in these patients, irreversible cell damage will have occurred, and these patients should be regarded as having had non-ST-segment elevation myocardial infarction (NSTEMI), according to the new definition of the Consensus Conference that replaced the WHO criteria.[13] Patients with acute coronary syndrome without raised concentrations of biomarkers can be regarded as having unstable angina (UA).[14] It should be noted that both NSTEMI and UA may or may not have changes on the surface ECG, including ST-segment depression or T-wave morphological changes. The ACC/AHA guidelines use the terms ST-segment elevation myocardial infarction and non-ST-segment-elevation myocardial infarction in place of Q-wave and non-Q-wave myocardial infarction; the latter terms are less useful in planning immediate management.[14]

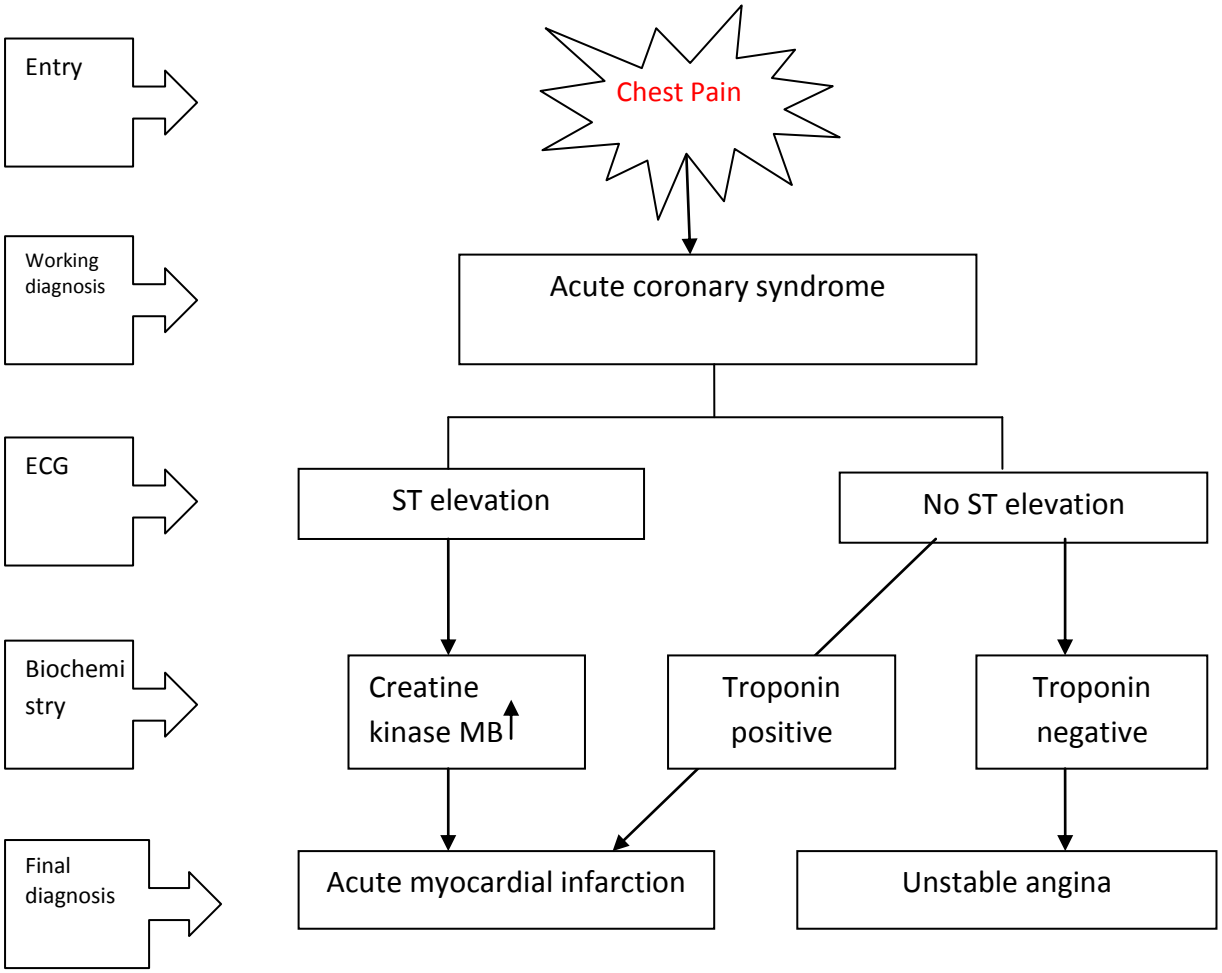


Figure 1: Acute coronary syndrome

1.2 EPIDEMIOLOGY

1.2.1 PREVALENCE AND INCIDENCE

In the United States, cardiovascular disease is the leading cause of morbidity and mortality among black, Hispanic, and white populations.[15] In 2003, there were 4,497,000 visits to US emergency departments for primary diagnosis of CVD.[16] Among these, coronary artery disease (CAD) was the most prevalent cause and was associated with high mortality and morbidity. Approximately 1.5 million cases of myocardial infarction occur annually in the United States; the yearly incidence rate is approximately 600 cases per 100 000 people.[15]

Acute myocardial infarction (AMI) still remains a major reason for ICU admission although mortality from Coronary heart disease (CHD) has declined steadily in the western world.[17] The average incidence of AMI in these societies is 3.5 per 1000 for males and 1 per 1000 for females aged 20 to 64 years.[17] The average incidence of myocardial infarction in United Kingdom (UK) is 600 per 100,000 for men aged 30-69 and 200 per 100,000 for women.[18] There are about 52,000 new cases of angina per year in all men living in the UK and about 43,000 new cases in women.[18] About 4% of men and 0.5% of women in the UK have had a heart attack.[18] Prevalence increases with age and is higher in men. Eight percent of men and 3% of women aged 55 to 64 years and about 14% of men and 8% of women aged 65 to 74 years have, or have had, angina.[18] According to the Quality and Outcomes Framework (QOF) data, the prevalence of CHD in Britain was 3.7% of all GP registrations.[18] The prevalence is higher in the North of England and Wales than in the South of England and is also higher in lower socio-economic groups. In France, the incidence of myocardial infarction leading to hospitalisation was estimated between 60,000 and 65,000 each year.[19] In Europe, the highest incidence of CHD is found in central and eastern European countries.[19] In general, a consistently, decreasing trend in the incidence of myocardial infarction is being observed in the developed Western World.[19] This may be related to effective measures taken for primary prevention in such societies.

However, coronary artery disease has also been reported to be on the rise in Asia.[20] In this continent in which over half the world's population live, it is estimated that the prevalence of coronary heart disease will rise by 115–127% for India and 81–110% for China from the level in 1990 until 2020.[20] These estimates are based on demographic changes alone and do not take into account major increases in risk factors which are likely on present trends. The prevalence of CAD and the incidence of ACS are said to be very high among Indians, with India having the highest burden of ACS in the world.[21-25] Coronary artery disease has been

reported to occur 5–10 years earlier in Indians than in other populations around the world and the major effect of this peculiar phenomenon is on the productive workforce of the country aged 35–65 years.[24] The rising incidence of ACS in Indians is said to be related to the changes in the lifestyle, westernization of food practices, increasing prevalence of diabetes mellitus and probably genetic factors.[24]

Data from across Africa suggests that coronary heart disease was rare until the mid-20th century.[26-31] Reviews of data on the evolution of CVD in Ghana (then the Gold Coast) revealed that the Annual Medical and Sanitary Reports (AMSR) sent regularly to the Colonial Secretary in London by the Gold Coast government, showed that coronary heart disease was distinctly rare from 1898 to 1960.[27,32] The AMSR from Nigeria during this period mentioned a similar spectrum of CVD but did not mention any coronary heart disease.[27] Review of hospital-based studies in thirteen Nigerian centres between 1955–2009, has shown that the prevalence of CAD/IHD has increased from 0.24% to 8.5%.[33-35] In a 10-year period (1961-70), a study done in Ibadan South-West Nigeria identified only 26 patients with myocardial infarction, an incidence of 1 in 20,000 hospitalised Nigerian adults.[36] Coronary artery disease was also reported to be rare in two Ugandan studies.[28, 29] Although CVD constituted 6–8% of medical admissions in both of these studies from Uganda, the major CVDs encountered were syphilitic heart disease, endomyocardial fibrosis, hypertension and rheumatic heart disease.[28,29] A South Africa study reported in 1946 revealed only a single death from CHD in an autopsy series of 352 adult Africans.[30] Several other studies conducted up to three decades later in Johannesburg and Durban also found coronary heart disease to be rare among blacks in South Africa, especially in rural areas.[31]

Changes in lifestyle, increasing urbanisation and industrialisation have led to a rapid epidemiological transition. This has resulted in an increase of both incidence and prevalence of CAD and ACS in Sub-Saharan Africa (SSA).[37-39] Thus, although other non-ischaemic

cardiovascular diseases (such as hypertensive heart disease, cardiomyopathy and rheumatic heart disease) predominate in the Sub-Saharan Africa, the burden of cardiovascular disease as a result of IHD has been reported to be on the increase. In another 10-year review of myocardial infarction (1990-1999) from the same Ibadan centre, found 52 patients with MI. This finding yielded an incidence of 1 in 10,000 compared to 1 in 20,000 in the previous report published in the early 70s.[38] Similarly, an increase in prevalence of IHD from 3.3% to 6.5% among patients with cardiovascular disease (CVD) was reported in Kano North-West Nigeria from 2004-2011. [40, 41] It is important to note that one of the Kano studies (3.3% prevalence) was a 5-year review done between 1999-2004 while the other study (6.5% prevalence) was a 1-year review done between 2010-2011. [40,41] This showed that the prevalence of the disease had doubled in less than a decade. A review of the case reports published in the preceding two decades across the African continent (Nigeria, South Africa, Ghana, Ivory Coast, Kenya, Uganda and Zimbabwe) suggested that the burden of coronary heart disease was already on the rise.[42]

Numerous differences exist between women and men with respect to the pathology of CHD and its incidence and prevalence.[43] Coronary artery disease is less common and occurs later in life in women than men.[44] Although men experienced higher age specific incidence rates for an initial MI during each study year, sex differences in the risk of initial AMI declined with advancing age.[45] In a study of sex differences in mortality following ACS, women constituted only 28% of the studied patients.[46] Both prevalence and incidence of CHD consistently remain higher in men than women according to the British CHD statistics.[18]

1.3 AETIOLOGY AND RISK FACTORS

Atherosclerosis is responsible for almost all cases of coronary heart disease (CHD).[47] It begins as a fatty streak on the wall of the artery, which progress to a plaque. The plaque may

rupture culminating into thrombotic occlusion and a coronary event. A variety of risk factors are associated with development of an atherosclerotic plaque in the coronary arteries and other arteries in the body, leading to CHD and CVD in general. These risk factors are usually grouped into two large groups, the modifiable and non-modifiable risk factors.

The non-modifiable risk factors include age, sex and family history of early coronary heart disease. The modifiable risk factors include hypertension, diabetes, dyslipidaemia, smoking or other tobacco use, obesity, sedentary lifestyle and or lack of exercise and type A personality.[15] In addition, there are also non-traditional or newer risk factors associated with increased risk of CHD such as carotid intima media thickness, leukocyte count, fasting blood sugar, high-sensitivity C-reactive protein, elevated homocysteine levels, ankle brachial index, lipoprotein (a) level, carotid artery calcification score and periodontal disease.[23]

1.3.1 MALE GENDER: Male gender alone has been found to contribute to the risk of CHD, although the potential mechanisms for such risk are not well understood. Population studies have identified male gender as a risk factor for higher rates of CHD.[48-50] The risk of CHD in men has been associated with variations in the Y chromosome. A study among 3233 biologically unrelated British men who underwent genotyping of their Y chromosome, with 13 ancient lineages (haplogroups) identified based on the genotype results, found that those descendent from one particular haplogroup (haplogroup I, almost entirely unique to Europeans) had significantly more CHD than men from other haplogroups (odds ratio 1.56, 95% CI 1.24-1.97).[51] These results suggest that differences in CHD risk within the male gender may be associated with inherited variations in sex chromosomes.

1.3.2 FAMILY HISTORY: Family history is an independent risk factor for CHD, particularly among younger individuals with a family history of premature disease.[52] The general agreement with regards to the definition of family history is that myocardial

infarction (MI) or death from CHD in a first degree relative (i.e. parent or sibling) prior to age 50 (males) or 60 (females) years, denotes a significant family history.[52] The importance of family history has been shown in several large cohort studies (Physician's Health Study, Women's Health Study, Reykjavik Cohort Study, Framingham Offspring Study, INTERHEART Study, and Cooper Center Longitudinal Study) that collectively followed over 163,000 patients, and all showed that a positive family history was associated with greater risk of developing CHD.[52-57]

1.3.3 HYPERTENSION: Hypertension is a well-established risk factor for adverse cardiovascular outcomes, including mortality from CHD and stroke.[58,59] In the INTERHEART study, hypertension accounted for 18% of the population-attributable risk of first myocardial infarction.[60] For adults aged 40-69 years, each 20mmHg rise over the usual systolic blood pressure or 10 mmHg rise of the diastolic blood pressure doubles the risk of death from CHD.[61] The INTERHEART study showed that 22% of myocardial infarctions (MI) in Western Europe were related to high blood pressure and those with hypertension had almost twice the risk of a MI.[60]

1.3.4 DYSLIPIDAEMIA: The prevalence of dyslipidaemia is increased in patients with premature CHD, being as high as 75-85% compared with approximately 40-48% in age-matched controls without CHD.[62, 63] In the INTERHEART study, dyslipidaemia (defined as a raised apo B to apo A-1 ratio) accounted for 49% of the population-attributable risk of a first MI.[60] The evidence of pathogenic role of dyslipidaemia in the development of CHD was derived by a series of randomised trials that showed reduction in the total and low density lipoprotein (LDL) cholesterol (usually with statins) reduced coronary events and mortality when given for primary and secondary prevention.[64-66] The INTERHEART study suggested that 45% of MIs in Western Europe are due to abnormal blood lipids.[60] The lipid abnormalities associated with increased risk of CHD are increased total and LDL cholesterol,

low high density lipoprotein (HDL) cholesterol, hypertriglyceridaemia, increased apolipoprotein C-III and LP(a) excess.[52]

1.3.5 SMOKING: Cigarette smoking is regarded as an important risk factor of CHD. The risk of MI was found to be six-fold in women and three-fold in men who smoke an average of 20 sticks per day compared to their counterparts who never smoke.[67,68] The risk of MI is proportional to tobacco consumption in both men and women and is higher in inhalers compared with non-inhalers.[68] In the INTERHEART study, smoking accounted for 36% of the population-attributable risk for first MI.[60] The risk of recurrent MI was found to reduce by 50% within a year of smoking cessation, and risk returns to that of non-smokers after two years of cessation of smoking.[69] The smoking cessation was found to be beneficial regardless of how long or how much the person previously smoked.

Regular exposure to passive smoking increases CHD risk by 25%.[70] WHO research estimates that over 20% of CVD is due to smoking.[71] In a study to find the impact of ban on smoking in public places, admission rates for MI was found to be significantly reduced within six months of the introduction of the law.[72]

1.3.6 DIABETES: Diabetes is regarded as one of the major risk factor for CHD. Men with type 2 diabetes have a 2 to 4 times greater annual risk of CHD; women have a 3 to 5 times greater risk.[73]

1.3.7 AGE: Coronary artery disease increases with age, and all of the major risk factors of CHD above continue to be relevant in older persons.

1.3.8 LACK OF PHYSICAL ACTIVITY: Recommended physical activity levels are 30 minutes of moderate physical activity on 5 or more days per week.[74] Physical activity is reported to significantly reduce the incidence of CHD.[52] The 2002 World Health Report

estimated that over 20% of CHD in developed countries was due to physical inactivity.[71] Exercise may have a variety of beneficial effects including an elevation of serum HDL-cholesterol, reduction in blood pressure, less insulin resistanc and weight loss. Men who engaged in moderately vigorous sports activity have been reported to have a 23% lower risk of death than those who were less active.[75] Persons with mild to moderate levels of physical activity as part of their occupation have lower risk of MI compared to sedentary workers.[76] In the INTERHEART study, lack of regular physical activity accounted for 12% of the population-attributable risk of a first myocardial infarction.[57]

1.3.9 OBESITY: Obesity is an independent risk factor for CHD. It is also a risk factor for hypertension, hyperlipidaemia, diabetes and impaired glucose tolerance. Central or abdominal obesity is most significant. Those with central obesity have over twice the risk of an acue MI.[60] In an analysis of data from 4,780 adults in the Framingham Offspring Study; obesity as measured by body mass index (BMI) significantly and independently predicted the occurrence of CHD and cerebrovascular disease after adjusting for traditional risk factors.[77]

1.3.10 PSYCHOSOCIAL WELL-BEING: Work stress, lack of social support, depression, anxiety and personality (particularly, hostility) can all increase CHD risk.[78] The link between psychological stress and atherosclerosis may be both direct, via damage of the endothelium, and indirect, via aggravation of traditional risk factors such as smoking, hypertension, and lipid metabolism.[52]

1.3.11 POOR NUTRITION: The WHO 2003 report stated that a diet high in fat (particularly saturated fats), sodium and sugar and low in complex carbohydrates, fruit and vegetables increases the risk of CVD.[79] It has been found that eating oily fish containing omega-3 fatty acid and fibre rich diet reduces CHD mortality.[80]

1.3.12 ETHNICITY: South Asians living in the UK (people from India, Pakistan, Bangladesh and Sri Lanka) have a higher premature death rate from CHD (46% higher for men; 51% higher for women).[81] Hypotheses proposed include link migration, disadvantaged socio-economic status, pro-atherogenic diet, lack of exercise, high levels of homocysteine, endothelial dysfunction and increased plaque inflammation.[82] The premature death rate from CHD in West Africans and people from the Caribbean is much lower (half the rate compared with the general population for men and two-thirds of the rate for women).[81]

Africa is a continent with various ethnic groups namely Black African, coloured African and European/other Africans.[83] The INTERHEART Africa study has shown different stages of epidemiological health transition among African ethnic groups.[83] Europeans were found to have advanced transition stage, with significantly high prevalence of dyslipidaemia, cigarette smoking and abdominal obesity but lower prevalence of hypertension and diabetes.[83] Coloureds have the highest prevalence of cigarette smoking as well as obesity, which lead to the higher rate of diabetes and hypertension compared to other ethnic groups.[83] Black/Africans are in the earlier stage of the epidemiological transition with higher prevalence of hypertension but lower smoking and atherogenic elements of their lipid profile.[83] It was also observed that low number of MI cases were recruited from other African countries outside South Africa and this may indicate that MI is still rare in less developed SSA, suggesting these countries may be in an earlier epidemiological transition stage.[83] In general, the INTERHEART Africa revealed that known risk factors of CHD accounted for 90% of cases of MI in African populations which is consistent with the overall INTERHEART study.[83] These data indicate that lifestyle modifications and established effective preventive therapy are needed to tackle the epidemic of CVD in Africa.

1.3.13 NON-ATHEROSCLEROTIC CAUSES OF MI

- Coronary occlusion secondary to vasculitis,
- Ventricular hypertrophy (eg, left ventricular hypertrophy, idiopathic hypertrophic subaortic stenosis [IHSS], underlying valve disease),
- Coronary artery emboli, secondary to cholesterol, air, or the products of sepsis,
- Congenital coronary anomalies,
- Coronary trauma,
- Primary coronary vasospasm (variant angina),
- Drug use (eg, cocaine, amphetamines, ephedrine),
- Arteritis,
- Coronary anomalies, including aneurysms of coronary arteries,
- Factors that decrease oxygen delivery, such as hypoxemia of severe anaemia,
- Aortic dissection, with retrograde involvement of the coronary arteries.

1.4 PATHOGENESIS

The atherosclerosis process starts with plaque formation. Within the coronary vasculature, flow dynamics and endothelial shear stress are implicated in the pathogenesis of vulnerable plaque formation.[84] This is followed by lipid accumulation and fibro-fatty stage. The lesion progresses with procoagulant expression and formation of thin fibrous cap. ACS develops when a plaque ruptures. The risk of plaque disruption depends on plaque composition, vulnerability (plaque type) and degree of stenosis (plaque size).[85] The most common underlying molecular and cellular pathophysiology of a disrupted atherosclerotic plaque is

arterial inflammation, caused by non-infectious (e.g. oxidized lipids) and possibly, infectious stimuli, which lead to plaque expansion, destabilization, erosion or rupture and thrombogenesis.[84] Activated macrophages and T-lymphocytes located at the shoulder of a plaque increase the expression of enzymes such as metalloproteinases that cause thinning and disruption of the plaque.[84] Thus, inflammation plays an important role in plaque instability, and subsequent acute coronary syndromes. Circulating levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 are correlated with the clinical course and outcome typical of an acute coronary syndrome.[86-88] The circadian variation of STEMI with a higher incidence in the early morning hours can be explained by the combination of b-adrenergic stimulation (increased vascular tone and blood pressure), hypercoagulability and hyper-reactivity of platelets.[89] Activities associated with increased sympathetic stimulation and vasoconstriction, such as physical or emotional stress, may also trigger plaque disruption and coronary thrombosis.[89]

The disrupted plaque releases procoagulant material that stimulates platelet aggregation, thrombin generation and thrombus formation.[90] The resultant thrombus interrupts blood flow to the myocardium leading to imbalance between oxygen supply and demand and if severe and persistent enough leads to MI. Most cases of STEMI results from complete or critical occlusion of the epicardial vessel involved.[91] UA/NSTEMI usually results from coronary artery narrowing caused by a thrombus that develops on a disrupted atherosclerotic plaque but which is non-occlusive.[84] However, an occlusive thrombus/plaque can also cause a syndrome of UA/NSTEMI in the presence of extensive collateral blood supply.[84]

Other mechanisms that may be responsible for UA/NSTEMI are intense focal spasm of the arterial segment, in the presence or absence of local stenosis.[84] Other mechanisms include dissection of the coronary artery. [84]

1.5 CLINICAL PRESENTATION

In ACS, a working diagnosis of STEMI must first be made. This is usually based on the history of chest pain/discomfort lasting for 10–20 min or more (not responding fully to nitroglycerine). Important clues are a previous history of coronary artery disease and radiation of pain to the neck, lower jaw, or left arm. The pain may not be severe and, in the elderly particularly, other presentations such as fatigue, dyspnoea, faintness, or syncope are common. There are no individual physical signs diagnostic of STEMI, but many patients have evidence of autonomic nervous system activation (pallor, sweating). Features may include irregularities of the pulse (bradycardia or tachycardia), a third heart sound, and basal rales.

