MONASH University

Rheumatic heart disease surgery in adult Indigenous and non-Indigenous Australians

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Epidemiology & Preventive Medicine

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Abstract

Background

Rheumatic heart disease (RHD) is an important cause of heart disease globally. In Australia it particularly affects older non-Indigenous Australians and Aboriginal Australian and Torres Strait Islander peoples. RHD primarily affects heart valves and, in advanced disease, can require surgery to repair or replace affected valves. Factors associated with the timing and choice of treatment for advanced RHD in adults and those influencing outcome following surgery for RHD remain variable and poorly understood.

Methods

The Australian and New Zealand Society of Cardiac and Thoracic Surgeons cardiac surgery registry was analysed. Demographics, co-morbidities, preoperative status and valve(s) affected were collated and associations with management and outcomes following RHD and non-RHD valve surgery evaluated. Associations between preoperative atrial fibrillation and surgical site and surgeon case load and complications and survival were determined.

Results

Surgical management of 1594 RHD and 19029 non-RHD adult valve procedures at 25 surgical sites and by 93 surgeons was analysed. RHD patients were younger, more likely to be female and Indigenous Australian, to have AF and previous percutaneous balloon valvuloplasty. There was a significant increase in the use of mitral bioprosthetic valves over time.

Following surgery, RHD patients required longer ventilation, experienced fewer strokes and had more hospital readmissions and anticoagulant complications. Those with preoperative AF had a longer hospital stay and reoperation was more likely. Mortality following RHD surgery at 30 days was 3.1% (95% CI 2.2 – 4.3), 5 years 15.3% (11.7 – 19.5) and 10 years 25.0% (10.7 – 44.9). Factors independently associated with poorer longer term survival included older age (OR1.03/additional year, 1.01 – 1.05), concomitant diabetes (1.7, 1.1 – 2.5) and chronic kidney disease (1.9, 1.2 – 2.9), longer ventilation time (OR 1.7 if greater than median, 1.1– 2.9) and prolonged hospital stay (1.02/additional day, 1.01 – 1.03). Survival in Indigenous Australians was comparable to non-Indigenous Australians. Increasing site and surgeon case load in adjusted analysis was associated with longer ventilation, less reoperation and more anticoagulant complications. Increasing surgeon case

load was also associated with less acute kidney injury. There was no consistent relationship between increasing site case load and survival.

Conclusions

Given RHD valve surgery is more common in young, female and Indigenous patients, the choice of valve surgery and need for anticoagulation has implications for future management of RHD and related morbidity, pregnancy and lifestyle plans. Bioprosthetic valve use in RHD is increasing. Survival following RHD valve surgery in Australia is comparable to earlier studies.

The adjusted association between surgeon and site case load was not simple or consistent. Mandating a particular site case load for valve surgery or minimum procedure load for individual surgeons, in Australia, cannot be supported.

A system of enhanced surveillance utilising standardised definitions for assessment of severity of disease, co-morbidities, intervention and health service data linkage to assess non-lethal outcomes will be an extension of this project and will assist in further informing the management of advanced RHD.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: 

Print Name: Elizabeth Anne Russell

Date: 27 June 2017

Publications during enrolment

Russell EA, Tran L, Baker RA, Bennetts JS, Brown A, Reid CM, Tam R, Walsh WF, Maguire GP. A review of valve surgery for rheumatic heart disease in Australia. *BMC Cardiovasc. Disord.* 2014 Oct 2;14:134. doi: 10.1186/1471-2261-14-134.

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Russell EA, Walsh WF, Costello B, McLellan AJA, Brown A, Reid CM, Tran L, Maguire GP. Medical management of rheumatic heart disease: a systematic review of the evidence. *Cardiology in Review.* Submitted.

Conference abstracts/presentations during enrolment

20th Asian Pacific Society of Cardiology Congress Abu Dhabi, April 2015

Russell EA, Maguire G. APSC2015-1125 A review of outcome following valve surgery for rheumatic heart disease in Australia. *Glob. Heart*. June 2015; 10(2): e2-e3. doi: http://dx.doi.org/10.1016/j.gheart.2015.03.009

63rd Scientific Meeting of the Cardiac Society of Australia and New Zealand, Melbourne, August 2015

Russell EA, Maguire G, Tran L, Reid C, Walsh W, Brown A, Baker R, Tam R, Bennetts J. Does annual site-specific caseload influence valve surgical outcome in Australia? *Heart Lung Circ*. December 2015; 4(3):S412. doi: http://dx.doi.org/10.1016/j.hlc.2015.06.695.

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Russell E, Maguire G, Bennetts J, Baker R, Reid C, Tran L. The burden and implications of preoperative atrial fibrillation in Australian heart valve surgery patients. *Heart Lung Circ*. August 2016; 25(8):e111. doi: http://dx.doi.org/10.1016/j.hlc.2015.12.071.

