ADHERENCE TO GUIDELINE MANDATED OPTIMAL MEDICAL THERAPY FOR ACUTE CORONARY SYNDROME AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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A dissertation submitted to the Wits Faculty of Health Sciences, University of the Witwatersrand in partial fulfilment of the requirements for the degree of Master of Medicine (MMed) in the Division of Internal Medicine.

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DECLARATION OF CANDIDATE

I, **Viwe Mtwesi**, hereby declare that this dissertation is my own work. It is being submitted for the degree of the Master of Medicine in the Division of Internal Medicine, University of Witwatersrand, Johannesburg. It has not been submitted for any degree/examination at this or any other university.

Signature: ……

Date: ……

DEDICATION

I dedicate this thesis to my late grandmother Nowini Radie Mtwesi, mother Vuyokazi Mtwesi, brother Mandisi Mtwesi, nephews Tiri and Amahle, and finally to my spiritual father Bishop Freddie Edwards for being my pillar of strength.

I am grateful to all of you.

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ABBREVIATIONS

ACE : Angiotensin-converting enzyme

ACS : Acute coronary syndrome

AMI : Acute myocardial infarction

AF : Atrial fibrillation

CABG : Coronary artery bypass graft surgery

CAD : Coronary Artery Disease

CMJAH : Charlotte Maxeke Johannesburg Academic Hospital

CKD : Chronic kidney disease

ECG : Electrocardiogram

HDL : High-density lipoprotein

HIV : Human immunodeficiency virus

IQR : Interquartile range

LBBB : Left bundle branch block

LDL : Low-density lipoprotein

MI : Myocardial infarction

NHLS : National Health Laboratory Service

NSTEMI : Non-ST-segment elevation myocardial infarction

PCI : Percutaneous coronary intervention

SD : Standard deviation

STEMI : ST-segment elevation myocardial infarction

UA : Unstable angina

ABSTRACT

Acute coronary syndrome (ACS) is the leading cause of death worldwide. Optimal medical therapy significantly reduces mortality resulting from ACS. Adherence to guideline medical mandatory therapy has been demonstrated to be suboptimal in most parts of the world, especially in developing countries. The current study assesses the effects of adhering to guideline mandatory therapy on the outcome in patients presenting with ACS.

METHODS

This is a retrospective record review of 1073 patients, who presented with ACS, admitted to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), from January 2013 to December 2014. Patients were over the age of 18. Records were retrieved from an existing database in the Cardiology Department. The use of commonly used prescribed medication was assessed, which included aspirin, statins, beta blockers, clopidogrel, ACE inhibitors, and spironolactone.

RESULTS

The majority of the patients were male (73.3%). The racial demographics of the patients were as follows: 46% were White, 22.8% were Indian, 19.8% were Black, and 10.3% were Coloured. STEMI was the most common presentation (52%), followed by unstable angina (30%), and NSTEMI (18%). Aspirin was the most prescribed drug at 85%, followed by statins, beta blockers, clopidogrel, ACE inhibitors, and spironolactone at 84%, 79%, 74%, 54% and 38% respectively. Creatinine levels were indirectly associated with the prescription of ACE inhibitors and clopidogrel. Age and gender were also found to influence drug prescription. The survival rates for the CMJAH admitted ACS patients on optimal medical therapy were high, at 96%, which was statistically significantly. Upon discharge, there was a 4% in-hospital mortality rate from ACS.

CONCLUSION

ACS presents most commonly as STEMI. Almost three-quarters of the ACS patients were males. There was a strong correlation between the use of guideline mandated therapy and reduced mortality rates. The findings of this study reinforce the need for proper diagnosis and appropriate medical treatment to improve the life expectancy of ACS patients.

CHAPTER 1

1. INTRODUCTION AND LITERATURE REVIEW

1.1 BACKGROUND

Acute coronary syndrome (ACS) encompasses a group of clinical disorders that include ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). These develop due to the partial or total occlusion of the coronary vasculature (Kumar & Cannon, 2009). These usually occur in the presence of underlying chronic atheromatous coronary disease, where an exacerbation may give rise to ischaemia or infarction (Davies, 2000). Atherosclerosis plays a vital role in the development of ACS. However, there are instances where patients may develop ACS in the absence of atherosclerosis. These include dissection, arteritis, myocardial bridging, and vasospasm (Fox et al., 2007) .

The process of atherosclerosis starts early in life as a 'fatty streak,' which progresses with time. When a patient develops risk factors for atherosclerosis, the endothelium changes its function, from an antiatherogenic endothelial state to a proatherogenic state. The dysfunctional endothelium exposes adhesion and vascular proteins, which in turn activate monocytes, leading to macrophage formation. Dysfunctional endothelium also promotes platelet aggregation and the release of cytokines, which ultimately cause penetration and deposition of circulating lipids into the intima (Fox et al., 2007; Santos-Gallego, Picatoste & Badimón, 2014) .

Thrombosis in the coronary arteries is caused by plaque rupture and fissuring, thus leading to partial or total vessel occlusion (Fuster et al., 1992; Shah, 2003).

Myocardial infarction (MI) is defined by the presence of myocardial cell necrosis due to decreased myocardial blood supply. The diagnosis requires elevation of cardiac biomarkers,

electrocardiographic (ECG) changes and symptoms according to the universal definition of MI (Virmani et al., 2006; Thygesen et al., 2007) .

The pathological diagnosis is divided into five types:

Type 1: Spontaneous MI – due to atheromatous plaque rupture

Type 2: Usually secondary to increased oxygen demand

Type 3: Myocardial infarction causing sudden death

Type 4a: Related to percutaneous coronary intervention (PCI)

Type 4b: Caused by stent thrombosis

Type 5: Related to Coronary artery bypass grafting

ACS is accelerated by age, menopause, hypertension, diabetes, smoking, genetic risk, human immunodeficiency virus, renal failure, rheumatoid arthritis, and certain recreational drugs (Yusuf et al., 2004a) . Coronary artery disease (CAD) remains the leading cause of death worldwide (Cade & Margetts, 1989), contributing to about a third of all mortalities in the adult population (Thom Thomas et al., 2006; Roger Véronique L. et al., 2011; Nichols et al., 2014). There is an increase in the incidence of non-communicable diseases in general in Africa (Cade & Margetts, 1989). In 2005, CAD was the eighth leading cause of death in Africa, and it is predicted that by 2020, seven out of 10 deaths in Africa will be due to non-communicable diseases (Boutayeb, 2006). Studies from South Africa, a country in an epidemiological transition, shows cardiovascular mortality as the second leading cause of death after human immunodeficiency virus related deaths (Manga, 2008; Peer et al., 2008) .

1.2 Risk factors for Coronary Artery Disease (CAD)

Over 90% of the population have at least one risk factor; more than 75% of patients presenting with CAD have major risk factors, which include cigarette smoking, dyslipidaemia, high blood pressure, and diabetes.

