CRITICAL ANALYSIS OF RHEUMATIC MITRAL VALVE SURGERY OUTCOMES IN CENTRAL SOUTH AFRICA

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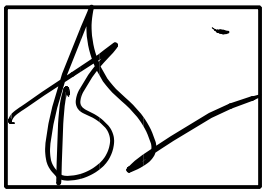
Declaration of Independent Work

I, Thabo J. De-huis declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education."



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October 2021

Signature **Date**

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i. Abstract for Dissertation

Introduction: Rheumatic heart disease (RHD) is still an important cause of acquired heart disease affecting children and young adults from poor socio-economic backgrounds. The most common presentation of RHD is mitral valve disease requiring surgical intervention. The study aim was firstly to describe peri-operative risk factors, procedures performed and surgical outcomes after mitral valve surgery for RHD in Central South Africa. Secondly, to compare these results in patients presenting with mitral regurgitation to those presenting with mitral stenosis and mixed mitral valve disease.

Methods: Patients undergoing mitral valve surgery for RHD, with or without concomitant tricuspid valve repair between January 2009 and December 2019 were identified from the departmental database. The lesions were grouped into mitral stenosis (MS), mitral regurgitation (MR), and mixed mitral (MX) disease. Statistical analyses was performed using the IBM SPSS program, version 26.0. A p-value of 0.05 or less was considered statistically significant.

Results: A total of 242 patients were included in the study of which 75.2% (n=182) were female. Black patients represented 74.4% (n=180), whites 13.6% (n=33) with Asian and mixed races at 12% (n=29). The mean age of the study population was 43.7 years. Distribution of patients according to the lesions was 25.6% (n=62) for MS, 45.0% (n=109) for MR and 29.3% (n=71) for MX disease. Patients presenting in NYHA status III and IV formed 44% of the MR group and 44% of the MS group and for 28% for the MX group. Calculated EuroSCORE > 5 was 29.4% (n=18) in the MS group, 29% (n=32) in the MR group, and 9.9% (n=7) in the MR group.

For the MS group, 96.7% (n=60) had mitral valve replacement and only 2.8% (n=2) were repaired (valvotomy); whilst in the MR and MX groups the replacement vs repair rate was 90.3% (n=93) and 94% (n=63) vs 9.7% (n=10) and 5.6% (n=4) respectively. The MS group had the highest number of concomitant tricuspid valve repair at 58.0% (n=36) as compared to MR (38.5%) and MX (35.2%) groups. There was no statistical difference across the groups with regards to the post-operative stroke rate (1%) as well as the rate of in-hospital complications

(14%). In-hospital mortality for the entire cohort was 3.8% (n=9), with 4.8% (n=3) for the MS, 3.7% (n=4) in the MR group and 2.8% (n=2) in the MX group. Of the 242 patients in the study 82 did not have their follow up at the UAH clinic. For the 160 patients followed up at UAH clinic, the median follow-up time was 2.68 years, with 35 patients having had follow-up visits > 5 years.

Conclusion: Patients received mitral valve surgery had RHD and were young females from poor socio-economic backgrounds with an average age in the 4th decade of life. MR was the most common lesion with replacement being the most performed operation in our unit. The post-operative complications rate as well as the in-hospital mortality were comparable to the published literature.

Word count: 484

Keywords

Rheumatic heart disease, mitral stenosis, regurgitation, mixed valve disease, bioprosthesis, mitral valve repair, balloon mitral valvotomy, mitral replacement, tricuspid valve, in-hospital mortality.

ii. Glossary

Acute Rheumatic Fever:
A sequela of streptococcal infection – typically following 2 to 3 weeks after a group A streptococcal throat infection that commonly occurs in children, and has rheumatological, cardiac, and neurological manifestations.

Aetiology:
Study or theory of the factors that cause diseases or disorders.

Aldosterone antagonist:
An agent that opposes the action of the adrenal hormone aldosterone on renal tubular mineralocorticoid retention, these agents (e.g., spironolactone) are useful in treating the hypertension of primary hyperaldosteronism, or the sodium retention of secondary hyperaldosteronism.

Angiotensin converting enzyme inhibitors:
A class of drugs (angiotensin-converting enzyme inhibitors) that block the conversion of angiotensin I to angiotensin II, used in the treatment of hypertension and congestive heart failure and in the prevention of microvascular complications of diabetes mellitus (DM).

Antibody cross-reactivity:
The ability of an antibody to react with similar antigenic sites on different proteins

Anticoagulation:
The process of hindering the clotting of blood.

Antigen mimicry:
The sharing of antigenic sites between microorganisms and mammalian tissue.

Aortic valve:
The aortic valve is a valve in the human heart between the left ventricle and the aorta.

Asymptomatic:
Presenting no symptoms of disease.

Atrial fibrillation:
An irregular, rapid heart rate that may cause symptoms like heart palpitations, fatigue, and shortness of breath.

Auscultation:
The action of listening to sounds from the heart, lungs, or other organs, typically with a stethoscope, as a part of medical diagnosis.

Autoimmune:
When the body tissues are attacked by its own immune system.

Beta blockers:
Any of a class of drugs which prevent the stimulation of the adrenergic receptors responsible for increased cardiac action, used to control heart rhythm, treat angina, and reduce high blood pressure.

Calcium channel blockers:
Prescription medications that relax blood vessels and increase the supply of blood and oxygen to the heart while also reducing the heart's workload.

Carditis:
The inflammation of the heart or its surroundings.

Chronic rheumatic heart disease:
Describes a group of long-term (chronic) heart disorders that can occur because of rheumatic fever.

Commissurotomy:
A surgical incision of a commissure in the body, as one made in the heart at the edges of the commissure formed by cardiac valve.

Diuretics:
Also called water pills, are medications designed to increase the amount of water and salt expelled from the body as urine.

Dyspnea:
Difficult or laboured breathing; shortness of breath.

Echocardiography:
The use of ultrasound waves to investigate the action of the heart.

Ejection fraction:
Is a measurement of the percentage of blood leaving your heart each time it contracts.

Endocarditis:
An infection of the inner lining of the heart or its valves.

Endoscopy:
A procedure in which an instrument is introduced into the body to give a view of its internal parts.

Embolic event:
Occurs when a blood clot that forms elsewhere in the body breaks loose and travels to the other part of the body via the bloodstream and causes an obstruction to blood flow.

Haemoptysis:
The coughing up of blood.

Haemorrhage:
A profuse discharge of blood, as from a ruptured blood vessel; bleeding.

Heparin:
A substance that slows the formation of blood clots.

Incidence:
The occurrence, rate, or frequency of a disease.

Left atrium:
The left upper chamber of the heart that receives blood from the pulmonary veins.

Left ventricle:
The chamber on the left side of the heart that receives arterial blood from the left atrium and pumps it into the aorta.

Mechanical valve:
Prosthetics designed to replicate the function of the natural valves of the human heart.

Mixed mitral valvular pathology:
Refers to coexisting mitral stenosis (MS) and mitral regurgitation (MR).

Morbidity:
The quality or state of being morbid.

Mortality:
The state of death.

Native valve:
Natural valve.

Nitrates:
Medications used for treating or preventing heart pain (angina, chest pain) caused by heart disease, usually of the arteries in the heart.

Palpitations:
The feelings of having a fast beating, fluttering, or pounding heart.

Pancarditis:
Inflammation of the entire heart (the epicardium and the myocardium and the endocardium) carditis - inflammation of the heart

Papillary muscle:
Are muscles located in the ventricles of the heart.

Percutaneous:
Made, done, or effected through the skin.

Pharyngitis:
Inflammation of the pharynx, causing a sore throat.

Prevalence:
A statistical concept referring to the number of cases of a disease that are present in a particular population at a given time.

Prosthetic valve:
A prosthetic heart valve is surgically implanted in the heart to replace a heart valve that has become damaged due to heart valve disease.

Pulmonary congestion:
Accumulation of fluid in the lungs, resulting in impaired gas exchange and arterial hypoxemia.

Regurgitation:
A leaky state of one or more of the cardiac valves, in which the valve not closing tightly, and blood is therefore regurgitating through it.

Robotic telemanipulations:
Indicate the capability of a human being of carrying out operations in a remote environment by means of a proper robotic system.

Scarlet fever:
An infectious bacterial disease affecting especially children and causing fever and a scarlet rash.

Stenosis:
The narrowing or restriction of a blood vessel or valve that reduces blood flow.

Sternotomy:
A type of surgical procedure in which a vertical inline incision is made along the sternum, after which the sternum itself is divided.

Streptococcus pyogenes:
Ubiquitous bacterium responsible for hundreds of millions of illnesses throughout the world each year, some of which are fatal.

Thoracotomy:
Surgical incision into the chest wall.

Thrombus:
A blood clot formed in situ within the vascular system of the body and impeding blood flow.

Valvulitis:
Inflammation of the valves of the heart.

Sources

(https://www.mayoclinic.org/diseases-conditions, https://reference.medscape.com/, https://medical-dictionary.thefreedictionary.com/source)

iii. List of Abbreviations

AF	Atrial fibrillation
ARF	Acute rheumatic fever
BMV	Balloon mitral valvotomy
CI	Confidence interval
CRHD	Chronic rheumatic heart disease
CTS	Cardiothoracic surgery
GAS	Group A streptococcus
GBD	Global burden of disease
GCP	Good clinical practice
HIV	Human deficiency virus
INR	International normalising ratio
LA	Left atrium
LVEF	Left ventricular ejection fraction
LV	Left ventricle
MV	Mitral Valve
NYHA	New York Heart Association
PI	Principal Investigator
PVR	Prosthetic valve replacement
RHD	Rheumatic heart disease
RHVD	Rheumatic heart valvular disease
SAMJ	South African Medical Journal
UAH	Universitas Academic Hospital
UFS	University of the Free State
VCAM1	Vascular cellular adhesion molecule 1
WHF	World Health Forum
WHO	World Health Organisation

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1. Literature Review

1.1 Introduction

There have been interesting theories about the causes of infectious diseases, which included the bad air (miasma) and the contagion theories, which date as far back as Hippocrates times (Pappas *et al*., 2008). These were also associated with rheumatic fever and its clinical manifestations noted in 1685 by Thomas Sydenham, and the association between rheumatism and heart disease was confirmed by Bouillaud, who was a French physician in the 1800s (Hajar, 2016). In 1889 Cheadle described the clinical presentation of ARF (Seckeler and Hoke, 2011). Rheumatic heart valvular disease (RHVD) remains an important acquired heart disease for children and young adults in under-developed and developing parts of the world (Carapetis *et al*., 2016).

An infection by a group A Streptococcus (GAS) bacterium, *Streptococcus pyogenes*, infects the pharynx and causes an autoimmune reaction resulting in a condition called acute rheumatic fever (ARF). This infection can present in different ways including joint pains, fever, heart valvular complications which include mitral valve disease such as regurgitation (MR), stenosis (MS) or a mixture (MX) of the two, chorea, and skin related manifestations as summarized in figure 1.1.

- Large joint arthritis and/or arthralgia, usually with fever, and sometimes with pansystolic murmur of mitral regurgitation.
- Acute fever, tiredness, and breathlessness from cardiac failure, with or without other manifestations (most commonly joint pain and/or swelling) and pansystolic murmur of mitral regurgitation.
- Choreiform movements, commonly with behavioural disturbance but often without other manifestations.
- Gradual onset of tiredness and breathlessness, which is indicative of cardiac failure, without fever or other manifestations, and pansystolic murmur of mitral regurgitation, which indicates the insidious onset of carditis.

*Skin manifestations (erythema marginatum and subcutaneous nodules).

Figure 1.1. Most common clinical presentations of acute rheumatic fever (Carapetis *et al*., 2016).

The infection with GAS organisms induces an autoimmune response in the host wherein the different immune response cell such as T cells and macrophages are activated. It is during this response against the antigens that there host's own tissues are damaged. These tissues include the heart, brain, skin and joint surfaces (Ellis *et al*., 2005).

RHVD develops due to either the chronicity of the infection or more commonly, to the repeated episodes of infection by GAS during ARF (Carapetis *et al*., 2005a). Mitral valve regurgitation is a condition in which the heart's mitral valve doesn't close tightly, which allows blood to flow backward in the heart. This leads to the left ventricle not being able to efficiently pump blood through the aorta as blood is pumped back into the left atrium. Mitral stenosis is a narrowing of the heart's mitral valve. This abnormal valve doesn't open properly, blocking blood flow into the main pumping chamber of your heart (left ventricle). Mixed mitral valve disease refers to coexisting MS and MR (Remenyi *et al*., 2012). Patients with RVHD can present with heart failure symptoms, with/without associated rhythm abnormalities, which may be complicated by peripheral thromboembolic events (Nishimura *et al*., 2017). Presence of the above-mentioned symptoms, with advanced age and severe valvular disease, were risk factors for poor outcomes (Zühlke *et al*., 2016).

In 2012, the World Heart Federation (WHF) described echocardiographic diagnostic guidelines to help with early diagnosis and initiation of appropriate management in patients with RHVD (Remenyi *et al*., 2012). The lack of surgical and medical interventions in low- and middle-income countries have been shown to have an adverse outcome (Zühlke *et al*., 2016).

In severe forms of ARF, the best way of management is generally hospitalization and symptomatic treatment until the patient stabilizes. Note that ARF has a potential to reoccur in patients who have recovered and that these subsequent infections can lead to more severe degrees of RHD. It is because of this possible reoccurrence of infection that long-term treatment with penicillin as a form of secondary prevention is important in the management strategy (Carapetis *et al*., 2016). In chronic cases of RHVD, the role of medical management is to treat symptoms such as heart failure and AF by using afterload reduction therapy such as diuretics and anticoagulation drugs such as warfarin, respectively (Elder *et al*., 2011).

There was a 16.9% 2-year fatality rate demonstrated in the REMEDY study in patients with RHD who were followed without surgical intervention. This high rate was common in patients with severe valve disease, congestive heart failure, NYHA class III/IV and advanced age (Zühlke *et al*., 2016).

Surgical interventions include percutaneous balloon mitral valvotomy (BMV), especially in younger and pregnant patients with isolated cases of MS and, have been shown to have comparable long-term outcomes to open mitral commissurotomy (Song *et al*., 2010). Open surgical intervention is another option in patients not suitable for BMV with complex disease process. Procedures include mitral valve commissurotomy (not commonly performed), valve repair or replacement with either a mechanical or biological prosthesis (Hajar, 2016). The choice between which procedure to do is dependent on patient factors, such as age, gender (with consideration to possible future pregnancies), severity of the valvular disease, whether early or advanced presentations, and surgeons experience with repair techniques (Moorthy *et al*., 2019). Tricuspid valve requiring intervention during mitral valve surgery, which is commonly associated with MS, is also attended to (Sarralde *et al*., 2010).

Late presentation with advanced disease process denoted by New York Heart Association (NYHA) class III/IV, severe heart failure, old age, extreme socio-economic status and complications from thromboembolic events such as stroke, are independent predictors of poor outcome both in pre- and post-operative periods (Zühlke *et al*., 2016).

Seventy-five percent of patients with isolated MS benefit from BMV in a long-term follow-up, with 8%-10% requiring a repeat procedure (Meneguz-Moreno *et al*., 2018). In institutions where repair is routinely performed, the long-term survival of patients has been reported to be superior to those who received replacement, though there is a fairly increased rate of reoperation due to repair failure in the rheumatic patients than the non-rheumatics (Antunes, 2018).

RHVD, still remains an important public health concern in low- and middle-income regions. Though some of the case series published may indicate a potential decline in the prevalence

of RHD, a concerted effort from affected governing structures needs to be applied in order to address this health burden and to allow for correct quantification. Financial as well as skilledpersonnel support are needed in areas where the disease is endemic in order to assist with early diagnosis and management.

1.2 Epidemiology

According to a 2005 review, about 241, 000 cases of ARF were reported each year and of these, 336,000 were of children between the ages of 5-14 years. Furthermore, it reported that the prevalence was between 15.6 and 19.6 million for RHD with the annual estimated deaths from RHD around 350,000 from both ARF and RHVD. It is imperative to note that all these deaths occurred in countries with low income as compared to high-income countries (Carapetis *et al*., 2005a).

A more recent study performed by the Global Burden of Disease showed that there is an estimated 33 million cases of RHD that are prevalent as shown in figure 1.2. This results in 275,000 mortality per annum and with the Disability-Adjusted Years (Daly) of about 9 million cases (Remenyi *et al*., 2012).

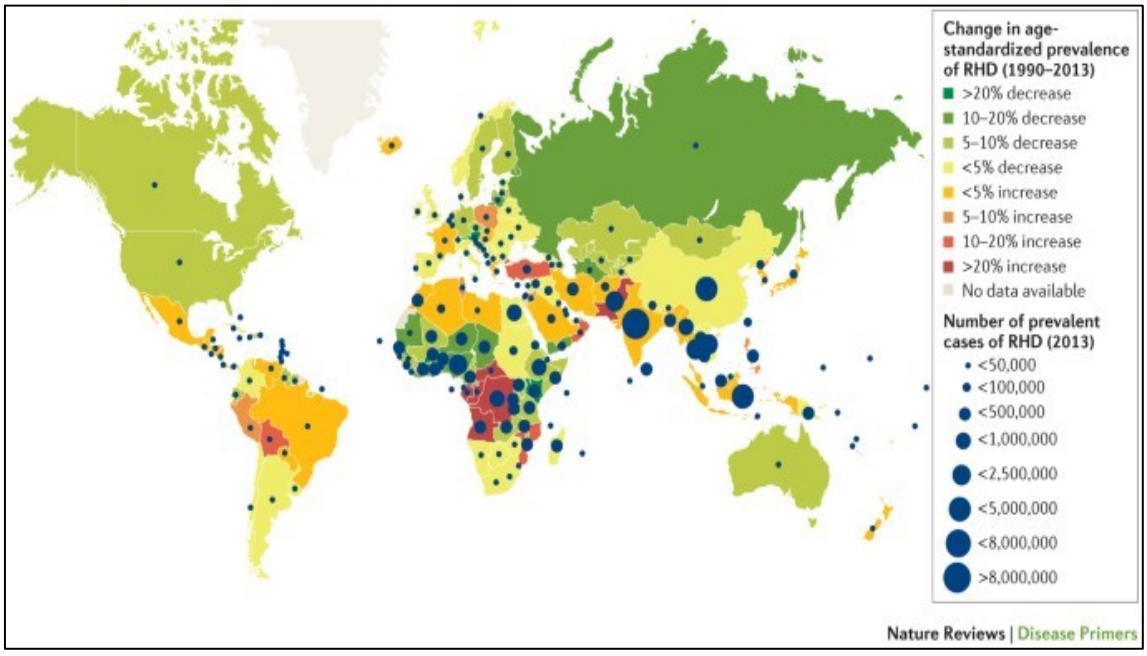


Figure 1.2. Number of prevalent cases of rheumatic heart disease in 2013 and the change in age standardized prevalence from 1990 to 2013 (Remenyi *et al*., 2012).

In a 2005 population-based study conducted on the continent of Africa, there was an estimated 5.7/1000 prevalence in the sub-Saharan populations and 1.8/1000 in the North African regions between the years 1980 to the 1990s as shown in figure 1.3 (Carapetis *et al*., 2005a).

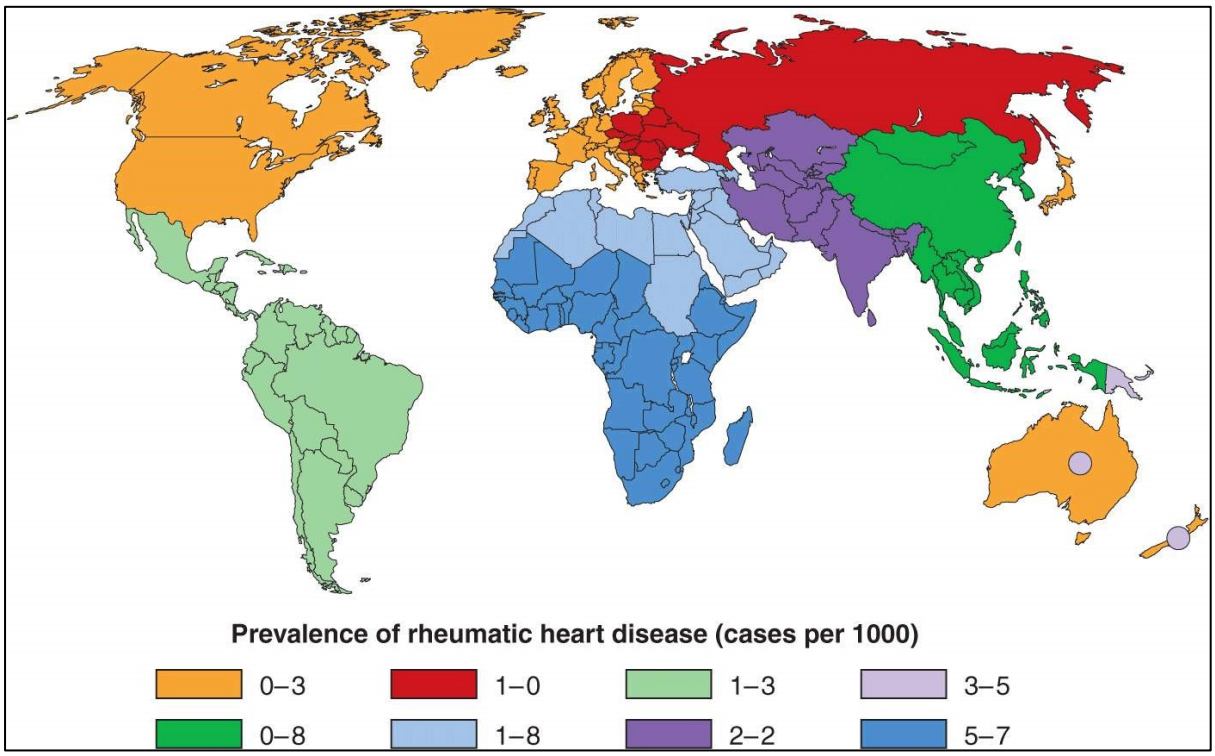


Figure 1.3. Prevalence of rheumatic heart disease in children aged between 5 and 14 years (Carapetis *et al*., 2005a).

In 1974, a school-screening program in South Africa reported that the prevalence of RHD in children who were asymptomatic and were clinically examined by an auscultation method to be 5.9/1000 (McLaren *et al*., 1975). In the age-related subgroup of 17-20 years a prevalence of 21/1000 was found. Surgical reviews that were published over a decade later showed an increase in RHD related mortality (Marcus *et al*., 1994).

In 2015, Engel published a prospective echocardiographic study on the prevalence of asymptomatic schoolchildren in Cape Town South Africa and Jimma Ethiopia. The Cape Town groups reported a high percentage of borderline RHD findings. If only definite RHD diagnoses are considered, the RHD prevalence was 2.3/1 000 in Bonteheuwel and 6.9/1 000 in Langa

(Engel *et al*., 2015). These prevalence findings were similar to a study done by Smit et al (2015) that conducted a prospective study on schoolchildren in central South Africa with a prevalence of 4.9/1000.

