LONG TERM OUTCOME AND THE VALIDITY OF EUROSCORE-II IN NATIVE-VALVE SURGERY FOR ACTIVE ENDOCARDITIS IN A SOUTH AFRICAN COHORT

BY

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KSHJIT001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
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DECLARATION

I, Jithan Jacob Koshy, 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, or is to be submitted for another degree in this or any other university.
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SIGNATURE:

DATE: 21st JULY 2014

ACKNOWLEDGEMENTS

I would like to dedicate this dissertation to my wife (Nisha Jacob) and daughter (Namitha Koshy) who supported me through my entire period of training.

I would like to acknowledge the Beit Trust for funding my postgraduate training and the production of this thesis. I would also like to extend my sincere gratitude to the members of the Beit Trust who were closely involved in supporting me through every step of my training. Special thanks go to Major General Ramsay (Secretary-Beit Trust) and Mrs Barton Wicks (Office Manager-Beit Trust). The trust was established in 1906 by the Will of Mr Alfred Beit, a director of the British South Africa Company. His fortune was bequeathed to various charitable causes in Zambia, Zimbabwe and Malawi, one of which is to provide a limited number of scholarships to deserving candidates domiciled within these countries. I am honoured to have received this scholarship with an extension for the lengthy training attributed to the cardiothoracic surgery career.

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I would like to acknowledge the contribution made by the research assistants in the labour intensive tasks of retrieving medical records, conducting telephonic interviews, tracing patients and data entry. The following research assistants contributed significantly:

- Justin Batcheller for assisting with the telephonic follow-up
- Mellinda Eller for the data retrieval and entry
- Elizabeth Kadow for the telephonic follow-up, and tracing of patients

I would also like to thank Paul Human and Henri Carrara for assisting with the statistical analysis of this study.

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PART A: PROTOCOL

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Part A: Protocol; Abstract

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ABSTRACT

BACKGROUND

Infective endocarditis was initially described in the early 16th century and only methodically reviewed after the 19th century when Osler gave the drive to the Royal College of Physicians in 1885, through his contribution.

The last 25 years has not shown much change in the mortality from infective endocarditis (IE) despite diagnostic and therapeutic advances. The current in-hospital mortality rate for patients with IE is 15% to 20%, with 1-year mortality approaching 40%. The morbidity associated with infective endocarditis includes valvular incompetence, embolization, cerebrovascular accidents and congestive heart failure and this has influenced the surgical options to a great extent. The EuroSCORE II is the current model available for predicting the early mortality after cardiac surgery.

HYPOTHESIS

Infective endocarditis has a high risk for mortality due to certain risk factors and the currently available EuroSCORE II model may not predict early mortality accurately and may not be suitable for our patient population.

Part A: Protocol; Abstract

OBJECTIVES

To evaluate the major risk factors for adverse short and long term outcomes in patients with active native valve infective endocarditis needing cardiac surgery, and to validate the EuroSCORE II in our cohort of patients.

PATIENTS AND METHODS

A retrospective review will be undertaken on patients with infective endocarditis requiring cardiac surgery from 2000-2012 at the Christian Barnard Division of Cardiothoracic surgery (Groote Schuur Hospital/UCT Private Academic Hospital) and follow-up with respect to mortality, re-operation and major adverse cardiac events, as well as an evaluation of the validity of the EuroSCORE II..

DATA COLLECTION AND ANALYSIS

The standardized data extraction form in the appendix will be used for extracting data from various databases and telephonic interviews. Data will be analyzed using STATA to determine the most significant predictors of adverse outcome and conducting Kaplan Meier actuarial analysis for early and late survival and freedom from adverse events. The EuroSCORE II will be evaluated and validated to our cohort of patients.

BACKGROUND

EPIDEMIOLOGY OF INFECTIVE ENDOCARDITIS

Infective endocarditis was initially described in the early 16th century and only methodically reviewed after the 19th century when Osler gave the drive to the Royal College of Physicians in 1885, through his contribution [1].

The last 25 years has not shown much change in the mortality from infective endocarditis despite diagnostic and therapeutic advances. The current in-hospital mortality rate for patients with IE is 15% to 20%, with 1-year mortality approaching 40%. The morbidity associated with infective endocarditis includes valvular incompetence, embolization, cerebrovascular accidents and congestive heart failure, and this has influenced the surgical options to a great extent [2].

A systematic review of rheumatic heart disease and its afflictions in the developing world shows that it poses an enormous burden on the limited health care resources in addition to the HIV pandemic. The review remarks of an unusually high incidence of infective endocarditis in sub-Saharan Africa and recommends the prevention of rheumatic fever and heart disease with primary and secondary antibiotic prophylaxis, endocarditis prevention with prophylaxis for high risk valvular pathologies and early diagnosis and management of endocarditis [3]

Infective endocarditis remains a complication for patients with rheumatic heart disease and as high as 20-25% of all rheumatic heart disease patients are afflicted by endocarditis during their lifetime. In areas with high endemicity of rheumatic heart disease, reports in the past have shown that as high as 90% of endocarditis was on rheumatic valves; and during the early half and mid-20th century this was the situation in the industrialized world [4].

In a cohort of 92 patients from Tygerberg hospital in the Western Cape of South Africa, the majority of patients were young males with underlying rheumatic heart disease (76%); and intravenous drug use and degenerative heart disease were rare; 77% were culture negative; and HIV infection was uncommon [5].

A Tunisian study in 2006 showed that infective endocarditis is still frequently associated with rheumatic disease among young adults, with a high frequency of negative blood cultures and high in-hospital mortality. [6].

MICROBIOLOGICAL ASPECTS

According to the prospective cohort study by the International Collaboration on endocarditis, infective endocarditis remains a disease fraught with major complications and high mortality. There is evidence to show that there is an increase in more acutely presenting patients and an increase in S. aureus endocarditis related to prior health care exposure. There is also documented evidence of geographic differences in the presentation, microbial etiology, treatment, and outcome of patients with IE [2].

In a multicentre study of 1622 patients more than one third were due to nosocomial infections, caused mostly by Staphylococcus aureus in 47% of cases. 57% of Methicillin resistant S. aureus were hospital acquired [7].

In a series of 108 patients with infective endocarditis in Algeria, 57% were culture negative and one third of these patients were found to have zoonoses (with Bartonella sp. comprising more than 50% of the zoonoses identified by positive PCR) [8].

A sub-study on coagulase negative staphylococci (CoNS) as a cause of native valve endocarditis (NVE) in the International Collaboration on Endocarditis-Prospective cohort study showed that CoNS in NVE occurred in only 7.8% of cases and almost half of these were health care-associated infections. There was a high rate of surgical intervention among this cohort of patients and they were associated with a high mortality of 25% [9].

In a review of infective endocarditis with negative blood cultures, prevalence rates range from 10 to 30% and even higher in some poorly developed countries due to prior antibiotic use, fastidious organisms and fungal infections; and this poses a huge problem in the choice of antibiotic regimens for these patients. Negative blood cultures were shown to be associated with a higher rate of major adverse cardiac events post-operatively [10].

PREDISPOSITION AND RISK FACTORS FOR INFECTIVE ENDOCARDITIS

A review by Carapetis et al in 2005 on the percentage of infective endocarditis with underlying rheumatic heart disease in developing countries, showed this in a median of 63% of cases. An estimated 33,700 cases of infective endocarditis in patients with underlying infective endocarditis occur annually in developing countries with a median mortality of about 25% [11].

a study published in 1951 on the incidence of infective endocarditis in rheumatic heart disease patients, followed up over a 20year period from childhood, showed that the risk increased in the older age with an incidence of 4.4% at 20 years [12].

HIV infection in Africa, unlike that in the developed world, has been the most significant health problem in the last 20 years. It has affected the general population, unlike most industrialized nations where it has been commonly associated with intravenous drug use. Studies have shown that the risk of infective endocarditis does not increase with HIV infection and marantic endocarditis has not been described in Africa [13].

In an Italian multicentre study of 895 cases of infective endocarditis, 108 episodes of infective endocarditis occurred in 105 HIV infected patients. Intravenous drug use was the predisposition in almost all patients, with staphylococcal infections in 60% and tricuspid involvement in 52%. Left sided infections and CD4 counts of less than 200/mm3 were associated with a higher mortality [14]

Current guidelines place rheumatic heart disease as medium risk for endocarditis precluding the need for antibiotic prophylaxis. Nkomo VT states that in Africa, rheumatic heart disease is classified as a disease with the greatest risk of poor outcome from infective endocarditis [15].

A review of prosthetic valve endocarditis by Piper et al shows that infective endocarditis occurs at a rate of 0.1-2.3% per patient year and is commonly associated with coagulase negative staphylococci. Prosthetic material has a higher propensity to get infected than other valvular pathologies [16].

PREVENTION AND MANAGEMENT OF INFECTIVE ENDOCARDITIS

In the current guidelines on the prevention, diagnosis and treatment of infective endocarditis, antibiotic prophylaxis is only recommended for high risk patients viz. those with prosthetic valves, intracardiac prosthetic material, previous episodes of infective endocarditis, and complex cyanotic congenital heart disease, shunts, conduits or other prosthesis. Prophylaxis is not recommended for any other pathology including rheumatic heart disease [17].

The therapeutic strategy for managing infective endocarditis lies in the identification of microorganisms, antibiotic sensitivities with directed antibiotic treatment, echocardiographic assessment and early surgical evaluation. Despite this approach infective endocarditis has a high mortality and risk of major adverse cardiac events [18].

Part A: Protocol; Background

In all patients with infective endocarditis approximately 20% require surgical intervention [19].

The trend in the management of infective endocarditis has moved towards a multidisciplinary approach with risk stratification, early diagnosis and antibiotic therapy and the early evaluation for surgical intervention. The most favourable outcome is seen when decisions on timing of surgery and ongoing management in infective endocarditis are made by a multidisciplinary team comprising the cardiologist, microbiologist and cardiac surgeon [20].

SURICAL ASPECTS

EUROSCORE II

The European system for cardiac operative risk evaluation was introduced in 1999 and in 2011 the improved EuroSCORE II was introduced with better prediction of operative risk [21]. Operative risk can be evaluated with EuroSCORE II using the online calculator by the EuroSCORE study group [22]. The validity of the scoring system can be evaluated by assessing the precision (calibration) and the accuracy (discriminatory ability). The Hosmer-Lemeshow test assesses the goodness of fit by estimating a chi-squared statistic from the difference between observed and expected values for mortality in 10 different risk groups. A p-value of >0.05 indicates that the EuroSCORE II fits the data well and accurately predicts mortality. The area under the receiver operating characteristic (ROC) curve can be used to evaluate the discriminatory power of the EuroSCORE II. The area under the curve ranges from 0.5 (no power) to 1.0 (absolute discriminatory ability) [23]. The specificity, sensitivity, positive and negative predictive values for the EuroSCORE II in predicting valve-related death can also be determined at different level cut points of prediction [24].

TIMING OF SURGERY

Acute aortic regurgitation, sinus of valsalva rupture and rupture into pericardium constitute an indication to operate within 24 hours as an emergency; and severe valvular stenosis, prosthesis instability, valvular regurgitation with overt cardiac failure, abscess formation, aortic true or false aneurysms or fistulisation, heart block, embolic risk from vegetations >1cm constitute an urgent indication to operate within 1-2 days [25].

There is evidence showing that early surgery for native valve infective endocarditis may benefit outcome, and earlier identification of surgical indications may substantially decrease mortality compared to medical therapy alone [26].

In a cohort of 291 patients with active infective endocarditis, early surgical intervention was associated with a greater risk of relapses with prosthetic valve endocarditis [27].

PREOPERATIVE STATE AND NEUROLOGIC COMPLICATIONS

Severe aortic or mitral valve regurgitation causing congestive cardiac failure is the most important indication for surgery, the most frequent cause of mortality and a significant risk factor for early mortality and morbidity [28].

In a study evaluating the risk factors for embolism and six month mortality in 216 patients with infective endocarditis, Hill et al showed that mobile vegetations, size >10mm were associated with new embolic episodes and the latter predicted six month mortality [29].

In a cohort of 288 consecutive patients with infective endocarditis, conservative management after an embolic stroke was associated with a poorer prognosis compared to early surgical intervention. The presence of neurologic complications such as ischaemic stroke or intracranial bleed also influences the timing of surgery with a delay of at least 4 weeks from the time of stroke being recommended unless there is progression of heart failure, decline of cardiac function, recurrent stroke, systemic embolization, or uncontrolled infection. And surgical intervention should be delayed if there is evidence of haemorrhagic conversion as this is associated with a higher rate of perioperative stroke and mortality [30].

SURGICAL TECHNIQUE AND VALVE SELECTION

A study of 78 patients operated for mitral endocarditis at a single center in France by Iung et al, revealed that 80% were feasible for repair. Repair in active endocarditis was associated with a higher rate of major adverse cardiac events but had equivalent survival to those with fully treated endocarditis [31].

When surgical management is the option for managing infective endocarditis, a thorough debridement and bioprosthetic or mechanical valve replacement has a low endocarditis recurrence risk [32].

In another North American study of 306 patients who had valve implantations for infective endocarditis, mechanical and bioprostheses were shown to have equivalent re-operation rates in patients above the age of 60 years. Younger patients benefited from mechanical prostheses with a lower re-operation rate. The decision to use a mechanical or stented bioprosthesis is based on the option to avoid either long term anticoagulation therapy or structural valve deterioration and this also holds for replacements in infective endocarditis [33].

EARLY MORTALITY AND MORBIDITY

In a study of 267 patients with infective endocarditis, critical physiological state, Staphylococcal infection, diabetes mellitus and embolic events were independent predictors of in-hospital mortality [34].

In a Canadian study by Davids TE et al, 383 patients who had surgery for infective endocarditis, staphylococci were the commonest organism. Prosthetic valve endocarditis, a critical preoperative state, and staphylococcal infection were independent risk factors for operative mortality. In addition age, recurrent endocarditis and ventricular ejection fraction of less than 40% were independent predictors of all-cause mortality [35].

The International Collaboration on Endocarditis–Prospective Cohort Study had 4075 patients with infective endocarditis and heart failure; the severity of heart failure was associated with surgical intervention and mortality [36].

Three hundred and sixty seven patients with prosthetic endocarditis were studied from the International Collaboration database and revealed that in-hospital mortality remained high with cerebral embolism and staphylococcal infection independently predicting 30 day mortality [37].

LONG TERM OUTCOME

Surgical intervention has been shown to be an independent predictor of long term survival whereas those with diabetes mellitus and paravalvular leaks had a poorer prognosis. Heart failure and intra-cardiac abscess predicted surgical intervention in these patients [38].

In a long-term outcome study the 10 and 15 year survival after valve replacement surgery for patients with infective endocarditis and no history of intravenous drug use was 56% and 42% respectively [39].

. A Tunisian experience showed that of the 186 patients with infective endocarditis, 79% were on native valves and 48% had surgery for active endocarditis. Severe cardiac failure was the most important predictor of mortality [40].

A review of 37 patients with active infective endocarditis had mitral valve repair surgery and a 10-year survival and freedom from re-operation of 80%. This study showed that mitral valve repair could be achieved with good long term survival and low rate of re-operation which was comparable to patients with no endocarditis [41].

STUDY JUSTIFICATION

There are a number of important themes influencing the indication, technique and outcome of surgery for infective endocarditis and these include:

- Native and prosthetic valve infections,
- Septic neurologic manifestations,
- Valve selection options (mechanical, stented tissue, or homograft)
- Replacement or repair of the affected valve
- Timing of surgery

The aim of this study is to determine the role of some of these risk factors in the overall management and outcome of patients at Groote Schuur Hospital in order to improve future management, to validate the EuroSCORE II in our patients and evaluate the applicability of this scoring system in the South African setting.

HYPOTHESIS

Infective endocarditis has a high risk for mortality and the currently available EuroSCORE II model may not predict early mortality accurately and may not be suitable for assessing the risk of mortality in our patients.

OBJECTIVES

To determine the most important predictors of adverse outcome with respect to the type of intervention in active native valve endocarditis and to evaluate the validity of the EuroSCORE II in our cohort of patients.

INCLUSION CRITERIA

- A diagnosis of infective endocarditis should have been made pre-operatively according to the modified Duke's criteria
- Active and fully treated infective endocarditis
- Native and prosthetic valve endocarditis
- Patients should have undergone cardiac surgery for infective endocarditis or its sequelae

EXCLUSION CRITERIA

- Patients with no evidence of infective endocarditis and no cardiac surgical intervention for endocarditis.

MAIN TYPES OF INTERVENTION

- Mitral valve repair
- Mitral valve replacement
- Aortic valve replacement
- Aortic and mitral valve replacement

PRIMARY OUTCOMES

- Valve related Mortality
    - Early (< 90 day) mortality
    - Late (≥90 day) mortality

SECONDARY OUTCOME

- Composite end point of early and late major adverse cardiac and cerebrovascular events (MACCE):
    - Valve related mortality
    - All valve related morbidity

- Reoperation
- Recurrence of infective endocarditis
- Cerebrovascular accident (embolic or haemorrhagic)
- Bleeding
- Significant arrhythmia
- Paravalvular leak, and

- Heart block requiring permanent pacemaker

PATIENTS AND METHODS

PROJECT TEAM

The project team constitutes the following contributors:

- **Dr. Jithan J. Koshy:** who will function as the primary investigator and be responsible for all aspects of the project including final data analysis and publication(s) that may arise
- **Justin Batcheller:** Research Assistant who will be responsible for data retrieval and entry under guidance by Dr J. Koshy
- **Paul Human:** Who will retrieve the list of patients and their demographic details from the cardiothoracic database and subsequently analyze the data and provide statistical services
- **Henri Carrara:** who will provide advice on statistical analysis
- **Mark Engel:** who will be the project co-supervisor and provide guidance for the write-up of this thesis.
- **Prof Peter Zilla:** who will be the project co-supervisor
- **Prof Johan Brink:** who will be the project supervisor

LITERATURE REVIEW

ELECTRONIC SEARCH

This process will include searching the following journals and search engines:

- European journal of Cardiothoracic Surgery
- Asian Annals of Thoracic Surgery
- Cardiothoracic surgery network
- OVID 1980 to June 2013
- MEDLINE 1966 to March 2013
- Google Scholar

Part A: Protocol; Patients and Methods

- The following search terms or phrases will be used: Infective endocarditis, rheumatic heart disease, prosthetic endocarditis, HIV infection and endocarditis, Staphylococcal endocarditis, valve replacement in endocarditis,

PATIENT IDENTIFICATION AND SELECTION

The study population will be from Groote Schuur Hospital, which serves as one of the referral centres for infective endocarditis amenable to surgery.