1.2.1 Modifiable Risk Factors

Smoking

The majority of the estimated 1.3 billion smokers globally come from developing countries. Smoking is responsible for six million deaths worldwide. In America, it accounts for approximately 400,000 deaths annually (Ambrose & Barua, 2004). It is estimated that smoking will kill approximately eight million people by 2030. Atherosclerotic cardiovascular disease, lung malignancy, and chronic obstructive airway disease are the leading causes of smoking related deaths (Jee et al., 1999).

Smoking is an independent risk factor for CAD and atherosclerotic cardiovascular disease. The incidence of ACS is increased threefold in males and six fold in females who smoke approximately 20 cigarettes per day (Yusuf et al., 2004a). Myocardial infarction patients who continue to smoke have higher rates of re-infarction and death. These patients also have a higher risk of STEMI and restenosis (World Health Organization, 2012) . Those with LV dysfunction who continue to smoke have an increased rate of myocardial infarction, death, and rehospitalisation (Yusuf et al., 2004a).

Smoking accelerates atherosclerosis by 50%, thus indicating an exponential relationship between MI and smoking. If a patient stops smoking, the process continues, but at a slower rate (Stamler et al., 1999; Vasan et al., 2005). Smoking is associated with an increase in LDL cholesterol and insulin resistance. The free radicals in cigarettes damage lipids and result in the formation of proatherogenic oxidised particles. It also increases activity of the sympathetic nervous system; this results in coronary vasoconstriction, which enhances the prothrombotic state via inhibition of tissue plasminogen activator release from the endothelium (Stamler et al., 1999; Reaven, 2003) .

Patients, who undergo percutaneous coronary intervention (PCI) and continue to smoke, have a higher risk of major adverse cardiovascular outcomes (Reaven, 2003). The dose and duration of smoking have very important mortality implications. Doses as low as five cigarettes per day portend an increased risk of coronary heart disease (Barbash G I et al., 1993; Reaven, 2003; Ruiz-Bailén et al., 2004). Patients who smoked 15 cigarettes per day had a 2.5-fold risk of CAD compared to non-smokers, and those who smoked less than 15 cigarettes had double the risk of non-smokers (van Domburg et al., 2000).

Passive smoking is also a risk for CAD, with an increased risk of 20% for coronary artery disease and death (van Domburg et al., 2000). Cigars contain the same toxins as cigarettes and thus they also convey some cardiovascular risk. Five cigars are equivalent to ten cigarettes (Wells, 1994). Pipe smoking is also associated with increased cardiovascular risk (Santo-Tomas et al., 2002).

Diet

Different food types can also contribute towards developing coronary artery disease. What we know is that higher intake of red meat and dairy products increases the risk of CAD. A study done on healthcare professionals showed a linear relationship with red meat intake and mortality due to CAD (Pan et al., 2012). Diets rich in fruit and vegetables are associated with a decrease the incidence of CAD. In the INTERHEART study lack of fruit and vegetable intake accounted for 14% of the attributable risk to first CAD presentation (Rimm et al., 1996; Yusuf et al., 2004a). Fibre intake has been also shown to decrease CAD. In a study done on health professionals, a10g increase in the total daily fibre intake was associated with reduced risk of myocardial infarction (Rimm et al., 1996). Diets high in glycaemic load may also contribute to the risk of CAD, mainly by increasing body weight and risk of insulin resistance especially in women (Mirrahimi Arash et al., n.d.).

Exercise

Exercise has a protective effect against development of CAD and death (Oster & Epstein, 1987; Powell et al., 1987). Exercise decreases the incidence of CAD through weight loss benefits, increasing HDL levels, decreasing insulin resistance, and decreasing blood pressure (Sandvik et al., 1993). In the INTERHEART study, lack of regular exercise accounted for 12% of the population attributable risk of a first CAD event (Yusuf et al., 2004a). Combination training, gave greater benefits for weight loss, fat loss and cardio-respiratory fitness than aerobic or resistance training modalities (Ho et al., 2012).

Obesity

A body mass index (BMI) above 30 defines obesity. It is an independent risk factor for CAD (Wilson Peter W.F. et al., 2008) and has a linear relationship with greater risk of CAD (Jensen Michael D. et al., 2014). Obesity is also associated with other risk factors for atherosclerosis like diabetes, hypertension and dyslipidaemia, factors which are fundamental in CAD development (Eckel Robert H. et al., 2004).

Psychosocial factors

These factors are believed to trigger early development of CAD directly through endothelial dysfunction or indirectly by increasing traditional risk factors which in turn accelerate atherosclerosis (Rozanski Alan, Blumenthal James A. & Kaplan Jay, 1999).

Diabetes

Pre diabetic states, insulin resistance and elevated plasma glucose are associated with development of myocardial infarction (Zavaroni et al., 1989; Singer et al., 1992). A small study of 300 patients looked at looked at a relationship between uncontrolled glucose and

development of myocardial infarction, and the found that a moderately increased glucose level was associated with a higher risk of developing myocardial infarction in patients with no prior diagnosis of diabetes (Gerstein, 1999).

The INTERHEART study described diabetes to be contributing to 10% of the population attributable risk for myocardial infarction (Yusuf et al., 2004a) . It has been referred to as coronary disease equivalent (Vaccaro et al., 2004).

Guidelines advocate for aggressive treatment and prevention of CAD risk factors like hypertension and dyslipidaemia in patients with diabetes ("Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report", 2002).

High blood pressure

High blood pressure is a well-established risk factor for cardiovascular diseases and outcomes (Miura et al., 2001). In a cohort of more than 1.25 million patients (20% with hypertension) without baseline cardiovascular diseases, showed that patients with hypertension had a 63.3% lifetime risk of cardiovascular diseases compared to 46.1% risk in patients with no hypertension (Rapsomaniki et al., 2014).

In the INTERHEART study hypertension contributed to 18% of the population attributable risk for first myocardial infarct (Yusuf et al., 2004a). Variations in blood pressure were also found to be associated with high risk of cardiovascular disease and mortality (Muntner et al., 2015).

Dyslipidaemia

Accelerated atherosclerosis accounts for 49% of the population attributable risk for first myocardial infarction (Yusuf et al., 2004b) .The prevalence of dyslipidaemia is high in patients with premature CAD with one study reporting a prevalence of dyslipidaemia as high as 75-85% compared with 40-48% in aged matched controls without CAD (Genest J J et al., 1992).

1.2.2 Non-Modifiable Risk Factors

Age and Gender

After adjusting for traditional risk factors, age still remains a significant risk for cardiovascular diseases (Dhingra & Vasan, 2012). Modifiable risk factors for CAD increase as the individual gets older, reaching a 45-50% increase for men (Larsson et al., 1992). CAD risk was found to be 3 times higher in men compared to women and mortality was also 5 times higher in men (Jousilahti Pekka et al., 1999).