64th Scientific Meeting of the Cardiac Society of Australia and New Zealand, Adelaide, August 2016

Russell E, Walsh W, Tran L, Reid C, Maguire G. Outcomes after rheumatic mitral valve surgery in Australia: replace or repair? CSANZ Victor Chang Memorial Lecture session. *Heart Lung Circ. August 2016; 25 (2):S293-S294.*
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Maguire G, Tran L, Reid C, Russell A. PM286 Surgery for Rheumatic Heart Disease - Factors Associated With Treatment Choice and Short and Long-Term Outcomes in Australia. *Glob. Heart*. June 2016; 11(2), e118–e119.
doi: http://dx.doi.org/10.1016/j.gheart.2016.03.412.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes six original papers published in peer reviewed journals and one submitted publication. The core theme of the thesis is "Rheumatic heart disease surgery in adult Indigenous and non-Indigenous Australians". The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Epidemiology & Preventive Medicine academic unit under the supervision of Professor Graeme Maguire.

(The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.)

In reference to the ten chapters, my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** *(published, in press, accepted or returned for revision, submitted)*	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution**	**Co-author(s), Monash student Y/N**
2	Medical management of rheumatic heart disease: a systematic review of the evidence	Submitted	70%. Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.	1) Prof Graeme Maguire, concept design and review 15%. 2) Prof Christopher Reid, review 4% 3) Dr Warren Walsh, review 3% 4) Dr Ben Costello, review 3% 5) Dr Alex McLellan, review 3% 6) Prof Alex Brown, review 1% 7) Dr Lavinia Tran, review 1%	N N N N N N N

3	Valve surgery for rheumatic heart disease in Australia.	Published	70%. Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.	1) Prof Graeme Maguire, concept design and review 15%. 2) Prof Christopher Reid, review 5% 3) Dr Warren Walsh, review 3% 4) Prof Robert Baker, review 2% 5) A/Prof Jayme Bennetts, review 2% 6) Prof Alex Brown, review 1% 7) Dr Robert Tam, review 1% 8) Dr Lavinia Tran, review 1%	N N N N N N N N
4	Outcome following valve surgery for rheumatic heart disease in Australia.	Published	70%. Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.	1) Prof Graeme Maguire, concept design and review 15%. 2) Prof Christopher Reid, review 5% 3) Dr Warren Walsh, review 3% 4) Prof Robert Baker, review 2% 5) A/Prof Jayme Bennetts, review 2% 6) Prof Alex Brown, review 1% 7) Dr Robert Tam, review 1% 8) Dr Lavinia Tran, review 1%	N N N N N N N N
5	Outcomes after mitral valve surgery for rheumatic heart disease.	Published	70%. Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.	1) Prof Graeme Maguire, concept design and review 15%. 2) Prof Christopher Reid, review 5% 3) Dr Warren Walsh, review 3% 4) Prof Robert Baker, review 2% 5) A/Prof Jayme Bennetts, review 2% 6) Prof Alex Brown, review 1% 7) Dr Robert Tam, review 1% 8) Dr Lavinia Tran, review 1%	N N N N N N N N

6	The burden and implications of preoperative atrial fibrillation in Australian heart valve surgery patients.	Published	70%. Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.	1) Prof Graeme Maguire, concept design and review 15%. 2) Prof Christopher Reid, review 5% 3) Dr Warren Walsh, review 3% 4) Prof Robert Baker, review 2% 5) A/Prof Jayme Bennetts, review 2% 6) Prof Alex Brown, review 1% 7) Dr Robert Tam, review 1% 8) Dr Lavinia Tran, review 1%	N N N N N N N N
7	Valve surgery outcome and case load in Australia.	Published	70%. Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.	1) Prof Graeme Maguire, concept design and review 15%. 2) Prof Christopher Reid, review 5% 3) Dr Warren Walsh, review 3% 4) Prof Robert Baker, review 2% 5) A/Prof Jayme Bennetts, review 2% 6) Prof Alex Brown, review 1% 7) Dr Robert Tam, review 1% 8) Dr Lavinia Tran, review 1%	N N N N N N N N
8	Outcome following valve surgery in Australia: development of an enhanced database module.	Published	72%. Conception and design, drafting of the article and revision; final approval of the version to be published.	1) Prof Graeme Maguire, concept design and review 15%. 2) Prof Christopher Reid, review 10% 3) Dr Warren Walsh, review 2% 4) Prof Alex Brown review 1%	N N N N

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 27 June 2017

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor signature: [redacted] **Date:** 29 June 2017

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Chapter 6 Preoperative atrial fibrillation: burden and implications in Australian heart valve surgery patients