Patients were identified by retrieving a list of patients from the Christian Barnard division of Cardiothoracic surgery Filemaker Database by inputting search terms which pools all patients with any input of "endocarditis" and then reviewing the selection criteria:

- A diagnosis of infective endocarditis should have been made pre-operatively according to the Duke's criteria
- Patients with active native valve infective endocarditis
- Patients should have undergone cardiac surgery for infective endocarditis or its sequelae at Groote Schuur Hospital or UCT Private Academic Hospital

DATA MANAGEMENT

DATA SOURCE IDENTIFICATION AND DATA RETRIEVAL

The following databases, hospital records, and interviews will form the main sources:

- Christian Barnard division of Cardiothoracic surgery Filemaker Database: Pre-op, Intra-Op and Immediate post-op details
- Clinicom Database: Death, Folder number, Date of birth, Dates of hospital events and telephone numbers and ID numbers
- Cardiology Buff room: Cardiology follow-up notes and
- Medical Records: Patient folders, telephone numbers etc
- Forensic medicine: Death and postmortem details
- Pathology/Microbiology Department: for Histology and microbiology results
- NHLS lab system: INR and Blood results, Histology and microbiology results
- Home Affairs: Alive or dead information, death certificate information

- Telephonic follow-up: retrieve all telephone and cell phone numbers and call patients, next of kin or friends; retrieve relevant information pertaining to survival, NYHA, Address, Re-operations, and major adverse cardiac events.
- Telephonic follow-up of untraceable patients: INR clinics, local day hospitals from NHLS data base
- Retrieve information by sending out local clinic staff from day hospitals to patient homes to find out basic information and contact details.
- Retrieve information by sending out the police to specific addresses to trace patients location and contact details

DATA EXTRACTION

Raw data will be initially captured in the standardized data forms after which they will be transferred to a Microsoft Excel spreadsheet with respect to the variables in the data capture sheets:

- Entry of data into Microsoft Excel data sheets with variables as noted in the appendices by constructing relevant columns for data collection
- The variables will be assigned to the following main themes:
    - Demographic characteristics
    - Preoperative clinical characteristics
    - Intraoperative characteristics
    - Post-operative characteristics and duration to specific outcomes
- Data input will be as follows:
    - Categorical data: Yes/No; 1,2,3….; I,II,III….; Consistent data entry.
    - Continuous Variables: SBP (mmHg) as numerical data only; only add absolute values and no SI units.
    - Certain numerical variables will be derived with specified formulae and entered as a numerical data.

DATA CLEANING

Involves making sure that all data entered is consistent and formatted for analytical purposes i.e. that continuous variables are absolute values or with decimal places and categorical data stay within the assigned categories.

ASSESSMENT OF RISK OF BIAS

The following factors can increase the risk of bias in this study:

- Retrospective nature of the study
- Referral patterns to the institution and within the institution
- Missing patients in the Cardiothoracic Database
- Missing data
- Incomplete outcome data

DEALING WITH MISSING DATA

Patients who are lost to follow-up will be evaluated up to the time of their last follow-up and then censored. Categorical or continuous variables that are missing due to incomplete medical records will be left blank in the data sheets and this will be accounted for during analysis.

PROFILES OF CONTRIBUTORS

PRIMARY INVESTIGATOR

Dr. Jithan Jacob Koshy, BScHB, MBChB: **Dr Koshy** trained as a medical doctor at the University of Zambia and then joined the University of Cape Town for further academic training in the sub-speciality of Cardiothoracic Surgery. He was involved in several research projects during his training and has co-authored a publication in the Journal of Heart Valve Surgery. He is a Beit Fellow and his training in Cardiothoracic Ssurgery has been funded by the Beit Trust. Relevant work includes:

- Geldenhuys A, Koshy J.J, Human PA, Mtwale JF, Brink JG, Zilla, P. Rheumatic mitral repair versus replacement in a threshold country: the impact of commissural fusion. J Heart Valve Dis 2012;21;424-32

STATISTICIAN

Paul Human, PhD is the research director at the Cape Heart Center, University of Cape Town in the field of cardiovascular medicine. He is involved in research activities related to bioprosthetic heart valves; xenotransplantation; bioprosthesis inflammatory/immune response; and calcification. He is also a biostatistician and manages the cardiothoracic surgery database for the Christian Barnard Division of Cardiothoracic surgery. Relevant work include:

- Trantina-Yates, A., Weissenstein, C., Human, P., & Zilla, P. Stentless bioprosthetic heart valve research: sheep versus primate model. The Annals of thoracic surgery, 2001; 71(5), S422-S427.
- Zilla, P., Bezuidenhout, D., & Human, P. Prosthetic vascular grafts: wrong models, wrong questions and no healing. Biomaterials, 2007; 28(34), 5009-5027.
- Human, P., & Zilla, P. Characterization of the immune response to valve bioprostheses and its role in primary tissue failure. The Annals of thoracic surgery, 2001; 71(5), S385-S388.
- Zilla, P., Brink, J., Human, P., & Bezuidenhout, D. Prosthetic heart valves: catering for the few. Biomaterials, 2008; 29(4), 385-406.

Part A: Protocol; Support and Funding

Henri Carrara, MPH is an analytical epidemiologist and biostatistician at the Faculty of Health Sciences, in the School of Public Health and Family Medicine, University of Cape Town. He assists with research activities for MMed and postgraduate students including:

• the choice of appropriate study designs to answer medical questions
• the design of questionnaires to efficiently collect good quality data and ensure that the data is in a format that is easy to analyse
• the choice of databases for data capture, to ensure good quality data is captured
• the statistical analysis of data
• the interpretation of study results and presentation of data in appropriate ways for reporting in medical literature
• in addition he assists with a general understanding of biostatistics and epidemiological studies so that the medical literature can be understood and assessed critically

He principally uses Epidata software for data capture (freeware) and Epicalc (also freeware) for elementary analysis, which is verified using STATA or SAS as required. Relevant works include:

- Sitas, F., Carrara, H., Beral, V., Newton, R., Reeves, G., Bull, D., ... & Weiss, R. Antibodies against human herpesvirus 8 in black South African patients with cancer. New England Journal of Medicine, 1999; 340(24), 1863-1871.
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- Moodley, J. R., Hoffman, M., Carrara, H., Allan, B. R., Cooper, D. D., Rosenberg, L., ... & Williamson, A. L. HIV and pre-neoplastic and neoplastic lesions of the cervix in South Africa: a case-control study. BMC cancer, 2006; 6(1), 135.

CO-SUPERVISOR

Mark Engel BSc(MED) Hons, MPH initially trained as a Medical Laboratory Scientist at the Cape Peninsula University of Technology. He was awarded a British Council award to undertake further studies in molecular biology techniques in the UK, after which he went on

to complete an honours degree in Human Genetics in the Faculty of Health Sciences at the University of Cape Town. Following a scholarship to Harvard University's School of Public Health in 2001/2002, Engel was appointed as a Research Fellow at the South African Cochrane Centre where he gained extensive experience in teaching and conducting systematic reviews. After completing a Masters in Public Health degree in Epidemiology and Biostatistics, also at the University of Cape Town, Engel joined the Department of Medicine at the University of Cape Town as a Project Manager of the ASAP Programme in Rheumatic Fever and Rheumatic Heart Disease. Currently, he is reading for a PhD in the area of Rheumatic Fever and Rheumatic Heart Disease; his research interest and activity focuses on genetic epidemiology of rheumatic fever. He has published NN papers in various fields, including systematic reviews. In addition, he has experience in teaching and the mentorship of MPH fellows. Relevant work includes:

- Dave JA, Engel ME, , Freercks R, Peter J, May W, Badri M, Van Niekerk L, Levitt NS. Abnormal glucose metabolism in non-diabetic patients presenting with an acute stroke: prospective study and systematic review. Q J Med, doi:10.1093/qjmed/hcq062
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- Engel ME, Matchaba P, Volmink J. Corticosteroids for tuberculous pleurisy. Cochrane Database Syst Rev. 2007: (4):CD001876.
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- Atkins SA, Lewin SA, Smith HJ, Engel M, Fretheim A, Volmink J. Conducting a meta-ethnography of qualitative literature: lessons learnt. BMC Medical Research Methodology 2008, 8:21.

CO-SUPERVISOR

Professor Peter Zilla, MD, PhD, FC Cardio SA

Professor Zilla obtained his academic qualifications from the Universities of Vienna (Austria), Zurich (Switzerland) and Cape Town (South Africa) and his clinical qualifications from the Austrian Physician's Board and the College of Medicine of South Africa.

After graduating as "Doctor of Medicine" at the University of Vienna, Austria in 1980 he obtained a DMed. degree from the University of Zurich, Switzerland in 1983, a PD degree (PhD equivalent) from the University of Vienna and another PhD degree from the University of Cape Town in 1990.

Professor Zilla is author of 185 peer reviewed full papers and patents (104 times first author or corresponding author) having been cited >5,400 times with a total of 420 impact points and an H-factor of 36 (i10 Factor 91). Apart from holding 33 US/PCT patents (23 issued, 8 published and 2 filed) he is the editor of 5 books and has authored 24 book chapters. He obtained international academic and industry grants of almost 80 million rand. For his research he has been awarded the Theodor Billroth Award (Austrian Surg Soc); Sigma Tau Award (Intern. Union of Angiology); Alexis Carrel Award (German Soc Vasc Surg); Goetz Award (SA Cardiac Soc); Eiselsberg Award (Austrian Physicians Assoc) and Alain Carpentier Award (Int. Soc. Heart Valve Dis). He was the organizer of 5 major international conferences in 4 different countries; is a member and executive council member of 10 international societies; was president of ISACB from 1994-98; is a regular reviewer of the 18 top journals in his field and is on the editorial board of 3 major international journals and Associate Editor of 'Biomaterials' (IF 8).

- See more at: http://www.cts.uct.ac.za/Staff/CVRU#sthash.z9dJmIpY.dpuf

SUPERVISOR

Professor Johan Brink, MBChB, FCS SA Cardio

Assoc. Prof Johan Brink obtained his academic qualifications and undergraduate and postgraduate training from the University of Cape Town and his clinical and specialist qualifications from the College of Medicine of South Africa.

After graduating as Medical Doctor at the University of Cape Town in 1976, he spent his early medical career and military service in a variety of disciplines in hospitals in South Africa and Namibia (then South West Africa). He commenced his training in Cardiothoracic Surgery at Barnes Hospital at Washington University in St Louis, Missouri USA in 1982 and completed his training at Groote Schuur (GSH) and Red Cross Children's (RXH) Hospitals at the University of Cape Town under Christiaan Barnard and his successors from1984 to 1988 when he was awarded the Fellowship in Cardiothoracic Surgery of the Colleges of Medicine

of South Africa. He was then appointed as Specialist Cardiothoracic Surgeon in the Christiaan Barnard Department of Cardiothoracic Surgery.

Over the last 15 years Prof. Brink has held many prestigious positions such as that of President of the South African Transplantation Society; President of the South African Society of Cardiothoracic Surgeons as well as President and Senator of the College of Cardiothoracic Surgery within the Colleges of Medicine of South Africa. See more at: http://www.cts.uct.ac.za/Staff/Core%20Divisional%20Staff#sthash.BxfQzSGp.dpuf

SUPPORT AND FUNDING

This research proposal has been approved by both the Surgical Research Council as well as the Research Ethics Committee. The administrative costs as well as telephonic costs will comprise the bulk of the budget:

- Stationery and printing: R2500
- Telephonic costs: R4000

The Chris Barnard Division of Cardiothoracic Surgery will provide funding.

LIMITATIONS OF THE STUDY

The major limitation of this study is the inherent bias related to its' retrospective and observational nature.. Patient selection and indication and timing of surgery may also affect the findings related to referral patterns and duration of antibiotic therapy. Another limitation is the heterogeneity of the procedures undertaken and the microorganisms involved in the disease process.

ETHICAL CONSIDERATION

Confidentiality and anonymity will be upheld by only using the folder numbers and initials in the study to identify the subjects during the data collection phase of the study.. No identification of individuals will be done under any circumstances during the data review, statistical analysis or publication phases of this study. This protocol has been submitted to the UCT Human research ethics committee for approval.

Permission has been obtained from the Groote Schuur Hospital Management to undertake the study.

An oral consent procedure will be followed during telephonic follow up contact with patients and information will be entered in the Data Capture form in Appendix

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

DECLARATIONS OF INTEREST

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

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LONG TERM OUTCOME AND THE VALIDITY OF EUROSCORE-II IN NATIVE-VALVE SURGERY FOR ACTIVE ENDOCARDITIS IN A SOUTH AFRICAN COHORT

BY

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KSHJIT001

PART B: LITERATURE REVIEW

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

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DEGREE

MASTER OF MEDICINE IN CARDIOTHORACIC SURGERY

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF CAPE TOWN

CONTENTS

Part B: Literature Review; Introduction

INTRODUCTION

Infective endocarditis was initially described in the early 16th century and only methodically reviewed after the 19th century when Osler gave the drive to the Royal College of Physicians in 1885, through his contribution[1].

The last 25 years has not shown much change in the mortality from infective endocarditis despite diagnostic and therapeutic advances. The current in-hospital mortality rate for patients with IE is 15% to 20%, with 1-year mortality approaching 40%. The morbidity associated with infective endocarditis includes valvular incompetence, embolization, cerebrovascular accidents and congestive heart failure and this has influenced the surgical options to a great extent[2].

OBJECTIVES

The objectives of this literature review are:

1. To review the current trends in the epidemiology of infective endocarditis in sub-Saharan Africa.
2. To review the most important risk factors for adverse outcomes after the surgical management of infective endocarditis
3. To review the EuroSCORE II model in predicting operative mortality in cardiac surgical patients particularly valve surgery.

LITERATURE SEARCH STRATEGY

For general background information, electronic sources such as MEDLINE, Google Scholar, and Pubmed were searched using key words such as: infective endocarditis, , rheumatic heart disease, prosthetic endocarditis, HIV infection and endocarditis, Staphylococcal endocarditis, valve replacement in endocarditis. The following databases were searched:

- European journal of Cardiothoracic Surgery
- Asian Annals of Thoracic Surgery
- Cardiothoracic surgery network
- OVID 1980 to June 2013
- MEDLINE 1966 to March 2013
- Google Scholar

THE LITERATURE REVIEW

THE EPIDEMIOLOGY OF INFECTIVE ENDOCARDITIS

A systematic review of rheumatic heart disease and its afflictions in the developing world shows that it poses an enormous burden on the limited health care resources, in addition to the HIV pandemic [3]. The review remarks of an unusually high incidence of infective endocarditis in sub-Saharan Africa and recommends the prevention of rheumatic fever and heart disease with primary and secondary antibiotic prophylaxis, endocarditis prevention with prophylaxis for high risk valvular pathologies and early diagnosis and management of endocarditis [3].

Infective endocarditis remains a complication for patients with rheumatic heart disease, and as high as 20-25% of all rheumatic heart disease patients are afflicted by endocarditis during their lifetime. In areas with high endemicity of rheumatic heart disease, reports in the past have shown that as high as 90% of endocarditis was on rheumatic valves; and during the early half and mid-20th century this was the situation in the industrialized world [4]. In a cohort of 92 patients from Tygerberg hospital in the Western Cape of South Africa, the majority of patients were young males with underlying rheumatic heart disease (76%); and intravenous drug use and degenerative heart disease were rare; 77% were culture negative; and HIV infection was uncommon [5].

A Tunisian study in 2006 showed that infective endocarditis is still frequently associated with rheumatic disease among young adults, with a high frequency of negative blood cultures and high in-hospital mortality [6]. A review of the historical perspective of the epidemiological trends in infective endocarditis in North America shows that the incidence rates of the disease remained relatively stable at 4.3 for 1950-1959, 3.3 for 1960-1969 and 3.9 for 1979-1981. Native valve endocarditis associated with rheumatic heart disease occurred in 26% of cases before the 1970's, after which prosthetic valves became an important underlying factor. Early mortality fell from over 45% to about 25% over the last 50 years [7].

THE MICROBIOLOGICAL TRENDS AND PATTERNS

According to the prospective cohort study by the International Collaboration on endocarditis, infective endocarditis remains a disease fraught with major complications and high mortality. There is evidence to show that there is an increase in more acutely presenting patients and an increase in S. aureus endocarditis related to prior health care exposure. There is also

documented evidence of geographic differences in the presentation, microbial etiology, treatment, and outcome of patients with IE [2].

In a series of 108 patients with infective endocarditis in Algeria, 57% were culture negative and one third of these patients were found to have zoonoses (with Bartonella *sp*. comprising more than 50% of the zoonoses identified by positive PCR) [8]. A literature review of culture negative endocarditis showed that 4-25% of blood cultures will be negative due to prior antibiotic use, fastidious organisms and fungal infections, and this poses a huge problem in the choice of antibiotic regimens for these patients[9]. Negative blood cultures were shown to be associated with a higher rate of major adverse cardiac events post-operatively [10]. Positive valve cultures were more common in staphylococcal infection which had a higher risk of re-operation [11].

A sub-study on coagulase negative staphylococci (CoNS) as a cause of native valve endocarditis (NVE) in the International Collaboration on Endocarditis-Prospective cohort study showed that CoNS in NVE occurred in only 7.8% of cases and almost half of these were health care-associated infections. There was a high rate of surgical intervention among this cohort of patients and they were associated with a high mortality of 25% [12]. In a multicenter study of 1622 patients, more than one third were due to nosocomial infections caused mostly by Staphylococcus aureus in 47% of cases. 57% of Methicillin resistant S. aureus were hospital acquired [13].

PREDISPOSING CARDIAC CONDITIONS AND RISK FACTORS

Rheumatic Heart Disease: A review by Carapetis et al in 2005 showed that a median of 63% of infective endocarditis cases had underlying rheumatic heart disease in developing countries, An estimated 33,700 cases of infective endocarditis in patients with underlying infective endocarditis occur annually in developing countries with a median mortality of about 25% [14]. In a study published in 1951 on the incidence of infective endocarditis in rheumatic heart disease patients followed up over a 20 year period from childhood showed that the risk increased in the older age with an incidence of 4.4% at 20 years [15]. The decline in the incidence of rheumatic heart disease in North America has resulted in the recognition of mitral valve prolapse as an emerging underlying risk factor for infective endocarditis and patients with no underlying cardiac pathology have also emerged due to intravenous drug use [16]. Current guidelines place rheumatic heart disease as medium risk for endocarditis precluding the need for antibiotic prophylaxis. Nkomo VT states that in

Africa, rheumatic heart disease is classified as a disease with the greatest risk of poor outcome from infective endocarditis [17].