Family History

Family history is an independent risk factor, especially in individuals with family history of premature CAD (Sesso Howard D. et al., 2001). Significant family history is defined by presence of cardiovascular disease in first degree relatives of any age or any other manifestation of atherosclerosis other than CAD (Patel et al., 2018). Data from NHANES survey reported that 12.2% of adults have a parent or sibling with a heart attack or angina before the age of 50 years (Benjamin Emelia J. et al., 2017). The risk of developing CAD ranges from 15-100% in various cohorts (Patel et al., 2018).

Ethnicity

Certain races are at an increased risk of developing cardiovascular disease; namely, non-Hispanic whites, Asians, and African Americans (Yusuf et al., 2004a). However, globally, whites are more susceptible to ACS.

1.3 Clinical presentation

ACS is a medical emergency, which should prompt early diagnosis and identification of the patient, to allow for timely and appropriate treatment and intervention (Yun & Alpert, 1997). Since the symptoms of ACS are similar, this challenges physicians when attempting to establish the appropriate diagnosis, risk stratification, treatment decision making, and monitoring response to treatment(Smith & Whitwam, 2006). Each condition can manifest itself as chest pain, discomfort, referred pain, nausea, light-headedness, faintness, dyspnoea, fatigue, or sudden loss of consciousness. Patients presenting such symptoms are immediately considered for ACS diagnosis. Typical chest pain, also known as angina, is the most common symptom that should initiate a diagnostic and treatment cascade. Aching, pressure, tightness, or burning pain over the anterior chest may last more than 15 minutes and extend to the epigastrium, shoulders, arms, back, neck, or mandible (Yun & Alpert, 1997; Smith & Whitwam, 2006). Ischaemic chest pain can be identified by the following features: it is usually gradual in onset, precipitated by activity, it is described as a discomfort rather than pain, and usually radiates to different parts of the body, mostly the upper body (Fox et al., 2007).

1.4 Risk stratification

In a Canadian registry, treating physicians found that risk stratifying the patient was vital as it helped improve treatment intensity in high risk patients. Patients labelled as high risk were likely to receive reperfusion therapy. Validated risk scores enhanced risk stratification, which

promotes appropriate intensive therapy. Before the use of validated risk scores, physicians used to objectively risk stratify patients. The problem was that most elderly patients were excluded. Elderly patients would have poor outcomes as they present atypically and would be incorrectly labelled as low risk. Risk stratification should be performed as soon as possible during admission and repeated just before discharge (Yan et al., 2009).

The most studied risk scores include the TIMI (Thrombolysis in Myocardial Infarction Score) and GRACE (Global Registry of Acute Coronary Events) score. The GRACE score performed much better than the TIMI score in stratifying ACS patients. The GRACE score predicts in-hospital and six-month mortality in ACS patients. The TIMI risk score predicts mortality, new, or recurrent events, and severe recurrent events requiring intervention in 14 days (de Araújo Gonçalves et al., 2005). There are many other risk scores, however, the above are the most validated.

1.5 Investigations

1.5.1 Electrocardiogram

This is an important diagnostic tool in patients suspected to have ACS. Changes can occur in the ST-segment, T-wave, and the QRS complex. The Electrocardiogram (ECG) is also important in identifying the location of the infarct and identifying arrhythmias. In 2012, the European Society of Cardiology formulated the following ECG criteria for myocardial infarction.

Table 1: ECG Manifestation of Acute Myocardial Ischaemia

ST ELEVATION

New ST-elevation at the J-point in two contiguous leads with the cut point: ≥0.1mV in all leads other than leads V2-V3, where the following cut points apply: ≥ 0.2mV in men ≥ 40years; ≥ 0.0.25mV in men ≤ 40years, or ≥ 0.15mV in women.
ST-depression and T-wave changes.
New horizontal or down-sloping ST depression ≥ 0.05mV in two contiguous leads and/or T inversion ≥ 0.1mV in two contiguous leads with prominent R wave or R/S ratio ≥ 1.

The ECG also helps with anatomical diagnosis of the infarct.

Anterior MI: ST-elevation or Q-waves in the precordial leads, V1– V6, indicative of left anterior descending artery obstruction. If there is AVR elevation, complete right bundle brunch block, ST depression in lead V5 or ST elevation in V1, this is highly suggestive of proximal LAD occlusion.

Inferior MI: ST-elevation or Q-waves in leads II, III, and aVF usually have occlusion in the right coronary artery or left circumflex coronary artery. Presence of ST elevation in V1 and V4R is indicative of right ventricular infarct.

Lateral MI: ST-elevation in aVL, lead 1.

Posterior MI: tall R wave in V1, ST-elevation in the posterior leads V3-V9 (Camm et al., 2012) .

1.5.2 Blood investigations

Biomarkers are measured to diagnose and risk stratify ACS. Myocardial infarction diagnosis is made when there is a rise or fall of cardiac troponins with at least one value above the 99th percentile of higher reference limit. The most important biomarkers of acute myocardial infarction are troponins and CKMB (Creatinine Kinase –Myocardial B). Cardiac troponins inform of infarct size, as they are at their highest within 12 hours, and stay high for up to 10 days. A positive troponin level is associated with an increased mortality and morbidity at 30

days. The rise of troponin can be seen in patients who do not have myocardial ischaemia, including myocarditis, renal failure, Takotsubo syndrome, pulmonary embolism, and heart failure (Aldous, 2013) .

C-reactive protein: part of the process of CAD is driven by inflammation, hence the elevation of this marker. It is a marker of a poor prognosis (Griselli et al., 1999).

1.6 Management of ACS

Universal to the management of all subtypes of ACS is primary and secondary prevention therapy. This includes the use of beta blockers, statins, angiotensin converting enzyme (ACE) inhibitors, and antiplatelet therapy. These drugs are, however, underutilised worldwide. Factors attributed to this include the economic status of the country, gender, age, and educational level (Shimony et al., 2014) .

High income countries show better adherence to guideline mandated therapies. Yet, approximately 12% of patients do not take their prescribed therapy after an ACS event. In upper-middle income countries, as many as 59% of ACS patients do not take their secondary prevention therapy. Factors related to non-adherence include a poor level of education and a lack of good primary healthcare system (Shimony et al., 2014) .

The management of ACS has improved over the years. In developed countries, this has resulted in a decrease in the mortality rates, reinfarction rates, strokes, and readmission within six months of an index event. In the United States, there has been an 18% reduction in mortality, reinfarction, and heart failure rates, however, the GRACE Registry reveals that management differs in hospitals according to geographical location and economic status (Fox et al., 2007) .

Old age, female sex, renal failure, and heart failure are associated with lower use of combination therapy, even in the absence of contraindications (Yan et al., 2009) .

Medical therapy needs to be started promptly in all patients presenting with ACS. Antiplatelet therapy should be initiated as soon as the diagnosis is suspected. This intervention alone has been shown to improve outcomes in patients who receive revascularisation therapy as well as those simply on medical therapy (Gitt & Betriu, 2008).

