# Ten-year propensity matched cohort analysis of mitral valve repair and replacement for rheumatic heart disease at Groote Schuur Hospital.

by

Agneta Geldenhuys
Student no: GLDAGN001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree:

**Master of Medicine in Cardiothoracic Surgery**

Faculty of Health Sciences

**UNIVERSITY OF CAPE TOWN**



Date of submission: 15 August 2011

Supervisor: Professor Peter Zilla, MD; PhD
Cardiothoracic Surgeon
Christiaan Barnard Division of Cardiothoracic Surgery, Faculty of Health Sciences
University of Cape Town and Groote Schuur Hospital

Co-Supervisor: Professor Johan Brink, MD
Cardiothoracic Surgeon
Christiaan Barnard Division of Cardiothoracic Surgery, Faculty of Health Sciences
University of Cape Town and Groote Schuur Hospital

**DECLARATION**

I, Agneta Geldenhuys, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

This work has not been published prior to registration for the abovementioned degree.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: …….

Date: …….

**TABLE OF CONTENTS**

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| HIV | Human Immunodeficiency Virus |
| INR | International normalised ratio |
| MRC | Medical research council |
| MV | Mitral valve |
| MVR | Mitral valve replacement |
| NHLS | National Health Laboratory Service |
| NS | Not significant |
| NYHA | New York Heart Association |
| WHO | World Health Organisation |

## PART A: RESEARCH PROTOCOL

**APPLICANT:**

Dr Agneta Geldenhuys

Cardiothoracic Surgery Registrar

Groote Schuur Hospital

University of Cape Town



**DEGREE REGISTERED:**

Master of Medicine in Cardiothoracic Surgery

University of Cape Town

**TITLE:**

**Ten-year propensity matched cohort analysis of mitral valve repair and replacement for rheumatic heart disease in Groote Schuur Hospital.**

## A.1 Background information

15.6 million people worldwide are affected by acute rheumatic fever and subsequent rheumatic heart disease according to World Health Organisation (WHO) estimates. The tonsillo-pharyngeal infection, caused by group A streptococcal infection, results in an inflammatory process which affects many organ systems, of which fibrotic changes to the heart valves leads to the most incapacitating clinical consequences. It is further estimated that 200 000 people die annually of rheumatic heart disease, affecting mostly young individuals of the developing world (1,2,3). Rheumatic heart disease remains the leading cause of valvular heart surgery in the developing world.

In non-rheumatic pathological processes, like degenerative mitral valve disease, mitral valve repair is known to be superior to mitral valve replacement in terms of operative mortality, functional outcomes and long-term survival (4,5). Furthermore, mitral valve repair excludes the possible complications associated with life-long anticoagulation as well as the risk of thrombo-embolism seen with mitral valve replacement (6,7). Mitral valve repair is clearly the procedure of choice in non-rheumatic mitral valve disease.

However, the appropriateness of valve repair for patients with rheumatic heart disease, even when repair appears to be technically feasible, remains controversial (8,9,10). Questions regarding the ongoing fibrotic process of cardiac valves in rheumatic pathology and the effect thereof on the repaired valve have been asked. At Groote Schuur Hospital, it has been our approach in rheumatic mitral valves to repair the valve rather than replace it, whenever the anatomical substrate of the valve appears to be favorable.

In view of the above, we propose to review our 10 year, single institution experience with repair and replacement of rheumatic mitral valves. This serves to determine the advisability of our strategy and the appropriateness of mitral valve repair whenever possible above mitral valve replacement in patients with rheumatic heart disease.

## A.2. Aims and objectives

*Broad aim*

To answer the question of whether the paradigm remains valid that in a developing country, the benefit of not requiring the insertion of a prosthetic heart valve truly outweighs the disadvantages of repeat surgery in the presence of a chronically progressing underlying disease.

*Objectives*

- To retrospectively analyse all cases of single mitral valve repair and single mitral valve replacements performed for rheumatic heart disease at Groote Schuur Hospital during the period from 1 January 2000 till 31 December 2010 with the aim of a propensity-matched outcome comparison, specifically emphasising the following aspects:
    - Patient related
    - Pathology related
    - Surgery related
    - Early clinical outcome with emphasis on early mortality and surgical related morbidity
    - Late clinical outcome with emphasis on late mortality and late valve related morbidity

      (see materials and methods section for further details of the above aspects which will be investigated)



## A.3. Institutional approval

This proposal was submitted for ethics approval to the University of Cape Town Research Ethics Committee and was approved (Annexure A).

## A.4 Methodology

The study population is from Groote Schuur Hospital, which serves as a referral centre in the Cape Town Central Health District of Western Cape Metro region for adult cardiac disease.

*Data collection*

The surgical database of the Chris Barnard Division of Cardiothoracic Surgery will be scrutinized for:

Inclusion criteria:

- All cases of rheumatic heart disease during the last decade where a single mitral valve repair or replacement was performed as a first open cardiac surgical procedure.
- Cases which had concomitant tricupsid valve annuloplasty for functional tricuspid regurgitation will be included.
- Cases where concomitant Cox-maze ablation therapy of atria was performed for treatment of pre-operative atrial fibrillation will be included
- All Patients above 13 years of age will be included

Exclusion criteria:

- Previous open cardiac surgery requiring cardiopulmonary bypass
- Any concomitant cardiac surgery procedures not related to mitral valve disease, like aortic valve replacement or coronary artery bypass grafting
- Mitral valve disease secondary to other pathological processes than rheumatic heart disease
- Patients below 13 years of age

The medical and surgical records of all the patients identified, will be retrospectively reviewed. A standardized data collection sheet (Annexure B) will be used to retrieve relevant information including:

1. Patient related: age at surgery, sex, race, contact telephone numbers, geographical area where patient stay, educational status of patient and type of housing (formal or informal)
2. Specific co-morbidities for surgery: hypertension, dyslipidemia, renal dysfunction, diabetes or other co-morbid factors
3. Classification of functional mitral valve pathology as pure mitral stenosis, pure mitral regurgitation or mixed mitral valve disease (both stenotic and regurgitant)
4. Presence of tricuspid regurgitation and if present graded as trivial, mild, moderate or severe
5. Specification of procedure performed: mitral valve repair or replacement, Cox-maze procedure, tricuspid annuloplasty
6. Functional status prior to surgery as graded by New York Heart Association (NYHA) grades I to IV and a follow up of the functional status immediately post surgery as well as at later follow up
7. Intra-operative details: Duration of cardiopulmonary bypass and aortic cross clamp, type of valve inserted if mitral valve replacement was performed, size of valve inserted of mitral valve replacement was performed, the reason for selecting a bioprosthesis if mitral valve replacement with bioprosthesis was performed, specific surgical repair methods when mitral valve was repaired
8. Histological evidence of valve pathology where specimens were obtained
9. The presence of pre-operative atrial fibrillation, post operative atrial fibrillation and whether a post operative permanent pacemaker needed to be inserted
10. Anticoagulation monitoring: whether the patient was previously placed on Warfarin and what the pre-operative International Normalized Ratio (INR) was. Number of annual INR checks performed by patient. Which INR clinic was used for monitoring purposes? National Health Laboratory System (NHLS) INR

profile and control over the last 12 months as well as the last therapeutic INR value.

11. Early clinical outcome (in hospital outcome during same admission as for this surgical procedure) will be reviewed with specific emphasis on:
    - status of repaired mitral valves as determined by intra-operative trans-oesophageal echocardiography
    - early mortality (during same hospital admission as for this surgical procedure)
    - early morbidity with specific emphasis on re-operation for bleeding, cerebrovascular events, requirements for permanent pacemaker insertion, requirements for renal dialysis and development of deep sternal sepsis
12. Late clinical outcome (outcome after discharge from hospital for this surgical procedure up to latest point of contact at recent follow-up) will be reviewed with specific emphasis on:
    - Late mortality with specific emphasis on valve related mortality and all cause mortality
    - Late morbidity with specific emphasis on morbidity associated with anti-coagulation, infective endocarditis, prosthesis failure, paravalvular leaks, the need for valve related redo surgery, cerebrovascular events and thromboembolism.
    - The presence of post operative atrial fibrillation as part of late follow up will specifically be mentioned and this will be referenced to the presence of pre-operative atrial fibrillation and whether a Cox-maze procedure was performed as anti-arythmia surgery
13. A telephonic follow up of all the patients will be performed with specific emphasis on:
    - Is the patient still alive? (especially if lost to follow-up at clinic attendance)
    - What is the current functional status of the patient? (New York Heart Association Classification)

- Has the patient had any re-operations since the primary valve related surgical procedure at any other institution, which we might not be aware of?
- Is the patient taking his/her Warfarin, what was the last INR value and which local clinic or hospital is used for INR monitoring?

14. Demographics and population migration patterns will be noted at follow-up with specific emphasis on:
    - How stable is the domicile of our patients population with relation to post-operative access to anti-coagulation and continuity of clinical follow-up?
    - Does patients migrate as much as generally perceived between Western Cape and other provinces after surgery?
    - Is there a significant percentage of our patients who travel from other African countries to the Western Cape for heart surgery?

None of the investigators, supervisors or co-workers involved in this study have any conflict of interest to declare.

The patient's anonymity will be protected by only using the folder numbers and initials in the study to indentify the subjects during the data collection phase of the study. Patient Jane Smith, folder number 81053623, will be identified in the study as JS 81053623 and under no circumstances will personal details of the patient be included or distributed during the study. No identification of individuals will be done under any circumstances during the data review, statistical analysis or during possible future publication phases of this study.

A simple oral consent procedure will be followed during telephonic follow up contact with patients. It will be conducted in the following way:

- I am Dr Agneta Geldenhuys, who is following up patients who had surgery for their heart valves at Groote Schuur Hospital.

- This follow-up is for the purposes of a research project where we are trying to establish how our patients is doing who had mitral valve surgery done during the last 10 years at Groote Schuur Hospital.
- Our records show that you had such an operation during this time.
- Are you willing to discuss your health with me? (you are under no obligation to this discussion).

The understanding that the ongoing ethical conduct of the study remains the responsibility of the Principle Investigators will be effective during all phases of this study.

