

https://dspace.org/

Valvular atrial fibrillation outcomes associated with the cox-maze procedure at Charlotte Maxeke Johannesburg academic hospital from 2000 to 2015

Kukulela, Nangamso

2018-02-11
https://hdl.handle.net/10539/29136

Downloaded from a DSpace repository. https://dspace.org/

Valvular Atrial Fibrillation Outcomes Associated with the Cox-maze Procedure at Charlotte Maxeke Johannesburg Academic Hospital from 2000 to 2015

Dr Nangamso Kukulela: MB ChB (UCT)

A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Masters in Medicine.

Johannesburg, 2018

Table of Contents

List of Figures and Tables IV

DECLARATION: V

ACKNOWLEDGEMENTS VII

NOMENCLATURE VIII

ABSTRACT IX

KEYWORDS: X

INTRODUCTION 1

1. METHODS AND MATERIALS 2

1.1 Study design and population 2

1.2 Ethics and consent 4

1.3 Statistics and Data analysis 4

2. RESULTS 4

3. DISCUSSION 7

4. CONCLUSION AND RECOMMENDATIONS 10

5. ACKNOWLEDGEMENTS 10

6. FUNDING: 11

7. CONFLICT OF INTEREST: 11

8. REFERENCES 11

9. TABLES AND FIGURES 15

APPENDIX A – Visual Abstract 20

APPENDIX B – Data Collection Sheet 21

APPENDIX C – Turn-it-in Report 26

APPENDIX D – Protocol Approval 28

APPENDIX E – Ethics Approval 29

APPENDIX F – Supervisors' Approval 30

APPENDIX G – Hospital Approval..... 31

APPENDIX H – Proof of Submission for Publication 32

APPENDIX I – Research Proposal 34

List of Figures and Tables

Figure 1: Study flow chart 15

Table 1: Baseline demographic and clinical characteristics according to post-operative rhythm 16

Table 2: Baseline demographic and clinical characteristics according rhythm at follow up 17

Table 3: Univariable regression analysis for independent predictors of atrial fibrillation 18

Table 4 Multivariable regression analysis for independent predictors of atrial fibrillation 19

DECLARATION:

I, Nangamso Kukulela, declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine (MMed) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

[Signature of candidate]

_____ day of_____2018

RE: Dr Nangamso Kukulela

Student number: 0506711

MMed Internal Medicine

This letter serves to certify that Dr Nangamso Kukulela has done his research in Internal Medicine. His topic: Valvular atrial fibrillation outcomes associated with the maze procedure at Charlotte Maxeke Johannesburg Academic Hospital from 2000 to 2015.

He compiled and analysed the data himself with the assistance of a statistician and followed the protocol of his study accordingly.

He entirely wrote the research report with the input from co-authors.

Kind Regards

Dr Nqoba Tsabedze

Prof Pravin Manga

ACKNOWLEDGEMENTS

I would like to show gratitude and appreciation to Dr Vanderdonck (department of cardiothoracic surgery, University of the Witwatersrand) for her assistance with patient records.

I would also like to show my appreciation to all my colleagues in the following departments for their assistance:

- Department of Cardiology, Department of Cardiothoracic surgery, INR clinic and records at Charlotte Maxeke Johannesburg Academic Hospital
- Department of Cardiology, Chris Hani Baragwanath Hospital
- Department of Cardiology, Helen Joseph Hospital

NOMENCLATURE

AF: Atrial Fibrillation

NYHA: New York Heart Association

EuroSCORE II: European System for Cardiac Operative Risk Evaluation

CHA2DS2-VASc: Congestive heart failure; Hypertension; Age >75; Diabetes Mellitus: Prior Stroke or Thromboembolism; Vascular disease; Age 65-75; Sex category (i.e. Female)

HASBLED: Hypertension; Abnormal renal function and abnormal liver function; Stroke; Bleeding; Labile INR; Elderly; Medication

ESC: European Society of Cardiology

ECG: Electrocardiogram

ECHO: Echocardiogram

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

ABSTRACT

Objectives: Outcomes data on the efficacy of the Cox-maze procedure for the treatment of valvular atrial fibrillation mostly originates from developed countries, with a paucity of data from the developing world. The primary objective of this study was to determine the outcomes of the Cox-maze procedure for valvular atrial fibrillation (AF) in a public tertiary academic centre in Johannesburg, South Africa.

Methods: We retrospectively reviewed inpatient and outpatient records of adult patients who underwent the Cox-maze procedure for valvular atrial fibrillation from January 2000 to December 2015. The study data collected included the primary indications for cardiac surgery, perioperative complications and follow-up outcomes data on the successful treatment of AF and restoration of sinus rhythm.

Results: We reviewed 144 patient records of which 98 (68.1%) were females. The mean age was 45.0 (SD: 12.4) years. Before surgery, 141 participants had a documented NYHA functional class. Of these, 117 (83.0%) participants were in NYHA class III with a mean ejection fraction of 55% (SD: 12.5). Rheumatic mitral stenosis was the primary indication for surgery in 73 (50.7%) participants. Immediately after surgery, sinus rhythm was restored in 106 (74%) patients. After a mean duration of 5.6 years (SD: 3.3), 104 patients had a documented rhythm. Of these, 81 (76.4%) remained in sinus rhythm. On multivariable analysis, none of the study variables could predict persistent atrial fibrillation

Conclusions: Our findings suggest that the Cox-maze procedure is effective in the management of valvular atrial fibrillation in symptomatic patients undergoing open heart surgery.

KEYWORDS:

- Atrial fibrillation
- Cox-maze procedure
- Open heart surgery
- Rheumatic valvular heart disease

INTRODUCTION

Since its description by Dr James Cox in 1987, and its subsequent modifications throughout the years, the Cox-maze procedure is said to be the gold standard for the surgical management of atrial fibrillation (AF). The Cox-maze procedure has been shown to increase the incidence of postoperative sinus rhythm, improved long-term sinus node function, fewer pacemaker requirements, less arrhythmia recurrence and improved long-term atrial contraction in patients with AF undergoing mitral valve repair or replacement (2, 3). Existing data also suggests that the procedure significantly reduces the incidence of late cerebrovascular accidents (CVA) and improves mortality rates associated with AF (3).

This study aims to analyse the long-term outcomes of the procedure in treating valvular AF in a tertiary academic centre in Johannesburg. This retrospective audit aims to determine the duration and the proportion of patients that remain free of AF post the Cox-maze procedure. The Cox-maze procedure is generally reserved for patients with a concomitant class-I indication for open heart surgery. Under these circumstances, the benefit of the procedure outweighs the risks associated with open heart surgery. The Cox-maze procedure is therefore performed during the same surgical sitting for patients with AF and another symptomatic cardiac condition requiring open heart surgery, mainly mitral valvular conditions (3).

1. METHODS AND MATERIALS

1.1 Study design and population

This was a retrospective review of records of patients who underwent the Cox-maze procedure concomitantly with a class-I indication for open heart surgery at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), between the years 2000 and 2015. The study included all adult patients above the age of 18. The principal investigator collected data from patient's records located in the department of cardiothoracic surgery at CMJAH and from the referring hospitals which included Helen Joseph Hospital (HJH) and Chris Hani Baragwanath Academic Hospital (CHBAH). These referring centres are all part of the academic teaching-hospital complex of the University of Witwatersrand, Johannesburg, South Africa.

1.1.1 Preoperative data

Data was collected from all three hospitals. The department of cardiothoracic surgery at CMJAH receives patients for definitive surgical management from these centres. Preoperative medical records consisting of patient’s demographic information, indications for surgery, co-morbid illnesses, pre-operative New York Heart Association (NYHA) classification, concomitant medication, echocardiogram findings, Euro II score, HASBLED score and blood biochemistry results including the international normalised ratio (INR), were all reviewed from the surgical referral notes in the respective cardiology units. All the patients in the study had either persistent and or long-standing AF. According to the 2016 European Society of Cardiology

(ESC) guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardiothoracic Surgery (EACTS), persistent AF is defined as AF that lasts for more than 7 days, including episodes that are terminated by cardioversion either with drugs or by direct current cardioversion after 7 days or more. Long-standing AF is continuous AF lasting for more than one year once it has been decided that a rate control strategy will be adopted (4).

1.1.2 Intra-operative data

Intra-operative data was obtained from the department of cardiothoracic surgery operative reports and discharge summaries. The intra-operative data included the type and location (left or right atrium) of Cox-maze procedure, cardiopulmonary bypass (CPB) time, aortic clamp time, duration of the procedure and the procedural outcomes. The rhythm, immediately post-surgery, was recorded as well as the duration of hospital stay.

1.1.3 Postoperative and follow up data

Post surgery, the cardiothoracic unit routinely refers patients back to their respective cardiology units for further follow-up. Thus, the post-operative follow-up data was collected at the respective referring cardiology units. Patient's post-surgical and follow-up data were also collected from the Prothrombin Index (PI) clinics which monitor INR levels for patients receiving warfarin. The post-operative and follow up data included the heart rhythm, concomitant medication, INR control, New York Heart Association classification (NYHA), and echocardiogram findings.