The choice of optimal medical therapy is a very important predictor of outcome. All patients who have had an MI should be on aspirin, unless contraindicated due to prior allergic reactions. Aspirin, a COX-1 inhibitor, blocks the formation of thromboxane A2, which is responsible for platelet aggregation and thrombus formation. As part of primary and secondary prevention, it has been shown to decrease mortality by 15% and fatal MIs by 30% (Cairns et al., 1985; Antithrombotic Trialists' (ATT) Collaboration, 2009). Clopidogrel, another antiplatelet drug, has demonstrated mortality and morbidity benefits (Yusuf et al., 2001). It works through irreversibly binding to P2Y12 ADP receptors, resulting in platelet inhibition. Clopidogrel should be started as soon as the patient is admitted and continued for one year in patients who present with ACS (Cannon, 2002; Fox Keith A.A. et al., 2004).

Dual antiplatelet therapy has been shown to decrease the relative risk of death, non-fatal MIs, and stroke by 20% compared to aspirin alone (Chen et al., 2005).

Beta blockers are vital in ACS patients. When started early, they decrease or limit infarct size. They also reduce early mortality from ACS. Long term use of beta blockers has also been shown to decrease mortality. Patients with ACS should be placed on a beta blocker unless the patient has a heart rate of less than 50 beats per minute, is in heart failure, or has a low output state, heart block, or bronchospasm (Chen et al., 2005; Kontos et al., 2011). Angiotensin

converting enzyme (ACE) inhibitors are indicated in all patients with ACS who have high blood pressure, diabetes, heart failure, or a left ventricular ejection fraction of less than 40%.

In patients with an ejection fraction of less than 40%, initiation of ACE inhibitors is associated with a 19% decrease in mortality (Swedberg et al., 1992; Pilote et al., 2004; Chen et al., 2005; Cannon et al., 2006). Contraindications to ACE inhibitors include severe renal dysfunction and allergic reactions, in which case the use of Angiotensin Receptor Blockers (ARB) is indicated.

Patients must be on lipid modifying agents or statins. These drugs should be started as soon as possible, and at higher doses, as higher doses are associated with better outcomes (Cannon et al., 2006). According to the South African dyslipidaemia guidelines, the target for LDL is to be less than 1.8 mmol/l in high risk patients (Klug et al., 2018).

Primary percutaneous coronary intervention (PCI) is most effective in patients who present timeously with STEMI (Windecker et al., 2014). Best results are achieved within the first 120 minutes from the onset of pain. However, there are benefits for patients presenting later, especially those patients with haemodynamic instability, ongoing chest pain, arrhythmias, and heart failure (Lim, Wee & Anantharaman, 2013; Windecker et al., 2014).

Where PCI facilities are not available or far away where significant delays are anticipated, patients should receive thrombolytic therapy (Windecker et al., 2014).

Fibrinolytic therapy is recommended within 12 hours of onset of the infarct, but the maximum benefit is achieved if administered in the first hour (Antman Elliott M. et al., 2004). The benefit of fibrinolytic therapy is in achieving TIMI 3 flow (normal epicardial flow), which occurs in 50%-60% compared to 93%-96% with primary PCI. Shortcomings of thrombolytic therapy include a 20%-30% risk of recurrence of ischaemia, 5%-15% rate of re-occlusion, and 3%-5% of reinfarction. Patients who have received thrombolytic therapy should delay PCI at least three

to 24 hours after therapy (Van de Werf et al., 2008). Urgent restoration of TIMI 3 flow in the coronary arteries is vital for myocardial salvage and mortality reduction (Van de Werf et al., 2008).

CHAPTER 2

2.0 HYPOTHESIS, CLINICAL SETTING, AND AIMS OF THE STUDY

2.1 CLINICAL SETTING OF THE STUDY

This study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary institution affiliated to the University of Witwatersrand, between January 2013 and December 2014. This hospital provides healthcare to a large drainage area, including the northern and eastern suburbs of Johannesburg. CMJAH is a referral hospital for patients from several secondary hospitals including Helen Joseph, Edenvale, Leratong, Germiston, Far East Rand, and Natalspruit hospitals. Cardiology is one of the divisions in the Department of Internal Medicine at CMJAH and it admits about 10 patients per week with a diagnosis of ACS.

2.2 ETHICAL APPROVAL

Permission to access all the patient data at CMJAH was obtained from the Chief Executive Officer of the hospital and ethical approval to conduct the study was obtained from the Postgraduate Ethics Committee of Wits and the Committee for Research on Human Subjects, South Africa (**Ethics Approval Number: M140615)**.

2.3 AIMS OF THE STUDY

The main aim of the study was to investigate the effectiveness of adherence to guideline mandated optimal medical therapy for ACS.

The specific objectives of the study were to:

1) Determine the characteristics of patients presenting with ACS.
2) Determine the degree of adherence to guideline mandated therapy.
3) Determine the outcome of in-hospital patients with ACS.

CHAPTER 3

3.1 METHODS

This is a retrospective study, which was conducted on patients diagnosed with ACS admitted to CMJAH from January 2013 to December 2014. The study cohort samples consisted of 1073 patients over 18 years of age. The patient records were retrieved from the Cardiology Database housed within the Division of Cardiology at CMJAH. Laboratory data were obtained from the National Health Laboratory Service (NHLS). Only the initial presentation data were taken into consideration for patients who presented more than once. Patients were identified by their hospital numbers, which were also used to track their blood results. All the above-mentioned reports were used to populate the datasheet in Appendix 1 and entered into a Microsoft Excel spreadsheet.

3.2 STATISTICAL ANALYSIS

All the Microsoft Excel spreadsheet data was imported into STATA® (version 12.5, series 0414) for statistical analysis. Descriptive statistics were computed. The description of categorical variables was illustrated with numbers, percentages, and continuous variables with means and standard deviations (SDs). Medians with interquartile ranges (IQRs) were also used for variables with non-parametric distribution. Associations between categorical values and patient outcomes were assessed with the Pearson's chi square tests. The Student's t-test was used for continuous variables and comparison of independent groups. A p-value < 0.05 was considered statistically significant.

CHAPTER 4

4.0 RESULTS

4.1 SOCIODEMOGRAPHIC CHARACTERISTICS

The analysis included a total of 1073 patients. There were 287 (26.7%) females and 786 (73.3%) males. Of these 1073 patients 46,9% of the patients were White, 22.8% were Indian, 19.8% were Black, and 10.3% were Coloured (**Table 2**).