*Statistical analysis*

Guidelines of the Society of Thoracic Surgeons for reporting mortality and morbidity after cardiac valve interventions will be used for the analysis and reporting of postoperative complications (11). All continuous numerical data will be expressed as means ± standard deviation and all actuarial estimates as percentage ± standard error. Inferential statistical analysis will be performed using the JMP® statistical software package (version 6.0.3, Cary; NC). Propensity score analysis using multiple logistic regression independent of outcome variables, will be performed against the pre-determined covariates of age, sex, body mass index, New York Heart Association classification, presence of pre-operative atrial fibrillation and left ventricular end systolic dimension. Actuarial curves will be based on Kaplan-Meier analysis with comparison between groups performed using the log-rank test. A p-value of $<0.05$ will be considered to be statistically significant.



**A.5 Research plan**

The project will be conducted over 7 months. The first 5 months will be dedicated to data collection of all relevant information. Once all data have been collected, data analysis and statistical analysis will be performed and conclusions drawn. This will

conclude over the next month. The last month will be dedicated to the specific write-up of the results and conclusions. Dr A Geldenhuys will be responsible for the conduct of the whole research plan, ethical conduct, data collection, data analysis and conclusions. She will be assisted by Dr J Koshy in the data collection and analysis and by Juliana Mtwale, elective research student, in data handling by creating a computerized database for this study. Statistical analysis of the data will be done with the help of Dr Paul Human and data analysis will be further reviewed with the help of the supervisors, Professors Peter Zilla and Johan Brink. All of the above individuals are members of the Christiaan Barnard Division of Cardiothoracic Surgery at Groote Schuur Hospital and University of Cape Town.



**A.6 OPERATIONAL BUDGET**

Administrative and telephonic costs comprises the bulk of the budget:

- Stationery and printing: R2000
- Telephonic costs: R5000

**A.7 FUNDING**

The Christiaan Barnard Division of Cardiothoracic Surgery, subject to ethics approval, will provide funding for this research project.

## A.8 REFERENCES


1. Carapetis JR. The Current Evidence of the Burden of Group A Streptococcal Disease. Geneva: World HealthOrg anization; 2004.:p1–57.
2. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005:685–94.
3. Carapetis JR. Rheumatic heart disease in developing countries. N Engl J Med 2007; 357:439 – 41.
4. Suri RM, Schaff HV, Dearani JA, Sundt 3rd TM, Daly RC, Mullany CJ, Enriquez-Sarano M, Orszulak TA. Survival advantage and improved dura- bility of mitral repair for leaflet prolapse subsets in the current era. Ann Thorac Surg. 2006;82:819-26.
5. Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation: A multivariate analysis. Circulation. 1995;91:1022-8.
6. David TE, Armstrong S, Sun Z, Daniel L. Late results of mitral valve repair for mitral regurgitation due to degenerative disease. Ann Thorac Surg. 1993;56:7-12.
7. Gillinov AM, Cosgrove DM, Blackstone EH, Diaz R, Arnold JH, Lytle BW, Smedira NG, Sabik JF, McCarthy PM, Loop FD. Durability of mitral valve repair for degenerative disease. J Thorac Cardiovasc Surg. 1998;116:734-43.
8. Grossi EA, Galloway AC, Miller JS, Ribakove GH, Culliford AT, Esposito R. Valve repair versus replacement for mitral insufficiency: when is a mechanical valve still indicated? J Thorac Cardiovasc Surg. 1998;115:389-94.
9. Duran CM, Gometza B, De Vol EB. Valve repair in rheumatic mitral disease. Circulation. 1991;84(Suppl):III:125-32.
10. Duran CM, Gometza BH, Saad E. Valve repair in rheumatic mitral disease: an unsolved problem. J Cardiol Surg. 1994;9:282-5.
11. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg. 2008 Apr;135(4):732-8.

# PART B: LITERATURE REVIEW

## B.1 Objectives

The objectives of this literature review were to obtain the following background information:

- The burden of rheumatic heart disease
- Appropriateness of different surgical therapies (repair and replacement) for rheumatic heart disease versus degenerative heart disease
- Difference between surgical treatment of rheumatic heart disease in children and adults
- Difference between therapeutic options in developing countries versus the developed world
- Previous studies in South Africa with different follow-up means from a previous era

## B.2 Search strategy

The literature search was initiated using the Pubmed Central digital archive. Further appropriate papers were identified by searching reference lists. Fourteen relevant research papers were identified. An author-year referencing method was used.

## B.3 Quality criteria

The keywords used for the Pubmed search included rheumatic heart disease and each of the following: South Africa, mitral valve disease, mitral valve repair, mitral valve replacement, and surgery for rheumatic heart disease. Studies involving mitral valve surgery for rheumatic heart disease were selected. Particular attention was given to studies performed in South Africa.

**B.4 Summary of the literature**

Almost 16 million people in the world are affected by rheumatic heart disease (1). The African continent with less developed countries carries the majority of the burden of this disease with the highest worldwide prevalence in sub-Saharan Africa (5.7 per 1000 school children) (2). Rheumatic heart disease most commonly affects the mitral valve and this is the leading cause of valvular heart surgery in the developing world (3).

In degenerative valvular disease (which predominates first world valvular pathology), mitral valve repair is the procedure of choice. The repair of these valves has low operative morbidity and mortality with superior functional outcome, late survival, freedom from re-operation and freedom from thrombo-embolic disease. The avoidance of complications associated with life-long anticoagulation in mechanical valve replacement serves as a further major advantage of valve repair (4,5,6).

On the other hand, the repair of rheumatic mitral valve disease remains controversial especially in view of the associated chronic, ongoing fibrotic process. Disease progression in the long term may necessitate mitral valve replacement making repair surgery redundant despite its advantages (7,8,9).

Evidence for surgical treatment differs depending on the age of the patient. In children with rheumatic heart disease, mitral valve repair is clearly indicated above replacement whenever the anatomic substrate permits it in view of a growing heart, accelerated degeneration of bioprostheses, and the possibility of orphanage through mass epidemics like Human Immunodeficiency Viral (HIV) infections. Antunes et al followed-up 241 rheumatic mitral valve patients in South Africa in the 1980s; almost half were children below 15 years of age (3). With pure or predominant regurgitation in three quarters of these patients and a mean follow-up period of 2.6 years, he unequivocally advised repair over replacement. In the 1990s, Kumar et al confirmed this conclusion in a paediatric series from New Delhi (10).

In adults the therapeutic dilemma of the superiority of repair over replacement in rheumatic mitral valve disease, forms the basis of an ongoing debate. From the developed world, Carpentier et al reported in 2001 on a long term (12 year) follow up of reconstructive valve surgery in rheumatic mitral valve insufficiency in France, showing a re-operation rate of only 2% per patient year with minimal risk of thrombo-embolic events and therefore clearly advocates for repair above replacement. (11) David et al echo this by showing improved late cardiac survival (independent of pre-operative characteristics) in rheumatic mitral valve repair above replacement in Toronto in 2001. (12)

Fewer studies are available from developing countries where unique problems exist like patient educated adherence to anti-coagulation therapy and infra-structural challenges to adhere to treatment and follow-up. Yankah et al followed up patients with endemic rheumatic heart disease and a migrant background post mitral valve repair in Germany, stating that these valves may be repairable but subsequently fail (13). The only data available from South Africa is from the work of Antunes et al in the 1980s in Johannesburg. As stated earlier, his patient population was young (mean age 21.5 years and 44.4% being below 15 years of age) with a 91% complete follow-up – a remarkable effort in a developing country with its limitations in retrospective follow-up of a migrant population with limited access to health care. With pure or predominant regurgitation in three quarters of these patients, he unequivocally advocated repair above replacement (3).



Sliwa et al confirmed in 2010 from The Heart of Soweto Study, Johannesburg, South Africa, that rheumatic patients become symptomatic for surgery later in life with a mean age of 43 years (14). This is in contrast to the previous work from Antunes et al in the 1980s.

## B.5 Identification of need for further research

The main possible disadvantages of disease progression on possible re-operation in rheumatic mitral valve repair need to be clearly reviewed against the dangers of a prosthetic valve in a developing country with difficult access to medical care. The current age shift of indigent rheumatic patients presenting for surgery may request a change in appropriate surgical therapy. It is important to identify treatment optimal for our local patient population with specific needs in difficult access to medical care (especially in rural areas), low average income and still generally inadequate access to proper patient education. The only study available in the South African context dates from more than 3 decades ago in Gauteng (3). No recent studies are available with no previous data from the Western Cape. Sub-Saharan Africa has the highest incidence of rheumatic heart disease (2) with an age shift towards later presentation for surgery in the modern era (16). It is therfor critical that the choice of appropriate therapy for rheumatic mitral valve disease in the modern era is based on more recent local evidence.



## B.6 References

1. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5:685–694.

2. Essop MR, Nkomo VT. Rheumatic and nonrheumatic valvular heart disease: epidemiology, management, and prevention in Africa. Circulation. 2005;112:3584–3591.

3. Antunes MJ, Magalhaes MP, Colsen PR, Kinsley RH. Valvuloplasty for rheumatic mitral valve disease. A surgical challenge. J Thorac Cardiovasc Surg. 1987 Jul;94(1):44-56.

4. Gillinov AM, Cosgrove DM, Blackstone EH, Diaz R, Arnold JH, Lytle BW, et al. Durability of mitral valve repair for degenerative disease. J Thorac Cardiovasc Surg 1998;116:734-43.

5. David TE, Omran A, Armstrong S, Sun Z, Ivanov J. Long-term results of mitral valve repair for myxomatous disease with and without chordal replacement with

expanded polytetrafluoroethylene sutures. J Thorac Cardiovasc Surg 1998;115:1279-85.

6. David TE, Armstrong S, Sun Z, Daniel L. Late results of mitral valve repair for mitral regurgitation due to degenerative disease. Ann Thorac Surg 1993;56:7-12.

7. Grossi EA, Galloway AC, Miller JS, Ribakove GH, Culliford AT, Esposito R, et al. Valve repair versus replacement for mitral insufficiency: when is a echanical valve still indicated? J Thorac Cardiovasc Surg 1998;115:389-94.

8. Duran CM, Gometza B, De Vol EB. Valve repair in rheumatic mitral disease. Circulation 1991;84(Suppl):III125-32.

9. Duran CM, Gometza BH, Saad E. Valve repair in rheumatic mitral disease: an unsolved problem. J Cardiol Surg 1994;9:282-5.

