CONTEMPORARY RISK FACTORS ASSOCIATED WITH ISCHEMIC HEART DISEASE IN CENTRAL SOUTH AFRICA: A SINGLE CENTER STUDY

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Dissertation

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Declaration of Independent Work

I, Michelle Louise Butler, do hereby declare that this research project submitted to the Central University of Technology for the degree MASTER OF HEALTH SCIENCES IN CLINICAL TECHNOLOGY is my own independent work that has not been submitted to any institution by me or any other person in fulfillment of the requirements for the attainment of any qualifications.

Signature

June 2022
Date

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Abbreviations and Symbols

ACS	Acute Coronary Syndrome
AHA	American Heart Association
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CMO	Cardiomyopathy
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
HDL	High Density Lipoprotein
HDL-C	High Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HPT	Hypertension
IHD	Ischemic Heart Disease
LDL	Low Density Lipoproteins
LDL-Ox	Oxidized Low Density Lipoproteins
MI	Myocardial Infarction
NC	Necrotic Core
NO	Nitric Oxide
NSTEMI	Non-ST Elevation Myocardial Infarction
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
SA	South Africa

STEMI	ST Elevation Myocardial Infarction
TC	Total Cholesterol
TG	Triglycerides
THUSA	Transition and Health during Urbanization in South Africans
UA	Unstable Angina
UAH	Universitas Academic Hospital
USA	United States of America
VDDL	Very Low Density Lipoproteins
WHO	World Health Organization
<	Less Than
≤	Less Than or Equal to
>	Greater Than
≥	Greater Than or Equal to

Definitions

Term	Definition
Acute coronary syndrome	Acute coronary syndrome is defined as myocardial infarction, unstable angina or sudden ischemic death (Fuster & Kovacic, 2014).
Aneurysm	A localized dilation of an artery, vein, or segment of the heart. This leads to the weakening of the wall, which may result in a rupture (Shiel et al., 2008).
Angina pectoris	Chest pain resulting from reversible myocardial ischemia (Yayan, 2014).
Angiogram	X-ray imaging of blood vessels with the use of a contrast dye (Shiel et al., 2008).
Arteriosclerosis	A process of the build-up of cholesterol that leads to the formation of plaque in the arteries, which present as hard, thick deposits that can lead to narrowing of the arteries (Kwiterovich, 2004).
Atheroma	A fatty deposit in the intima of an artery, which is a result of atherosclerosis (Shiel et al., 2008).
Atherosclerosis	A form of arteriosclerosis. It is the presence of fatty lipid deposits in the intima of an artery (Shiel et al., 2008).
Cardiovascular disease	Includes all diseases of the circulatory system (Benjamin et al., 2019).
Complication	An unanticipated problem arising as a result of a procedure, illness or treatment (Shiel et al., 2008).
Coronary artery bypass graft (CABG)	A surgical procedure in which a narrowed or blocked artery is given a new route for blood flow to increase oxygen and nutrient delivery to the heart muscle (Shiel et al., 2008).

Coronary artery disease	A disease of the arteries that supply the heart muscle with blood and is a chronic and mostly progressive disease (Roversi et al., 2014).
Chronic obstructive pulmonary disease (COPD)	COPD is a preventable and treatable respiratory disease characterized by persistent airflow limitation and chronic respiratory symptoms resulting from abnormal inflammatory responses to irritants (Shiel et al., 2008).
Diabetes mellitus	Diabetes mellitus is a chronic condition associated with abnormally high levels of glucose in the urine and blood. It is caused by either insufficient production of insulin, autoimmune resistance to, or complete absence of insulin secreted from the pancreas (Shiel et al., 2008).
Dyspnea	Shortness of breath; difficult or laboured breathing (Shiel et al., 2008).
Embolism	The obstruction of a blood vessel by a blood clot or foreign substance that travels in the bloodstream (Shiel et al., 2008).
Endothelial	Related to endothelium, which is the single layer of cells that line the inner surfaces of blood vessels and the heart (Shiel et al., 2008).
Haemorrhage	Abnormal bleeding (Shiel et al., 2008).
Hypercholesterolemia	High blood cholesterol levels (Shiel et al., 2008).
Hypertension	Blood pressure repeatedly exceeding 140/90mmHg (Shiel et al., 2008).
Inflammation	A localized reaction as a result of injury, irritation or infection leading to swelling, redness and pain (Shiel et al., 2008).
Metabolic syndrome	A cluster of cardiometabolic alterations including the presence of arterial hypertension, abdominal obesity, dyslipidemia and insulin resistance (Fuentes et al., 2013).

Myocardial infarction	A sudden blockage of a coronary artery which may lead to death of the heart muscle due to loss of blood supply (Shiel et al., 2008).
Non-ST elevation myocardial infarction	Biochemical evidence of myocyte necrosis without new ST elevation or left bundle branch block appearance on the electrocardiogram (Shavadia et al., 2012).
Obesity	A body mass index (BMI) of ≥30 kg/m² (Lavie et al., 2007).
Risk factors	Something that increases the chances of a person developing a disease (Shiel et al., 2008).
ST elevation myocardial infarction	Elevation of the ST segment at the J point of ≥1mm at any location or the development of a new left bundle branch block found on the electrocardiogram with biochemical evidence of myocyte necrosis (Shavadia et al., 2012).
Stroke	The sudden death of brain cells leading to the death of brain tissue which is caused by a rupture or blockage of an artery in the brain (Shiel et al., 2008).
Unstable angina	Chest pain which may be present in one of three ways: a) occurring at rest and for more than 20 minutes at a time; b) new onset of angina of moderate to severe intensity; or c) crescendo angina, which is previous angina which progressively increases in both severity and intensity (Knuuti et al., 2020).

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Executive Summary

Introduction:

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Urbanization of low- to middle-income countries, such as South Africa, and the transition to a more Westernized lifestyle and diet may increase the prevalence of cardiovascular disease (CVD).

Established risk factors associated with CVD include non-modifiable (age, sex, ethnicity and family history of CAD) and modifiable risk factors [hypertension, diabetes mellitus, obesity, elevated low-density lipoprotein (LDL) levels]. Modifiable risk factors, especially hypertension, are considered global epidemics and a particular concern in Sub-Saharan Africa. As early as 1995, Mollentze et al. reported a high incidence of hypertension among the Black population in South Africa, studying CVD risk factors. Yet, there is a lack of information regarding the risk profile for CAD of individuals residing in the central South African region.

Due to the alarming increase in CVD in Sub-Saharan Africa, emphasis must be placed on prevention, early diagnosis and proper management of the disease. However, there is a paucity of data describing the prevalence of non-modifiable and modifiable risk factors for central SA. This study aimed to describe the modern-day modifiable and non-modifiable risk factors for CAD in a central South African public sector population.

Methods:

A retrospective descriptive single-centre study was conducted, describing patients with angiographically confirmed CAD evaluated in the catheterization laboratory for the first time. The study was performed at Universitas Academic Hospital in Bloemfontein, Free State, South Africa, from January 2016 to December 2017. Demographic, anthropometric and clinical data were collected from the patient's medical records.

Results:

Four hundred and eighty-two patients out of 1859 met the inclusion criteria and were included in this study. More than half of these patients resided in the Free State (59%). The majority of patients were male (66%) and primarily Caucasian (46%), followed by Mixed Race (24%), Black African (23%) and Asian (6%) patients. Females were significantly older than males (60.3±9.6 vs 57.4±11.1 years; $p<0.05$). Asians were substantially younger than Caucasians (49.8±10.5 vs 59.1±10.8 years; $p<0.05$). A positive family history of CAD was more common in Caucasians than in Black Africans and Mixed Race ethnicities ($p<0.05$).

Most patients (63%) had three or more risk factors for CAD. Hypertension was the most common risk factor and was present in ≥87% of all patients. Hypertension was significantly more prevalent in Black Africans than Caucasians (96% vs 87%; $p<0.05$). Smoking was the second most common risk factor (67%), with significantly more males being smokers than females (73% vs 55%; $p<0.05$) and more common in Caucasians than Black Africans (68% vs 55%; $p<0.05$). Obesity was the third most common risk factor (41%), with Asians being significantly less obese than Caucasians (23% vs 45%; $p<0.05$). Diabetes mellitus was present in a third of all patients but considerably less common in Caucasians (25%) than Black Africans (37%; $p<0.05$), Asians (50%; $p<0.05$) and Mixed Race ethnicities (45%; $p<0.05$).

Clinically, 72% of patients presented with acute coronary syndrome (ACS). In general, patients presenting with ST-elevation myocardial infarction (STEMI) were younger than those presenting with non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) (56.6±10.4 vs 59.2±11.3 and 59.1±9 years). Asians presenting with STEMI and UA were significantly younger when compared to Caucasians (STEMI: 48.3±9.2 vs 57.1±10.2; $p<0.05$ and UA: 45.8±5.9 vs 60.0±8.1; $p<0.05$). The majority of patients in the study had 3 or more vessel disease [STEMI (53%); NSTEMI (49%) and UA (43%)]. Nearly half of the patients received the percutaneous coronary intervention (PCI) for CAD, while 22% were referred for coronary artery bypass graft (CABG) surgery.

Conclusion:

This study shows that CAD in South Africa occurs in all ethnic groups and similar risk factors are present to those of the classical risk factors observed in the rest of the world. Most patients presented with more than one risk factor, but the prevalence of hypertension is particularly concerning. The high prevalence of hypertension highlights the need for preventative strategies and creating awareness in the South African population. Most patients with proven atherosclerotic disease presented with ACS, particularly STEMI. The average age of these patients was younger than those documented in the rest of the world. ACS should be considered in any patient presenting with chest pain in central South Africa.

Chapter 1 - Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide and accounts for more than one-third of total deaths in both men and women (Pathak et al., 2017). CAD is a disease involving the heart's blood vessels and led to more than 116 per 100 000 deaths in the United States in 2009 (Roversi et al., 2014). An increase in age correlates with an increase in CAD prevalence, with the age group of 40-59 years having a 35-40% prevalence of CAD and increasing to almost 70% in the age group of 60-79 years (Roversi et al., 2014). Approximately 4 million deaths per year in Europe are due to cardiovascular disease (CVD) in both men and women (Duda-Pyszny et al., 2018).

The most well-known risk factors for CAD are non-modifiable risk factors and modifiable risk factors. The non-modifiable risk factors include age – men over the age of 40 and women over the age of 45 years (Thomson et al., 2009), gender, and family history of CAD. Modifiable risk factors are divided into major and minor risk factors. The major risk factors are hypercholesterolemia, diabetes mellitus, and hypertension (Canto et al., 2011), and minor risk factors are obesity, sedentary lifestyle, psychological stress, smoking and chronic obstructive pulmonary disease (COPD) (Kulkarni, 2015; Eriksson et al., 2013).

During the development of CAD, the arterial walls thicken and become stiff, contributing to the development of hypertension. Atherosclerosis is the hardening of an artery primarily due to an atheromatous plaque (Petlad et al., 2009). In atherosclerosis, small patches of wall thickening occur, referred to as atheromas. These atheromas can then encroach on the vessel's lumen leading to the narrowing of the vessel. Arterial spasms or emboli can now completely occlude a vessel due to the narrowed lumen (Marieb & Hoehn, 2013). The first step in the development of atherosclerosis is lipid retention in the artery walls, followed by a process of chronic inflammation. This chronic inflammation leads to the formation of a fatty streak which then further progresses to fibroatheromas (Aziz & Yadav, 2016).

In the past, coronary artery disease had a remarkably low prevalence in Black South Africans. However, a study conducted by Pieters et al. (2011) showed an increase in the prevalence of CAD, especially in the urban areas of South Africa. Urbanization also brings an increase in socioeconomic status, leading to increased risk factors such as decreased physical activity and obesity. The literature on CVD in developed countries is well documented (Laslett et al., 2012; Bansilal et al., 2015) but limited in low to middle-income countries. Therefore, knowledge about the effects of CVD in countries like South Africa is limited, especially in the rural population (Keates et al., 2017; Shavadia et al., 2012; Yuyun et al., 2020).

CVD, which includes stroke, hypertensive heart disease and coronary artery disease, is responsible for more than one-third of deaths in South Africans in patients over 65 years (Sliwa et al., 2008). Different African countries suggest that CVD and its associated risk factors are changing, particularly in areas undergoing rapid urbanization (Pieters et al., 2011). Due to the increase in the prevalence of CAD in South African individuals, a better understanding of the risk factor profile that contributes to the development of atherosclerosis and CAD needs to be better understood and recognized in an attempt to decrease the morbidity and mortality due to coronary heart disease (CHD). Therefore, this study aims to investigate and determine the modern-day risk factors for CAD patients in central South Africa by auditing patient medical files from 2016 and 2017.

1.1. Research Question

What are the contemporary cardiac risk factors, modifiable and non-modifiable, seen in patients presenting to the catheterization laboratory for the first time in 2016 and 2017 at Universitas Academic hospital?

1.2. Aim

This study aimed to investigate the modern-day risk factors for angiographically proven coronary artery disease in 2016 and 2017 in patients presenting to the catheterization laboratory for the first time in a tertiary health care hospital in central South Africa.

1.3. Objectives

- To describe the non-modifiable and modifiable risk factors for CAD over two years (2016 and 2017).
- To determine the clinical presentation of patients with ACS.

1.4. Research Hypothesis

The hypothesis of this research study is that there are different modifiable risk factors amoungst the different ethnicities in central South Africa.