There are three principal presentations of UA:

(1) Resting angina that commences when the patient is at rest and prolonged usually lasting for more than 20 minutes,

(2) New-onset (less than 2 months): severe angina of at least Canadian Cardiovascular Society classification (CCS) class III severity,

(3) Increasing angina that has become more frequent and longer in duration.[92] Criteria for the diagnosis of UA are based on the duration and intensity of angina as graded according to the CCS classification (see Table 1).[93] Non–ST-elevation MI generally presents as prolonged, more intense rest angina or angina equivalent.[84]

Table 1: Grading of angina pectoris according to CCS classification[84]

Class	Description of stage
I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
IV	"Inability to carry on any physical activity without discomfort— anginal symptoms may be present at rest."

CCS- Canadian Cardiovascular Society

1.6 INVESTIGATIONS

1.6.1 ELECTROCARDIOGRAPHY (ECG) This is the simplest and most important investigation carried out in all suspected ACS patients. A patient who is considered to have ACS should be placed in an environment with continuous ECG monitoring and defibrillation capability, where a 12-lead ECG can be obtained expeditiously and definitively interpreted, ideally within 10 minutes of arrival to the Emergency Department.[84] In the case of STEMI or new or presumed new left bundle-branch block, reperfusion therapy needs to be started as soon as possible. However, an ECG can be equivocal in the early hours, and even in proven infarction it may never show classical features of ST-segment elevation and new Q-waves. Additional recordings of lead V7–V8 or V4R are helpful to make the diagnosis in selected

cases (true posterior infarction or right ventricular infarction, respectively). In patients with a slowly evolving or stuttering myocardial infarction, serial ECGs should be taken to detect evolving infarction.[91] In patients with acute coronary syndrome but without ST elevations, the ESC Task Force regards ST-segment depression of at least 0·1mV and T-wave inversion of more than 0.1 mV to signify ischaemia, whereas the ACC/AHA sets the cut-offs at 0.05 mV and 0.2 mV or more, respectively. Both reports emphasize that a normal electrocardiogram does not rule out myocardial infarction.[94]

1.6.2 CARDIAC ENZYMES: Blood sampling for serum markers of necrosis is routinely done in the acute phase, but one should not wait for the results to initiate reperfusion treatment.[91] Creatine kinase and its MB isoenzyme have been the gold standard markers of myocardial necrosis for three decades. However, the ACC/AHA and ESC reports acknowledge the superiority of troponins T and I in detecting minor myocardial injury and for risk stratification. Many studies have shown that about 30% of patients with ACS but without persistent ST elevation have raised troponin concentrations.[95, 96]

Estimation of cardiac biomarkers is important to differentiate UA from NSTEMI in the absence of ST-elevation. Once it has been established that no biomarker of myocardial necrosis has been released (based on 2 or more samples collected at least 6 hours apart, with a reference limit of the 99th percentile of the normal population)[97], the patient with ACS may be considered to have experienced UA. Diagnosis of NSTEMI is established if a biomarker has been released. Markers of myocardial injury can be detected in the bloodstream with a delay of up to several hours after the onset of ischemic chest pain, which then allows the differentiation between UA (no biomarkers in circulation; usually transient, if any, ECG changes of ischemia) and NSTEMI (elevated biomarkers). Thus, at the time of presentation, patients with UA and NSTEMI can be indistinguishable.[84] The finding of elevated markers

of necrosis may sometimes be helpful in deciding to perform coronary angiography (e.g. in patients with left bundle-branch block).[91]

The decision of measuring troponins quantitatively in the central laboratory or qualitatively at point-of-care or bedside depends on the facilities available and time period before the result is available. According to the ACC/AHA guidelines, a turnaround time of 30-60 minutes is required. The US National Academy of Clinical Biochemistry advises the implementation of point-of-care test systems if the hospital logistics cannot consistently deliver cardiac marker results within 1 hour.[98] Although troponins T and I are regarded as equivalent, several troponin I assays have still not been adequately validated or standardised.[96] Both ECS and ACC/AHA reports agree that a single test for troponins on arrival of the patient in hospital is insufficient. The ACC/AHA guidelines suggest a repeat measurement 8–12 hours after the onset of symptoms (evidence level B). The ESC task force recommends a second test 6–12 hours after admission (evidence level C).[94]

Of recent the new high sentivity cardiac troponin T (hs-cTnT) assay has been introduced as a most reliable marker of cardiac damage.[99] The hs-cTnT assay can measure very small elevations which are undetectable using other troponin assays. The sensitivity for detecting ACS using hs-cTnT has greatly improved, but some chronic conditions may now cause abnormal results.[99] Thus follow up testing should be done 3-6 hours after the initial test. A changing troponin indicates an acute event while unchanging elevation indicates chronic cardiac disease.[99] A study on MI patients had revealed more patients with myocardial damage and who were at an increased risk of new cardiac events. The normal result is <15 ng/L and result above this level indicates cardiac damage.

1.6.3 ECHOCARDIOGRAPHY

Two-dimensional echocardiography has become a useful bedside technique in the triage of patients with acute chest pain. Regional wall motion abnormalities occur within seconds after coronary occlusion, well before necrosis occurs. However, wall motion abnormalities are not specific to STEMI and may be due to ischaemia or old infarction. Two-dimensional echocardiography is of particular value when the diagnosis of STEMI is uncertain, and other causes of chest pain such as acute aortic dissection, pericardial effusion, or pulmonary embolism are being considered. The performance of echocardiography should not delay the initiation of treatment. The absence of wall motion abnormalities excludes major myocardial ischaemia.[91]

1.7 DIAGNOSIS

The initial working diagnosis for STEMI includes the following:[91]

- History of chest pain/discomfort,
- Persistent ST-segment elevation or (presumed) new left bundle-branch block.
- Elevated markers of myocardial necrosis (CK-MB, troponins).
- 2-D echocardiography to diagnose wall motion abnormality and to rule out other causes of chest pain/discomfort.

The initial diagnosis and evaluation of the syndrome of UA/NSTEMI is described above.

According to the revised criteria for the diagnosis of MI, any one of the following criteria satisfies the diagnosis for acute, evolving or recent MI.[90]

(1) Typical rise or fall of biochemical makers of myocardial necrosis with at least one of the following:

- Ischaemic symptoms,
- Development of pathological Q wave in the ECG,
- Electrocardiographic changes indicative of ischaemia (ST-elevation or depression),
- Imaging evidence of new loss of myocardium or new regional wall motion abnormality.

(2) Pathologic finding of acute MI.

However, it has been emphasized that because of the time urgency for reperfusion in STEMI, 12-leads ECG is sufficient to initiate such strategies.[90]

Acording to the revised universal definition of myocardial infarction, MI is additionally classified into 5 types; based on pathological, clinical and prognostic differences, as well as different treatment strategies (see table II).[100]

Table II. Universal Classification of Myocardial Infarction[100]

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, Assuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values _5 x 99th percentile URL in patients with normal baseline values (_99th percentile URL) or a rise of cTn values _20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values _10 x 99th percentile URL in patients with normal baseline cTn values (_99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium

or new regional wall motion abnormality.

1.8 MANAGEMENT

The first step in the management of patients with ACS is the prompt recognition of STEMI, since the beneficial effects of therapy with reperfusion are greatest when performed soon after presentation. Once the diagnosis of an acute STEMI is made, the early management of the patient involves the simultaneous achievement of several goals, as outlined below. [101, 102]

- Relief of ischemic pain,
- Assessment of hemodynamic state and correction of abnormalities that are present,
- Initiation of reperfusion therapy (primary PCI or fibrinolysis),
- Antithrombotic therapy to prevent rethrombosis or acute stent thrombosis,
- Beta-blocker therapy to prevent recurrent ischemia and ventricular arrhythmias.

This is then followed by the in-hospital initiation of different drugs that may improve the long-term prognosis. [101]

- Antiplatelet therapy to reduce the risk of recurrent coronary artery thrombosis or coronary artery stent thrombosis,
- Angiotensin converting enzyme (ACE) inhibitor therapy to prevent remodelling of the left ventricle,
- Statins therapy,
- Anticoagulation in the presence of left ventricular thrombus or chronic atrial fibrillation to prevent embolization.

1.8.1 RELIEF OF PAIN AND ANXIETY:

Relief of pain and anxiety is important as the latter increases sympathetic activity which causes vasoconstriction, increased cardiac workload and increased oxygen demand thereby worsening ischaemia. Intravenous opioids (usually morphine) are the analgesics most commonly used in this context. Some of the side-effects include nausea, vomiting, hypotension and respiratory depression. Hypotension and bradycardia usually respond to atropine. Sublingual nitroglycerin is administered to patients presenting with ischemic type chest pain, followed by intravenous nitroglycerin in patients with persistent pain. Oxygen should be administered to those with oxygen saturation <90%, those who are breathless or who have any features of heart failure or shock. The role of supplemental oxygen in patients without hypoxia has not been well studied.[103]

1.8.2 ASSESSMENT OF HAEMODYNAMIC ABNORMALITIES

Evidence of systemic hypo-perfusion (hypotension; tachycardia; impaired cognition; cool, clammy, pale), cardiogenic shock complicated with acute MI requires aggressive evaluation and management. Patients who present with dyspnoea, hypoxia, pulmonary oedema, and/or impending respiratory compromise require aggressive oxygenation, airway stabilization, diuretic therapy and afterload reduction in addition to standard treatment. Sustained ventricular tachyarrhythmias in the peri-infarction period must be treated immediately because of their deleterious effect on cardiac output, possible exacerbation of myocardial ischemia, and the risk of deterioration to ventricular fibrillation (VF).[101]

1.8.3 REPERFUSION STRATEGY

Prompt restoration of myocardial blood flow is essential to optimize myocardial salvage and to reduce mortality.[104] A decision must be made as soon as possible as to whether reperfusion

will be achieved with fibrinolytic agents or primary (direct) percutaneous coronary intervention (PCI) (figure 2).

If high-quality PCI is available, multiple randomized trials have shown enhanced survival compared to fibrinolysis with a lower rate of intracranial haemorrhage and recurrent MI.[105] As a result, the guidelines for the management of patients with STEMI recommends the use of primary PCI for any patient with an acute STEMI who can undergo the procedure within 90 minutes of first medical contact by persons skilled in the procedure.[102] Patients with typical and persistent symptoms in the presence of a new or presumably new left bundle branch block are also considered eligible.[91]

For patients presenting 12 to 24 hours after symptom onset, the performance of primary PCI is reasonable if the patient has severe HF, haemodynamic or electrical instability, or persistent ischemic symptoms.[102]

If primary PCI is not available on site, rapid transfer to a PCI centre can produce better outcomes than fibrinolysis, as long as the door-to-balloon time, including inter-hospital transport time, is less than 90 minutes. For patients who present within two hours of the onset of symptoms, full-dose lytic therapy and transfer to a PCI centre is suggested.[91] The assumption made is that primary PCI cannot be performed in less than 90 minutes at a local PCI centre. For patients who present with symptoms greater than two to three hours transfer for primary PCI is suggested. However, there are times when the patient presents after two hours that PCI cannot be accomplished in less than 120 minutes. In this scenario, clinical judgement needs to be exercised; fibrinolytic therapy may be appropriate in patients with up to 12 hours of symptoms.[91]

FIBRINOLYSIS: Fibrinolysis is given to any patient with STEMI who presents within 12 hours of symptoms onset with no contraindication for fibrinolysis and presents to a facility

without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact.[102] It is given to patients who present to a facility in which the relative delay necessary to perform primary PCI (the expected door-to-balloon time minus the expected door-to-needle time) is greater than one hour.[102] The time interval from first patient contact to initiation of fibrinolytic drug (door to needle time) infusion should be less than 30 minutes.[102] Fibrinolytic therapy has generally not improved outcomes in patients presenting at 12 hours or later and is therefore not indicated in those who are stable and asymptomatic. However, fibrinolysis can be considered up to 24 hours after symptom onset if the patient has ongoing or stuttering chest pain and PCI is not available.[102]

Angiography and possible PCI, if applicable, should be considered within 24 hours after fibrinolysis, called post-thrombolytic PCI.[91] In the CARESS trial, a more conservative strategy with sending patients for angiography only in the case of failed fibrinolysis was associated with a worse clinical outcome when compared with a strategy of referring all patients for angiography and PCI.[91] In order to avoid early PCI during the prothrombotic period following fibrinolysis, on the one hand, and to minimize the risk of re-occlusion, on the other hand, a time window of 3–24 hours following successful fibrinolysis is recommended.[90] Rescue PCI is defined as PCI performed on a coronary artery which remains occluded despite fibrinolytic therapy. The non-invasive identification of failed fibrinolysis remains a challenging issue, but less than 50% ST-segment resolution in the lead(s) with the highest ST-segment elevation 60–90 min after start of fibrinolytic therapy has increasingly been used as a surrogate.[91] Rescue PCI has been shown to be feasible and relatively safe.[102] In a randomized study of 427 patients (REACT), the event-free survival at 6 months after failed fibrinolysis was significantly higher with rescue PCI than with repeated administration of a fibrinolytic agent or conservative treatment.[106] Rescue PCI should be considered when there is evidence of failed fibrinolysis based on clinical signs and

insufficient ST-segment resolution (50%), if there is clinical or ECG evidence of a large infarct, and if the procedure can be performed within a reasonable time delay (up to 12 hours after onset of symptoms).[91]

Facilitated PCI is defined as a pharmacological re-perfusion treatment delivered prior to planned PCI, in order to bridge the PCI-related time delay. Full-dose lytic therapy, half-dose lytic therapy with a glycoprotein (GP) IIb/IIIa inhibitor and GPIIb/IIIa inhibitor alone have been tested for this indication. There is no evidence of a significant clinical benefit with any of these agents, but more bleeding complications were observed.[107, 108]

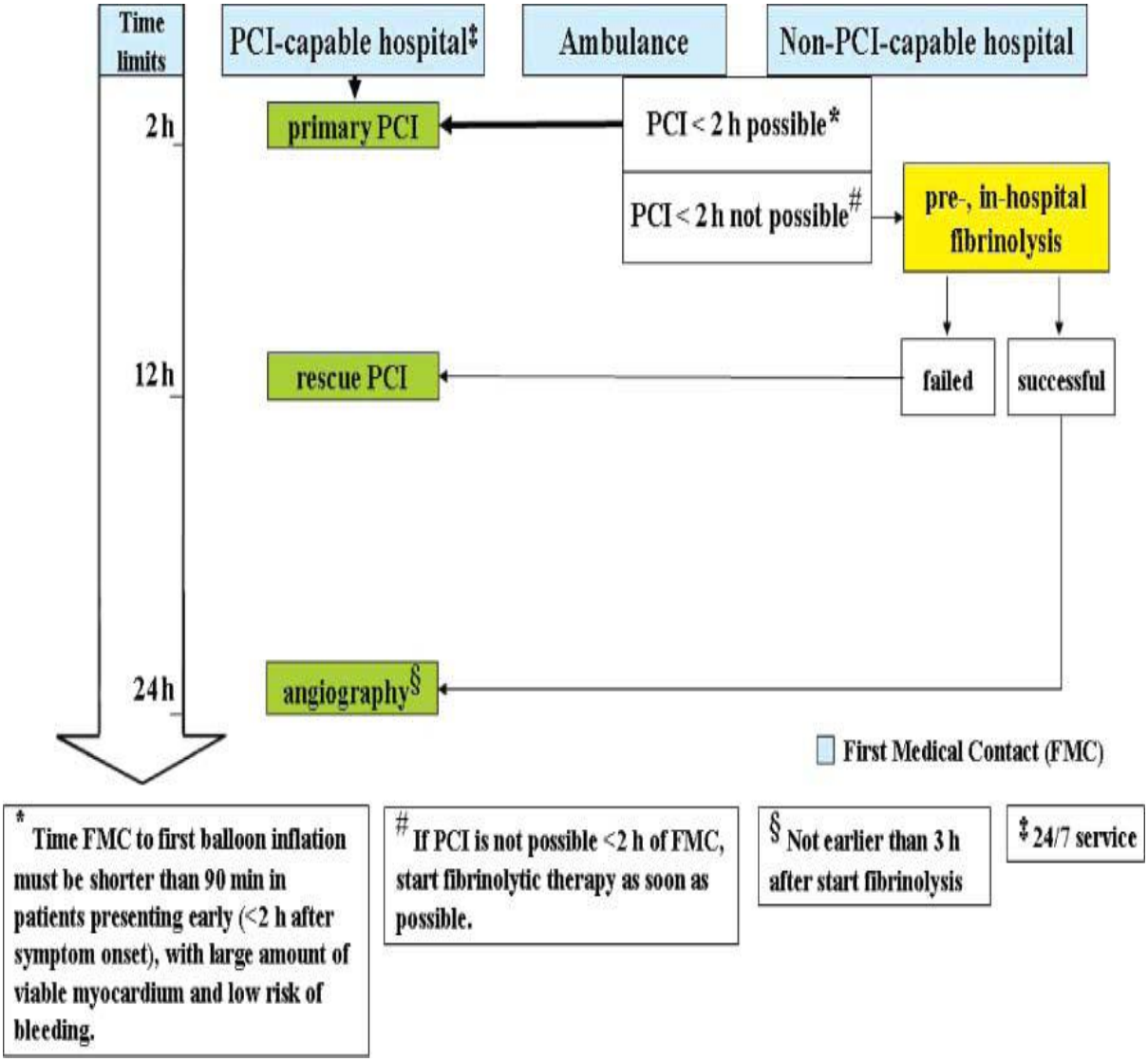


Figure 2: Reperfusion strategies.[91]

1.8.4 BYPASS SURGERY

Coronary-artery-bypass-graft surgery (CABG) is infrequently performed in patients with STEMI. The main indications are for emergent or urgent CABG related to failure of fibrinolysis or PCI, cardiogenic shock, or life-threatening ventricular arrhythmias associated with left main or three-vessel disease.[101] The benefit of revascularization must be weighed up against the increase in mortality associated with CABG in the first three-to-seven days after STEMI. Thus, if the patient has stabilized, surgery should be delayed to allow myocardial

recovery. Patients with critical anatomy should undergo CABG during the initial hospitalization.[101]

1.8.5 ADJUNCTIVE THERAPY

ANTI-COAGULATION THERAPY: The choice of agent depends upon the overall treatment strategy designed for each patient: fibrinolytic therapy with a fibrin specific or non-fibrin specific agent, primary PCI or no reperfusion.[102] Heparin is standard anticoagulant therapy during PCI. The lack of randomized clinical trials of heparin vs. placebo during PCI in STEMI is due to the strong belief that anticoagulation therapy is a requirement during the procedure.[91] It should be given at a dose able to maintain an ACT of 250–350s. Low-molecular-weight heparins (LMWHs) have been studied in a limited number of STEMI patients undergoing primary PCI. Thus, there is little evidence to support their use instead of heparin in this setting.[91] The direct thrombin inhibitor, bivalirudin, has been investigated as an adjunct anti-thrombotic therapy in patients undergoing PCI. In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, bivalirudin was found to significantly reduce the incidence of major bleeding by 40%. [109] The all-cause mortality at 30 days was 1% lower, but acute stent thrombosis occurred more frequently.[109] Fondaparinux, a factor Xa inhibitor, was found to be associated with a non-significant 1% higher incidence of death or recurrent infarction at 30 days.[110] These findings together with the occurrence of catheter thrombosis do not lend support to the use of fondaparinux as the sole anticoagulant in patients undergoing primary PCI.[91]

1.8.6 ANTIPLATELET THERAPY: Aspirin should be given to all patients with STEMI as soon as possible after the diagnosis is deemed probable unless there is contraindication. Aspirin should be started at a dose of 150–325mg in a chewable form (enteric-coated aspirin should not be given because of slow onset of action).[91] An alternative approach, especially if

oral ingestion is not possible, is for IV administration of aspirin at a dose of 250–500mg, although no specific data are available on the relative merits of this strategy.[91] A lower dose (75–160mg) is given orally daily thereafter for life.[91] NSAIDs (apart from aspirin) and selective cyclo-oxygenase (COX-2) inhibitors have been demonstrated to increase the risk of death, re-infarction, cardiac rupture, and other complications in STEMI patients. Thus discontinuation of these drugs is indicated at the time of STEMI.[91]

Clopidogrel has been shown to be especially useful in addition to aspirin in patients undergoing PCI.[111,112] Based on these data, clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI. It is given as a loading dose of 300 mg, however, a 600 mg loading is more effective followed by maintenance dose of 75 mg.[91] Platelet GP IIb/IIIa inhibitors block the final pathway of platelet aggregation. Most of the studies on the role of GP IIb/IIIa antagonists in STEMI have focused on abciximab rather than on the other two members of the family, tirofiban and eptifibatide. However, it remains to be seen whether abciximab provides additional benefit to STEMI patients who receive an optimal clopidogrel treatment prior to PCI.[91]

1.8.7 ADJUNCTIVE ANTICOAGULANT AND ANTIPLATELET THERAPY AFTER FIBRINOLYSIS AND IN THOSE WITHOUT REPERFUSION THERAPY.

Aspirin has been found to be very effective after fibrinolytic therapy; however, it has shown to have additive effect.[91] A similar result was found when clopidigrel was added to aspirin after fibrinolysis. It was found to significantly reduce the odds of the composite end-point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischaemia, leading to a reduction in the need for urgent revascularization of 20%. The rates of major bleeding and intracranial haemorrhage were similar in the two groups.[113] Enoxaparin treatment was associated with a significant reduction in the risk of death and re-infarction at

30 days when compared with a weight-adjusted heparin dose, however, this comes at the cost of a significant increase in non-cerebral bleeding complications. The net clinical benefit (absence of death, non-fatal infarction, or intracranial haemorrhage) favours enoxaparin. Benefit was observed regardless of the type of fibrinolytic agent and the age of the patient.[114] For patients presenting within 12 hours after symptom onset and in whom reperfusion therapy was not given, or in patients presenting after 12 hours aspirin, clopidogrel and an antithrombin agent (heparin, enoxaparin, or fondaparinux) should be given as soon as possible.[115]

1.8.8 MEDICAL THERAPY

β –BLOCKERS: Several trials and meta-analyses have demonstrated that b-blockers reduce mortality and re-infarction by 20–25% in those who have recovered from infarction.[91] The significant mortality reductions observed with b-blockers in heart failure in general further support the use of these agents after STEMI. Evidence from all available studies suggests that b-blockers should be used indefinitely in all patients who have recovered from STEMI and do not have contraindication.[116]

1.8.8.1 ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-I) AND ANGIOTENSIN RECEPTOR BLOCKERS (ARBs).

