MASTERS OF MEDICINE (MMED) IN MEDICINE

RESEARCH DISSERTATION

UNIVERSITY OF CAPE TOWN

Study Title

The South African Cardiovascular Magnetic Resonance (SA-CMR) Registry: An Interim Analysis of Clinical Utility, Indications and Baseline Characteristics of Patients Undergoing CMR in a Single Centre in South Africa

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Declaration

I, Cecilia Beatrice Irene Coccia, declare that this dissertation/ thesis is my own original work (except where acknowledgements indicate otherwise). It is being submitted for the degree of Masters of Medicine (MMed) in Medicine. Neither the whole work nor any part of it has been, or is being submitted for another degree in this or any other university. This work has not been reported or published prior to registration for the above-mentioned degree. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. Full ethics approval has been granted by the local ethics committee.

Signed ________________________ Signed by candidate

On this __20th__ (day) of _January 2019

Table of Contents

Abstract

Background

Cardiovascular magnetic resonance (CMR) is a clinically useful imaging modality that is fast becoming a routine tool in clinical practice. In 2013, the results of the first multi-national registry, EuroCMR, were published. The study highlighted the clinical significance and impact of CMR in Europe. More recently, the global CMR registry (GCMR) has been established to standardise data from international centres in order to support the role of CMR across diverse patient demographics. Despite South Africa joining the GCMR network, the role of CMR in the South African context remains undefined and at present there is limited research pertaining to its use. The South African CMR (SA-CMR) registry was founded in 2016 with a view to gain insight into CMR in the South African setting. This interim analysis of the first 1,142 patients aims to establish the clinical use and indications for CMR, to assess the quality of CMR images and to the assess the baseline demographic and clinical characteristics of the cohort. Secondary objectives aim to ascertain the impact of CMR on patient management.

Methods

SA-CMR was designed to be a national registry that consists of both retrospective and prospective CMR data. This analysis reports on the single-centre experience at Groote Schuur Hospital, Cape Town. The retrospective arm consists of patients that underwent CMR at Groote Schuur Hospital (GSH) from its introduction in 2005 to April 2017. This interim analysis will assess the first 1,142 patients in this retrospective arm.

Results

Of the indications for use of CMR in Cape Town, the ascertainment of the presence of cardiomyopathies or their delineation accounted for 54% of scans performed. 15% were utilised to define congenital cardiac anomalies. The average age of patients undergoing CMR was 40 years old and there was a slightly increased percentage of female to male patients (52.65% vs 47.32%). Image quality was diagnostic in 99% of cases and adverse reactions from gadolinium contrast agent use only occurred in 0.18% of patients – of which none were fatal. 34% of scans showed either an alternative diagnosis or additive information which subsequently resulted in an alteration in clinical management of the patient.

Conclusion

In comparison with the European cohort, where the most important indication for CMR was risk stratification in suspected coronary artery disease, SA-CMR showed that, in the South African setting, CMR was utilised predominantly for investigation of cardiomyopathies. SA-CMR further supported CMR as a safe imaging technique which has assisted in diagnostics and clinical management of patients with cardiovascular disease in South Africa.

Acknowledgements

Immense gratitude to Prof. Ntobeko Ntusi for having the vision to run this project as well as the confidence bestowed upon me to complete it.

Furthermore, a special thank you to Mr Stephen Jermy, who collected the data from patient records. Without his invaluable assistance, this study would not have been possible.

Tables

Table 1 – Demographic Data of SA-CMR Cohort

Total Number Patients= 1142

Patient Characteristics	
Age (years), mean ± SD	41± 16
Female sex, %	52.68%
Male sex, %	47.32%
Height (cm), mean ± SD	167.3± 11.8
Weight (kg), mean ± SD	73.4± 20.4
BSA (m^2), mean ± SD	1.84± 0.28

Table 2 – Imaging Data of SA-CMR Cohort

Cardiac parameters		
LVEDV (ml)	169.6	± 78.4
LVESV (ml)	84.2	± 75.1
LVEF (%)	55.3	± 17.6
LV mass (gram)	133.6	± 62.5
RVEDV (ml)	169.9	± 74.2
RVESV (ml)	87.7	± 60.1
Image quality		
Good	90%	
Moderate	9%	
Poor	1%	
Indication met	66%	
Altered management plan	34%	

Values are %(n) or mean +- standard deviation

Figures

Figure 1: Timeline representing the milestones in CMR. ***SCMR: Society of Cardiovascular Magnetic Resonance, JCMR: Journal of Cardiovascular Magnetic Resonance, EuroCMR: European Cardiovascular Resonance, SA-CMR: South African Cardiovascular Magnetic Resonance, GCMR: Global Cardiovascular Magnetic Resonance***

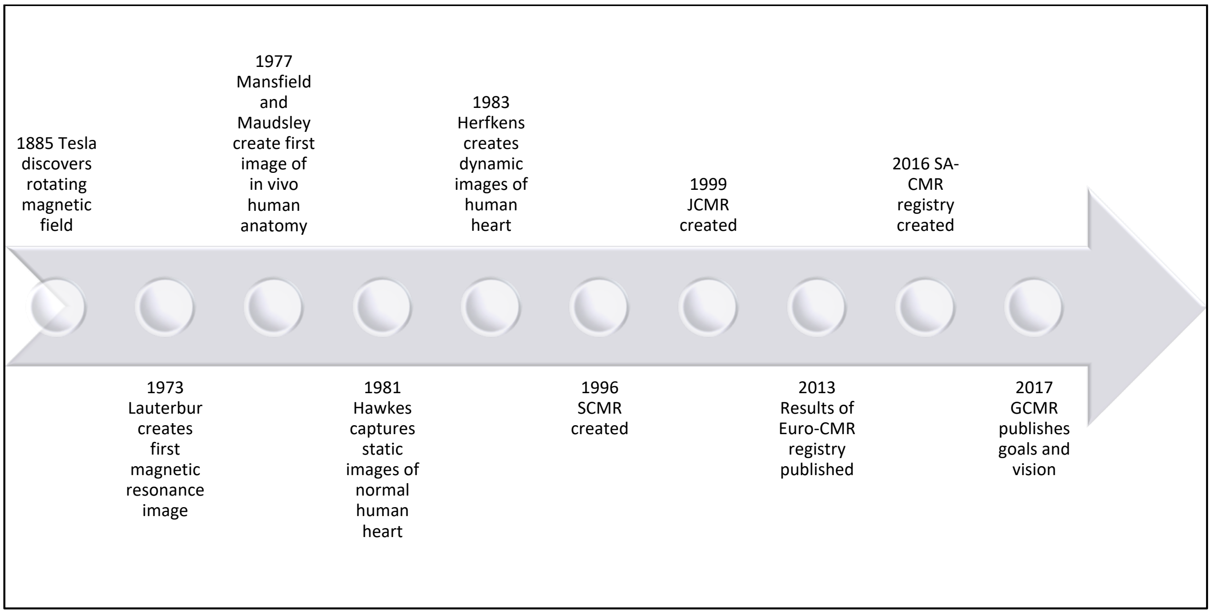


Figure 2: World Health Organization – *Non-communicable Diseases Country Profiles,* 2018. [www.who.int]

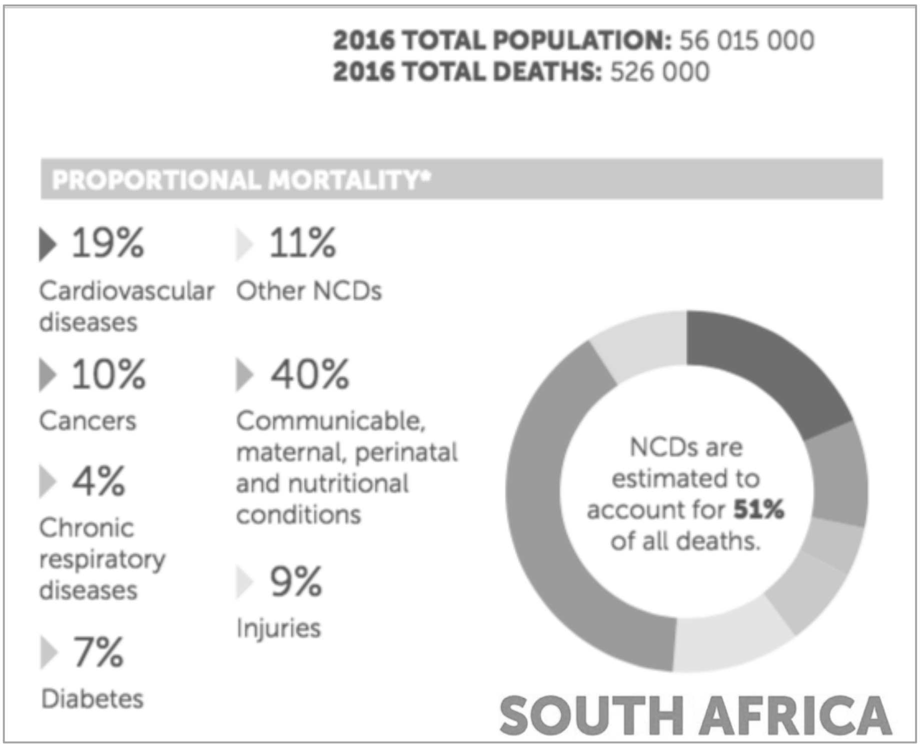
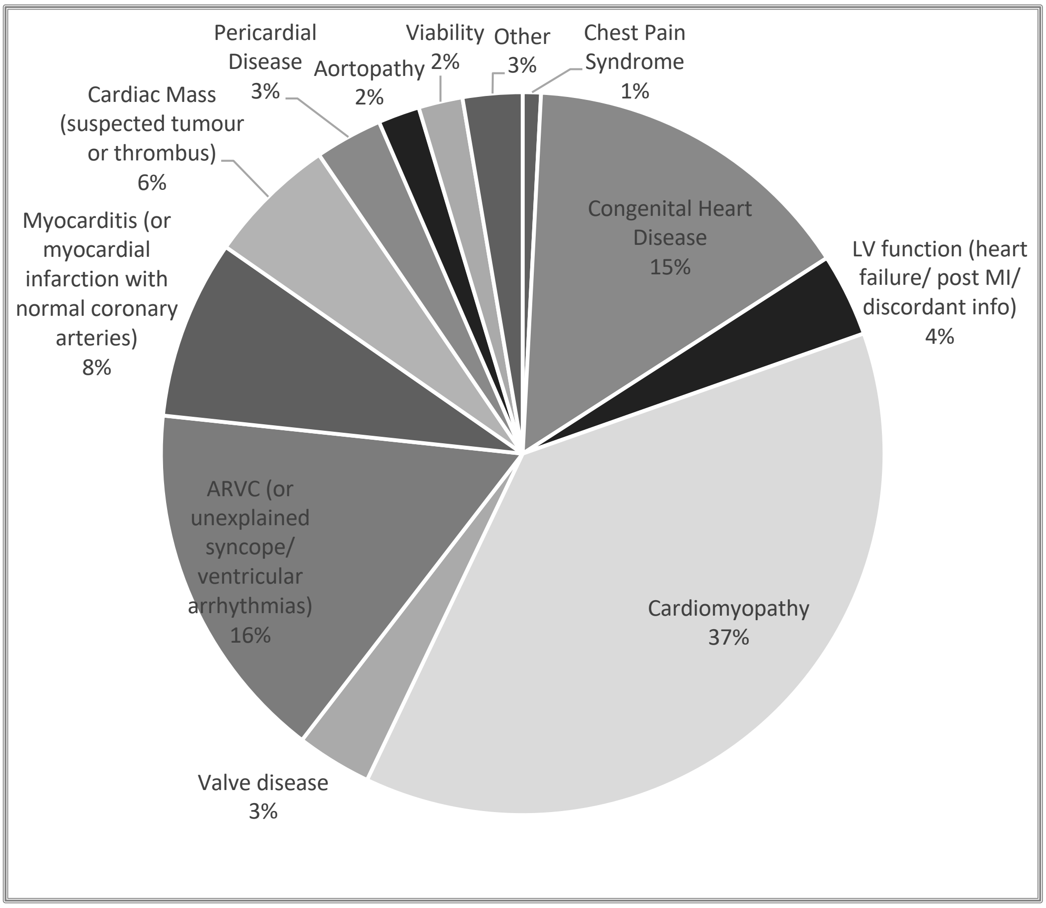


Figure 3 – Indications for CMR (SA-CMR)



Abbreviations

ACCF: American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria working Group

ACR: American College of Radiology

ARVC: arrhythmogenic right ventricular cardiomyopathy

ASNC: American Society of Nuclear Cardiology

CAD: coronary artery disease

CMR: cardiovascular magnetic resonance imaging

CT: computerised tomography

CVD: cardiovascular disease

EuroCMR: European Cardiovascular Magnetic Resonance registry

GCMR: Global Cardiovascular Magnetic Resonance registry

GSH: Groote Schuur Hospital

HIV: Human immunodeficiency virus

LVEDV: Left ventricular end diastolic volume

LVESV: Left ventricular end systolic volume

LVEF: Left ventricular ejection fraction

MRI: magnetic resonance imaging

NASCI: North American Society for Cardiac Imaging

RVEDV: Right ventricular end diastolic volume

RVESV: Right ventricular end systolic volume

SA-CMR: South African Cardiovascular Magnetic Resonance registry

SCAI: Society for Cardiovascular Angiography and Interventions

SCCT: Society of Cardiovascular Computed Tomography

SCMR: Society for Cardiovascular Magnetic Resonance

SIR: Society of Interventional Radiology

Chapter 1 – Structured Literature Review

Objectives of literature review

- To review the evolution of cardiovascular magnetic resonance imaging
- To provide an overview on the developments and clinical use of cardiovascular magnetic resonance imaging
- To establish the role of cardiovascular magnetic resonance imaging on a global scale
- To provide a broad overview of the cardiovascular disease burden in South Africa
- To ascertain the role of cardiovascular magnetic resonance imaging in South Africa at present
- To justify the need for further research in cardiovascular magnetic resonance imaging in South Africa

Literature search strategy

The following databases were accessed for literature: Google Scholar, Pubmed and Biomed Central (and individual website for World Health Organization), using a combination of the following terms: "burden of disease", "cardiac magnetic resonance", "cardiovascular disease", "cardiovascular magnetic resonance", "EuroCMR", "magnetic resonance imaging", "protocols" "registry", "South Africa". Studies referenced from the articles found in the search were also reviewed and included in the literature review if relevant. Due to a paucity of South African publications related to cardiovascular magnetic resonance imaging, editorials and webpages were utilised, if applicable.

Literature summary

<u>Cardiovascular magnetic resonance: Background</u>

Cardiovascular magnetic resonance (CMR) imaging is a state-of-the-art imaging modality that has greatly evolved over the past 30 years and has significantly impacted cardiovascular clinical practice. Although the rotating magnetic field was discovered by Nikola Tesla in 1885, it took nearly a century before the first nuclear magnetic resonance image was produced by Lauterbur in 1973. These two-dimensional imaging strategies where subsequently utilised by Peter Mansfield and Andrew Maudsley in 1977 to create the first image of *in vivo* human anatomy. By the 1980s there was immense interest in the field and this brought about the advent of magnetic resonance imaging (MRI) as a clinical tool.[1]

The first notable mention of cardiovascular or cardiac magnetic resonance (CMR) imaging was in 1981 when Hawkes *et al*. published a paper on the use of MRI to capture static graphics of the normal human heart.[2] Dynamic imaging of the heart soon followed, with initial visualisation of a live rabbit heart in 1982 and thereafter images of human hearts in 1983.[3][4] Due to the challenges of imaging an organ in motion, technology for cardiac imaging took longer to develop.[5] Whereas previously it was difficult to utilise and extremely time-consuming; in recent years, MRI technology has undergone significant advances. Subsequently, MRI has evolved into a clinically useful imaging tool in diagnostic medicine and in both clinical and basic science research. There have been marked improvements in scanning methods, increasing field strength, sequences for optimal image acquisition, radio-frequency coil design, and software programs for post-processing and analysis, all resulting in shorter imaging time, improvement in image quality and greater acceptance of MRI as the ‘gold standard’ imaging tool for many clinical contexts.

Cardiovascular magnetic resonance: Clinical utility

With the significant advances in CMR as an imaging modality and the overcoming of hurdles related to cardiac motion, CMR now provides unparalleled information relating to cardiovascular medicine. CMR provides an array of anatomical, pathological and functional information using high spatial and temporal resolution and image contrast along with haemodynamic assessment and tissue characterisation.[6] It is a safe imaging modality that is not only non-invasive but avoids the hazards of ionising radiation.

CMR plays an essential role in the diagnosis of cardiac disease and provides an answer to the majority of questions during a single examination.[7] It has the capability of providing more combined information about cardiac morphology, chamber size, mass, regional and global function, oedema, focal and diffuse fibrosis, flow and haemodynamics, viability, energetics and lipidosis, than any other imaging modality. Applying different CMR modules for both left and right ventricular structure and function, as well as the appropriate use of gadolinium, first pass perfusion and late gadolinium enhancement (LGE) modules allows for evaluation of normal cardiac function as well as specific cardiac pathology.[8][9] Further, CMR angiography provides a non-invasive approach to diagnosing pathology of the vasculature. Importantly, CMR, as well as the use of gadolinium, is safe and does not involve ionising radiation or radioactive substances.[5][10]

Current recommendations for CMR have been established by an expert consensus panel and the usefulness is based not only the procedure providing clinically relevant information but also being appropriate as a first-line imaging technique.[11][12][13]

CMR can be utilised for both congenital and acquired heart and vascular disease. In patients with congenital heart disease, despite echo remaining the more readily available and cost effective imaging modality, CMR is the preferred technique in children, adolescents and adults as it can illustrate the anatomical pathology completely, allowing for assessment of shunt size, anomalies of the atria, ventricles, valves and arteries. Furthermore, specific protocols to shorten the acquisition period have been provided to ensure imaging quality remains optimal in younger patients who have faster heart rates.[14]

In the case of acquired vascular disease, CMR can readily be utilised for assessment of disease in both the aorta and peripheral vessels. The main indications for CMR in coronary artery disease are for the assessment of global ventricular function and mass, myocardial viability and the detection and assessment of acute and chronic myocardial infarction.[11] Compared to standard angiography, which illustrates coronary artery patency, CMR studies show the downstream microvascular blood flow within the myocardium and therefore allows for risk stratification in patients undergoing perfusion studies or vasodilator stress CMR.[15][16]

CMR is further indicated for patients with pericardial disease, cardiac tumours and cardiomyopathies (including dilated, hypertrophic, restrictive, arrhythmogenic cardiomyopathies, left ventricular non-compaction and overlap syndromes). Valvular heart disease can readily be assessed with visualisation of all parts of the valve (papillary muscles, leaflets and chordae tendinae) throughout the cardiac cycle. CMR provides assessment of cardiac chamber anatomy and function, severity of stenotic lesions as well as quantification of regurgitation.[11][17]

With its vast use in diagnosis of cardiac pathology, CMR has been described as a "one-stop-shop" and much research has gone into establishing its current role in clinical practice.

Cardiovascular magnetic resonance: Global standing

Since great advances were rapidly being made in the field of magnetic resonance, and specifically CMR; in 1996, the Society for Cardiovascular Magnetic Resonance (SCMR) was established. SCMR goals were to further develop CMR through education, quality control, research, and training. This initiative led to the creation of the Journal of Cardiac Magnetic Resonance (JCMR) in 1999. In 2013, seventeen years after the establishment of SCMR, results from the first multi-national CMR registry were produced which brought to light the clinical value of this powerful imaging tool.

The first multi-national registry pertaining to CMR was the European Cardiovascular Magnetic Resonance registry (EuroCMR) of which the results were published in January 2013. Although CMR is routinely used in the European and American settings, prior to this study, the clinical value of CMR regarding impact on decision-making and patient safety was not well understood.[18] EuroCMR consisted of a multi-center registry of 27,000 patients from 15 centres in 15 countries in order to include a multi-national and multi-ethnic population. Its purpose was to establish the indications for CMR in Europe, assess image quality, the safety of the procedure and the impact on clinical management. Prospective follow-up of suspected CAD (coronary artery disease) and HCM (hypertrophic cardiomyopathy) was also assessed to highlight the prognostic potential of CMR in these subsets.[19]

Outcomes of EuroCMR illustrated that the most important indications for CMR in Europe were risk stratification in suspected CAD (34.2%), work-up of myocarditis and cardiomyopathies

(32.2%), and the assessment of myocardial viability (14.6%). EuroCMR further demonstrated that CMR was a safe technique: 96.3% of all CMR procedures were complication free, with mild complications occurring in 3.6% and severe in 0.026% of patients. All severe complications were related to stress perfusion testing. Regarding image quality, good or diagnostic image quality was achieved in 88% of patients, moderate quality in 10.3% and poor or non-diagnostic in 1.7% of patients.[19] The importance, however, of SCMR-trained personnel in producing good quality images was highlighted by the Greek CMR experience where 65% of initial diagnosis made by SCMR-untrained personnel made no impact compared to results after re-evaluation by SCMR personnel where imaging needs where satisfied in 83% of patients.[7]

EuroCMR further showed a significant impact on clinical management of 61.8% of patients that underwent CMR as it resulted either in a new diagnosis being made or in change in current treatment, with 45% of patients being worked up for suspected CAD avoiding angiography. Lastly, the interim analysis of the prognostic value of CMR in suspected CAD and HCM illustrated that patients who had a normal CMR in the work-up for CAD had a major adverse event rate of 1.0% per annum compared to 2.7% in the group with an abnormal CMR. In patients with HCM, the absence of late gadolinium enhancement (LGE) was linked to an event rate of 2.2% compared to 4.3% in patients with LGE.[19]

The creation of EuroCMR fueled the drive for more research into the utilisation of CMR as an imaging modality, with JCMR publishing 109 articles in 2013, 102 in 2014, and 116 in 2015.[20][21] Further publications from the EuroCMR registry highlighted the impact of CMR on clinical decision making in heart failure patients (where an entirely new diagnosis was made in 30% of cases and a change in clinical management occurred in 52% of patients)[22] and the cost benefits of in-patient CMR versus in-patient coronary angiography.[23]

With the evolution of CMR and the establishment of multiple, other, smaller-scale registries worldwide, SCMR further initiated and developed a Global Cardiovascular Magnetic Resonance Registry (GCMR). In 2017, the goals, rationale and data infrastructure of GCMR were published, highlighting the vision of GCMR, which is "to provide a central, representative collective platform to demonstrate the impact of clinical CMR applications on patient care and on how CMR's diagnostic and prognostic value impact patient management". GCMR has enrolled 45 centres, of which 17 have signed the participating agreement. South Africa is included in this subset however is yet to contribute clinical data.[24] Furthermore, at present no results from SA-CMR have been published and its impact on cardiovascular disease in South Africa remains undefined. (Figure 1. illustrates SA-CMR in relation to other milestones in the evolution of CMR).

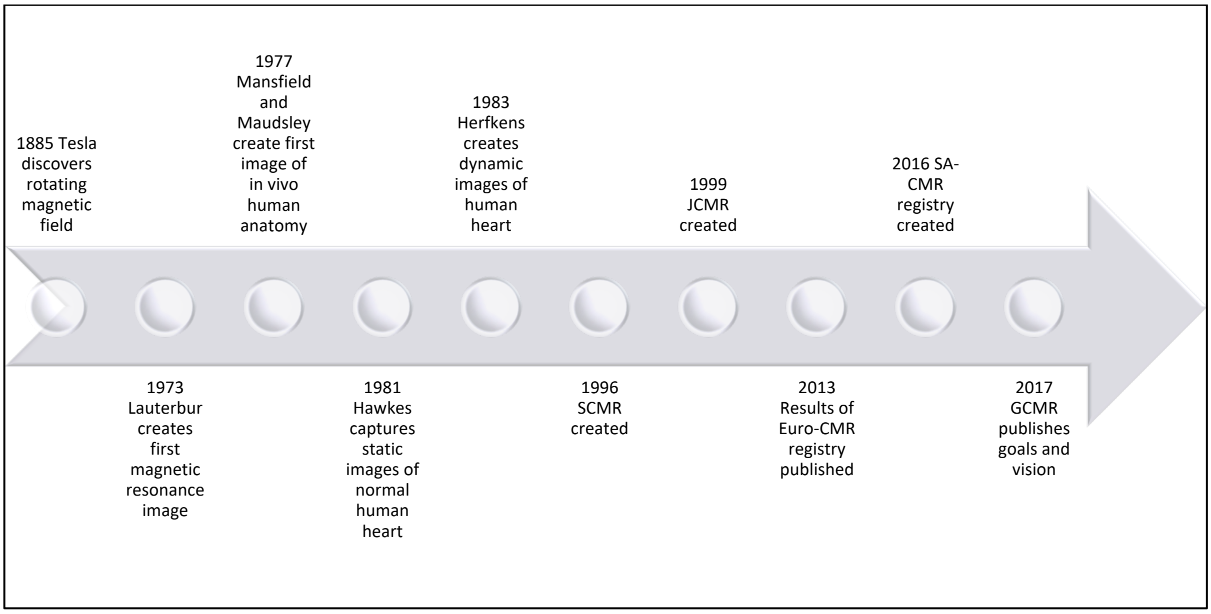


Figure 1: Timeline representing the milestones in CMR. ***SCMR: Society of Cardiovascular Magnetic Resonance, JCMR: Journal of Cardiovascular Magnetic Resonance, EuroCMR: European Cardiovascular Resonance, SA-CMR: South African Cardiovascular Magnetic Resonance, GCMR: Global Cardiovascular Magnetic Resonance***

Cardiovascular disease burden in South Africa

At present the global burden of cardiovascular disease (CVD) is escalating, with CVD currently being ranked as the leading cause of death worldwide and the second leading cause of death in most African countries.[25] Furthermore, the majority of individuals affected are from low- to middle-income countries, with 78% of global mortality and 86% of mortality and morbidity from CVD occurring in developing countries.[26][27]In South Africa, the 2018 World Health Organization (WHO) update illustrated that noncommunicable diseases accounted for more than 50% of deaths and of this 19% were from cardiovascular disease (Figure 2).[28] In addition, CAD predominates as the leading cause of death amongst Caucasian and Indian populations in South Africa.[29] In 1976, Mokhobo had already illustrated the presence of hypertension in rural African populations, and subsequently, in 1982, Seedat *et al* showed urban/rural differences in a similar study, with the prevalence of hypertension being higher in urban populations owing to an increase in risk factors and urbanisation. At that stage, Seedat *et al* had already suggested the implementation of preventative and therapeutic programs.[30][31] Over the past few decades, this rapid epidemiological transition characterised by an increase in socioeconomic state and urbanisation has resulted in further exposure to unfavorable lifestyle behaviour, tobacco use, human immunodeficiency virus (HIV) infection and psychosocial as well as economic stressors. Gersh *et al* describe this exposure as a 'hostile' cardiovascular environment which they fear may lead to an epidemic in the developing world.[32]

South Africa not only suffers the burden of CAD attributable to lifestyle and modifiable factors, but experiences a high burden of CVD from other causes as well. Keates *et al* highlighted the epidemiological profile of CVD in Africa, illustrating that South Africa and other African countries not only bear the weight of increasing CAD but also diseases such as rheumatic heart

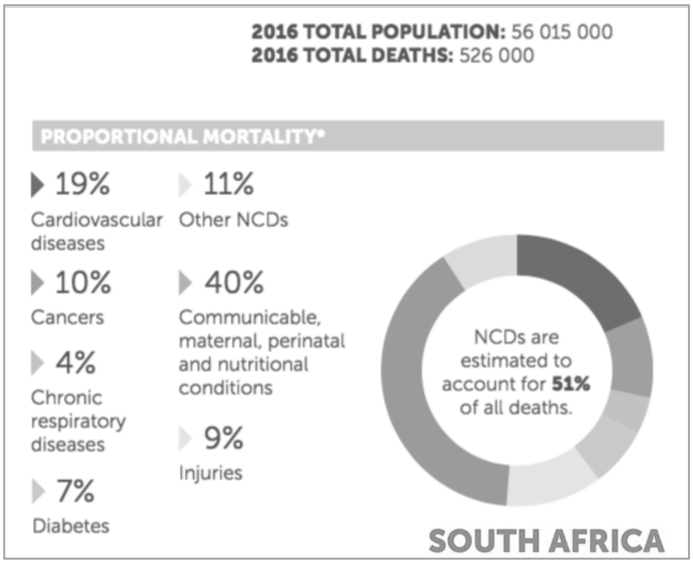


Figure 2: World Health Organization – *Non-communicable Diseases Country Profiles,* 2018. [www.who.int]

disease (RHD) – which although considered historic- remain to be optimally prevented and treated.[33] Although RHD is no longer the most common form of cardiac disease in sub-Saharan Africa (SSA), it still remains prevalent with the current incidence of symptomatic RHD being 24.7 per 100,000 population per annum among adults and the prevalence of asymptomatic RHD being up to 20.2 cases per 1000 school children.[34] Other causes of CVD in South Africa include cardiomyopathies, congenital heart disease, pericardial disease (mostly from tuberculosis), dysrhythmias, HIV-related cardiomyopathies, and heart failure.[33] Additional factors contributing to cardiac failure in SSA included hypertensive heart disease (more frequently in younger African patients) and chronic lung disease.[35]

South Africa currently carries a high burden of CVD with a wide-spectrum of pathologies ranging from CAD to RHD to cardiomyopathies. Considering this, prevention, diagnostic and management strategies are imperative in addressing the approaching epidemic. Resources are limited, and efforts should be made to find modalities that are not only cost-effective but that significantly impact the disease process in these patients. The use of CMR as an imaging modality in the developed world has been shown to greatly impact patient management. Whether this modality can impact cardiovascular disease in the developing world is yet to be ascertained.

Cardiovascular magnetic resonance: Current standing in South Africa

Cardiovascular magnetic resonance imaging is a rapidly advancing imaging modality. On a global scale much interest has been shown in the field, with research highlighting its use in the clinical setting. Ongoing CMR development and improvement in software and hardware has resulted in its use in routine clinical practice in Europe and North America. The extent of this evolution has even resulted in the ACC/AHA/AAP guidelines recommending that every adult and paediatric cardiology fellow be trained in CMR in order to keep up with the demand for CMR-trained physicians.[36][37] In Africa, however, there is significant underutilisation of this non-invasive technique[38] and minimal training is offered in the field. The University of Cape Town is the only centre on the African continent with a fellowship program in CMR.

South Africa currently has 128 MRI machines in use, throughout the country, with approximately 80% of these located in the private sector. Most of these MRI scanners have a field strength of 1.5T, with a very small proportion with 3T magnets. Most of the MRI scanners, situated within the private sector, are owned by radiology practices, and are used exclusively for diagnostic imaging. There are only two units in South Africa, both located in Cape Town, with an established CMR research program: - the Cape Universities Brain Imaging Centre (CUBIC), a collaboration between Medical Research Council, University of Cape Town and Stellenbosch University located at the University of Cape Town; and the University of

Stellenbosch. Incidentally, these two universities are also the only ones conducting regular CMR research on the entire African continent. This is likely to change in the near future as several other centres in the country have clinicians now trained in CMR.

Data pertaining to CMR in South Africa is limited and there are currently very few published articles relating to the field. South African research published in the JCMR is either related to CMR imaging specifications or to specific clinical subsets. Burger *et al* highlighted a novel non-rigid elliptical model for subject specific motion correction for respiratory motion,[39] whereas the Auger and Zhong produced articles related to quantifying right ventricular strain, motion and myocardial mechanics as well the evaluation of 2D and 3D cine DENSE (Displacement Encoding with Stimulated Echoes) imaging.[40][41] Specific clinical subsets that Ntusi *et al* investigated included patients with tuberculosis pericarditis with or without HIV-co-infection: illustrating a unique category of patients that would not have been assessed in the developed world.[42] Despite these studies, at this point, however, there remains no research pertaining to larger cohorts and the overall use of CMR in the South African setting remains undefined. Ntusi and colleagues in the UK have recently published on the use of CMR in pregnancy, including data from South Africa.[43]

The need for further research in South Africa

There is a paucity of CMR research centres on the African continent. The drawbacks relating to CMR in South Africa include limited infrastructure, expertise, skills and personnel.[44] In 2015, the Radiology Society of South Africa (RSSA) in collaboration with SCMR hosted the first CMR course in South Africa in attempt to increase the number of trained radiologists and initiate a local training program. Following this course; numerous smaller workshops run by CUBIC UCT were established, aiming at creating training opportunities. Until recently, however, South African clinicians were still required to train in centres abroad. Since 2016, Ntusi and colleagues have established an annual South African CMR congress, which includes modules for level I and II certification, to improve local training in CMR. More recently, UCT has started offering clinical and research fellowships in CMR.

Compared to the European and American settings, CMR in South Africa is not readily accessible and, in many settings, is far from a routine investigation, with echocardiography, nuclear scintigraphy and invasive angiography predominating as primary imaging modalities for CVD. In addition, high cost has further limited the use of CMR,[5] despite the fact that cost analysis of the EuroCMR registry showed cost savings compared to outpatient coronary angiography.[22]

With the rising incidence of CVD in Africa and the limited resources available, there is an increasing need for appropriate cardiac investigations and interventions. CMR has been shown to be a safe, non-invasive modality that not only provides diagnostic information but also significantly impacts clinical management. Currently, there is a paucity of data on the clinical use and indications of CMR in South Africa. In 2016 data collection commenced for the first South African CMR registry. The rationale behind the establishment of the SA-CMR registry was to serve as an initial attempt to address these gaps in knowledge in a systematic fashion. This interim analysis aims to glean insights into the clinical indications and use of CMR in the South African population and whether its role as an imaging modality will have positive outcomes on patient care in South Africa.

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Chapter 2- Publication- Ready Manuscript

The South African Cardiovascular Magnetic Resonance (SA-CMR) Registry: An Interim Analysis of Clinical Utility, Indications and Baseline Characteristics of Patients Undergoing CMR in a Single Centre in South Africa

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Abstract

Background

The South African Cardiovascular Magnetic Resonance (SA-CMR) registry was founded in 2016 with a view to gain insight into cardiovascular magnetic resonance imaging (CMR) in the South African setting. This interim analysis of SA-CMR aimed to establish the clinical use and indications for CMR, to assess the quality and safety of CMR, to the assess the baseline demographic and clinical characteristics of the cohort, and to determine the impact on clinical management. This study is largely modelled on European Cardiovascular Magnetic Resonance (EuroCMR) registry, a multi-national European registry, which highlighted the impact of CMR in the clinical setting.

Methods

This study reports on a single-center experience of the founding site for the SA-CMR registry that consists of both retrospective and prospective data. The retrospective arm consists of patients that underwent CMR at Groote Schuur Hospital from its introduction in 2005 to April 2017. This interim analysis is a descriptive study of the first 1,142 patients in the retrospective arm.

Results

Of the indications for use of CMR in South Africa, the ascertainment of the presence of cardiomyopathies or their delineation accounted for 54% scans performed, followed by 15% for congenital cardiac anomalies. The average age of patients undergoing CMR was 41 years old and there was a slight female preponderance (52.65% vs. 47.32%). Image quality was diagnostic in 99% of cases and CMR was shown to be safe with mild, adverse contrast reactions only occurring in 2 patients (0.18%) – of which none were fatal. 34% of scans revealed an

alternative diagnosis which subsequently resulted in an alteration in the clinical management of the patient.

Conclusion

This interim analysis of SA-CMR showed that, in the South African setting, CMR was utilised predominantly for investigation of cardiomyopathies. Image quality was in the vast majority of cases and SA-CMR further supported CMR as a safe imaging technique which assisted in diagnostics and clinical management of cardiovascular disease in South Africa.

Condensed Abstract

The South African Cardiovascular Magnetic Resonance (SA-CMR) Registry was established to delineate the role of CMR in South Africa. The purpose of this interim analysis was to assess the clinical use and indications for CMR, to assess the quality and safety of CMR, to the assess the baseline demographic and clinical characteristics of the cohort, and to determine the impact on clinical management. The data showed, in 1,142 patients, that the predominant indication for CMR is the investigation of cardiomyopathies. In the South African setting, CMR image quality is diagnostic in 99% of cases, it is a safe imaging modality, and it has had a major impact on clinical management.

Keywords

Cardiovascular magnetic resonance, registry, South Africa, cardiovascular imaging, magnetic resonance imaging

Background

Cardiovascular magnetic resonance (CMR) imaging is a state-of-the-art imaging modality that has greatly evolved over the past 30 years and has significantly impacted cardiovascular clinical practice.[1] EuroCMR was the first multi-national registry to give insight into the clinical utility and impact of CMR as an imaging tool.[2] Subsequent to this, the Global Cardiovascular Magnetic Resonance Registry (GCMR) was created with South Africa being included as one of the 45 participating centers.[3] Despite CMR being utilised in South Africa, at present, the role of CMR and its impact on cardiovascular disease (CVD) in the South African context remains undefined. The South African Cardiovascular Magnetic Resonance (SA-CMR) registry was therefore established in 2016 to address whether its role as an imaging modality in a resource-limited setting would have positive outcomes on patient care in South Africa. This interim analysis sought to assess the clinical indications, baseline characteristics, image quality, safety and clinical impact of CMR in the first 1,142 patients in the retrospective arm of this registry.

Methods

Study design and population

The SA-CMR registry consists of both retrospective and prospective data. The retrospective arm consists of all patients that underwent CMR at Groote Schuur Hospital (GSH), Cape Town, South Africa, from its introduction in 2005 to April 2017. As the registry is ongoing, this interim analysis assesses the 1,142 patients that fall into the retrospective arm only. Patients included in the registry and for whom CMR is clinically indicated were referred by their attending physician or cardiologist according to the report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria working Group, American College of Radiology, Society of Cardiovascular Computed

Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology (ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR) consensus appropriate-use criteria for CMR.[4] The registry includes all patients that underwent CMR at GSH, thus there are no exclusion criteria.

Research procedures and data management

Retrospective data was extracted from medical records at GSH and manually transposed onto a password protected database. Prospective CMR scans were recorded on data collection sheets and added directly to the registry database for future study (not included in this interim analysis). Data and patient details were only accessible to members of the research team involved in SA-CMR. The lead investigator was responsible for data interpretation and analysis, which was supervised by the principal investigator who is Level III SCMR trained and accredited. Data interpretation and analysis did not involve patient names or identification in order to maintain anonymity. The SA-CMR registry and interim analysis had been reviewed by the University of Cape Town Human Research Ethics Committee and study conduct and data management was approved.

Variables and Definitions

The variables assessed included patient demographics, clinical features; as well as the indications for, quality of, and results of the CMR scans performed (including complications and impact of CMR on patient management). Indications for CMR are grouped according to the "Appropriate Use Criteria" categories.[4] As with EuroCMR, the quality was defined as good, moderate or poor; where good is high image quality which is clearly diagnostic, moderate has some impairment in image quality but is largely diagnostic and poor refers to substantially impaired image quality and is undiagnostic.[5]

Data analysis

This interim analysis is a descriptive breakdown and interpretation of retrospective data collected in the SA-CMR registry. The patient demographics and CMR results were described using percentages and absolute numbers (and range given, where appropriate). Where required, the mean ± standard deviations were used for continuous variables. In the case of skewed distribution, median values and interquartile ranges were used. Values recorded were expressed as a percentage of the available data for that specific variable. No formal hypothesis testing was done, as this is a retrospective review of existing data.

Procedural Characteristics

CMR is performed in keeping with the current South African Heart Association position statement on appropriateness/competency,[6] which is based on American College of Cardiology (ACC) /American Heart Association (AHA) and European Society of Cardiology (ESC) clinical competency statement on cardiac computerized tomography (CT) and CMR,[7] and ACCF/ACR/SSCT/ASNC/NASCI/SIR appropriateness criteria for cardiac CT and CMR.[4] In our institution, CMR is performed and interpreted in consensus fashion by a cardiologist with SCMR training and by an experienced radiologist with an interest in CMR, and done in accordance with the standardised SCMR protocols.[8][9] A gadolinium dose of 0.15 to 0.2 mmol/kg body weight is used. At present, no routine stress perfusion testing is undertaken at GSH, but this is likely to change in the near future.

Results

Baseline demographics

1142 scans performed between 2005 and 2017 were included in this analysis. Table 1 and 2 illustrate the demographic data as well as cardiac parameters. The mean age of patients in the cohort was 41 years, and there was a slight female preponderance (52.68% female vs. 47.32% male).

Clinical indications for CMR

1,142 patients underwent CMR in this period. Clear indications and conclusions were recorded in 862 cases (75%), done for clinical indications, while these were not recorded for the 25% of scans done for research purposes. In South Africa, the main indication for performing CMR was for the diagnosis or delineation of cardiomyopathies (54%, out of a total of 862 recorded indications). This included suspected diagnosis of arrhythmogenic right ventricular cardiomyopathy, unexplained syncope or ventricular arrhythmias. The diagnosis or assessment of congenital heart disease accounted for 15% of scans. A small proportion of patients were investigated for the consequences of coronary artery disease (CAD), with only 1% (n=7) of scans being performed for chest pain syndromes, 4% (n=32) for evaluation of left ventricular function following myocardial infarction (or heart failure patients), and 2% (n=17) performed for viability testing. Indications for CMR in this cohort are illustrated in Figure 1.

Image quality and safety

Image quality was documented in 689 of the scans performed. However, a further 244 scans had a clear diagnosis with no comment on impairment in image quality. It was thus deducted that 90% of scans (n=835) were deemed good or diagnostic, 9% (n=86) were moderate image quality and only 1% (n=12) were poor image quality or undiagnostic.

In the 1,142 patient cohort, there were 2 (0.18%) adverse events. Both events were related to mild gadolinium allergy; one patient developed facial oedema and the other developed a mild bronchospasm: both responded to promethazine and hydrocortisone. There were no severe or fatal complications.

Impact of CMR on patient management

862 scans showed documented conclusions. In 66% (n=571) the indication for imaging was met; where the result either supported the clinical question, clarified the diagnostic uncertainty, or provided further information regarding the known pathology investigated. In 34% (n=291) of scans either an alternate diagnosis was made with subsequent modification of the management plan, or doubt remained surrounding the diagnosis, leading to further diagnostics.

Discussion

This interim analysis of the SA-CMR registry has provided a brief understanding of the role of CMR in the South African context. Its utilisation as a diagnostic modality in a single centre has been predominantly for assessment of structural heart disease in the form of cardiomyopathies, and congenital heart disease. To a much lesser extent, it had been utilised for investigation of CAD, assessment of cardiac viability, and left ventricular function in unexplained heart failure. The CMR image quality was shown to be diagnostic in 99% of cases, and it proved to be a safe imaging modality with minimal complications. Clinical management was impacted in over a third of patients who underwent CMR highlighting its importance as an emerging diagnostic tool in South Africa.

South Africa, like other sub-Saharan countries, bear a significant burden of cardiovascular disease. Over the past few decades, a rapid growth of socioeconomic state and urbanisation in developing countries has resulted in exposure to a ‘hostile’ cardiovascular environment with unfavorable lifestyle behaviour, tobacco use, HIV infection and psychosocial as well as economic stressors.[10] Furthermore, epidemiologically, illnesses such as rheumatic heart disease still account for a significant disease burden. The result is a country that experiences both the weight of CAD attributable to lifestyle and modifiable factors, as well as CVD from other causes such as cardiomyopathy, congenital heart disease, heart failure, dysrhythmias, HIV-related CVD, and pericardial disease. [11] In light of this, diagnostic and management strategies that can address the combination of pathologies in this population are essential when considering the approaching epidemic. SA-CMR has been shown to be an imperative tool in diagnostics of an array of cardiovascular diseases, providing further knowledge and influencing management. CMR, however remains under-utilised in South Africa. Contributing factors include limited infrastructure, expertise, skills and personnel. CMR is furthermore time consuming with both physicians and technologists needing to be actively involved in image acquisition and planning. Colleagues without background knowledge of basic cardiovascular pathology offered during cardiology fellowship training may need to spend time in units offering this specific training. At present efforts are being made through the Radiology Society of South Africa (RSSA), South African Heart Society (in collaboration with SCMR), and the annual CMR Congress of South Africa to improve training and clinical research. Obtaining a better understanding of the role of CMR in South Africa, through SA-CMR, will help to drive these initiatives.

The creation of SA-CMR was largely modelled on the EuroCMR, the first multi-national registry relating to CMR, which consisted of data from multiple centres in Europe and highlighted the role of CMR as a clinical utility. [5] When comparing the results of the SA-CMR interim analysis to EuroCMR, it has shown that overall, the use of CMR is used in a relatively young population of patients with CVD. Furthermore, the main indications for CMR were for the investigation of cardiomyopathies and congenital heart disease. This contrasts to the European setting where CMR is predominantly used in an older age group (mean 60 years) and the main indications included risk stratification in suspected CAD/ ischaemia in known CAD, the work-up of myocarditis and cardiomyopathies and the assessment of myocardial viability.[2] The disparities in results are likely due to lack of access of CMR in most centres and the lack of exposure of older cardiologists to CMR training coupled with the preference for use of invasive angiography for assessment of likely CAD. In the European setting, CMR is utilised as a clinical routine in many centres, whereas in South Africa it is a limited resource with echocardiography and angiography prevailing as primary diagnostic modalities in cardiology. CMR is therefore being predominantly used only in special diagnostic circumstances where other imaging strategies have not yielded the required results. Despite studies showing some cost benefits of CMR versus angiography,[12] [13] as of yet, no data regarding cost evaluation is available in South Africa. Consequently, justifying the use of CMR above angiography for the diagnosis of suspected CAD remains a challenge with very few scans being performed for chest pain syndromes or viability testing. Moreover, SA-CMR supported CMR as a safe imaging modality with only 2 minor adverse events occurring. Its use as an alternative for invasive diagnostics may potentially result in fewer complications and hospitalisations. SA-CMR showed that in a third of patients the management plan was altered, with either a new diagnosis being made or further diagnostics being performed. In the remaining two-thirds of patients the indication was met, with CMR supporting the clinical question, clarifying the diagnostic uncertainty, or providing further information regarding the known pathology investigated. The direct impact on clinical management in EuroCMR however, yielded higher results with CMR changing management in nearly two-thirds of patients. Additionally, in EuroCMR, stress CMR resulted in nearly half of their patients undergoing stress testing avoiding invasive angiography [2]. At present, CMR perfusion stress testing is not available at GSH and may account for the lesser degree of impact on management when compared to EuroCMR. The role of CMR as a modality to reduce invasive techniques in our setting remains to be determined and further research would be valuable in rationalising resources in patients with suspected CAD.

With the rise of CVD in Sub-Saharan Africa, there is a need to reconsider the current diagnostic strategies and potentially relocate resources to provide more accurate and less invasive imaging modalities. This interim analysis of SA-CMR has shown that, in the South African population, CMR may fulfill this role, as an imaging modality that is safe and has positive outcomes on patient care.

Study Limitations

1) This interim analysis included patients from the retrospective arm of SA-CMR dating back to 2005. In the earlier years record keeping was not optimal and some data was missing in this cohort. This study suffers from all the inherent drawbacks of a retrospective design. Future analysis of the results of the prospective arm may change significantly due to both adequate record keeping and expansion of the referral pattern.
2) Multiple scans were performed in patients with HCM or ARVC to answer a specific research question thereby contributed to the quarter of patients without a formal conclusion in the report. Percentages calculated in this interim analysis were based on the available data therefore the results do not represent the full cohort.
3) Due to a special interest in ARVC research at GSH a higher number of scans may have been performed for that indication thereby skewing results.

4) As the data from this single-centre reflects clinical experience in a single tertiary centre, there is inherent referral bias in the results, which may not reflect the reality in primary and secondary levels of care. Furthermore, institutional practice, clinical investigational pathways and resource availability may vary in tertiary centres resulting in generalizability of results. Future research involving more centres to reflect different clinical practices will hopefully provide a better perspective of trends in South Africa.

Conclusions

This interim analysis of SA-CMR is the first known study to illustrate the clinical use and indications of CMR in the South African setting. 1,142 patients who underwent CMR at Groote Schuur Hospital in Cape Town were assessed. SA-CMR has been able to show that the main indications for CMR in South Africa are the investigation of cardiomyopathies, and congenital heart disease. SA-CMR further showed that image quality was comparable international reports, with 99% of images being diagnostic. It further supports CMR as a safe imaging technique which has assisted in diagnostics and clinical management of patients with CVD in South Africa.

List of abbreviations

ACCF: American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria working Group

ACR: American College of Radiology

ARVC: arrhythmogenic right ventricular cardiomyopathy

ASNC: American Society of Nuclear Cardiology

CAD: coronary artery disease

CMR: cardiovascular magnetic resonance imaging

CT: computerised tomography

CVD: cardiovascular disease

EuroCMR: European Cardiovascular Magnetic Resonance registry

GCMR: Global Cardiovascular Magnetic Resonance registry

GSH: Groote Schuur Hospital

HIV: Human immunodeficiency virus

LVEDV: Left ventricular end diastolic volume

LVESV: Left ventricular end systolic volume

LVEF: Left ventricular ejection fraction

MRI: magnetic resonance imaging

NASCI: North American Society for Cardiac Imaging

RVEDV: Right ventricular end diastolic volume

RVESV: Right ventricular end systolic volume

SA-CMR: South African Cardiovascular Magnetic Resonance registry

SCAI: Society for Cardiovascular Angiography and Interventions

SCCT: Society of Cardiovascular Computed Tomography

SCMR: Society for Cardiovascular Magnetic Resonance

SIR: Society of Interventional Radiology

Declarations

Ethics approval and consent to participate

Both the SA-CMR Registry as well as this interim analysis have been approved by the local Human Ethics and Research Committee (HREC REF R055/2015 and REF 771/2016). As data for the interim analysis was extracted anonymously from the SA-CMR registry, informed consent was not required.

Consent for publication

This manuscript does not contain identifying data from any individual person and all data collected remained anonymous.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The lead investigator, Dr CBI Coccia, was responsible for both data interpretation and analysis, as well as for drafting the manuscript. This was supervised by the principal investigator, Prof

N Ntusi, who is SCMR-trained. Both authors reviewed the draft and approved the final manuscript.

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Tables

Table 1 – Demographic Data of SA-CMR Cohort

n= 1142

Patient Characteristics	
Age (years), mean ± SD	41± 16
Female sex, %	52.68%
Male sex, %	47.32%
Height (cm), mean ± SD	167.3± 11.8
Weight (kg), mean ± SD	73.4± 20.4
BSA (m^2), mean ± SD	1.84± 0.28

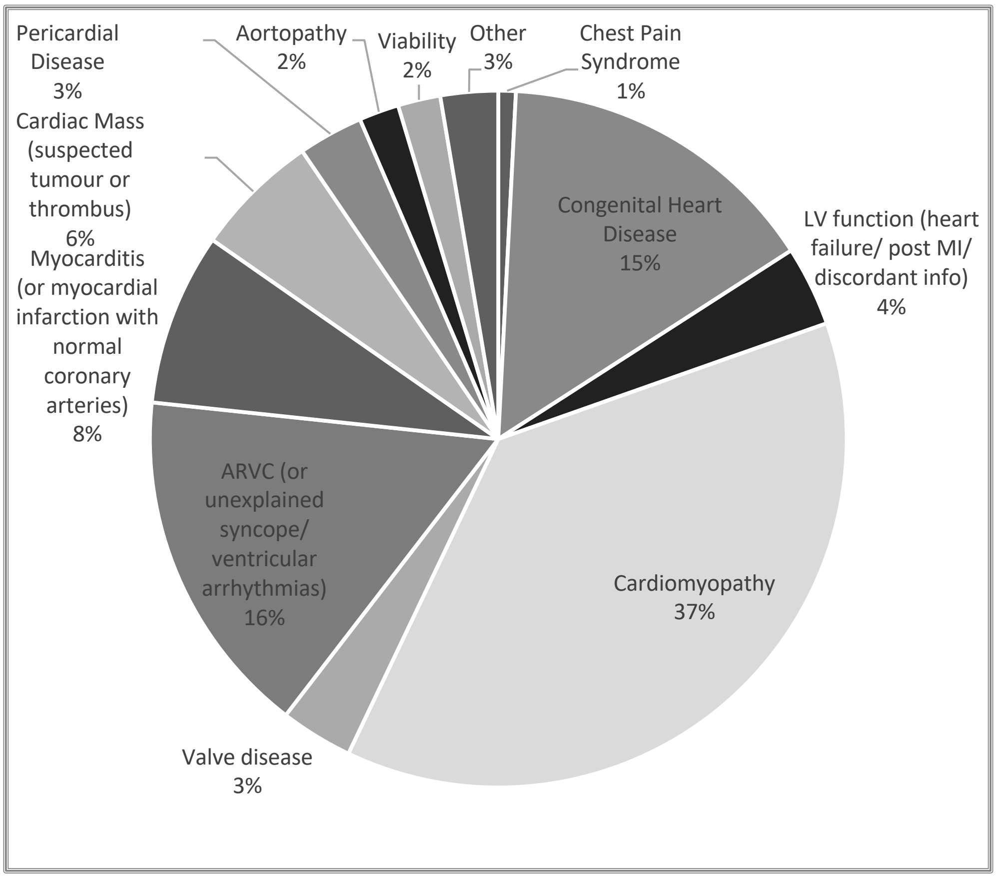
Table 2 – Imaging Data of SA-CMR Cohort

Cardiac parameters		
LVEDV (ml)	169.6	± 78.4
LVESV (ml)	84.2	± 75.1
LVEF (%)	55.3	± 17.6
LV mass (gram)	133.6	± 62.5
RVEDV (ml)	169.9	± 74.2
RVESV (ml)	87.7	± 60.1
Image quality		
Good	90%	
Moderate	9%	
Poor	1%	
Indication met	66%	
Altered management plan	34%	

Values are %(n) or mean +- standard deviation

Figures

Figure 1 – Indications for CMR (SA-CMR)



Appendices

Appendix 1: Data collection variables

Demographics

Age

Gender

Clinical Features

Height

Weight

Body Surface Area (BSA)

Cardiac Function

Left Ventricular End Diastolic Volume (LVEDV) (ml)

Left Ventricular End Systolic Volume (LVESV) (ml)

Left Ventricular Ejection Fraction (LVEF) (%)

Left Ventricular Mass (gram)

Right Ventricular End Diastolic Volume (RVEDV) (ml)

Right Ventricular End Systolic Volume (RVESV) (ml)

Image Quality

Good

Moderate

Poor

Indications

Chest pain syndrome

Chest pain syndrome by stress MRI

Congenital heart disease

Left ventricular function (heart failure/ post myocardial infarction/ discordant information)

Cardiomyopathy

Valve disease

ARVC (or unexplained syncope/ ventricular arrhythmias)

Myocarditis (or myocardial infarction with normal coronary arteries)

Cardiac Mass (suspected tumour or thrombus)

Pericardial Disease

Aortopathy

EP or pulmonary vein anatomy

Viability

Research

Other

Impact on clinical management

Indication met

New diagnosis

Appendix 2: Standardised CMR variable collection sheet

LEFT VENTRICLE:

LV EDV (ml)____________ LV ESV (ml)___________ LV SV (ml)___________

LV EF (%)___________ LV mass (g)___________ LV mass index (g/m2)

LV size: ☐Normal ☐Dilated

LV hypertrophy: ☐None ☐Present

LV wall thickness: ☐Septal ☐Anterior ☐Lateral ☐Inferior ☐Apical

☐Regional

☐Septal ☐Anterior ☐Posteriolateral ☐Inferior Submitral ☐Apical

☐Global

Abnormal fat in LV:

☐None ☐Septal ☐Anterior ☐Posteriolateral ☐Inferior Submitral ☐Apical

Thinning of the LV wall:

☐None ☐Septal ☐Anterior ☐Posteriolateral ☐Inferior Submitral ☐Apical

LV wall motion abnormalities:

Description:

☐None ☐Hypokinesia ☐Akinesia ☐Dyskinesia

☐aneurysms ☐Other:

Specify____

Position:

☐Diffuse

☐Septal ☐Anterior ☐Posteriolateral ☐Inferior Submitral ☐Apical

Severity: ☐Mild ☐Moderate ☐Severe

T1W imaging:

T2W imaging:

LGE findings:

Pattern of LGE:

Additional comments:____

RIGHT VENTRICLE:

RV EDV (ml)________________ RV ESV (ml)_______________ RV EF (%)_____________

RV size: ☐Normal ☐Dilated

Abnormal fat in RV:

☐None ☐RVOT ☐Anteroseptal free wall ☐Subtricuspid Posterobasal ☐Apical

RV wall thickness: ☐Septal ☐Free wall ☐Inferior ☐Apical

Thinning of the RV wall:

☐None ☐RVOT ☐Anteroseptal free wall ☐Subtricuspid Posterobasal ☐Apical

RV wall motion abnormalities:

Description:

☐None ☐Hypokinesia ☐Akinesia ☐Dyskinesia

☐aneurysms ☐Other:

Specify____

Position:

☐N/A ☐RVOT ☐Anteroseptal free wall ☐Subtricuspid

Posterobasal ☐Apical

☐Presence of bulges ☐Aneurysms

LGE findings:

Pattern of LGE:

Additional comments:____

Additional structures:

MV ☐Not assessed ☐Absent ☐Stenotic ☐Regurgitant

☐Severity of MR – Grade (1-3+): ________

Other comments;____

AV ☐Not assessed ☐Absent ☐Stenotic ☐Regurgitant

☐Severity of AR – Grade (1-3+): ________

Other comments;____

TV ☐Not assessed ☐Absent ☐Stenotic ☐Regurgitant

☐Severity of TR – Grade (1-3+): ________

Other comments;____

PV ☐Not assessed ☐Absent ☐Stenotic ☐Regurgitant

☐Severity of PR – Grade (1-3+): ________

Other comments;____

LA ☐Not assessed ☐Normal ☐Dilated LA area: __________ cm2

LA dimension: __________ cm

Other comments:____

RA ☐Not assessed ☐Normal ☐Dilated RA area: _________ cm2

Other comments:____

Aorta ☐Not Assessed ☐Normal

☐____

Annulus: ________cm Sinuses: ________cm STJ:________cm

AscAoMPA:________cm Arch:________cm

DescAoMPA:________cm

PA ☐Not Assessed ☐Normal

☐____

MPA:________cm RPA:________cm LPA:________cm

SVC ☐Not Assessed ☐Normal ☐Dilated

Other comments: ____

IVC ☐Not Assessed ☐Normal ☐Dilated

Other comments: ____

Pericardium ☐Not Assessed ☐Normal ☐Thickened ☐Effusion

Other:____

Appendix 3: HREC approval for SA-CMR Registry

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 April 2016

REF NO: R055/2015

Dr N Ntusi
Cardiology
E:7
NGSH

Dear Dr Ntusi

PROJECT TITLE: South African Cardiovascular Magnetic Resonance (SA-CMR) REGISTRY SITE Groote Schuur Hospital, Cape Town

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 8 April 2016.

The HREC has **approved** the registration of your registry.

Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

The registration of this database is valid until **30 April 2019.**

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Appendix 4: HREC approval for study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

03 November 2016

HREC REF: 771/2016

Dr N Ntusi
Department of Medicine / Cardiology
J-Floor
OMB

Dear Dr Ntusi

PROJECT TITLE: THE SOUTH AFRICAN CARDIOVASCULAR MAGNETIC RESONANCE (SA-CMR) REGISTRY: AN INTERIM ANALYSIS OF CLINICAL UTILITY, INDICATIONS AND BASELINE CHARACTERISTICS OF PATIENTS UNDERGOING CMR IN SOUTH AFRICA (MMeD-candidate-C Coccia)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Cecilia Coccia will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that institutional approval is required from Groote Schuur Hospital.
Formal approval from the HREC is subject to appropriate institutional approval being obtained from Groote Schuur Hospital.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 771/2016

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 771/2016

Appendix 5: **Journal of Cardiovascular Magnetic Resonance Instructions to Authors**

Journal of Cardiovascular Magnetic Resonance

Aims and scope

Journal of Cardiovascular Magnetic Resonance (JCMR) publishes high-quality articles on all aspects of basic, translational and clinical research on the design, development, manufacture, and evaluation of cardiovascular magnetic resonance (CMR) methods applied to the cardiovascular system. Topical areas include, but are not limited to:

- New applications of magnetic resonance to improve the diagnostic strategies, risk stratification, characterization and management of diseases affecting the cardiovascular system.
- New methods to enhance or accelerate image acquisition and data analysis.
- Results of multicenter, or larger single-center studies that provide insight into the utility of CMR.

Basic biological perceptions derived by CMR methods.

Fees and funding

Article-processing charges

Open access publishing is not without costs. Journal of Cardiovascular Magnetic Resonance therefore levies an article-processing charge of £1370/$2145/€1745 for each article accepted for publication. We routinely waive charges for authors from low-income countries. For other countries, article-processing charge waivers or discounts are granted on a case-by-case basis to authors with insufficient funds. Authors can request a waiver or discount during the submission process. For further details, see our article-processing charge page.

JCMR is the official journal of the Society for Cardiovascular Magnetic Resonance. If the submitting author is a Member of the Society, the cost of the article-processing charge is covered by the membership, and no further charge is payable. Members can request this by using the Society's membership number in the payment page. This number can be obtained from the society.

For non-members of the Society, some or all of the publication cost may be covered if the corresponding author's institution participates in our open access membership program (more details available on the membership page).

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Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

◦ or for non-clinical or non-research studies a description of what the article reports

- list the full names, institutional addresses and email addresses for all authors

◦ if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below

- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

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If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and

its supplementary information files].

- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each author's competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section.

Guidance and criteria for authorship can be found in our editorial policies.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission.

Examples of the BioMed Central reference style are shown below. Please ensure that the reference style is followed precisely.

See our editorial policies for author guidance on good citation practice.

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link (e.g. for blogs) they should be included in the reference.

Example reference style:

Article within a journal

Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Med. 2013;11:63.

Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

Online First chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

Figures, tables additional files

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- Figures should be provided as separate files, not embedded in the main manuscript file.
- Each figure of a manuscript should be submitted as a single file that fits on a single page in portrait format.
- Tables should NOT be submitted as figures but should be included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
- Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order.
- Figures should be uploaded in the correct orientation.
- Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.
- Figure keys should be incorporated into the graphic, not into the legend of the figure.
- Each figure should be closely cropped to minimize the amount of white space surrounding

the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site. For more information on individual figure file formats, see our detailed instructions.

- Individual figure files should not exceed 10 MB. If a suitable format is chosen, this file size is adequate for extremely high quality figures.
- **Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures (or tables) that have previously been published elsewhere.** In order for all figures to be open access, authors must have permission from the rights holder if they wish to include images that have been published elsewhere in non open access journals. Permission should be indicated in the figure legend, and the original source included in the reference list.

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- EPS (suitable for diagrams and/or images)
- PDF (suitable for diagrams and/or images)
- Microsoft Word (suitable for diagrams and/or images, figures must be a single page)
- PowerPoint (suitable for diagrams and/or images, figures must be a single page)
- TIFF (suitable for images)
- JPEG (suitable for photographic images, less suitable for graphical images)
- PNG (suitable for images)
- BMP (suitable for images)
- CDX (ChemDraw - suitable for molecular structures)

For information and suggestions of suitable file formats for specific figure types, please see our author academy.

Figure size and resolution

Figures are resized during publication of the final full text and PDF versions to conform to the BioMed Central standard dimensions, which are detailed below.

Figures on the web:

- width of 600 pixels (standard), 1200 pixels (high resolution).

Figures in the final PDF version:

- width of 85 mm for half page width figure
- width of 170 mm for full page width figure
- maximum height of 225 mm for figure and legend
- image resolution of approximately 300 dpi (dots per inch) at the final size

Figures should be designed such that all information, including text, is legible at these dimensions. All lines should be wider than 0.25 pt when constrained to standard figure widths. All fonts must be embedded.

Figure file compression

- Vector figures should if possible be submitted as PDF files, which are usually more compact than EPS files.
- TIFF files should be saved with LZW compression, which is lossless (decreases file size without decreasing quality) in order to minimize upload time.
- JPEG files should be saved at maximum quality.
- Conversion of images between file types (especially lossy formats such as JPEG) should be

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When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.
- Larger datasets, or tables too wide for A4 or Letter landscape page can be uploaded as additional files. Please see [below] for more information.
- Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). Please use the standard file extensions.
- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.
- Tables should not be embedded as figures or spreadsheet files, but should be formatted using 'Table object' function in your word processing program.
- Color and shading may not be used. Parts of the table can be highlighted using superscript, numbering, lettering, symbols or bold text, the meaning of which should be explained

in a table legend.

- Commas should not be used to indicate numerical values.

If you have any questions or are experiencing a problem with tables, please contact the customer service team at info@biomedcentral.com.

Preparing additional files

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As the length and quantity of data is not restricted for many article types, authors can provide datasets, tables, movies, or other information as additional files.

All Additional files will be published along with the accepted article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files, if requested, should be sent by email to the journal's editorial email address, quoting the manuscript reference number. Please do not send patient consent forms unless requested.

Results that would otherwise be indicated as "data not shown" should be included as additional files. Since many web links and URLs rapidly become broken, BioMed Central requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. Do not include any individual participant details. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission. Each additional file should be cited in sequence within the main body of text.

If additional material is provided, please list the following information in a separate section of the manuscript text:

- File name (e.g. Additional file 1)

- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
- Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

Appendix 6: **Approved Protocol**

Study title:

The South African Cardiovascular Magnetic Resonance (SA-CMR) Registry: An Interim Analysis of Clinical Utility, Indications and Baseline Characteristics of Patients Undergoing CMR in South Africa

Internal reference number: M007

Ethics reference number: HREC REF R055/2015 and 771/2016

Date and version number: 19 June 2016, V3

Investigators:

Lead investigator and research co-ordinator: Dr Cecilia Coccia

Principal Investigator: Dr Ntobeko Ntusi

Funding:

National Research Foundation of South Africa grant to Dr Ntusi (TTK14050566787)

Table of Contents

1. Study synopsis

Study Title	The South African Cardiovascular Magnetic Resonance (SA-CMR) Registry: An Interim Analysis of Clinical Utility, Indications and Baseline Characteristics of Patients Undergoing CMR in South Africa
Internal Reference Number	M007
Ethics Reference Number	HREC REF R055/2015
Study Design	Retrospective study
Study Participants	Patients referred for CMR at Groote Schuur Hospital
Number of participants	~1000 patients
Planned study period	12 months

Primary Objectives	• Assess clinical use and indications for CMR
	• Assess image quality
	• Assess baseline characteristics of the cohort
	    • Demographic
	    • Clinical

Secondary Objectives	• Correlate CMR findings with patient demographics and medical history • Impact of CMR on management of patients
Intervention	None

2. Abbreviations

CAD	Coronary artery disease
CMR	Cardiovascular magnetic resonance
CT	Computerised tomography
CUBIC	Cape Universities Brain Imaging Centre
CVD	Cardiovascular disease
EuroCMR	European Cardiovascular Magnetic Resonance Registry
GSH	Groote Schuur Hospital
HCM	Hypertrophic cardiomyopathy
HIV	Human immunodeficiency virus
LGE	Late gadolinium enhancement
MRI	Magnetic resonance imaging
SA-CMR	South African Cardiovascular Magnetic Resonance Registry
SCMR	Society for Cardiovascular Magnetic Resonance

3. Abstract

Cardiovascular magnetic resonance (CMR) is a clinically useful imaging modality that is fast becoming a routine tool in clinical practice. In 2013 the results of the first multi-national registry, EuroCMR, were published. The study highlighted the clinical significance and impact of CMR in Europe. As of yet the role of CMR in the South African context remains undefined and at present there is limited research pertaining to its use. The South African CMR (SA-CMR) registry aims to glean insights into the clinical use and indications for CMR in South Africa as well as to establish its quality, safety and role in altering clinical management. This study aims to provide an interim analysis of the clinical utility, indications and baseline demographic features of patients undergoing CMR in South Africa and forms part of the pilot phase of the SA-CMR registry.

4. Background and rationale

Cardiovascular magnetic resonance (CMR) imaging is a state-of-the-art imaging modality that has greatly evolved over the past 30 years and has significantly impacted cardiovascular clinical practice. Although the rotating magnetic field was discovered by Nikola Tesla in 1885, it took nearly a century before the first image of in vivo human anatomy was created by Peter Mansfield and Andrew Maudsley in 1977. The first nuclear magnetic resonance image was produced in 1973 by Lauterbur. By the 1980s there was immense interest in the field and this brought about the advent of MR imaging (MRI) as a clinical tool.[1] Subsequently, MRI has evolved into a clinically useful imaging tool in diagnostic medicine and in clinical and basic science research. In recent years, MRI technology has undergone significant advances in scanning methods, increasing field strength, sequences for optimal image acquisition, radio-frequency coil design, and software programs for post-processing and analysis, all resulting in shorter imaging time, improvement in image quality and greater acceptance of MRI as the 'gold standard' imaging tool for many clinical contexts. In 1996 the Society of Cardiac Magnetic Resonance (SCMR) was established, with the creation of the Journal of Cardiac Magnetic Resonance (JCMR) in 1999. In 2013, seventeen years after the establishment of SCMR, the first multi-national CMR registry was produced which brought to light the clinical value of this powerful imaging tool.

CMR provides an array of anatomical, pathological and functional information, is non-invasive, and avoids the hazards of ionising radiation. Ongoing CMR development and improvement in software and hardware has resulted in its use in routine clinical practice in Europe and North America. In Africa, however, there is significant underutilisation of this non-invasive technique.[2] South Africa currently has 115 MRI machines in use, throughout the country, with approximately 80% of these located in the private sector. The vast majority of these MRI scanners have a field strength of 1.5T, with a very small proportion with 3T magnets. Most of the MRI scanners, situated within the private sector, are owned by radiology practices, and are used exclusively for diagnostic imaging. There are only two units in South Africa, both located in Cape Town, involved in MRI research: - the Cape Universities Brain Imaging Centre (CUBIC), a collaboration between Medical Research Council, University of Cape Town and Stellenbosch University; - the other unit located at University of Cape Town. Incidentally, these two universities are also the only ones conducting MR research on the entire African continent.

CMR plays an essential role in the diagnosis of cardiac disease and provides an answer to the majority of questions during a single examination.[3] It has the capability of providing more combined information about cardiac morphology, chamber size, mass, regional and global function, oedema, focal and diffuse fibrosis, flow and haemodynamics, viability, energetics and lipidosis than any other imaging modality.[4] Applying different CMR modules for both left and right ventricular structure and function, as well as the appropriate use of gadolinium, first pass perfusion and late gadolinium enhancement (LGE) modules allows for evaluation of normal cardiac function as well as specific cardiac pathology.[5] Further CMR angiography provides a non-invasive approach to diagnosing pathology of the vasculature. Importantly, CMR is safe and does not involve ionising radiation or radioactive substances.[4]

Current recommendations for CMR have been established by an expert consensus panel and the usefulness is based not only the procedure providing clinically relevant information but also being appropriate as a first-line imaging technique. CMR can be utilised for both congenital and acquired heart and vascular disease. In patients with congenital heart disease CMR is the first line technique in children, adolescents and adults as it is capable of illustrating the anatomical pathology completely, allowing for assessment of shunt size, anomalies of the atria, ventricles, valves and arteries. In the case of acquired vascular disease CMR can readily be utilised for assessment of disease in both the aorta and peripheral vessels. The main indications for CMR in coronary artery disease are for the assessment of global ventricular function and mass, myocardial viability and the detection and assessment of acute and chronic myocardial infarction.[6] Compared to standard angiography, which illustrates coronary artery patency, CMR perfusion studies show the downstream microvascular blood flow within the myocardium.[7] CMR is further indicated for patients with pericardial disease, cardiac tumours, cardiomyopathies (including dilated, hypertrophic, restrictive, arrhythmogenic cardiomyopathies, left ventricular non-compaction and overlap syndromes), and in valvular heart disease where the cardiac chamber anatomy and function as well as quantification of regurgitation can be assessed.[6] With its vast use in diagnosis of cardiac pathology, CMR has been described as a "one-stop-shop" and much research has gone into establishing its current role in clinical practice.

The first multi-national registry pertaining to CMR was the European Cardiovascular Magnetic Resonance Registry (EuroCMR) which was published in January 2013. Although CMR is routinely used in the European and American setting, prior to this study, the clinical value of CMR regarding impact on decision-making and patient safety was not well understood.[8] EuroCMR consisted of a multicenter registry of 27000 patients from 15 centres in 15 countries in order to include a multi-national and multi-ethnic population. Its purpose was to establish the indications for CMR in Europe, assess image quality, the safety of the procedure and the impact on clinical management. Prospective follow-up of suspected CAD (coronary artery disease) and HCM (hypertrophic cardiomyopathy) was also assessed to highlight the prognostic potential of CMR in these subsets.[9]

Outcomes of EuroCMR illustrated that the most important indications for CMR in Europe were risk stratification in suspected CAD (34.2%), work-up of myocarditis and cardiomyopathies (32.2%), and the assessment of myocardial viability (14.6%). EuroCMR further demonstrated that CMR was a safe technique: 96.3% of all CMR procedures were complication free, with mild complications occurring in 3.6% and severe in 0.026% of patients. All severe complications were related to stress perfusion testing. Regarding image quality, good or diagnostic image quality was achieved in 88% of patients, moderate quality in 10.3% and poor or non-diagnostic in 1.7% of patients.[9] The importance, however, of SCMR-trained personnel in producing good quality images was highlighted by the Greek CMR experience where 65% of initial diagnosis made by SCMR-untrained personnel made no impact compared to results after re-evaluation by SCMR personnel where imaging needs where satisfied in 83% of patients.[3] EuroCMR further showed a significant impact on clinical management of 61.8% of patients that underwent CMR as it resulted either in a new diagnosis being made or in change in current treatment, with 45% of patients being worked up for suspected CAD avoiding angiography. Lastly, the interim analysis of the prognostic value of CMR in suspected CAD and HCM illustrated that patients who had a normal CMR in the work up for CAD had a major adverse event rate of 1.0% per annum compared to 2.7% in the group with an abnormal CMR. In patients with HCM, the absence of LGE was linked to an event rate of 2.2% compared to 4.3% in patients with LGE.[9]

At present the global burden of cardiovascular disease (CVD) is escalating, with CVD currently being ranked as the leading cause of death worldwide[2] and the second leading cause of death in most African countries.[12] Furthermore, the majority of individuals affected are from developing countries, with 78 percent of global mortality and 86 percent of mortality and morbidity from CVD occurring in developing countries.[13][14] In South Africa, CAD predominates as the leading cause of death amongst Caucasian and Indian populations[15] with an increasing prevalence amongst African populations owing to an increase in risk factors and urbanisation.[16] In addition to CAD, there is a high burden of CVD from other causes, rheumatic heart disease, systemic hypertension, dilated and HIV-related cardiomyopathies, congenital heart disease and pericarditis.[12]

As of yet the clinical value of CMR in Africa is not clearly defined. Data pertaining to CMR in South Africa is limited as there are currently very few published articles. At present Cape Town is the only CMR research centre on the African continent. The drawbacks relating to CMR in South Africa include limited infrastructure, expertise, skills and personnel. Currently, there are no sites in South Africa for training in cardiovascular CT (Computerised Tomography) and MRI[10] and clinicians are required to train in centres abroad. Compared to the European and American settings, CMR in South Africa is not readily accessible and, in many settings, is far from a routine investigation, with echocardiography, nuclear scintigraphy and invasive angiography predominating as primary imaging modalities for CVD. In addition, high cost has further limited the use of CMR[4], despite the fact that cost analysis of the EuroCMR registry showed cost savings compared to outpatient coronary angiography.[11]

With the rising incidence of CVD in Africa and the limited resources available, there is an increasing need for appropriate cardiac investigations and interventions. CMR has been shown to be a safe, non-invasive modality that not only provides diagnostic information but also significantly impacts clinical management. Currently, there is a paucity of data on the clinical use and indications of CMR in South Africa. In 2015 data, collection commenced for the first South African CMR registry. The rationale behind the establishment of the SA-CMR registry was to serve as an initial attempt to address these questions in a systematic fashion. This interim analysis aims to glean insights into the clinical indications and use of CMR in the South African population.

5. Aims and objectives

5.1 Primary objectives

The primary aim of this study is to gain knowledge regarding clinical use and indications for CMR in South Africa. Through retrospective review of data from the SA-CMR registry it further aims to assess the baseline demographic and clinical characteristics of the cohort as well as to delineate the quality of the CMR images.

5.2 Secondary objectives

The secondary objectives of the interim analysis study are to correlate CMR findings with patient demographics and medical history, as well as too assess the safety of CMR in this population.

6. Hypotheses

Since the goals of this study are descriptive, no formal hypotheses will be tested.

7. Methods

7.1 Study design

The SA-CMR registry consists of both retrospective and prospective data. The retrospective arm consists of all patients that underwent CMR at Groote Schuur Hospital (GSH) from its introduction in 2005 to date. This interim analysis will assess the first 1000 patients in this retrospective arm.

7.2 Characteristics of study population

There are no pre-selected criteria for patients included in the study. The study includes all patients that underwent CMR at GSH, thus there are no exclusion criteria.

7.3 Recruitment and enrollment

This study is a retrospective analysis of data in the SA-CMR registry. Patients included in the registry and for whom CMR is clinically indicated are referred by their attending physician or cardiologist according to the ACCF/ ESC/ ACR/ SCCT/ SCMR/ ASNC/ NASCI/ SCAI/ SIR consensus appropriateness criteria for CMR.[17]

7.4 Research procedures and data collection methods

Data will be extracted from the retrospective arm of SA-CMR registry and manually transposed on a data collection sheet in Microsoft Excel. The original data incorporated into the registry would have been collected from medical records at GSH. The lead investigator will be responsible for data interpretation and analysis. This will further be supervised by the principal investigator who is SCMR-trained.

7.5 Data safety and monitoring plan

Data and patient details are only accessible to members of the research team involved in SA-CMR. The SA-CMR registry has been reviewed by the local Human Ethics and Research Committee and data management has been approved. Data used for the interim analysis will only be stored on password protected systems. Data interpretation and analysis will not involve patient names or identification in order to maintain anonymity.

7.6 Variables and Definitions

The variables assessed will include patient demographics clinical features; as well as the indications for, quality of, and results of CMR. As with EuroCMR, the quality will be defined as good, moderate or poor; where good is diagnostic, moderate leaves doubt surrounding the diagnosis and poor is un-diagnostic.[8] See Appendix 1 for the variables that will be collected.

7.7 Data analysis

The data collected will subsequently be expressed as mean ± standard deviations for continuous variables (or median in the case of skewed deviation). Categorical variables will be assessed using chi-square whereas continuous variables will be compared using the correlation coefficient or Wilcoxon rank test. A p-value< 0.05 is deemed significant.

7.8 Procedural Characteristics

CMR is performed in keeping with the current South African Heart Association position statement on appropriateness/competency,[10] which is based on ACC/AHA clinical competency statement on cardiac CT and MRI[18] and ACCF/ACR/SSCT/ASNC/NASCI/SIR appropriateness criteria for cardiac CT and MRI.[17] In this institution, CMR is performed and interpreted in consensus fashion by a cardiologist with SCMR training and by a radiologist with an interest in CMR, and done in accordance with the standardised SCMR protocols.[5]A gadolinium dose of 0.15 to 0.2 mmol/kg body weight is used. At present, no routine stress perfusion testing is undertaken at GSH, but this is likely to change in the near future.

8. Description of risks and benefits

8.1 Risks

CMR is a safe and non-invasive technique with no known risk when appropriately supervised. It does not involve ionising radiation. Potential participants with ferromagnetic objects in their bodies or with implanted devices which can be damaged by the CMR magnet would have been assessed by the clinical team for suitability for such imaging. As per standard operating procedures, all participants entering the scanner room are screened for such objects. Gadolinium contrast is widely used for clinical indications in CMR and is safe. Occasionally it may cause a mild headache, nausea, itching and very rarely (< 1 in 1000) a more severe allergic reaction. It is cleared within hours by the body. Gadolinium has been associated with nephrogenic systemic fibrosis in patients with severe renal dysfunction; hence, as per our departmental guidelines based on Food and Drug Administration guidelines, all patients with glomerular filtration rate (GFR) < 30 ml/min (stage 3-5 renal disease) should be not be given gadolinium unless they are on dialysis. For this study, all potential participants with a GFR < 30 ml/min will not have been included. Venipuncture carries a risk of local discomfort, bruising and a very rare risk of nerve damage or arteriovenous fistula. Our CMR unit is fully equipped for resuscitation (including defibrillation).

8.2 Benefits

The investigation is non-invasive and avoids ionising radiation. It not only has diagnostic capability but has also been shown to influence clinical management and further limit the use of unnecessary invasive investigations. However, there are no direct benefits to the participants whose data will be utilised.

9. Informed consent process

As data will be extracted from the SA-CMR registry, informed consent will not be required. Further, as noted above, SA-CMR has been approved by the Human Ethics and Research Committee.

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