In a Cape Town study conducted in 2016 amongst schoolchildren using an echocardiography, it was shown that the actual prevalence of RHD was higher than that which was reported in earlier studies conducted about three decades ago. It was reported be about 20.2/1000, which is much higher than other estimates (Shung-King *et al*., 2016). This could possibly be attributed to interpretation of echocardiography results in which possible cases were interpreted as definite.

Another study conducted in Soweto, South Africa, demonstrated that there is an inverse relationship between the prevalence of ARF which is declining as compared to that of RHD in the adult population as shown in figure 1.4 (Mayosi 2016).

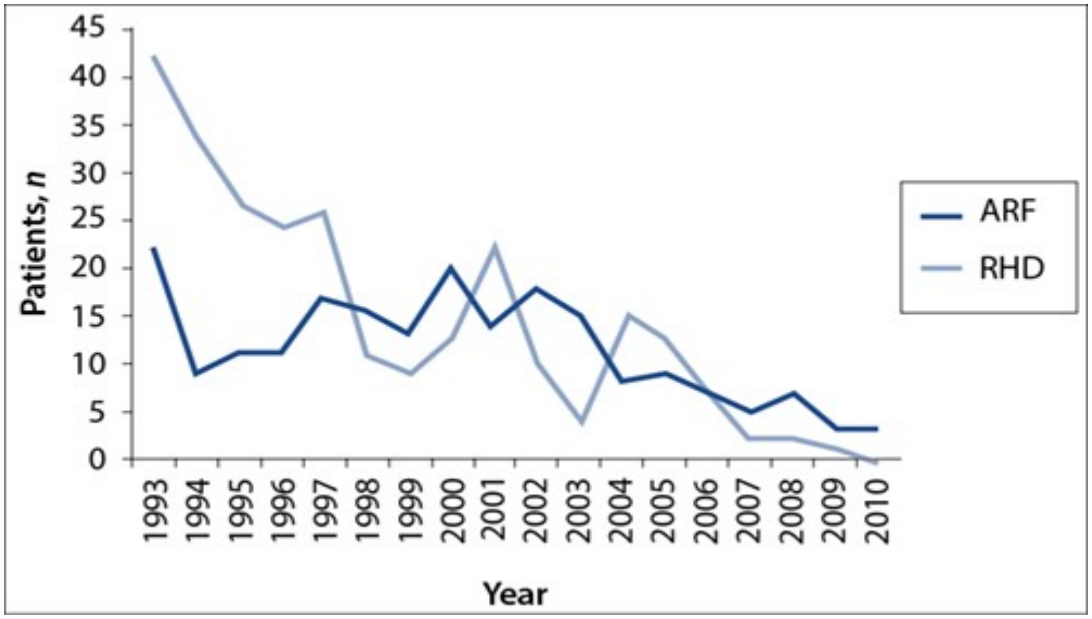


Figure 1.4. Rheumatic heart disease and acute rheumatic fever trends in Soweto, 1993– 2010 (Mayosi 2016).

These changes could, to an extent, be attributed to the changing in socio-economic conditions of most of the people in South Africa who were subjected to poverty and malnutrition during

the apartheid era, which seem to improve somewhat after the 1994 change in political leadership (Mayosi 2016).

1.3 Risk Factors

1.3.1 Age

Most cases of ARF occur in children between the ages of 5-14 years old. There are instances where cases of ARF have been reported in children as young as 2-3 years old (Lawrence *et al.,* 2013). First time cases can also occur in older people, though not so common. Recurrent infections turn to be common in older children as well as young adults, but rarely in patients above the ages of 35-40 years (Parnabay and Carapetis, 2010). RHD is a chronic disease that results from accumulated injuries to the heart valves due to either a single or more commonly, recurrent episodes of infection with GAS from ARF. Thus, RHD turns to peak later in life between the ages 25-45 years (Carapetis *et al*., 2005a).

1.3.2 Sex

Although the ARF prevalence is similar between males and females, RHD affects women more than males (Hajar, 2016; Rothenbuhler *et al*., 2014). Reasons for these differences are not obvious, however certain factors such as increased autoimmune susceptibility (intrinsic) and close contact with GAS during child rearing (extrinsic), have been proposed as some of the possible causes (Sawhney *et al*., 2003; Yacoub2004). Other factors that still need to be investigated include the possible unequal access to health care between girls and women compared to boys and men in certain parts of the world, which might be due to many reasons intrinsic to these regions. About 25% of maternal deaths during pregnancy in data from South Africa and Senegal are noted to be indirectly related to RHD (Diao *et al*., 2011). It should be noted that this complication during pregnancy is related to the worsening of hemodynamics that occur during pregnancy in patients with pre-existing RHD and not because of the severity of ARF or RHD (Sawhney *et al*., 2003).

1.3.3 Environmental Factors

Environmental factors seem to affect the differences that are seen amongst different populations. Many of these factors overlap and thus make it difficult to tease each of them out individually. What seems to be common however is the poor socio-economic background that most of these patients come from (Steer *et al.,* 2002).

An association between overcrowding in households and high prevalence of ARF and RHD have been described and that reduction of this towards smaller households has had a great impact in the reduction of the disease entities (Jaine *et al*., 2011). In other parts of the world where ARF and RHD prevalence is high, there is an association with the geographical location the given population is found. For example, there might be high prevalence in the people who stay in a rural area of a given region as opposed to those who stay in urban areas, highlighting the possibility of access to medical services as well as economic inequalities (Steer *et al*., 2002). Other important factors, which form part of access to medical services, include health education as was shown in the French Caribbean and Cuba programs (Nordet *et al*., 2008). Other social injustices such as war, which result in displacement and crowding, have shown that the incidence of ARF and RHD turns to increase in these populations (Omurzakova *et al*., 2009).

1.4 Pathophysiology

The initial reaction after throat infection by the GAS is that the inflammatory cells such as neutrophils and macrophages attack and destroy the bacteria as well as presentation of antigen to T cells (Ben-Pazi *et al*., 2013). The initial reaction of T and B cells to this antigen is through the production of antibodies, which is then followed by T cells activation. An autoimmune reaction can occur against the patient's own tissues leading to injuries of some organ systems such as the cardiovascular, brain, joints, as well as the skin. The molecular mimicry is the process by which this autoimmune response is mediated as shown in figure 1.5 (Ellis *et al*., 2005). The process of molecular mimicry is the sharing of T cell epitopes of the infecting organism and the infected organism (Cunningham *et al*., 2014). Therefore, during this process, the antibodies, which are produced to fight off the infection also attack the host tissues (Fae *et al*., 2006).

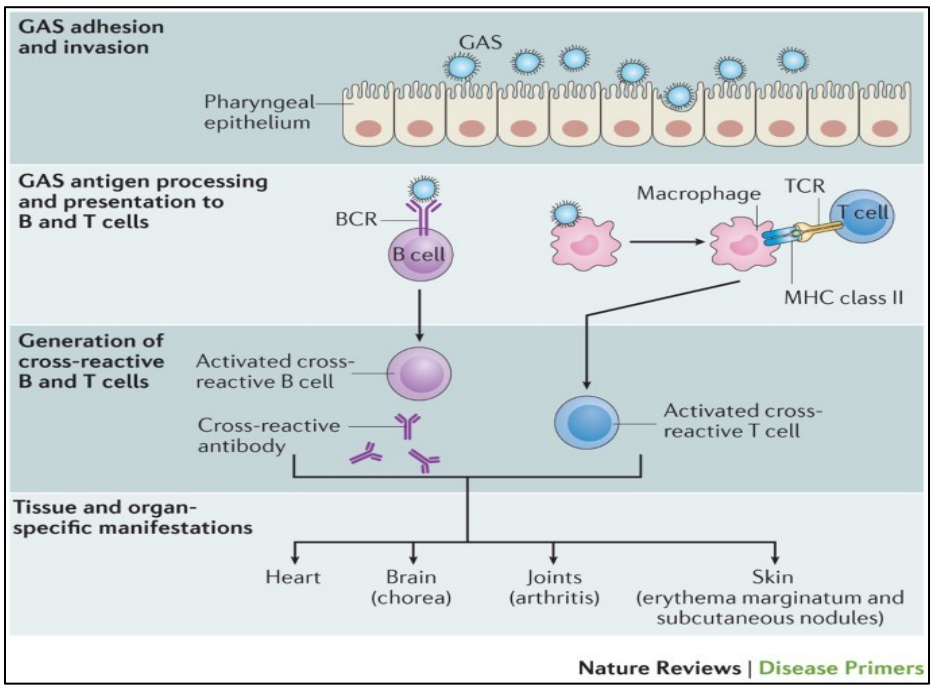


Figure 1.5. Generation of a cross-reactive immune response in acute rheumatic fever (Ellis *et al*., 2005).

Because of this autoimmune reaction, there is also a generalized cross-reaction between the immune system's response and the host tissue, resulting in multiple joints being affected as shown in figure 1.6. Arthritis might be a result of the formation of immune complexes that bind to the synovial membrane and/or collagen in joints, which leads to recruitment of inflammatory cells (Carapetis *et al*., 2016).

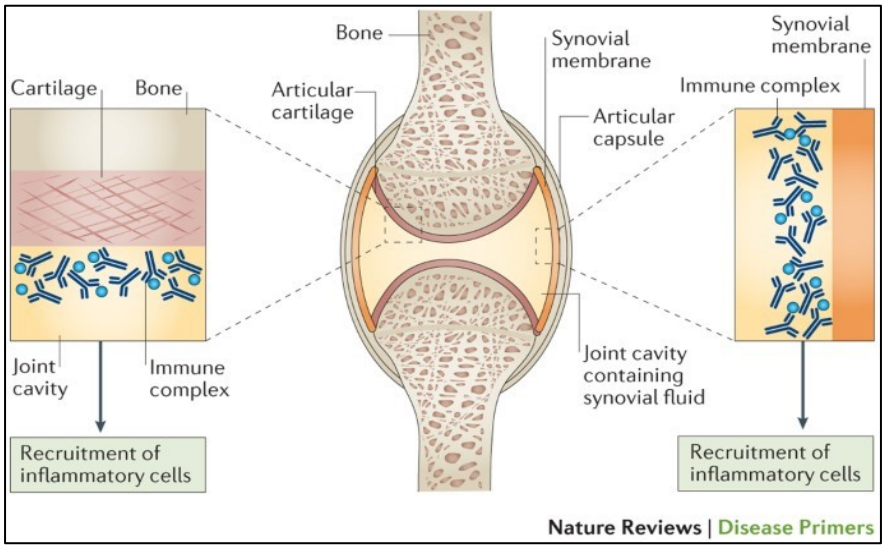


Figure 1.6. Manifestations of acute rheumatic fever in the joints (Carapetis *et al*., 2016).

Other systems which are affected include the central nervous system in which the immune complex react with the basal ganglia of the brain tissue (figure 1.7), resulting in a condition called Sydenham's chorea. In the skin when the antibodies react with keratin result in a condition known as erythema, marginatum as well as subcutaneous nodules (figure 1.8). Lastly, in the cardiovascular system, the heart muscle and its valves are affected (figure 1.9) (Carapetis *et al*., 2016)**.**

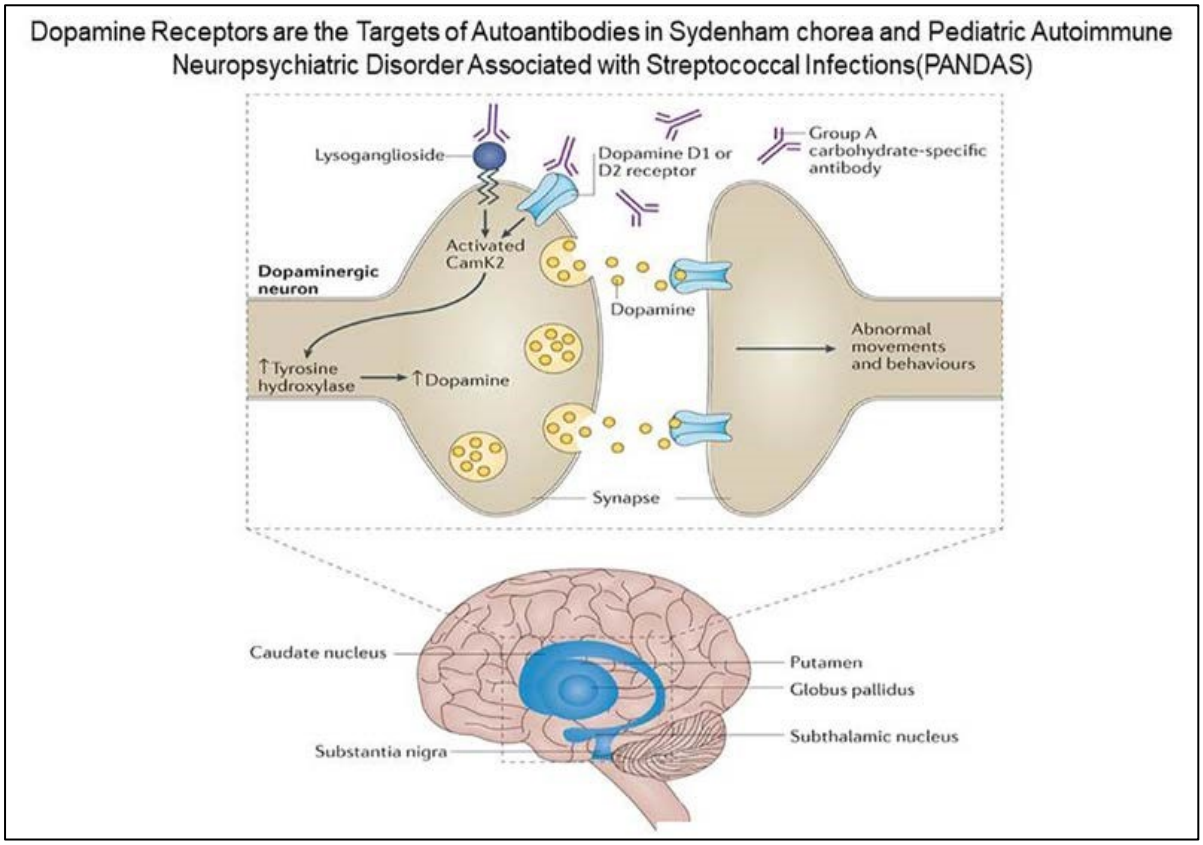


Figure 1.7. Molecular and cellular basis of Sydenham's chorea (Carapetis *et al*., 2016).

In Sydenham's chorea as shown in figure 1.7, neurons in the basal ganglia are attacked by antibodies against the group A carbohydrate of Streptococcus spp. that react with the surface of the neuron. This reaction activates signalling through calcium/calmodulin-dependent protein kinase type II (CAMK2), which involves an increase in tyrosine hydroxylase in dopaminergic neurons. Receptors, such as the D1 and D2 dopamine receptors, and lysoganglioside might be autoantibody targets on the neuronal cell. This targeting could lead

to altered cell signalling and increased levels of dopamine, in turn leading to abnormal movements and behaviours (Carapetis *et al*., 2016).

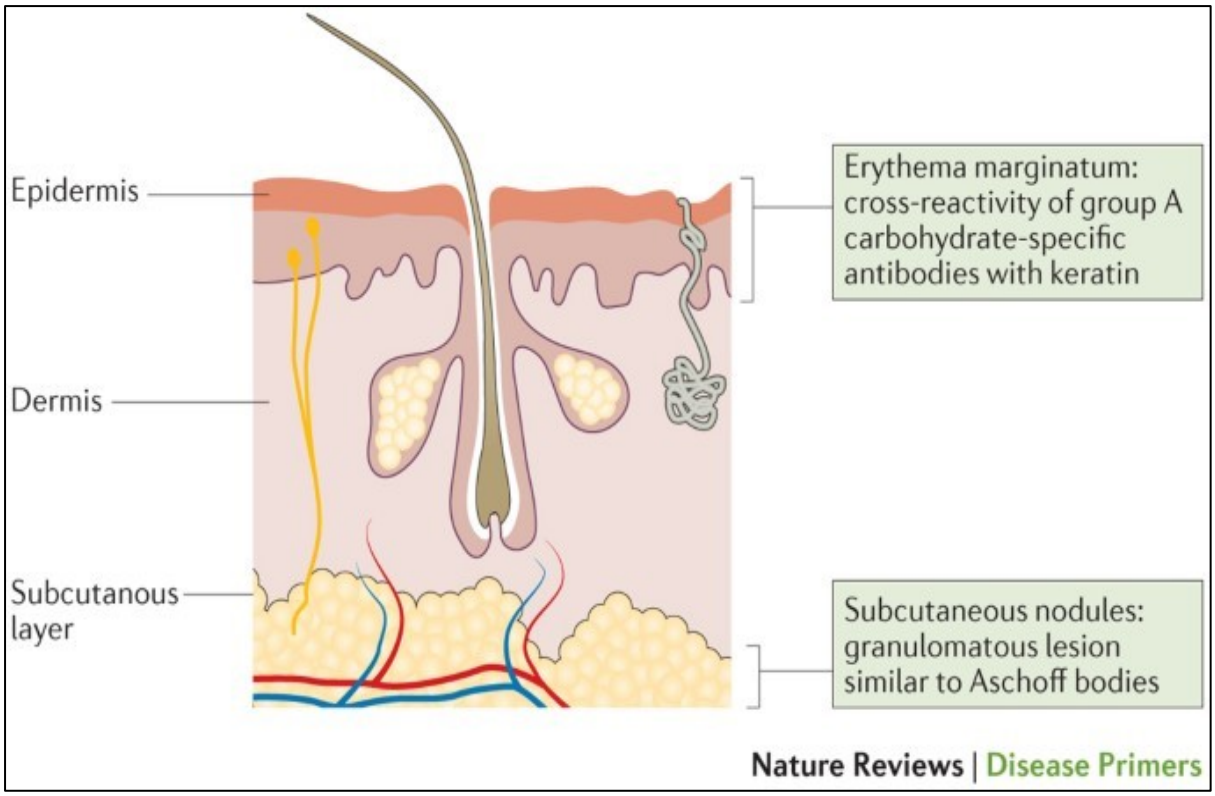


Figure 1.8. Skin manifestations of acute rheumatic fever (Carapetis *et al*., 2016).

Erythema marginatum as shown in figure 1.8 might be due to antibodies against group-A carbohydrates cross-reacting with keratin and subcutaneous nodules might be caused by delayed hypersensitivity against group A streptococcal antigens (Carapetis *et al*., 2016).

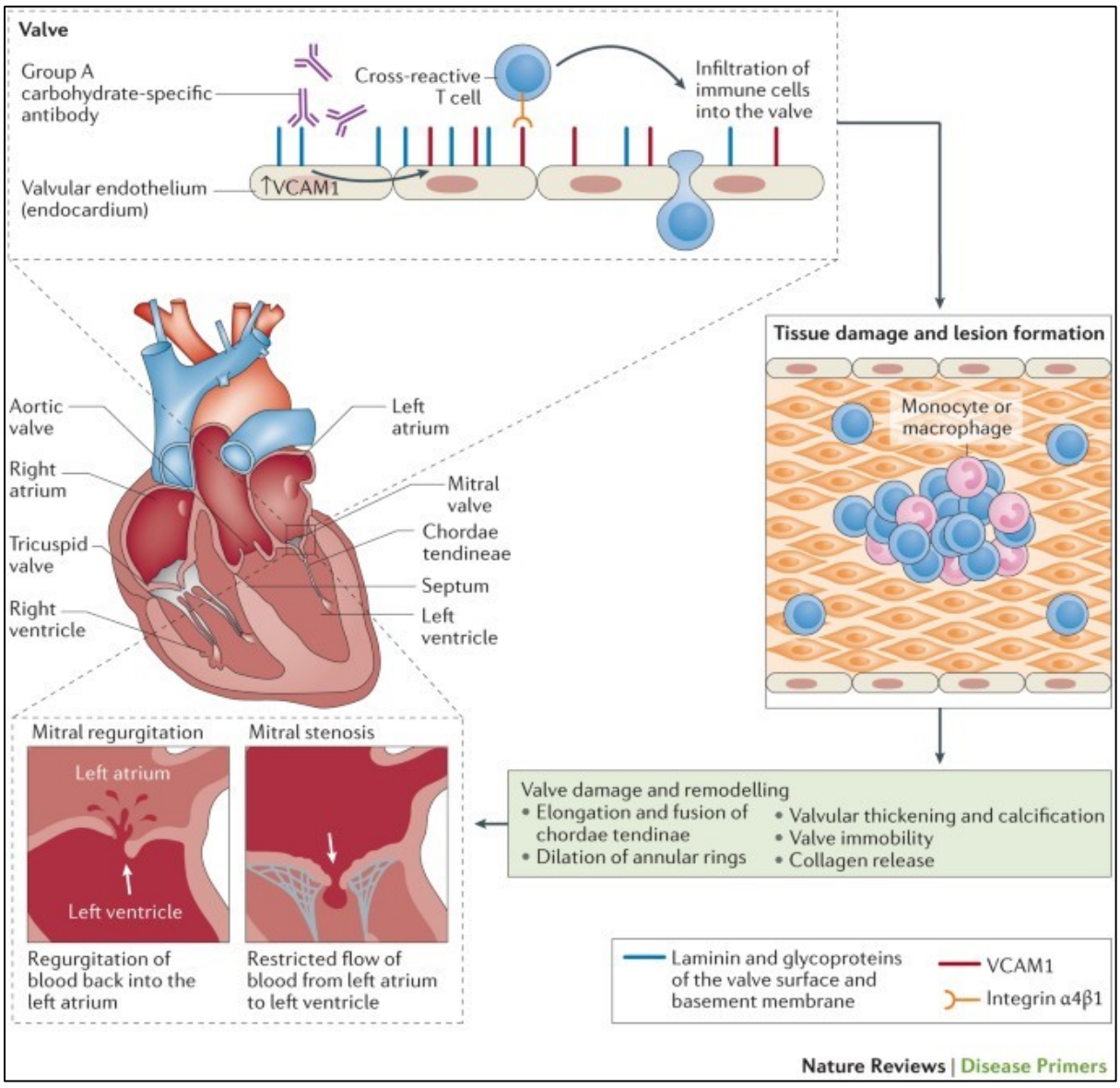


Figure 1.9. The GAS cross-reactive immune response in the heart (Carapetis *et al*., 2016).

The heart is affected by antibodies (generated by B cells) against the group A carbohydrate binding to the surface of the valve and upregulating vascular cell adhesion molecule 1 (VCAM1) on the surface of the valve endothelium as shown in figure 1.9. The upregulation of VCAM1 allows T cells expressing integrin α4β1 (also known as VLA4) to adhere to the endothelium and to extravasate into the valve. The inner valve becomes infiltrated by T cells, primarily CD4+ T cells, and Aschoff bodies or granulomatous lesions form underneath the endocardium. Damage to the endothelium and infiltration of T cells into the valve remodels the valve structure, including the chordae tendineae, with malformation of the valve leading

to regurgitation or stenosis of the valve. Breakdown of the valve releases collagen and results in further immune-mediated damage to the valve (Carapetis *et al*., 2016).