Several trials have established that ACE-inhibitors reduce mortality after STEMI with reduced residual LV function.[117] There is a strong case for administering ACE-inhibitors to patients who have experienced heart failure in the acute phase, even if no features of this persist and who have an EF of ≤40%. Use of ACE-inhibitors should be considered in all patients with atherosclerosis, but given the relatively modest effect, their long-term use cannot be considered as mandatory for post-STEMI patients who are normotensive, without heart failure or compromised systolic LV function.[91] However, caution should be applied in

acute phase as it may precipitate hypotension and acute renal failure. Valsartan has been shown to be a better alternative to ACE-inhibitors in patients who do not tolerate ACE-inhibitors and have clinical signs of heart failure and/or an EF ≤ 40%.[118]

1.8.8.2 ALDOSTERONE BLOCKADE: Aldosterone blockade may be considered for post-STEMI patients with an EF < 40% and heart failure or diabetes provided that creatinine is < 2.5 mg/Dl in men and 2.0 mg/dL in women, and potassium is < 5.0 mEq/L.[119] Routine monitoring of serum potassium is warranted and should be done with great care when other potential potassium-sparing agents are used.

1.8.8.3 CALCIUM ANTAGONISTS: The use of verapamil and diltiazem may be appropriate when b-blockers are contraindicated, especially in obstructive airways disease. Caution must be exercised in the presence of impaired LV function.[91] Trials with dihydropyridines have failed to show a benefit in terms of improved prognosis and these should, therefore, only be prescribed for clear clinical indications such as hypertension or angina.[120]

1.8.8.4 STATIN THERAPY

Statin therapy should be initiated as early as possible in all patients with STEMI.[91] Several trials have unequivocally demonstrated the benefits of long-term use of statins in the prevention of new ischaemic events and mortality in patients with coronary heart disease. The targets established by the Fourth Joint Task Force of the ESC and other societies in patients after infarction are: for total cholesterol, 4.5 mmol/L with an option of 4.0 mmol/L if feasible, and for lower LDL cholesterol 1.8 mmol/L with an option of 80 mg/dL 2.0 mmol/L, if feasible.[121]

1.8.8.5 ANTIPLATELETS AND ANTICOAGULANTS COMBINATION

Aspirin can be replaced by oral anticoagulants at the recommended international normalized ratio (INR) if there is an indication for oral anticoagulation (e.g. atrial fibrillation, LV thrombus, mechanical valves).[91] However, in a large meta-analysis of ACS patients the combination of aspirin and oral anticoagulation prevented three major adverse events and caused one major bleed per 100 patients treated compared with aspirin alone.[122] This combination, therefore, seems to be a reasonable treatment for STEMI survivors who have a high risk of thrombo-embolic events. In some patients, there is an indication for dual antiplatelets therapy and oral anticoagulation (e.g. stent placement and AF) called 'triple therapy'.[91] Triple therapy seems to have an acceptable risk–benefit ratio provided clopidogrel co-therapy is kept short and the bleeding risk is low.[123] Oral anticoagulants may also be considered in patients who do not tolerate aspirin or clopidogrel.[91] Treatment duration of 12 months is recommended for clopidogrel whether or not a stent has been placed.[111]

1.8.9 MANAGEMENT OF NSTEMI/UA

Once the diagnosis of either UA or an acute NSTEMI is made, medical therapy should be started immediately. At the same time, early risk stratification in patients with ACS is essential to identify those patients at highest risk for further cardiac events who may benefit from a more aggressive therapeutic approach.[84] Clinical trials have identified a number of factors in predicting high risk and benefit from an early invasive strategy.[124-126] These include the presence and extent of ST segment depression, elevated cardiac biomarkers, evidence of hemodynamic instability and persistent chest pain despite appropriate medical therapy. These variables have been used to create risk scores such as TIMI, GRACE, and PURSUIT which allow decision for early invasive therapy.

1.8.9.1 EARLY REPERFUSION AND REVASCULARIZATION

Avoidance of fibrinolysis: Prospective trials have demonstrated that fibrinolytic therapy is not beneficial in patients with non-ST elevation ACS.[124, 125] The ACC/AHA and ACCP have recommended **against** the routine use of fibrinolytic agents in patients with non-ST elevation ACS.[126,127]

Immediate angiography and revascularization: Patients who have non-ST elevation ACS and one or more of the following characteristics are at extremely high risk of an adverse cardiovascular event in the short term:

- Haemodynamic instability or cardiogenic shock,
- Severe left ventricular dysfunction or heart failure,
- Recurrent or persistent rest angina despite intensive medical therapy,
- New or worsening mitral regurgitation or new ventricular septal defect,
- Sustained ventricular arrhythmias.

It is recommend that patients with any of these five characteristics be referred for immediate coronary arteriography and revascularization.[126, 127]

For those patients without one of the above extremely high risk characteristics, randomized trials have shown benefit of an early invasive approach in high-risk ACS. While the optimal timing is uncertain, the majority of patients undergo coronary revascularization early (ie, within 24 hours).[128] The TIMI risk score is a widely-used predictive model used to guide invasive versus conservative strategy which is based upon seven variables available at presentation:[129]

- Age ≥65 years,
- Presence of at least three risk factors for CHD (hypertension, diabetes, dyslipidemia, smoking, or positive family history of early MI),
- Prior coronary stenosis of ≥50%,
- Presence of ST segment deviation on admission ECG,
- At least two anginal episodes in 24 hours prior,
- Elevated serum cardiac biomarkers,
- Prior use of aspirin in the last seven days (which is probably a marker for more severe coronary disease).[130]

A value of '1' is assigned when a factor is present and '0' when it is absent.[129] Patients are considered to be at 'low risk' with a score of '0 to 2'; 'intermediate risk' with a score of '3 to 4'; and 'high risk' with a score of '5 to 7'. Patients with high-risk and intermediate TIMI scores are found to benefit from early invasive strategy. 'High risk' criteria have also been defined by the 2007 ACC/AHA guidelines on unstable angina and non-ST elevation MI and the 2005 European Society of Cardiology guidelines as cardiac biomarker elevations, ST segment depression, recurrent angina, haemodynamic instability, sustained VT/VF, prior PCI within the prior six months or CABG, and diabetes.[84,131]

The choice of revascularization procedure after angiography depends upon the location and extent of disease. Among patients with an appropriate lesion, PCI is most often performed, but coronary artery bypass grafting (CABG) is usually preferred for the treatment of patients with left main or left main equivalent disease, or three or two vessel disease involving the left anterior descending artery with left ventricular dysfunction or treated diabetes.[132]

1.9 MYOCARDIAL INFARCTION WITH NORMAL CORONARY ARTERIES

In clinical trials, 9 to 14% of patients with a non-ST elevation ACS who underwent early angiography had no significant coronary stenosis.[125, 133-135] Possible mechanisms include rapid clot lysis, vasospasm, myocarditis, and coronary microvascular disease. Such patients have a much better short-term prognosis than those with a culprit lesion.[134, 135]

1.10 MYOCARDIAL INFARCTION IN SPECIAL POPULATION

1.10.1 ELDERLY PATIENTS: It is estimated that 60 to 65% of MIs occur in patients ≥65 years of age and 33% occur in patients ≥75 years of age.[136] Although patients 75 years and older have been under-represented in clinical trials of ACS, the following observations concerning acute MI in older adults compared to younger patients are generally accepted:[128]

- Elderly patients are more likely to have NSTEMI rather than STEMI. However, STEMI is not uncommon and it is estimated that 60 to 65% of STEMIs occur in patients ≥65 years of age and 28 to 33% occur in patients ≥75 years of age.[137]
- Elderly patients more frequently have an atypical presentation, including silent or unrecognized MI due to presenting symptoms of syncope, weakness, or confusion (delirium).[126] Delays in diagnosis have been well-documented and often lead to delays in therapy.[128]
- Patients ≥75 years of age have higher in-hospital mortality (19 versus 5 percent in one series). Both bleeding and recurrent MI are also more frequent.[128]
- Elderly patients are more likely to have frequent and severe bleeding as a consequence of antithrombotic therapy.[137]

Some of the worse outcomes after acute MI probably result from comorbidities in elderly patients, but also can be attributed in part to a lower likelihood of receiving potentially beneficial therapies due to concerns about toxicity. Therapies such as beta-blockers, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) are all utilized to a lesser degree in elderly patients.[138-140] A retrospective review of almost 57,000 patients with non-ST elevation acute coronary syndrome found that after adjustment, patients (including those ≥75 years of age) who received more recommended therapies had lower in-hospital mortality rates than those who did not.[141] Thus, although concern about risks and side effects is appropriate, older age alone should not be an indicator to withhold recommended therapy.

The 2007 ACC/AHA guidelines recommend that elderly patients (defined as greater than 75 years of age) with unstable angina and NSTEMI should receive the same treatment as younger patients with the following cautions:[84]

- The patient's general health, comorbidities, cognitive status, and life expectancy should be taken into account.
- Increased sensitivity to hypotension-inducing drugs and possible altered drug pharmacokinetics should be considered. Calculation of the creatinine clearance is recommended for all patients ≥75 years of age at the time of initial care.[128] This calculation requires a stable serum creatinine concentration.
- Intensive medical and interventional management can be undertaken with close monitoring for adverse effects.

1.10.2 COCAINE ASSOCIATED MYOCARDIAL INFARCTION: Myocardial infarction is a well-described complication among patients presenting with cocaine-induced

ischemic symptoms. According to the 2008 American Heart Association scientific statement on the management of cocaine-associated chest pain and myocardial infarction, patients should be managed in a manner similar to other ACS patients with the following points to be considered. [142]

- Benzodiazepines should be administered early,
- Beta-blockers should not be used in the setting of acute cocaine intoxication with chest pain due to the possibility of exacerbation of coronary artery vasoconstriction.

1.11 PROGNOSIS

Coronary heart disease is the leading cause of morbidity and mortality worldwide.[4] It is the most common cause of death in Europe.[4] It is the most common cause of death (and premature death) in the UK.[18] In UK, one in 5 men and 1 in 7 women die from CHD. The death rates from CHD is said to have fallen by 45% for people aged less than 65 years in the last 10 years.[18] This fall is greatest in those aged 55 years and over. It is largely due to a reduction in the major risk factors (mostly smoking) and improvement in treatment and secondary prevention. A similar decline in the mortality rate from MI was observed in a hospital surveillance for myocardial infarction and of in-hospital and out-of-hospital deaths due to CHD among 35-to-74-year-old residents of four communities of varying size in the United States.[17] However, there was no evidence of a decline in the incidence of hospitalization for first myocardial infarction among either men or women. In fact, such hospital admissions have increased by 7.4% per year among black women and 2.9% per year among black men.[17]

Analysis of data from the MONICA centres over a 10-year trend indicates an average of 4% reduction in CHD for men and women.[143] Thus, studies across the western world have

reported a substantial decline in the mortality which is a result of the improved medical care particularly the widespread use of reperfusion techniques and the adjunctive use of multiple medical therapies.[17,144,145] However, while the CHD mortality has declined in the last few decades, the use of age-adjusted rates to describe the CHD mortality obscures the fact that the decline largely represents the postponement of CHD deaths until older age. Thus, the burden of CHD is increasing in parallel with the increase in life expectancy.[146, 147] In other words, as more persons live with heart disease, the burden of prevalent disease with its assorted co-morbid complications is increasing. Also, the decline in the death rate of CHD among the developed economies of Europe, North America Australia and New Zealand is contrasted with an increase in mortality in several countries of eastern and central Europe, most notably countries of the former USSR.[148] For example, age adjusted CHD death rates in Ukraine between 1989 and 1999 rose by 60% in both men and women.[148]

Despite the falling age adjusted mortality for myocardial infarction in the Western world, the disease prevalence for non-fatal component of ACS remains high and the economic costs are immense. The annual cost of CHD ranks highest of all diseases for which comparable analysis are performed.[149] The economic cost is related to the direct cost to the health care system, the lost of productivity and to the provision of formal and informal care of patients.[148] For example, in the UK the economic burden of CHD has been estimated at €2.6 billion for direct health care costs in 1999 and a further €3.6 billion for the provision of care for CHD patients and €4.4 billion for the loss of productivity.[148]

Previous studies in Sub-Saharan Africa revealed the low prevalence of ischaemic heart disease among Africans.[150,151] However, recent studies revealed ischaemic heart disease as one of the emerging cardiovascular diseases in Africa and other developing countries.[38,39,152] The WHO estimated that in 2005, IHD caused approximately 361,000 deaths in the African region, and current projections suggest that this number will nearly double by 2030.[5] More

significant is that for people aged >60 years in the African region., IHD is already the leading cause of death in men and the second leading cause of death in women.[153] Ischaemic heart disease may be complicated by an episode of sudden death. In a review of the causes of sudden cardiac death in Ile-Ife Nigeria, there was an increase of sudden cardiac death due to myocardial infarction from 4% in 1998 to 6.2% in 2004.[154,155] A study done in North Central Nigeria, reported MI to be responsible for 9% of sudden cardiac death among the causes of deaths reported to coroner for medico-legal autopsies.[156] Ischaemic heart disease is said to be the leading cardiovascular cause of death and the fifth commonest cause of death in the Western Cape province of South Africa.[157] In the discussion accompanying the report of an autopsy study of coronary atherosclerosis and myocardial infarction in Ethiopia in 1989, Maru reviewed case reports published in the preceding two decades from Ethiopia, Ghana, Ivory Coast, Kenya, Nigeria, South Africa, Uganda and Zimbabwe and concluded that the burden of coronary heart disease was already on the rise.[158]

1.12 OUTCOMES PREDICTORS

Certain demographics and clinical characteristics have been identified as prognostic risk factors among patients with ACS.

1.12.1 Demographic prognostic risk factors

Age has been increasingly recognized as a critical determinant of outcome in patients with acute ischemic heart disease.[2,159] In one study, this relation was relatively flat until the age of 60, when the risk of death accelerated dramatically.[160] In the TIMI III registry, patients over the age of 75 with UA/NSTEMI had more diffuse and severe coronary disease and more adverse outcomes both in hospital and within the first six weeks after discharge than those less than 75 years of age.[161] Some previous studies have revealed sex as a prognostic factor in ACS, however, those studies have found that when other baseline characteristics were

adjusted for, the impact of sex was weakened but not eliminated.[161] Most studies report higher in-hospital and 30-day mortality after MI in women compared to men.[162-165] This effect is primarily seen in younger women (less than 55 years), and differences between the sexes declines progressively with age.[164,165] It is thought that the higher early mortality in women may be accounted for by differences in symptoms at presentation.[166] In a study to determine the predictors of 30-day mortality after myocardial infarction after adjustment for multiple other baseline characteristics, female gender was only a marginally independent prognostic factor.[159]

1.12.2 Medical history

Several baseline features have been previously identified as important prognostic factors among patients with ACS.[8, 159] Patients with prior MI have been shown to be at increased risk of subsequent death in a previous study.[8] Similarly, peripheral and cerebral vascular diseases have been associated with more extensive atherosclerosis.[167] Recent studies have shown that patients with diabetes have more extensive coronary atherosclerosis and worse left ventricular function.[159,168] A history of hypertension was also associated with increased risk, although the strength of the relation was much less than that of diabetes.[169] The influence of smoking, family history, and elevated cholesterol were paradoxical: they were associated with lower mortality despite being traditional risk factors for coronary artery disease.[159] Several other studies also reported lower mortality in patients with a history of smoking.[170-172] Negative prognostic implications of prior coronary artery bypass grafting has been reported.[159] This probably reflects the presence of more left ventricular dysfunction and multi-vessel coronary disease, leaving patients at increased risk of adverse outcomes in the setting of an acute event.[159]

1.12.3 Haemodynamic and infarct site

Systolic blood pressure is a critical factor for survival among in-hospital patients admitted with ACS.[159] In a study of poor prognostic factors associated with mortality among ACS, survival rate began to decline at SBP of 120 mmHg.[159] In a study to determine the importance of SBP at admission on mortality among ACS patients revealed that as SBP increased, there was a reduction for in-hospital mortality risk.[1] This effect was greater in patients presenting with SBP levels between 90 and 160 mm Hg compared with those with SBP levels >160 mm Hg on admission.[1] SBP value of 135 mmHg constitutes the optimal cut off point for classification between patients who died during hospitalization and the rest of the patients.[1] In another study in Japan, SBP lower than 106 mmHg was significantly associated with higher mortality.[173] In the same study, death due to the cardiogenic shock, congestive heart failure and ventricular fibrillation was found to be more common among patients with a SBP lower than 106 mm Hg.[173] An Indian study revealed that those AMI patients having SBP of less than 140 mm Hg at admission were 5.39 times more likely to die than those with admission SBP measurement of more than 140 mm Hg.[174]

The association between SBP on hospital admission and prognosis of patients with MI is not new. Several clinicians have observed that the higher the blood pressure level at presentation, the better the prognosis of MI patients.[1, 2] It is well known that SBP levels depend on a combination of cardiac output and peripheral resistance. SBP value within normal limits during the acute phase of ACS indicates a preserved combination of cardiac output and systemic resistance. This may reflect more limited necrosis in myocardial tissue, without severe atrioventricular conduction system disorders and with less pronounced adrenergic neurohormonal system activation.[1]

Heart rate on admission is frequently overlooked as an important prognostic indicator. Indeed, patients with significant sinus tachycardia or bradycardia at hospital admission had an increased risk of death.[166] Previous studies have identified sinus tachycardia as an independent prognostic factor, presumably because it represents activation of the sympathetic nervous system as a consequence of infarct size.[175] The physiological significance of bradycardia may represent a variety of underlying pathophysiological problems, ranging from conduction system disturbances to agonal rhythms.

The relation between outcome and location of infarction is complicated. Multiple previous studies have reported that patients with anterior infarction have the highest risk of death, and that isolated inferior infarction has been associated with the lowest risk.[159, 176, 177] A detailed analysis from the GISSI I trial showed that the number of leads with ST-segment elevation was more important than infarction location.[177] The Killip classification have also been found to be a predictor of outcomes among ACS.[5, 173] The Killip classification, published in 1967, categorizes patients with an acute MI based upon the presence or absence of simple physical examination findings that suggest LV dysfunction.[178]

- Class I - no evidence of HF,
- Class II - findings consistent with mild to moderate HF (S3, lung crepitations less than one-half way up the posterior lung fields, or jugular venous distension),
- Class III - overt pulmonary oedema,
- Class IV - cardiogenic shock.

Evidence of even lesser degrees of HF on physical examination or chest x-ray indicates extensive LV systolic and/or diastolic dysfunction and is associated with a worse prognosis compared to those with no pulmonary congestion.[179] The higher the Killip class on

presentation, the greater the subsequent mortality.[180,181] Killip class is applicable in all the spectrum of ACS. For example, Killip class ≥3 was found to be an independent positive predictor of mortality[173] as well as being the most powerful predictor, with a two-fold increased risk for death with each worsening of class respectively.[8]

The occurrence of atrial fibrillation (AF) in patients with non-ST elevation ACS is associated with increased mortality, similar to observations in ST elevation MI.[182] In an analysis from the PURSUIT trial, 6.4% of patients with non-ST elevation ACS developed AF during hospitalization .[182] These patients had a higher mortality at 30 days (adjusted hazard ratio 4.4) and at six months (adjusted hazard ratio 3). The incidence of all-cause death from 48 hours to 30 days was greater in those with VT/VF within 48 hours of randomization than in those without (13.0% versus 2.2%; adjusted odds ratio 6.73, 95% CI 2.68-16.90).[183] When compared to patients without VT/VF, those with VT/VF >48 hours had a higher risk of death at one year than was seen for those with VT/VF ≤48 hours (hazard ratios 20.70 versus 7.45).[183]

1.12.4 ECG FEATURES: The ECG can provide prognostic information. The highest rate of mortality and morbidity occurred in patients with transient ST elevation and substantial myocardial damage.[184] In those with NSTEMI/UA, the prognosis is worse in patients with ST segment depression compared to those with T-wave inversion alone or a normal ECG.[184] In a study of over 5000 patients in a patient-pooled dataset (from the FRISC II, ICTUS, and RITA-3 databases), the presence of left-bundle-branch-block on the admission electrocardiogram was independently associated with a significantly increased rate of long-term cardiovascular death or myocardial infarction (adjusted hazard ratio 1.64, 95% CI 1.18-2.28).[184] This finding appeared to be due in part to the increased age and increased frequency and severity of left ventricular dysfunction. Patients with NSTEMI who have QRS duration

≥100 ms in the absence of bundle-branch-block may have significant increases in-hospital mortality at one and five years.[185]

1.12.5 SERUM BIOMARKERS: A number of serum biomarkers can be measured to assist in risk stratification of patients with UA/NSTEMI. The two most commonly used are serum troponins and CK-MB. Other biomarkers, such as myoglobin, C-reactive protein (CRP), and brain natriuretic peptide (BNP), also have prognostic significance. Cardiac troponin I (cTnI) and cTnT are sensitive and specific markers of myocardial necrosis. The largest experience on the magnitude of the predictive value of serum troponin-T comes from the GUSTO IV ACS trial of over 7,000 patients who did not undergo early revascularization.[186] The patients were stratified by quartiles of troponin T (≤ 0.01, 0.01 - 0.12, 0.12 - 0.47, and > 0.47). The 30 day mortality rate increased from 1.1% to 7.4% from the first to fourth quartiles of cTnT. There is also a graded relationship between serum CK-MB elevations and prognosis in ACS.[187, 188] The relationship between peak CK-MB level and outcome in patients with a non-ST elevation ACS was evaluated in the PURSUIT trial of 8,250 patients from whom at least one CK-MB sample was obtained.[187] Mortality was related to the presence of an elevated CK-MB level. The 30-day and six-month mortality was 1.8% and 4%, respectively, when peak CK-MB levels were normal; these patients were considered to have UA. Mortality increased progressively to 8.3% and 11% at 30 days and six months when peak CK-MB levels were more than 10 times normal.[187]

A serum myoglobin above 110 µg/l was associated with the following significant changes; a lower incidence of TIMI grade III flow, a greater likelihood of thrombus in the infarct-related artery, and an increase in six-month mortality (adjusted odds ratio 3.0). These effects were independent of other prognostic variables such as ECG changes and serum cTnI and CK-MB.[189] The predictive value of plasma BNP was best illustrated in a study of 2,525 patients in whom plasma BNP was measured at a mean of 40 hours after the onset of symptoms.[190]

After adjusting for other predictors of risk, the odds ratios for death at 10 months were 3.8, 4.0, and 5.8 for concentrations in the second, third, or fourth quartiles compared to those in the lowest quartile. Higher plasma BNP was also associated with an increased risk of new or recurrent myocardial infarction and new or worsening heart failure. Plasma N-terminal pro-BNP (N-pro-BNP) has similar predictive value.[191-193]

The largest experience on the magnitude of the predictive value of serum CRP and its interaction with serum troponin T comes from the GUSTO IV ACS trial of over 7,000 patients.[186] The patients were stratified by quartiles of CRP and troponin T at enrolment. The 30-day mortality rate increased from 2% to 6.3% from the first to fourth quartiles of CRP. Data from TACTICS-TIMI 18 suggest that women with a non-ST elevation ACS are more likely to have elevations of CRP and BNP, and less likely to have elevations of troponins and CK-MB than men, despite similar levels of risk .[194] As a result, a multimarker approach that incorporates CRP and BNP as well as troponins may more accurately predict risk for both genders.