Table 2: Sociodemographic characteristics

		Frequency	Percent
Ethnicity (n=1073)	White	503	46.9%
	Indian	245	22.8%
	Black	212	19.8%
	Coloured	110	10.3%
	Unknown	3	0.3%
Gender (n=1073)	Female	287	26.7%
	Male	786	73.3%

Of the 1073 patients entered into the study the percentages of STEMI, NSTEMI and UA patients were 52%, 18% and 30%, respectively (Fig 1)

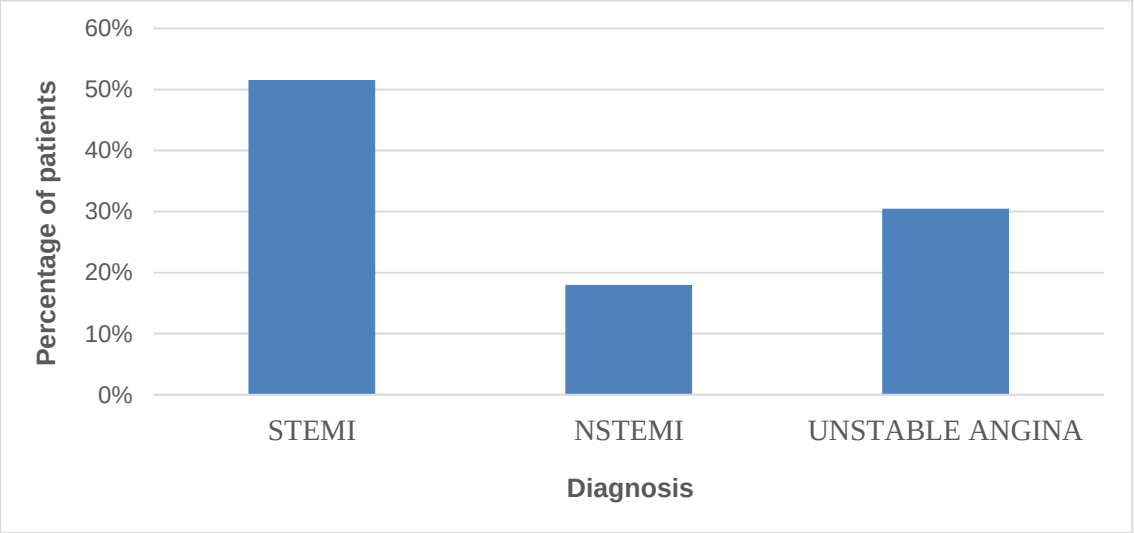

Figure 1: Percentage distribution of the three types of ACS (n = 1073)

The following important laboratory values were analysed in this cohort of patients (Table 3) The mean creatinine value was 115.42 ± 131.23 µmol/l. The average haemoglobin was 13.96 ± 2.21 g/dL, with a mean of 13.96 g/dL. The average HBA1c was 7.23± 1.96% g/dL, with a mean of 7.20% mg/dL. The average high-density lipoprotein (HDL) cholesterol level was 1.09 ± 0.54 mmol/l, with a mean of 1.09 mmol/l, while the mean low-density lipoprotein (LDL) cholesterol level was 2.68 ± 1.173 mmol/l. The total cholesterol level was found to be at a mean level of 4.60 ± 1.607 mmol/l.

Table 3: Laboratory investigations in ACS patients

	N	Reference ranges	Mean	Std. Deviation
Creatinine	1037	47-90umol/L	115.42	131.228
Haemoglobin	1018	12.1-16.3g/dL (females) 14.3-18.3g/dL (males)	13.96	2.209
HBA1c (%)	584	<7%	7.20	1.961
HDL	885	>1.2mmol/L (females) >1.0mmol/L (males)	1.09	0.538
LDL	863	<3.0mmol/L	2.68	1.173
Total Cholesterol	888		4.60	1.607

Hypertension, smoking, and dyslipidaemia were the leading risk factors for ACS, with a frequency of 62%, 52%, and 43%, respectively. Obesity and diabetes mellitus were only found in 28% of patients with ACS (**Figure 2)**.

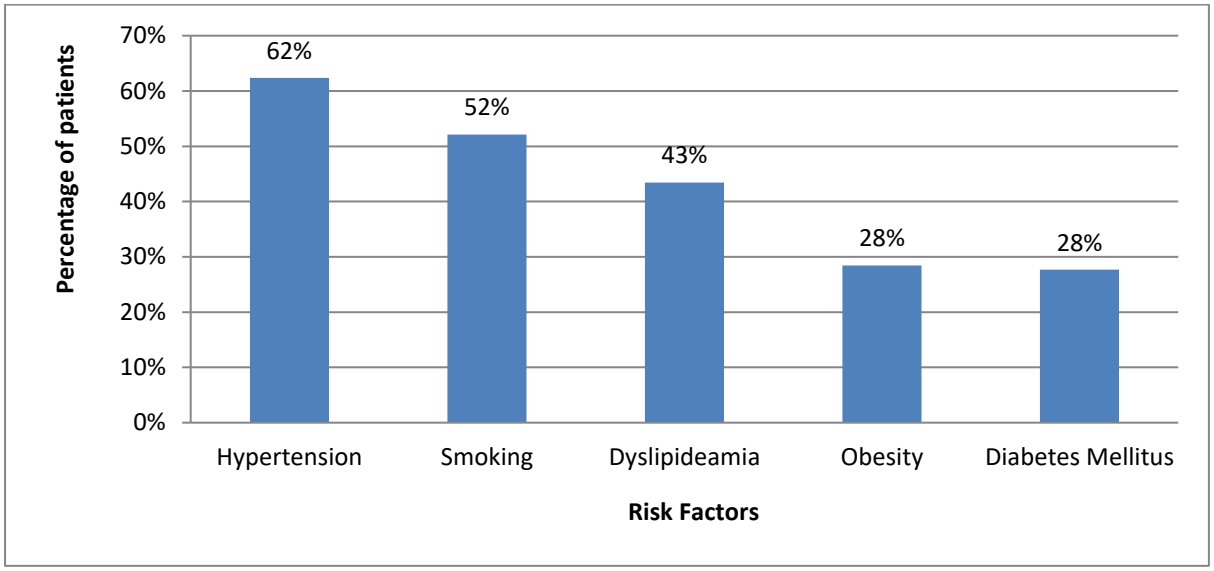

Figure 2: Risk factors associated with ACS.

Table 4 highlights the association of known risk factors (like hypertension, dyslipidaemia or smoking) with development of ACS (from STEMI, NSTEMI and UA) in our study population. Hypertension, dyslipidaemia and being a smoker at time of admission was significantly associated with the risk of developing ACS. However, there was no difference in the risk of ACS susceptibility in the obese vs. non-obese or diabetic vs. non-diabetic groups.