1.2 Ethics and consent

Ethics for the study was sought from the University of Witwatersrand Human Research Ethics Committee and the relevant hospital authorities. The study observed all protocols and principles outlined in the declaration of Helsinki 2017 (5).

1.3 Statistics and Data analysis

All statistical analyses were generated using STATA version 13.1 (StataCorp, Texas). Continuous variables were expressed as the mean and standard deviation (SD) when normally distributed and as a median and interquartile ranges when the distribution is skewed. Odds ratio (OR) are presented with their 95% confidence interval (CI). A p-value of less than 0.05 was considered statistically significant. A multivariable regression analysis was also performed. The following parameters were included in the multivariable regression analysis: participant's age, hypertension, diabetes mellitus, LA size, left ventricular internal diameter at diastole, left ventricular ejection fraction, duration of AF and associated mitral valve disease. These variables were selected according to known risk factors for AF. The REDCap (Research Electronic Data Capture) electronic data capture tool hosted at the University of Witwatersrand, Johannesburg, was used as the data collection and management tool.

2. RESULTS

The study successfully identified 144 adults who had open heart surgery and a concomitant Cox-maze procedure (Figure 1). The study population consisted of 98

(68.1%) female patients who had a mean age of 45 (SD: 12) years. There were 110 (76.4%) black patients and only 22 (15.3%) were white patients. The postoperative demographic and clinical parameters are summarised in Table 1. The Cox-maze procedure was performed in the left atrium in 119 (82.6%), right atrium in 2 (1.4%) and both atria in 21 (14.6%) participants. The site was not specified in two (1.4%) participants. Hundred and thirty six (94.4%) patients had successful surgical interventions with no documented complications. The mortality and complications data were missing in 7 (4.9%) patients. Only one patient demised post surgery. . The median duration of hospital stay was 17 (13-24) days.

Rheumatic mitral stenosis was the primary indication for surgery in 73 (50.7%) patients of the study population. In our study cohort only 105 participants had a documented ejection fraction. The mean ejection fraction was 55% (SD: 12.0) with 66 (62.9%) participants having preserved ejection fraction (EF > 50%) and 12 (11.4%) participants having reduced ejection fraction (EF< 40%). The left atrial size was documented in 96 participants in our cohort population. The mean left atrial size was 6cm (SD: 1), with 64 (66.7%) participants having a severely enlarged LA. The NYHA functional class was documented in 141 participants. Prior to surgery 7 (5.0%) were in NYHA functional class IV, 117 (83.0%) patients were in NYHA functional class III,, 15 (10.6%) were in NYHA functional class II and only 2 (1.4%) were in functional class I. After a mean duration of follow-up for 5.6 (SD: 3.3) years, NYHA functional class was documented in 76 participants. Of these, 55 (72.4%) of patients were in NYHA functional class I and 21 (27.6%) in NYHA functional class II. The CHA_2DS_2VASc score, which predicts the thrombotic risk for stroke in AF was documented in 141 participants and reported as low risk in 103 (73.0%) and

intermediate risk in 38 (27.0%) participants. A hundred and fourty three participants were assessed for the risk of bleeding using the HASBLED score. One hundred and eighteen were found to be at low risk and only 24 reported to have an intermediate risk.

Pre-operatively, all patients were in persistent or long-standing AF. The rhythm analysis immediately after surgery revealed that 106 (73.6%) of patients were in sinus rhythm with only 24 (16.7%) remaining in atrial fibrillation (Table 1). One patient had atrial flutter and 9 (6.25%) patients had an atrioventricular block. The rhythm after surgery was not specified in four patients. Only 130 participants, those in sinus rhythm (n=106) and those in AF (n=24), of the study population were used for post operative rhythm analysis as demonstrated in table 1 and figure 1. The patient's rhythm at follow-up visits was indicated in 104 participants. Of these, 81 (76.4%) of patients were in sinus rhythm and 23 (21.2%) in AF. Two patients had no documented record of the rhythm at follow-up (Table 2 and figure 1). Analysis of the biochemistry results indicated that most patients had optimal haemoglobin and therapeutic INR levels before the surgical operation. In this study, there were no patients with a labile INR, where a labile INR was defined as less than 60% of time spent in the INR therapeutic range.

Univariable and multivariable analyses (Tables 3 and 4) were performed to identify independent predictors of persistent atrial fibrillation. Procedural factors that are generally associated with AF were analysed. These included the participant's age, hypertension, diabetes mellitus, LA size, left ventricular internal diameter at diastole,

left ventricular ejection fraction, duration of AF and associated mitral valve disease (4). In this model, none of the variables predicted persistence of atrial fibrillation.

3. DISCUSSION

This retrospective audit found that the Coz-Maze procedure is a viable option for the surgical management of persistent or long-standing AF in patients who also require concomitant, open-heart valve surgery. Our study results also indicate that the majority of patients in our setting that undergo cardiac surgery are young with a mean age of 45 (SD: 12.0) years. This is a direct consequence of the disease burden of rheumatic heart disease (RHD), which is endemic in young adults living in our geographic region (6). The prevalence of rheumatic valvular disease remains high in developing countries with associated morbidity and mortality complications (6, 7). The majority of patients in our cohort had mitral valve pathology secondary to rheumatic valve disease with concomitant AF. This is consistent with findings from the developed world demonstrating that over 50% of maze surgery occurs in the setting of mitral valve surgery (8).

Rheumatic heart disease is a major burden in developing countries where it causes significant cardiovascular mortality and morbidity in young people. It has been estimated to cause approximately 250 000 deaths per annum worldwide (9). It has also been reported that mortality is high in RHD related heart failure, although post-surgical morbidity and mortality were reported to be low (9). These findings are also reflected in our study, which found a high prevalence of patients with mitral valve

pathology secondary to RHD undergoing surgery and who had improved functional status post-operation.

Freedom from arrhythmias and thrombotic complications of AF also greatly improve the quality of life in this age group (10). Atrial fibrillation poses major medical and socioeconomic consequences and is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5 fold increased risk in men (11). The health-related costs of AF continue to increase yearly unless the AF is prevented and treated effectively (11). AF is the most common cardiac arrhythmia with a prevalence of 5 - 6% in patients older than 65 years, increasing up to 10% in those over 80 years (12).

In South Africa, the prevalence of AF in the urban black population is reported to be 7%. This data was derived from a cardiovascular disease cohort with heart failure affecting 8%, hypertension affecting 4%, and valvular heart disease affecting 13 % of the study participants respectively (13).

There is an increased utilisation of electrophysiological (EP) techniques in the management of valvular AF in developed nations. However, this modality is still scarce in the developing world. A study by Miyalazi et al. evaluated the efficacy of AF ablation in patients with moderate valvular heart disease (VHD). AF ablation outcomes for patients with moderate VHD (n=45) were compared to a control group without VHD (n=436). The study concluded that patients with VHD undergoing AF ablation were less likely to remain in sinus rhythm at long-term without antiarrhythmic drugs than those without VHD (14). These findings suggest that the Cox-maze

procedure may be a valuable surgical management option of AF for patients with concomitant valvular heart disease.

A significant number of patients undergoing cardiac surgery with AF have mitral valve pathology (8). For patients with AF and a concomitant class-I indication for cardiac surgery, the decision to offer the Cox-maze procedure is influenced by the patients underlying co-morbid illness (8). Furthermore, it has been suggested that the short, medium and long-term efficacy of the Cox-maze procedure in restoring sinus rhythm is generally the same regardless of the underlying valvular lesion (15). A Cochrane database systematic review by Huffman et al., showed that a concomitant Cox-maze procedure for patients undergoing open-heart surgery doubles the likelihood of freedom from AF, atrial flutter or atrial tachycardia and being free of anti-arrhythmic drugs, although it may increase the risk of permanent pacemaker implantation. (16).

A fifteen year retrospective study of 438 participants, by Musharbarsh et al., showed that for patients with a history of AF undergoing cardiac surgery, a concomitant Cox-maze procedure did not significantly add to the post-operative morbidity and mortality (17). The study showed that the Cox-maze procedure was associated with an improved late survival compared to patients with untreated AF and similar survival to patients without AF (17). These findings were also demonstrated in our cohort with 98.6% surviving surgery with a mortality rate less than 1%. Many reports also indicate that the Cox-maze procedure is not associated with an increase in morbidity and mortality in patients undergoing open heart surgery (15). Similar findings were also reported in a study by Han et al (20). This study showed that the Cox-maze procedure is safe and effective for patients with AF associated with rheumatic mitral

valve disease (18). A recent study from New Zealand also found that the Cox-maze procedure was a safe and effective surgical management option for patients with AF and was associated with low rates of mortality and stroke long term, than what would have been expected with anti-coagulation strategies alone (19).

The study limitations include its retrospective nature. Post-operative echocardiography was not routinely done on all patients. This limited our ability to perform pre and post-operative echocardiogram comparisons. The prevalence of paroxysmal AF post Cox-maze surgery was also not evaluated as routine Holter ECG monitoring was not performed. Despite these limitations, our data reflects real-world Cox-maze procedural outcomes in a developing country.

4. CONCLUSION AND RECOMMENDATIONS

The Cox-maze procedure remains a safe and a viable option for the surgical management of concomitant symptomatic AF. This procedure should be considered in all patients with symptomatic structural heart disease undergoing open heart surgery.

5. ACKNOWLEDGEMENTS

We would like to acknowledge Dr Vanderdonck (department of cardiothoracic surgery, University of the Witwatersrand) for her assistance with patient records and colleagues at the Department of Cardiology at Helen Joseph Hospital, Chris Hani Baragwanath Hospital and Charlotte Maxeke Johannesburg Academic Hospital. We

are grateful for the support from staff members at the Department of Cardiothoracic surgery and the INR clinic at Charlotte Maxeke Johannesburg Academic Hospital.

6. FUNDING:

None

7. CONFLICT OF INTEREST:

None declared

8. REFERENCES

1. Lall SC, Melby SJ, Voeller RK, Zierer A, Bailey MS, Guthrie TJ, et al. The effect of ablation technology on surgical outcomes after the Cox-maze procedure: A propensity analysis. The Journal of thoracic and cardiovascular surgery. 2007;133(2):389-96.
2. Philpott JM, Zemlin CW, Cox JL, Stirling M, Mack M, Hooker RL, et al. The ABLATE Trial: Safety and Efficacy of Cox Maze-IV Using a Bipolar Radiofrequency Ablation System. The Annals of thoracic surgery. 2015;100(5):1541-6.
3. Cox JL. The first Maze procedure. The Journal of thoracic and cardiovascular surgery. 2011;141(5):1093-7.
4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European heart journal. 2016;37(38):2893-962.
5. Helsinki. WMA declaration of Helsinki - Ethical principles for medical research involving human subjets. https://wwwwmanet/policies-post/wma-declaration-of-

helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (date accessed: 22/03/2018).

6. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. The New England journal of medicine. 2017;377(8):713-22.
7. Wang B, Xu ZY, Han L, Zhang GX, Lu FL, Song ZG. Impact of preoperative atrial fibrillation on mortality and cardiovascular outcomes of mechanical mitral valve replacement for rheumatic mitral valve disease. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2013;43(3):513-9.
8. Saint LL, Damiano RJ, Jr., Cuculich PS, Guthrie TJ, Moon MR, Munfakh NA, et al. Incremental risk of the Cox-maze IV procedure for patients with atrial fibrillation undergoing mitral valve surgery. The Journal of thoracic and cardiovascular surgery. 2013;146(5):1072-7.
9. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet. 2012;379(9819):953-64.
10. Ad N, Henry L, Holmes SD, Stone LE, Hunt S. The association between early atrial arrhythmia and long-term return to sinus rhythm for patients following the Cox maze procedure for atrial fibrillation. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2013;44(2):295-300; discussion -1.
11. Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, et al. Causes of death and influencing factors in patients with atrial fibrillation: a

competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation. 2013;128(20):2192-201.

12. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.
13. Jardine RM, Fine J, Obel IW. A survey on the treatment of atrial fibrillation in South Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2014;104(9):623-7.
14. Miyazaki S, Kuwahara T, Kobori A, Takahashi Y, Takei A, Sato A, et al. Catheter ablation of atrial fibrillation in patients with valvular heart disease: long-term follow-up results. J Cardiovasc Electrophysiol. 2010;21(11):1193-8.
15. Labin JE, Haque N, Sinn LA, Schuessler RB, Moon MR, Maniar HS, et al. The Cox-Maze IV procedure for atrial fibrillation is equally efficacious in patients with rheumatic and degenerative mitral valve disease. The Journal of thoracic and cardiovascular surgery. 2017.
16. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM, et al. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. The Cochrane database of systematic reviews. 2016(8):Cd011814.
17. Musharbash FN, Schill MR, Sinn LA, Schuessler RB, Maniar HS, Moon MR, et al. Performance of the Cox-maze IV procedure is associated with improved long-term survival in patients with atrial fibrillation undergoing cardiac surgery. The Journal of thoracic and cardiovascular surgery. 2017.
18. Han JS, Wang HS, Wang ZW, Yin ZT, Han HG, Tang CY. [Safety and efficacy of Cox-maze procedure for patients with atrial fibrillation associated with rheumatic mitral valve disease]. Zhonghua yi xue za zhi. 2016;96(13):1011-5.

19. Borrie AJ, Wademan BH. Outcomes of surgical ablation for atrial fibrillation: a 10-year experience. The New Zealand medical journal. 2016;129(1433):17-24.

9. TABLES AND FIGURES

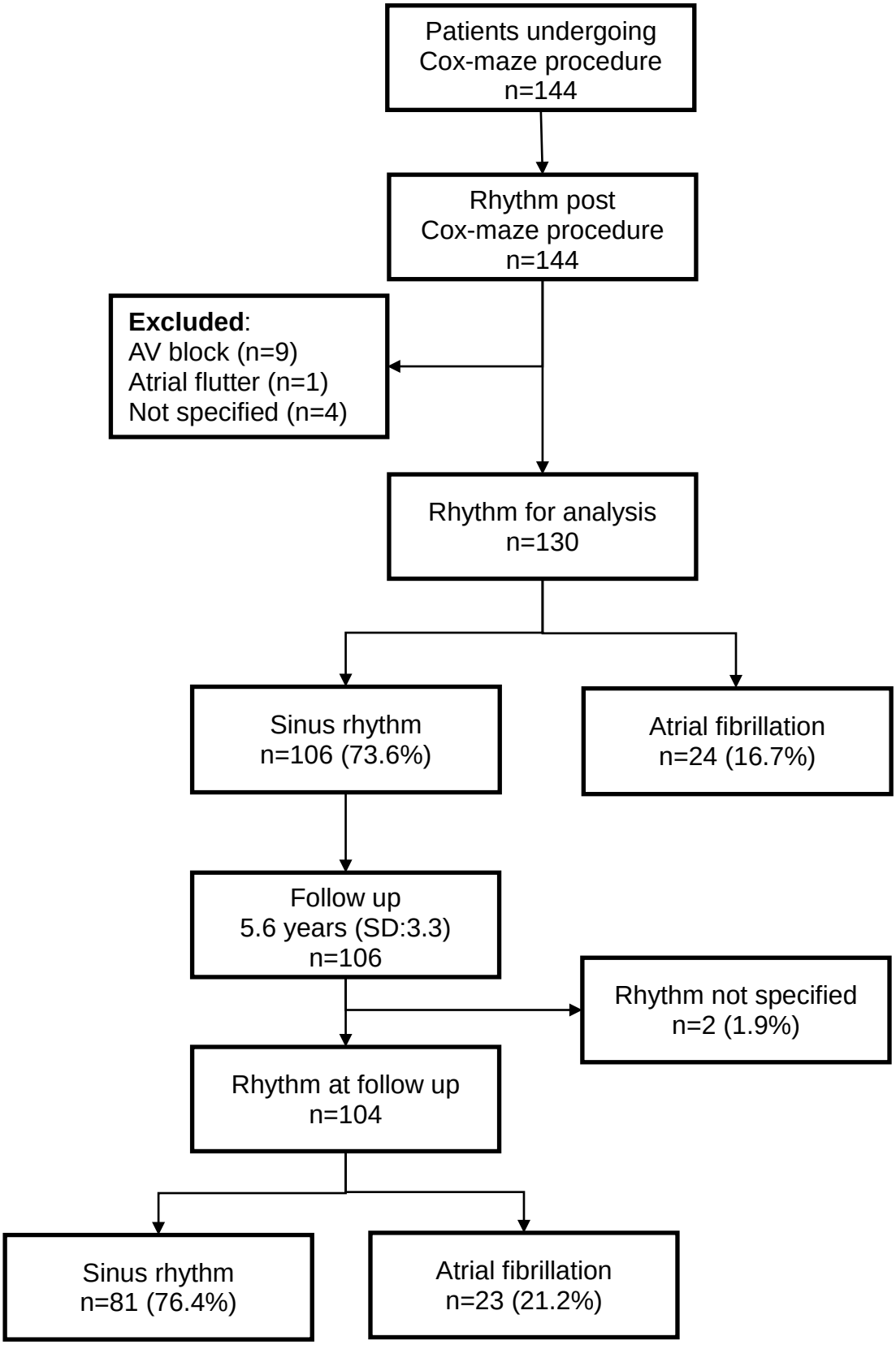


Figure 1: Study flow chart

Table 1: Baseline demographic and clinical characteristics according to post-operative rhythm