Chapter 2 - Literature Review

2.1. Background

In the 2004 update, the World Health Organization (WHO) estimated that global deaths attributed to cardiovascular disease (CVD) will increase from 17.1 million to 23.4 million by the year 2030 (World Health Organization: Global Burden of Disease, 2008). In 2008, CVD was responsible for almost half of the deaths worldwide, with the majority occurring in low to middle-income countries and more than 50% in individuals over 70 years of age (Keates et al., 2017). The prevention of developing CVD can be accomplished with a healthy lifestyle, avoiding smoking, eating a balanced diet, increasing physical activity levels, and maintaining a healthy body weight (Knuuti et al., 2020). Coronary heart disease (CHD) accounts for up to one-third of total CVD cases, with a lifetime risk of 48.6% for men and 31.4% for women at the age of 40 years, and 34.9% and 24.2% for men and women respectively at the age of 70 years (Yahagi et al., 2015).

The WHO defines CAD as a disease of the blood vessels responsible for supplying the heart muscle with blood (Roversi et al., 2014). It is a chronic and mostly progressive disease, thus making it a serious disease even though there are clinically silent periods where none of the classic symptoms of CAD is present (Knuuti et al., 2020). The pathological process responsible for CAD is that of atherosclerotic plaque accumulation within these arteries, which can be obstructive or non-obstructive. If these arteries are diseased, an individual may suffer from a myocardial infarction (MI), which can be fatal depending on the severity and location of the disease. Atherosclerosis is essentially initiated by endothelial dysfunction that occurs due to factors such as genetics, environmental and lifestyle-related factors (Arbab-Zadeh et al., 2012).

Managing the controllable or modifiable risk factors for CAD can significantly decrease the chances of developing CAD or suffering from an acute myocardial infarction (AMI) later in life. These modifiable risk factors include smoking, hypertension, diabetes, obesity, dyslipidemia, decreased physical activity, psychological stress and poor dietary choices (Onen, 2013; Aziz & Yadav, 2016). Diets that are very high in carbohydrates along with increased alcohol consumption

lead to increased levels of triglycerides in the blood, which is known to be a risk factor for the development of atherosclerosis. Diets high in fats also lead to increased levels of cholesterol in the blood (Jiang et al., 2016). Thus, improving one's lifestyle by decreasing calorie intake and increasing physical activity with adequate pharmacological therapy will significantly improve CVD prevention and management (Almahmeed et al., 2012).

An important strategy for decreasing CVD mortality would be smoking cessation and control of blood pressure (Gupta et al., 2017). Smoking is one of the most common risk factors for CVD. It predisposes individuals to several atherosclerotic syndromes such as MI and other acute coronary syndromes (ACS), stable angina, and sudden death. The risk of smokers dying from CAD is 70% greater than non-smokers (Tonstad & Johnston, 2006). Smoking habits present an additional risk for CAD due to increased oxidative stress caused by the compounds of cigarette smoke. This risk is quadrupled in young premenopausal women suffering from MI due to the anti-estrogenic effects of smoking tobacco products (Pathak et al., 2017).

Risk factors related to urbanization, which is on the rise in Southern Africa, as recognized by the Transition and Health during Urbanization in South Africans (THUSA) study, include obesity, hypertension and smoking (Pieters et al., 2011). A build-up of cholesterol leads to the formation of plaque in the arteries, which present as hard, thick deposits that can lead to narrowed arteries, a process known as atherosclerosis (Kwiterovich, 2004). Currently, no data exist for central South Africa regarding the modern-day risk factors for ischemic heart disease (IHD) and the changes seen due to urbanization. Central South Africa includes areas such as the Free State, Northern Cape and Lesotho, which are all areas undergoing rapid urbanization.

Environmental factors such as air pollution and exposure to toxic chemicals may contribute to the development of respiratory ailments such as asthma or chronic bronchitis, which may lead to chronic obstructive pulmonary disease (COPD). COPD is associated with lower levels of physical activity, increased age and the use of tobacco products (Onishi, 2017). The risk factors for the development of atherosclerosis are primarily driven by urbanization and the consequences of lifestyle changes such as diet and physical activity, contributing to an increase in these risk factors (Ntsekhe & Damasceno, 2013).

2.1.1. Global Prevalence of CAD

Arbab-Zadeh et al. (2012) reported that during post-mortem investigations, adults in the United States (mean age 36 ±14 years) died from non-natural causes. More than 80% of patients showed signs of atherosclerosis at a relatively young age, with approximately 8% presenting with obstructive coronary artery disease (Arbab-Zadeh et al., 2012).

Epidemiological studies in developing countries like India, a third-world country, have shown an increase in trends and a high burden of common risk factors for CAD such as hypertension, diabetes and metabolic syndrome. CAD in adults increased from 3% to 10% from 1960 to 1995 in urban Indians, and around 2% to 4% in rural Indians, with men and women displaying comparable rates (Pathak et al., 2017). The National Health and Nutrition Examination Survey from 2007 to 2010 in the United States summarized the prevalence and mortality of CVD, IHD and MI (Table 2.1.) (Roversi et al., 2014).

Table 2.1. The prevalence and mortality of cardiovascular disease, ischemic heart disease and myocardial infarction according to the National Health and Nutritional Examination Survey in the United States from 2007 to 2010 (adapted from Roversi et al., 2014).

Prevalence	Men	Women	Total
CVD prevalence % (age >20 years)	36.7	34	35.3
CVD deaths per 100 000 per year	281.4	190.4	236.1
IHD prevalence % (age >20 years)	7.9	5.1	6.4
IHD deaths per 100 000 per year	155.9	84.9	116.1
MI prevalence % (age >20 years)	4.2	1.7	2.9

2.1.2. African Prevalence

There is a heavy burden of CVD in African and Middle Eastern countries, with the prevalence of risk factors leading to CVD being high and on the increase, such as smoking, hypertension, dyslipidemia and sedentary lifestyle, all leading to patients in these areas presenting with MI at a younger average age compared to other regions (Almahmeed et al., 2012). Sub-Saharan Africa is home to the largest portion of the poorest individuals worldwide. In 2013, it was estimated that 1 million deaths in Sub-Saharan Africa were due to CVD, constituting 5.5% of global CCVD-

related deaths and 11.3% of deaths in Africa (Keates et al., 2017). Northern Africa's prevalence of CAD in Tunisia between 1997 and 2009 revealed that CAD-related mortality increased from 70 to 80 deaths per 100 000 in men ≥55 years and 28 to 41 deaths per 100 000 in women ≥65 years. However, the younger age groups in this region revealed a decline in CAD-related mortality. Sudan was estimated to have 205 per 100 000 deaths due to age-adjusted CAD-related mortality in 2002 (Keates et al., 2017).

2.1.3. South African Prevalence

There is a lack of current literature and statistics regarding the prevalence of CAD and the causative risk factors in South Africa. More studies are focused on CVD as a whole, and acute MI, most of which are not current research and only provide limited data on the subject (Bourne et al., 1991; Mollentze et al., 1995; Alberts et al., 2005; Masina et al., 2017; Kabongo et al., 2018; Sookan et al., 2018; Hamid et al., 2019).

Sliwa et al. (2008) reported on 4162 patients (The Heart of Soweto Study) with confirmed cardiovascular disease from 1 January 2006 to 31 December 2006. Of these patients, 1593 (38%) were newly diagnosed with CVD, and 2569 (62%) were previously diagnosed with CVD. The average age of the newly diagnosed CVD patients was 52.8 years, with the age profile for men being slightly higher than for women (men 55 years of age, while women averaged 53 years of age). On the other hand, the average age of newly diagnosed CAD was found to be 56.7 years. Of the total 1593 patients, 77 (47%) diagnosed with CAD were of African ethnicity, and 68 (41%) were women, as summarized in Table 2.2.

Table 2.2. Socio-demographic data for patients with newly diagnosed cardiovascular disease and coronary artery disease (adapted from Sliwa et al., 2008).

Socio-demographic profile	**All (n=1593)**	**CAD (n=165)**
Age (years)	52.8	56.7
African ethnicity	1359 (85%)	77 (47%)
Women	939 (59%)	68 (41%)

Coronary artery disease in Black South Africans has been historically rare, yet studies are now revealing an increase in the prevalence, mainly due to factors such as urbanization (Pieters et al., 2011). Hypertension is a major contributing risk factor to CAD in South Africa, as demonstrated by a study performed by Peltzer & Phaswana-Mafuya (2013). The data indicated that 77.3% of subjects older than 50 suffered from hypertension in Sub-Saharan Africa. Studies regarding prevalence relating to recent CAD statistics in South Africa are limited, although a change in the trend in prevalence rates is to be expected. Updated statistics about CAD prevalence and the causative risk factors in South Africa are needed to assist in planning and implementing health care practices. Furthermore, establishing whether the risk profile of patients presenting with CAD is contributing to a change in CAD prevalence rates also warrants further investigation.

2.2. Coronary Artery Disease

By 2030, the WHO predicts that coronary heart disease will be responsible for up to 14.9% of deaths for men and 13.1% for women worldwide (Kulkarni, 2015). Coronary heart disease, or ischemic heart disease, is a disease of the blood vessels that supply the heart's muscle with blood and is of significant concern (Roversi et al., 2014). CAD is a pathological process characterized by the accumulation of atherosclerotic plaque in the epicardial arteries and can either be obstructive or non-obstructive. This functional alteration of coronary circulation is a process that can be modified by changes in lifestyle, optimal pharmacological therapy, or invasive interventions. Invasive interventions include percutaneous coronary interventions (PCI), also referred to as cardiac stenting or ballooning, or coronary artery bypass graft (CABG) surgery (Knuuti et al., 2020).

Coronary artery disease is defined as the development of atherosclerosis within the coronary arteries, leading to coronary insufficiency (Yayan, 2014). Complete blockage of these arteries can then occur due to deposits of fat, blood clots and calcium within the walls of the blood vessels (Lind, 2003). Coronary artery disease may consist of long and stable periods but may become unstable at any time. This may be due to plaque rupture or erosion, resulting in an acute atherothrombotic event (Knuuti et al., 2020).

Angina pectoris, the main symptom of coronary insufficiency, is a pain caused by reversible ischemia (Valgimigli & Biscaglia, 2014) localized to the retrosternal area and triggered by both mental and physical stress. The pain usually subsides within 15 minutes or 2 minutes after nitro-glycerine administration (Yayan, 2014).

ACS is the collective term used for unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), which are classified as an immediately life-threatening stage of coronary heart disease (Yayan, 2014). STEMI is defined as an elevation of ≥1mm at the J point in any location or the development of a new left bundle branch block on the electrocardiogram (ECG) and biochemical evidence of necrosis of the myocytes (Shavadia et al., 2012). Shavadia et al. (2012) define the diagnosis of NSTEMI as the absence of a new left bundle branch block or ST-elevation, yet biochemical markers indicate myocardial necrosis. Unstable angina is considered in patients with symptoms of ischemia, although no ECG changes or biochemical indications suggest the presence of ischemia (Shavadia et al., 2012).

2.2.1. Atherosclerosis

Atherosclerosis leads to thickening and stiffening of the arterial walls, resulting in the development of hypertension, which places more significant stress on a pre-existing plaque, making it more vulnerable to rupture (Marieb & Hoehn, 2013). The lumens of the vessels are narrowed and constricted, which causes the walls of the artery to fray and ulcerate, encouraging the backup of blood, platelet adhesion and formation of a thrombus in the arterial wall. Thrombus development is due to damage to the endothelial cells causing diminished nitric oxide and prostaglandin release, chemicals that are supposed to vasodilate and inhibit aggregation of platelets. The formation of these plaques increases the risk of MI, stroke and aneurysm formation within the arterial walls (Marieb & Hoehn, 2013).

CAD is characterized by the accumulation of atherosclerotic plaque in the epicardial arteries and is considered a chronic inflammatory disease (Aziz & Yadav, 2016), which is progressive in nature and is the underlying condition responsible for coronary events. Coronary events may also occur due to arteritis, coronary dissection, myocardial bridging, coronary vasospasm, and thromboembolisms without obvious CAD, yet these are rare (Arbab-Zadeh et al., 2012).

Four stages occur in the development of atherosclerosis, namely; (i) endothelial injury; (ii) accumulation of lipids in the tunica intima that oxidize; (iii) proliferation of smooth muscle cells that results in the formation of a fibrous cap; and finally (iv) the plaque becoming unstable as it continues to enlarge (Marieb & Hoehn, 2013). The progression of atherosclerosis is illustrated in Figure 2.1. (Groenendyk & Mehta, 2018).

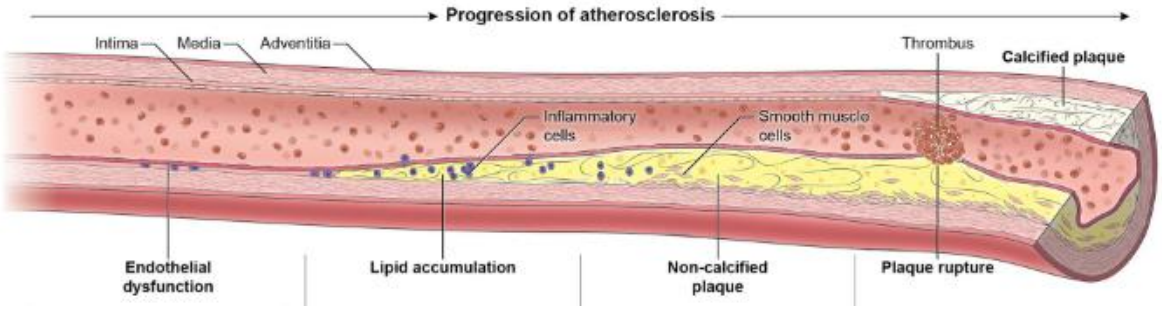

Figure 2.1. The progression of atherosclerosis from endothelial dysfunction to plaque rupture (adapted from Groenendyk & Mehta, 2018).