As much as the heart muscle heals from this acute infection, permanent damage can still ensue, leading to the development of RHD. ARF inflammatory process has both structural as well as functional effects on the structures of the heart, which with time can develop into RHD. Some of the changes that develop over time include the dilatation of the annuli of the heart, as well as the supporting structures of the respective valves. The cumulative effect of these structural and functional changes is that the valves may fail to close or adequately close during the cardiac cycle as shown in figure 1.9 (Veasy and Tani, 2005).

1.4.1 Genetic susceptibility

The nature of host-microorganism reaction is to a large extent dependent on the characteristics of both the host and the infecting organism. Evidence of this is in the changing trend of ARF over time. For example, the ARF epidemics during World War II period were caused mainly by the GAS strain, which were characteristically rich in M protein and had hyaluronic acid capsule (Stollerman, 2001). These strains also had a particular geographical prevalence and specific clinical manifestation. For example, this highly mucoidappearing strain affected the pharynx more than it did the skin and was more common in the Utah ARF out brakes in the United States (Veasy *et al*., 2004). The more recently cultured strains in the tropical areas have shown a different clinical manifestation with a predilection of skin-manifestations than throat infections (Bessen *et al*., 2000).

Factors such as the use of penicillin prophylaxis and treatment could have played a role in the development of these differences in GAS strains and therefore the clinical manifestations of ARF. The other reason could be the change in the profile of the host as those children who were affected adversely by ARF epidemics fared worse and some could not even bear children post this. Genetic predisposition in this generation was also a strong contender making this population more susceptible to worse forms of infections (Stollerman, 2001).

Changes that have taken place in the past 100 years or so might have contributed to the reduced transmission of the severe forms of genetic predisposition to the post epidemic generations and together with improved general living standards and industrialization could have contributed to the overall decline in the incidence and prevalence of ARF as well as RHD. The extent to which the above factors have influenced these disease entities in developing countries is unclear. The true numbers of burden of disease have not been accurately captured for about 500 years and that due to the lack of treatment for severe RHD, suggests that many patients might have prematurely died (Zülke *et al*., 2016).

1.4.2 Humoral Immune Response

Rheumatic carditis, which is inflammation of the layers of the heart, is initiated by the humoral immune response following GAS infection. RHD results from infiltration of heart's layers and valves by inflammatory cells (Galvin *et al*., 2000). The brain can also be affected by this process where you have the vessels in brain undergoing a lymphocytic perivascular cuffing which results in Sydenham's chorea (Greenfield and Wolfson, 1922).

1.4.2.1 Rheumatic carditis

Valve and heart muscle tissue of patients who died from ARF and RHD have shown antibodies deposition on these structure because of cross-reaction with cardiac epitopes (Kaplan *et al*., 1964). Studies that were later conducted on mouse and human monoclonal antibodies (mAbs) confirmed these findings (Cunningham *et al*., 1997). Note that there was a cross reaction that occurred between the antibodies produced by the host and the group A carbohydrate or streptococcal M protein (Veasy *et al*., 2004) and that this targeted myocardium myosin and laminin in the endothelium as well as the basement membrane of the valves (Galvin *et al*., 2000). This leads to chronic inflammation and valvular damage (Roberts *et al.,* 2001).

There is evidence that suggests that the α-helical structure that is common amongst the streptococcal M protein, myosin of the heart, keratin in the skin and laminin is responsible for the inability of the antibodies to distinguish between host's epitopes and microorganism's group A carbohydrate epitope *N*-acetyl-β-D-glucosamine (Shikhman and Cunningham, 1994).

There are S2 fragments of the myocardial myosin heavy chain, which have been used in episodes of active rheumatic inflammation of the heart to monitor response to treatment as this reaction is related to humoral response. It is worth noting that the S2 epitopes among all populations worldwide where rheumatic endocarditis is endemic, are similar irrespective of the M protein gene sequencing carried by the GAS in the region (Ellis *et al*., 2010).

Impairment of immune tolerance as well as epitope spreading induction lead to more cardiac myosin epitopes recognition. This has been attributed to repeated infections of the throat by GAS, resulting in the molecular mimicry described above (Cunningham *et al*., 1997). During ARF autoantibodies against collagen I are produced which results in structural damage of the cardiac valve, but these autoantibodies do not cross react (Martins *et al*., 2008). From the studies that have been conducted over time, it has been shown that damage to collagen by the immune system that occurs after the initial rheumatic carditis, is the continuous process in RHD (Tandon *et al*., 2013).

Infiltration of myocardium by autoreactive T cells, valvular endothelial activation as well as the formation of Aschoff nodules in the valve are some of the structural changes that occur because of autoimmune response in rheumatic carditis as shown in figure 1.10 (Carapetis, 2015).

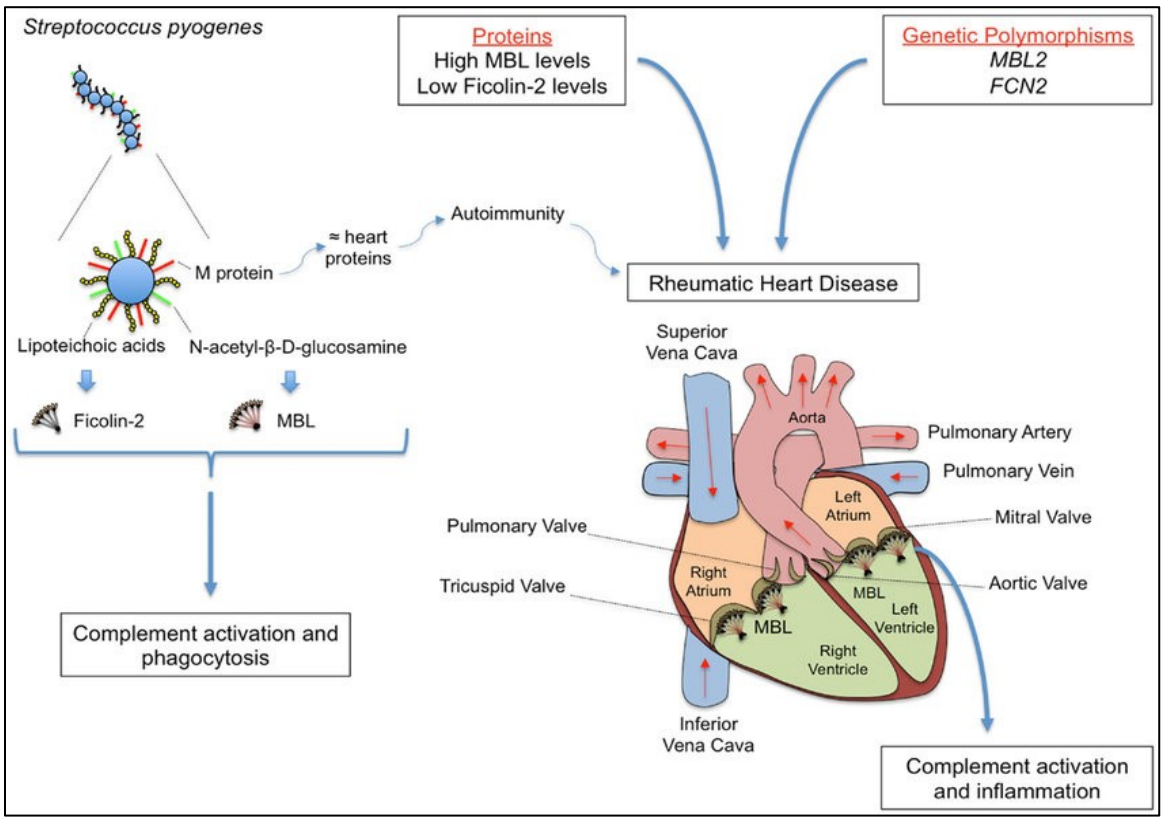


Figure 1.10. Cellular immune response in rheumatic heart disease (Carapetis, 2015).

Infiltration of T cells into activated endothelium of heart valve occurs due to the upregulation of the vascular cell adhesion protein 1 (VCAM1) that takes place on the surfaces of the endothelial layer triggered by immunoglobulins G (IgG) antibodies reaction (Chopra *et al*., 1988). In ARF $CD4^+$ T cells predominates in the valvular infiltration though both $CD4^+$ and $CD8^+$ occurs in the inflamed rheumatic valve (Roberts *et al*., 2001). Lesion called Aschoff nodules or bodies are seen under the endocardium near or on the valve. They may also be seen on the myocardium itself, which in rheumatic carditis will later heal. T cells and macrophages are contained in these nodules, and they are because of intense inflammation, which is mediated by $CD4^+$ T cells (Aschoff, 1906).

There are several inflammatory adhesion molecules and chemokines together with their receptors, which are upregulated by VCAM1. To name but a few, molecules such as integrin α4β1, intracellular adhesion molecule 1 (ICAM1), P-selectin, CC-chemokine ligand 3, CCL1 and CXC-chemokine ligand 9, are examples of these inflammatory molecules (Faē *et al*., 2005). Structural valvular dysfunction results from the imbalance that occurs in the quantity of the

intrinsic valvular tissue components. These include an increase in the levels of proteins such as vimentin and lumican as well as an increase in the levels of molecules such as apolipoprotein A1. A decrease is observed in molecules such as collagen VI, haptoglobin-related protein, rolargin, biglycan and cartilage oligomeric matrix protein (Martins *et al*., 2014).

1.4.2.2 Sydenham's chorea

Chorea and neuropsychiatric manifestations are characteristic for Sydenham's chorea in ARF (Taranta and Stollerman, 1956). The basal ganglia in Sydenham's chorea is targeted by the immunoglobulin G (IgG), which are neuron-specific antibodies, and this results in the excessive release of dopamine from the neural cells (Kirvan *et al*., 2003). Antigens found in the basal ganglia of the human brain, such as D1 and D2 dopamine receptors31, lysoganglioside side and tubulin, together with the group A carbohydrate epitope Nacetylβdglucosamine, react with the mAbs through a process of molecular mimicry in patients with Sydenham's chorea (Kirvan *et al*., 2003).

Because of the structural similarity between the host and the microbial agents, there is a cross-reactivity that occurs during the response against group A streptococcal carbohydrate by the neuron-specific antibodies. The presence of dopamine D2 receptors on dopaminergic neurons in the substantia nigra and ventral tegumental area that project to the striatum could be the reason for specific antibody targeting, though this is not entirely clear (MeadorWoodruff *et al*., 1991).

Because in some studies patients with Sydenham's chorea had improvement in their symptoms after they received plasmapheresis with plasma from healthy donors, strongly suggest the antibody-mediated pathogenicity of the disease, and that patients would therefore respond positively to immunotherapy or corticosteroids administration (Garvey *et al.,* 2003). The role of antibiotics on behavioural and neurochemical changes in Sydenham's chorea were investigated in a study using rats-models using ampicillin, and this showed that there was prevention of the motor symptoms development as well as some behavioural alterations usually noted in GAS infections (Lotan *et al*., 2014).

1.5 Diagnosis

1.5.1 Diagnostic Criteria

The Jones Criteria is used for the clinical diagnosis of ARF and to exclude other possible diagnosis. The Jones Criteria, which has undergone modifications, is divided into major and minor clinical manifestations as shown in Table 1.1 (Gewitz *et al*., 2015).

Table 1.1. Summary of the 2015 Jones criteria (Gewitz *et al*., 2015).

Jones criteria for the diagnosis of ARF		
	Low-risk population ARF incidence ≤2 per 100 000 school-aged children or all-age RHD prevalence of ≤1 per 1000 population year	**Moderate/high-risk population** Children not clearly from a low-risk population
Major criteria		
Carditis	Clinical and/or **subclinical***	Clinical and/or **subclinical***
Arthritis	Polyarthritis	**Monoarthritis, polyarthritis and/or polyarthralgia**
	Chorea	Chorea
	Erythema marginatum	Erythema marginatum
	Subcutaneous nodules	Subcutaneous nodules
Minor criteria		
Carditis	Prolonged PR interval†	Prolonged PR interval†
Arthralgia	Polyarthralgia	**Monoarthralgia**
Fever	≥38.5°C	**≥38°C**
Markers of inflammation	Peak ESR ≥60 mm in 1 h and/or CRP ≥3.0 mg/dL	Peak **ESR ≥30 mm** in 1 h and/or CRP ≥3.0 mg/dL

Changes compared with the 1992 revision[7] are highlighted in **bold**.
*Subclinical carditis: Seen only on echocardiography without ausculatory findings.
†Accounting for age variability and only if carditis NOT counted as a major criteria.
ARF, acute rheumatic fever; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; RHD, rheumatic heart disease.

For the diagnosis of ARF to be made, the patient must have at least two major criteria or one major with a minimum of two minor criteria (Gewitz *et al*., 2015). Evidence of prior GAS infection using blood serology is also important part of the diagnosis. The challenge of diagnosis is in patients who present with subclinical features or those who present with chorea. In these patients, even serological testing might not yield positive tests (Taranta *et al*., 1956).

Arthritis and fever are the most common presenting features of ARF, each with a rate of 75% and more than 90% respectively. In patients who present with a single joint involvement, the diagnosis of ARF related arthritis can pose a challenging diagnosis. Note that in patients who present with a single joint involvement, it always important to exclude a possible septic arthritis. Usually within two to three days after having started the patients with a suspected

ARF on aspirin and other non-steroidal antiinflammatory drugs, there should be a satisfactory response, failure of should prompt towards a possible different diagnosis (Carapetis and Currie, 2001). In less than 10% of cases, other rare clinical manifestations of ARF such as subcutaneous nodules that develop over the bony prominences and bright pink, blanching papules called erythema marginatum develop over the body or the proximal aspects of the limbs (Steer *et al*., 2009).

Pathology of mitral valve as part of the carditis is the most common presentation, occurring in more than 50% of cases, resulting in mitral valve regurgitation, which is the inability of the valve to closing during ventricular contraction, thus allowing blood to flow back into the atrium of the heart. The second most common valve that is affected by ARF carditis is the aortic valve, though at a lesser rate compared to the mitral valve (Vijayalakshmi *et al*., 2008).

Cardiac enlargement can be a complication of severe forms of valvular lesions at a later stage. In the recent past the usefulness of cardiac echocardiography in the diagnosis of cardiac ARF has contributed to the revised Jones Criteria (Figueroa *et al*., 2001). Considering this, echocardiography is recommended in all patients with suspicion of ARF as part of the new Jones Criteria of 2015 as shown in figure 1.11. Note that even if clinically there is a negative finding with auscultation, both clinical and subclinical carditis still fulfil the major criteria (Gewitz *et al*., 2015).

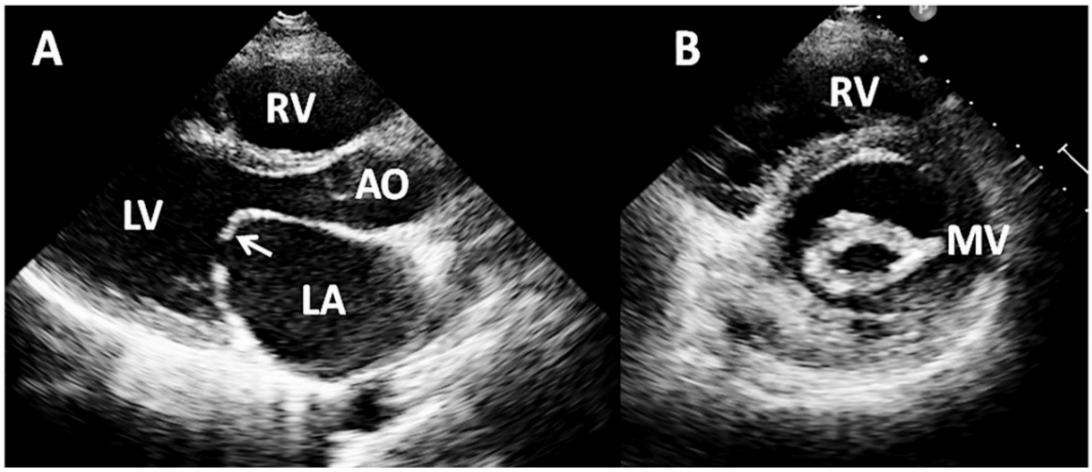
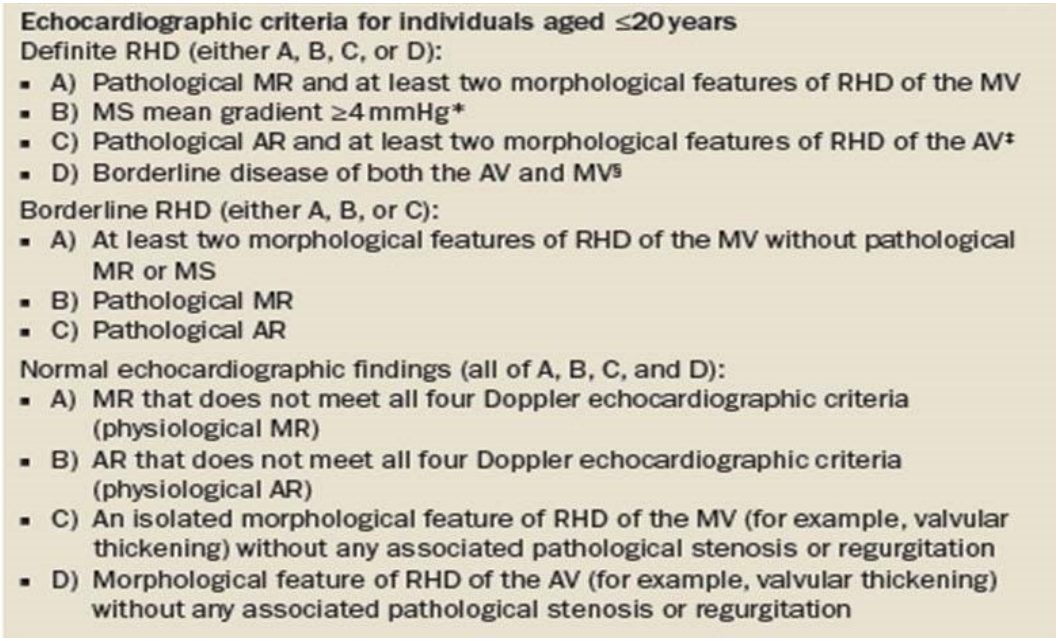


Figure 1.11. Transthoracic echocardiography from patient with severe mitral stenosis, in parasternal long axis **(A)** and short-axis **(B)** views. Both leaflets are thickened with pliable anterior leaflet on long-axis view (arrow) and fusion of both commissures on short-axis view. **AO:** aorta; **LA:** left atrium; **LV:** left ventricle; **MV:** mitral valve; **RV:** right ventricle (Matheus *et al*., 2019).

There is a World Heart Federation echocardiographic guideline document on the diagnosis of rheumatic mitral valve pathology, which is published in 2012 that assist clinicians treating patients with either diagnosed or suspected RHD to appropriately manage these patients (figure 1.12). Amongst the recommendations, the thickness of the mitral leaflets as well as their mobility are used for the evaluation of the pathology and determine the severity thereof. Other measures used to quantify the severity of stenosis include the sub-valvular apparatus thickness and the gradient created by blood flow across the stenotic valve (Reményi *et al*., 2012).



Echocardiographic criteria for individuals aged ≤20 years

Definite RHD (either A, B, C, or D):

- A) Pathological MR and at least two morphological features of RHD of the MV
- B) MS mean gradient ≥4 mmHg*
- C) Pathological AR and at least two morphological features of RHD of the AV‡
- D) Borderline disease of both the AV and MV§

Borderline RHD (either A, B, or C):

- A) At least two morphological features of RHD of the MV without pathological MR or MS
- B) Pathological MR
- C) Pathological AR

Normal echocardiographic findings (all of A, B, C, and D):

- A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR)
- B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR)
- C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
- D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation

Figure 1.12. World Heart Federation for Echocardiographic criteria for individuals < 20years for diagnosis of RHD (Reményi *et al*., 2012).

For assessment of mitral valve regurgitation, there are various factors that are taken into consideration in order to quantify the severity of the pathology. These include the size of the anulus, the mobility of the mitral valve leaflets, the coaptation depth – described as the area of both the anterior and posterior mitral valve leaflets that meet during valve closure, the amount or volume of blood that flows in the opposite direction during left ventricular contraction, (Figure 1.13) (Reményi *et al*., 2012).

Pathologic MR (all four Doppler criteria must be met)
Seen in two views
In at least one view, jet length ≥ 2 cm
Velocity ≥ 3 m/sec for one complete envelope
Pansystolic jet in at least one envelope
Pathologic AR (all four Doppler criteria must be met)
Seen in two views
In at least one view, jet length ≥ 1 cm
Velocity ≥ 3 m/sec in early diastole
Pandiastolic jet in at least one envelope

Figure 1.13. World Heart Federation for Echocardiographic diagnosis of RHD (Reményi *et al*., 2012).

In about 30% of patients, chorea, which is an aimless and involuntary movement of the body, can be a presenting symptom of ARF. Chorea can also occur in the absence of other ARF clinical manifestations or even a history of prior streptococcal infection. In the latter instance, exclusion of other possible causes of chorea such as drug reactions as well as systemic lupus erythematosus and to perform a heart sonar for the evaluation of possible carditis (Carapetis *et al*., 2016).

With the recently revised 2015 Jones Criteria for the diagnosis of ARF, moderate-high risk group is regarded as originating from a population with the incidence of ARF more than 2 per 100 000 school children per annum or in all ages if there is more than 1 per 100 000 prevalence in a year for RHD. Arthritis of single joint can fulfil the diagnostic criteria for ARF in moderate-high risk patients (Gewitz et al., 2015). This update was done so that in endemic areas, patients with possible ARF who present atypically are not missed (Padmavati and Gupta, 1988).

In regions of the world with less access to medical services patients most commonly present with established RHD rather than ARF as it was the case in a cohort of patients in Uganda

whom none reported ever having a prior ARF infection (Okello *et al*., 2013). The most common presentation of patients with RHD is cardiac failure. They may however also present with complications such as stroke, infective endocarditis as well as heart rhythm abnormalities such as atrial fibrillation. Extreme cases of dysrhythmia can result in sudden death (Singh *et al*., 2008). Echocardiography has helped in the diagnosis of RHD in patients with a cardiac murmur. The diagnosis of RHD in patients who are pregnant poses a challenge in their management due to the hemodynamic changes related to pregnancy (Carapetis *et al*., 2016).

1.5.2 Screening for rheumatic heart disease

The development of a screening programme that would be able to detect the large numbers of patients with RHD as compared to the few with ARF would significantly reduce the possible complications associated with RHD and afford those who are identified early the opportunity to receive secondary prophylaxis. With the use of portable echocardiography for screening, even remote regions are reached and thus patients who would otherwise not have access to the health facilities are diagnosed early and appropriate interventions instituted (Zülke & Mayosi, 2013). There is an association between old age RHD presentation and poor socio-economic status. Prior knowledge of ARF was less common in most patients who were diagnosed with RHD through echocardiographic screen, thus highlighting the significance of image screening in order to accurately determine the actual burden of disease (Beaton *et al*., 2012).