HIV Infection: In Africa, unlike that in the developed world, HIV infection has been the most significant health problem in the last 20 years. It has affected the general population, unlike most industrialized nations where it has been commonly associated with intravenous drug use. Studies have shown that the risk of infective endocarditis does not increase with HIV infection and marantic endocarditis has not been described in Africa [18]. In the developed world the prevalence of infective endocarditis is 6.3-34% in intravenous drug users with concomitant HIV infection. Infective endocarditis in advanced HIV infection is associated with a 30% greater mortality than HIV negative patients. Marantic endocarditis is a non-infective form of endocardial vegetation found in 3-5% of patients with advanced HIV infection [19].

A prospective study in Spain on a cohort of 109 episodes of infective endocarditis showed a shift in the predisposing condition, being more commonly injecting drug use (36%) and prosthetic valves (16.5%), and the former being mostly HIV infected patients. Staphylococcal infections comprised more than 90% of the episodes and 47% were due to Staphylococcus aureus [20]. In an Italian multicentre study of 895 cases of infective endocarditis, 108 episodes of infective endocarditis occurred in 105 HIV infected patients. Intravenous drug use was the predisposition in almost all patients, with staphylococcal infections in 60% and tricuspid involvement in 52%. Left sided infections and CD4 counts of less than 200/mm3 were associated with a higher mortality [21]. In a Spanish series of 31 HIV infected patients who had cardiac surgery, 68% were for infective endocarditis mostly related to intravenous drug use and an overall mortality of 50% with no AIDS related deaths [22].

Prosthetic Valve Endocarditis: A review of prosthetic valve endocarditis by Piper et al shows that infective endocarditis occurs at a rate of 0.1-2.3% per patient year and is commonly associated with coagulase negative staphylococci. Prosthetic material has a higher propensity to get infected than other valvar pathologies [23]. An observational multicentre cohort study of prosthetic valve endocarditis shows that despite frequent early diagnoses and surgical intervention, the mortality of this condition remains high [24].

PREVENTION AND MANAGEMENT OF INFECTIVE ENDOCARDITIS

Prevention of Endocarditis: In the current guidelines on the prevention, diagnosis and treatment of infective endocarditis, antibiotic prophylaxis is only recommended for high risk patients viz. those with prosthetic valves, intracardiac prosthetic material, previous episodes of infective endocarditis and complex cyanotic congenital heart disease, shunts, conduits or other prosthesis. Prophylaxis is not recommended for any other pathology including rheumatic heart disease [25].

Medical and Surgical Management: The therapeutic strategy for managing infective endocarditis lies in the identification of microorganisms, antibiotic sensitivities with directed antibiotic treatment, echocardiographic assessment and early surgical evaluation. Despite this approach, infective endocarditis has a high mortality and risk of major adverse cardiac events [26]. Surgery remains a lifesaving procedure in high risk patients with severe aortic regurgitation, overt cardiac failure due to advanced valvar destruction and locally destructive complications [27]. In all patients with infective endocarditis, approximately 20% require surgical intervention [28]. The trend in the management of infective endocarditis has moved towards a multidisciplinary approach with risk stratification, early diagnosis and antibiotic therapy and the early evaluation for surgical intervention. The most favourable outcome is seen when decisions on timing of surgery and ongoing management in infective endocarditis are made by a multidisciplinary team comprising the cardiologist, microbiologist and cardiac surgeon [29].

IMPORTANT ASPECTS OF SURICAL MANAGEMENT

Timing of Surgery: Acute aortic regurgitation, sinus of valsalva rupture and rupture into pericardium constitute an indication to operate within 24 hours as an emergency; and severe valvar stenosis, prosthesis instability, valvar regurgitation with overt cardiac failure, abscess formation, aortic true or false aneurysms or fistulisation, heart block, embolic risk from vegetations >1cm constitute an urgent indication to operate within 1-2 days [30].

There is evidence showing that early surgery for native valve infective endocarditis may benefit outcome and earlier identification of surgical indications may substantially decrease mortality compared to medical therapy alone [31]. In a study of 252 patients with infective endocarditis, early surgery showed an improved long term survival in those patients with Staphylococcus aureus infection compared with other infections ($p=0.03$) [32]. In a prospective randomized controlled trial, 76 patients were assigned to two groups, early

surgery and conventional treatment, with the primary endpoint being in-hospital mortality and embolic events at 6 weeks. Early surgery was shown to effectively reduce the risk of embolic events and mortality by reducing the embolic load [33]. In a cohort of 291 patients with active infective endocarditis, early surgical intervention was associated with a greater risk of relapses with prosthetic valve endocarditis [34]. In patients with native valve endocarditis, early surgical intervention is not uniformly beneficial in all sub-groups of these patients, and may be beneficial in only certain select groups with specific indications [35].

Surgical intervention has been shown to be an independent predictor of long term survival, whereas those with diabetes mellitus and paravalvar leaks had a poorer prognosis. Heart failure and intracardiac abscess predicted surgical intervention in these patients [36]. In 61 cases of Staphylococcus aureus, prosthetic valve endocarditis was identified in the International Collaboration on Endocarditis merged database with an all-cause mortality rate of 47.5%. Early valve surgery in patients with cardiac complications had a lower mortality rate of 28.6% compared to other sub-groups [37].

Preoperative State and Neurologic Complications: Severe aortic or mitral valve regurgitation causing congestive cardiac failure is the most important indication for surgery, the most frequent cause of mortality and a significant risk factor for early mortality and morbidity [38]. In a study evaluating the risk factors for embolism and six month mortality in 216 patients with infective endocarditis, Hill et al showed that mobile vegetations, size >10mm were associated with new embolic episodes and the latter predicted six month mortality [39]. In a cohort of 288 consecutive patients with infective endocarditis, conservative management after an embolic stroke was associated with a poorer prognosis compared to early surgical intervention. The presence of neurologic complications such as ischaemic stroke or intracranial bleed also influences the timing of surgery with a delay of at least 4 weeks from the time of stroke being recommended unless there is progression of heart failure, decline of cardiac function, recurrent stroke, systemic embolization, or uncontrolled infection [40]. In a series of 145 episodes of infective endocarditis, vegetation size and mitral valve endocarditis were independent predictors of stroke and vegetation size a predictor of 1 year mortality [41]. The location, size and mobility of vegetations as assessed by transoesophageal echocardiography on 178 patients with infective endocarditis, showed that a higher rate of embolic events was associated with mobile vegetations greater than 1 cm [42].

Surgical Technique and Valve Selection: A study of 78 patients, operated for mitral endocarditis at a single center in France, by Iung et al revealed that 80% were feasible for

repair. Repair in active endocarditis was associated with a higher rate of major adverse cardiac events but had equivalent survival to those with fully treated endocarditis [43]. When surgical management is the option for managing infective endocarditis, a thorough debridement and bioprosthetic or mechanical valve replacement has a low endocarditis recurrence risk [44]. In another North American study of 306 patients who had valve implantations for infective endocarditis mechanical and bioprostheses were shown to have equivalent re-operation rates in patients above the age of 60 years. Younger patients benefited from mechanical prostheses with a lower re-operation rate. The decision to use a mechanical or stented bioprosthesis is based on the option to avoid either long term anticoagulation therapy or structural valve deterioration and this also holds for replacements in infective endocarditis [45].

EUROSCORE II

The European system for cardiac operative risk evaluation was introduced in 1999, and in 2011 the improved EuroSCORE II was introduced, with better prediction of operative risk [46]. Operative risk can be evaluated with EuroSCORE II using the online calculator by the EuroSCORE study group [47]. The validity of the scoring system can be evaluated by assessing the precision (calibration) and the accuracy (discriminatory ability). The Hosmer-Lemeshow test assesses the goodness of fit by estimating a C statistic from the difference between observed and expected values for mortality in 10 different risk groups. A lower C statistic and a p-value of >0.05 indicates that the EuroSCORE II fits the data well and accurately predicts mortality [48]. The area under the receiver operating characteristic (ROC) curve can be used to evaluate the discriminatory power of the EuroSCORE II. The area under the curve ranges from 0.5 (no power) to 1.0 (absolute discriminatory ability) [48]. The specificity, sensitivity, positive and negative predictive values for the EuroSCORE II in predicting valve related death can also be determined at different levels of cut-off points of prediction [49]. A recent prospective study validating the EuroSCORE II in Argentina showed a good discriminatory capacity and calibration for the population, but an underestimation of early mortality in the lowest risk groups. This was attributed to inadequate model behaviour and/or poor surgical performance [50].

RISK FACTORS FOR EARLY MORTALITY AND MORBIDITY

In a study of 267 patients with infective endocarditis, critical physiological state, Staphylococcal infection, diabetes mellitus and embolic events were independent predictors

of in-hospital mortality [51]. In a Canadian study by Davids TE et al, 383 patients who had surgery for infective endocarditis, staphylococci were the commonest organism. Prosthetic valve endocarditis, a critical preoperative state, and staphylococcal infection were independent risk factors for operative mortality. In addition age, recurrent endocarditis and ventricular ejection fraction of less than 40% were independent predictors of all-cause mortality [52].

The International Collaboration on Endocarditis–Prospective Cohort Study had 4075 patients with infective endocarditis and heart failure; the severity of heart failure was associated with surgical intervention and mortality [53]. Another European study, looking at the short term and 1 year outcome of infective endocarditis, showed that cardiac failure, embolic events, neurologic complications predicted a poorer prognosis and need for surgery. In this study, a high CRP >100mg/l predicted a higher mortality during the study period [54]. A European study with 193 patients with 203 episodes of infective endocarditis showed that prosthetic endocarditis was emerging as an important underlying problem. Patients with staphylococci, a contraindication to surgery or advanced age were associated with a high early mortality [55].

In a Turkish study of 112 patients with infective endocarditis, hemodialysis and mobile vegetations were independently associated with mortality, and the 30 day mortality was 28% [56]. Cerebral embolism and staphylococcal infection were independent predictors of 30 day mortality in 367 patients with prosthetic endocarditis from the International Collaboration database [57]. In-hospital mortality among 107 patients with active infective endocarditis was 27%, and this was independently predicted by multiple valve involvement, vegetations > 15mm, admission serum creatinine ≥2mg/dl and previous episodes of infective endocarditis [58].

FACTORS AFFECTING LONG TERM OUTCOME

Surgical intervention has been shown to be an independent predictor of long term survival whereas those with diabetes mellitus and paravalvar leaks had a poorer prognosis. Heart failure and intracardiac abscess predicted surgical intervention in these patients [36]. In a long-term outcome study, the 10 and 15 year survival after valve replacement surgery for patients with infective endocarditis and a history of non-intravenous drug use was 56% and 42% respectively [59]. A study of 308 patients with infective endocarditis followed up over a 21 year period showed that prosthetic endocarditis, positive valve culture and persistent fever

for more than a week were associated with an increased risk of recurrent infective endocarditis [60]. A Tunisian study showed that of the 186 patients with infective endocarditis, 79% were on native valves and 48% had surgery for active endocarditis. Severe cardiac failure was the most important predictor of mortality [61].

SUMMARY OF THE LITERATURE

Infective endocarditis was initially described in the early 16th century and only methodically reviewed after the 19th century when Osler gave the drive to the Royal College of Physicians in 1885, through his contribution [1].

The last 25 years has not shown much change in the mortality from infective endocarditis despite diagnostic and therapeutic advances. The current in-hospital mortality rate for patients with IE is 15% to 20%, with 1-year mortality approaching 40%. The morbidity associated with infective endocarditis includes valvular incompetence, embolization, cerebrovascular accidents and congestive heart failure and this has influenced the surgical options to a great extent [2].

Infective endocarditis is a significant problem in sub-Saharan Africa and is related to a high prevalence of rheumatic heart disease among the young indigent population. Africa has the highest burden of rheumatic heart disease with an incidence of 17-43% of all heart diseases [17]. The incidence of infective endocarditis in patients with rheumatic heart disease has not been clearly documented in literature.

The microbiological profile of infective endocarditis is dependent on patient risk factors and exposure. Coagulase negative staphylococci and Staphylococcus aureus endocarditis have been shown to be associated with hospital acquired infections and streptococcal endocarditis with community acquired infections [62]. Early mortality has been associated with staphylococcal infections, vegetation size, embolic load and most importantly the immediate preoperative physiologic state [51]. Studies have shown that there is not much difference in the recurrence of infective endocarditis when comparing mechanical and bioprosthetic implants [45]. However, few studies have been done to show the role of mitral valve repair in patients with active native valve endocarditis. The studies that have been done seem to show that the benefit of repair over replacement also holds true for active native mitral valve endocarditis. In one study, mitral valve repair in active endocarditis has been shown to have a good overall survival and low reoperation rate, but few studies compare this with outcomes for mitral repair in fully treated endocarditis or mitral replacement in active endocarditis [63].

In a cohort of 92 patients from Tygerberg hospital in the Western Cape of South Africa, the majority of patients were young males with underlying rheumatic heart disease (76%). Intravenous drug use, HIV infection and degenerative heart disease were rare and 77% of patients were culture negative [5]. In a review of infective endocarditis with negative blood

cultures, prevalence rates range from 10 to 30% and even higher in some poorly developed countries due to prior antibiotic use, fastidious organisms and fungal infections. This poses a huge problem in the choice of antibiotic regimens for these patients. Negative blood cultures were shown to be associated with a higher rate of major adverse cardiac events post-operatively [10].

HIV infection in Africa, unlike that in the developed world, has been the most significant health problem in the last 20 years. It has affected the general population unlike most industrialized nations, where it has been commonly associated with intravenous drug use. Studies have shown that the risk of infective endocarditis does not increase with HIV infection, and marantic endocarditis has not been described in Africa [18].

The therapeutic strategy for managing infective endocarditis lies in the identification of microorganisms, antibiotic sensitivities with directed antibiotic treatment, echocardiographic assessment and early surgical evaluation. Despite this approach, infective endocarditis has a high mortality and is a risk of major adverse cardiac events [26]. In all patients with infective endocarditis, approximately 20% require surgical intervention [28] and the predicted mortality can be assessed with a number of scoring systems. The European system for cardiac operative risk evaluation was introduced in 1999, and in 2011 the improved EuroSCORE II was introduced with better prediction of operative risk [46]. The applicability and validity of this scoring model in the South African setting has not yet been evaluated.

The aim of our study is to determine the role of various risk factors in early and late mortality and major adverse cardiac and cerebrovascular events (MACCE), and to validate the EuroSCORE II in our cohort of patients undergoing surgical treatment for active native valve endocarditis.

FUTURE RESEARCH

Further research needs to be done to accurately evaluate the incidence of infective endocarditis in rheumatic heart disease. The recommendations set forth in the current guidelines on antibiotic prophylaxis in rheumatic heart disease needs to be reviewed in the context of the high burden of the disease in Africa.

Randomized control trials are needed to improve our understanding on the timing of surgical intervention, as this has remained a controversial aspect of management, particularly in the face of neurological complications. The role of mitral valve repair for active native valve endocarditis is also an aspect that is not clearly understood and further trials may provide more information.

In order to adequately assess the validity of the EuroSCORE II model in the South African context, a large cohort of patients with various cardiac surgical procedures from multiple centers need to be reviewed.

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LONG TERM OUTCOME AND THE VALIDITY OF EUROSCORE-II IN NATIVE-VALVE SURGERY FOR ACTIVE ENDOCARDITIS IN A SOUTH AFRICAN COHORT

BY

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KSHJIT001

PART C: MANUSCRIPT

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FACULTY OF HEALTH SCIENCES
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CONTENTS

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ABSTRACT

OBJECTIVES

To evaluate the major risk factors for adverse short and long term outcomes in patients with active native valve infective endocarditis needing cardiac surgery and to validate the EuroSCORE II in our cohort of patients.

METHODS

We retrospectively studied all patients (n=149) who had cardiac surgery for infective endocarditis between June 2000 and May 2011 at our tertiary referral center. Ninety-six patients met the inclusion criteria for the study and those included in the analysis were 29 aortic valve replacements (AVR), 27 mitral valve replacements (MVR), 28 aortic/mitral (double) valve replacements (DVR), and 12 mitral valve repair (MV Repair).

RESULTS

Mechanical valves were implanted in 68 patients (70.8%), bioprosthetic valves in 16 (16.7%), mitral annuloplasty rings in 12 (12.5%). Cox proportional hazard model showed that the most important risk factors for early 30 day mortality were critical preoperative state, emergency surgery, EuroSCORE II > 12%, low cardiac output state (LCOS), HIV positive status, preoperative embolic episodes, vegetation size > 1cm and postoperative ventilation > 24 hours. The EuroSCORE II underestimated early mortality for the entire cohort but overestimated mortality in the lower risk groups (AVR and MV repair) and underestimated

mortality in the higher risk groups (MVR and DVR). The discriminatory ability was evaluated with the receiver operating characteristic (ROC) curve which showed an area under the curve of 0.796. Hosmer-Lemeshow test was used to assess goodness of fit with a chi-squared statistic of 12.4 (p-value = 0.13). When the discriminatory ability was evaluated within the subgroups, the AUROC curve was poorer for MVR (0.696), 0.837 for DVR and better for AVR group (0.92). The highest sensitivity (76%) and specificity (88%) of the EuroSCORE II was identified at a cut point of 12% and confirmed with a maximal Youden's index. Kaplan Meier analysis of patients with a EuroSCORE II >12% versus ≤12% showed that the former had significantly lower early to midterm survival and similar late survival (55.0 ± 11.1% vs. 94.7 ± 2.5% at 90 days; 55.0 ± 11.1% vs. 83.3 ± 4.7% at 5 years; and 45.8 ± 12.5 vs. 39.1 ± 27.8 with p = 0.0001).

CONCLUSIONS

We concluded that the EuroSCORE II underestimated mortality in the highest risk groups and overestimated mortality in the lowest risk groups. This may be due to poor surgical performance in the higher risk group and good surgical performance in the lower risk groups. The discriminatory ability and model fit were evaluated to be good and a EuroSCORE II > 12%, predicted a significantly higher early and medium term mortality.

INTRODUCTION

Infective endocarditis was initially described in the early 16th century and only methodically reviewed after the 19th century when Osler made his contribution to the Royal College of Physicians in 1885 [1].

There has been little change in the mortality from infective endocarditis despite diagnostic and therapeutic advances in the last 25 years. The current in-hospital mortality rate for patients with IE is 15% to 20%, with 1-year mortality approaching 40%. The morbidity associated with infective endocarditis includes valvular incompetence, embolization, cerebrovascular accidents and congestive heart failure and this has influenced the surgical approaches to a great extent [2].

Infective endocarditis is a significant problem in sub-Saharan Africa and is related to a high prevalence of rheumatic heart disease among the young indigent population. Africa has the highest burden of rheumatic heart disease contributing to 17-43% of all heart disease [3]. The incidence of infective endocarditis in patients with rheumatic heart disease has not been clearly documented in literature.