10. Kumar AS, Talwar S, Saxena A, Singh R, Velayoudam D. Results of mitral valve repair in rheumatic mitral regurgitation. Interact Cardiovasc Thorac Surg. 2006 Aug;5(4):356-61.

11. Chauvaud S, Fuzellier JF, Berrebi A, Deloche A, Fabiani JN, Carpentier A. Long-Term results of reconstructive surgery in rheumatic mitral valve unsufficiency. Circulation 2001:102[suppl I]:I-12-I-15.

12. Yau TM, El-Ghoneimi YAF, Armstrong S, Ivanov J, David TE. Mitral valve repair and replacement for rheumatic heart disease. J Thorac Cardiovasc Surg 2000;119:53-61.

13. Yankah C, Siniawski H, Detschades C, Stein J, Hetzer R. Rheumatic mitral valve repair: 22-year clinical results. J Heart Valve Dis. 2011;20:257-64.

14. Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. Eur Heart J. 2010 Mar;31(6):719-27.

## PART C: MANUSCRIPT

This manuscript was compiled in accordance with the author guidelines of The Journal of Heart Valve Disease (Annexure D) and submitted to this journal.

# Ten-year propensity-matched cohort analysis of mitral valve repair and replacement for rheumatic heart disease at Groote Schuur Hospital.

**Agneta Geldenhuys, Jithan J Koshy, Paul A Human, Juliana F Mtwale, Johan G Brink, Peter Zilla**

Christiaan Barnard Department of Cardiothoracic Surgery, Groote Schuur Hospital, University of Cape Town; South Africa.

**Key words**: Rheumatic heart disease, mitral valve repair, commissural fusion.

**Running title**: Commissural fusion predicts poor outcome in repair of rheumatic mixed mitral disease

Corresponding Author:
Agneta Geldenhuys, MBChB.
Christiaan Barnard Department of Cardiothoracic Surgery
D24, Groote Schuur Hospital
Anzio Road Observatory, 7925
Cape Town, South Africa
Facsimile: +27-21-448-1145
Telephone: +27-21-406-6181
E-mail: agneta.geldenhuys@uct.ac.za

## ABSTRACT

**Background and aim of the study:** In developing countries rheumatic heart disease is the predominant indication for cardiac surgery. As the disease tends to progress, re-operation rates for mitral valve repairs are high. Against this background we assessed predictors of failure and compared the overall performance of repairs with replacements in a 10-year cohort of rheumatic single mitral valve (MV) procedures.

**Methods:** Between 2000 and 2010, 560 consecutive adult (>13yrs) patients had a primary, single mitral valve procedure. Of the 215 primary MV repairs **69** were rheumatic (32%) as opposed to 281 out of 345 in primary MV replacements (81%). Of the 281 single MV replacements for rheumatic disease an equal number of **69** were propensity-matched with the repair group. Based on propensity score analysis, Kaplan-Meier actuarial analysis with log-rank testing was used to evaluate survival and morbidity.

**Results:** Follow-up was 100% complete (n=138) and ranged from 0.6 months to 132.5 months [Mean 53.32±36.48]. Of all rheumatic single MV procedures, 19.7% were repaired. Actuarial freedom from valve-related mortality was 95.6±3.1% and 91.7±3.6% at 5 years and 95.6±3.1% and 80.2±11.2% at 10 yrs for repairs and replacements, respectively (NS). Actuarial freedom from all valve related events (deaths, re-operations and morbidity) was 79.8±5.8%and 85.6±4.5% at 5 years and 69.8±8.4%and 69.2±10.7% at 10 years (NS). Actuarial freedom from all valve related events was 57.1±11.1% and 95.5±3.1% at 5 years (p=0.0008) and 41.6±12.4% and 95.5±3.1% at 10 years (p<0.001) for those mitral valve repairs with and without commissural fusion, respectively (p=0.0002 overall).

**Conclusions:** The long-term results for mitral valve replacement in an indigent, rheumatic heart disease population of a developing country are distinctly better than generally perceived. Notwithstanding, mitral valve repair has a superior long-term outcome in those patients who do not show commissural fusion at operation.

# INTRODUCTION

Mitral valve repair has become the undisputed procedure of choice for degenerative mitral incompetence, the predominant cause of mitral disease in the industrialized world. Yet, there remains uncertainty whether repair should also be the preferential therapy in the predominantly rheumatic patients of developing countries (1). In a disease that is chronic and progressive, there is concern that repair would result in re-operation rates that would put additional strain on the limited resources of a developing country. Moreover, re-operation may potentially not even be available due to limited access to cardiac surgery. These concerns are opposed by the complications of life-long anticoagulation for mechanical prostheses in an environment where "non-compliance" is often due to logistical impediments such as access to uninterrupted supply of anti-coagulation medication and regular INR controls. In an uneducated population, patient ignorance of the necessity for anti-coagulation is also a factor. Similarly, absence from work or even the fare for transport to the nearest clinic, may be another insurmountable obstacle to anticoagulation.

In children and young adults, a growing heart, accelerated degeneration of bioprosthesis, and the possibility of orphanage through mass epidemics like Human Immunodeficiency Viral (HIV) infections clearly favour mitral valve repair over replacement. In the 1980s Antunes et al followed-up 241 rheumatic mitral valve patients in South Africa; almost half were children below 15 years of age (2). With pure or predominant regurgitation in three quarters of these patients and a mean follow-up period of 2.6 years, he unequivocally advised repair over replacement. In the 1990s, Kumar et al confirmed this conclusion in a paediatric series from New Delhi (3).

In adult patients, however, the situation is less clear-cut. Yankah et al concurred with others that 'in regions with endemic rheumatic fever 'mixed mitral valve lesions may be repairable but subsequently fail'(1),(2-5). This conclusion was based on the ability to follow-up rheumatic patients with migrant backgrounds in an industrialized country and may not stand up to a holistic analysis of circumstances in a developing country. Yet, to be able to weigh the overall dangers of disease progression and re-operation, against the dangers of living with a prosthetic valve in a developing country, follow-up studies

would be needed. Except for isolated heroic follow-up efforts such as Antunes'(2), however, little information is available on post-operative adult rheumatic patients in developing or threshold countries. In the absence of such follow-up studies, centres that provide cardiac surgery often relied on common sense rather than facts for therapeutic decisions. In contrast to the 1980s when Antunes reported his results, the rapid and broad penetration of mobile phones into developing countries has dramatically changed the follow-up conditions. Together with advancements in information technology such as centralized population registries and nation-wide database-linked laboratory-services, patient follow-up studies in developing countries have higher chances of success today than two decades ago.

Utilizing these contemporary means of communication we attempted to clarify, in a retrospective cohort study, whether the avoidance of anti-coagulation outweighs the disadvantages of disease progression in rheumatic patients undergoing mitral valve repair in a threshold country.

## PATIENTS AND METHODS

### *Patients*

Between January 2000 and December 2010, 560 consecutive, single, first time mitral valve procedures with or without tricuspid annuloplasty and modified Maze procedures were performed in adult patients (>13years) at Groote Schuur Hospital, University of Cape Town, South Africa. 215 MV repairs (69 for rheumatic heart disease, 53 for ischemic heart disease, 45 for degenerative disorders, 23 for adult congenital heart disease, 21 for infective endocarditis and 4 for trauma) and 345 MV replacements (281 rheumatic; 46 infective and 18 degenerative) were performed. Of the total of 350 patients who had single mitral valve procedures for rheumatic heart disease, 69 (19.7%; 54 women; 15 men) had MV repair performed by two experienced surgeons. A further 12 had an attempted repair, which failed and had immediate replacement.

281 single MV replacements were performed for rheumatic heart disease and from this group an equal number of 69 (58 women; 11 men) were propensity-matched with the repair group. The clinical data of these patients are shown in table I.

All study patients had a strong history of rheumatic fever; 99.3% gave a domiciliary address within the Western Cape Province of South Africa at the time of surgery and 6.5% were HIV positive.

Preoperatively, trans-thoracic echocardiography was performed to assess the mitral valve features as listed in table II. Patients were excluded from attempted repair if the leaflets were too extensively diseased and immobile. The degree of regurgitation was based on Doppler echocardiography criteria (6, 7). Intra-operative trans-oesophageal echo was performed in all repair patients.



### *Surgery*

A conventional median sternotomy approach with ascending aorta and bi-caval cannulation, moderate hypothermia (32ºCelsius), antegrade cardioplegia and a left atriotomy was used in all patients. In mitral valve replacements, the posterior leaflet could be preserved in 37.7%. In the replacement group 63 patients (91.3%) received a bi-leaflet prosthesis [On-X: 25; St Jude: 24; Edwards Mira: 14]. If socioeconomic circumstances predicted poor compliance with anticoagulation or if pregnancies were

planned, tissue valves were used [Medtronic Mosaic: 4; Carpentier Edwards Pericardial: 2]. Details of MV repair techniques are summarized in table II. Patients were commenced on Warfarin therapy on post-operative day 1 and monitored by regular INR testing. Subcutaneous Heparin was used as an adjunct anti-coagulant until a stable therapeutic INR was obtained within the range of 2.0-3.5.

***Data Collection and Postoperative Follow-up***

Approval was obtained from the institutional ethics review board of the University of Cape Town to perform this retrospective, propensity-matched cohort study including permission to access national databases.

Post-operatively, patients from the metropolitan area were reviewed at the cardiac clinic at Groote Schuur Hospital and patients from outside the metropole were reviewed at regional hospitals. Routine visits were scheduled for 6 weeks and 6 months post-operatively, and thereafter, annually. All patients on anti-coagulation (those with mechanical valve prostheses and those in atrial fibrillation) were scheduled for monthly INR testing at their local health-care facility.

Active data collection for this study was undertaken between January and June 2011. Seventy-one percent of patients were contactable telephonically (land telephone lines: 28.2% and/or mobile phones: 42.8%). 8.7% of patients were traced through the metropolitan hospital-link database (Clinicom) to determine their point of care in the healthcare system. In 14.5% of cases, patients were found via the National Health Laboratory Service's database that was consulted for the patient's INR testing. Their functional status were then verified by their local health care providers or a community health care worker that visited the patient's physical address. A further 5% of patients were uncontactable but returned for a routine appointment to the cardiac clinic at Groote Schuur Hospital during this January to June period. Less than 1% of patients were traced by means of the National Department of Interior's population registry.