Chapter 7 Valve surgery outcome and case load in Australia

Abbreviations

ABS	Australian Bureau of Statistics
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AIHW	Australian Institute of Health and Welfare
ANZSCTS	Australian and New Zealand Society of Cardiac and Thoracic Surgeons
AR	Aortic regurgitation
ARF	Acute rheumatic fever
AS	Aortic stenosis
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ASGS	Australian Statistical Geography Standard
AV	Aortic valve
CABG	Coronary artery bypass grafting
CEC	Clinical Excellence Commission
CI	Confidence interval
DOAC	Direct oral anticoagulant
eGFR	Estimated glomerular filtration rate
RF	Rheumatic fever
HIC	High income country
HR	Hazard ratio
ICU	Intensive care unit
IE	Infective endocarditis
INR	International normalized ratio
IQR	Interquartile range
LA	Left atrium
LMIC	Middle and low-income countries
LMW	Low molecular weight
LOS	Length of stay
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end systolic diameter
MAPE	Major adverse prosthesis-related events

MDRD	Modification of Diet in Renal Disease
MR	Mitral regurgitation
MS	Mitral stenosis
MTR	The Massive Transfusion Registry
MV	Mitral valve
NDI	National Death Index
MUHREC	Monash University Human Research Ethics Committee
NHMRC	National Health and Medical Research Council
NOAC	Non-vitamin K antagonist oral anticoagulants
NYHA	New York Heart Association
OIS	Operational Infrastructure Support Program
OR	Odds ratio
PASP	Pulmonary artery systolic pressure
PBV	Percutaneous balloon valvuloplasty
POC	Point of care
PREVAIL	Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTMV	Percutaneous transluminal (balloon) mitral valvotomy
RA	Remoteness area
RBC	Red blood cell
RF	Rheumatic fever
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RHD	Rheumatic heart disease
ROCKET AF	Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF
RR	Relative risk
SD	Standard deviation
SR	Sinus rhythm
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TAVI	Transcatheter aortic valve implantation
TIA	Transient ischaemic attack
TR	Tricuspid regurgitation
TS	Tricuspid stenosis
UF	Unfractionated

Chapter 1

Introduction

Rheumatic Fever (RF) occurs as a consequence of an inappropriate host immune response to group A streptococci bacterial infection (2, 3). A particular target of the associated inflammation is the heart valves which can become inflamed. Rheumatic Heart Disease (RHD) arises as a consequence of RF with this earlier heart valve inflammation leading to scarring and abnormal valve functioning. RHD is a condition of global health importance affecting between 15.6 and 19.6 million people. Most (almost 80%) reside in low and middle-income countries (LMICs), where the estimated population prevalence is 2.5 - 3.2 cases per 1 000 (4). It is estimated that 1% to 5% of people with RHD will die each year with the total number of RHD-related deaths estimated at 233 000 to 294 000 per year, 23 877 in high income countries (HICs) and 468 164 in LMICs (4).

Whilst RHD is now rare in HICs (2), it remains an important cause of preventable heart disease in some Indigenous populations including Canadian First Nations people (5), New Zealand Māori (6) and Australian Aboriginal and Torres Strait Islander peoples (7) who are often subject to a combination of educational, economic and environmental disadvantage, often with limited access to primary and specialist health care (3). In 2010 the prevalence of RHD amongst Australia's Aboriginal and Torres Strait Islander people was estimated to be 6.45 per 1 000 or 26 times that of non-Indigenous Australians (8). A recent survey of more than 5 000 Indigenous and non-Indigenous Australian children found 8.6 per 1 000 (95% CI 6.0-12.0) of Indigenous Australian children aged 5-14 years had echocardiographic evidence of RHD with none detected in non-Indigenous children (9, 10). RHD also continues to affect older non-Indigenous Australians, presumably relating to RF decades earlier.

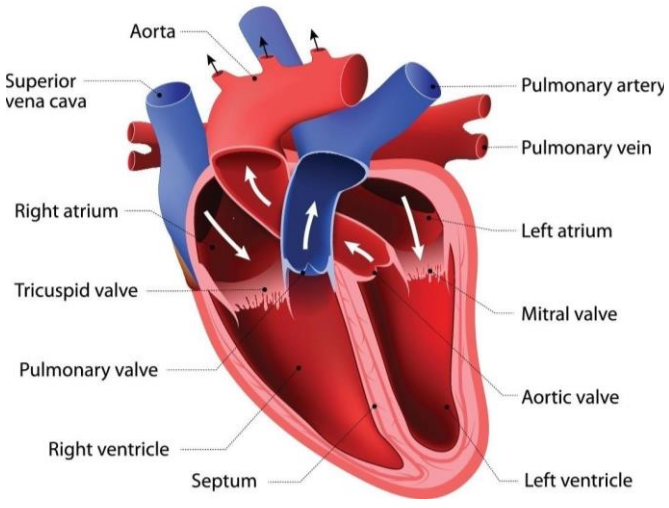

Figure 1 Human heart anatomy (1)

According to the Australian Institute of Health and Welfare (8), between 2007 and 2009, there were 12 deaths in Australia where ARF was the underlying (main) cause of death and 897 (1.3 per 100,000 population) with RHD as the underlying cause of death.

The most common heart valves affected by RHD are the mitral and aortic valves, less commonly the tricuspid and rarely the pulmonary valve (see Figure 1). Damage to these valves can alter their function in two ways. RHD commonly leads to regurgitation (10, 11) where blood moves backwards across a normally closed valve and/or, less commonly, valves may become stenosed (12) whereby the normal forward flow of blood across the valve is limited due to incomplete opening. Such valve damage is associated with an increased risk of heart failure, stroke and endocarditis (13).

The natural history of RHD-related valve damage is variable but in many cases the damage may progress as a result of further episodes of RF, through a process of chronic and progressive fibrosis, or as a consequence of ensuing heart failure or endocarditis. Fortunately the majority of RHD patients are only mildly affected (4) and only a minority have disease or complications requiring intervention (13). Such intervention can include percutaneous procedures to open stenosed valves and heart surgery to repair or replace damaged valves.

In some populations at elevated risk of RHD, such as Aboriginal Australian and Torres Strait Islander peoples, outcomes following cardiac surgery have been reported as being inferior (14, 15) despite these people being younger at time of surgery (14). This has been assumed to be related to factors including comorbidities (3, 14, 15), barriers to primary and specialist health care and the inability to achieve safe anticoagulation during long-term follow-up (11), a treatment required in patients with mechanical valve replacement or the heart arrhythmia atrial fibrillation (AF).

Management of RHD involves a combination of regular primary and specialist health care review, monitoring echocardiography and secondary antibiotic prophylaxis to prevent further episodes of RF. In selected patients medication may be used and interventions, including catheter and surgical-based approaches, may be required in those with more advanced disease. From a patient and clinician perspective, the aim in managing advanced RHD is to intervene to prevent progression and the development of complications and irreversible heart damage and at a time that ensures the lowest possible risk of complications with the best short and long-term outcome.

There are a paucity of published data on the choice and timing of intervention for advanced RHD. Many studies are single centre case series with associated methodologic limitations and the broad range of settings where patients with RHD live makes generalisation between studies difficult. Clinician preferences and experience and limited evidence regarding the outcome of different treatment options has led to a lack of consistency in the timing and choice of interventions for the management of advanced RHD (16). There is also a lack of evidence regarding the choice of interventions (11) and a need for greater consistency in management that takes into account the needs and aspirations of patients, their families and local health care providers. Randomised controlled trials of different interventions used in the management of advanced RHD are rarely possible. Many existing recommendations are based on the still relatively limited evidence pertaining to studies that have a focus on non-RHD related valvular heart disease. The broad range of settings where RHD occurs ranging from LMICs to HICs also means recommendations must be cognisant of local health care systems and resourcing for implementing management and follow-up.

Whilst existing national Australian guidelines (3) for RHD management acknowledge that outcomes may be affected by treatment choice, valve replacement type and timing of referral for intervention, there is limited information provided regarding how these factors interact and how they might be anticipated to influence outcomes and treatment recommendations.

This thesis therefore aims to address deficits in current knowledge regarding the timing, choice of intervention and broader health care service structures for managing advanced RHD, by analysing data from a large multi-site cardiac surgery enhanced surveillance register, The Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database. This is an Australia-wide prospective registry for the collection and analysis of adult cardiac surgical procedures. The Database commenced in 2001 with six surgical centres and currently encompasses 28 Australian sites. This thesis focuses on specific elements of surgical management of RHD that have been contentious in the broader clinical practice and policy context.

In particular, papers summarised in the thesis plan and presented in detail in subsequent chapters will first review existing knowledge regarding the medical management of RHD. They then describe the patient population requiring surgery and overall outcomes before focusing on how patient factors, surgical choice, and surgeon and site-specific case load influence short-term morbidity and mortality and longer term survival. In addition, these papers provide associated reviews on the existing state of knowledge regarding the surgical

management of advanced RHD specifically and valvular disease more generally. Finally this thesis concludes by providing a protocol for future research in this area.

While the ultimate aim in addressing RF and RHD in Australia will remain its eradication, the nature of this condition will mean there will remain people living with RHD in HICs and LMICs for some time yet. This thesis provides a suite of linked studies that will be important in informing the national Australian and global response to the management of advanced RHD and will serve as a resource for informing the future health care response both at an individual and health service level.

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Thesis plan

The work underlying this thesis is presented in seven chapters that address specific elements of advanced RHD care. Each is accompanied by a paper that has been published or submitted to a peer review journal

Chapter 2 Medical management of rheumatic heart disease: a systematic review of the evidence

While this thesis focuses on the surgical management of RHD, it is cognisant that many patients with this condition may also benefit from medical management. Despite its importance there is limited evidence to inform the medical non-procedural management of RHD. This chapter outlines the existing evidence regarding such medical management including symptom control, left ventricular dysfunction, rate control in mitral stenosis (MS), atrial fibrillation (AF) and anticoagulation. It provides an perspective on when to treat, the outcomes associated with different treatment choices and, where possible, how treatment choice can take account of health service resourcing.

This chapter includes the following paper submitted for peer review and publication:
Russell EA, Walsh WF, Brown A, Reid CM, Tran L, Baker RA, Bennetts JS, Tam R, Maguire GP. Medical management of rheumatic heart disease: a systematic review of the evidence. *Cardiology in Review* (Submitted)

Chapter 3 Valve surgery for rheumatic heart disease in Australia

There have been no Australian multi-centre studies of RHD valve surgery published and limited data available regarding factors that might affect the choice of surgery in patients with RHD. This chapter examines the Australian patient population requiring valve surgery for RHD and reviews the pre-operative factors that are associated with surgical choice.

This chapter includes the following peer-reviewed and published report:
Russell EA, Tran L, Baker RA, Bennetts JS, Brown A, Reid CM, Tam R, Walsh WF, Maguire GP. A review of valve surgery for rheumatic heart disease in Australia. *BMC Cardiovascular Disord*ers 2014 Oct 2;14:134. doi: 10.1186/1471-2261-14-134.

Chapter 4 Outcome following valve surgery for rheumatic heart disease in Australia

This chapter expands on the areas highlighted in Chapter 3 and extends this to an examination of the factors associated with RHD and non-RHD surgery outcome. Significant independent predictors of short or long term outcome overall and for Indigenous Australians specifically are addressed, both alone and in association with procedure type.

This chapter includes the following peer-reviewed and published report:
Russell EA, Tran L, Baker RA, Bennetts JS, Brown A, Reid CM, Tam R, Walsh WF, Maguire GP. A review of outcome following valve surgery for rheumatic heart disease in Australia. *BMC Cardiovascular Disord*ers 2015 Sep 23;15(1):103. doi: 10.1186/s12872-015-0094-1.

Chapter 5 Outcomes after mitral valve surgery for rheumatic heart disease

The most common heart valve affected by RHD is the mitral valve. Mitral valve replacement is generally associated with poorer survival compared with mitral repair. This chapter examines the Australian patient population having mitral valve surgery for RHD and non-RHD related valve disease and reviews the factors associated with the choice of surgical management and with short and long-term outcome following valve surgery.

This chapter includes the following peer-reviewed and published report:
Russell EA, Walsh WF, Reid CM, Tran L, Brown A, Bennetts JS, Baker RA, Tam R, Maguire GP. Outcomes after mitral valve surgery for rheumatic heart disease. *Heart Asia.* 2017;9:1-7. doi**:** 10.1136/heartasia-2017-010916

Chapter 6 The burden and implications of preoperative atrial fibrillation in Australian heart valve surgery patients

Atrial fibrillation (AF) is the most common preoperative cardiac surgery arrhythmia and, as highlighted in Chapter 2, particularly prevalent in patients with valvular disease due to RHD. In the setting of RHD, AF often requires consideration of anticoagulation, a treatment that can be particularly difficult to provide in a remote Indigenous Australian setting. This chapter describes the burden and assesses the impact of AF on valve surgery, early post-operative complications and short and long term survival, overall and with particular reference to RHD and Indigenous Australians.

This chapter includes the following peer-reviewed and published report:
Russell EA, Walsh WF, Tran L, Tam R, Reid CM, Brown A, Bennetts JS, Baker RA, Maguire GP. The burden and implications of preoperative atrial fibrillation in Australian heart valve surgery patients. *International Journal of Cardiology*. 2017; 227:100-105. doi: 10.1016/j.ijcard.2016.11.070.

Chapter 7 Valve surgery outcome and case load in Australia

In Australia there are a significant number of centres that undertake valve surgery and it has been suggested that heart valve surgery in general and that for RHD specifically, should be consolidated in a small number of higher volume centres as a mechanism for enhancing treatment choice and short and longer term outcome. Whilst multiple cardiac surgical units may be argued to enhance access (particularly for residents of regional and remote centres) and reduce waiting times, for more specialised valve surgery, including for RHD, a smaller number of specialised units may be preferable. This chapter examines the independent association between site and/or surgeon-specific average annual case load and short and long-term outcome following valve surgery.

This chapter includes the following peer-reviewed and published report:
Russell EA, Baker RA, Bennetts JS, Brown A, Reid CM, Tam R, Tran L, Walsh WF, Maguire GP. Case load and valve surgery outcome in Australia. *International Journal of Cardiology*. 2016;221:144-151. doi: 10.1016/j.ijcard.2016.06.179

Chapter 8 Outcome following valve surgery for rheumatic heart disease in Australia: development of an enhanced database module

The seventh and final paper presented in this thesis outlines a protocol for a study that will further inform the management of advanced RHD. This study will involve the development of a multicentre, enhanced baseline assessment and data linkage surveillance system to better understand short and longer term non-lethal outcomes associated with surgical management of RHD. It will collect and incorporate more detailed information regarding pre and postoperative factors at four Australian cardiothoracic surgical sites caring for patients with both RHD and non-RHD related valvular heart disease and link this to hospital separation and other registry data sources.

This chapter includes the following peer-reviewed and published report:
Russell EA, Reid CM, Walsh WF, Brown A, Maguire GP. Outcome following valve surgery in Australia: development of an enhanced database module. *BMC Health Services Research* 2017:17:43 doi 10.1186/s12913-017-2002-0

Chapter 9 Discussion

The implications of the findings of the studies and publications comprising this thesis and how they may inform systems and protocols for management of RHD in the future are highlighted here. This includes the results of pre-operative factors associated with the choice of surgical management and how patient, disease (AF) and system factors (case load) may influence short and long term outcome.

Chapter 10 Conclusion

This thesis concludes by outlining the original contributions this project has made to the knowledge and understanding of factors associated with RHD surgical management and outcomes. The major conclusions from the research are presented and recommendations made regarding future research priorities.

Chapter 2

Medical management of rheumatic heart disease:

a systematic review of the evidence

While this thesis focuses on the surgical management of RHD it is cognisant that many patients with this condition may also benefit from medical management. Despite its importance there is limited evidence to inform the medical non-procedural management of RHD. This chapter outlines the existing evidence regarding such medical management including symptom control, left ventricular dysfunction, rate control in mitral stenosis (MS), atrial fibrillation (AF) and anticoagulation. It provides a perspective on when to treat, the outcomes associated with different treatment choices and, where possible, how treatment choice can take account of health service resourcing.

The criteria for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were applied in undertaking the literature search. All studies which reported on the stated criteria were included so there were no excluded studies. They were reported on as to their contribution to evidence for current medical management of RHD, with differences acknowledged when there was a range of outcomes reported. There were not enough studies in any one area to complete a meta-analysis.

Follow up in the studies ranged from one day to 12 months with on average 90.2% (75% to 100%) of the study participants being followed for the stated time period. Sub-studies using data from larger studies did not always fit with pre-defined criteria, participant selection and definitions. Studies where data was obtained only from medical record review or self-reporting were also associated with incompleteness of data. Finally generalisability was compromised by studies that were from single centres or which had restrictive inclusion criteria, short follow-up, or small sample sizes.

This chapter includes the following submitted paper submitted for peer review and publication:
Russell EA, Walsh WF, Brown A, Reid CM, Tran L, Baker RA, Bennetts JS, Tam R, Maguire GP. Medical management of advanced rheumatic heart disease: a systematic review of the evidence. *Cardiology in Review* (Submitted)

Medical management of rheumatic heart disease: a systematic review of the evidence

Authors:

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ABSTRACT

Background Rheumatic heart disease (RHD) is an important cause of heart disease globally. Management can encompass medical and procedural (catheter and surgical) interventions.

Methods Literature pertaining to medical management of RHD from PubMed 1990-2016 and via article reference reviews. Areas included symptoms, left ventricular (LV) dysfunction, rate control in mitral stenosis (MS), atrial fibrillation (AF) and anticoagulation.

Results Diuretics, angiotensin blockade and beta blockers for LV dysfunction, and beta blockers and I_f inhibitors for rate control in MS reduced symptoms and improved LV function but did not alter disease progression. Rhythm control for AF was preferred and where this was not possible rate control with beta blockers was recommended. Anticoagulation was indicated where there was a history of cardioembolism, AF, spontaneous left atrial contrast and mechanical prosthetic valves. While warfarin remained the agent of choice for mechanical valve replacement, non-vitamin K antagonist oral anticoagulants (NOACs) may have a role in RHD-related AF, particularly with valvular regurgitation. Evidence for anticoagulation following bioprosthetic valve replacement or mitral valve repair was limited.

Conclusions In RHD medical management of LV dysfunction and rate control in MS improves symptoms. There is limited evidence rhythm control of AF may be preferable to rate control and emerging evidence that NOACs have a role in patients at high risk of cardioembolic complications. Warfarin remains the mainstay of anticoagulation in mechanical valve replacements and, to a lessor extent, in MS. There is little evidence to support anticoagulation in patients in sinus rhythm following bioprosthetic valve replacement or repair.

INTRODUCTION

Rheumatic heart disease (RHD) occurs after one or more episodes of rheumatic fever (RF), a condition associated with an inappropriate host immune response to infection with group A streptococci (1-3). RHD is a condition of global health importance that is estimated to affect 15.6 to 19.6 million people, most in middle and low-income countries (LMIC) (4). Of those people with RHD, 1% to 5% are estimated to die each year with the total number of RHD-related deaths estimated at 233-294 000 per year, with the majority (468 164) in LMIC (4).

While RHD is now rare in high income countries (1), it remains an important cause of preventable heart disease in some Indigenous populations including Canadian First Nations people (5), New Zealand Māori (6) and Australian Aboriginal and Torres Strait Islander peoples (7) who are often subject to environmental disadvantage and variable access to primary and specialist health care (2). A recent echocardiographic screening study of Indigenous Australian children aged 5-14 years, found a prevalence of RHD (8) of 0.9% with none detected in a comparably aged non-Indigenous cohort (9). Nonetheless, older non-Indigenous residents are also affected by RHD, presumably relating to RF decades earlier. Thus, in an Australian review of RHD surgery outcome, 87% of patients requiring surgery for RHD-related valve disease were non-Indigenous (10).

The most common heart valves affected by RHD are the mitral and aortic valves, less commonly the tricuspid and rarely the pulmonary valve (10). Valve regurgitation and stenosis may occur in isolation or together. Such valve damage is associated with an increased risk of heart failure, stroke and endocarditis (11). The natural history of RHD-related valve disease is variable but in many cases valve damage and dysfunction can progress as a result of further episodes of RF, through a process of chronic and progressive scarring and/or as a consequence of ensuing heart failure or endocarditis. The majority of RHD patients are only mildly affected (4) and only a small minority have more severe disease or complications requiring intervention (11).

Management of RHD involves a combination of regular primary and specialist health care review, monitoring echocardiography and secondary antibiotic prophylaxis to prevent further episodes of RF. In the small but important group with more severe valvular disease, medications and other interventions, including catheter and surgical-based approaches, may be required. From a patient and clinician perspective, the aim in managing advanced RHD is therefore to intervene to prevent progression and the development of complications and

irreversible heart damage at a time that ensures the lowest possible risk of complications with the best short and long-term outcome.

Despite its importance, there is limited evidence to inform the medical non-procedural management of RHD. Many existing recommendations are based on the relatively limited evidence pertaining to studies that have a focus on non-RHD related valvular heart disease. The broad range of settings where RHD occurs ranging from LMIC to high income countries also means recommendations must be cognisant of local health care systems and resourcing.

This review will therefore aim to outline the existing evidence regarding the medical management of RHD-related valvular disease. Specific areas of interest will include management of symptoms, left ventricular dysfunction, rate control in mitral stenosis (MS), atrial fibrillation (AF) and anticoagulation. It will provide an emphasis on when to treat, the outcomes associated with different treatment choices and, where possible, how treatment choice can take account of health service resourcing.

METHODS

The criteria for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were applied in undertaking this review (12). Published evidence regarding the medical management of RHD was identified by performing a PubMed (13) search for English language articles, published between 1990 and 2016. The reference lists of retrieved articles were also searched. The search strategy included a combination of “rheumatic heart disease”, “management of rheumatic heart disease”, “rheumatic valve intervention”, and “rheumatic valve surgery”. After review, any sources that did not specify that the primary focus was RHD-related valve disease, were restricted to very young children, only included patients having re-operation or which were review articles were eliminated. Studies were included if they reported on data for type and timing of intervention, assessment of severity, medical management, or assessment of outcome. Sample size, duration of follow-up, subject demographics and country of origin were recorded.

RESULTS

The results of the search strategy are outlined in Figure 1 below. Of the 42 included studies 18 were randomised clinical trials, 10 other prospective and 14 retrospective case series of interventions with follow-up ranged from initial hospital discharge to 24 years.

Outcome measures reported differed between studies with 23 including survival, 18 bleeding, 19 thromboembolic events and eight, New York Heart Association (NYHA) functional status.