Variable	Overall Population (n=130)	Sinus Rhythm (n=106)	Atrial fibrillation (n=24)	p-value
Age (years)	44.7 (SD: 13.0)	44.5 (SD:13.0)	45.7 (SD: 12.6)	0.351
Female	87 (66.9)	72 (67.9)	15 (62.5)	0.610
Ethnicity				0.442
African	98 (75.4)	81 (76.4)	17 (71.0)	
Indian	3 (2.3)	3 (2.8)	0 (0.0)	
Coloured	8 (6.2)	5 (4.7)	3 (12.5)	
White	21 (16.1)	17 (16.0)	4 (16.7)	
Comorbidities				
Hypertension	20 (15.4)	16 (15.1)	4 (16.7)	0.847
Diabetes Mellitus	5 (3.9)	5 (4.7)	0 (0.0)	0.278
Dyslipidaemia	3 (2.3)	3 (2.8)	0 (0.0)	0.404
HIV	7 (5.4)	6 (5.7)	1 (4.2)	0.770
Medication				
Beta Blocker	101 (77.7)	81 (76.4)	20 (83.3)	0.462
Aspirin	27 (20.8)	22 (20.75)	5 (20.8)	0.993
Statins	23 (17.7)	17 (16.0)	6 (25.0)	0.299
CCB	9 (6.9)	7 (6.6)	2 (8.3)	0.763
Digoxin	22 (16.9)	18 (17.0)	4 (16.7)	0.970
NYHA:				0.073
I	1 (0.8)	0 (0.0)	1 (1.0)	
II	14 (11.0)	10 (9.6)	4 (17.4)	
III	106 (83.5)	88 (84.6)	18 (78.3)	
IV	6 (4.7)	6 (5.8)	0 (0.0)	
Echo parameters				
LVEF (%) (n=105)	55.9 (SD:12.5)	56.5 (SD: 12.8)	53.4 (SD: 11.0)	0.175
LVIDd (cm) (n=81)	1.2 (SD:1.1)	1.2 (SD:1.2)	1.2 (SD:1.1)	0.945
LA size (cm) (n=96)	5.9 (5.3-6.9)	6.1 (SD: 1.3)	6.3 (SD: 1.1)	0.280
Biochemistry				
CRP	16.6 (10.0-24.5)	25.0 (SD: 25.8)	14.6 (SD: 7.2)	0.001
Hb (g/dL)	13.5 (12.4-14.2)	1 5.6 (SD: 16.0)	13.0 (SD: 1.6)	0.055
Creatinine (umol/L)	76.4 (SD: 18.9)	76.8 (SD: 19.3)	74.6 (SD: 17.2)	0.310
Procedural Factors				
CPB time (minutes)	131.9 (SD: 39.9)	130.9 (SD: 37.3)	135.5 (49.2)	0.331
AC time (minutes)	89.4 (SD: 31.4)	87.1 (SD: 30.3)	99.6 (SD: 34.6)	0.063
Hospital stay (days)	20.5 (SD: 11.9)	20.8 (SD: 12.3)	18.6 (SD: 9.3)	0.186
HASBLED score (n=143)				0.880
Low risk	108 (83.7)	88 (83.8)	20 (83.3)	
Intermediate risk	20 (15.5)	16 (15.2)	4 (16.7)	
High risk	1 (0.8)	1 (0.9)	0 (0.0)	
CHA2DS2VASc (n=141)				0.039
Low risk	95 (74.8)	81 (78.6)	14 (58.3)	
Intermediate risk	32 (25.2)	22 (21.4)	10 (41.7)	
EuroSCORE II (n=144)				0.453
Low risk	3 (2.3)	3 (2.8)	0 (0.0)	
Moderate risk	85 (65.4)	67 (63.2)	18 (75.0)	
High risk	42 (32.3)	36 (34.0)	6 (25.0)	

Data shown as mean, standard deviation (SD) for continuous variable and as absolute number (percentage) for dichotomous variables. AC: Aortic clamp time; CCB: calcium channel blocker; CPB: cardiopulmonary bypass time; CRP: c-reactive protein; Hb: haemoglobin; HIV: Human Immunodeficiency Virus; LA: left atrium; LVEF: left ventricular ejection fraction; LVIDd: left ventricular internal diameter end diastole; NYHA: New York Heart Association

Table 2: Baseline demographic and clinical characteristics according rhythm at follow up

Variable	Overall Population (n=104)	Sinus Rhythm (n=81)	Atrial fibrillation (n=23)	p-value
Age years	45.0 (SD: 12.9)	45.2 (SD: 13.0)	43.8 (SD: 13.0)	0.35
Female	71 (68.3)	54 (66.7)	17 (74.0)	0.51
Ethnicity:				0.21
African	79 (76.0)	61 (75.3)	18 (78.2)	
Indian	3 (2.9)	1 (1.2)	2 (8.7)	
Coloured	5 (4.8)	4 (5.0)	1 (4.3)	
White	17 (16.3)	15 (18.5)	2 (8.7)	
Comorbidities:				
Hypertension	16 (15.4)	14 (17.3)	2 (8.7)	0.31
Diabetes Mellitus	5 (4.8)	3 (3.7)	2 (8.7)	0.32
Dyslipidaemia	3 (2.9)	3 (3.7)	0 (0.0)	0.35
HIV	6 (5.8)	4 (5.0)	2 (8.7)	0.50
NYHA (n=76):				0.83
I	34 (77.3)	25 (78.1)	1 (1.0)	
II	10 (22.7)	7 (21.9)	3 (25.0)	

Data shown as mean, standard deviation (SD) for continuous variable and as absolute number (percentage) for dichotomous variables. HIV: Human Immunodeficiency Virus; NYHA: New York Heart Association

Table 3: Univariable regression analysis for independent predictors of atrial fibrillation

Variable	OR	CI	p-value
Hypertension	0.87	0.24-3.20	0.84
Diabetes mellitus	2.48	0.39-15.79	0.34
Age (26-35 years)	0.40	0.06-2.57	0.33
LA size (4.7 - 5.2 cm)	0.87	0.24-3.20	0.84
LVEF (40-50%)	2.85	0.28-29.0	0.37
LVEF (>50%)	2.20	0.25-19.53	0.48
EuroSCORE II (2-5%)	0.48	0.19-1.25	0.14
CHADVASc Score (moderate)	0.47	0.12-1.74	0.26

CI: Confidence interval; EuroSCORE II: European system for cardiac operative risk evaluation II; LA: left atrial size; LVEF: left ventricular ejection fraction; OR: odds ratio

Table 4 Multivariable regression analysis for independent predictors of atrial fibrillation

Variable	OR	CI	p-value
Hypertension	0.10	0.00-2.51	0.16
Age (26-35 years)	0.76	0.02-27.1	0.88
LVEF (40-50%)	0.90	0.02-34.7	0.96
LVEF (>50%)	0.63	0.02-24.4	0.81

CI: Confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio

APPENDIX A – Visual Abstract

VISUAL ABSTRACT

Key question

What is the efficacy of Cox maze procedure in management of valvular atrial fibrillation?

Key findings

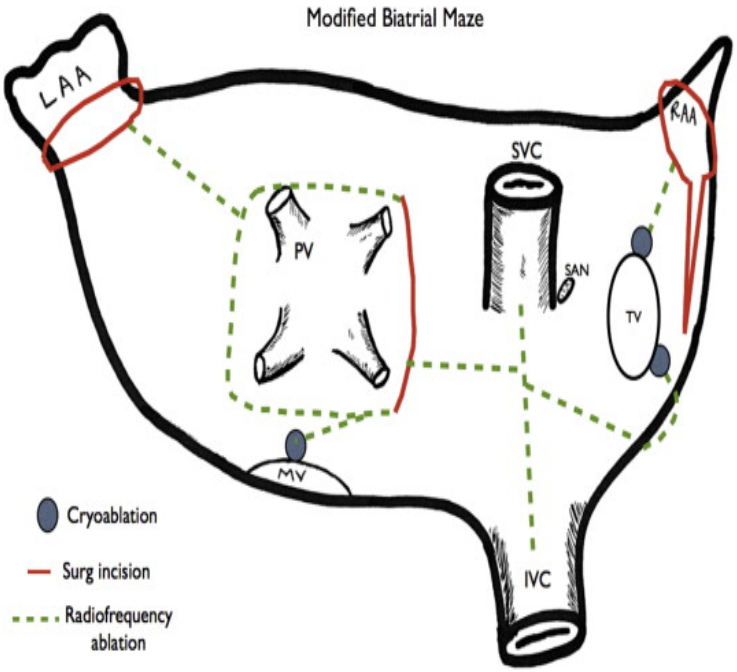
Immediately post
Cox-maze procedure
n=144
e procedure
n=144

- % of patients
- After a mean duration of 5.6 years (SD:

Take home message

Cox maze procedure is valuable in the management of symptomatic valvular atrial fibrillation.

CENTRAL IMAGE (1)



APPENDIX B – Data Collection Sheet

Data Collection Sheet

VALVULAR ATRIAL FIBRILLATION OUTCOMES ASSOCIATED WITH THE MAZE PROCEDURE AT CHARLOTTE MAXEKE JOHANESSBURG ACADEMIC HOSPITAL FROM 2000 TO 2015

1. *Patient Data*

Patient Information Study Form Number: | | | | | | |

Name:
Surname:
GT NO:

Date of data collections:
Demographic data:
Date of Surgery:
Age at Surgery:
Gender: Male [1] Female [2] | | |

Documented Ethnic group: | | |
African [1]; Indian [2]; Coloured [3]; White [4]; Unknown [5]

2. *PeriOperative Data*

Indications for Surgery: | | | |

Rheumatic Heart disease with MR [1]; Rheumatic heart disease with MS [2]; SBE with MR [3]; Papillary Muscle Rupture [4];

Trauma [5]; Myxomatous MVP [6]; Dilated CMO with functional MR [7]; ASD [8]; VSD [9] Tetrallogy of Fallot [10]; Ebstein,s anomaly [11]; Other [12]

Patient Risk Factors:

Co-morbidities | | | |
Hypertension [1]; Diabetes [2]; Thyroid [3]; Dyslipidaemia [4], CKD [5]; HIV [6]; Family History of Valvular heart condition [7], smoking [8]; Other (specify) [9]; none [10].

Clinical Presentation:
NYHA prior the procedure:
Euro SCORE:
CHAD2VASc score:

Rhythm prior the procedure:

Sinus [1]; AF [2]; Atrial Flutter [3]; AV block [4]; other [5]

Rhythm post procedure:

Sinus [1]; AF [2]; Atrial Flutter [3]; AV block [4]; other [5]

Echo findings:
LViDd
LViDs
LA
EF
MR mild [1]; Moderate [2]; severe [3]

TR mild [1]; Moderate [2]; severe [3]

AR mild [1]; moderate [2]; severe [3]

AS mild [1]; moderate [2]; severe [3]

Regional Wall motion: Normal [1]; Abnormal [2], Anterior [3]; Septal [4]; Inferior [5]; Lateral [6]
TAPSE
PAP
Diastolic Function: E/A ..... E/E' .....

PeriOperative Blood Results:
ProBNP:
Trop T:
CK-MB:
CRP:
Haemoglobin:
RVD: YES [1] No [2]
CD4:
Viral laod:
Creatinine:
INR:

Labile [1] YES [2] No [3]

Concomitant Medication:

Beta-blockers [1]; Loop Diuretics [2]; ACE-I [3]; Amiodarone [4]; Warfarin [5]; ASA [6]; Statins [7]; Ca Channel Blocker [8]; Metformin [9]; Insulin [10]; Thiazide Diuretics [11]; ACE-I [12]; ARB [13]; other [14]

Procedural Factors:
Maze Procedure:
RA [1]; LA [2]; Both [3]; Unknown [4]

Durations:
CPB time:
Aortic clamp time:

Perioperative Outcomes:
Survival [1]; Mortality [2]; unknown [3]

Durations of hospital stay (days):
[from date of surgery to date of discharge]

Follow up visits:

Visit 1

Date of follow up:
NYHA:
BP:
INR:
Rhythm at follow up:

Sinus [1]; AF [2]; Flutter [3]; AV block [4]; other [5]

Medication:
Beta-blockers [1]; Loop Diuretics [2]; ACE-I [3]; Amiodarone [4]; Warfarin [5]; ASA [6]; Statins [7]; Ca Channel Blocker [8]; Metformin [9]; Insulin [10]; Thiazide Diuretics [11]; ACE-I [12]; ARB [13]; other [14]

Visit 2:

Date of follow up:
NYHA:
BP:
INR:
Rhythm at follow up:
Sinus [1]; AF [2]; Flutter [3]; AV block [4]; other [5]

Medication:
Beta-blockers [1]; Loop Diuretics [2]; ACE-I [3];
Amiodarone [4]; Warfarin [5]; ASA [6]; Statins [7]; Ca Channel Blocker [8];
Metformin [9]; Insulin [10]; Thiazide Diuretics [11]; ACE-I [12]; ARB [13]; other [14]

Visit 3:

Date of follow up:
NYHA:
BP:
INR:
Rhythm at follow up:
Sinus [1]; AF [2]; Flutter [3]; AV block [4]; other [5]

Medication:
Beta-blockers [1]; Loop Diuretics [2]; ACE-I [3];
Amiodarone [4]; Warfarin [5]; ASA [6]; Statins [7]; Ca Channel Blocker [8];
Metformin [9]; Insulin [10]; Thiazide Diuretics [11]; ACE-I [12]; ARB [13]; other [14]

Visit 4:

Date of follow up:
NYHA:
BP:
INR:
Rhythm at follow up:

Sinus [1]; AF [2]; Flutter [3]; AV block [4]; other [5]

Medication:
Beta-blockers [1]; Loop Diuretics [2]; ACE-I [3];
Amiodarone [4]; Warfarin [5]; ASA [6]; Statins [7]; Ca Channel Blocker [8];
Metformin [9]; Insulin [10]; Thiazide Diuretics [11]; ACE-I [12]; ARB [13]; other [14]

Visit 5:
Date of follow up:
NYHA:
BP:
INR:
Rhythm at follow up:
Sinus [1]; AF [2]; Flutter [3]; AV block [4]; other [5]

Medication:
Beta-blockers [1]; Loop Diuretics [2]; ACE-I [3];
Amiodarone [4]; Warfarin [5]; ASA [6]; Statins [7]; Ca Channel Blocker [8];
Metformin [9]; Insulin [10]; Thiazide Diuretics [11]; ACE-I [12]; ARB [13]; other [14]

Visit 6:
Date of follow up:
NYHA:
BP:
INR:
Rhythm at follow up:
Sinus [1]; AF [2]; Flutter [3]; AV block [4]; other [5]

Medication:
Beta-blockers [1]; Loop Diuretics [2]; ACE-I [3];
Amiodarone [4]; Warfarin [5]; ASA [6]; Statins [7]; Ca Channel Blocker [8];
Metformin [9]; Insulin [10]; Thiazide Diuretics [11]; ACE-I [12]; ARB [13]; other [14]

APPENDIX C – Turn-it-in Report

turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Nangamso Kukulela
Assignment title:	RESEARCH REPORT
Submission title:	0506711n:Valvular_Atrial_Fibrillatio…
File name:	lvular_Atrial_Fibrillation_Outcomes…
File size:	131.26K
Page count:	26
Word count:	4,231
Character count:	25,105
Submission date:	21-Aug-2018 12:37PM (UTC+0200)
Submission ID:	991796195



Valvular Atrial Fibrillation Outcomes Associated with the Cox-maze Procedure at Charlotte Maxeke Johannesburg Academic Hospital from 2000 to 2015

Dr Nangamso Kukulela: MB ChB (UCT)
Dr Nqoba Tsabedze: MB BCh (Wits), FCP (SA), Cert. Cardiology (SA), MMed (Wits), PhD (Candidate)
Prof Pravin Manga: MB BCh (Wits), FCP (SA), PhD (Wits), FRCP
Miss Brenda Kagodora: MSc

Copyright 2018 Turnitin. All rights reserved.

0506711n:Valvular_Atrial_Fibrillation_Outcomes_Associated_..

ORIGINALITY REPORT

12%	11%	10%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Nqoba Tsabedze, Keir McCutcheon, Lancelot Mkhwanazi, Riaz Garda et al. "Periprocedural myocardial infarction during percutaneous coronary intervention in an academic tertiary centre in Johannesburg", International Journal of Cardiology, 2017 Publication	3%
2	"Abstracts : Abstracts", European Journal of Heart Failure, 2015. Publication	2%
3	academic.oup.com Internet Source	1%
4	journalfilter.com Internet Source	1%
5	aorticconference.org Internet Source	1%
6	Robert Čihák, Luděk Haman, Miloš Táborský. "2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS", Cor et Vasa, 2016	1%

APPENDIX D – Protocol Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

07 January 2017
Person No: 0506711N
PAG

Dr N Kukulela
10 Kanahura
Van Dalan Street
Willow Brook
Ruimsig
1724
South Africa

Dear Dr Kukulela

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Valvular atrial fibrillation outcomes associated with the maze procedure at Charlotte Maxeke Johannesburg Academic Hospital from 2000 to 2015* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX E – Ethics Approval

R14/49 Dr Nangamso Kukulela

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160855

NAME: (Principal Investigator)	Dr Nangamso Kukulela
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Valvular Atrial Fibrillation Outcomes Associated with the Maze Procedure at Charlotte Maxeke Johannesburg Academic Hospital from 2000 to 2015
DATE CONSIDERED:	26/08/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Pravin Manga and Dr Nqoba Tsabedze
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/09/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX F – Supervisors' Approval

Division of Cardiology

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Johannesburg Hospital
PO Box 1481
Houghton, 2041, Johannesburg, South Africa

Tel: +27-11-488 3611/3842
Fax: +27-11-642-9041
Email: Pravin.Manga@.wits.ac.za

21 September, 2016

To whom it may concern:

Re: Dr Nangamso Kukulela, Student No. 0506711N, Protocol Ref. No. M160855

This letter serves to notify that Dr Nangamso Kukulela has successfully addressed all MMed protocol assessment corrections and recommendations from the MMed assessor committee meeting. I am satisfied with his revised protocol.

Yours sincerely,

NQOBA TSABEDZE MBBCh, FCP(SA), Cert. Cardiology (SA)
Specialist Physician and Cardiologist
University of the Witwatersrand

PRAVIN MANGA MBBCh, FCP (SA), PhD (WITS), FRCP
Professor and Head of Division of Cardiology
University of the Witwatersrand

APPENDIX G – Hospital Approval



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Email:johannes.maepa@gauteng.gov.za
17 August2016

Dear Dr. Nangamso Kukulela

STUDY TITLE: Valvular Atrial Fibrillation Outcomes Associated with the Maze Procedure at Charlotte Maxeke Johannesburg Academic Hospital from 2000 to 2015.

Permission to conduct the above mentioned study is provisionally approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your ethics clearance as soon as the study is approved by the Ethics committee for the CEO's to give you the final approval to conduct the study.

Supported/~~not supported~~

Dr M.I. Mofokeng
Clinical Director
DATE: 17/08/2016

Approved/~~not approved~~

Ms G. Bogoshi
Chief Executive Officer
Date: 17/08/2016

APPENDIX H – Proof of Submission for Publication

EJCTS <em@editorialmanager.com>
to me

Re: EJCTS-2018-701751 - Valvular Atrial Fibrillation Outcomes Associated with the Cox-maze Procedure, Valves, Original Article (received: 24.09.2018)

Dear Dr. Kukulela,

You have been listed as a contributing author for the above-mentioned manuscript submitted to the European Journal of Cardio-Thoracic Surgery. Please verify your contribution by clicking one of the below links.

Yes, I am affiliated: https://ejcts.editorialmanager.com/l.asp?i=167302&l=OREFALA7

No, I am not affiliated: https://ejcts.editorialmanager.com/l.asp?i=167303&l=OSKPKFOB

IMPORTANT: Please check that your contributions to this paper and conflict of interest statement as declared by the corresponding author (Dr Dineo Mpanya) are correct. These are included at the bottom of this e-mail.

With kind regards,

Friedhelm Beyersdorf, MD, Editor-in-Chief

European Journal of Cardio-Thoracic Surgery,
Editorial Office,
University Freiburg - Medical Center,
Department of Cardiovascular Surgery,
Hugstetter Str. 55,
79106 Freiburg,
Germany

tel: +49-761-27090860
fax: +49-761-27090870
e-mail: info@ejcts.org

http://www.editorialmanager.com/ejcts
https://academic.oup.com/ejcts

****

Author contribution Nangamso Kukulela:
Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing

SA Heart Congress 2018
04 – 07 October, Sun City, North West Province

Oral Abstract Acceptance

Dear Dr Kukulela

On behalf of the SA Heart Congress 2018, we are pleased to advise that your abstract has been accepted for**Oral Presentation.**

Abstract ID: 9125
Abstract Title: Valvular Atrial Fibrillation Outcomes Associated with the Cox maze Procedure at Charlotte Maxeke Johannesburg Academic Hospital from 2000 to 2015

The SA Heart Reviewers require you to make the below edits and resubmit your abstract via the portal.

Portal link: http://www.exbo.co.za/abstracts/index.php
Comments:
Reviewer 1: This is a unique series and experience of the COX MAZE procedure in a South African setting. How was AF diagnosed and looked for post operatively e.g. ECGs or Holter monitoring? Were patients on antiarrhythmic drugs post ablation? What was the exact lesion set created with the COX procedure.

Reviewer 2: Excellent topic - thanks for taking the initiative. It will be important to note whether the patients had persistent or paroxysmal atrial fibrillation prior to surgery and whether any patients were on long term amiodarone therapy during follow-up.

Please note the length of your presentation, as well as date and session will be advised shortly.

Oral Abstracts will be judged, and winners announced at the Celebration Dinner, Saturday 06 October.
The Best Clinical Excellence Award will receive R50 000.00.

Kindly confirm with the Congress Office by return email whether you accept, as well as confirm the presenting author's details by no later than Friday, 29 June 2018.

Please note, all abstract presenters are required to register for the Congress under the Early Bird Rate, please visit the congress website for online registration: www.saheartcongress.org/

Should you have any queries please do not hesitate to contact the congress office.

We look forward to welcoming you to the SA Heart Congress 2018.

SA Heart Congress Office 2018
Contact person: Claire Jettke
Tel: +27 (0)11 325 0020
Fax: +27 (0)11 325 0028
Email: claire@eoafrica.co.za
Website: www.saheartcongress.org/

APPENDIX I – Research Proposal

The Research Proposal

Table of contents

1. Introduction 3
2. Background/Literature review.....4
3. Study objectives.....8
4. Methods
    - 4.1 study design.....9
    - 4.2 study population and sample.....9
    - 4.3 study site 10
    - 4.4 estimated population size.....10
    - 4.5 Data collection.....10
5. Data Management and Analyses 11
6. Ethics 12
7. Timing 12
8. Funding.....12
9. Problems.....13
10. References 13

VALVULAR ATRIAL FIBRILLATION OUTCOMES ASSOCIATED WITH THE MAZE PROCEDURE AT CHARLOTTE MAXEKE JOHANESSBURG ACADEMIC HOSPITAL FROM 2000 TO 2015

Student: Dr Nangamso Kukulela; Student No: 0506711N; Masters Degree in Medicine

Supervisor: Prof Pravin Manga; Head of Cardiology; Charlotte Maxeke Johannesburg Academic Hospital

Co-supervisor: Dr Nqoba Tsabedze; Specialist physician and Cardiologist; Wits; Faculty of Health Sciences

Abbreviations:

- **Euro II Score**: European System For cardiac Operative Risk Evaluation
- **AF**: Atrial Fibrillation
- **CHA2DS2-VASc**: Congestive heart failure; Hypertension, Age >75; Diabetes Mellitus; Prior Stroke or Thromboembolism; Vascular disease; Age 65-65;Sex category (i.e. Female sex)
- **NYHA**: New yolk heart associated
- **ESC**: European Society Of Cardiology
- **ECG**: Electrocardiogram
- **CMJAH**: Charlotte Maxeke Johannesburg Academic Hospital

1. Introduction

The surgical maze procedure is an open-heart surgical operation performed to treat atrial fibrillation (AF) (1). During open-heart surgery a number of incisions are made on the left atrium (and sometimes the right) to form scar tissue, which prevents conduction of AF electrical impulses. This disrupts the propagation of chaotic abnormal electrical impulses seen in AF (1, 2).

'Maze' refers to the series of incisions arranged in a maze like pattern in the atria (2, 3). The procedure was first developed by James Cox and associates in 1987 at Barnes-Jewish Hospital located at St. Louis, Missouri, USA (3). After the introduction of the initial procedure, a series of improvements were made culminating in Cox maze IV procedure (3).

The maze IV is now considered as the gold standard for effective surgical cure of AF (3). Cox maze IV consists of a pattern of linear scars created by incision or ablative technology such as radiofrequency or cryothermal ablation. Traditionally, the original maze procedure (maze I) created lines of scar by making several small incisions (referred to as 'cut and sew') around the sinoatrial node as well as one to the atrial-superior vena caval junction through the sinus tachycardia region of the sinoatrial node. This resulted in unwanted events such as chronotropic incompetence and prolonged intra-atrial conduction delay.

This led to the development maze II procedure that modified the location of the incision to prevent these problems with the maze I procedure. The technical challenges of the maze II procedure, such as approach to the left atrium, resulted in the maze III procedure, which reduced the frequency of chronotropic incompetence, improve atrial transport function and shortened the procedure time (14 -17).

Indications for surgical management of AF include the following: 1. Patients with AF who undergo surgery for structural heart disease. 2. Patients complicated with left atrial thrombosis refractory to thrombolytic therapy or with a history of thromboembolism despite proper anticoagulant therapy. 3. Patients with failed catheter ablations for AF or with recurrent AF. 4. Isolated AF patients with refractory medically intolerable symptoms and a significant impaired quality of life. 5. Patients with medically refractory paroxysmal AF with repeated emergency visits. 6. Patients with severely dilated atria and a severely increased cardiothoracic ratio, with low voltage fibrillary-waves on the Electrocardiogram (ECG), in which there is little chance to maintain sinus rhythm and effective atrial contraction postoperatively (4, 5).

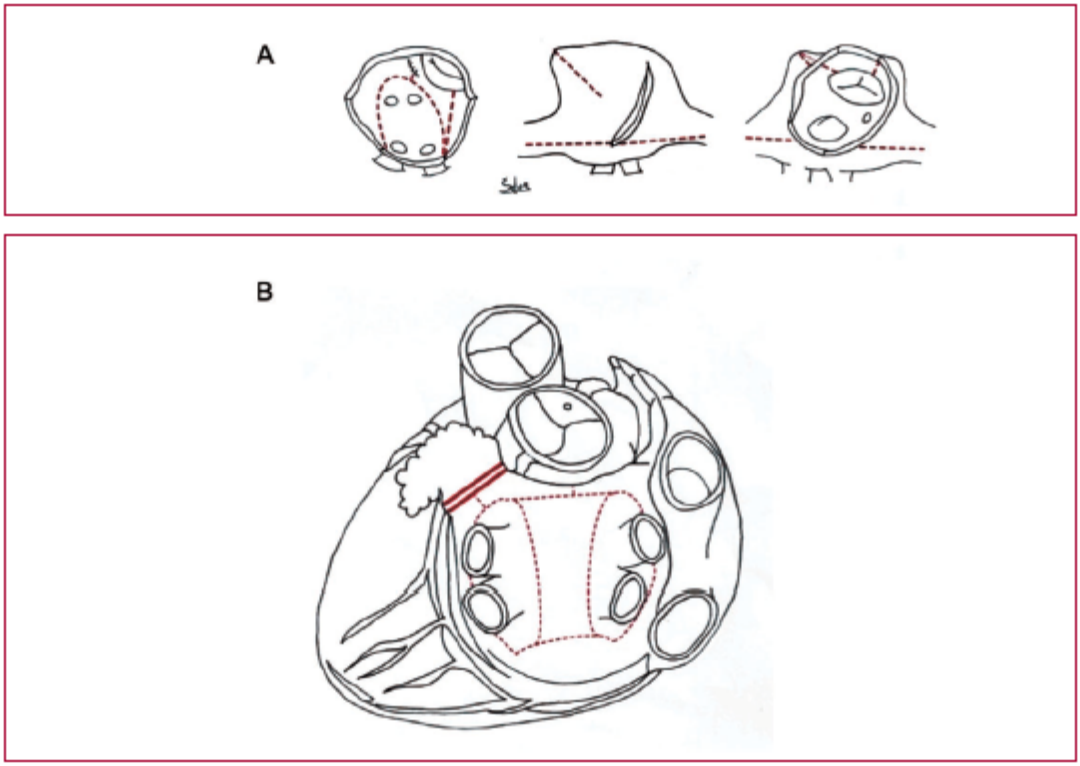


Illustration A: Surgical lesion sets for biatrial Cox maze procedure. Surgeon's view showing left atrial lesions (left panel) and right atrial lesions (middle and right panel). B: Left atrial lesions in a thoracoscoping minimally invasive surgical procedure (dashed lines) including left atrial exclusion (double line). (16)

The complications of the maze procedure are similar to those of an open heart surgery and depend on individual risk factors. Most common complications include the following: bleeding, infections (including mediastinitis), stroke, pneumonia, myocardial ischaemia, new arrhythmias and death (4, 6).

Outcomes data on the maze procedure is currently only from the developed world, with a paucity of data from developing regions, including South Africa. Due to limited Electrophysiology (EP) theatres in the developing regions, the maze procedure remains a relevant therapeutic modality for valvular AF management.

This study aims to analyse the long term outcomes of the procedure in treating valvular AF in a tertiary academic centre in Johannesburg. This retrospective audit aims to determine the duration and the number of patients that remain AF free post maze procedure. As elucidated above, the maze procedure is generally reserved for patients with a concomitant class-A indication for open heart surgery. Under these circumstances, the benefit of the procedure outweighs the risks associated with open heart surgery. The maze procedure is therefore done during the same surgical sitting for patients with AF and another cardiac condition requiring open heart surgery. This is predominantly for mitral valvular conditions.

2. Background/ Literature Review

Atrial fibrillation is characterised by disorganised, rapid and irregular atrial activation (7). It results in abnormal chaotic electrical impulses in the atria. AF is diagnosed clinically by pulse palpation and confirmed by the ECG in those patients with irregular pulses. The ECG shows absent P waves.

It is a common arrhythmia with a prevalence of 5-10% in patients over the age of sixty five (8). The incidence of AF increases with age. It is extremely unusual in children unless a structural heart disease is present or there is another arrhythmia that precipitates the AF (7). The arrhythmia is associated with a fivefold risk of stroke and a threefold incidence of congestive heart failure (7, 9). It is a major cardiovascular challenge in modern societies with worsening medical, social and economic implications (7).

According to the definitions given by ACC/ESC/AHA 2006, society of thoracic (STS), ESC and EACTS clinical guidelines committee, there are five types of AF. These are defined: First diagnosis; Paroxysmal; persistent; long-standing persistent and permanent AF (4).

The causes of AF can be divided into cardiac and non cardiac causes. The cardiac can further be divided into ‘valvular’ and ‘non valvular (7). Valvular AF is used to imply that AF is related to rheumatic heart disease, predominantly mitral stenosis (7). The cardiac causes include hypertension, congestive heart disease, valvular heart disease, coronary artery diseases and myocardial infarction, cardiac surgery and cardiac tumours. The non-cardiac causes include thyrotoxicosis, electrolyte imbalances, acute and chronic pulmonary diseases and phaeochromocytomas. In some patients no cause can be found and this group is labelled as ‘lone’ AF (7). The term ‘lone’ AF was introduced in 1954 to refer to patients with AF and without any other evident cardiac or other disease (10). The treatment of AF is usually with pharmacological agents. Due to the perioperative complications associated with open heart surgery, the maze procedure is rarely done for AF alone without another compelling indication for open heart surgery.

The maze procedure has been reported to be effective in restoring sinus rhythm in patients with AF. A study in Japan sought to determine the effectiveness of the maze procedure for maintaining sinus rhythm and atrial contraction for a long period in patients with mitral valve disease (1). The study was a retrospective study that included 94 patients between June 1992 and October 1994 with mitral valve disease and AF. These patients underwent a modified maze procedure simultaneously with open heart surgery for refractory AF and the underlying valvular lesion. The ECG results found that in the early stage, a regular rhythm was noted in 75 of the 90 patients and 19 had AF (1). In the late stage, a regular rhythm was seen in 66 patients and 28 had AF. The incidence of patients with regular rhythm was not statistically different between the early and the late stages (p=0.14) (1). The study thus found that sinus rhythm and atrial contraction recovered early after the maze procedure in most patients and was maintained for more than two years (1). They concluded that the maze procedure is effective for a long period in patients with mitral valve disease. This study is one of the very few reports attempting to define the long term outcomes of the cardiac rhythm and atrial function after the maze procedure in patients with AF and mitral valve disease (1). A similar study by Ko Bando et al, sought to determine whether the Cox maze procedure provides additional benefit to patients with atrial fibrillation undergoing mitral valve operations. This retrospective study compared 258 patients between 1992 and 2000 who had the maze procedure at the same time with mitral valve replacement (n=147) or mitral valve repair (n=111) and 61 control patients with perioperative atrial fibrillation who had mitral valve replacement alone during the same interval. This study showed that freedom from AF at 5 years was significantly higher in the mitral valve replacement

plus maze group (78%) and the mitral repair plus maze group (81%) than in the mitral valve replacement alone group (6%, P<.0001) (11).

A more recent study published in 2013 by Ad et al aimed to assess the effect of the Cox maze procedure on operative and follow up outcomes. This prospective study divided 817 patients into 3 groups. The first group consisted of patients who had isolated mitral valve or mitral valve plus tricuspid valve surgery without history of AF (n=506). The second group was for patients with untreated AF (n=75) and the last group was for patients who underwent the Cox maze procedure (n=236). The study found that there was no increased morbidity associated with the Cox maze procedure with the benefit of very low thrombotic rate (2). Lindsey et al studied the incremental risk of the Cox maze procedure for patients with atrial fibrillation undergoing mitral valve surgery. The purpose of their study was to quantify the additional risk of performing the Cox maze IV procedure for patients undergoing mitral valve surgery. This was a retrospective study that included 312 patients between January 2002 and June 2011. This study concluded that the addition of Cox maze procedure to patients with AF undergoing a mitral valve surgery did not significantly affect the procedural mortality (12).

A study in Milan by Alberto Pozzoli et al also evaluated the clinical and functional outcomes of the maze procedure in symptomatic refractory lone AF patients. The study enrolled 39 highly symptomatic patients, with European Heart Rhythm Association class III-IV, in whom the maze procedure was done. The results showed that freedom from arrhythmias was 93% at 36 months (13). Freedom with anti-arrhythmic drugs was 85% at 36 months (13). The left ventricular ejection fraction also normalised in all study participants and AF-related symptoms score decreased from class III to class I in 93% of cases with a p-value of <0.001. Thus the maze

procedure may provide a complete reversal of arrhythmia related myocardial dysfunction. The results from the study concluded that the maze procedure has excellent outcomes, with symptom relief and negligible risk (13).

Prasad et al studied the long term efficacy in patients undergoing maze procedure for lone AF versus AF concomitant with other valvular heart procedures. This was because it was largely unknown whether the operation has similar efficacy in patients with lone atrial fibrillation compared with that in patients with atrial fibrillation associated with coronary, valvular, or congenital heart disease (3). They showed that the Cox maze has equivalent operative risk and long term efficacy in patients undergoing both lone AF surgery and concomitant heart disease operations.

Several studies have been done in first world countries to evaluate the outcomes of the maze procedure. These studies have documented the success rate of the maze procedure in converting AF into sinus rhythm. Due to the risk associated with open heart surgery, the maze procedure is reserved for patients with AF requiring open heart surgery. This is commonly a mitral valve disease requiring surgical treatment. There is limited data on the long term outcomes of the maze procedure performed in this group of patient, both in developed and in developing countries.

This study aims to audit short and long term outcomes of the maze procedure in patients with valvular AF in our local setting.

3. Study Objectives

a) The primary objective of this study is to determine the perioperative complications and the AF burden free duration of the maze procedure in treating valvular AF.

b) The secondary objectives of the study are to:

- Describe the demographics of the patients undergoing the maze procedure in our local setting.
- To describe the associated open heart surgery indications associated with the procedure.
- To describe the prevalence of AF related complications in this population.
- To describe the prevalence of warfarin related complications in this population.

4. Methods

4.1 Study design

This is a Retrospective audit of all the patients who underwent the maze procedure at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) department of cardiothoracic surgery from 2000 to 2015

4.2 Study population and sample

The participants of this study will be all the patients that have the maze procedure done at Charlotte Maxeke Johannesburg Hospital, department of cardiothoracic

surgery for valvular AF. We will include patients from 2000 to 2015. The study includes both male and female patients from age 15 and above from all race groups.

Eligibility Criteria

All the patients in whom the maze procedure was done at CMJAH are eligible for this study.

Patient Factors

- Age, gender, ethnicity
- Co-morbidities: hypertension, diabetes, dyslipidaemia, HIV, chronic kidney disease, valvular heart condition, history of Rheumatic heart disease, history of thromboembolism, thyroid disease, smoking
- Clinical presentation: NYHA, Euro II SCORE, CHADA2DS-VASc score, Haemoglobin, Creatinine, urea, INR, D-Dimer, pro-BNP, Trop T, CKMB, pre-operative ECG, Left ventricular ejection fraction
- Concomitant medications: Anticoagulation, anti-hypertensive medication, HMG CoA reductase inhibitors, Antiarrhythmic drugs, Anti-Diabetic Medication.

Procedural factors:

- Indications
- Duration of the procedure
- Outcome of the procedure
- Peri operative complications

Duration of Hospital stay (days)

Review at Follow up (OPD): follow up ECGs will be reviewed to document the presence or absence of AF. NYHA will be analysed at each visit to determine if AF free patients had a better functional status.

4.3 Study site

The study will be conducted at Charlotte Maxeke Johannesburg Academic Hospital, department of cardiothoracic surgery and department of cardiology.

4.4 Estimated sample size

All patients who underwent maze procedure for a valvular AF at CMJAH from 2000 to 2015 with a minimum 100 patients for Analysis.

4.5 Data collection

The data will be collected by the principal investigator (PI). The PI will review all surgical postoperative notes, filed in the department of cardiothoracic surgery, to identify all patients who have had the maze procedure. The surgical operative notes will also be evaluated for any perioperative complications encountered and acute mortality and morbidity outcomes.

Patients identified to have had the maze procedure will then have their outpatients' follow-up clinic files in the department of cardiology reviewed. During this phase of the study, the PI will review each follow-up visit's ECG for the presence or absence of AF. Other relevant clinical data that will be collected will include the documented clinical condition of the patient according to the New York Heart Association (NYHA) classification of the patient, the chronic medication used, the dose of warfarin used

and the international normalised ratio (INR) control among others. The ultimate aim of the study is to be able to determine how many patients remain AF free after the maze procedure and for how long

5. Data Management and Analysis

For this retrospective analysis, we will use descriptive statistics-frequency tables to describe clinical and demographic parameters. Normally distributed continuous data will be summarised as mean +/- SD and skewed data will be presented in median and inter quartile ranges. Multivariate analyses of the risk factors will be done. Student t-test will be used for normally distributed continuous variables and Wilcoxon rank sum test will be used for non-normal continuous data. The 95% confidence interval will be calculated for all data with a p value of <0.05 considered significant. REDcap software will be used as the data management tool for all the data. All statistical analyses will be generated using STATA version 13.1 (StataCorp, Texas).

6. Ethics

Ethics approval for the study will be sought from the University of Witwatersrand Human Research Ethics Committee, CMJAH CEO and the head of department of the cardiothoracic surgery and head of the department of cardiology. All patient information will be protected and not published. Patient's details will only be used during the data collection process to track the individual patient's records and follow

up notes. Outcomes of the study will be published in a peer reviewed journal and will be shared with all clinicians participating in valvular AF patient care.

7. Timing

	June	July	Aug	Sept Oct	Nov Dec	Jan Feb	March
Literature review							
Preparing Protocol							
Protocol							
Assessment							
Ethics Application							
Collecting Data							
Data analysis							
Writing up – thesis							
Writing up-paper							

8. Funding

No funding will be required for this study.

9. Problems

We anticipate some challenges during collecting data and finding patient's records, especially perioperative notes and outpatient files from many years ago.

References:

1. Yuda S, Nakatani S, Kosakai Y, Yamagishi M, Miyatake K. Long-term follow-up of atrial contraction after the maze procedure in patients with mitral valve disease. Journal of the American College of Cardiology. 2001;37(6):1622-7.

2. Ad N, Holmes SD, Massimiano PS, Pritchard G, Stone LE, Henry L. The effect of the Cox-maze procedure for atrial fibrillation concomitant to mitral and tricuspid valve surgery. The Journal of thoracic and cardiovascular surgery. 2013;146(6):1426-34; discussion 34-5.

3. Prasad SM, Maniar HS, Camillo CJ, Schuessler RB, Boineau JP, Sundt TM, 3rd, et al. The Cox maze III procedure for atrial fibrillation: long-term efficacy in patients undergoing lone versus concomitant procedures. The Journal of thoracic and cardiovascular surgery. 2003;126(6):1822-8.

4. Kyprianou K, Pericleous A, Stavrou A, Dimitrakaki IA, Challoumas D, Dimitrakakis G. Surgical perspectives in the management of atrial fibrillation. World journal of cardiology. 2016;8(1):41-56.

5. Shi J, Bai ZX, Zhang BG, Ren WJ, Guo YQ. A modified Cox maze IV procedure: a simpler technique for the surgical treatment of atrial fibrillation. Interactive cardiovascular and thoracic surgery. 2016.

6. Almashrafi A, Alsabti H, Mukaddirov M, Balan B, Aylin P. Factors associated with prolonged length of stay following cardiac surgery in a major referral hospital in Oman: a retrospective observational study. BMJ open. 2016;6(6):e010764.

7. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2012;14(10):1385-413.

8. Jardine RM, Fine J, Obel IW. A survey on the treatment of atrial fibrillation in South Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2014;104(9):623-7.

9. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, et al. The impact of atrial fibrillation type on the risk of

thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. European heart journal. 2016;37(20):1591-602.

10. Evans W, Swann P. Lone auricular fibrillation. British heart journal. 1954;16(2):189-94.

11. Bando K, Kobayashi J, Kosakai Y, Hirata M, Sasako Y, Nakatani S, et al. Impact of Cox maze procedure on outcome in patients with atrial fibrillation and mitral valve disease. The Journal of thoracic and cardiovascular surgery. 2002;124(3):575-83.

12. Saint LL, Damiano RJ, Jr., Cuculich PS, Guthrie TJ, Moon MR, Munfakh NA, et al. Incremental risk of the Cox-maze IV procedure for patients with atrial fibrillation undergoing mitral valve surgery. The Journal of thoracic and cardiovascular surgery. 2013;146(5):1072-7.

13. Pozzoli A, Taramasso M, Coppola G, Kamami M, La Canna G, Della Bella P, et al. Maze surgery normalizes left ventricular function in patients with persistent lone atrial fibrillation. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2014;46(5):871-6.

14. Cox JL, Boineau JP, Schuessler RB, Kater KM, Ferguson TB, Jr., Cain ME, et al. Electrophysiologic basis, surgical development, and clinical results of the maze procedure for atrial flutter and atrial fibrillation. Advances in cardiac surgery. 1995;6:1-67.

15. Kosakai Y, Kawaguchi AT, Isobe F, Sasako Y, Nakano K, Eishi K, et al. Modified maze procedure for patients with atrial fibrillation undergoing simultaneous open heart surgery. Circulation. 1995;92(9 Suppl):Ii359-64.

16. Cox JL, Jaquiss RD, Schuessler RB, Boineau JP. Modification of the maze procedure for atrial flutter and atrial fibrillation. II. Surgical technique of the maze III procedure. The Journal of thoracic and cardiovascular surgery. 1995;110(2):485-95.

17. Lonnerholm S, Blomstrom P, Nilsson L, Oxelbark S, Jideus L, Blomstrom-Lundqvist C. Effects of the maze operation on health-related quality of life in patients with atrial fibrillation. Circulation. 2000;101(22):2607-11.