Follow-up was 100% complete (n=138) and ranged from 0.6 months to 132.5 months [Mean 53.32±36.48 (Repairs: 54.36±35.76, Replacements 52.68± 36.0)]. Total follow-up was 615 patient-years.

***Statistical Analysis***

Guidelines of the Society of Thoracic Surgeons for reporting mortality and morbidity after cardiac valve interventions were used for the analysis and reporting of postoperative complications(8). All continuous numerical data were expressed as means ± standard deviation and all actuarial estimates as percentage ± standard error. Inferential statistical analysis was performed using the JMP® statistical software package (version 6.0.3, Cary; NC). Propensity score analysis using multiple logistic regression independent of outcome variables, was performed against the pre-determined covariates of age, sex, body mass index, New York Heart Association classification, presence of pre-operative atrial fibrillation and left ventricular end systolic dimension. Nearest-neighbour matching (non-caliper) of repair group and replacement patient population propensity scores was performed using an in-house iterative algorithm using Filemaker Pro® (version 6.0; Santa Clara; CA). Actuarial curves were based on Kaplan-Meier analysis with comparison between groups performed using the log-rank test. Comparison at discrete time points was by Fisher's Exact test. Post-hoc comparison of normally distributed continuous numerical data, based on Shapiro-Wilk testing, was performed using the unpaired Student's T-test or, alternatively the non-parametric Wilcoxon test. Comparison of categorical data was performed using Fisher's exact or rectangular Chi-squared tests. A p-value of $<0.05$ was considered to be statistically significant.

# RESULTS

***Early Clinical Outcome***

Post-operative echocardiography of all mitral repair patients indicated no regurgitation in 23 patients (33.3%); trivial regurgitation in 35 patients (50.7%) and mild regurgitation in 11 (15.9%). There was no echocardiographic evidence of significant mitral stenosis. There was no hospital mortality in the repair group versus 1 death (1.5%) in the replacement group. Re-exploration for bleeding was necessary in 2 patients in both the repair and replacement groups. No post-operative cerebro-vascular event occurred in the repair group versus one in the replacement group. Permanent pacemaker insertion for conduction disturbances was necessary in 3 patients in the repair group and 2 in the replacement group. No patient required dialysis for acute renal failure or developed deep sternal sepsis.

***Late Clinical Outcome***

*Late Mortality:* There were 6 late deaths (8.7%) in the repair group after a median period of 36.9 months (range 12-132) and 8 (11.6%) in the replacement group after median 19.9 months (range 6-113). The causes of death are listed in table III.

In the repair group, 3 deaths were valve related: one patient died of a stroke 16 months after surgery; one died of a sudden cardiac arrest 55 months following mitral valve repair and 11 months after redo mitral valve replacement; and one of congestive heart failure with rapid atrial fibrillation with a well-functioning repaired valve after 12 months. Two died of cancer, and one of a community acquired pneumonia.

In the replacement group, 5 of the 8 deaths were valve related: two due to clotted valves (both after 14 months); one haemorrhagic stroke (after 120 months); one untreated paravalvular leak after 6 months (probable prosthetic endocarditis); and one 'sudden cardiac arrest' (after 38 months). Two died of HIV related infections and one was murdered.

Actuarial freedom from **all-cause** mortality was 90.5±4.1% and 90.2±3.8% at 5 years and 90.5±4.1% and 74.0±11.4% at 10 years for the repairs and replacements respectively. (NS) (Figure 1a). Actuarial freedom from **valve-related** mortality was

95.6±3.1% and 91.7±3.6% at 5 years and 95.6±3.1% and 80.2±11.2% at 10 years for the repairs and replacements respectively. (NS) (Figure 1b).

*Re-operations:* 11 patients (8.0%) required reoperation. In the repair group 10 (14.5%) required a valve replacement for progressive valve deterioration (3.1 events/100 patient years; median period 43.8 months; range 0.9-127.4 months); 4 required replacement within the first year (2 for pure regurgitation; 2 for mixed mitral disease) and 6 had a late re-operation (5 for mixed mitral valve disease and 1 for regurgitation.)

In the replacement group, one patient required reoperation within two months for valve thrombosis (0.3 events/100 patient years) (Table IV).

Freedom from re-operation was 82.2±5.8% and 98.5±1.5% at 5 years and 76.3±7.8% and 98.5±1.5% at 10 years for repairs and replacements, respectively (p=0.007)(Figure 2a).

Within the repair group, several parameters were analyzed to determine factors associated with failure of repair. The most striking determinant for the latter was the presence of commissural fusion at the initial intraoperative assesment. Sub-analysis of the repair group regarding those with and without commissural fusion, ("Fused" and "Non-fused" groups respectively), demonstrated an actuarial freedom from re-operation of 62.3±11.8% and 95.5±3.1% at 5 years and 53.4±13.0% and 95.5±3.1% at 10 years for the two groups, respectively (p=0.004)(Figure 2b).

*Valve-Related Morbidity:* In the repair group there was one Warfarin-related gastro-intestinal bleed due to erosive gastritis (in a patient in atrial fibrillation) versus 3 Warfarin related bleeding episodes in the replacement group: Two abnormal uterine bleeds and one upper gastrointestinal bleed. Infective endocarditis developed on one repaired valve, versus three in the replacement group. No prosthesis failures were encountered in the replacement group. Three patients in the replacement group developed a paravalvular leak. Two minor leaks were treated conservatively and one developed infective endocarditis and died. In the replacement group, only one valve thrombosed and underwent an early redo replacement.

Two late cerebrovascular accidents due to thromboembolism occurred, one in each group.

Actuarial freedom from all valve related events (deaths, re-operations, and morbidity) was 79.8±5.8% and 85.6±4.5% at 5 years and 69.8±8.4% and 69.2±10.7% at 10 years for the repairs and replacements respectively (N.S.) (Figure 3a). Actuarial freedom from all valve related events was 57.1±11.1% and 95.5±3.1% at 5 years (p=0.008) and 41.6±12.4% and 95.5±3.1% at 10 years (p<0.001) for those mitral valve repairs with and without commissural fusion, respectively (p=0.0002 overall)(Figure 3b)

***Atrial fibrillation***

In the repair group, 20 (29%)(45% "Fused/ 20% "Non-Fused) were pre-operatively in permanent atrial fibrillation versus 27 (39%) in the replacement group. In 13 of these 47 cases a modified Maze procedure was performed with six (46%) remaining in sinus rhythm. In each of the "Fused" and "Non-fused" commissural groups, two remained in sinus rhythm.

New onset post-operative atrial fibrillation occurred in 6 patients (8.7%) in the repair group and 3 patients (4.3%) in the replacement group.

***Demographics, Population Migration and Follow-up***

Almost two thirds of the patients were of mixed race mirroring the demographics of South Africa's Western Cape Province. Only one of 138 patients came from another province with 87% of patients living within 100km of the hospital. At the last follow-up (mean of 4.46±3.00 years after surgery) two thirds of patients had not changed their domicile. Most who had changed (25.4%) did so within the metropolitan area. Only 2.9% moved to another province and 0.7% to another African country.

## DISCUSSION

In the rapidly urbanizing societies of threshold countries such as Brazil, India, China and South Africa rheumatic heart disease still accounts for a significant proportion of their 350,000 annually performed cardiac operations. In contrast to previous eras, however, modern means of communication have thoroughly penetrated all levels of society, allowing even remote, indigent patient groups to be followed-up. The 100% follow-up rate in our present study gives testimony to these changed circumstances, opening the door to the optimization of therapies previously reserved for industrialized countries. By comparing disease progression after mitral valve repair with the adverse events associated with mitral valve replacement, we could demonstrate that:

- the ten-year survival was not significantly different in replacements and repairs
- while freedom from re-operation was significantly lower in the repair group, freedom from valve related events was identical in both groups
- within the repair group, 10-year freedom from valve related events was 96% in those patients without fused commissures as opposed to 42% in those with fused commissures.

In developing countries, perceived non-compliance with anticoagulation therapy had led to a strong advocacy of mitral valve repairs over replacements (2, 9). A significant 5-year re-operation rate of 8% (10) to 23% (1) as a consequence of disease progression seemed acceptable in view of severe thromboembolic complications (11) and lethal thromboses of the prostheses (12). It was therefore an unexpected observation of our study that adverse events were less prevalent than anticipated in the replacement group with an identical survival rate as for mitral repairs. The reasons for this improved performance of mitral-valve replacements in a developing country may lie in an increased patient age at the time of surgery (associated with greater maturity and reliability), and better communication means between patients and health facilities. In our present study the mean patient age was 39 years. This trend towards rheumatic patients becoming symptomatic for surgery at a later stage in life was confirmed by Sliwa et al. At the same hospital where Antunes' study was performed in 1986 the mean age of patients needing surgery in 2010 was 43 years (13) as opposed to 21 years (44% being younger than 15 years) in the original study 25 years earlier (2). As the incidence

was still 25/100,000 patients/year it represents a true age-shift with advancing development rather than disease eradication - a trend reflected in a mean age at surgery of 49 years in South Korea (14) and 55 years in Taiwan (15). Notwithstanding, the large series of mitral valve repairs in rheumatic children in India and China (9) emphasizes the fact that the disease still affects many young patients.

An additional explanation for our better outcomes may be that bi-leaflet prostheses had a higher impact in developing countries than in industrialized ones. A previous series from South Africa with tilting disc valves showed a 75% freedom from valve related mortality (11) at 5 years, compared to 90% in our present study.

