THE DEMOGRAPHICS OF CARDIOVASCULAR MORTALITY AMONG CARDIAC PATIENTS ADMITTED IN A CARDIAC INTENSIVE CARE UNIT (2010–2017) AT THE CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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DECLARATION

I, Amir Abe Idris, declare that this dissertation is my own work. It is being submitted for the degree Master of Medicine (MMed) in Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination at any other university.

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DEDICATION

I dedicate this work to my late father, Gen. Abe Idris, my late mother, Mecca Idris Suleiman, my son, Bilal Idris and my daughter, Layla Idris, for their love and support throughout my career.

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EXECUTIVE SUMMARY

Statement of purpose

The purpose of this retrospective study was to describe the demographic and clinical characteristics, laboratory biochemical findings and the prevalence of associated risk factors among patients with coronary artery disease, who demised in the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Coronary Care Unit (CCU) during the period 2010–2017.

Overview

Cardiovascular diseases (CVDs) are the leading cause of death globally, with more than four out of five CVD deaths being attributable to stroke and heart attack. The prevalence of total CVD cases has almost doubled from 271 million in 1990 to 523 million in 2019. Furthermore, it is estimated that 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. An increase in non-communicable diseases (NCDs) has been noted in sub-Saharan Africa (SSA), with a higher incidence in CVDs noted to be affecting the general SSA population. Of the top ten causes of natural death in South Africa, CVDs ranked third and showed an increase over the past years. In 2011, the Word Economic Forum (WEF) projected a US$47 trillion loss in economic output by 2030 due to the increasing burden of NCDs.

A reduction in mortality from acute myocardial infarction (AMI) has occurred with the development of the coronary care unit (CCU). The CCU has been termed the most significant innovation in cardiology concerning the management of AMI. Its contribution to the decrease in mortality from AMI has been well documented in the literature over the past 30 years. However, the CCU has evolved remarkably over the past decades. The modern-day CCU has transformed into a blended integration between the CCU and cardiology wards, and CCU and intensive care units (ICU) or high care units. Cardiologists must be trained and competent in skills generally mastered by ICU specialists, such as the management of septic shock, critical illness neuropathy, renal replacement therapy (RRT), provision of ventilatory support and neuropsychiatric complications such as delirium.

Despite the increasing burden of NCDs and the changing face of the CCU, SSA is still confronted with an insufficient healthcare infrastructure, poor delivery systems, lack of specialist cardiology services and drug shortages. There is a severe shortage of percutaneous

coronary intervention (PCI) capable facilities in South Africa, with a total of less than 70 facilities in both the public and private healthcare sectors. Currently, there is no standardised source of data for CVD mortality in SSA and, in particular, South Africa. Locally, there is also a paucity of data reporting mortality rates in CCUs, with specific emphasis on risk factors related to acute coronary syndrome (ACS).

This study provides vital information regarding the demographic and clinical characteristics, biochemical parameters and risk factors of the non-surviving patients admitted to a modern-day CCU. The aim of the study was to contribute towards the development of management guidelines, resource allocation, employing severity scoring systems for predicting mortality in the CCU population, as well as developing patient selection criteria for CCU admission based on mortality risk scoring, to improve overall patient care.

In this retrospective study, a cohort of patients who died at the CMJAH CCU from January 2010 to December 2017 was identified. Data were collected from the patients' CCU discharge summary forms and the cardiology department database. Data from this study will be submitted for publication in the *Cardiovascular Journal of Africa* and presented to the relevant health authorities.

Keywords

acute coronary syndrome; acute myocardial infarction; cardiac care unit; cardiovascular disease; cause of death; CCU; comorbidities; coronary artery disease; mortality; non-communicable diseases; risk factors

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACCESS	Acute Coronary Events – a multinational Survey of current management Strategies
ACE-I	angiotensin converting enzyme inhibitors
ACS	acute coronary syndrome
AHA	American Heart Association
AHF	acute heart failure
AKD	acute kidney disease
AKI	acute kidney injury
AMI	acute myocardial infarction
APACHE	Acute Physiology and Chronic Health Evaluation
APS	acute physiology score
ARB	angiotensin receptor blockers
ARDS	acute respiratory distress syndrome
ARNI	angiotensin receptor neprilysin inhibitor
ART	antiretroviral therapy
BNP	B-type natriuretic peptide
BTS	British Thoracic Society
CABG	coronary artery bypass graft
CAD	coronary artery disease
CANVAS	Canagliflozin Cardiovascular Assessment Study trial
CAUTI	catheter-associated urinary tract infection
CCU	coronary care unit
CHD	coronary heart disease
CICU	cardiac intensive care unit
CKD	chronic kidney disease
CK-MB	creatinine kinase MB
CLABSI	central line-associated blood stream infection
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CoBaTrICE	Competency-Based Training in Intensive Care Medicine in Europe
COX	cyclo-oxygenase
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CRP	C-reactive protein

CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
DAPT	dual anti-platelet therapy
DCMO	dilated cardiomyopathy
DECLARE-TIMI 58	Dapagliflozin Effect in Cardiovascular Events – Thrombolysis In Myocardial Infarction 58 trial
DOAC	direct oral anticoagulant
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
EHFS	EuroHeart Failure Survey
ELAIN	Early versus Late Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury Randomized Clinical Trial
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction trial
EMS	emergency medical services
ESC	European Society of Cardiology
GCS	Glascow Coma Scale
GFR	glomerular filtration rate
GISSI	Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico trial
GIT	gastrointestinal tract
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
HAI	hospital-acquired infection
Hb	haemoglobin
HDL	high-density lipoprotein
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HHF	hospitalisation for heart failure
HIV	human immunodeficiency virus
HOCM	hypertrophic obstructive cardiomyopathy
HREC	Human Research Ethics Committee

hs-CRP	high-sensitivity CRP
IABP	intra-aortic balloon pump
ICMO	ischaemic cardiomyopathy
ICU	intensive care unit
IE	infective endocarditis
IHD	ischaemic heart disease
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	low-density lipoprotein
LMWH	low molecular weight heparin
LOS	length of stay
LV	left ventricle
MCS	mechanical circulatory support
MIRU	Myocardial Infarction Research Unit
MRA	mineralocorticoid receptor antagonists
MRI	magnetic resonance imaging
NCD	non-communicable diseases
NSTE-ACS	non-ST segment elevation acute coronary syndrome
NSTEMI	non-ST segment elevation myocardial infarction
NYHA	New York Heart Association
PARADIGM-HF	Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure trial
PCI	percutaneous coronary intervention
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrillin (eptifibatide) Therapy
RDW	red cell distribution width
REDCap™	Research Electronic Data Capture
RHD	rheumatic heart disease
RRT	renal replacement therapy
SBP	systolic blood pressure
SFA	superficial femoral artery
SGLT-2	sodium-glucose co-transporter 2
SOFA	Sequential Organ Failure Assessment
SPECT	single-photon emission computed tomography
SSA	sub-Saharan Africa
STEMI	ST-segment elevation myocardial infarction

SYNTAX	Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery trial
THESUS-HF	The Sub-Saharan African Survey of Heart Failure
TIBC	total iron-binding capacity
TIMI	thrombolysis in myocardial infarction
tPA	tissue plasminogen activator
TTM	targeted temperature management
UA	unstable angina
UMass	University of Massachusetts
US	United States
VAD	ventricular assist device
VALI	ventilator-associated lung injury
VAP	ventilator-associated pneumonia
VKA	vitamin K antagonists
VTE	venous thromboembolism
WHO	World Health Organization

CHAPTER 1
LITERATURE REVIEW

1.1 INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death globally, with more than four out of five CVD-related deaths being attributable to stroke and heart attack. These diseases are a heterogenous group of disorders that affect the heart and the blood vessels. The spectrum of disease includes rheumatic heart disease (RHD), coronary heart disease (CHD), cardiomyopathy and heart Failure (HF), dysrhythmias, cerebrovascular disease, congenital heart disease and venous thromboembolism (VTE).[1]

The prevalence of CVD is on the rise and has thus been labelled a true pandemic. This pandemic, however, is dynamic due to changes in risk factors and advancements in interventions for prevention and treatment.[2] The changes in risk factors can be explained by urbanisation of communities that has led to lifestyle changes, changes in dietary intake, prevalence of comorbid conditions and an aging population.[2,3]

Morbidity and mortality rates vary globally, with noted increases in developing countries. This reflects that CVDs transcend borders, socioeconomic and racial borders.[2]

An escalation in non-communicable diseases has also been observed in sub-Saharan Africa (SSA), with an increase in CVDs noted to be affecting the general population of this region.[3] Although CVD-related mortality has decreased over the past few decades, the disease burden not only stems from mortality, but also from the morbidity and number of people living with the diseases.[3,4]

In South Africa, mortality from diseases of the cardiovascular system showed an increase from 18.4% in 2016 to 18.9% in 2018. Of the top 10 causes of natural death in South Africa, CVDs ranked third. This is one position higher compared to the previous years (2016–2017). Ischaemic heart disease (IHD), although ranked eighth, also moved up one position. Diabetes and hypertension ranked second and sixth position, respectively. These two conditions are important traditional risk factors for CVD.[5]

Currently, there is no standardised source of information on CVD mortality in SSA and in particular, South Africa. Locally, there is also a paucity of data regarding mortality rates in coronary care units (CCUs), with more emphasis on risk factors associated with acute coronary

syndromes (ACS). In a multinational survey of current management strategies, Schamroth *et al*. analysed 642 South African patients with ACS, and found an all-cause death rate of 5.7% at 12 months after an ACS event. The mortality rate was higher among patients with ST-segment elevation myocardial infarction (STEMI) compared to non-STEMI (NSTEMI) patients.[6] Furthermore, other non-ischaemic aetiologies have been documented to contribute to CCU mortalities. In the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF study),[7] acute heart failure (AHF) of non-ischaemic aetiology (hypertension, rheumatic heart disease and endemic cardiomyopathies) was associated with a high mortality rate. Enakpene *et al*.[8] reported that a risk factor notably associated with both ischaemic and non-ischaemic heart disease was human immunodeficiency virus (HIV) infection. The prevalence of hypertension was increased three-fold in patients on combination antiretroviral therapy (ART).[8]

1.2 EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES

In 2021, the World Health Organization (WHO) reported that globally, the prevalence of total CVD cases has almost doubled from 271 million in 1990 to 523 million in 2019. It has been estimated that 17.9 million people died in 2019 from CVDs, representing 32% of all global deaths.[1]

Cardiovascular diseases were formerly regarded as a disease of high-income countries but the opposite is now true. Over three quarters of CVD deaths occur in low- and middle-income countries.[9,10] By the turn of the 21st century, IHD ranked eighth among the leading killers on the African continent in both men and women, slightly behind cerebrovascular disease. Ample data are available from sub-Saharan Africa, implicating that CHD was rare up until the mid-20th century.[11]

Cardiovascular diseases are a growing cause of mortality and disability in South Africa and SSA in general, partly as a result of the increasing prevalence of determinants and risk factors for CVD in these societies in transition.[12] One of the postulated explanations for this shift from the predominance of communicable diseases to an increased occurrence of non-communicable diseases is that life expectancy has increased in these countries. This can further be explained in the context of a decline in infant and child mortality rates and socioeconomic development. Socioeconomic development has also led to changes in environmental and behavioural determinants such as smoking and a sedentary lifestyle. Improvement in healthcare services and vaccination programmes has also occurred as a result of socioeconomic development.[12]

1.3 EVOLUTION OF CORONARY CARE UNITS

Although the development of the concept and significance of coronary care units (CCUs) in the early 1960s has most commonly been credited to Desmond Julian, a senior registrar and cardiologist at the Edinburgh Royal Infirmary, United Kingdom,[13,14] Hughes Day in the United States of America (USA) and Kenneth Brown in Canada have been recognised for development of the concept in their parts of the world.[15] Moreover, in the articles by Fye *et al*.[16] and Gidwani *et al*.,[17] recognition and credit had been given to Morris Wilburne for defining the concept of the CCU in the USA and terming it as such, on the basis of his abstract published in *Circulation* in October 1961.[16,17] At an almost similar time in 1961, in a different part of the world, in a different context, Julian's article to the British Thoracic Society (BTS) was also published in the *Lancet.* As such, it is difficult to attribute the development of the concept of CCU to one particular person. Furthermore, the pioneers of the CCU could be described in two cohorts: those that played a critical role in developing the concept and those implementing the concept.[16]

From the perspective that early recognition and management of arrhythmias post-MI would prevent death, Julian's vision of the CCU was based on four principles, namely:[14]

i. continuous electrocardiogram (ECG) monitoring with arrhythmia alarms;
ii. cardiopulmonary resuscitation (CPR) with external defibrillator capabilities;
iii. admission of patients with acute MI (AMI) to a single unit of the hospital where trained personnel, cardiac medications and specialised equipment were immediately available; and
iv. the ability of trained nurses to initiate resuscitation attempts in the absence of immediate physician presence.

Unlike the intensive care unit (ICU) that provided care for patients with wide medical and surgical conditions, the CCU was targeted at providing care for a specific group of patients – those that were at high risk of sudden death from AMI-related complications. It was, however, not until the following year in 1962 that the first CCU was developed by Hughes Day at the Bethany Hospital in Kansas City, Kansas, in the USA. It comprised four private rooms situated adjacent to a seven-bed Medical and Surgical ICU.[17]

The history or development of the CCU has been typically described in four phases, with a fifth phase having been recently added given the increasing need for critical care services in the CCU.[13] These developmental phases are summarised in Table 1.1.

Table 1.1. Phases in the evolution of coronary care units (CCUs).

Years	Phase	Summary of key points
1912	Clinical observation	James Herrick's first English description of acute myocardial infarction.
1961	CCU	Specialised and dedicated areas based on Julian's vision/principles of CCU.
1970s–1980s	Technological advancements	• Pulmonary artery catheterisation • Angiography • Thrombolysis • Percutaneous coronary intervention (PCI) • Beta blockade
1980s–1990s	Evidence-based medicine	• Randomised controlled trials for therapies. • Development of management guidelines.
2003	Critical care phase	• Subspeciality in acute cardiac care. • Recognise requirement for validated intensive care knowledge skills and behaviours for cardiologists (CoBaTrICE – Competency-Based Training in Intensive Care Medicine in Europe).

1.3.1 The coronary care unit phase

The development of the CCU has been termed the greatest innovation in cardiology regarding the management of AMI.[16] Its contribution to the reduction of mortality from AMI has been well documented over the past 30 years.[17,18] From its early days, it has been testified that CCUs improved patient outcomes. A report by Killip and Kimball in the 1960s, which was based on their experience with 250 AMI patients treated in CCU, reaffirmed the importance of CCUs by showing reduced mortality rates from 26% to 7%.[13,14,17,18]

Similar to his colleagues, Day recognised that the success of resuscitation efforts was limited by delays in detecting arrhythmia. This led to him, Julian and Brown constructing crash carts for the resuscitation of AMI patients in general wards. Contrary to the article in *Circulation* by Fye *et al*. on the 50th anniversary of the CCU concept,[16] Day is credited for inventing not only the term CCU, but also the term "Code Blue".[18]

This era also saw an important shift in dynamics between nurses and doctors. Through the recognition that cardiac arrest resulted in severe brain damage after four minutes, physicians began empowering specific nurses to deal with emergencies, initiating emergency protocols including closed-chest compressions and defibrillation, without the immediate supervision or presence of the doctor.[17] The technique of closed-chest cardiac massage combined with mouth-to-mouth respiration had already been developed at this time.[16]

Furthermore, Eliot Corday, a Los Angeles-based cardiologist, played a key role in the development of CCUs. Through his power as President of the American College of Cardiology (ACC) in 1965, he contributed to the growth and rapid dissemination of CCUs in the USA, resulting in over 200 units by 1966.[16,17]

The development of the direct current (DC) defibrillator to restore normal heart rhythm and use of prophylactic lidocaine to decrease the chances of cardiac arrest in AMI patients were Bernard Lown's contributions to the growth of the CCU.[16]

1.3.2 The phase of technological advancements

The period stretching across the 1970s and 1980s saw the birth of many devices and interventions, some of which are still being used today and have been perfected over time with more research and knowledge.[13] The Swanz Ganz catheter was developed in 1970[16,17] through the Myocardial Infarction Research Unit (MIRU) programme that was funded by the National Institutes of Health (NIH) in the USA. One of the primary aims of this programme was to study and understand the pathophysiology of AMI and develop treatments that were more effective in managing its complications.[16] There were nine such MIRU centres located in various public and private research universities and academic hospitals across the USA. This invention provided information regarding intracardiac pressures and cardiac output but its role, however, has become limited with the upswing in evidence-based medicine.[15,16]

Although the thrombolytic effects of streptokinase had been known as early as the 1930s, its use in the management of AMI became standard of care during the 1980s.[17] The Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico (GISSI) trial standardised the use of thrombolysis in the management of AMI in 1986.[17,19] Furthermore, in 1993, the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) Investigators showed that tissue plasminogen activator (tPA) was superior to standard thrombolytic therapy.[17]

The first reported coronary angiograph was actually performed by a paediatrician, F. Mason Sones Jr., who experimented with cardiac catheterisation techniques. During the procedure, he inadvertently injected contrast dye into the right coronary artery instead of the aorta of the patient. This incident occurred in 1959, even before the establishment of the CCU.[17]

Transluminal angioplasty of the superficial femoral artery (SFA) was reported by Charles Dotter and Melvin Judkins in 1964. The catheter was later modified by Andreas Gruentzig in

1975, who added a balloon to the tip and dilated the iliac artery with success. He then went on to perform the first coronary balloon angioplasty two years later.[17]

The use of stents and dual anti-platelet therapy (DAPT) were introduced when restenosis and sudden vessel closure became more evident with the increasing use of balloon angioplasty. The Global Use of Strategies To Open Occluded Coronary Arteries In Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators proved that primary angioplasty as a therapeutic approach was superior to fibrinolysis in the management of acute STEMI.[17,20] This finding was later supported by Andersen *et al*.[21] They continued to assert that the intervention was even more effective when delivered within two hours of symptomatic indications of a cardiac event. This approach led to the development of the practice of acute STEMI patients being taken to hospitals with percutaneous coronary intervention (PCI) facilities, preferably within 90 minutes after the onset of symptoms.[17,21]

1.3.3 The critical care phase

Modern day CCUs have transformed into a blended integration of CCUs and cardiology wards, ICUs and high care units.[13] They have certainly evolved from the CCUs of the 1960s and 1970s, observing a change in the patient population admitted and the variety of conditions that involve multiple organ system dysfunction.[17] Cardiologists of today must be trained and competent in skills generally mastered by ICU specialists, such as the management of septic shock, critical illness neuropathy, renal replacement therapy (RRT), provision of ventilatory support and neuropsychiatric complications, for example, delirium. Given the changing needs of the CCU, this unit has seen a name change from coronary care unit to cardiac care unit in some areas, even referred to a cardiac ICU (CICU) in others.[13,15]

1.4 DEFINING THE CORONARY INTENSIVE CARE UNIT (CICU)

A CICU refers to a specialised unit in the hospital physically and administratively reserved for the care of acute cardiovascular conditions. Equipped with continuous ECG and multi-parametric monitoring capabilities, and medical/nursing staff trained in the management of acute cardiovascular emergencies, a CICU offers around-the-clock care to these patients. Its primary objective is to provide monitoring and support failing organ systems in acute and/or critically ill cardiovascular patients. CCUs provide care to the spectrum of CVDs including heart failure and ACS. The unit is primarily under the supervision and care of the cardiovascular team led by the cardiologist or cardiac intensivist; however, more often than not, a

multidisciplinary approach is required between the intensivists, physicians and rehabilitation team.[22]

The system of grading the levels of care has also been adapted to accommodate acute cardiovascular care. This system promotes decision-making pertaining to the level of care needed by the patient in terms of nursing and medical capabilities, intervention required and the area in which the patient should be managed. The system also contributes to facilitate decisions regarding the allocation of resources in terms of staffing and equipment, resulting in patient flow between healthcare facilities being better directed. This ultimately promotes improved outcomes and reduces mortality and the length of hospital stay.[22] The sections that follow (cf. 1.4.1 to 1.4.3) describe the levels of CICU care as defined by the European Society of Cardiology (ESC).

1.4.1 Level 1 care and facilities

Level 1 patients are at high risk of having their condition deteriorate and thus require closer observation, mainly careful cardiac rhythm observation and non-invasive haemodynamic monitoring. They may also require specific treatment such as vasoactive drugs or continuous positive airway pressure (CPAP), and can therefore not be supervised in the general cardiology ward. Conditions managed in a level 1 CICU include heat failure without shock, complex non-fatal arrhythmias, ACS and post-intervention monitoring.[22]

1.4.2 Level 2 care and facilities

Level 2 care generally requires more advanced procedures, techniques and monitoring compared to level 1 care. Care at this level includes the monitoring of central venous and/or arterial pressures, administration of continuously infused medication, temporary transvenous pacing and pericardiocentesis. A level 2 facility should be equipped to take care of patients requiring both level 1 and level 2 care. They can also serve as an initial admission point for patients that require level 3 care and are awaiting transfer. A level 2 CICU facility should have a full-time coronary interventional catheter laboratory and a minimum of six beds in the facility.[22]

1.4.3 Level 3 care and facilities

Acute cardiovascular complications that require critical care define level 3 CICUs. Interventions such as invasive mechanical ventilation, RRT and extracorporeal life support are offered at

this level of care. A level 3 facility should be equipped to provide this level of care and should be under the supervision of a cardiovascular intensivist or, alternatively, a cardiologist and intensivist.[22]

It should be noted that in South Africa, such a system of grading the levels of CICU care has not been adopted in the public healthcare sector. Such units are generally found in tertiary academic hospitals and the private sector. ICU beds in general are a scarce resource in South Africa, with a reported number of less than 5 000 ICU and high-care beds in both the public and private sector for a population approaching 60 million individuals.[23]

Although CCUs originated for the singular purpose of rapidly resuscitating patients with arrhythmic complications of AMI, they have indeed rapidly transformed into CICUs that deliver comprehensive critical care for patients with CVDs over the years.[13] Such developments, however, raise the issue of heterogeneity of conditions managed in such units, which may have an impact of the outcomes of management. Several surveys have been designed to assess CICUs' activities and developmental progress. CCUs are no longer only dealing with monitoring of arrythmias but have evolved to dealing with critically ill patients with multi-organ system involvement and failure, often requiring emergency interventions.[13]

The distinction between a CCU and a medical ICU has become blurred. Cardiologists often have to deal with patients with multiple critical care issues from the onset. The required skill set for a cardiologist has also evolved with technological advancements that occurred mostly during the 1970s to the 1980's.[13]

Sinha *et al*.[24] reported that in a study of 3.4 million acute admissions to CICU across the USA over a 10-year period, the proportion of noncardiac primary diagnoses increased from 38.0% to 51.7%. This increase was mostly attributed to infectious and respiratory diseases, and renal failure. The fastest declining cardiac primary diagnosis over the 10-year period was coronary artery disease, which decreased from 32.3% to 19.0%. Despite this decrease in coronary artery disease, heart failure, pulmonary vascular and valvular heart diseases were reported to be escalating, with a resultant increase in non-percutaneous coronary interventions such as mechanical ventilation and renal replacement therapies. Despite these shifts toward greater comorbidity, the unadjusted mortality rate decreased from 9.3% to 8.9%.[24]

Similar findings were reported by Holland and Moss, who demonstrated sepsis to be the most frequent noncardiac primary diagnosis (5%). Furthermore, acute coronary syndromes were the most common primary cardiac diagnosis (25%). The overall CCU mortality rate was 7%,

mostly related to acute kidney injury, sepsis and respiratory failure.[25]

Coronary care units have revolutionised the management of patients with AMI and a wide range of cardiovascular diseases. They have provided a setting in which research on coronary syndromes could be conducted and continue to provide a platform for future studies on cardiac critical care.[13,17]

1.5 INTERNATIONAL COMPARISON OF CRITICAL CORONARY CARE PROVISION IN SOUTH AFRICA

Although non-communicable diseases (NCDs) are the leading cause of death worldwide, this group of diseases is the second most common cause of death in SSA.[26] Similar to the global scenario, CVDs are a major contributor to NCD-related deaths. It has also been predicted that by 2030, NCDs will account for more than half of all deaths in SSA. Despite the increasing burden of NCDs, SSA is still challenged by insufficient healthcare infrastructure, poor delivery systems, lack of specialist cardiology services and drug shortages.[26]

Historically, South Africa has been characterised by unequal distribution/development of healthcare systems and transport infrastructure according to racial segregation.[26,27] Geography (urban/rural), racial group, socioeconomic status and lack of reliable emergency medical services (EMS) are still a barrier to healthcare in the country.[26,27] On occasion, it may take patients hours to days before arriving at referral centres. Consequently, timely reperfusion is often not possible due to late arrivals.[27] There is a serious shortage of PCI-capable facilities in South Africa, with, according to the latest available figures, only 62 facilities in both the public and private healthcare sectors. Slightly more than half of these are located in Gauteng province with one province, Northern Cape, having no PCI-capable facility at all. Two other provinces, Northwest and Limpopo, have no PCI-capable facility in the public sector.[28] Furthermore, 77% of these facilities are accessible to only 18.1% of the population, as reported by Stassen *et al*.[28]

On the contrary, a study performed in the USA reported that 83.7% of the population live within one hour of a PCI facility, with only 16.3% living over 60 minutes away from a PCI centre. Furthermore, the median pre-hospital time was 30 minutes (interquartile range [IQR] 24–39 minutes).[29]

Although the study by Stassen *et al*. was based in SA, the access barriers noted are likely to apply to the African continent as a whole.[28] A consensus statement from 10 SSA countries

supports this assertion. Transportation delays, lack of facilities and specialists and costs of medication are significant barriers in providing adequate ACS care. Among the 10 countries participating in this study, only five have cardiac catheterisation labs.[30]

The British Cardiac Society (BCS) Guidelines and Medical Practice Committee recommends one PCI facility for every 350 000–400 000 population, if angiography and pacing services were both offered in that facility.[31] Looking at these recommendations, the Western Cape and Gauteng provinces are at an almost comparable level with internationally recommended standards, both provinces having a ratio of one PCI facility for approximately 470 000.[28] However, the PCI facility-to-population ratio in the other seven provinces in South Africa is significantly higher than what international guidelines recommend, with one facility for 5.7 million people in Limpopo and two facilities for 2.1 million people in Mpumalanga.[28]

Another major obstacle to combating CVDs in SSA is the lack of specialised skilled labour.[26] This problem is not only restricted to cardiologists, but also includes nursing and support staff.[27] Most SSA countries have fewer than five doctors per 10 000 population.[26] It has been reported that six countries in SSA did not have a registered cardiologist.[26,32]

Electrophysiological studies are available in seven countries in Africa including SA; however, most are situated in North Africa. Despite being widely available, ECG machines are mostly used in secondary and tertiary healthcare centres. Ambulatory and stress ECG testing is available in 76% and 61%, respectively, of the countries in Africa. Echocardiography is mostly limited to tertiary centres.[32] In 2013, the median pacemaker implantation rate in Africa was 2.66 per million population. In comparison, the rate of pacemaker implantations in Europe during the same year was 552 per million population,[33] emphasising the extreme disparity between the two continents.

Based on findings from the ACute Coronary Events – a multinational Survey of current management Strategies (ACCESS) study, it could be argued that the availability of interventional cardiology facilities in South Africa is comparable to international standards. However, most of the participating centres in the South African cohort in this study were located in the private sector and at tertiary institutions.[6,26]

In a Pretoria-based South African study, fibrinolytic therapy was given to 37% of patients who presented with STEMI to Steve Biko Academic Hospital. Therapy was administered late in the majority of cases. Slightly more than 80% of patients used private vehicles to get to hospital and 16% used an ambulance,[34] reflecting the limited access to speedy EMS services in South

Africa.[28] This finding is also significant as patient self-transport is discouraged by the American College of Cardiology/American Heart association (ACC/AHA).[35] In a prospective study by Meel and Gonçalves[34] of patients with a diagnosis of STEMI, none of the patients received pre-hospital fibrinolytic therapy. This is an area of potential intervention in order to improve ACS management in South Africa and subsequently reduce morbidity and mortality.[34]

In a South African qualitative study, which entailed interviewing various medical professionals including paramedics, registered nurses and cardiologists in the public and the private healthcare sectors, one of the respondents explained the low rate of fibrinolytic therapy by highlighting the lack of seniority among casualty doctors, and often feeling apprehensive when administering fibrinolytic therapy due to an unjustified fear of complications.[27] Other reasons for in-hospital delays of fibrinolytic therapy have also been noted, ranging from opening of patient folders, inefficiencies at triage, poor recognition and diagnosis of STEMI and high patient volumes in understaffed hospitals.[27,34]

1.6 COMPLICATIONS IN THE CORONARY CARE UNIT

Given the changing CCU population, many of the patients admitted to CCUs are susceptible to a number of complications associated with critical illness, related to the severity of the underlying disease and the need for intensive care therapies. Although most of these complications are preventable, many are also associated with an increased risk of morbidity and mortality, as well as an increase in utilisation of CCU resources and prolonged stay. The majority of these complications may be similar across general medical and surgical ICUs, although some are unique to the CCU setting.[36] The following sections explore complications that may occur in patients treated in a CCU.

1.6.1 Infections and sepsis

Infections and sepsis are common in the CICU setting and may already be present on admission to the unit or may be acquired while hospitalised. This patient population is at an increased risk for hospital-acquired infections (HAI) as they are increasingly exposed to invasive haemodynamic monitoring by means of medical devices, short-term medical support, renal replacement therapy and targeted temperature management (TTM).[36] Examples of HAIs occurring in this patient population include surgical site sepsis, ventilator-associated pneumonia (VAP), central line-associated blood stream infection (CLABSI) and urinary catheter-associated urinary tract infection (CAUTI).[17,36] Varying rates of infection have been reported with the use of mechanical circulatory support (MCS) devices. This is influenced by

several factors such as the type of MCS device and the duration of use. An infection rate of 1% has been reported with the use of an intra-aortic balloon pump and rates as high as 29% when using extracorporeal membrane oxygenation (ECMO) support.[36]

1.6.2 Pain and anxiety

Pain may be a direct cause of agitation or delirium and may also be a presenting feature of the underlying disease, for example, with ischaemic pain. Although data related to acute and chronic pain in the CICU have not been described, it has been reported that up to two thirds of patients in ICU experience pain and anxiety. At times, the patients are intubated and cannot communicate with the care providers, or the use of analgesics and sedatives may have altered the patient's level of consciousness.[36]

1.6.3 Renal complications

Impaired renal function in patients admitted to the CCU is often multifactorial and complex. This may be as a result of pre-existing underlying conditions, such as hypertension and/or diabetes mellitus and even chronic kidney disease (CKD). Deterioration in renal function may also be as a consequence of conditions such as heart failure and the administration of nephrotoxic agents, such as contrast-induced nephropathy related to angiography.[37]

Acute kidney injury (AKI) has been identified as an independent predictor of mortality in critically ill patients. A study conducted in a CCU and cardiac rehabilitation ward in Kuala Lumpur, Malaysia, revealed that slightly more than 10% of the patients admitted met the criteria of AKI, of which heart failure was identified as the aetiological factor in 72.7% of these patients. Furthermore, 36.4% of the patients with AKI in this study died. Lower glomerular filtration rates (GFR) and a higher proportion of patients requiring RRT were found in the group that died, together with an increase in the length of CCU stay.[38]

Buargub and Elmokhtar reported a mortality rate of 25.7% in patients with AKI in CCU compared to 6.12% in the non-AKI group.[39] Similar to the findings of the study performed in Kuala Lumpur, the patients in the mortality group were found to have lower GFR, longer length of CCU stay and decompensated heart failure in the majority of cases.[38,39] A Taiwanese study revealed an incidence of acute kidney disease (AKD) of 47.6% in the CCU population, of which 4.8% died while being hospitalised.[37]

1.6.4 Neuromuscular complications

Bed rest is a risk factor for ICU-acquired weakness. It has been defined as a clinically appreciable myopathic or neuropathic weakness that develops due to critical illness, with no other risk factors present. ICU-acquired weakness has been reported in up to one third of ICU patients, with data in CICU cohorts lacking. The limited evidence available does, however, highlight the benefits of early mobilisation in CICU patients, with reduced length of stay, shorter duration of mechanical ventilation and non-pharmacological management of delirium.[36]

1.6.5 Psychiatric and cognitive complications

Neuropsychiatric complications have been reported in the ICU population, which include anxiety, depression, post-traumatic stress disorder (PTSD) and delirium.[40] Delirium, also referred to as an acute confusional state, usually fluctuates and is characterised by a change in cognition or alteration in consciousness.[41] This condition may be a result of the underlying medical condition, medication side-effects and withdrawal, or as a consequence of the environment. Identification of modifiable risk factors and reversible causes is vital as this condition is associated with high morbidity and mortality. The spectrum of presentation can range from withdrawal or somnolence to psychosis and agitation.[36,41] The AHA reported the incidence of delirium in CICU cohorts as ranging between 8% and 20%. The Richmond-Agitation Sedation Scale is a helpful tool that may be used to minimise the risk of excessive sedation in mechanically ventilated patients.[36]

1.6.6 Respiratory complications

Respiratory failure is the leading indication for CICU admission. It has been reported that up to one in five patients admitted to CICU require mechanical ventilation. Given the growing number of patients requiring this level of respiratory intervention in the CICU, attending clinicians need to be familiar with potential complications and be thoroughly aware of safe mechanical ventilation parameters. Complications include VAP, ventilator-associated lung injury (VALI), tracheal trauma and muscle weakness. VAP is defined as pneumonia that develops in patients who are endotracheally intubated and mechanically ventilated for a period exceeding 48 hours. VALI is defined as a range of lung damage occurring in mechanically ventilated patients, which results in inflammation, hyaline membrane formation and increased vascular permeability. This includes volutrauma (from alveolar overdistension), atelectrauma (from repetitive alveolar opening and closing) and barotrauma (from elevated airway

pressures). The most common damage in acute respiratory distress syndrome (ARDS) survivors is diffusion impairment.[36]

1.6.7 Gastrointestinal (GIT) system complications

Comprehensive data on gastrointestinal complications in the CICU population are still lacking. Malnutrition is quite prevalent and occurs in up to 78% of ICU patients. It has been associated with adverse outcomes such as increased length of stay, sepsis and in-hospital mortality. Therefore, guidelines from professional societies on nutritional support in the ICU are likely applicable to the CICU population as well. Trophic enteral feeding is considered reasonable in patients with compensated or resolving shock, patients undergoing TTM and in those with compensated respiratory failure, including patients stabilised on ECMO.[36] Overt upper GIT bleeding has been reported in approximately 2%–4% of the ICU population. Due to incomplete evidence, it has been postulated that this patient population may be at a higher risk of upper GIT bleeding as they frequently receive antiplatelet and anticoagulation therapy.[36]

1.6.8 Glycaemic complications

Data on hyperglycaemia in CICU may be extrapolated from medical ICU patients where hyperglycaemia has been linked to an increased mortality rate. The AHA recommends starting insulin therapy when blood glucose levels are exceeding 8.3 mmol/L.[36] Prevention of hypoglycaemia is also important as it may result in neurocognitive impairment and neuroglycopenic brain injury.[40]

1.6.9 Mortality

With the advancement of technology, medications and intervention related to the management of AMI, the overall in-hospital mortality has been reduced to below 5%. Improvements in the prevention of MI and pre-hospital care has been noted as some of the contributors to the reduction in mortality.[15]

A decrease in mortality resulting from AMI has been observed in CCU patients. However, a trend towards an increase in ischaemic cardiomyopathy together with heart failure has been reported and consequently, in the majority of patients with a fatal outcome, death has been attributed to pump failure.[17]

With regard to CICU mortality in particular, the Critical Care Cardiology Trials Network (CCCTN) reported an overall mortality rate of 8.3% (range 4%–19.7%) across 16 CICUs located in tertiary healthcare centres across the USA and Canada between September 2017 and September 2018. When stratified by indication for CICU admission, cardiac arrest (45.3%), cardiogenic shock (30.6%), need for RRT (34.5%), neurological emergencies (30.6%) and respiratory failure (24.1%) carried the highest mortality rates. Patients who were admitted to the CICU for frequent monitoring or post-procedural monitoring had the lowest mortality rate ranging between 0.2% and 0.4%.[42]

In an Irish study performed earlier between 1993 and 1994 in a CCU a morality rate of 20% was reported. Furthermore, all patients (n=6) that presented with cardiogenic shock, demised. Patients in this study were treated with thrombolytic therapy according to the Thrombolysis in Myocardial Infarction (TIMI) risk factor scoring, with 54.19% having received the therapy. Reasons for not administering thrombolytic therapy included absolute contraindications to thrombolytics, non-diagnostic ECG changes, patients presenting too late and hypertension; however, in some cases no reason was stated.[43]

Similar findings were reported in a study performed in the late 1970s in a CCU at the RK Khan Hospital in Durban, South Africa, with a mortality rate of 22.8%. Of these deaths, 17.4% occurred while the patient was treated in the CCU, with the remainder of deaths having occurred after transfer from the CCU to the general medical ward.[44] No literature could be located reporting the current mortality rates in South African CCUs.

1.7 PREDICTORS OF OUTCOME/MORTALITY

1.7.1 Demographic factors

Advanced age is a well-recognised risk factor for mortality and other adverse outcomes in patients with CVD or other critical illness.[45] In acute ischaemic heart disease, age is also acknowledged as an established non-modifiable risk factor for mortality.[46] An increase in age has been associated with an increase in mortality rates. In the Tokyo CCU Network in-hospital mortality analysis, it was found that a 10-year age increase had an odds ratio of 1.84 for mortality, with female gender also being associated with a higher odds ratio for mortality.[47]

The reasons for this observed increase in mortality with an increasing age is multifactorial. Padkins *et al*. attempted to explain in their study that older patients generally had more comorbidities, a higher illness severity and often more critical care needs. Older patients

generally presented with frailty as well and limited physical and physiological reserves. Furthermore, it was found that older age was associated with higher short-term and long-term mortality, even after adjusting for factors such as cardiogenic shock. However, older patients with severe shock had a much poorer outcome when compared to younger patients or those with a lesser degree of shock.[45]

1.7.2 Past medical history

Diabetes has been reported as a major risk factor for death in patients with MI. Hypertension has also been reported as a risk factor for mortality in these patients, although to a lesser extent when compared to diabetes.[46] Diabetic patients with ACS also have a 50% higher chance of presenting with an adverse event when compared to those without diabetes.[48]

Smoking has traditionally been described as a modifiable risk factor for coronary artery disease (CAD), also contributing to an increased CAD-related mortality rate. Several studies have shown that smoking cessation had a benefit of lower rates of developing CAD and that non-smokers also had a reduced risk of developing CAD.[49] In a different study by Barbash *et al*., however, it was reported that smokers with CAD actually had a better in-hospital and 6-month outcome when compared to non-smoking patients with AMI that received thrombolysis. In addition, they also found that individuals who had never smoked, had a higher in-hospital re-infarction rate, stroke and bleeding rates, whereas the smokers consisted predominantly of males, were older with a higher prevalence of diabetes and had a higher Killip classification.[50] These findings could be related to how smokers, non-smokers and ex-smokers were defined in various studies.[49]

1.7.3 Haemodynamic parameters

Systolic blood pressure (SBP) on admission in patients with AMI is a widely reported and accepted prognostic indicator of in-hospital mortality.[51,52] It has been found to bear an inverse relationship to in-hospital mortality, with SBP ≤120 mmHg associated with a higher mortality rate.[51] In a Japanese study, it was reported that an SBP of ≤106 mmHg carried a significantly higher mortality rate (25.7%), while an SBP of 141–159 mmHg on admission might be associated with a better in-hospital prognosis.[51] In another study also based in Japan,[53] similar findings were reported. However, they further added that SBP ≤105 mmHg was likely to be associated with a higher creatinine kinase level and thus carried higher mortality rates. Death resulting from cardiogenic shock, ventricular fibrillation, congestive heart failure and left

ventricular rupture occurred more commonly in patients with SBP ≤105 mmHg. On the contrary, left ventricular rupture was common in patients with SBP ≥159 mmHg.[53]

A possible explanation for the fact that higher SBP on admission has been associated with a better in-hospital prognosis, might be related to blood pressure being a product of cardiac output (CO) and total peripheral vascular resistance (TPR). A higher BP might reflect a higher TPR and thus preserved LV systolic function, thereby implying a lesser degree of myocardial injury.[53] Similar to hypotension, cardiac arrest was associated with higher in-hospital mortality.[47]

Cardiogenic shock, conversely, was reported to be associated with a higher in-hospital mortality rate, similar to a low SBP.[53] The Killip class scoring of AMI has been identified as an independent predictor of in-hospital mortality, with a score of ≥3 carrying a significantly higher in-hospital mortality rate.[53]

1.7.4 Killip classification of acute myocardial infarction[54]

The different Killip classes of AMI are defined as follows:

- Class I No clinical evidence of heart failure.
- Class II Findings consistent with mild to moderate heart failure (e.g., S3 gallop, rales less than halfway up the posterior lung fields, or jugular venous distension).
- Class III Overt acute pulmonary oedema.
- Class IV Cardiogenic shock or hypotension (systolic blood pressure <90 mmHg) and evidence of low cardiac output (oliguria, cyanosis or impaired mental status).

Heart rate is another important prognostic indicator where patients with a significant sinus tachycardia or sinus bradycardia have an increased mortality rate. Physiologically, sinus tachycardia serves as an indicator of activation of the sympathetic nervous system as a result of the infarct size. Sinus bradycardia, on the contrary, is indicative of multiple pathophysiological disturbances such as underlying conduction abnormalities and/or agonal rhythms.[46]

1.7.5 Infarct size and location

The size of the infarct plays a vital role in the management of patient with STEMI. This information can be obtained through various modalities. Absence or presence of Q-waves on ECG can help the clinician decide if the myocardium is infarcted or not. Regional or global wall motions on the echocardiogram can also provide useful information. Further imaging with a radionuclide using the technetium-99m-sestamibi single-photon emission computed tomography (SPECT) approach or cardiac magnetic resonance imaging (MRI) can provide information on the infarct size and whether the myocardium is still viable or not. Further decisions regarding reperfusion can then be taken when viability status is known.[35]

The relationship between infarct size, location and outcome is complicated. It has been reported that an anterior infarct carried a higher mortality rate, with an isolated inferior infarct being having the lowest risk of mortality. All other infarct locations were found to pose an intermediate risk of mortality. The GISSI-I trial reported that rather than location of the infarct, the number of leads with ST segment elevation was of more importance.[46]

1.7.6 Serum biomarkers

Serum biomarkers, such as cardiac troponin, creatinine kinase MB (CK-MB), B-type natriuretic peptide (BNP) and C-reactive protein (CRP) levels, were found to have prognostic significance in patients with acute cardiac ischaemia, where an elevation in levels was associated with an increase in adverse outcomes.[48] Cardiac biomarkers were reported to be higher in patients that had demised in the CCU.[47] A linear correlation between high-sensitivity CRP (hs-CRP) levels have been observed with coronary atherosclerosis complexity and troponin levels.[55]

1.7.7 Haematology and biochemistry

Anaemia has been identified as a marker of unfavourable outcome, particularly in ACS and AHF patients. Between 17.5% and 28% of patients treated in a CICU for ACS had anaemia, while in 52% to 68% of patients with heart failure, anaemia was observed. The risk of long-term mortality showed a statistically significant increase in relation to decreasing levels of haemoglobin (Hb), serum iron concentration, total iron-binding capacity (TIBC) and the need for red cell concentrate transfusion. Furthermore, a 1 g/dL decline in Hb was found to increase mortality risk by 19%. The complexities of these factors in cardiac diseases are not clearly understood, although anaemia in these patients could result from both iron deficiency or anaemia of chronic disease occurring with chronic inflammatory states.[55]

Inflammation is associated with atherosclerotic vascular disease. An increase in the level of hs-CRP has been shown to correlate with the severity and complexity of atherosclerotic CAD. Furthermore, it has been suggested that patients with elevated hs-CRP were more likely to benefit from statin therapy compared to those with low levels of hs-CRP.[55]

1.7.8 Red blood cell distribution width

Red blood cell distribution width (RDW), which is a measure performed as part of the routine full blood count (FBC), is used to determine the size of the circulating red blood cells. In a single-centre, prospective, observational study, Hu *et al*. found that RDW was an independent predictor of AKI and mortality in patients admitted to a CCU. A higher incidence of AKI was reported in the patient group with elevated RDW percentage values. The in-patient mortality rate in the high RDW group was approximately double that of the lower RDW group (22% versus 11.6%). Patients with low RDW values had a two-year mortality rate of 7.1%, which was increased more than four-fold to 33.3% in the high RDW group.[56]

The exact role of RDW in a patient's outcome is still unclear, with several mechanisms having been postulated, including inflammation, oxidative stress and undernutrition, of which inflammation is the most widely accepted mechanism. Inflammation can inhibit bone marrow function and suppress erythrocyte maturation.[56,57] It is an important underlying mechanism in CVD with plaque formation and atherosclerosis, and results in disrupted vascular endothelial barriers, increases pro-inflammatory cytokines and neutrophil accumulation.[56] Oxidative stress leads to death of erythrocytes and their removal from circulation via haemolysis. Premature red cells are consequently released into the circulation resulting in various sizes of erythrocytes and thus a higher RDW.[56,57] Markers of nutritional state (albumin, prealbumin and serum triglyceride) are also inversely related to RDW.[57]

1.8 PROGNOSTIC SCORING SYSTEMS

Risk stratification systems play a central role in patients with non-ST segment elevation myocardial infarction (NSTEMI), as this group of patients have a diverse risk-of-death spectrum and recurrent cardiac events. These risk scoring systems are useful in predicting both short-term and long-term outcomes. These scores are calculated based on findings from the patient's initial clinical history, ECG findings and laboratory results. The Global Registry of Acute Coronary Events (GRACE) risk score was developed from database registries of patients across the ACS spectrum. Additionally, the Thrombolysis in Myocardial Infarction (TIMI) and Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using

Integrillin (eptifibatide) Therapy (PURSUIT) risk scores were developed from database registries of patients with NSTEMI. Early risk stratification facilitates the classification of patients into low, intermediate and high risk categories and contributes information on suggested management therapies and site of management.[58,59]

1.8.1 GRACE risk score

The GRACE score was developed based on data from hospitals in 14 countries around the world. It is used as a predictor of in-hospital mortality, six-month death or non-fatal MI in patients presenting with ACS. It is also aligned to treatment recommendations.[60] This scoring system is based on eight variables, namely:[58–60]

- age;
- heart rate;
- systolic blood pressure;
- Killip class;
- creatinine concentration;
- elevated biomarkers of myocardial injury;
- cardiac arrest on admission; and
- ST-segment deviation.

GRACE risk scores are categorised as 'low' (0 to 108), 'intermediate' (109 to 140) or 'high' (≥141). After a patient has been stratified according to risk category, the risk scoring nomogram that lists recommended therapies is applied.[61] This scoring system has been validated in several observational studies.[58–60]

1.8.2 TIMI score

The TIMI score takes into account seven variables, whereby the presence of the variable scores 1 and its absence scores 0. It is useful for predicting short-term prognosis, i.e., the risk of mortality or recurrent MI events at day 14. Based on the TIMI score, patients are classified into low (0–2), intermediate (3–4) and high (5–7) risk categories.[59]

The criteria taken into consideration when determining the TIMI score are the following:

- age ≥65 years;
- ≥3 risk factors for coronary artery disease (CAD);
- use of aspirin in the last 7 days;
- known CAD (stenosis ≥50%);
- severe angina (≥2 episodes in 24 hours);
- ST-segment deviation; and
- elevated cardiac markers.

1.8.3 PURSUIT risk score

The PURSUIT trial, which enrolled 9 461 patients admitted 726 hospitals across Western and Eastern Europe and North and South America, formed the basis of the development of the PURSUIT Risk Score. It is used for risk stratification of patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS). It is based on the following five variables:[59]

- age;
- sex;
- worst Canadian Cardiovascular Society (CCS) class of angina during the previous six weeks;
- signs of heart failure; and
- ST-depression on presenting ECG.

These risk scoring systems (GRACE, TIMI and PURSUIT) have been validated and overall, no significant difference between the three has been found with regard to predicting death and recurrent MI at 30 days. However, the GRACE risk score showed superiority at predicting outcome at one year.[58]

1.8.4 Sequential Organ Failure Assessment (SOFA) score

The SOFA score is a simple scoring system used in many ICUs to quantify organ dysfunction and predict mortality in the critically ill population. Its use has been validated in multiple studies for the ICU population but few studies have validated its use for the CICU population.[62]

This scoring system focuses on the presence of organ dysfunction in six organ systems, each system scored out of four. The systems include the cardiovascular system, central nervous system, respiratory, renal, coagulation and hepatic system. A change in the score of two or more is definitive of sepsis syndrome, with an increasing score reflective of deteriorating organ dysfunction. It is generally used as a serial scoring system, with an admission SOFA score being calculated based on the maximum values for each subcategory in the 24 hours preceding ICU admission; thereafter, a daily maximum score is calculated.[63]

Although initially developed for the objective quantification of organ dysfunction, it has been shown through various studies to have a good correlation between increasing score and mortality. Moreno *et al*. demonstrated this correlation in their study. Furthermore, they found that the change in the SOFA score (determined by subtracting the admission SOFA score from the maximum SOFA score) correlated strongly with mortality in the ICU.[63]

Jentzer *et al*. evaluated the use of the SOFA score in predicting mortality in the CICU population. They found that the day-one SOFA score had a good discriminatory value in predicting short-term mortality. In addition, they reported that it exhibited similar discriminatory value in predicting short-term mortality as the Acute Physiology and Chronic Health Evaluation (APACHE) III and APACHE IV scores. Moreover, the SOFA score was simpler to use and calculate, and its discriminatory value improved with serial calculations. A higher SOFA score was associated with a higher risk of mortality, whereas patients with a low score (<2) had a low risk of mortality. The cardiovascular and renal subscores were found to be the strongest predictors of mortality.[62] Table 1.2 summarises the system-specific components and values allocated to determine the SOFA score.

Table 1.2. Systemic variables taken into consideration when calculating the SOFA score.

System	SOFA SCORE				
	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg)	≥400	301–400	201–300	101–200	≤100
or kPa	≥5.3	4.1–5.3	2.8–4.0	1.4–2.7	≤1.3
Coagulation					
Platelets (X $10^3/mm^3$)	>150	101–150	51–100	21–50	≤20
Liver					
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥12.0
or µmol/L	<20	20–32	33–101	102–204	≥204
Cardiovascular					
Hypotension	None	Mean arterial pressure <70 mmHg	Dopamine ≤5 or dobutamine (any dose)*	Dopamine >5	Dopamine >15
Central nervous system					
Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	≥5.0
or µmol/L	<110	110–170	171–299	300–440	>440
Or urine output	–	–	–	< 500 mL/day	< 200 mL/day

*Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/minute).

1.8.5 Acute Physiology and Chronic Health Evaluation (APACHE) score

The APACHE score is a scoring system developed in 1981 to estimate the risk of mortality in critically ill patients. Initially, the scoring system comprised two major components: the acute physiology component that assessed the severity of the current illness, and the patient's chronic health evaluation status before admission.[64,65] The APACHE II score, which was an updated and simplified version of the initial scoring system, consisted of 12 physiologic parameters and included age, the Glascow Coma Scale (GCS) conversion score and chronic health score, which were used to estimate mortality risk, calculated in the first 24 hours of admission to the ICU.[64] The APACHE II remained in use until 1991 when another update resulted in the APACHE III score. The current most updated version, the APACHE IV, comprises 17 physiological parameters with additional variables that include mechanical ventilation, thrombolytic therapy and the effects of sedation on the GCS.[64,65]

A single-centre prospective study by Argyriou *et al*., evaluating the use of the APACHE II and SOFA scores in a CICU, concluded that although the APACHE II score had superior calibration and accuracy over the SOFA score, both scoring systems had good discriminative ability in predicting patient outcome.[66] Table 1.3 summarises the physiological components and variables of the APACHE II score.

Table 1.3. Acute physiological points of the APACHE II score.

Physiologic variables	High abnormal range				Low abnormal range				
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal) (°C)	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
Mean arterial pressure (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (beats per minute)	≥180	140–179	110–139		70–109		6–9	40–54	≤39
Respiratory rate (breaths per minute)	≥50	35–49		25–34	12–24	10–11			≤5
Oxygenation (mmHg)	≥500	350–499	200–349		<200	PaO_2		PaO_2 55–60	PaO_2 <55
A-aDO_2 or PaO_2 a. FiO_2 ≥0.5 record A-aDO_2 b. FiO_2 ≤0.5 record only PaO_2					PaO_2 >70	61–70			
Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.3–7.49		7.25–7.32	7.15–7.24	<7.15
Serum sodium (mmol/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Serum potassium (mmol/L)	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
Serum creatinine (mg/dL)	≥3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
Haematocrit (L/L)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
White cell count (X 10^9/L)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Serum HCO_3 (mmol/L) (if pH is not available)	≥52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15
Glasgow Coma Scale [19] = 15 – actual GCS Total APS = sum of 12 variable points									

A-aDO_2, alveolar-arterial oxygen gradient; APS, acute physiology score; FiO_2, fraction of inspired oxygen; HCO_3, bicarbonate; PaO_2, arterial oxygen pressure.

1.9 CORONARY CARE UNIT THERAPIES

Various resources have described the changing landscape of the CICU in terms of patient demographics, diagnosis, therapies and the increasing need for ICU interventions and care.[42] Care in the contemporary CICU not only includes the use of vasopressors, inotropic drugs and vasodilators, but also extends to more advanced therapies including invasive mechanical ventilation, mechanical circulatory support devices such as intra-aortic balloon pump, ventricular assist devices and ECMO.[42]

1.9.1 Medical drugs

1.9.1.1 Antiplatelet therapy

Antiplatelet therapy is used to decrease the recurrence rate of native coronary artery thrombosis and prevent thrombosis of coronary artery stents. Aspirin, a non-selective cyclo-oxygenase (COX) inhibitor, is used commonly in the CCU. Guidelines recommend that it be used as soon as the diagnosis of STEMI is considered. A dosage of 150–325 mg in a chewable form should be taken as an immediate dose, or 250–500 mg intravenously (IV) if the patient is unable to take it orally. It is thereafter continued at a dose of 75–160 mg orally daily for life. Caution should be taken to exclude contraindications for aspirin use such as known hypersensitivity, active gastrointestinal bleeding and known bleeding disorders.[67]

Clopidogrel is the most frequently used P2Y12 inhibitor used as adjunctive antiplatelet therapy together with aspirin in patients that will undergo PCI. It is administered as soon as possible in patients with STEMI who will undergo PCI at a loading dose of 300–600 mg orally, followed by a daily dose of 75 mg.[67]

1.9.1.2 Anticoagulation

Anticoagulation has several uses in the CCU including in patients with ACS, during PCI, as thromboprophylaxis in patients with dysrhythmias and/or stroke, and valve replacement surgery. This is achieved through the use of antiplatelet, vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs). In general, choice of therapy is informed by the indication, ischaemic risk and bleeding risk.[68]

Anticoagulation in ACS

The choice of anticoagulation therapy is made with the overall management plan for the patient in mind, e.g., invasive procedures and bleeding risk. In NSTEMI, anticoagulation forms part of the mainstay of therapy, in addition to antiplatelet therapy. The following agents have been used for anticoagulation in patients with ACS:[68]

- Enoxaparin at a loading dose of 30 mg IV, followed by 1 mg/kg subcutaneously (S/C) 12-hourly.
- Unfractionated heparin (UFH) at 60 IU/kg loading dose (maximum 4000 IU), then followed by 12 IU/kg/hour (maximum 1000 IU/hour).
- Fondaparinux 2.5 mg daily.
- Bivalirudin 0.10 mg/kg loading dose, followed by 0.25 mg/kg/hour if an early invasive strategy is selected.

In patients diagnosed with STEMI, anticoagulation should be started immediately. If the patient undergoes fibrinolytic therapy, anticoagulation should be given for a minimum period of 48 hours up to eight days in hospital or until reperfusion.[68]

Anticoagulation and PCI

It has been estimated that 5–10% of patients undergoing PCI will require systemic anticoagulation. The decision regarding duration and choice has to be balanced against the patient's risk for ischaemia and bleeding.[68]

Anticoagulation in valve replacements

Both the ACC and ESC recommend lifelong use of VKAs in patients with prosthetic valve replacement. Furthermore, aspirin therapy should be considered as a supplementary agent in patients with concomitant atherosclerotic disease and low bleeding risk. DOACs are contraindicated for use in patients with prosthetic valves. A multicentre randomised controlled trial (RCT) was discontinued early due to a high incidence of adverse outcomes and bleeding when dabigatran was compared to VKAs.[68]

1.9.1.3 Angiotensin-converting enzyme inhibitors (ACE-I) / angiotensin receptor blockers (ARB)

Angiotensin-converting enzyme inhibitors (ACE-I), e.g., enalapril, have been shown through multiple trials to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF), i.e., an ejection fraction (EF) of ≤40%. Unless contraindicated or with

intolerance, all patients with HFrEF should be initiated on this drug class and doses up-titrated to the maximum tolerable dose.[69] In cases where an ACE-I is not tolerated, the use of ARBs instead of an ACE-I is recommended.[69]

1.9.1.4 Beta (β-) blockers

As with ACE-I, beta-adrenergic blocking agents (β-blockers) have been shown to provide a mortality benefit and improve symptoms in patients with HFrEF. They are used in conjunction with ACE-I and diuretics. β-blockers should be started at a low dose in euvolemic, haemodynamically stable patients and up-titrated to the highest tolerable dose.[69]

1.9.1.5 Mineralocorticoid receptor antagonists (MRA)

Spironolactone or eplerenone are MRAs that form part of the triad of heart failure treatment drugs, together with ACE-I and β-blockers. These agents are considered the cornerstone of heart failure management. They also reduce morbidity and mortality in HFrEF patients and improve symptoms. However, these drugs should be used with caution in patients with renal impairment and hyperkalaemia.[69]

1.9.1.6 Angiotensin receptor neprilysin inhibitor (ARNI)

Sacubitril/valsartan is recommended for use in ambulant patients with HFrEF who continue to have symptoms, despite optimal therapy with an ACE-I, MRA and β-blocker. The recommendation is that the ACE-I/ARB be replaced with an ARNI. ARNIs have shown multiple benefits over ACE-I, including a reduction in all-cause and cardiovascular mortality, decreasing the number of hospitalisations with heart failure and improvement of symptoms and quality of life. Furthermore, their use was associated with a lower incidence of insulin-requiring diabetes, and a reduction in lower eGFR rates and hyperkalaemia. These findings were part of the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial.[69]

1.9.1.7 Sodium-glucose co-transporter 2 (SGLT-2) inhibitors

Dapagliflozin or empagliflozin are SGLT-2 inhibitors that have recently been added to the HF management guidelines. It has been recommended that all patients with HFrEF should be

started on this drug class regardless of whether they have diabetes or not. This is in addition to the patient already receiving an ACE-I/, β-blocker and an MRA.[69]

The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) study is an ongoing phase III international, multi-centre randomised, double blind, parallel-group placebo-controlled trial studying the use of SGLT-2 inhibitors in the management of heart failure. Compared to other trials investigating heart failure and the use of SGLT-2 inhibitors, this trial's population consisted of patients with a high risk of cardiovascular (CV) death and hospitalisation, thus with more severe HF. 29lso It has also been found that in patients without heart failure, there was a decreased risk of new onset HF by approximately 30%. Moreso, these benefits are thought to be unrelated to the effect of this drug class on glycaemic control. The benefits were particularly more appreciable in patients with HfrEF, with an EF of <30%.[70]

SGLT-2 inhibitors exhibit their beneficial effects in HF through various mechanisms on the renal and cardiovascular systems and metabolism. In the cardiovascular system, these agents work via inhibition of the sodium-hydrogen exchanger-1 (NHE-1) in the myocardium, thereby inhibiting toxic intracellular calcium overload and subsequently reducing myocardial injury, hypertrophy and fibrosis. This, in turn, causes an overall improvement in the energetics of the myocardium and decreases oxidative stress.[70,71]

Furthermore, through its effect of increasing sodium and glucose excretion in the urine, there is an increase in natriuresis and osmotic diuresis, and therefore, a reduction in intravascular volume, preload and afterload and a decrease in blood pressure.[72,73] SGLT-2 inhibitors also improve vascular compliance and endothelial function. Furthermore, empagliflozin is associated with weight loss, decrease in visceral fat, increase in insulin sensitivity and a reducing effect on uric acid levels.[71]

Its use has been associated with a higher incidence of urinary tract infections (UTI) and genital tract infections. Furthermore, volume depletion due to diabetic ketoacidosis (DKA), despite co-administration of diuretics, remained low at <1% for DKA and 5% for volume depletion.[74]

Similar to the EMPEROR-Reduced trial, the Dapagliflozin Effect in Cardiovascular Events-Thrombolysis In Myocardial Infarction 58 (DECLARE-TIMI 58) trial also showed a reduction in cardiovascular death and hospitalisation for heart failure (HHF) rates with the use of SGLT-2 inhibitors.[73] This is the largest study by far investigating the effects of SGLT-2 inhibitors in HF among 17 160 patients.[73] When compared to the Empagliflozin Cardiovascular Outcome

Event Trial in Type 2 Diabetes Mellitus Patients (EMPA REG) trial, both studies focussed on patients with type 2 diabetes. Apart from a difference in sample size, the DECLARE-TIMI 58 trial included patients with established CVD or those who had multiple risk factors for CVD and preserved renal function with the exclusion of New York Heart Association (NYHA) class-4 patients.[73] Overall, only approximately 41% of the study population had established CV disease compared with 100% of patients in the EMPA REG trial, and 66% in the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial.[75] The study observations of a reduction in CV mortality and HHF were found to be more significant in patients with HFrEF, although an EF of <45% was used as the cut-off value for HFrEF.[73]

A limitation of this study, however, was that the EF was available in roughly a third of the patients.[73] Although this may in part be due to the fact that the study was not specifically designed to evaluate patients with HF, it still translated to slightly over 5 000 patients having a recorded EF. Ultimately, a similar conclusion was drawn that SGLT-2 inhibitors do reduce HHF and CV death, as found in the EMPA REG and CANVAS trials.[75] The findings of this study were also thought to be more generalisable overall to patients with type 2 diabetes, as the sample apparently was more representative of this particular patient population.[75] In addition, it was found that HF without reduced EF was more common in older females who were hypertensive, whereas HFrEF was more common in males with established atherosclerotic CVD.[73]

1.9.1.8 Other drugs

Diuretics are commonly used in the CCU to alleviate symptoms of congestion associated with heart failure and improve the patients exercise capacity, and consequently, reduce hospitalisations. Loop diuretics are preferred over thiazide diuretics due to their more potent and shorter effect. However, agents in the two classes of diuretics may be combined in the treatment of diuretic resistance.[69]

Ivabradine is recommended for use in patients with HFrEF (EF ≤35%), NYHA class II or III, who are in sinus rhythm but continue to have a resting heart rate of ≥70 beats per minute, despite being on a maximum tolerated β-blocker dose.[69]

Digoxin, often used as well, can be considered for use in patients with HFrEF who are in sinus rhythm and remain symptomatic despite optimal medical therapy with an ACE-I/ARNI, a β-blocker and MRA. It offers a reduced hospitalisation rate in this patient group. Caution should be exercised when using digoxin, as it has a narrow therapeutic window and can result in

toxicity. Digoxin is also used in patients with atrial fibrillation with a fast ventricular response (>110 beats per minute) despite therapy with β-blockers.[69]

A combination of hydralazine and isosorbide dinitrate has shown to reduce the risk of death in patients of African Black ethnicity with symptomatic HFrEF (EF ≤35%) or NYHA class III or IV in the presence of a LVEF <45% and a dilated LV, despite optimal medical therapy.[69]

Unless contraindicated, statin therapy should be provided to AMI patients regardless of their low-density lipoprotein (LDL) cholesterol level on admission.[48,76] Several studies have shown a mortality benefit with the use of statins, in addition to the prevention of new ischaemic events. Statin therapy is also recommended for use in patients with a high risk for developing CVD or those with established CVD, in order to prevent the onset of HF and prevent admissions related to HF.[69] With regard to ACS management, the ESC recommended that patients be given lipid-lowering statin therapy to a LDL cholesterol target of less than 1.8 mmol/L, or a 50% reduction when the baseline LDL level is between 1.8 and 3.5 mmol/L.[76]

1.9.2 Intravenous inotropes, vasopressors and vasodilators

Intravenous vasodilators, i.e., nitrates and nitroprusside, may be considered in acute heart failure and/or acute pulmonary oedema in the setting of a hypertensive emergency. Their overall mechanism of action results in vasodilatation and therefore a reduction of preload and afterload, resulting in an increased stroke volume and a reduction in myocardial oxygen demand.[69]

Inotropic support is often indicated in patients with poor cardiac output and LV systolic dysfunction and hypotension. They should be initiated at a low dose and up-titrated to doses that will ensure adequate organ perfusion. Due to their mechanism of action, inotropic agents may result in arrythmias, myocardial ischaemia and mortality.[69]

Vasopressors generally work through inducing peripheral arterial vasoconstriction and subsequent improvement of vital organ perfusion. This, however, may also result in an increase in afterload. For advanced heart failure and cardiogenic shock, norepinephrine has proven superior to dopamine and epinephrine, as the latter was found to cause higher rates of tachycardia and lactic acidosis.[69]

1.9.3 Coronary angiography

A cardiac catheterisation laboratory is an important facility that contributes to a positive impact on patient outcome. It has set diagnostic and therapeutic indications as specified below:

- Diagnostic indications:[13,77;
  - primary or rescue PCI;
  - revascularisation candidates in cardiogenic shock patients;
  - patients with ventricular septal rupture or valvular heart disease in pre-operative evaluation; and
  - persistent haemodynamic and/or electrical instability.

- Therapeutic indications:[13,77]
  - primary or rescue PCI;
  - haemodynamic support in the form of intra-aortic balloon counterpulsation (IABC);
  - temporary/permanent pacemaker implantation in symptomatic bradyarrythmias and CRT in refractory heart failure;
  - Implantable cardioverter defibrillator (ICD) implantation in refractory ventricular tachycardia; and
  - radiofrequency ablation of incessant tachyarrythmias.

Major complications related to coronary angiography include death, MI and stroke. Some of the minor complications include localised access-site complications, adverse reactions to the contrast media, renal impairment, intracoronary thrombosis, perforation of the coronaries and arrythmias.[78]

1.9.4 Percutaneous coronary intervention (PCI)

Primary PCI is the reperfusion therapy of choice in STEMI patients, showing lower mortality, reinfarction and stroke rates. It offers a benefit over fibrinolytic therapy if performed within 12 hours of symptom onset and within 2 hours from the diagnosis of STEMI. It should, however, be taken into consideration that PCI may not be easily accessible in some areas and therefore, fibrinolysis remains a better option as it is more readily available in most centres.[76]

In the case of a patient presenting more than 12 hours after symptom onset, primary PCI may be considered when there is clinical evidence of ongoing ischaemia in terms of continuous or

recurrent chest pain, electrical instability based on ECG findings or complications of MI such as heart failure, shock or malignant arrhythmias.[76]

In the South African cohort of the ACCESS study, 93% of the patients with the diagnosis of ACS underwent coronary angiography, while 18% received fibrinolytic therapy. Of those that underwent angiography, slightly over 50% of them also had PCI. This actually showed a higher intervention rate compared to the entire ACCESS cohort statistics, and may reflect the study population in the South African cohort, as most of the participating centres participating were tertiary and private institutions with on-site facilities available. Therefore, these findings may not accurately represent the South African population in its entirety.[6]

The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial investigated the 12-month major adverse cardiac or cerebrovascular event rate among patients with left main coronary artery disease. They found that the rate of such events was similar in both the patients that underwent PCI compared to those that underwent coronary artery bypass graft (CABG). It was noteworthy, however, that PCI had higher revascularisation rates at 12 months. Furthermore, the stroke rate associated with CABG was almost 10 times higher when compared to the group that underwent PCI (2.7% versus 0.3%). Regarding patients with three-vessel disease, excluding the left main coronary artery, higher revascularisation and major cardiac and cerebrovascular event rates were observed in the PCI group compared to the CABG group, although the rate of mortality from any cause at 12 months was similar in both groups.[79]

A meta-analysis by Daemen *et al*. showed that the safety profile and survival rates between PCI and CABG were similar at five years, which was a substantially longer period compared to the SYNTAX trial. It was also found that at five-year follow-up, PCI resulted in higher repeat revascularisations compared to CABG. Although the rates of patients being angina free were similar at five years, the rate of angina was higher with CABG at one year, and PCI required more repeat revascularisation to achieve the same rate as CABG at five years.[80]

Rescue PCI is performed after failed fibrinolytic therapy. Fibrinolytic therapy is considered to be successful when there is a >50% ST-segment resolution 60–90 minutes after fibrinolytic therapy, a typical reperfusion arrythmia and resolution of chest pain. In the absence of these variables, it may be considered as evidence for ongoing occlusion in the coronary vessels or reinfarction.[67,76] In this case, re-administering of fibrinolytic therapy has not proven effective.[67] A meta-analysis of several randomised trials evaluated the advantages and risks associated with rescue PCI and repeat fibrinolysis versus conservative management in patients with

STEMI who failed fibrinolysis. An association with increased risk for minor bleeding and no significant improvement for all-cause mortality or reinfarction with repeat fibrinolysis were found.[81] Furthermore, rescue PCI was associated with a significant relative risk reduction for heart failure and reinfarction, while an association with an increased risk of stroke and minor bleeding with rescue PCI was also observed.[81] Rescue PCI should be considered when there is clinical or ECG-based evidence of a large infarct, or if the procedure could be carried out within a reasonable time delay, i.e., up to 12 hours after symptom onset.[67]

Facilitated PCI uses a pharmaco-invasive strategy that combines fibrinolysis and rescue PCI or routine early PCI after successful fibrinolysis.[67] Routine early PCI refers to angiography performed within 2–24 hours after successful fibrinolytic therapy.[76]

1.9.5 Thrombolysis

The ACC/AHA and ESC both recommended that when primary PCI is unavailable, or a travel time of more than 60 minutes to the nearest PCI-capable centre is inevitable, fibrinolysis should be given as an alternative reperfusion therapy. The recommended door-to-needle time is within 30 minutes. Should the patient present to a PCI-capable facility, a door-to-balloon time of 90 minutes is advised.[35,76]

STEMI patients who developed symptoms within the preceding 12 hours should receive fibrinolytic therapy, provided there are no contraindications.[35] Fibrinolytic therapy is also recommended for STEMI patients with symptom onset within the previous 12 hours and a new/presumably new left bundle branch block (LBBB), provided that no contraindications exist. In the presence of contraindications and the absence of symptoms, with symptom onset more than 24 hours ago, fibrinolytics should not be administered.[35]

The tissue plasminogen activator (tPA) class of medications, such as tenecteplase, forms part of the newest fibrinolytic agents. They are easier to administer, thus having a diminished possibility of administration errors, and could be used more easily outside the hospital setting, making pre-hospital fibrinolysis easier.[82]

1.9.6 Cardiac pacing

Temporary pacing leads are most commonly inserted for bradyarrythmias. These often occur as a result of AMI (anterior/inferior), complete heart block, sick sinus syndrome or as a result of a failed permanent pacemaker.[83] Cardiac pacing is not usually necessary unless the

bradyarrythmia is associated with hypotension, impaired renal perfusion or a heart rate of less than 40 beats per minute.[84] Less commonly, temporary pacing leads are placed prophylactically for control of tachyarrythmias or diagnostic purposes.[83,84] In an emergency situation, transthoracic pacing should be considered while preparing for placement of a transvenous wire.

Major complications associated with this procedure include pneumothorax, perforation of the right ventricle, pacing/sensing failure, arrythmias and septicaemia. Haematoma formation and diaphragmatic stimulation are some of the minor complications associated with cardiac pacing.[83,84]

1.9.7 Invasive mechanical ventilation

Endotracheal intubation and mechanical ventilation are indicated when a patient's spontaneous respiratory effort is insufficient to keep them alive.[85] It may occasionally be indicated as a prophylactic measure in patients with impending failure of physiological processes of the body systems. In addition, it may be used to keep a critically ill patient's ventilation under control.[85] These indications can largely be grouped into the following scenarios:[85,86]

- acute respiratory failure: arterial PO_2 <60 mmHg, arterial PCO_2 >60 mmHg or respiratory rate >40 respirations/minute;
- clinical deterioration;
- decline in level of consciousness with inability to maintain the airway;
- cardiac arrest or haemodynamic instability; and/or
- respiratory muscle fatigue or neuromuscular disease.

These interventions form an essential part of management of the critically ill patient. However, it should be kept in mind that invasive mechanical ventilation is not without the potential to cause harm to the patient.

1.9.8 Mechanical circulatory support

Due to the rising number of patients admitted to the CCU with heart failure and cardiogenic shock, the use of acute mechanical circulatory support (MCS) devices is becoming central to CCU care.[87,88] Several types of MCS devices are available, classified according to pump haemodynamics, at which site blood is withdrawn and returned, catheter/cannula sizes,

method of placement (percutaneous or surgical) and whether a gas exchange unit is used.[88]

1.9.8.1 Intra-aortic balloon pump (IABP)

An intra-aortic balloon pump is an MCS device recommended for use in the management of impaired cardiac function. While generally recommended for short-term use, the following indications are applicable:[87]

- cardiogenic shock*;
- refractory unstable angina;
- refractory ventricular tachycardia;
- pre-/post-operative cardiac surgery support;
- interim therapy while awaiting more advanced therapies;
- acute ischaemic mitral regurgitation secondary to papillary muscle rupture;
- ventricular septal rupture; and
- failed PCI.

*Cardiogenic shock is a class IIb/B recommendation according to the ESC guidelines.[89]

An IABP is contraindicated in patients with aortic dissection, severe aortic regurgitation and thoracic aortic aneurysms. Complications include infection, bleeding and thrombus formation, damage to the blood vessels, catheter rupture and migration.[87]

1.9.8.2 Extracorporeal membrane oxygenation (ECMO)

In essence, ECMO functions as a modified cardiopulmonary bypass circuit, using a pump that has the ability to take over the patient's' entire cardiac output (CO) and gaseous exchange. It is considered for use in cardiac and/or respiratory failure.[87,88]

Patients are generally supported on either veno-arterial or veno-venous ECMO.[87] Often, it is used for patients with cardiorespiratory failure who continue to deteriorate despite optimal therapy with medication, inotropic support, vasopressors and other MCS devices, such as IABP.[87,89] Complications of ECMO include limb ischaemia, acute pulmonary oedema as a result of left ventricular myocardial damage and thrombus formation. In the event of mechanical-related complications such as air/clots in the circuit, pump/oxygenator failure or rupture of the tubing, patient should be taken off the system and reinitiated as soon as possible. Mechanical complications are considered an emergency.[87]

1.9.8.3 TandemHeart®

The TandemHeart® is a system based on centrifugal-flow pump mechanics. Inserted percutaneously, it serves to establish a left atrium-to-femoral artery bypass. With the capacity to deliver up to five litres of flow to replace the patient's cardiac output, it offloads the left ventricle preload, stroke work and myocardial oxygen consumption. It is indicated for high-risk PCI and patients with cardiogenic shock. Furthermore, it is used as a bridging therapy to more definitive advances such as cardiac transplant or ventricular assist devices. Some of the complications related to this system include catheter migration, bleeding, ischaemia of the distal extremities and transseptal puncture. Use of the TandemHeart® is contraindicated in patients with thrombi in the atria and those with severe peripheral vascular disease.[87]

1.9.8.4 Impella group devices

The Impella group of devices, which includes the Impella Recover and the Impella heart pump, are axial flow pumps that can be inserted percutaneously in order to provide transvalvular left ventricular assistance. These devices are generally able to provide flows of 2.5 L/min up to 5 L/min.[89] These devices are generally designed to provide left ventricular assistance, with the exception of the Impella RP, which is a right ventricular assistance device. Generally, indications include cardiogenic shock refractory to medical management/IABP, high-risk PCI or decompensation after left VAD implantation, acute myocardial infraction or heart transplantation. Contraindications to use this device include LV thrombus, mechanical aortic valve replacement or valvular regurgitation, tortuous course of the vessels and LV rupture or tamponade. Similar to the other MCS devices, catheter migration, bleeding and distal extremity ischaemia are possible complications associated with the use of Impella devices, in combination with haemolysis.[87]

1.9.9 Renal replacement therapy (RRT)

The decision of when to initiate RRT in the critically ill patient is of crucial importance and often not easy to make.[90,91] This decision includes consideration of the recommended indications for RRT, vascular access and its complications, anticoagulation, dosing and when to discontinue therapy.[91] The classical indications include metabolic acidosis and fluid overload not responding to medical therapies, hyperkalaemia, signs of uraemia such as encephalopathy/pericarditis and certain drug intoxications.[91]

In a systematic review by Karvellas *et al*., it has been implicated that early initiation of RRT in critically ill patients with AKI was associated with improved survival.[90] Similarly, the Early versus Late Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury (ELAIN) Randomized Clinical Trial in Germany, also found that early RRT in critically ill patients with AKI was significantly better compared to the delayed initiation group. However, this was a single-centre study involving surgical patients, although 47% of the patients in this study population was postcardiac surgery cases.[92]

1.9.10 Venous access and arterial pressure monitoring

Assessment of a patient's haemodynamic status is crucial in the CCU and all patients admitted should be monitored either through non-invasive or invasive measures. Invasive intra-arterial pressure monitoring should be performed in patients with severe hypotension (SBP ≤80 mmHg), cardiogenic shock or those on vasopressors or IV inotropes.[81]

1.10 CONCLUDING COMMENTS

The development of the CCU has played a significant role in reducing ACS-related mortality. However, the patient profile, conditions that need to be managed and interventions required have evolved over the years. At present, a high burden of non-cardiovascular conditions and complications are seen in the CCU. The skill set of contemporary cardiologists has also evolved. They are often faced with patients that have multiple organ dysfunction and require ICU interventions. These increasing complexities in patients, the requirement for the involvement of various subspecialities and the multidisciplinary approach is expected to continue. Numerous knowledge gaps are still prevalent in this new era, with ample opportunity for research. To the best of our knowledge, this is the first study conducted to describe the epidemiology of patients that demised in the modern-day CCU in South Africa.

1.11 AIM AND OBJECTIVES, STUDY DESIGN AND METHODOLOGY

1.11.1 Aim and objectives

The aim of this research was to describe the demographic and clinical characteristics, laboratory biochemical findings and associated prevalence of risk factors among patients who demised (non-survivors) in the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) CCU during the eight-year period from 2010 to 2017.

The objectives of the study were:

i. to describe the demographic, clinical and laboratory features of patients who died in the CCU;
ii. to analyse and document the prevalence of major risk factors associated with mortality in the CCU and compare our findings to previously published data;
iii. to describe the most common admission diagnosis of this cohort; and
iv. to compare the major risk factors between the ACS and non-ACS cohort.

1.11.2 Study design and setting

A single-centre, retrospective study was conducted that included all patients who died in the period from January 2010 to December 2017, admitted to the CCU of the CMJAH.

1.11.3 Sample population

Patients 18 years and older who were admitted and died at CMJAH CCU from January 2010 to December 2017 represented the patient population. The sample identified for inclusion consisted of 96 patients.

1.11.3.1 Inclusion criteria

- Patients who died in CMJAH CCU from January 2010 to December 2017.
- Both men and women aged 18 years and older.

1.11.3.2 Exclusion criteria

- Patients with incomplete medical records were excluded from the study.

1.11.4 Data collection

Data of patients that died at CMJAH CCU from 2010 to 2017 were collected retrospectively from patient records. A data collection sheet (cf. Appendix A) was compiled to collect information relevant to the study.

During data collection, the following details were obtained:

- demographic variables: age, gender, racial group;
- habits: smoking;
- comorbidities: HIV status, hypertension, diabetes, obesity and dyslipidaemia;
- diagnosis at death;
- laboratory investigation results;
- echocardiogram findings;
- length of CCU stay;
- treatment/interventions received; and
- complications

The data collected were entered into Research Electronic Data Capture (REDCap™) (Vanderbilt University; Nashville, TN, USA) and exported to Microsoft Excel, version 2016 (Microsoft Corporation; Redmond, WA, USA). REDCap™ is a web-based application that allows for capturing of data, analysis, exportation of data to a statistical program of choice and safe storage of data using a password-protected system. Patient information was stored by means of a numbering system to ensure confidentiality.

1.11.5 Data analysis

Analysis of results was done using Stata 16 software (StataCorp, 2019; *Stata Statistical Software: Release 16.* StataCorp LLC, College Station, TX, USA). Groups were compared using Student's t-test (parametric or normally distributed data), the Kruskal Wallis test (non-parametric data or data not normally distributed) for continuous variables and the chi-square test for proportions. Demographic data were analysed using descriptive statistical analysis (mean, median). Continuous variables were described using the mean and standard deviation, or median and interquartile range (IQR) when variables were not normally distributed. Pearson's correlation coefficients determined the association between risk factors for heart disease and ACS status, using a statistical significance threshold of 0.05. Multiple linear regression analysis was used to determine predictors of risk factors associated with mortality in the CCU. Confidence intervals of 95% (95% CI) were calculated and a p-value of less than 0.05 was regarded as statistically significant.

1.11.6 Ethical considerations

Ethics approval was granted unconditionally by the University of the Witwatersrand Human Research Ethics Committee (HREC), with ethics clearance certificate number M190955. Informed consent was not applicable to this type of study given its retrospective nature and using only archived patient records to obtain information.

1.12 DEFINITION OF TERMS

For the purpose of this study, the following definitions of terminology were applicable:

1.12.1 Anaemia

Anaemia was defined according to the World Health Organization (WHO) criteria of haemoglobin levels <13 g/dL in men and <12 g/dL in women.[93]

1.12.2 Obesity

Although obesity by definition is regarded as a body mass index (BMI) of ≥30 kg/m^2, for the purpose of this study, patients were classified as either obese or not based on the clinician's discretion. The information was obtained from the discharge summary and no formal measurement of weight and height were recorded to calculate BMI.

1.12.3 Diabetes mellitus

Diabetes mellitus was defined as a previous diagnosis of diabetes, the need for oral hypoglycaemic agents or a random plasma glucose level of ≥11.1 mmol/L, fasting plasma glucose of ≥7.0 mmol/L, or glycated haemoglobin (HbA1c) of ≥6.5% if the patient has symptoms of hyperglycaemia. In asymptomatic individuals, an abnormal value as set out above, found on two separate occasions within a two-week period, was indicative of diabetes.[94]

1.12.4 Hypertension

Patients were regarded as hypertensive if they had a history of hypertension, were on antihypertensive medication or had a persistent elevation in blood pressure of ≥140/90 mmHg.[95]

1.12.5 Acute coronary syndromes (ACS)

Acute coronary syndromes were defined as a spectrum of clinical symptoms and signs that occur as a result of acute myocardial ischaemia and range from unstable angina (UA) to non-ST-segment elevation myocardial infraction (NSTEMI) and ST-segment myocardial infarction (STEMI).[96]

1.12.6 Acute myocardial infarction (AMI)

A diagnosis of AMI requires detection of an increase and/or decrease in cardiac biomarkers (preferably troponin) with at least one value above the 99th centile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following:[97]

- symptoms of myocardial ischaemia;
- ECG changes indicative of new ischaemia;
- development of pathological Q-waves on the ECG;
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; and/or
- presence of a coronary thrombus observed by angiography or at autopsy.

1.12.7 Acute kidney injury (AKI)

Acute kidney injury has been defined according to Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI as follows:[98]

- increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or
- increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the preceding seven days; or
- urine volume of <0.5 mL/kg/h for six hours.

1.12.8 Acute kidney disease (AKD)

was Acute kidney disease has been defined according to KDIGO clinical practice guidelines for AKI as follows:[98]

- AKI; or
- GFR of <60 mL/min per 1.73 m^2 for <3 months; or
- a decrease in GFR by ≥35% or an increase in serum creatinine by >50% for <3 months.

1.12.9 Chronic kidney disease (CKD)

Chronic kidney disease has been defined according to KDIGO guidelines. Diagnosis of CKD was made according to the patient's known medical history as obtained from the records. The KDIGO criteria are as follows:[98]

- GFR of <60 mL/min per 1.73 m^2 for >3 months; or
- kidney damage for >3 months.

1.12.10 Coronary care unit

For the purpose of this study, the terms coronary care unit (CCU) and coronary intensive care unit (CICU) have been used interchangeably.

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CHAPTER 2
PUBLISHABLE MANUSCRIPT

The demographic and clinical profile of cardiovascular mortality among patients admitted to a coronary care unit (2010–2017) at the Charlotte Maxeke Johannesburg Academic Hospital, South Africa

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Abstract

Background: Patient management in coronary care units (CCUs) has evolved over the years. However, limited data are available on the causes of morbidity and all-cause mortality in sub-Saharan African patients admitted to CCUs.

Methods: This retrospective study analysed data of consecutive patients who died between 2010 and 2017 at the Charlotte Maxeke Johannesburg Academic Hospital CCU, Johannesburg, South Africa.

Results: The study included 96 patients; 50.0% were male. The median age was 63 years (interquartile range 45–76). Hypertension was the most common risk factor (52.1%), followed by diabetes mellitus (32.3%). The majority of deaths (65.6%) were from non-acute coronary syndromes (ACS)-related diagnoses, with ACS being the most common cause of cardiovascular death (34.3%). Pneumonia and chronic kidney disease (CKD) were the major causes of non-cardiovascular death (both 26.3%).

Conclusion: Cardiovascular diseases primarily affected younger patients compared with international studies, with hypertension and diabetes being the most prevalent risk factors.

Keywords: coronary care unit, acute coronary syndromes, cardiovascular diseases, cardiovascular death, Africa

2.1 Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally, with more than four out of five CVD deaths being attributable to stroke and heart attack.[1] These diseases are a heterogeneous group of disorders that affect the heart and blood vessels. The spectrum of disease includes rheumatic heart disease (RHD), coronary heart disease (CHD), cardiomyopathy and heart failure (HF), dysrhythmias, cerebrovascular disease, congenital heart disease and venous thromboembolism (VTE).[1]

The prevalence of CVD is increasing and has thus been labelled a true pandemic. This pandemic, however, is dynamic due to changes in risk factors and advancements in the interventions to prevent and treat CVDs.[2] The changes in risk factors can be explained by urbanisation of communities, which has led to lifestyle changes, changes in dietary intake, the prevalence of comorbid conditions and an ageing population.[2,3]

In South Africa, mortality from diseases of the cardiovascular system showed an increase from 18.4% in 2016 to 18.9% in 2018.[4] Of the top 10 causes of natural death in South Africa, cerebrovascular diseases ranked third. This is one position higher compared to the previous years (2016–2017). Ischaemic heart disease (IHD), although ranked as eight, also moved up one place. Diabetes and hypertension were in second and sixth position, respectively. These two conditions are notable traditional risk factors for CVD.[4]

Currently, there is no standardised source of data for CVD mortality in sub-Saharan Africa (SSA) and, in particular, South Africa. There is also a paucity of data on the mortality rates in CCUs, with more emphasis on acute coronary syndromes (ACS) risk factors locally. In a multinational survey of the current management strategies registry, Schamroth *et al*. analysed 642 South African patients with ACS, and found an all-cause mortality rate of 5.7% at 12 months.[5] In The Sub-Saharan African Survey of Heart Failure Study (THESUS-HF study), acute heart failure (AHF) with a non-ischaemic aetiology (hypertension, rheumatic heart disease and endemic cardiomyopathies) was associated with a mortality rate of 17.8%.[6]

Modern-day CCUs have transformed into a blended integration between CCU and cardiology wards, and CCU and intensive care (ICU) or high care units.[7] They have certainly evolved from the CCUs established in the 1960s and 1970s, reflecting a change in the patient population admitted and the variety of conditions, which now involve multiple organ system dysfunction.[8] Cardiologists must be competent and trained in skills generally mastered by ICU specialists, such as managing septic shock, critical illness neuropathy, renal replacement therapy (RRT),

provision of ventilatory support and neuropsychiatric complications such as delirium. Given the changing needs of the CCU, this unit has seen a name change from coronary care unit to cardiac care unit in some areas, even being called a cardiac ICU (CICU) in others.[7,9]

The aim of this research was to describe the demographic and clinical characteristics, laboratory biochemical findings and the prevalence of associated risk factors for coronary artery disease among patients who demised (non-survivors) in the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) CCU during the period 2010 to 2017.

2.2 Methods

2.2.1 Study design and setting

A single-centre, retrospective study was performed on consecutive patients who died at the CMJAH CCU between January 2010 and December 2017. The CMJAH is a tertiary academic centre in Johannesburg, South Africa, providing cardiology services to patients in Gauteng, North West and parts of Mpumalanga and Limpopo provinces.

2.2.2 Participants

Records of all patients ≥18 years of age, who were admitted and died at CMJAH CCU from January 2010 to December 2017, were included in the study. Incomplete medical records were excluded.

2.2.3 Data collection

Retrospective data of the patients were collected from the CMJAH CCU patient registry and the electronic health record system, which stores the data of all patients hospitalised in the CCU and general cardiology wards. A data collection sheet (Appendix A) was used to capture information on patients' demographic variables, habits (i.e. smoking), comorbidities, laboratory results, echocardiogram (ECG) findings, length of CCU stay, treatment and interventions, diagnosis at death, and complications.

The data were collected using Google Forms and entered into a password-encrypted Microsoft Excel (version 2016/365) spreadsheet. Patient information was stored using a numbering system allocating a unique number to each patient. A total of 96 patients were included in the final analysis. The process of patient report collection is illustrated in Figure 2.1.

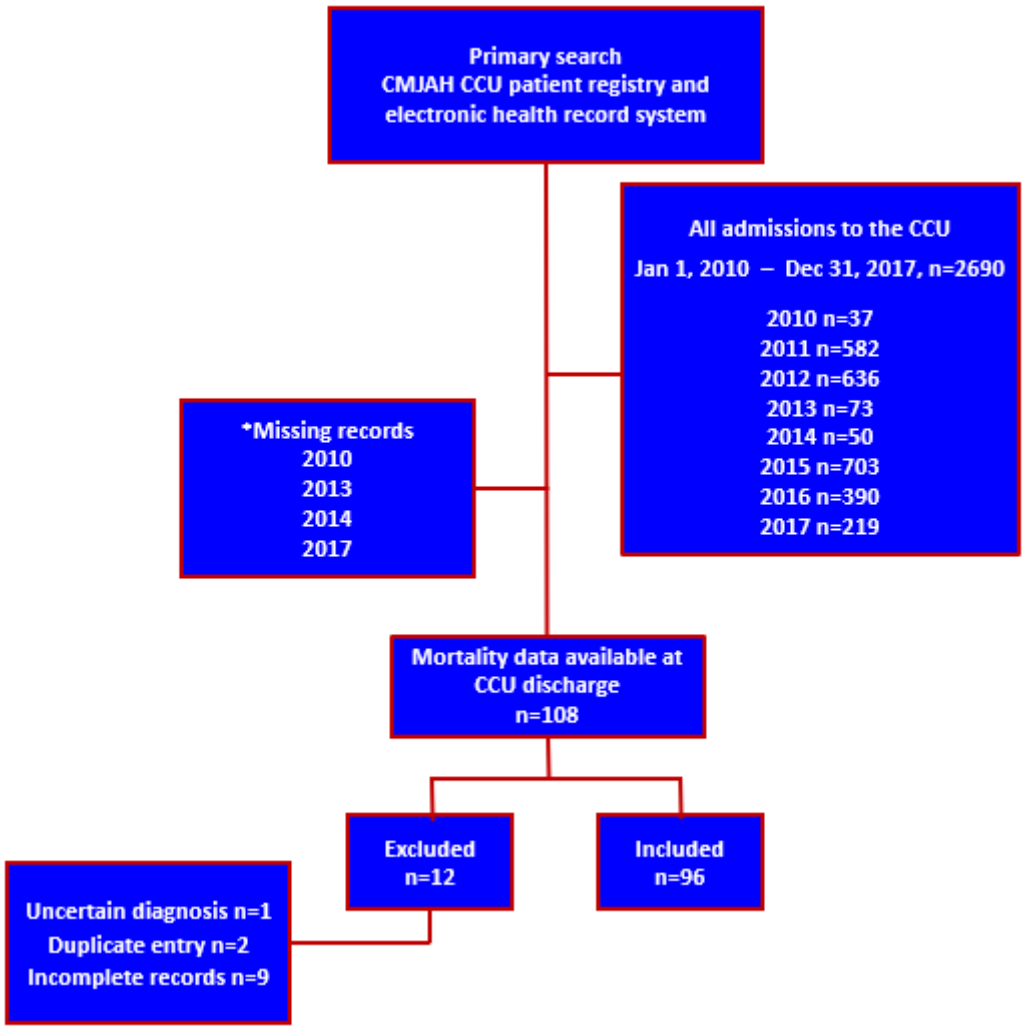

Figure 2.1. Selection of patient records.

Abbreviations: CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; CCU, coronary care unit.

2.2.4 Statistical analysis

Data were collected and analysis of results was done by a biostatistician using Stata 16 software (Stata Statistical Software: Release 16; StataCorp LLC, 2019; College Station, TX). Groups were compared using the Student's t-test (parametric or normally distributed data) and Kruskal Wallis test (non-parametric data or data that were not normally distributed) for continuous variables and the chi-square test for proportions. Demographic data were analysed using descriptive statistical analysis. Continuous variables were described using the mean and standard deviation or median and interquartile range (IQR) when variables were not normally distributed. Pearson's correlation coefficients were calculated to determine the association between risk factors for heart disease and ACS status, using a statistical significance threshold of 0.05. Multiple logistic regression analysis was used to determine predictors of risk factors

associated with mortality in the CCU. Confidence intervals (CI) were set at 95% and a *p*-value of less than 0.05 was regarded as representative of statistical significance.

2.2.5 Ethical considerations

Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) (ethics clearance certificate number: M190955; Appendix B – ethics letter; Appendix C – approved study protocol). Permission was also obtained from the Gauteng Province Department of Health (Appendix D). Given the retrospective nature of the study and using archived patient records to obtain information, informed consent was waived. No identifying patient data were collected. All data collected were encrypted and stored on a password-protected device.

2.3 Results

2.3.1 Baseline demographic profile and risk factors

The final study population included 96 patients who died while hospitalised in the CCU Table 2.1 summarises the findings of the demographic and clinical characteristics of the patients presented as frequencies and percentages, while Table 2.2 shows the variables presented as medians and IQRs. The gender of the patients was equally distributed (male and female each *n* = 48; 50.0%. The median age among all patients who died was 63 years (IQR 45–76) (Table 2.2). As shown in Table 2.1, the majority of patients (*n* = 58; 60.4%) were 60 years of age or older, while, with regard to race, 50.0% (*n* = 48) were reported as Black. Hypertension was identified as a comorbidity in 52.1% (*n* = 50), while 34 (35.4%) patients had dyslipidaemia and 19 (19.8%) patients had diabetes mellitus.

Table 2.1. Demographic and clinical characteristics of patients who died at CMJAH CCU 2010–2017 (*n* = 96, unless specified otherwise).

Variables and categories	*n* (%)
Gender	
Female	48 (50.0)
Male	48 (50.0)
Age (years)	
<40	16 (16.7)
40–49	9 (9.4)
50–59	13 (13.5)
≥60	58 (60.4)
Year of admission	
2010	1 (1.0)
2011	24 (25.0)
2012	11 (11.0)
2013	1 (1.0)
2014	N/A
2015	N/A
2016	39 (40.6)
2017	20 (20.8)
Race	
Black	48 (50.0)
White	30 (31.3)
Indian	12 (12.5)
Mixed ancestry	5 (5.2)
Not recorded	1 (1.0)
Risk factors (n = 96)	
Hypertension	50 (52.1)
Dyslipidaemia	34 (35.4)
Diabetes	31 (32.3)
Obesity	19 (19.8)
Smoking	14 (14.6)
HIV status	
Negative	33 (34.4)
Positive	8 (8.3)
Unknown	55 (57.3)
Diagnosis at death	
Cardiovascular disease related (n = 96)	
Unclassified	3 (3.1)
Acute coronary syndrome	33 (34.4)
Coronary heart disease	1 (1.0)
Valvar heart disease	8 (8.3)
Heart failure	9 (9.4)
Dilated cardiomyopathy	13 (13.5)
Infective endocarditis	4 (4.7)
Dysrhythmia	9 (9.4)
Ischaemic cardiomyopathy	4 (4.2)
Pulmonary embolism	4 (4.2)
Conduction disorder	2 (2.1)
Hypertrophic obstructive cardiomyopathy	2 (2.1)
Aortic aneurysm	1 (1.0)
Aortic dissection	1 (1.0)
Cerebrovascular accident	2 (2.1)

Table 2.1. Continued.

Variables and categories	*n* (%)
Diagnosis at death	
Non-cardiovascular disease related (n = 19)	
HIV	3 (15.8)
Asthma	1 (5.3)
Chronic kidney disease	5 (26.3)
Acute kidney injury	4 (21.0)
Pneumonia	5 (26.3)
Hypothyroid	1 (5.3)
Complications	
Sepsis	6 (6.3)
Bleeding	1 (1.0)
KDIGO staging of acute kidney injury (n = 53)	
Stage 1	12 (22.6)
Stage 2	16 (30.2)
Stage 3	25 (47.2)
Killip classification (n = 94)	
Class 1	42 (44.9)
Class 2	34 (36.2)
Class 3	8 (8.5)
Class 4	10 (10.6)

CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; CCU, coronary care unit; HIV, human immunodeficiency virus; KDIGO, Kidney Disease Improving Global Outcomes; N/A, not available.

Table 2.2. Demographic and clinical characteristics of patients who died at CMJAH CCU 2010–2017: results for variables with medians and interquartile ranges (IQR).

Variables and categories	Median (IQR)
Age (years)	63 (45–76)
Duration of CCU stay (days)	3.5 (2–7)
Ejection fraction (%) observed on ECG	41.5 (30–57.7)
Laboratory results	
Urea (mmol/L)	10.4 (7–20.55)
Creatinine (µmol/L)	134 (98–249.5)
$HbA1_C$ (%)	6.25 (5.9–9.05)
LDL-C (mmol/L)	2.34 (1.6–3.66)
TIMI score	3 (2–4)

CMJAH, Charlotte Maxeke Johannesburg Academic Hospital CCU, coronary care unit; ECG, electrocardiogram; HbA1C, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; TIMI, Thrombolysis in Myocardial Infarction

The distribution of cardiovascular diagnoses at death is illustrated in Figure 2.2, while Figure 2.3 represents the distribution of the 19 patients who had a noncardiovascular-related cause of death.

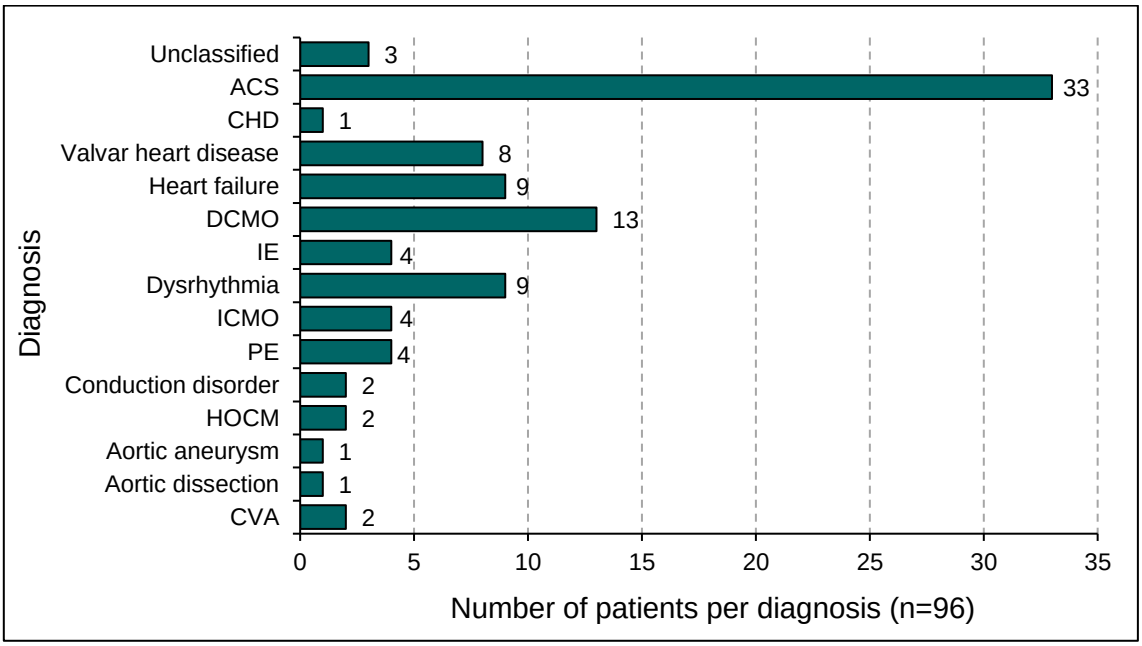

Figure 2.2. Cardiovascular cause of death.

Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; DCMO, dilated cardiomyopathy; IE, infective endocarditis; ICMO, ischaemic cardiomyopathy; PE, pulmonary embolus; HOCM, hypertrophic obstructive cardiomyopathy; CVA, cerebrovascular accident.

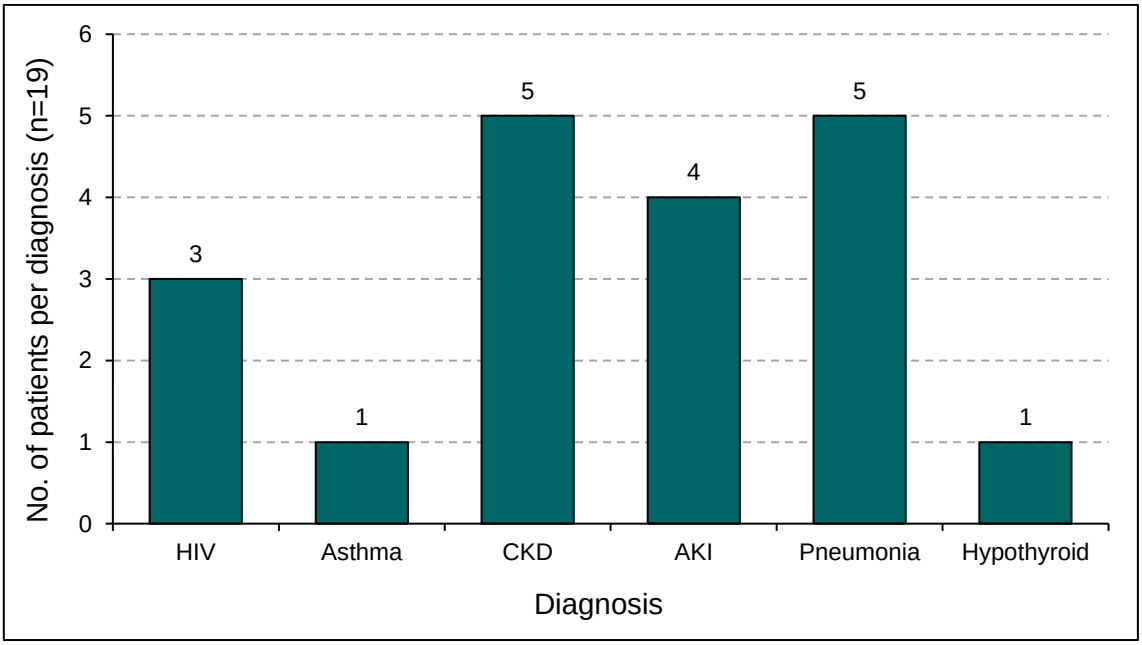

Figure 2.3. Non-cardiovascular cause of death.

Abbreviations: HIV, human immunodeficiency virus; CKD, chronic kidney disease; AKI, acute kidney injury.

2.3.2 Echocardiographic parameters

Among patients with documented ECG findings (n=79), 23 (29.1%) were documented to have abnormal wall motion. The median ejection fraction (EF) was 41.5% (IQR 30–57.7). Vegetations were present in four (5.1%) patients, while 13 (16.5%) patients had pericardial effusion. Twenty (25.3%) patients had a dilated right ventricle. Mitral valve disease was documented in 45 (57.0%) patients, of whom 43 (95.6%) had mitral regurgitation and two (4.4%) had mitral stenosis.

2.3.3 Acute coronary syndromes

Table 2.3 summarises a comparison of findings between patients diagnosed with ACS (*n* = 33) and those with non-ACS (*n* = 63). Twenty (60.0%) of the 33 patients who presented with ACS were male. Hypertension was the most prevalent risk factor, documented in 21 (63.6%) patients in the ACS group and 29 (46.0%) of the patients with non-ACS. Hypertension was followed by dyslipidaemia in 16 (48.5%) patients and diabetes mellitus in 14 (42.4%) patients compared to 18 (28.6%) and 17 (27.0%) with dyslipidaemia and diabetes, respectively, in the non-ACS cohort. Smokers were significantly more likely to present with ACS, compared to non-smokers (*n* = 11 [33.3%] versus *n* = 3 [4.76%]; $p < 0.001$). In the non-ACS group, only three (4.8%) of patients who died were smokers.

Table 2.3. Major risk factors for heart disease: comparison of the acute coronary syndrome (ACS) and non-ACS cohorts.

Risk factor	Group		*p*-value
	ACS (*n* = 33)	Non-ACS (*n* = 63)	
Hypertension			0.10
Yes	21 (63.6)	29 (46.0)	
No	12 (36.4)	34 (54.0)	
Diabetes mellitus			0.12
Yes	14 (42.4)	17 (27.0)	
No	19 (57.6)	46 (73.0)	
Obesity			0.061
Yes	10 (30.3)	9 (14.3)	
No	23 (69.7)	54 (85.7)	
Dyslipidaemia			0.053
Yes	16 (48.5)	18 (28.6)	
No	17 (51.5)	45 (71.4)	
Smoking			<0.001
Yes	11 (33.3)	3 (4.8)	
No	22 (66.7)	60 (95.2)	
Gender			
Male	20 (60.0)	28 (50.0)	
Female	13 (40.0)	28 (50.0)	
Age (years)			
Median	60	61	
Interquartile range	(64–72)	(44–76)	

We fitted a logistic regression model to evaluate covariates associated with clinical presentation of ACS among all patients who died. The results are shown in Table 2.4. The model was adjusted for age and gender. Smokers were 8.27 times more likely to present with ACS [95% confidence interval 1.86; 36.76; $p = 0.006$].

Table 2.4. Univariate logistic regression model for risk factors associated with a patient being diagnosed with acute coronary syndrome.

Risk factor	Level	Odds ratio	95% CI	LR *p*-value
Hypertension	Yes	1.15	(0.32; 4.06)	0.82
Diabetes mellitus	Yes	1.13	(0.35; 3.60)	0.84
Obesity	Yes	2.4	(0.73; 7.78)	0.14
Dyslipidaemia	Yes	1.48	(0.50; 4.33)	0.47
Smoking	Yes	8.27	(1.86; 36.76)	0.006
Gender	Male	2.19	(0.78; 6.10)	0.13
Age		1.02	(0.98;1.05)	0.25

CI, confidence interval; LR, likelihood ratio.

2.3.4 Complications and causes of death

Approximately one third of the cohort that died from a cardiovascular cause of death had ACS (*n* = 33/96; 34.4%), followed by dilated cardiomyopathy (*n* = 13/96; 13.5%). Congenital heart disease, aortic aneurysm and dissection were among the least common causes of cardiovascular death, which occurred in one case each. The majority of the study population demised from non-ACS diagnoses (*n* = 63/96, 65.6%).

As shown in Table 2.1, pneumonia and CKD (both *n* = 5/19; 26.3%) were the major causes of death in patients whose diagnosis at death was not primarily related to a cardiac cause. Sepsis occurred in six (*n* = 6.3%) patients and bleeding in one (*n* = 1.0%). A total of 53 (55.2%) patients had documented AKI, with the majority (*n* = 25/53; 47%) being classified as KDIGO stage 3.

2.4 Discussion

In this study, we reviewed the medical records of consecutive patients who experienced in-hospital all-cause mortality while admitted to the CMJAH CCU in Johannesburg, South Africa. The median age among the 96 patients who demised was 63 years, which was notably lower than the median age of 72 years found in two separate Italian studies.[10,11] The youngest person in the study by Campanile *et al*. was 61 years,[10] compared to 16.7% of the patients in our study being younger than 40 years of age. Similarly, the age IQR of approximately 7 000 patients in the study by Casella *et al*. was 61–80 years,[11] compared to an IQR of 45–76 years in our study.

Similar findings with regard to age were observed in the United States, with a reported mean age of 67 and 70 years, respectively, among CCU patients.[12,13] Moreover, approximately 40% of the patients who demised in our study were younger than 60 years of age. This was a noteworthy finding as it reflects that a significant proportion of the study population was in their productive years and most probably still actively working and providing for their families. A similar trend in CVDs affecting younger patients across Africa, such as hypertensive, rheumatic and ischaemic heart diseases and cardiomyopathy, has been reported in several publications.[14–16]

The Word Economic Forum (WEF) projected a US$47 trillion loss in economic output by 2030 resulting from the increasing burden of non-communicable diseases (NCDs), particularly because NCDs are now more prevalent in the younger, economically productive population.[17] The elements contributing to CVDs occurring prematurely in Africa compared to other regions in the world, are not clear and may be multifactorial.[15,16,18]

The male-to-female ratio of patients in this study was equally distributed at 1:1. This finding is uncommon, with literature reporting a male predominance in patients with CVDs and even in the CCU setting. The proportion of males in a study performed locally at the RK Khan Hospital in Durban, was 77%.[19] A similar finding of a male predominance was found in an Italian study, with females comprising only 36.1% of the study population of 1 165 consecutive patients admitted to a CICU of a tertiary hospital in Italy. Nearly one quarter of the patients admitted had coronary artery disease (24.8%).[10] In the present study, 39 males died from a cardiovascular diagnosis at death, whereas more females had a non-cardiovascular diagnosis at death compared to males (13 females and 9 males). Once more, this finding is unusual as it has generally been reported that females with CVD tended to be older than males, and that females had a higher mortality rate from CVD when compared to males.[10,19,20]

An Israel-based study that compared mortality trends in women and men with AMI admitted to CCU before and during the reperfusion era using thrombolytic therapy or coronary angioplasty, reported a higher mortality rate in females of 24% in the pre-reperfusion era and 15% during the reperfusion era. In comparison, the mortality rate among male patients was 17% pre-reperfusion and 10.8% during the reperfusion era.[20] These authors postulated that the higher mortality rate in women might be due to women being older than the males, the presence of a higher prevalence of comorbidities and other unmeasurable factors such as time to seeking medical care.[20] Campanile *et al*. found that 41.5% of the females in their study were older than 75 years of age, and >50% of the females had three or more comorbidities.[10] Our findings possibly might have resulted from the data collection method and incomplete records being excluded from the study. However, an almost similar ratio was found in a study performed in a tertiary hospital in Bangladesh, with 55% of the non-survivors in CCU being male.[21]

Half of the patients who demised were Black (Table 2.1). In contrast, Ratcliffe *et al*. found that Asians (9.7%) had a higher mortality rate in their CCU, followed by Hispanics (8.2%), Whites (6.3%), with African-Americans having the lowest mortality at 5.8%.[12] The racial distribution in our study might in part be due to the overall population composition in Johannesburg. The 2011 Census reported 76.4% of the Johannesburg population as Black African, followed by 12.3% being white.[22] Although this study focused on all-cause mortality in the CCU, it should be noted that CAD has traditionally been reported as uncommon in Black people, with an increase in prevalence noted recently,[23,24] which is probably due to urbanisation and lifestyle changes in these communities. Factors that were postulated for the lower incidence of CAD in Africans included an inherent immunity to development of CAD and higher high-density lipoprotein HDL cholesterol levels in African patients.[23]

In our study, the median length of CCU stay was 3.5 days (IQR 2–7), in keeping with international data. Studies from America and Italy reported a median length of stay (LOS) of 2–4 days.[11,12,25] Patients with AKI and acute respiratory failure stayed on average a six to seven days longer in the CCU, compared to those without these factors.[25] The University of Massachusetts (UMass) found that patients admitted to their CCU that died from a cardiac cause, had a shorter CCU stay and that troponin-I levels negatively affected the LOS. Additionally, the left ventricular ejection fraction (LVEF) and serum sodium level had no effect on the LOS.[13]

Amit *et al.*[26] postulated that with the new definition of AMI and the introduction of routine troponin measurements, an increased burden in CCU admissions has occurred. More patients with unstable angina (UA) are reclassified as NSTEMI. There was an observable increase in patient load, with a decline in the median LOS. This finding was thought to reflect an increasing demand for CCU facilities and thus bed pressure due to an increase in NSTEMI admissions, but with resources remaining more or less the same.[26]

The patients admitted to our CCU had a high burden of coronary artery risk factors. In a study by Nethononda *et al*., the presence of traditional risk factors for CAD was similar amongst African and non-African study groups, although hypertension had a significantly higher incidence in the African population.[23] Hypertension has indeed been reported as the most prevalent risk factor for CAD in Africa in various publications, followed by diabetes mellitus. The converse was found in the EuroHeart Failure Survey (EHFS II) where diabetes was identified as the most prevalent risk factor.[16] Similar to studies from CCUs across the world, the incidence of hypertension, diabetes, obesity and dyslipidaemia was found to be higher in females compared with males.[19,20,27] Diabetes has been reported as a strong predictor for mortality in various studies.[12,13,28] Smoking was more prevalent in males and although tobacco use varies according to regions, a similar gender difference trend with more males smoking compared to females, has been observed.[3,20]

Close to 20% of patients with a documented HIV status were positive. This is important because of an increased risk of early atherosclerosis and stroke among HIV-positive individuals. Furthermore, with improvement in the management of HIV and the availability and distribution of antiretroviral therapy (ART), persons living with HIV now have a longer life expectancy, with hypertension becoming more prevalent as this population is aging ART. Moreover, HIV is associated with an increased risk for impaired glucose tolerance (IGT) and diabetes.[3]

Acute coronary syndrome (ACS) was the most common cause of death, followed by cardiomyopathies and heart failure of various aetiologies. This was in line with findings from the Italian, French and American-based studies.[10,11,29] Despite an increase in the number of non-cardiovascular admissions to the CCU, ACS remains the most common admission diagnosis. The trend in gender differences remained the same over time, with more males being diagnosed with ACS compared to females. Hypertension persists as the most prevalent risk factor for ACS, together with dyslipidaemia and diabetes. Although smoking was the only risk factor that increased the likelihood of being diagnosed with ACS, this might be influenced by our sample size. Surprisingly, just over half of the patients had Killip class 1 AMI. It is known that the higher the Killip classification, the poorer the outcome,[30]which could point to the effect of other variables in patient outcome in our study.

Renal dysfunction (both AKI and CKD), which accounted for approximately 50% (*n* = 9/19) of the deaths from non-cardiovascular causes, emphasises the need for advanced interventions, such as dialysis, in the CCU.[25] Furthermore, the number of non-cardiovascular deaths resulting from pneumonia (*n* = 5/19; 26.3%) and sepsis (*n* = 6/96; 6.3%) explains why mechanical ventilation has become a critical intervention in the CCU over the years.[25]

2.4.1 Study limitations

Given the retrospective nature of the study, missing data, particularly regarding the management of patients, was challenging, as data collection relied on the CCU discharge summary. These records were compiled by various clinicians and contained limited information. It was also a single-centre study, with our centre being a tertiary specialised centre, posing the chance of referral bias. Furthermore, treatments offered at our centre might not be available in other centres; therefore, results might not be fully generalisable to patients receiving care in the private healthcare setting. Data regarding diagnosis at death were based on the attending clinician's assessment. The cause of death was deduced from the ICD10 code documented by the attending clinician. Furthermore, data from 2010, 2014 and 2015 were largely missing, which further limited our study population. Disease severity scoring systems, such as the SOFA and APACHE scores that are commonly applied in ICU settings, were not used consistently. The term ACS encompasses the spectrum from UA, NSTEMI and STEMI. Only data of patients that died were collected, which we did not compare with the data of the survivors. This, in turn, could result in the inability to calculate the overall mortality rate in our CCU. Additionally, there is the potential of missing patients that died while in casualty or in the ward after discharge from the CCU.

2.5 Conclusion

The study has demonstrated that CVD are affecting a younger patient population that should still be economically active. ACS remains the primary cardiovascular cause of death in the CCU despite advances in therapies and interventions. There was, however, a high number of deaths that resulted from cardiac causes other than ACS and non-cardiovascular causes, such as renal failure and pneumonia. There also was a high burden of hypertension, dyslipidaemia and diabetes in our patient population, highlighting a potential gap for intervention. Regardless of the study limitations, the findings study are valuable because it demonstrates the changing role of the CCU with its evolved patient profile, and also how the role of the modern-day cardiologist has changed over time. To our knowledge, this is the first study in the country profiling the demographic characteristics of the patients that died in a modern-day CCU and documenting the use of interventions and therapies traditionally presumed to be performed by intensivists. The need for critical care training in cardiology is evident.

Declaration: The research for this study was conducted by AI in partial fulfilment of the requirements for the degree Master of Medicine (MMed) in Internal Medicine at the University of the Witwatersrand, Johannesburg, South Africa.

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Author contributions: AI was responsible for data collection and drafting of the manuscript. NT supervised the study and contributed great knowledge to the final production of the final manuscript. DM contributed to the final production of the manuscript.

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Conflict of interest: None.

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APPENDIX A
DATA COLLECTION SHEET

Study number:

Demographics
Gender: Male ☐ Female ☐

Age:

Total number of days of CCU stay:

Nationality: RSA: ☐ Non-RSA: ☐

Race: B ☐ W ☐ C ☐ I ☐ Other ☐

Significant medical family history:

Diagnosis at death:

Risk factors:

HPT ☐ DM ☐ Obesity ☐ Dyslipidaemia ☐ Smoking ☐

Echocardiography

LV: Normal wall motion:☐ Abnormal wall motion☐

LVIDd: LVIDs: EF: LA:

RV: Normal☐ Dilated☐ RA: Normal☐ Dilated:☐

Mitral valve: Normal ☐ MR☐ MS☐

Aortic valve: Normal☐ AR☐ AS☐

Tricuspid valve: Normal ☐ TR ☐ TS ☐

Pulmonary valve: Normal ☐ PR ☐ PS ☐

Pericardial effusion: None ☐ Present☐ Size

Vegetations: Present ☐ Absent ☐

Blood Results:

HIV: Positive Negative

HB:

Na K Urea Cr HbA1C

TC LDL-C HDL-C Triglycerides

KDIGO Stage if AKI

Killip:

TIMI:

Treatment /Intervention:

Thrombolysis: Yes ☐ No ☐

Aspirin ☐ Plavix ☐ B-Blocker ☐ ACE-I ☐ Statin ☐ Diuretic ☐

PCI ☐ NIV ☐ Invasive ventilation ☐ Temporary pacing ☐

Dialysis ☐ Intra-aortic balloon pump ☐

Inotropic support ☐ 1 – Adrenaline ☐ 2 – Dobutamine ☐ 3 – Phenylpherine ☐

Complications: Sepsis ☐ Bleeding ☐ Other ☐

APPENDIX B
ETHICS APPROVAL

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Amir Idris

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190955 MED19-04-151

NAME: (Principal Investigator)	Dr Amir Idris
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The demographics of cardiovascular mortality among cardiac patients admitted in a cardiac Intensive Care Unit (2010-2017) at the Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	27/09/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Nqoba Tsabedze
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/11/2019

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C

STUDY PROTOCOL

RESEARCH PROPOSAL

The Demographics of Cardiovascular Mortality Among Cardiac Patients admitted in a Cardiac Intensive Care Unit (2010 – 2017) at the Charlotte Maxeke Johannesburg Academic Hospital

Student: Dr AA IDRIS
Student no:
1253070

Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand

Supervisor:
Dr Nqoba Tsabedze
Academic and Clinical Head: Cardiology
University of Witwatersrand

1. BACKGROUND

Cardiovascular diseases are a heterogeneous group of disorders that affect the heart and blood vessels. Coronary heart disease (CHD), in particular affects the blood supply to the heart and is the main cause of death in many countries (1). Among CHD, Ischaemic heart disease (IHD) and stroke are the world's biggest killers, accounting for a combined 15.2 million deaths in 2016 (2). These diseases have remained the leading causes of death globally in the last 15 years, including South Africa (2). However, at the turn of the 21st century, IHD ranked eighth among the leading killers in the African continent, just behind cerebrovascular disease in both men and women. There is ample data from Western, Eastern, Central and Southern Africa suggesting that coronary heart disease was rare up until the mid-20th century (3).

The term Acute Coronary Syndrome (ACS) is applied to patients in whom there is suspicion of myocardial ischemia. There are three types of ACS: ST-segment elevation Myocardial Infarction (STEMI), non-ST-segment elevation Myocardial Infarction (NSTEMI), and unstable angina. The first two are characterized by a typical rise and/or fall in biomarkers of myocyte injury (4). Several factors related to the severity of the disease have been identified, such as smoking, diabetes mellitus, systemic arterial hypertension, dyslipidaemia, the number of arteries diseased and the degree of functional impairment of the left ventricle. Furthermore, age, sex, obesity, heavy alcohol consumption and physical inactivity are all recognized as clinically relevant contributory factors (5). The principal coronary risk factors in Africa are similar to those identified in other regions of the world. However, definitive data from Africa on the magnitude of the burden of these risk factors, the strength of associations between the various risk factors and the incidence of myocardial infarction have generally been lacking (6).

The contribution of the Coronary Care Unit (CCU) to the reduction of mortality from acute myocardial infarction (MI) has been well documented over the past 30 years (7). CCUs originated for the singular purpose of rapidly resuscitating patients from arrhythmic complications of acute MI but have transformed into Cardiac Intensive Care Units (CICUs) that deliver comprehensive critical care for patients with cardiovascular diseases (8).Such evolution raises the issue of heterogeneity of conditions being cared for in such units, impacting on outcome of management. Several surveys have been designed to assess CICUs activities and evolution.

One notable study was done by Sinha and colleagues (9). In a study of 3.4 million acute admissions to CICU over a 10-year period, the proportion of non-cardiac primary diagnoses, increased from 38.0% to 51.7%, and this was attributed to infectious, respiratory diseases and

renal failure. There was a decrease in cardiac primary diagnoses from 32.3% to19.0%. Despite this, heart failure, pulmonary vascular disease and valvular heart diseases were reported to be on the rise, with resultant increase in non-percutaneous coronary interventions such as mechanical ventilation and renal replacement therapies. Despite these shifts toward greater comorbidity, unadjusted mortality decreased from 9.3% to 8.9% (9).

Similar findings were reported in a study by Holland and Moss (10), which demonstrated sepsis to be the most frequent non-cardiac primary diagnosis (5%). Furthermore, acute coronary syndromes were the most common primary cardiac diagnosis (25%). Overall CCU mortality was 7%, being accounted mostly by acute kidney injury, sepsis and respiratory failure.

Locally, there is a paucity of data with regards to mortality rates in CCUs with more emphasis on ACS risk factors. In a multinational survey of current management strategies registry, Schamroth and colleagues, analysed 642 South African patients with ACS, and found all cause death at twelve months to be 5.7%. The mortality rate was higher among patients with ST-segment elevation Myocardial Infarction (STEMI) (11).

In Sub-Saharan Africa there are a few notable studies addressing risk factors in ACS. The INTERHEART-Africa study demonstrated traditional risk factors (hypertension, diabetes, smoking, obesity and dyslipidaemia), with hypertension being the commonest risk factor in the black African population. However, the study did not include all the racial groups, with specific exclusion of the Asian Indian population (6, 12). The AIR (Acute Coronary Syndromes in Indian patients admitted to RK Khan hospital) study, investigated risk factors specifically in the Asian Indian population as this population group was not included in the INTERHEART-Africa study (13). Similar to the African population in the INTERHEART study, hypertension was found to be the significant risk factor in the older age group. Of note the AIR study reported family history of ACS, peripheral vascular disease, hypercholesterolemia and smoking to be the common risk factors in the younger age group with male predominance. Moreover, a study of black African patients with acute MI and acute ischemic syndromes admitted to Chris Hani Baragwanath Hospital, showed a clear increase in prevalence of risk factors for CHD (14). This study which included all racial groups, with documented angiographic evidence of ACS, found hypertension to be the most common risk factor in the black African population. In contrast to the INTERHEART and AIR study, it demonstrated that cholesterol levels were within the normal target values in the black African population. Surprisingly, the study also found that the female gender was at a higher risk for ACS than males.

Furthermore, there are other non-ischemic aetiologies that have been documented to contribute in CCU mortalities. In the Sub-Saharan Heart Failure Study (THESUS-HF study) (15), acute heart failure from non-ischemic aetiology (hypertension, rheumatic heart disease and endemic cardiomyopathies) were associated with high mortality. One notable aetiology contributing to both ischemic and non-ischemic heart disease is Human Immunodeficiency Virus (HIV) infection. The prevalence of hypertension was also increased 3-fold in patients on combination Anti-Retroviral Therapy (ART) (16).

2. STUDY AIM, OBJECTIVES, DESIGN AND METHODOLOGY

2.1 Statement of the problem

Other than the international studies mentioned, there are few studies describing the mortality trends in Coronary Care Unit (CCU) settings in South Africa and in other sub-Saharan countries with CCU capabilities. This study will investigate and describe the demographics of all non-surviving patients in a Tertiary (Academic) hospital CCU. To the best of our knowledge this will be the first study conducted in a state tertiary centre, to investigate and describe the demographics and clinical characteristics of fatalities in a CCU.

2.2 Aims of the study

The aims of the study are to describe the demographic, clinical characteristics, laboratory biochemical findings and associated prevalence of risk factors among patients who demised in the CMJAH CCU during the period of 2010 to 2017.

2.3 Objectives of the study

- To describe the demographic, clinical and laboratory features of patients who died in CCU.
- To analyse and document the major prevalence of risk factors associated with mortality in CCU and compare our findings to data published elsewhere.
- To describe the most common admission diagnosis of this cohort.
- To describe the major risk factors between the ACS and Non - ACS cohort.

2.4 Methodology

2.4.1 Study design

This is a retrospective study that will include all patients who died in the period from January 2010 to December 2017, admitted to the Coronary Care Unit (CCU) of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). CMJAH is a Tertiary university teaching hospital with sub specialized units, that has a ten bedded CCU with interventional facilities on site. It is a referral hospital servicing multiple surrounding public and private hospitals.

2.4.2 Study population, sample size and inclusion criteria

The population will include all patients who died in CCU from January 2010 to December 2017, both men and women aged 18 years and older. This study will only include patients with complete medical records. It is projected that approximately 100 patients will be included in the study.

2.4.3 Data Collection and variable description

Data will be collected from patient records and will be entered into REDCap™ and exported to excel. Mortality will be defined as number of deaths in each year. Details such as demographics (age, gender, racial group), habits such as smoking, comorbidities (HIV status, hypertension, diabetes, obesity, dyslipidaemia), and both laboratory investigation results and imaging (Echocardiogram) findings. Date of admission and date of death will also be collected with length of stay to be calculated. (See Appendix A)

2.4.4 Data management and analysis

Data cleaning and analysis will be conducted using statistical software Stata (Stata Corp, 2017: version15. College Station, TX: StateCorp LLC). Data will be checked for validity and excluded if there are any discrepancies in patient data. The data will then undergo a descriptive analysis with attention to specific objectives and variables as per the data collection sheet. Should there be a need for comparison - groups will be compared using the Student t test (parametric or normally distributed data) and Kruskal Wallis test (non-parametric or data that is not normally distributed) for continuous variables and chi-square test for proportions. We will then undertake a logarithmic regression analysis in order to determine possible factors influencing mortality.

3. Ethics

The research proposal for this study will be submitted to the postgraduate committee of the University of the Witwatersrand and the Human Research Ethics committee (HREC) to get permission and clearance to perform this study. All the study data collected will be extracted from the patient records. Written permission will be obtained from the Head of Division of Cardiology and the Hospital CEO. During data collection, patient details will be documented using a numbering system. The study will be conducted in adherence to the Declaration of Helsinki.

4. Potential limitations of the study

In view of the retrospective nature of the study, completeness of records may be a challenge in some patients, patient records may have missing data that is essential to the study. Moreover, in view of the location of the study site, being in an urban area, the results may be biased towards an urban population.

5. Funding

All necessary costs will be incurred by myself, including stationery, printing and other paperwork.

6. GANTT chart

2018/2019	Nov	Dec	Jan	Feb	Mar	April	May	June	July	Aug	Sept
Literature review											
Preparing protocol											
Protocol Assessment											
Ethics Application											
Collecting Data											
Write Up Report											
Write Up-Paper											

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APPENDIX D

PERMISSION: GAUTENG PROVINCE DEPARTMENT OF HEALTH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email:Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
04 March 2019

Dear Dr. A. Idris

STUDY TITLE: The Demographics of Cardiovascular Mortality Among Cardiac Patients Admitted in a Cardiac Intensive Care Unit (2010-2017) at Charlotte Maxeke Johannesburg Academic Hospital.

.

Permission to conduct the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 5/03/2019

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 05.03.2019

APPENDIX E

AUTHOR GUIDELINES: *CARDIOVASCULAR JOURNAL OF AFRICA*

Cardiovascular Journal of Africa

INFORMATION FOR AUTHORS

The *Cardiovascular Journal of Africa* is pleased to consider original articles, reviews, discussions on topical issues, case studies, meeting reports and other contributions relevant to the understanding, treatment and care of vascular disease.

Original articles and reviews are sent for independent peer-review. Material is accepted for publication on the understanding that it has not been published elsewhere. Authors will be asked to confirm this in writing and transfer copyright to the Journal.

Authors submitting papers to *CVJA* should also register as a reviewer as a quid pro quo for authors for reviewers reviewing your submission. If authors do not register as reviewers it may be taken in consideration when deciding on acceptance and rejection, and the time of publication. We do try not to call on a reviewer more than once a year but in rare circumstances it may be twice.

Important Notice to all Authors:
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It has become necessary for the *Cardiovascular Journal of Africa* to charge a manuscripts submission fees for all articles submitted for publication. On acceptance of a manuscript an additional Article Processing Fee will apply before publishing.

- **Manuscript Submission Fee:** South African and International Authors: ZAR 1000.
  Paid on Submission of Manuscript.

- **Article Processing/Publishing Fee:** South African and International Authors: ZAR 6000.
  Paid on Article Acceptance for Publication in the CVJA.

This is normal for most, if not all, journals. We so far have been able to survive without charging authors for submissions and processing but can no longer do so. We regret that we have to implement this as from the 13 of December 2016. Payment will need to be made online and once payment has been received, the manuscript will be further processed for possible publication.

The payment of the manuscript submission fee and does not guarantee publication of the article. The manuscript submission fee is not refundable in the event of rejection as processing cost will have been incurred. **(Payment can be made online with a valid credit card)**

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The *Cardiovascular Journal of Africa (CVJA)*, which incorporates the *Cardiovascular Journal of South Africa*, is particularly concerned with publication of scientific articles related to Cardiac and Vascular conditions and situations, concerning adults and children, in Sub Saharan Africa. But will accept articles from all parts of the world.

Basic Science publications related to clinical aspects either for elucidation, in-depth understanding or therapeutic approaches are accommodated. The Journal functions as official medium for other related societies which do not as yet have own Journals such as, Hypertension, Stroke, Nuclear Medicine and Magnetic Resonance in Cardiology, Paediatrics, Molecular and Cellular Cardiology, and Vascular disease in Diabetes and Obesity.

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All categories of manuscripts for the *Cardiovascular Journal of Africa* must be submitted on-line to Editorial Manager. You will be assigned your own password and user name. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (download off-line document). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to info@clinicscardive.com

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format		**Alternative Image Format**	
Image Format	.tif	**Image Format**	.jpg
Image Width	Greater than or equal to intended display size	**Image Width**	Greater than or equal to intended display size
Colorspace	RGB	**Colorspace**	RGB
DPI	500+	**DPI**	500+
Alpha Channels	None	**Compression Quality**	Maximum
Layers	Flattened		

References numbered in the order of appearance in the text, according to Vancouver style.

For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183.

For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139.

DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures and tables as above.

Reviews

Title page as above. Abstract (150 words) setting out the scope, key messages and conclusions of the review. Body of text liberally partitioned with headings and subheadings leading to a synopsis with conclusions at the end. Key messages in a separate box itemising two to five short principal statements. Acknowledgements, references, tables and figures as above.

Other articles should adopt a concise style consistent with similar articles previously published in the journal. Manuscripts should include a title page, and appropriate subheadings for text. Style of tables, figures and references as above.

Figures be sent to us in a high resolution JPEG format, but they MUST be sent separately from the Word document. If not in high resolution JPEG, then PowerPoint will do.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (download off-line document). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to info@clinicscardive.com

The status of progression of the peer-review system will be directly accessible by authors. The Editorial Manager system is particularly useful to authors and reviewers as there is a direct link to PubMed for viewing all related articles on the subject matter.

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Authors submitting papers to *CVJA* should also register as a reviewer as a quid pro quo for authors for reviewers reviewing your submission. If authors do not register as reviewers it may be taken in consideration when deciding on acceptance and rejection, and the time of publication. We do try not to call on a reviewer more that once a year but in rare circumstances it may be twice.

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APPENDIX F

TURNITIN REPORT SUMMARY

CHAPTER 1

Submission date: 24-Jun-2024 07:46PM (UTC+0200)
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