In Uganda, the use of the hand-held echocardiographic (HHE) machines improved the identification of children with RHD from those without the disease and that the sensitivity and specificity were 79% and 87% respectively (Beaton *et al*., 2015). There is always a debate regarding prophylaxis of patients with moderate RHD. In some studies, it was shown that not all patients with mild RHD go on to develop severe carditis, and that about two thirds of these will either have no disease progression or even regression of the disease (Paar *et al*., 2010).

In other parts of the world, such as in Fiji, it has been demonstrated that training of the health care providers such as nurses in the use of echocardiography has resulted in the detection of large numbers of patients with RHD (Colquhoun *et al*., 2013). Whether the use of

echocardiography as a screening tool is cost effective, still needs to further be investigated (Zühlke & Mayosi, 2013). In a particular study, it was shown that using Markov model, in patients with early RHD, it was cost effective employing echocardiography as a screening tool and providing secondary prophylaxis than when primary prophylaxis is used (Manji *et al*., 2013).

Therefore, an ideal public health programme would be the one that utilizes the combination of these above-mentioned strategies to effectively deal with ARF and RHD prevalence (Carapetis *et al*., 2015).

1.6 Prevention

1.6.1 Primordial prevention

Strategies to avoid GAS infection are part of the primordial prevention. Having the knowledge of some of the factors involved in the cause and transmission of GAS leading to the development of ARF should help in instituting measures that can at least in part, reduce the incidence and thus the prevalence of ARF in endemic areas. Factors such as improved leaving conditions with better hygiene as well as access to primary health care. Health education amongst the community about the association between a throat infection and the potential development of ARF in endemic areas is also paramount (Gordis *et al*., 1969).

1.6.2 Primary prevention

This entails identification of patients with GAS throat infection and treating them with appropriate antibiotics, thus preventing the development. Because of the varying degrees of severity with regards to throat infection, prophylaxis will only be possible in those people who are sick enough to seek medical attention (Denny *et al*., 1950). Another important factor in this prevention is the understanding of both the community as well as the health care providers that sufficient treatment of a throat infection is important. It is important to note that though this intervention may be appealing, there is yet to a study that shows statistical significance of actively treating patients with GAS positive swabs (Lennon *et al*., 2008).

In the majority studies seeking to institute primary prevention against ARF, the patients were treated with injectable penicillin regardless of whether the sore throat they had was because of GAS or the common cold virus. In other places, more stringent measures were instituted to try and minimize inappropriate use of antibiotics, but this resulted in poor outcomes also (LeMarechal *et al*., 2013). The best way to deal with the above-mentioned challenges is that, whenever possible, a throat swab should be performed to identify those patients with GASpositive throat infection and thus institute proper antibiotics against the development of ARF (Carapetis *et al.,* 2016).

Another important factor that may result in the development of ARF following a throat infection by GAS is the duration of the infection (Catanzaro *et al*., 1958). There have been studies regarding the effective course of antibiotics to provide satisfactory bacterial eradication, and these suggested that either treating patients with a 10-day oral course of penicillin twice a day or oral amoxycillin once a day or using benzathine penicillin which can be injected will produce the required results (Clegg *et al*., 2006). The best period to reduce the development of ARF from a sore throat, treatment should ideally be started within nine days of the infection (Denny *et al*., 1950).

1.6.3 Secondary prevention

The importance of secondary prevention of ARF and thus of the development of RHD has been shown in several randomized controlled trials (Manyemba and Mayosi, 2002). It has been shown that compared to oral penicillin, benzathine penicillin injections are more effective and that this reduces the progression of the disease to RHD (Tompkins *et al*., 1972).

There have been studies conducted to evaluate whether a four-weekly penicillin dose versus a three-weekly dose was better, but the important factor to reducing the progression of ARF into RHD was shown to be more related to the compliance of the treatment regimen and thus not to the type of the regimen (Lue *et al*., 1994). In one study, it was found that 50% of patients who went on to develop persistent or even deterioration of the disease, the prevalence of subclinical carditis was 18% post ARF (Tubridy-Clark and Carapetis, 2007). Drug safety and treatment adherence form important part of secondary prevention (Remenyi *et al*., 2013). It

has been shown that failure to adhere to these methods have led to recurrence in ARF in a Brazilian study (Pelajo *et al*., 2010). Another factor which has contributed to the development of RHD is the late presentation of post ARF infection, such as patients in a Uganda study which showed that about 85% of cardiovascular presentation were at mean age of 30 years with a diagnosis of RHD (Okello *et al*., 2013). Most of these patients on presentation presented with complications of long-standing heart disease such as heart failure, rhythm abnormalities as well as embolic stroke. The most common cardiac lesion that patients from underdeveloped countries tend to present with is mitral stenosis (Tadele *et al*., 2013).

There are few factors, which influence the duration of prophylaxis. These include amongst others the duration post the last ARF infection episode, the age at which the infection occurred, which in turn influences the possibility of recurrence, whether there is carditis at the time of presentation as well as the extent of RHD (Spinetto *et al*., 2011). Thus, the recommended duration for secondary prophylaxis is at least a period of 10 years with regards to the initial date of presentation post ARF infection, or until the ages of 18-21 years (Heart Foundation New Zealand, 2014). However, patients with moderate RHD should continue with prophylaxis until age 30-35 years and those with severe forms of the disease up to the ages of 40 years according to the recent guidelines (Nishimura *et al*., 2014).

1.7 Management

1.7.1 Acute rheumatic fever

Presentation of patients with complaints such as sore throat, single or multiple joints pains and fever in endemic ARF areas, should prompt one to exclude ARF amongst other potential diagnosis such as septic arthritis. The hallmark of the disease progression namely, polyarthritis might be masked by the administration of NSAIDS. Confirmation of the diagnosis of ARF is a crucial undertaking in the first days of presentation. Patients who are suspected to having ARF should be admitted for thorough diagnostic work up, including echocardiography as well as streptococcal titres. It is important to exclude other possible causes of arthritis as well as throat infection other than GAS. The pillars of management are based on the eradication of GAS throat infection, symptomatic treatment as well as management of potential cardiac complications from carditis as shown in figure 1.14 (Carapetis, 2015).

Diagnosis

- Hospitalization for assessment and investigations, including echocardiography, acute phase reactants, streptococcal serology and tests for other differential diagnoses

Eradication of group A Streptococcus from the throat

- Single dose benzathine penicillin G

Symptomatic treatment of joint involvement and fever

- Nonsteroidal anti-inflammatory drugs (paracetamol may be used until diagnosis has been confirmed

Management of heart failure

- Bed rest, fluid restriction and cardiac medications

Corticosteroids may be considered for severe heart failure

- Deferral of surgery, if possible, until acute inflammation has subsided

Management of chorea

- Rest and calm environment
- For severe or refractory cases, administration of valproic acid, carbamazepine or corticosteroids may be considered

Commencement of long-term care

- Education and registration for long-term care
- First dose of benzathine penicillin G (to eradicate group A Streptococcus from the throat

Figure 1.14. Key management priorities in acute rheumatic fever and the main actions used to address them (Carapetis, 2015).

Benzathine penicillin given as a single intramuscular injection or a full 10-day course of òral penicillin or amoxicillin is essential for the eradication of GAS infection (Catanzaro *et al*., 1954). Educating the community about the disease as well as the significance of secondary prophylaxis is an important part of treatment (New Zealand Heart Foundation, 2006). Studies that have been conducted in the past have not yet shown any significant effect in patients treated with penicillin post ARF and the subsequent development of valvular RHD in a period of 1 year (Carter *et al*., 1962). It has been shown that in patients with AFR carditis, on top of penicillin treatment, bed rest also improved the patient's conditions and resulted in a short disease duration, less relapses, and complications such as cardiac enlargement from heart failure (Markowitz and Gordis 1972).

Measures that can be used to determine improvement in the clinical picture and thus the possibility of the patient to start mobilizing, should amongst others include inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). This will

guide on how soon the patient with a significant carditis can start mobilizing. In those patients with mild to moderate disease forms, the decision to start mobilizing will depend more on the clinical picture (National Heart Foundation of Australia (*RF/RHD Guideline Development Working Group) & the Cardiac Society of Australia and New Zealand, 2006*).

1.7.2 Carditis

Note that RHD develops as a result of ARF and the extent to which it affects the heart as well as the possible recurrent infections. Although there is little data to support the specific use of corticosteroids in the overall management of carditis associated with ARF, they have been used as part of the management together with other previously mentioned measures (Albert *et al*., 1995). There was no benefit shown in randomized controlled trials (RCT) which sought to see the effectiveness of using intravenous immunoglobulin therapy in the management of ARF (Voss *et al*., 2001). There is clearly a need for a large multicentre study to accurately define the role of corticosteroids in the management of ARF related carditis and the course of the disease and the development of complications related to carditis (Cilliers *et al*., 2012).

1.7.3 Heart Failure

Patients presenting with signs of heart failure and chronic RHD needs to be seen by cardiologist and an echocardiograph examination is vital. It is important to immediately institute measures to treat the heart failure, which include fluid restriction as well as diuretics. In patients with aortic valve leakage (regurgitation), drugs such as angiotensin-converting enzymes inhibitors (ACE-I) can be added to the treatment regime (New Zealand Heart Foundation, 2006). ACE-I can also be used in patients with abnormal left ventricular function noting that for those patients requiring surgery should not be delayed in that regard (Nishimura *et al*., 2014).

The timing for surgical intervention is usually reserved for later in those patients whom it is indicated to allow for the acute phase of the disease to pass and thus making surgery less technically challenging. In acute conditions, which results in complications such as rupture of the chordae tendineae, which are the supporting structures of the valve, urgent surgery may be indicated. It is important to be able to distinguish this complication from potential similar

disease such as pneumonia, which may lead to mismanagement of patients (Anderson *et al*., 2008). In cases presenting with free mitral or aortic valve regurgitation will also require emergency surgery. Repair is preferred in cases presenting at young age or those in which it is possible to do so, otherwise replacement of the valve carried out (Finucane and Wilson, 2013). There are clearly demonstrated advantages to repair than replacement such as decreased incidence of endocarditis and complications relating to thromboembolic events, to mention but a few (Remenyi *et al*., 2012).

1.7.4 Sydenham's chorea

Symptoms last beyond 2 years have been reported in patients with chorea, though the general trend is the self-limiting course of the disease (Cardoso *et al*., 1999). Rest and reassurance are usually all the treatment needed for those patients with mild to moderate forms of the disease. Thus, medical treatment with drugs is only reserved for those patients in which symptoms are severe and impair the daily functioning of the patient (New Zealand Heart Foundation, 2006). Short course of corticosteroids have been shown to improve the shown to improve symptoms and lessen the duration of thereof (Barash *et al*., 2005). Valproic acid, which is a neurotransmitter enhancer and mood stabilizer, as well as carbamazepine, which is benzodiazepine anticonvulsant and an analgesic drug, are now the mainstay treatment for rheumatic chorea (Genel *et al*., 2002). Studies have shown that valproic acid is the most effective of the three drugs, but it is reserved for the refractory forms of the disease due to its potential to cause liver toxicity (New Zealand Heart Foundation, 2006). Chorea that occurs during pregnancy known as chorea gravidarum can be caused by ARF (Carapetis *et al*., 2016).

1.7.5 Arthritis

The preferred initial management of patients with arthritis and fever is usually paracetamol, to which response is generally satisfactory. This is so that the progression of the disease to polyarthritis should not be masked by the early administration of NSAIDS. Aspirin and naproxen have both proven effective alternatives to the treatment of ARF arthritis. Ibuprofen can also be used as the NSAIDS of choice together with paracetamol and this has been included in the guideline management of ARF. Note that aspirin when used in children with

acute viral infection in children can cause Reye's syndrome, which can result in multiorgan system failure, and for this reason, naproxen is more preferred as the first line of treatment (Uziel *et al*., 2000). As soon as the arthritis is controlled, aspirin and NSAIDs can be stopped as they have little benefit in the treatment of carditis. In cases of rebound arthritis, then the course can be prolonged until control is achieved (Carapetis *et al*., 2016).

1.7.6 Erythema marginatum and subcutaneous nodules

There is no specific treatment for erythema marginatum, and local treatment can be applied in cases of painful ulcers of the skin that can potentially develop over the nodules (Carapetis *et al*., 2016).

1.7.7 Rheumatic valvular heart disease

There is a comprehensive management of RHD, which includes secondary prophylaxis with penicillin antibiotics, serial echocardiography follow-ups of patients by specialist to monitor the heart as well as valve function. Patients should be referred as soon as possible for heart surgery in where it is indicated, not forgetting monitoring of coagulation in patients who might have developed atrial fibrillation and are on warfarin (New Zealand Heart Foundation, 2012). Prevention of ARF recurrence as well as close follow up of the left ventricular (LV) and valvular function are central to the overall management of RHD. Resolution of RHD is usually noted in patients with mild forms of the disease and minimal involvement of the ventricle (Wilson *et al*., 1998). In contrast, those patients who have the severe forms of the disease, there is an observed progression of RHD resulting in valvular dysfunction. This severity of the disease results in chronic left ventricular volume overload which then leads to the development of LV dysfunction (Walsh, 2010).

In order to follow the disease process and pick up any significant deterioration in the function of LV as well as the valves, echocardiography has [played an important role. The evolution of valvular disease associated with ARF is a subtle process and the disease present usually before the second decade of life (Walsh, 2010).

1.7.8 Pregnancy and childbirth

A complete cardiac assessment should be undertaken ideally in all women with a history of RHD before they fall pregnant *(Australia (ARF/RHD Writing Group), National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand, 2012*). Elective cardiac surgery should be considered in women who are symptomatic from RHD before they fall pregnant to avoid the potential morbidity and mortality associated to cardiac complications in this group due to the cardiovascular physiological changes that occur during pregnancy (Carapetis *et al*., 2016).

Mitral stenosis is the most common valvular lesion that has a high adverse outcome in this group of patients and for this reason, mitral balloon valvotomy is a potential intervention that can be offered in patients with moderate to severe degrees of stenosis. Women with moderate to severe forms of mitral stenosis are at risk of developing peripartum complications as well as foetal related complications such as foetal growth restriction. Other life-threatening complications during pregnancy that occur include pre-eclampsia. Thus, a multidiscipline team approach is pivotal in the management of pregnant women with a diagnosis of RHD. Those patients with severe disease forms should be referred to tertiary institutions for their delivery (Carapetis *et al*., 2016).

1.7.9 Anticoagulation

Patients with RHD related atrial fibrillation and those who have had mitral valve surgery with a mechanical valve prosthesis are ideally put-on warfarin as an anticoagulation method. Once patients are placed on warfarin, their international normalising ratio (INR) needs to be regularly monitored as it is influenced, amongst other things, by food *(New Zealand Heart Foundation, 2006*).

1.7.10 Infective endocarditis

The risk of development of infective endocarditis in RHD patients differs from patient populations and usually it is not recommended to prophylactically treat patients with RHD except in specific situations such as those who have had prosthetic valve replacement and are

due to undergo procedures that potentially can introduce bacteraemia (Nishimura *et al*., 2008).

1.7.11 Indications for heart surgery

In patients who present with severe forms of valvular disease such as mitral or aortic regurgitation, stenosis or combination of these, cardiac surgery will be indicated (Nishimura *et al*., 2014). Each valve is assessed according to the established guidelines, and for mitral; valve regurgitation the indication for surgery is based on the severity of regurgitation and the development of LV dysfunction as shown in figure 1.15.

	Mild	Moderate	Severe
Vena contracta width (mm)	<3	3–7	>7
Regurgitant volume (mls/beat)	<30	30–59	≥60[a] / ≥30[b]
Regurgitant fraction (%)	<30	30–49	>50
Regurgitant orifice area (cm^2)	<0.2	0.2–0.39	≥0.4[a] / ≥0.2[b]

Adapted from Vanhanian *et al.*[9] and Lancellotti *et al.*[32]

Key: [a] = threshold for primary mitral regurgitation; [b] = threshold for secondary mitral regurgitation

Figure 1.15 Severity grading of mitral regurgitation (Nishimura *et al*., 2014).

For mitral stenosis, the indication to intervene surgically is more dependent on the symptoms of the patient as well the gradient across the diseased valve is shown in Table 1.2.

Table 1.2 European association of echocardiography/American society of echocardiography classification of mitral valve stenosis (JIndianAcadEchocardiogrCardiovascImaging *et al.,* 2013).

	Mild	Moderate	Severe
Specific findings (cm^2)			
Valve area	>1.5	1.0-1.5	<1.0
Supportive findings (mmHg)			
Mean gradient	<5	5-10	>10
Pulmonary artery pressure	<30	30-50	>50
*Heart rate between 60-80 in sinus rhythm			

Note that with mitral valve surgery, due to association with elevated pulmonary pressures, there might be a need to also perform a repair surgery on the tricuspid valve. There is generally a high threshold for valvular surgery in children, especially if the valve has to be replaced and thus the numbers of valvular surgery in this patient population are generally low (Finucane and Wilson, 2013).

Once the decision has been taken to offer the patient a surgical intervention, the choice of the type of surgical intervention best for the given patient will be based on several factors. These include amongst others, the age of the patient, presence, or absence of atrial fibrillation, to an extent, the ability of the patient to comprehend the disease and its consequences, access to health facilities, possibility of feature pregnancies, and patient preference (Essop and Nkomo, 2005).

Mitral valve repair is the operation of choice in patients who have regurgitation as the primary lesion and has been shown to carry little morbidity and mortality, however there is a high reoperation rate associated with repair than there is with replacement (DiBardino *et al.,* 2010). There are different forms of repair techniques that can be employed depending on the severity of the valve pathology, the patient physiological status as well as the experience of the operating team. These include leaflet resection with annuloplasty rings, chordae tendinea replacement with artificial chords as well other forms of percutaneous repairs such as the Mitra-clip technique, but to mention a few (Klaar *et al*., 2011).

Either a mechanical or a bioprosthesis can be used in those patients considered not ideal candidates for repair, and the decision for which method of valve operation to be offered the patient is taken before the operation itself using preoperative echocardiographic data. It is important to note that in some instances this decision can change intraoperatively depending on the valve visualization. There is a reported mortality of about 3-5% associated with mitral valve replacement with certain factors influencing the long term variably (Holmes *et al*., 2017). Bio prosthesis will be preferred in women who still want to have children at a later stage in order to avoid warfarin during pregnancy and thus the complications that might occur to the mother and the foetus (Sadler *et al*., 2009).

Another form of intervention that is employed for symptomatic and severe disease is valvoplasty even though nowadays intervention in general is recommended for asymptomatic patients with echocardiographic evidence of worsening disease as shown in figure 1.16. To decide which patients will be suitable candidates for balloon valvuloplasty, a grading score called the Wilkins score is used. This score assesses factors such as the mobility of the valve leaflets, the thickness of the leaflets, thickness of the sub-valvular apparatus and valvular calcification. Depending on the extent of these factors, values are assigned, and a total calculated which if less than 8, then the patient can be referred for valvotomy (Rifaie *et al*., 2009). Valvuloplasty seems to be more successful in younger patients with pliable valvular tissue than older ones, and thus once diagnosis has been confirmed and the patient qualifies for an intervention, early referral should be sought (Carapetis *et al*., 2016).

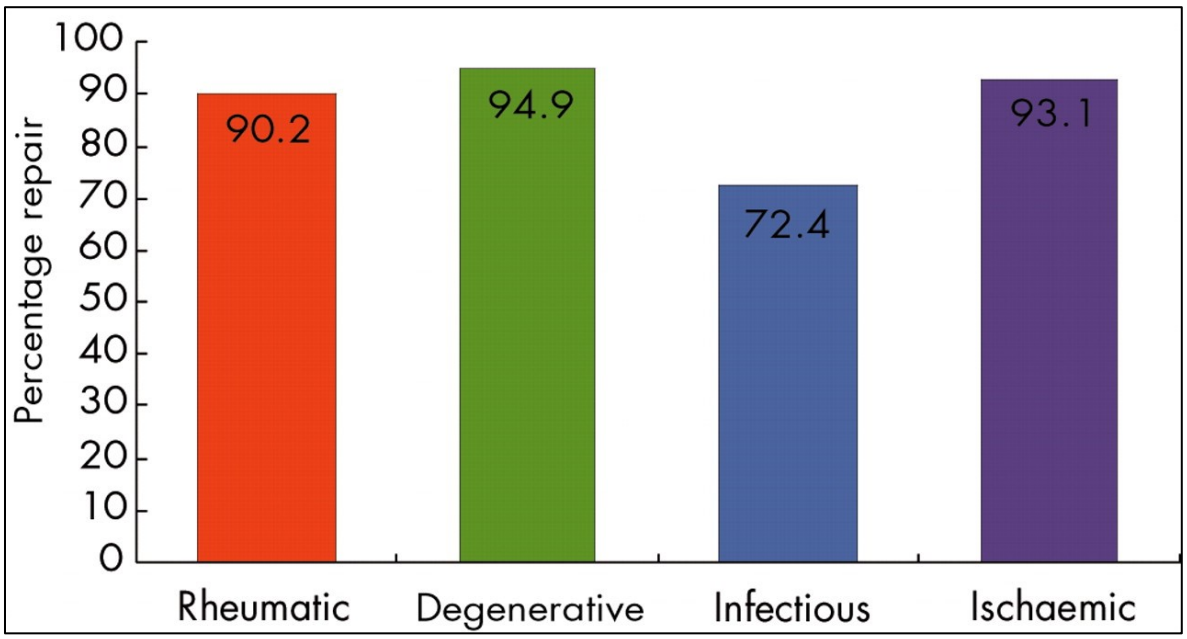


Figure 1.16. Feasibility of mitral valvoplasty according to pathology (De Oliveira and Antunes, 2006).

Other forms of mitral valve surgeries that have been on the increase in the recent past include minimal mitral valve surgery in which the approach to the valve is through small incisions with reported similar benefits and post-operative course which matches that of the traditional approaches. Other modalities that have been gaining steady increase in their usage include the robotic telemanipulations (Seco *et al*., 2013).

1.8.1 Surgical outcomes

Post mitral valve repair results show a better outcome as compared to replaced valves with regards to morbidity and mortality, and this has made repair the operation of choice valvular pathologies amenable to this method of operation (Mohty *et al*., 2001), see Figure 1.17. There is however, an observed increase in the incidence of repeat valvular surgery in those patients who have undergone repair (Christina *et al*., 2013).

There are common postoperative complications that are associated with mitral valve surgery and the type of surgery the patients have undergone. These include in-hospital complications such as bleeding requiring re-exploration, respiratory complications requiring reintubation with or without antibiotics, rhythm abnormalities requiring anticoagulation and/or artificial

permanent pacing, renal dysfunction requiring haemodialysis, and blood transfusions. Medterm complications include deep sternal sepsis, rhythm abnormalities, and paravalvular leaks. Long-term complications include wound sepsis, paravalvular leaks, dysrhythmia, and anticoagulation treatment complications in patients receiving warfarin, such as bleeding or stroke. Mortality can occur in-hospital or post hospital discharge (Christina *et al*., 2013).

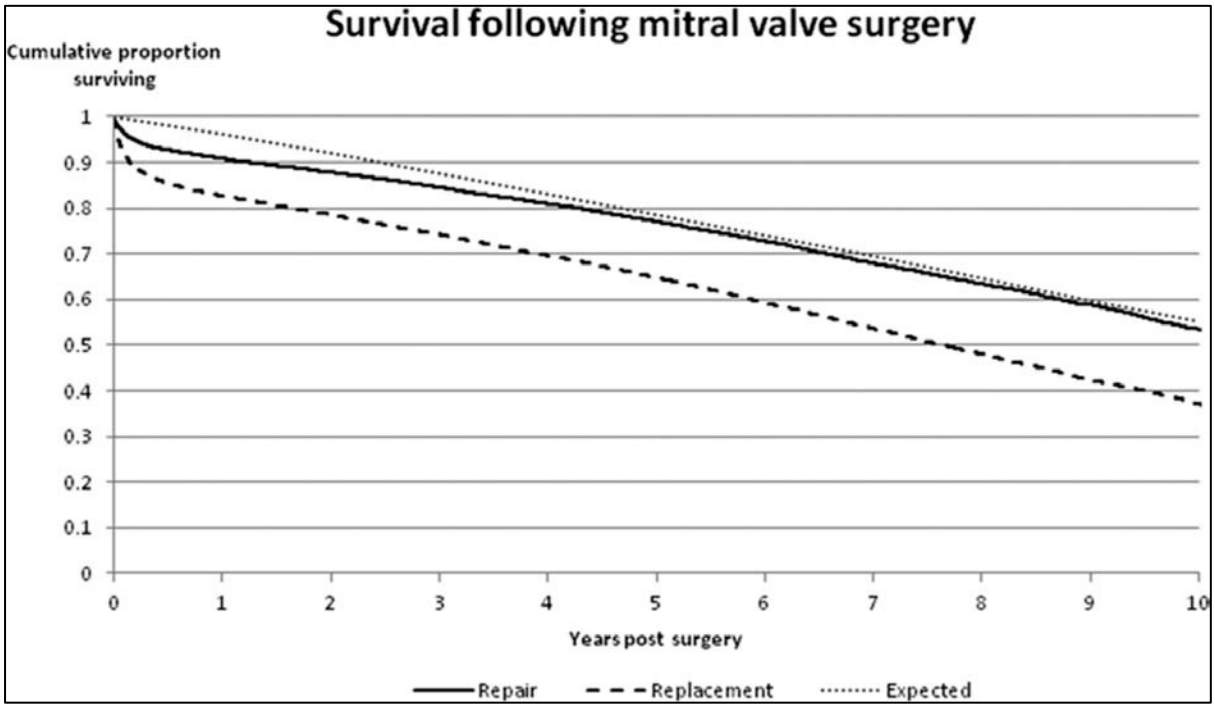


Figure 1.17. Long-Term Survival of Patients Undergoing Mitral Valve Repair and Replacement (Christina *et al*., 2013).

1.8.2 Quality of life

Though there are formal studies that investigated the effect that RHD and its complications have on the patients, close relatives as well as the communities it affects, a number of questionnaires that have been carried out in regions where RHD is prevalent have shown that there is physical, emotional, psychological as well financial burden that RHD. This then suggest that formal studies need to be undertaken in these areas to clearly outline the impact on the quality of life. This is defined as the perception that individuals have in relation to the life they lead with regards to their culture and value systems they identify with as well as goals, expectations, standards, and concerns regarding life which RHD and its complications have on (Petricca *et al*., 2009).

1.8.3 Outlook

Interest in RHD has decreased in the developed countries, which are well resourced in the due to the decline in the disease prevalence. There has equally been an increase in research in the areas where the disease is still endemic (Mayosi 2016). There are three main goals that have identified to assist in the alleviation of the disease burn in these endemic areas, namely: implementation of evidence-based interventions, generation of knowledge and interventions, and advocacy of ARF and RHD control measures shown in figure 1.18.

Effective implementation of known evidence-based treatments

- Integration of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) control efforts into existing child-health programmes
- Disease-specific and register-based case finding, treatment and tracking (Where feasible)

Generation of new knowledge and interventions

- Contemporary data on disease characteristics and outcomes
- Health technology assessment and economic evaluation
- Vaccine development
- Genetic studies
- Plasma and tissue proteomic studies
- Development of longer acting penicillin formulations

Advocacy

- Reliable data on disease burden and effects on populations
- Adaptation of elements from advocacy models of the 'big three' diseases

Figure 1.18. Potential strategies for ARF and RHD control (Carapetis *et al.,* 2016).

1.9 Problem identification

It is widely ascertained that prosthetic valve replacement (PVR) reduces life expectancy, especially in children and young adults regardless of native valve pathology, due to prosthetic valve related complications (Mvondo 2016). De Santo and colleagues reported a 25year survival of 70% in young women (mean age: 30 years) after mechanical valve replacement (De Santo *et al*., 2005).

Rheumatic valvular heart disease remains an important acquired heart disease for children and young adults in under-developed and developing parts of the world. Most of these people come from poor socio-economic backgrounds with limited resources. This makes it difficult for their voices to be heard and assisted by the so-called first world health systems and governments with both monetary and technological advances. Part of the challenge could be the misinformation that the incidence of ARF and RHD are in the decline due to the skewed data that has been collected over the recent past.

Health consequences as well as financial burden that ARF and RHD have on the already strained economies make this disease entity one of the important health conditions that need to be closely monitored and managed. The effects of this disease entity extend beyond management, whether medical and/or surgical, influencing the quality of life of patients. Thus, in the Sub-Saharan regions with a burden of other diseases such as human immune deficiency (HIV), tuberculosis (TB) and malaria, intensified awareness regarding the prevalence and management of ARF and RHD is crucial.

As part of this, we have undertaken to evaluate a cohort of patients who were diagnosed with RHD requiring intervention for their mitral valves with or without tricuspid valves in Central South Africa.

1.9.1 Aim

The aim of this study was to describe the surgical outcomes of patients who underwent mitral valve surgery with/without tricuspid valve repair between 2009 and 2019 at Universitas Academic Hospital for RHD.

1.9.2 Objectives

- To identify adult patients above the age of 14 years, who had Rheumatic mitral valve disease requiring surgical intervention, from the departmental database.

- To describe the prevalence of MR, MS, and MX in the cohort.

- To describe the preoperative patient demographics, pre-operative risk factors and surgical procedure/s in these patients.

- To analyze the post-surgical outcomes and complications in relation to pre-operative risk factors and surgical procedures.

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2. Publishable Article

Critical Analysis of Rheumatic Mitral Valve Surgery Outcomes in Central South Africa

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Abstract

Introduction: The study aim was to analyze the rheumatic mitral surgery risk factors and outcomes of a surgical unit in Central South Africa.

Methods: Patients 14 years or older operated for mitral valve surgery with/without tricuspid valve repair between 01 January 2009 and 31 December 2019 were included in the study. Demographics, pre-, peri- and post-operative cardiovascular risk factors, including in-hospital morbidity and mortality, as well as long-term follow up were analyzed. The lesions were grouped into mitral stenosis (MS), mitral regurgitation (MR) and mixed mitral (MX) disease.

Results: A total of 242 patients were included in the study of which females were the majority with 75.2% (n=182). Black patients represented 74.4% (n=180), white 13.6% (n=33) with Asian and mixed race 12% (n=29). The mean age of the study population was 43.7 years. Distribution of patients according to the lesions was 25.6% (n=62) for MS, 45.0% (n=109) for MR and 29.3% (n=71) for MX disease. Most patients with New York Heart Association (NYHA) status III and IV were in the MR (44%) and MS (43.5%) respectively, whereas the MX group only accounted for 27.8%. Hypertension and atrial fibrillation were prevalent in the MS (64.5%; 53.2%) and MX (63.4%; 53.5%) groups. The most performed surgery across all groups with a mean of 94% was mitral valve replacement. Concomitant tricuspid valve repair was mostly performed in the MS group (58.1%). There was no statistical difference across the groups with regards to the post-operative stroke rate (1%) as well as the rate of in-hospital complications (14%). In-hospital mortality was 4.8% (n=3) for the MS, 3.7% (n=4) in the MR group and 2.8% (n=2) in the MX group, with the overall mortality being 3.8%.

Conclusion: MR was the most common lesion with replacement being the most performed operation in our unit. The post-operative complications rate as well as the in-hospital mortality were comparable to the published literature.

Keywords

Rheumatic heart disease, mitral stenosis, regurgitation, mixed valve disease, bioprosthesis.

Introduction

Rheumatic heart disease (RHD) is still an important cause of morbidity and mortality in poor socioeconomic regions[1]. RHD is the most common form of acquired heart disease in children and young adults in low- and middle-income countries of the world is rheumatic heart valvular disease (RHVD)[2].

In 2015, Engel published a prospective echocardiographic study on the prevalence of asymptomatic schoolchildren in Cape Town South Africa and Jimma Ethiopia. If only definite RHD diagnoses are considered, the RHD prevalence was 2.3/1 000 in Bonteheuwel and 6.9/1 000 in Langa[3]. These prevalence findings were similar to a study done by Smit that conducted a prospective study on schoolchildren in central South Africa with a prevalence of 4.9/1000[4]. A Cape Town study published in 2016 showed a very high prevalence with using echocardiography as a diagnostic method compared to auscultation alone with a prevalence of 20.2/1000[5].

RHD remains a significant cause of morbidity and mortality, particularly in regions with poor socio-economic backgrounds[2]. The most seen valve pathology in RHD is mitral valve regurgitation (MVR)[6], particularly in young females, where pure MVR is the most usual form of RHD presentation[2,7], which in Cameroon study was 59.7%[8]. The second common lesion affecting the mitral valve (MV) is stenosis (25%), which is seen commonly in the older generation, with mixed form of the above-mentioned pathologies making up the third possible variety of MV disease at 13.7% seen in RHD patients[5,9,10].

The diagnosis as well as the assessment of the severity of the disease are made by echocardiography, and the primary surgical indications in chronic RHD are the development of cardiovascular (CV) symptoms and/or decreased left ventricular ejection fraction (LVEF)[11]. These CV symptoms include heart failure (HF), rhythm abnormalities such as atrial fibrillation (AF) and complications related to AF such as stroke[12].

The role of medical management in RVHD is directed at managing complications such as HF with diuretics and fluid restrictions, as well as AF management with anticoagulation medication to prevent stroke and other systemic embolic complications[6], but no long-term survival benefit was demonstrated when compared to surgical intervention[13].

Surgical interventions include closed balloon mitral valvotomy (BMV), open mitral valve commissurotomy, valve repair and replacement with either mechanical or biological

prosthesis. Tricuspid valve repair/replacement may be performed during open mitral valve surgery depending on the extent of the disease[14].

In appropriately selected patients, BMV has been shown to produce comparable results to open techniques[15]. MV repair is the most commonly performed surgical intervention for MVD[14], with comparable results in appropriately selected patients with RVHD[10]. It has been shown to have better survival outcomes, lower morbidity post-operatively, as well as lower use of anticoagulation therapy[17], although there is an increased rate of reoperation in the RVHD group compared to the non-RVHD, as well as in repair generally than in replacement[18,19].

Reported mortality post MV surgery is 1.5% to 5.5% on average[20], although in the REMEDY study the 2-year case fatality rate was higher (500 deaths, 16.9%)[21]. This study aims to analyze the rheumatic MV surgery risk factors and outcomes of a surgical unit in Central South Africa (SA).

Methodology

A retrospective descriptive study was conducted that included patients 14 years and older who underwent primary MV surgical intervention for RHD with/without concomitant tricuspid valve repair between 01 January 2009 and 31 December 2019 in the Department of Cardiothoracic Surgery, Bloemfontein. The operations were performed at Universitas Academic Hospital (UAH), which is a 600-bed tertiary hospital and is the only referral center offering a tertiary service for cardiac surgery in central SA serving a population of approximately 3 million people.

The cohort was divided into three groups, namely mitral regurgitation (MR), stenosis (MS) and the mixed mitral disease (MX). MR was compared to both MS and MIX groups.

The department of cardiothoracic database and UAH medical files were used to collect data, which included demographics, preoperative, perioperative, postoperative risk factors, and

outcomes. In-hospital mortality was recorded, and follow-up determined from last visit to the Department of Cardiology.

Statistical Analysis

This data was analyzed using IBM SPSS program, version SPSS 26.0. A p-value of 0.05 0r less was considered statistically significant. Where applicable, standard deviations of variables were determined as well as analysis of the mean and any relation between variables using Pearson chi square test.

Ethical Approval

The University of the Free State, Health Science Research Ethics Committee (HSREC) approved the research protocol with the assigned number (UFS-HSD2019/1530/2807).

Results

Demographics

Two hundred and forty-two patients who underwent primary MV surgery with or without tricuspid valve repair for RHD between 2009 and 2019 were included in the study. There was an overall female preponderance of 75.2% (n=182) and the mean age of the study population was 43.7 years (range: 14 years – 80 years). Most of the patients were Black (74.4%), with the White and others accounting for 13.6% and 12% respectively. The most prevalent pathology observed was MR 45% (n= 109) followed by MX 29.3% (n=71) and MS
25.6% (n=62) (see table I).

Risk Profile

A total of 57.4% of all patients presented with preoperative NYHA I and II (see table I). Those with pre-operative residual stroke or TIA were the MS group with 6.5% (n=4) compared to the other groups. Preoperative renal dysfunction was 4.8% in the MS, which was higher than in

the other groups. With regards to pre-operative AF, the MS and the MX group had 53.2% (n=33) and 53.5% (n=38) patients respectively, with MR group at 28.4% (n=31).

DM being more prevalent as a risk factor in MS than in MR with P = 0.0092. Atrial fibrillation was more prevalent in MS and MX than in MR with P values of 0.0022 and 0.0013 respectively. The MR group had a greater proportion of patients with a Euroscore > 5 in comparison to MX at P = 0.0035 (see table I).

Table I. Demographics and Pre-operative Risk Factors According to Lesion.

Variable	MR n= 109 *(%)*	MS n=62 *(%)*	P MR vs MS	MX n=71 *(%)*	P MR vs MX
Age	43.7 years (range: 14 years – 80 years)				
Male	29 (*26.6)*	16 (*25.8)*	0.9095	15 (*21.1)*	0.8690
Female	80 (*73.4)*	46 (*74.2)*	0.9092	56 (*78.9)*	0.5102
Black	86 (*78.9)*	36 *(58.1)*	**0.0065**	58 (*81.7)*	0.7896
White	10*(9.2)*	14 (*22.6)*	**0.0280**	9 (*12.8)*	0.6177
Other	13 (*11.9)*	12 (*19.4)*	0.2728	4 *(5.6)*	0.1976
HPT	43 (*39.4)*	40 (*64.5)*	**0.0028**	45 (*63.4)*	**0.0028**
Neuro deficit	3 *(2.8)*	4 (*6.5)*	0.2566	3 (*4.2)*	0.6816
DM	3 (*2.8)*	9 (*14.5)*	**0.0092**	2 (2.8)	>0.9999
AF	31 (*28.4)*	33 (*53.2)*	**0.0022**	38 (53.5)	**0.0013**
Renal dysfunction	2 *(1.8)*	3 (*4.8)*	0.3541	3 (4.2)	0.3843
NYHA I+II **III+IV**	60 *(55.0)* 49 *(44.9)*	35 *(56.5)* 27 *(43.5)*	0.9858 0.9858	43 *(60.7)* 28 *(39.4)*	0.5639 0.5639
EuroSCORE (> 5)	32 *(29.4)*	18 *(29.0)*	0.9641	7 *(9.9)*	**0.0035**

MS – Mitral stenosis, MR – Mitral regurgitation, MX – Mixed disease, AF – Atrial fibrillation, HPT – Hypertension, DM – Diabetes mellitus, NYHA – New York Heart Association Classification.

Preoperative Echocardiography

Most patients had pre-operative LVEF above 50% (see table II), and the pre-operative left atrial (LA) size was more than 5 cm in most of the patients in the MS group at 66.1% (n=41) (see table II). The preoperative LA size > 5 cm was higher in the MS group (66.1%) than in MR (19.2%) and MX (11.3%) groups with MR vs MS group at p= < 0.0001. RVPSP was more than

55 mmHg in the MR, MS, and MX groups with 53.4%, 67.2% and 55.9% respectively. The mean pre-operative RVPSP was 67.1 mmHg, which decreased to 51.0 mmHg postoperatively. The preoperative LVEF mean was 53.5%, which came down to 48.1% postoperative.

Table II. Pre-operative Echocardiography.

Variable	**MR n=109** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=71** ***(%)***	**P MR vs MX**
LVEF %					
< 30	5 *(4.6)*	3 *(4.8)*	>0.9999	3 *(4.2)*	>0.9999
30-39	9 *(8.3)*	4 *(6.4)*	0.7714	7 *(9.9)*	0.7910
40-49	18 *(16.5)*	12 *(19.4)*	0.7945	10 *(14.1)*	0.8188
>50	77 *(70.6)*	43 *(69.4)*	0.9976	51 *(71.8)*	0.9970
LA size cm	**MR n=109** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=71** ***(%)***	**P MR vs MX**
<4	31 *(28.4)*	1 *(1.5)*	**0.0001**	46 *(64.9)*	**0.0001**
4 - 4.5	32 *(29.3)*	7 *(10.6)*	**0.0118**	9 *(12.7)*	**0.0153**
4.6 – 5	25 *(22.9)*	13 *(20.9)*	0.9154	8 *(11.3)*	0.0513
>5	21 *(19.2)*	41 *(66.1)*	**0.0001**	8 *(11.3)*	0.2228
RVPSP mmHg	**MR n=73** ***(%)***	**MS n=58** ***(%)***	**P MR vs MS**	**MX n=59** ***(%)***	**P MR vs MX**
17 - 24	-	-	-	-	-
25 – 40	16 *(21.9)*	6 *(10.3)*	0.1273	3 *(5.1)*	**0.0055**
41 - 55	18 *(24.7)*	13 *(22.4)*	0.9257	13 *(22)*	0.8831
>55	39 *(53.4)*	39 *(67.2)*	0.1553	33 *(55.9)*	0.9109
LVESD cm	**MR n=109** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=57** ***(%)***	**P MR vs MX**
2 – 4	31 *(28.4)*	42 *(67.7)*	**0.0001**	41 *(71.9)*	**0.0001**
4.1 – 4.5	32 *(29.3)*	12 *(19.3)*	0.2089	6 *(10.5)*	**0.0063**
4.6 – 5	25 *(24.1)*	3 *(4.8)*	**0.0021**	5 *(8.8)*	**0.0414**
>5.1	21 *(22.9)*	5 *(8.1)*	0.0819	5 *(8.8)*	0.1232

MS – Mitral stenosis, MR – Mitral regurgitation, MX – Mixed disease, LVEF – Left ventricle ejection fraction, LA – Left atrium, CM - centimeter, RVPSP - Right ventricular peak systolic pressure, mmHg - Millimeter of mercury, LVESD - Left Ventricular End-Systolic Diameters.

Intra-operative Data.

Table III. Intra-Operative Data.

Type of operation	**MR n=109** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=71** ***(%)***	**P MR vs MX**
Repair	10 *(9.7)*	2 *(2.8)*	0.2147	4 *(5.6)*	0.5705
Replacement	99 *(90.8)*	60 *(96.7)*	0.2491	67 *(94.4)*	0.5605
Tricuspid repair	42 *(38.5)*	36 *(58.1)*	0.0211	25 *(35.2)*	0.7697
Aortic cross-clamp time (min):	**MR n=97** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=71** ***(%)***	**P MR vs MX**
<60	12 *(12.4)*	7 *(11.2)*	>0.9999	7 *(10)*	0.8059
60 – 90	37 *(38.1)*	23 *(37.1)*	0.8037	41 *(58.6)*	**0.0027**
>90	48 *(49.5)*	32 *(51.6)*	0.9210	22 *(31.4)*	**0.0248**
Cardio-pulmonary bypass time (min):	**MR n=103** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=68** ***(%)***	**P MR vs MX**
<60	0	2 *(3.2)*	-	0	-
60 – 120	36 *(34.9)*	21 *(33.9)*	0.8876	24 *(35.3)*	0.9633
>120	67 *(65.0)*	39 *(62.9)*	0.9118	44 *(64.7)*	0.9633

MS – Mitral stenosis, MR – Mitral regurgitation, MX – Mixed disease, min – Minutes.

Most of the study cohort patients received MV replacement (93.7%) and only 6.2% had repair of their valves, with concomitant tricuspid valve repair in 38.2% (majority being in the MS group ~ 58%) (Table III).

The mean cardiopulmonary bypass (CPB) cumulative and aortic-cross clamp times were 138 and 90 minutes respectively, see distribution figures 2.1 and 2.2.

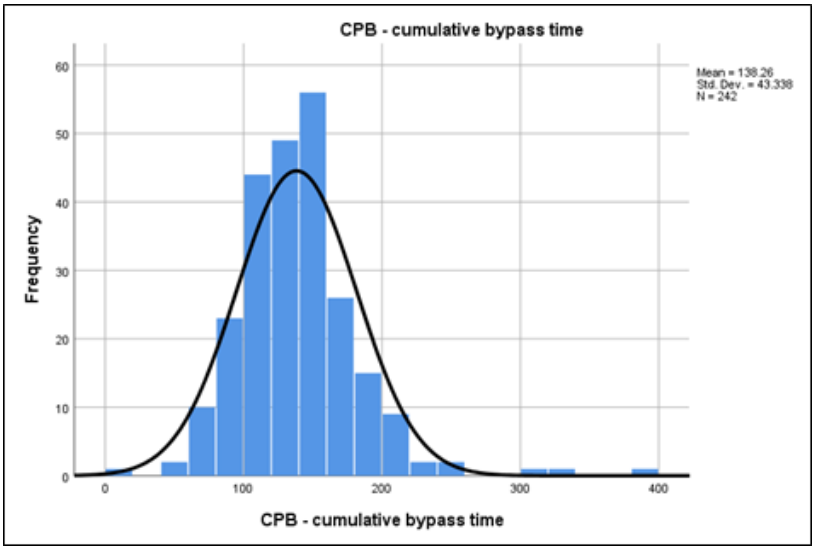

Figure 2.1. Cumulative CPB time distribution graph.

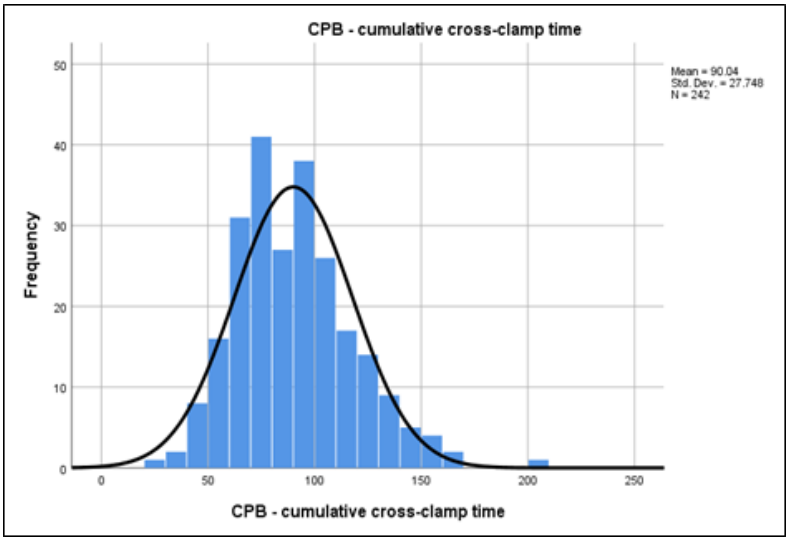

Figure 2.2. Cumulative cross-clamp time distribution graph.

Follow-up Echocardiography

There was a reduction of LVEF >50% in the MR group from 70.6% to 50%. With the LVEF between 40 and 49 the MX group had a much lower proportion of patients as compared to the largest group namely MR at p = 0.0102. With regards to LVESD the MS group had a much lower proportion of patients > 5.1 cm as compared to MR with p = 0.0021 (Table IV).

Table IV. Post-operative Echocardiography.

LVEF	**MR n=106** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=65** ***(%)***	**P MR vs MX**
<30	16 *(15.1)*	2 *(3.2)*	**0.0188**	3 *(4.6)*	**0.0439**
30 – 39	11 *(10.4)*	5 *(8.1)*	0.7873	12 *(18.5)*	0.1666
40 – 49	26 *(24.5)*	14 *(22.5)*	0.9217	5 *(7.7)*	**0.0071**
>50	**53 *(50)***	41 *(66.1)*	0.0613	45 *(69.2)*	**0.0210**
LVESD cm	**MR n=107** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=59** ***(%)***	**P MR vs MX**
2 – 4	59 *(55.1)*	44 *(71.0)*	0.0616	40 *(67.8)*	0.5066
4.1 – 4.5	17 *(15.9)*	13 *(20.9)*	0.5326	10 *(16.9)*	0.9299
4.6 – 5	10 *(9.3)*	3 *(4.8)*	0.3846	5 *(8.5)*	>0.9999
>5.1	21 *(19.8)*	2 *(3.2)*	**0.0021**	4 *(6.8)*	**0.0395**
AF	**MR n=109** ***(%)***	**MS n=62** ***(%)***	**P MR vs MS**	**MX n=71** ***(%)***	**P MR vs MX**
	30 *(27.5)*	28 *(45.2)*	**0.0297**	21 *(29.6)*	0.8968

MS – Mitral stenosis, MR – Mitral regurgitation, MX – Mixed disease, LVEF – Left ventricle ejection fraction, CM - centimeter, LVESD - Left Ventricular End-Systolic Diameters, AF – Atrial fibrillation.

With the comparison of pre- vs post-operative echocardiography there was a statistically significant difference found with LVEF having worsened from 5 to 11 patients whose initial LVEF was <30 to >30 with p = 0.0180. The LVESD also changed significantly from pre op to post op with p = 0.0001 (Table V).

Table V. Echo Pre op vs post op echocardiography.

	Pre Op	**Post Op**		**Pre OP**	**Post Op**		**Pre Op**	**Post Op**	
LVEF	**MR n=109 *(%)***	**MR n=106 *(%)***	**P**	**MS n=62 *(%)***	**MS n=62 *(%)***	**P**	**MX n=71 *(%)***	**MX n=65 *(%)***	**P**
<30	5 *(4.6)*	16 (15.1)	**0.0180**	3 (4.8)	2 (3.2)	>0.999	3 (4.2)	3 (4.6)	>0.999
30 – 39	9 (8.3)	11 (10.4)	0.7639	4 (6.4)	5 (8.1)	>0.999	7 (9.9)	12 (18.5)	0.2153
40 – 49	18 (16.5)	26 (24.5)	0.1980	12 (19.4)	14 (22.5)	0.8258	10 (14.1)	5 (7.7)	0.2812
>50	77 (70.6)	53 (50)	**0.0031**	43 (69.4)	41 (66.1)	0.8477	51 (71.8)	45 (69.2)	0.8855
	Pre Op	**Post Op**		**Pre Op**	**Post Op**		**Pre Op**	**Post Op**	
LVESD cm	**n=109 (%)**	**MR n=107 (%)**	**P**	**n=62 (%)**	**MS n=62 (%)**	**P**	**n=57 (%)**	**MX n=59 (%)**	**P**
2 – 4	31 (28.4)	59 (55.1)	**0.0001**	42 (67.7)	44 (71.0)	0.8456	41 (71.9)	40 (67.8)	0.7832
4.1 – 4.5	32 (29.3)	17 (15.9)	**0.0277**	12 (19.3)	13 (20.9)	>0.999	6 (10.5)	10 (16.9)	0.2878
4.6 – 5	25 (24.1)	10 (9.3)	**0.0125**	3 (4.8)	3 (4.8)	>0.99	5 (8.8)	5 (8.5)	>0.999
>5.1	21 (22.9)	21 (19.8)	0.9197	5 (8.1)	2 (3.2)	0.4395	5 (8.8)	4 (6.8)	>0.999

MS – Mitral stenosis, MR – Mitral regurgitation, MX – Mixed disease, LVEF – Left ventricle ejection fraction, CM - centimeter, LVESD - Left Ventricular End-Systolic Diameters.

Post-operative Complications and Mortality

The observed post-operative complications rate was 14% across the three groups, with 3.6% pulmonary complications requiring re-intubation. Only 1.2% of the total number of patients developed new neurological dysfunction post-operatively. The development of new AF postoperatively was common in the MS group (1.6%). Other complications included renal dysfunction, sternal wound sepsis, bleeding requiring re-look, IE, and MODS.

The average ICU stay was 3.3 days. In-hospital mortality was 3.8% (n = 9), with the MS group accounting for 4.8% (n=3) which was proportionally the highest between the three groups.

The risk factors that were common in mortality group included age above 60 yrs. (n=5), female gender (n=8), patients requiring concomitant TV repair (n=5), preoperative AF (n=5) and CPB of more than 120 min (n=5) (Table VI).

Table VI In-hospital mortality.

Age	m/f	Race	Dx	Proc	NYHA	Rhythm	LVEF	EuroSCORE	Clamp time	CPB time	Causes of death
43	F	B	MX	R	3	AF	41	6.5	35	65	-
62	F	W	MS	R	2	AF	-	7.8	206	310	RF
61	F	B	MR	r/TV	-	Sin	-	7.0	83	113	-
66	F	O	MS	r	3	Sin	70	6.8	27	54	RF, Sepsis
36	F	B	MX	R	2	Sin	-	6.7	79	113	Sepsis
66	F	B	MR	R/TV	2	Sin	46	4.9	129	332	Bleeding
42	F	B	MX	R/TV	2	AF	57	2.1	80	132	CVA
48	M	W	MR	R/TV	4	AF	21	4.3	96	185	IE, MODS
72	F	B	MS	R/TV	2	AF	60	5.8	156	380	-

m/f: male/female, *Dx*: diagnosis, *Proc*: procedure, *NYHA*: New York Heart Association, *EuroSCORE*: European System for Cardiac Operative Risk Evaluation, *Clamp time*: Aortic Cross-clamp time, *CPB*: Cardiopulmonary Bypass Time, *O*: Asian and mixed race, *IE*: infective endocarditis, *CVA*: cerebrovascular accident, *MODS*: multiple organ dysfunction syndrome, *AF*: atrial fibrillation, *R/TV*: replacement with tricuspid valve repair, *r/TV*: repair with tricuspid valve repair, *Sin*: sinus rhythm, *RF*: renal failure, *W*: white, *B*: black.

Last Date for Patient Follow Up

There were 160 patients with follow up visits to the Cardiology Clinic > 10 days post-operatively at UAH with the other followed up in periphery. The median last visit to Cardiology Clinic 977.5 days (2.68 years) with Range - (11: 3796). A total of 35 patients had been seen at the Cardiology Clinic > 5 years.

Discussion

Of the acquired valvular heart diseases, RHD remains the common cause of MVD in low- and middle-income regions[22]. Our findings confirmed that RHD was still the common cause of mitral valve pathology requiring intervention when compared to other aetiologies such as degenerative and congenital causes.

Some of the factors that increase the risk of developing RHD include low income, crowded living spaces and poor nutrition[23]. This has been confirmed in our study population with most patients being black females (75.2%) from poor socio-economic backgrounds, a comparable finding to literature[9]. The skewed gender distribution seen in RHD studies has also been observed in our study with 73.4% females[24].The average age on presentation for surgical intervention was 43.7 years in keeping with the published literature[1].

The mean number of patients in NYHA class III and IV at presentation for surgery was 43%, indicating the late presentation and/or referral for surgical intervention. Hypertension was prevalent in the MS (64.5%) and MX (63.4%) groups than in the MR (39.4%). This could be attributed to the late presentation in the MS and MX groups, a finding consistent with the published literature[2]. A coincidental finding was type 2 DM which was high in the MS group compared to the MR group with a statistical significance of a p-value 0.0121.

The mean pre-operative AF rate was 45.0%, higher than published literature and there was a correlation between pre-operative AF and neurological dysfunction, confirming the increased risk of stroke in patients diagnosed with RHD complicated by dysrhythmia and blood stasis[9,13]. AF was higher in the MS (53.2%) and MX (53.5%) groups than the MR (28.4%). This finding supports the assertion that patients in the two groups (MS, MX) were older and with advanced disease processes than in the MR group[9].

Pre-operative LVEF was above 50% in most of the patients across the three groups. As expected, the preoperative LA size above 5 cm was higher in the MS (66.1%) group than in others, with a statistical significance when this variable was compared between MR vs MS group. The preoperative LVEF mean percentage was 53.5% which came down to 48.1% post-operative, and this could be that most patients operated had MR with impaired ventricular function, which was unmasked after the surgery.

The LVESD mean value was 4.04 cm across all the groups, a value, which was expected to reverse remodel after the operation. This was confirmed by the last follow-up LVESD mean value of 3.8 cm, with the majority of patients who reversed remodeled found in the MR group when pre- and post-operative values were compared in this a group.

No relationship was demonstrated between CPB and aortic cross-clamp times to the postoperative length of hospital stay. Most of the patients received MV replacement and only 6.2% had repair of their valves, with concomitant tricuspid valve repair in 38.2% (majority being in the MS group ~ 58%). This was in contrast to the published literature wherein the most performed MV procedure for RHD is repair. This difference could be attributed to the

low rate of MV repair performed at our institution due to either late presentation, as in the cases of MS, or if they present early (MR), they are operated by registrars with little, if any, experience for repair. Another factor to consider is that some of the patients with MS who presented early with Wilkins scores amenable to closed valvotomy procedure were referred to Cardiology for closed mitral valvotomies (n=34) over a period of 5 years. Mechanical prosthesis represented the most used replacement valve method (77.5%). Although this was an expected finding with regards to the age of most patients, it did not explain the choice of a mechanical valve in a population where most patients are females of a child-bearing age. There was a high number of concomitant tricuspid valve repair in the MS (58.1%) group as compared to the other two (MR, MX) as expected due to increased number of patients with PHT affecting the RV in this group.

A total of 1.2% of the total number of patients developed new neurological dysfunction post-operatively, which was in keeping with the published literature[25]. The development of new AF post-operatively was prevalent in the MS group (1.6%)[26] as was expected. The in-hospital mortality rate was 3.8% (n=9). The risk factors common in patients who demised in-hospital included age above 60 yrs. (n=5), female gender (n=8), patients requiring concomitant TV repair (n=5), preoperative AF (n=5) and CPB of more than 120 min (n=5).

Study Limitations

There were few limitations to the study, which included missing data on some variables, especially on the post-operative course complications, which prevented any reasonable analysis to be performed. Late mortality data was also not available because the National Department of Home Affairs refused to provide us with the requested information for our patient cohort.

Other limitations are the general ones inherent to a retrospective study, which include the differential bias and a loss to follow up bias, both of which were present in our study.

Conclusion

Most of the observed outcomes in our study were in keeping with the internationally published literature regarding demographics and risk profiles. The surgical intervention mostly performed in our setting was MV replacement with a mechanical prosthesis than repair. The post-operative morbidity and mortality were similar to the general findings in the literature, with the in-hospital mortality seen commonly in patients above sixty years of age with preoperative AF, majority of which were black females, with prolonged CPB times.

Acknowledgements

Benyam Tesfaye for helping with the statistical data analysis.

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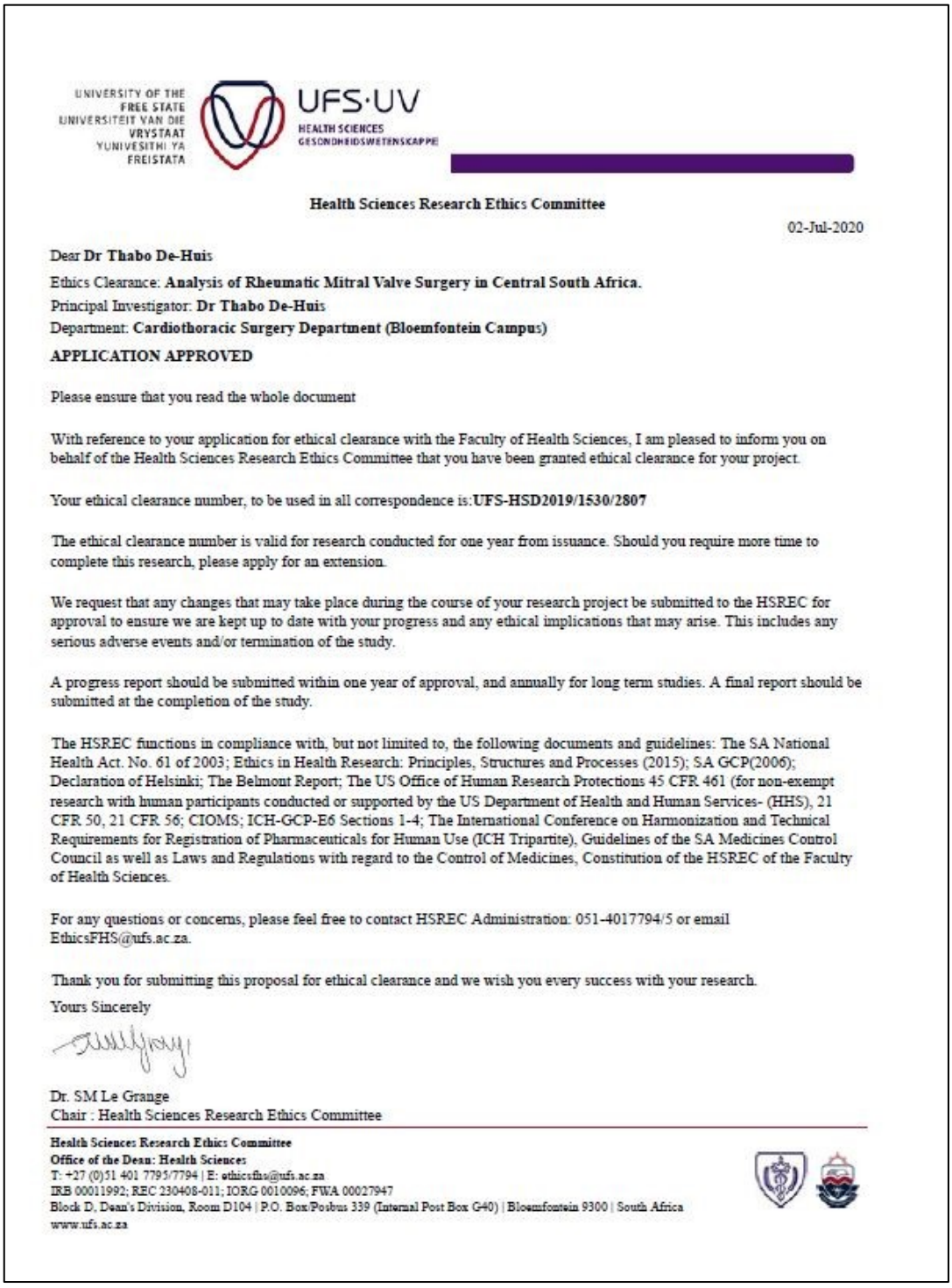
3. Appendices

3.1 Appendix A – Letter of approval from HSREC



UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

02-Jul-2020

Dear **Dr Thabo De-Huis**

Ethics Clearance: **Analysis of Rheumatic Mitral Valve Surgery in Central South Africa.**

Principal Investigator: **Dr Thabo De-Huis**

Department: **Cardiothoracic Surgery Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/1530/2807**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
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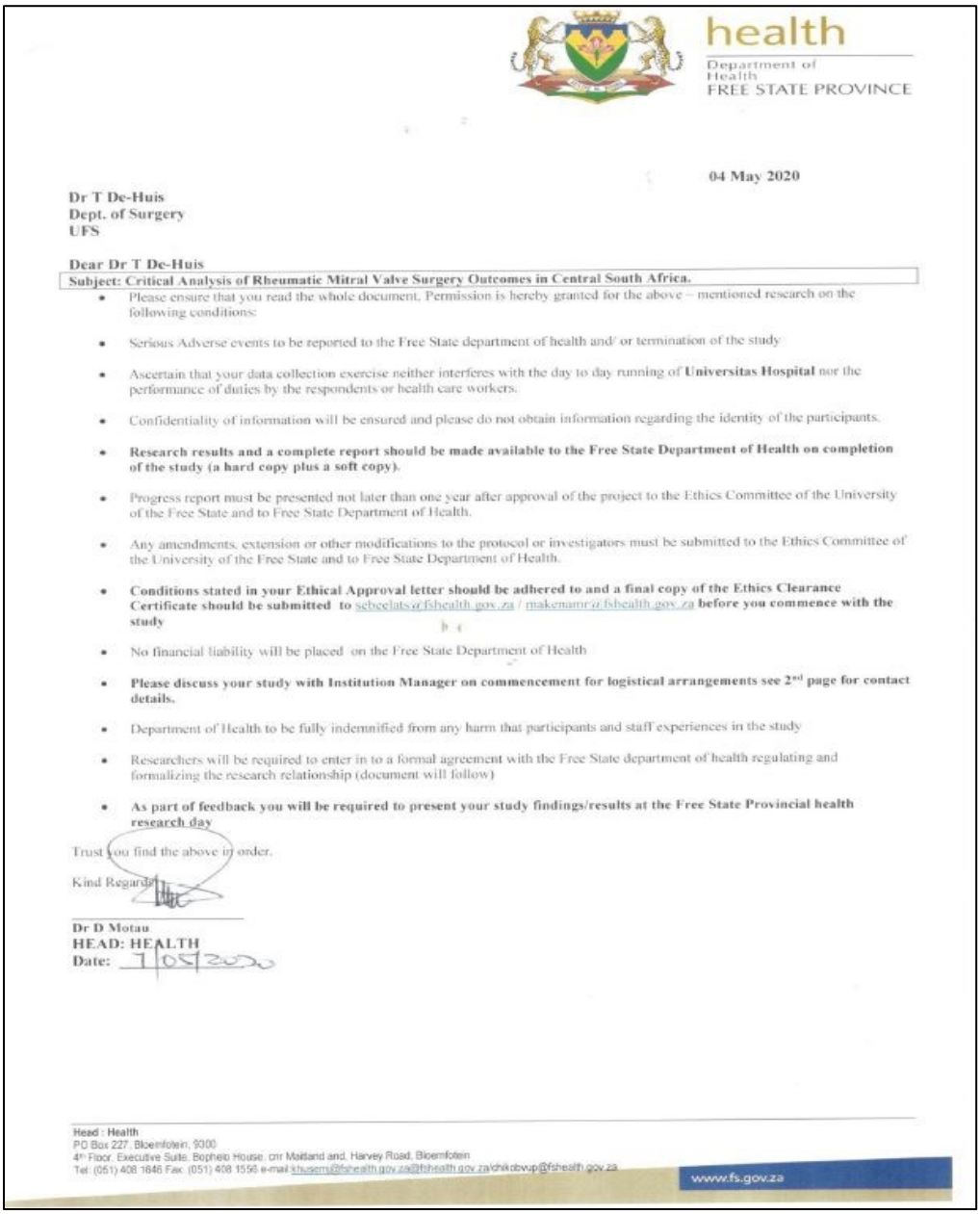
www.ufs.ac.za

3.2 Appendix B – Letter of approval from DOH



health
Department of Health
FREE STATE PROVINCE

04 May 2020

Dr T De-Huis
Dept. of Surgery
UFS

Dear Dr T De-Huis
Subject: Critical Analysis of Rheumatic Mitral Valve Surgery Outcomes in Central South Africa.

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

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 7/05/2020

Head : Health
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www.fs.gov.za

3.3 Appendix C – Letter of approval from HOD

PERMISSION FROM HEAD OF DEPARTMENT OF CARDIOTHORACIC SURGERY

Dear HSREC/Whom it may concern

PROJECT TITLE:

Critical Analysis of Rheumatic Mitral Valve Surgery Outcomes in Central South Africa

I, Prof Francis Smit am the Head of Department in the Cardiothoracic Surgery and grant Dr Thabo De Huys, the principal investigator for the above-mentioned project permission to conduct his study. He may use the patient data in the departmental database and patient files to conduct and complete his MMED study as he will be aiming to evaluate and analyse patients who received mitral valve surgery in the Department of Cardiothoracic Surgery.

The research study can commence as soon as the Health Sciences Research Ethics Committee grant him approval.

Yours faithfully

20/02/2020

HEAD OF DEPARTMENT DATE

CRITICAL ANALYSIS OF RHEUMATIC MITRAL VALVE SURGERY OUTCOMES IN CENTRAL SOUTH AFRICA

By

Dr TJ De-huis

Department of Cardiothoracic Surgery

University of the Free State

June 2019

Critical Analysis of Rheumatic Mitral Valve Surgery Outcomes in Central South Africa

by

Dr T.J. De-huis

MBChB, ATLS, University of the Free State

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Glossary

Acute Rheumatic Fever:

A sequela of streptococcal infection – typically following 2 to 3 weeks after a group A streptococcal throat infection that commonly occurs in children, and has rheumatological, cardiac, and neurological manifestations.

Aetiology:

Study or theory of the factors that cause diseases or disorders. (https://www.encyclopedia.com)

Aldosterone antagonist:

An agent that opposes the action of the adrenal hormone aldosterone on renal tubular mineralocorticoid retention; these agents (e.g., spironolactone) are useful in treating the hypertension of primary hyperaldosteronism, or the sodium retention of secondary hyperaldosteronism.

Angiotensin converting enzyme inhibitors:

A class of drugs (angiotensin-converting enzyme inhibitors) that block the conversion of angiotensin I to angiotensin II, used in the treatment of hypertension and congestive heart failure and in the prevention of microvascular complications of diabetes mellitus (DM).

Antibody cross-reactivity:

The ability of an antibody to react with similar antigenic sites on different proteins

Anticoagulation:

The process of hindering the clotting of blood.

Antigen mimicry:

The sharing of antigenic sites between microorganisms and mammalian tissue.

Aortic valve:

The aortic valve is a valve in the human heart between the left ventricle and the aorta.

Asymptomatic:

Presenting no symptoms of disease. **Atrial fibrillation:**

An irregular, rapid heart rate that may cause symptoms like heart palpitations, fatigue, and shortness of breath.

Auscultation:

The action of listening to sounds from the heart, lungs, or other organs, typically with a stethoscope, as a part of medical diagnosis. **Autoimmune:** When the body tissues are attacked by its own immune system.

(https://www.medicinenet.com)

Beta blockers:

Any of a class of drugs which prevent the stimulation of the adrenergic receptors responsible for increased cardiac action, used to control heart rhythm, treat angina, and reduce high blood pressure.

Calcium channel blockers:

Prescription medications that relax blood vessels and increase the supply of blood and oxygen to the heart while also reducing the heart's workload.

Carditis:

The inflammation of the heart or its surroundings.

Chronic rheumatic heart disease:

Describes a group of long-term (chronic) heart disorders that can occur as a result of rheumatic fever.

Commissurotomy:
A surgical incision of a commissure in the body, as one made in the heart at the edges of the commissure formed by cardiac valve.

Diuretics:
Also called water pills, are medications designed to increase the amount of water and salt expelled from the body as urine.

Dyspnea:
Difficult or labored breathing; shortness of breath.

Echocardiography:
The use of ultrasound waves to investigate the action of the heart.

Ejection fraction:
A measurement of the percentage of blood leaving your heart each time it contracts.

Endocarditis:
An infection of the inner lining of the heart or its valves.

Endoscopy:
A procedure in which an instrument is introduced into the body to give a view of its internal parts.

Embolic event:
Occurs when a blood clot that forms elsewhere in the body breaks loose and travels to the other part of the body via the bloodstream and causes an obstruction to blood flow.

Haemoptysis:
The coughing up of blood.

Haemorrhage:
A profuse discharge of blood, as from a ruptured blood vessel; bleeding.
Heparin:
A substance that slows the formation of blood clots.
Incidence:
The occurrence, rate, or frequency of a disease.

Left atrium:
The left upper chamber of the heart that receives blood from the pulmonary veins. **Left ventricle:**

The chamber on the left side of the heart that receives arterial blood from the left atrium and pumps it into the aorta.
Mechanical valve:
Prosthetics designed to replicate the function of the natural valves of the human heart.
Mixed mitral valvular pathology:
Refers to coexisting mitral stenosis (MS) and mitral regurgitation (MR).
Morbidity:
The quality or state of being morbid.
Mortality:
The state of death.
Native valve:
Natural valve.
Nitrates:
Medications used for treating or preventing heart pain (angina, chest pain) caused by heart disease, usually of the arteries in the heart. **Palpitations:**
The feelings of having a fast beating, fluttering or pounding heart.

Pancarditis:
Inflammation of the entire heart (the epicardium and the myocardium and the endocardium) carditis - inflammation of the heart

Papillary muscle:
Are muscles located in the ventricles of the heart.

Percutaneous:
Made, done, or effected through the skin.

Pharyngitis:
Inflammation of the pharynx, causing a sore throat.
Prevalence:
A statistical concept referring to the number of cases of a disease that are present in a particular population at a given time.
Prosthetic valve:
A prosthetic heart valve is surgically implanted in the heart to replace a heart valve that has become damaged due to heart valve disease.

Pulmonary congestion:

Accumulation of fluid in the lungs, resulting in impaired gas exchange and arterial hypoxemia.

Regurgitation:

A leaky state of one or more of the cardiac valves, in which the valve not closing tightly, and blood is therefore regurgitating through it.

Robotic telemanipulations:

Indicate the capability of a human being of carrying out operations in a remote environment by means of a proper robotic system.

Scarlet fever:

An infectious bacterial disease affecting especially children and causing fever and a scarlet rash.

Stenosis:

The narrowing or restriction of a blood vessel or valve that reduces blood flow.

Sternotomy:

A type of surgical procedure in which a vertical inline incision is made along the sternum, after which the sternum itself is divided.

Streptococcus pyogenes:

Ubiquitous bacterium responsible for hundreds of millions of illnesses throughout the world each year, some of which are fatal.

Thoracotomy:

Surgical incision into the chest wall.

Thrombus:

A blood clot formed in situ within the vascular system of the body and impeding blood flow.

Valvulitis:

Inflammation of the valves of the heart.

Abbreviations

AF	Atrial fibrillation
ARF	Acute rheumatic fever
CI	Confidence interval
CRHD	Chronic rheumatic heart disease
CTS	Cardiothoracic surgery
GCP	Good clinical practice
INR	International normalising ratio
LA	Left atrium
LVEF	Left ventricular ejection fraction
LV	Left ventricle
MV	Mitral Valve
NYHA	New York heart association
PI	Principle investigator
PVR	Prosthetic valve replacement
RHD	Rheumatic heart disease
RVHD	Rheumatic valvular heart disease
SAMJ	South African Medical Journal
UFS	University of the Free State
VCAM1	Vascular cellular adhesion molecule 1
WHO	World Health Organisation

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CHAPTER 1

Introduction

Rheumatic valvular heart disease (RVDH) is the most common form of acquired heart disease in children and young adults in many parts of the world. In a 2005 summary report commissioned by the World Health Organisation (WHO), the overall burden of this disease was estimated to be 15.6 million prevalent cases, with 282 000 new cases and 233 000 deaths

per year (Carapetis *et al*., 2005)

Sub-Saharan Africa was long thought to be the area of the world with the most prevalence of RVHD; a school screen study using clinical examination conducted in Soweto in 1974 reported a prevalence of 5.9/1000 in asymptomatic school children (McLaren *et al.,* 1975*)* while several surgical reviews published in the following decade reported significant mortality associated with chronic rheumatic heart disease (RHD) (Marcus *et al.,* 1994)

The recent study published in the South African Medical Journal (SAMJ) in 2016 has shown that the prevalence of chronic RHD is actually higher than what was reported 30 years ago when using echocardiography as a diagnosis than auscultation method. It reports the prevalence to be 20.2/1000 in a Cape Town study (Shung-King *et al.,* 2016).

Acute rheumatic fever (ARF) results from the body's autoimmune response to a throat infection caused by Streptococcus pyogenes, also known as the Group A Streptococcus bacterium. RHD refers to the long-term cardiac damage caused by either a single severe episode or recurrent multiple episodes of ARF. It is RHD that remains a significant worldwide cause of morbidity and mortality, particularly in resource poor settings (Carapetis *et al.,* 2007)

Factors that lead to the development of chronic RHD include a younger age at first episode of ARF, severe carditis at first episode of ARF, and frequency and recurrent episodes of ARF (Bland & Jones, 1951).

While the carditis associated with ARF is a pancarditis, valvular pathology almost exclusively dominates chronic RHD. Left-sided cardiac involvement is most commonly seen and involves the mitral valve almost 100% of the time and the aortic valve in 20-30% of cases (Kitchin *et al*., 1964). The tricuspid valve is affected histologically in 15 – 40% of patients with RHD, but this finding is rarely of clinical importance except in the most severe cases (Carpentier *et al*., 1974).

Mitral valve regurgitation is the most commonly seen valvular pathology in RHD (Tissie*r et al*., 2005) particularly in children and young adults, where pure mitral regurgitation is the most common form of RHD presentation as reported by the Rheumatic Fever working Party of The Medical Research Council of Great Britain. RHD is the most common aetiology of mitral stenosis (Ratnakar *et al*., 1989). The development of mitral stenosis is associated with the number, though not necessarily the severity, of carditis during ARF reoccurrences (Bland *et al*., 1951), and is more common in women as noted by Rheumatic Fever Working Party of The Medical Research Council of Great Britain.

Except in the young, where pure mitral regurgitation dominates, mixed valvular pathology is the most common finding in chronic RHD (Zülke *et al*., 2014). Mitral regurgitation and mitral stenosis most often develop along a continuum of disease, and many patients have both important regurgitation and stenotic components (Bland *et al*., 1951).

Not all patients who develop chronic RHD have a clinical history of ARF (Sliwa *et al*., 2010). RHD also typically shows a relatively long period between the initial cardiac insult and presentation with symptomatic cardiac disease. While the highest risk for ARF is in childhood, symptomatic RHD commonly presents in the third and fourth decade (Zülke *et al*., 2014).

Screening by echocardiography has revealed a large burden of “borderline RHD”, a diagnostic category in the 2012 World Health Federation (WHF) criteria, which includes isolated functional or isolated morphological changes to either the mitral or aortic valves (Remènyi *et al*., 2012)

There is no role for medical management in patients with severe mitral regurgitation and preserved left ventricular function. Medical management for mitral stenosis centres on the prevention of thromboembolic events. Anticoagulation is indicated for patients with mitral stenosis and atrial fibrillation, and/or a prior embolic event, and/or a left atrial thrombus (Nishimura, *et al*., 2014).

The primary indications for surgery in chronic RHD are the development of cardiovascular symptoms and/or decreased left ventricular function (Nishimura, *et al*., 2014). When a good result can be achieved, mitral valve repair is preferable to mitral valve replacement, particularly in children. A 2013 meta-analysis that compared mitral valve repair to mitral valve replacement found lower early and late mortality and fewer major adverse events in patients undergoing mitral valve repair. As compared to replacement, repair avoids the need for anticoagulation, a decrease in haemorrhagic and thromboembolic complications contributed to the reduction in risk. However, patients undergoing repair showed a higher rate of reoperation (Wang *et al*., 2013).

It is widely ascertained that prosthetic valve replacement (PVR) reduces life expectancy, especially in children and young adults regardless of native valve pathology, due to prosthetic valve related complications (Mvondo *et al*., 2016). De Santo and colleagues reported a 25 years survival of 70% in young women (mean age: 30 years) after mechanical valve replacement (De Santo *et al*., 2005).

Thus, this retrospective analytical study will evaluate our patients’ profiles, including demographics, preoperative risk factors, peri and postoperative outcomes, complications and survival, and compare these with those of other centres.

CHAPTER 2

Literature Review

2.1 Rheumatic Heart Disease

2.1.1 Background and Pathophysiology

Rheumatic fever is an inflammatory disease that occurs following a streptococcus pyogenes infection, such as Streptococcal pharyngitis or scarlet fever. Believed to be caused by antibody cross-reactivity that can involve the heart, joints, skin and brain, the illness typically develops two to three weeks after a Streptococcal infection. ARF commonly appears in children between the ages of 6 and 15, with only 20% of the first-time attacks occurring in adults (Kumar V *et al*., 2007).

Antigenic mimicry in association with an abnormal immune response is the cornerstone of the pathophysiology, based on the triad of rheumatogenic group A Streptococcal strains, genetically susceptible host, and aberrant host immune response (Bisno *et al*., 2003). **See Figure 2.1.**

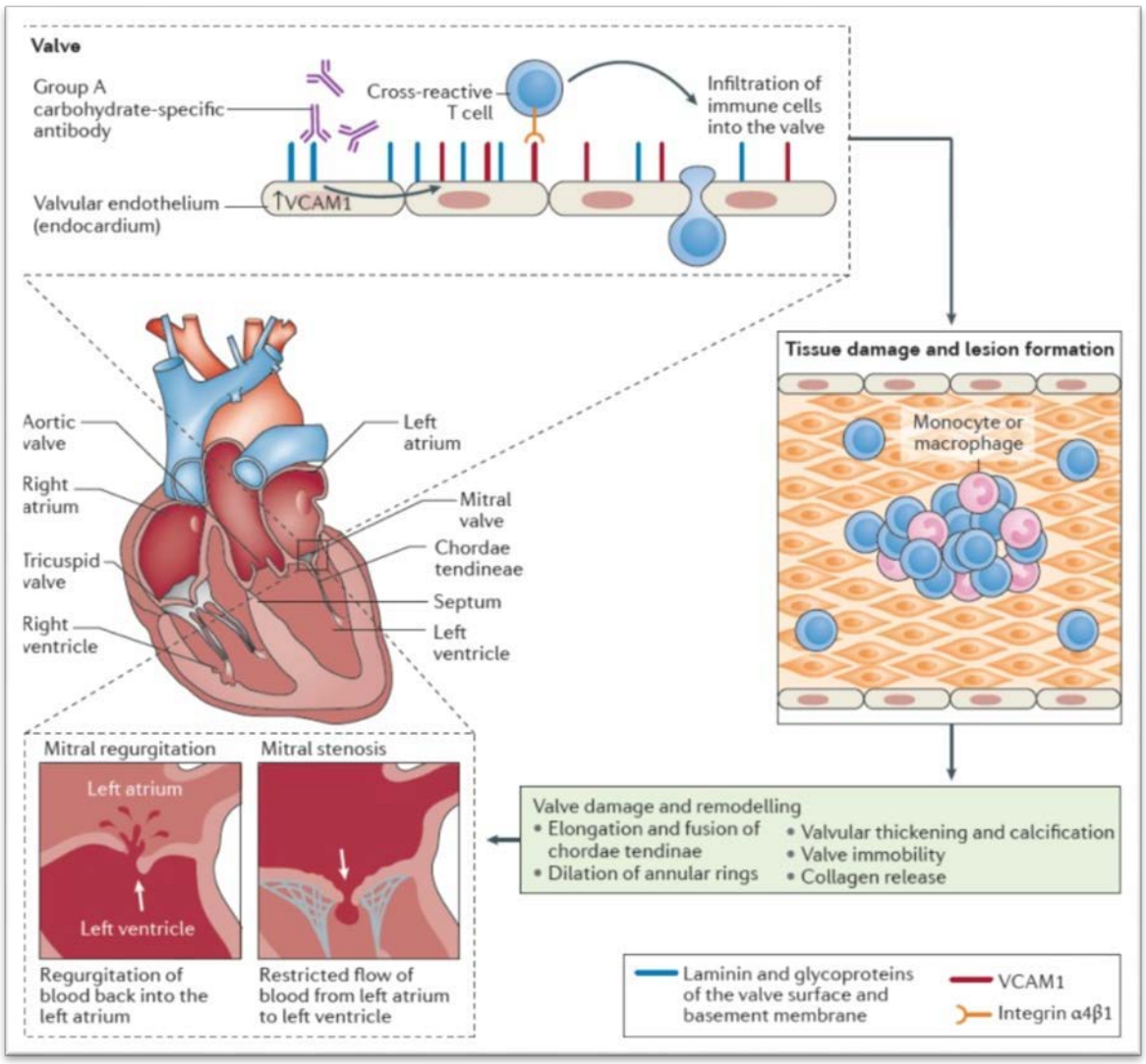

Figure 2.1 Pathogenesis of carditis in ARF (VCAM1: vascular cell adhesion molecule1) (Carapetis et al.,2016).

2.1.2 Epidemiology

The estimated prevalence of RHD in Sub-Saharan Africa is 5.7 per 1000 and in North Africa 1.8 per 1000 derived from all relevant population-based data from the 1980s and 1990s (Carapetis *et al*., 2005), **see figure 2.2 below.**

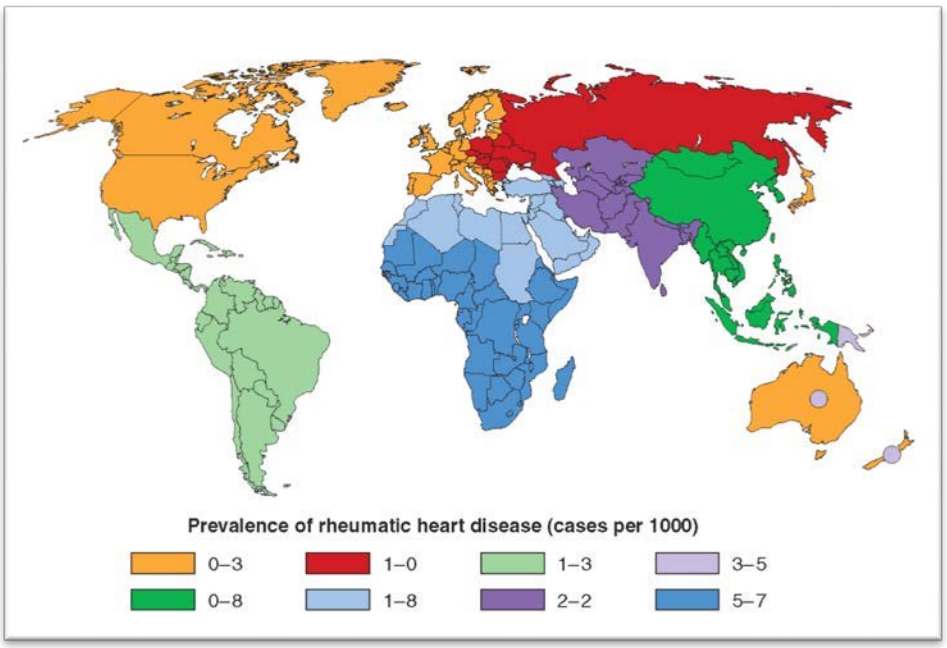

Figure 2.2 Prevalence of RHD in children aged between 5 and 14 years: (Carapetis *et al*., 2005)

Determinants of the persistence of rheumatic fever and RHD in Africa are poverty, overcrowding, malnutrition, low level of disease awareness in communities, shortage of resources for providing quality care and inadequate expertise of health care providers, underlying genetic susceptibility and more virulent Group A Streptococcal infection (Hafejee *et al*., 1982).

Although the frequency of RHD has diminished in Europe and North America, it is still endemic in Third World countries where it represents by far the leading predisposing factor (Thiene *et al*., 2006). **See figure 2.2 above.**

South African studies reveal a changing pattern of the disease at hospital and population levels. Hospital based studies show a high incidence of congestive heart failure caused by RHD (average of 25 cases/ 100 000/ year in Soweto) that is associated with high 60 day and 180day mortality rates of *24.8% (95% confidence interval (CI) 13.6 -42.5)* and *35.4% (95% CI 21.6-54.4), respectively* (Sliwa *et al*., 2010).

The high burden of heart failure and mortality in adults must be contrasted with a falling caseload of ARF and RHD in children, as demonstrated in Soweto recently (see figure 2.3 below). These changes are consistent with a transition of ARF/RHD from a condition of childhood to a mature endemic disease of the adults (Mayosi *et al*., 2016)

The changes may reflect a "Mandela dividend" associated with the improvement in access to primary health care and rising socioeconomic status of South Africans since the advent of the new South Africa in 1994 (Mayosi *et al*., 2014).

However, the recent study from Cape Town, South Africa, published in the SAMJ showed that the prevalence of chronic RHD diagnosed with the echocardiography is higher (20.2/1000) than what was previously found with auscultation alone (5.9/1000) (Shung-King *et al*., 2016).

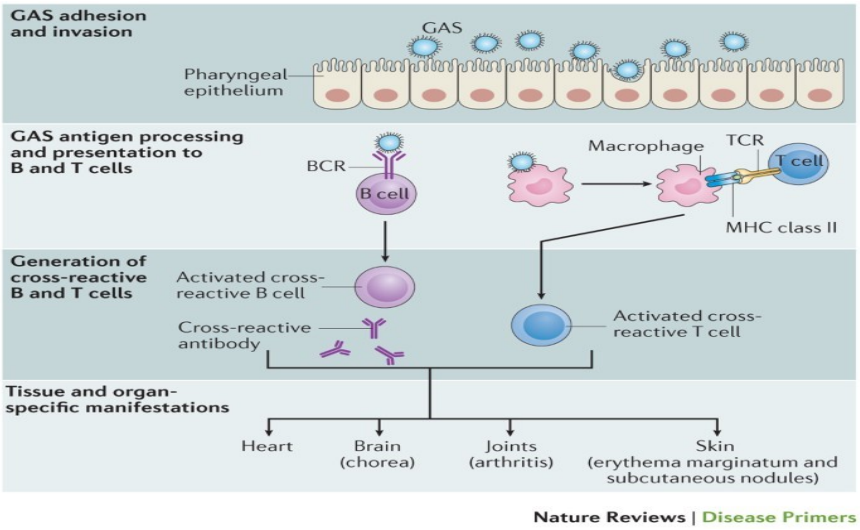

Figure 2.3 RHD and ARF trends, 1993 – 2010, *(*Mayosi *et al*., 2014).

2.1.3 Natural History and Presentation

2.1.3.1 Acute Rheumatic Fever

The disorder manifests as a combination of fever, polyarthritis, carditis, chorea erythema magnutum and subcutaneous nodules in a patient about 3 weeks after they have had pharyngitis caused by a group A Streptococcal infection (diagnosed by a positive throat swab culture or a high or rising Streptococcal antibody titre, and most often affects children, adolescents, and young adults (Carapetis *et al*., 2005*).* ***See figure 2.4****.*

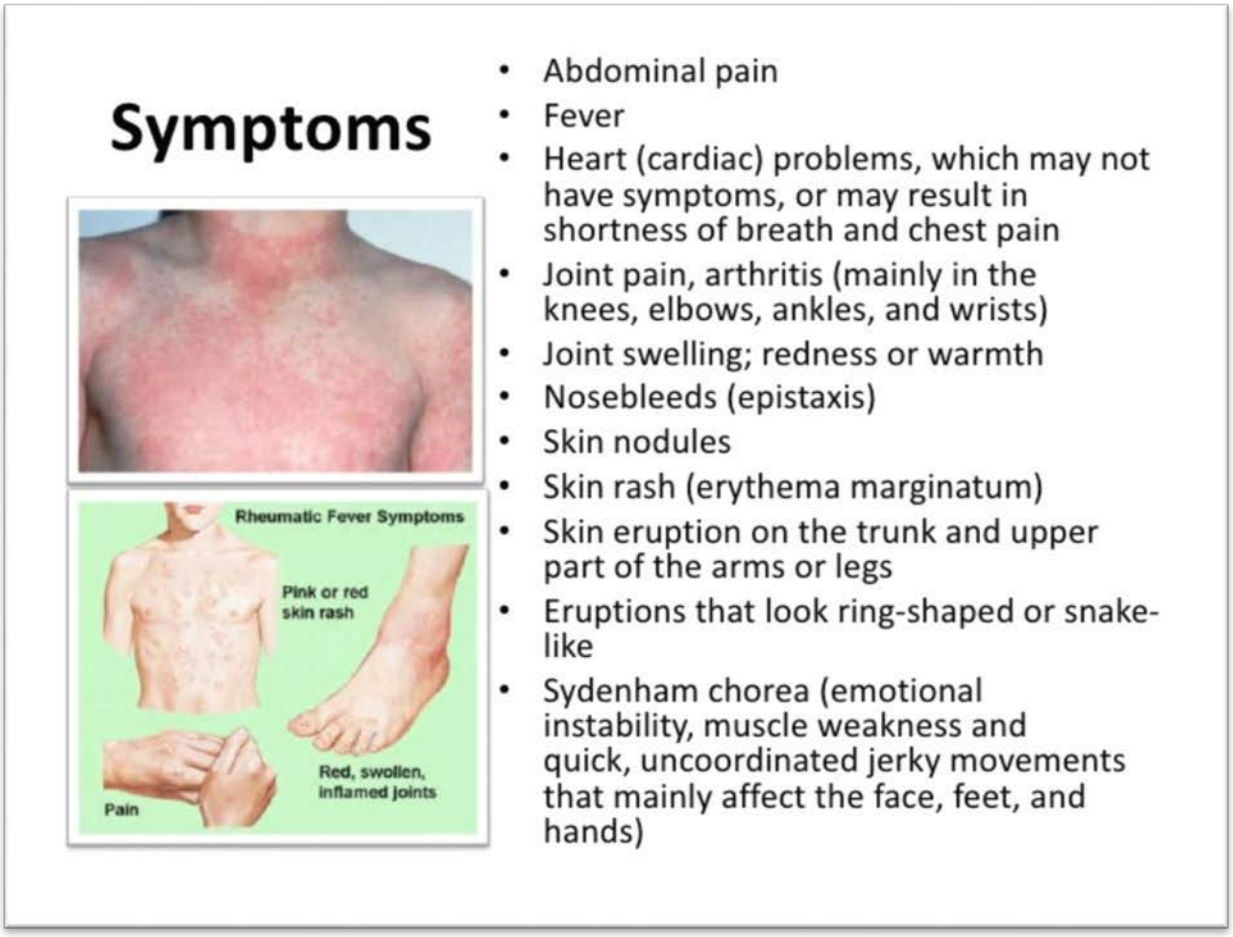

Figure 2.4 ARF clinical symptoms.
(Carapetis, et al., 2005).

2.1.3.2 Chronic Rheumatic Heart Disease

Patients might be diagnosed with RHD after a known ARF attack; however, the disease is often diagnosed in patients who were previously asymptomatic or who do not recall acute rheumatic fever symptoms or episodes. Most patients present after the onset of shortness of breath at the ages of 20-50 years (Sliwa *et al*., 2010). These patients then present with a valvular heart murmur detected during auscultation.

Mitral valve regurgitation is the most common valvular lesion in patients with RHD, particularly in the early stages (Sanyal *et al*., 1974). Mitral valve stenosis result from a persistent or recurrent valvulitis with bicommissural fusion (Marcus *et al*., 1994).

Patients with mitral regurgitation can remain asymptomatic for up to 10 years as a result of compensatory left atrial (LA) and left ventricular (LV) dilatation before the onset of LV systolic dysfunction (Marijon *et al*., 2007). The natural cause of severe valvular disease leads to severe heart failure in the absence of appropriate intervention. In very advanced stages of the disease, surgery might become contraindicated when myocardial dilatation and dysfunction prevail (Wisenbaught *et al*., 1994).

2.1.4 Diagnosis of Mitral Valve Disease *Clinical:*

Mitral stenosis:

A common clinical presentation is a middle-aged female complaining of easy fatigability, dyspnea on exertion or palpitations. Other less presentations include haemoptysis, thromboembolic events, and endocarditis (Richard, et al., 2009).

Mitral regurgitation:

Can be asymptomatic in early stages of the disease and with progression of the disease fatigue, palpitations and pulmonary congestion can develop.

Echocardiography:

Mitral valve stenosis is classified based on valve area and pressure gradients across the valve.

Table 2.1

	Mild	Moderate	Severe
Specific findings (cm^2)			
Valve area	>1.5	1.0-1.5	<1.0
Supportive findings (mmHg)			
Mean gradient	<5	5-10	>10
Pulmonary artery pressure	<30	30-50	>50
*Heart rate between 60-80 in sinus rhythm			

European association of echocardiography/American society of echocardiography classification of mitral valve stenosis.

*The grading of **mitral valve regurgitation** is complex and involves several techniques, table 2.2. **Table***

2.2

MR grade	Rvol (ml)	ERO (mm^2)
Mild	< 30	< 20
Moderate	30 – 59	20 – 39
Severe	≥ 60	≥ 40

(www.mitralvalverepair.org)

2.1.5 Treatment

Medical Treatment:

Mitral stenosis*:*

In severe mitral stenosis, up to 40% of patients will develop atrial fibrillation as reported by the European Heart Rhythm Association and European association for cardio-Thoracic Surgery in their report of 2010.

Rate control reduces symptoms and is generally easier to achieve than rhythm control in a heart with dilated atria and fibrosis from previous inflammation. It can be achieved with either beta blockers or calcium channel blockers according to the Joint Task Force on Management of Valvular Heart Disease of European Society of Cardiology in their 2012 report.

Diuretics are used to reduce dyspnoea, and long-acting nitrates can also provide some relief (Holmes *et al*., 2017). Patients with atrial fibrillation, prior embolic events, or with a demonstrated left atrial thrombus should be anti-coagulated with warfarin (target INR 2-3) or heparin (Nishimara *et al*., 2014).

Mitral Regurgitation:

In chronic mitral regurgitation with signs of heart failure, the treatment is in line with standard heart failure management including beta blockers, angiotensin converting enzyme inhibitors, aldosterone antagonists, with diuretics used where heart failure is present. However, there is no proven benefit to any medical therapy for mitral regurgitation without LV dysfunction, and generally when such dysfunction does develop, it is an indication for surgery (Holmes *et al*., 2017).

Surgical Treatment:

Mitral Stenosis:

Either open or percutaneous surgical approaches, are the treatment of choice in severe symptomatic mitral stenosis. In patients with valves with mobile leaflets that are free of calcium, percutaneous mitral commissurotomy is the preferred option **(figure 2.5).**

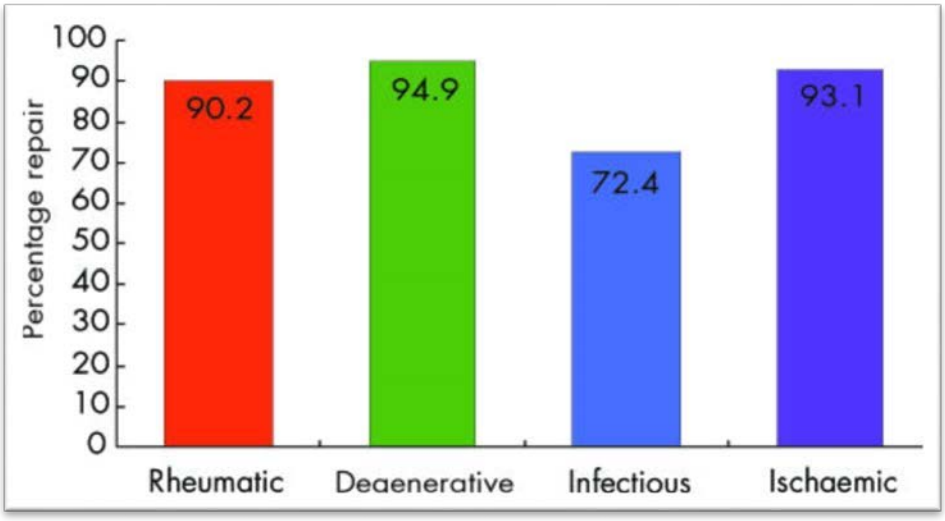

Figure 2.5 Feasibility of mitral valvoplasty according to pathology, in more than 2500 patients in Coimbra, Portugal, during the past 16 years (heart.bmj.com/content/92/2/275.full).

Surgery is recommended in the presence of atrial thrombus, heavy valve calcification, or when another open cardiac procedure needs to be performed. Mitral valve replacement has an operative mortality of 3-5%, but long-term outcomes are highly variable and related to multiple patient related factors (e.g., bi ventricular function, pulmonary pressures, atrial fibrillation (Holmes *et al*., 2017).

Mitral Regurgitation:

In primary mitral regurgitation, the evidence to operate is clear: surgery is indicated if the mitral regurgitation is severe and acute in nature, such as from a ruptured papillary muscle.

If the mitral regurgitation is chronic and causing symptoms, and there are no contraindications to surgery, repair is also indicated (Holmes *et al*.,2017).

Minimal Invasive surgery:

Mitral valve repair and replacement can also be performed through a small right thoracotomy and several small instruments ports with a femoral incision for bypass cannula insertion. Standard operative techniques are used under endoscopic view. The safety and efficacy of this approach has been well demonstrated and is similar to the traditional midline sternotomy approach in the hands of experienced surgeons.

Robotic telemanipulations are developing a place in mitral valve surgery since their first use in 1998 (Seco *et al*., 2013).

Percutaneous Mitral Valve Repair:

Recent trials have shown efficacy of the Mitraclip system for percutaneous repair in moderate to severe mitral regurgitation in patients deemed too high risk for surgery (Klaar *et al*., 2011). The Mitraclip system is less effective at reducing mitral regurgitation in the short term but has similar outcomes at 12 months. It results in improved LV ejection fraction (LVEF), New York Heart Association (NYHA) score and quality of life compared to baseline (Holmes *et al*., 2017).

2.1.6 Outcomes and Complications

It is generally accepted that operative mortality and long-term survival after mitral valve repair is better than that after mitral valve replacement **(figure 2.6),** and valve repair operation has become the first choice in most patients with degenerative mitral valve disease (Mohty *et al*., 2001).

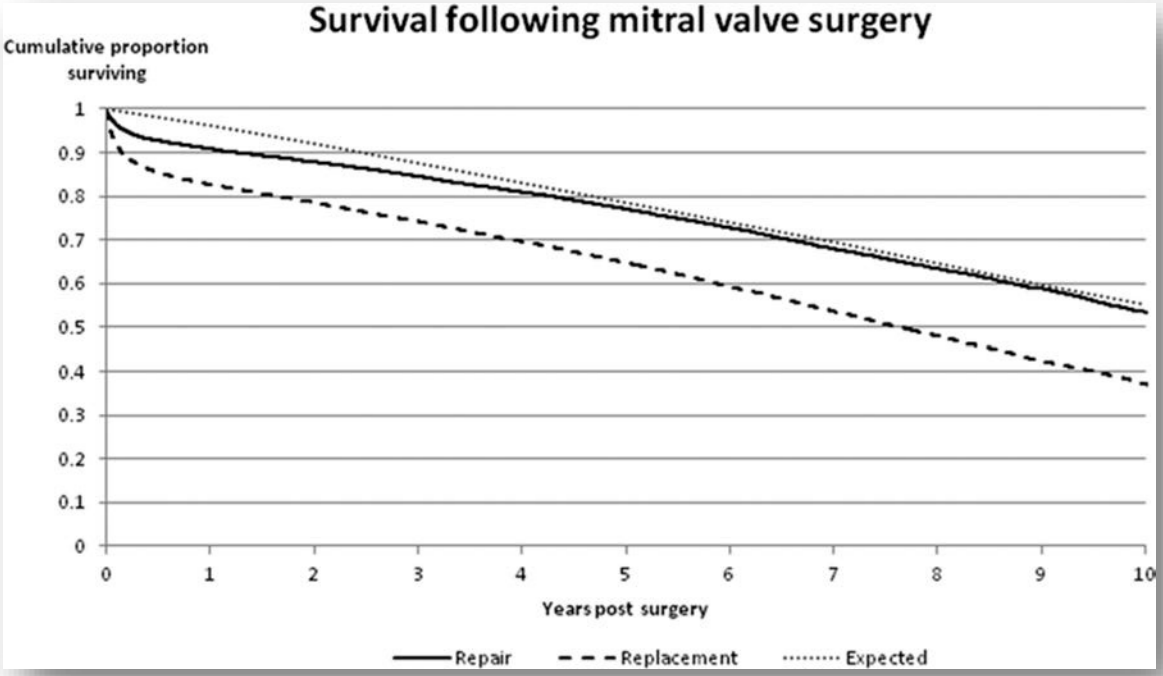

Figure 2.6 Survival following mitral valve surgery compared to the general population. CIRCULATIONAHA.113.002200Circulation. 2013; 127:1870–1876

With the progress in surgical techniques and utilization of many new surgical approaches for mitral valve repair, the feasibility and results are improving, with an increasing number of patients considered likely candidates for this procedure (David *et al*., 2003).

When comparing outcomes of mitral valve repair with those of mitral valve replacement, selection bias could affect the results because the patients with high risk factors tend to undergo mitral valve replacement (Jung *et al*., 2018).

Complications:

Complications can occur after valve surgery. Valve related complications include thromboembolism, bleeding complications and prosthetic valve endocarditis, followed by structural and non-structural prosthetic valve dysfunction (Hurle *et al*., 1997).

2.1.7 Study Rational

It is widely ascertained that prosthetic valve replacement (PVR) reduces life expectancy, especially in children and young adults regardless of native valve pathology, due to prosthetic valve related complications (Mvondo *et al*., 2016). De Santo and colleagues reported a 25year survival of 70% in young women (mean age: 30 years) after mechanical valve replacement (De Santo *et al*., 2005).

Rheumatic valvular heart disease still remains an important acquired heart disease for children and young adults in under-developed and developing parts of the world. The majority of these people come from poor socio-economic backgrounds with limited resources. This makes it difficult for their voices to be heard and assisted by the so-called first world health systems and governments with both monetary and technological advances. Part of the challenge could be the misinformation that the incidence of ARF and RHD are in the decline due to the skewed data that has been collected over the recent past.

Health consequences as well as financial burden that ARF and RHD have on the already strained economies make this disease entity one of the important health conditions that need to be closely monitored and managed. The effects of this disease entity extends beyond management, whether medical and/or surgical, influencing the quality of life of patients.

Thus, in the Sub-Saharan regions with a burden of other diseases such as human immune deficiency (HIV), tuberculosis (TB) and malaria, intensified awareness regarding the prevalence and management of ARF and RHD is crucial.

As part of this, we have undertaken to evaluate a cohort of patients who were diagnosed with RHD requiring intervention for their mitral valves with or without tricuspid valves in Central South Africa.

2.1.8 Aim

The aim of this study was to describe the surgical outcomes of patients who underwent mitral valve surgery with/without tricuspid valve repair between 2009 and 2019 at Universitas Academic Hospital for RHD.

2.1.8 Objectives

- To identify adult patients above the age of 14 years, who had Rheumatic mitral valve disease requiring surgical intervention, from the departmental database.
- To describe the prevalence of MR, MS and MX in the cohort.
- To describe the preoperative patient demographics, pre-operative risk factors and surgical procedure/s in these patients.
- To analyse the post-surgical outcomes and complications in relation to pre-operative risk factors and surgical procedures.

CHAPTER 4

Methodology

4.1. Study Location:

The research study will be conducted in the Department of Cardiothoracic surgery, Faculty of Health Sciences, University of The Free State, Bloemfontein, South Africa.

4.2. Study Population:

4.2.1. The number of subjects:

The data file of patients that presented with primary rheumatic mitral valve disease with or without secondary tricuspid valve disease requiring repair, for surgical treatment from 2009 to 2019 will be included in this study. Only patients older than 14 years will be included and the demographics age, gender, race, diagnosis, predisposing factors, outcomes, and complications, as well as long-term survival will be recorded for each patient.

4.2.2. Inclusion and Exclusion Criteria

4.2.2.1 Inclusion Criteria

- All patients that presented with rheumatic mitral valve pathology who underwent surgical intervention between 2009 and 2019.
- Patients with primary rheumatic mitral valve disease who underwent surgery for mitral valve with or without concomitant tricuspid valve repair due to sequelae of mitral valve disease.

- sequelae of mitral valve disease.
- Only patients above 14 years old.

4.2.2.2 Exclusion Criteria

- Patients younger than 14 years old.
- Patients with infective mitral valve pathology (i.e., infective endocarditis)
- Patients with secondary mitral valve pathology, i.e., ischaemic mitral valve regurgitation.
- Patients for redo mitral valve surgery
- Primary aortic valve pathology

4.3. Study Design

The study will be a retrospective analytical study that will include all patients who underwent surgery for isolated rheumatic mitral valve pathology with or without tricuspid valve repair between the period of 2009 to 2019 only.

4.4. Study Outline

RHD of MV 2009-2019

Demographics

↓

Age, gender, race, predisposing factors

↓

Echo criteria for mitral valve disease

↓

Perioperative records

↓

Post op outcomes and complications

4.5. Research Team

Project Leader

Dr T.J. De-huis

Cardiothoracic surgery registrar

Department of Cardiothoracic surgery

University of The Free State (UFS)

Supervisor

Prof F.E. Smit

PhD Cardiothoracic surgery

Head: Department of cardiothoracic surgery

University of The Free State (UFS)

Co-supervisor

Dr L. Botes

D-Tech Biomedical Technology

Senior Lecturer: Clinical Technology

Central University of Technology

Co-Supervisor

Mr H A. Hanekom

MMedSc

Scientist: Department of cardiothoracic surgery

University of The Free State (UFS)

4.6 Data Recorded

Demographics, clinical presentations, operative and postoperative data, as well as postoperative complications will be recorded. All the data will be sourced from patient's medical file and the departments' online data base from 2009 to 2019.

4.6.1. Preoperative Data:

The following demographic and clinical data will be recorded for each participant:

- *Age* (years)
- *Gende*r (male/female)
- *Race* (Black/coloured/Indian/white)
- *Predisposing factors* (previous ARF, atrial fibrillation, pulmonary hypertension, heart failure)
- *Echocardiography criteria*
- *Date of surgery*

4.6.2. Intraoperative Data:

- *Type of valve surgery* (replacement/repair including valvotomy)
- *Type of valve prosthesis* (mechanical/bioprosthesis)

4.6.3. Postoperative Data:

- Complications (cardiac and extracardiac)
- Outcomes (in hospital mortality)
- Survival (long-term mortality)

4.7. Statistical Analysis

The data will be captured electronically by a researcher on to the data sheet (Appendix…). The captured data will be analysed by a statistician.

4.8. Ethical Aspects and Good Clinical Practice

4.8.1. Ethical clearance:

The study will commence as soon as the ethical clearance is granted.

4.8.2. Safety Variables:

The study will pose no risk to the patients as it will be a retrospective study.

4.8.3. Premature discontinuation of The Study:

The study will be prematurely discontinued in the event any of the study leaders feels that the patients' confidentiality might in anyway be breached or if any unethical procedure occurs.

4.8.4. Good Clinical Practice (GCP)

The researchers shall adhere to the South African Good Clinical Practice guidelines.

4.9 Financial Implications to The Patients

There will be no financial implications to the patients.

4.10. Confidentiality

Personal details of every patient participating in this study shall be kept confidential. At no time during the research may any of the patents' details be made known to any person than the researchers.

4.11. Contact details of the researchers:

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Chapter 5

Time Frame

Date	Task	Responsible person	Date of completion
June – July 2019	Literature search	PI, Dept Cardiothoracic	End of July
July – August 2019	Protocol draft & submission	PI, Dept Cardiothoracic	End of August
August – Oct 2019	Retrospective analysis data	Research team, Dept CTS	End of October
October- Nov 2019	Data analysis	Statistician Dept CTS	End of November
Nov - December 2019	Prepare article for publication	Researchers, Dept CTS	End of December
December - January 2020	Submit article	PI, Dept CTS	End January 2020

Chapter 6 Budget

Literature searches and printing costs as well as publication costs will be covered by the Department of Cardiothoracic surgery, UFS.

Clinical data gathering will not amount to any expenses for the patients, researcher or the hospital.

Item	Cost
Publication fee	ZAR 5000 (depending on the journal, fee estimated from publication in Cardiovascular Journal of Africa)
Statistician	ZAR 5000
Language editing	ZAR 5000
Total	**ZAR 15000**

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3.5 Appendix E – Data collection sheet

Case number	Identification Code		Initials	Date of Birth	Age	Date of admission	Gender	
Race	NHHA	HIV status	CD4 count	Viral Load	ARV Treatment	Underlying Condition		
COMORBIDITIES	COMORB. SPECIFICATION	pulmonary HTP	EuroScore	Atrial Fib				
operative priority	Date of surgery	indication For Operation	Mitral Repair	Mitral Replacement				
Tricuspid Repair	Aortic Cross Clamp Time	CardioPulmonary Bypass Time	Complications/Morbidity					
Dicharge Date	FollowUp Data	Mortality Date						

3.6 Appendix F – Instructions to authors

South African Heart Journal

SA HEART IS AN OFFICIAL JOURNAL OF THE SOUTH AFRICAN HEART ASSOCIATION AND APPEARS ON A QUARTERLY BASIS

Instructions for authors

SA Heart publishes peer reviewed articles dealing with cardiovascular disease, including original research, topical reviews, state-of-the-art papers and viewpoints. Regular features include an ECG quiz, image in cardiology and local guidelines. Case reports are considered for publication only if the case or cases are truly unique, incorporates a relevant review of the literature and makes a contribution to improved future patient management.

Publication policy

Articles must be the original, unpublished work of the stated authors. Written permission from the author or copyright holder must be submitted with previously published material including text, figures or tables. Articles under consideration elsewhere or previously published (except as abstracts not exceeding 400 words) may not be submitted for publication in SA Heart. On acceptance transfer of copyright to the South African Heart Association will be required. No material published in SA Heart may be reproduced without written permission. Permission may be sought from the Editor (Email: afd@sun.ac.za).

Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (http://www.wma.net/en/30publications/10policies/b3/17c.pdf) and the South African MRC ethics guidelines (http://www.sahealthinfo.org/ethics/index.htm). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.
2. Authors are solely responsible for the factual accuracy of their work.
3. Articles should be between 3 000 and 5 000 words in length.
4. A 200-word abstract should state the main conclusions and clinical relevance of the article.
5. All articles are to be in English.
6. Abbreviations and acronyms should be defined on first use and kept to a minimum.
7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.
8. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. ...trial.[15]

The following format should be used for references:

Articles
Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. Clin Orthop 1993;294:73-8. (If there are more than six authors, list only the first three followed by et al.)

Chapter in a book
Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). Spinal Trauma. Philadelphia: JB Lippincott; 1991:377-94.

Online media
Norback JS, Llwellyn DC and Hardin JR (2001). Shoptalk 101. Integrating workplace communication into undergraduate engineering curricula [online]. Retrieved February 15, 2012. http://www.lionhrtpub.com/orms/orms-8-01/norback.html.

9. Articles are to be submitted by email. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.
10. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a MS Word or PowerPoint document. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure and table must have a separate self-explanatory legend.
11. Remove all markings such as patient identification from images and radiographs before photographing.

Submission of manuscripts

Please submit the manuscript to the Editor (afd@sun.ac.za) and copy it to the Guest Editor (if applicable) and the secretary of the South African Heart Association (erika@saheart.org).

3.7 Appendix G – Turnitin Plagiarism Report

Submission ID: 1547146864

Critical Analysis of Rheumatic Mitral Valve Surgery Outcomes in Central South Africa

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