The most significant outcome of our study, however, was the dramatic difference in freedom from valve related events of mitral valve repairs in those patients without commissural fusion versus those with fused commissures. As much as previous studies had concluded that repairs in mixed mitral valve disease perform worse than in pure regurgitation (1, 2, 9) fused commissures are also a hallmark of pure mitral stenosis where commissurotomy leads to excellent long-term results. Whether an incompetence-component in stenotic valves is a reflection of a more aggressive constrictive response of the fibrotic tissue remains speculative. It is, however, conceivable that additional anterior leaflet augmentation most recently advocated for the treatment of mixed mitral valve disease in order to counteract transversal leaflet traction (16-18) would have addressed this constriction and preempted the recurrence of incompetence. The fact that the predominant failure mode of valves that had commissural fusion in our study was incompetence rather than stenosis supports this explanation as does Acar's report of a significantly lower re-operation rate in mixed mitral valve disease if anterior leaflet augmentation was employed (16). In the absence of anterior augmentation in past rheumatic repairs, our study identified commissural fusion as the one component of stenotic mitral valve disease that strongly suggests measures going beyond conventional repair strategies. Should long-term results with anterior leaflet augmentation in the subgroup with commissural fusion fall short of expectations, we have shown that replacement is less detrimental in such patients than perceived from historical reports.

**Study limitations**

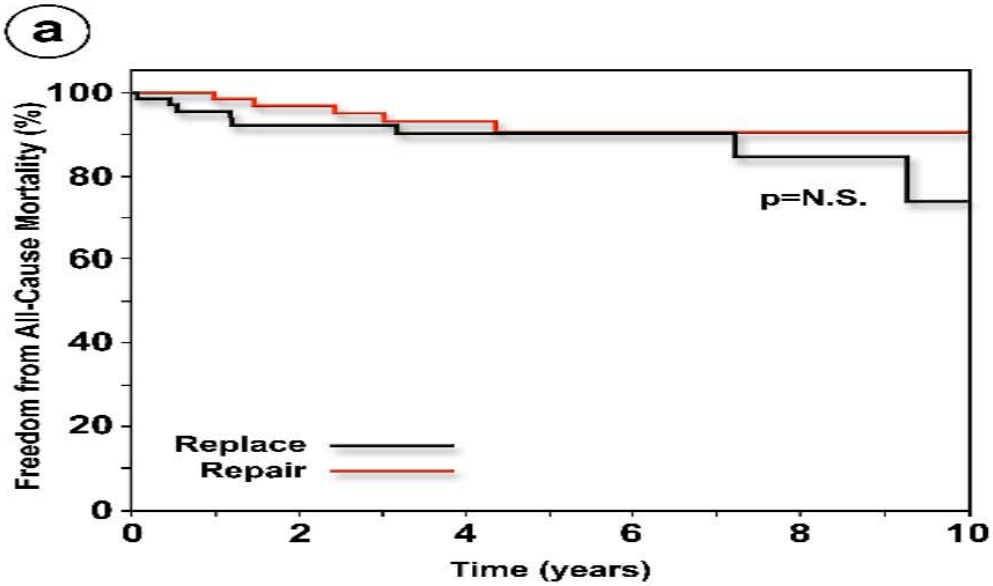
This was a retrospective study of patients with all the well-known associated short-comings, compared to a prospective study. The latter was not possible, predominantly due to problems with patient follow-up ten years ago when mobile phone penetration was low and there was more inter-provincial migration of patients. Reliance on mainly telephonic assessment at varying time points represents another weakness. Echocardiographic follow-up at predetermined time points would have been desirable but not implementable in the given population. As no strategy was implemented for late cardioversion of patients in atrial fibrillation, a less aggressive approach to Maze procedures was adopted. Anterior leaflet augmentations only became a reported modality in the latter half of the study but may have benefited the worst performing patients.

**Conclusions**

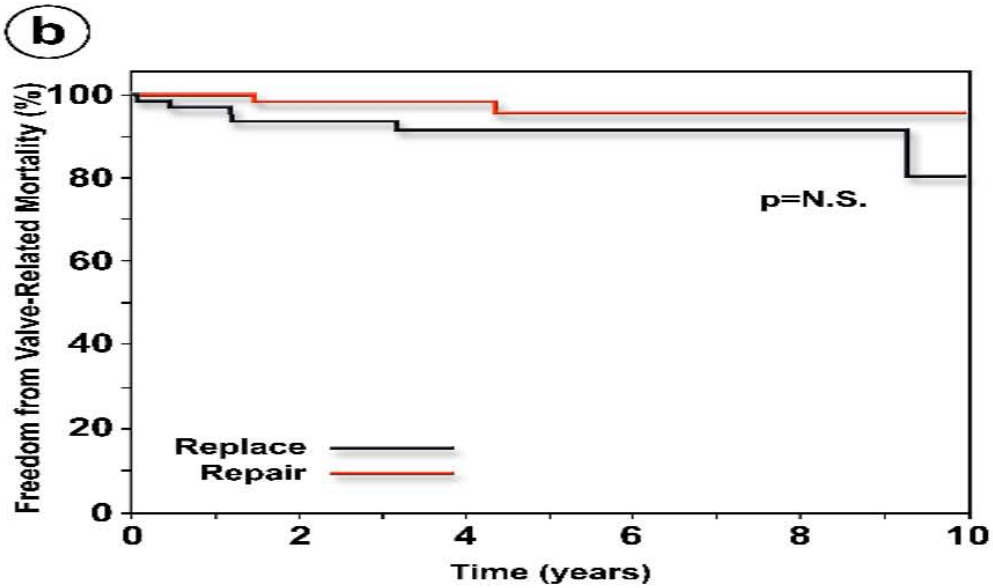
The long-term results for mitral valve replacement in an indigent, rheumatic heart disease population of a developing country in a modern era are distinctly better than generally perceived. Conventional mitral valve repair in rheumatic patients is an excellent, durable procedure if restricted to patients that do not have commissural fusion. Adding anterior leaflet augmentation in those valves showing commissural fusion and a Maze procedure in chronic atrial fibrillation may yet create a rheumatic patient population with a minimal risk of re-operation rarely requiring anticoagulation.

## LEGEND

***Figure 1:*** Actuarial curves (Kaplan Meier) comparing overall survival (a) and survival from valve related death (b) between mitral valve replacement and repairs.

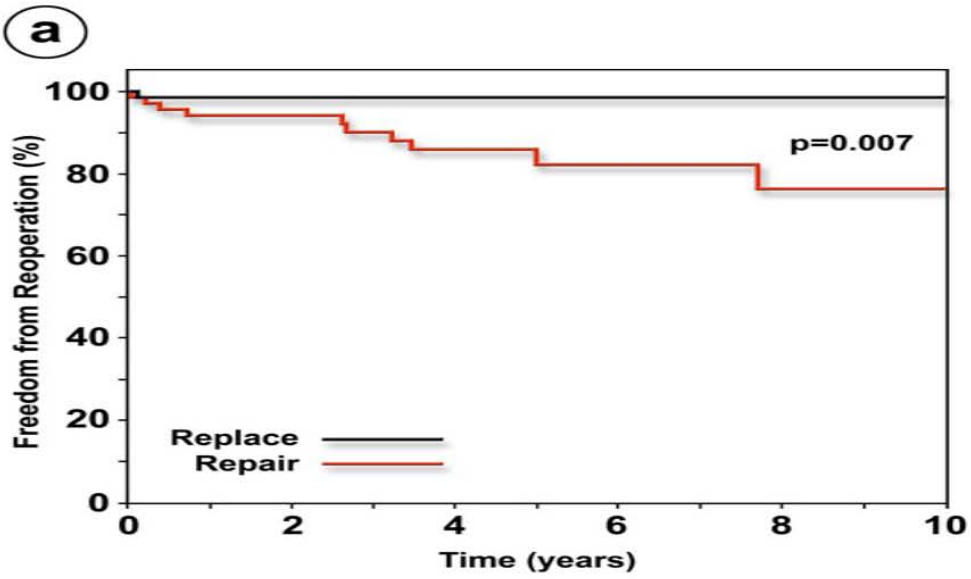



| Time (Years) | Procedure | 0 | 1 | 2 | 5 | 10 |
|---|---|---|---|---|---|---|
| Patients At Risk (n) | Replace | 69 | 59 | 55 | 28 | 3 |
| | Repair | 69 | 64 | 60 | 27 | 7 |
| Estimate (%) | Replace | 100 | 95.4±2.6 | 92.2±3.4 | 90.2±3.8 | 74.0±11.4 |
| | Repair | 100 | 98.4±1.6 | 96.8±2.2 | 90.5±4.1 | 90.5±4.1 |

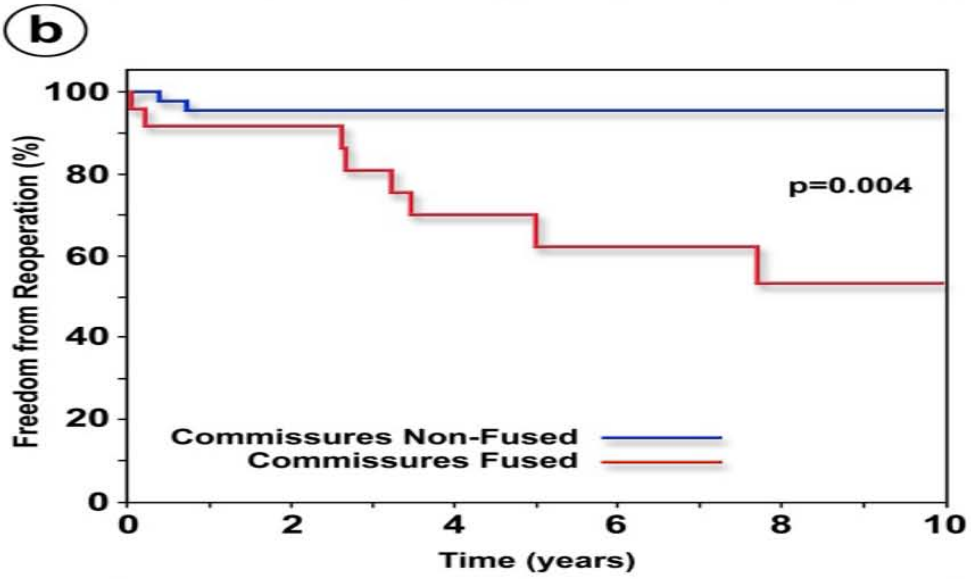



| Time (Years) | Procedure | 0 | 1 | 2 | 5 | 10 |
|---|---|---|---|---|---|---|
| Patients At Risk (n) | Replace | 69 | 59 | 55 | 28 | 3 |
| | Repair | 69 | 64 | 60 | 27 | 7 |
| Estimate (%) | Replace | 100 | 97.0±2.1 | 93.7±3.1 | 91.7±3.6 | 80.2±11.2 |
| | Repair | 100 | 100 | 98.4±1.6 | 95.6±3.1 | 95.6±3.1 |

***Figure 2:*** Actuarial freedom from re-operation (Kaplan Meier) comparing mitral valve replacement with all mitral valve repair patients (a) and between the subgroups of mitral valve repair showing commissural fusion or freedom from commissural fusion (b).