(i) *Endothelial injury*

Atherogenesis is the process of plaque build-up within the arterial wall. It begins with endothelial dysfunction inside the lumen of the artery, leading to the release of pro-adhesion molecules which recruit immune (monocytes) cells in response to certain stimuli, such as hypertensive pressure and lipid build-up (Groenendyk & Mehta, 2018). This endothelial dysfunction leads to the inhibition of nitric oxide (NO) production, a vasodilator, and leads to the stimulation of the production of adhesive molecules. The adhesive molecules stimulate the attraction of inflammatory cells, which ultimately results in the binding of monocytes and T cells to the endothelial cells that then migrate to the subendothelial space (Aziz & Yadav, 2016).

(ii) *Lipid accumulation in the tunica intima that oxidizes*

Inflammatory cells, monocytes and T cells migrate into the subendocardial space once they have bonded to endothelial cells. Endothelial cells that are injured release growth factors and chemotactic agents, which modify and transport lipids circulating in the blood, particularly low-density lipoprotein (LDL) and very-low-density lipoproteins (VLLD) (Aziz & Yadav, 2016).

Oxidation of the LDL and VLLD occurs in the inflammatory environment when they bind with the endothelial cells in the subendocardial space, damaging the neighbouring cells, causing macrophage attraction. Some macrophages engulf and become engorged with oxidized LDLs and transform into foam cells, forming a fatty streak when they accumulate, indicating the first sign of an atheroma (Marieb & Hoehn, 2013). The patchy intimal plaques, known as atheromas, are the hallmark of atherosclerosis and are commonly located in the lumens of medium to large arteries. The plaque has cellular and fibrous components, which are inflammatory cells and smooth muscle cells, while the fibrous components are fat components of lipids and connective tissue (Aziz & Yadav, 2016).

(iii) *Proliferation of smooth muscle cells resulting in fibrous cap formation*

Smooth muscle cell proliferation is stimulated by proinflammatory cytokines, causing the growth of the smooth muscle cells into the tunica intima. The dense extracellular matrix increases as these smooth muscle cells replicate (Aziz & Yadav, 2016). Fats and plasma cholesterol then access the tunica intima and tunica media as permeability increases within the endothelial layer (Lazenby, 2011). This leads to the development of a subendocardial fibrous plaque comprised of a lipid core surrounded by connective tissue fibres and smooth muscle cells (Aziz & Yadav, 2016). When this plaque grows, it can compromise blood flow within the vessel's lumen leading to ischemia, producing symptoms such as angina (Groenendyk & Mehta, 2018).

(iv) *Plaque becomes unstable*

Subsequently, the arterial layers involved include the intimal, medial, and adventitial layers. The fibrous plaque, or lesion, with a cholesterol-rich lipid core, distorts the medial and adventitial walls, decreasing the size of the vessel lumen while at the same time increasing the calibre of the vessel. Haemorrhages may occur within the arterial wall due to new vasa vasorum invading the diseased intima, leading to intramural haemorrhage and increased fibrous tissue (Aziz & Yadav, 2016). Enlargement of the plaque continues as the cells at the centre die, smooth muscle production of collagen fibre declines and calcium is deposited, resulting in a complicated plaque that is unstable and may rupture (Marieb & Hoehn, 2013). Plaque rupture or erosion may occur, resulting in the formation of a clot responsible for an estimated 60-70% of MI's (Groenendyk & Mehta, 2018). If thin fibrous caps do rupture, thrombosis and healing may occur. Cyclic recovery can have

disastrous effects on silent ruptures, as this process leads to multiple layers of tissue that have healed and may potentially result in sudden cardiac death (Aziz & Yadav, 2016).

2.2.1.1. Atherosclerotic Plaque Morphologies

Two morphologies of atherosclerotic plaques commonly lead to acute coronary events: plaque erosion and plaque rupture (Arbab-Zadeh et al., 2012). A less typical plaque morphology, a calcific nodule, is responsible for only around 2-7% of acute coronary events. Plaque erosion, or denudation of the coronary arterial endothelium, is present in 19% of plaques in sudden cardiac death cases. This resulted from an autopsy study that included 241 deceased patients who succumbed to sudden coronary death and were found to be present in 36-44% of plaques with acute thrombus (Arbab-Zadeh et al., 2012). Plaque erosion can be associated with a non-occlusive thrombus (Figure 2.2) and an occlusive thrombus (Figure 2.3).

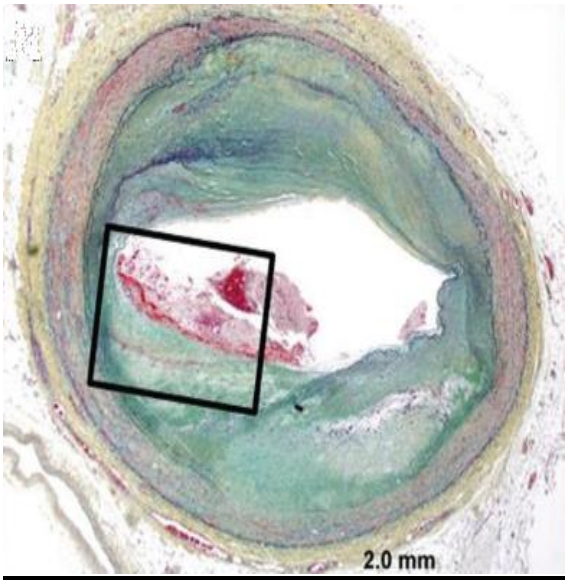

Figure 2.2. A histopathological example of plaque erosion within a coronary artery with a non-occlusive thrombus (adapted from Arbab-Zadeh et al., 2012).

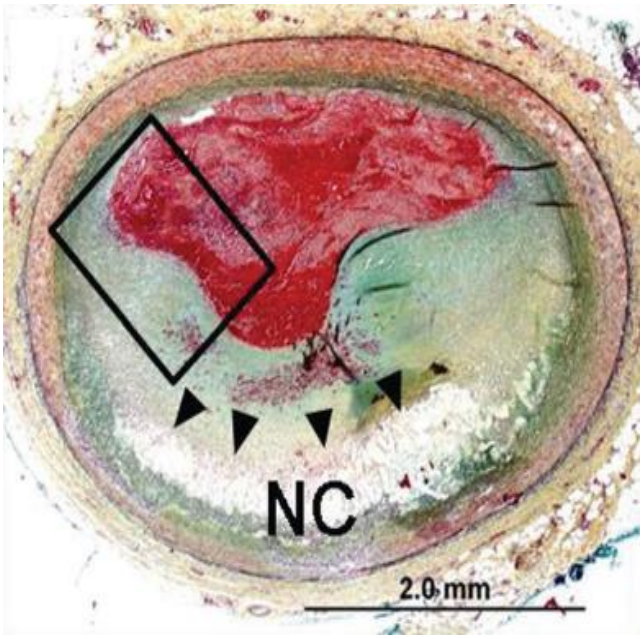

Figure 2.3. A histopathological example of plaque erosion with occlusive thrombus with an early necrotic core (NC) in black arrows (adapted from Arbab-Zadeh et al., 2012).

Plaque rupture was the causative factor for 31% of sudden cardiac death cases. If acute thrombus cases are considered (Figure 2.4), plaque rupture is found to be responsible for a higher death rate, around 59-75% (Gimbrone & García-Cardeña, 2016).

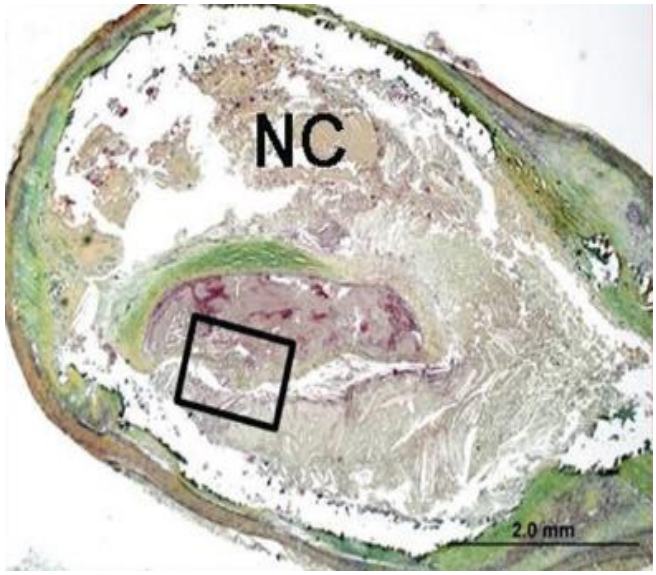

Figure 2.4. A histopathological example of a plaque that has ruptured with an occlusive thrombus (adapted from Arbab-Zadeh et al., 2012).

2.3. NYHA Classification

The New York Heart Association (NYHA) classification system allows for the classification of the extent of heart failure in individuals. Table 2.3 shows how the NYHA classification categorize individuals into one of four functional categories based on limitations in physical activity and symptoms they suffer from during physical activity, such as shortness of breath, palpitations, fatigue and anginal pain (Raphael et al., 2007).

Table 2.3. New York Heart Association Classification Table (adapted from Raphael et al., 2007).

Class	Patient Symptom
I	Cardiac disease is present with no limitation with physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea or angina.
II	Cardiac disease resulting in slight limitation of physical activity, yet comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or angina.
III	Cardiac disease resulting in marked limitation of physical activity, yet comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea or angina.
IV	Cardiac disease resulting in not being able to perform physical activity without discomfort, symptoms may be present even at rest. Any physical activity results in increased discomfort.

2.4. Risk Factors

The risk factors for coronary artery disease are divided into non-modifiable and modifiable risk factors. The non-modifiable risk factors include aspects that an individual has no control over and cannot change, including age, gender, ethnicity, genetics, or family history of a disease (Yayan, 2014). On the other hand, modifiable risk factors can be changed or improved by medical therapy or changes in one's lifestyle. These risk factors include hypertension, obesity, smoking and COPD, diabetes mellitus and hypercholesterolemia (Weber et al., 2016).

2.5. Non-Modifiable Risk Factors

2.5.1. Age

Despite men and women having a similar plaque burden, women tend to be on average 10 years older than men when first showing manifestations of CAD. However, women lose this advantage if they are diabetic, smokers, or have premature menopause (Pathak et al., 2017). CAD prevalence for men is higher before 50 years of age, then equalizes and becomes more significant in women during the sixth decade of life (Pathak et al., 2017). Older patients usually present with atypical symptoms of CAD, leading to a delay in diagnosis and treatment. Increased age predisposes individuals to an increased incidence of CAD in both men and women, with those over 75 presenting with the most significant morbidity and mortality (Knuuti et al., 2020). Younger women with ACS have an increased risk for mortality of up to 50% compared to men of the same age. This increased risk may be due to the perceived notion that younger women have a very low risk for CAD, leading to minimal diagnostic and therapeutic management (Pathak et al., 2017).

The incidence of hypertension and arterial stiffness related to CVD is more significant in the aged population than in the younger population (Sun, 2016). With advanced age, hypertension prevalence increases to around half of the people between 65-69 years and up to three-fourths in people 70 years and older (Chobanian et al., 2003). According to Kaess et al. (2012), an increase in arterial stiffness increases the incidence of developing hypertension. Arterial stiffness results from decreased compliance due to a decrease in the ratio of elastin and collagen fibres, which occurs naturally with ageing. Three mechanisms are associated with cardiovascular ageing: metabolic syndrome, inflammation, and neuro-hormonal disorders. Combined with advanced age, these mechanisms predict cardiovascular disease (Sun, 2016).

2.5.1.1. Metabolic Syndrome

Metabolic syndrome is a group of abnormalities that are all risk factors for the development of CVD and include the following (Canale et al., 2013):

- Morbid obesity
- Hypertension
- Dyslipidemia
- Diabetes mellitus

As age increases, there is an increase in the amount of visceral fat in the body and an increase in circulating leptin levels, which results in increased blood pressure (Intapad et al., 2013). This, along with the above mention conditions, results in endothelial dysfunction of the blood vessels and ultimately results in hypertension. Metabolic syndrome increases the stiffness of the arteries, thus accelerating the cardiovascular ageing process that inevitably leads to the development of hypertension (Sowers, 2013).

2.5.1.2. Inflammation

Inflammation causes tissue injury due to increased chemokines and cytokines in the bloodstream, leading to macrophage and T cell infiltration. These processes occur more frequently with advanced age and an increase in the sympathetic nervous system activation, which is responsible for the inflammatory response (Barnes et al., 2014). Aldosterone plays a role in the inflammatory response and the infiltration of T cells. However, aldosterone regulation becomes dysfunctional with advanced age, thus contributing to age-related inflammation (Sun, 2016).

Inflammation is linked to metabolic syndrome and obesity, as these two mechanisms increase the inflammatory process. Obesity results in chronic inflammation, which ultimately leads to increased arterial stiffness and obesity-induced endothelial dysfunction in the vascular system due to the inflammatory response that occurs in adipose tissue (Fuentes et al., 2013).

2.5.1.3. Neuro-Hormonal

The autonomic nervous system is responsible for regulating peripheral vascular resistance and blood pressure. In the case of metabolic syndrome, there is an increase in the activation of the sympathetic nervous system, which disrupts this regulation (Canale et al., 2013). Metabolic syndrome related to obesity shows resistance to insulin and adipokine production dysregulation. This accelerates the sympathetic nervous system, ultimately contributing to metabolic syndrome-induced hypertension (Sun, 2016).

In women, hormonal changes that occur with menopause also contribute to the development of hypertension, as autonomic support is more pronounced in older women than in younger women (Pathak et al., 2017). Post-menopausal women generally have an increased sympathetic nervous

system activation. The sympathetic nervous system has a positive association with arterial blood pressure, leading to increased hypertension in older women and a blunted baroreflex sensitivity responsible for this age-associated increase in the sympathetic nervous system activity. Advanced age is associated with hypertension due to salt sensitivity (renal inflammation contributes to salt sensitivity) – mediated by increased inflammation (Figure 2.5.) (Sun, 2016).

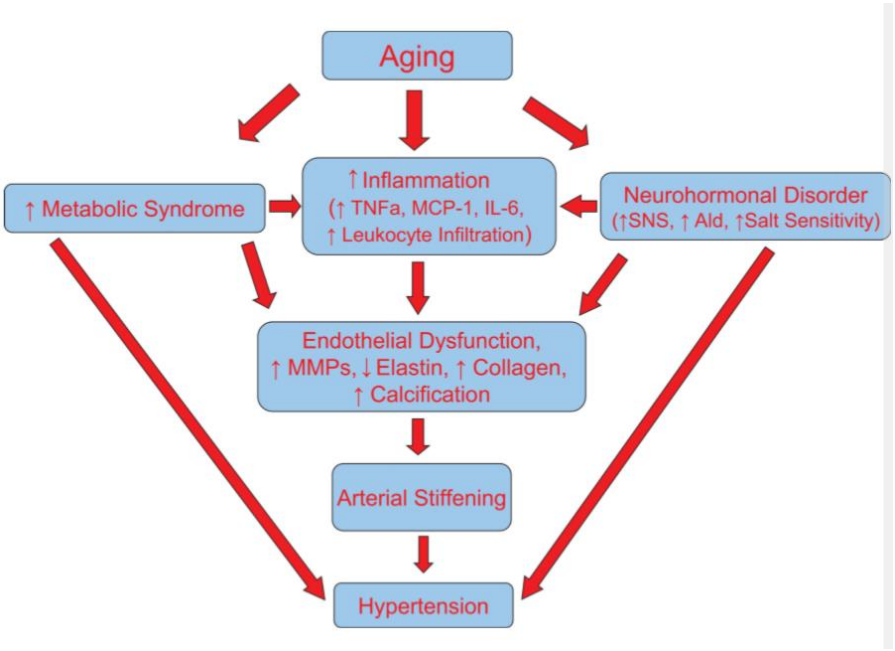

Figure 2.5. Diagram of the mechanism that links age, arterial stiffness and hypertension (adapted from Sun, 2016).

2.5.2. Gender

CVD, including CAD, are the leading cause of death in both men and women, with a greater mortality rate in women than in men (Duda-Pyszny et al., 2018). Epidemiological studies in India have shown an increased burden of common risk factors for CAD, such as hypertension, diabetes and metabolic syndrome. CAD in adults increased from 3% to 10% from 1960 to 1995 in urban Indians and around 2% to 4% in rural Indians, with both men and women having similar rates (Pathak et al., 2017).

Women present with more atypical symptoms (atypical chest pain with nausea, dyspnea and increased sweating) of angina than men, which in clinical practice does not always warrant further CAD diagnostics, causing a delay in treatment and ultimately, a worse outcome (Duda-Pyszny et

al., 2018). Although both genders over the age of 40 develop an increased risk for CAD, women tend to be underdiagnosed and undertreated. On average, women present 7-10 years later than men, and older women are often burdened with several risk factors and comorbidities for CAD (Duda-Pyszny et al., 2018). When women present with CAD at a younger age, they tend to receive lower evidence-based treatment than men (Khamis et al., 2016). The worldwide INTERHEART study (Steyn et al., 2005), which included 52 000 individuals that experienced an MI, has revealed that, on average, women first present with coronary heart disease around 10 years later than men, mainly after menopause (Pathak et al., 2017). Lipid profiles deteriorate in postmenopausal women, with high-density lipoprotein (HDL) cholesterol levels decreasing and LDL cholesterol levels increasing. Women have developed higher cholesterol levels than men by the time they are in their 50's (Brewer et al., 2015).

As women age, they experience increased arterial pressure, especially systolic blood pressure, leading to increased risk for stroke and all-cause mortality (Duda-Pyszny et al., 2018). Obesity, with a body mass index (BMI) of $\geq 30 kg/m^2$, increases women's risk for CAD by 64%, whereas for men, CAD risk increases by 46%. In contrast, diabetes mellitus (DM) is associated with a higher CAD risk for women than men (Brewer et al., 2015).

2.5.3. Ethnicity / Cultural

Cardiovascular disease development is influenced by race and ethnicity (Winham et al., 2015). Black Africans are more susceptible to hypertension than Caucasians. On the other hand, Black Africans have a more favourable lipid profile than Caucasians by having lower LDL and total cholesterol (TC) levels and higher HDL cholesterol levels (Pieters et al., 2011).

Data regarding CAD and CVD disease in Black South Africans has been poorly documented in the past (Loock et al., 2006), with a low prevalence of risk factors. Still, previous studies indicated that there might be an increase in prevalence, especially in the urban areas of South Africa (Akinboboye et al., 2003; Loock et al., 2006). There is limited data on CVD prevalence, and CAD in particular, particularly in South African populations, especially on racial profiles (Akinboboye et al., 2003).

2.5.4. Genetics / Family History

A significant risk factor for the development of CAD is a family history of the disease due to the possibility of susceptible gene inheritance and the shared lifestyle (Kulkarni, 2015).

There are three ways how a positive family history may relate to CAD development (Conroy et al., 1985):

- as an index of the inheritance of risk factors
- as a truly independent risk factor
- as a vulnerability factor potentiating the action of risk factors.

A history of MI or sudden death in a female sibling before age 55 is associated with MI risk to a greater extent than a brother or parent. Family history involving a sister with CAD is associated with a 12-fold greater risk, versus only a 6-fold increase in risk for a brother and a 3-fold for a parent (Lazenby, 2011).

2.6. Modifiable Risk Factors

2.6.1. Hypertension

The aorta in young individuals is compliant, yet with increased age, the elastin in the aorta's medial layer degrades, causing the aorta to stiffen. This stiffness leads to an increase in systolic blood pressure (Weber et al., 2016). Optimal blood pressure ranges are less than 120mmHg for systolic blood pressure and less than 80mmHg for diastolic blood pressure. Hypertensive values are systolic values ≥140mmHg and/or diastolic values ≥90mmHg (Xavier Gómez-Olivé et al., 2018). Individuals fall into the pre-hypertensive range when the values are between 120-139mmHg for systolic blood pressure and between 80-89mmHg for diastolic blood pressure (Lazenby, 2011). Early detection and increased hypertension awareness are necessary to reduce overall morbidity and mortality.

Hypertension is arguably the most common risk factor for CVD, especially in Africa (Onen, 2013; Byrne et al., 2016). Hypertension is frequently underdiagnosed and thus undertreated in Sub-Saharan Africa, leading to more frequent and severe complications (Twagirumukiza et al., 2011; Ataklte et al., 2015). Hypertensive complications are associated with increased risk for stroke and

heart disease morbidity and mortality. According to Onen (2013), the most significant challenge surrounding hypertension is the lack of awareness of the disease, the frequency of under-diagnosis and the severity of the complications resulting from hypertension. Men generally develop hypertension at a younger age than women, leading to a more significant life-long burden of the disease, thus increasing their risk of adverse events, such as stroke and CAD (Winham et al., 2015).

Bloch (2016) revealed an increase of 5.2% in the global prevalence of hypertension from 2000 to 2010. In 2010 the prevalence of hypertension worldwide was 31% of all adults, equating to 1.39 billion people. The data shows disparities between high-income and middle to low-income countries in the prevalence of hypertension. From 2000 to 2010, high-income countries showed a 2.6% decrease, while middle- to low-income countries showed a 7.7% increase in hypertension prevalence. This is attributed to decreased awareness, treatment and control rates in the middle to low-income countries (Bloch, 2016).

Hypertension in South Africa was estimated in 2000 to have caused 46 888 deaths (Peltzer & Phaswana-Mafuya, 2013). Bourne et al. (1991) conducted a community-based cross-sectional study that included 986 Black subjects in the Cape Peninsula of South Africa. They reported a hypertension prevalence of 13.7% in women and 14.4% in men. Primary hypertension prevalence is high among Black African communities, according to Akinboboye et al. (2003), with Nigeria having a prevalence of 10-12% in the general adult population. This study demonstrated that hypertension is prevalent in urban and rural Black African communities, with a slightly higher frequency in the urban setting (Akinboboye et al., 2003).

The Heart of Soweto study (Sliwa et al., 2008) reported that in 2006, 4506 participants presented for the first time to the Chris Hani Baragwanath Hospital, and 897 (19.9%) were newly diagnosed hypertensive patients, and 1330 (25.9%) were patients with known hypertension. In Africans with hypertension, around 40% are undiagnosed, <30% of those diagnosed with hypertension are on treatment, and <20% who are on treatment have an adequately controlled blood pressure of <140/90mmHg (Onen, 2013). Ataklte et al. (2015) reviewed the data from 33 surveys involving over 100 000 participants. They found a 30% prevalence of hypertension in Sub-Saharan Africa, with only 27% of the participants being aware of their hypertensive status before the survey. Only

18% were receiving treatment for hypertension, of which only around 7% had controlled blood pressure.

Hypertension is a major contributing risk factor to CAD in South Africa, as demonstrated by a study performed by Peltzer & Phaswana-Mafuya (2013). This study reported that the advanced age population (over 50 years of age) has a very high prevalence of hypertension in South Africa and should be addressed. In total, 3840 subjects were studied, of which 2053 (74%) were Black Africans, 269 (9.3%) were Caucasians, 655 (12.8%) were Coloured, and 307 (3.8%) were Asian (Table 2.4),

Table 2.4. Prevalence of confirmed hypertension among older South Africans (adapted from Peltzer & Phaswana-Mafuya, 2013).

Gender and Ethnicity	Total (n=3840)	Over 50 years (n=2842)
Male	1638	1159
Female	2202	1683
Black African	2053	1150
Caucasian	269	193
Coloured	655	545
Asian	307	214

2.6.2. Obesity

The prevalence of obesity worldwide has been increasing over the past few decades in both adults and children, with adults being classified as obese when they have a body mass index (BMI) of ≥30 kg/m² (Lavie et al., 2007). Obesity is a growing health concern worldwide, with an estimated prevalence of 36% in 2015 in the USA, 32% in China and 24% in Canada (Wang et al., 2015). In 2014, obesity was estimated as the second leading cause of preventable death due to numerous health implications associated with obesity (Jahangir et al., 2014). In some countries from North Africa, Oceania and the Middle East, the prevalence of obesity in 2013 was greater than 50% in the adult population. North America had a prevalence of ±33%, or one-third of the population, while Western Europe showed a prevalence of ±20%, or one-fifth of the adult population. Japan has the lowest percentage of obese adults, with only 3.8% of the population being categorized as

obese. This can be attributed to healthier diets and better public transport leading to more daily walking than in other countries (Ortega et al., 2016). Obesity is associated with the increased risk of developing hypertension, dyslipidemia, diabetes mellitus type 2 and metabolic syndrome, which are risk factors associated with CAD (Jahangir et al., 2014).

The leading cause of obesity is the imbalance between energy intake and expenditure, defined as the abnormal accumulation of body fat ≥20% (Jiang et al., 2016). With obesity, inflammatory responses have been found to occur, such as increased clotting factors and factors associated with decreased fibrinolysis, which leads to an increase in CAD (Jahangir et al., 2014). Factors contributing to weight gain and obesity include sedentary lifestyles, depression, low esteem and inadequate sleeping patterns (Jiang et al., 2016). Abnormally high BMI values increase the risk of developing dyslipidemia. Increased BMI is associated with increased levels of triglycerides (TG) and low-density lipoprotein (LDL) cholesterol and decreased levels of HDL cholesterol, which increase the risk of developing CAD (Jahangir et al., 2014).

Body mass index (BMI) is calculated with the formula of weight (kg) divided by height (m) squared (Wang et al., 2015). The WHO's BMI classification is summarized in Table 2.5.

Table 2.5. Classification of BMI ranges (adapted from Wang et al., 2015).

Range	**BMI (kg/m²)**
Underweight	<18.5
Normal range	18.5–<25
Overweight	≥25.0–<30
Grade I obesity	≥30.0–<35
Grade II-III obesity	≥35

There are numerous adverse effects of obesity on cardiovascular structures, functions, and hemodynamics. Obesity results in increased blood volume and cardiac output because of an increased stroke volume (Ortega et al., 2016). Due to increased blood volume and filling pressures, left ventricular chamber dilation usually occurs, leading to heart failure over time (Ortega et al.,

2016). This increases the risk of developing ventricular hypertrophy, leading to increased myocardial oxygen demand (Lavie et al., 2007).

2.6.3. Smoking

Smoking contributes to an increased risk of stroke and coronary heart disease. Tobacco found in cigarettes is the second leading risk factor for mortality globally, claiming almost 6 million lives in 2010 (Kumar et al., 2012). The WHO MONICA project revealed that in the age group of 35-39 years, 81% of men and 77% of women who experienced nonfatal MI were smokers (Mähönen et al., 2004). Smoking is responsible for around one-third of the global mortality associated with CVD (Hammal et al., 2014).

The prevalence of smoking among adults in India in 2012 was 14%, and in the Russian Federation, 39%, while adolescents (aged 13 to 15 years) showed a prevalence of 7% in girls and 12% in boys who smoke cigarettes, while 8% of girls and 12% of boys use other tobacco products (Kumar et al., 2012). Data collected by the WHO for 29 African countries revealed the prevalence of tobacco smoking among adults to have different patterns across the continent. For example, in the adult population of Morocco and Egypt, tobacco smoking is estimated to be 45-50%, in Cameroon and the Republic of Congo, 43-44%, and in Mauritius and Sierra Leone, 44-60% (Keates et al., 2017). Countries such as Ethiopia and Ghana, on the other hand, revealed a lower prevalence of smokers with 9% and 13%, respectively. However, smoking prevalence has been consistently higher in men than in women (Keates et al., 2017). The number of smokers in Sub-Saharan Africa is expected to increase to over 200 million by 2030 (Keates et al., 2017).

Smoking tobacco products increases CVD risk. Exposure to smoking can be categorized by whether the individual is a current smoker, former smoker, or never smoked or used tobacco products before. Smoking cigarettes damages all the organs in the body and can cause many diseases leading to an overall reduction in health. One of the most common risk factors for cardiovascular disease is smoking. It predisposes individuals to several atherosclerotic syndromes such as MI and other ACS, stable angina, and sudden death (Tonstad & Johnston, 2006). Literature suggests that the intensity of smoking increases the risk of coronary heart disease and death - the higher the number of cigarettes smoked per day, the greater the risk (Nance et al., 2017).

Smokers have a two to four times greater risk for sudden cardiac death than non-smokers, with the risk even higher in heavy smokers. The risk of coronary heart disease death is 70% greater in smokers than non-smokers and increases further in the presence of other CAD risk factors (Tonstad & Johnston, 2006). Smoking accelerates established atherosclerosis progression and leads to an increased risk of coronary events (Metz & Waters, 2003). Smoking even a single cigarette may lead to arterial wall stiffness, thus increasing the chances of plaque rupturing (Kool et al., 1993).

The three constituents of cigarette smoke, nicotine, carbon monoxide and oxidant gases, contribute to CVD development (Tonstad & Johnston, 2006). Smoking leads to injury and dysfunction of the endothelium in the coronary and peripheral arteries. The damage to the endothelium can result in atherogenesis and acute cardiovascular events. Nitric oxide regulates leukocyte adhesion, platelet activation, inflammation and thrombosis. The oxidant chemicals from cigarette smoking contribute to a hypercoagulable state noted in smokers. Evidence has shown that smokers have a higher portion of single-vessel disease than non-smokers, and thrombosis plays a significant role in the acute coronary events' pathogenesis (Metz & Waters, 2003). Nicotine increases the heart rate and blood pressure, thus increasing myocardial work. There is evidence that in patients with coronary heart disease, nicotine causes vasoconstriction leading to decreased coronary blood flow. Carbon monoxide exposure and increased carboxyhemoglobin levels cause a decrease in oxygen-carrying capacity and increased red cell mass (Tonstad & Johnston, 2006).

Smoking cessation has significant beneficial effects on all smoking-induced CVD. Upon smoking cessation, the effects of multiple mechanisms from smoking can be reversed within weeks. These effects are clotting factors, carboxyhemoglobin and platelet activation. However, some effects of smoking are not reversible, yet smoking cessation can at least prevent smoking-mediated progression of atherosclerosis and lipid deposits in the arterial intima (Tonstad & Johnston, 2006). Hammal et al. (2014) reported that smoking cessation was the most effective method for reducing mortality for smokers with CAD. They also showed that non-smokers had a much higher long-term survival rate than current smokers. Smokers who quit smoking one year after revascularization had a much greater long-term survival rate than those who continued to smoke after revascularization.

2.6.4. Chronic Obstructive Pulmonary Disease (COPD)

There is a 9-10% prevalence of COPD in individuals aged 40 years and older, with prevalence increasing to over 20% in those over the age of 70 years (Roversi et al., 2014). A population-based study by Eriksson et al. (2013) revealed that CAD was reported in 7-13% of patients suffering from COPD, while COPD was reported in 26-35% of patients with CAD. The prevalence of IHD increases along with an increase in COPD severity, reaching rates of up to 60% in individuals affected by advanced COPD (Eriksson et al., 2013).

COPD is an independent risk factor for CVD morbidity and shares several risk factors with CAD, such as smoking and sedentary lifestyles. COPD is associated with increased risk for CAD, and CAD is associated with both the diagnosis and severity of COPD. COPD prevalence is more significant in men than women, with a ratio of 1.64 for men to women (Cazzola et al., 2012).

COPD is a preventable and treatable respiratory disease characterized by persistent airflow limitation and chronic respiratory symptoms resulting from abnormal inflammatory responses to irritants, such as cigarette smoke (Roversi et al., 2014). Figure 2.6. illustrates the common pathogenic mechanisms of CAD and COPD; and is centred around chronic inflammation that leads to tissue injury and repair and the subsequent parenchymal damage that results from this process of injury and repair, as well as the clinical manifestations (Roversi et al., 2014).

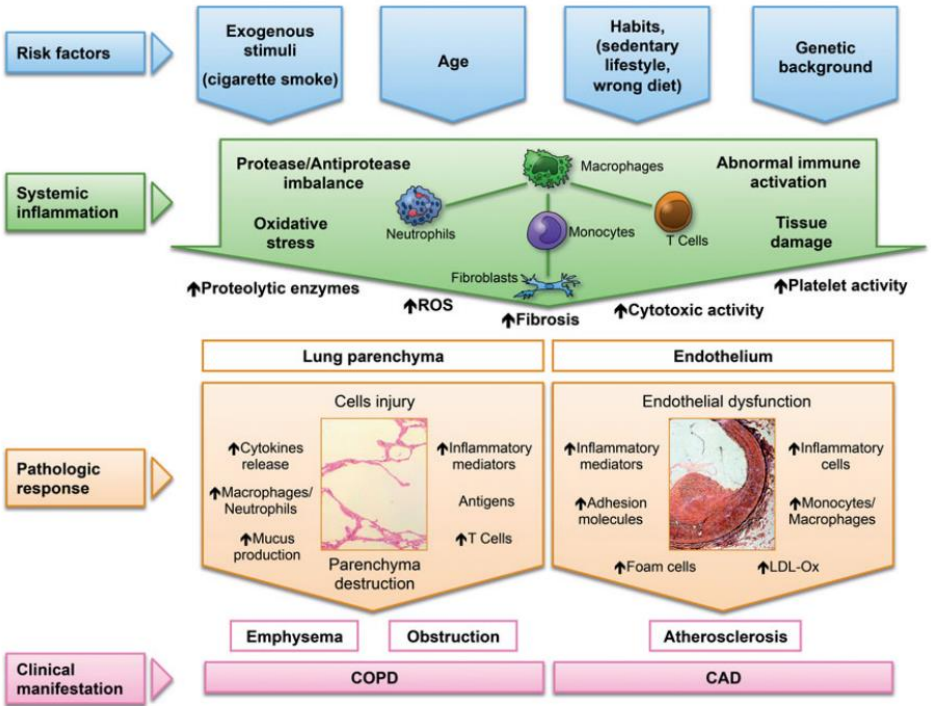

Figure 2.6. The common pathogenic mechanism of CAD and COPD (adapted from Roversi et al., 2014).

2.6.5. Diabetes

Over the past few decades, the prevalence of diabetes mellitus (DM) has increased, leading to an increased incidence of CVD. In 2014, the worldwide estimation of DM prevalence, as reported by The International Diabetes Federation, was 387 million individuals, an overall prevalence of 8.3%, and is expected to continue to increase to 552 million by 2030 (Yahagi et al., 2017).

DM is a disorder with inadequate insulin production or abnormal insulin receptors in the body. Without the insulin, or the lack of functional receptors for insulin, the body cannot absorb glucose, leaving blood glucose levels to remain elevated (hyperglycemia), and most glucose is excreted in the urine. This can lead to metabolic acidosis, weight loss and protein wasting as fats and tissue proteins must be used as energy sources (Marieb & Hoehn, 2013). Cardiovascular risk in DM type 1 is primarily caused by hyperglycemia. In contrast, DM type 2 features are caused by many factors such as dyslipidemia, hypertension and obesity, which are not always present in DM type 1 (Yahagi et al., 2017). DM increases the risk of developing CAD due to the association of DM with

dyslipidemia and endothelial dysfunction, both of which are steps in the process of atherogenesis (Jahangir et al., 2014).

There is a high incidence of asymptomatic ischemic disease in both type 1 and type 2 DM, which suggests that there is a high frequency of healed plaque ruptures in individuals with DM, which is likely the result of silent plaque ruptures that occur with the absence of symptoms (Yahagi et al., 2017). DM type 1 is associated with a high 10-year risk for cardiovascular events, thus making it a decisive CAD risk factor. Other possible mechanisms for CAD risk associated with DM include increased vasoconstriction (this is related to circulating free fatty acids being elevated), insulin-related sympathetic nervous system being stimulated, a decrease in insulin-mediated vasodilation and an increase in the insulin-mediated renal sodium reabsorption (Jahangir et al., 2014). Plaques in individuals with DM generally have larger necrotic cores with increased inflammation consisting mainly of macrophages and T lymphocytes relative to individuals without DM (Yahagi et al., 2017). Suggestions of more active atherogenic processes in individuals with DM type 1 and 2 can be seen with the increased incidence of healed plaque ruptures, positive remodeling of the heart, and more extensive lesion calcifications (Yahagi et al., 2017).

Important factors leading to atherosclerotic calcification in DM individuals include, oxidative stress, increased inflammatory cytokine production, endothelial dysfunction, and alterations in mineral absorption (Yahagi et al., 2017). The presence of one or more risk factors (e.g. elevated cholesterol levels, cigarette smoking and systolic hypertension) in individuals with DM has a more significant impact on increasing the mortality of CVD in individuals with DM than in those without (Sowers et al., 2001). Calcification of the vasculature is classified into two forms depending on their location, either within the intima or the media. Type 2 DM most commonly presents with medial calcification but mainly affects the peripheral arteries, resulting in loss of elasticity of smooth muscle cells (Yahagi et al., 2017).

A vast amount of our understanding of diabetes' role in atherosclerosis has been obtained through autopsy investigations of sudden coronary death. A recent autopsy analysis showed evidence that plaque rupture and erosion episodes had lower incidence values in individuals with DM than in those without, yet a more significant plaque burden was observed in DM type 1 and type 2 than in

non-diabetics (Yahagi et al., 2017). A histopathological study of 47 coronary atherectomy specimens revealed that patients with DM had increased percentages of lipid-rich atheromas than non-diabetics. The thrombus occupies a larger area in diabetic than non-diabetic patients (Moreno et al., 2000). There is a greater tendency for significant atherosclerotic plaque burden in individuals with DM compared to non-diabetics, likely explaining the more considerable amount of coronary calcium observed in the DM population (Raggi et al., 2004).

2.6.6. Hypercholesterolemia

Individuals with a known family history of premature coronary artery disease should be screened for familial hypercholesterolemia (Knuuti et al., 2020). Concerning lipid profiles, a hallmark of cardiovascular disease is an increase in LDL cholesterol and total cholesterol (TC) and a decrease in HDL cholesterol levels (Winham et al., 2015). In 2016, the Heart and Stroke Foundation of South Africa stated that 23.9% of adults have high TC, 28.8% have high LDL cholesterol, and 47.9% have low HDL cholesterol (Byrne et al., 2016). Therefore, substantial evidence links cholesterol to atherosclerosis development (Onen, 2013). A national survey by Shisana et al. (2014) indicated that only 4.2% of participants knew they had high blood cholesterol levels.

Since 1980, cholesterol levels in Africa have been among the lowest globally, possibly attributed to the low LDL cholesterol levels and thus atherosclerosis documented on the continent (Ntsekhe & Damasceno, 2013). Due to high levels of physical activity and low-fat diets historically seen across Africa, lipid profiles were considered largely favourable due to traditional lifestyles, resulting in lower atherosclerosis rates (Keates et al., 2017). Most Black Africans reported having low levels of total cholesterol and higher levels of HDL cholesterol (Onen, 2013; Pieters et al., 2011; Keates et al., 2017), with the relatively high HDL cholesterol levels considered to have an inverse influence on the risk of CAD (Akinboboye et al., 2003). Normal blood levels of cholesterol are summarized in Table 2.6.

Table 2.6. Reference range for cholesterol levels (adapted from (Kwiterovich, 2004).

Blood Test	Ideal value
Total cholesterol	<200mg/dL OR <5.2 mmol/L
Triglycerides	<200mg/dL OR <2.3 mmol/L
HDL	≥60mg/dL OR ≥1.6 mmol/L
LDL	<130mg/dL OR <3.4 mmol/L

Familial hypercholesterolemia is a hereditary disorder of LDL cholesterol metabolism and is characterized by high LDL cholesterol levels affecting 1 in 250 individuals. Individuals with this disorder have a 3 to 4-fold increased risk of developing CAD (Besseling et al., 2016). High levels of LDL cholesterol in the arteries can lead to premature CVD. In patients with heterozygous familial cholesterolemia, if left untreated, CVD symptoms can manifest in the fourth decade of life for men and the fifth decade of life for women (Hovingh et al., 2013).

2.7. Treatment

Prevention and treatment of the risk factors should be the primary concern of healthcare professionals, with early detection of the diseases that are attributed to the development of atherosclerosis and, ultimately CAD (Perk et al., 2012). Improved management strategies and resources should be implemented, especially in the country's rural areas, to ensure fewer deaths within the population. However, if the risk factors allow for the development of atherosclerosis and CAD, appropriate therapy should be initiated, including changes in lifestyle, medical treatment, or revascularization (Knuuti et al., 2020).

2.7.1. Medical Therapy

The main approach for primary prevention of CAD is statin therapy (Winham et al., 2015). Statins are administered to lower LDL cholesterol and decrease plaque size. The main action of statins is anti-inflammatory, stabilising the plaque and preventing rupture (Marieb & Hoehn, 2013). In the setting of a STEMI, the administration of fibrinolytic therapy should occur within 30 minutes (Meel & Gonçalves, 2016).

2.7.2. Percutaneous Coronary Intervention (PCI)

Coronary revascularization has been the mainstay in CAD treatment for many decades, with PCI being the most commonly used procedure for reperfusion (Boschetto et al., 2012). PCI is an invasive procedure (yet less invasive and traumatic than open heart surgery) and poses fewer complications. Yet, there is a high rate of restenosis of greater than 10% (Boschetto et al., 2012). PCI has been shown to have better outcomes in the setting of acute MI than thrombolysis therapy (Metz & Waters, 2003).

2.7.3. Coronary Artery Bypass Grafting (CABG)

CABG has been used as a reperfusion procedure since the 1960s (Boschetto et al., 2012). CABG procedures allow for complete revascularization and ensure patency of the vessels at follow-up. Yet, the procedure is extremely invasive as it is done via a sternotomy/thoracotomy approach and has added risks due to the need for extracorporeal circulation (Boschetto et al., 2012). CABG procedures are performed for critical and/or multiple lesions. Veins are removed from the legs, or even small arteries from the thoracic cavity, that are then replanted in the heart, bypassing the occluded or diseased segment of the artery and restoring blood flow (Marieb & Hoehn, 2013).

Chapter 3 - Journal Article

Contemporary risk factors associated with ischemic heart disease in central South Africa: a single-centre study

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Abstract

Introduction: The study aimed to investigate modifiable and non-modifiable risk factors in coronary artery disease (CAD) patients in central South Africa.

Methods: Patients with angiographically confirmed CAD evaluated in the catheterization laboratory for the first time over a two-year period (2016-2017) were included. Data was extracted from the patient's medical records.

Results: Four-hundred-and eighty-two patients met the inclusion criteria, presenting at a mean age of 58.4±10.8 years and were predominantly male (66%). Female patients presented significantly older than males (60.3±9.6 vs 57.4±11.1 years; $p<0.05$). The mean age at presentation was comparable between ethnic groups, with only Asians presenting significantly younger than Caucasians (49.8±10.5 vs 59.1±10.8; $p<0.05$). Hypertension (91%) was the most common risk factor, followed by smoking (67%) and obesity (40%). Black Africans demonstrated a higher incidence of hypertension when compared to Caucasians (96% vs 87%; $p<0.05$). Smoking was more prevalent in Caucasians than Black Africans (68% vs 54%; $p<0.05$) and occurred more commonly in males than females (73% vs 55%; $p<0.05$). Most patients presented with acute coronary syndrome (ACS) (72%), mainly with ST-elevated myocardial infarction (STEMI) (36%). The majority of patients presenting with ACS were in the age interval 51-60 years. The ACS risk factor profile was similar to the total study group.

Conclusion: CAD is present in all ethnic groups, and modifiable and non-modifiable risk factors are similar to the classical risk factors described worldwide. Minor interracial differences were observed and hypertension was the most prevalent risk factor recorded in central South Africa. Most patients with CAD presented with ACS, particularly STEMI.

Keywords: Coronary artery disease; acute coronary syndrome; risk factors; modifiable risk factors; non-modifiable risk factors

3.1. Introduction

In 2010, middle to low-income countries accounted for 80% of the global cardiovascular disease (CVD) burden (Sliwa & Mocumbi, 2010). In Sub-Saharan Africa, CVD is responsible for 13% of all deaths and accounts for up to 37% of all non-communicable disease deaths, making CVD the leading cause of non-communicable disease deaths in Sub-Saharan Africa (Yuyun et al., 2020).

Sub-Saharan Africa is home to the most significant proportion of the world's poorest individuals. It includes countries geographically located in the "central belt", East to West Africa and Central Africa (Keates et al., 2017). Several countries in Sub-Saharan Africa reported an increase in CVD prevalence (Hamid et al., 2019). Urbanization of low to middle-income countries, such as South Africa, as well as the transition to a more Westernized lifestyle and diet, causes an increase in CVD prevalence, as well as an increase in the risk factors responsible for CVD (Oladapo et al., 2010; Mollentze et al., 1995; Stewart et al., 2011; Vorster et al., 2005; Vorster, 2002). This presents significant challenges to healthcare, as low to medium-income countries are already overburdened by expenditure on nutrition and communicable diseases.

Established risk factors associated with CVD include non-modifiable (age, sex, ethnicity and family history of coronary artery disease) and modifiable risk factors [hypertension, diabetes mellitus, obesity and elevated low-density lipoproteins (LDL levels)] (Canto et al., 2011). Modifiable risk factors, especially hypertension, are considered global epidemics and are of particular concern in Sub-Saharan Africa, where it is still under-detected and under-diagnosed due to poverty and disease ignorance (Ogah & Rayner, 2013). Cardiac risk factors responsible for causing CVD worldwide include age, sex, dyslipidemia, diabetes mellitus, smoking, obesity and diet or lifestyle factors (Knuuti et al., 2020; Maddox et al., 2014; Yahagi et al., 2015). In 1995, Mollentze et al. reported a high incidence of hypertension among the Black population in South Africa, with a 29% and 30.3% prevalence in QwaQwa and Mangaung, respectively. Mollentze et al. (1995) also predicted that due to urbanization, the prevalence of risk factors, morbidity and mortality from CVD in the Black African population was expected to increase dramatically within the next few years.

Oladapo et al. (2010) reported that more than 80% of CVD and accompanied risk factors are preventable with cost-effective measures such as health education and lifestyle modification. Due to the alarming increase in CVD in Sub-Saharan Africa, emphasis must be placed on prevention, early diagnosis and proper management of the disease. The INTERHEART Africa study (Steyn et al., 2005) indicated that known risk factors are present in 90% of patients presenting with myocardial infarctions (MI) in Sub-Saharan Africa. However, recent data describing the prevalence of non-modifiable and modifiable risk factors causing CVD is unavailable for central SA. Published South African studies focus on acute myocardial infarctions (AMI) rather than coronary artery disease (Sirkar et al., 2018; Sookan et al., 2018; Masina et al., 2017). The latest study addressing CVD risk factors in central SA was published by Mollentze et al. in 1995. This study aimed to determine the current non-modifiable and modifiable risk factors in patients with established coronary artery atherosclerosis in central South Africa to highlight the need for preventive strategies.

3.2. Methods

3.2.1. Study Design

A retrospective descriptive single-centre study was conducted describing the modifiable and non-modifiable risk factors for public sector patients. Patients with angiographically confirmed atherosclerotic coronary artery disease (CAD) presenting for the first time at the catheterization laboratory from January 2016 to December 2017 were included in the study.

3.2.2. Study Setting

The study was conducted at Universitas Academic Hospital (UAH) in Bloemfontein, the only tertiary referral hospital in the central South African region with a population of ±6.3 million. Patients are referred from the Free State, Northern Cape and Lesotho.

3.2.3. Study Population

Only patients with proven atherosclerotic CAD confirmed by coronary angiography were included in this study. Atherosclerosis leading to narrowing of the lumen in one or more of the major coronary arteries reported by a qualified cardiologist confirmed the presence of CAD. Patients

with evidence of primary myocardial muscular, valvular and congenital heart disease were excluded.

3.2.4. Data Collection

Patient data was captured from the patient's medical records and catheterization laboratory reports and included; demographic [age (years), sex, ethnicity, hospital classification], anthropometry [height (cm), weight (kg), and body mass index (BMI) (kg/m²)] and clinical data (clinical diagnosis and cardiac risk factors). BMI was calculated using the weight/height² formula (Oladapo et al., 2010). Modifiable (age, sex, ethnicity and family history of CAD) and non-modifiable (hypertension, diabetes mellitus, smoking, obesity, COPD and hypercholesterolemia) risk factors were recorded for each patient.

3.2.5. Definitions

Hospital classification (https//www.westerncape.gov.za/general-publication/western-cape-government-hospital-tariffs-overview?toc_page=3)

H1: Single annual income of less than R70 000 or family annual income less than R100 000;

H2: Single annual income between R70 000 to R100 000 or family annual income between R250 000 to R300 000;

H3: Single annual income more than R250 000 or family annual income more than R350 000;

H4: Externally funded patients.

The diagnosis was captured as specified by the treating physician in the medical record.

Hypertension

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (Kaess et al., 2012). Patients on antihypertensive treatment were also included.

Smoking

Smoking refers to the use of any tobacco product as an inhalant; both current and previous/ex-smokers were included.

Obesity

Patients were classified as obese if they had a BMI of ≥30 kg/m² (Lavie et al., 2007).

Diabetes

Type I and II DM as specified in the patient's medical file and/or reference to diabetic medication in treatment.

Acute coronary syndrome (ACS)

Standard definitions were applied (Yayan, 2014).

3.2.6. Ethics

Ethical approval was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (UFS-HSD2019/1351/011001) and the Free State Department of Health.

3.2.7. Statistics

Statistical analysis was done in collaboration with a biostatistician. Raw data was captured on an Excel spreadsheet and a t-test was used to compare normally distributed data. Non-parametric data were compared using a Mann-Whitney U test. Where required, a Chi² or Fisher's exact test was utilized for comparisons. Analysis was done using standard Statistical Analysis Software. Statistical significance was noted if $p>0.05$.

3.3. Results

Coronary angiograms were performed in 1859 patients over the 2-year study period. Seven hundred and twenty-five (n=725) patients met the inclusion criteria for this study. However, 243 patients had to be excluded due to incomplete data files. The study group analyzed consisted of 482 patients who had complete clinical records.

3.3.1. Geographic Location

Most patients were from the Free State (59%) and Northern Cape (37%), with only 4% from Lesotho and other provinces. More than half (57%) of patients from the Free State were from rural

areas outside the Mangaung Metropolitan Metro. Ninety percent (n=435) of patients included in the study were from low-income groups (H0-H2).

3.3.2. Non-Modifiable Cardiac Risk Factors

Demographic data can be viewed in Table 3.1. The study population (n=482) showed a male preponderance (66%). Males also presented significantly younger than females (57.4±11.1 years vs 60.3±9.6 years; $p<0.05$). Noteworthy, atherosclerosis was observed in all ethnic groups, with Caucasians making up less than half (46%) of the total group. Coronary atherosclerosis was present in 24% and 23% of Mixed-race and Black Africans, respectively. Of note, compared to the rest of the group, Asian patients presented significantly younger than Caucasians (49.8±10.5 vs 59.1±10.8; $p<0.05$). The ages of Black Africans and Mixed-race were similar to that of Caucasians ($p>0.05$). Family history was unknown or not recorded in a third of the patients (n=165; 34%). A positive family history of CAD was recorded significantly more in Caucasians than Black Africans ($p<0.05$) and Mixed-race ethnicities ($p<0.05$).

Table 3.1. Non-modifiable cardiac risk factors of the study population

Parameter	**1st-time presenters with atherosclerotic disease (n=482)**		
	n (%)	**Age (years) Mean ± SD**	**p-value (age)**
Sex	482	58.4 ± 10.8	0.01*
Male	317 (65.8%)	57.4 ± 11.1	
Female	162 (33.6%)	60.3 ± 9.6	
Ethnicity	482		
Caucasian	223 (46.3%)	59.1 ± 10.8	-
Black African	112 (23.2%)	59.4 ± 9.5	0.80
Asian	30 (6.2%)	49.8 ± 10.5	<0.01*
Mixed-race	117 (24.3%)	58.1 ± 11	0.42
Positive family history per ethnicity	141		
Caucasian (n=223)	82 (36.8%)	58.4 ± 10.6	
Black African (n=112)	13 (11.6%)	57.5 ± 9.5	0.77
p-value	<0.01*		
Asian (n=30)	16 (53.3%)	49.2 ± 9.7	<0.01*
p-value	0.08		
Mixed-race (n=117)	30 (25.6%)	57.5 ± 9.3	0.68
p-value	0.04*		

*All p values in comparison to Caucasians. * Significant difference (p<0.05).*

3.3.3. Clinical Presentation

The majority of patients (72%) presented clinically with ACS. Twelve percent (12% with non-specific chest pain, and the remaining 16% with other clinical conditions such as ischemic

cardiomyopathy, positive stress tests, or incidental findings during routine cardiac catheterization (Table 3.2.).

Table 3.2. Clinical presentation for study population per sex and race

Parameter	1st-time presenters with atherosclerotic disease (n=482)						
	ACS (n=348)			Non-specific chest pain n (%)	Ischemic CMO n (%)	Positive stress/mibi n (%)	Incidental atherosclerosis finding n (%)
	STEMI n (%)	NSTEMI n (%)	UA n (%)				
Clinical presentation	171 (35.5%)	112 (23.2%)	65 (13.5%)	57 (11.8%)	36 (7.5%)	10 (2.1%)	31 (6.4%)
Sex							
Male (n=317)	119 (37.5%)	71 (22.4%)	40 (12.6%)	36 (11.4%)	27 (8.5%)	6 (1.9%)	18 (5.7%)
Female (n=162)	50 (30.9%)	40 (24.7%)	25 (15.4%)	21 (13%)	9 (5.6%)	4 (2.5%)	13 (8%)
Unknown (n=3)							
Ethnicity							
Caucasian (n=223)	66 (29.6%)	54 (24.2%)	35 (15.7%)	29 (13%)	14 (6.3%)	8 (3.6%)	17 (7.6%)
Black African (n=112)	39 (34.8%)	22 (19.6%)	10 (8.9%)	20 (17.9%)	13 (11.6%)	0 (0%)	8 (7.1%)
Asian (n=30)	16 (53.3%)	4 (13.3%)	4 (13.3%)	1 (3.3%)	3 (10%)	2 (6.7%)	0 (0%)
Mixed-race (n=117)	50 (42.7%)	32 (27.4%)	16 (13.7%)	7 (6%)	6 (5.1%)	0 (0%)	6 (5.1%)

STEMI = ST Elevation Myocardial Infarction; NSTEMI = Non-ST Elevation Myocardial Infarction; UA = Unstable angina; CMO = Cardiomyopathy.

3.3.4. Modifiable Cardiac Risk Factors

Figure 3.1. illustrates the modifiable cardiac risk factors for the study population. Most patients presented with 3 or more risk factors (n=304; 63%); 27% (n=128) had 2 risk factors, and 10% (n=46) presented with only 1 risk factor for CAD.

Hypertension was the most frequently documented risk factor in all ethnic groups (≥87%) as well as in both male (91%) and female (91%) patients. Hypertension was significantly more common in Black African patients than in Caucasians (96% vs 87%; $p<0.05$). Smoking was the second most common risk factor and occurred in two-thirds of the patients, but significantly more in Caucasians than Black Africans (68% vs 55%; $p<0.05$). Caucasian patients presented with significantly more chronic obstructive pulmonary disease (COPD) than Black Africans (10% vs 2%; $p<0.05$). Smoking was substantially more prevalent in males than females (73% vs 55%; $p<0.05$).

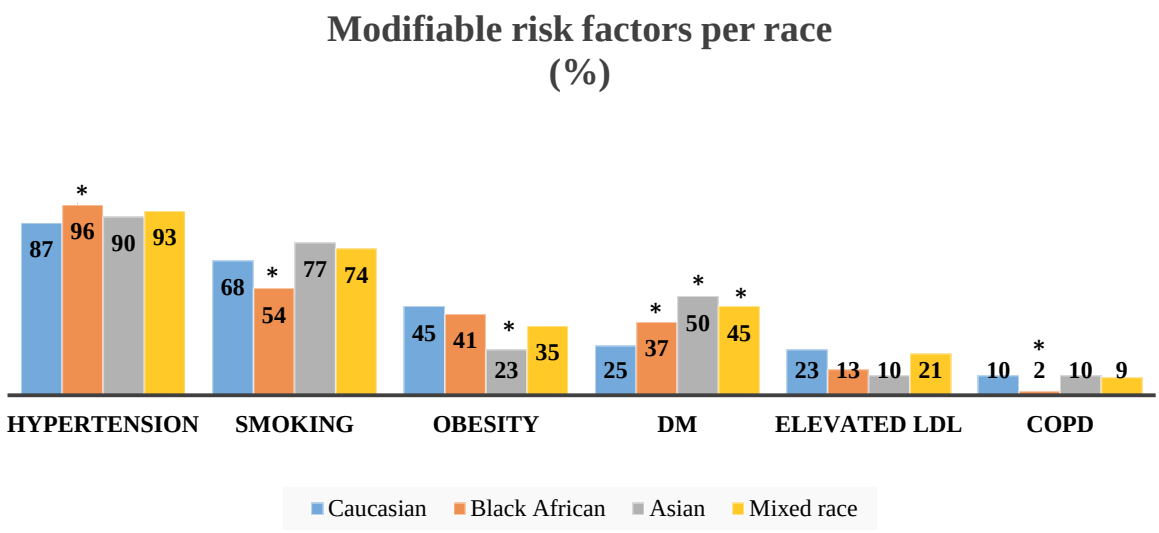

Figure 3.1. Modifiable risk factors per race (*statistically significant <0.05)

The mean BMI for the study population was 30±6.1 kg/m^2; it is noteworthy that 70% of patients were classified as overweight, while 40% of those were obese (BMI ≥30kg/m^2). Asians were significantly less obese compared to Caucasians (23% vs 45%; p<0.05). No sex differences in obesity were observed (Table 3.3).

DM was present in 34% of the study group, of which most presented with type II diabetes (n=128; 78%). No sex differences were observed, yet DM was present in significantly more Black African (37%; p<0.05), Asian (50%; p<0.05) and Mixed-race patients (45%; p<0.05) when compared to Caucasians (25%). Elevated LDL levels (≥3.4mmol/l) were noted more in female patients than male patients (25% vs 16%; p<0.05), yet there were no significant differences among ethnicities (Table3.3).

Table 3.3. Modifiable cardiac risk factors for study population per sex and race

Parameter	Cardiac risk factors of 1st-time presenters with atherosclerotic disease (n=482)					
	HPT	Smoking	Obesity	DM	LDL	COPD
All patients (n=482)	438 (90.9%)	323 (67%)	195 (40.5%)	164 (34%)	94 (19.5%)	38 (7.9%)
Sex						
Male (n=317)	288 (90.9%)	232 (73.2%)	125 (39.4%)	103 (32.5%)	52 (16.4%)	30 (9.5%)
Female (n=162)	148 (91.4%)	89 (54.9%)	70 (43.2%)	61 (37.7%)	41 (25.3%)	8 (4.9%)
Unknown (n=3)	2	2	0	0	1	0
p-value (Fishers exact)	1.0	<0.01*	0.43	0.27	0.03*	0.12
Ethnicity						
Caucasian (n=223)	194 (87%)	152 (68.2%)	101 (45.3%)	55 (24.7%)	51 (22.9%)	23 (10.3%)
Black African (n=112)	108 (96.4%)	61 (54.5%)	46 (41.1%)	41 (36.6%)	15 (13.4%)	2 (1.8%)
p-value (Yates)	0.01*	0.02*	0.54	0.03*	0.06	0.01*
Asian (n=30)	27 (90%)	23 (76.7%)	7 (23.3%)	15 (50%)	3 (10%)	3 (10%)
p-value (Yates)	0.86	0.46	0.04*	<0.01*	0.12	0.96
Mixed-race (n=117)	109 (93.2%)	87 (74.4%)	41 (35%)	53 (45.3%)	25 (21.4%)	10 (8.5%)
p-value (Yates)	0.12	0.29	0.09	<0.01*	0.86	0.74

HPT = hypertension; Smoking includes both current and ex-smokers; LDL ≥3.4mmol/l; Obesity is BMI ≥30kg/m^2; DM=diabetes mellitus; COPD = chronic obstructive pulmonary disease. * Significant difference (p<0.05). *All p values in comparison to Caucasians.*

3.3.5. Acute Coronary Syndrome

3.3.5.1. Clinical Presentation of ACS Patients

Three hundred and forty-eight patients had a confirmed diagnosis of ACS. Almost half of the patients in the ACS group presented with STEMI (49%), followed by NSTEMI (32%) and UA (19%) (Table 3.4).

3.3.5.2. Non-Modifiable Cardiac Risk Factors of ACS Patients

The ACS group of patients had a male preponderance (66%) and were predominantly Caucasian (n=155; 45%). Of note, females with ACS presented at an older age than men (59.7±10 years vs 57±10.6 years; p<0.05). Similar to the findings observed for the total study group with atherosclerosis, Asian patients presented at a younger age than their Caucasian counterparts in the ACS group (48.3±9.2 vs 58.9±10.5; p<0.05). Positive family history was significantly more common in Asians than Caucasians presenting with STEMI (p<0.05).

Table 3.4. Non-modifiable cardiac risk factors for ACS group per clinical diagnosis, age, sex and race

Parameter	ACS patients (n=348)					
	STEMI (n=171)		NSTEMI (n=112)		UA (n=65)	
	n (%)	Age (years) Mean ± SD	n (%)	Age (years) Mean ± SD	n (%)	Age (years) Mean ± SD
Total group (n=348)	171 (49.1%)	56.6 ± 10.4	112 (32.2%)	59.2 ± 11.3	65 (18.7%)	59.1 ± 9
Sex						
Male (n=230)	119 (51.7%)	56.2 ±10.1	71 (30.9%)	58.2 ± 11.9	40 (17.4%)	57.6 ± 9.4
Female (n=115)	50 (43.5%)	57.9 ±10.4	40 (34.8%)	60.9 ± 10.3	25 (21.7%)	61.5 ± 7.8
Unknown (n=3)						
p-value	0.18	0.32	0.54	0.23	0.41	0.09
Ethnicity						
Caucasian (n=155)	66 (42.6%)	57.1 ± 10.2	54 (34.8%)	60.3 ± 11.7	35 (22.6%)	60.0 ± 8.1
Black African (n=71)	39 (54.9%)	57.7 ± 9.4	22 (31%)	60.0 ± 10.6	10 (14.1%)	58.4 ± 4.5
p-value	0.11	0.77	0.68	0.92	0.19	0.55
Asian (n=24)	16 (66.7%)	48.3 ± 9.2	4 (16.7%)	51.3 ± 9.7	4 (16.7%)	45.8 ± 5.9
p-value	<0.05*	<0.01*	0.11	0.14	0.61	<0.01*
Mixed-race (n=98)	50 (51%)	57.7 ± 10.5	32 (32.7%)	57.7 ± 10.9	16 (16.3%)	60.8 ± 10.8
p-value	0.24	0.76	0.85	0.31	0.30	0.77

*All p values in comparison to Caucasian.*Significant difference (p<0.05).*

For the ACS group, regardless of sex and ethnicity, most patients presented in the age interval of 51-60 years (36%). Most Caucasian patients presented in the 61-70 age group (n=57; 37%), while most Black African and Mixed-race patients presented in the 51-60 years age group (n=35; 49% and n=36; 37%) and the majority of Asian patients presented in the age group of 41-50 years (n=10; 42%).

Table 3.5. Age intervals per ACS diagnosis for each ethnic group

Parameter	Age-interval (years)	ACS patients (n=348)					
		STEMI (n=171)		NSTEMI (n=117)		UA (n=65)	
		n (%)	*p-value*	n (%)	*p-value*	n (%)	*p-value*
Caucasian (n=155)	41-50	16 (10.3%)	-	9 (5.8%)	-	5 (3.2%)	-
	51-60	20 (12.9%)	-	15 (9.7%)	-	11 (7.1%)	-
	61-70	23 (14.8%)	-	18 (11.6%)	-	16 (10.3%)	-
	71-80	3 (1.9%)	-	7 (4.5%)	-	3 (1.9%)	-
Black African (n=71)	41-50	5 (7%)	*NC*	4 (5.6%)	*NC*	0	-
	51-60	19 (26.8%)	0.02*	9 (12.7%)	0.66	7 (9.9%)	0.65
	61-70	7 (9.9%)	0.42	5 (7%)	*NC*	3 (4.2%)	*NC*
	71-80	5 (7%)	*NC*	3 (4.2%)	*NC*	0	-
Asian (n=24)	41-50	7 (29.2%)	0.03*	1 (4.2%)	*NC*	2 (8.3%)	*NC*
	51-60	5 (20.8%)	*NC*	1 (4.2%)	*NC*	1 (4.2%)	*NC*
	61-70	1 (4.2%)	*NC*	1 (4.2%)	*NC*	0	-
	71-80	0	-	0	-	0	-
Mixed-race (n=98)	41-50	10 (10.2%)	0.98	7 (7.1%)	0.87	1 (1%)	*NC*
	51-60	18 (18.4%)	0.32	11 (11.2%)	0.89	7 (7.1%)	0.99
	61-70	11 (11.2%)	0.53	9 (9.2%)	0.69	5 (5.1%)	*NC*
	71-80	8 (8.2%)	0.04*	3 (3.1%)	0.80	1 (1%)	*NC*

*All p values in comparison to Caucasian.*Significant difference (p<0.05). NC=not calculated due to small sample size.*

3.3.5.3. Modifiable Cardiac Risk Factors of ACS Patients

As expected, the modifiable risk factors in the ACS group showed similar patterns to that of the total study population.

Most ACS patients presented with three or more vessel disease (STEMI = 53%; NSTEMI = 49%; UA = 43%). There were no racial differences in patients having three-vessel disease presenting with STEMI. One hundred and sixty patients (46%) from the ACS group had PCI (balloon angioplasty/stent), 75 patients (22%) were referred for CABG surgery, 82 patients (24%) received only medical therapy, and 31 patients (9%) treatment was not recorded.

3.4. Discussion

Non-communicable diseases are the second most common cause of death in Sub-Saharan Africa, with CVD documented as the leading cause of death (Yuyun et al., 2020). This is the only recent study in central South Africa that describes current cardiac risk factors for patients with angiographically confirmed CAD. The main findings of this study showed that cardiovascular risk factors occur in all population groups and concur with risk factors documented worldwide. The majority of the patients included in this study (90%) were from low socio-economic status groups (H0-H2). The study demonstrated that coronary artery atherosclerosis is present in all ethnic

groups in central South Africa. CAD occurred most frequently in males, who presented 2.9 years younger than females.

Our results concur with the INTERHEART study (Steyn et al., 2005) and a study conducted by Masina et al. (2017), which also demonstrated a male preponderance (75% and 85%, respectively) with males presenting three years earlier compared to female patients. Compared to the other ethnic groups in our study, Asian patients presented significantly younger. Similar findings were reported by Patil et al. (2020) in a study conducted in rural India, where 41.8% of patients with premature CAD were under the age of 35.

Classic modifiable cardiac risk factors were observed in all ethnic groups in central South Africa. Numerous risk factors were present, with most patients having three or more risk factors (63%). Hypertension was the most prevalent modifiable risk factor in the total study population and occurred in ≥87% of all patients, significantly more in Black African patients. Smoking, or a history of smoking, was reported in 67% of patients, followed by obesity (40%), diabetes mellitus (34%) and elevated LDL levels (20%).

The high prevalence of modifiable cardiac risk factors, especially hypertension, in our central South African group is cause for concern. Despite the differences in methodology, hypertension was markedly higher than that reported in INTERHEART (Steyn et al., 2005) and Masina et al. (2017) (21.9% and 46%, respectively). Cognizance should be taken that INTERHEART (Steyn et al., 2005) included patients from 9 countries in Sub-Saharan Africa (1107 of 1363 were from South Africa) and Masina et al. (2017) studied 94 Black patients with acute myocardial infarction (AMI). Interestingly, hypertension occurred in 50% of Black patients in the INTERHEART (Steyn et al., 2005) study, which was higher compared to the 34% of the European/other African cases (Steyn et al., 2005). This supports our observation that hypertension appears to be a significant risk factor in Black patients with coronary artery atherosclerosis. Our results agree with Loock et al. (2006), demonstrating an 88.8% hypertension prevalence in 89 cases of coronary heart disease in rural Black South Africans attending the Kalafong Hospital between 1982 and 1986. Hypertension showed no significant differences between sexes, as supported by Bosu et al. (2019) evaluating hypertension in older adults in Africa.

Geographical differences may also exist; in a study on risk factors in central South Africa conducted in 1990, the authors showed that a blood pressure of >140/90 mmHg was present in more than 70% of males and females over the age of 55 years (Mollentze et al., 1995).

Smoking was frequently observed and was the second most common modifiable risk factor in the patient population (67%). This resembles the findings of Patil et al. (2020), where a prevalence of 60.4% smoking history was observed. Similar results were also reported by INTERHEART (Steyn et al., 2005), where smoking/ex smoking was present in 65% of cases in the overall group and 72% of patients from Africa. However, these results are in contrast with Masina et al. (2017), observing a population in Kwa-Zulu Natal, South Africa, where smoking was the most common modifiable risk factor but with a 48% prevalence, which is also high but lower than our findings. The high prevalence of smoking is not unexpected, as several studies have reported a high prevalence of smoking (Arshad & Pasha, 2013; Patil et al., 2020; Stewart et al., 2011; Mollentze et al., 1995). Our results showed that males smoked significantly more than females, which has also been observed in several other studies (Alberts et al., 2005; Mollentze et al., 1995; Onen, 2013; Xavier Gómez-Olivé et al., 2018).

Asian populations were significantly less obese than the other ethnic groups. However, no statistical differences were observed between the sexes in all groups. Notably, 70% of all patients with coronary artery atherosclerosis in our study were overweight, of which 40% were obese (BMI of $\geq 30 kg/m^2$). The presence of overweight and obesity is remarkably similar to the Heart of Soweto study findings (Sliwa et al., 2008), where 70% of their adult population were also overweight. However, their study showed that more females than males were overweight, and is supported by several other studies (Loock et al., 2006; Mollentze et al., 1995; Alberts et al., 2005). The African cohort in the INTERHEART study had an average BMI of $27.59 kg/m^2$ (overweight), higher than that of the overall group, emphasizing the high prevalence of this modifiable problem in Sub-Saharan Africa (Steyn et al., 2005).

Diabetes is a noteworthy risk factor in our study population. Similar to Kabongo et al. (2018), who observed a South African population with NSTEMI, a prevalence of 39.3% of diabetes was observed, while 34% of our patients had diabetes. DM was significantly more common in Black

African, Asian and Mixed-race patients, comparable to the reported results of Masina et al. (2017). More females than males had elevated LDL levels, which concur with other studies (Duda-Pyszny et al., 2018; Xavier Gómez-Olivé et al., 2018; Mollentze et al., 1995).

Although this study did not focus on metabolic syndrome, the high prevalence and combination of hypertension, obesity, diabetes and hypercholesterolemia in our population is cause for concern. Masina et al. (2017) recorded metabolic syndrome in 45% of their patients studied.

Clinical Presentation

This study shows that 72% of patients with coronary artery atherosclerosis presented with ACS. STEMI was the most common clinical presentation and accounted for nearly half of the ACS patients (49%). Our results are lower than the 83% ACS cases observed by Masina et al. (2017) but higher than that of Shavadia et al. (2012) (56%), who described 111 patients with ACS in an Urban Hospital in Sub-Saharan Africa, and Sookan et al. (2018) (63%), who studied 117 patients with acute MI at a hospital in Kwa-Zulu Natal.

The ACS group mainly consisted of male patients (n=230; 66%), similar to studies by Shavadia et al. (2012), Maharaj et al. (2012), Meel & Gonçalves (2016) and Sookan et al. (2018), who also demonstrated a high male prevalence (80.6%; 66.5%; 70%; 70%). Overall, Asians presented significantly younger in the STEMI and UA groups than other ethnicities. The Worldwide INTERHEART (Steyn et al., 2005) study reported a mean age of 58 years, while the African INTERHEART (Steyn et al., 2005) study population had a mean age of 54 years for myocardial infarctions; therefore, patients in Africa appear to be younger (Steyn et al., 2005). Of note, the sub-analysis results of modifiable and non-modifiable risk factors in the ACS group were virtually indistinguishable from the results of all patients with radiologically confirmed coronary artery atherosclerosis.

Based on our patients' non-modifiable and modifiable risk profiles, we postulate that central South Africa may be in the process of an epidemiological transition phase with subtle differences among the various ethnic groups. It is also evident that classical risk factors are responsible for CVD in all the ethnic groups represented in the study. Hypertension and smoking in patients in central

South Africa appear to be significant risk factors in all ethnic groups and emphasize the need for screening and patient education. Our study shows that CAD occurs in all ethnic groups and that STEMI is the dominant clinical presentation. Therefore, this diagnosis should be considered in any patient presenting with chest pain and should not be ignored in patients of any ethnicity. The results of this study emphasize the importance of epidemiological studies such as these, especially if certain risk factors may be region-specific. Data such as this is essential for healthcare providers planning and organizing service delivery. It highlights preventable areas that regional and primary healthcare services should target. Primary healthcare services in central SA should prioritise hypertension education and screening.

3.5. Limitations

Limitations of this study relate to its retrospective nature and the fact that it was a relatively small study population. Results for smaller subgroups need to be interpreted cautiously as 34% of files were not used due to incomplete data, which may influence results. However, the African group in the INTERHEART (Steyn et al., 2005) study conducted in 2005 included 373 patients. Masina et al. (2017) studied 94 patients compared to our 482 total study population and 348 ACS patients. In neither of these studies, angiography was performed, whilst all patients in our study had coronary angiograms. Although only patients with angiographically significant atherosclerosis were included, the degree of obstruction was not quantified – this would have added value to the study. This study did not investigate the prevalence of human immunodeficiency virus (HIV) and its contribution to premature CAD in ethnic groups.

3.6. Conclusion

This study demonstrates that CAD in South Africa is present in all ethnic groups and modifiable and non-modifiable risk factors seen in this study are similar to the classical risk factors described for CAD in the rest of the world. Hypertension is a significant risk factor in central South Africa and warrants further investigation. Most patients with proven coronary artery atherosclerosis presented with ACS, particularly STEMI. The average age of patients with ACS was younger than those documented in the rest of the world but similar to recorded data for Sub-Saharan Africa. Regional epidemiological studies similar to this are essential for planning health services and increasing awareness of CAD.

3.7. List of Abbreviations

ACS	Acute Coronary Syndrome
BMI	Body Mass Index
CAD	Coronary Artery Disease
CMO	Cardiomyopathy
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
HIV	Human Immunodeficiency Virus
HPT	Hypertension
LDL	Low Density Lipoproteins
MI	Myocardial Infarction
NSTEMI	Non-ST Elevation Myocardial Infarction
SA	South Africa
STEMI	ST Elevation Myocardial Infarction
UA	Unstable Angina
UAH	Universitas Academic Hospital

3.8. References

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Chapter 4 - General Conclusion

This study is the first of its kind conducted in central South Africa, describing the modern-day risk factors for ischemic CAD based on coronary angiographic diagnosis. This study highlighted CAD being present in all ethnic groups and ages. The modifiable and non-modifiable risk factors observed correspond with the classic risk factors described for CAD in the rest of the world.

More than half of the patients from the Free State resided outside the Mangaung Metropolitan District, in rural areas and small towns. This is an important finding since these patients do not have quick access to emergency cardiac care facilities.

Females with CAD presented at an older mean age than males. The female population in our country tend to ignore the signs of ischemic heart disease, unlike their male counterparts which could account for our study's predominantly male population and differences in age at presentation. Further studies are needed to address the lack of understanding of the signs and symptoms of AMI in the central SA population, particularly in our female population.

A large portion of the study population had a combination of three or more risk factors for CAD, which increases the chances (and severity in most cases) of developing CAD at an earlier age. Hypertension is the most prominent risk factor in central South Africa for all ethnic groups, particularly Black Africans, in both males and females. More attention needs to be placed on early diagnosis and proper treatment to decrease the risk of developing CAD. Hypertension is a worldwide phenomenon, and several studies have proven that hypertension prevalence is on the rise in Sub-Saharan Africa. Hypertension has been a significant concern in our central South Africa population with CAD as early as 1995. More effort needs to be placed on hypertension awareness and treatment, particularly in our rural populations, to reduce the morbidity and mortality from this very treatable risk factor for CAD.

Smoking is also a significant risk factor that should not be ignored, particularly in males and our younger population. Many individuals are unaware of the effects of smoking on the body; individuals tend to think that smoking is a harmless habit with no adverse side effects. Elevated LDL levels are a major concern for females. The population lacks knowledge of it as it is not something the individual is aware of, unlike the other common risk factors such as hypertension and obesity. Due to the considerable rate of urbanization occurring in South Africa, obesity has become a prominent issue, especially among the Caucasian, Black African and Mixed-race individuals, along with diabetes which was more commonly observed in Black Africans, Asians and Mixed-race individuals.

The majority of patients in all ethnic groups with proven coronary artery atherosclerosis presented with ACS, particularly STEMI. Males and females had similar prevalence rates in all ACS groups and the average age of females in the ACS group was consistently older than that of the males. Therefore, it is of utmost importance that any form of chest pain syndrome should not be ignored in any ethnic group, both in males and females. We can speculate that due to a lack of education and awareness of the common signs and symptoms of CAD and the risk factors thereof are ignored. Our population does not understand the importance of treating the risk factors before CAD is so severe that they suffer an acute MI, which can be fatal.

Nearly half of the patients with ACS had PCI performed, and 22% were referred for CABG surgery, which means that the degree of disease observed in our population was considerable.

Limitations

Limitations of this study include the record-keeping of medical files for our patients, as only 482 of the 725 could be used for this study as 243 files were either missing or had incomplete information. Another limitation is that the angiographic reports were not specific regarding the degree and severity of CAD in each patient.

Recommendations

Regional epidemiological studies such as these are important for the planning and implementation of health services and increasing awareness and patient education of CAD in central South Africa.

It is recommended that screening and patient education should be a priority for our country's healthcare system, particularly in rural regions. Hypertension, in particular, should be identified and treated at an early age in all ethnic groups. If a larger portion of our population has knowledge about the risk factors for CAD and realise the importance thereof, we may see a decrease in the morbidity and mortality of CAD. Many of the risk factors for CAD are lifestyle-related diseases that can be improved with changes in diet and lifestyle; therefore, patient education is essential. It is also recommended that education on CAD should not only be limited to patients. The nurses and doctors treating these patients in the rural areas and clinics must be informed of the risk factors and prevalence thereof to improve treatment strategies. The planning of healthcare services can be adjusted to treat our patients before CAD progresses to such an extent that medical intervention is required.

Chapter 5 - References

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Chapter 6 - Appendices

Appendix A: HSREC Approval Letter

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

10-Sep-2019

Dear **Miss Michelle Whittemore**

Ethics Clearance: **Contemporary risk factors associated with ischemic heart disease in central South Africa: a single center study**

Principal Investigator: **Miss Michelle Whittemore**

Department: **Clinical Technology - CUT**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/1351/0110**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
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Appendix B: Approval from HOD

Central University of Technology, Free State

FACULTY OF HEALTH AND ENVIRONMENTAL SCIENCES

2019-06-19

Health Science Research Ethics Committee (HSREC)

Master of Health Sciences in Clinical Technology

Dear HSREC

Ms M Whittemore (student no: 214038602) is a registered Masters student in Clinical Technology at the Central University of Technology in the program Clinical Technology.

The title of her research dissertation is:
Contemporary risk factors associated with ischemic heart disease in Central South Africa: a single-centre study

Her evaluation committee was conducted at 29/05/2019 and approved.

If you need any additional information, please do not hesitate to contact me.

Kind Regards

Mr D Mokgawa
Acting Head of Department: Health Sciences

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