Table 4: Association between risk factors and diagnosis

Risk factors		**Diagnosis**				**P-value**
		STEMI	**NSTEMI**	**UA**	**Total**	
Diabetes Mellitus	Yes	27.3%	26.9%	28.7%	27.7%	.871
	No	72.7%	73.1%	71.3%	72.3%	
Hypertension	Yes	55.0%	64.8%	73.4%	62.3%	.001
	No	45.0%	35.2%	26.6%	37.7%	
Dyslipidaemia	Yes	34.4%	43.0%	59.0%	43.4%	.001
	No	65.6%	57.0%	41.0%	56.6%	
Smoker	Yes	54.6%	57.5%	44.6%	52.1%	.004
	No	45.4%	42.5%	55.4%	47.9%	
Obesity	Yes	28.2%	25.9%	30.3%	28.4%	.559
	No	71.8%	74.1%	69.7%	71.6%	

The most common medical therapy prescribed in the study group was aspirin, which was prescribed to 85% of the patients, followed by statins (84%), beta blockers (79%), clopidogrel (74%), ACE inhibitors (59%), and spironolactone (38%). (Fig 3)

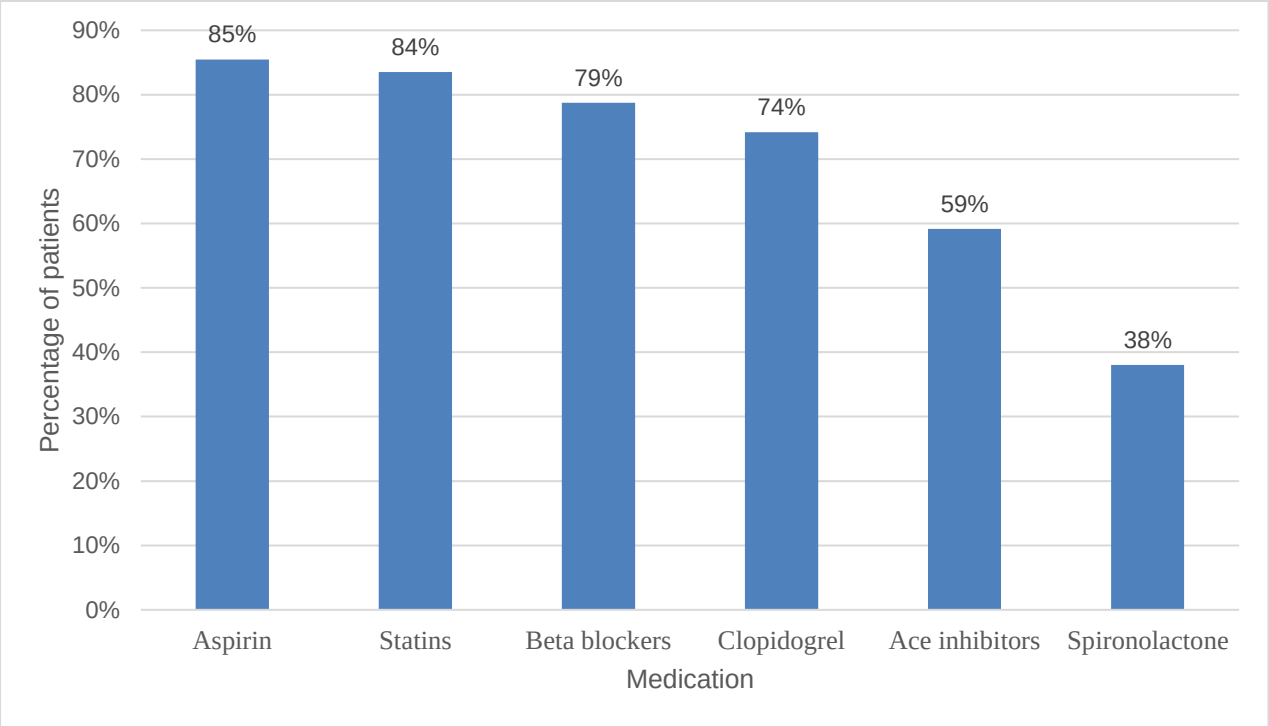

Figure 3: Commonly used therapeutic drugs in the management of ACS.

Table 5 highlights the association of ACS diagnosis and medication prescribed in hospital. In this study cohort, all classes of drugs were significantly associated with receiving guideline recommended medication for ACS.

Table 5: Association between ACS diagnosis and receiving medication

		NSTEMI	STEMI	UA	Total	p value
Aspirin	Yes	85.7%	90.7%	82.0%	85.5%	.024
	No	14.3%	9.3%	18.0%	14.5%	
Clopidogrel	Yes	84.4%	85.0%	50.6%	74.3%	.000
	No	15.6%	15.0%	49.4%	25.7%	
Beta blockers	Yes	79.2%	85.9%	74.0%	78.8%	.005
	No	20.8%	14.1%	26.0%	21.2%	
Statin	Yes	81.7%	89.6%	83.1%	83.6%	.037
	No	18.3%	10.4%	16.9%	16.4%	
Ace inhibitors	Yes	58.6%	68.4%	56.2%	59.6%	.018
	No	41.4%	31.6%	43.8%	40.4%	
Spironolactone	Yes	44.0%	40.4%	29.0%	38.9%	.000
	No	56.0%	59.6%	71.0%	61.1%	

Mortality was directly correlated to drug prescription (Table 6). Thus only 28.3% of patients who died were taking aspirin compared to 88% among the 1027 who survived ($p<0.001$), implying a strong association between taking aspirin and outcome. A similar association with death and the use of clopidogrel, beta blockers, ACE inhibitors and spironolactone was found ($p<0.01$)

Table 6: Association between treatment and the death of ACS patients

Medication		Deceased		Total (n=1073)	P-value
		Yes (n=46)	No (n=1027)		
Aspirin	Yes	28.3%	88.0%	85.5%	<0.001
	No	71.7%	12%	14.5%	
Clopidogrel	Yes	28.3%	76.3%	74.3%	<0.001
	No	71.7%	23.7%	25.7%	
Beta blockers	Yes	13.0%	81.8%	78.8%	<0.001
	No	87.0%	18.2%	21.2%	
Statins	Yes	26.1%	86.2%	83.6%	<0.001
	No	73.9%	13.8%	16.4%	
ACE inhibitors	Yes	6.5%	62.0%	59.6%	<0.001
	No	93.5%	38.0%	38.9%	
Spironolactone	Yes	4.3%	40.4%	38.9%	<0.001
	No	95.7%	59.6%	61.1%	

There was a significant interaction between the prescription of aspirin, clopidogrel, statins, ACE inhibitors, and age. Those who were on aspirin were on average were younger as compared to patients that were not on aspirin therapy (58.7 ± 11.9 years vs 61.2 ± 12.7; p-value = 0.02). Patients on clopidogrel were also younger as compared to those not on clopidogrel (58.3 ± 11.9 vs 61.4 ± 12.6; $p<0.001$). Patients prescribed statins were also younger as compared to those not on statins (58.72 ± 12.083 vs 60.73 ± 12.220; $p<0.04$). This was also true for those prescribed ACE inhibitors ($p<0.027$).

It can be noted that in all cases younger patients were more likely to be prescribed guideline mandated therapy than older patients. However, a similar relationship did not hold for those receiving beta blockers and spironolactone therapy.