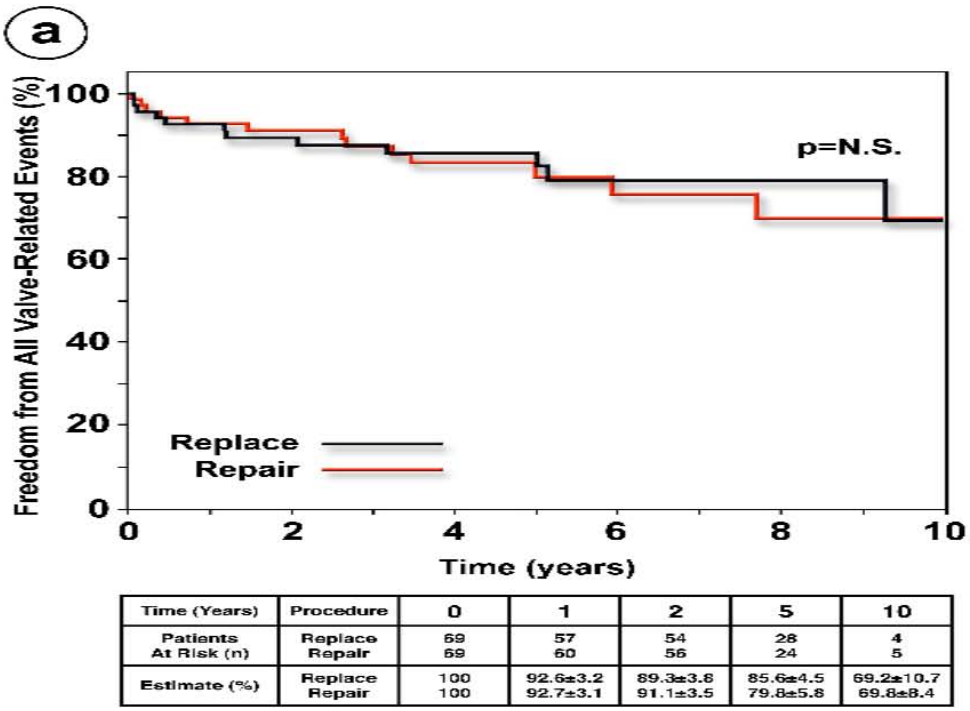



| Time (Years) | Procedure | 0 | 1 | 2 | 5 | 10 |
|---|---|---|---|---|---|---|
| Patients At Risk (n) | Replace<br>Repair | 69<br>69 | 58<br>60 | 54<br>56 | 28<br>23 | 3<br>5 |
| Estimate (%) | Replace<br>Repair | 100<br>100 | 98.5±1.5<br>94.2±2.8 | 98.5±1.5<br>94.2±2.8 | 98.5±1.5<br>82.2±5.8 | 98.5±1.5<br>76.3±7.8 |

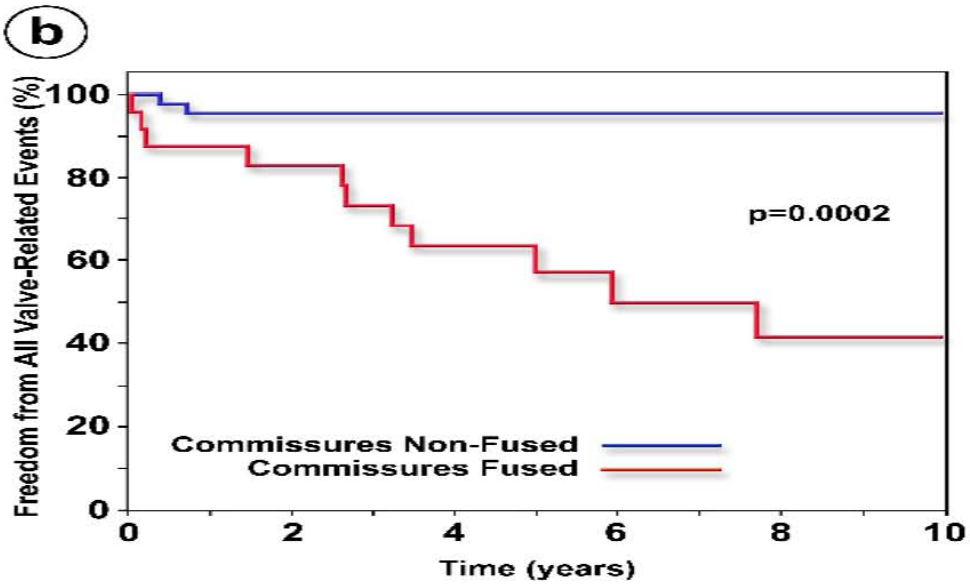



| Time (Years) | Commissures | 0 | 1 | 2 | 5 | 10 |
|---|---|---|---|---|---|---|
| Patients At Risk (n) | Non-Fused<br>Fused | 45<br>24 | 40<br>21 | 38<br>19 | 15<br>9 | 3<br>3 |
| Estimate (%) | Non-Fused<br>Fused | 100<br>100 | 95.5±3.1<br>91.7±5.6 | 95.5±3.1<br>91.7±5.6 | 95.5±3.1<br>62.3±11.8 | 95.5±3.1<br>53.4±13.0 |

***Figure 3:*** Actuarial freedom from valve related events (Kaplan Meier) between mitral valve replacement and repair (a) and between repairs in mitral valves that had commissural fusion and those free of commissural fusion (b).




| Time (Years) | Procedure | 0 | 1 | 2 | 5 | 10 |
|---|---|---|---|---|---|---|
| Patients At Risk (n) | Replace<br>Repair | 69<br>69 | 57<br>60 | 54<br>56 | 28<br>24 | 4<br>5 |
| Estimate (%) | Replace<br>Repair | 100<br>100 | 92.6±3.2<br>92.7±3.1 | 89.3±3.8<br>91.1±3.5 | 85.6±4.5<br>79.8±5.8 | 69.2±10.7<br>69.8±8.4 |




| Time (Years) | Commissures | 0 | 1 | 2 | 5 | 10 |
|---|---|---|---|---|---|---|
| Patients At Risk (n) | Non-Fused<br>Fused | 45<br>24 | 40<br>21 | 38<br>19 | 15<br>10 | 3<br>3 |
| Estimate (%) | Non-Fused<br>Fused | 100<br>100 | 95.5±3.1<br>87.5±6.8 | 95.5±3.1<br>82.9±7.8 | 95.5±3.1<br>57.1±11.1 | 95.5±3.1<br>41.6±12.4 |

## TABLES

### Table I

| | MV Repairs | MV Replacements | P-value |
|---|---|---|---|
| Number of patients | 69 | 69 | |
| Age (Years) | 36.9±14.5<br>Range: 12-68 | 40.9±11.7<br>Range: 15-69 | 0.0768 |
| Female:Male ratio | 54:15 | 58:11 | 0.5143 |
| Valve lesions (%) | | | |
| Pure stenosis | 3 | 7 | 0.325 |
| Regurgitation | 39 | 13 | 0.0001 |
| Stenosis and Regurgitation | 27 | 49 | 0.0003 |
| Left atrial size (cm) | 5.2±0.97 | 5.3±0.85 | 0.5206 |
| Pre-operative atrial fibrillation | 29% | 39% | 0.2811 |
| Requiring additional tricuspid annuloplasty | 5.7% | 13% | 0.2431 |
| Modified Maze procedure performed | 13% | 5.8% | 0.2431 |

**Table II**

| **Operative Repair Data** | **No. Of Patients** |
|---|---|
| Intra-Operative Findings (%) | |
| Anterior Prolapse | 52%(19) |
| Anterior Restriction | 18%(13) |
| Posterior Prolapse | 16%(11) |
| Posterior Restriction | 48%(33) |
| Chordal Rupture | 39%(27) |
| Chordal Restriction | 41%(28) |
| Chordal Elongation | 23%(16) |
| **Commissural Fusion** | **35%(24)** |
| **No Commissural Fusion** | **65%(45)** |
| Annular Calcification | 13%(20) |
| Annular Dilatation | 90%(19) |
| Mitral Valve Repair Procedures | |
| Annuloplasty | 90%(19) |
| Medtronic CG-Future Band | 68%(47) |
| Carpentier-Edwards Physio Ring | 13%(20) |
| Carpentier Edwards Classic Ring | 7.2%(20) |
| Duran | 1.4%(20) |
| Commissurotomy | 35%(24) |
| Papillary muscle splitting | 1.4%(20) |
| Leaflet Cleft closures | 10%(7) |
| Chordal shortening | 8.7%(6) |
| Artificial chordae | 49%(34) |
| Leaflet Resection | 11.6%(20) |
| Leaflet Augmentation | 19% (13) |
| Alfieri “edge to edge” suture | 22% (15) |

**Table III**

| **Reason for late Death % (events per 100 patient-years)** | | |
|---|---|---|
| | **Repair** | **Replacement** |
| Valve-Related | | |
| Valve Thrombosis | **-** | **2** |
| Stroke | **1** | **1** |
| Paravalvular Leak | **0** | **1** |
| Post Redo MVR sudden cardiac arrest | **1** | **0** |
| 'Sudden cardiac arrest' | **0** | **1** |
| Congestive Cardiac Failure | **1** | **0** |
| Community Acquired Pneumonia | **1** | **0** |
| HIV | **0** | **2** |
| Cancer | **2 *** | **0** |
| Murder | **0** | **1** |
| **Total** | **6** | **8** |

***(* One cancer developed following a redo mitral replacement)***

**Table IV**

| **Follow-up** | | | |
|---|---|---|---|
| | **MV Repairs** | **MV Replacements** | **p-value** |
| Mean follow-up period (years) | 4.53±2.98 | 4.39±3.04 | 0.785 |
| 30 day mortality | 0% | 1.5% (20) | 1.000 |
| Late Mortality | 8.7% (6) | 13% (20) | 0.770 |
| Re-Operation Rate | 14.5% (10) | 1.5%(20) | 0.009 |
| Mean time to re-operation (days) | 954±890 | 46 (1 patient) | - |
| New onset atrial fibrillation | 6 (8.7%) | 3 (4.3%) | 0.493 |
| Valve related events: | | | |
| Post-op mitral valve endocarditis | 1 (1.4%) | 3 (4.3%) | 0.619 |
| Warfarin related bleed | 1 (1.4%) | 3 (4.3%) | 0.619 |
| Paravalvular leak | - | 3 (4.3%) | - |
| Thrombosed valve (re-operated) | - | 1 (1.4%) | - |
| Stroke due to thrombo-embolism | 1 (1.4%) | 1 (1.4%) | - |

# REFERENCES


1. Yankah C, Siniawski H, Detschades C, Stein J, Hetzer R. Rheumatic mitral valve repair: 22-year clinical results. J Heart Valve Dis. 2011;20:257-64.

2. Antunes MJ, Magalhaes MP, Colsen PR, Kinsley RH. Valvuloplasty for rheumatic mitral valve disease. A surgical challenge. J Thorac Cardiovasc Surg. 1987 Jul;94(1):44-56.

3. Kumar AS, Talwar S, Saxena A, Singh R, Velayoudam D. Results of mitral valve repair in rheumatic mitral regurgitation. Interact Cardiovasc Thorac Surg. 2006 Aug;5(4):356-61.

4. Talwar S, Rajesh MR, Subramanian A, Saxena A, Kumar AS. Mitral valve repair in children with rheumatic heart disease. J Thorac Cardiovasc Surg. 2005 Apr;129(4):875-9.

5. Skoularigis J, Sinovich V, Joubert G, Sareli P. Evaluation of the long-term results of mitral valve repair in 254 young patients with rheumatic mitral regurgitation. Circulation. 1994 Nov;90(5 Pt 2):II167-74.

6. Grossman W. Profiles in valvular heart disease. In: Baim DS, Grossman W, editors. Cardiac catheterization, angiograph, and intervention. Baltimore: Williams & Wilkins; 1996. p. 742-4.

7. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. Circulation. 1987 Jan;75(1):175-83.

8. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg. 2008 Apr;135(4):732-8.

9. Kumar AS, Rao PN, Saxena A. Results of mitral valve reconstruction in children with rheumatic heart disease. Ann Thorac Surg. 1995 Oct;60(4):1044-7.

10. Talwar S, Mathur A, Choudhary SK, Singh R, Kumar AS. Aortic valve replacement with mitral valve repair compared with combined aortic and mitral valve

replacement. Ann Thorac Surg. 2007 Oct;84(4):1219-25.

11. Antunes MJ, Wessels A, Sadowski RG, Schutz JG, Vanderdonck KM, Oliveira JM, et al. Medtronic Hall valve replacement in a third-world population group. A review of the performance of 1000 prostheses. J Thorac Cardiovasc Surg. 1988 Jun;95(6):980-93.

12. Copans H, Lakier JB, Kinsley RH, Colsen PR, Fritz VU, Barlow JB. Thrombosed Bjork-Shiley mitral prostheses. Circulation. 1980 Jan;61(1):169-74.

13. Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. Eur Heart J. 2010 Mar;31(6):719-27.

14. Kim JB, Kim HJ, Moon DH, Jung SH, Choo SJ, Chung CH, et al. Long-term outcomes after surgery for rheumatic mitral valve disease: valve repair versus mechanical valve replacement. Eur J Cardiothorac Surg. 2010 May;37(5):1039-46.

15. Wang Y-C, Tsai F-C, Chu J-J, Lin P-J. Midterm outcomes of rheumatic mitral repair versus replacement. Int Heart J. 2008;49:565-76.

16. Acar C, de Ibarra JS, Lansac E. Anterior leaflet augmentation with autologous pericardium for mitral repair in rheumatic valve insufficiency. J Heart Valve Dis. 2004 Sep;13(5):741-6.

17. Zegdi R, Ould-Isselmou K, Fabiani JN, Deloche A. Pericardial patch anterior leaflet extension in rheumatic mitral insufficiency. Eur J Cardiothorac Surg. Jun;39(6):1061-3.

18. Gupta A, Gharde P, Kumar AS. Anterior mitral leaflet length: predictor for mitral valve repair in a rheumatic population. Ann Thorac Surg. Dec;90(6):1930-3.

## PART D: SUPPORTING DOCUMENTATION

**Acknowledgements:**

Dr Paul Human were responsible for specific statistical analysis of the results. Dr Jithan J Koshy helped with data collection and analysis and Juliana F Mtwale helped with data handling by creating a computerized database for this study. Professors Peter Zilla and Johan Brink assisted in the analysis as well as the concluding phases of the study.

The Department of Cardiology at Groote Schuur Hospital made relevant current and archived data available on patients in the study population for perusal.

A sincere word of thank you to all the sisters and health care workers at the local health care clinics for your great effort in assisting us in order to make contact with these patients.

## Annexure A: University of Cape Town ethics approval.

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

11 April 2011

Sent via Internal mail & Email

HREC REF: 189/2011

DR A GELDENHUYS,
CARDIOTHORACIC SURGERY
CHRIS BARNARD DIVISION
D 24
NGSH

Dear DR GELDENHUYS,

PROJECT TITLE: **A RESTROSPECTIVE REVIEW OF MITRAL VALVE REPAIR AND MITRAL VALVE REPLACEMENT IN RHEUMATIC HEART DISEASE IN GROOTE SCHUUR HOSPITAL DURING THE LAST DECADE.**

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

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

**Approval is granted until 15 April 2012**

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

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

**Please quote the HREC. REF in all your correspondence.**

Yours sincerely

A/PROF MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

## Annexure B: Mitral valve repair data collection sheet

Data Collection Sheet MVREP for RHD

| | | | |
|---|---|---|---|
| 1 | Name | | |
| 2 | Folder # | | |
| 3 | Sex | | |
| 4 | Race | | |
| 5 | Date of Birth | | |
| 6 | Age | | |
| 7 | Date of Surgery | | |
| 8 | Hypertension | | |
| 9 | Dyslipidemia | | |
| 10 | Renal dysfunction | | |
| 11 | NYHA Pre-op | | |
| 12 | NYHA Post-op f/u | | |
| 13 | Previous Cardiac surgery | | |
| 14 | AF Initial | | |
| 15 | AF Long term | | |
| 16 | Anticoagulation Initial | | |
| 17 | Anticoagulation Long term/stopped | | |
| 18 | Diagnosis MS | | |
| 19 | Diagnosis MR | | |
| 20 | Diagnosis MMVD | | |
| 21 | VD Etiology Mitral | | |
| 22 | VD SBE Mitral | | |
| 23 | VD TEE Mitral Pre anatomy | | |
| 24 | VS Mitral Proc Classification | | |
| 25 | VS Mitral Proc Procedure | | |
| 26 | MS gradient | | |
| 27 | MS MVA | | |
| 28 | MR Grade | | |
| 29 | VD Vegetations Mitral | | |
| 30 | Tricuspid Regurgitation | | |
| 31 | LV-EF | | |
| 32 | LV ESD | | |
| 33 | LV EDD | | |
| 34 | LA Size | | |
| 35 | PHT Mean | | |
| 36 | PHT Peak | | |
| 37 | A-Cross clamp | | |
| 38 | CPB Time | | |
| 39 | Associated procedures (MAZE etc) | | |
| 40 | Intr-op Valve characteristics | | |
| 41 | Intra-op Vegetations Mitral | | |
| 42 | Intra-op Ant Leaf A1 | | |
| 43 | Intra-op Ant Leaf A2 | | |
| 44 | Intra-op Ant Leaf A3 | | |
| 45 | Mitral Comm Fus L | | |
| 46 | Mitral Comm Fus R | | |
| 47 | Mitral Proc Leaflet Resect | | |
| 48 | VS Mitral Proc Post Leaf P1 | | |
| 49 | VS Mitral Proc Post Leaf P2 | | |
| 50 | VS Mitral Proc Post Leaf P3 | | |

## Annexure C: Mitral valve replacement data collection sheet

| DATA COLLECTION SHEET FOR MITRAL VALVE REPLACEMENTS | | | | | |
|---|---|---|---|---|---|
| NAME | | | | | |
| FOLDER No | | | | | |
| CONTACT NUMBER | | | | | |
| SEX | | | | | |
| RACE | | | | | |
| DATE OF BIRTH | | | | | |
| AGE | | | | | |
| SOCIO-ECONOMIC STATUS | Domicile: | | | | |
| EDUCATIONAL STATUS | Standard: | | | | |
| | | | | | |
| DATE OF SURGERY | | | | | |
| COMORBIDITIES | Hypertension | Dyslipidemia | Renal Dysfunction | Diabetes | Others |
| MITRAL VALVE DISEASE | MS | | | | |
| | MR | | | | |
| | MMVD | | | | |
| NYHA | Pre-op | | | | |
| | Post-op | | Date | | |
| | F/U-1 | | Date | | |
| | F/U-2 | | Date | | |
| | Last F/U | | Date | | |
| INTRA-OP | CPB Time | | | | |
| | Cross Clamp Time | | | | |
| | Valve Type | | | | |
| | Valve Size | | | | |
| | Tissue Valve Reason | | | | |
| HISTOLOGICAL EVIDENCE | | | | | |
| PRE-OP AF | | | | | |
| POST-OP AF | | | | | |
| POST-OP PPM | | | | | |

| POST-OP ICU Stay (Hrs) | | | | | |
|---|---|---|---|---|---|
| POST-OP Hospital Stay (Days) | | | | | |
| ANTICOAGULATION | Pre-Op Anticoagulation | | | | |
| | No. of Annual INR Checks | | | | |
| | INR Clinic Location | | | | |
| | NHLS INR Profile Last 12mo | | | | INR Data |
| | | | | | |
| ANTICOAGULATION COMPLICATIONS | Side Effects | | | | |
| | Bleeding | | | | |
| | Supratherapeutic INR | | | | |
| | Subtherapeutic INR | | | | |
| | Thromboembolic Events | | | | |
| VALVE COMPLICATIONS | Infective Endocarditis | Date | | | |
| | Paravalvar Leak | Date | | | |
| | Prosthesis Failure | Date | | | |
| | Valve Thrombosis | Date | | | |
| | Complete Heart Block | Date | | | |
| CURRENT SURVIVAL (Telephonic Rev) | | | | | |
| MORTALITY (Telephonic Rev) | Cause | Date | | | |
| REOPERATION | Cause | Date | | | |
| | SBE | | Organism | | |
| | Paravalvar Leak | | | | |
| | Prosthesis Failure | | | | |
| | Valve Thrombosis | | | | |
| | PPM Insertion | | | | |

**Annexure D: Journal of Heart Valve Disease Author Guidelines.**

# Instruction to Authors

**Editorial policy**

The Journal of Heart Valve Disease publishes peer-reviewed scientific communications pertaining to heart valves and heart valve disease, including but not limited to all issues related to the scientific activity of The Society for Heart Valve Disease. These encompass all relevant clinical, surgical and laboratory specialties, multicenter trials, morphology, physiology, molecular biology, pathology as well as design, materials, test data and performances of replacement devices, relevant instruments and equipment. The scope of articles includes original publications, editorials, current and collective reviews, technical know-how papers both in surgery and cardiology, case reports, correspondence and book reviews.
Submission of a manuscript to the Journal implies the authors' assertion that (a) it is original, (b) has not been published before and (c) is not under consideration, or under publication elsewhere. Prior publication of an abstract of 400 words or less does not prejudice the originality of a manuscript.