1.12.6 GLYCAEMIC CONTROL: Diabetic patients have a worse long-term outcome after a non-ST elevation of ACS than those without diabetes.[195] In addition, there is increasing evidence that suboptimal glycaemic control in diabetic patients and stress hyperglycaemia in non-diabetic patients are associated with worse in-hospital outcomes after an acute MI and that strict glycaemic control may be beneficial.[195]

1.12.7 WHITE BLOOD CELL COUNT: Patients with a higher white blood cell (WBC) count, which is a marker of inflammation, have an increased risk for an adverse event, in-hospital mortality, and short and long-term mortality after non-ST elevation ACS as well as acute ST elevation MI.[196-198]

1.12.8 ANAEMIA: The presence of anaemia appears to be an adverse predictor of prognosis in patients with a non-ST elevation ACS. In a review of clinical trials that included over 14,500 patients with non-ST elevation ACS, the likelihood of cardiovascular mortality, non-fatal MI, or recurrent ischemia at 30 days was increased in patients with haemoglobin below 11 g/dL compared to those with haemoglobin of 15 to 16 g/dL.[199]

1.12.9 IMPAIRED RENAL FUNCTION: Patients with end-stage renal disease have a higher risk for and a worse outcome after, myocardial infarction. However, lesser degrees of renal dysfunction also predict an adverse prognosis in patients with acute MI. The magnitude of this effect has been examined in several studies.[200-202] In addition to renal dysfunction; the blood urea nitrogen (BUN) level may be an independent risk factor for mortality.[203]

1.12.10 Modifiable factors

Of the predictors of adverse outcome that can be modified, time from the onset of symptoms to hospital arrival or treatment is the most important.[159] After adjustment for other factors in the model, each additional hour is associated with a measurable increase in the risk of death.[159] In the same study, after adjustment for all known prognostic factors, the favorable effect of treatment with accelerated TPA and intravenous heparin remained significant compared with other treatment strategies.[159] In another report, AMI patients reporting after more than 24 hours of onset were 4.27 times more likely to die during hospital stay compared to those reporting within 6 hours of onset of AMI.[174]

1.13 RISK STRATIFICATION

The American College of Cardiology/American Heart Association and the European Society of Cardiology Consensus guidelines recognize the importance of early risk stratification in the management of ACS and recommend an integrated approach to risk assessment.[204]

Because patients with ischaemic discomfort are heterogeneous in terms of risk of cardiac death and non-fatal ischaemic events, an assessment of prognosis guides the initial evaluation and treatment. An estimation of the risk is useful in (1) Selection of the site of care (coronary care unit, monitored step-down unit, or outpatient setting) and (2) Selection of therapy, and invasive management strategy.[205]

The level of risk is estimated by integrating the variables from the history, physical examination, ECG, assessment of renal function and cardiac biomarker measurements in a patient presenting with the features suggestive of ACS.[205] The patients can then be categorised into 'low', 'intermediate' and 'high risk' of cardiovascular events respectively.[205] However, optimal risk stratification requires accounting for multiple prognostic factors (see above prognostic factors) simultaneously by a multi-variable approach.[205]

There are number of risk assessment tools available to assist in assessing risk of death and ischaemic events in patients with ACS, thereby providing a basis of therapeutic decision making.[205]

Antman et al developed a 7-point risk score, the "TIMI Risk Score" (Thrombolysis In Myocardial Infarction) comprised of age ≥65 years, more than 3 coronary risk factors, prior angiographic coronary obstruction of ≥50%, ST-segment deviation, more than 2 angina events within 24 hours, use of aspirin within 7 days and elevated cardiac makers.[206] The score was defined as the simple sum of these individual prognostic variables. The risk of developing an adverse outcome, death, re-infarction or recurrent severe ischaemia that requires revascularisation, ranged from 5% with a score of 0-1 to 41% with a score of 6 or 7.[206] The TIMI risk index, a modification of the TIMI risk score that uses the variables: age, systolic blood pressure and heart rate, has not only been shown to predict short term mortality

in STEMI but has also been useful in prediction of 30 days and 1 year mortality across the spectrum of patients with ACS, including UA/NSTEMI.[207]

The PURSUIT risk model, developed by Boersma et al.[208] based on patients enrolled in the Receptor Suppression Using *Integrilin* (PURSUIT) trial, is another useful tool to guide in the clinical decision making process when a patient is admitted to hospital. In this risk model, clinical features associated with increased 30 day incidence of death and the composite of death or myocardial re-infarction were (in order of strength) age, heart rate, systolic blood pressure, ST-segment depression, sign of heart failure (HF) and cardiac biomarkers.[208]

The GRACE risk model, which was developed from Global Registry of Acute Coronary Events (GRACE) is useful in predicting in-hospital mortality (and death or MI) and subsequent treatment and intensity in STEMI, NSTEMI and UA.[8] The eight variables used in the GRACE risk model are: older age; Killip class; SBP; ST-segment deviation; cardiac arrest during presentation; serum creatinine level; positive initial cardiac biomarkers and heart rate.[8] The sum of scores is applied to a reference nomogram to determine the risk of mortality from hospital discharge to 6 months.[8]

An analysis comparing the 3 risk score (TIMI, PURSUIT and GRACE) concluded that all the three tools demonstrated good predictive accuracy for death and MI at one-year, thus identifying patients who may benefit from aggressive therapy, including early myocardial revascularisation.[209]

1.14 JUSTIFICATION FOR THE STUDY

Despite therapeutic advances, recent large-scale randomized clinical trials reported 6% to 9% early mortality rates among ACS patients, even for those receiving thrombolytic therapy within 6 hours of symptom onset.[8-11] Often, choices among alternative therapies or decisions

regarding the allocation of clinical resources are based on assessment of patient risk. Therefore, careful attention to the pivotal factors that increase risk of in-hospital morbidity and mortality might illuminate the role of second-tier interventions or adjunctive pharmacotherapeutics that would further lower the fatality rate of ACS.

Studies across Europe and America have shown that SBP on admission is an independent predictor of in-hospital mortality among patients admitted with myocardial infarction.[1-3, 12] However; populations in Africa constitute individuals with different ethnicity including Black, Coloured, Asian and European origin. Consequently, it is not known whether information derived from Western Europe and America is applicable to African populations. There is a scarcity of data with regard to relationship of admitting SBP level and outcomes of ACS from Africa. The purpose of this study is therefore, to determine the relationship of admission SBP, clinical characteristics and outcomes among patients admitted with features of ACS to Charlotte Maxeke Johannesburg Academic hospital (CMJAH), South Africa.

1.15 GENERAL OBJECTIVE

To determine the relationship of SBP on admission, clinical characteristics and mortality among in-hospital patients admitted with features of ACS to CMJAH.

1.15.1 SPECIFIC OBJECTIVES

1) To determine the demographic and clinical characteristics of patients admitted with ACS.
2) To determine the relationship between different groups of SBP on admission and clinical characteristics among in- hospital patients with ACS.
3) To determine the relationship between different groups of SBP on admission and outcome of patients admitted with ACS.
4) To determine the mortality predictors among patients admitted with ACS to CMJAH.

CHAPTER 2

METHODOLOGY

The protocol for this study was approved by the Human Ethics Committee of the University of the Witwatersrand with ethics clearance certificate number of M130336.

2.1 Study Site: Cardiology division of CMJAH.

2.2 Study Design: Single centre retrospective study.

2.3 Study population: Patients 18 years and older hospitalised at CMJAH with a diagnosis of ACS from January 2010 to June 2012.

2.3.1 Inclusion criteria;

(1) Patients 18 years and above,

(2) Patients admitted with primary diagnosis of ACS.

2.3.2 Exclusion criteria;

(1) Patients whose data was incomplete from the records.

(2) Patients diagnosed with peri-procedural or in-hospital MI.

2.4 Methods

All patient data was obtained from the patient records in the database unit of the cardiology division of CMJAH. A standard patient datasheet was used to collect patient details with regard to demographic information, cardiovascular history, and risk factors. Detailed cardiovascular, general and other systemic examination findings of the patients were collected as well. Records of the blood chemistry, lipid profile, cardiac biomarkers as well as a full blood count were included. Electrocardiographic and echocardiographic findings were collected. All the drugs given to the patients as well as the type of interventional or surgical procedures performed were collected and documented on the datasheet. Those patients with missing information on the database had their information retrieved from the main Records department of the hospital. Patients were classified into 4 quartiles based on systolic blood

pressure at admission as follows: ‘SBP <100mmHg’, ‘SBP 100-129mmHg’ (Normal), ‘SBP 130-139 mmHg (pre-hypertension) and ‘SBP ≥140mmHg’ (hypertension).

2.5 Definition of terms:

2.5.1 Acute coronary syndrome (ACS)

ACS was defined as a constellation of clinical symptoms that are compatible with acute myocardial ischaemia and comprised both MI and UA.[205]

2.5.2 Acute MI

MI was defined as biomarker elevation (troponin I > 0.4ng/mL or CKMB > 8.8 ng/mL) and any one of the following; (1) ischaemic symptoms, (2) development of pathologic Q wave/s on ECG, (3) Electrocardiographic changes indicative of ischaemia (ST-segment elevation or depression). Thus, this definition encompassed both ST-segment MI (STEMI) and non ST-segment MI (NSTEMI).[13]

2.5.3 Unstable angina

This was defined as occurrence of angina at rest and lasting for > 20 minutes with or without ECG changes of ischaemia (ST-segment depression of at least 0.05 mV and T wave invertion of >0.1 mV) but without elevation of biomarkers.[205]

2.5.4 Systolic blood pressure (SBP) on admission

This was defined as the first SBP recorded in the supine or sitting position at presentation to the emergency department. The SBP was measured by a cardiology fellow or a physician on call/duty using mercury sphygmomanometers under standardised techniques.

2.5.5 Dyslipidaemia and obesity

This was defined as TC ≥ 5.2 mmol/L, LDL ≥ 3.37 mmol/L, or HDL <1 mmol/L.[208] Fasting lipid profile was used for the assessment of lipid abnormality. Obesity was diagnosed if the BMI was ≥ 30kg/m^2 as obtained from the patients' records.[210]

2.5.6 Diabetes Mellitus (DM)

Defined as a history of diabetes, need for anti-diabetic agents, or a fasting plasma glucose greater than or equal to 7 mmol/L , two-hour plasma glucose greater or equal to 11.1 mmol/L in the presence of the classic symptoms of DM.[210]

2.5.7 Renal impairment

This was defined as a serum Cr of >114 μmol/l.[205]

2.5.8 Hypertension

Patients were considered to be hypertensive if they had history of hypertension, were on anti-hypertensive medication or had SBP and DBP persistanly greater than 140 mmHg and 90 mmHg respectively.[211]

2.5.9 Alcohol consumption

'Non-drinker': a person who is generally abstinent of alcohol or only drinks on special occasions.[212]

'Moderate drinker': a person that drinks not more than 2 standard drinks per day for a man aged 65 years or less, or not more than 1 standard drink per day for a man more than 65 years or a woman of any age. One standard drink is equivalent to 350ml can of beer or one glass of wine or a mixed drink containing 45ml of 80-proof spirit.[212]

'Heavy drinker': a person that consumes alcohol in excess of the amount consumed by a moderate drinker.[212]

2.6 Data analysis

All data generated were collated, checked and analysed using computer-based Statistical Package for Social Sciences [SPSS] version 16.0. Quantitative variables were described using mean and standard deviation. Qualitative variables were presented as percentages and bar charts. The non-parametric test χ^2 (chi-squared) or Fisher's exact test was used to test for significance among categorical variables. Multiple logistic regression analysis was used to determine predictors of in-hospital mortality. Confidence interval of 95% was used and a p-value of less than 0.05 was regarded as significant.

CHAPTER 3

RESULTS

A total of 658 consecutive patients with a diagnosis of ACS admitted at cardiology division of CMJAH were recruited during the two and half years study period (from January 2010 to June 2012). Of these 159 (24.2%), 299 (45.4%), and 200 (30.4%) patients were recruited for the year 2010, 2011 and 2012 respectively (see figure 3). The first six-month (January-June) prevalence of ACS progressively increased along the 3 years of this study (see figure 4). The total cardiovascular admission during the study period was 3016 patients, giving a 21.8% prevalence of ACS in this study. However, a total of 613 patients who had complete clinical data from their records were used for the rest of the study. The remaining 45 patients with incomplete data from their records were excluded from further analyses.

3.1 Socio-demographic characteristics of the patients.

The 613 patients consisted of 451 males (73.6%) and 162 females (26.4%), with male to female ratio of 2.8:1. The mean age of the study patients was 58.9 ±12.5 years (range from 18 to 94 years), with the mean age of 57.4 ±11.9 years and 63.0 ±12.6 years for male and female respectively. Females were significantly older than males in this study ($p < 0.0001$). The majority of patients were in the 58-67 year age group (figure 5).

The demographics of the four racial groups Black, Coloured, White and Indian were recorded for the study. In this study, White patients predominated with 334 patients (55%) followed by Blacks 134 patients (22%), while the Coloureds were the least represented racial group with 26 patients (4.2%) (figure 6). The mean ages of the racial groups were 56.7±12.2 years, 59.3 ±12.9 years, 59.4±12.4 years, and 61.2±13.9 years for Black, Indian, White and Coloured racial groups respectively. Differences in the mean age between the race groups was not statistically significant ($p=0.123$).

3.2 Baseline characteristics of patients and the SBP quartiles.

Figure 7 shows the frequency of the established major ACS risk factors among the study patients. Hypertension predominated among the risk factors and this was closely followed by cigarette smoking and they were present in 259 (27.3%) and 246 (25.9%) patients respectively. The distribution of clinical characteristics among the 4 quartiles of SBP is shown in Table III. Patients who presented with SBP quartile ≥140mmHg were more likely to be smokers and hypertensives. Those patients with SBP level <100mmHg had significantly high frequency of Killip class ≥3 and high mean HR. Other clinical parameters were not significantly different among the four SBP quartiles.

Black patients recorded the highest proportion of patients (29.2%) in the highest SBP quartile (SBP≥140mm Hg). However, this difference was not statistically significant (p= 0.117) when compared to other racial groups. Gender and age were also not significantly different among the SBP quartiles (see Table IV).

Table V shows the mean values of the laboratory parameters among the SBP quartiles. Those patients who presented with the highest SBP quartile (SBP ≥140mmHg) had significantly higher LDL cholesterol levels compared to the other SBP quartiles. Although the mean serum urea was higher and mean haemoglobin and total cholesterol levels were lowest among the patients in the lowest SBP (<100mmHg) quartile, compared to other SBP quartiles the differences were not statistically significant.

3.3 Coronary angiographic findings

Coronary angiographic findings in the 4 SBP quartiles are shown in Table VI. A total of 407 (66.4%) patients underwent angiography. Normal coronary anatomy was present in only 21 (5.2%) patients, while left anterior descending artery (LAD) lesion was most frequently,

found to be present in 248 (60.9%) patients who had angiography. Systolic blood pressure <100mmHg quartile had the least number of patients with normal coronary arteries on angiography. However, the frequencies of the angiographic findings were not significantly different among the four groups of SBP.

3.4 Types of acute coronary syndrome

The most frequent form of ACS diagnosed was STEMI; followed by NSTEMI. Unstable angina was the least form of ACS diagnosed among the study patients (figure 8). The distribution of the types of ACS among the 4 SBP quartiles showed no significant differences. Males predominated in all 3 types of ACS but again the differences were not statistically significant (p= 0.49, 0.63 and 0.72 for STEMI, NSTEMI and UA respectively).

3.5 Medications and intervention procedure received by the patients

A total of 91 (30.5%) patients were thrombolysed out of 298 patients who qualified for such therapy (ie patients with STEMI). One hundred and eighty patients (29.4%) had PCI (table VII). The SBP <100mmHg quartile recorded the highest percentage of patients who received fibrinolysis compared to the percentages of thrombolysed patients in other quartiles, but the differences were not statistically significant. No statistically significant differences were recorded among patients who had PCI in the 4 SBP quartiles. Streptokinase was used as thrombolytic agent in 73 (80.2%) patients while 18 (19.8%) patients were thrombolysed with alteplase.

Statistically significant differences were detected among patients who received the maximum number of drugs with proven medical benefits in ACS patients (i.e. aspirin, clopidogrel, ACE-I/ARBs, statins and beta-blockers) (see Table VII). The lowest percentage of patients who received such combination of drugs was recorded in the SBP <100 mm Hg quartile. The

percentage of patients who received the drug combinations increased progressively along the 4 quartiles with the highest percentage recorded by those with prehypertension and hypertension groups.

Figure 9 depicts the type of PCI performed on patients. Ischaemia guided PCI was most frequent and was performed in 109 (60.6%) patients. Rescue PCI was the least performed strategy, done in only 2 (1,1%) patients. Primary PCI was done in 42 (23.3%) patients.

3.6 Clinical parameters and in-hospital mortality

Of the 613 patients studied, 27 (4.4%) died in the hospital. Table VIII shows the uni-variate analysis of some of the established risk factors for in-hospital mortality. Systolic blood pressure ≤100mmHg, Killip class classification ≥3, atrial fibrillation, age >65years, lack of optimal medical therapy and high mean heart rate >96bpm were significantly associated with mortality. Those with SBP 100-129 mm Hg had significantly lower mortality rate. No statistically significant differences were detected in the other major ACS risk factors between survivors and non survivors.

Table IX shows the relationship between the laboratory parameters and mortality. Patients who died had significantly higher levels of serum creatinine and urea compared to survivors. Haemoglobin level of <11.4mg/dl was significantly associated with mortality. Other laboratory parameters were not significantly different between survivors and non survivors.

3.7 Predictors of in-hospital mortality

Table X shows the results obtained after multiple logistic regression analysis. Systolic blood pressure of ≤100 mm Hg, Killip class ≥ 3, atrial fibrillation, age > 65years, HR ≥ 96bpm and Hb level of <11.4mg/dl were found to be independent predictors of in-hospital mortality. Patients with SBP ≤100mmHg and those >65years of age had more than twice the risk of

death compared to others. The risk of death was more than 4 and 5 fold among those with Killip class 3-4 and those in AF respectively (table X). Those with HR ≥ 96bpm and Hb level of <11.4mg/dl had more than 2 and 4 times higher risk of death respectively. Those that received higher number of drugs with proven medical benefit (optimal medical therapy) had better survival compared to those that did not or only received a minimum number of such medications. Although SBP level of 100-129 mm Hg showed trend toward lower mortality, the group could not independently predict survival after inclusion of other co-variables in the multiple logistic regression analyses.

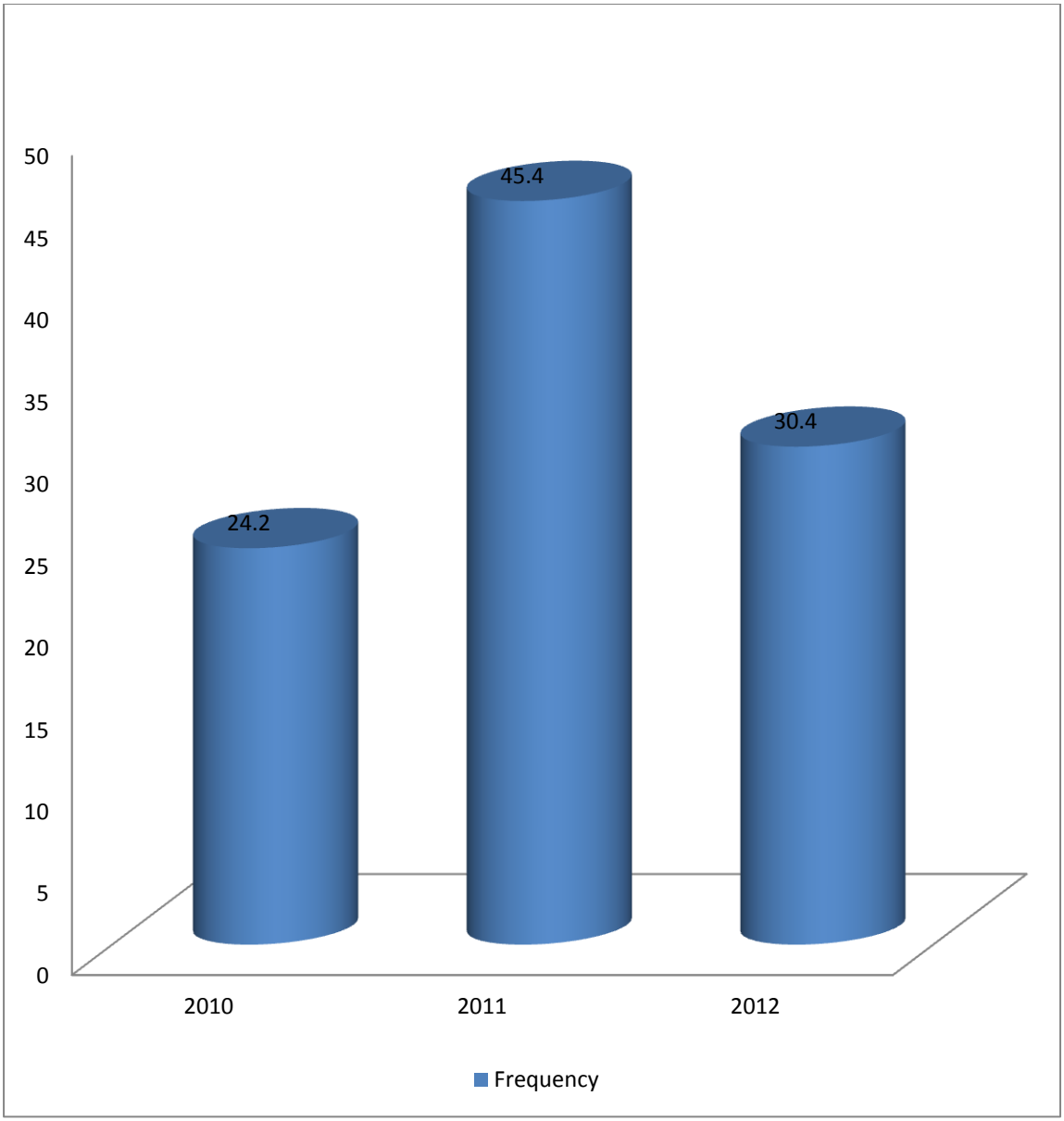


Figure 3: The frequency of ACS by year. 2012 is only till June.

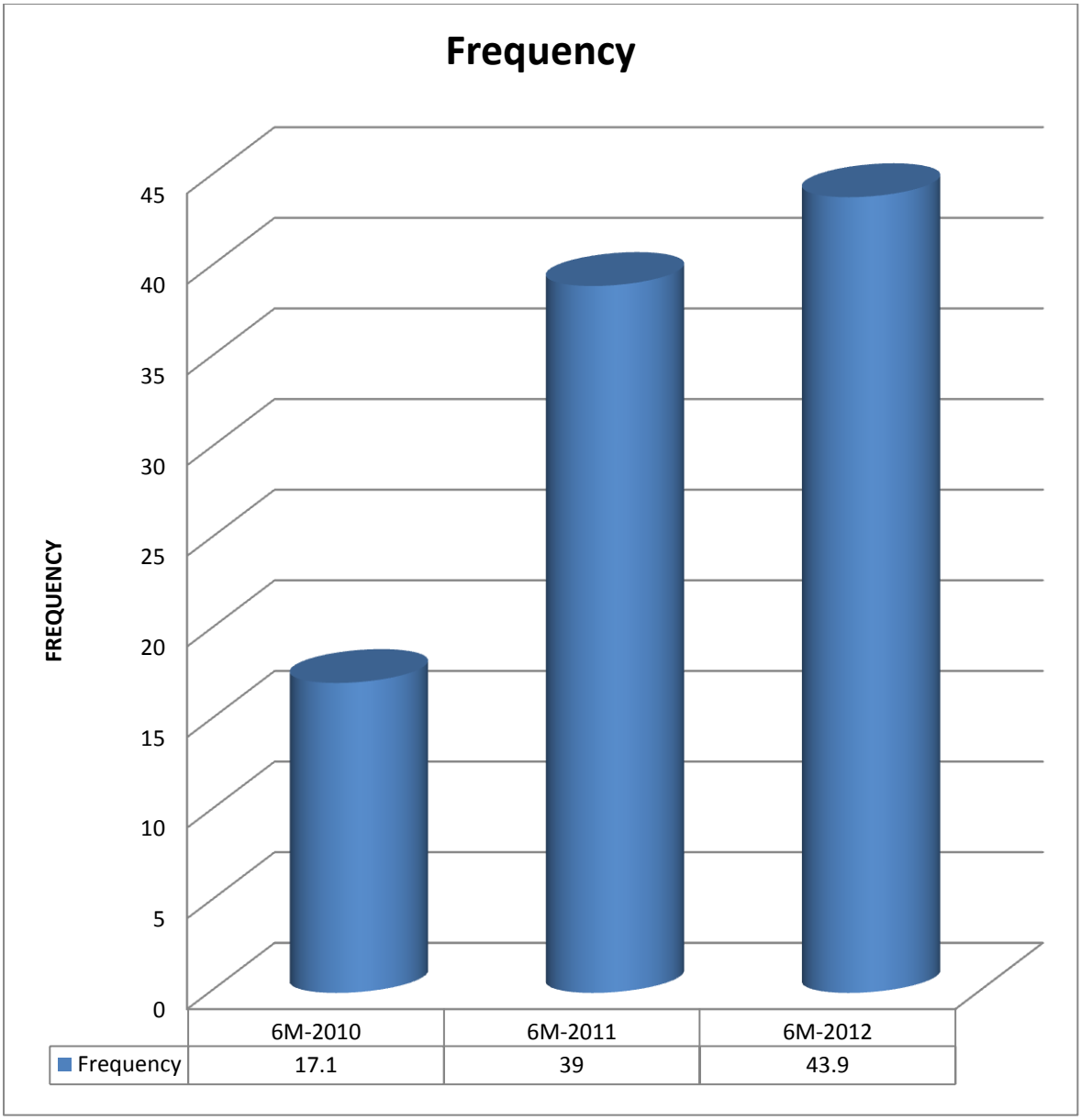


Figure 4: The first six months (January-June) frequency of ACS in each year of study.

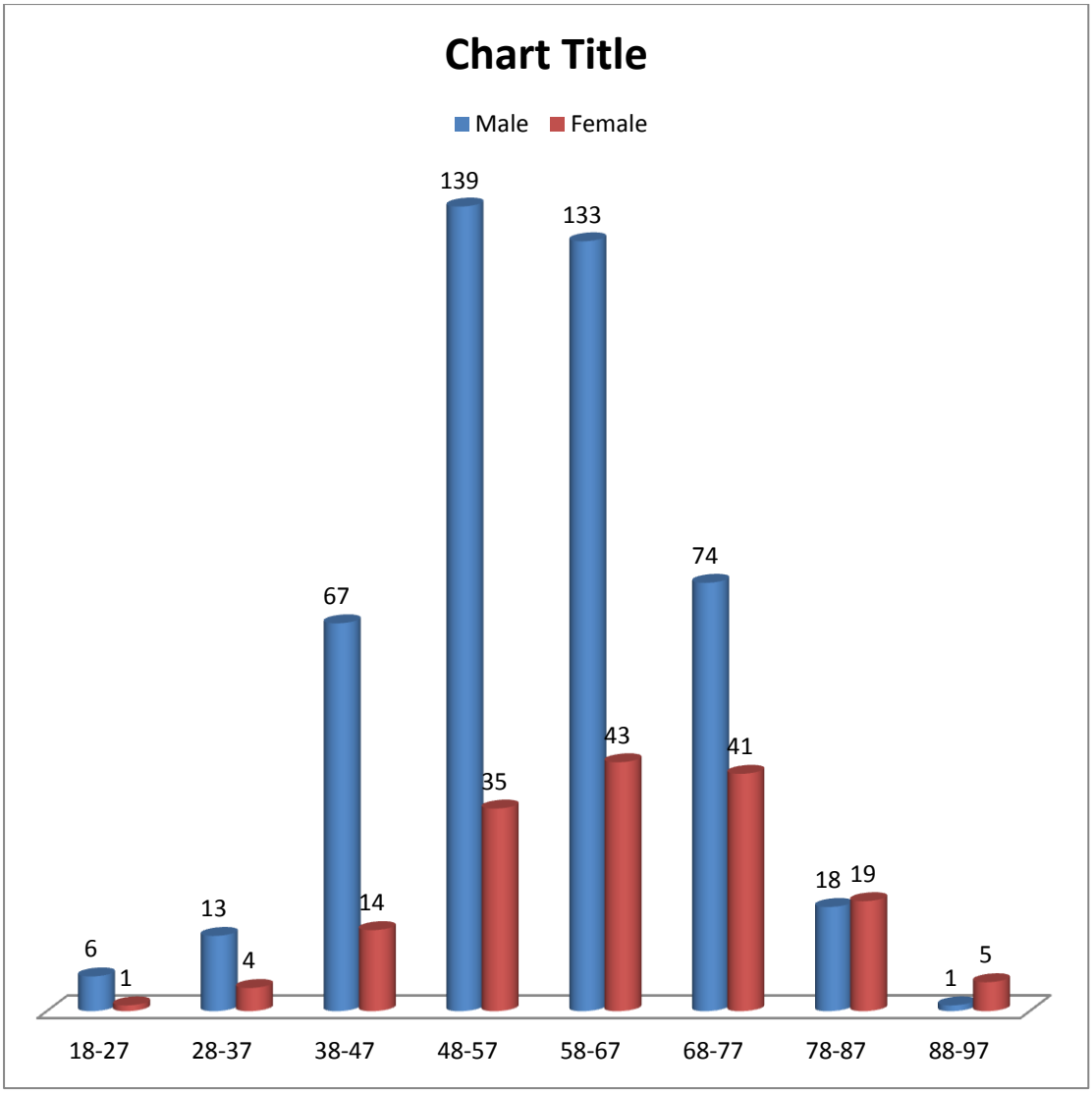


Figure 5: Age-sex distribution of the study patients.

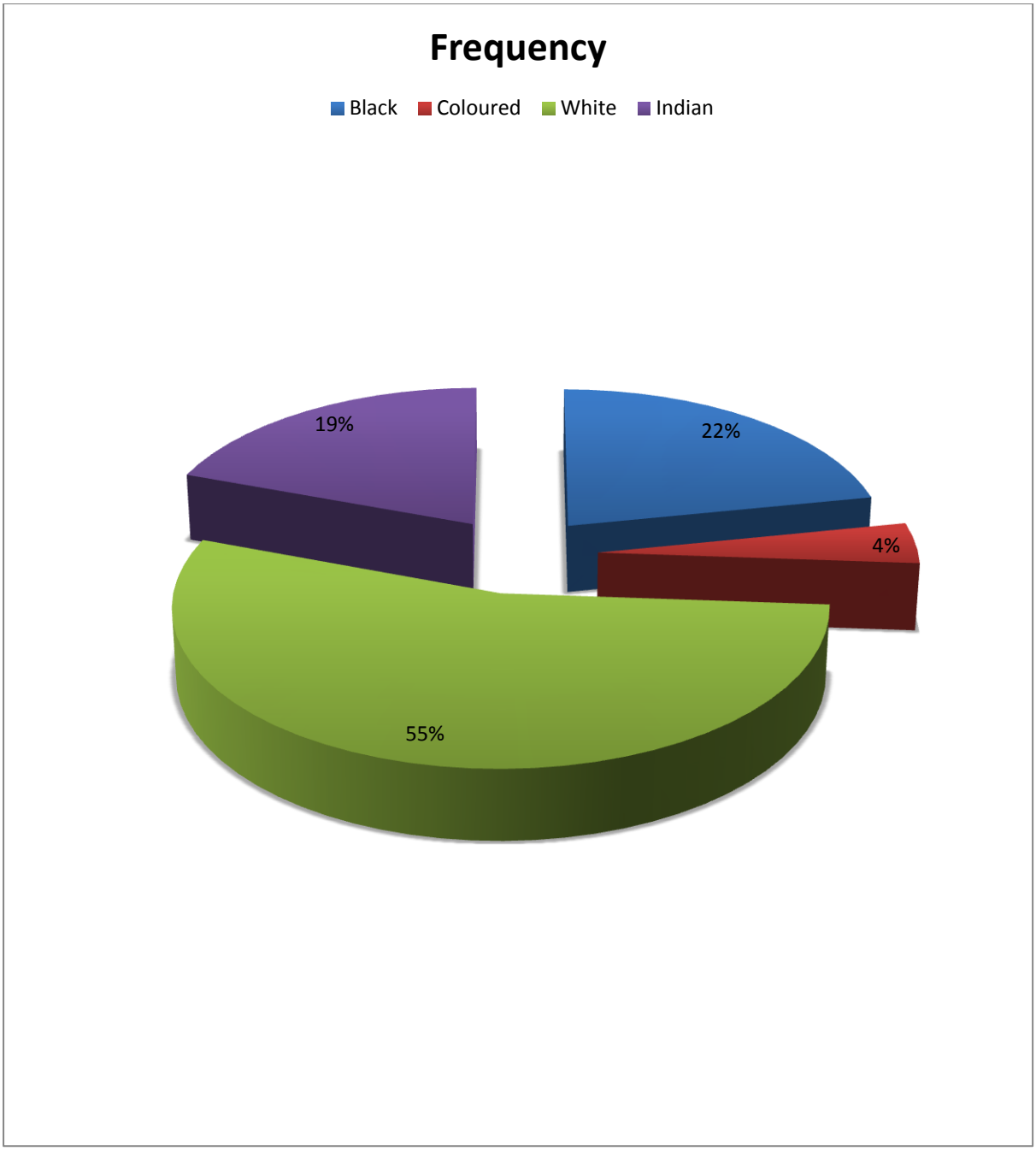


Figure 6: Racial groups among the patients.

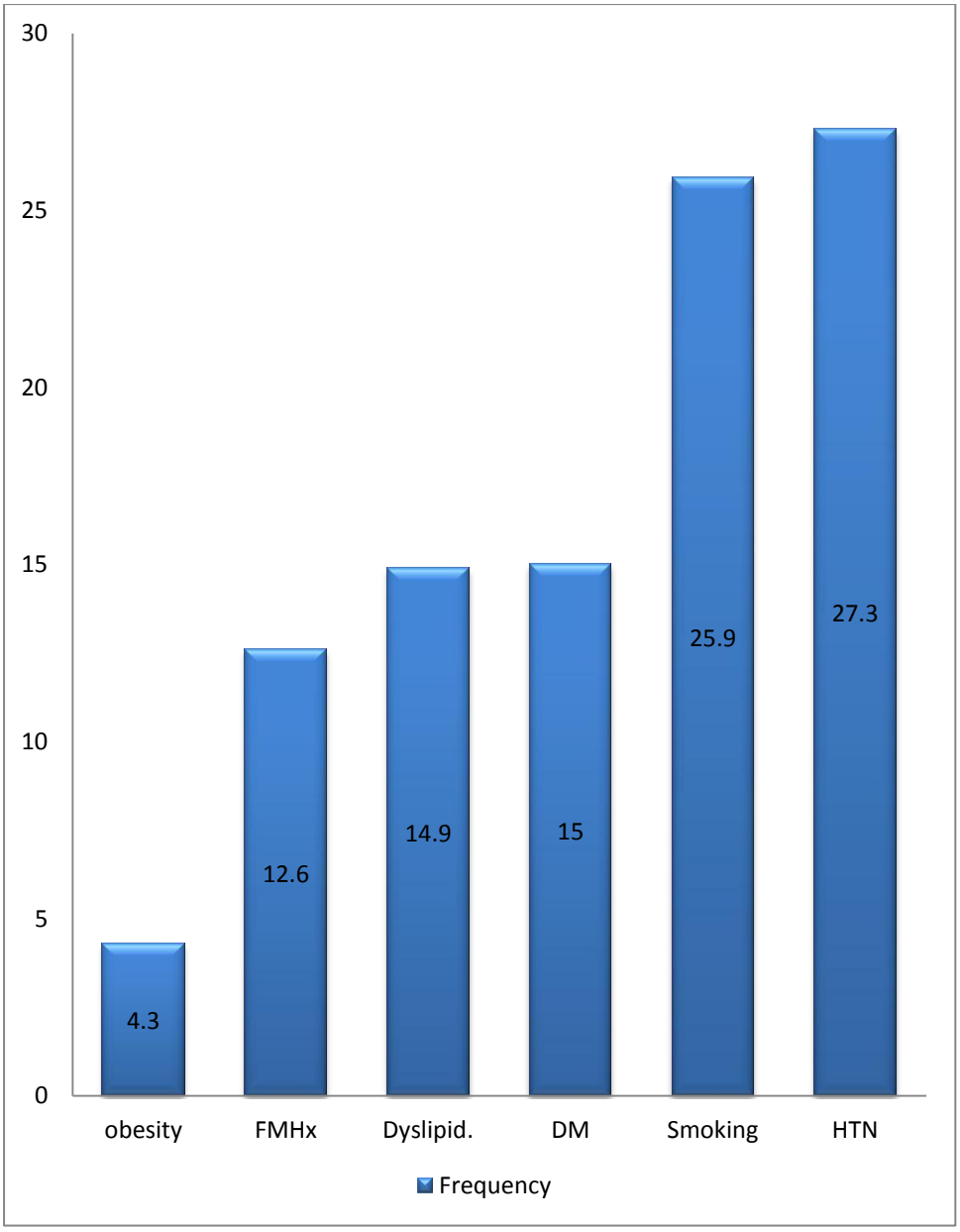


Figure 7: Major risk factors of ACS.

Key: FMHx= Family history, Dyslipid,= Dyslipidaemia, DM= Diabetes mellitus, HTN= Hypertension.

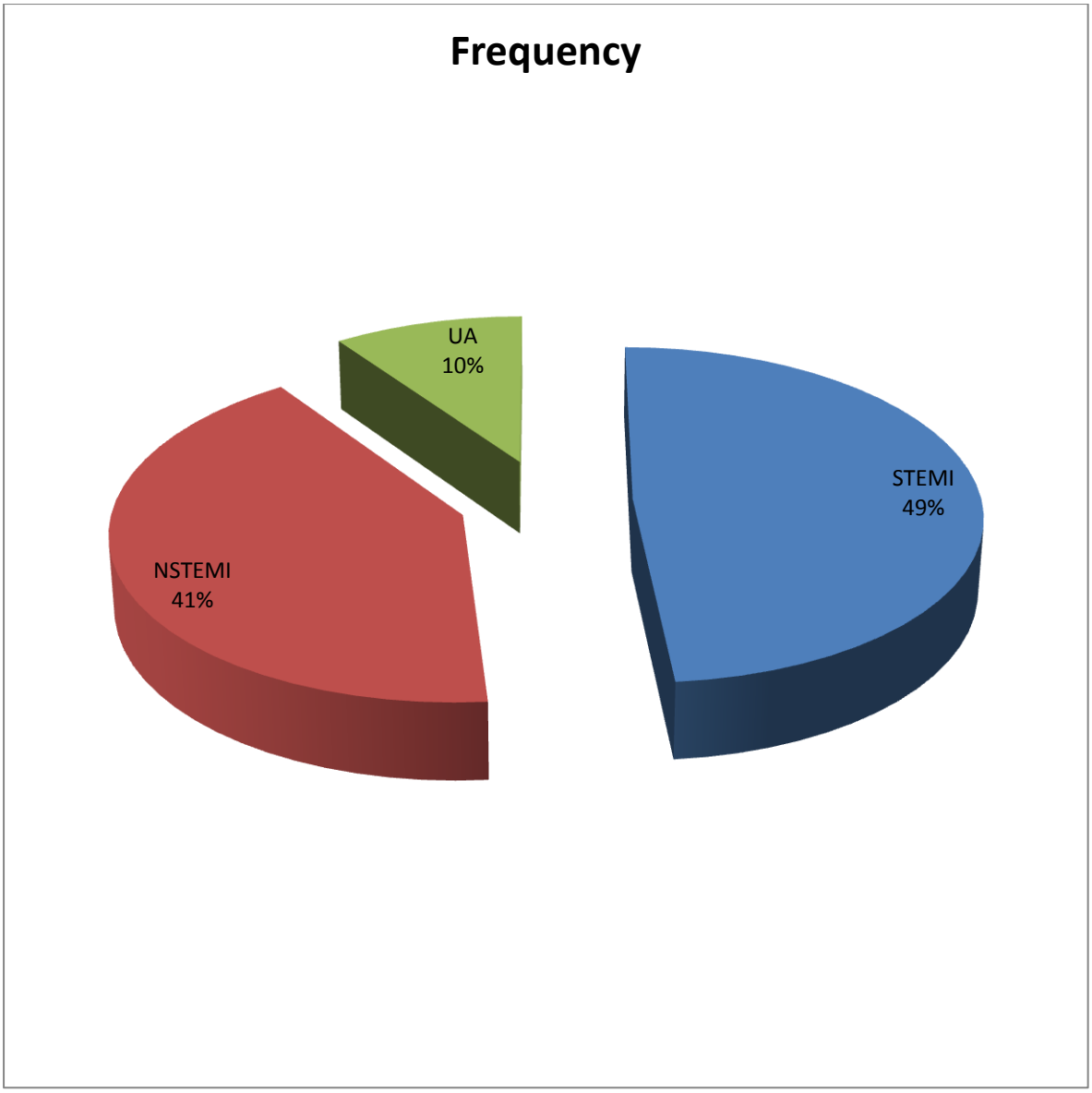


Figure 8: Types of ACS

Table III: Clinical parameters by systolic blood pressure at admission.

	Systolic blood pressure quartile, mmHg				
Variables	<100	100-129	130-139	≥140	P- Value
	n= 82	n= 305	n= 82	n= 144	
Risk factors					
HTN (%)	17(20.7)	90(29.5)	37(45.1)	115(79.9)	<0.0001
DM (%)	19(23.2)	65(21.3)	17(20.7)	41(28.5)	0.370
Smoking (%)	23(28.0)	130(42.6)	27(32.9)	66(45.8)	0.023
Dyslipidaemia (%)	10(12.2)	75(24.6)	21(25.6)	35(24.3)	0.098
HR (bpm)	92.9±25.5	83.6±19.9	80.5±19.4	85.4±22.4	0.005
AF (%)	4(4.9)	8(2.6)	2(2.4)	9(6.3)	0.215
Killip ≥3 (%)	11(13.4)	8(2.6)	1(1.2)	9(6.3)	<0.0001

Key: SD= standard deviation, HTN= Hypertension, DM= Diabetes mellitus, HR= Heart rate, AF= Atrial fibrillation, Killip≥3= Killip class classification 3 or 4.

Table IV: Demographic parameters by systolic blood pressure

	Systolic blood pressure quartile, mmHg				
Variables	<100	100-129	130-139	≥140	P- Value
	n= 82	n= 305	n= 82	n= 144	
Age(years ±SD)	57.9±13.6	57.9±12.0	61.3±12.3	60.0±12.9	0.095
Gender					
Male (%)	56(68.3)	228(74.8)	65(79.2)	102(70.8)	0.345
Female(%)	26(31.7)	77(25.2)	17(20.7)	42(29.2)	
Black (%)	16(19.5)	60(19.7)	16(19.5)	42(29.2)	0.117
Coloured (%)	4(4.9)	15(4.9)	4(4.8)	3(2.1)	0.540
White (%)	44(53.7)	168(55.1)	45(54.9)	77(53.5)	0.988
Indian (%)	18(22.0)	62(20.3)	17(20.7)	22(15.3)	0.539

Table V: Laboratory parameters by systolic blood pressure at admission.

	Systolic blood pressure quartile, mmHg				
Variables	<100 n= 82	100-129 n= 305	130-139 n= 190	≥140 n= 144	P- Value
TC (mean±SD)	4.4±1.1	4.7±1.5	4.9±1.3	5.0±1.5	0.055
LDL (mean±SD)	2.5±1.1	2.7±1.2	2.8±1.1	3.1±1.3	0.045
HDL (mean±SD)	1.1±0.6	1.0±0.5	1.1±0.4	1.2±0.5	0.126
Urea (mean±SD)	9.6±13.9	8.4±10.9	6.5±3.3	7.2±4.5	0.115
SCr (mean±SD)	114.4±96.9	105.4±98.8	100.2±41.3	114.9±99.0	0.597
Hb (mean±SD)	13.4±2.5	13.7±2.6	14.5±2.3	13.9±2.4	0.095
Troponins (mean±SD)	10.8±14.9	48.2±522.9	37.0±150.1	7.9±14.3	0.456

Key: SD= Standard deviation, TCHOL = Total cholesterol, LDL= Low density lipoprotein, HDL= High density lipoprotein, SCr= Serum creatinine, Hb= Haemoglobin.

Table VI: Coronary angiographic findings by systolic blood pressure at admission.

	SBP quartile, mmHg				
Culprit lesions	<100	100-219	130-139	≥140	P- Value
	n= 82	n= 305	n= 82	n= 144	
RCA (%)	35(42.7)	108(35.4)	28(34.1)	46(31.9)	0.438
LMT (%)	3(3.7)	11(3.6)	5(6.1)	5(3.5)	0.752
LAD (%)	31(37.8)	131(43.0)	36(43.9)	50(34.7)	0.334
LCX (%)	17(20.7)	69(22.6)	18(22.0)	29(20.1)	0.939
MX vessels (%)	10(12.2)	29(9.5)	10(12.3)	16(11.1)	0.834
Normal (%)	2(2.4)	10(3.3)	3(3.7)	6(4.2)	0.916

Key: SBP= Systolic blood pressure, RCA= Right coronary artery, LMT= Left main trunk, LAD= Left anterior descending artery, LCX= Left circumflex artery, MX vessels= Multiple vessels disease (≥3 vessels).

Table VII: Medications/intervention by systolic blood pressure at admission.

	Systolic blood pressure quartile, mmHg				
	<100	100-129	130-139	≥140	
Variables	n= 82	n= 305	n= 82	n= 144	
Fibronolysis (%)	46(18.3)	49(16.1)	8(9.8)	19(13.2)	0.373
PCI (%)	25(30.5)	97(31.8)	25(30.1)	33(22.9)	0.277
Optimal med.(%)	46(56.1)	227(74.4)	65(79.3)	114(79.2)	0.001

Key: SBP= Systolic blood pressure, PCI= percutaneous coronary intervention, Optimal med.= Combination of maximum number of drugs with proven benefit (4-5 of aspirin, clopidogrel, statins, ACE-I/ARBs and beta blockers) received by a patient.

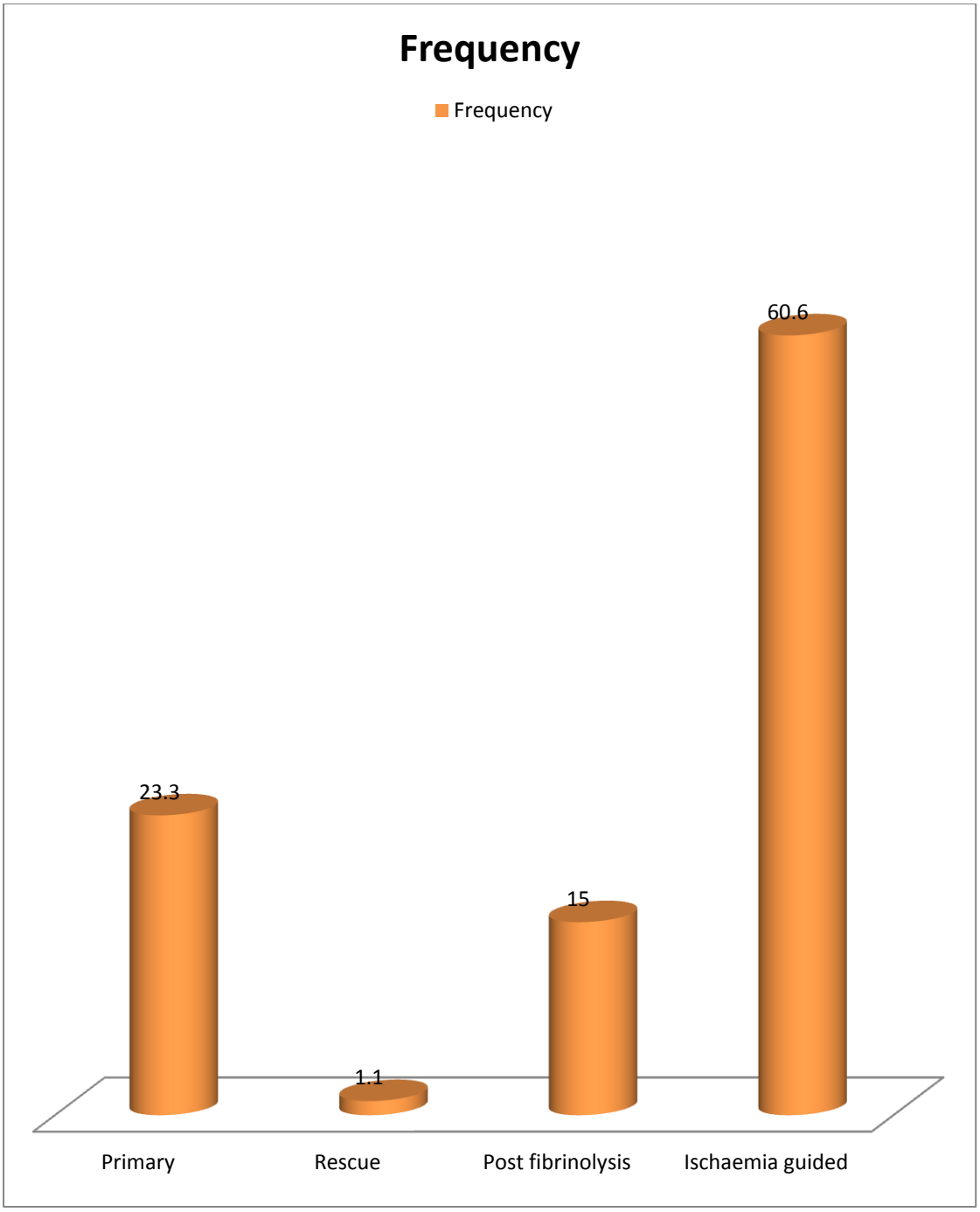


Figure 9: Types of PCI done to the patients.

Table VIII: Clinical parameters and in-hospital mortality

Variables	Deceased n= 27	Survivors n= 586	P-Value
SBP mm Hg			
<100(%)	12(44.4)	70(11.9)	<0.0001
100-129(%)	7(25.9)	298(50.9)	0.011
130-139(%)	2(7.4)	80(13.7)	0.351
≥140 (%)	6(22.2)	138(23.5)	0.874
Killip ≥3 (%)	7(25.9)	22(3.8)	<0.0001
Age >65y (%)	16(59.3)	166(28.3)	0.001
AF (%)	5(18.5)	18(3.1)	<0.0001
Optimal med. (%)	7(25.9)	445(75.9)	<0.0001
HR ≥96bpm (%)	10(37.0)	122(20.8)	0.045
Male (%)	19(70.4)	432(73.7)	0.700
DM (%)	7(25.9)	135(23.0)	0.728
HTN (%)	9(33.3)	250(42.7)	0.337
Smoking (%)	6(22.2)	240(40.9)	0.052
Dyslipidaemia (%)	5(18.5)	136(23.2)	0.571

Key: SD= standard deviation, SBP- Systolic blood pressure, Killip≥3= Killip class classification 3 or 4. AF= Atrial fibrillation, Optimum med.= Maximum number of drugs with proven benefit (4-5 of aspirin, clopidogrel, statins, ACE-I/ARBs and beta blockers) received by a patient. HR≥96bpm= Heart rate ≥96 beat per minute, DM= Diabetes mellitus, HTN= Hypertension.

Table IX: Laboratory parameters and in-hospital mortality

Variables	Deceased n= 27	Survivors n= 586	P-Value
TCHOL(mean±SD)	4.6±1.1	4.8±1.5	0.644
LDL(mean±SD)	2.6±1.6	2.8±1.2	0.434
HDL(mean±SD)	1.3±0.7	1.1±0.5	0.096
SCr(mean±SD)	178.8±144.6	104.1±88.1	<0.0001
UREA(mean±SD)	16.5±23.1	7.7±8.3	<0.0001
Hb≤11.4mg/dl (%)	7(23.9)	54(9.2)	0.004
Troponins(mean±SD)	5.2±10.1	3.4±403.8	0.731

Key: SD= Standard deviation, TCHOL= Total cholesterol, LDL= Low density lipoprotein, HDL= High density lipoprotein, SCr= Serum creatinine, Hb= Haemoglobin.

Table X: Predictors of in-hospital mortality among the study patients.

Variables	OR	95% CI	P- Value
SBP mm Hg			
≤100	2.953	1.172-7.435	0.022
120-139	3.931	0.892-17.323	0.098
Age>65y	2.765	1.152-6.637	0.023
Killip≥3	4.073	1.285-12.905	0.017
AF	5.389	1.443-20.122	0.012
Optimal med.	0.168	0.065-0.436	<0.0001
HR≥96bpm	2.692	1.033-7.012	0.043
Hb<11.4mg/dl	4.609	1.449-14.665	0.010
SCrμmol/l	0.999	0.996-1.002	0.364
Urea mmol/l	0.982	0.954-1.012	0.235

Key: OR= Odds ratio, CI= Confidence intervals SBP= Systolic blood pressure, Killip≥3= Killip class classification 3 or 4. AF= Atrial fibrillation, Optimal med.= Maximum number of drugs with proven benefit (4-5 of aspirin, clopidogrel, statins, ACE-I/ARBs and beta blockers) received by a patient, HDL= High density lipoprotein, HR= Heart rate, LDL= Low density lipoprotein, SCr= Serum creatinine, Hb= Haemoglobin.

CHAPTER 4

DISCUSSION

This work aimed to study the demographic and clinical characteristics, in-hospital mortality as well as their relationship to systolic blood pressure on admission in patients admitted with a diagnosis of ACS to a large urban public hospital in Johannesburg.

4.1 Demographic characteristics

The mean age of patients in this study was 58.9 ±12, which is 5-6 years lower than the mean age of patients with AMI reported in Europe and America.[210] In the INTERHEART Africa study, it was found that the mean age of the African patients presenting with MI was 54.3 ±11. African patients with MI presented 3.8 years earlier than the overall INTERHEART cohort.[83] A similar mean age was also reported in African and Indian studies.[213, 214] A study in Cape Town, South Africa, reported the mean age of patients that was 4 years lower than the mean age obtained in this study.[157] Overall, the results suggest that AMI occurs more prematurely in Africa than in the developed world. The reasons for this finding are not clear but it may be the result of lack of prevention, late detection and lack of effective management of risk factors for MI in Africa as compared to the developed world.

In this study, males dominated with a male to female ratio of 2.8:1. This is the usual pattern in the literature.[83,173,210] Although the mechanisms of increased risk for CHD is not well understood, studies have consistently identified male gender as a risk factor for higher rate of CHD.[48-50] In this study, it was also found that women were significantly older than men at time of ACS presentation. Studies across the world also reported an older age at presentation for women as compared to men.[2,49,148-149,173] As compared to pre-menopausal women, the risk for CHD in men is approximately 10 years earlier.[148] In post-menopausal women, the risk increases but still remains lower than for men of the same age. Generally, interpretation of

the impact of gender in ACS is complex and potentially influenced by referral bias and by differences in the diagnostic sensitivity of the ECG and stress tests with gender.[2]

With regards to racial differences, this study found that the Whites constituted the largest group of patiens presenting with ACS. The second largest group, surprisingly, were Black patients then followed by Indian patients, whilst the Coloureds formed the smallest group. Among the various racial groups of South Africa there exists a striking difference in the prevalence of myocardial infarction. The White population is afflicted to a degree which approximates that of the United States, but for the age group between 25 to 44 years, the incidence in White South Africans may be the highest in the world.[215] In contrast, the Black population was thought to be almost immune to the disease.[215] Schwartz and colleagues, in an analysis of 30 cases among 417,000 medical admissions to Baragwanath Hospital for the period 1951 to 1961, determined a prevalence rate of MI among Black to be 0.01 per cent.[216] In a study in Natal, only 10 patients were Black out of a total of 794 patients presenting with MI, yielding a prevalence of 0.013 for Black patients.[217] Another study at the Johannesburg General Hospital in 1970, Seftel and Kew found a prevalence rate of 0.6% among 3 000 admissions to the medical wards.[218] Later, in 1978 a Cape Town study revealed a MI prevalence rate of 1.4% among Blacks, a figure much higher than reported from other centres.[219] It is believed that increased urbanisation and adoption of a Western lifestyle has led to the increase in the number of cases of MI among the Black population which were previously thought to be immune from CHD. In the current study, Black patients recorded a prevalence of 22%, which is second only to that of 55% recorded by White patients.

In this study, the Indian ethnic group which is said to have one of the highest prevalence of CHD in the world, ranked third behind White and Black populations, with a prevalence of 19%.[214] It must be remembered that the prevalence rates as found in this study do not necessarily reflect the true prevalence rates of each population group for ACS. There was no

adjustment made for the different ratios of each group in the general population. Furthermore no adjustment was made for different referral patterns to hospitals in the different regions of Johannesburg.

4.2 Clinical characteristics and the risk factors of ACS

(i) The major risk factors of ACS identified were: hypertension, cigarette smoking, diabetes, dyslipidaemia, family history and obesity. These risk factors have been implicated for the rise in cases of CAD, particularly among Black Africans, more than four decades ago.[218] A study at the Johannesburg General Hospital in 1970, revealed that a large proportion of black patients with MI were cooks (indicating sedentary lifestyle) and who were frequently hypertensives and diabetics with higher serum lipid levels.[218] The recent INTERHEART Africa study reported that only five of these risk factors accounted for as much as 89.2% of the risk of an initial MI.[83] These risk factors included: hypertension, diabetes, cigarette smoking, dyslipidaemia and obesity, which also mirrors the most frequent risk factors reported in this study.

Studies in other parts of Africa have also reported similar risk factors of IHD. Hypertension, diabetes, cigarette smoking and dyslipidaemia were reported to be among the most common risk factors of IHD in some Nigerian studies.[220,221] Increasing industrialisation and urbanisation, while raising living standards and increasing lifespan for many, is also accompanied by a change of diet (increased calories, fat and salt), cigarette smoking, lack of exercise, and obesity. The consequences of this lifestyle are diabetes, hypertension, and coronary artery disease.

(ii) In the evaluation of the differences of clinical characteristics among SBP quartiles, those with lower SBP on admission were more likely to have higher mean HR and higher Killip class while those with a higher SBP were more likely to be hypertensive, smokers and have

significantly higher LDL level. These findings are similar to those reported in two studies to determine the impact of SBP on clinical characteristics and outcomes in Greece and Japan.[1, 173] As blood pressure is dependant on good left ventricular function, those with lower SBP may suggest patients having LV dysfunction or even cardiogenic shock and hence a higher Killip class. Also, a low SBP activates the sympathetic nervous system which explains the higher heart rate among these patients. Those with higher SBP, positive history of cigarette smoking and higher lipids suggest a clustering of multiple cardiovascular risk factors. Epidemiological data have shown that hypertensive patients differ markedly from normotensive patients not only in terms of high blood pressure level.[222] There is a tendency for hypertension to occur in combination with other lifestyle, metabolic, and anthropometric factors, all of which are independently associated with increased risk of cardiovascular diseases. According to data from the Framingham Heart Study, less than 20% of hypertension occurs in the absence of one or more risk factors, including high triglycerides and LDL cholesterol levels, reduced HDL cholesterol levels, glucose intolerance, hyperinsulinaemia, obesity, and left ventricular hypertrophy.[223]

(iii) In this study, the number of patients who received optimal medical therapy among the four SBP quartiles differed significantly. Patients in the lowest quartile of SBP received the least number of optimal therapies whilst patients in the higher SBP quartiles received the highest number of optimal therapies. More than likely patients within the lowest SBP quartile had a contraindication to the use of some of these optimal agents. For example, the use of ACEI or beta-blockers is contraindicated in patients with hypotension.[101,224] Furthermore, factors like high Killip class, renal dysfunction and advanced age also determines the choice of medications for these patients. In a prospective, multicentre observational study involving 6,853 patients admitted for ACS, it was demonstrated that advanced age, female sex, history of heart failure, and renal dysfunction were independently associated with lower use of

combination therapy, even in the absence of known contraindications.[224] Cardiogenic shock was among the clinical factors associated with high risk of mortality among ACS patients in a study of ACS in developing countries.[225] In this study, patients within the lowest SBP quartile on admission had a higher percentage of patients in Killip class III or IV and were more likely to have impaired renal function compared with those patients in the higher SBP quartiles. Thus it is not surprising that they had the lowest rate of prescription of optimal medical therapies.

4.3 Predictors of in-hospital mortality

The mortality rate recorded in this study was 4.4%. This is rather lower than the mortality rate among ACS patients in other similar studies in Japan and Greece, where a mortality rate of 9% and 8.9% was recorded respectively.[1,173] However; those studies had a larger sample of patients compared to the number of patients in our study. While our study involved 613 patients, the Japanese and Greek studies involved 1211 and 2172 patients respectively.[1,173] One of the possible reasons for the lower mortality in our study is probably related to time of presentation to hospital. In South Africa, the public hospitals cater to the poorer sectors of the community, who in general present very late to hospital. Thus patients with early mortality do not even make to the hospital. In other words, largely survivors of ACS get admitted to hospital. A one-year mortality rate of 5.7% was recorded in a study of ACS in South Africa.[226] A multi-national observational study has shown a significant decline in the mortality rate among ACS patients due to the remarkable improvement of patient's care by using evidence-based pharmacological and interventional therapy.[227] Similarly, the majority of patients in this study benefited from such care as the cardiac centre has the required facilities and expertise, as well as its strict adherence to the latest guidelines with regards to the management of ACS.

One of the important findings in this study was that a low SBP on admission, advanced age, higher Killip class, AF, HR ≥ 96beats/minute and Hb <11.4g/dl were independent predictors of mortality among ACS patients. Previous studies have shown similar findings with significantly higher mortality rate among ACS patients with lower SBP, advanced age and a high Killip class at time of admission.[1, 173]

The association between SBP on hospital admission and prognosis of patients with MI is not new. Several observations of MI patients, have noted that a higher blood pressure at presentation is associated with a better prognosis.[1, 2, 173, 228] Moreover, it has been estimated that a 10mmHg increase in SBP at the time of admission was associated with almost a 20% decrease in the risk of in-hospital death.[173, 228] In the current study patients with a SBP of more than 100 mm Hg at admission were found to have better in-hospital outcome (lower mortality rate) compared to those with SBP <100 mm Hg. In a similar study in Greece, the reduction of mortality associated with increased SBP was observed to be greater in patients presenting with SBP levels >120mmHg compared with those with SBP levels <100mmHg on admission.[1] Furthermore this study found that a 10-mm Hg increment in SBP was associated with a 27% lower likelihood of death during hospitalization. In Japanese patients with AMI an admission SBP of 141-159mmHg was found to have a better in-hospital outcome.[173]

The higher mortality rate recorded among ACS patients with a lower SBP more than likely is related to the poor prognostic factors present in this group of patients. In this study, patients with a lower SBP were found to be significantly in a higher Killip class and were less likely to receive evidence-based pharmacological therapies. Studies have shown that a higher Killip class on admission is associated with a higher mortality and that a Killip class ≥ 3 is one of the most powerful predictors of mortality with a two-fold increased risk of death with each worsening of class.[8, 173, 180] In our study, Killip class was indeed among the strongest positive

predictors of mortality with more than four-fold increased risk of death among those in Killip class ≥3.

Likewise, it has been found that optimal medical therapy is associated with making a remarkable impact on outcomes among the ACS patients.[224, 227] In a study on optimal medical therapy among ACS patients, after adjusting for other validated prognosticators, patients receiving optimal medical therapy had significantly lower 1-year mortality compared with those given a '0' or '1' evidence-based drug at discharge.[222] In this study optimal medical therapy was found to be an independent predictor of survival among patients with ACS.

It is well known that SBP levels depend on a combination of cardiac output and peripheral resistance. A SBP value within normal limits during the acute phase of ACS indicates a preserved combination of cardiac output and systemic resistance. This may reflect a more limited necrosis of myocardial tissue without severe atrioventricular conduction system disorders and with a less pronounced activation of the adrenergic neurohormonal system.

As reviewed in this study, previous studies have identified HR as an independent predictor of mortality.[175] Patients with significant sinus tachycardia on admission were found to have an increase risk of death.[175] In a study to determine the prognostic significance of sinus tachycardia following admission for ACS, sinus tachycardia was identified as an independent prognostic factor of mortality.[175] The higher heart rate following MI is usually related to the unbalanced activity of the autonomic nervous system characterised by activation of sympathetic nervous system.[229] The post-infarct sympathetic activity leads to higher myocardial concentration of catecholamines which may precipitate arrhythmias and increase mortality.[230] Studies have also shown that resting HR is correlated with hypoglycaemia, hyperinsulinaemia, metabolic syndrome and increased mortality.[231]

This study has also revealed anaemia as one of the independent risk factor of mortality among patients admitted with ACS. A review of clinical trials revealed that the likelihood of death, recurrent ischaemia and non-fatal MI was greatly increased in patients with Hb <11mg/dl compared to those with normal haemoglobin.[199] In animal models, a high level of Hb was found to prevent ischaemia even in the presence of significant coronary artery stenosis.[232]

Anaemia worsens myocardial ischaemia both by increasing myocardial oxygen demand due to the high hyperdynamic flow and by decreasing oxygen content of the already compromised myocardium.[233] Anaemia is also associated with some poor prognostic factors of ACS. A study on association of Hb level with clinical outcomes in ACS has shown that those with lower levels of haemoglobin were more likely to be older, female, less likely to be current smokers, lower estimated creatinine clearance and less likely to undergo revascularisation during their initial hospitalisation for MI.[199]

4.4 LIMITATIONS

- The study is a retrospective observational analysis. Thus limitations of all retrospective analyses apply to this study as well.
- The analysis was over a period of 2.5 years. Analysis over a longer period may have yielded more robust data.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

This study describes the relationship between the SBP on admission, clinical characteristics and outcomes among patients admitted with ACS at CMJAH. The following findings are highlighted.

- The patients were relatively young and there were more males than females with male to female ratio of 2.8:1.
- Whites were the largest racial group identified, with a significant (22%) of the cohort being Black.
- Patients with SBP ≤100mm Hg had high frequency of Killip class ≥ 3 and higher mean HR. Those with higher SBP level were more likely to be hypertensives, smokers and higher serum lipid levels. Patients with lower SBP level were also more likely to receive less optimal medical therapy.
- The key independent positive predictors of mortality that were found include; SBP ≤100mmHg, Killip class ≥3, AF, HR ≥ 96bpm, Hb <11.4mg/dl and age > 65 years.
- Optimal medical therapy was found to be positive predictors of survival.

5.2 Recommendations for clinical practice

Based on the findings in this study, the following recommendations are made:

- As a low SBP level on admission is associated with a poorer prognosis in ACS patients, these patients need to be identified early in their presentation for more aggressive revascularization therapies.
- Other simple clinical and lab parameters should be assessed and managed promptly on admission (e.g. Killip class, AF, HR and Hb) particularly in the elderly, in order to reduce in-hospital mortality.
- All ACS patients should receive optimal medical therapy unless there is an absolute contraindication.

5.3 Recommendations for future work

A larger prospective study is suggested in order to validate and extend the scope of the findings of this study.

- A longitudinal study will be a more reliable way of determining the ACS outcomes and their predictors.
- African multi-centre prospective studies are needed to generate protocols for the prevention and management of IHD/ACS in Africa, which may be different from the current protocols that are mostly derived from Western countries.

REFERENCES

1) Pitsavos C, Panagiotakos D, Zombolos S, Mantas Y, Antonoulas A, Stravopodis P et al. Systolic Blood Pressure on Admission Predicts In-Hospital Mortality Among Patients Presenting With Acute Coronary Syndromes: The Greek Study of Acute Coronary Syndromes. *J Clin Hypertens* 2008;10:362-366

2) Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS et al.ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2002;40:1366–1374

3) Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST-segment elevation. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000;21:1406–1432

4) American HEART Association. 2005 Heart and Stroke Statistical Update. Dallas, Texas: American Heart Association. 2005. Available at www.americanheart.org. Accessed Dec. 5, 2012

5) World Health Organization. The World Health report 2001: reducing risks, promoting healthy life. Geneva, Switzerland: WHO, 2002

6) Mathers CD, Lopez AD, Murray CJL. The burden of disease and mortality by condition: data, methods, and results for 2001. In: Lopez AD, Mathers CD, Ezzati M, et al, eds.Global burden of disease and risk factors. New York, NY, and Washington, DC: Oxford University Press & the World Bank, 2006:45–240

7) Rao C, Lopez AD, Hemed Y. Causes of death. In: Jamison DT, Feachem RG, Makgoba MW, et al, eds. Disease and mortality in Sub-Saharan Africa. 2nd ed. Washington, DC: The World Bank, 2006:67–82

8) Granger CB, Goldberg RJ, Dabbous O, et al; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345–2353

9) Nikus KC, Eskola MJ, Virtanen VK, et al. Mortality of patients with acute coronary syndromes still remains high: a follow-up study of 1188 consecutive patients admitted to a university hospital. *Ann Med* 2007;39:63–71

10) Sanz G, Castaner A, Betriu A, Magrina J, Roig E, Coll S, et al. Determinants of prognosis in survivors of myocardial infarction.
N Engl J Med 1982;306:1065-1070

11) Norris RM, Brandt PWT, Caughey DE, Lee AJ, Scott PJ. A new coronary prognostic index. *Lancet* 1969;1:274-278

12) Moss AJ, DeCamilla J, Davis H, Bayer L. The early post hospital phase of myocardial infarction: prognostic stratification. *Circulation* 1976;54:58-64

13) Thygesen K, Alpert JS, White HD et al. Universal definition of myocardial infarction. *Circulation* 2007;116:2634

14) Schachinger V, Britten M, Zeiher A. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;100:2153-2157

15) Rathore SS, Gersh BJ, Weinfurt KP, Oetgen WJ, Schulman KA, Solomon AJ. The role of reperfusion therapy in the paced patients with acute myocardial infarction. *Am Heart J* 2001;142(3):516-519

16) Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007;115:e69 –171

17) Wayne D. Rosmond, Lloyd E. Chambless. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med* 1998:339. 13, 867-67

18) British Heart Foundation. 2010 Coronary Heart Disease Statistics. British Heart Foundation promotion research group.Department of Public Health, University of Oxford. Available at www.heartstats.org. Accessed Nov. 12, 2013.

19) Danchin N, Puymirat E, Aissaoui N, Adavane S, Durand E. Epidemiology of acute coronary syndromes in France and in Europe.
Annales de Cardiologie et d'Angéiologie 2010;59: S37–S41

20) Sanderson JE, Tse Tf. Heart failure: a global disease requiring a global response. *Heart* 2003; 89:585–586

21) Prabhakaran D, Yusuf S, Mehta S, Pogue J, Avezum A, Budaj A, et al. Two-year outcomes in patients admitted with non-ST elevation acute coronary syndrome: results of the OASIS registry 1 and 2.
Indian Heart J 2005; 57: 217-225

22) Tan AT, Emmanuel SC, Tan BY, Teo WS, Chua TS, Tan BH. Myocardial infarction in Singapore: a nationwide 10-year study of multiethnic differences in incidence and mortality. *Ann Acad Med Singapore* 2002; 31: 479-86

23) Mak KH, Chia KS, Kark JD, Chua T, Tan C, Foong BH, et al. Ethnic differences in acute myocardial infarction in Singapore.
Eur Heart J 2003; 24: 151-160

24) Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet* 2008; 371(9622): 1435-1442

25) Sharma M, Ganguly NK. Premature coronary artery disease in Indians and its associated risk factors. *Vasc Health Risk Manag* 2005;1:217-225

26) Biritwum RB, Amoah AGB, Pobee JOM. Cardiovascular diseases in sub-Saharan Africa. Accra, Ghana: ASCOM Publishers, 2005.

27) Pobee JO. Cardiovascular research: a luxury in tropical Africa? *East Afr Med J* 1987;64:396-410

28) Cooke AR. Notes on the disease met with in Uganda, central Africa. *J Trop Med* 1901;4:175-178

29) Shaper AG, Shaper LJ. Analysis of medical admissions to Mulago Hospital. *East Afr Med J* 1958;35:647–678

30) Becker BJP. Cardio-vascular disease in the Bantu and coloured races of South Africa. IV. Atheromatosis. *S Afr Med J* 1946;11:97–105

31) Walker AR, Sareli P. Coronary heart disease: outlook for Africa. *J R Soc Med* 1997;90:23-27

32) Pobee JOM. A view of cardiovascular disease in the African continent. *Cardiovasc Epidemiol Newslet* 1979;26:23

33) Ojji DB, Alfa J, Ajayi SO, Mamven MH, Falase AO. Pattern of heart failure in Abuja, Nigeria. An echocardiographic study. *Cardiovasc J Afr* 2009; 20(6):349-52

34) Karaye KM, Sani MU. Factors associated with poor prognosis among patients. admitted with heart failure in a tertiary medical centre. *BMC cardiovascular Disorder* 2008;8:8-16

35) Onwuchekwa AC, Asekomeh GE. Pattern of heart failure in a Nigerian Teaching Hospital. *Vascular Health and Risk Management* 2009;5:745-750

36) Falase AO, Cole TO, Osuntokon BO. Myocardial infarction in Nigerians. *Trop Geogr Med* 1973;25(2):147-150

37) Mayosi BM. Contemporary trends in the epidemiology and management of cardiomyopathy and pericarditis in sub-Saharan Africa. *Heart* 2007 93:1176–1183

38) Falase AO, Oladapo OO, Kanu EO. Relatively low incidence of myocardial infarction in Nigerians. *Tropical Cardiology* 2001; 45-47

39) Sanderson JE, Chan S, Chan WW. The aetiology of heart failure in the Chinese population of Hong Kong – a prospective study of 730 consecutive patients. *Int J Cardiol* 1995; 51:29-35

40) Sani MU, Adamu B, Mijinyawa MS, Abdu A, Karaye KM, Maiyaki MB. Ischaemic heart disease in Aminu Kano Teaching Hospital, Kano, Nigeria: a 5 year review. *Niger J Med* 2006;15(2): 128-131

41) Sani MU, Miinyawa MS, Shehu MN, Kareem LO, Yusuf SU, Ibrahim DA, Abdu A. Rising Incidence of Acute coronary syndromes in Aminu Kano Teaching Hospital. (Unpublished data)

42) Maru M. Coronary atherosclerosis and myocardial infarction in autopsied patients in Gondar, Ethiopia. *J R Soc Med* 1989;82:399–401

43) Vera Bittner. Perspectives on Dyslipidemia and Coronary Heart Disease in Women. *J A m Coll Cardiol* 2005;46:1628 –1635

44) American Heart Association. Statistical Fact Sheet: Populations. Women and Cardiovascular Diseases: Statistics. Available at: http://www.

americanheart.org/downloadable/heart/1104938287787FS10WM05rev. pdf. Accessed January 26, 2013

45) Goldberg RJ, Gorak EJ, Yarzebski J, Hosmer DW, Dalen P Jr, Gore JM, et al. A communitywide perspective of sex differences and temporal trends in the incidence and survival rates after acute myocardial infarction and out-ofhospital deaths caused by coronary heart disease. *Circulation* 1993;87:1947-1953

46) Jeffrey SB, Laine E, Dianne G, Matthew R, Christopher BG, Paul WA. Sex Differences in Mortality Following Acute Coronary Syndromes. *JAMA* 2009;302(8):874-882

47) Wilson PW. Established risk factors and coronary artery disease: the Framingham Study. *Am J Hypertens* 1994; 7:7S

48) Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999; 353:1547-1598

49) D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117:743-790

50) Kappert K, Böhm M, Schmieder R, et al. Impact of sex on cardiovascular outcome in patients at high cardiovascular risk: analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). *Circulation* 2012; 126:934-993

51) Charchar FJ, Bloomer LD, Barnes TA, et al. Inheritance of coronary artery disease in men. An analysis of the role of the Y chromosome.
Lancet 2012; 379:915-945

52) Sesso HD, Lee IM, Gaziano JM, et al. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation* 2001; 104:393-430

53) Andresdottir MB, Sigurdsson G, Sigvaldason H, et al. Fifteen percent of myocardial infarctions and coronary revascularizations explained by family history unrelated to convetional risk factors. The Reykjavik Cohort Study. *Eur Heart J* 2002; 23:1655-1690

54) Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004; 291:2204-2220

55) Murabito JM, Pencina MJ, Nam BH, et al. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults.
JAMA 2005; 294:3117-3140

56) Bachmann JM, Willis BL, Ayers CR, et al. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. *Circulation* 2012; 125:3092-3120-3145

57) Chow CK, Islam S, Bautista L, et al. Parental history and myocardial infarction risk across the world: the INTERHEART Study.
J Am Coll Cardiol 2011; 57:619-634

58) Miura K, Daviglus ML, Dyer AR, et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all

causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med* 2001; 161:1501-1540

59) Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903-1940

60) Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364:937-968

61) Lewington S, Clarke R, Qizilbash N, et al; Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.
Lancet 2002 Dec 14;360(9349):1903-1913 [abstract]

62) Roncaglioni MC, Santoro L, D'Avanzo B, et al. Role of family history in patients with myocardial infarction. An Italian case-control study. GISSI-EFRIM Investigators. *Circulation* 1992; 85:2065-2085

63) Genest JJ Jr, Martin-Munley SS, McNamara JR, et al. Familial lipoprotein disorders in patients with premature coronary artery disease.
Circulation 1992; 85:2025-2055

64) Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; 333:1301-1360

65) Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279:1615

66) Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators.

N Engl J Med 1996; 335:1001-1028

67) Njølstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. *Circulation* 1996; 93:450-475

68) Prescott E, Hippe M, Schnohr P, et al. Smoking and risk of myocardial infarction in women and men: longitudinal population study.

BMJ 1998; 316:1043-1090

69) Sesso HD, Lee IM, Gaziano JM, et al. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation* 2001; 104:393-420

70) Law MR, Morris JK, Wald NJ; Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence.

BMJ 1997 Oct 18;315(7114):973-980 [abstract]

71) Guilbert JJ; The world health report 2002 - reducing risks, promoting healthy life. *Educ Health (Abingdon)* 2003 Jul;16(2):230-302

72) Richard PS, Robert MS, Stanton AG. Reduced incidence of admissions for myocardial infarction associated with public smoking ban: before and after study. *BMJ* 2004;328:977–983

73) Garcia MJ, McNamara PM, Gordon T, et al; Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study.

Diabetes 1974 ;23(2):105-110

74) Recommended amount of physical activity, World Health Organization, accessed May 2013

75) Paffenbarger RS Jr, Hyde RT, Wing AL, et al. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 1993; 328:538-578

76) Held C, Iqbal R, Lear SA, et al. Physical activity levels, ownership of goods promoting sedentary behaviour and risk of myocardial infarction: results of the INTERHEART study. *Eur Heart J* 2012; 33:452-477

77) Wilson PW, Bozeman SR, Burton TM, et al. Prediction of first events of coronary heart disease and stroke with consideration of adiposity. *Circulation* 2008; 118:124-167

78) Brezinka V, Kittel F; Psychosocial factors of coronary heart disease in women: a review. *Soc Sci Med* 1996 May;42(10):1351-13 65 [abstract]

79) Diet, Nutrition and the prevention of chronic diseases. World Health Organization, 2003; Report of a Joint AHO/FAO Expert Consultation

80) Bays HE, Tighe AP, Sadovsky R, et al; Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications. *Expert Rev Cardiovasc Ther* 2008 Mar;6(3):391-409 [abstract]

81) British Heart Foundation. 2008 Coronary Heart Disease Statistics. British Heart Foundation promotion research group.Department of Public Health, University of Oxford. Available at www.heartstats.org. Accessed Oct. 6, 2013.

82) Kuppuswamy VC, Gupta S; Excess coronary heart disease in South Asians in the United Kingdom. *BMJ*. 2005 May 28;330(7502):1223-1224

83) Steyn K, Sliwa K, Hawken S, Commerford P, Onen C, Damasceno A et al. Risk factors associated with myocardial infarction in Africa : The INTERHEART Africa Study. *Circulation* 2005;112:3554-3561

84) Adams DC, Antman EM, Bridges CR, Antman RM, Casey, JR, DE, Chavey WE et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2007; 50:e1–157.

85) Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol* 2005;46:937–954

86) Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685–1695

87) Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005; 111:3481–3488

88) Lee KW, Lip GY, Tayebjee M, Foster W, Blann AD. Circulating endothelial cells, von Willebrand factor, interleukin-6, and prognosis in patients with acute coronary syndrome. *Blood* 2005;105:526–532

89) Stone PH. Triggering myocardial infarction. *N Engl J Med* 2004;351: 1716–1718

90) Antman EM. ST-Segment Elevation Myocardial Infarction: Pathology, Pathophysiology and Clinical Features. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds. Braunwald's heart diseases; A textbook of cardiovascular medicine. 8th ed. Philadelphia: Saunders an imprint of Elsevier;2012.1087-1110

91) Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. *European Heart Journal* 2008 29, 2909–2945

92) Braunwald E. Unstable angina: a classification. *Circulation* 1989;80:410-414

93) Campeau L. Letter: grading of angina pectoris. *Circulation* 1976;54:522-523

94) Hamm CW, Bertrand M, Braunwald U. Acute coronary syndrome without ST elevation: implementation of new guidelines. *Lancet* 2001; 358: 1533–1538

95) Klootwijk KP, Hamm CW. Acute coronary syndromes: diagnosis. *Lancet* 1999; 353**:** 10–15

96) Jaffe AS, Ravkilde J, Roberts R, et al. It's time for a change to troponin standard. *Circulation* 2000; 102: 1216–20

97) Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: The present and the future. *J Am Coll Cardiol* 2006;48:1–11

98) Wu AH, Apple FS, Gibler B, et al. National Academy of Clinical Biochemistry Standards of Laboratory Practise: recommendation for the use of cardiac markers in coronary artery diseases. *Clin Chem* 1999; 5**:**1104–1121

99) Lindahl B, Verge P, James S. The new high sensitivity cardiac troponin T assays improves risk assessment in ACS. *Am Heart J* 2011; 161:425-437.

100) Kristian T, Joseph SA, Allan SJ, Maarten LS, Bemard R, Havey DW et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:0735-1097

101) Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the

American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction).

Circulation 2004; 110:e82

102) www.acc.org/qualityandscience/clinical/statements.htm (Accessed on September 18, 2007). www.acc.org/qualityandscience/clinical/statement.htm (Accessed on September 18, 2012)

103) Moradkhan R, Sinoway LI. Revisiting the role of oxygen therapy in cardiac patients. *J Am Coll Cardiol* 2010; 56:1013-1056

104) Anderson JL, Karagounis LA, Califf RM. Metaanalysis of five reported studies on the relation of early coronary patency grades with mortality and outcomes after acute myocardial infarction. *Am J Cardiol* 1996; 78:11-45

105) Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; 361:13-57

106) Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction.

N Engl J Med 2005; 353:2758–2768

107) Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006;367:579–588

108) Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4PCI): randomised trial. *Lancet* 2006;367:569–578

109) Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;358: 2218–2230

110) Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: The OASIS-6 randomised trial. *JAMA* 2006;295:1519–1530

111) Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004;110:1202–1208

112) Beinart SC, Kolm P, Veledar E, Zhang Z, Mahoney EM, Bouin O, et al. Long-term cost effectiveness of early and sustained dual oral antiplatelet therapy with clopidogrel given for up to one year after percutaneous coronary intervention results: from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. *J Am Coll Cardiol* 2005;46:761–769

113) Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179–1189

114) Giraldez RR, Nicolau JC, Corbalan R, Gurfinkel EP, Juarez U, Lopez-Sendon J, et al. Enoxaparin is superior to unfractionated heparin in patients with ST elevation myocardial infarction undergoing fibrinolysis regardless of the choice of lytic: an ExTRACT-TIMI 25 analysis. *Eur Heart J* 2007;28:1566–1573

115) Cohen M, Gensini GF, Maritz F, Gurfinkel EP, Huber K, Timerman A, et al. The safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and tirofiban versus placebo in the treatment of acute ST-segment elevation myocardial infarction patients ineligible for reperfusion (TETAMI): a randomized trial. *J Am Coll Cardiol* 2003;42:1348-1356

116) Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;318:1730-1737

117) Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669–677

118) Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893–1906

119) Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321

120) Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies.
Am J Cardiol 1991;67:1295–1297

121) Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines disease prevention in clinical practice: executive summary. *Eur Heart J* 2007;28:2375-2414

122) Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur Heart J* 2006;27:519–526

123) Karjalainen PP, Porela P, Ylitalo A, Vikman S, Nyman K, Vaittinen MA, et al. Safety and efficacy of combined antiplatelet–warfarin therapy after coronary stenting. *Eur Heart J* 2007;28:726-732

124) Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994; 89:1545-1590

125) Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban.
N Engl J Med 2001; 344:1879-1898

126) Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest. Results of the Thrombolysis in Myocardial Ischemia (TIMI IIIA) Trial. *Circulation* 1993; 87:38-67

127) Gibson RS, Hansen JF, Messerli F, et al. Long-term effects of diltiazem and verapamil on mortality and cardiac events in non-Q-wave acute myocardial infarction without pulmonary congestion: post hoc subset analysis of the multicenter diltiazem postinfarction trial and the second danish verapamil infarction trial studies. *Am J Cardiol* 2000; 86:275-289

128) Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation* 2007; 115:2549-2578

129) Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *AJAM* 2000; 284:835-890

130) Borzak S, Cannon CP, Kraft PL, et al. Effects of prior aspirin and anti-ischemic therapy on outcome of patients with unstable angina. TIMI 7 Investigators. Thrombin Inhibition in Myocardial Ischemia. *Am J Cardiol* 1998; 81:678-690

131) Silber S, Albertsson P, Avilés FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005; 26:804-867

132) Eagle KA, Guyton RA, Davidoff R. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 2004; 110:e340-e390

133) Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during Instability in Coronary artery disease Investigators. *Lancet* 1999; 354:708-720

134) Diver DJ, Bier JD, Ferreira PE, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). *Am J Cardiol* 1994; 74:531-540

135) Roe MT, Harrington RA, Prosper DM, et al. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. *Circulation* 2000; 102:1101-1101

136) Goldberg RJ, McCormick D, Gurwitz JH, et al. Age-related trends in short- and long-term survival after acute myocardial infarction: a 20-year population-based perspective (1975-1995). *Am J Cardiol* 1998; 82:1311-1340

137) Alexander KP, Newby LK, Armstrong PW, et al. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation* 2007; 115:2570-2598

138) Paul SD, O'Gara PT, Mahjoub ZA, et al. Geriatric patients with acute myocardial infarction: Cardiac risk factor profiles, presentation, thrombolysis, coronary interventions, and prognosis. *Am Heart* J 1996; 131:710-756

139) Mehta RH, Rathore SS, Radford MJ, et al. Acute myocardial infarction in the elderly: differences by age. *J Am Coll* Cardiol 2001; 38:736-779

140) Stone PH, Thompson B, Anderson HV, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: The TIMI III registry. *JAMA* 1996; 275:1104-1167

141) Alexander KP, Roe MT, Chen AY, et al. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol* 2005; 46:1479-1501

142) McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation* 2008; 117:1897-1920

143) Marques-Vidal P, Ruidavets JB, Cambou JP, Ferrieres J. Incedence, recurrence and case fatality rates for myocardial infarction in South Western France, 1985 to 1993. *Heart*. 200;84: 171-175

144) Heidenreich PA, McClellan M. Trends in treatment and outcomes for acute myocardial infarction: 1975-1995. *Am J Med* 2001; 110:165-201

145) Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. *Arch Intern Med* 2002; 162:2405-2467

146) Bishop E. Heart disease may actually be rising; researchers claim deaths are now being delayed to a later age group. *Wall Street Journal* 1996; pB3(W)-pB6(E)

147) Gerber Y, Jacobsen SJ, Killian J, Weston S, Roger VL. Impact of Participation Bias in a Based Study of Myocardial Infarction in Olmsted County, Minnesota, 2002 to 2004. *Circulation* 2006;13:e827-e862

148) British Heart Foundation. 2004 Coronary Heart Disease Statistics. British Heart Foundation promotion research group.Department of Public Health, University of Oxford. Available at www.heartstats.org. Accessed March 5 2013.

149) Liu JI, Mantadakis N, Gray A, Rayner M. The economic burden of coronary heart disease in the UK. *Heart* 2002;8: 567-603

150) Oyoo GO, Ogola EN. Clinical and socio demographic aspects of congestive heart failure patients at Kenyatta National Hospital, Nairobi.
East Afr Med J 1999; 76:23–27

151) Ladipo GO, Fraude JR, Parry EH. Pattern of heart disease in adults of the Nigerian Savannah. A Prospective study. *Afr J Med Sci* 1977; 6: 185-192

152) Damasceno A, Cotter G, Dzudie A, Sliwa K, Mayosi BM: Heart failure in Sub-Saharan Africa: time for action. *J Am Coll Cardiol* 2007; 50 (17):1688-1693.

153) World Health Organization, Department of Measurement and Health Information. Projections of mortality and burden of disease by region, 2006. Available at http://www.who.int/healthinfo/statistics/bod_deathbyregion.xls (accessed 30 March 2013).

154) Rotimi O, Ajayi AA, Odesanmi WO. Sudden unexpected death from cardiac causes in Nigerians. A review of 50 autopsied cases.
Int J Cardiol 1998;63(2): 111-119.

155) Rotimi O, Fatusi AO, Odesanmi WO. Sudden cardiac death in Nigerians—the Ile-Ife experience. *West Afr J Med* 2004;23(1):27-31

156) Olubenga AS, Adeyi AA, Agabus NM, Godwin OE, Barnabas MM, Rahila OS. The role of necropsy in diagnostic dilemmas as seen in a Tertiary Hospital in North Central Nigeria. *East Afr Med J* 2006;83(11):626-630

157) Maharaj CR, Geduld H, Wallis LA. Door to needle time for the administration of fibrinolytics in acute myocardial infarction in Cape Town.
SAMJ 2012;102(4):55-61

158) Maru M. Coronary atherosclerosis and myocardial infarction in autopsied patients in Gondar, Ethiopia. *J R Soc Med* 1989;82:399–401

159) Kerry LL, Lynn H. Woodlief MS; Eric JT, Douglas W, Amadeo B, et al. Predictors of 30-Day Mortality in the Era of Reperfusion for Acute.
Circulation 1995;91:1659-1668

160) Stone PH, Thompson B, Anderson HV, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: The TIMI III registry. *JAMA* 1996; 275:1104-1190

161) Becker RC, Terrin M, Ross R, Knatterud GL, Desvigne-Nickens P, Gore JM, Braunwald E, for the Thrombolysis in Myocardial Infarction Investigators. Comparison of clinical outcomes for women and men after acute myocardial infarction. *Ann Intern Med.* 1994;120:638-645

162) Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. *Circulation* 1991; 83:484-897

163) Gottlieb S, Harpaz D, Shotan A. Sex differences in management and outcome after acute myocardial infarction in the 1990s: A prospective observational community-based study. Israeli Thrombolytic Survey Group.
Circulation 2000; 102:2484-2499

164) Vaccarino V, Parsons L, Every NR. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med* 1999; 341:217-239

165) Vaccarino V, Parsons L, Peterson ED. Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006.
Arch Intern Med 2009; 169:1767-1798

166) Berger JS, Elliott L, Gallup D. Sex differences in mortality following acute coronary syndromes. *JAMA* 2009; 302:874-889

167) Kornowski R, Goldbourt U, Zion M, Mandelzweig L, Kaplinsky E, Levo Y, et al, for the SPRINT Study Group. Predictors and long-term prognostic significance of recurrent infarction in the year after a first myocardial infarction. *Am J Cardiol* 1993;72:883-888

168) Granger CB, Califf RM, Young S, Candela R, Samaha J, Worley S, et al, for the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. *J Am Coll Cardiol* 1993;21:920-925

169) Barbash GI, White HD, Modan M, Van de Werf F. Significance of diabetes mellitus in patients with acute myocardial infarction receiving thrombolytic therapy. *J Am Coll Cardiol* 1993;22:707-713

170) Barbash GI, White HD, Modan M, Diaz R, Hampton JR, Heikkila J, et al. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial.*Circulation* 1993;87:53-58

171) Ockene IS, Ockene JK. Smoking after acute myocardial infarction: a good thing? *Circulation* 1993;87:297-299

172) Mueller HS, Cohen LS, Braunwald E, Forman S, Feit F, Ross A, et al. Schweiger M, Cabin H, Davison R, Miller D, Solomon R, Knatterud GL, for the TIMI Investigators. Predictors of early morbidity and mortality after

thrombolytic therapy of acute myocardial infarction: analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase II. *Circulation* 1992;85:1254-1264

173) Shuraishi J, Sawada T, Kimura M, Matsui A, Irie H, Shima T, et al. Systolic blood pressure at admission, clinical manifestations, and in-hospital outcomes in patients with acute myocardial infarction. *Journal of Cardiology* 2011;58:54-60

174) Frederick SV, Ferreira AM, Kulkarni MS, Motghare DD. Utility of Logistic Regression Analysis to Estimate Prognosis in Acute Myocardial Infarction. *Indian Journal of Community Medicine* 2009;34:371-372

175) Crimm A, Severance HW Jr, Coffey K, McKinnis R, Wagner GS, Califf RM. Prognostic significance of isolated sinus tachycardia during first three days of acute myocardial infarction. *Am J Med* 1984;73:983-988

176) Taylor GJ, Humphries JO, Millits ED, Pitt B, Schulze RA, Griffith LS,et al. Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. *Circulation* 1980;62:960-970

177) Mauri F, Gasparini M, Barbonaglia L, Santoro E, Franzosi KMG, Tognoni G et al. Prognostic significance of the extent of myocardial injury in acute myocardial infarction treated by streptokinase (the GISSI Trial).
Am J Cardiol 1989;63:1291-1295

178) Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967; 20:457

179) Becker RC, Burns M, Gore JM, et al. Early assessment and in-hospital management of patients with acute myocardial infarction at increased risk for adverse outcomes: a nationwide perspective of current clinical practice. The National Registry of Myocardial Infarction (NRMI-2) Participants.

Am Heart J 1998; 135:786-801

180) Steg PG, Dabbous OH, Feldman LJ. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE).
Circulation 2004; 109:494-509

181) Khot UN, Jia G, Moliterno DJ. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA* 2003; 290:2174-2190

182) Al-Khatib SM, Pieper KS, Lee KL. Atrial fibrillation and mortality among patients with acute coronary syndromes without ST-segment elevation: results from the PURSUIT trial. *Am J Cardiol* 2001; 88:A7, 76-109

183) Piccini JP, White JA, Mehta RH. Sustained Ventricular Tachycardia and Ventricular Fibrillation Complicating Non-ST-Segment-Elevation Acute Coronary Syndromes. *Circulation* 2012; 126:41-98

184) Damman P, Holmvang L, Tijssen JG. Usefulness of the admission electrocardiogram to predict long-term outcomes after non-ST-elevation acute coronary syndrome (from the FRISC II, ICTUS, and RITA-3 [FIR] Trials).
Am J Cardiol 2012; 109:670

185) Brilakis ES, Mavrogiorgos NC, Kopecky SL, et al. Usefulness of QRS duration in the absence of bundle branch block as an early predictor of survival in non-ST elevation acute myocardial infarction. *Am J Cardiol* 2002; 89:1013-1037

186) James SK, Armstrong P, Barnathan E, et al. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a GUSTO-IV substudy.
J Am Coll Cardiol 2003; 41:916-947

187) Alexander JH, Sparapani RA, Mahaffey KW, et al. Association between minor elevations of creatine kinase-MB level and mortality in patients with acute coronary syndromes without ST-segment elevation. PURSUIT Steering Committee. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *JAMA* 2000; 283:347-369

188) Savonitto S, Granger CB, Ardissino D, et al. The prognostic value of creatine kinase elevations extends across the whole spectrum of acute coronary syndromes. *J Am Coll Cardiol* 2002; 39:22-67

189) de Lemos JA, Morrow DA, Gibson CM, et al. The prognostic value of serum myoglobin in patients with non-ST-segment elevation acute coronary syndromes. Results from the TIMI 11B and TACTICS-TIMI 18 studies.
J Am Coll Cardiol 2002; 40:238-289

190) de Lemos JA, Morrow DA, Bentley JH. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes.
N Engl J Med 2001; 345:1014-1067

191) Richards AM, Nicholls MG, Espiner EA. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction.
Circulation 2003; 107:2786-2804

192) James SK, Lindahl B, Siegbahn A. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003; 108:275-288

193) Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. *J Am Coll Cardiol* 2002; 40:437-478

194) Wiviott SD, Cannon CP, Morrow DA. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non- ST- elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) sub study.
Circulation 2004; 109:580-598.

195) Donahoe SM, Stewart GC, McCabe CH. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007; 298:765-798

196) Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment.
J Am Coll Cardiol 2004; 44:1945-1987

197) Barron HV, Harr SD, Radford MJ. The association between white blood cell count and acute myocardial infarction mortality in patients > or =65 years of age: findings from the cooperative cardiovascular project.
J Am Coll Cardiol 2001; 38:1654-1690

198) Cannon CP, McCabe CH, Wilcox RG. Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. OPUS-TIMI 16 Investigators. *Am J Cardiol* 2001; 87:636-678

199) Sabatine MS, Morrow DA, Giugliano RP. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes.
Circulation 2005; 111:2042-2078

200) Al Suwaidi J, Reddan DN, Williams K. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 2002; 106:974-1034

201) Anavekar NS, McMurray JJ, Velazquez EJ. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; 351:1285-1327

202) Freeman RV, Mehta RH, Al Badr W. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol* 2003; 41:718-778

203) Kirtane AJ, Leder DM, Waikar SS. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol* 2005; 45:1781-1798

204) Weintraub WS. Prediction scores after myocardial infarction. Value, limitations, and future directions. *Circulation* 2002;106:2292–2293

205) Anderson JL, Adams DC, Antman ME, Bridges RC, Califf NR, Casea DR Jr, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2007;50:1e-157e

206) Antman EM, Cohen M, Bernink PJ. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–42

207) Morrow DA, Antman EM, Giugliano RP. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an In TIME II sub study. *Lancet* 2001;358:1571–1575

208) Boersma E, Pieper KS, Steyerberg EW. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;101:2557-2567

209) Giugliano RP, Braunwald E. The year in non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2005;46:906 –919

210) Park YW, Zhu S, Palaniappan L. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994.
Arch Intern Med 2003; 163:427-436

211) Moser M: World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension- Do These Differ From the U.S. Recommendations? Which Guidelines Should the Practicing Physician Follow? *J Clin Hypertens (Greenwich).* 1999, 1:48 54

212) Gaziono MJ, Buring JE, Breslow IJ, Goldhaber ZS, Rosner B VanDenburgh M et al. Moderate alcohol intake, increased level of high density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *The New England Journal of Medicine* 1993; 329: 1829-1834.

213) Seyoum Y, Leake N. Clinical features of acute myocardial infarction: A report from Halibet Referral Hospital in Eritrea.
Journal of Eritrean Medical Association (JEMA) 2002;28-30

214) Misiriya KJR, Sudhayakumar N, Abdul Khadar S, Raju G, Jayaprakash VL**,** Pappachan JM. The Clinical Spectrum of Acute Coronary Syndromes: Experience from a Major Center in Kerala. *JAPI* 2009; 57:377-383

215) Yap TG, Duong T, Bland JM, Malik M, Torp-Pedersen C, Kober L, et al. Prognostic Impact of Demographic Factors and Clinical Features on the Mode of Death in High-Risk Patients after Myocardial Infarction – A Combined Analysis from Multicenter Trials. *Clin. Cardiol* 2005; 28: 471–478

216) Schwartz, M. B., Schamroth, L., and Seftel, H. C.: The pattern of heart disease in the urbanised (Johannesburg) African. *Med. Proc.*1958;4:275-289

217) Schrire V. Heart disease in Southern Africa with special reference to ischemic heart disease, S. Afr. *Med. J* 45:634, 1971-1997

218) Seftel, H. C., and Kew, M. C.: Myocardial infarction in the Johannesburg Bantu, S. -Afr. *Med. J* 1970; 44:8-15

219) Elliot C, Abdul SM, Weir EK, Rodney EM, Peter JH. Myocardial infarction in the Black population of South Africa: Coronary arteriographic findings. *American Heart Journal* 1978;95:691-696

220) Sani MU, Adamu B, Mijinyawa MS, Abdu A, Karaye KM, Maiyaki MB, Borodo MM. ischaemic heart disease in Aminu Kano Teaching Hospital Kano, Nigeria: a 5 year review. *Niger J Med* 2006; Apr – Jun 15(2): 128 – 131

221) Anjorin CO, Buba F, Ene AC. Myocardial Infarction at University of Maiduguri Teaching Hospital, North eastern Nigeria: a long term review.
J Med Sci 2005; 5(4): 358 – 362

222) Barreto MS, Passos VMA, Firmo JOA, Guerre HL, Vidigal PG, Lima-Costa MF. Hypertension and Clustering of Cardiovascular Risk Factors in a Community in Southeast Brazil - The Bambuí Health and Ageing Study.
Arq Bras Cardiol 2001;77: 576-581

223) Kannel WB. Risk stratification in hypertension: new insights from the Framingham study. *Am J Hypertens* 2000; 13: 3S-10S

224) Yan AT, Yan RT, Tan M, Huynh T, Soghrati K, Brunner LJ et al. Optimal medical therapy at discharge in patients with acute coronary syndromes: Temporal changes, characteristics, and 1-year outcome.
Am Heart J 2007;154:1108-1115

225) The ACCESS Investigators. Management of acute coronary syndromes in developing countries: ACute Coronary Events—a multinational Survey of current management Strategies. *Am Heart J* 2011;162:852-859

226) Colin S. ACCESS South Africa investigators. Management of acute coronary syndrome in South Africa: insights from the ACCESS (Acute Coronary Events – a Multinational Survey of Current Management Strategies) registry. *Cardiovasc J Afr* 2012; 23: 365–370

227) Keith AA, Philippe GS, Kim AE, Shaun GG, Frederick AA, Christopher BG, et al. Decline in Rates of Death and Heart Failure in Acute Coronary Syndromes, 1999-2006. *JAMA. 2007;297:1892-1900*

228) Gheorghiade M, Abraham WT, Albert NM. OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure.
JAMA 2006;296:2217–2226

229) Iwasaki M, Yuasa F, Yuyama R, Mimura J, Kawamura A Motohiro M, Yo M, Sugura T, I wasaka T. Correlation of heart rate turbulence with sympathovagal balance in patients with acute myocardial infarction.

Clin Exp Hypertens 2005;27:251−257

230) Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 2000;102:742-747

231) Beddhu S, Nigwekar SU, Ma X, Greene T. Association of resting heart rate with insulin resistance, cardiovascular events and mortality in chronic kidney disease. *Nephrol Dial transplant* 2009; 24:2482−2488

232) Yoshikawa H, Powell WJ Jr, Bland JH, Lowenstein E. Effect of acute anaemia on experimental myocardial ischaemia. *Am J Cardiol* 1973;32:670-678

233) Most AS, Ruocco NA Jr, Gewirtz H. Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis. *Circulation* 1989;74:1085-1092

5.5 APPENDIX A

DATA COLLECTION SHEET; FROM DATABASE

SYSTOLIC BLOOD PRESSURE ON ADMISSION, CLINICAL CHARACTERISTICS AND MORTALITY IN PATIENTS HOSPITALISED FOR ACUTE CORONARY SYNDROME

DEGREE: MSc MEDICINE

INVESTIGATOR: DR MUHAMMAD NAZIR SHEHU

SUPERVISOR: PROF. P. MANGA MB BCH FCP (SA) PhD FRCP

1. PERSONAL BIODATA: STUDY No: DATE:

Age (years)-------- Sex: [M] [F] Race----------

2.HISTORY

A. Chest pain: Duration (in hours)----------

II) Severity: a) Mild { } b) Moderate { } c) Severe { }

B. Risk factors of ACS Yes No

Diabetes [ ] [ ]

Hypertension [ ] [ ]

Family history [ ] [ ]

Cigarette smoking: Active smoker [ ] Former smoker [ ] Non smoker [ ]

C. Other medical history Yes No

History of previous ACS [ ] [ ]

HIV test positive [ ] [ ] [ ] Unknown

Renal disease [ ] [ ]

Heart failure [ ] [ ]

Alcohol drinking: Non drinker [ ] Moderate drinker [ ] Heavy drinker [ ]

3.PHYSICAL FINDINGS

Heart rate beats/min. ---------- ----------

Blood pressure syst./diast. ------/----- --------/-----

Yes No

Pedal oedema [ ] [ ]

Raised JVP (CM) [ ] [ ]

Third heart sound [ ] [ ]

Cardiomegaly [ ] [ ]

Tender hepatomegaly [ ] [ ]

Pulmonary rales [ ] [ ]

4. LABS FINDINGS

	VALUE	**PARAMETER**	**VALUE**
Urea (mmol/l)		**TC** (mmol/l)	
SCr (umol/l)		**LDL** (mmol/l)	
Na (mmol/l)		**TG** (mmol/l)	
Glucose (mmol/l)		**HDL** (mmol/l)	
Hb g/Dl		**Troponin I/T** U/L	
Total WBC x 10^9 /L		**CK-MB** U/L	

ECG

- Arrhythmia : [ ] Yes [ ] No

  If yes, specify…….

- ACS features STEMI [ ] NSTEMI [ ]
- Left ventricular hypertrophy [ ]Yes No[ ]
- Other ECG Findings ----------

Echocardiography: EF ---------% SF--------% IVSDs---------(CM) IVSDd----------(CM)

LVPWDs---------(CM) LVPWDd---------(CM) LVIDd---------(CM)

LVIDs--------(CM) LA--------(CM) AO---------(CM) E-vel.------(m/s)

A-vel. --------(m/s). E/A --------

Wall motion abnormality: Akinesia [ ] Hypokinesia [ ] Dyskinesia[ ]

Aneurhysmal [ ]

Echo diagnosis.....

Angiography: Type of artery involved---------- Number of arteries involved----------

Severity of the stenosis: Significant [ ] Non significant [ ].

Cardiac region(s) affected----------

5. In-hospital death: [ ] date of death: ___ ___ /___ ___ ___ /200 ___

R14/49 Dr Muhammad Nazir Shehu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130336

NAME: (Principal Investigator)	Dr Muhammad Nazir Shehu
DEPARTMENT:	Department of Internal Medicine Division of Cardiology Charlotte Maxeke Johannesburg Academic
PROJECT TITLE:	Systolic Blood Pressure on Admission, Clinical Characteristics and Mortality in Patients admitted for Acute Coronary Syndrome at Charlotte Maxeke Johannesburg Academic
DATE CONSIDERED:	05/04/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof P Manga
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/04/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 17-04-2013

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES