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CORONARY CARE NETWORKS IN THE RESOURCE-LIMITED SETTING: SYSTEMS OF CARE IN SOUTH AFRICA

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CORONARY CARE NETWORKS IN THE RESOURCE-LIMITED SETTING

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the millions of patients that do not enjoy optimum care in resource-limited settings; may research expose these inequities and propose contextual solutions to your disease burdens.

ABSTRACT

BACKGROUND: Owing to an epidemiological transition observed throughout Sub-Saharan Africa, South Africa is experiencing an increase in the incidence of myocardial infarction. ST-elevation myocardial infarction (STEMI) occurs commonly in South Africa and at much younger ages than observed elsewhere in the world. Emergent treatment in the form of coronary reperfusion is required to reduce morbidity and mortality following STEMI. Political and socio-economic factors have led to large disparities in emergency healthcare access for many South Africans. Well organised networks of care (coronary care networks, CCNs) that seamlessly integrate prehospital care, in-hospital assessment and percutaneous coronary intervention is recommended to reduce mortality for these patients. CCNs are underdeveloped and under-studied in South Africa. To this end, the aims of this project was to examine the current state of Coronary Care Networks in South Africa, a low- to middle income country and to provide recommendations for future development of such networks.

METHODS: This project was comprised of four studies. **Study I** was a cross-sectional descriptive study that aimed at determining the current PCI-capable facilities in South Africa and sought correlations between the resources, population, poverty and insurance status using Spearman's Rho. **Study II** utilised proximity analysis to determine the average drive times of South African municipal wards (geopolitical subdivisions used for electoral purposes) to the closest PCI-capable facility for each South African province. It further determined the proportion of South Africans living within one and two hours respectively, from such a facility. **Study III** combined data obtained from Studies I and II with network optimisation modelling to propose an optimised reperfusion strategy for patients with STEMI, based on proximity, using the North West province as a case study. Finally, **Study IV** employed qualitative methodology to determine the barriers and facilitators to developing CCNs in South Africa by performing interviews with individuals working with the South African contexts of coronary care.

RESULTS: South Africa has 62 PCI-capable facilities, with most PCI-facilities (n=48; 77%) owned by the private healthcare sector. A disparity exists between the number of private and state-owned PCI-facilities when compared to the poverty (r=0.01; p=0.17) and insurance status of individuals (r=-0.4; p=0.27) **(Study I)**. This means that reperfusion by PCI is likely inaccessible to many despite approximately, 53.8% and 71.53% of the South African population living within 60 and 120 minutes of a PCI facility **(Study II)**. Yet, we provide an efficient and swift model that provides a recommendation for the best reperfusion strategy even in the instance of a large amount of ward data with these additional constraints. This model can be run in real-time and can guide reperfusion decisions at the bedside or form the basis of regional reperfusion guidelines, and CCN development priorities **(Study III)**. When considering the local CCN, we found an under-resourced CCN that is not prioritised by policy-makers and displays considerable variation in performance based on time of day and geographic locale. Specific barriers to the development of CCNs in South Africa included poor recognition and diagnosis of STEMI, inappropriate transport and treatment decisions, and delays. Facilitators to the development of CCNs were regionalised STEMI treatment guidelines, further research and prehospital thrombolysis programmes **(Study IV)**.

CONCLUSION: South Africa has a shortage of PCI facilities. Even in areas with high concentrations of PCI facilities. In addition, many patients may not be able to access care due to socio-economic status. When considering proximity alone, most South Africans are able to access PCI within guideline timeframes. Despite this, prehospital thrombolysis should still be considered in some areas – as demonstrated by a novel approach that combines geospatial analysis and network optimisation modelling. This approach is able to efficiently determine the optimum reperfusion strategy for each geographic locale of South Africa. Current CCNs in South Africa are under-resourced, over-burdened and not prioritised. Future efforts should aim at improving STEMI recognition and diagnosis to decrease delays to reperfusion. The findings described should be considered and integrated into a future model of CCNs within South Africa, towards improving reperfusion times and finally morbidity and mortality.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following four studies.

I. **Study I**

Stassen W, Wallis LA, Vincent-Lambert C, Castren M, Kurland L. Percutaneous coronary intervention still not accessible for many South Africans. Afr J Emerg Med. 2017;7:105-7.

II. **Study II**

Stassen W, Wallis LA, Vincent-Lambert C, Castren M, Kurland L. The proportion of South Africans living within 60 and 120 minutes for a percutaneous coronary intervention facility. Cardiovasc J Afr. 2018;29(1):6-11.

III. **Study III**

Stassen W, Olsson L, Kurland L. A coronary care network model for patients requiring reperfusion in the North West province of South Africa: Recommendations based on optimisation modelling and geospatial analysis. 2018. *Manuscript.*

IV. **Study IV**

Stassen W, Kurland L, Wallis LA, Castren M, Vincent-Lambert C. Barriers and facilitators to implementing coronary care networks in South Africa: A qualitative study. 2018. *Manuscript.*

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AIDS	Acquired Immunodeficiency Syndrome
ALS	Advanced Life Support
AMI	Acute Myocardial Infarction
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	Cardiovascular Disease
D2B	Door-to-balloon
EC	Emergency Centre
EC	Eastern Cape Province
ECG	Electrocardiograph
ECP	Emergency Care Practitioner
EMS	Emergency Medical Services
EP	Emergency Physician
FMC	First Medical Contact
FS	Free State Province
GP	Gauteng Province
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
KZN	Kwazulu Natal Province
LI	Limpopo Province
LMIC	Low- to middle income country

MIN	Medical Insurance
MP	Mpumalanga Province
NC	Northern Cape Province
NSTEM	non-ST-segment elevation myocardial infarction
NW	North West Province
PCI	Percutaneous coronary intervention
PHT	Prehospital Thrombolysis
RN	Registered Nurse
RSA	Republic of South Africa
SES	Socio-economic status
SSA	Sub-Saharan Africa
STEMI	ST-segment elevation myocardial infarction
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
TB	Tuberculosis
UA	Unstable Angina
WC	Western Cape Province

1. INTRODUCTION

South Africa has historically been characterised by racial segregation and inequitable development of healthcare and transport infrastructure to areas where specific racial groups settled. This has further contributed to poor socio-economic development of these groups. Previously only thought to be prevalent as a disease of affluence, cardiovascular diseases and in particular, myocardial infarction (and ST-elevation myocardial infarction, STEMI) is increasing.

To reduce the morbidity and mortality associated with STEMI, early care and coronary reperfusion is recommended. Clear guidelines on the management of patients with STEMI are available. These guidelines provide specific reperfusion timeline targets that will maximise good outcome. Unfortunately, South Africa consistently falls short on achieving these targets.

Coronary care networks (CCNs) are comprised when elements of recognition, EMS activation, early diagnosis, and early reperfusion (via prehospital thrombolysis, in-hospital thrombolysis or PCI) seamlessly integrate. The aim of the CCN is to optimise each aspect of care and deliver reperfusion based on accepted, evidence-based guidelines.

In South Africa, CCNs are underdeveloped and under-studied. This thesis integrates a series of four studies and illuminates some of the specific shortfalls and potential solutions for the intricacies of the South Africa coronary care system.

2. BACKGROUND

In recent times, the shift of care for patients with myocardial infarction has gone from one where single, standalone hospitals aim at improving care for specific patients, to a focus on rather developing coronary care networks. [1] A coronary care network (CCN) can be defined as the integration of the different aspects of a healthcare system, from access to transport, patient assessment and diagnosis, and optimal treatment towards time to reperfusion therapy in patients experiencing coronary events. [1] Focusing on CCN development, has been shown to reduce mortality, as delays in care are often related to system-wide barriers, rather than individual aspects. To harness these benefits, developing a CCN should take into consideration the geographic diversity, availability of resources and infrastructure (including hospitals and roads), the specific context of a healthcare system and healthcare funding models. [1] Furthermore, prioritising the development of CCNs should also be contextual to the epidemiology of cardiovascular disease within a particular setting. In South Africa, the epidemiology of cardiovascular disease is on the increase. [2] In order to appreciate the complexities of developing CCNs in South Africa, it is essential to provide a background of the geography, history and socio-economic development within the country.

a. SOUTH AFRICA IN CONTEXT

i. SOUTH AFRICAN GEOGRAPHY

The Republic of South Africa (RSA) is the Southern-most country on the African continent and extends across a landmass of 1 220 813km^2. RSA is bordered by the Atlantic Ocean on the West and the Indian Ocean on the Eastern shores. On the North, RSA is bordered by Namibia, Botswana, Zimbabwe and Mozambique.

RSA has three capitals; Pretoria (executive), Bloemfontein (judicial) and Cape Town (legislative). The country has a bicameral legislature that is elected democratically by party-list proportional representation: National Parliament and the National Council of Provinces. There are nine provinces in RSA (Figure 1) which are in turn divided into district or local municipalities. Each municipality is responsible for developmental planning, bulk supply of utilities, road maintenance and public transport systems. Further administrative subdivisions exist, as each of these municipalities are divided into a series of municipal wards where a local councillor is elected to the municipal council and provides local representation and operationalisation of municipal plans. Provision of healthcare and emergency medical services may be a provincial (regional hospitals) or district municipal (smaller hospital and clinics) function. In order to, contextualise healthcare access in RSA, it is essential first touch on politics, socio-economics and historical inequities that South Africans faced. In light of this, the racial terms used are consistent with terms in the South African census, is in common use in RSA and does not promote or accept racial profiling of any kind.

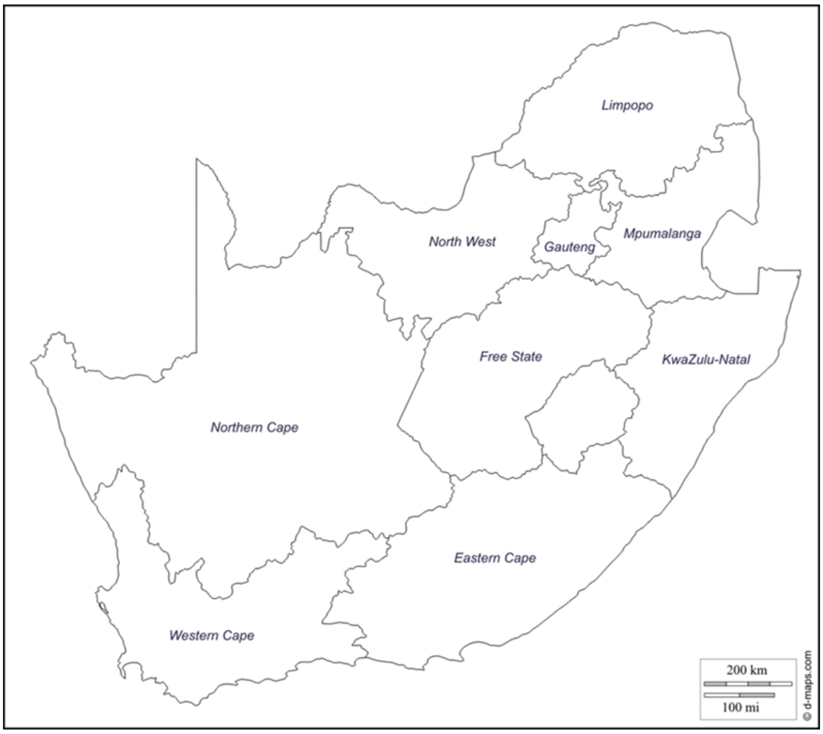

Figure 1 The 9 South African provinces

ii. SOUTH AFRICAN HISTORY

South Africa was largely inhabited by indigenous KhoiKhoi, San and black African tribes. [3,4] In 1652, the first European settlers arrived at the Southernmost tip of South Africa, Cape of Good Hope (now in the Western Cape province, Fig 1). Despite resistance, early tribes were violently dispossessed of their land, belongings and cattle and forced to work on the farms of the settlers. By 1654, slaves were imported from Africa, India and Indonesia to supplement the labour of local indigenous South Africans. [3] Under British rule from 1814, further inland invasion and forced removal of indigenous tribes continued. Furthermore, Afrikaans-speaking Dutch farmer settlers also continued inland claiming land and cattle. [4] The African Zulu tribe, under the direction of Shaka kaSenzangakhona (son of the Zulu tribe chief), lead a series of militaristic operations where other tribes were forcibly removed and driven away from their own land extending eastward. The Zulu homeland was situated in what is now known as Kwazulu Natal (Fig.1). [4] These series of militant land occupation by British, Afrikaners (Boers) and

African tribes continued for close on a century. Those who could not resist, were reduced to tenant labourers, and driven into pre-circumscribed areas of land where they would live in poverty, unable to own land. [4] Such enslavement is the cornerstone of the white Boer economy. The discovery of gold and diamonds in the late 18th Century, lead to further large scale importation of slaves and ruthless measures to secure cheap black labour as miners. [3] Due to restrictive laws on land-ownership, and racial segregation these workers were mostly housed in over-crowded and unsanitary hostels with limited access to healthcare services. [3]

After British victory in the Anglo-Boer Wars, British rule was later handed over to the South African white minority and the Union of South Africa was born in 1910. [3,4] The constitution of the Union gave rights to the white minority yet removed the right to vote from many South Africans. Racial segregation had been entrenched in South Africa from early on, but it was not signed into law until the right wing National Party came into rule in 1948. Hereafter, a series of laws that excluded non-whites from economic and political participation. When South Africa became a republic in 1961, a second constitution was adopted, which largely took away the rights of non-white citizens. Under this constitution, all South Africans were required to be racially classified at birth into European (white), Asian (Indian), coloured, or Bantu (black). A racial hierarchy was created where white people were most superior. [3] Where a person could live and work was determined based on their racial classification. Furthermore, the quantity of resources provided for education, healthcare and infrastructure development was also throttled based on race and consequently, geographic locale. [3] This was termed, *apartheid*, an Afrikaans term which means apartness. This saw the forced eviction of millions to return them to their “original tribal homes” within rural and underdeveloped areas. Limited opportunities for employment were available here, and those employed in urban areas had to carry passes that provided permission for them to live and work there. This meant that many breadwinners left their families impoverished, in order to seek employment elsewhere. In these areas, healthcare complaints were mainly related to infectious diseases. [3] Healthcare services were also segregated and infrastructure development was inequitably funded based on race. The result was poor healthcare infrastructure, under-resourced hospitals and clinics and poor healthcare access. Even to this day, the lack of historic healthcare infrastructure development in these areas result in inequitable healthcare access for these marginalised communities. [3] This is also seen in the context of coronary care resources. [5]

The African National Congress (ANC) was formed in 1912 and protested all manners of discrimination and segregation based on race or gender however, these protests were left unheeded. The ANC became progressively more militant after the 1940s and were banned in the 1960s. [3] Violent skirmishes between the South African police, the ANC and other anti-apartheid movements increased as resistance escalated. The United Nations condemned apartheid policies and urged member states to break diplomatic and trade relations. [4] Large scale boycotts of the import of South African products to many countries were implemented, and sanctions against the country were intensified; culminating in a declaration by the United Nations that apartheid was "a crime against humanity" in the late 1960s. [4] Nelson Mandela, an anti-apartheid revolutionary and political activist, was arrested and found guilty of sabotage and conspiracy to violently overthrow the Apartheid Government in 1964. He was sentenced to life imprisonment at Robben Island, a maximum-security prison that was used for political prisoners during the apartheid regime. [4] Political uprising and community violence escalated in the 1980s, leaving many districts ungovernable. A state of emergency was declared. [4] Further boycotts to investment in South Africa and trade restrictions saw a slowing down of the South African economy. RSA was fast becoming an outlaw to other nations who applied pressure and called for the release of Nelson Mandela. In 1989, F.W. de Klerk became the new president of RSA. In his opening parliamentary address as president in 1990, de Klerk announced the abolishment of apartheid laws, lifting the ban against anti-apartheid organisations and the release of political prisoners who were not convicted of common law crimes. This included the release of Nelson Mandela a few days later. [4] A transition period of negotiations ensued in RSA, culminating in South Africa's first democratic election in 1994. Nelson Mandela, leader of the ANC was elected as president of the new Republic of South Africa. Under Mandela's leadership, RSA adopted a new constitution in 1996, and is considered one of the most advanced in the world. Under this Bill of Rights, no South African may experience prejudice or oppression based on race, gender, sexuality or religious creed. [4]

Despite reform in the Bill of Rights, many South Africans are still suffering due to historic disparate infrastructure development and limited opportunities for education and employment. Furthermore, due to current socio-economic conditions, almost a quarter of a century later adequate healthcare access may still not be possible for many.

iii. Socio-economic Conditions in Modern Day South Africa

South African poverty lines are calculated using a multimodal approach called the cost-of-basic-needs approach. [6] This approach considers three costing aspects; the cost of a reference basket of groceries which determines the food aspect of welfare, calculating the cost of reference basket to meet normative nutritional standards (the food poverty line), and finally adding non-food items to the cost of living (housing, education, transportation). [6] The reference food basket is comprised of the overall food consumption patterns of South Africans. This is done by determining common foods consumed by 10% of households, and then stratifying these items to be representative of the majority of households at different income and expenditure levels. The non-food item cost of living is determined in a similar fashion. [6] These calculations are then added to the food poverty line and compared between two sets of household income cohorts, and thus provides a lower- and upper-bound poverty line. [6]

The food poverty line for RSA is R441 (SEK 310) per capita per month. The lower-bound poverty line is calculated at R647 (SEK 456) while the upper-bound poverty line is R992 (SEK 699). [7] These values are adjusted for inflation as at April 2015. [7]

According to a report released in 2017, approximately 55.5% of South Africans live in poverty (upper-bound poverty line, R992/SEK 699 per person/month). [7] Even more concerning is that more than a quarter of South Africans live *below* the food poverty line (R441/SEK 310 per person/month). [7] Approximately 20% of the South African population live in informal dwellings, 16% have no access to electricity and 54% have no access to piped water in their household. Up to 5% of South Africans still don'´not have access to sanitation services or use bucket toilets, while 18% of the population felt that their physical safety was threatened when using shared or communal toilets. [8]

From an educational perspective, only 28% of the population completed secondary school, while only 4.5% of South Africans attended tertiary education. Five percent of the population had no formal schooling. Despite this, RSA has a 94% literacy rate. The black majority is mostly affected by poverty, poor basic services and poor education, [8] and is largely due to expenditure disparities during apartheid regimes. [3] Importantly, an increase in the incidence of lifestyle diseases such as hypertension and hypercholesterolaemia, and ischaemic heart disease is appreciable in these marginalised populations. [9–11] The chronic management of lifestyle diseases, as well as acute presentations such as myocardial infarction, it is essential to ensure adequate access to coronary care services for South Africans. Socio-economic status (SES), poverty and education has been found to influence healthcare service use and healthcare access. Considering that a large majority of South Africans live in poverty, they may not have the means to fund healthcare, or transport to healthcare services. Access to healthcare still remains a significant challenge in South Africa. [12,13]

iv. Healthcare access in South Africa

Every South African has a constitutional right to healthcare access. [13] In this context, healthcare access is defined as the provision of necessary medical services universally to the entire population, while taking the individualised need of each patient into consideration. [13] In essence, healthcare access should further allow a patient the opportunity to seek medical attention and exercise educated choices within the healthcare system, while providing conditions that are favourable to accessing this care. [13] These conditions relate to the social and economic circumstances of the patient and healthcare system as well as the infrastructures that connect the patient to the service. [13]

RSA has two distinct healthcare systems, private healthcare and state healthcare. State healthcare is that provided by the South African government to citizens while private healthcare is only accessible to patients through funds to pay for the services, or those with healthcare insurance aid. Membership to healthcare insurance was restricted to white people until the 1970s. [3] Only 17% of South Africans currently belong to a healthcare insurance scheme. [8]

The private healthcare sector is much better resourced than the state sector. Healthcare expenditure in the private sector is up to ten times per capita that reported in the state sector. [13,14] Furthermore, in the private sector there is one medical specialist for every 500 patients, while one specialist serves around 11 000 patients in the state sector. [13] The state healthcare system also only contains 20-30% of the cardiology resources of the country.[3,15] Poor healthcare resources in the state sector, has been shown to limit the opportunities for healthcare access in patients. [13] However, even in the higher resourced private sector there remains inequitable distribution of hospitals as 70% of facilities are located in 30% of the country's provinces. [3]

Rural geographic, (and historically displaced and underdeveloped areas), poverty and race still largely account for significant barriers to healthcare access. [13] Within coronary care, healthcare access should universally relate to prevention and chronic control of risk factors, and during acute coronary events such as myocardial infarction, emergency medical services, and prompt transport to a healthcare facility that is able to provide the necessary treatment. The specific integration of the latter aspects, are key elements of a CCN, which is largely underdeveloped in South Africa. [1] This is particularly concerning when considering an increasing burden of cardiovascular disease and its risk factors, among rural and impoverished communities. [16,17] The need for developing these networks of care to facilitate healthcare access becomes apparent.

b. Epidemiology of Cardiovascular Disease

i. Global cardiovascular disease burden

Cardiovascular disease (CVD) is considered one of the leading causes of death worldwide, accounting for approximately 32% of deaths in 2013. [18] Globally, the risk of premature death between the ages of 30-70 years that is attributable to CVD was estimated to be 0.108 for men and 0.067 for women. [18] CVD also accounted for 11% of all premature deaths attributable to non-communicable diseases (NCD)s. [18] Finally, cardiovascular disease accounts for the leading cause of death globally in patients older than 40 years of age. [18] Globally, the age standardised prevalence of CVD was 6,304 (6,196–6,383) per 100 000 population, in 2015. [19] Ischaemic heart disease (IHD) had a global incidence of 1,663 (1,519–1,828) per 100 000 population in 2015. [19] IHD accounted for the largest proportion of CVD in the world, in patients over the age of 40 years, the economically active population. [19] In fact, with 8.92 million deaths it was the leading cause of death in the world, in 2015. [19] Since 1990 many higher income countries (United States of America, Canada, Western Europe, Australia and New Zealand) have seen a significant decrease the prevalence of CVD. [19] Similarly, there has also been a decrease in mortality in many of these countries. Unfortunately, this has not been the case in Sub-Saharan Africa and low- to middle income countries (LMICs). [19]

ii. Sub-Saharan cardiovascular disease burden

Urbanisation of the Sub-Sahara African population (SSA) has lead to a so-called “epidemiological transition” of the disease burden. [10] This transition sees a decrease in the incidence of infectious diseases and an increase in the non-communicable disease burden, including CVD. [10] The epidemiological transition is fuelled by declining infant and child mortality, declining mortality due to infectious diseases, and increased lifestyle risk factors (obesity, diabetes mellitus, high stress, tobacco use, sedentary lifestyles), secondary to urbanisation. [10,20–22] Such a transition is occurring at a much higher rate than was observed during the urbanisation of higher income countries. [10]

Despite a paucity of epidemiological data on CVD within SSA, [23] it is suggested to be the second leading cause of death after HIV/AIDS and, the leading cause of death in patients over 30 years. [22,24] In 2015, the estimated prevalence of CVD in southern SSA exceeded that of the global prevalence at 7,668 (7,495–7,844) per 100 000 population. [19] IHD in turn, had a reported prevalence of 1,415 (1,264–1,595) per 100 000 population. [19]

Alarmingly, the incidence of CVD in SSA is expected to double between 1990 and 2030.[10,22–25] Such increases in CVD and IHD are also expected in South Africa. [10,26,27]

iii. SOUTH AFRICAN CARDIOVASCULAR DISEASE BURDEN

South Africa is currently experiencing a four-factor burden of disease. [2] Despite dealing with a large HIV/TB burden, continuing infectious disease burden and a high incidence of violence and injury, South Africa is also facing an increasing burden of non-communicable and lifestyle diseases – which is estimated to be two- to three-fold in prevalence as in higher income countries. [2,26,27] In keeping with the epidemiological transition seen in SSA, RSA is experiencing large-scale increases in the incidence of CVD. This is again, predominantly due to an increase in the lifestyle risk factors, secondary to urbanisation. [2]

There is limited epidemiological data related to CVD and IHD available in South Africa. [23] However, some reports suggest the age-standardised prevalence of CVD in 2015 to be between 7,101-8,400 and 8,001-10,100 per 100 000 persons for females and males respectively. [19] When considering IHD in isolation, the prevalence in 2015 was estimated to be 500-1500, while the death rate was 258 [9] (40 – 1800) [19] per 100 000 population. In 2015 and 2016, ischaemic heart disease accounted for 2.7% and 2.8% of deaths in South Africa. [28]

Within South Africa, CVD presents much earlier in life when compared to higher income countries. Almost half the deaths related to CVD occurs in patients between the ages 30 and 69 years, up to 10 years younger than that seen internationally. [10,26] ST-segment elevation myocardial infarction (STEMI, discussed below), which carries a higher mortality, also tends to present more often in younger patients. [29,30] These premature deaths create further socio-economic hardship as the breadwinners of impoverished families are likely to be affected. In addition, it appears as though the impoverished, rural communities in South Africa carry a disproportionately high CVD burden, [16,17] but also have poorer access to care. [5,13,31] In some of these rural areas, up to 77% of patients report having had angina (or acute coronary syndromes) previously. [31] When CVD and IHD progresses, it may present emergently as acute coronary syndromes.

c. Acute Coronary Syndromes: UA, NSTEMI, STEMI

i. Definitions

The European Resuscitation Council (ERC) defines an acute coronary syndrome (ACS) as the manifestation of coronary heart disease (CHD) and refers to three related, yet distinct clinical entities: unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction. [32] The most common pathophysiologic aetiology for the clinical manifestation of ACS is the rupture or erosion of an atheromatous plaque within a coronary artery. This rupture and consequent thrombus formation may lead to partial or total occlusion of the coronary artery leading to myocardial ischaemia and eventually, necrosis. [33,34] Clinically, ACS most often presents with cardiac ischaemic chest pain, diaphoresis and shortness of breath. In the elderly, patients with diabetes and in the female population however, symptoms may be atypical or absent. [32] Nevertheless, the suspicion of ACS in any patient constitutes a time-critical emergency that needs to be assessed further for risk stratification. [33,34] Following assessment, the most appropriate management strategy is selected based on the manifest clinical entity: UA, NSTEMI or STEMI. [34,35]

Although similar in pathophysiology and clinical presentation, unstable angina (UA) is different to NSTEMI and STEMI in its severity. [35] UA normally presents with chest pain at rest that lasts longer than 20 minutes and often has a crescendo pattern (increasing in intensity, frequency and duration) over time. [35] However, the ischaemia produced is not severe enough to cause significant myocardial damage which results in cardiac-specific biomarkers (troponin) to be detected on blood analysis. [33,35] Although, UA reflects developing severity of IHD.

Non-ST-segment elevation myocardial infarction (NSTEMI) does produce sufficient myocardial ischaemia to cause injury that is detected on cardiac biomarker analysis. [33,35] Cardiac Troponin T and I (cTn T & cTn I) are components of the myocardial contractile apparatus and are found almost exclusively in the heart. [33] A diagnosis of NSTEMI can be made in the presence of a cTn result exceeding the 99th percentile of the upper reference limit of a normal reference population by at least one value; coupled with a high pretest probability of myocardial infarction. [33] Although not specifically diagnostic, both UA and NSTEMI may be associated with electrocardiographic (ECG) findings of myocardial ischaemia (ST-segment depression, T-wave inversion) may be present in up to 50% of patients. [35] These findings have been shown to be predictive of poor outcome later, prompting expedited reperfusion. [36]

ST-segment elevation myocardial infarction (STEMI) is distinguishable from UA and NSTEMI by the presence of new ST-elevation in two contiguous leads above the J-point reference of at least ≥0.1mV in all leads except in leads V2-V3. [33] In V2-V3 the following diagnostic cut-offs apply: ≥0.25mV in men <40 years of age, ≥0.2mV in men 40 years and older, and ≥0.15mV in women. [33] In this manner, STEMI is a diagnosis based on ECG findings, and therefore does not require the Cardiac Troponin T and I results to initiate life-saving therapy. [29] STEMI accounts for just under half of all acute myocardial infarctions (AMIs) in LMICs, [37] including South Africa. [30]

Although clinically similar entities, UA, NSTEMI and STEMI represent three different spectra of the same pathophysiological processes and carry distinctly different risks of outcome. [35] Based on the risk of death, each of the entities are also managed in different manners. Reperfusion in STEMI should be facilitated promptly, as delays may have a significant impact on morbidity and mortality. [38–48] Studies suggest that every one hour delay may increase the one-year mortality by 10-15% (Hazard Ratio 1.10; 95% CI 1.04-1.16). [40,49] In patients who survive, delays to reperfusion were independent predictors of development of cardiac failure (Hazard Ratio 1.10; 95% CI 1.02 to 1.17). [47] A more recent retrospective study suggests a 3% (OR 0.97; 95% CI 0.96-0.99) increase in mortality for every one minute delay in PCI. [48] Essentially, every minute matters. For this reason, STEMI will be the focus of further discussion in the coming sections. The mainstay of STEMI management is coronary reperfusion, either by means of percutaneous coronary intervention (PCI), or thrombolysis. [29] If accessed timeously, PCI is the preferred strategy. [29]

d. Management of STEMI

To facilitate the prompt management of STEMI, numerous interventions should occur at various levels. The linking of these elements, recognition, diagnosis and reperfusion, comprises a Coronary Care Network (CCN). When reconsidering the earlier definition of a CCN, (the integration of the different aspects of a healthcare system towards decreased times to reperfusion therapy in patients experiencing myocardial infarction) these elements of management links seamlessly. Recognition is the first aspect that initiates access to transport, diagnosis relates to patient assessment and optimal treatment relates to the specific modes of reperfusion (PCI or thrombolysis) based on geographic diversity, availability of resources and infrastructure (including hospitals and roads), the specific context of a healthcare system and healthcare funding models. [1]

i. Early Recognition

The first step in the management of ST-elevation myocardial infarction is recognition of symptoms. Recognition occurs at two levels: patient level and first medical contact.

Access into the CCN starts with symptom recognition by the patient. [29,50] Often, patients delay seeking care after symptom onset. [15,50–57] Patient delays may account for up to 59% of the entire prehospital delay, [50] which delays first medical contact (see below). In South Africa, only 64% of STEMI patients seek care within 6 hours. [30] Reasons for patient delays have been cited as misinterpretation of the symptoms by patients and [50,53–59] waiting for spontaneous symptom relief. [53,55] Other factors associated with a delay in presentation are low SES, [55,57,60] poor level of education, [55,59] and difficulty with arranging transport. [54,55,57] Such delays in seeking care have been associated with increased mortality. [48,49,61]

First medical contact (FMC) is defined as the point where a patient is initially assessed by a healthcare provider that is able to obtain an ECG and make the diagnosis of STEMI. [29] FMC is essential in providing initial life-saving interventions (such as defibrillation), or initiating the STEMI care pathways and expediting reperfusion. [29] FMC may either be a prehospital provider, a general practitioner (family physician) or a physician in the emergency department. [29]

The importance of FMC in early recognition of AMI and its impact on mortality has been demonstrated in numerous studies. [29,44,53,57,58,62–67] Utilising Emergency Medical Services (EMS) as FMC has been found to decrease the times to reperfusion, [57,58,62–64,68] while self-transport, [15,62,68] or presenting to a general practitioner [53,58] was associated with significant delays (in reperfusion). Similarly, ambulance use in STEMI is associated with improved mortality. [65] In South Africa, only 16%-51% of patients utilise ambulance transport when presenting with STEMI. [53,69] At the lower end, this is considerably less than rates reported in Singapore (35%), [70] China (40%), [64] Ireland (40%), [71] Sweden (51%), [58] and Canada (68%). [65] The higher end of ambulance use, again highlights the different disparities in access to healthcare within South Africa. Reasons for low EMS usage in STEMI have been cited as unfamiliarity with the emergency number, [53,72] a belief that own transport was faster [53,58,71,72] or easier, [58,72] and an ignorance of the severity of the situation. [53,58,71,72] Widespread public education campaigns have been suggested to improve ambulance usage in STEMI however, [73–75] no such campaigns have been implemented in RSA.

In South Africa, the cost of transport to healthcare was previously subsidised but these subsidies have since been withdrawn. [76] This has resulted in many South Africans being unable to access healthcare even in emergency situations, as EMS access has been cited as *inadequate at best and non-existent at worst.* [76] Considering the historic effects of infrastructure development and current socio-economic situation within South Africa, it is not surprising that delays occur. This is in stark contrast to higher income countries where basic education and social development have underpinned economic growth.

Assuming the barriers of access to healthcare and transport can be overcome, further efforts should be directed at early diagnosis of STEMI. [29] To this end, the European Resuscitation Council recommends that a 12 lead ECG be obtained within 10 minutes of FMC, preferably in the prehospital environment. [29] EMS, when accessible can therefore play a pivotal role in early diagnosis.

ii. Early Diagnosis

Expeditious STEMI diagnosis by 12 lead ECG is recommended by the European Resuscitation Council. [29] This recommendation rests on the presumption that early diagnosis will mobilise faster reperfusion, towards an eventual improved outcome. [77] Notwithstanding diagnosis by general practitioners or at the emergency department, which has been associated with delays in reperfusion; [15,53,58,62,68] prehospital diagnosis of STEMI has been associated with decreased time to reperfusion [78] and concomitant improvements in mortality. [79,80]

A 2016 systematic review and meta-analysis demonstrated a decrease of 35 (95% CI 44.02 - 26.61) minutes in reperfusion when prehospital 12 lead ECGs were performed to confirm STEMI diagnosis by EMS (pooled sample of 27,524 patients). Furthermore, in a pooled sample of 71,315 patients, the use of prehospital 12 lead ECGs for STEMI diagnosis were associated with a significant decrease in mortality (relative risk of 0.68; CI 95% 0.63-0.74). [81] When prehospital 12 lead ECG STEMI diagnosis is combined with advanced notification of impending patient arrival, a 39% reduction in short-term mortality (risk ratio 0.61; 95% CI 0.42-0.89) is appreciable if PCI is performed while a 29% (risk ratio 0.71; 95% CI 0.54-0.93) reduction in short-term mortality is seen if thrombolysis is performed.[82] Prehospital 12 lead ECG acquisition was not associated with prolonged scene time. [83,84]

Despite some studies showing acceptable accuracy of prehospital providers' identification of ST-elevation, [85–87] false STEMI pre-notification rates have been reported between 14% and 39%. [88–91] When considering the low resource setting of LMICs, [3] with limited cardiology resources [5,15] such high rates of false cardiac team activations may lead to significant waste. One way of improving the accuracy is through telemetry – sending the ECG to a central, experienced resource in order to assist with decision-making. [92] Twelve lead ECG telemetry has been shown to significantly decrease the reperfusion times of patients with STEMI,[93–96] even in rural settings where smaller hospitals are bypassed for preferential referral to facilities capable of performing PCI. [97,98] The prehospital 12 lead ECG can therefore be utilised to expedite the diagnosis of STEMI patients, [93] telemetry can be utilised to ensure shared decision-making on the best reperfusion strategy, [96,99] and patients can be transported preferentially to PCI-capable facilities. [79,96,97,100–102]

In a South African study, only 34% of STEMI patients received a prehospital 12 lead ECG prior to hospital arrival. [69] To our knowledge, there is currently no South African literature investigating the reasons for such low rates of prehospital 12 lead ECG acquisition. However, the results of international studies could perhaps be extrapolated. Reasons for poor prehospital 12 lead ECG acquisition have been cited to include lack of funding and the cost of equipment,[103,104] limited advanced life support resources [15,104] (the only prehospital providers trained in 12 lead ECG acquisition and interpretation), [105] limited 12 lead ECG resources, [15,104] lack of ongoing training and quality assurance systems, [103] and poor integration of the varying aspects of the coronary care networks. [103] Overcoming some of these barriers may assist South Africa in harnessing the benefit that prehospital 12 lead ECG acquisition and transmission can bring to the local CCNs. Notwithstanding instances where PCI may be undertaken as primary reperfusion strategy, by understanding geographic diversity, availability of resources and infrastructure, the specific context of the South African CCN and healthcare funding models, specific recommendations can be made on where healthcare resources should be distributed in order to facilitate early diagnosis and reperfusion.

iii. Early Reperfusion

The European Resuscitation Council recommends (Class IA) preferential reperfusion via percutaneous coronary intervention (PCI), if PCI can be performed within less than 120 minutes from FMC and STEMI diagnosis, by an experienced PCI team. [29] Failing this, thrombolysis is recommended as soon as possible, but preferably within 30 minutes of FMC or 10 minutes from STEMI diagnosis. [29]

A recent meta-analysis of a pooled sample of 11 429 patients showed improved in-hospital (OR 0.61; 95% CI 0.46-0.82; P=0.001) and long-term (OR 0.82; 95% CI 0.71-0.96; P=0.01) survival in patients with AMI treated with PCI over thrombolysis. [106] These findings were echoed by an earlier meta-analysis that showed a 24% reduction in one year mortality for patients treated with PCI over thrombolysis. [107] It is further recommended that patients who present to a non-PCI capable facility, be transferred to PCI-capable facilities promptly for PCI instead. [108]

Secondary transfer of STEMI patients for PCI has been associated with significant delays [15,109,110] and worsened outcome. [111,112] This brings a particular focus on EMS to act as "gatekeepers" to identify STEMI patients and directly transport them to a PCI-capable facility. These direct referrals or transports have been associated with improved reperfusion times and ultimately, improved mortality. [111,113–116] However, considering the South African context of few PCI-capable facilities [5] and inaccessible healthcare, [13] such an approach may not be feasible for all regions in South Africa. For these reasons, prehospital thrombolysis may be considered. [29]

When comparing prehospital versus in-hospital thrombolysis, a recent Cochrane Review concluded that prehospital thrombolysis reduces time to reperfusion and should be considered in low- to middle-income country settings where timely PCI is not easily achievable. [117] Interestingly, another meta-analysis found similar short-term mortality (relative risk 0.94; 95 % CI 0.67-1.31) when early prehospital thrombolysis was compared to PCI, yet at the expense of increased risk of stroke (relative risk 3.57; 95 % CI 1.39-9.17). [118] Therefore, such an approach with further referral to PCI later (a pharmaco-invasive approach) might be acceptable for the South African milieu. [119] A prehospital thrombolysis programme should function within a well-organised, regional coronary care network. [29]

A coronary care network (CCN) is comprised when the elements of recognition, EMS activation, early diagnosis at FMC, and early reperfusion (via prehospital thrombolysis, in-hospital thrombolysis or PCI) seamlessly integrate. The aim of this network is to optimise each aspect and deliver reperfusion based on accepted, evidence-based guidelines, such as that provided by the European Resuscitation Council [29] and the American Heart Association. [120]

e. Coronary Care Networks

South Africa consistently fails in delivering timely reperfusion. [15,30,53,69] A study based in Cape Town, showed a median time to thrombolytics administration (door-to-needle time) to be 54 minutes. Thrombolytic administration within 30 minutes only occurred in 20.5% of the time. [69] A Pretoria-based study showed that only 37% of eligible patients received thrombolytic therapy and of these, only 3% received the medication within one hour. [53] Finally, a national study revealed that only 36% of STEMI patients received thrombolytics, while only 1% had a contra-indication to thrombolytic therapy. In patients with STEMI, PCI was performed within 24 hours in only 51.8% of patients. [30]

To optimise reperfusion and expedite care, it is recommended by the European Resuscitation Council and American Heart Association that regional reperfusion strategies be developed based on the geographic and system factors at play within each unique setting. [29] In other words, the development and implementation of CCNs. In areas where primary PCI is unlikely, it is recommended that systems development should focus on rapid thrombolysis at the site of STEMI diagnosis, and organised direct transfer to a PCI facility within two to 24 hours, a so-called pharmaco-invasive strategy. [29]

The development of such CCNs have been shown to decrease reperfusion time and improve mortality in many different settings, such as Austria, [121] the United States, [122,123] Canada, [124] and Spain. [125] Success of such coordinated efforts have also been shown to improve reperfusion timelines (and consequently mortality) in rural regions that are traditionally underserved. [126] Such applications may therefore be of particular value in the South African setting where historic inequities have left rural patients impoverished and without healthcare access.

In the Austrian model, guideline implementation and network organisation between the ambulance service and high-volume PCI centres showed a 6.5% decrease in mortality. [121] In Spain, developing CCNs has shown a 14% decrease in risk standardised mortality rates. [125] Improvements associated with CCNs are not isolated to high income settings. [127–130] A recent Indian study showed improvements in reperfusion times, higher utilisation of PCI (29.5% vs. 707 46.5%; $P < .001$) and improved 1-year mortality (adjusted odds ratio 0.76; 95% CI 0.58-0.98; $P = .04$) after the implementation of a CCN. [127]

The following essential elements of a CCN have been proposed: a single emergency number, emergency vehicles with 12-lead ECG equipment, sufficient resources of well-trained advanced life support paramedics, ECG telemetry, direct telephone access to the PCI suite, standardised protocols of care for diagnosis, therapy and transport (that is specific to the geographic and traffic diversity), cardiology leadership as the head of every network, involvement of healthcare authorities, public information campaigns and prospective audit registries. [1]

The South African CCN falls particularly short. Although a national emergency number exists, it has been found that patients are unfamiliar with the number. [53] Furthermore, every private emergency service markets their own unique number, which may add to the confusion. It is uncertain how many emergency vehicles have access to 12-lead ECG equipment, while there is a shortage of advanced life support paramedics. [131] Standardised, and regionalised protocols do not exist, and is likely due to fragmentation of the CCN and lack of foundational data to base these recommendations on, [15,23] owing to a lack of ongoing registries. Finally, public awareness campaigns have mainly been related to the infectious and HIV/AIDS disease burdens, and non-communicable diseases have been left to the wayside.

One other aspect to consider when outlining the South African CCN, is related to the EMS system and the qualifications and scopes of practice as it relates to STEMI management, locally. Firstly, South Africa has a three-tiered “level of care” model; basic, intermediate and advanced life support (BLS, ILS, ALS). In this manner, prehospital care is provided by “paramedics” as opposed to prehospital nurses or emergency physicians. The South African EMS is currently going through a period of transition. Until now, a dual pathway to become a prehospital provider was either through vocational or short course training, or through formalised tertiary education. After six weeks of training, an individual can register with the Health Professions Council of South Africa (HPCSA) as a Basic Ambulance Assistant (BLS), and within the context of coronary can perform cardiopulmonary resuscitation and use an automated external defibrillator. [105] After approximately six months of work experience, a BLS may complete a six- to eight-month course, registering as an Ambulance Emergency Assistant (ILS), and can now perform manual defibrillation, have basic three lead ECG rhythm analysis ability and administer oral aspirin. [105] Finally, after another six months of work experience, the ILS can complete a nine- to twelve-month course and register as a Critical Care Assistant (ALS). In addition to the skills of the BLS and ILS, the ALS can administer morphine, glyceryl trinitrate and perform and diagnose 12 lead electrocardiography. [105] This means of qualification is now being phased out, as promulgated by the Minister of Health of South Africa. [132] Going forward, formal academic training at a higher education institute is required to register as a prehospital provider. The courses are between one (basic) and four years in duration. After four years, an individual may register as an emergency care practitioner (ECP) with the HPCSA. In addition to the capabilities of BLS to ALS, the ECP also has the ability to perform prehospital thrombolysis. [105] Unfortunately, there is a large shortage of ALS [133] and ECPs [134] in South Africa, especially in rural areas.

Despite a paucity of data, considerable variation (based on socio-demographic and geographic factors) exists within the South African CCN, and a single patient care pathway is therefore difficult to describe. Yet, two antipodes of care might be expected. with other patients having a care pathway on a scale between these antipodes.

A STEMI patient who lives in an urban area with medical insurance will likely be transported by a private ambulance service to hospital promptly, after requesting an ambulance via a private emergency call centre. This service may or may not perform a 12 lead ECG, confirming the diagnosis and alerting the receiving PCI hospital of an incoming STEMI case. Considerable delays may occur at the receiving facility however, the patient will likely receive primary PCI, be admitted into a cardiac intensive care unit, discharged and followed up later.

In contrast, a patient without medical insurance living in rural or peri-urban areas may experience chest pain and attempt requesting for ambulance assistance. The ambulance may take a considerable amount of time responding to the incident, and might be staffed by two basic ambulance attendants who are unable to perform a 12 lead ECG or provide other life-saving care. After a long transport time to the closest hospital (unlikely to be a PCI capable facility), the patient may be assessed by a junior medical officer, the availability of 12 lead ECG diagnostic capabilities and thrombolytic agents cannot be guaranteed. The patient might be transferred to a referral hospital later for care or cardiology consultation. PCI might still not be performed, and the benefit of thrombolysis might have expired. For other patients, their care pathway within the South African CCN might be on a scale between these two antipodes.

In summary, the incidence of cardiovascular diseases and myocardial infarction is projected to increase in the South Africa, doubling in incidence between 1990 and 2030. Small studies show that myocardial infarction (and in particular STEMI) care in RSA does not currently comply with the international best practices guideline recommendations regarding reperfusion timelines. This may have a significant impact on the morbidity and mortality of the South Africans suffering AMI and have a negative impact on the socio-economic development in the country. Literature suggests that single interventions do not improve care substantially but that an integrated, multidisciplinary approach should be taken. To this end, one of the first recommended change actions is to develop coronary care networks towards expediting reperfusion. Before making change, it is essential to understand the different factors at play within a complex healthcare system.

There is currently a paucity of literature describing the state and resources available within the underdeveloped South African coronary care network. For this reason it is essential to evaluate and analyse the current situation and determine the barriers to timely reperfusion. Furthermore, it is needed to develop regional systems of care by contextualising solutions that have been found to improve care internationally. This thesis addresses some of the questions arising from these knowledge gaps by describing the current situation, contextualising access to reperfusion care, proposing methods of network development and finding barriers and facilitators to development of these networks.

3. AIMS OF THE THESIS

The aim of the current thesis was to evaluate and analyse the existing Coronary Care Networks (CCNs) in South Africa, a low- to middle income country. The objectives were to:

i. Determine the amount and location of PCI-facilities in South Africa and to relate coverage to population; and access in relation to socio-economic status for each South African province.
ii. Determine the proportion of South Africans who live within 60 and 120 minutes from a PCI facility by determining the driving times and distances from each municipal ward to the closest PCI facility. .
iii. Propose a coronary care network reperfusion model for patients who present with STEMI in the North West province of South Africa by making use of geospatial analysis and optimisation modelling.
iv. Explore the perceptions of healthcare providers work within the South African coronary care network and identify facilitators and barriers to an effective coronary care network in South Africa.

4. ETHICAL CONSIDERATIONS

In this section specific ethical considerations for this project as well as accessible dissemination of findings will be discussed next. None of the authors of constituent papers have any conflict of interest to declare. The project was conducted based on the principles of the Helsinki Declaration and accepted international Good Clinical Practice guidelines, with specific contextual reference to South African cultural norms.

ETHICAL APPROVAL

Ethical approval for each of the studies was obtained from the Human Research Ethics Committee (HREC) of Stellenbosch University. (Studies I-III HREC reference number M14.07.027; Study IV HREC reference number N16.10.120).

PERMISSIONS AND CONFIDENTIALITY

Permission to access data was obtained from relevant stakeholders, hospital groups and Departments of Health prior to data collection and write-up. Anonymity was maintained throughout the data collection procedure and identifying data has been removed and is not reported on. Data analyses were performed on the group level, and individuals are therefore not identifiable. The interviews were self-transcribed, and identifying data were not recorded on the transcriptions. Audio recordings were deleted after data analysis. Further confidentiality was ensured by limiting data access to the research team.

CONSENT AND ENROLMENT

Written informed consent was obtained from all participants. Particular consent was obtained from each participant for the audio recording of the qualitative interviews. Participants were also permitted to withdraw from the study at any time prior to transcription, as each individual participant would no longer be identifiable hereafter. Participants in the focus groups were also requested to treat the opinions of other participants in confidence and with respect.

Risks and Benefits

No direct risks were anticipated for enrolled organisations and participants in the qualitative interviews as identities were protected. Participants also enjoyed no direct benefits for participation in the studies. No compensation was provided for participation.

Fair Dissemination of Findings

Owing to different disease burdens, patient presentations and resources available, not all research emanating from high income countries are relevant to the low- and middle-income African setting. [135,136] For this reason it is essential that research relevant to these settings be published and accessible to clinicians and policymakers from such settings. [135] Only approximately 59% of African emergency care articles are published in open access journals. [135] One in every six articles pertaining to African emergency is not accessible through self-archiving websites or from the author directly. Accessing subscription-based publications may be costly and these publications can charge up to 3.5 times the standard access or publication charges to African researchers. [135] This is cost-prohibitive to many African researchers. In order for African emergency care to develop, improved output and access to contextual research is needed. [135] Furthermore, African research on non-communicable diseases (such as CVD) was lacking, and a call to increased research in this field was made. [135] When we consider that the average doctor in Tanzania earns $600/month, [137] $283/month in Zimbabwe, [138] $685/month in Mozambique [139] and $2660/month in South Africa, [140] it is clear that buying an article at $36 per publication [135] is not an option. For this reason, as far as possible, the science generated should be published in open access journals to ensure that the findings are fairly disseminated to the individuals to which it pertains, and to which the milieu it speaks. For this reason, specific journals of the constituent papers are chosen, to provide maximum impact by reaching policymakers from these settings.

5. METHODS

i. STUDY I

Study design

A cross-sectional design was employed, and data were obtained from literature, online and local directories, organisational databases and correspondence with the relevant Departments of Health and private or independent hospital groups. Stakeholders were contacted and requested to provide information on which of their facilities had PCI capabilities. Failing this, additional information was gained by searching local directories and hospital databases online. [141] The hospitals and their physical addresses that were obtained were then consolidated, analysed and compared. The availability of PCI was validated by two methods. First, a 10% random sample was selected, and the availability of PCI was confirmed by telephone. Furthermore, the data of each province was sent to a local cardiologist within that province to verify. These validations yielded no inaccuracies. The current study is reported in accordance with the STROBE guidelines for the reporting of observational research.

Data sources

Population, [142] and socio-economic status data [143] were obtained from the 2015 mid-year population estimates and 2014 reporting data of StatsSA, the National statistics service of South Africa.

In South Africa, poverty rates are calculated using a multidimensional approach (cost-of-basic-needs approach) that considers food and non-food items to establish a lower, upper and absolute (food) poverty line. The food poverty line is R335 ($20) per capita per month, while the upper and lower poverty lines are R779 ($45) and R501 ($30) per capita per month. [6] Poverty and medical insurance rates (percentage of individuals in each province falling below the poverty line and possessing medical insurance), were extracted from the census data. [143]

Data analysis

The number of PCI-facilities in South Africa was analysed descriptively and presented as absolute numbers. Proportions of PCI facilities per province are presented as percentage of total PCI facilities nationally. Furthermore, absolute numbers and proportions of PCI facilities per province are further divided into state-owned or owned by private hospital groups. Correlations between data variables (population, poverty rate and proportion of persons with medical insurance in each province) and distribution of PCI facilities were sought by means of Spearman's Correlation Coefficient. The significance level was set at p=0.05, two-tailed.

ii. Study II

Study design

We assessed timely access to PCI facilities by a series of geospatial analyses. Firstly, we determined the driving times and distances to the closest (private and/or state) PCI facility of each of the municipal wards within South Africa. Hereafter, we determined the proportion of the South African population who live within 60 and 120 minutes from these facilities based on the average drive times. We purposefully selected these timeframes as they are in line with local and International PCI reperfusion guidelines.[34,144]

Data sources

PCI facility availability data from a previously published cross-sectional study were utilised.[5] We plotted state and private PCI facilities in turn using the physical address of each. From here we used ArcGIS 10 and ArcGIS Online (Esri, California, United States) to plot a 60 and 120 minute drive-time polygon around each of the PCI facilities. ArcGIS calculates the drive-time polygons around created points (PCI facilities, in this case) that can be accessed within a specified time of travel from that point. These drive times are calculated using predicted typical traffic trends. Typical traffic trends for each road are determined within ArcGIS by averaging a week's real-time travel speeds, in five minute intervals.

Using ArcGIS, a join was created between the current South African ward boundary lines and the 2011 population census data.[145] Ward (district) level data was used as this is the smallest geographical area available with population data, and therefore improves accuracy of results. Ward level data was not available for the 2016 community survey. The mathematical mid-point (centroid) of each ward was calculated and the population was added to this point on the map datasets.

Analysis of proximity

Proximity analysis was used to determine the projected drive time from each ward centroid to the closest PCI facility in all provinces. These drive times were again calculated based on the typical traffic trends for each area. These data are presented descriptively. Medians and inter-quartile ranges are reported as the data showed heterogeneity between provinces.

Using the drive-time polygons and the "Select by Location" feature of ArcGIS 10, it was possible to extract those wards whose centres fell within the 60 and 120 minute drive-time polygons. [146] Integrity of the data was ensured by performing a series of manual verifications. We extracted the specific wards and their populations that fell within these polygons to determine the population who live within these referral areas.

iii. Study III

Study design

We applied geospatial analysis [146] with network optimisation modelling, [147] to determine which strategy (thrombolysis or PCI) is most appropriate for patients presenting within each of the municipal wards of the North West province. These recommendations are based on the proximity of the patient to the closest hospital, with priority given to PCI capable facilities. The geospatial analyses aggregate and analyse the data and send it to the optimisation software that selects the best treatment option swiftly. This is presented graphically. We describe the data sources, the geospatial analysis and the optimisation model next.

Data sources

We obtained PCI location data from a previous study. [5] The locations of non-PCI hospitals were obtained through local directories and correspondence with the relevant Departments of Health and private hospital groups. We plotted these points within the North West province using ArcGIS 10 and ArcGIS Online (Esri, California, United States). We used the current South African ward demarcation lines and determined the mathematical mid-point of each ward, the ward centroid.

Reperfusion timelines

Reperfusion can be done my two means: thrombolysis or percutaneous coronary intervention (PCI). PCI shows a mortality benefit should it occur within 120 minutes of first medical contact. [29] First medical contact (FMC) is defined as the moment that the patient presents with signs and symptoms to the initial healthcare provider. In our context, first medical contact is therefore defined as the moment that the ambulance arrives first on scene. [29] Thrombolysis should be initiated within 10 minutes of STEMI diagnosis, preferably in the prehospital setting should PCI not be reachable within 120 minutes,. [29] Unfortunately, the cost for ambulances to carry these medications might preclude widespread availability in LMICs, such as South Africa; notwithstanding the waste of expensive medications should they expire at an ambulance base. For this reason, our model suggests a preference for in-hospital thrombolysis should it be reachable within 30 minutes. This is in accordance with previous recommendations. [15,29,34,144] Failing this, we suggest prehospital thrombolysis (PHT). Figure 2 outlines the reperfusion strategies and timelines used in this model.

Analysis of proximity

Proximity analysis [146] was used to determine the projected driving time from each ward centroid to the closest PCI-capable and PCI non-capable facility. ArcGIS Online (Esri, California, United States) calculates drive times using predicted typical traffic trends. Typical traffic trends for each road are determined within ArcGIS by averaging a week's historic real-time travel speeds, in five minute intervals. These travel times were then imported into an optimisation model and solved iteratively with integer programming using Lingo 13 (Lindo Systems Inc. Illinois, United States). [147]

Optimisation model

We describe the optimization model using standard mathematical notations. Table 1 defines the data input and required definitions for the model. This model is used to choose the reperfusion strategy after the STEMI diagnosis in accordance with Figure 2.

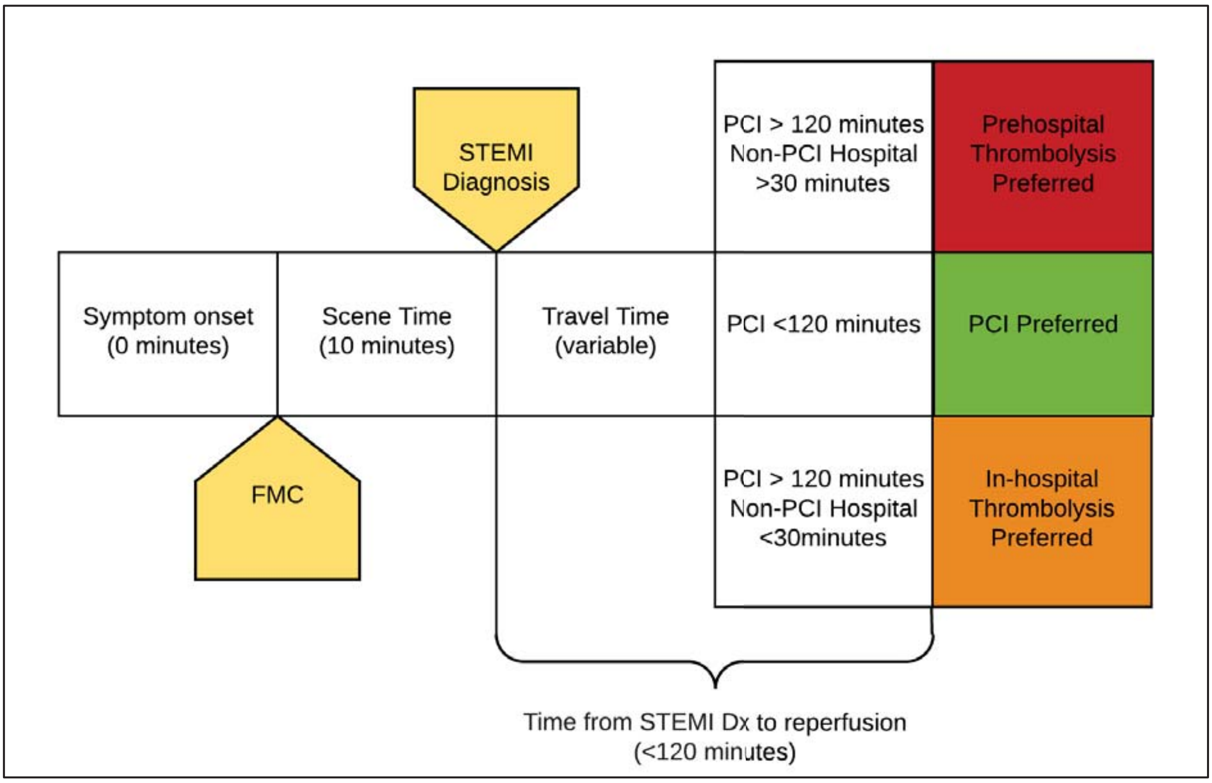

Figure 2 Reperfusion Decisions

Table 1 Defined data of model

Sets	S = Available treatment options (PCI, in-hospital thrombolysis, or prehospital thrombolysis)
	H = Type of available hospitals (, PCI or Non-PCI hospital)
	W = Ward identification number for every independent ward centroid
Parameters	p_j = Priority of treatment type *j* is set by this weight. (in our case this weight is PCI < in-hospital thrombolysis < prehospital thrombolysis; the smallest is chosen first, if possible).
	c_j = Time limit for the ambulance transport to the hospital of type *j* (in our case set by regulation to 120 minutes for PCI hospital and 30 minutes to Non-PCI hospital. If none is possible, prehospital thrombolysis is chosen).
Calculated values	t_{ij}= Transport time with ambulance from the ward centroid *i* to the nearest hospital of type *j.*
Variable	x_{ij} = Binary variable that is set to 1 if treatment option *j* is chosen for ward centroid *i*, otherwise 0.

Since the geospatial analysis provides the nearest hospital (PCI, or otherwise) for every ward centroid we use the best of two worlds and can solve the optimisation problem below swiftly in an iterative way decomposing for every ward centroid in the following manner (Fig 3):

Objective function (1) minimize z that is the sum of all weights for different treatments *j* for every ward centroid *i*.

Constraint (2) sets the time limit for ambulance transport to different type of hospitals *j* from every ward centroid *i.*

Constraint (3) ensure us that we can only choose one treatment option for every ward centroid *i.*

Constraint (4) selects the optimal treatment *j* for every ward centroid *i,* and set 1 if it is chosen, otherwise it is 0.

Calculate ***for*** $i \in W$:

$$\min z = \sum_{j \in S} p_j x_{ij} \quad (1)$$

$$s.t$$

$$t_{ij} x_{ij} \leq c_j, \forall j \in H \quad (2)$$

$$\sum_{j \in S} x_{ij} = 1 \quad (3)$$

$$x_{ij} \in \{0,1\}, \forall j \in S \quad (4)$$

Figure 3 The optimisation model expressed as an integer programming model

The reperfusion decision results were then combined with ward data and colour coded (based on Fig. 2). These results are presented graphically and presented descriptively.

Geographic representation

After solving the optimisation equation, reperfusion decision results were extracted to Microsoft Excel (Microsoft Corporation, Washington, United States). Using the coded number of each ward as unique identifier, a geospatial join was created between the optimisation results and the ward centroid files in ArcGIS (Esri, California, United States). Hereafter, each ward centroid was colour coded based on proximity and the recommended reperfusion strategy. These results are presented descriptively and graphically.

iv. STUDY IV

Study design

Using purposeful sampling, this exploratory study employed a qualitative research design, and made use of individual and focus group interviews. Qualitative designs have been used previously to describe complex phenomena, generate new ideas within an underexplored field, and to provide meaning to human experience. [148]

Setting

The principal author is an Emergency Care Practitioner (ECP) with 7 years' experience within the South African prehospital context in road, aeromedical and mobile intensive care units. Primarily based within the City of Johannesburg of the Gauteng province, he has experience of other South African provinces and the greater African continent secondary to aeromedical exposure. He has also received formal training in qualitative research, and interview techniques.

At the time of the study, the North West and Northern Cape provinces had no emergent access to PCI-capable facilities. Variable access to these facilities within the Western Cape and Gauteng provinces were appreciable. South Africa has a tremendous shortage in PCI-capable facilities, [5] have significant delays to reperfusion [30,53,69] and is characterised by poor access to PCI based on geography and socio-economic status. [5]

Data collection procedure

Qualitative data collection was completed between June and October 2017. We developed an interview schedule using current literature on the barriers to the implementation of coronary care networks, as well as specific contextual insight by the principal investigator's experience. An initial in-depth interview was conducted to develop and refine the interview schedule and to gather ideas that were planned to be explored further during focus group interviews.

The discussion schedule firstly addressed what participants felt the current state of CCNs in South Africa was. From here, prompts and probes aimed to elucidate specific data of each participants' perception and experiences of barriers within their own setting and solutions that they might consider worth implementing to facilitate the development of effective CCNs.

After finalising the discussion schedule, two focus group interviews were completed to gain an integrated view of the CCNs of South Africa with people who would normally be expected to work together.

We selected participants from the prehospital and in-hospital context of both state and private healthcare settings with variable PCI access. We expressly aimed to interview participants working in areas of both PCI-capable facilities and those who do not have immediate PCI access. The qualitative approach of focus groups was selected in order to generate insights into the different perspectives between individuals from different settings, thus making results more representative of the South African context. [149] The demographic profile of the participants is shown in Table 2. We felt that these stakeholders would have sufficient experience and knowledge to unpack the problem of implementing coronary care networks within the South African context and that they would provide appropriate content that could lead to meaningful analysis.

During the focus group interviews, many aspects related to the role of the cardiologist surfaced. We therefore decided to triangulate the results by conducting a final depth interview with an interventional cardiologist who has experience in both state and private healthcare sectors. Hereafter, it was felt that data saturation had occurred, and interviews were concluded.

Data analysis

With specific permission, all interviews were recorded in duplicate via iPhone 6S (Apple Inc. California, United States) Voice Memo Application (iOS 11) and H1 Handy Audio Recorder (ZOOM Corporation, Tokyo, Japan). Hereafter, recordings were downloaded onto a secured computer and transcribed verbatim by the principal author. All identifying data were omitted from the transcripts, which were stored under password protection.

Using methods described previously, [148] transcripts were subjected to descriptive content analysis after immersion in the data. Using Atlas.ti (Scientific Software Development GmbH; Berlin, Germany) specific meaning units were condensed, coded and categorised according to themes. These themes are presented descriptively and discussed according to the three central questions to this project: 1) What is the current perceived state of coronary care networks within the South African context? 2) What are some of the barriers to implementing coronary care networks? 3) What are some suggested facilitators to implementing a coronary care network? The thematic development is exemplified in Table 3.

Table 2 Demographic profile of participants

Participant	Position	Province of work	Sector of work	PCI Access
P1	ECP	Gauteng	Private	Yes
P2	RN: ICU	North West	Private	No
P3	RN: EC	North West	Private	No
P4	ALS	North West	Private	No
P5	EC Doctor	North West	Private	No
P6	ECP	Western Cape	State	No
P7	EP	Gauteng	State	Yes
P8	EP	Gauteng	State	No
P9	EP	Northern Cape	State	No
P10	ECP	Gauteng	Variable	Variable
P11	Cardiologist	Gauteng and Mpumalanga	State and Private	Yes

P: Participant; ECP: Emergency Care Practitioner; RN: Registered Nurse; ICU: Intensive Care Unit; EC: Emergency Centre; ALS: Advanced Life Support; EP: Emergency Physician; PCI: Percutaneous Coronary Intervention. Shaded participants indicate the focus group interviews.

Trustworthiness

The trustworthiness of data presented within this qualitative approach was ensured by considering aspects of credibility, transferability, dependability and confirmability. [150]

We ensured credibility by employing qualitative methods that are well-established; by making use of a discussion schedule consistently applied by the same interviewer; by triangulation (the use of both focus groups and individual depth interviews); by using participants who freely volunteered their time, thus ensuring that participants were genuinely interested in giving data freely (promotes honesty); and by examining the results in the context of previous research findings for congruence, as presented in this report. [150]

As this was a qualitative work, transferability is difficult to ascertain. However, we believe by selecting a heterogenous sample, our participants were broadly representative of most aspects of CCNs within the South African context. Furthermore, a thick description of the participants and the South African context may provide opportunity for the reader to establish transferability to their context on an individual basis. [150]

Dependability is ensured by providing a description of the data collection procedures and the specific discussion schedule utilised. Further method error was mitigated by ensuring that only the principal author completed all interviews, thereby interview techniques should have been similar for all interviews. [150]

To ensure confirmability, the transcribed research was checked by the other authors. Further to this, reflective admission of the interviewer’s own beliefs were written down before and after each interview. Furthermore, data was triangulated between two methods (focus groups and individual depth interviews), and corroborated by previous research findings. [150]

Table 3 Thematic development using qualitative content analysis

Meaning Unit	**Code**	**Theme**
“So in that particular setting the number of coronary care unit beds is so miniscule”	Limited CCU beds	There are many resource constraints
“most GPs don't know what an ECG is, they don't know how to interpret it,”	ECG Interpretation	Poor recognition and diagnosis
“we can’t adjust the system based on no data.”	Limited data available	Research is needed

6. RESULTS

i. STUDY I

State healthcare facilities in all nine provinces and thirteen private hospital groups were sampled. Table 4 shows the distribution of PCI facilities and the population of each province. There is a total of 62 PCI facilities in South Africa, 45.9% of which are located within the Gauteng province, the most densely populated province. Nationally, there is one PCI facility for every 887,096 people. In Limpopo and the North West one PCI facility serves 5.1 and 3.7 million people, respectively. There are no PCI facilities in the Northern Cape.

Table 4 Population and number of PCI-facilities per province

PROVINCE	TOTAL POPULATION n(% nationally)	TOTAL PCI n(% nationally)	POPULATION/ PCI
GP	13.2 mil (24.0%)	28 (45.9%)	471 439
WC	6.2 mil (11.3%)	13 (21.3%)	476 930
NC	1.1 mil (2.2%)	0 (0%)	--
EC	6.9 mil (12.6%)	4 (6.6%)	1 729 050
NW	3.7 mil (6.7%)	1 (1.6%)	3 707 000
KZN	10.9 mil (19.9%)	10 (16.4%)	1 091 910
FS	2.8 mil (5.6%)	3 (4.9%)	939 300
MP	4.28 mil (7.8%)	2 (3.8%)	2 141 950
LI	5.7 mil (10.4%)	1 (1.6%)	5 726 800
TOTAL	**55 mil (100%)**	**62 (100%)**	**887 096**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo

There is a strong positive correlation between the population share of each province and their PCI facility share (r=0.82; p=0.007).

Table 5 shows the proportion of private to state-owned PCI facilities for each province, poverty rates and the ratio of individuals with medical insurance. Locally, 48 (77%) of the PCI facilities are privately owned and are therefore only accessible to 18.1% (those with medical insurance) of the population. The remaining 82% of the population without insurance share 23% (n=14) of PCI facilities. In the province with the highest poverty level, Limpopo (78.9%), there are no state-owned PCI-facilities.

Table 5 Private and state-owned PCI-facilities, and medical insurance and poverty rates per province

PROVINCE	TOTAL PCI n(% nationally)	PRIVATE PCI n(%/province)	STATE PCI n(%/prov)	POVERTY RATE	% w/ MIn
GP	28 (45.9%)	22 (78.6%)	6 (21.4%)	33.0%	28.2%
WC	13 (21.3%)	10 (77%)	3 (23%)	35.4%	26.3%
NC	0 (0%)	0 (0%)	0 (0%)	63.0%	19.8%
EC	4 (6.6%)	3 (75%)	1 (25%)	70.6%	10.5%
NW	1 (1.6%)	1 (1.6%)	0 (0%)	61.4%	14.8%
KZN	10 (16.4%)	8 (80%)	2 (20%)	65.0%	12.8%
FS	3 (4.9%)	2 (66.7%)	1 (33.3%)	61.9%	17.9%
MP	2 (3.8%)	1 (50%)	1 (50%)	67.1%	14.9%
LI	1 (1.6%)	1 (100%)	0 (0%)	78.9%	8.6%
TOTAL	**62 (100%)**	**48 (77%)**	**14 (23%)**	**59.6%**	**18.1%**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo. MIn: Medical Insurance

A very weak correlation exists between the poverty levels and number of state PCI facilities in each province (r=0.01; p=0.17). The amount of private PCI facilities and individuals with medical insurance was moderately, negatively correlated (r=-0.4; p=0.27).

ii. STUDY II

PCI facilities are concentrated around major cities and along the coastal areas of South Africa. Wards within the 60 and 120 minute drive-time polygons to PCI facilities are presented in Figure 4.

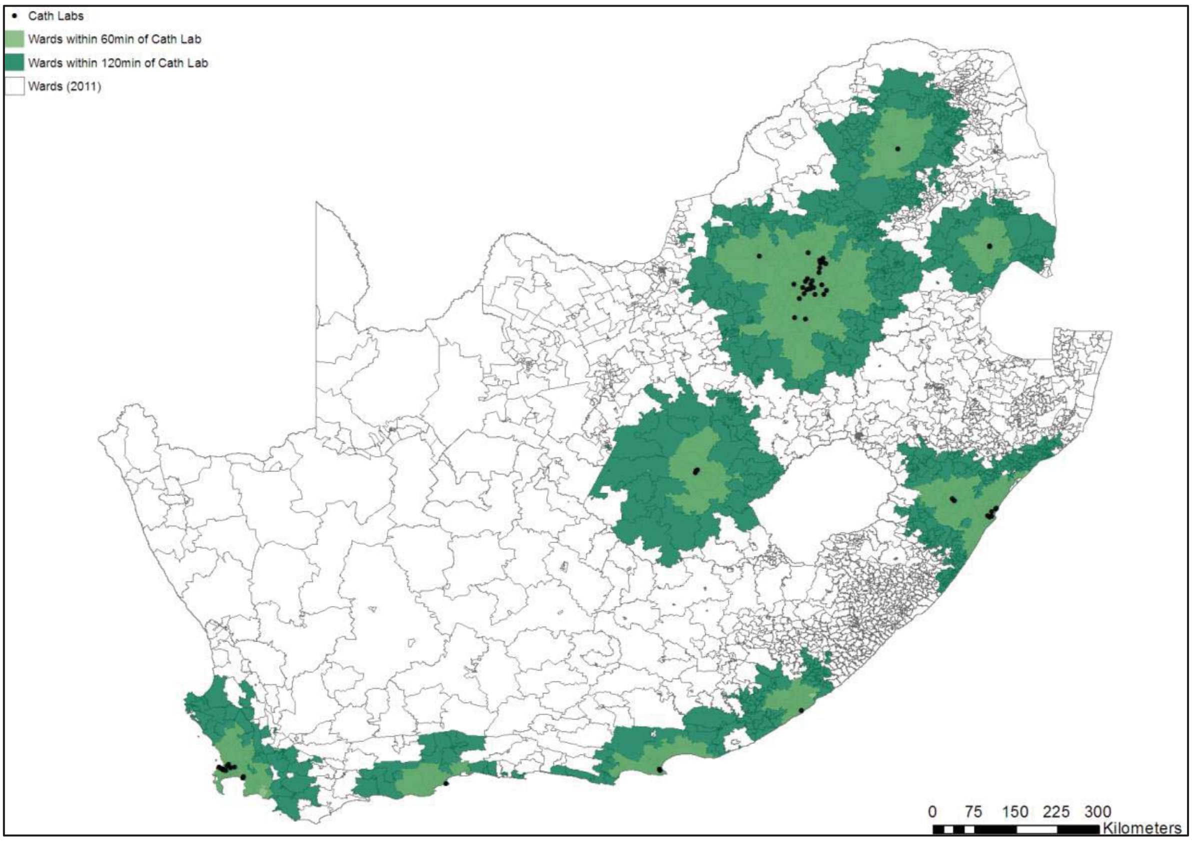

Figure 4 Drive-time polygons and wards within 60 and 120 minutes from PCI facility (ArcGIS 10, Esri, California, United States)

Table 6 displays the driving distances to PCI facilities in South Africa. The median driving distance to the closest PCI facility nationally is 123.6 km (IQR 157.6 km). The Northern Cape has the longest driving distance to a PCI facility of 940.8 km while the shortest distance is 0.3km in the Eastern Cape and the Free State provinces, jointly. The median driving distance to the closest state PCI facility (Table 7) is 100km (IQR 157.6km), while the shortest driving distances are in the Free State and the Gauteng provinces, jointly (0.9km) and the furthest is in the Northern Cape (1085km).

Table 6 Driving distances to a PCI facility (state or private) in South Africa

PROVINCE	MINIMUM DRIVE DISTANCE	MEDIAN DRIVE DISTANCE (IQR)	MAXIMUM DRIVE DISTANCE
GP	0.5km	15.1km (15.9km)	71.5km
WC	0.8km	52.9km (110.3km)	363km
NC	155.5km	406.9km (305.4km)	940.8km
EC	0.3km	206.9km (157.2km)	395km
NW	1.1km	144km (162.6km)	573.3km
KZN	1.6km	137.5km (166.6km)	413.8km
FS	0.3km	140.1km (118.1km)	278km
MP	2km	109.7km (51.7km)	313.1km
LI	2.3km	132km (73.9km)	342.9km
South Africa	**0.3km**	**123.6km (157.6km)**	**940.8km**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo

Table 7 Driving distances to a state PCI facility in South Africa

PROVINCE	MINIMUM DRIVE DISTANCE	MEDIAN DRIVE DISTANCE (IQR)	MAXIMUM DRIVE DISTANCE
GP	0.9km	28.7km (28.5km)	90.6km
WC	1.4km	93km (227.8km)	495.6km
NC	155.5km	406.8km (311.6km)	1085.8km
EC	2.4km	302.3km (140.4km)	551.7km
NW	7km	172.3km (173.9km)	653.7km
KZN	2.4km	146.3km (173.8km)	434.8km
FS	0.9km	158.3km (107.8km)	301.8km
MP	7.4km	125.5km (52.5km)	320.4km
LI	77km	289.2km (158.1km)	607.8km
South Africa	**0.9km**	**170.7km (22.35km)**	**1085.8km**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo

Table 8 displays the drive-times to the PCI facilities in South Africa. The longest drive to PCI is in the Northern Cape at 751 minutes while the shortest drive is in the Free State province (0.7 minutes). Nationally, the median drive-time to PCI is 100 (IQR 120.4) minutes. The closest state PCI facility (Table 9) is a median of 123.7 (IQR 164.1) minutes away. The shortest time to the closest state PCI facility is in Kwazulu Natal (1.5 minutes away) while the furthest is in the Northern Cape (900.1 minutes away).

Table 8 Drive-times to a PCI facility (state or private) in South Africa

PROVINCE	MINIMUM DRIVE TIME	MEDIAN DRIVE TIME (IQR)	MAXIMUM DRIVE TIME
GP	0.8 min	18.3 min (13.8 min)	59.6 min
WC	1.6 min	43.8 min (79.3 min)	277.9 min
NC	111.7 min	300.4 min (640.1 min)	751.8 min
EC	0.8 min	164 min (137.5 min)	318.6 min
NW	3.1 min	115.4 min (117.3 min)	453.6 min
KZN	3 min	109.8 min (133.6 min)	345.1 min
FS	0.7 min	103.1 min (79.9 min)	227 min
MP	4.2 min	94.4 min (54.6 min)	249.2 min
LI	3.5 min	114.1 min (63.2 min)	344.3 min
South Africa	**0.7 min**	**100 min (120.4 min)**	**751.8 min**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo

Table 9 Drive-times to a state PCI facility in South Africa

PROVINCE	MINIMUM DRIVE TIME	MEDIAN DRIVE TIME (IQR)	MAXIMUM DRIVE TIME
GP	1.7 min	29.1 min (20.6 min)	68.3 min
WC	3 min	77.8 min (160.4 min)	328.7 min
NC	105.4 min	298.1 min (210.9 min)	900.1 min
EC	4.3 min	238.6 min (127.2 min)	432.6 min
NW	10.5 min	134.2 min (125.8 min)	486.7 min
KZN	1.5 min	90.9 min (108 min)	270.2 min
FS	1.7 min	112.5 min (79.1 min)	242.9 min
MP	12.6 min	102.6 min (53.4 min)	257.8 min
LI	80.8 min	230 min (88.3 min)	515.2 min
South Africa	**1.5 min**	**123.7 min (164.1 min)**	**900.1 min**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo

Just over half of the population (53.8%) of South Africa lives within 60 minutes of a PCI facility while 71.53% of the country's population can reach a PCI facility within two hours (Table 10). Practically all inhabitants of the Gauteng province live within 60 minutes of PCI while 2.5% of the Northern Cape's inhabitants are within two hours of the closest PCI facility, whether state or privately owned. When only considering state PCI facilities (Table 11), only 47.8% and 63% of the population can access these facilities within 60 and 120 minutes respectively.

Table 10 Proportion of South African population living within 60 and 120 minutes of a state or private PCI facility

PROVINCE	**PCI WITHIN 60 MINUTES n(% per province)**	**PCI WITHIN 120 MINUTES n(% per province)**
GP	12.27 mil (99.7%)	12.3 mil (100%)
WC	4.44 mil (76.1%)	5.1 mil (87.6%)
NC	0 (0%)	29k (2.5%)
EC	1.96 mil (29.9%)	2.68 mil (40.8%)
NW	1.28 mil (36.4%)	2.13 mil (60.6%)
KZN	4.89 mil (47.6%)	6.64 mil (64.7%)
FS	0.99 mil (36.4%)	1.9 mil (69.3%)
MP	0.95 mil (23.5%)	3.19 mil (78.9%)
LI	1.06 mil (19.8%)	3.04 mil (56.3%)
Total n(%SA)	**27.86 mil (53.8%)**	**37.0 mil (71.5%)**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo; mil: million; k: thousand

Table 11 Proportion of South African population living within 60 and 120 minutes of a state PCI facility

PROVINCE	PCI WITHIN 60 MINUTES n(% per province)	PCI WITHIN 120 MINUTES n(% per province)
GP	12.27 mil (99.7%)	12.27 mil (99.7%)
WC	4.19 mil (71.9%)	4.78 mil (82%)
NC	0 (0%)	0 (0%)
EC	1.22 mil (18.6%)	1.48 mil (22.6%)
NW	0.66 mil (18.8%)	1.93 mil (55%)
KZN	4.78 mil (46.6%)	6.72 mil (65.4%)
FS	0.82 mil (29.9%)	1.81 mil (65.9%)
MP	0.73 mil (18.1%)	3.13 mil (77.5%)
LI	6 k (0.1%)	0.26 mil (4.9%)
Total n(%SA)	**24.6 mil (47.8%%)**	**32.6 mil (63.0%)**

GP: Gauteng, WC: Western Cape, NC: Northern Cape, EC: Eastern Cape, NW: North West, KZN: Kwazulu Natal, FS: Free State, MP: Mpumalanga, LI: Limpopo; mil: million; k: thousand

iii. STUDY III

The number of wards and population for each reperfusion strategy is presented in Table 12. For most patients, primary PCI is the preferred reperfusion strategy based on their proximity.

Figure 5 presents the recommended reperfusion strategies for each ward in the North West province, by colour coding each ward according to Figure 2.

Table 12 Wards and reperfusion strategy

	Wards, n(%)	Population, n(%)
PCI preferred	204 (53%)	938 380 (60%)
In-hospital thrombolysis preferred	44 (11%)	185 994 (12%)
Prehospital thrombolysis preferred	138 (36%)	452 525 (28%)

PCI: Percutaneous Coronary Interventions

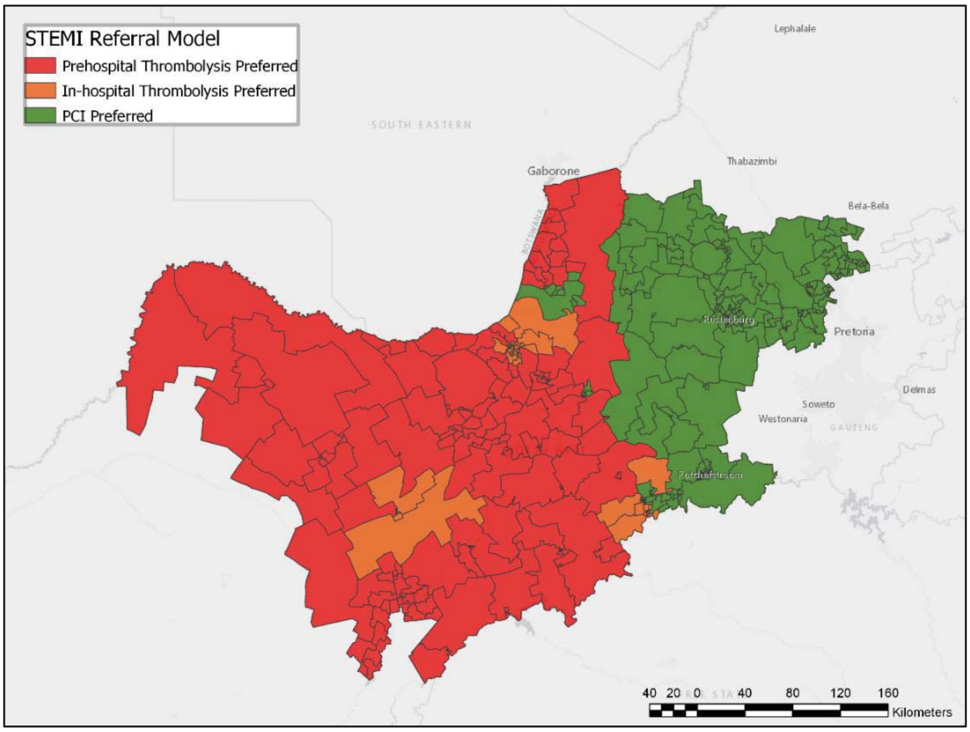

Figure 5 The North West province with reperfusion strategy recommendations

iv. STUDY IV

Eleven participants were interviewed. Inclusion of participants was diverse (Table 2). Interviews lasted approximately 60 minutes. Despite having a diverse range of participants, common themes (summarised in Table 15) emerged universally.

Table 13 Emerging Themes

1. What is the current perceived state of CCNs within the South African context?
Increasing patient numbers, with more lifestyle diseases
Non-communicable diseases are not prioritised
The network is characterised by considerable variation
The network is perceived to be fragmented
There are many resource constraints
2. What are some of the barriers preventing the implementation of a CCN that prescribes to international guidelines?
Poor recognition and diagnosis
Inappropriate transport decisions
Inefficiencies at patient triage
There are considerable delays
3. What are some suggested facilitators to overcoming these barriers?
Prehospital Thrombolysis
Locally appropriate guidelines
Improved clinical governance
Research is needed

7. DISCUSSION

The aim of the current thesis was to evaluate and analyse the existing Coronary Care Networks (CCNs) in South Africa, a low- to middle income country. This was achieved through four studies. South Africa has a shortage of PCI facilities. Many patients may not be able to access care due to socio-economic status. When considering proximity alone, most South Africans are able to access PCI within guideline timeframes. Despite this, prehospital thrombolysis should still be considered in some areas – as demonstrated by a novel approach that combines geospatial analysis and network optimisation modelling. This approach can efficiently determine the optimum reperfusion strategy for each geographic locale of South Africa. Current CCNs in South Africa were perceived to be under-resourced, over-burdened and not prioritised. Future efforts should aim at improving STEMI recognition and diagnosis to decrease delays to reperfusion. The findings described should be considered and integrated into a future model of CCNs within South Africa, towards improving reperfusion times and finally morbidity and mortality.

There are currently 62 PCI facilities in South Africa, more than three quarters of which are contained within the private healthcare sector (Study I). The sheer amount of PCI facilities in South Africa is lacking – there is one PCI facility for every 878 096 people in the country. International guidelines recommend one PCI facility for every 350 to 400 thousand population. [151] A doubling of the amount of facilities might therefore be required. Yet other studies suggest that one PCI facility per million population might suffice should patients be able to reach such a facility within two hours. [152] In South Africa, more than two thirds of the population may access a PCI facility within this timeframe (Study II). This is less when compared to the United States, where 79% of the adult population live within one hour of a PCI facility, with close on 90% of the population living within ninety minutes of a PCI facility. [153]

Access however, is not simply a product of proximity within the South African context of poor healthcare service provision. One of the nine South African provinces has no PCI facilities, while two only have a single private facility each (Study I). The proportion of state-owned PCI facilities do not correlate with the number of patients of poor socio-economic and insurance status within the provinces. (Study I) It was consequently shown that the poor and those without healthcare insurance have a disproportionate share of the PCI resources, and access to PCI may therefore be impossible to these patients, [5] even when only considering proximity alone, [154] unless they are able to fund the treatment privately. Disparities in PCI access are in part, remnants of the apartheid healthcare systems that were fragmented and provided disproportionate healthcare funding based on racial biases and segregation, [13,155] and in part related to current socio-economic conditions. The South African Government accepts that the dual (private and state) healthcare system of South Africa limits healthcare access, and is costly and unsustainable. [155] A National Health Insurance (NHI) has been proposed that aims at providing universal health coverage for all, that is both of high quality and is cost-effective. [155] NHI is currently in its pilot phases in some regions but it is still unclear how NHI might affect access to emergency coronary reperfusion for poor South Africans.

To expedite care, participants (Study IV) highlighted the need for preferential transport of patients to PCI facilities after confirming prehospital STEMI diagnosis (with or without prehospital thrombolysis). Preferential transport to PCI facilities is supported by international literature [111,113–116] and guideline recommendations. [29] This does not seem to occur in South Africa where secondary transfer often delays reperfusion. [15,53,69] Due to proximity and access barriers, certain patients may not have timely reperfusion even if transported to PCI facilities. By utilising a novel approach that combines geospatial analysis and network optimisation modelling, a recommended CCN model for patients with STEMI in the North West province was presented (Study III). This model is scalable and can be applied efficiently in real time. In the event that PCI is not immediately accessible, international guidelines suggest that reperfusion be achieved through thrombolysis instead; [29] and the model accounts for such an eventuality.

Thrombolysis in the South African setting has been found to be marred by considerable delays. [53,69] International guidelines appreciate the complexity of hospital systems, and how this may contribute to delays in the administration of thrombolytic agents. In order to overcome these delays, guidelines suggest that it be initiated in the prehospital setting. [29] Literature supports this, showing significant reductions in reperfusion time and, consequently mortality. [117,156,157] Prehospital thrombolysis still forms the cornerstone of reperfusion strategies in many rural areas of Europe [1,158] and Australia [1] where PCI is not accessible. In fact, based on proximity and PCI access associated with socio-economic and insurance status, prehospital thrombolysis may be of particular value in South Africa. [117,159] A prehospital thrombolysis programme was supported as a facilitator to early reperfusion and implementation of a South African CCN by participants of Study IV. In low resource settings such as South Africa and other LMICs, it is essential to consider the cost of acquiring thrombolytic medications as well as the potential waste of expired medications being carried by ambulances.

A successful prehospital thrombolysis programme is dependant on the following essential components: prehospital personnel being trained in 12 lead ECG acquisition and diagnosis, [29,144] the availability of 12 lead ECG equipment, clearly defined eligibility criteria (clinical and logistic) for prehospital thrombolysis, access to cardiology input and consultation [144,160] and immediate referral to a PCI capable facility for a pharmaco-invasive strategy. [29,160]

Prehospital providers in Study IV echoed that 12 lead ECG telemetry and consultation with a receiving cardiologist was essential for a prehospital thrombolysis programme; without this they would be hesitant to administer the agents. This is likely due to unfamiliarity with the decision-making and administration of thrombolysis. In a Swedish model, such hesitance was short-lived. [161] Interestingly, one study showed a delay in thrombolytics administration when telemetry was used. [162] These findings should be considered in the context of a nascent prehospital thrombolysis network.

International guidelines recommend regionalised protocols outlining the reperfusion strategies for patients based on proximity timelines. [29] Participants in the qualitative study also suggested that a *"geographical referral process"* document would be a helpful facilitator in improving transport decision-making and guiding reperfusion. Providing standard referral guidelines have been found to improve the performance of CCNs. [121] By employing the referral model developed and presented in Study III, this can be done efficiently for the entire country, as well as in other settings. By utilising technology, this could be achieved in real time, using current traffic trends and bed occupancy constraints.

One cannot improve a system that one does not measure. [163] The systematic implementation of metric performance data to inform quality improvement projects have been found to lead to significant reductions in reperfusion times, and increased adherence to international standards of care. [164,165] Regular clinical governance and research was also suggested as facilitators to developing and implementing CCNs by the panel in Study IV. These views are corroborated by international literature - by utilising a process of regular audits and feedback, CCNs perform better. [29,144,166] Feedback on performance and data metrics have also been associated with improved utilisation of prehospital 12 lead ECGs which has been found to be lacking in the South African setting. [69]

8. LIMITATIONS

Some important limitations should be considered. When considering PCI facility data, it is possible that single PCI facilities might not be listed. This was however, mitigated by two levels of validation, verification by local expertise and telephonic confirmation of a random sample.

Population calculations were based on 2011 South African census data because more recent publications do not provide population data at the ward level. This may lead to small inaccuracies due to migration and population growth since.

When considering the proximity analysis, drive-time polygons are calculated based on typical (average) drive times and traffic trends, and does not consider any traffic anomalies or outliers. The time taken to dispatch a vehicle in the EMS control centre, ambulance response and scene times were not taken into consideration. This may prolong the total prehospital time and therefore ischaemic time. However, guideline timeframes are calculated from first medical contact. Similarly, patient delay was not taken into consideration. In-hospital delays were also not considered. Yet, such constraints could easily be implemented into the proposed model and can therefore be accounted for.

The qualitative study (Study V) is strengthened by the purposive selection of a heterogenous sample that ensures representation from a variety of aspects within the South African CCN. Consequently, there was representation from in- and prehospital phases of care, state and private healthcare, five of the nine South African provinces and participants with and without PCI access. Despite such a diverse sample, the qualitative and descriptive design of this study limits the transferability. A further limitation is that the barriers and facilitators to the implementation of CCNs in South Africa was not interrogated from the patient's perspective, which might provide valuable data for consideration.

By consolidating and interpreting the results of the four studies, the lessons learnt from their undertaking and some of the barriers and facilitators to CCNs in South Africa (obtained from Study IV), several recommendations for future perspectives can be made.

9. FUTURE PERSPECTIVES

India, also an LMIC, has a tremendous burden of CVD and STEMI. [127] Similar to South Africa, a large majority of the Indian population also lives in poverty, with poor sanitation and under poor socio-economic hardship. [127] However, despite these circumstances, India has managed to develop successful CCNs that show promise in reducing the time to reperfusion and improving mortality. [127] Many lessons can be learned from their experience.

Mehta et. al. proposes a conceptual framework for confronting failures within coronary care networks in resource-limited settings such as South Africa. [167] This framework describes six distinct but integrated aspects of a coronary care network. These six aspects are: patients, insurance, transport, hospital (and healthcare) systems, healthcare providers (physician in the original model), and technology. [167]

It is felt that by focusing on these aspects, South Africa can harness the success of our Indian counterparts, providing a point of departure for the development of CCNs locally. For this reason, and taking the findings of this thesis into consideration, recommendations for the future development of CCNs in South Africa are provided.

PATIENTS

This thesis did not particularly examine the role of the patient within the South African CCN however, some important aspects should be highlighted. These aspects relate to the need for epidemiological data, prevention strategies and patent education.

During the completion of these studies, it was impossible to obtain good quality, representative epidemiological data on the prevalence and incidence of CVD and STEMI in South Africa. Authors have previously emphasised the need for such data in SSA, [23] while others have exposed the lack of research output concerning non-communicable diseases. [135] By providing policymakers with good quality data showing the increasing burden of STEMI in South Africa, and highlighting areas of high incidence, it is believed that future developments can be targeted to these specific populations. By focusing on high incidence populations, a larger impact can be achieved with lower resource expenditure - a large consideration in LMICs. Two of these interventions may be prevention and patient education.

A proposed explanation for the increase in the burden of CVD seen in SSA is an increase in the incidence of lifestyle risk factors such as hypertension, diabetes and hypercholesterolaemia. [10,20–22] The impact of prevention on mortality has been demonstrated.

[168] Similarly, failing at prevention programmes might have major implications to healthcare expenditure. [168] The feasibility of prevention programmes should be explored within the South African setting. One such an intervention suggested by participants, is patient education campaigns.

In a small South African cohort, a lack of education regarding the risks of AMI and STEMI was determined to be a cause of delayed patient presentation and poor ambulance use. [53] Public education campaigns have been shown to reduce patient delays and improve ambulance use when experiencing symptoms of AMI. [73–75] It is recommended as a part of primary and secondary prevention programmes. [169,170] Education campaigns in South Africa should be tailored to each community's local SES, language profile and level of education and take into consideration access to print, social and broadcast media of each community.

It is further recommended that a future study investigate the barriers and facilitators to CCN access from the perspective of the patient.

INSURANCE

According to Section 27(3) of 1996 of the South African constitution, emergency medical care may not be refused to any South African, regardless of their ability to pay. [171] Within this context an emergency may be defined as "*the sudden and, at the time, unexpected onset of a health condition that requires immediate medical or surgical treatment, where failure to provide medical or surgical treatment would result in serious impairment to bodily functions or serious dysfunction of a bodily organ or part, or would place the person's life in serious jeopardy.*" [172] What emergency medical care entails however, has not been clearly defined and is largely open to interpretation. [173] Practically, this means that a STEMI patient with stable vital signs, may be directed from one hospital to another without receiving reperfusion therapy. For this reason, it is recommended that the definition of "emergency medical care" in the context of STEMI include the provision of reperfusion.

Until such time as NHI is well-established, we recommend the provision of alternative funding models with integrated state and private partnerships to allow for timely reperfusion in STEMI. Assuming education campaigns are effective at decreasing patient delays to presentation and improving ambulance use, and access can be facilitated through sustainable funding models, the emergency medical services play a pivotal role in transporting STEMI patients to appropriate care facilities within the CCN.

Transport

Under the apartheid regime, inequitable development of road and transport infrastructure in racially segregated areas have left some South Africans inaccessible by formal roads. [13] Public transport systems in South Africa are also unsafe, expensive and often inaccessible to some communities. [13,174] Furthermore, some informal settlements in South Africa lack formal addresses. This may prolong ambulance response times, which may increase the total ischaemic time of patients with STEMI and increase mortality. [48] Considering that ambulance response times of greater than 3-4 hours are not uncommon in some rural parts of South Africa, [175] it is not surprising that patients have a distrust of EMS when experiencing symptoms of AMI. [53] Some propose that these poor response times are due to a lack of ambulance resources, and while it is definitely a consideration, Stein et. al. demonstrates that more efficient use rather than increased resources may be effective at honouring target response times. [176] Epidemiological data are required to make meaningful recommendations on where vehicles should be placed. As an interim measure, a community first responder programme could be explored, [177] which could expedite healthcare access while providing some prehospital care.

Ideally, patients with STEMI should be transported by advanced life support (ALS) paramedics that are able to perform 12 lead ECGs to confirm diagnosis, and similarly manage any severe complications. [29,105] There is currently a shortage of ALS in South Africa. [131] It is therefore imperative that ALS resources are reserved for response only to the patients that truly need such a level of care. As the first point of contact for patients seeking an EMS response, [178] emergency dispatch centre triage tools can be used to predict the acuity of the patient, and the need for an ALS response. [179] Such triage tools rely completely on the presentation and symptomatology described by the callers. In a country with eleven official languages and varied levels of education [8] these descriptions may be myriad. Triage tools tailored to the South African setting, that take these socio-demographic aspects into consideration should be developed and validated. By utilising these triage tools, dispatch PCI activation could reduce reperfusion times even further. [180]

By combining proximity analysis and network optimisation models, an efficient means of providing reperfusion recommendations is presented (Study III). In some instances, it is recommended that patients undergo prehospital thrombolysis before being referred to a PCI facility – a pharmaco-invasive strategy. It is currently unclear whether these areas have 12 lead ECG resources, emergency care practitioners licensed to administer thrombolysis, [105] or thrombolytic medications. Similarly, it is also unclear whether such resources exist at hospitals in areas where in-hospital thrombolysis is recommended. A national audit of thrombolytic, human and diagnostic resources is recommended.

TECHNOLOGY

Notwithstanding the application of technology for telephonic triage, location-based services and efficiency modelling, as described above; technology should also be considered in aiding the diagnosis of STEMI. Prehospital twelve lead ECG telemetry has been used successfully in other settings. [93–96] By utilising 12 lead ECG telemetry to facilitate shared decision-making, cohesion could be facilitated in the South African CCN. It may further facilitate early pre-notification to emergency centre staff that a STEMI patient is en route. This has been found to improve in-hospital reperfusion times. [82] Considering the lack of ALS paramedics, centralised ECG diagnosis can be facilitated through basic and intermediate prehospital providers using telemetry. [84] An attractive alternative for paramedic-initiated STEMI diagnosis in resource-limited areas. Twelve lead ECG telemetry can also support regional prehospital thrombolysis programmes, followed by immediate PCI referral. Such a pharmaco-invasive approach seems more feasible in LMICs, like South Africa with limited resources or prolonged transport times. [181]

HEALTHCARE PROVIDERS

Inappropriate triage and missed STEMI diagnosis seems to occur often in South Africa. [53,69] In order to remedy this, education programmes should not only target patients but also healthcare providers. Within the continuum of a CCN, these providers include local family physicians and general practitioners, emergency call-takers, prehospital providers, triage officers, nurses, doctors and emergency and cardiology specialists. It is recommended that training should be based on regional referral networks that are tailored to the specific resource and barrier constraints within the particular setting.

One way of delivering such training programmes is through a self-paced, online learning programme. Online learning has been implemented successfully in the South African setting to improve traumatic brain injury guideline adherence. [182] It is recommended that such training programmes be integrated into data feedback and clinical governance systems that continuously measure performance of the CCN, providing dynamic improvement projects. Hospital (and healthcare) systems are essential in managing these data repositories.

Hospital Systems

A national STEMI performance metric registry is suggested, which currently does not exist in South Africa. [183] It is further suggested that such a registry be populated by each of the different healthcare sectors to allow for data sharing. State and private partnerships, as well as agreement between different private hospital groups should be undertaken to achieve this.

It is therefore recommended that each specific setting in South Africa seek bottlenecks (e.g. administrative processes) within their jurisdiction and implement healthcare improvement strategies to improve STEMI care. [29] Such improvement projects should encompass the entire CCN, from prehospital care, to in-hospital systems.

Presenting PCI facility data, such as in Study I, simply provides an overview of where these facilities are located. Yet, it does not comment on or guarantee a 24 hour PCI service. Literature has exposed considerable variation in the reperfusion times between patients who present within working hours, or outside of these. [69,184] Considering the shortage of cardiology resources in South Africa, hospital systems should further focus on the provision of 24 hour PCI facilities to avoid such variations in care.

In an attempt to ratify these recommendations, a final recommendation is to subject these to a consensus process to present the priorities of CCN development in South Africa.

10. CONCLUSION

Consisting of four interrelated studies, this project aimed to examine and explore Coronary Care Networks in South Africa, a low- to middle income country and to describe and study aspects that could improve timely access to coronary care in patients experiencing ST-elevation myocardial infarction within this context.

South Africa has a shortage of PCI facilities. When considering proximity alone, most South Africans can access PCI within guideline timeframes. Yet, due to socio-economic conditions, PCI may still not be accessible for many patients. Subsequently, thrombolysis (particularly prehospital thrombolysis) should be considered to expedite reperfusion. We propose a novel approach that combines geospatial analysis and network optimisation modelling to efficiently determine the optimum reperfusion strategy for each geographic locale of South Africa. Current CCNs in South Africa are under-resources, over-burdened and unprioritised. Based on these findings, we provide recommendations that could be studied and integrated into future CCN models applicable to the South African context.

To propose an encompassing coronary care network for the South African context based on the findings of this thesis would be premature. Results have left me with more questions than answers. Furthermore, the immense diversity of South Africa may mean that regional network recommendations should be developed instead. This will require significantly more scientific inquiry. However, some research and development recommendations can be provided. These are based on current results, and aspects highlighted in the discussion.

In a country suffering a quadruple burden of disease, poverty, limited healthcare access and poor living conditions one might argue that there are bigger socio-economic and healthcare priorities than cardiovascular diseases and ST-elevation myocardial infarction. However, considering that CVD and STEMI will continue to rise as further urbanisation and life-expectancy gains are made through other health and social initiatives, we simply cannot afford not to invest in the preparedness to manage these patients. CVD also affects the economically active population, and decreasing morbidity and mortality is essential to ensure sustainable economic and social development of many communities.

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