The microbiological profile of infective endocarditis is dependent on patient risk factors and exposure; Coagulase Negative Staphylococci and Staphylococcus Aureus endocarditis have been shown to be associated with hospital acquired infections and streptococcal endocarditis with community acquired infections [4]. Early mortality has been associated with staphylococcal infections, vegetation size, embolic load and most importantly the immediate preoperative pathophysiologic state [5]. Studies have shown that there is little difference in the recurrence of infective endocarditis when comparing mechanical and bioprosthetic implants [6]. However, few studies have been done to show the role of mitral valve repair in patients with active native valve endocarditis. The few studies show that the benefit of repair over replacement for non-infective mitral valve disease also holds true for active native mitral valve endocarditis. In one study, mitral valve repair in active endocarditis has been shown to have a good overall survival and low reoperation rate, but few studies compare this with outcomes for mitral repair in fully treated endocarditis or mitral replacement in active endocarditis [7].

In a cohort of 92 patients with active endocarditis from Tygerberg hospital, a fellow tertiary referral hospital in the Western Cape of South Africa, the majority of patients were young

males with underlying rheumatic heart disease (76%). Intravenous drug use, HIV infection and degenerative heart disease were rare. 77% of patients were culture negative. [8]. In a review of infective endocarditis with negative blood cultures, prevalence rates of culture negativity ranged from 10 to 30% and even higher in some poorly developed countries due to prior antibiotic use, fastidious organisms and fungal infections. This poses a problem in the choice of antibiotic regimens for these patients. Negative blood cultures were shown to be associated with a higher rate of major adverse cardiac events post-operatively [9].

HIV infection in Africa, unlike that in the developed world, has been a major health problem in the last 20 years. HIV infection has widely affected the general population, unlike in most industrialized nations were HIV has been commonly associated with intravenous drug use and social instability. Studies have shown that the risk of infective endocarditis does not increase with HIV infection and marantic endocarditis has not been described in Africa [10].

The therapeutic strategy for managing infective endocarditis lies in the identification of microorganisms and their antibiotic sensitivities with directed antibiotic treatment, echocardiographic assessment and early surgical intervention. Despite this approach, infective endocarditis has a high mortality and risk of major adverse cardiac events [11]. In all patients with infective endocarditis, approximately 20% require surgical intervention [12] and the predicted mortality can be assessed with a number of scoring systems. The European system for cardiac operative risk evaluation (EuroSCORE) was introduced in 1999, and in 2011 the updated EuroSCORE II was introduced with better prediction of operative risk [13]. The applicability and validity of this scoring model in the South African setting has not been evaluated.

The aim of our study is to determine the role of various risk factors in early and late mortality and in major adverse cardiac and cerebrovascular events (MACCE), as well as to validate the EuroSCORE II in predicting mortality in our cohort of patients undergoing surgical treatment for active native valve endocarditis.

PATIENTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

We retrospectively studied all patients (n=149) who had cardiac surgery for infective endocarditis between June 2000 and May 2011 at our tertiary referral center. The indications for surgery were elective in 73 (48.3%), urgent in 51 (34.2%) and emergent in 25 patients (16.8%). Native valve endocarditis was present in 123 patients (82.6%) and prosthetic valve endocarditis in 26 patients (17.3%). The patients' clinical characteristics, i.e. demographics, microbiology, predisposing cardiac conditions, symptoms, previous cardiac surgery, echocardiographic parameters and operative techniques were recorded and postoperative morbidity and mortality were followed-up, analyzed and the data is summarized in Table 1. Active native valve endocarditis was seen in 100 patients (67.1%) and 29 had AVR, 27 had MVR, 28 had DVR, 12 had MV repair, 3 had isolated tricuspid valve surgery and one had aortic valve repair. Ninety-six patients met the inclusion criteria for the study and were thus included in the analysis. Exclusion factors were: fully treated endocarditis (n=23), prosthetic endocarditis (n=26), isolated tricuspid valve surgery (n=3) and primary aortic valve repair (n=1).

BACTERIOLOGIC CHARACTERISTICS

The microbiological etiology of endocarditis in our patients is shown in Table 1. The most frequent organisms isolated were Staphylococci in 28 patients, comprising approximately equal numbers of Staphylococcus *Aureus* and Coagulase-negative Staphylococci. Streptococci were isolated from 29 patients. Various gram-negative organisms including some from the HACEK group occurred in 15% and no organisms were seen, cultured or identified from blood, valve tissue, serology or PCR in 26% of patients. Preoperative blood cultures were negative in 47% of patients.

PREDISPOSING CARDIAC CONDITIONS

The predisposing cardiac conditions associated with infective endocarditis are reported in Table 1. The most common underlying cardiac condition was rheumatic heart disease in 84% of patients which was either known on history preoperatively, identified intra-operatively or detected histologically. Rarer predispositions included degenerative disease in 2%, calcific degeneration in 2%, congenital heart disease in 2%, previous infective endocarditis on normal

valves in 1%, mitral prolapse in 1%, and pacemaker device infection in 1%. There was no known underlying heart disease in 7% of patients.

PREOPERATIVE CHARACTERISTICS AND THE EUROSCORE II

The preoperative characteristics are recorded in Table 1. Operative risk was evaluated by the EuroSCORE II using the online calculator provided by the EuroSCORE study group [14]. The patients were also assessed as being critically ill if they had the following: pulmonary oedema, mechanical ventilation, cardiogenic or septic shock or renal failure requiring dialysis. Emergency surgery was defined as occurring within 24 hours of presentation, urgent surgery defined between 24-48 hours of presentation and elective surgery thereafter. The variables included patient-related, cardiac-related and operation related factors

OPERATIVE CHARACTERISTICS AND SURGICAL TECHNIQUES

All surgical procedures were performed via a median sternotomy on cardiopulmonary bypass with systemic cooling to 28 and 32 degrees Celsius in all cases. Myocardial protection was by antegrade cardioplegia with or without additional retrograde cold blood cardioplegia. Aortic valve exposure was through an oblique aortotomy and mitral valve exposure was either through the Waterstons groove or via a biatrial transeptal approach.

Gross pathological findings were leaflet destruction, vegetations, intracardiac abscesses and fistulae. The affected valves and surrounding structures were debrided off all macroscopically infected material after which repair or replacement was performed.

The types of prosthetic material implanted were mechanical valves, bioprosthetic valves, annuloplasty rings, and bovine pericardial patches for reconstruction of the aortic root. Concomitant procedures were atrial fibrillation ablation (1%), coronary artery bypass surgery (1%) and tricuspid annuloplasty in (13%).

FOLLOW-UP

The patients were traced through telephonic contact, email contact, friends and relatives, through their local clinic, prison system, local police and the South African National Health Laboratory Service (NHLS). Long-term follow-up was completed in 98.6% of patients. Cause of death was determined through the records of forensic pathology examination, death certificates and clinical notes prior to death in those patients who were in hospital. Out-of-hospital deaths were determined from feedback of patients' relatives, death certificates in the patients' folders and the South African Home Affairs death registry. In-hospital mortality and

less than 90 day mortality was classified as early and >90 day mortality as late. For the purpose of evaluating the EuroSCORE II which predicts 30-day mortality, the early mortality category was further subdivided into ≤30-day mortality (Table 3). In the reporting of death and MACCE, the guidelines for the reporting of mortality and morbidity after cardiac valve intervention were followed [15].

The results of long term follow up were evaluated using NYHA functional status, hospital readmissions, thromboembolic events, bleeding episodes, prosthetic endocarditis, arrhythmias and heart block, paravalvular leaks, reoperations, and mortality. The dates of these events were determined and the time to events calculated from the time of operation. Categorical or continuous variables that were missing due to incomplete medical records were left blank in the data sheets and this was accounted for during analysis.

STATISTICAL METHODS

In the analysis of the data, variables were systematically expressed with standard definitions. The continuous variables were presented as median (range) and mean ± standard deviation in the manuscript where appropriate. Categorical variables were expressed as percentages. The Kaplan-Meier analysis was used to present actuarial survival estimates and freedom from major adverse valve related/cardiac events. The Cox proportional hazard regression model was used to evaluate hazard ratios for both short and long term outcome after adjusting for confounding factors. The primary endpoints included in the study were: early 30 day mortality, early 90 day mortality and late mortality (>90days); and secondary endpoints were: early MACCE and late MACCE. Significant hazard ratios at 95% confidence interval were identified and tabulated. A p-value of <0.05 was considered to be statistically significant.

The validity of the EuroSCORE II was evaluated by its goodness of fit and discriminatory capacity. The Hosmer-Lemeshow test assessed the goodness of fit by estimating a statistic from the difference between observed and expected values for mortality in 10 different risk groups. A p-value of >0.05 indicates that the EuroSCORE II fits the data well and accurately predicts mortality. The EuroSCORE II's ability to discriminate was assessed by its capacity to distinguish between patients who died within 30 days from those who did not. The area under the receiver operating characteristic (AUROC) curve was used to evaluate the discriminatory power of the EuroSCORE II in our cohort of patients and the treatment sub-groups. The area under the curve ranges from 0.5 (no power) to 1.0 (absolute discriminatory ability). A cut point of predicted operative mortality, at which the highest specificity and

sensitivity coincided, was determined for the entire cohort and confirmed by a maximal Youden's index. The entire cohort was divided into two groups, one above and the other equal to or below this cut point. The two groups were then compared with Kaplan Meier survival estimation and freedom from MACCE.

The entire cohort was also divided into DVR and non-DVR groups (single valve replacement and mitral valve repair) and their long term survival and freedom from MACCE were compared with Kaplan Meier curves.

RESULTS

SURGICAL PROCEDURE AND STUDY POPULATION

The preoperative demographic and clinical characteristics of the 96 included patients are summarized in Table 1. Gross pathological findings were vegetations in 76 patients (79%), intra-cardiac abscess in 30 (31%), ventricular septal defect in 3 (3%), and all had various degrees of leaflet damage. Mechanical valves were implanted in 68 patients (70.8%), bioprosthetic in 16 (16.7%), isolated mitral valve repair with a mitral annuloplasty ring in 12 (12.5%), pericardial patch reconstruction of the aortic root in 6 patients (6.3%) and tricuspid annuloplasty rings in 13 patients (14%).

The cut point of the EuroSCORE II model was evaluated to be 12% at which the sensitivity and specificity were maximal (Youden's index), and 21% of the entire cohort of patients had a score >12%. At the 12% cut point, the sensitivity of the EuroSCORE II to predict 30-day operative mortality was 73%, specificity of 88% and the positive predictive value was 44%.

Aortic Valve Replacement (Table 1): Of those patients who had an AVR (n=29): the mean age was higher than the other sub-groups (42.8±13.6 years) and the majority were males (86%), More than half the patients had a poor functional status (NYHA ≥ III) and only 7% were HIV positive. Thirty eight percent of patients had vegetation > 1cm and only 3% had a preoperative stroke. A pericardial patch repair of the debrided aortic root was undertaken in 10% of patients. The majority of patients (72%) had a mechanical valve implanted and 14% had a concomitant mitral annuloplasty ring. The mean EuroSCORE II was 5.8±6.1% and 14% of patients had a EuroSCORE II >12%. Among the eight patients who were in a critical preoperative state, seven required an emergency operation. The commonest organisms isolated were staphylococci in 7 (24%) patients and streptococci in 4 (14%).

Mitral Valve Replacement (Table 1): In those patients who had MVR (n=27), the male to female ration was not significantly different and more than half were in a poor functional status (NYHA ≥ III) This group had the highest HIV positive rate (15%) and 52% had vegetations >1cm with a preoperative stroke rate of 26%. The majority of patients (85%) had a mechanical valve implanted. The mean EuroSCORE II was 5.39±6.16 and 19% of patients had a score >12%. Among the eight patients who were in a critical preoperative state seven required emergency surgery. The commonest organisms were again staphylococci (41%) and streptococci (38%)

Aortic and Mitral Valve Replacement-DVR (Table 1): In patients with active native endocarditis who had DVR (n=28): the majority were males (71%), and more than half had an NYHA class ≥ III. Most of the patients (86%) had mechanical valves implanted and 11% required a pericardial patch to reconstruct the aortic root. The mean EuroSCORE II was 10.6±9.4 and eleven patients (39%) had a EuroSCORE II >12%. There were nine patients (32%) who were in a critical preoperative state, six of whom required emergency surgery (21%), and a further 10 (36%) patients needed urgent surgery.

Mitral Valve Repair (Table 1): A total of 12 patients had isolated mitral valve repair for active native mitral valve endocarditis. The male to female ratio was not significantly different and only 25% were in NYHA class ≥ III. None of the patients were HIV positive. The preoperative stroke rate was 25% and 42% had vegetations > 1cm. The pathology found at surgery included: leaflet perforation in 67%; chordal rupture and prolapse in 83%, and all had annular dilation. All the patients received Colvin-Galloway future band annuloplasty prosthesis, chordi were replaced with Goretex in 83% and one patient required a pericardial patch augmentation of the posterior leaflet. The mean EuroSCORE II was 3.0±3.9% and only one patient had a EuroSCORE II >12%.Only one patient required emergency surgery and was in a critical condition preoperatively. The commonest organism isolated was Streptococci in 42% of patients.

POSTOPERATIVE MORBIDITY AND EARLY MORTALITY

Table 2 shows the early and late postoperative outcomes of the 96 patients with active native valve endocarditis. Two patients (2%) died immediate postoperatively and a total of 14 patients (15%) died early (90-day mortality). Postoperative inotropic support was needed in 73% of patients and 5% of patients developed low cardiac output state out of which 1 patient required IABP support. Postoperatively, 6% of patients underwent re-exploration for tamponade or bleeding.

The commonest causes of in-hospital 30-day mortality were septicaemia (5 patients) and stroke (4 patients), and the other three were due to cardiogenic shock (2 patients) and tamponade (1 patient). Two more patients died of sepsis within 60 days and one of cancer within 90 days. The patient with cardiogenic shock developed a low cardiac output state after AVR: trans-esophageal echocardiography showed possible valve dehiscence, after emergent relook and repair on bypass the patient died 2 hours postoperatively in ICU due to cardiogenic shock.

The intensive care duration of stay was more than 24 hours in all of patients who had valve replacement and survived in ICU, and the ventilation period was greater than 24 hours in more than two thirds in each subgroup. DVR had the highest early mortality with 7 patients (24%) dying within 90 days.

Out of the six patients who had reoperations: 3 were early (one for cardiogenic shock due to suspected prosthetic endocarditis but no paravalvular leak noted at surgery, one for definite prosthetic endocarditis and the other iatrogenic native aortic regurgitation after MVR). The commonest early MACCE after aortic valve replacement was heart block in 2 patients and reoperation in 2 other patients. Relook for tamponade/bleeding occurred in 3 patients post DVR (11%) and 3 patients post AVR (11%).

The Cox proportional hazards model (Table 4) shows that the most significant hazard ratios for early 30 day mortality were critical pre-operative state, emergent surgery, EuroSCORE II >12%, HIV positive, LCOS, preoperative embolic episodes, vegetaions >1cm, NYHA ≥ III, and ventilation > 24 hours. After adjusting for age, sex, DVR, HIV positive status and NYHA class; LCOS, preoperative embolic episodes and ventilation > 24 hours were the most significant hazard ratios. When we evaluated early 90 day mortality (Table 5), the most significant hazard ratios after adjusting for these risk factors were: critical preoperative state, EuroSCORE II > 12%, LCOS, preoperative embolic episodes, and ventilation > 24 hours. The most significant adjusted hazard ratios for early MACCE (Table 6) were: critical pre-operative state, EuroSCORE II > 12%, LCOS, pre-op embolic episodes, pre-op dialysis and NYHA ≥ III.

The EuroSCORE II had a Hosmer-Lemeshow statistic of 12.4 (p-value = 0.13) and an AUROC of 0.796. When the discriminatory ability was evaluated within the subgroups the AUROC curve was poorer for MVR (0.696), 0.837 for DVR, better for AVR (0.92) and not assessed for MV repair, as there were no early deaths (Figure 3). The EuroSCORE II underestimated mortality in the entire cohort as well as the subgroups except in the AVR and MV repair groups, where the observed mortality was lower or absent respectively (Table 7).

LONG TERM OUTCOME, REOPERATION AND MAJOR ADVERSE CARDIAC EVENTS

A total of 98% of the patients were followed-up completely and 2 patients were lost to follow-up at 62 and 64 months after surgery. After excluding 90-day early mortality (14 patients), the median follow-up was 51 months and ranged from 7 to 140 months during which period 12 patients died. Kaplan-Meier survival analysis was used to estimate the

actuarial survival at 5 years (77.6% ± 4.6%) and 10 years (52.6% ± 15.9%) for the entire cohort of 96 patients. All-cause mortality after 90 days was 13% and valve related mortality was 10%. The commonest causes of >90-day valve related mortality were stroke (6%) and clotted valve (3%) and one patient died of prosthetic endocarditis (Table 3). The two patients that died of non-valve related causes were due to HIV related infection in one (11 months) and bowel obstruction in the other (63 months).

The three late reoperations were for prosthetic endocarditis (2 patients at 59 and 100 months) and bioprosthetic mitral valve stenosis (one patient at 58 months after DVR); and all three patients who had late reoperation died. Recurrence of endocarditis on the prosthetic valve occurred in 3 patients (3%) with 100% mortality and all were on mechanical valves (NS).

The Cox proportional hazards model (Table 8) showed that the most significant adjusted hazard ratios for late mortality were: female sex, HIV positive status and patients who had DVR; and for late MACCE (Table 9) were: DVR and the use of pericardial patch reconstruction of the aortic root.

Figure 1, shows the Kaplan Meier survival analysis of patients with a EuroSCORE II >12% versus ≤12%. The higher risk group had a significantly lower early to midterm survival and similar late survival when compared to the lower risk group (55.0 ± 11.1% vs. 94.7 ± 2.5% at 90 days; 55.0 ± 11.1% vs. 83.3 ± 4.7% at 5 years; and 45.8 ± 12.5 vs. 39.1 ± 27.8 with p = 0.0001).

Actuarial survival estimates of freedom from valve related mortality determined for the four main treatment groups at 5 and 10 years (AVR was 84.9 ± 7.1% and 84.9 ± 7.1%; for MVR was 79.1 ± 8.6% and 39.6 ± 28.3%; for DVR was 59.3 ± 9.5% and 19.8 ± 16.5%; and no valve related mortalities in the MV repairs. A comparison of the long-term survival of DVR versus the rest of the patients (non-DVR group) shows that former group had a significantly higher mortality and lower freedom from MACCE (Figure 2: p = 0.0002 and p = 0.007 respectively).