Table 7: Descriptive statistics for age at incident for ACS patients, according to drugs

Drug			Age by drug		
		N	Mean	Std. Deviation	P-value
Aspirin	Yes	914	58.70	11.990	.018
	No	154	61.20	12.713	
Clopidogrel	Yes	793	58.26	11.862	.000
	No	274	61.38	12.605	
Beta blockers	Yes	841	58.91	11.971	.413
	No	226	59.65	12.706	
Statins	Yes	891	58.72	12.083	.044
	No	176	60.73	12.220	
Ace inhibitors	Yes	632	58.45	11.573	.027
	No	428	60.13	12.748	
Spironolactone	Yes	407	58.16	12.309	.055
	No	638	59.63	11.969	

There was a significant relationship between the prescription of clopidogrel and creatinine levels. Those who were on clopidogrel had a lower average creatinine level compared to those not receiving clopidogrel (105.9 ± 88.9 vs142.94 ± 208; p <0.006).

There was also a significant relationship between ACE inhibitors and creatinine levels. Patients on ACE inhibitors had an average creatinine value of (105.58 ± 90.257 vs 130.24 ± 175.429) for those not on ACE inhibitors.

There was, however, no significant relationship between creatinine level and prescription of the other drugs.

Table 8: Descriptive statistics for creatinine and drug therapy

			Creatinine Results		
Drug		N	Mean	Std. Deviation	P-value
Aspirin	Yes	890	112.10	129.679	0.057
	No	147	135.54	139.017	
Plavix	Yes	772	105.96	88.940	0.006
	No	264	142.94	208.848	
Beta blockers	Yes	818	114.61	138.234	0.694
	No	218	118.55	101.278	
Statins	Yes	868	112.04	130.120	0.066
	No	168	133.13	136.187	
ACE inhibitors	Yes	617	105.58	90.257	0.009
	No	412	130.24	175.429	
Spironolactone	Yes	399	112.96	110.285	0.623
	No	615	117.15	145.046	

There was a statistically significant ($p<0.05$) relationship between prescription of clopidogrel, beta blockers, spironolactone, and gender, with p-values of 0.004, 0.001, and 0.002, respectively.

There was no significant relationship with gender and the prescription of aspirin, statins, and ACE inhibitors since the p-values were greater than 0.05.

Table 9: Association between gender and drug prescription

Variable	Category	Female (n=287)	Male (n=786)	Total (n=1073)	P-value
Aspirin	Yes	81.9%	86.8%	85.5%	.0502
	No	18.1%	13.2%	14.5%	
Clopidogrel	Yes	67.8%	76.6%	74.3%	.004
	No	32.2%	23.4%	25.7%	
Beta blockers	Yes	72.0%	81.3%	78.8%	.001
	No	28.0%	18.7%	21.2%	
Statins	Yes	80.8%	84.6%	83.6%	.162
	No	19.2%	15.4%	16.4%	
ACE inhibitors	Yes	55.4%	61.2%	59.6%	.105
	No	44.6%	38.8%	40.4%	
Spironolactone	Yes	31.1%	41.7%	38.9%	.002
	No	68.9%	58.3%	61.1%	

CHAPTER 5

5.1 DISCUSSION AND CONCLUSION

Non-communicable diseases, including CAD, are the leading cause of deaths and are estimated to account for 43% of total adult deaths in South Africa (Mayosi et al., 2009; Lee et al., 2012). Atherosclerosis is a prerequisite for CAD and it has been shown that post revascularization this process progresses, hence the importance of optimal medical therapy (Hawn et al., 2013).

Adherence to guideline mandated therapy has been proven to improve mortality and other adverse cardiovascular outcomes, but we still see suboptimal prescription of therapy as low as 43% in some parts of the world (Serruys et al., 2009).

There are many contributors to paucity of guideline mandated prescription for ACS known as barriers to optimal medical therapy. These include health beliefs and low perceived need for therapy (Lauffenburger et al., 2020). The current study aimed to assess the adherence to guideline mandated therapy at CMJAH of patients admitted with ACS.

Similar to global trends, we observed that ACS mostly affects males compared to females with more than two thirds of our cohort being male. This is similar with a study by Yusuf et al that showed that males dominate the incidence of CAD globally (Yusuf et al., 2004b; Khan et al., 2013).

Acute coronary syndrome presentation in the different race groups was similar to what is described in studies such as the INTERHEART study, with white patients having the highest incidence and mixed race having the least. Interestingly, in the current study the percentage of black patients (19.8%) is considerably higher to that what has been previously reported in the African continent. This has been attributed to urbanisation and an increase in risk factor

profile (increase in obesity, diabetes, hypertension) among black patients (Mayosi et al., 2009). However, our findings are contrary to an American study of over 6000 ACS patients which found that African American females had the highest rates of ACS (Allabban, Hollander & Pines, 2017). This may highlight the biases of study reports due to location. For example, hospitals servicing neighbourhoods with more individuals of specific ancestry. However, we will need further data from more studies with longer periods, conducted across South Africa, as well as, meta-analyses to elucidate this.

The commonest risk factors were high blood pressure and smoking at 62% and 52% respectively , this is lower than what we have seen in a Canadian registry and a small Asian study with prevalence of high blood pressure and smoking at 89%, 39% and 74%, 67.8 % respectively (Oxner Adam et al., n.d.; Qanitha et al., 2019).

Patient characteristics that were associated with poor drug prescription include the female sex, older age, and creatinine levels. This is on par with most studies. Female sex as a factor is difficult to understand, but a small study by (Yan et al., 2007). demonstrated that females were less likely to get optimal medical therapy. In the current study this was more significant for prescription of clopidogrel, beta blockers, and spironolactone.

One can argue that older individuals tend to have comorbidities that affect prescription of drugs, renal failure being one of the most common comorbidities. We have seen this in a study done by Safwan et al where some of the factors affecting prescription to the elderly were heart failure, hypotension, bradycardia, and gastrointestinal bleeds (Safwan et al., 2017).

On the contrary, an Israeli study had younger patients less likely to adhere to medication, with interpersonal interactions and knowledge about drug side effects profile literature being the reason for low adherence (Hamood et al., 2015).

Defining what is an acceptable limit for adherence to medical therapy is difficult as patients have different factors that sometimes lead to nonadherence of certain drugs and sometimes the drug is not indicated. What we do know is that adherence tends to be higher in acute and obvious conditions like STEMI compared to UA and NSTEMI with this observation getting a sharp decline after 6 months (Jackevicius, Mamdani & Tu, 2002).

Prescription of medication is also affected by type of revascularization, with patients who get PCI more likely to get treatment compared to patients who undergo bypass surgery. In this instance it is likely that PCI patients are looked after by cardiologists who are more likely to be more knowledgeable about medical therapy compared to surgeons (Hlatky et al., 2013).

In our cohort we did not define the type of revascularization the patient underwent, however the fact that they were discharged from the department of cardiology means the cardiologists were the primary care givers.

