International Journal of Cardiology 333 (2021) 119–126

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Rationale and design of the African Cardiomyopathy and Myocarditis Registry Program: The IMHOTEP study

Sarah M. Kraus [a], Gasnat Shaboodien [a], Veronica Francis [a], Nakita Laing [a,d], Jacqui Cirota [a], Ashley Chin [a], Shahiemah Pandie [a], John Lawrenson [b,c], George A.M. Comitis [b], Barend Fourie [c], Liesl Zühlke [a,b], Ambroise Wonkam [a,d], Helen Wainwright [e], Albertino Damasceno [f], Ana Olga Mocumbi [g], Lungile Pepeta [h], Khulile Moeketsi [i], Baby M. Thomas [i], Kandathil Thomas [i], Makoali Makotoko [j], Stephen Brown [j], Mpiko Ntsekhe [a], Karen Sliwa [a], Motasim Badri [a,k], Freedom Gumedze [l], Heather J. Cordell [m], Bernard Keavney [n], Vanessa Ferreira [o], Masliza Mahmod [o], Leslie T. Cooper [p], Magdi Yacoub [q], Stefan Neubauer [o], Hugh Watkins [o], Bongani M. Mayosi [a], Ntobeko A.B. Ntusi [a,*], for the IMHOTEP Investigators:

Julius Mwita [1], Ahmed El-Guindy [2], Sir Magdi Yacoub [2], Tolno Sandy Kola [3], F. Ayub Barasa [4], Albertino Damasceno [5], Ana Olga Mocumbi [6], Okechukwu Ogah [7], Motasim Badri [8], James Russell [9], Ashley Chin [10], Sarah Kraus [10], Bongani Mayosi [10], Mpiko Ntsekhe [10], Ntobeko Ntusi [10], Karen Sliwa [10], Ambroise Wonkam [10], Nakita Laing [10], Shaheen Pandie [10], Blanche Cupido [10], George Comitis [11], John Lawrenson [11], Rik De Decker [11], Liesl Zühlke [11], Paul Brink [12], Barend Fourie [12], Marshall Heradien [12], Lungile Pepeta [13], Nomlindo Makubalo [13], Mahlubandile Nxele [13], Benjamin Longo-Mbenza [14], Khulile Moeketsi [14], Baby Thomas [14], Kandithalal Thomas [14], Makoali Makotoko [15], Stephen Brown [15], Ahmed Suliman [16], Sulafa Ali [17], Kemilembe Tibazarwa [18], Charles Mondo [19], Michael Mungoma [20], Bernard Keavney [21], Heather Cordell [22], Vanessa Ferreira [23], Masliza Mahmod [23], Stefan Neubauer [23], Hugh Watkins [23], Leslie T. Cooper [24], Ellise Tapiwa Gambahaya [25]

[1] *University of Botswana, Gaborone, Botswana*
[2] *Aswan Heart Centre, Aswan, Egypt*
[3] *Hospital De L'amitie Sino-Guineenne, Conakry, Guinea*
[4] *Moi University, Eldoret, Kenya*
[5] *Eduardo Mondlane University, Maputo, Mozambique*
[6] *Instituto Nacional de Saúde, Ministério da Saúde, Maputo, Mozambique*
[7] *University College Hospital, Ibadan, Nigeria*
[8] *King Saud Bin Abdalaziz University for Health Sciences, Riyadh, Saudi Arabia*
[9] *Connaught Hospital, Freetown, Sierra Leone*
[10] *Groote Schuur Hospital, Cape Town, South Africa*
[11] *Red Cross War Memorial Children's Hospital, Cape Town, South Africa*
[12] *Tygerberg Hospital, Cape Town, South Africa*
[13] *Dora Nginza Hospital, Port Elizabeth, South Africa*
[14] *Nelson Mandela Academic Hospital, Mthatha, South Africa*
[15] *University of the Free State, Bloemfontein, South Africa*
[16] *University of Khartoum, Khartoum, Sudan*
[17] *Sudan Heart Centre, Khartoum, Sudan*
[18] *Muhimbili National Hospital, Dar es Salaam, Tanzania*
[19] *St. Francis Hospital Nsambya, Kampala, Uganda*
[20] *Mulago Hospital, Kampala, Uganda*
[21] *University of Manchester, Manchester, United Kingdom*
[22] *University of Newcastle-upon-Tyne, Newcastle, United Kingdom*
[23] *University of Oxford, Oxford, United Kingdom*
[24] *Mayo Clinic, Jacksonville, United States of America*
[25] *Parirenyatwa Hospital, Harare, Zimbabwe*

* Corresponding author at: Department of Medicine, Faculty of Health Sciences, J46.53, Groote Schuur Hospital, Main Road, Observatory, 7925, South Africa.
E-mail address: Ntobeko.Ntusi@uct.ac.za (N.A.B. Ntusi).

https://doi.org/10.1016/j.ijcard.2021.02.026

[a] The Cardiac Clinic and Hatter Institute of Cardiovascular Research in Africa, Department of Medicine, University of Cape Town (UCT) and Groote Schuur Hospital, Cape Town, South Africa
[b] Division of Paediatric Cardiology, Department of Paediatrics and Child Health, UCT and Red Cross War Memorial Children's Hospital, Cape Town, South Africa
[c] Division of Paediatric Cardiology, Department of Paediatrics and Child Health, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa
[d] Division of Human Genetics, Department of Medicine, UCT, Cape Town, South Africa
[e] Department of Pathology, National Health Laboratory Service and UCT, Cape Town, South Africa
[f] Department of Medicine, Eduardo Mondlane University, Maputo, Mozambique
[g] Instituto Nacional de Saúde and Eduardo Mondlane University, Maputo, Mozambique
[h] Department of Paediatrics, Port Elizabeth Hospital Complex and Nelson Mandela Metropolitan University, Port Elizabeth, South Africa
[i] Division of Cardiology, Nelson Mandela Academic Hospital and Walter Sisulu University, Mthatha, South Africa
[j] Division of Cardiology, Universitas Hospital and University of the Free State, Bloemfontein, South Africa
[k] College of Medicine, King Saudi Bin Abdulaziz University for Medical Sciences, Riyadh, Saudi Arabia
[l] Department of Statistics, UCT, Cape Town, South Africa
[m] Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
[n] Division of Cardiovascular Sciences, University of Manchester, Manchester, United Kingdom
[o] Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom
[p] Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, USA
[q] Heart Science Centre, Harefield, London, UK

ARTICLE INFO

Article history:
Received 10 July 2020
Received in revised form 27 January 2021
Accepted 10 February 2021
Available online 16 February 2021

Keywords:
Cardiomyopathy
Heart failure
Myocarditis
Africa
Genetics
Cardiovascular outcomes

ABSTRACT

Background: Heart failure (HF), the dominant form of cardiovascular disease in Africans, is mainly due to hypertension, rheumatic heart disease and cardiomyopathy. Cardiomyopathies pose a great challenge because of poor prognosis and high prevalence in low- and middle-income countries (LMICs). Little is known about the etiology and outcome of cardiomyopathy in Africa. Specifically, the role of myocarditis and the genetic causes of cardiomyopathy are largely unidentified in Africans.
Method: The African Cardiomyopathy and Myocarditis Registry Program (the IMHOTEP study) is a pan-African multi-centre, hospital-based cohort study, designed with the primary aim of describing the clinical characteristics, genetic causes, prevalence, management and outcome of cardiomyopathy and myocarditis in children and adults. The secondary aim is to identify barriers to the implementation of evidence-based care and provide a platform for trials and other intervention studies to reduce morbidity and mortality in cardiomyopathy. The registry consists of a prospective cohort of newly diagnosed (i.e., incident) cases and a retrospective (i.e., prevalent) cohort of existing cases from participating centres. Patients with cardiomyopathy and myocarditis will be subjected to a standardized 3-stage diagnostic process. To date, 750 patients have been recruited into the multi-centre pilot phase of the study.
Conclusion: The IMHOTEP study will provide comprehensive and novel data on clinical features, genetic causes, prevalence and outcome of African children and adults with all forms of cardiomyopathy and myocarditis in Africa. Based on these findings, appropriate strategies for management and prevention of the cardiomyopathies in LMICs are likely to emerge.

1. Introduction

Akinkugbe et al observed several decades ago that "the cardiomyopathies pose the greatest challenge of all the cardiovascular diseases (CVDs) in Africa because of their greater prevalence in societies still plagued by diseases of famine and pestilence; the difficulty in diagnosis, which often requires specialised cardiological investigations that are lacking in resource-poor environments; the lack of access to effective interventions; and the high mortality associated with these often irreversible disorders of heart muscle" [1]. Cardiomyopathy contributes 20–30% of cases of heart failure (HF) in adults in Africa [2]. There is, however, limited information on the etiology, treatment, outcome, and prevention of cardiomyopathy in Africans [3]. The relatively younger age of onset of HF in African patients (mean age 52 years) compared with their North American/European counterparts (70–72 years), is a significant epidemiological finding recently confirmed by the sub-Saharan Africa (SSA) Survey of Heart Failure (THESUS-HF) [4]. The younger age of onset of HF in African patients has major economic and social implications [5].

Over the past 25 years, molecular genetic investigations conducted outside of Africa have identified specific genetic causes of cardiomyopathy and this information has been applied increasingly in clinical practice to diagnose and manage these conditions [6]. Diagnostic genetic screening is not widely available on the African continent and our knowledge of genetics of cardiomyopathy in Africans is limited to a few small studies [7–13].

Dilated cardiomyopathy (DCM) is a major cause of HF in Africa [4], but due to the lack of readily available diagnostic tools, myocarditis has rarely been identified and consequently data regarding the contribution of myocarditis to the pathogenesis of DCM are limited [14]. A number of studies from different regions of the world report acute myocarditis as an important cause of sudden cardiac death (SCD) and chronic DCM in both adults and children [15,16]. The dearth of information on the causes, outcome and treatment of myocarditis in Africa is well recognized [17].

2. Rationale for the study

The paucity of data on etiology, treatment and outcome of cardiomyopathy and myocarditis limits our ability to diagnose, manage and prevent these conditions at population and individual levels in SSA [3]. The African Cardiomyopathy and Myocarditis Registry Program (IMHOTEP) has been designed to elucidate the etiology, clinical features, outcome, and management of all forms of cardiomyopathy and myocarditis in children and adults presenting to referral centres from all regions of Africa.

The design of IMHOTEP as a single registry that includes all forms of cardiomyopathies is based on several observations: (1) it is well recognized there is significant genetic and phenotypic overlap between the different morphological and functional types of cardiomyopathy [18], raising the possibility that different morpho-functional types of cardiomyopathy may be on a phenotypic and genotypic continuum;

(2) cardiomyopathies are caused by both familial (genetic) and nonfamilial (secondary) aetiologies [19], but the interplay between genetics and environment is not well understood; (3) myocarditis may be present in a significant proportion of cases where it serves as a causative factor in nonfamilial cardiomyopathy or a triggering factor for the symptomatic presentation of genetic disease, which may be expected to be more likely in SSA where there is a high prevalence of infectious disease with cardiac involvement, such as human immunodeficiency virus (HIV) infection; and (4) endomyocardial fibrosis (EMF) is endemic in certain peri-equitorial regions of Africa, including northern Mozambique where the prevalence is as high as 19.8%, affecting young individuals between the ages of 10 and 19 predominantly [20], and carrying a case fatality rate of up to 75% at 2 years [21]. Although the pathogenesis of EMF is not known, it has been postulated that the conditioning factors may be geography, poverty and diet, the triggering factor may be an as yet unidentified infective agent, and the perpetuating factor is eosinophilia [22–24]. Although there have been reports of familial aggregation and putative genetic association in the human leucocyte antigen (HLA) region in EMF, there are no definitive studies of genetic susceptibility and protective factors in this condition [20,25–27].

The IMHOTEP study includes adults and children because cardiomyopathies affect individuals of all ages. Certain conditions, such as EMF, that are endemic on our continent affect children and adolescents predominantly [20]. Patients presenting in childhood with severe disease provide a unique opportunity to study both genetic and environmental factors contributing to the development of cardiomyopathy, without the influence of co-morbidities and lifestyle confounders often present in adults (Fig. 1).

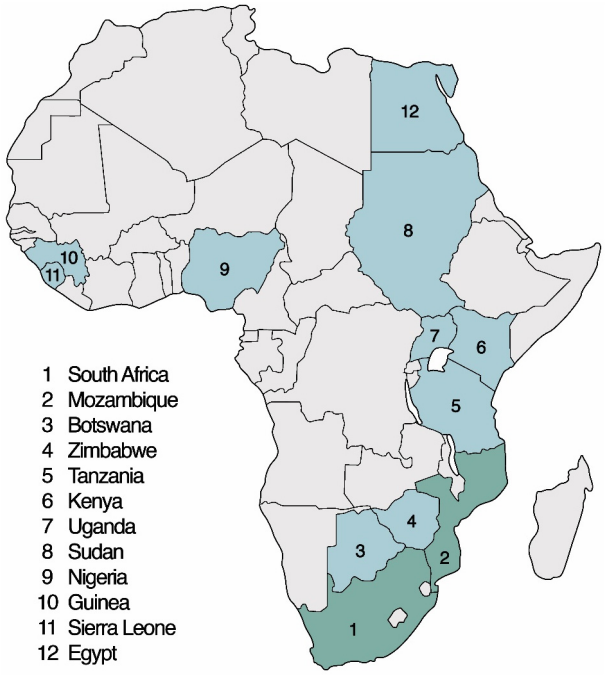


Fig. 1. IMHOTEP collaborating countries. The pilot phase of the IMHOTEP study will be conducted in (1) South Africa and (2) Mozambique (green). Recruitment sites for the pilot phase include Cape Town (3 sites), Bloemfontein, Port Elizabeth and Mthatha in South Africa, and Maputo in Mozambique. Following the pilot phase, participating sites from countries 4–12 (blue) will initiate recruitment. Additional collaborating institutions not represented here include Oxford University (United Kingdom), Mayo Clinic (United States) and King Saud Bin Abdalaziz University for Health Sciences (Saudi Arabia).

3. Materials and methods

3.1. Study design

3.1.1. Study population

IMHOTEP is a pan-African, multi-centre, hospital-based cohort study with two arms: (1) the 'incident cases' arm will involve the enrolment of new cases of cardiomyopathy and myocarditis; and (2) the 'prevalent cases' arm will involve the enrolment of existing cases of cardiomyopathy and myocarditis. In addition, the prevalent cases arm of the study will involve the integration of existing studies from Cape Town – the Clinical and Genetic Study of Familial Dilated Cardiomyopathy in South Africa initiated in 1996 and the Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Registry of South Africa initiated in 2004 [28–30]. Furthermore, in cases of familial cardiomyopathy, both affected and unaffected relatives of incident and prevalent cases will be recruited. Incident cases, prevalent cases and relatives will be followed prospectively from the time of enrolment in IMHOTEP.

3.1.2. Objectives

The IMHOTEP study has been designed to address the following objectives:
Primary objectives

1. To describe the clinical, electrocardiographic, imaging, histological and genetic characteristics of cardiomyopathy and myocarditis in children and adults in Africa;
2. To describe the management of cardiomyopathy and myocarditis in children and adults in Africa;
3. To estimate the complications associated with cardiomyopathy and myocarditis in children and adults in Africa;
4. To determine the overall survival experience of children and adults diagnosed with cardiomyopathy and myocarditis in Africa.

Secondary objectives

1. To identify barriers to the use of evidence-based guidelines in the management of patients with cardiomyopathy and myocarditis in Africa;
2. To provide a platform for studies of the pathogenesis, and trials of treatment and prevention of mortality and morbidity in patients with cardiomyopathy and myocarditis in Africa.

3.1.3. Study eligibility

Patients, with known (i.e., prevalent cases) or newly diagnosed (i.e., incident cases) cardiomyopathy or myocarditis who have undergone diagnostic evaluation at a participating centre, are eligible for inclusion in IMHOTEP. The European Society of Cardiology (ESC) definitions and classification of cardiomyopathy will be used as the inclusion and exclusion criteria for IMHOTEP (Table 1) [19]. In keeping with the ESC classification, secondary cardiomyopathies have been included. The diagnosis of myocarditis will be made according to the clinical classification system described in Table 2 [31].

3.1.4. Diagnostic approach

Clinical algorithms, specifically adapted for the limited resource setting, have been developed to guide clinicians in the appropriate work-up of patients with suspected cardiomyopathy and myocarditis. These algorithms illustrate a diagnostic approach that has been adopted in Cape Town and is based on three stages of investigation: (1) non-invasive stage, (2) invasive stage, and (3) genetic stage (Table 3). This approach is based on standard of care guidelines [31–34] and highlights the use of core investigations for all patients, and extended tests that will be optional depending on clinical indication and the availability of resources.

Cardiovascular magnetic resonance (CMR) will be conducted on incident cases at centres with appropriate equipment and expertise, such as Cape Town. Standardized protocols will be utilised to evaluate chamber size and ventricular function, left ventricular mass, strain, haemodynamic assessment, tissue characteristics (including native T1 and T2 and postcontrast T1 and extracellular volume mapping techniques) and late gadolinium enhancement [35–40].

Endomyocardial biopsy (EMB) will be recommended in patients with suspected myocarditis based on clinical suspicion or CMR findings at centres with appropriate facilities and expertise to conduct EMB safely and pathologists with the requisite experience.

3.1.5. Medical genetics, counselling and genetic testing

Blood samples for DNA analysis will be collected and processed using standard protocols from prevalent and incident cases. Patients will receive genetic counselling and be required to sign a consent form for DNA analysis prior to sample collection. Specimens will be transferred to Cardiovascular Genetics Laboratory, Hatter Institute of Cardiovascular Research in Africa, University of Cape Town (UCT) for DNA extraction, storage and analysis. The molecular genetic approach will follow three stages. First, all index cases will be screened for known molecular genetic causes of cardiomyopathy using targeted Next Generation Sequencing (NGS). A family pedigree will be constructed at the time of sample collection, and family screening will be conducted in selected cases of unexplained and familial cardiomyopathy, with an emphasis on identifying large multiplex families (>5 affected members) and family trios in children under the age of 12 years. Second, genotype-negative probands of multiplex families and children with severe early-onset cardiomyopathy in family trios will be subjected to whole exome sequencing (WES) to identify novel genetic causes of cardiomyopathy. We aim to apply this approach to approximately 10 multiplex families and 40 family trios. Finally, the genotype-negative cases not included in stage two (and with no DNA sample from an affected family member) will be screened for the novel genetic mutations that are identified in this and

Table 1
Inclusion and exclusion criteria.

Inclusion criteria: Persons of all ages living in Africa with any of the following	
Autopsy diagnosis	Cardiomyopathy or myocarditis
Idiopathic cardiomyopathies	Etiology unknown
Familial cardiomyopathies	Hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, restrictive cardiomyopathy, left ventricular noncompaction, mixed forms of cardiomyopathy
Neuromuscular disorders with cardiac involvement	Disorders that are atypical and/or are genotype negative for classical neuromuscular disorders on genetic screening
Non-familial or secondary causes of cardiomyopathy	Myocarditis (infective/toxin/immune), human immunodeficiency virus (HIV), drugs/toxins, peripartum, endocrine, nutritional, obesity, alcohol, tachycardiomyopathy, eosinophilic, Kawasaki disease, Takotsubo cardiomyopathy, amyloidosis, autoimmune, endomyocardial fibrosis, carcinoid heart disease, Radiation
Myocarditis	Acute or chronic myocarditis
Exclusion criteria: Persons with any of the following	
Systemic arterial hypertension	Blood pressure ≥ 160/100 mmHg documented and confirmed at repeated measures Consider HHD in patients in patients with BP < 160/100: • History of longstanding hypertension with dilated LV and impaired systolic function • High normal (BP ≥ 130/85) or grade 1 hypertension (BP ≥ 140/90) in patients with systolic dysfunction and concentric LVH, particularly if on blood pressure lowering medications • Evidence of hypertensive target organ damage – nephropathy, retinopathy, LVH, small vessel disease
Coronary artery disease (ischaemic heart disease)	Coronary artery obstruction >50% of the luminal diameter of a major branch on coronary CTA or coronary angiography Where coronary CTA or coronary angiography not available, consider CAD in patients with: • History of angina, ACS, or previous MI in a patient with risk factors for CAD, and/or evidence of previous infarction or ischaemia on ECG (Q waves, ST elevation or depression), echocardiogram (regional wall motion abnormalities) and/or CMR (subendocardial or transmural LGE) • Positive exercise stress test
Pericardial diseases	Primary pericardial disease, e.g. pericarditis, pericardial constriction, pericardial effusion (not associated with heart failure)
Congenital heart disease	Ventricular septal defect, atrial septal defect, patent ductus arteriosus, coarctation of the aorta, anomalous origin of the left coronary artery from pulmonary artery, Tetralogy of Fallot, pulmonary or aortic valve stenosis, transposition of the great vessels, hypoplastic right or left ventricle, Ebstein's anomaly, other
Cor pulmonale	Primary pulmonary hypertension, pulmonary disease
Valvular heart disease	Rheumatic heart disease, degenerative valve disease, infective endocarditis, valve prolapse, congenital bicuspid valve, other

LVH, left ventricular hypertrophy; ACS, acute coronary syndrome; HHD, hypertensive heart disease; CTA, computed tomography; CAD, coronary artery disease; ECG, electrocardiogram; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement.

other studies. This approach will provide a comprehensive analysis of established and new genetic causes of cardiomyopathy in Africans.

3.1.6. Data collection and management

All clinical and demographic information will be captured on a web-based database accessible to all participating centres via the internet. Data will be stored on a secure server governed by the University of Cape Town. Access to the database will be controlled by a username and password system. Data will be collected using electronic case report forms (CRFs) accessible either via tablet or computer devices. Paper CRFs will be available for use in the event that electronic systems become inaccessible, where data can be captured on the form by hand and subsequently entered manually onto the database. Patients will be asked to complete a personal information sheet containing contact details at the time of recruitment, and this information will be updated at the time of follow-up. All patient identifiers will be anonymized and recorded separately from clinical and demographic data to ensure the confidentiality of participants. Each participant will be assigned a unique identification number at the time of recruitment.

As this will be a longitudinal study of patients with cardiomyopathy or myocarditis managed according to standard of care guidelines at multiple centres with varied resource availability, the amount of data recorded will vary between centres. Mandatory data required at recruitment will include demographics, medical history and presenting symptoms, physical examination findings, drug therapy and basic investigations including electrocardiography and echocardiography. Additionally, CRFs for all specialized investigations and procedures will be available for completion, to accommodate facilities with the relevant expertise (Table 3).

Data entry will be done via voluntary submission by participating centres under the guidance of the local site coordinator. Incentives to clinicians include the use of an established data collection tool for collecting patient information and access to data for their site for purposes of audit and publication. An active system of data collection instituted by an outreach team will be required once multiple sites are recruited.

Source documents will be stored according to the hospital record keeping protocols at each centre. Informed consent forms, contact information, copied source documents and paper CRFs will be stored in a securely locked area on site. If facilities allow for secure electronic storage of the above-mentioned documents, such will be utilised in preference to hard copy storage. An annual audit check on a randomly selected sample of cases from all sites will be conducted to look for data discrepancies and to ensure data quality control.

3.1.7. Follow-up

Follow-up clinic visits will be scheduled according to clinical necessity in accordance with standard practice guidelines. The attending physician will arrange follow-up based on the patients' clinical condition. If additional events, investigations or procedures have occurred, the attending clinician will be required to record the data using the relevant CRF(s). IMHOTEP requires an annual follow-up CRF to be completed that can be done at the time of a follow-up visit or by means of a hospital folder and telephonic review to ensure that all symptoms, events, investigations and procedures are recorded, thus enabling review of primary and secondary outcomes on an annual basis (Table 4). A random sample of 10% of the locally adjudicated events will be audited by an independent committee for consistency with the study definitions.

3.1.8. Genotype analysis

Extracted DNA samples from all index cases will be batched and transferred to Oxford Medical Genetics Laboratory (PMID: 27532257) for targeted Next Generation Sequencing (NGS) analysis of the cardiomyopathy related genes. Selected genotype-negative probands of multiplex families and children with severe early-onset cardiomyopathy in family trios will be subjected to whole exome sequencing (WES) to identify novel genetic causes of cardiomyopathy. The WES analysis will be carried out as previously described by our group [41] and will also be based on the recent guidelines [42–44] for assigning causality and will rely on familial transmission over biological plausibility. We note that for detection of causative mutations in Mendelian disorders, formal statistical testing is often not required; nevertheless, Fisher's exact test will be used to determine the level

Table 2
Clinical classification for the diagnosis of myocarditis.

Diagnosis	Criteria
Probable acute myocarditis based on clinical features	In the clinical context of possible myocardial injury with cardiovascular symptoms and no evidence of coronary artery disease where the following criteria are met: 1. Biomarkers of cardiac injury raised; and 2. Either of the following: a. Wall motion abnormalities and/or left ventricular systolic dysfunction on echocardiography; or b. Abnormal left ventricular systolic function, left ventricular wall motion abnormalities, and abnormal tissue characteristics on CMR (increased signal intensity ratio on T2--weighted imaging; increased T1 value and increased T2 value on parametric mapping; increased signal intensity on early gadolinium imaging; and/or typical pattern on enhancement on late gadolinium imaging)
Definite myocarditis	Histological or immune-histological evidence of myocarditis

CMR, cardiovascular magnetic resonance.

Table 3
Three stage investigative approach to cardiomyopathy and myocarditis.

Stage 1: Non-invasive							
Confirm diagnosis of cardiomyopathy; morphofunctional phenotype and etiology; exclude alternative causes (see Table 1); SCD risk							
	All cardiomyopathies	DCM	HCM	ARVC	RCM	Myocarditis	Children*
Core investigations	History Examination Chest X-ray Electrocardiogram Echocardiogram Basic blood investigations: (Hb, WCC, renal and liver function)	HIV, TSH, CK Ferritin/Iron CMP Glucose (HbA1C) Cholesterol Proteinuria	CK Proteinuria		Ferritin/Iron Eos count Proteinuria	Troponin (CK) CRP/ESR WCC and differential count	HIV TSH Troponin CK CMP Lactate CRP/ESR
Extended investigations	Additional diagnostic investigations done at the physician's discretion according to clinical indications and resource availability	CMR SACE[a] Autoantibodies[b] CRP/ESR[b] Lactate[c] Myoglobinuria[c] Eos count[d] (Thiamine)	CMR Urine and plasma protein immunofixation, free light chains,[e] alpha-Galactosidase A levels[f]	SAECG Holter (EST) CMR	CMR SACE[a] Urine and plasma protein immunofixation, free light chains[e]	CMR	CMR Viral screen* Metabolic screen (plasma acylcarnitine, urine reducing substances, urine organic acid, urine ketones) Autoantibodies[b]
	SCD risk assessment	Holter and/or EST according to published guidelines					
	Exclusion of CAD	EST, and/or MIBI, and/or coronary CTA according to published guidelines					
Stage 2: Invasive	– Only undertaken at institutions that have the facilities and expertise, in the following circumstances						Not routinely undertaken
Diagnostic or etiologic uncertainty, exclusion of CAD, transplantation assessment, SCD risk assessment, arrhythmias							
Extended investigations	TOE: Exclusion of left atrial thrombus prior to cardioversion/EPS, or poor transthoracic views where CMR is not available Cardiac catheterization: Exclusion of coronary artery disease OR haemodynamic assessment (diagnostic, transplantation) EMB: Indications according to published guidelines, including: • New onset heart failure of <2 weeks' duration, a normal sized or dilated LV, and haemodynamic compromise • New onset HF with a dilated ventricle, 2 weeks - 3 months of symptoms, new ventricular arrhythmias or Mobitz type 2 s-degree HB or third-degree HB, or who fail to respond to usual care within 1–2 weeks • Diagnostic purposes that will alter management (e.g. giant cell myocarditis, amyloidosis, cardiac sarcoidosis, ARVC) or post-transplantation (organ rejection) EPS: For assessment of arrhythmias or ablation procedure where required SMB: If myopathy or muscular dystrophy suspected						Indications must be individualized and according to the attending physicians' discretion SMB (myopathy, muscular dystrophy)
Stage 3: Genetics (screening for familial/genetic cardiomyopathy)							
All patients	Family history and pedigree						As for adults
Extended investigations	Family screening – indicated in ARVC and HCM, and in DCM and RCM cases with positive family histories Molecular genetic testing						As for adults Screen parents

Abbreviations; ARVC, arrhythmogenic right ventricular cardiomyopathy; CK, creatinine kinase; CMP, calcium magnesium phosphate; CMR, cardiovascular magnetic resonance; CRP, C-reactive protein; CTA, computerized tomography angiography; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; Eos, eosinophil; EPS, electrophysiology study; ESR, erythrocyte sedimentation rate; EST, exercise stress test; HbA1C, glycosylated haemoglobin; HB, heart block; HCM, hypertrophic cardiomyopathy; HF, heart failure; HIV, human immunodeficiency virus; LV, left ventricle; LVNC, left ventricular cardiomyopathy; MIBI, myocardial perfusion imaging; RCM, restrictive cardiomyopathy; SACE, serum angiotensin converting enzyme; SAECG, signal average electrocardiogram; SCD, sudden cardiac death; SMB, skeletal muscle biopsy; TOE, transoesophageal echocardiogram; TSH, thyroid stimulating hormone.

[a] Sarcoidosis suspected;
[b] Autoimmune conditions such as systemic lupus erythematosus or rheumatoid arthritis suspected;
[c] Mitochondrial disorder suspected;
[d] Hypereosinophilic syndrome suspected;
[e] Amyloidosis suspected;
[f] Anderson-Fabry disease suspected,
* Viral screen includes coxsackie A/B, parvovirus B19, mumps, rubella, cytomegalovirus, Ebstein Barr virus, echovirus, respiratory viruses. Normative data for z-score calculations to be applied.

of significance for mutations detected in any of our 750 cases and not present (or present at much lower frequencies) in ethnically matched control chromosomes.

3.1.9. Statistical analysis

Descriptive statistics will be used to describe the study population; all continuous variables will be tested for distribution using a histogram for visualisation and Shapiro-Wilks for test of normality. Normally distributed data will be reported as mean and standard deviation. Non-normally distributed data will be reported as median and interquartile range. Categorical data will be summarised in tables and reported as number and proportion. Chi-squared test of equal proportions will be used to determine differences between categorical data. Wilcoxon sum rank (2 samples) and Kruskal-Wallis (more than 2 samples) will be used to determine differences between non-normally distributed continuous data. Student's *t*-test (2 samples) and ANOVA (more than 2 samples) will be used for normally distributed data. Cox proportional hazards regression analysis will be used to explore the risk of sudden death. Kaplan-Meier survival analysis will be used to explore the survival of cardiomyopathy and myocarditis patients in relation to different treatments. All statistical tests will be two-sided, at $\alpha = 0.05$.

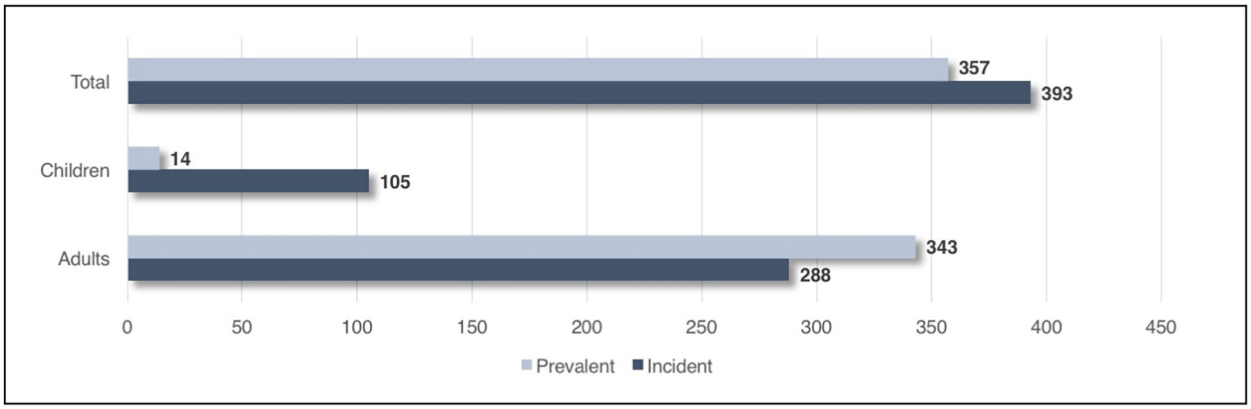
We aim to recruit a minimum of 750 unrelated probands with cardiomyopathy in the pilot phase of this study which will be conducted over three years (2017–2019), involving sites in South Africa and Mozambique. This sample size will be adequate for testing the genetic hypothesis, and will provide preliminary data on outcomes. These data will be used to estimate the minimum sample size for the full study that will be conducted involving all the participating centres in this study.

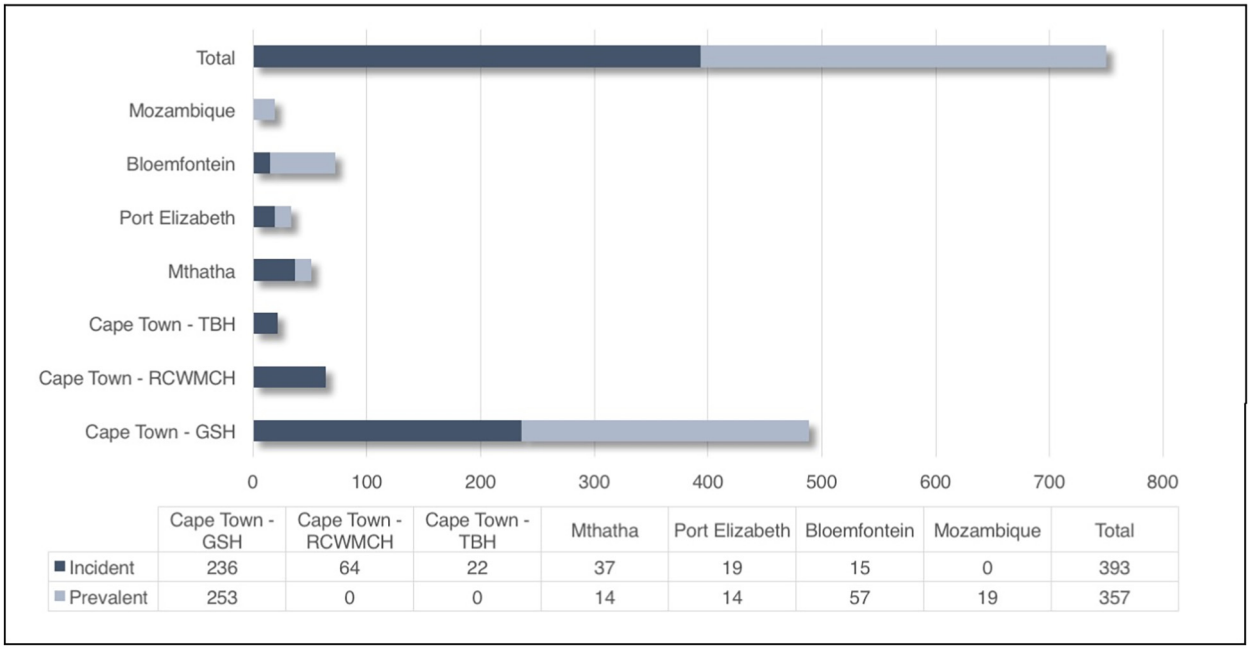
Table 4
Primary and secondary outcome measures.

Primary endpoint/outcome measures	Secondary endpoints/outcome measures
Death from all causes	Death from cardiovascular disease
Hospitalization for heart failure[a]	Pulmonary embolism
Embolic stroke/transient ischaemic attack	Systemic embolism (other than stroke)
Heart failure (new or decompensated)	
Resuscitated cardiac arrest[b]	
New onset atrial fibrillation	

[a] Heart failure (HF) is defined as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

[b] Cardiac arrest is defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation. Resuscitated cardiac arrest is defined by the restoration of life by establishing or maintaining airway (or both), breathing, and circulation through CPR, defibrillation, and other related emergency care techniques.





	Cape Town - GSH	Cape Town - RCWMCH	Cape Town - TBH	Mthatha	Port Elizabeth	Bloemfontein	Mozambique	Total
Incident	236	64	22	37	19	15	0	393
Prevalent	253	0	0	14	14	57	19	357

Fig. 2. Recruitment status of IMHOTEP. Total number of adults and children recruited to IMHOTEP (above). Recruitment according to site (below). ARVC; arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; GSH, Groote Schuur Hospital; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy; RCWMCH, Red Cross War Memorial Children's Hospital; TBH, Tygerberg Hospital.

3.1.10. Study management

The Project Coordinating Office (PCO) for IMHOTEP is based in the Department of Medicine at the University of Cape Town. The PCO is responsible for the management of the registry, the co-ordination of the different centres, overseeing data collection and quality assurance. The PCO has been responsible for the development of the CRFs, consent forms, patient information sheets, and management algorithms, in addition to the development and maintenance of the web-based database. A data management plan outlining standard operating procedure has been developed and a data manager has been appointed at the PCO to oversee all data collection. Additionally, the PCO is the statistical consulting site responsible for analysis of data. Local site investigators have been appointed at each participating site (Appendix). A Steering Committee (decision-making body) comprised of the principal and co-investigators, and a scientific panel comprised of experts in the fields of cardiomyopathy, cardiovascular imaging, cardiac electrophysiology, histopathology and molecular genetics, have been established.

Support from the Pan-African Society of Cardiology (PASCAR), as well as proposed collaborators from other centres, was obtained prior to the establishment of this registry.

3.1.11. Ethics

The study has been approved by the UCT Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 766/2014). Participating centres will require institutional ethics committee approval prior to being established as part of the registry. For the incident case cohort, informed consent for inclusion into the registry must be obtained prior to enrolment. In the case of participants under the age of 18 years, the participant's parent/guardian will sign consent. In addition, children aged eight and above may sign an assent form. In accordance with current practices, a separate consent form must be signed for DNA specimen collection, storage and analysis. Regarding the prevalent case cohort, informed consent for participation in research and DNA analysis was obtained from participants when they were recruited into the previous studies. Detailed information sheets have been developed and will be provided to each participant.

All invasive investigations performed will be performed according to prevailing standard of care guidelines for cardiomyopathy and myocarditis [31–34,45], or as part of an approved research protocol. There will be no anticipated additional costs incurred by the participants, as treatment, investigations and follow-up will be conducted according to clinical indications.

3.1.12. Status of the study and study participants

The pilot phase of the study commenced at Groote Schuur Hospital in Cape Town on February 1, 2015, followed by staggered initiation of recruitment sites in Cape Town, Mthatha, Port Elizabeth, Bloemfontein and, most recently, Mozambique. We have enrolled 750 unrelated patients (631 adults and 119 children) at the time of writing (30 March 2020) (Fig. 2), reaching target recruitment for the vanguard phase of the study, with 18 months (average) follow-up data collection underway.

4. Discussion

Cardiomyopathy is an endemic noncommunicable disease of high importance to the poor majority in Africa and is a locally relevant unmet need for research [3,22]. The IMHOTEP study aims to fill knowledge gaps in our understanding of cardiomyopathy and myocarditis, in

the African population, by delineating clinical features and molecular genetics of the different morpho-functional forms of cardiomyopathy, and obtaining important outcome data. As access to health care and the availability of sophisticated investigations and interventions vary considerably across the African continent, IMHOTEP has been designed to record core information required to make a diagnosis of cardiomyopathy or myocarditis and key outcome events over a minimum follow-up period of two years in the pilot phase. In addition, IMHOTEP has the facility to record detailed reports of specialized investigations and procedures, which can be utilised by facilities that have the equipment and expertise. We have proposed a standardized three-stage investigative approach to the work-up of cardiomyopathy and myocarditis that can be easily adapted according to resource availability (Table 3).

We postulate that myocarditis is underdiagnosed in Africa, due to the requirement of sophisticated imaging (like CMR) or invasive investigations (specifically EMB) to confirm the diagnosis; and that by utilizing a tailored clinical classification system (Table 2), we hope to not only improve diagnostic yield but facilitate better use of available resources. Infectious diseases contribute significantly to the burden of disease in African countries [46], highlighting the importance of establishing the role of myocarditis in the etiology, pathophysiology and outcomes of cardiomyopathies in Africans. IMHOTEP aims to establish the prevalence of myocarditis in patients presenting with new-onset HF in Africa, and contribute to the development of innovative diagnostic strategies more suitable for resource-limited settings.

Internationally, there is a recognized need to conduct more extensive genomic studies in much larger cohorts of rigorously phenotyped probands and family members to improve our understanding of the genomic basis of inherited cardiomyopathies [18,47]. By incorporating the prevalent cases that includes the amalgamation of several existing studies in which phenotypic information and DNA have been collected over the last 20 years, in addition to the collection of DNA samples in incident cases, IMHOTEP seeks to assemble one of the largest cohorts of cardiomyopathies in African individuals, whereby the genetic origin of disease can be studied. The variable expressivity and penetrance seen in genetic cardiomyopathies suggest that genetic, epigenetic and environmental modifiers influence disease manifestation, in addition to single pathogenic mutations [18]. IMHOTEP will provide the platform to address the environmental modifying factors that alter the natural history of genetic cardiomyopathy. Importantly, IMHOTEP will stimulate the establishment of cardiogenetics clinical services in Africa, and facilitate the development of cost-effective diagnostic strategies to diagnose genetic cardiomyopathy in low-to-middle-income settings.

5. Strengths and limitations

IMHOTEP is a hospital-based registry and will therefore not address disease burden at the population level. Participating centres will be selected based on the availability of expertise required to diagnose cardiomyopathy and myocarditis, and exclude alternative cardiac conditions such as ischemic heart disease, hypertension, valvular heart disease, congenital heart disease and pericardial disease. This will likely result in an overrepresentation of advanced disease and disease-related adverse events as patients will be recruited from tertiary centres. The pilot phase will provide an opportunity to address operational problems prior to scaling up the study multiple sites in all regions of Africa (see participating sites in Appendix).

6. Summary

Cardiomyopathy and myocarditis contribute significantly to the burden of CVD in Africa and result in considerable morbidity and mortality [4,12,14,48]. Sufficient information on cardiomyopathies and myocarditis in the African population is currently lacking. There is a need for large, well designed, prospective studies to evaluate the clinical, genetic and molecular epidemiology, as well as modifiable risk factors for cardiomyopathy, and the impact cardiomyopathy and myocarditis have on the burden of HF in the population [3,5]. To the best of our knowledge, this is the first multi-national study to record clinical characteristics, adverse events and long-term outcomes of children and adults with heart muscle disease in Africa, with the aim of addressing diagnostic and management deficiencies. The ultimate goal of IMHOTEP is to improve the quality of life and prognosis in affected individuals living in Africa.

Contributions

BMM conceived the idea for this study. BMM, NABN, and SMK developed the first protocol of this work. All authors have contributed to the revision of the protocol and improved upon the design of this study. All authors have approved the final manuscript. NN takes overall responsibility for the contents of this manuscript.

Author statement

Sarah M. Kraus – developed the first protocol of this work, contributed to the revision of the protocol and improved the design of this study, approved the final manuscript.

Gasnat Shaboodien, Veronica Francis, Nakita Verkijk, Jacqui Cirota, Ashley Chin, Shahiemah Pandie, John Lawrenson, George A.M. Comitis, Barend Fourie, Liesl Zühlke, Ambroise Wonkam, Helen Wainwright, Albertino Damasceno, Ana Olga Mocumbi, Lungile Pepeta, Khulile Moeketsi, Baby Thomas, Kandithalal Thomas, Makoali Makotoko, Stephen Brown, Mpiko Ntsekhe, Karen Sliwa, Motasim Badri, Freedom Gumedze, Heather J Cordell, Bernard Keavney, Vanessa Ferreira, Masliza Mahmod, Stefan Neubauer, Leslie T. Cooper, Magdi Yacoub, Hugh Watkins – read and approved the final manuscript.

Bongani M Mayosi – conceived of the idea for the study.

Ntobeko A.B. Ntusi – conceived of the idea for the study, contributed to the revision of the protocol and improved upon the design of this study, approved the final manuscript, and takes overall responsibility for the contents of this manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

This project is funded in part by grants from the International Centre for Genetic Engineering and Biotechnology (ICGEB), the National Research Foundation, the Lily and Ernst Hausmann Research Trust, and is jointly supported by the South African Medical Research Council, Medical Research Council UK (via the Newton Fund) and GSK. Dr. Sarah Kraus is a Helen and Morris Mauerberger Clinical Research Scholar. We are grateful to Sr. Unita September, Ms. Marnie De Waal, Ms. Alexia Joachim, Mr. Lwazi Mhlanti, Ms. Annemie Stewart, Ms. Chedwin Grey, Ms. Lesley Workman, Ms. Sinoxolo Bhovula, Dr. Zita Kerbelker and Ms. Melissa De Vries for expert support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.02.026.

References

[1] O.O. Akinkugbe, G.D. Nicholson, J.K. Cruickshank, Heart disease in blacks of Africa and the Caribbean, Cardiovasc. Clin. 21 (1991) 377–391.

[2] K. Sliwa, B.M. Mayosi, Recent advances in the epidemiology, pathogenesis and prognosis of acute heart failure and cardiomyopathy in Africa, Heart 99 (2013) 1317–1322.

[3] O. Alfieri, B.M. Mayosi, S.J. Park, N. Sarrafzadegan, R. Virmani, Exploring unknowns in cardiology, Nat. Rev. Cardiol. 11 (2014) 664–670.
[4] A. Damasceno, B.M. Mayosi, M. Sani, et al., The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries: results of the sub-saharan africa survey of heart failure, Arch. Intern. Med. 172 (2012) 1386–1394.
[5] B.J. Gersh, K. Sliwa, B.M. Mayosi, S. Yusuf, Novel therapeutic conceptsThe epidemic of cardiovascular disease in the developing world: global implications, Eur. Heart J. 31 (2010) 642–648.
[6] H. Watkins, H. Ashrafian, C. Redwood, Inherited cardiomyopathies, N. Engl. J. Med. 364 (2011) 1643–1656.
[7] B.M. Mayosi, S. Khogali, B. Zhang, H. Watkins, Cardiac and skeletal actin gene mutations are not a common cause of dilated cardiomyopathy, J. Med. Genet. 36 (1999) 796–797.
[8] S.S. Khogali, B.M. Mayosi, J.M. Beattie, W.J. McKenna, H. Watkins, J. Poulton, A common mitochondrial DNA variant associated with susceptibility to dilated cardiomyopathy in two different populations, Lancet 357 (2001) 1265–1267.
[9] P.A. Brink, J.C. Moolman-Smook, V.A. Corfield, Mendelian-inherited heart disease: a gateway to understanding mechanisms in heart disease Update on work done at the University of Stellenbosch, Cardiovasc. J. Afr. 20 (2009) 57–63.
[10] D.A. Watkins, N. Hendricks, G. Shaboodien, et al., Clinical features, survival experience, and profile of plakophylin-2 gene mutations in participants of the Arrhythmogenic Right Ventricular Cardiomyopathy Registry of South Africa, Heart Rhythm. 6 (2009) S10–S17.
[11] M. Fish, G. Shaboodien, S. Kraus, et al., Mutation analysis of the phospholamban gene in 315 South Africans with dilated, hypertrophic, peripartum and arrhythmogenic right ventricular cardiomyopathies, Sci. Rep. 6 (2016) 22235.
[12] N.A. Ntusi, G. Shaboodien, M. Badri, F. Gumedze, B.M. Mayosi, Clinical features, spectrum of causal genetic mutations and outcome of hypertrophic cardiomyopathy in South Africans, Cardiovasc. J. Afr. 27 (2016) 152–158.
[13] B.M. Mayosi, M. Fish, G. Shaboodien, et al., Identification of cadherin 2 (CDH2) mutations in arrhythmogenic right ventricular cardiomyopathy, Circ. Cardiovasc. Genet. 10 (2017).
[14] G. Shaboodien, C. Maske, H. Wainwright, et al., Prevalence of myocarditis and cardiotropic virus infection in Africans with HIV-associated cardiomyopathy, idiopathic dilated cardiomyopathy and heart transplant recipients: a pilot study, Cardiovasc. J. Afr. 23 (2013) 1–6.
[15] L.T. Cooper Jr., A. Keren, K. Sliwa, A. Matsumori, G.A. Mensah, The global burden of myocarditis: part 1: a systematic literature review for the Global Burden of Diseases, Injuries, and Risk Factors 2010 study, Glob. Heart 9 (2014) 121–129.
[16] B.J. Maron, J.A. Towbin, G. Thiene, et al., Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention, Circulation 113 (2006) 1807–1816.
[17] L. Blauwet, L.T. Cooper, Cardiotropic viral infection in HIV-associated cardiomyopathy: pathogen or innocent bystander? Cardiovasc. J. Afr. 24 (2013) 199–200.
[18] T.J. Cahill, H. Ashrafian, H. Watkins, Genetic cardiomyopathies causing heart failure, Circ. Res. 113 (2013) 660–675.
[19] P. Elliott, B. Andersson, E. Arbustini, et al., Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases, Eur. Heart J. 29 (2008) 270–276.
[20] A.O. Mocumbi, M.B. Ferreira, D. Sidi, M.H. Yacoub, A population study of endomyocardial fibrosis in a rural area of Mozambique, N. Engl. J. Med. 359 (2008) 43–49.
[21] P.G. D'Arbela, T. Mutazindwa, A.K. Patel, K. Somers, Survival after first presentation with endomyocardial fibrosis, Br. Heart J. 34 (1972) 403–407.
[22] B.M. Mayosi, K. Somers, Cardiomyopathy in Africa: heredity versus environment, Cardiovasc. J. Afr. 18 (2007) 175–179.
[23] A. Grimaldi, A.O. Mocumbi, J. Freers, et al., Tropical endomyocardial fibrosis: natural history, challenges, and perspectives, Circulation 133 (2016) 2503–2515.
[24] K. Sliwa, A. Damasceno, B.M. Mayosi, Epidemiology and etiology of cardiomyopathy in Africa, Circulation 112 (2005) 3577–3583.
[25] F.C. Adi, Endomyocardial fibrosis in two brothers, Br. Heart J. 25 (1963) 684–688.
[26] A.K. Patel, J.L. Ziegler, P.G. D'Arbela, K. Somers, Familial cases of endomyocardial fibrosis in Uganda, Br. Med. J. 4 (1971) 331–334.
[27] A.M.D. Beaton, C.M.D. Sable, J.P. Brown, et al., Genetic susceptibility to endomyocardial fibrosis, Global Cardiol. Sci. Pract. 2014 (2014) 473–481.
[28] N.B.A. Ntusi, M. Badri, F. Gumedze, A. Wonkam, B.M. Mayosi, Clinical characteristics and outcomes of familial and idiopathic dilated cardiomyopathy in Cape Town: a comparative study of 120 cases followed up over 14 years, S. Afr. Med. J. 101 (2011) 399–404.
[29] N.B.A. Ntusi, A. Wonkam, G. Shaboodien, M. Badri, B.M. Mayosi, Frequency and clinical genetics of familial dilated cardiomyopathy in Cape Town: implications for the evaluation of patients with unexplained cardiomyopathy, S. Afr. Med. J. 101 (2011) 394–398.
[30] M.A. Latib, K. Michaels, B.M. Mayosi, Initial report of the Arrhythmogenic right ventricular cardiomyopathy registry of South Africa: 2004, Cardiovasc. J. S. Afr. 15 (2004) 237–238.
[31] S. Sagar, P.P. Liu, L.T. Cooper Jr., Myocarditis, Lancet 379 (2012) 738–747.
[32] C. Rapezzi, E. Arbustini, A.L. Caforio, et al., Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases, Eur. Heart J. 34 (2013) 1448–1458.
[33] P.M. Elliott, A. Anastasakis, M.A. Borger, et al., 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy, Eur. Heart J. 35 (2014) 2733–2779.
[34] I. Kindermann, C. Barth, F. Mahfoud, et al., Update on myocarditis, J. Am. Coll. Cardiol. 59 (2012) 779–792.
[35] C.M. Kramer, J. Barkhausen, S.D. Flamm, R.J. Kim, E. Nagel, Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized P. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols, J. Cardiovasc. Magn. Reson. 10 (2008) 35.
[36] C.M. Kramer, J. Barkhausen, S.D. Flamm, R.J. Kim, E. Nagel, Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized P. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update, J. Cardiovasc. Magn. Reson. 15 (2013) 91.
[37] American College of Cardiology Foundation Task Force on Expert Consensus D, W.G. Hundley, D.A. Bluemke, et al., ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents, J. Am. Coll. Cardiol. 55 (2010) 2614–2662.
[38] J.C. Moon, D.R. Messroghli, P. Kellman, et al., Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of cardiology consensus statement, J. Cardiovasc. Magn. Reson. 15 (2013) 92.
[39] J. Schulz-Menger, D.A. Bluemke, J. Bremerich, et al., Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing, J. Cardiovasc. Magn. Reson. 15 (2013) 35.
[40] V.M. Ferreira, S.K. Piechnik, M.D. Robson, S. Neubauer, T.D. Karamitsos, Myocardial tissue characterization by magnetic resonance imaging: novel applications of T1 and T2 mapping, J. Thorac. Imaging 29 (2014) 147–154.
[41] S. Mercier, S. Kury, G. Shaboodien, et al., Mutations in FAM111B cause hereditary fibrosing poikiloderma with tendon contracture, myopathy, and pulmonary fibrosis, Am. J. Hum. Genet. 93 (2013) 1100–1107.
[42] D.G. MacArthur, T.A. Manolio, D.P. Dimmock, et al., Guidelines for investigating causality of sequence variants in human disease, Nature 508 (2014) 469–476.
[43] J.C. Taylor, H.C. Martin, S. Lise, et al., Factors influencing success of clinical genome sequencing across a broad spectrum of disorders, Nat. Genet. 47 (2015) 717–726.
[44] M.A. Kelly, C. Caleshu, A. Morales, et al., Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel, Genet. Med. 20 (2018) 351–359.
[45] B. Bozkurt, M. Colvin, J. Cook, et al., Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association, Circulation 134 (2016) e579–e646.
[46] B.M. Mayosi, S.R. Benatar, Health and health care in South Africa - 20 years after Mandela, N. Engl. J. Med. 371 (2014) 1344–1353.
[47] R.E. Hershberger, D.J. Hedges, A. Morales, Dilated cardiomyopathy: the complexity of a diverse genetic architecture, Nat. Rev. Cardiol. 10 (2013) 531–547.
[48] N.A.B. Ntusi, G. Shaboodien, M. Badri, F. Gumedze, B.M. Mayosi, Clinical features, spectrum of causal genetic mutations, and outcome of hypertrophic cardiomyopathy in South Africans, Cardiovasc. J. Afr. 27 (3) (2016) 152–158.