**Address**

Manuscripts and all editorial correspondence should be sent electronically to:
rwemery@healtheast.org

**Review policy**

A manuscript will be evaluated not only with respect to its scientific competence and accuracy but also to its relative importance in the field of heart valve and heart valve disease and for its probable interest to our readership. Each manuscript will be reviewed by the Editor and/or Associate Editor and at least 2-3 additional outside reviewers. Invited reviewers will evaluate each manuscript based on the following criteria:

*Originality*

The importance of the research question as it pertains to heart valves and heart valve disease;

*Scientific integrity*

Analytical methods appropriate for data presented;
Data presented in a clear concise method;
Tables, figures, illustrations and references are appropriate for the topic;
Appropriate statistical methods applied and determination if statistical review should be considered;

*Manuscript format and content*

Are structure, content, grammatical, length and writing style consistent with guidelines;
Is the discussion section relevant;
Is the conclusion section reasonable and support the discussion.

**Acknowledgement of manuscript receipt**

The corresponding author will receive an acknowledgement by e-mail and an assigned unique tracking number. Any and all communication with the Editor regarding the status of a manuscript will be provided only to authors who identify the manuscript number. **When corresponding with the editorial office manuscripts must be referenced using the assigned number.**

**Manuscript acceptance, revision and re-review**

The corresponding author will be notified by e-mail about the acceptance of a manuscript. If it accepted only conditionally pending revision, the corresponding author will receive all reviewer comments together with the editor's recommendations. Revised manuscripts must be submitted in three parts: 1) a cover letter that provides a point-by-point response to reviewers' comments; 2) the revised manuscript containing the deletions noted strikethrough and additions in bold; 3) the unmarked revised manuscript. Revised manuscripts received after 3 months from the 'Request to Revise" receipt date may be required to resubmit as a new manuscript and will be subject to the entire submission review process.
Manuscripts that have been either undergone substantial revision or contain techniques/technology of controversial topics or articles discussing complex issues are subject to re-review at the discretion of the Editor.

**Copyright**

If the manuscript is accepted for publication in the Journal, the copyright of it must be transferred to ICR

Publishers Ltd., and the copyright transfer document, which will be sent with the page proofs, should be signed by all authors of the article.

**Medical ethics**

*Human studies*. Manuscripts reporting on human studies must adhere to the principles of the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm). Reports describing data obtained from research conducted in human participants must contain a statement in the Methods section indicating approval by the Institutional Review Board. If patients are identifiable from illustrations, photographs, study data or figures, release forms giving permission for publication must be submitted with the manuscript.

*Animal experiments*. Manuscripts reporting experiments on living animals should adhere to the principles provided in the Guide for Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) . Manuscripts should also include in the Methods section a statement by the authors that the relevant regulations of the country where the experiments were carried out were fully observed.

**Conflict of interest**

All authors submitting any type of communication to be considered for publication in the Journal are expected to disclose any type of commercial association that might pose a conflict of interest in connection with that communication. All sources of funding of the work should be declared and acknowledged in a footnote. If the corporate or institutional affiliation of an author might constitute a conflict of interest, this fact should be communicated with the Editor in writing when the manuscript is submitted.

**Scientific contribution**

The maximum number of authors is eight, except in the case of multicenter studies. If there are more than three authors, each author will be required to state the type of scientific participation in the work. This can be (a) conception or design of protocol, collection, assessment or interpretation of data, (b) drafting the manuscript or revising its contents and (c) approval of the final version to be sent for publication.

**Language**

The language of the Journal is the American version of medical/technical English.

Checklist for manuscript preparation

GENERAL

- All manuscripts must be submitted electronically to: rwemery@healtheast.org, with a formal letter of submission. Hard copy submission is not necessary anymore.
- Type the manuscript double spaced throughout, including title page, abstract, text, references, tables, figure legends.
- Arrange the manuscript pages as follows: Cover letter, title page abstract, text, acknowledgements if applicable, references, tables, figure legends. Each figure should be attached as a separate JPEG or TIFF file with an original resolution of 300 dpi.
- Number all pages consecutively with arabic numbers, beginning with title page, ending with the (last) page of figure legends.

LENGTH

- The length of an original article should not exceed 4,500 words to include figure legends, tables and references. The combined total number of illustrations, tables and/or figures should not exceed eight and the number of references should not exceed 40.
- Case reports should not exceed 1500 words, two figures or tables and eight references.
- Authors of review articles should consult the editor.
- Brief communications that contain substantive information concerning new, innovative or evolving technologies of clinical and/or scientific data pertaining to heart valves or heart valve disease are encouraged. They should not exceed 1000 words, two tables or figures and no more than five references.
- Readers are encouraged to submit Letters to the Editor on articles published in the Journal. Submitted commentary letters will be provided to the original author and author replies will be published along with the commentary. If the original author does not respond, a notation indicating. "Response Declined" will be published. Letters to the Editor should not exceed 750 words, 1 table or figure and 5 references.

TITLE PAGE

- Keep the title as short as possible, not exceeding 12 words. Provide a short title not exceeding four words. This will be used as running title on the printed pages.

- Give three to five keywords for cross-indexing.
- Give first names, middle initial(s) and last names of all authors with the respective highest academic qualification. Give the full name and location of not more than four institutional affiliation(s).
- Give the name, full postal address, telephone and fax numbers, and e-mail address of the author to whom all correspondence, including page proofs and requests for reprints should be sent (corresponding author).
- If the paper has been or is to be presented at a meeting of a scientific organization, give the name, venue and date of that meeting at the bottom of the title page.

ABSTRACT

Keep the length between 250 - 300 words for original publication and review articles, 150 - 200 words for case reports and other short communications. Organize the abstract in four major parts:

- Background and aim of the study
- Materials and methods
- Results
- Conclusions

TEXT

- Use the American version of medical/technical English, including spelling. Do not use abbreviations or acronyms, except for measurements. For the latter, follow the recommendations in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals, 2nd Edition", published in Ann Intern Med 1982;96:766-71 and Br Med J 1982;284:1766-70.
- Mention every reference, figure (Fig.) and table (Table) in the text and number them consecutively as they first appear.

REFERENCES

- Mark all references with arabi numbers in brackets on the line. Personal communication, manuscript in preparation or sent for publication cannot be quoted as reference; they should be mentioned within parentheses in the text. Manuscript accepted for publication by a journal can be used as reference, stating the name of the journal and specifying "in press".
- The references should be numbered sequentially in the text and listed, on separate sheets, at the end of the text in that order. Reference format should conform to that known as the "Vancouver" style (http://www.library.uq.edu.au/training/citation/vancouv.pdf ) for biomedical journals. Journal abbreviations should conform to the style used in the Index Medicus. The page numbers should be inclusive, providing the first and last pages of the reference. Do not use full stop after the last page number. Each reference should include:

  - For journals: authors' names and initials, title of article, journal name, year of publication, volume number, and inclusive pages (list all authors when six or less, when seven or more, list only three and add et al.) e.g.:

  Josa M, Khuri SF, Braunwald NS, et al. Delayed sternal closure: an improved method of dealing with complications after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1986;90:593-598

  - For book chapters: authors' names, chapter title, editors' name, book title, edition, city, publisher, year of publication and pages, e.g.:

  Berger HJ, Zaret BL, Cohen LS. Cardiovascular nuclear medicine. In Goldberger E, ed. Textbook of Clinical Cardiology. 1st ed. St Louis: CV Mosby, 1982:326-345

  - For books: authors' names, book title, edition, city, publisher, year of publication, e.g.:

  Acar J, Bodnar E (eds). Textbook of Acquired Heart Valve Disease, Volume I and II, 1st edition, London, ICR Publishers, 1995

ILLUSTRATIONS

- All illustrations, graphics and figures should be in JPEG or TIFF format. The original resolution of the illustrations should be a minimum of 300 dpi. Bear in mind that the illustrations will be reproduced as single column width (8.25 cm, 3.25 inches) or double column width (17.15 cm, 6.75 inches). Intermediate width will be considered only exceptionally.
- The Journal cannot commit itself to reproduce unlimited color illustrations. If color is not absolutely necessary in the Editors' opinion, the authors will be asked to share the additional expenses by advancing a payment of $ 1,500.00 and $ 350.00 for the first and every subsequent color illustration on a page, respectively.
- Suitable legends should be typewritten, double spaced, listed on a separate page and included at the end of the manuscript.

TABLES

Tables should be self-explanatory and should supplement, not duplicate, the text. They should be typed on individual pages separate from the text. Provide a brief title for each. Abbreviations used in tables should be defined at the bottom of the table.

LETTER OF PERMISSION

Supply permission from both the publisher and the author to reproduce any previously published illustration or table. This letter of permission should be submitted at the time the final revised manuscript is submitted.

COPY EDITING

The Editors reserve all rights to make editorial revisions to aid clarity and understanding without altering the meaning.