The highest prescription was for aspirin and the lowest was for spironolactone. This can be explained by the fact that spironolactone is only recommended for patients with low left ventricular systolic function and patients with normal renal function.

The level of prescription and adherence to therapy was higher than most studies at 85% for aspirin and 38% for spironolactone. In the REACH registry aspirin use was at 76%, statins at 76% and beta blockers at 63% which is lower than what we recorded (Mehta et al., 2001). This could be as a result of the academic nature of our institution, which would imply that most

things are done according to the latest guidelines and most patients are seen by experts in the field and not by general physicians.

Creatinine levels above the normal range have been associated with limited drug prescription, especially for ACE-inhibitors, mainly because in renal failure these drugs are contraindicated. However, in our cohort we described a very unusual pattern, where patients who had low creatinine levels were less likely to get guideline indicated medication. It is possible that these are patients had low blood pressure and thus not prescribed guideline suggested therapy and secondly it could be related to drug sensitivity. Further research is needed.

Clopidogrel was less likely to be prescribed to patients with high creatinine levels. The reason behind this ispossibly that the physicians were concerned about the high bleeding risk in renal failure patients.

We are seeing more academic bodies emphasise the use of medical therapy after a myocardial event and we are seeing an improvement in drug prescription and adherence. This is evidenced by the STABILITY trial and EUROASPIRE, where drug prescription was above 90% for aspirin, statins and beta blockers. (Kotseva et al., 2009; White et al., 2010). This is a marked improvement from earlier studies like SYNTAX where adherence was documented at only 41.3%. (Serruys et al., 2009). The current study data is from around the same period when SYNTAX was reported, so the adherence in the current study to guideline recommended therapies being above 80% for most drugs is excellent, but there is always room for improvement.

The SYNTAX trial had a low adherence to guideline recommended therapies for patients with comorbidities like renal failure, heart failure and COPD compared to patients with just one risk factor and no other organ involvement (Serruys et al., 2009). These findings are similar to findings in the current study

Part of the reason for non-adherence is polypharmacy, which has been shown to have a negative impact on adherence for many reasons, like drug interactions and patients getting discouraged by taking many pills (Gnjidic et al., 2015). However, we do know that mortality benefit was improved with combination therapy as compared to individual drugs as shown in the PREVENT IV trial, with the exception of antiplatelet drugs (Goyal et al., 2007).

In terms of the type of ACS, STEMI patients received more drugs compared to NSTEMI and UA. This is similar to another report which showed that STEMI patients received more comprehensive treatment compared to other types of ACS (Tra et al., 2015). The postulated reasons for this are that most people tend to underestimate the critical nature or the seriousness of NSTEMI and UA and that STEMI patients tend to be sicker compared to other patients.

The mortality rate in our study was lower than the reported rates in previous studies. We observed that 96% of patients who survived received guideline recommended optimal medical therapy versus those patients who died mostly did not receive optimal medical therapy. However, mortality rates are related to additional comorbidities, severe illness and complexity. Thus, the low mortality rate in the current study could be the absence of additional co-morbidities and complexity during the sampling period of the study.

In summary, this study has shown that at the time of study, there was a high level of administration and adherence to optimal medical therapy guidelines at CMJAH for ACS cases. We also observed this to co-segregate with a low mortality rate. In comparison to previously reported studies on ACS, this study has shown that patients at CMJAH receive appropriate medical therapy on discharge. For CMJAH, we hope that the high adherence rate to guideline recommended therapies and low mortality rate will be maintained over time and strongly recommend ongoing future audits.

5.2 STUDY LIMITATIONS

This study had a few limitations. This study is only a single center audit; thus, its generalizability is limited. Some variables excluded were linked to putative ACS diagnostic assessment criteria such as ECG results, as well as measurement of adherence using pill count. However, the recorded cardiac enzyme elevation, clinical presentation and recorded ECG changes make it highly likely that the diagnostic criteria for ACS diagnosis were robust. Being a retrospective analysis some putative variables that were excluded were a result of using stringent quality control thresholds on our retrospective study data, which excluded variables with >5% missingness or incorrect values. The other limitations reflect the common weaknesses of the public health facilities and their supporting structures. I also did not have information on contraindications and reasons for not prescribing certain drugs. This study also performed data analyses on a secondary database used to capture existing clinical and NHLS laboratory data collected for CMJAH. As a result, some medical tests during hospital visits were not routinely tested/recorded, such as HIV status, HBA1C. Also, the patient database was not designed to assist with patient follow-ups nor assist in reporting beyond short-term patient outcomes in the hospital.

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Appendix 1: Data collection Sheet

DATA COLLECTION SHEET

Management and Outcome of Acute Coronary Syndromes at
Charlotte Maxeke Johannesburg
Academic Hospital

Degree:

MMed (Internal Medicine)

Student Name:

Dr. V Mtwesi

Supervisors:

Prof. P. Manga MB BCh FCP (SA) PhD FRCP

Dr. A. Vachiat MB BCh FCP (SA) MMed (Internal Medicine)

DEMOGRAPHIC DATA

Date of Admission:				**Discharge Date:**			
	Day	*Mon*	*Year*		*Day*	*Mon*	*Year*
Age of Participante:		**Date of Birth:**					
	Number				*Day*	*Mon*	*Year*

Gender:

Male	**1**
Female	***2***
Missing	**3**

Race:

African	**1**
White	**2**
Coloured	**3**
Indian	**4**
Missing	**5**

TYPE OF ACUTE CORONARY SYNDROME (ACS)

Type of ACS:

N-STEMI	**1**	*1 = non-ST segment elevation myocardial infarction*
UA	**2**	*2 = Unstable angina*
STEMI	**3**	*3 = ST segment elevation myocardial infarction*

Treatment

PCI	**1**
Thrombolytic	**2**

Discharge Medication:

ACE Inhibitor/ARB	**1**
Beta-blockers	**2**
Aspirin	**3**
Statins	**4**
Clopido	**5**

Blood Investigation	**Result**
Trop-T	
CKMB	
Urea	
Creat	
CRP	

Lipogram	**Result**
Trig	
LDL	
HDL	
Tchol	

Angiogram Findings:

RCA	LAD	CX	LVA	LM	STENT	
					YES	*NO*

HEALTH QUESTIONNAIRE

Condition	*Yes = 1*	*No = 2*	*Unknown = 3*
Smoking			
Diabetes			
Hypertension			
Dyslipidimia			
Family History			
Previous ACS			
HIV Status			

Appendix 2: Ethics approval letter

R14/49 Dr Vivwe Mbwesi et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140615

NAME: (Principal Investigator)	Dr Vivwe Mbwesi et al
DEPARTMENT:	Cardiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Adherence to Guideline Mandated Optimal Therapy in ACS Patients at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	27/06/2014
DECISION:	Approved unconditionally
CONDITIONS:	(Title Change 27/02/2017)
SUPERVISOR:	Dr A Vachiat and Prof P Manga
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/10/2014

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.The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was intially review in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES