Association between carotid intima-media thickness and patient outcomes in coronary artery disease in central South Africa

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Declaration of Independent Work

I, Victor Teboho Mokoena, do hereby declare that this research project submitted to the Central University of Technology for the degree MASTERS 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 fulfilment of the requirements for the attainment of any qualification.

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Executive Summary

Background

Acute coronary syndrome (ACS) is the most common form of cardiovascular disease (CVD), with 17.6% being the rate of death in South Africa and 31% (17.9 million) globally. Carotid intima-media thickening (CIMT) is an imaging technique that allows non-invasive assessment of vascular anatomy using B-mode (Bright mode) ultrasound. In multiple studies, carotid intima-media thickness (IMT) has been shown to predict cardiovascular (CV) risk.

An increase in carotid intima-media thickness may result from hypertrophy of the intimal or medial layers or both. Cellular and molecular mechanisms that increase CIMT are also responsible for the development and progression of atherosclerosis. CIMT evaluation is a safe, non-invasive, and cost-effective method to detect early atherosclerotic vascular diseases.

However, the application of CIMT as a measure of adverse events following coronary artery bypass surgery (CABG) is not well described in the literature. The aim of this study is to determine the pre-operative CIMT values (CABG) and establish whether an association exists between pre-operative CIMT and outcomes in ACS patients undergoing coronary artery bypass surgery in central South Africa.

Methods

This retrospective analytical cohort study was conducted at Universitas Academic Hospital (UAH) within the Department of Cardiothoracic Surgery. Universitas is a state/private hospital located in Bloemfontein, the capital city of the Free State, South Africa.

The clinical data of 89 ACS patients with recorded CIMT measurements were included in the study. The study group (n=89) was divided into two cohorts, group 1 and group 2. Group 1 included patients with normal CIMT values (<0.070 cm) and group 2 patients with abnormal CIMT values (≥0.070 cm). The medical records of all patients with a measured CIMT that received

CABG surgery from 2008 to 2014 were evaluated. Pre-operative risk factors, intra-operative risk factors, and post-operative complications were recorded.

Results

The study included 89 patients, of which 77 (86.5%) were male and 12 (13.5%) female. As expected, the CIMT differs significantly between group 1 and group 2 (p-value <0.0001) in terms of categorising normal and abnormal reference ranges for CIMT between groups. Pre-operative mean body mass index (BMI) was significantly higher (p=0.03) in group 2 than in group 1 (29.2 kg/m^2 vs 26.6 kg/m^2). Patients in group 2 had significantly more diabetes (p=0.008), hypertension (p=0.009) and an increased NT pro-BNP (p=0.02) than patients in group 1. The intra-operative and post-operative variables between groups were comparable, with no significant differences.

Conclusion

Currently, no studies have evaluated the outcomes of patients who present with an elevated pre-operative CIMT undergoing CABG surgery. There are significant and acceptable traditional pre-operative risk factors correlating with CIMT, although the study could not demonstrate an assosiation with intra- and post-operative outcomes. In this population, CIMT does not correlate with adverse patient outcomes and cannot be used as a tool to predict post-operative adverse events.

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List of Abbreviations and symbols

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ARIC	Atherosclerosis Risk In Communities
ASE	American Society of Echocardiography
BMI	Body Mass Index
BSA	Body Surface Area
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCA	Common Carotid Artery- Intima Media Thickening
CCA-IMT	Common Carotid Artery
CHD	Coronary Heart Disease
CIMT	Carotid Intima-Media Thickening
CK-MB	Creatinine Kinase-MB
cm	Centimetre
CO_2	Carbon Dioxide
CPB	Cardiopulmonary Bypass
CVD	Cardio Vascular diseases
DAPT	Dual Antiplatelet Therapy
DES	Drug-Eluting stent
DM	Diabetes Mellitus
EDV	End Diastolic Volume
ESV	End Systolic Volume
EUROSCORE	European System for Cardiac Operative Risk Evaluation

EUROSCORE II	European System for Cardiac Operative Risk Evaluation II
GM-GSF	Granulocyte-macrophage colony-stimulating factor
HDL	High Density Lipoprotein
HDLc	High Density Lipoprotein cholesterol
HSREC	Health Science Research Ethics Committee
ICAM-1	Intercellular Adhesion Molecule 1
ICU	Intensive Care Unit
IMT	Intima-Media Thickening
Kg/m^2	Kilogram per square metre
LDL	Low-Density-Lipoprotein
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
M-CSF	Macrophage Colony-Stimulating factor
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial Infraction
MONICA	Monitoring trends and determinants in cardiovascular disease
MORGAM	MONICA Risk, Genetics, Archiving, and Monograph
NHLS	National Health Laboratory Service
NIRS	Near-Infrared Spectroscopy
NSTEMI	Non-ST elevation Myocardial-Infarction
NT-proBNP	N-Terminal-pro-B-type Natriuretic Peptide
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
rSO2	Regional Brain Saturation
SA	South Africa
SBP	Systolic Blood Pressure
SD	Standard Deviation

SIRS	Systemic Inflammatory Response Syndrome
SOP	Standard Operating Procedure
SSA	sub-Saharan Africa
STEMI	ST-Elevation Myocardial Infarction
STS	Society of Thoracic Surgeons
SVR	Systemic Vascular Resistance
TTE	Transthoracic Echocardiograms
UFS	University of the Free State
VCAM-1	Vascular Cell Adhesion Molecule 1
WHO	World Health Organisation

SYMBOLS

%	Percent
<	Less than
=	Equals
>	Greater than
±	Plus minus
≥	Equal or greater than

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Chapter 1- INTRODUCTION

As nations develop, previous third-world countries are now finding themselves in a second to first-world environment riddled with an increased risk of developing cardiovascular disease (CVD) due to lifestyle changes. According to the World Health Organisation (WHO), these lifestyle factors dramatically increased the number of cardiovascular deaths globally, with an estimated 17.9 million deaths from CVDs in 2019, representing 31% of all global deaths. In sub-Saharan Africa, non-communicable diseases are the second most common cause of death, accounting for 2.6 million deaths, equivalent to about 35% of deaths (Yuyun et al., 2020).

Acute coronary syndrome (ACS) is the umbrella term used for the clinical signs and symptoms of myocardial ischemia; unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), and any other manifestations which are the result of sudden myocardial ischemia (Smith & Negrelli, 2015). Atherosclerosis is the leading cause of vascular diseases, contributing to ACS development (Herrington et al., 2016). Evaluating atherosclerotic lesions in the carotid and peripheral arteries are mainly conducted by performing contrast angiography, an invasive method (Paech & Weston, 2011). In the 1980s, other approaches entailed taking tissue specimens to be examined microscopically to examine and measure arterial wall thickness. However, these methods are invasive and may be associated with increased risk and complication rates (Pignoli et al., 1986).

Carotid intima-media thickness (CIMT) measures the combined thickness of the intima and media layers of the carotid artery, most commonly assessed by B-mode (bright mode) ultrasound (Zhang et al., 2014). An increase in carotid intima-media thickness may result from hypertrophy of the intimal or medial layers or both. Cellular and molecular mechanisms that increase CIMT are also responsible for the development and progression of atherosclerosis (Kasliwal et al., 2014). CIMT analysis is a safe, non-invasive, and cost-effective method to detect early atherosclerotic vascular diseases. As CIMT is regarded as a marker predicting early stages of the atherosclerotic process (Liu et al., 2020), and atherosclerosis causes CAD leading to CABG surgery, it is important to determine the association between CABG surgery outcomes and CIMT. This knowledge will significantly contribute to pre-operative risk factor analysis and potentially contribute to a more accurate prediction of patient outcomes whilst improving intra-operative patient care.

Near-infrared spectroscopy (NIRS) monitors brain tissue oxygen saturation to evaluate the balance between brain oxygen supply versus consumption (Vretzakis et al., 2013). NIRS has been extensively used in cardiac surgery patients to determine the association between cerebral oxygenation measurements and post-operative outcomes (Scheeren et al., 2012). Murkin et al. (2007) found an association between intra-operative cerebral oxygen desaturation and post-operative cognitive dysfunction, stroke, and prolonged hospital stay. The influence of thickened carotid intima on a patient's baseline NIRS value will provide us with a better understanding of the correlation of these variables to patient outcomes after cardiac surgery.

The aim of this study is to determine the pre-operative CIMT values in ACS patients undergoing coronary artery bypass surgery (CABG) by evaluating if a correlation exists between pre-operative atherosclerotic burden and pre-, intra- and postoperative outcomes and complications in patients diagnosed with ACS. NIRS will be used to evaluate the relationship between CIMT thickness and cerebral oxygen saturation.

Aims and objectives

The aim of this study was to investigate whether pre-operative CIMT measurements in ACS patients undergoing elective CABG surgery affect intra- and post-operative surgical outcomes.
Objectives:

- Identify all ACS patients with a pre-operative CIMT measurement between January 2008-November 2014 from the Cardiothoracic database.
- Compare the CIMT values between gender and race.
- Correlate the CIMT value with the pre-operative patient risk factors.
- Correlate the CIMT value with the intra-operative data.
- Correlate the CIMT value with patient post-operative outcomes.

Chapter 2 – LITERATURE REVIEW

2.1 BACKGROUND

In 2010, cardiovascular disease mortality in sub-Saharan Africa was 892 deaths per 100,000 people. The combined fatal and non-fatal burden of disease was 18,825 disability-adjusted life years per 100,000 people. For this reason, CVD contributes to the highest death and disability rate of the top 10 CVDs in sub-Saharan Africa (Keates et al., 2017).

Atherosclerosis is the most frequent cause of CAD and underlies most ACS. ACS can be treated pharmacologically or surgically. Pharmacological treatment involves the use of statins (Rosenson et al., 2018), antithrombotics and antihypertensive drugs. Surgically, myocardial revascularisation can be done using coronary artery bypass surgery or percutaneous coronary intervention to restore blood flow to the area distal to the blockage (Hamilton et al., 2013).

The measurement of CIMT has been demonstrated as a marker for the presence (Geroulakos et al., 1994), risk (Kitagawa et al., 2007) and extent (Kablak-Ziembicka et al., 2004) of CVD. Several studies (Bots et al., 2016; Saxena et al., 2017) have validated the application of this imaging technique because it can detect slight changes over time associated with future cardiovascular events.

2.2 ACUTE CORONARY SYNDROME (ACS)

2.2.1 Definition

CAD is the leading cause of mortality in Westernised countries (Mills et al., 2016). ACS can be defined as a constellation of clinical presentations ranging from those with (i) unstable angina, (ii) non-ST-elevation myocardial infarction (NSTEMI) and (iii) ST-elevation myocardial infarction (STEMI). The three clinical conditions have similar pathophysiologies, but each condition presents with specific clinical features, therapies, and prognoses (Lusis, 2010).

Acute thrombosis can contribute to ACS development and can be aggravated by a ruptured or eroded atherosclerotic plaque, which can occur with or without vasoconstriction. This can lead to partial or total occlusion in blood flow to the myocardium, causing ischemia, injury, or infarction (Alfarisi et al., 2020).

2.2.2 Aetiology of acute coronary syndrome

Fibrous plaque formation or thrombosis can cause occlusion of a coronary artery, thus decreasing or impeding blood flow to the myocardium. Atherosclerosis is the leading cause contributing to the formation of these plaques or thrombi (Insull, 2009).

2.2.2.1 Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of large- and medium-sized arteries, characterised by subendothelial accumulation and subsequent oxidative modification of lipoproteins, immune cells, and the extracellular matrix (Libby, 2012). Atherosclerosis is characterised by the accumulation of fatty deposits, platelets, neutrophils, monocytes, and macrophages throughout the tunica intima (endothelial cell layer) and eventually into the tunica media (smooth muscle layer). The arteries most often affected are the coronaries, aorta and the cerebral arteries (Aziz, 2016) due to high blood pressure and arterial vessel tortuosity in these regions (Ciurică et al., 2019). Atherosclerosis progresses relentlessly before ultimately manifesting as an acute ischemic event (Kumar & Cannon, 2009).

2.2.2.2 Pathophysiology of atherosclerosis

Atherosclerosis is caused by endothelium dysfunction and can be caused by various factors (Hamad et al., 2020). Deleterious modifications in the physiology or metabolism of endothelial cells initiate the development of atherosclerosis, and the development of plaque and the occurrence of atherosclerosis (Yang et al., 2020). The sequential event includes focal permeation, trapping, and physicochemical modification of circulating lipoprotein particles in the sub-endothelial space constructing an inflammatory lesion (Linton et al., 2019).

Once endothelium damage occurs, the inflammatory cells, mainly monocytes, migrate into the sub-endothelium by binding to endothelial adhesion molecules. Once in the sub-endothelium, they undergo differentiation, becoming macrophages. Macrophages digest oxidised low-density lipoproteins (LDL) that penetrate the arterial wall, transforming into foam cells and causing fatty streak formation (Ross, 1999).

The formation of atherosclerosis occurs in four stages (Stage I-IV), as summarised below.

Stage I: Endothelial dysfunction

The normal vascular endothelium is taken as a gatekeeper of cardiovascular health. In contrast, abnormal vascular endothelium contributes significantly to many cardiovascular ailments, such as atherosclerosis, ageing, hypertension, obesity, and diabetes (Sun et al., 2020).

The endothelium regulates vessel tonus through vasoactive substances (nitric oxide, endothelin and cycloxygenase). Besides regulating vessel tonus, endothelial cells are also responsible for; (i) the regulation of cell adhesion, (ii) tissue growth and metabolism, (iii) angiogenesis, (iv) inflammatory responses, (v) vessel integrity, hemostasis, (vi) vascular permeability, (vii) vascular smooth muscle cell proliferation, (viii) platelet activation and (ix) thrombus formation (Boulanger, 2016).

Damage to the endothelium upsets the balance between vasoconstriction and vasodilation and initiates a number of events/processes that promote or exacerbate atherosclerosis. These events are summarised in figure 2.1 and include:

- increased endothelial permeability,
- hemodynamic stress-induced damage (Franck et al., 2019) causing platelet aggregation (Patzelt et al., 2015),
- leukocyte adhesion is triggered by the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) (Habas & Shang, 2018) and
- the generation of cytokines and monocyte adhesion to the endothelium.

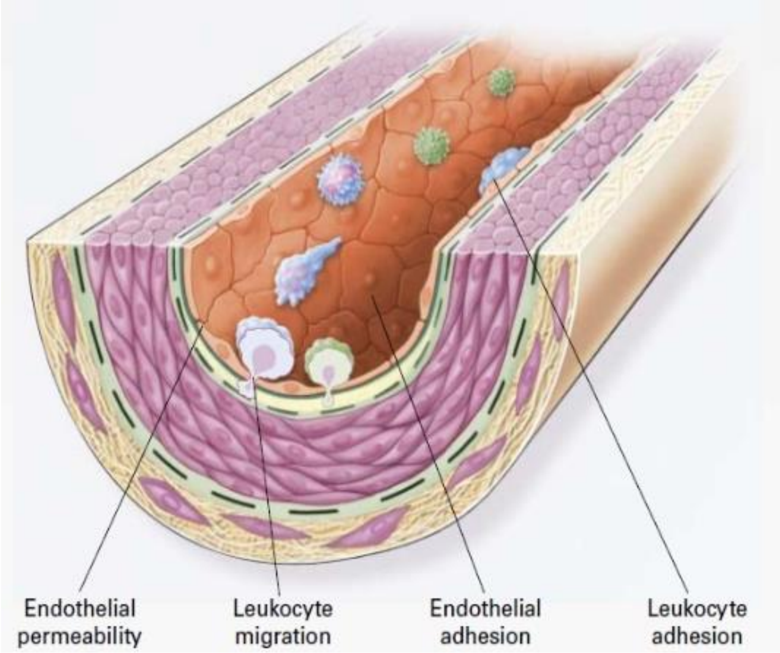

Figure 2.1 Pathophysiology of atherosclerosis- Stage I: endothelial dysfunction in atherosclerosis development (adapted from Ross, 1999)

Stage II: Fatty-streak formation

Endothelial activation triggers platelet aggregation and monocyte adhesion, followed by the secretion of chemokines (monocyte chemoattractant protein-1). Platelet aggregation occurs when platelets are activated. These platelets adhere to the endothelial monolayer and release inflammatory mediators. Platelet-derived inflammatory mediators promote activation of the endothelial monolayer and recruitment of circulating blood cells, including monocytes and endothelial progenitor cells. These cells signal additional inflammatory mediators to the compromised area (Franck et al., 2019). The chemokines recruit circulating monocytes to transmigrate into the intima. The monocytes differentiate into macrophages in response to macrophage colony-stimulating factor (M-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Čejková et al., 2016) (Figure 2.2).

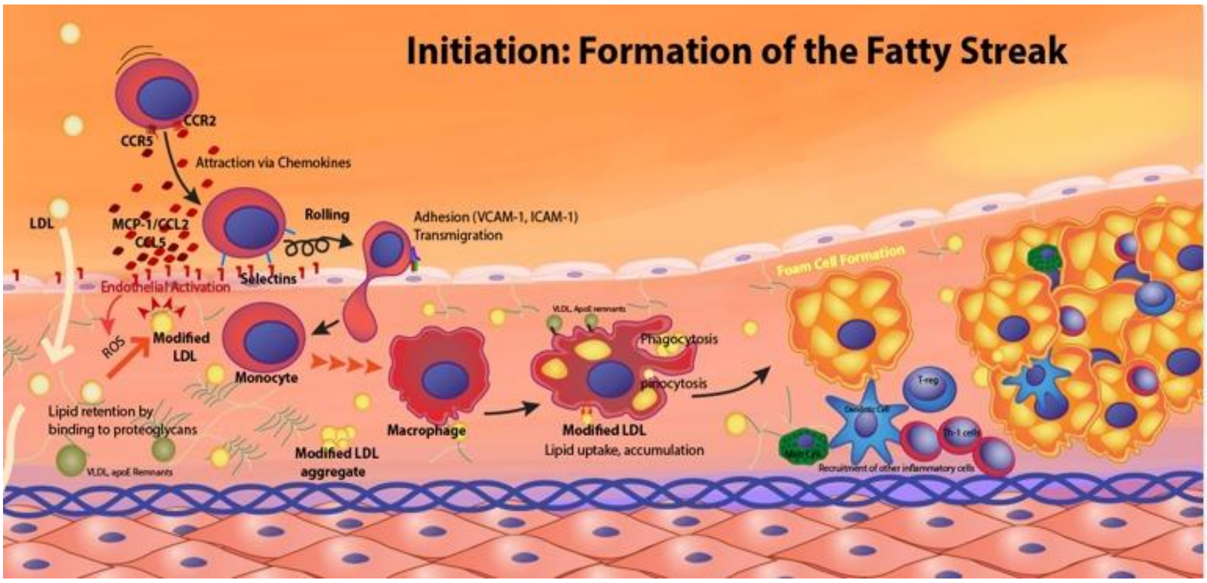

Figure 2.2 Transmigration of monocytes into the intima (adapted from Linton et al., 2019)

Cholesterol-carrying low-density lipoproteins (LDL) stimulate innate and adaptive immune responses. Fatty streaks initially consist of lipid-laden macrophages (foam cells) caused by oxidatively-modified LDL, consisting of protein components modified by aldehyde products. Negative charges are created that render the oxidised LDL very attractive to macrophages (Ganesan et al., 2018). Exaggerated macrophage phagocytosis of accumulating lipids in arterial walls leads to the formation and accumulation of foam cells (Colin et al., 2014). The accumulation of the oxidised LDL in macrophage-derived foam cells directly affects foam cell migration. It increases focal adhesion kinases, which drives foam cell accumulation in the arterial intima (Lu & Weiser-evans, 2019).

Although macrophages are the primary infiltrating cells, other cells contribute to the development of atherosclerotic lesions, including dendritic cells, mast cells, T cells, and B cells (Libby, 2012). Adaptive immunity is mediated by T cells and B cells, which recognise modified auto-antigens presented by antigen-presenting cells, such as macrophages or dendritic cells (Bartlett et al., 2019). T cells are among the first to be recruited into the atherosclerotic lesion and are later accompanied by numerous smooth-muscle cells (Minelli et al., 2020) (Figure 2.3).

The lesion will progress to fibrotic plaques due to continued inflammation and the macrophage chemoattractants will stimulate the infiltration and proliferation of vascular smooth muscle cells. The smooth muscle cells produce the extracellular matrix, thus providing a stable fibrous barrier between plaque prothrombotic factors and platelets (Basatemur et al., 2019)(Figure 2.3).

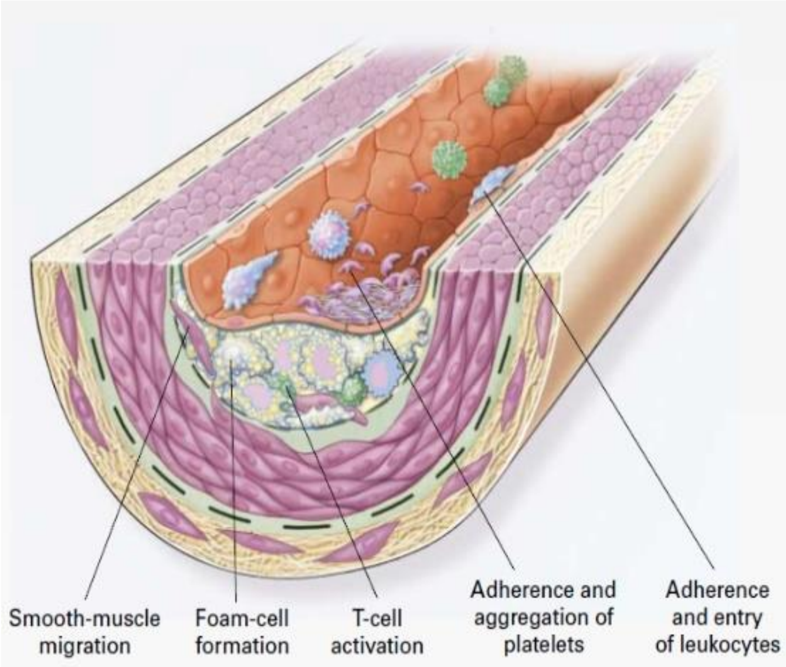

Figure 2.3 Stage 2: Fatty-streak formation in atherosclerosis (adapted from Ross, 1999)

Stage III: Formation of an advanced, complicated lesion of atherosclerosis

Figure 2.3 illustrates fatty streak progression to intermediate and advanced lesions. It forms a fibrous cap that walls off the lesion from the lumen. This represents a type of healing or fibrous response to the injury. The fibrous cap covers a mixture of leukocytes, lipids, and debris, which may form a necrotic core (Gonzalez & Trigatti, 2017).

The triggering of the macrophage inflammatory pathways and the accumulation is also a critical event in lesion development. The principal factors associated with macrophage accumulation include macrophage colony-stimulating factor, monocyte chemotactic protein 1, and oxidised LDL (Figure 2.4). The necrotic core results from apoptosis and necrosis, increased proteolytic activity, and lipid accumulation (Gonzalez & Trigatti, 2017). The fibrous cap forms due to increased activity of platelet-derived growth factor, transforming growth factor b, interleukin-1, tumour-necrosis factor-alpha (Colin et al., 2014).

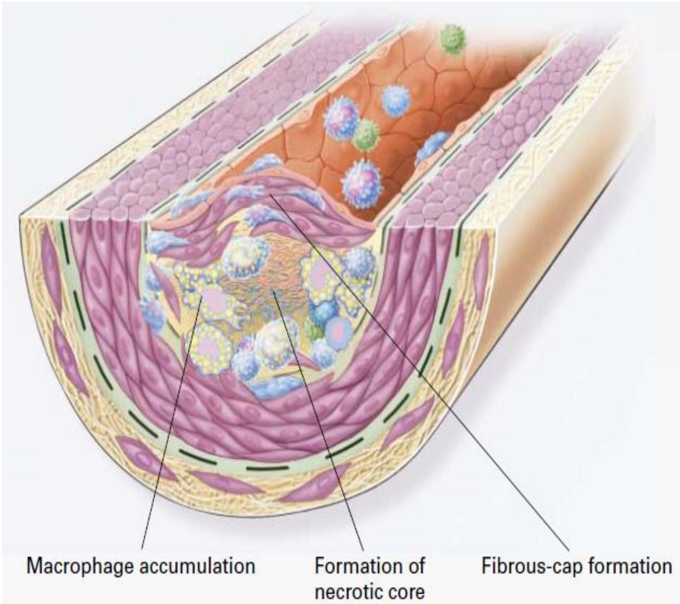

Figure 2.4 Stage 3: Formation of an advanced, complicated lesion of atherosclerosis (adapted from Ross, 1999)

(D) Stage 4: Unstable fibrous plaques in atherosclerosis

Slowly growing plaques expand gradually due to lipid accumulation in foam cells and the migration and proliferation of smooth muscle cells (Basatemur et al., 2019). These plaques tend to stabilise because of the vascular smooth muscle cells that synthesise structurally important collagens that provide stability to the plaque and are not prone to rupture and the fibrin cap on the lesion matures. In contrast, other plaques grow more rapidly because of rapid lipid deposition and inflammatory cells that release matrix metalloproteinases, which degrade collagen and extracellular matrix, potentially weakening the plaque. These have thin fibrin caps that are prone to rupture (Figure 2.5) (Dave et al., 2013). Neutrophils also further increase inflammation by releasing pro-inflammatory molecules, such as tissue necrosis factor-α, interleukin-1, 6, 8 and granulocyte-macrophage colony-stimulating factors, well as the pro-oxidant enzymes, setting the stage for plaque disruption, acute thrombosis with subsequent vascular occlusion (Silvestre-Roig et al., 2020).

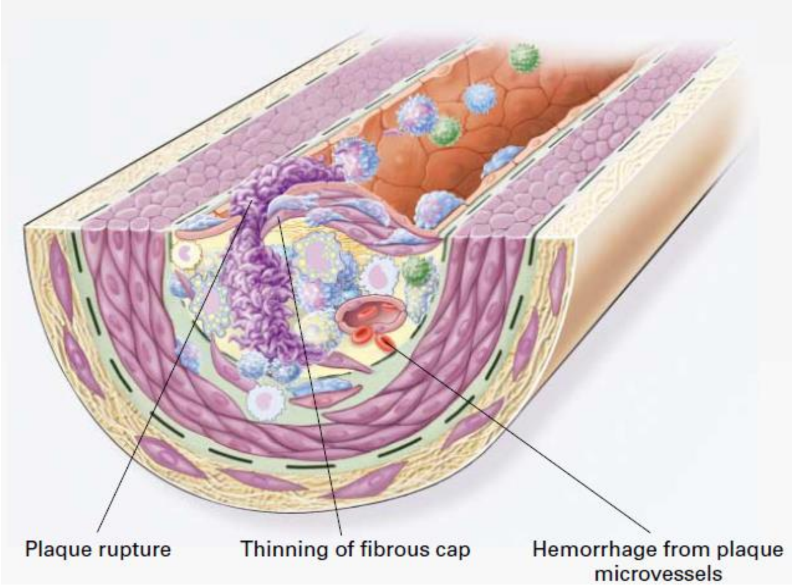

Figure 2.5 Pathophysiology of atherosclerosis Stage 4: unstable fibrous plaques in atherosclerosis (adapted from Ross, 1999)

2.2.3 Treatment of ACS

Several treatment methods are available to treat patients diagnosed with ACS. Treatment of ACS patients includes, revascularisation of the obstruction to restore the blood supply to the ischemic myocardium to limit ongoing harm, reduce ventricular irritability, and improve short- and long-term outcomes. The treatment methodologies for revascularisation include thrombolysis (dissolving and breaking blood clots) with fibrinolytic drugs (pharmacological treatment), percutaneous coronary intervention (PCI) and CABG with the use of CPB (Bergheanu, 2017).

2.2.3.1 Pharmacological/Medical treatment of ACS

Numerous drugs are available to treat ACS, but the most commonly used drugs and their mode of action are summarised below (Strange, 2008):

- **anti-ischemic therapy**: -e.g. nitroglycerin,β-blockers, calcium channel blockers, inhibitors of the renin-angiotensin-aldosterone system (Clopidogrel), morphine and other analgesics (Amsterdam et al., 2014).
- **antithrombotic therapy:** -aspirin.

- platelet populations and specific platelet responses are promising targets for the new antithrombotic treatment of patients with cardiovascular disease(van der Meijden & Heemskerk, 2019).
- **anticoagulant therapy:** -unfractionated heparin and low–molecular-weight heparin (Amsterdam et al., 2014).
- **lipid-lowering therapy** -in the absence of contraindications, lipid-lowering treatment with statins should be initiated for all patients with unstable angina/ NSTEMI, regardless of baseline LDL cholesterol levels. Currently, it is known that the addition of anti-PCSK9 (proprotein convertase subtilisin/kexin type 9) antibody significantly reduces plasma LDL-C and the incidence of cardiovascular events (Rosenson et al., 2018).

2.2.3.2 Revascularization

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are recommended for revascularization treatments for patients with diabetes mellitus (DM) with obstructive CAD (Head et al., 2017).

Myocardial revascularization has been the golden standard in treating CAD for over 50 years. CABG was used in clinical practice since the 1960s (Rocha, 2017), while Grüntzig first introduced PCI. In the mid-1980s, PCI was promoted as an alternative to CABG (Iqbal et al., 2013). Between 2001 and 2006, the number of PCIs performed annually for multivessel disease increased by 56%, and the total number of CABG surgeries decreased by 24% and continued to decline at a rate of approximately 5% per year subsequently (Riley et al., 2011).

While both interventions have witnessed significant technological advances, in particular the use of drug-eluting stents (DESs) in PCI and arterial grafts in CABG, their role in the treatment of patients presenting with stable CAD is being challenged by advances in medical treatment, referred to as optimal medical therapy, which include intensive lifestyle and pharmacological management (Nerlekar et al., 2016).

2.2.3.3 *Coronary bypass graft surgery with cardiopulmonary bypass (CPB)*

Cardiac surgery has been consistently performed using CPB ever since its clinical introduction during the 1950s. The first successful CPB procedure was done in 1953 on a woman with an atrial septal defect, and soon CPB became the standard for all cardiac procedures (Alexi-meskishvili & Konstantinov, 2003).

CABG had been hampered by limitations arising from the impossibility of exposing the lateral and posterior coronary arteries while dependent on the heart's pumping function. The invention of the CPB machine allowed physicians to stop the heart and be able to manipulate the heart to the desired position (Passaroni et al., 2015).

CPB circuits include pumps, cannulae, tubing, reservoir, oxygenator, heat exchanger and arterial line filter. Modern CPB machines have systems for monitoring pressures, temperature, oxygen saturation, haemoglobin, blood gases, electrolytes, and safety features such as bubble detectors, oxygen sensors, and reservoir low-level detection alarms (Sarkar & Prabhu, 2017).

To bypass severely stenotic arteries, transplanted saphenous veins are used as auto-grafts in coronary artery bypass operations. The graft extends from the proximal ascending aorta to just beyond the stenotic area of the artery. After a few years, venous grafts exhibit atherosclerotic plaques indistinguishable from those found in native coronary arteries. Half of these grafts occlude within 5 to 10 years, owing to neo-intimal hyperplasia and atherosclerosis (Fitzgibbon et al., 1996; Harskamp et al., 2013).

2.2.3.4 *Percutaneous coronary intervention (PCI)*

Percutaneous coronary intervention (PCI) is a non-surgical, invasive procedure to relieve the narrowing or occlusion of the coronary artery and improve blood supply to the ischemic tissue. Percutaneous coronary intervention is performed during an angiogram in the angiography suite. Different methods usually achieve this, the most common being ballooning the narrow segment or deploying a stent to keep the artery open (Nerlekar et al., 2016).

2.2.3.5 *Balloon angioplasty*

PCI can involve the inflation of a balloon inside a coronary artery to open the narrowing. It leads to the disruption of plaque. This procedure is not the primary intervention anymore because, over time, the ballooned artery returns to the stenotic state. It is, however, performed when stent placement is either not possible or will be harmful. It can also be performed as a bridge to CABG or future PCI (Levine et al., 2016).

There are different types of stents available such as (Stefanini & Holmes, 2013):

- **Bare metal stents are preferred if the patient cannot** take a longer duration of dual antiplatelet therapy (DAPT). A minimum of 1 month of DAPT is required.
- **Drug-eluting stents (DES) were** found to have reduced restenosis and revascularization rates compared with bare-metal stents.
- **Bioresorbable vascular scaffold and**
- **Drug-eluting balloons**

2.3. PRE-OPERATIVE CLINICAL RISK FACTORS AND COMORBIDITIES

Careful evaluation of patient characteristics should lead to proper risk stratification, identifying areas that can be neutralised through intervention. The incorporation of advances in the treatment of coronary bifurcation summit can lead to improved coronary bypass results. The following core variables are described by the American Heart Association (AHA) and American College of Cardiology (ACC) as predictors of mortality after CABG surgery (Hills et al., 2011):

i. the urgency of operation,
ii. age,
iii. prior heart surgery,
iv. gender,
v. left ventricular ejection fraction,
vi. and percentage stenosis on the left main coronary artery (with more than 70% stenosis).

Additionally, other variables were identified that, when added to the core variables, had a modest influence on predictive capabilities (Eagle et al., 2004):

i. height,
ii. weight,

iii. percutaneous coronary intervention during admission,
iv. recent (less than 1 week) myocardial infarction,
v. history of angina,
vi. ventricular arrhythmia,
vii. chronic heart failure,
viii. mitral regurgitation, and
ix. comorbidities.

These comorbidities refer to important risk factors associated with CAD and attempts to reduce CAD are based on modifying these risk factors. The Framingham Heart Study (1960s) identified significant risk factors associated with CAD and included modifiable and non-modifiable risk factors. Modifiable risk factors include diabetes, smoking, hypertension, hyperlipidaemia, sedentary lifestyle, obesity, stress and depression. Non-modifiable factors are advanced age, male gender and a family history of premature CAD (Tabei et al., 2014).

2.4 INTIMA-MEDIA THICKNESS (IMT)

Atherosclerosis is more or less equally present in the coronary, cerebral, and carotid arteries (Svanteson et al., 2017). IMT measures the common carotid artery (CCA) and is a marker for atherosclerosis (Weber et al., 2015).

Pignoli et al. (1986) were the first to report the measurement of IMT of carotid arteries using ultrasound. Salonen & Salonen (1991) followed, reporting on the *in vivo* use of ultrasound imaging to evaluate atherosclerotic changes in the carotid arteries. They demonstrated a close histological relationship between coronary, cerebral, and carotid atherosclerotic diseases. Since then, the ultrasonographic assessment of easily accessible arteries has become a surrogate marker for evaluating less accessible vessels such as the coronary and cerebral arterial systems (Amato et al., 2017). Ultrasound imaging provides information on IMT, the presence and type of plaque, calcification, and wall diameter. Therefore, ultrasound imaging aids in assessing pre-symptomatic lesions and atherosclerotic burden (Zhang et al., 2014).

2.4.1. Science of ultrasound

As ultrasound pulse waves propagate through the body and encounter the boundary between two tissues, a certain amount of sound energy is reflected at the interface, while the remainder propagates on into the second tissue. The amount that is reflected depends on the difference in acoustic impedance of the two tissues. Acoustic impedance is defined as the product of material density and the speed of sound. When ultrasound pulse (wave) propagates through the layers of the carotid artery, reflections of echoes may occur at the interface between the adventitia and media, media and intima, intima and lumen if a significant difference in acoustic impedance exists between the different tissue structures (Zhang et al., 2014). Whether the reflected echoes will be detected depends on the amount of reflected energy in relation to the sensitivity of the ultrasound instrumentation. Better resolution is achievable at higher transducer frequencies.

On the other hand, attenuation of sound energy loss is caused when scattering and absorption become more pronounced at higher frequencies. Therefore, a compromise between resolution and penetration depth that affects the attenuation degree is required. A transducer can achieve a good ultrasound imaging quality of the carotid artery with a wavelength between 5 and 10 MHz, depending on the vessel's depth (Hannawi et al., 2018).

2.4.2. Performing carotid intima-media thickness evaluation

Three layers compose the wall of an artery. From the lumen outwards, the tunica intima (or intima), the tunica media, and the tunica adventitia. The vessel wall nearest to the transducers is called the “near wall”, and the farthest one is the “far wall”, as illustrated in figure 2.6. After processing these signals, a typical two-layered image will be generated, as shown in figure 2.7 (Touboul et al., 2013).

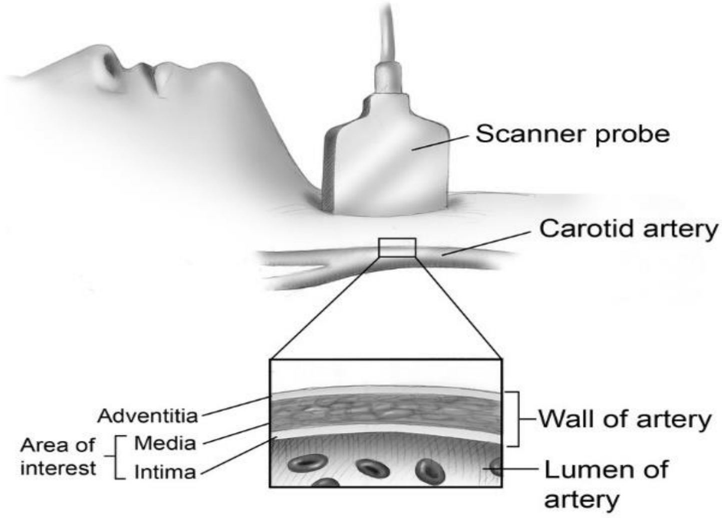

Figure 2.6: Scanner probe position and cross-sectional view of the carotid artery (adapted from https://preventivecardiologist.wordpress.com/2012/05/18/whats-so-great-about-carotid-artery-thickness/)

CIMT measurement is a double-line pattern visualised by echotomography on the common carotid artery (CCA) walls in a longitudinal image (El-saadany et al., 2012). It is formed by two parallel lines consisting of the leading edges of two anatomical boundaries: the lumen-intima and media-adventitia interfaces (Touboul et al., 2013) (Figure 2.7).

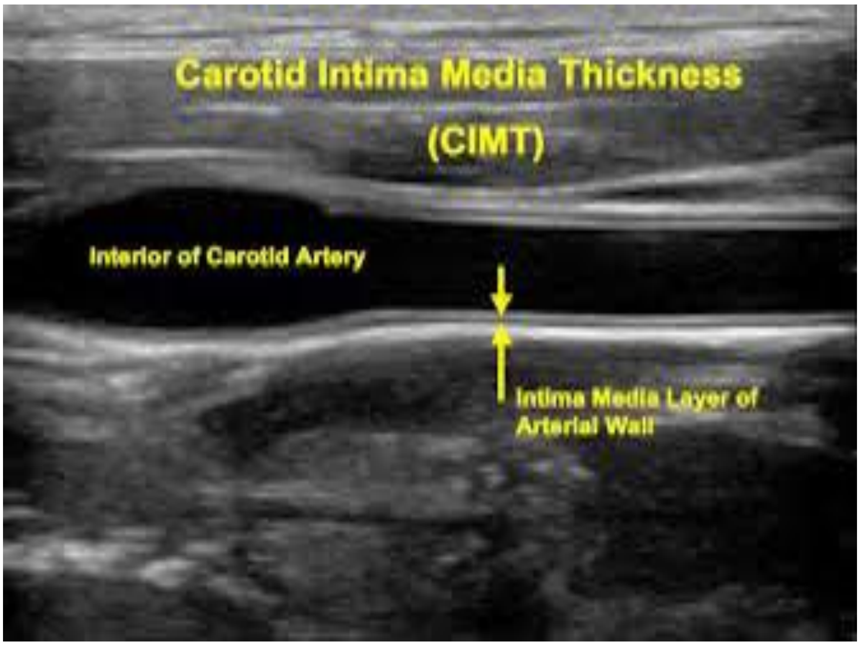

Figure 2.7 Typical view of CIMT (adapted from El-saadany, Ahmed and Dharmadhikan, 2012)

2.4.2.1 Application of CIMT

Non-invasive testing is recommended in patients with suspected stable ischemic heart disease (Weissgerber et al., 2016). Carotid ultrasound provides information about IMT, presence of plaque, plaque volume, lumen narrowing, and shear stress (Kim & Youn, 2016). This method is safe, relatively inexpensive, available and reliable for evaluating carotid arteries (Touboul et al., 2013). IMT evaluations may help detect coronary artery disease in the early stages of the disease and might predict the risk of a future stroke or cardiovascular event (Zhang et al., 2020; Gautam et al., 2019).

2.4.2.2 Ultrasound equipment settings

CCA acquisition with ultrasound should include standard equipment such as a high-resolution B-mode system operating with preferentially linear ultra-sound transducers at frequencies of 17 MHz. Appropriate depth of focus (e.g. 30–40 mm), frame rate optimally 25 Hz (115 Hz), and gain settings (minimal intraluminal artefacts) are recommended to obtain optimal image quality. Log gain compensation should be around 60 dB. It must be adjusted to obtain a symmetrical brightness on the near and far wall, decreasing the gain in the mid-part of the field to avoid intraluminal artefacts if needed (Touboul et al., 2013).

2.4.3. Advantages of CIMT

In clinical practice, ultrasonographic assessment of CIMT outperforms angiography when observing atherosclerotic vascular changes and the development of atherosclerosis. These advantages include (Kasliwal et al., 2014):

- CIMT can be used repeatedly and reproducibly with no adverse effects on the patients. It can be performed non-invasively with no risk of vessel dissection, vessel closure, or coronary spasm.
- CIMT scanning protocol can detect atherosclerotic diseases in early and asymptomatic stages.
- CIMT directly visualises vasculature, unlike indirect biomarkers such as low-density LDL-C or even the more advanced biomarkers like high-sensitivity C-reactive protein or lipoprotein-associated phospholipase A2.
- CIMT with plaque interrogation can be performed in any basic ultrasound ambulatory setting with favourable speed and cost factors.

- CIMT can be easily quantified via automated boundary detection software, and the carotid interrogation is radiation-free and thus safer than other imaging tests such as coronary calcium scoring.
- CIMT allows for observation of the arterial wall, the actual site of the atherosclerotic disease, rather than the lumen.
- CIMT is not dependent on calcification of the plaque, as are some of the other assessment tools, such as the coronary artery calcification score.

2.4.4. Association between carotid intima-media thickness and cardiac risk factors

An increase in IMT can be associated with cardiac risk factors, e.g. age, gender (male/female), smoking, hypertension, hypercholesterolemia and diabetes mellitus (Cheng et al., 2002). There is an association between carotid IMT and local atheromatous plaque. Therefore, the baseline common carotid artery inter media thickening (CCA-IMT) is an independent predictor of carotid plaque occurrence, with a prevalence of plaque threefold higher in a patient with a high IMT baseline (Singh et al., 2013). It is possible to conclude that increased wall thickness precedes plaque formation and that non-invasive B-mode ultrasonographic measurement of CCA-IMT could be considered a useful marker for the development of carotid atherosclerosis (Cazaubon, 2006). However, Willeit et al. (2020) concluded that the extent of intervention effects on CIMT progression predicts the degree of CVD risk reduction and provides a missing link supporting the usefulness of CIMT progression as a surrogate marker for CVD risk in clinical trials.

Gautam et al., (2019) reported that the mean CIMT was significantly higher in patients with triple-vessel disease than in control subjects and patients with single-vessel disease. However, Touboul et al. (2013) demonstrated that CIMT values in a healthy population differ between countries and are related to many factors, such as methodological variability and differences in cardiovascular risk and factor profiles. Since 2000, several guidelines (Mancia et al., 2007; Touboul et al., 2013; Amer et al., 2010; Greenland et al., 2010; Aboyans et al., 2018) have suggested that carotid artery B-mode ultrasound imaging is a safe, non-invasive and relatively inexpensive method to assess subclinical atherosclerosis in asymptomatic individuals (>45 years of age) and could provide valuable information on traditional risk factor assessment.

However, matching reference values to specific imaging protocols remains important (Magnussen, 2017).

2.4.5. Reference ranges for carotid intima-media thickening

Although the importance of CIMT measurements has been confirmed, there is still a lot of controversy in the literature about set reference limits (Ravani et al., 2015). Studies such as the Atherosclerosis Risk in Communities (ARIC) (Chambless et al., 1997) and Multi-Ethnic Study of Atherosclerosis (MESA) (Polak et al., 2017) reported the use of different CIMT values according to age, gender and geographical origin. Therefore, the suggestion is that normative CIMT values should be defined, considering age, gender, and geographical origin. The American Society of Echocardiography supports these statements and recommends that population-specific normative CIMT reference values be set according to age, gender, and ethnicity (Stein et al., 2008).

CIMT values greater than or equal to the 75th percentile are considered high and indicate increased CVD risk. The 25th to 75th percentile values are considered average and indicate unchanged CVD risk. Values less than or equal to the 25th percentile are considered low for CVD risk (Stein et al., 2008; Greenland et al., 2010; Barili et al., 2016). CCA-IMT 'normal values' in the absence of plaque should help characterise populations at intermediate risk (Touboul et al., 2013).

CIMT reference ranges are available for different age groups and gender, as summarised in Table 2.1 (Randrianarisoa et al., 2015). Furthermore, the atherosclerosis risk in communities (ARIC) study has published a calculator incorporating CIMT and plaque assessment to determine an adjusted Framingham risk (Kats et al., 2016).

Table 2.1 Normal CIMT values (Randrianarisoa et al., 2015)

Age	**18-29**	**30-39**	**40-49**	**50-59**
Women	0.47mm	0.59mm	0.67mm	0.70mm
Men	0.47mm	0.62mm	0.72mm	0.80mm

The CIMT cut-off value of 0.07 cm in this study was selected with reference to the findings of Youn et al. (2011), which demonstrated the mean value and 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles value of carotid intima-media thickness among men and women according to age group. The 75th percentile values observed in Youn et al. (2011) were selected as cut-off values for our study. The 75th percentile is also described by the Manneheim consensus study (Touboul et al., 2013).

2.5 NEAR-INFRARED SPECTROSCOPY (NIRS)

Jöbsis (1977) first reported using near-infrared spectroscopy to monitor regional cerebral oxygen saturation (rSO_2). rSO_2 is a non-invasive monitoring technique used to measure bedside cerebral oxygen saturation. Its rapid, sensitive and ongoing monitoring capability allows it to provide real-time cerebral oxygenation values (Scheeren et al., 2012).

Figure 2.8: Near-infrared spectroscopy (adapted from http://www.wemed1.com/downloads/dl/file/id/7947/product/10495/manual_for_mo_s_5100c.pdf

2.5. NIRS sensor placement

Since near-infrared light quickly penetrates the skull, it is possible to perform a real-time assessment of regional (frontal) cortical oxygenation (rSO_2) using electrodes placed on the patient's forehead. This region contains blood in a so-called watershed area, which is the area situated between the regions receiving blood from the anterior and medial cerebral artery. Brain tissue oxygen haemoglobin saturation derives mainly from the grey matter in the cerebral cortex and reflects the balance between oxygen delivery and utilisation in that region (Figure 2.8) (Scheeren et al., 2012).

2.5.1. Interpretation of NIRS values

A decline in the rSO_2 <50% or a 20% drop from the individual rSO_2 baseline is cause for concern and warrants clinical intervention. Absolute values below 50% and a decline of more than 25% from baseline are associated with neurological dysfunction and other adverse outcomes (Edmonds et al., 2004; Wang et al., 2020).

2.5.2. The value of NIRS in cardiopulmonary bypass

The typical range of rSO_2 is 55–80%. The incidence of desaturation in cerebral oximetry below 50%; or a decline of 20% from baseline in patients undergoing CABG surgery using CPB, can be as high as 42 %, as reported by Vretzakis et al. (2014). The effect of non-physiological blood flow, temperature fluctuations and anaesthesia during CPB gives rise to the importance of measuring rSO_2. These elements constantly vary peri-operatively and rSO_2 makes timeous intervention possible to mitigate the unfavourable neurological outcome (McDonagh et al., 2018).

2.5.3. Association between NIRS and post-operative outcome

Cerebral oximetry is useful during coronary artery bypass surgery. Its use is associated with a shorter ICU stay, lower incidence of stroke, renal failure, deep sternal infection, prolonged ventilation, reoperation and death (Murkin et al., 2007). Neurologic injury is still a common complication after cardiac surgery, post-operative neurocognitive decline and stroke account for up to 50% and 1-3% of the complication rates, respectively (de Tournay-Jetté et al., 2011).

Neurocognitive dysfunction is a complication of cardiac surgery that can restrict the improved quality of life that patients usually experience after cardiac surgery (Newman et al., 2006).

2.6. INTRA- AND POST-OPERATIVE OUTCOMES AND COMPLICATIONS AFTER CARDIOPULMONARY BYPASS SURGERY

CABG surgery is a standard surgical procedure, representing annual volumes of approximately 200,000 cases in the United States and an average incidence rate of 62 per 100,000 inhabitants in Western European countries (Melly et al., 2018). The peri-operative mortality in elective CABG surgery patients is approximately 1-2%, while other complications range between 5% and 7% (Jan et al., 2021). Reiche et al. (2021) reported a significant peri-operative mortality rate of 11.2% in a Johannesburg hospital in South Africa, which is much higher than worldwide statistics (Jan et al., 2021).

Advanced age, a lower left ventricular ejection fraction, smoking, increased CPB time, and a higher European System for Cardiac Operative Risk Evaluation (EuroSCORE) II are all associated with increased mortality (Reiche et al., 2021).

Risk prediction models such as the Society of Thoracic Surgeons (STS) (Shahian et al., 2009; O'Brien et al., 2018) and the European System for Cardiac Operative Risk Evaluation (EuroSCORE I&II) were developed as tools for patient risk stratification. These tools are widely used as risk stratification models in patients presented for cardiac surgery. EuroSCORE I (Nashef et al., 1999), revised in 2011 as EuroSCORE II (Nashef et al., 2012) due to substantial improvement in quality of care, use cardiac-specific and procedure-based variables to predict the patient's risk of mortality following cardiac surgery.

2.6.1. Pre-operative risk factors and predictors of in-hospital mortality after CABG

2.6.1.1. Age at surgery

As the population ages, an increasing number of older patients are undergoing adult cardiac surgery. Older age has been recognized as an independent predictor of short- and long-term mortality and adverse outcome after CABG surgery (Kamal et al., 2017).

According to Lemaire et al., (2020), patients aged ≥ 80–89 years had worse post-operative outcomes and female octogenarians had a higher mortality rate compared to their male counterparts.

2.6.1.2. Obesity

Obesity, defined as a body mass index (BMI) ≥30 kg/m^2 has been associated with increased pulmonary morbidity. Severe obesity (BMI ≥ 40 kg/m^2) has been deemed an independent risk factor for an extended hospital stay after CABG surgery (Kamal et al., 2017). However, (Stamou et al., 2011) documented that overweight and obese people with cardiovascular disease have a better prognosis than patients with a normal BMI.

2.6.1.3. Diabetes mellitus

The association of metabolic disorders with diabetes mellitus led to accelerated atherosclerotic progression and complexity of coronary lesions (Ryde'n et al., 2014). For this reason, patients with diabetes are at increased risk of developing major adverse events and death after CABG surgery with prolonged hospital stay than patients without diabetes (Kamal et al., 2017).

2.6.1.4. Hypertension

Isolated systolic hypertension (systolic blood pressure (SBP) >140 mmHg, after adjusting for other potential risk factors) increased the risk of adverse outcomes by 30% and is associated with a 40% increase in the possibility of cardiovascular morbidity peri-operatively in CABG patients (Aronson et al., 2002). Hypertension also increases the potential for atrial fibrillation after CABG (Gorczyca et al., 2018).

2.6.1.5. Renal impairment

Post-operative acute renal failure develops in 5-30% of patients who undergo cardiac surgery and is associated with a high risk of death (up to 80%) (Serraino et al., 2021).

Alramadan et al. (2019) concluded that pre-existing renal dysfunction is a significant predictor of 30-day and long-term mortality, length of ICU stay, and other significant post-operative complications.

2.6.1.6 Low left ventricular ejection fraction (LVEF)

Patients with severely reduced LVEF are at a higher risk of mortality after CABG than those with lower ejection fraction levels (Valezquez et al., 2016). Surgery remains superior to medical therapy alone in patients with a low LVEF (Lerman et al., 2019).

2.6.2. Intra-operative outcomes

CPB use is unique due to its overall effect on a patient's physiology compared to other types of surgery. Because patients undergo intense surgery for an extended period, the duration of CPB is significantly related to increased post-operative complications (Madhavan et al., 2018).

2.6.2.1. Cumulative bypass time (minutes)

Prolonged duration of CPB time is associated with an increased incidence of prolonged mechanical ventilation (Nadeem et al., 2019) and SIRS response (Roberto et al., 2002). Numerous studies comparing on-pump versus off-pump cardiovascular surgery have documented more significant adverse outcomes in on-pump conventional CPB patients (Madhavan et al., 2018; Gaudino et al., 2018; Nadeem et al., 2019). CPB duration positively correlates with interleukin-6 response responsible for the systemic inflammatory response associated with adverse outcomes in cardiac surgery (Shultz et al., 2016).

2.6.2.2. Cumulative cross-clamp time (minutes)

Prolonged cross-clamp time correlates with post-operative morbidity and mortality in both low- and high-risk patients (Al-Sarraf et al., 2011). Despite advances in surgical techniques and procedure refinement, prolonged cross-clamp time remains a significant predictor of morbidity and mortality (Iino et al., 2017). Extended cross-clamp times are associated with low cardiac output, prolonged ventilation, renal compromise, and neurological deficits noted immediately after CPB surgery (Shultz et al., 2016).

2.6.2.3. Total number of grafts >3

Most commonly used in CABG surgery, vascular conduits include the major saphenous vein and the internal left thoracic artery (mammary artery). The major saphenous vein is used for its length and ease of access. However, long-term patency remains suboptimal with a 10-year patency rate of 50-60% and is associated with leg wound infection and increased hospital stay (Head et al., 2017). The mammary artery is the gold standard conduit and is anastomosed to the left anterior descending artery with a 10-year patency rate of >90%, with only 1% of patients having hemodynamically significant atherosclerosis (Hussain & Harky, 2019).

The poor prognosis of patients presenting with ACS is related to an increased risk of acute myocardial infarction, the incidence of heart failure, cardiac arrest and dysrhythmias. However, event-free survival rates are higher after bypass surgery, independent of the number of vessels diseased (Hussain & Harky, 2019).

Ultimately, the long-term clinical outcomes after CABG surgery result from the complex interplay involving conduit selection, handling and salvage, bypass technique, surgeon experience or competence, patient factors and compliance, and post-operative medical therapy (McNichols et al., 2021).

2.6.2.4. Inotropic and vasopressor administration during CPB

Vasoactive, inotropic and vasopressor therapies improve end-organ perfusion by enhancing the adrenergic pathway (Belletti et al., 2015). Severe systemic vasodilation (vasoplegia), characterized by markedly decreased systemic vascular resistance (SVR) and low mean arterial blood pressure (MAP) during and after CPB, occurs in 5-25% of patients undergoing cardiac surgery (Belletti et al., 2015). According to the 2019 European Society for Cardiothoracic Surgery, European Society for Cardiothoracic Anesthesia and European Board of Cardiovascular Perfusion Guidelines on CPB in adult cardiac surgery, it is recommended that vasoplegic syndrome during CPB be treated with alpha-1 adrenergic agonist vasopressors to combat low SVR (Wahba et al., 2020). Norepinephrine is classified as an alpha-1 adrenergic agonist, which is considered the first-line agent and may have a mortality benefit over other drugs (Shaefi et al., 2018).

Targeting a normal physiological MAP during CPB is important to maintain appropriate perfusion pressures in all end organs, particularly the kidneys, the brain and the gastrointestinal tract (Brown et al., 2019). Vasoplegic syndrome during CPB may result from the release of proinflammatory cytokines, anaesthetic drugs, active endocarditis and the pre-operative use of angiotensin-converting enzyme inhibitors and calcium channel blockers (Wahba et al., 2020). Appropriate maintenance of mean arterial pressure (MAP) during CPB prevents deleterious effects on the patient's post-operative outcomes. In contrast, low and non-targeted MAP causes a marked increase in mortality, acute kidney injury (Kanji et al., 2010) and neurological complications (post-surgical delirium and stroke) (Brown et al., 2019).

2.6.2.5. *Hyperlactatemia during cardiac surgery*

Hyperlactemia during CPB is associated with increased post-operative outcomes (Matteucci et al., 2020). Demers et al. (2000) demonstrated that a blood lactate concentration of 4.0 mmol/L or higher during CPB identifies a subgroup of patients with an increased risk of post-operative morbidity and mortality. Lactate is often used to predict clinical outcomes, but the question remains if it is correctly interpreted in clinical decision-making. Elevated lactate levels during CPB is an indication of a troublesome operative course and has a significant sensitivity (78%) and specificity (83%) for mortality within 3 days (Kogan et al., 2012).

Hypoperfusion causing increased lactate levels is associated with high post-operative morbidity (Ranucci et al., 2006). Hyperlactatemia may also be due to hemodilution or problematic oxygen delivery to various tissues (Ranucci et al., 2015). Therefore, hyperlactatemia is an indicator of circulatory failure or insufficiency (Garcia-Alvarez et al., 2014).

During CPB, systemic microvascular control may deteriorate, inducing peripheral arteriovenous shunting associated with a rise in lactate levels (Trzeciak & Rivers, 2005). It is important to fulfil the metabolic O_2 needs of the patient to avoid hyperlactatemia (acidosis Type-A) and to keep maximum flow rates to prevent adverse post-operative outcomes (Demers et al., 2000).

Critical oxygen delivery is based on the hypothesis that when a patient is perfused below maximal flow rates (taking temperature into consideration), the oxygen expenditure becomes dependent on the oxygen delivery (Dunn et al., 2016). Energy production is then, to a certain extent, supplied by anaerobic glycolysis. Thus, when a decrease in peripheral oxygen supply occurs during CABG, an increase in lactate production will follow (Ranucci et al., 2006).

2.6.2.6. *The mechanisms leading to hyperlactatemia during CABG surgery:*

Several mechanisms are involved in the development of hyperlactatemia during CABG surgery and are summarized as:

a) Type A lactic acidosis (Cohen-Woods classification) is caused by poor tissue perfusion, shock (hypovolaemic, cardiogenic, haemorrhagic, or septic), acute hypoxaemia or CO_2 poisoning (Mizock, 2016).
b) Increased lactate production may be stimulated irrespective of tissue dysoxia, as a response to inflammatory mediators or through other mechanisms and is referred to as Type-B lactic acidosis (Chioléro et al., 2000).
c) Decreased utilisation of lactate by under perfused liver or muscle cells or glucose failing to enter the oxidative pathway and being broken down to lactate by the glycolytic pathway (Ranucci et al., 2006). Tissue dysoxia and inflammatory mediators are significant stimuli for lactate production. However, hyperglycemia and increased nonoxidative glucose disposal indicate glucose-induced stimulation of tissue glucose uptake and glycolysis. This suggests that hyperglycemia itself is a significant contributor to the development of hyperlactatemia (Chioléro et al., 2000).

An intra-operative peak lactate of 4.4 mmol/L predicts post-operative mortality in adult patients undergoing cardiac surgery with CPB (Kogan et al., 2012). Hyperlactatemia is associated with prolonged ICU and hospital stay (Minton & Sidebotham, 2017).

2.6.3. Post-operative outcomes

2.6.3.1. Systemic inflammatory response syndrome (SIRS)

At CPB initiation, blood comes in contact with tubing, a non-physiological surface that induces a SIRS response (Roberto et al., 2002). This response includes a variety of metabolic, endocrine, and immune changes known as the "stress response," which may lead to prolonged in-hospital stay (Bulow et al., 2014). The clinical manifestations of this reaction include post-operative complications such as respiratory complications, sternal wound infections, contractile dysfunction, renal impairment, coagulopathy and neurological dysfunction (Bulow et al., 2014).

2.6.3.2. Neurological dysfunction

Pre-operative neurological events are risk factors for postoperative neurologic events and in-hospital mortality, particularly in patients undergoing CPB surgery. Pre-operative stroke was associated with mortality, increased risk of early and late post-operative stroke and prolonged length of hospital stay (Kamal et al., 2017). With advancements in technology and surgical technique, neurological complications (ischemic stroke, delirium and post-operative cognitive decline) after cardiovascular surgery remain 1-5% (McDonagh et al., 2018).

2.6.3.3. Sepsis

Sepsis can lead to a low cardiac output, causing tissue hypotension and hypoperfusion. Although sepsis is rare after cardiac surgery, those who develop the condition experience high mortality rates (Kaufmann & Kung, 2019).

Correlation between carotid intima-media thickness and patient outcomes in coronary artery disease in central South Africa

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Abstract

Objectives

Atherosclerosis is responsible for significant cardiovascular morbidity and mortality. Carotid intima medial thickness (CIMT) is a useful non-invasive tool to detect atherosclerosis to diagnose cardiovascular disease. The aim of the study was to assess the correlation between pre-operative CIMT measurements and intra- and post-operative surgical outcomes in acute coronary syndrome (ACS) patients undergoing coronary artery bypass graft (CABG) surgery.

Methods

This retrospective analytical cohort included 89 patients diagnosed with ACS who received CABG surgery. Patients were divided into two cohorts: group 1 (normal CIMT <0.07cm) and Group 2 (abnormal CIMT ≥0.07cm). B-mode ultrasound was used to measure the CIMT in all patients. Pre-, intra- and post-operative data and complications were recorded for each patient.

Results

The study included 77 (86.5%) males and 12 (13.5%) females. Pre-operative mean body mass index (BMI) was significantly higher (p=0.03) in group 2 than in group 1 (29.2 kg/m^2 vs 26.6 kg/m^2). Patients in group 2 had significantly more diabetes (p=0.008), hypertension (p=0.009) and an increased NT pro-BNP (p=0.02) than patients in group 1. The intra-operative and post-operative outcomes between groups were comparable, with no significant differences.

Conclusion

The study showed no correlation between abnormal CIMT and increased adverse intra- and post-operative patient outcomes. Therefore, based on the results of this study, CIMT should not be considered a tool to predict adverse events in patients undergoing CABG surgery.

Keywords: Carotid intima-media thickness; Acute Coronary Syndrome; Outcomes; Complications; Coronary artery bypass graft surgery

Introduction

Global cardiovascular deaths are estimated at 17.9 million annually, representing 31% of all deaths (Mc Namara et al., 2019). In sub-Saharan Africa (SSA), non-communicable diseases are the second most common cause of death, accounting for 2.6 million deaths or 35% (Yuyun et al., 2020). From the year 2000 to 2016, SSA experienced a 37% increase in CHD with a projected increase of 21% by 2030 (Abdelatif et al., 2021). The early detection of high-risk individuals has significant clinical value.

CIMT measurement has been used as a marker to establish the presence (Geroulakos et al., 1994), risk (Kitagawa et al., 2007) and extent (Kablak-Ziembicka et al., 2004) of CVD. Several studies have validated the application of this imaging technique because it can detect slight changes over time associated with future cardiovascular events (Bots et al., 2016; Saxena et al., 2017). The 2010 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommended measurements of CIMT as a class IIa (reasonable to perform) recommendation for cardiovascular risk assessment in asymptomatic adults with intermediate cardiovascular risk (Greenland et al., 2010). The Mannheim Carotid Intima-Media Thickness and Plaque Consensus update from the advisory board of the "Watching the Risk" symposium in 2004 stated that CIMT and the measurement of plaque presence are recommended for the initial detection of CVD risk in asymptomatic patients at intermediate risk or if risk factors were present. Several authors (Chambless et al., 1997; Van Der Meer et al., 2004) investigated the correlation between CIMT and an increased risk for the development of coronary artery disease (CAD) and concluded that, with an increase in CIMT, the risk of CAD and myocardial infarction (MI) becomes correspondingly higher.

Cardiac surgery with cardiopulmonary bypass (CPB) causes a systemic inflammatory response syndrome (SIRS), of which 2-6% of cases are associated with severe morbidity and death (Bulow et al., 2014). Lactate production is a well-established indicator of tissue perfusion and regional brain oxygen saturation (rSO_2) (Koch et al., 2015) during CPB (Matteucci et al., 2020). Atherosclerosis adversely affects endothelium and is associated with an abnormal inflammatory response (Ross, 1999; Kaperonis et al., 2006; Libby, 2012). Since the mechanism of SIRS is linked to the endothelial response during CPB circulation, changes in endothelial function and tissue oxygenation are negatively affected by SIRS (Brezzo et al., 2020). CIMT is a valuable marker to predict the severity of coronary artery atherosclerosis; it may be postulated that CIMT can be used to predict surgical outcomes. Limited data is available on CIMT and its correlation to operative outcomes in CABG patients (Aboyans et al., 2005; Ham et al., 2018), with no data being available for the central South African population.

The aim of this study was to investigate whether pre-operative CIMT measurements in ACS patients undergoing elective CABG surgery affect intra- and post-operative surgical outcomes.

Methods

Study design

This retrospective analytical cohort included ACS patients that received elective CABG surgery as the mode of treatment between 2008-2014. During this period, 200 patients received CIMT evaluations, of whom 89 patients met the inclusion criteria and had complete data sets.

Study setting

The study was performed at the Cardiothoracic Surgery Department at Universitas Academic Hospital, Bloemfontein, the only public tertiary referral hospital in the central South African region, mainly servicing patients from the Free State, Northern Cape and Lesotho.

Ethics

Ethical clearance was obtained from the Health Science Research Ethics Committee (HSREC) of the University of the Free State (UFS-HSD 2020/1708/2601) and the Free State Department of Health. This study was a sub-study of a prospective investigation conducted on all ACS patients (ETVOS NR 51/07).

Patient population

Eighty-nine patients were included in the study and divided into two cohorts as per gender-specific CIMT reference ranges. Group 1 included patients with normal CIMT values and Group 2 patients with abnormal CIMT values

Patient demographics, clinical history, pre-operative risk factors, EuroSCORE II, CPB, near-infrared spectroscopy (NIRS) and post-operative outcomes and complications were recorded from the patient's medical records and the departmental database.

Laboratory sampling

Pre-operative results for cholesterol, creatine, total creatine kinase, glucose, insulin, N-terminal-pro-b-type natriuretic peptide (NT-proBNP) and creatinine kinase-MB (CK-MB) isoform were captured. Blood analysis was performed by the National Health Laboratory Service (NHLS) according to the laboratory standard operating procedures (SOPs), applying local laboratory reference ranges for each parameter.

Definitions

BMI was calculated using Du Bois formula (Du Bois & Du Bois, 1989) and categorized as underweight (>18.5 kg/m^2), normal or healthy weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (>30 kg/m^2) (Nuttall, 2015).

Hypertension was defined as isolated systolic hypertension (>140/90 mmHg) according to the definitions of Mancia et al. (2007). Patients with "normal 120–129/ 80-89 mmHg" and/or "high normal 130–139/ 85/89 mmHg" blood pressures were classified as not having hypertension.

Carotid intima-media thickness (CIMT) measurements

The CIMT measurements were performed pre-operatively one day prior to surgery. Patient positioning and the examination procedure were done according to standardized methods published in the Mannheim CIMT and plaque consensus (Touboul et al., 2013). Standard equipment included a high-resolution B-mode system operating in black and white mode, with linear ultrasound transducers at frequencies >7 MHz. A Phillips EnVisor sonar machine and Phased/Sector Array 2-8 MHz L12-3 sonar probe were used to obtain the CIMT images. Three

CIMT measurements were recorded and averaged. For our study normal CIMT cutoff were set at <0.07cm (males), <0.065cm (females) for normal CIMT and ≥0.07cm (males), ≥0.065cm (females) for abnormal CIMT. Since there are no consistent reference guidelines for CIMT cut-off in the literature, groups were divided based on the primary cut-off values per gender, as Youn et al. (2011) recommended.

Due to the literature's lack of standard reference guidelines, a second limited sub-analysis was done using a cut-off CIMT value of ≥0.09cm as abnormal, irrespective of gender or age (Hennerici & Neuerburg-Heusler, 1998). However, only the intra- and post-operative outcomes and complications were compared between groups.

Lactate measurements

Lactate levels were analyzed at specified time intervals: (i) after the insertion of an intra-arterial catheter (T1-baseline), (ii) after intubation (T2), and (iii) at approximately 15-minute intervals for the duration of surgery (T3, T4 etc.). Post-operatively, lactate values were recorded at 1hour (hr), 2hr, 4hr, 8hr, 12hr, 24hr, 48hr and 72hr after the patient was admitted to the intensive care unit (ICU). Only peak lactate values were used for intra- and post-operative analysis. This study defines peak lactate as lactate >4 mmol/dL during and after surgery.

Near-infrared spectroscopy (NIRS) measurements

Two NIRS electrodes were placed on the patient's forehead before the patient was induced, and baseline values were set. Results were interpreted as either satisfactory (NIRS values > 50% or < 20% drop from baseline) or as compromised cerebral blood flow (NIRS values ≤ 50% or > 20% drop from baseline). It should be noted that not all patients received NIRS measurements because not all theatres were equipped with a NIRS monitor. Only 32 of the 89 patients had recorded NIRS measurements.

Echocardiogram (Left ventricular ejection fraction)

Standard transthoracic echocardiograms (TTE) were performed on all patients in line with the British Society of Echocardiography protocol for comprehensive adult TTE studies (Wharton et al., 2015) A Phillips EnVisor echocardiography machine was used and the patients' left ventricular ejection fraction (LVEF) was calculated peri-operatively. The American Society of Echocardiography (ASE) define LVEF as the percentage of blood ejected during a left ventricular contraction of the heart using quantitative measures. LVEF was calculated using the formula: LVEF=([EDV-ESV]/EDV) × 100. The cut-off value for normal LVEF for our study was determined at >55%.

Statistical Analysis

Statistical analyses were done using R Software version 3.2.2 (2015/08/14). T-tests and the calculation of confidence intervals were done with XLSTAT version 2016.03.30846. Data were compared using Student's t-test for normally distributed continuous variables, the Mann-Whitney test for continuous data that were not normally distributed and the χ^2 or Fisher's exact χ^2 test (where cell counts were less than 5) for categorical variables. Statistical significance was noted if the *p*-value was less than 0.05.

Results

Pre-operative data

Anthropometrics and demographics

Eighty-nine ACS patients received CIMT measurements prior to elective CABG surgery. Twenty-eight patients (31%) presented with a normal CIMT and 61 patients (69%) with an abnormal CIMT. Seventy-seven (86.5%) were male and 12 (13.5%) were female patients. The mean age of the groups was comparable; both groups presented with a preponderance of Caucasian males (80%). The mean BMI was significantly higher in group 2 compared to group 1 (29.2 kg/m2 vs 26.6 kg/m2) (p<0.05). The demographic and anthropometric data are summarized in Table I.

Table I Demographic and anthropometric data of normal and abnormal CIMT groups

Variable (unit)	Statistic	Group 1 Normal CIMT (n=28, 31%)	Group 2 Abnormal CIMT (n=61, 69%)	p-value
Age (years)	Mean ± SD	58.9 ± 8.88	59.6 ± 9.15	0.72
Gender:				
Male	n (%)	23 (82.1%)	54 (88.5%)	
Female	n (%)	5 (17.9%)	7 (11.5%)	
Ethnicity:				
Caucasian (n=69)	n (%)	22 (78.57%)	47 (77.05%)	>0.99
Mixed Race (n=9)	n (%)	2 (7.14%)	7 (11.48%)	0.71
Black African (n=9)	n (%)	4 (14.29%)	5 (8.20%)	0.45
Asian (n=2)	n (%)	0	2 (3.28%)	-
BMI (kg/m^2):	Mean ± SD	26.6 ± 4.88	29.2 ± 5.85	0.03*
Overweight	n (%)	12 (42.9%)	19 (31.2%)	
Obese	n (%)	13 (46.4%)	16 (26.2%)	
Severely obese	n (%)	0	4 (6.6%)	

[Normal CIMT males <0.07cm; Abnormal CIMT males ≥0.07cm; Normal CIMT females <0.065cm; Abnormal CIMT females ≥0.065cm] (CIMT, corotid intima-media thickness; SD, standard deviation) (*statistically significant p-value <0.05)

Clinical data

Significantly more patients in group 2 with an abnormal CIMT presented with hypertension (p=0.009), diabetes (p=0.008), and an increased NT pro-BNP (p=0.017). Cholesterol (LDL) could not be analysed due to incomplete data sets. All other clinical parameters were comparable between groups (p>0.05). The pre-operative CK-MB isoform, total cholesterol and NT pro-BNP values exceeded the upper reference limit in group 2 (Table II). The mean

EuroSCORE II of both groups was high, but patients were evenly distributed in the three severity classifications with no differences between groups.

Table II Pre-operative clinical data of normal and abnormal CIMT groups

Variable (unit)	Statistic	Group 1 Normal CIMT (n=28, 31%)	Group 2 Abnormal CIMT (n=61, 69%)	p-value
CIMT (mm)	Mean ± SD	0.1 ± 0.01	0.1 ± 0.03	<0.0001*
Hypertension	n (%)	16 (57.14%)	52 (85.25%)	0.009*
Diabetes	n (%)	2 (7.14%)	21 (34.43%)	0.008*
Cholesterol (LDL) > 3mmol	n (%)	24 (85.71%)	28 (45.90%)	No analysis, incomplete data sets
	Mean ± SD	4.4 ± 0.07)	4.09 ± 0.94	
Statins use	n(%)	22 (78.57%)	44 (67.21%)	-
Hypercholesterolaemia	n (%)	14 (50.0%)	24 (39.34%)	0.57
NT pro-BNP [ng/L]	Mean ± SD	562.9 ± 591.2	1344.4 ± 1646.7	0.017*
Current / Ex-smoker	n (%)	12 (42.86%)	31 (50.82%)	0.64
CK-MB isoform [ng/mL]	Mean ± SD	32.8 ± 96.39	20.8 ± 49.28	0.58
Glucose [mmol/L]	Mean ± SD	6.05 ± 2.053	6.37 ± 2.70	0.58
Insulin [mU/L]	Mean ± SD	24.8 ± 39.49	28.06 ± 30.71	0.74
LVEF	Mean ± SD	54.4 ± 14.39	52.2 ± 15.07	0.52
EuroSCORE II	n(%)	6 (21.4%)	16 (26.2%)	-
0-2 Low risk	n(%)	11 (39.3%)	20 (32.8%)	-
3-5 Medium risk	n(%)	7 (25.0%)	20 (32.8%)	-
>5 High risk	Mean ± SD	6.18 ± 9.60	7.53 ± 13.85	0.61

[Normal CIMT males <0.70mm; Abnormal CIMT males ≥0.07cm; Normal CIMT females <0.065cm; Abnormal CIMT females ≥0.065cm] (CIMT, corotid intima-media thickness; SD, standard deviation; LVEF, left ventricular ejection fraction) (*statistically significant p-value <0.05)

Intra-operative data

The intra-operative clinical variables were similar between groups and no significant differences were detected (Table III).

Table III Intra-operative clinical data of normal and abnormal CIMT groups

Variable (unit)	Statistic	Group 1 Normal CIMT (n=28, 31%)	Group 2 Abnormal CIMT (n=61, 69%)	p-value
Peak lactate (mmol/dL)	Mean ± SD	4.7 ± 1.6	4.02 ± 1.8	0.085
Cumulative bypass time (min)	Mean ± SD	112 ± 22.7	111.4 ± 31.5	0.92
Cumulative cross-clamp time (min)	Mean ± SD	60.5 ± 14.3	59.3 ± 18.5	0.75
Total number of grafts ≥3	n (%)	21 (75.00%)	43 (70.5%)	0.85
Intra-Aortic Balloon pump	n (%)	15 (53.6%)	21 (34.4%)	0.14
NIRS >50%; drop of <20%	n (%)	3 (10.7%)	17 (27.9%)	0.13
NIRS <50%; drop of >20%	n (%)	13 (46.5%)	24 (39.3%)	
Phenylephrine bolus at 100ug/ml during bypass	n (%) Mean ± SD	23 (82.1%) 15.07 ± 22.04	49 (80.3%) 20.7 ± 17.8	>0.99 0.30
Adrenaline during anaesthesia at more than 20µg/kg/min	n (%) Mean ± SD	6 (21.4%) 0.07 ± 0.04	9 (14.8%) 0.3 ± 0.4	0.63 0.16
Adrenaline bolus during bypass 1:1000000 mg/ml	n (%) Mean ± SD	4 (14.3%) 3 ± 1.8	17 (27.9%) 7 ± 9.4	0.20 0.13
Effortil bolus during bypass (mg)	n (%) Mean ± SD	2 (7.1%) 14.5 ± 7.8	5 (8.2%) 11.6 ± 5.4	>0.99 0.69

[Normal CIMT males <0.07cm; Abnormal CIMT males ≥0.07cm; Normal CIMT females <0.065cm; Abnormal CIMT females ≥0.065cm] (CIMT, corotid intima-media thickness; SD, standard deviation) (*statistically significant p-value <0.05)

Post-operative outcomes and complications

The post-operative outcomes between groups were similar with no significant differences (Table IV). Most patients in both groups had an ICU stay of less than 3-days, with only 21.43% in group 1 and 14.75% in group 2 exceeding a 3-day ICU stay. The mortality rate was low, with only 1 (2%) fatality in the abnormal IMT group due to sepsis.

Table IV Post-operative outcomes of normal and abnormal CIMT groups

Variable (unit)	Statistic	Group 1 Normal CIMT (n=28, 31%)	Group 2 Abnormal CIMT (n=61, 69%)	p-value
Peak lactate (>4 mmol/dL)	Mean ± SD	5.3 ± 3.4	5.8 ±3.2	0.52
Length of stay in ICU >3 days	Mean ± SD n (%)	3.1 ± 0.7 6 (21.4%)	3.13 ± 2.2 9 (14.8%)	0.63
Length of stay in ICU >3 days	Mean ± SD	2.94 ± 0.1	3.54 ± 0.6	0.33
Mortality	n (%)	0 (0%)	1 (2%)	-

[Normal CIMT males <0.07cmm; Abnormal CIMT males ≥0.07cm; Normal CIMT females <0.065cm; Abnormal CIMT females ≥0.065cm] (CIMT, corotid intima-media thickness; SD, standard deviation) (*statistically significant p-value <0.05)

Post-operative complications in both groups were limited. Patients with an abnormal CIMT tended to have more post-operative complications than those with a normal CIMT (34.4% vs 21.4%) (Figure 1). The prevalence of post-operative complications was too low to analyze statistically.

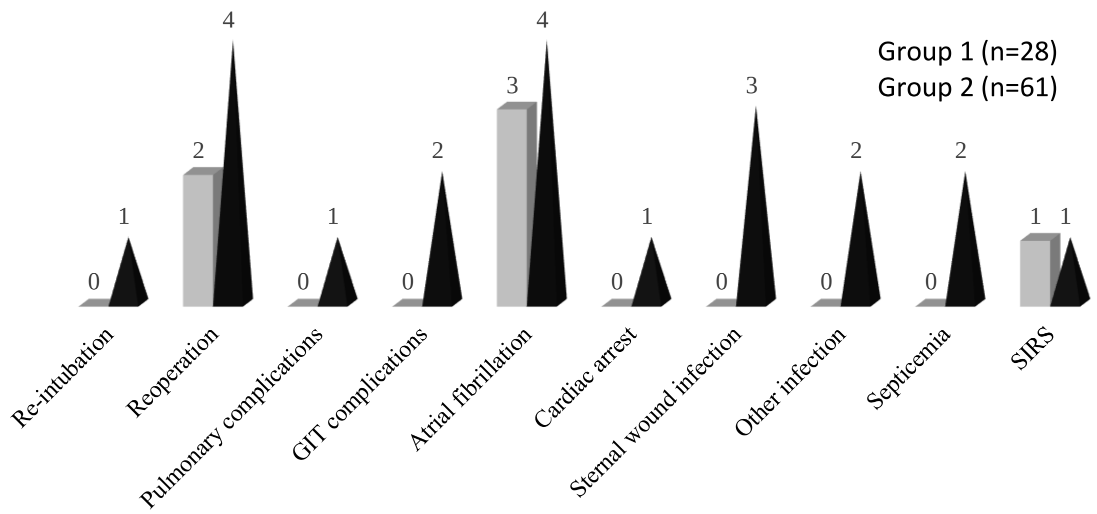

Figure 1 Post-operative complications of normal and abnormal CIMT groups

Sub-analysis at 0.09cm CIMT cut-off

When a higher CIMT cut-off value was used as an abnormal indicator for CIMT (0.09cm), the pre-operative, intra-operative, and post-operative limited sub-analysis demonstrated similar results between groups with no statistically significant differences (Table V). Post-operative complications did not show any differences.

Table V **Pre-, intra- and post-operative outcomes compared to normal (<0.09cm) and abnormal (≥0.09cm) CIMT values regardless of gender**

Variable (unit)	Statistic	Group 1 Normal CIMT <0.09cm (n=61, 68.5%)	Group 2 Abnormal CIMT ≥0.09cm (n=28, 31.5%)	p-value
Pre-operative clinical data:				
NT pro-BNP [ng/L]	Mean ± SD	936.1 ± 165.7	1391 ± 650.5	0.51
LVEF	Mean ± SD	53.6 ± 1.7	52.1 ± 3.3	0.69
CK-MB isoform [ng/mL]	Mean ± SD	21.8 ± 10.3	36.10 ± 27.9	0.62
Intra-operative clinical data:				
Peak lactate (mmol/dL)]	Mean ± SD	4.3 ± 0.2	3.9 ± 0.4	0.29
Cumulative bypass time (minutes)	Mean ± SD	112.9 ± 3.8	109.6 ± 6.6	0.66
Post-operative outcomes:				
Peak lactate (>4 mmol/dL)	Mean ± SD	5.8 ± 0.4	5.69 ± 0.70	0.93

Discussion

This study aimed to assess the impact of an abnormal CIMT on intra- and post-operative variables in ACS patients receiving CABG surgery. It was hypothesized that patients with pronounced/thickened CIMTs would present with worse intra- and post-operative measurable abnormalities, outcomes and complications. The study results showed that patients with abnormal CIMTs had more pre-operative risk factors than patients with normal CIMTs. However, no significant differences were observed between intra- and post-operative variables comparing normal and abnormal CIMT groups, even at a higher abnormal CIMT cut-off value of ≥0.09cm.

The anthropometric analysis showed that patients with an abnormal CIMT had a significantly higher BMI and were significantly more overweight than patients with a normal CIMT. This finding is in agreement with studies conducted by Rashid & Mahmud (2015) and El Jalbout et al. (2018), who reported an increased CIMT in adolescents with an increased BMI.

Pre-operative risk factors

In this cohort, 69% of ACS patients who required CPB surgery due to severe coronary artery disease had an abnormal CIMT. This finding concurs with several other studies that concluded that CIMT is elevated with advanced CAD (Kablak-Ziembicka et al., 2004; Zhang et al., 2014). In our study, patients with an abnormal CIMT, risk factors such as hypertension, diabetes and NT pro-BNP were significantly more frequent than in those with a normal CIMT. Diabetes directly impacts CIMT due to vascular endothelial dysfunction (Baba et al., 2018). The authors reported that patients presenting with diabetes have higher CIMT values than healthy controls and that the prevalence of increased CIMT is very high (82.8%) in the Nigerian population. In our study, 34% of patients with diabetes had abnormal CIMTs, significantly more than patients with normal CIMTs.

Hypertension is multifactorial in cause, including but not limited to high sodium intake, cigarette smoking, unhealthy diet, low potassium intake, lack of physical activity (Mills et al., 2016) and familial history of hypertension (Li et al., 2021). Evidence suggests that hypertension is strongly associated with increased CIMT thickening (Zhang et al., 2019). The carotid artery has a relatively small media compared with muscular arteries. Thus an increased CIMT is thought to primarily represent intimal rather than medial thickening supporting atherosclerotic-related cardiovascular events rather than hypertrophy of the medal later of the carotid artery (Magnussen, 2017). Our results (Table II) show that an association between hypertension and an increased CIMT exists with significantly more patients presenting with hypertension in the abnormal CIMT group (85.25%) compared to the normal CIMT group (57.14%). Similar observations were reported by Rashid & Mahmud (2015), Chen et al. (2015) and Magnussen (2017).

The MONICA Risk, Genetics, Archiving, and Monograph (MORGAM) biomarker project demonstrated that adding NT-proBNP to a conventional risk model can improve a 10-year risk estimation for cardiovascular events (Blankenberg et al., 2010). This study showed that NT-pro BNP was significantly higher pre-operatively in patients with an abnormal CIMT. A response to left ventricular strain or ischaemia causes a release of NT-proBNP, which has been found to be an important biomarker for left ventricular systolic dysfunction and left ventricular stress in the general population (Mirjafari et al., 2014).

Intra-operative risk factors

There was no correlation between CIMT and intra-operative factors, even when a higher abnormal CIMT cut-off value was used. A possible reason is that the study population was too small and that subtle differences may not have been detected. Interestingly, no difference in lactate values was found between groups. Insufficient oxygen delivery and hypoperfusion during CPB contribute to hyperlactatemia (Ranucci et al., 2006). CIMT is a marker of subclinical atherosclerosis and endothelial dysfunction (Yang et al., 2020), which is a factor that would increase lactate production intra-operatively due to the systemic inflammatory response caused by CPB (Laffey et al., 2002). An increase in lactate is associated with poor outcomes and increased mortality in cardiac surgery patients (Minton & Sidebotham, 2017).

Post-operative complications

The post-operative complications were comparable between groups with no statistically significant differences. Our study's overall post-operative complication rate is low but corresponds with the overall rate of complications reported after CABG surgery (1-3%) (Safaie et al., 2015). Considering the low number of complications reported in our study, patients with an abnormal CIMT tended to have more post-operative complications than those with a normal CIMT.

Abnormal CIMT ≥0.09 cm

Data on the accepted normative values are unavailable because there is no widely accepted cut-off value for what constitutes an adverse/abnormal CIMT value. Many variables affect the thickening of the carotid intima in different populations, whether it be age, ethnicity, or diet (Magnussen, 2017). Even when using a higher abnormal CIMT cut-off value of 0.09 cm, there was no relation between higher CIMT values and increased post-operative outcomes and complications. Our results agree with Aboyans et al., (2005), who also found little value in pre-operative CIMT. In contrast, some value was reported in off-pump CABG where increased CIMT (0.9mm) was associated with increased 30-day morbidity (Ham et al., 2018). However, based on our results, CIMT should not be considered a predictor for surgical outcomes in ACS patients undergoing CABG surgery using CPB. Before a criteria for abnormal CIMT can be set, there is a need for measurement consensus and population reference values. There are currently no set CIMT population values for SA.

Limitations

The study is limited by its retrospective design. The sample size was small; for this reason, only assumptions can be made. A larger patient population may reveal more definite answers on whether increased CIMT values can predict surgical outcomes.

Conclusion

Our study demonstrated an association between abnormal CIMT and pre-operative risk factors such as BMI, diabetes, hypertension and NT-Pro BNP. However, there was no correlation between abnormal CIMT and an increased rate of adverse intra- and post-operative patient outcomes. Therefore, it seems that CIMT should not be used to predict adverse events in patients undergoing CABG surgery. Further studies that include larger patient numbers are needed to confirm our observations.

References

Aboyans, V., Lacroix, P., Yildiz, C., Postil, A. & Laskar, M. 2005. Common carotid intima-media thickness measurement is not a pertinent predictor for secondary cardiovascular events after coronary bypass surgery . A prospective study. *European Journal of Cardio-thoracic Surgery*, 28(3): 415–419.

Baba, M.M., Abdullahi Talle, M., Ibinaiye, P.O., Abdul, H. & Buba, F. 2018. Carotid Intima-Media Thickness in Patients with Diabetes Mellitus Attending Tertiary Care Hospital in Nigeria. *Angiology: Open Access*, 6(2): 1-5.

Blankenberg, S., Zeller, T., Saarela, O., Havulinna, A.S., Kee, F., Tunstall-Pedoe, H., Kuulasmaa, K., Yarnell, J., Schnabel, R.B., Wild, P.S., Münzel, T.F., Lackner, K.J., Tiret, L., Evans, A. & Salomaa, V. 2010. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: The MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. *Circulation*, 121(22): 2388–2397.

Du Bois, D. & Du Bois, E.F. 1989. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*, 5(5): 303-313.

Bots, M.L., Evans, G.W., Tegeler, C.H. & Meijer, R. 2016. Carotid Intima - media Thickness Measurements : Relations with Atherosclerosis , Risk of Cardiovascular Disease and Application in Randomized Controlled Trials. *Chinese Medical Journal*, 129(2): 215–226.

Brezzo, G., Simpson, J., Ameen-ali, K.E., Berwick, J. & Martin, C. 2020. Brain , Behavior , & Immunity - Health Acute effects of systemic in fl ammation upon the neuro-glial-vascular unit and cerebrovascular function. *Brain, Behavior, & Immunity - Health*, 5: 1–12.

Bulow, N.M.H., Colpo, E., Duarte, M.F., Correa, E.F.M., Schlosser, R.S., Lauda, A., Kade, I.J. & Rocha, J.B.T. 2014. Inflammatory Response in Patients under Coronary Artery Bypass Grafting Surgery and Clinical Implications: A Review of the Relevance of Dexmedetomidine Use. *International Scholarly Research Network Anesthesiology*, 2014(3): 1–28.

Chambless, L.E., Heiss, G., Folsom, A.R., Rosamond, W., Szklo, M., Sharrett, A.R. & Clegg, L.X. 1997. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: The Atherosclerosis Risk in Communities (ARIC) study, 1987-1993. *American Journal of Epidemiology*, 146(6): 483–494.

Chen, Y., Xiong, H., Wu, D., Pirbhulal, S., Tian, X., Zhang, R., Lu, M., Wu, W. & Huang, W. 2015. Relationship of short-term blood pressure variability with carotid intima-media thickness in hypertensive patients. *BioMedical Engineering Online*, 14(1): 1–15.

Geroulakos, G., O'Gorman, D.J., Kalodiki, E., Sheridan, D.J. & Nicolaides, A.N. 1994. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. *European Heart Journal*, 15(6): 781–785.

Greenland, P., Alpert, J.S., Beller, G.A., Benjamin, E.J., Budoff, M.J., Fayad, Z.A., Foster, E., Hlatky, M.A., Hodgson, J.M.B., Kushner, F.G., Lauer, M.S., Shaw, L.J., Smith, S.C., Taylor, A.J., Weintraub, W.S. & Wenger, N.K. 2010. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults. *Journal of the American College of Cardiology*, 56(25): 50–103.

Ham, S., Song, J., Shim, J., Soh, S. & Kim, H. 2018. Prognostic role of carotid intima- media thickness in off-pump coronary artery bypass surgery. *Scientific Reports*, 8(1): 1–8.

Hennerici, M.G. & Neuerburg-Heusler, D. 1998. *Vascular diagnosis with ultrasound : clinical reference with case studies / Michael Hennerici, Doris Neuerburg-Heusler*. Stuttgart : New York: Thieme.

El Jalbout, R., Cloutier, G., Cardinal, M.H.R., Henderson, M., Lapierre, C., Soulez, G. & Dubois, J. 2018. Correction to: Carotid artery intima-media thickness measurement in children with normal and increased body mass index: a comparison of three techniques. *Pediatric Radiology*, 48(8): 1080.

Kablak-Ziembicka, A., Tracz, W., Przewlocki, T., Pieniazek, P., Sokolowski, A. & Konieczynska, M. 2004. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart*, 90(11): 1286–1290.

Kaperonis, E.A., Liapis, C.D., Kakisis, J.D., Dimitroulis, D. & Papavassiliou, V.G. 2006. Inflammation and atherosclerosis. *European Journal of Vascular and Endovascular Surgery*, 31(4): 386–393.

Kitagawa, K., Hougaku, H., Yamagami, H., Hashimoto, H., Itoh, T., Shimizu, Y., Takahashi, D., Murata, S., Seike, Y., Kondo, K., Hoshi, T., Furukado, S., Abe, Y., Yagita, Y., Sakaguchi, M., Tagaya, M., Etani, H., Fukunaga, R., Nagai, Y., Matsumoto, M. & Hori, M. 2007. Carotid intima-media thickness and risk of cardiovascular events in high-risk patients. Results of the Osaka Follow-Up Study for Carotid Atherosclerosis 2 (OSACA2 Study). *Cerebrovascular Diseases*, 24(1): 35–42.

Koch, C., Ro, R., Uhle, F., Schneck, E., Andreas, M., Weigand, M.A. & Lichtenstern, C. 2015. Prospective evaluation of regional oxygen saturation to estimate central venous saturation in sepsis. *Journal of clinical monitoring and computing*, 29: 443–453.

Laffey, J.G., Boylan, J.F. & Cheng, D.C.H. 2002. The systemic inflammatory response to cardiac surgery. *Anesthesiology*, 97(1): 215–252.

Li, A. le, Peng, Q., Shao, Y. qin, Fang, X. & Zhang, Y. ying. 2021. The interaction on hypertension between family history and diabetes and other risk factors. *Scientific Reports*, 11(1): 1–7.

Libby, P. 2012. Inflammation in atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 32(9): 2045–2051.

Magnussen, C.G. 2017. Carotid artery intima-media thickness and hypertensive heart disease: a short review. *Clinical Hypertension*, 23(1): 1–4.

Mancia, G., Backer, G. De, Uk, A.D., Cifkova, R., Republic, C., Heagerty, A.M., France, S.L., Poland, K.N., Poland, A.R., Germany, R.E.S., Struijker, H.A.J., France, V.D., Germany, U.S., Germany, S.S., Poland, M.T., Widimsky, P., Republic, C., Cifkova, R., Republic, C., Dominiczak, A., Kingdom, U., Fagard, R., Germany, R.E.S. & Uk, B.W. 2007. 2007 Guidelines for the management of arterial hypertension The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European Heart Journal*, 28(12): 1462–1536.

Matteucci, M., Ferrarese, S., Cantore, C., Cappabianca, G., Massimi, G., Mantovani, V., Rossi, M.B. & Beghi, C. 2020. Hyperlactatemia during cardiopulmonary bypass: risk factors and impact on surgical results with a focus on the long-term outcome. *Perfusion (United Kingdom)*, 35(8): 756–762.

Mc Namara, K., Alzubaidi, H. & Jackson, J.K. 2019. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? *Integrated Pharmacy Research and Practice*, 8: 1–11.

Van Der Meer, I.M., Bots, M.L., Hofman, A., Del Sol, A.I., Van Der Kuip, D.A.M. & Witteman, J.C.M. 2004. Predictive Value of Noninvasive Measures of Atherosclerosis for Incident Myocardial Infarction: The Rotterdam Study. *Circulation*, 109(9): 1089–1094.

Mills, K.T., Stefanescu, A. & He, J. 2016. The global epidemiology of hypertension Katherine. *Physiology & behavior*, 176(1): 139–148.

Minton, J. & Sidebotham, D.A. 2017. Hyperlactatemia and cardiac surgery. *Journal of Extra-Corporeal Technology*, 49(1): 7–15.

Mirjafari, H., Welsh, P., Verstappen, S.M.M., Wilson, P., Marshall, T., Edlin, H., Bunn, D., Chipping, J., Lunt, M., Symmons, D.P.M., Sattar, N. & Bruce, I.N. 2014. N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) and mortality risk in early inflammatory polyarthritis: Results from the Norfolk Arthritis Registry (NOAR). *Annals of the Rheumatic Diseases*, 73(4): 684–690.

Nuttall, F.Q. 2015. Body Mass Index. *Nutrition Today*, 50(3): 117–128.

Ranucci, M., Isgrò, G., Ranucci, M., Toffol, B. De, Isgrò, G., Romitti, F. & Conti, D. 2006. Hyperlactatemia during cardiopulmonary bypass : Determinants and impact on postoperative outcome Hyperlactatemia during cardiopulmonary bypass : determinants and impact on postoperative outcome. *Critical Care*, 10(6): 1-9.

Rashid, S.A. & Mahmud, S.A. 2015. Correlation between carotid artery Intima-media thickness and luminal diameter with body mass index and other cardiovascular risk factors in adults. *Sultan Qaboos University Medical Journal*, 15(3): e344–e350.

Ross, R. 1999. Atherosclerosis--an inflammatory disease. *The New England journal of medicine*, 340(2): 115–126.

Safaie, N., Montazerghaem, H., Jodati, A. & Maghamipour, N. 2015. In-Hospital Complications of Coronary Artery Bypass Graft Surgery in Patients Older Than 70 Years. *Journal of Cardiovascular Thoracic Research*, 7(2): 60–62.

Saxena, Y., Saxena, V., Mittal, M., Srivastava, M. & Raghuvanshi, S. 2017. Age-wise association of carotid intima media thickness in ischemic stroke. *Annals of Neurosciences*, 24(1): 5–11.

Touboul, P., Hannerici, M., Meairs, S. & Adams, H. 2013. Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004–2006–2011): An Update on Behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgi. *Cerebrovascular Disease Disease*, 34(4): 290–296.

Wharton, G., Steeds, R., Allen, J., Phillips, H., Jones, R., Kanagala, P., Lloyd, G., Masani, N., Mathew, T., Oxborough, D., Rana, B., Sandoval, J. & Wheeler, R. 2015. A minimum dataset for a standard adult transthoracic echocardiogram : a guideline protocol from the British Society of Echocardiography. *Echo Research and Practice*, 2(1): G9–G24.

Yang, C.W., Guo, Y.C., Li, C.I., Liu, C.S., Lin, C.H., Liu, C.H., Wang, M.C., Yang, S.Y., Li, T.C. & Lin, C.C. 2020. Subclinical atherosclerosis markers of carotid intima-media thickness, carotid plaques, carotid stenosis, and mortality in community-dwelling adults. *International Journal of Environmental Research and Public Health*, 17(13): 1–14.

Yuyun, M.F., Sliwa, K., Kengne, A.P., Olga, A. & Bukhman, G. 2020. Cardiovascular Diseases in Sub-Saharan Africa Compared to High-Income Countries : An Epidemiological Perspective. *Global Heart*, 15(1): 1–18.

Zhang, L., Fan, F., Qi, L., Jia, J., Yang, Y., Li, J. & Zhang, Y. 2019. The association between carotid intima- media thickness and new-onset hypertension in a Chinese community-based population. *BMC Cardiovascular Disorders*, 19(269): 1–6.

Zhang, Y., Guallar, E., Qiao, Y. & Wasserman, B.A. 2014. Is carotid intima-media thickness as predictive as other noninvasive techniques for the detection of coronary artery disease? *Arteriosclerosis, Thrombosis, and Vascular Biology*, 34(7): 1341–1345.

Chapter 4 – GENERAL CONCLUSION

This is the first study in central SA describing the profile of patients with CAD based on CIMT measurements. This study aimed to assess the impact of an abnormal CIMT on intra- and post-operative outcomes in ACS patients receiving CABG surgery. It was hypothesized that patients with pronounced/thickened CIMTs would present with worse intra- and post-operative measurable outcomes and complications. Although the study demonstrated no association between abnormal CIMT and increased intra- and post-operative outcomes, it did indicate that an abnormal CIMT is associated with certain pre-operative risk factors.

Currently, the early detection of atherosclerosis is receiving increased attention as an important topic in medicine. Change in CIMT over time can be readily assessed, and clinical trials showed that the rate of change is modifiable with treatment.. A preventive approach that is driven by measurement of CIMT may result in a decreased rate of cardiovascular events at a reasonable cost.

The clinical significance of using CIMT to predict future cardiovascular risk is well described in large epidemiological studies. This study is pivotal in discussing CIMTs clinical utility in the primary prevention of CHD in the population investigated. CIMT using carotid ultrasonography is a non-invasive method used during medical examinations to evaluate carotid plaque formation to help prevent increased risk of future CVD.

This study demonstrated an association between abnormal CIMT and pre-operative risk factors such as diabetes, hypertension and NT-Pro BNP. The anthropometric analysis showed that patients with an abnormal CIMT had a significantly higher BMI and were significantly more overweight than those with a normal CIMT. These findings emphasise the importance of maintaining a healthy BMI, especially in the current environment of increased consumption of processed, high sodium food, decreased physical activity and smoking. These lifestyle choices increase the chances of stroke and CHD dramatically.

Nevertheless, there was no correlation between abnormal CIMT and increased intra- and post-operative patient outcomes. The post-operative complication rate was very low and could be the reason why no association was found between abnormal CIMT and increased post-operative outcomes. Even when ≥0.09 cm was considered the abnormal CIMT cut-off value, no association was found between abnormal CIMT and increased intra- and post-operative outcomes.

The emphasis remains that increased CIMT does not indicate the use of CIMT as a tool for predicting adverse events in patients undergoing CABG surgery. However, CIMT measurement has been extensively studied and has shown to have a high potential for predicting future cardiovascular risk in patients. Data on the accepted normative values are not available because there is no widely accepted cut-off value for what constitutes an adverse/abnormal CIMT value. Many variables affect the thickening of the carotid intima in different populations, whether age, ethnicity or diet. The current guidelines show that increased CIMT is a worthwhile predictor of subsequent coronary heart disease (CHD) and stroke.

Therefore, studies with increased patient numbers are needed to confirm our observations due to the low post-operative complication rates observed. Prospective studies with adequate patient numbers will enhance the understanding of the prognostic value of CIMT, especially in the South African population, where limited data is available. These studies will also assist in establishing normative CIMT values specific to the central South African population.

Future recommendations for CIMT measurement in our facility would be to adapt automated edge detector programs instead of manual measurements to make measurements faster and less variable. An outreach programme for long-term assessment and follow-up of CIMT progression in pre-adolescence and adolescent phase must be established to develop risk stratification in those with an intermediate 10-year risk estimate.

As this study was the first in South Africa, it is important to establish a countrywide database to address the challenge of insufficient data available for analysis. As coronary heart disease is the leading cause of death worldwide, investigations into the value of non-invasive techniques such as CIMT are warranted.

Abdelatif, N., Peer, N. & Manda, S.O.M. 2021. National prevalence of coronary heart disease and stroke in South Africa from 1990–2017: a systematic review and meta-analysis. *Cardiovascular Journal of Africa*, 32(3): 156–160.

Aboyans, V., Lacroix, P., Yildiz, C., Postil, A. & Laskar, M. 2005. Common carotid intima-media thickness measurement is not a pertinent predictor for secondary cardiovascular events after coronary bypass surgery . A prospective study. *European Journal of Cardio-thoracic Surgery*, 28(3): 415–419.

Aboyans, V., Ricco, J.-B., Bartelink, M.-L.E.L., Björck, M., Brodmann, M., Cohnert, T., Collet, J.-P., Czerny, M., De Carlo, M., Debus, S., Espinola-Klein, C., Kahan, T., Kownator, S., Mazzolai, L., Naylor, A.R., Roffi, M., Röther, J., Sprynger, M., Tendera, M., Tepe, G., Venermo, M., Vlachopoulos, C. & Desormais, I. 2018. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal,. *European Heart Journal*, 39(9): 763–816.

Al-Sarraf, N., Thalib, L., Hughes, A., Houlihan, M., Tolan, M., Young, V. & McGovern, E. 2011. Cross-clamp time is an independent predictor of mortality and morbidity in low- and high-risk cardiac patients. *International Journal of Surgery*, 9(1): 104–109.

Alexi-meskishvili, V. V & Konstantinov, I.E. 2003. Surgery for Atrial Septal Defect : From the First Experiments to Clinical Practice. *Annals of Thoracic Surgery*, 76(1): 322–327.

Alfarisi, H.A.H., Mohamed, Z.B.H. & Ibrahim, M. Bin. 2020. Basic pathogenic mechanisms of atherosclerosis. *Egyptian Journal of Basic and Applied Sciences*, 7(1): 116–125.

Alramadan, M.J., Karim, N., Hossain, N., Smith, J.A., Cochrane, A., Reid, C.M. & Billah, B. 2019. Renal Disease Is Associated With Poor Outcomes Following Isolated Coronary Artery Bypass Grafting. *Global Heart*, 14(4): 347–353.

Amato, M., Veglia, F., Faire, U. De, Giral, P., Rauramaa, R., Smit, A.J., Kurl, S., Ravani, A., Frigerio, B., Sansaro, D., Bonomi, A., Tedesco, C.C., Castelnuovo, S., Mannarino, E., Humphries, S.E., Hamsten, A., Tremoli, E. & Baldassarre, D. 2017. Carotid plaque-thickness and common carotid IMT show additive value in cardiovascular risk prediction and reclassification. *Atherosclerosis*, 263: 412–419.

Amer, M.S., Maher, M.M., Omar, O.H., Reda, R.A., Elawam, A.E. & Sweed, H.S. 2010. Carotid Intima-Media Thickness Can Predict Coronary Atherosclerosis in Diabetic Elderly Patients. *European Journal of General Medicine*, 7(3): 245–249.

Amsterdam, E.A., Wenger, N.K., Brindis, R.G., Casey, D.E., Ganiats, T.G., Holmes, D.R., Jaffe, A.S., Jneid, H., Kelly, R.F., Kontos, M.C., Levine, G.N., Liebson, P.R., Mukherjee, D., Peterson, E.D., Sabatine, M.S., Smalling, R.W. & Zieman, S.J. 2014. AHA / ACC Guideline 2014 AHA / ACC Guideline for the Management of Patients With Non – ST-Elevation Acute Coronary Syndromes : Executive Summary A Report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines. *Circulation*, 130(25): 2354–2394.

Aronson, S., Boisvert, D. & Lapp, W. 2002. Isolated Systolic Hypertension Is Associated with Adverse Outcomes from Coronary Artery Bypass Grafting Surgery. *International Anesthesia Research Society*, 95(5): 1079–1784.

Aziz, M. 2016. Pathogenesis of Atherosclerosis A Review Pathophysiology. *Medical and Clinical Reviews*, 2(3): 1–6.

Barili, F., Pacini, D., D'Ovidio, M., Dang, N.C., Alamanni, F., Di Bartolomeo, R., Grossi, C., Davoli, M., Fusco, D. & Parolari, A. 2016. The Impact of EuroSCORE II Risk Factors on Prediction of Long-Term Mortality. *Annals of Thoracic Surgery*, 102(4): 1296–1303.

Bartlett, B., Ludewick, H.P., Misra, A., Lee, S. & Dwivedi, X.G. 2019. Macrophages and T cells in atherosclerosis: a translational perspective. *American journal of physiology-Heart and circulatory physiology*, 317(2): 375–386.

Basatemur, G.L., Jørgensen, H.F., Clarke, M.C.H., Bennett, M.R. & Mallat, Z. 2019. Vascular smooth muscle cells in atherosclerosis. *Nature Reviews Cardiology*, 16(12): 727–744.

Belletti, A., Castro, M.L., Silvetti, S., Greco, T., Pasin, L., Zangrillo, A., Landoni, G., Hospitalar, C., Central, L., Hospital, E.P.E., Marta, D.S., Marta, R.D.S., Medica, S., Epidemiologia, B., Maccacaro, G.A., Cliniche, S. & Festa, V. 2015. The Effect of inotropes and vasopressors on mortality : a meta-analysis of randomized clinical trials. *British journal of anaesthesia*, 115(5): 656–675.

Bergheanu, S.C. 2017. Pathophysiology and treatment of atherosclerosis: Current view and future perspective on lipoprotein modification treatment. *Netherlands heart Journal*, 25(4): 231–242.

Blankenberg, S., Zeller, T., Saarela, O., Havulinna, A.S., Kee, F., Tunstall-Pedoe, H., Kuulasmaa, K., Yarnell, J., Schnabel, R.B., Wild, P.S., Münzel, T.F., Lackner, K.J., Tiret, L., Evans, A. & Salomaa, V. 2010. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: The MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. *Circulation*, 121(22): 2388–2397.

Du Bois, D. & Du Bois, E.F. 1989. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*, 5(5): 303–313.

Bots, M.L., Evans, G.W., Tegeler, C.H. & Meijer, R. 2016. Carotid Intima - media Thickness Measurements : Relations with Atherosclerosis , Risk of Cardiovascular Disease and Application in Randomized Controlled Trials. *Chinese Medical Journal*, 129(2): 215–226.

Boulanger, C.M. 2016. Endothelium. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 36(4): e26–e31.

Brezzo, G., Simpson, J., Ameen-ali, K.E., Berwick, J. & Martin, C. 2020. Brain , Behavior , & Immunity - Health Acute effects of systemic in fl ammation upon the neuro-glial-vascular unit and cerebrovascular function. *Brain, Behavior, & Immunity - Health*, 5: 1–12.

Brown, C.H., Neufeld, K.J., Tian, J., Probert, J., Laflam, A., Max, L., Hori, D., Nomura, Y., Mandal, K., Brady, K., Hogue, C.W., Shah, A., Zehr, K., Cameron, D., Conte, J., Bienvenu, O.J., Gottesman, R., Yamaguchi, A. & Kraut, M. 2019. Effect of Targeting Mean Arterial Pressure during Cardiopulmonary Bypass by Monitoring Cerebral Autoregulation on Postsurgical Delirium among Older Patients: A Nested Randomized

Clinical Trial. *Journal of American Medical Aassociation Surgery*, 154(9): 819–826.

Bulow, N.M.H., Colpo, E., Duarte, M.F., Correa, E.F.M., Schlosser, R.S., Lauda, A., Kade, I.J. & Rocha, J.B.T. 2014. Inflammatory Response in Patients under Coronary Artery Bypass Grafting Surgery and Clinical Implications: A Review of the Relevance of Dexmedetomidine Use. *International Scholarly Research Network Anesthesiology*, 2014(3): 1–28.

Čejková, S., Králová-Lesná, I. & Poledne, R. 2016. Monocyte adhesion to the endothelium is an initial stage of atherosclerosis development. *Cor et Vasa*, 58(4): e419–e425.

Chambless, L.E., Heiss, G., Folsom, A.R., Rosamond, W., Szklo, M., Sharrett, A.R. & Clegg, L.X. 1997. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: The Atherosclerosis Risk in Communities (ARIC) study, 1987-1993. *American Journal of Epidemiology*, 146(6): 483–494.

Chen, Y., Xiong, H., Wu, D., Pirbhulal, S., Tian, X., Zhang, R., Lu, M., Wu, W. & Huang, W. 2015. Relationship of short-term blood pressure variability with carotid intima-media thickness in hypertensive patients. *BioMedical Engineering Online*, 14(1): 1–15.

Cheng, K., Mikhailidis, D.P., Hamilton, G. & Seifalian, A.M. 2002. A review of the carotid and femoral intima-media thickness as an indicator of the presence of peripheral vascular disease and cardiovascular risk factors. *Cardiovascular Research*, 54(3): 528–538.

Chioléro, R.L., Revelly, J.-P., Leverve, X., Gersbach, P., Cayeux, M.-C., Berger, M.M. & Tappy, L. 2000. Effects of cardiogenic shock on lactate and glucose metabolism after heart surgery. *Critical Care Medicine*, 28(12): 3784–3791.

Ciurică, S., Marilucy, L.-S., Loeys, B.L., Radhouani, I., Natarajan, N., Miikka Vikkula, A.H.E.M.M., Adlam, D. & Persu, A. 2019. Arterial tortuosity. *Australasian Physical and Engineering Sciences in Medicine*, 13(2): 67–70.

Colin, S., Chinetti-Gbaguidi, G. & Staels, B. 2014. Macrophage phenotypes in atherosclerosis. *Immunological reviews*, 262(1): 153–166.

Dave, T., Ezhilan, J., Vasnawala, H. & Somani, V. 2013. Plaque regression and plaque stabilisation in cardiovascular diseases. *Indian Journal of Endocrinology and Metabolism*, 17(6): 983–989.

Demers, P., Martineau, R. & Cartier, R. 2000. Outcome With High Blood Lactate Levels During Cardiopulmonary Bypass in Adult Cardiac Operation. *Annals of Thoracic Surgery*, 70(6): 2082–2086.

Dunn, J., Mythen, M. & Grocott, M. 2016. Physiology of oxygen transport. *British journal of anaesthesia*, 16(10): 341–348.

Eagle, K.A., Guyton, R.A., Davidoff, R., Edwards, F.H., Ewy, G.A., Gardner, T.J., Hart, J.C., Herrmann, H.C., Hillis, L.D., Jr, A.M.H., Lytle, B.W., Marlow, A., Nugent, W.C., Orszulak, T.A., Antman, E.M., Jr, S.C.S., Joseph, S., Anderson, J.L., Faxon, D.P., Fuster, V., Gibbons, R.J., Gregoratos, G., Halperin, J.L., Hiratzka, L.F., Hunt, S.A., Jacobs, A.K. & Ornato, J.P. 2004. ACC / AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery: Summary Article. *Circulation*, 110(9): 1168–1176.

Edmonds, H.L., Ganzel, B.L. & Austin, E.H. 2004. Cerebral oximetry for cardiac and vascular surgery. *Seminars in Cardiothoracic and Vascular Anesthesia*, 8(2): 147–166.

El-saadany, H.M., Ahmed, A. & Dharmadhikan, V. 2012. Carotid Artery Intima Media Thickness In Relation With Microalbuminuria In Patients With Type 2 Diabetes Mellitus. *Al- Azhar Assuit Medical Journal*, 10(3): 363–378.

Fitzgibbon, G.M., Kafka, H.P., Leach, A.J., Keon, W.J., Hooper, G.D. & Burton, J.R. 1996. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *Journal of the American College of Cardiology*, 28(3): 616–626.

Franck, G., Even, G., Gautier, A., Salinas, M., Loste, A., Procopio, E., Gaston, A., Morvan, M., Deschildre, C., Berissi, S., Laschet, J., Nataf, P., Nicoletti, A., Michel, J. & Caligiuri, G. 2019. Haemodynamic stress-induced breaches of the arterial intima trigger inflammation and drive atherogenesis. *European Heart Journal*, 40(11): 928–937.

Ganesan, R., Henkels, K.M., Wrenshall, L.E., Kanaho, Y., Di Paolo, G., Frohman, M.A. & Gomez-Cambronero, J. 2018. Oxidized LDL phagocytosis during foam cell formation in atherosclerotic plaques relies on a PLD2-CD36 functional interdependence. *Journal of leukocyte biology*, 103(5): 867–883.

Garcia-Alvarez, M., Marik, P. & Bellomo, R. 2014. Sepsis-associated hyperlactatemia. *Critical Care*, 18(503): 1–11.

Gaudino, M., Benedetto, U., Bakaeen, F., Rahouma, M., Tam, D.Y., Abouarab, A., Franco, A. Di, Leonard, J., Elmously, A., Puskas, J.D., Angelini, G.D., Girardi, L.N., Fremes, S.E. & Taggart, D.P. 2018. Off- Versus On-Pump Coronary Surgery and the Effect of Follow-Up Length and Surgeons ' Experience: A Meta-Analysis. *Journal of the American Heart Association*, 7(21): 1–8.

Gautam, B., Sherpa, K., Poudel, R., Shrestha, P., Sharma, D., Sah, R.K., Malla, R., Maskey, A., K.C, M.B. & Rajbhandari, S. 2019. Association of Carotid Intima Media Thickness with the severity of Coronary Artery Disease in patients undergoing Coronary Artery Bypass Graft Surgery in a tertiary care center. *Nepalese Heart Journal*, 16(2): 35–40.

Geroulakos, G., O'Gorman, D.J., Kalodiki, E., Sheridan, D.J. & Nicolaides, A.N. 1994. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. *European Heart Journal*, 15(6): 781–785.

Gonzalez, L. & Trigatti, B.L. 2017. Macrophage Apoptosis and Necrotic Core Development in Atherosclerosis: A Rapidly Advancing Field with Clinical Relevance to Imaging and Therapy. *Canadian Journal of Cardiology*, 33(3): 303–312.

Gorczyca, I., Michta, K., Pietrzyk, E. & Wożakowska-kapłon, B. 2018. Predictors of post-operative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting. *Kardiologia Poliska*, 76(1): 195–201.

Greenland, P., Alpert, J.S., Beller, G.A., Benjamin, E.J., Budoff, M.J., Fayad, Z.A., Foster, E., Hlatky, M.A., Hodgson, J.M.B., Kushner, F.G., Lauer, M.S., Shaw, L.J., Smith, S.C., Taylor, A.J., Weintraub, W.S. & Wenger, N.K. 2010. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults. *Journal of the American College of Cardiology*, 56(25): 50–103.

Habas, K. & Shang, L. 2018. Alterations in intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in human endothelial cells. *Tissue and Cell*, 54: 139–143.

Ham, S., Song, J., Shim, J., Soh, S. & Kim, H. 2018. Prognostic role of carotid intima- media thickness in off-pump coronary artery bypass surgery. *Scientific Reports*, 8(1): 1–8.

Hamad, H.A.A., Mohamed, Z.B.H. & Ibrahim, M. Bin. 2020. Basic pathogenic mechanisms of atherosclerosis. *Egyptian Journal of Basic and Applied Sciences*, 7(1): 116–125.

Hamilton, B., Kwakyi, E., Koyfman, A. & Foran, M. 2013. Diagnosis and management of acute coronary syndrome. *African Journal of Emergency Medicine*, 3(3): 124–133.

Hannawi, S.M., Hannawi, H. & Al Salmi, I. 2018. Carotid Intima Media Thickness as a Surrogate Measure for Cardiovascular Disease in Rheumatoid Arthritis: Literature Review. *Journal of Integrative Cardiology*, 4(4): 1–5.

Harskamp, R.E., Lopes, R.D., Baisden, C.E., de Winter, R.J. & Alexander, J.H. 2013. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. *Annals of surgery*, 257(5): 824–833.

Head, S., Milojevic, M., Taggart, D.P. & Puskas, J.D. 2017. Current Practice of State-of-the-Art Surgical Coronary Revascularization. *Circulation*, 136(14): 1331–1345.

Hennerici, M.G. & Neuerburg-Heusler, D. 1998. *Vascular diagnosis with ultrasound : clinical reference with case studies / Michael Hennerici, Doris Neuerburg-Heusler*. Stuttgart : New York: Thieme.

Herrington, W., Lacey, B., Sherliker, P., Armitage, J. & Lewington, S. 2016. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. *Circulation Research*, 118(4): 535–546.

Hussain, S.M.A. & Harky, A. 2019. Complications of Coronary Artery Bypass Grafting. *International Journal of Medical Reviews*, 6(1): 1–5.

Iino, K., Miyata, H., Motomura, N., Watanabe, G., Tomita, S., Takemura, H. & Takamoto, S. 2017. Prolonged Cross-Clamping During Aortic Valve Replacement Is an Independent Predictor of Postoperative Morbidity and Mortality: Analysis of the Japan Cardiovascular Surgery Database. *The Annals of Thoracic Surgery*, 103(2): 602–609.

Insull, W. 2009. The Pathology of Atherosclerosis : Plaque Development CONTINUUM OF CHANGES IN ARTERIAL. *The American journal of Medicine*, 122(1): S3–S14.

Iqbal, J., Gunn, J. & Serruys, P.W. 2013. Coronary stents: historical development , current status and future directions. *British Medical Bulletin*, 106(1): 193–211.

El Jalbout, R., Cloutier, G., Cardinal, M.H.R., Henderson, M., Lapierre, C., Soulez, G. & Dubois, J. 2018. Correction to: Carotid artery intima-media thickness measurement in children with normal and increased body mass index: a comparison of three techniques. *Pediatric Radiology*, 48(8): 1080.

Jan, A., Hayat, M.K., Khan, M.A.A. & Ullah, R. 2021. Trends in per-operative parameters and postoperative complications associated with coronary artery bypass graft surgery (CABG); a four-year retrospective study. *Pakistan Journal of Medical Sciences*, 37(7): 1734–1739.

Jöbsis, F.F. 1977. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science*, 198(4323): 1264–1267.

Kablak-Ziembicka, A., Tracz, W., Przewlocki, T., Pieniazek, P., Sokolowski, A. & Konieczynska, M. 2004. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart*, 90(11): 1286–1290.

Kamal, Y.A., Al-elwany, S., Ghoneim, A. & El-minshawy, A. 2017. Traditional predictors of in-hospital mortality after coronary artery bypass grafting : Current status. *Cardiothoracic and Vascular Science*, 1(2): 1–5.

Kanji, H.D., Schulze, C.J., Hervas-Malo, M., Wang, P., Ross, D.B., Zibdawi, M. & Bagshaw, S.M. 2010. Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. *Journal of Cardiothoracic Surgery*, 5(1): 1–9.

Kaperonis, E.A., Liapis, C.D., Kakisis, J.D., Dimitroulis, D. & Papavassiliou, V.G. 2006. Inflammation and atherosclerosis. *European Journal of Vascular and Endovascular Surgery*, 31(4): 386–393.

Kasliwal, R.R., Bansal, M., Desai, D. & Sharma, M. 2014. Carotid intima–media thickness: Current evidence, practices, and Indian experience. *Indian Journal of Endocrinology and Metabolism*, 18(1): 13–22.

Kats, D., Patel, M.D., Palta, P. & Meyer, M.L. 2016. Social support and cognition in a community- based cohort: the Atherosclerosis Risk in Communities (ARIC) study. *Age and Ageing*, 25(4): 475–480.

Kaufmann, J. & Kung, E. 2019. Factors Affecting Cardiovascular Physiology in Cardiothoracic Surgery: Implications for Lumped-Parameter Modeling. *Frontiers in Surgery*, 6(62): 1–7.

Keates, A.K., Mocumbi, A.O., Ntsekhe, M., Sliwa, K. & Stewart, S. 2017. Cardiovascular disease in Africa: epidemiological profile and challenges. *Nature Publishing Group*, 14(5): 1–21.

Kim, G. & Youn, H. 2016. Is Carotid Artery Ultrasound Still Useful Method for Evaluation of Atherosclerosis ? *Korean Circulation Journal*, 47(1): 1–8.

Kitagawa, K., Hougaku, H., Yamagami, H., Hashimoto, H., Itoh, T., Shimizu, Y., Takahashi, D., Murata, S., Seike, Y., Kondo, K., Hoshi, T., Furukado, S., Abe, Y., Yagita, Y., Sakaguchi, M., Tagaya, M., Etani, H., Fukunaga, R., Nagai, Y., Matsumoto, M. & Hori, M. 2007. Carotid intima-media thickness and risk of cardiovascular events in high-risk patients. Results of the Osaka Follow-Up Study for Carotid Atherosclerosis 2 (OSACA2 Study). *Cerebrovascular Diseases*, 24(1): 35–42.

Koch, C., Ro, R., Uhle, F., Andreas, M., Schneck, E., Weigand, M.A. & Lichtenstern, C. 2015. Prospective evaluation of regional oxygen saturation to estimate central venous saturation in sepsis. *Journal of clinical monitoring and computing*, 29: 443–453.

Kogan, A., Sternik, L., Spiegelstein, D., Preisman, S., Lavee, J., Bar, A., Malachy, A., Berkenstadt, H. & Raanani, E. 2012. The impact of hyperlactatemia on postoperative outcome after adult cardiac surgery. *Journal of Anesthesia*, 26(2): 174–178.

Kumar, A. & Cannon, C.P. 2009. Acute coronary syndromes: diagnosis and management, part I. *Mayo Clinic proceedings*, 84(10): 917–38.

Laffey, J.G., Boylan, J.F. & Cheng, D.C.H. 2002. The systemic inflammatory response to cardiac surgery. *Anesthesiology*, 97(1): 215–252.

Lemaire, A., Soto, C., Salgueiro, L., Ikegami, H., Russo, M.J. & Lee, L.Y. 2020. The impact of age on outcomes of coronary artery bypass grafting. *Journal of Cardiothoracic*

Surgery, 3: 1–8.

Lerman, B.J., Popat, R.A., Assimes, T.L., Heidenreich, P.A. & Wren, S.M. 2019. Association of Left Ventricular Ejection Fraction and Symptoms With Mortality After Elective Noncardiac Surgery Among Patients With Heart Failure. *American Medical Association*, 321(6): 572–579.

Levine, G.N., Bates, E.R., Blankenship, J.C., Bailey, S.R., Bittl, J.A., Cercek, B., Chambers, C.E., Ellis, S.G., Guyton, R.A., Hollenberg, S.M., Khot, U.N., Lange, R.A., Mauri, L., Mehran, R., Moussa, I.D., Mukherjee, D., Ting, H.H., O'Gara, P.T., Kushner, F.G., Ascheim, D.D., Brindis, R.G., Casey, D.E., Chung, M.K., De Lemos, J.A., Diercks, D.B., Fang, J.C., Franklin, B.A., Granger, C.B., Krumholz, H.M., Linderbaum, J.A., Morrow, D.A., Newby, L.K., Ornato, J.P., Ou, N., Radford, M.J., Tamis-Holland, J.E., Tommaso, C.L., Tracy, C.M., Woo, Y.J., Zhao, D.X., Halperin, J.L., Anderson, J.L., Albert, N.M., Al-Khatib, S.M., Birtcher, K.K., Bozkurt, B., Cigarroa, J.E., Curtis, L.H., Fleisher, L.A., Gentile, F., Gidding, S., Hlatky, M.A., Ikonomidis, J., Joglar, J., Kovacs, R.J., Ohman, E.M., Pressler, S.J., Sellke, F.W., Shen, W.K. & Wijeysundera, D.N. 2016. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarctionAn update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the. *Circulation*, 133(11): 1135–1147.

Li, A. le, Peng, Q., Shao, Y. qin, Fang, X. & Zhang, Y. ying. 2021. The interaction on hypertension between family history and diabetes and other risk factors. *Scientific Reports*, 11(1): 1–7.

Libby, P. 2012. Inflammation in atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 32(9): 2045–2051.

Linton, M.F., Yancey, P.G., Davies, S.S., Jerome, W.G., Linton, E.F., Song, W.L., Doran, A.C. & Vickers, K.C. 2019. *The Role of Lipids and Lipoproteins in Atherosclerosis*. MDText.com, Inc.

Liu, D., Du, C., Shao, W. & Ma, G. 2020. Diagnostic role of carotid intima-media thickness for coronary artery disease: A meta-analysis. *BioMed Research International*, 2020: 1–7.

Lu, S. & Weiser-evans, M.C.M. 2019. Nuclear Focal Adhesion Kinase. *Circulation Research*, 125(2): 167–169.

Lusis, A.J. 2010. Atherosclerosis. *Nature*, 407(6801): 233–241.

Madhavan, S., Chan, S.-P., Tan, W.-C., Eng, J., Li, B., Luo, H.-D. & Teoh, L.-K.K. 2018. Cardiopulmonary bypass time: every minute counts. *The Journal of cardiovascular surgery*, 59(2): 274–281.

Magnussen, C.G. 2017. Carotid artery intima-media thickness and hypertensive heart disease: a short review. *Clinical Hypertension*, 23(1): 1–4.

Mancia, G., Backer, G. De, Uk, A.D., Cifkova, R., Republic, C., Heagerty, A.M., France, S.L., Poland, K.N., Poland, A.R., Germany, R.E.S., Struijker, H.A.J., France, V.D., Germany, U.S., Germany, S.S., Poland, M.T., Widimsky, P., Republic, C., Cifkova, R., Republic, C., Dominiczak, A., Kingdom, U., Fagard, R., Germany, R.E.S. & Uk, B.W. 2007. 2007 Guidelines for the management of arterial hypertension The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European Heart Journal*, 28(12): 1462–1536.

Matteucci, M., Ferrarese, S., Cantore, C., Cappabianca, G., Massimi, G., Mantovani, V., Rossi, M.B. & Beghi, C. 2020. Hyperlactatemia during cardiopulmonary bypass: risk factors and impact on surgical results with a focus on the long-term outcome. *Perfusion (United Kingdom)*, 35(8): 756–762.

Mc Namara, K., Alzubaidi, H. & Jackson, J.K. 2019. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? *Integrated Pharmacy Research and Practice*, 8: 1–11.

McDonagh, D., Burger, M., Mathew, J.P., Graffagnino, C., Milano, C.A. & Newman, M.F. 2018. Neurologic Complications of Cardiac Surgery. *Lancet Neurol*, 13(5): 490–502.

McNichols, B., Spratt, J.R., George, J., Rizzi, S., Manning, E.W. & Park, K. 2021. Coronary Artery Bypass : Review of Surgical Techniques and Impact on Long-Term Revascularization Outcomes. *Cardiology and Therapy*, 10(1): 89–109.

Van Der Meer, I.M., Bots, M.L., Hofman, A., Del Sol, A.I., Van Der Kuip, D.A.M. & Witteman, J.C.M. 2004. Predictive Value of Noninvasive Measures of Atherosclerosis for Incident Myocardial Infarction: The Rotterdam Study. *Circulation*, 109(9): 1089–1094.

van der Meijden, P.E.J. & Heemskerk, J.W.M. 2019. Platelet biology and functions: new concepts and clinical perspectives. *Nature Reviews Cardiology*, 16(3): 166–179.

Melly, L., Torregrossa, G., Lee, T., Jansens, J.L. & Puskas, J.D. 2018. Fifty years of coronary artery bypass grafting. *Journal of Thoracic Disease*, 10(3): 1960–1967.

Mills, K.T., Stefanescu, A. & He, J. 2016. The global epidemiology of hypertension Katherine. *Physiology & behavior*, 176(1): 139–148.

Minelli, S., Minelli, P. & Montinari, M.R. 2020. Reflections on Atherosclerosis: Lesson from the Past and Future Research Directions. *Journal of Multidisciplinary Healthcare*, 13: 621–633.

Minton, J. & Sidebotham, D.A. 2017. Hyperlactatemia and cardiac surgery. *Journal of Extra-Corporeal Technology*, 49(1): 7–15.

Mirjafari, H., Welsh, P., Verstappen, S.M.M., Wilson, P., Marshall, T., Edlin, H., Bunn, D., Chipping, J., Lunt, M., Symmons, D.P.M., Sattar, N. & Bruce, I.N. 2014. N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) and mortality risk in early inflammatory polyarthritis: Results from the Norfolk Arthritis Registry (NOAR). *Annals of the Rheumatic Diseases*, 73(4): 684–690.

Mizock, B.A. 2016. *Specifi c Disorders Lactic Acidosis — Clinical Syndrome*.

Murkin, J.M., Adams, S.J., Novick, R.J., Quantz, M., Bainbridge, D., Iglesias, I., Cleland, A., Schaefer, B., Irwin, B. & Fox, S. 2007. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesthesia and analgesia*, 104(1): 51–58.

Nadeem, R., Agarwal, S., Jawed, S. & Yasser, A. 2019. Impact of Cardiopulmonary Bypass Time on Postoperative Duration of Mechanical Ventilation in Patients Undergoing Cardiovascular Surgeries : A Systemic Review and Regression of Metadata. *Cureus*, 11(11): 1–7.

Nashef, S.A.M., Roques, F., Michel, P., Gauducheau, E., Lemeshow, S. & Salamon, R. 1999. European system for cardiac operative risk evaluation (Euro SCORE). *European Journal of Cardio-thoracic Surgery*, 16(1): 9–13.

Nashef, S.A.M., Roques, F., Sharples, L.D., Nilsson, J. & Smith, C. 2012. EuroSCORE II. *European Journal of Cardio-thoracic Surgery*, 41(4): 734–745.

Nerlekar, N., Ha, F.J., Verma, K.P., Bennett, M.R., Cameron, J.D., Meredith, I.T. & Brown, A.J. 2016. Percutaneous Coronary Intervention Using Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Unprotected Left Main Coronary Artery Stenosis. *Circulation Cardiovascular Interventions*, 9(12): 1–8.

Newman, M.F., Mathew, J.P., Grocott, H.P., Mackensen, G.B., Monk, T., Welsh-Bohmer, K.A., Blumenthal, J.A., Laskowitz, D.T. & Mark, D.B. 2006. Central nervous system injury associated with cardiac surgery. *Lancet (London, England)*, 368(9536): 694–703.

Nuttall, F.Q. 2015. Body Mass Index. *Nutrition Today*, 50(3): 117–128.

O'Brien, S.M., Feng, L., He, X., Xian, Y., Jacobs, J.P., Badhwar, V., Kurlansky, P.A., Furnary, A.P., Cleveland, J.C., Lobdell, K.W., Vassileva, C., Wyler von Ballmoos, M.C., Thourani, V.H., Rankin, J.S., Edgerton, J.R., D'Agostino, R.S., Desai, N.D., Edwards, F.H. & Shahian, D.M. 2018. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2—Statistical Methods and Results. *The Annals of Thoracic Surgery*, 105(5): 1419–1428.

Paech, D.C. & Weston, A.R. 2011. A systematic review of the clinical effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of suspected coronary artery disease. *BMC Cardiovascular Disorders*, 11(32): 1–11.

Passaroni, A.C., Augusto, M. & Silva, D.M. 2015. Cardiopulmonary bypass: development of John Gibbon's heart-lung machine. *Brazilian Journal of Cardiovascular Surgery*, 30(2): 235–245.

Patzelt, J., Verschoor, A. & Langer, H.F. 2015. Platelets and the complement cascade in atherosclerosis. *Vascular Pathology*, 6(49): 1–9.

Pignoli, P., Tremoli, E., Poli, A., Oreste, P. & Paoletti, R. 1986. Intimal plus medial thickness of the arterial wall : direct measurement with ultrasound imaging a. *Circulation*, 74(6): 1399–1406.

Polak, J.F., Szklo, M. & Leary, D.H.O. 2017. Carotid Intima-Media Thickness Score, Positive Coronary Artery Calcium Score, and Incident Coronary Heart Disease: The Multi-Ethnic Study of Atherosclerosis. *Journal of the American Heart Association*, 6(1): 1–8.

Randrianarisoa, E., Rietig, R., Jacob, S., Blumenstock, G., Haring, H., Rittig, K. & Balletshofer, B. 2015. Normal values for intima-media thickness of the common carotid artery – An update following a novel risk factor profiling. *European Journal of Vascular Medicine*, 44(6): 444–450.

Ranucci, M., Carboni, G., Cotza, M., Bianchi, P., Di Dedda, U. & Aloisio, T. 2015. Hemodilution on Cardiopulmonary Bypass as a Determinant of Early Postoperative Hyperlactatemia C. Lazzeri, ed. *Public Library of Science One*, 10(5): 1–10.

Ranucci, M., Isgrò, G., Ranucci, M., Toffol, B. De, Isgrò, G., Romitti, F. & Conti, D. 2006. Hyperlactatemia during cardiopulmonary bypass: Determinants and impact on postoperative outcome Hyperlactatemia during cardiopulmonary bypass : determinants and impact on postoperative outcome. *Critical Care*, 10(6): 1–9.

Rashid, S.A. & Mahmud, S.A. 2015. Correlation between carotid artery Intima-media thickness and luminal diameter with body mass index and other cardiovascular risk factors in adults. *Sultan Qaboos University Medical Journal*, 15(3): e344–e350.

Ravani, A., Werba, J.P., Frigerio, B., Sansaro, D., Amato, M., Tremoli, E. & Baldassarre, D. 2015. Assessment and relevance of carotid intima-media thickness (C-IMT) in primary and secondary cardiovascular prevention. *Current pharmaceutical design*, 21(9): 1164–1171.

Reiche, S., Mpanya, D., Vanderdonck, K., Mogaladi, S. & Motshabi-chakane, P. 2021. Perioperative outcomes of coronary artery bypass graft surgery in Johannesburg, South Africa. *Journal of cardiothoracic surgery*, 16(7): 1–8.

Riley, R.F., Don, C.W., Powell, W., Maynard, C. & Dean, L.S. 2011. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circulation. Cardiovascular quality and outcomes*, 4(2): 193–197.

Roberto, P., Evora, B., Ii, C.B., Iii, L.A., Afrodite, A., Albuquerque, S., Martinez, P., Évora, V., José, A. & Vi, R. Key Points for Curbing Cardiopulmonary Bypass Inflammation 1. *Acta Cirurgia Brasileria*, 31(1): 45–52.

Rocha, E.A.V. 2017. Fifty Years of Coronary Artery Bypass Graft Surgery. *Brazilian Journal of Cardiovascular Surgery*, 32(4): II–III.

Rosenson, R.S., Hegele, R.A., Fazio, S. & Cannon, C.P. 2018. The Evolving Future of PCSK9 Inhibitors. *Journal of the American College of Cardiology*, 72(3): 314–329.

Ross, R. 1999. Atherosclerosis--an inflammatory disease. *The New England journal of medicine*, 340(2): 115–126.

Ryde'n, L., Grant, P.J. & Anker, S.D. 2014. ESC Guidelines on diabetes , pre-diabetes , and cardiovascular diseases developed in collaboration with the EASD – Summary : The Task Force on diabetes , pre-diabetes , and Cardiology (ESC) and developed in collaboration with the European Association fo. *Diabetes and Vascular Disease Research*, 11(3): 133–173.

Safaie, N., Montazerghaem, H., Jodati, A. & Maghamipour, N. 2015. In-Hospital Complications of Coronary Artery Bypass Graft Surgery in Patients Older Than 70 Years. *Journal of Cardiovascular Thoracic Research*, 7(2): 60–62.

Salonen, J.T. & Salonen, R. 1991. Ultrasonographically Assessed Carotid Morphology and the Risk of Coronary Heart Disease. *Atherosclerosis and Thrombosis*, 11(5): 1245–1249.

Sarkar, M. & Prabhu, V. 2017. Basics of cardiopulmonary bypass. *Indian Journal of Anesthesia*, 61(9): 72–79.

Saxena, Y., Saxena, V., Mittal, M., Srivastava, M. & Raghuvanshi, S. 2017. Age-wise association of carotid intima media thickness in ischemic stroke. *Annals of Neurosciences*, 24(1): 5–11.

Scheeren, T.W.L., Schober, P. & Schwarte, L.A. 2012. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. *Journal of clinical* *monitoring and computing*, 26(4): 279–287.

Serraino, G.F., Provenzano, M., Jiritano, F., Michael, A., Ielapi, N., Mastroroberto, P., Andreucci, M. & Id, R.S. 2021. Risk factors for acute kidney injury and mortality in high risk patients undergoing cardiac surgery. *The Public Library of Science One*, 16(5): 1–13.

Shaefi, S., Mittel, A., Klick, J., Evans, A., Ivascu, N.S., Gutsche, J. & Augoustides, J.G.T. 2018. Vasoplegia After Cardiovascular Procedures & Pathophysiology and Targeted Therapy. *Journal of Cardiothoracic and Vascular Anesthesia*, 32(2): 1013–1022.

Shahian, D.M., O'Brien, S.M., Filardo, G., Ferraris, V.A., Haan, C.K., Rich, J.B., Normand, S.-L.T., DeLong, E.R., Shewan, C.M., Dokholyan, R.S., Peterson, E.D., Edwards, F.H. & Anderson, R.P. 2009. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. *The Annals of thoracic surgery*, 88(1): 2–22.

Shultz, B., Timek, T., Davis, A.T., Heiser, J., Murphy, E., Willekes, C. & Hooker, R. 2016. Outcomes in patients undergoing complex cardiac repairs with cross clamp times over 300 minutes. *Journal of Cardiothoracic Surgery*, 11(1): 1–8.

Silvestre-Roig, C., Braster, Q., Ortega-Gomez, A. & Soehnlein, O. 2020. Neutrophils as regulators of cardiovascular inflammation. *Nature Reviews Cardiology*, 17(6): 327–340.

Singh, S., Nagra, A., Maheshwari, P., Panwar, R., Hecht, H., Fukumoto, T., Bansal, M., Panthagani, D., Lammertin, G., Kasliwal, R., Mishra, H., Hofstra, L., Singh, M.P., Fuster, V., Sengupta, P.P. & Narula, J. 2013. Rapid Screening for Subclinical Atherosclerosis by Carotid Ultrasound Examination. *Global Heart*, 8(2): 83–89.

Smith, J.N. & Negrelli, J.M. 2015. Diagnosis and Management of Acute Coronary Syndrome : An Evidence-Based Update. *Journal of the American Board of Family Medicine*, 28(2): 283–293.

Stamou, S.C., Nussbaum, M., Stiegel, R.M., Reames, M.K., Skipper, E.R., Robicsek, F. & Lobdell, K.W. 2011. Effect of Body Mass Index on Outcomes After Cardiac Surgery: Is There an Obesity Paradox? *The Annals of Thoracic Surgery*, 91(1): 42–47.

Stefanini, G.G. & Holmes, D.R. 2013. Drug-Eluting Coronary-Artery Stents. *The New England* *journal of medicine*, 386(3): 254–265.

Stein, J.H., Korcarz, C.E., Hurst, R.T., Lonn, E., Kendall, C.B., Mohler, E.R., Najjar, S.S., Rembold, C.M. & Post, W.S. 2008. Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force Endorsed by the Society for Vascula. *Journal of the American Society of Echocardiography*, 21(2): 93–111.

Strange, J.W. 2008. Assessment and management of acute coronary syndrome. *The Foundation Years*, 4(3): 99–105.

Sun, H.J., Wu, Z.Y., Nie, X.W. & Bian, J.S. 2020. Role of endothelial dysfunction in cardiovascular diseases: The link between inflammation and hydrogen sulfide. *Frontiers in Pharmacology*, 10(1568): 1–15.

Svanteson, M., Rollefstad, S., Kløw, N.E., Hisdal, J., Ikdahl, E., Semb, A.G. & Haig, Y. 2017. Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. *Rheumatic and Musculoskeletal Disease Open*, 3(2): 1–8.

Tabei, S.M.B., Senemar, S., Saffari, B., Ahmadi, Z. & Haqparast, S. 2014. Non-modifiable Factors of Coronary Artery Stenosis in Late Onset Patients with Coronary Artery Disease in Southern Iranian Population. *Journal of cardiovascular and thoracic research*, 6(1): 51–55.

Touboul, P., Hannerici, M., Meairs, S. & Adams, H. 2013. Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004–2006–2011): An Update on Behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgi. *Cerebrovascular Disease Disease*, 34(4): 290–296.

de Tournay-Jetté, E., Dupuis, G., Bherer, L., Deschamps, A., Cartier, R. & Denault, A. 2011. The Relationship Between Cerebral Oxygen Saturation Changes and Postoperative Cognitive Dysfunction in Elderly Patients After Coronary Artery Bypass Graft Surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, 25(1): 95–104.

Trzeciak, S. & Rivers, E.P. 2005. Clinical manifestations of disordered microcirculatory perfusion in severe sepsis Review Clinical manifestations of disordered microcirculatory perfusion in severe sepsis. *Critical care*, 9(4): S20–S26.

Valezquez, E.J., Lee, K., Jones, R., Al-Khalid, H., Hill, J.A., Panza, J.A., Michler, R.E., Bonow, R.O., Doenst, T., Petrie, M.C., Oh, J.K., She, L., Ph, D., Moore, V.L., Nickens, P.D., Sopko, G. & Rouleau, J.L. 2016. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *The New England Journal of Medicine*, 374(16): 1511–1520.

Vretzakis, G., Georgopoulou, S., Stamoulis, K., Stamatiou, G., Tsakiridis, K., Zarogoulidis, P., Katsikogianis, N., Kougioumtzi, I., Machairiotis, N., Tsiouda, T., Mpakas, A., Beleveslis, T., Koletas, A., Siminelakis, S.N. & Zarogoulidis, K. 2014. Cerebral oximetry in cardiac anesthesia. *Journal of Thoracic Disease*, 6(1): 60–69.

Vretzakis, G., Georgopoulou, S., Stamoulis, K., Tassoudis, V., Mikroulis, D., Giannoukas, A., Tsilimingas, N. & Karanikolas, M. 2013. Monitoring of brain oxygen saturation (INVOS) in a protocol to direct blood transfusions during cardiac surgery : a prospective randomized clinical trial. *Journal of Cardiothoracic Surgery*, 8(145): 1–9.

Wahba, A., Milojevic, M., Boer, C., De Somer, F.M.J.J., Gudbjartsson, T., Van Den Goor, J., Jones, T.J., Lomivorotov, V., Merkle, F., Ranucci, M., Kunst, G., Puis, L., Alston, P., Fitzgerald, D., Nikolic, A., Onorati, F., Steen Rasmussen, B. & Svenmarker, S. 2020. 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. *European Journal of Cardio-thoracic Surgery*, 57(2): 210–251.

Wang, X., Wang, T. & Jiang, W. 2020. Non-Invasive Regional Cerebral Oxygen Saturation (rSO 2) and Postoperative Neurological Dysfunction. *Gerontology & Geriatrics Research*, 6(1): 1–4.

Weber, L.A., Cheezum, M.K., Reese, J.M., Lane, A.B., Haley, R.D., Lutz, M.W. & Villines, T.C. 2015. Cardiovascular Imaging for the Primary Prevention of Atherosclerotic Cardiovascular Disease Events. *Current Cardiovascular Imaging Reports*, 8(36): 1–13.

Weissgerber, A., Scholz, M., Teren, A., Sandri, M., Teupser, D., Gielen, S., Thiery, J. & Schuler, G. 2016. The value of noncoronary atherosclerosis for identifying coronary artery disease: results of the Leipzig LIFE Heart Study. *Clinical Research in Cardiology*, 105(2): 172–181.

Willeit, P., Tschiderer, L., Allara, E., Reuber, K., Seekircher, L., Gao, L., Liao, X., Lonn, E., Gerstein, H.C., Yusuf, S., Brouwers, F.P., Asselbergs, F.W., Van Gilst, W., Anderssen, S.A., Grobbee, D.E., Kastelein, J.J.P., Visseren, F.L.J., Ntaios, G., Hatzitolios, A.I., Savopoulos, C., Nieuwkerk, P.T., Stroes, E., Walters, M., Higgins, P., Dawson, J., Gresele, P., Guglielmini, G., Migliacci, R., Ezhov, M., Safarova, M., Balakhonova, T., Sato, E., Amaha, M., Nakamura, T., Kapellas, K., Jamieson, L.M., Skilton, M., Blumenthal, J.A., Hinderliter, A., Sherwood, A., Smith, P.J., Van Agtmael, M.A., Reiss, P., Van Vonderen, M.G.A., Kiechl, S., Klingenschmid, G., Sitzer, M., Stehouwer, C.D.A., Uthoff, H., Zou, Z.Y., Cunha, A.R., Neves, M.F., Witham, M.D., Park, H.W., Lee, M.S., Bae, J.H., Bernal, E., Wachtell, K., Kjeldsen, S.E., Olsen, M.H., Preiss, D., Sattar, N., Beishuizen, E., Huisman, M. V., Espeland, M.A., Schmidt, C., Agewall, S., Ok, E., Aşçi, G., De Groot, E., Grooteman, M.P.C., Blankestijn, P.J., Bots, M.L., Sweeting, M.J., Thompson, S.G. & Lorenz, M.W. 2020. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: Meta-Analysis of 119 clinical trials involving 100 667 patients. *Circulation*, 142(7): 621–642.

Yang, C.W., Guo, Y.C., Li, C.I., Liu, C.S., Lin, C.H., Liu, C.H., Wang, M.C., Yang, S.Y., Li, T.C. & Lin, C.C. 2020. Subclinical atherosclerosis markers of carotid intima-media thickness, carotid plaques, carotid stenosis, and mortality in community-dwelling adults. *International Journal of Environmental Research and Public Health*, 17(13): 1–14.

Youn, Y.J., Lee, N.S., Kim, J.Y., Lee, J.W., Sung, J.K., Ahn, S.G., You, B.S., Lee, S.H., Yoon, J., Choe, K.H., Koh, S.B. & Park, J.K. 2011. Normative values and correlates of mean common carotid intima-media thickness in the Korean rural middle-aged population: The atherosclerosis RIsk of rural areas iN Korea general population (ARIRANG) study. *Journal of Korean Medical Science*, 26(3): 365–371.

Yuyun, M.F., Sliwa, K., Kengne, A.P., Olga, A. & Bukhman, G. 2020. Cardiovascular Diseases in Sub-Saharan Africa Compared to High-Income Countries : An Epidemiological Perspective. *Global Heart*, 15(1): 1–18.

Zhang, K., Qian, S.C., Pan, X.D., Dong, S.B., Zheng, J., Liu, H., Wang, Y.L. & Sun, L.Z. 2020. The use of cIMT as a predictor of postoperative stroke in patients undergoing surgical repair of acute type a aortic dissection. *Journal of Cardiothoracic Surgery*, 15(1): 1–8.

Zhang, L., Fan, F., Qi, L., Jia, J., Yang, Y., Li, J. & Zhang, Y. 2019. The association between carotid intima- media thickness and new-onset hypertension in a Chinese community-based population. *BMC Cardiovascular Disorders*, 19(269): 1–6.

Zhang, Y., Guallar, E., Qiao, Y. & Wasserman, B.A. 2014. Is carotid intima-media thickness as predictive as other noninvasive techniques for the detection of coronary artery disease? *Arteriosclerosis, Thrombosis, and Vascular Biology*, 34(7): 1341–1345.

APPENDICES

Appendix A1: 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

08-Jan-2021

Dear **Mr Victor Mokoena**

Ethics Clearance: **Association between carotid intima-media thickness and patient outcomes in coronary artery disease in Central South Africa**
Principal Investigator: **Mr Victor Mokoena**
Department: **Environmental Health Sciences - 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-HSD2020/1708/2601**

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 A2: Department of Health Approval Letter

health
Department of Health
FREE STATE PROVINCE

02 December 2020

Mr V Mokoena
Depart. Of Environmental Health Science
CUT

Dear Mr. V Mokoena

Subject: Association between carotid intima-media thickness and patient outcomes in coronary artery disease in Central South Africa.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Unversitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / makenamr@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 7/12/2020

Head : Health
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