DISCUSSION

Our retrospective study describes the early and long-term outcomes of four main surgical options for active native valve endocarditis and the validity of the EuroSCORE II in the cohort of patients at a single center. We have shown that the overall early 30-day mortality was high (11%) and the most significant risk factors were: LCOS, preoperative embolic episodes and ventilation > 24hrs after adjusting for age, sex, NYHA class ≥ III, DVR and HIV status. The most significant risk factor for late mortality was the female sex, HIV positive status and patients who had DVR (after adjusting for HIV status and female sex). When we looked at the composite end point of MACCE, the most significant preoperative adjusted risk factors were: critical pre-operative state, EuroSCORE II > 12%, pre-operative embolic episodes, pre-operative dialysis and NYHA ≥ III. The most important immediate postoperative risk factor for MACCE was low cardiac output state (LCOS). Within the AVR sub-group, preoperative stroke, critical physiologic state and the use of pericardial patch (marker of extensive root pathology) were significant risk factors for valve related mortality. In the MVR group the significant risk factors for valve related mortality were LCOS. And finally in the DVR group, the significant risk factors were LCOS and the use of the pericardial patch. Our patients with mitral valve repairs had no valve related mortality and the significant risk factor for adverse events was prolonged ventilation > 24 hours. The DVR group had a significantly higher early and late mortality and lower freedom from major adverse cardiac events ($p = 0.0002$) than the other treatment groups.

Post-operative low cardiac output state (LCOS) was the most significant risk factor for early mortality and MACCE. This risk factor was more common in patients with DVR (11%) and may be attributed to the more severe form of valvular destruction seen in patients with double valve involvement. More extensive destruction can cause ventricular dysfunction and lead to low cardiac output state after surgical reconstruction.

The EuroSCORE II underestimated 30-day mortality in the combined and sub-groups except the AVR group and the discriminatory power was the least in the MVR group. We determined that at a cut-point of 12%, the EuroSCORE II had the highest sensitivity (73%) and specificity (88%) for the entire cohort with a positive predictive value of 44%.

In a review by Anguera et al, severe aortic or mitral valve regurgitation causing congestive cardiac failure is the most important indication for surgery, the most frequent cause of mortality and a significant risk factor for early mortality and morbidity [16]. In a study evaluating the risk factors for embolism and six month mortality in 216 patients with infective endocarditis, Hill et al showed that mobile vegetations, size >10mm were associated with new embolic episodes and the latter predicted six month mortality [17] which was a consistent finding in our study. When surgical management is the option for managing infective endocarditis, a thorough debridement and bioprosthetic or mechanical valve replacement has a low endocarditis recurrence risk [18]. There was no significant difference in rate of recurrent endocarditis between mechanical and bio-prostheses in our patient cohort although no endocarditis was reported on bio-prostheses. The current literature shows that there is no significant difference between the incidence of mechanical and bioprosthetic endocarditis [6].

In a study of 78 patients operated for mitral endocarditis at a single center in France by Iung et al, 80% were amenable for repair. Repair in active endocarditis was associated with a higher rate of major adverse cardiac events but had equivalent survival to those with fully treated endocarditis [19]. Only 30% of our patients with mitral endocarditis were amenable for repair and they had no valve related mortality but 33% had major adverse cardiac events.

A retrospective study by Chu et al, on 267 patients with infective endocarditis, critical physiological state, staphylococcal infection, diabetes mellitus and embolic events were independent predictors of in-hospital mortality [5]. In another study by Tyrone Davids et al, 383 patients having surgery for infective endocarditis had staphylococci as the commonest organism. A critical preoperative state and staphylococcal infection were independent risk factors for operative mortality. In addition age, recurrent endocarditis and ventricular ejection fraction of less than 40% were independent predictors of all-cause mortality [20]. Our study showed that a critical pre-operative state but not staphylococcal infection was associated with early mortality, and recurrent endocarditis was associated with reoperation and mortality in over 60%.

In a long-term outcome study of 346 patients between 1986 and 2005, the 10 and 15 year survival after valve replacement surgery for patients with infective endocarditis without intravenous drug use was 56% and 42% respectively [21]. Our cohort had a similar 10-year survival at 52.6 ± 15.9. A review of 37 patients with active infective endocarditis had mitral valve repair surgery and a 10-year survival and freedom from re-operation of 80% [7]. This

study showed that mitral valve repair could be achieved with good long-term survival and low rate of re-operation that was comparable to patients with no endocarditis and were consistent with our findings.

Most of the studies reviewing active native valve endocarditis had a heterogeneous cohort of patients with different treatment modalities, and assessed outcomes of the overall group. Our study shows that the cohort consists of a heterogeneous group and analyzing them based on different treatment modalities reveals that patients who had DVR had a significantly higher valve related mortality compared to the non-DVR treatment groups (59.3±9.5 Vs. 78±6.3 at 5 years p=0.009), probably related to the more extensive degree of infection.

In a study evaluating the EuroSCORE II in 3479 Chinese patients, the model gave a more accurate prediction for single valve (AUROC of 0.792) than multiple valve surgery (AUROC of 0.605) with respect to discriminatory ability and calibration. This was attributed to the lack of the incorporation of certain valve related risk factors such as left ventricular dimensions into the EuroSCORE II model [22]. The EuroSCORE II was developed from a predominantly European population with a different risk factor profile compared to our South African cohort. External validity may be influenced by general differences in socioeconomic status and access to health care with respect to the South African context. In addition, the lack of inclusion of certain risk factors such as ventricular dimensions that markedly influence the outcomes in valvular heart disease may explain the overall underestimation of mortality and the poor predictive value of the EuroSCORE II in our cohort. In another study comparing the EuroSCORE II in a Turkish cohort of 428 patients, the model was shown to underestimate mortality risk for the entire cohort [23]. Our study cohort, though small, showed a similar pattern with the predicted mortality being underestimated in the entire cohort but overestimated in the lower risk AVR and MV repair groups. In addition, the EuroSCORE II had a better discriminatory ability for early mortality in the AVR group than the other sub-groups in our study. In general, the EuroSCORE II had good discrimination and calibration for our entire cohort. Contrary to the results of our study, a recent prospective validation of the EuroSCORE II in Argentina showed that it underestimated in-hospital mortality in the lowest risk cases but performed well in the higher risk patients. They attributed this to inadequate model behaviour and/or surgical care [24]. However, in our situation the EuroSCORE II overestimated operative mortality in the lower risk groups and underestimated mortality in the higher risk groups. This may be explained by good surgical performance in the lower risk groups and poor surgical performance in the higher risk groups.

An alternate scoring system which takes into account the major risk factors such as ventricular dimensions may more accurately predict operative mortality in our cohort of patients. In order to develop an appropriate risk stratification model for patients undergoing valve surgery in South Africa, a multi-center database of heart valve surgery is required.

STUDY LIMITATIONS

The major limitation of this study is the inherent bias related to the retrospective and observational nature of the study. Patient selection, indication and timing of surgery may also affect the findings related to referral patterns and duration of antibiotic therapy. Another limitation is the heterogeneity of the procedures undertaken and microorganisms involved in the disease process. The small sample size also affects the assessment of the validity of the EuroSCORE II in our cohort of patients. Our cohort of patients is a high-risk category due to the underlying nature of the disease and this can have an influence on the underestimation of the predicted mortality by the EuroSCORE II.

CONCLUSION

We concluded that the most important risk factor for early outcome was LCOS, and for long term outcome was DVR. The EuroSCORE II had a good discriminatory ability and calibration, but generally underestimated mortality for the entire cohort of patients. Underestimation occurred particularly in the DVR and MVR groups, whereas, the EuroSCORE II overestimated mortality in the AVR and MV repair groups. This may be due to poor surgical performance in the higher risk patients and good surgical performance in the lower risk patients, respectively. When evaluating the EuroSCORE II at a cut point of 12%, it was evident that the higher risk group (>12%) had a significantly higher early and medium term mortality than the lower risk group (≤12%).

We will, however, need to evaluate a larger cohort of patients with other underlying cardiac conditions in order to make a more robust validation of the EuroSCORE II model in the South African context.

APPENDIX

TABLES

Table 1

Demographic and clinical characteristics of patients with active left sided native valve infective endocarditis for the entire cohort and treatment sub-groups

	Combined *N=96*	AVR *n=29*	MVR *n=27*	DVR *n=28*	MVRep *n=12*
Demographics					
Age (years)	35.2±14.0	42.8±13.6	29.7±11.0	33.5±11.8	33.7±18.6
Male	66 (69%)	24(83%)	14(52%)	21(75%)	7(58%)
BMI	20.9±4.5	22.1±4.5	20.9±5.6	20.2±3.9	20.1±2.9
LVEF (%)	61.5±11.9	57.1±11.5	64.6±13.1	62.5±11.4	62.8±9.5
LVEDD (mm)	6.0±1.0	6.4±0.8	5.9±0.9	6.1±1.1	5.3±0.8
NYHA III-IV	55 (57%)	19 (66%)	17 (57%)	16 (57%)	3 (25%)
Comorbidities					
HIV positive	8 (8%)	2(7%)	4(15%)	2(7%)	0
Dialysis	6 (6%)	3(10%)	0	3(11%)	0
Stroke	14 (15%)	1(3%)	7(26%)	3(11%)	3(25%)
Atrial fibrillation	10 (10%)	1(3%)	4(15%)	5(18%)	0
Indications for surgery					
Vegetation size >1cm	43 (45%)	11(38%)	14(52%)	13(46%)	5(42%)
CCF	79 (82%)	27(93%)	23(85%)	19(68%)	10(83%)
Failed medical therapy	83 (87%)	24(83%)	23(85%)	27(96%)	9(75%)
Embolic phenomena	38 (40%)	8(28%)	15(56%)	12(43%)	3(25%)
Preoperative state					
Critical pre-op state	26 (27%)	8(28%)	8(30%)	9(32%)	1(8%)
Emergency	20 (21%)	6(21%)	7(26%)	6(21%)	1(8%)
Urgent	35 (36%)	14(48%)	10(37%)	10(36%)	2(17%)
Elective	39 (41%)	8(28%)	10(37%)	12(43%)	9(75%)
EuroSCORE II>12%	20 (21%)	4 (14%)	5 (19%)	10 (36%)	1 (8%)
Concomitant procedures					
Tricuspid Annuloplasty	13 (14%)	1(3%)	3(11%)	7(25%)	2(17%)
CABG	1 (1%)	0	0	1(4%)	0
Prosthesis material					
Mechanical	68 (71%)	21(72%)	23(85%)	24(86%)	0
Bioprosthesis	16 (17%)	8(28%)	4(15%)	4(14%)	0
Pericardial patch	6 (6%)	3(10%)	0	3(11%)	0
Annuloplasty ring	12 (13%)	0	0	0	12(100%)
Microbiologic profile					
Unidentified	26 (27%)	8(28%)	5(19%)	12(43%)	1(8%)
Staphylococci	26 (27%)	7(24%)	11(41%)	5(18%)	3(25%)
Streptococci	27 (28%)	4(14%)	10(38%)	8(29%)	5(42%)
Gram negative	17 (18%)	10(34%)	1(4%)	3(11%)	3(25%)

AVR, Aortic valve replacement; MVR, Mitral valve replacement; DVR, Double valve replacement; MV, mitral valve; BMI, Body mass index; LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end diastolic dimension; NYHA, New York heart association; HIV, Human immunodeficiency virus; CCF, Congestive cardiac failure; EuroSCORE, European system for cardiac operative risk evaluation

Table 2

The early and late postoperative characteristics of the entire cohort and the treatment sub-groups

	Combined *N=96*	AVR *n=29*	MVR *n=27*	DVR *n=28*	MV rep *n=12*
Early postoperative course					
Inotropic support	70 (73%)	26(90%)	21(78%)	19(68%)	4(33%)
LCOS	5 (5%)	0	2(7%)	3(11%)	0
Dialysis	6 (6%)	3(10%)	0	3(11%)	0
Tamponade/Relook	6 (6%)	3(10%)	0	3(11%)	0
30-day mortality	11 (11%)	1 (3%)	4 (15%)	6 (21%)	0
90-day mortality	14 (15%)	2 (7%)	4(15%)	7(24%)	1 (8%)
ICU stay >24 hours	91 (95%)	29 (100%)	26 (96%)	26 (93%)	10 (83%)
Ventillation >24 hours	78 (81%)	26 (90%)	22 (81%)	20 (71%)	10 (83%)
Early MACE					
Bleeding	3 (3%)	1(3%)	0	1 (4%)	1(8%)
Clotted valve	1 (1%)	0	0	1 (4%)	0
Embolic stroke	4 (4%)	1(3%)	3(11%)	0	0
Heart block	3 (3%)	2 (7%)	1 (4%)	0	0
Hemorrhagic stroke	2 (2%)	0	0	2 (7%)	0
Paravalvular leak	1 (1%)	0	0	1 (4%)	0
Repaired valve failure	1 (1%)	0	0	0	1(8%)
Reoperation					
Other valve failure	1 (1%)	0	1 (4%)	0	0
Paravalvular leak	2 (2%)	2 (7%)	0	0	0
Late MACE					
Clotted valve	3 (3%)	1(3%)	0	2 (7%)	0
Embolic stroke/endocarditis	1 (1%)	0	0	1 (4%)	0
Embolic stroke	1 (1%)	0	0	1 (4%)	0
Hemorrhagic stroke	2 (2%)	1(3%)	1 (4%)	0	0
Paravalvular leak	1 (1%)	1(3%)	0	0	0
Repaired valve failure	1 (1%)	0	0	0	1(8%)
Reoperation					
Embolic stroke/endocarditis	2 (2%)	0	1 (4%)	1 (4%)	0
Embolic stroke/bioprosthesis failed	1 (1%)	0	0	1 (4%)	0
>90-day all mortality	12 (13%)	3(10%)	3(11%)	6 (21%)	0
>90-day valve mortality	10 (10%)	2(7%)	2(7%)	6(21%)	0
All-cause mortality	26 (27%)	5(17%)	7(26%)	13(46%)	1(8%)
Valve related mortality	23 (24%)	4(14%)	6(22%)	13(46%)	0

AVR, Aortic valve replacement; MVR, Mitral valve replacement; DVR, Double valve replacement; MV repair, mitral valve repair; LCOS Low cardiac output state; ICU, intensive care unit; MACE, major adverse cardiac event;

Table 3

The causes of early and late mortality in the entire cohort of patients (N=96)

Mortality cause	≤30 day mortality *n=11*	≤90 day mortality *n=14*	>90 day mortality *n=12*
Valve related			
Cardiac tamponade	1	1	0
Cardiogenic shock	2	2	0
Clotted valve	0	0	3
Prosthetic valve endocarditis	0	0	1
Septic Shock	4	6	0
Embolic CVA	2	2	4
Hemorrhagic CVA	2	2	2
Non valve related			
Bowel Obstruction	0	0	1
Cancer	0	1	0
HIV related	0	0	1

CVA, cerebrovascular accident; HIV, human immunodeficiency virus

Table 4

Cox Proportional Hazard Analysis: The statistically significant risk factors for early mortality (30 day) in the entire cohort of patients (Hazard Ratio)

Variable for Early mortality 30D		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Critical Pre-op State	No	70	100,400	3	0.03	1.0 (ref)	1.0 (ref)
	Yes	26	32,991	8	0.24	8.1 (2.1-30.0)	NS
Emergency	No	76	108,100	5	0.04	1.0 (ref)	1.0 (ref)
	Yes	20	25,328	6	0.24	4.9 (1.5-16.0)	NS
EuroSCORE II>12	No	70	102,200	3	0.03	1.0 (ref)	1.0 (ref)
	Yes	26	31,237	8	0.26	7.1 (2.2-23.3)	NS
HIV positive	No	88	128,900	8	0.06	1.0 (ref)	1.0 (ref)
	Yes	8	4,571	3	0.66	5.0 (1.3-18.9)	5.4 (1.4-20.7)
LCOS	No	91	133,400	6	0.05	1.0 (ref)	1.0 (ref)
	Yes	5	42	5	119.00	30.9 (7.9-120.0)	36.4 (6.5-203.7)
Pre-op emboli	No	58	82,440	2	0.02	1.0 (ref)	1.0 (ref)
	Yes	38	50,989	9	0.18	7.9 (1.7-36.4)	10.2 (1.8-58.0)
Vegetation size >1cm	No	53	83,545	2	0.02	1.0 (ref)	1.0 (ref)
	Yes	43	49,883	9	0.18	5.8 (1.3-27.0)	NS
NYHA ≥ III	No	41	57,565	1	0.01	1.0 (ref)	1.0 (ref)
	Yes	55	75,863	10	0.13	7.9 (1.0-61.5)	NS
Ventillation > 24 hours	No	76	115,900	4	0.03	1.0 (ref)	1.0 (ref)
	Yes	17	16,577	5	0.30	6.4 (1.7-24.1)	6.9 (1.4-33.4)

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

Table 5

Cox Proportional Hazard Analysis: The statistically significant risk factors for early mortality (90 day) in the entire cohort of patients (Hazard Ratio)

Variable for 90 day Mortality		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Critical Pre-op State	No	70	100,400	5	0.05	1.0 (ref)	1.0 (ref)
	Yes	26	32991	9	0.27	5.7 (1.9-17)	5.6 (1.2-26.9)
Emergency	No	76	108,100	7	0.06	1.0 (ref)	1.0 (ref)
	Yes	20	25,328	7	0.28	4.3 (1-12)	NS
EuroSCORE II>12	No	70	102,200	4	0.04	1.0 (ref)	1.0 (ref)
	Yes	26	31,237	10	0.32	6.5 (2.3-18.6)	4.2 (1.2-15.7)
LCOS	No	91	133,400	9	0.07	1.0 (ref)	1.0 (ref)
	Yes	5	42	5	119.00	31 (7.9-120)	39.5 (7.7-203.4)
Pre-op emboli	No	58	82,440	4	0.05	1.0 (ref)	1.0 (ref)
	Yes	38	50,989	10	0.20	4.5 (1-14)	5.6 (1.6-19.9)
Pre-op dialysis	No	90	131,500	11	0.08	1.0 (ref)	1.0 (ref)
	Yes	6	1890	3	1.59	4.5 (1.2-16.1)	NS
HIV	No	88	128,900	11	0.09	1.0 (ref)	1.0 (ref)
	Yes	8	4571	3	0.66	3.8 (1-13)	4.9 (1.3-18.3)
Pre-op AF	No	85	122,800	9	0.07	1.0 (ref)	1.0 (ref)
	Yes	10	10,529	4	0.38	3.9 (1.2-12.6)	NS
Vegetation > 1cm	No	53	83,545	4	0.05	1.0 (ref)	1.0 (ref)
	Yes	43	49,883	10	0.20	3.3 (1.0-10.6)	NS
Pericardial patch	No	90	130,000	11	0.05	1.0 (ref)	1.0 (ref)
	Yes	6	3432	3	0.28	5.5 (1.5-19.7)	NS
Ventillation>24hrs	No	76	115,900	6	0.05	1.0 (ref)	1.0 (ref)
	Yes	17	16,577	6	0.36	5.4 (1.7-16.9)	6.1 (1.6-23.1)

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

Table 6

Cox Proportional Hazard Analysis: The statistically significant risk factors for early major adverse cardiac and cerebrovascular events in the entire cohort of patients, adjusted for age, sex, NYHA, DVR, & HIV status.

Variable for Early MACCE		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Critical Pre-op State	No	70	92,484	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	26	23,956	12	0.50	7.1 (2.7-19.1)	3.5 (1.2-10.1)
Emergency	No	76	97,536	9	0.09	1.0 (ref)	1.0 (ref)
	Yes	20	18,904	9	0.48	4.7 (1.2-11.9)	NS
EuroSCORE II>12	No	70	94,238	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	26	22,202	12	0.54	6.1 (2.4-15.6)	4.4 (1.5-12.9)
LCOS	No	91	116,400	15	0.13	1.0 (ref)	1.0 (ref)
	Yes	5	42	3	71.43	8.7 (2.3-33.2)	6.1 (1.5-24.6)
Pre-op emboli	No	58	77,493	7	0.09	1.0 (ref)	1.0 (ref)
	Yes	38	38,947	11	0.28	2.9 (1.0-7.6)	3.1 (1.1-8.5)
Pre-op dialysis	No	90	115,900	13	0.11	1.0 (ref)	1.0 (ref)
	Yes	6	531	5	9.42	8.2 (2.8-23.5)	5.0 (1.5-17.1)
Pericardial patch	No	90	113,500	15	0.13	1.0 (ref)	1.0 (ref)
	Yes	6	2,928	3	1.02	4.2 (1.2-14.6)	NS
NYHA ≥ III	No	41	55,681	1	0.02	1.0 (ref)	1.0 (ref)
	Yes	55	60,759	17	0.28	15.6 (2.1-117.8)	16.8 (2.2-128.3)

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

Table 7

Observed and predicted 30-day mortality of the combined and treatment sub-groups with the AUROC curve

	Average Predicted 30-day mortality-Euro SCORE II (%)	Observed 30-day mortality %	P-value	AUROC
AVR (n=29)	5.8	3.4	0.54	0.92
MVR (n=27)	5.4	14.8	0.03	0.696
DVR (n=28)	10.6	21.4	0.06	0.837
MV repair (n=12)	3	0	0.54	-
Combined (n=96)	6.6	11.5	0.06	0.796

AUROC, area under receiver operating characteristic; AVR, aortic valve replacement: MVR, mitral valve replacement; DVR, aortic and mitral valve replacement; MV repair, mitral valve repair

Table 8

Cox Proportional Hazard Analysis: The statistically significant risk factors for late mortality (>90 day) in the entire cohort of patients, adjusted for age, sex, NYHA, DVR, & HIV status.

Variable for Late Mortality		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Female	No	66	90,331	5	0.06	1.0 (ref)	-
	Yes	30	43,098	7	0.16	3.4 (1.0-11.8)	-
HIV	No	88	128,900	10	0.04	1.0 (ref)	1.0 (ref)
	Yes	8	4571	2	0.11	4.9 (1.1-23.1)	6.6 (1.0-42.9)
DVR	No	68	106,300	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	28	27,147	6	0.22	4.6 (1.4-15.4)	8.1 (1.9-34.0)

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

Table 9

Cox Proportional Hazard Analysis: The statistically significant risk factors for late major adverse cardiac and cerebrovascular events in the entire cohort of patients adjusted for age, sex, NYHA & HIV status.

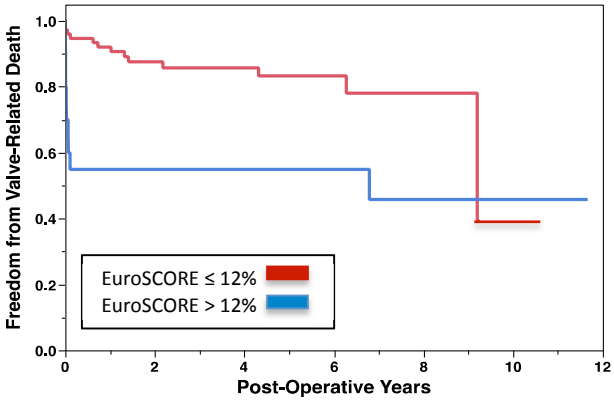
Variable for Late MACCE		N	Person-time	N events		"Crude" HR (95% CI)	Adj. HR (95% CI)
DVR	No	68	104,900	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	28	27,147	6	0.22	4.6 (1.3-15.2)	6.0 (1.6-22.2)
Pericardial patch	No	90	128,600	11	0.09	1.0 (ref)	1.0 (ref)
	Yes	6	3432	1	0.29	3.1 (0.4-24.8)	NS

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

FIGURES

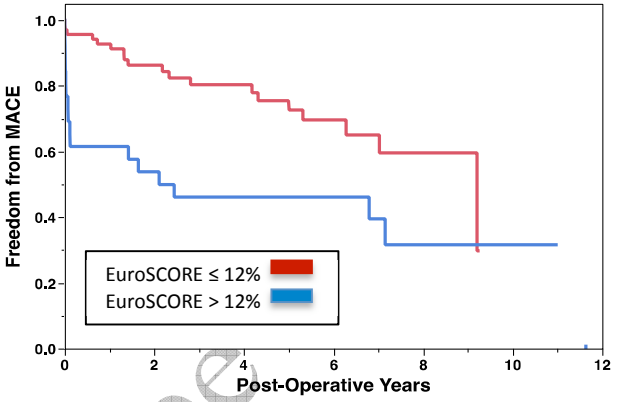
Figure 1: Long term freedom from (A) Valve related mortality and (B) Major adverse cardiac events (MACCE) in patients with a EuroSCORE II of >12% and ≤12%. Difference in survival was statistically significant in the early half compared to the latter half in both graphs.

A



P-Value = 0.0001		90-day	5 yrs.	10yrs.
EuroSCORE II ≤12% (n=76)	Percent	94.7±2.5	83.3±4.7	39.1±27.8
	No. at risk	72	30	1
EuroSCORE II >12% (n=20)	Percent	55.0±11.1	55.0±11.1	45.8±12.5
	No. at risk	12	7	3

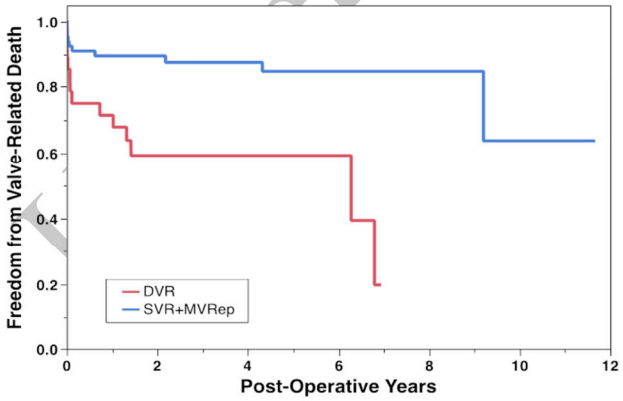
B



P-Value = 0.0002		90-day	5 yrs.	10yrs.
EuroSCORE II ≤12% (n=76)	Percent	97.1±2.0	75.5±5.9	29.8±21.5
	No. at risk	72	31	1
EuroSCORE II >12% (n=20)	Percent	61.5±9.5	46.2±9.8	31.7±10.9
	No. at risk	13	5	2

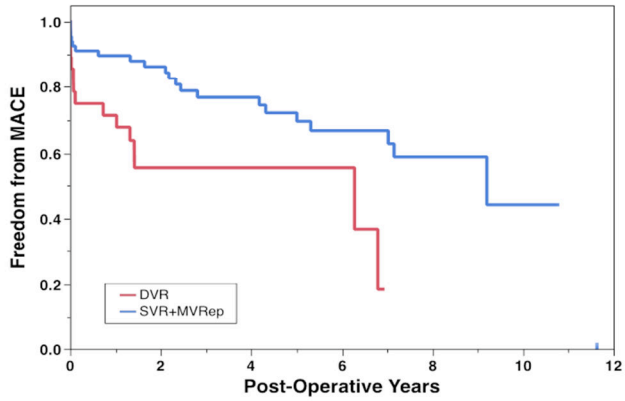
Figure 2: Long term freedom from (A) Valve related death and (B) Major adverse cardiac events in patients who had double valve replacement (DVR) compared to those who had single valve replacements and mitral valve repair. DVR is shown to be a higher risk group with higher mortality and MACE.

A



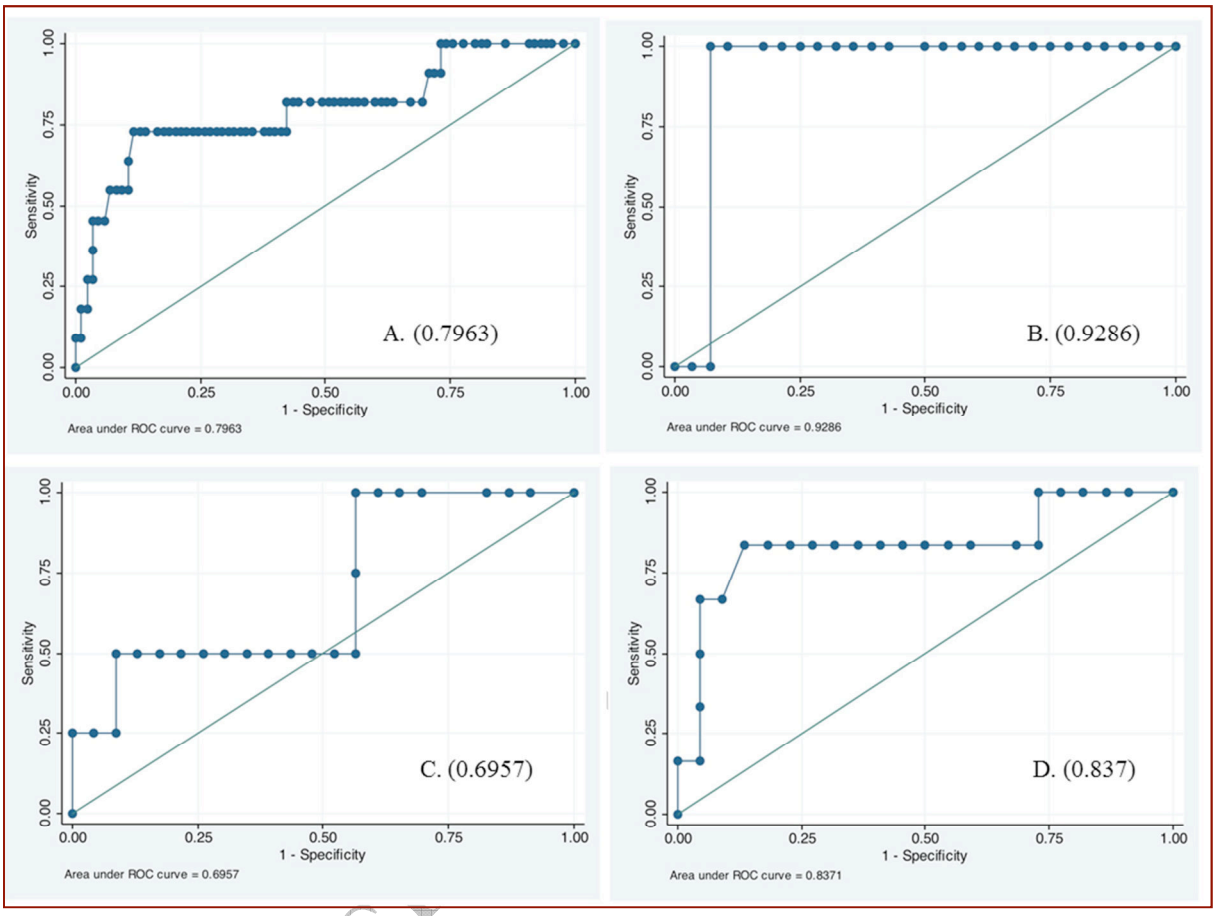
P-Value = 0.0002		90-day	5 yrs.	10 yrs.
DVR (n=28)	Percent	75±8.2	59.3±9.6	19.8±16.5
	No. at risk	22	8	1
SVR/MVRep (n=68)	Percent	91.2±3.4	85.0±4.8	63.7±18.8
	No. at risk	62	29	3

B



P-Value = 0.007		90-day	5 yrs.	10 yrs.
DVR (n=28)	Percent	85.7±6.6	55.4±9.7	18.5±15.4
	No. at risk	25	8	1
SVR/MVRep (n=68)	Percent	98.5±1.5	72.2±6.1	44.2±14.1
	No. at risk	68	29	3

Figure 3: Receiver operating characteristic curves for the EuroSCORE II in (A) Combined cohort, n = 96, (B) Aortic valve replacement, n = 29, (C) Mitral valve replacement, n = 27, and (D) Double valve replacement, n = 28.



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LONG TERM OUTCOME AND THE VALIDITY OF EUROSCORE-II IN NATIVE-VALVE SURGERY FOR ACTIVE ENDOCARDITIS IN A SOUTH AFRICAN COHORT

BY

JITHAN JACOB KOSHY, MARK ENGEL, PAUL HUMAN, HENRI CARRARA, PETER ZILLA, JOHAN BRINK
KSHJIT001

PART D: APPENDICES

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE
MASTER OF MEDICINE IN CARDIOTHORACIC SURGERY
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF CAPE TOWN

CONTENTS

Part D: Letters of Intent

UNIVERSITY OF CAPE TOWN MASTER OF MEDICINE LETTERS OF INTENT

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21st July 2014

Adri Winkler
Manager of the Postgraduate Unit
Postgraduate Office
University of Cape Town

RE: Submission of Master of Medicine in Cardiothoracic Surgery Thesis

This is to confirm that I, Jithan Jacob Koshy, intend to submit my MMed Dissertation in order to qualify for graduation in December 2014.

Student Details: Jithan Jacob Koshy
BScHB, MBChB
KSHJIT001

Supervisor: Johan Brink
MBChB, FC Cardio SA
Chris Barnard Division of Cardiothoracic Surgery
University of Cape Town

Please contact me if there are any queries.

Regards,

Jithan Koshy

Part D: Letters of Intent

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BScHB, MBChB (UNZA)
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21st July 2014

Adri Winkler
Manager of the Postgraduate Unit
Postgraduate Office
University of Cape Town

RE: Format of Master of Medicine (MMed) Thesis Submission

My Master of Medicine Dissertation is a retrospective review entitled:

LONG TERM OUTCOME AND THE VALIDITY OF EUROSCORE-II IN NATIVE-VALVE SURGERY FOR ACTIVE ENDOCARDITIS IN A SOUTH AFRICAN COHORT

The final document has been submitted in four parts:

Part A – Protocol for the retrospective review

The protocol has been completed and approved by the Surgical Departmental Research Committee and the Faculty Research Ethics Committee.

Part B – Literature Review

The literature review focuses on the epidemiology of infective endocarditis in Africa and the influence of rheumatic heart disease, the microbiologic profile of the disease, predisposing factors, the current guidelines in the prevention and management of the disease, and the risk factors for early and long-term adverse events. Part B has been completed in a general style fit for publication in most journals.

Part C – Manuscript

The final manuscript has been completed using the guidelines for submission for the European Journal of Cardiothoracic Surgery. The document has not yet been officially published in the journal and for this reason the published document and original document may differ slightly after review.

Part D – Appendices

All data sheets, resource material, style guidelines and original documentation have been included in Part D as appendices, some of these appendices may also appear in parts A to C.

Regards,

Jithan Koshy

Part D: Instructions to Authors

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Maximum number of Videos	2	2	2	2	2	2	0

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*Figures including composite parts a,b,c etc. will only be allowed if ALL of the constituting parts are mounted into 1 image / 1 electronic file.

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The submission should be classified into one of the following types: Original articles (OA); Editorials (ED); Review articles (REV); Case reports (CR); Images in Cardio-thoracic Surgery (ICTS); How-to-do-it (HTDI); Letters to the Editor (LTTE) - see the journal for examples. The specification for each submission category should contain but not exceed the following.

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Multi-author books

[3] Huang GJ, Wu YK. Operative technique for carcinoma of the esophagus and gastric cardia. In: Huang GJ, Wu YK, editors. Carcinoma of the esophagus and gastric cardia. Berlin: Springer, 1984:313–348.

On-line-only publications (note: DOI is the only acceptable on-line citation)

[4] Kazaz M, Celkan MA, Ustunsoy H, Baspinar O. Mitral annuloplasty with biodegradable ring for infective endocarditis: a new tool for the surgeon for value repair in childhood. Interact CardioVasc Thorac Surg doi: 10.1510/icvts.2005.105833

Authors are encouraged to cite previous key references from EJCTS/ICVTS in order to establish that their studies are well founded.

Figures: All artwork and lettering must be of professional quality. Reproduction of color figures is possible, but the authors will be asked to pay the extra printing costs (approximately €270 per color page). Figures should be numbered in the order they appear in the text.

Videos: Where appropriate, video sequences may be submitted using standard digital video formats. Videos must be relevant and contain only vital/novel information and should ideally run no longer than 30 seconds (see specifications below). One still image (screen shot) per video must also be submitted. Videos will be displayed in the on-line journal only - the video URL address will be printed in the hardcopy journal to link to the video in the on-line journal. Videos should be numbered in the order they appear in the text.

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Part D: Instructions to Authors

(2) Artwork for on-line review (creation of optimal **PDF**): .jpg files preferred (specification: 72 dots per inch/600 pixel screen width, grayscale for black andwhite,RGBfor color).One file per figure - upload as **I**mage files.

(3) **Orig**inal artwork for print (all revised manuscripts only): .tif files obligatory (specification: sized to 8.4 cm column width, resolution: 1000 dots per inch for line art, 300 dots per inch for grayscale/combine/color, CMYK for color) – upload as Supplemental files. This specification enables your artwork to be reproduced with the best possible printing quality. Failure to upload print quality artwork files with the revision will delay eventual publication. If unable to supply artwork electronically in the required format (only), post hard-copies (GLOSSY PRINTS) to the address below for scanning.

(4) Video (on-line viewing only): .avi, .mov, .mpg or .rm files preferred (specification: frame size: 320 × 240 pixels, duration: maximum 30 seconds, number of frames/second: 20–30). Corresponding still images also required: .jpg preferred (specification: 72 dots per inch) – upload as Supplemental files.

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One complete copy of the manuscript and three sets of original illustrations – including still image(s) for any video(s) (marked on the back to indicate the corresponding author's name, the figure number and the top edge) should be submitted together with the electronic file of the text (and artwork/videos if possible) on disk, zip disk or CD.

Note that the review system is totally electronic so you must be prepared to register and work on-line to further process your submission – even if you submitted on paper with disk. Also, processing of hard-copy manuscripts is generally slower than for electronic submissions.

Revised manuscripts

Label accordingly (2nd, 3rd version) including new figures, videos and tables; provide a covering letter, replying point-by-point to the Editor's and referees' comments, and describing the changes which have been made in the revised version. Highlight the changes in the revised manuscript to facilitate editorial reassessment.

Reprints. After publication, 25 reprints will provided free of charge. Additional reprints (100 minimum) can be ordered at prices quoted on the reprint order form which will be sent out with the proofs.

Part D: Data Extraction Sheet

DATA EXTRACTION SHEET

DATA CAPTURE SHEET				
Variable	**Category**	**Entry**	**Formula**	**Value**
Patient Study Code		1-150		
Patient Folder Number		xxxxxxxxxx		
Patient ID number		xxxxxxxxxxxxxxxx		
Age at Surgery (years)		years		
Male		Yes=1/No=0		
Female		Yes=1/No=0		
Pre-op AF		Yes=1/No=0		
Weight		Kg		
BMI			Weight/Height2	
Echo Parameters:EF		Percentage		
LVEDD		millimeters		
Poor Socioeconomics		Yes=1/No=0	At least 2 of (Education<Standard 8, Informal settlement or Unemployed)	
HIV Positive		Yes=1/No=0		
Pre-op Dialysis		Yes=1/No=0		
Pre-op CVA		Yes=1/No=0		
Rheumatic Heart Disease		Yes=1/No=0		
Vegetation size >1cm		Yes=1/No=0		
Indication-CCF		Yes=1/No=0		
Indications for Surgery-Failed Medical Tx		Yes=1/No=0		
Indication-Embolization		Yes=1/No=0		
Native Valve IE		Yes=1/No=0		
Active IE		Yes=1/No=0		
Previous IE		Yes=1/No=0		
Prosthetic IE		Yes=1/No=0		
Unidentified organism		Yes=1/No=0		
Staph		Yes=1/No=0		
Staphylococcus Aureus		Yes=1/No=0		
Coag -ve Staph		Yes=1/No=0		
Streptococcus		Yes=1/No=0		
Gram negative Organisms		Yes=1/No=0		
Interval from ATB start (Days)		Days		
ASA State		1,2,3,4,5 or 6		
Emergency		Yes=1/No=0		
Urgent		Yes=1/No=0		
Elective		Yes=1/No=0		
Euro score II		Percentage		
Age at Surgery (years)		years		
Gender	male/female	male = 1/female = 0		
Creatinine clearance		ml/min	(140-age(years) X weight (kg) X (0.85 if female)/(72 X serum creatinine (mg/dl)	
Serum creatinine		micromol/l		
Extracardiac arteriopathy	claudication	Yes=1/No=0		
	carotid occlusion	Yes=1/No=0		
	amputation for arterial disease	Yes=1/No=0		
	intervention on abdominal aorta, limb arteries or carotids	Yes=1/No=0		
Poor mobility		Yes=1/No=0		
Previous Cardiac Surgery		Yes=1/No=0		
Chronic lung disease		Yes=1/No=0		
Active endocarditis		Yes=1/No=0		
Critical Preop State		Yes=1/No=0		
Diabetes on insulin		Yes=1/No=0		
NYHA	I, II, III or IV			
CCS class IV angina		Yes=1/No=0		
LV Function	Good (LVEF > 50%)	Yes=1/No=0		
	Moderate (LVEF 31-50%)	Yes=1/No=0		
	Poor (LVEF 21-30%)	Yes=1/No=0		
	Very poor (LVEF<20%)	Yes=1/No=0		
Recent MI		Yes=1/No=0		
Pulmonary hypertension	No	Yes=1/No=0		
	Moderate(PA systolic 31-55mmHg)	Yes=1/No=0		
	Severe (PA systolic >55mmHg)	Yes=1/No=0		
Urgency	Elective	Yes=1/No=0		
	Urgent	Yes=1/No=0		
	Emergency	Yes=1/No=0		
	Emergency salvage	Yes=1/No=0		
Weight of intervention	Isolated CABG	Yes=1/No=0		
	Single non CABG	Yes=1/No=0		
	2 procedure	Yes=1/No=0		
	3 procedure	Yes=1/No=0		
Aortic IE		Yes=1/No=0		
Mitral IE		Yes=1/No=0		
Aortic/Mitral IE		Yes=1/No=0		
Operation-SVR		Yes=1/No=0		
Operation-AVR/MVR		Yes=1/No=0		
Mitral Valve Repair		Yes=1/No=0		
Mechanical prosthesis		Yes=1/No=0		
Bioprosthesis		Yes=1/No=0		
Pericardial patch		Yes=1/No=0		
Duration of Death &Survival(Days)		Days		
MACE-All Cause Mortality		Yes=1/No=0		
MACE- Valve Related death		Yes=1/No=0		
Mortality Category	Cardiac tamponade	Yes=1/No=0		
	cardiogenic shock	Yes=1/No=0		
	clotted valve	Yes=1/No=0		
	prosthetic endocarditis	Yes=1/No=0		
	septic shock	Yes=1/No=0		
	embolic CVA	Yes=1/No=0		
	hemorrhagic CVA	Yes=1/No=0		
	Others	Yes=1/No=0		
MACE category	Valve mortality	Yes=1/No=0		
	Reoperation for the valve	Yes=1/No=0		
	bleeding	Yes=1/No=0		
	clotted valve	Yes=1/No=0		
	embolic CVA	Yes=1/No=0		
	hemorrhagic CVA	Yes=1/No=0		
	heart block	Yes=1/No=0		
	paravalvar leak	Yes=1/No=0		
	repaired valve failure	Yes=1/No=0		
MACE-Reop		Yes=1/No=0		
30 Day Mortality		Yes=1/No=0		
>30 Day Mortality		Yes=1/No=0		
90 day mortality		Yes=1/No=0		
>90 day mortality		Yes=1/No=0		
Post Op Tamponade		Yes=1/No=0		
ICU (Hrs)		Hours		
Ventilation (Hrs)		Hours		
Duration to All MACE and current survival		Days		
MACE-ALL		Yes=1/No=0		
MACE-Category		Yes=1/No=0		

Part D: Telephonic Participation Sheet

TELEPHONIC PARTICIPATION SHEET

Patient name			
Relative/Friend			
Doctor Involved in care at local clinic			
Nurse Involved in care at local clinic			
Telephonic Details			
Address			
Name of Local Clinic			
Annual Clinic visit	Yes/No		
Cardiology clinic visit	Yes/No		
INR Clinic visit	Yes/No		
Regular monthly INR	Yes/No		
If working, what kind of work	Yes/No	Type	
Is there shortness of breath when walking, climbing stairs? Mild	Yes/No		
Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.	Yes/No		
Shoprtness of breath when walking short distances (20–100 m), comfortable only at rest	Yes/No		
Severe limitations. Experiences symptoms even while *at rest* . Mostly bedbound patients	Yes/No		
NYHA status	I,II,III or IV		
Hospitalization after surgery: if yes then reason	Yes/No	Reason	
Stroke after surgery	Yes/No		
Major bleeding after surgery	Yes/No		
Heart rhythm disturbance after surgery requiring hospitalisation	Yes/No		
Reoperation after surgery	Yes/No		
Valve complications: if so what happened (clotted valve, leaking valve, valve infection)	Yes/No	Type	
Clots in other parts of the body	Yes/No	Where	
Dates for any of the above complications	Date	Type of Complcation	
Did the patient get admitted to hospital for the complication, when and where	Yes/No	when	where
If relative interviewed in case of death: what were the circumstances leading to death			
Was death sudden, unexpected	Yes/No		
Was death at home	Yes/No		
Was death in the hospital	Yes/No		
Did the patient develop stroke before he/she died	Yes/No		
If in hospital death, what did the doctors say was the cause of death	Yes/No	Cause	
Date of death	Date		

TECHNICAL APPENDICES; TABLES

Table 1: Demographic and clinical characteristics of patients with active left sided native valve infective endocarditis for the entire cohort and treatment sub-groups

	Combined *N=96*	AVR *n=29*	MVR *n=27*	DVR *n=28*	MVRep *n=12*
Demographics					
Age (years)	35.2±14.0	42.8±13.6	29.7±11.0	33.5±11.8	33.7±18.6
Male	66 (69%)	24(83%)	14(52%)	21(75%)	7(58%)
BMI	20.9±4.5	22.1±4.5	20.9±5.6	20.2±3.9	20.1±2.9
LVEF (%)	61.5±11.9	57.1±11.5	64.6±13.1	62.5±11.4	62.8±9.5
LVEDD (mm)	6.0±1.0	6.4±0.8	5.9±0.9	6.1±1.1	5.3±0.8
NYHA III-IV	55 (57%)	19 (66%)	17 (57%)	16 (57%)	3 (25%)
Comorbidities					
HIV positive	8 (8%)	2(7%)	4(15%)	2(7%)	0
Dialysis	6 (6%)	3(10%)	0	3(11%)	0
Stroke	14 (15%)	1(3%)	7(26%)	3(11%)	3(25%)
Atrial fibrillation	10 (10%)	1(3%)	4(15%)	5(18%)	0
Underlying cardiac conditions					
RHD	83 (87%)	24(83%)	24(89%)	26(93%)	9(75%)
No underlying pathology	6 (6%)	1(3%)	1(4%)	1(4%)	3(25%)
Degenerative	2 (2%)	1(3%)	1(4%)	0	0
Others	5 (5%)	3 (10%)	1 (4%)	1 (4%)	
Indications for surgery					
Vegetation size >1cm	43 (45%)	11(38%)	14(52%)	13(46%)	5(42%)
CCF	79 (82%)	27(93%)	23(85%)	19(68%)	10(83%)
Failed medical therapy	83 (87%)	24(83%)	23(85%)	27(96%)	9(75%)
Embolic phenomena	38 (40%)	8(28%)	15(56%)	12(43%)	3(25%)
Preoperative state					
Critical pre-op state	26 (27%)	8(28%)	8(30%)	9(32%)	1(8%)
Emergency	20 (21%)	6(21%)	7(26%)	6(21%)	1(8%)
Urgent	35 (36%)	14(48%)	10(37%)	10(36%)	2(17%)
Elective	39 (41%)	8(28%)	10(37%)	12(43%)	9(75%)
EuroSCORE II>12	20 (21%)	4 (14%)	5 (19%)	10 (36%)	1 (8%)
Concomitant procedures					
Tricuspid Annuloplasty	13 (14%)	1(3%)	3(11%)	7(25%)	2(17%)
CABG	1 (1%)	0	0	1(4%)	0
Prosthesis material					
Mechanical	68 (71%)	21(72%)	23(85%)	24(86%)	0
Bioprosthesis	16 (17%)	8(28%)	4(15%)	4(14%)	0
Pericardial patch	6 (6%)	3(10%)	0	3(11%)	0
Annuloplasty ring	12 (13%)	0	0	0	12(100%)
Microbiologic profile					
Unidentified	26 (27%)	8(28%)	5(19%)	12(43%)	1(8%)
Staphylococci	26 (27%)	7(24%)	11(41%)	5(18%)	3(25%)
Streptococci	27 (28%)	4(14%)	10(38%)	8(29%)	5(42%)
Gram negative	17 (18%)	10(34%)	1(4%)	3(11%)	3(25%)

AVR, Aortic valve replacement; MVR, Mitral valve replacement; DVR, Double valve replacement; MV, mitral valve; BMI, Body mass index; LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end diastolic dimension; NYHA, New York heart association; HIV, Human immunodeficiency virus; RHD, Rheumatic heart disease; CCF, Congestive cardiac failure; EuroSCORE, European system for cardiac operative risk evaluation

Part D: Technical Appendices; Tables

Table 2: The early and late postoperative characteristics of the entire cohort and the treatment sub-groups

	Combined *N=96*	AVR *n=29*	MVR *n=27*	DVR *n=28*	MV rep *n=12*
Early postoperative course					
Inotropic support	70 (73%)	26(90%)	21(78%)	19(68%)	4(33%)
LCOS	5 (5%)	0	2(7%)	3(11%)	0
Dialysis	6 (6%)	3(10%)	0	3(11%)	0
Tamponade/Relook	6 (6%)	3(10%)	0	3(11%)	0
30-day mortality	11 (11%)	1 (3%)	4 (15%)	6 (21%)	0
90-day mortality	14 (15%)	2 (7%)	4(15%)	7(24%)	1 (8%)
ICU stay >24 hours	91 (95%)	29 (100%)	26 (96%)	26 (93%)	10 (83%)
Ventillation >24 hours	78 (81%)	26 (90%)	22 (81%)	20 (71%)	10 (83%)
Early MACE					
Bleeding	3 (3%)	1(3%)	0	1 (4%)	1(8%)
Clotted valve	1 (1%)	0	0	1 (4%)	0
Embolic stroke	4 (4%)	1(3%)	3(11%)	0	0
Heart block	3 (3%)	2 (7%)	1 (4%)	0	0
Hemorrhagic stroke	2 (2%)	0	0	2 (7%)	0
Paravalvar leak	1 (1%)	0	0	1 (4%)	0
Repaired valve failure	1 (1%)	0	0	0	1(8%)
Reoperation					
Other valve failure	1 (1%)	0	1 (4%)	0	0
Paravalvar leak	2 (2%)	2 (7%)	0	0	0
Late MACE					
Clotted valve	3 (3%)	1(3%)	0	2 (7%)	0
Embolic stroke/endocarditis	1 (1%)	0	0	1 (4%)	0
Embolic stroke	1 (1%)	0	0	1 (4%)	0
Hemorrhagic stroke	2 (2%)	1(3%)	1 (4%)	0	0
Paravalvar leak	1 (1%)	1(3%)	0	0	0
Repaired valve failure	1 (1%)	0	0	0	1(8%)
Reoperation					
Embolic stroke/endocarditis	2 (2%)	0	1 (4%)	1 (4%)	0
Embolic stroke/bioprosthesis failed	1 (1%)	0	0	1 (4%)	0
>90-day all mortality	12 (13%)	3(10%)	3(11%)	6 (21%)	0
>90-day valve mortality	10 (10%)	2(7%)	2(7%)	6(21%)	0
All-cause mortality	26 (27%)	5(17%)	7(26%)	13(46%)	1(8%)
Valve related mortality	23 (24%)	4(14%)	6(22%)	13(46%)	0

AVR, Aortic valve replacement; MVR, Mitral valve replacement; DVR, Double valve replacement; MV repair, mitral valve repair; LCOS Low cardiac output state; ICU, intensive care unit; MACE, major adverse cardiac event;

Part D: Technical Appendices; Tables

Table 3: The causes of early and late mortality in the entire cohort of patients (N=96)

Mortality cause	≤30 day mortality *n=11*	≤90 day mortality *n=14*	>90 day mortality *n=12*
Valve related			
Cardiac tamponade	1	1	0
Cardiogenic shock	2	2	0
Clotted valve	0	0	3
Prosthetic valve endocarditis	0	0	1
Septic Shock	4	6	0
Embolic CVA	2	2	4
Hemorrhagic CVA	2	2	2
Non valve related			
Bowel Obstruction	0	0	1
Cancer	0	1	0
HIV related	0	0	1

CVA, cerebrovascular accident; HIV, human immunodeficiency virus

Part D: Technical Appendices; Tables

Table 4: Cox Proportional Hazard Analysis: The statistically significant risk factors for early mortality (30 day) in the entire cohort of patients (Hazard Ratio)

Variable for Early mortality 30D		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Critical Pre-op State	No	70	100,400	3	0.03	1.0 (ref)	1.0 (ref)
	Yes	26	32,991	8	0.24	8.1 (2.1-30.0)	NS
Emergency	No	76	108,100	5	0.04	1.0 (ref)	1.0 (ref)
	Yes	20	25,328	6	0.24	4.9 (1.5-16.0)	NS
EuroSCORE II>12	No	70	102,200	3	0.03	1.0 (ref)	1.0 (ref)
	Yes	26	31,237	8	0.26	7.1 (2.2-23.3)	NS
HIV positive	No	88	128,900	8	0.06	1.0 (ref)	1.0 (ref)
	Yes	8	4,571	3	0.66	5.0 (1.3-18.9)	5.4 (1.4-20.7)
LCOS	No	91	133,400	6	0.05	1.0 (ref)	1.0 (ref)
	Yes	5	42	5	119.00	30.9 (7.9-120.0)	36.4 (6.5-203.7)
Pre-op emboli	No	58	82,440	2	0.02	1.0 (ref)	1.0 (ref)
	Yes	38	50,989	9	0.18	7.9 (1.7-36.4)	10.2 (1.8-58.0)
Vegetation size >1cm	No	53	83,545	2	0.02	1.0 (ref)	1.0 (ref)
	Yes	43	49,883	9	0.18	5.8 (1.3-27.0)	NS
NYHA ≥ III	No	41	57,565	1	0.01	1.0 (ref)	1.0 (ref)
	Yes	55	75,863	10	0.13	7.9 (1.0-61.5)	NS
Ventillation > 24 hours	No	76	115,900	4	0.03	1.0 (ref)	1.0 (ref)
	Yes	17	16,577	5	0.30	6.4 (1.7-24.1)	6.9 (1.4-33.4)

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

Part D: Technical Appendices; Tables

Table 5: Cox Proportional Hazard Analysis: The statistically significant risk factors for early mortality (90 day) in the entire cohort of patients (Hazard Ratio)

Variable for 90 day Mortality		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Critical Pre-op State	No	70	100,400	5	0.05	1.0 (ref)	1.0 (ref)
	Yes	26	32991	9	0.27	5.7 (1.9-17)	5.6 (1.2-26.9)
Emergency	No	76	108,100	7	0.06	1.0 (ref)	1.0 (ref)
	Yes	20	25,328	7	0.28	4.3 (1-12)	NS
EuroSCORE II>12	No	70	102,200	4	0.04	1.0 (ref)	1.0 (ref)
	Yes	26	31,237	10	0.32	6.5 (2.3-18.6)	4.2 (1.2-15.7)
LCOS	No	91	133,400	9	0.07	1.0 (ref)	1.0 (ref)
	Yes	5	42	5	119.00	31 (7.9-120)	39.5 (7.7-203.4)
Pre-op emboli	No	58	82,440	4	0.05	1.0 (ref)	1.0 (ref)
	Yes	38	50,989	10	0.20	4.5 (1-14)	5.6 (1.6-19.9)
Pre-op dialysis	No	90	131,500	11	0.08	1.0 (ref)	1.0 (ref)
	Yes	6	1890	3	1.59	4.5 (1.2-16.1)	NS
HIV	No	88	128,900	11	0.09	1.0 (ref)	1.0 (ref)
	Yes	8	4571	3	0.66	3.8 (1-13)	4.9 (1.3-18.3)
Pre-op AF	No	85	122,800	9	0.07	1.0 (ref)	1.0 (ref)
	Yes	10	10,529	4	0.38	3.9 (1.2-12.6)	NS
Vegetation > 1cm	No	53	83,545	4	0.05	1.0 (ref)	1.0 (ref)
	Yes	43	49,883	10	0.20	3.3 (1.0-10.6)	NS
Pericardial patch	No	90	130,000	11	0.05	1.0 (ref)	1.0 (ref)
	Yes	6	3432	3	0.28	5.5 (1.5-19.7)	NS
Ventillation>24hrs	No	76	115,900	6	0.05	1.0 (ref)	1.0 (ref)
	Yes	17	16,577	6	0.36	5.4 (1.7-16.9)	6.1 (1.6-23.1)

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

Part D: Technical Appendices; Tables

Table 6: Cox Proportional Hazard Analysis: The statistically significant risk factors for early major adverse cardiac and cerebrovascular events in the entire cohort of patients, adjusted for age, sex, NYHA, DVR, & HIV status.

Variable for Early MACCE		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Critical Pre-op State	No	70	92,484	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	26	23,956	12	0.50	7.1 (2.7-19.1)	3.5 (1.2-10.1)
Emergency	No	76	97,536	9	0.09	1.0 (ref)	1.0 (ref)
	Yes	20	18,904	9	0.48	4.7 (1.2-11.9)	NS
EuroSCORE II>12	No	70	94,238	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	26	22,202	12	0.54	6.1 (2.4-15.6)	4.4 (1.5-12.9)
LCOS	No	91	116,400	15	0.13	1.0 (ref)	1.0 (ref)
	Yes	5	42	3	71.43	8.7 (2.3-33.2)	6.1 (1.5-24.6)
Pre-op emboli	No	58	77,493	7	0.09	1.0 (ref)	1.0 (ref)
	Yes	38	38,947	11	0.28	2.9 (1.0-7.6)	3.1 (1.1-8.5)
Pre-op dialysis	No	90	115,900	13	0.11	1.0 (ref)	1.0 (ref)
	Yes	6	531	5	9.42	8.2 (2.8-23.5)	5.0 (1.5-17.1)
Pericardial patch	No	90	113,500	15	0.13	1.0 (ref)	1.0 (ref)
	Yes	6	2,928	3	1.02	4.2 (1.2-14.6)	NS
NYHA ≥ III	No	41	55,681	1	0.02	1.0 (ref)	1.0 (ref)
	Yes	55	60,759	17	0.28	15.6 (2.1-117.8)	16.8 (2.2-128.3)

EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation

Table 7: Observed and predicted 30-day mortality of the combined and treatment sub-groups with the AUROC curve

	Average Predicted 30-day mortality-Euro SCORE II (%)	Observed 30-day mortality %	P-value	AUROC
AVR (n=29)	5.8	3.4	0.54	0.92
MVR (n=27)	5.4	14.8	0.03	0.696
DVR (n=28)	10.6	21.4	0.06	0.837
MV repair (n=12)	3	0	0.54	-
Combined (n=96)	6.6	11.5	0.06	0.796

AUROC, area under receiver operating characteristic; AVR, aortic valve replacement: MVR, mitral valve replacement; DVR, aortic and mitral valve replacement; MV repair, mitral valve repair

Part D: Technical Appendices; Tables

Table 8: Cox Proportional Hazard Analysis: The statistically significant risk factors for late mortality (>90 day) in the entire cohort of patients, adjusted for age, sex, NYHA, DVR, & HIV status.

Variable for Late Mortality		N	Person-time	N events	Event Rate/1000	"Crude" HR (95% CI)	Adj. HR (95% CI)
Female	No	66	90,331	5	0.06	1.0 (ref)	-
	Yes	30	43,098	7	0.16	3.4 (1.0-11.8)	-
HIV	No	88	128,900	10	0.04	1.0 (ref)	1.0 (ref)
	Yes	8	4571	2	0.11	4.9 (1.1-23.1)	6.6 (1.0-42.9)
DVR	No	68	106,300	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	28	27,147	6	0.22	4.6 (1.4-15.4)	8.1 (1.9-34.0)
EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation							

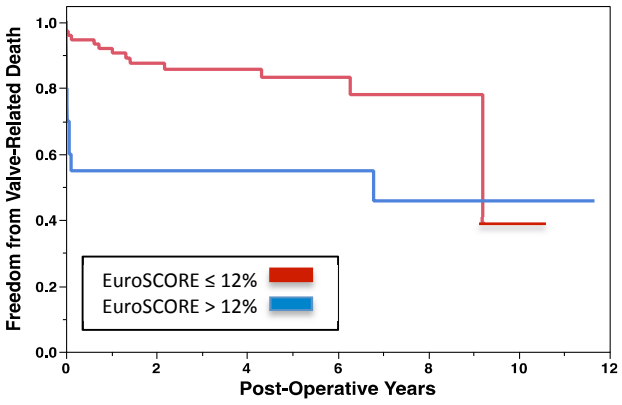
Table 9: Cox Proportional Hazard Analysis: The statistically significant risk factors for late major adverse cardiac and cerebrovascular events in the entire cohort of patients adjusted for age, sex, NYHA & HIV status.

Variable for Late MACCE		N	p-t	N events		"Crude" HR (95% CI)	Adj. HR (95% CI)
DVR	No	68	104,900	6	0.06	1.0 (ref)	1.0 (ref)
	Yes	28	27,147	6	0.22	4.6 (1.3-15.2)	6.0 (1.6-22.2)
Pericardial patch	No	90	128,600	11	0.09	1.0 (ref)	1.0 (ref)
	Yes	6	3432	1	0.29	3.1 (0.4-24.8)	NS
EuroSCORE, European system for cardiac operative risk evaluation; LCOS, low cardiac output state; Pre-op, preoperative; AF, atrial fibrillation							

TECHNICAL APPENDICES; FIGURES

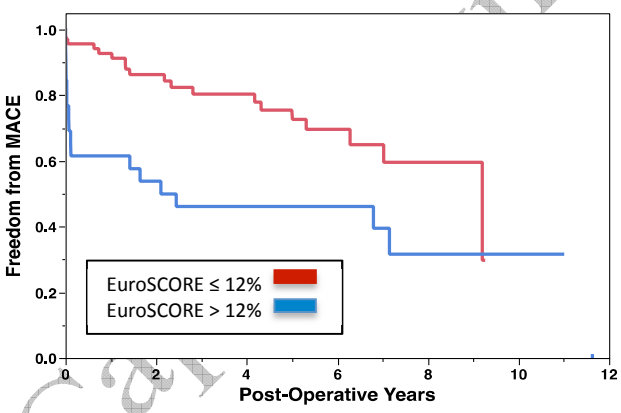
Figure 1: Long term freedom from (A) Valve related mortality and (B) Major adverse cardiac events (MACCE) in patients with a EuroSCORE II cut-off of > 12% and ≤ 12%. Difference in survival was statistically significant in the early half compared to the latter half in both graphs.

A



P-Value = 0.0001		90-day	5 yrs.	10yrs.
EuroSCORE II ≤12% (n=76)	Percent	94.7±2.5	83.3±4.7	39.1±27.8
	No. at risk	72	30	1
EuroSCORE II >12% (n=20)	Percent	55.0±11.1	55.0±11.1	45.8±12.5
	No. at risk	12	7	3

B

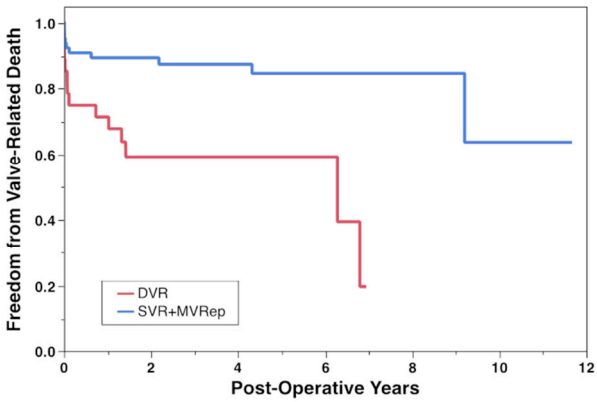


P-Value = 0.0002		90-day	5 yrs.	10yrs.
EuroSCORE II ≤12% (n=76)	Percent	97.1±2.0	75.5±5.9	29.8±21.5
	No. at risk	72	31	1
EuroSCORE II >12% (n=20)	Percent	61.5±9.5	46.2±9.8	31.7±10.9
	No. at risk	13	5	2

Part D: Technical Appendices; Figures

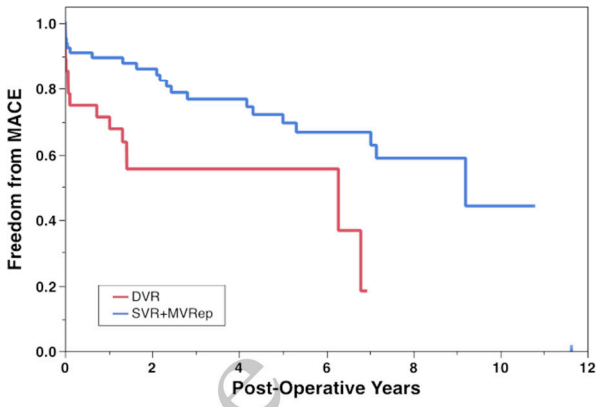
Figure 2: Long term freedom from (A) Valve related death and (B) Major adverse cardiac events in patients who had double valve replacement (DVR) compared to those who had single valve replacements and mitral valve repair. DVR is a higher risk group with higher mortality and MACE.

A



P-Value = 0.0002		90-day	5 yrs.	10 yrs.
DVR (n=28)	Percent	75±8.2	59.3±9.6	19.8±16.5
	No. at risk	22	8	1
SVR/MVRep (n=68)	Percent	91.2±3.4	85.0±4.8	63.7±18.8
	No. at risk	62	29	3

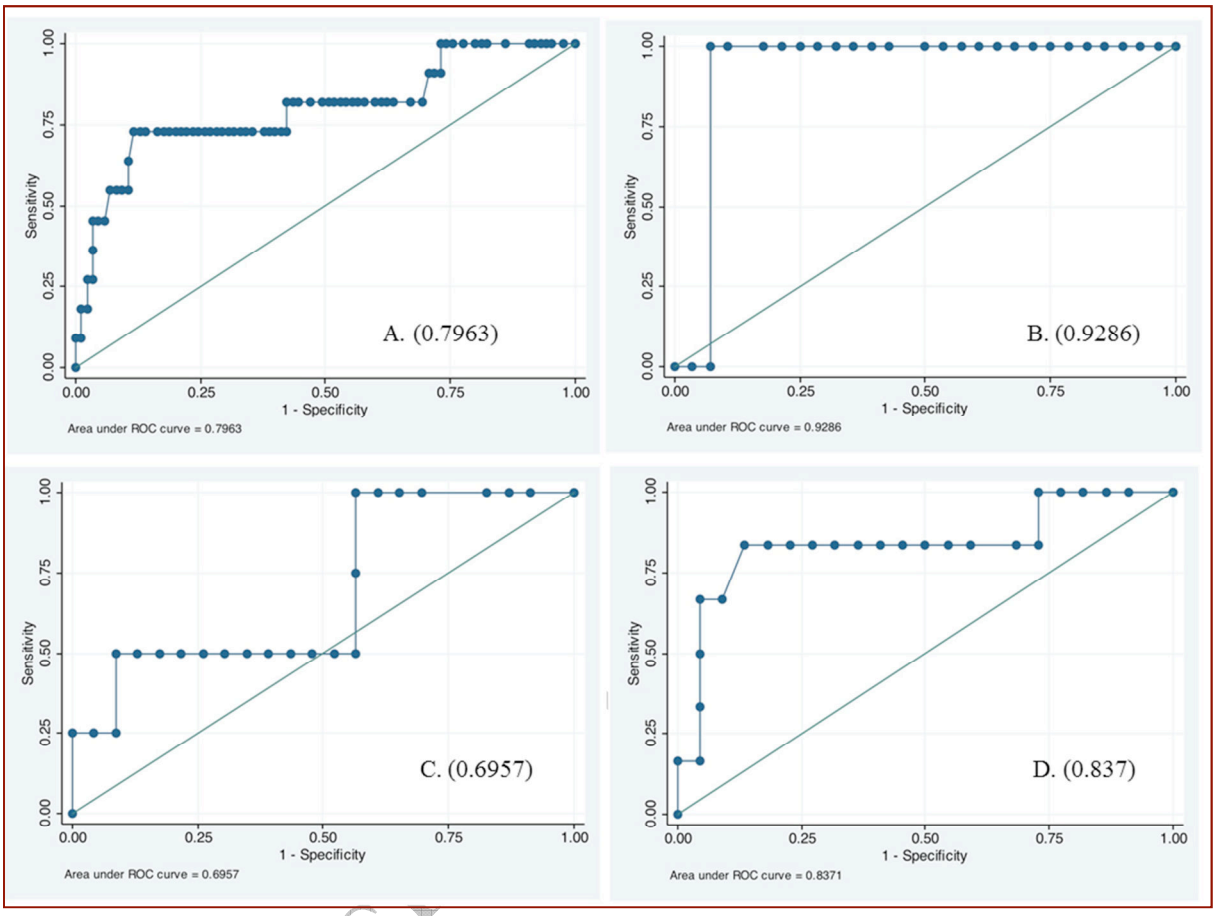
B



P-Value = 0.007		90-day	5 yrs.	10 yrs.
DVR (n=28)	Percent	85.7±6.6	55.4±9.7	18.5±15.4
	No. at risk	25	8	1
SVR/MVRep (n=68)	Percent	98.5±1.5	72.2±6.1	44.2±14.1
	No. at risk	68	29	3

Part D: Technical Appendices; Figures

Figure 3: Receiver operating characteristic curves for the EuroSCORE II in (A) Combined cohort, n = 96, (B) Aortic valve replacement, n = 29, (C) Mitral valve replacement, n = 27, and (D) Double valve replacement, n = 28.



Part D: Cover Sheet

COVER SHEET

Title	**LONG TERM OUTCOME AND THE VALIDITY OF THE EUROSCORE-II IN NATIVE-VALVE SURGERY FOR ACTIVE ENDOCARDITIS IN A SOUTH AFRICAN COHORT**
Authors	**JITHAN JACOB KOSHY, MARK ENGEL, PAUL HUMAN, HENRI CARRARA, JOHAN BRINK, PETER ZILLA**
Contribution of author(s)	J.J. Koshy was responsible for the development of the protocol, data extraction, analysis of results, interpretation of the findings and writing the final report. J.J. Koshy was also responsible for independently performing the literature search. J.G. Brink, M. Engel, and P. Zilla were the project supervisors. H. Carrara and P. Human provided assistance in statistical analyses.
Issue Protocol first published	2012
Review first published /	/
Date of most recent amendment /	06/05/2015
What's new /	/
Date new studies sought but not found /	/
Date new studies found but not yet included/excluded	/
Date new studies found and included/excluded	/
Date authors' conclusion section amended	/
Contact Address	Dr Jithan Jacob Koshy D24 Department of Cardiothoracic Surgery Christian Barnard Division of Cardiothoracic Surgery Groote Schuur Hospital Observatory Cape Town 7925 South Africa Jiths20@yahoo.com
DOI /	/
Editorial Group /	/
Editorial Group Code	/
	/

Part D: Official Ethics Approval & Amendment Letters

OFFICIAL ETHICS APPROVAL & AMENDMENT LETTERS

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	28/07/2014
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	16/7/13

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	16/07/13		
HREC REF Number	083/2012	Current Ethics Approval was granted until	15/03/2013
Protocol title	RETROSPECTIVE REVIEW OF VALVE SURGERY FOR INFECTIVE ENDOCARDITIS AT THE GROOTE SCHUUR HOSPITAL DURING THE LAST 10 YEARS		
Principal Investigator	JITHAN JACOB KOSHY		
Department / Office Internal Mail Address	D24 - CARDIOTHORACIC SURGERY NEW GROOTE SCHUUR HOSPITAL		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only

RESEARCH ETHICS COMMITTEE
2013 -07- 16
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		150
Total number of records or specimens collected, reviewed or stored since last progress report		150
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature

Signature of PI		Date	16/07/13
Signature of Supervisor (if PI is a student)		Date	16/07/13

Part D: Official Ethics Approval & Amendment Letters

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Ms S Ariefdien - Tel: [021]4066492 • Fax: [021]4066411
email: sumayah.ariefdien@uct.ac.za

29 February 2012

HREC REF: 083/2012

Dr J Koshy,
Cardiothoracic Surgery-Division
D24
New Groote Schuur Hospital

CC. Prof P Zilla

Dear Dr Koshy,

PROJECT TITLE: RETROSPECTIVE REVIEW OF VALVE SURGERY FOR INFECTIVE ENDOCARDITISAT THE GROOTE SCHUUR HOSPITAL DURING THE LAST 10 YEARS

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 March 2013

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 (FHS010).

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

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH 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.

Part D: Official Ethics Approval & Amendment Letters

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	☑ Type of review: Expedited	☐ Full committee	
This serves as notification that all changes and documentation described below are approved			
Signature Chairperson of the HREC	pp T Burges	Date	07.10.2014

Note: All amendments should include a Synopsis justifying the changes for the amendment (please see notice dated 23 April 2012)

HUMAN RESEARCH ETHICS COMMITTEE
06 JAN 2014
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	27th December 2013		
HREC REF Number	083/2012		
Protocol title	RHEUMATIC HEART DISEASE IS THE UNDERLYING RISK FACTOR FOR INFECTIVE ENDOCARDITIS THAT NEEDS SURGERY IN SOUTHERN AFRICA		
Protocol number (if applicable)	N/A		
Principal Investigator	JITHAN JACOB KOSHY		
Department / Office Internal Mail Address	CARDIOTHORACIC SURGERY, D24 NEW GROOTE SCHUUR HOSPITAL		
1.1 Is this a major or a minor amendment? (see FHS006hlp)		☐ Major	✓ Minor
1.2 Does this protocol receive US Federal funding?		☐ Yes	✓ No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval?		☐ Yes	✓ No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval.
This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.

TITLE CHANGE FROM OLD WORDING:
(RHEUMATIC HEART DISEASE IS THE UNDERLYING RISK FACTOR FOR INFECTIVE ENDOCARDITIS THAT NEEDS SURGERY IN SOUTHERN AFRICA)

DUE TO NEW FINDINGS IN THE ANALYSIS TO NEW WORDING:

[LONG TERM OUTCOME AND THE VALIDITY OF EUROSCORE-II IN NATIVE-VALVE SURGERY FOR ACTIVE ENDOCARDITIS IN A SOUTH AFRICAN COHORT]