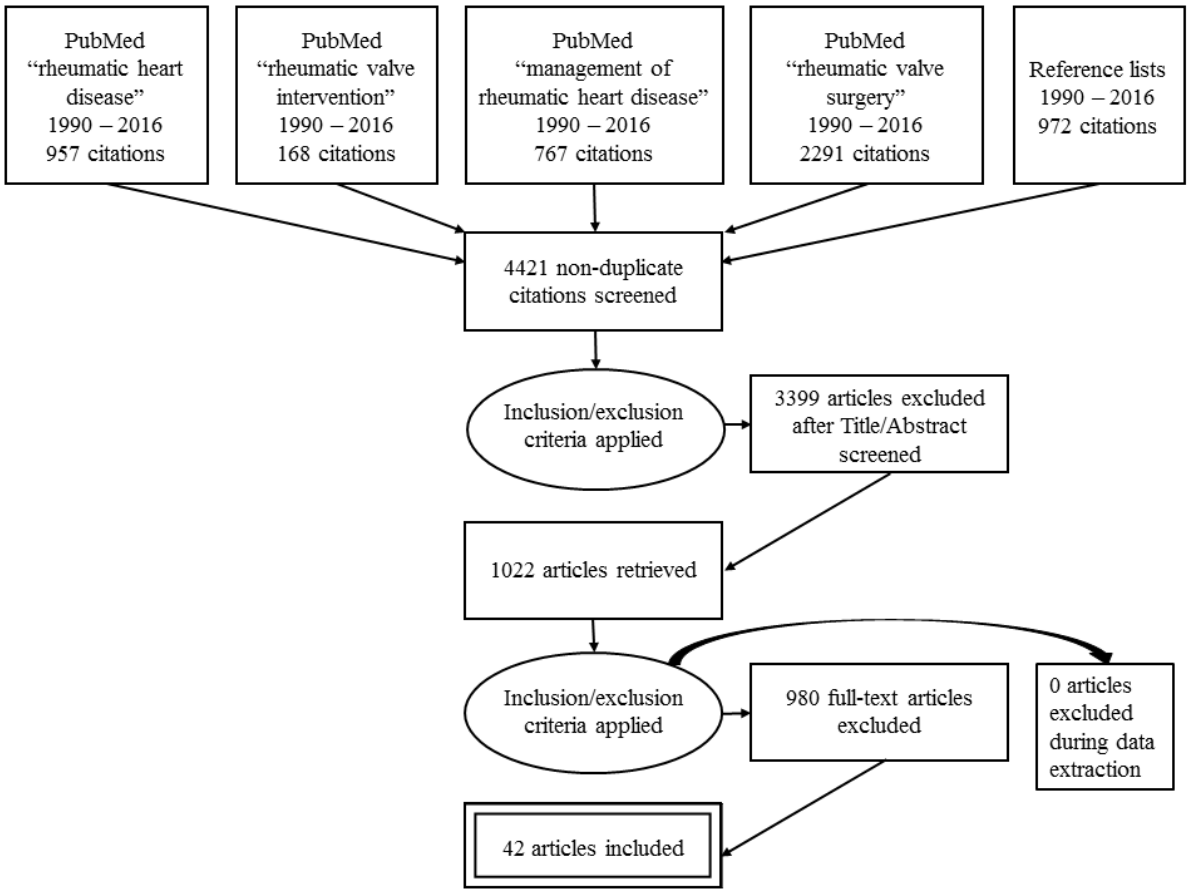

Figure 1 Search strategy

Principles of medical management

Medical management of all patients with RHD may include regular review by primary and specialist health care incorporating evaluation of severity of disease based on symptom history and imaging (typically echocardiography) and antibiotic prophylaxis to reduce the risk of RF and infective endocarditis. The focus here will be on additional elements of management in the subset of patients with more advanced disease as evidenced by the

onset of symptoms (typically exercise limitation or dyspnoea) or imaging suggestive of severe valvular dysfunction, AF or those at high risk of complications including stroke. While surgical or other invasive interventions in addition to medical management may be more accessible in high-income countries, in LMICs this is not necessarily the case. Indeed in a study of 551 Ugandan RHD patients the majority of patients (91.1%) were found to have received medical management for RHD without proceeding to surgery or other interventions (14).

The medical management of advanced RHD may include non-medication and medication based interventions. Non-medication based interventions in other forms of heart disease may include exercise training/rehabilitation and implantable devices including biventricular-pacing/cardiac resynchronisation. No studies relating to the efficacy of such non-medication medical management in advanced RHD were identified.

Potential targets for the medication-based medical management of advanced RHD are summarised in the box below.

- diuretics for fluid overload
- beta blockers and angiotensin blockade (angiotensin converting enzyme inhibitors (ACE inhibitors) and/or angiotensin receptor blockers) for left ventricular dysfunction
- heart rate lowering in mitral stenosis
- rate and rhythm control for AF
- anticoagulation to reduce cardioembolic events and valve thrombosis following surgery

Fluid overload

A particular marker of severe RHD is exercise limitation and dyspnoea either on exertion or at rest. Diuretics such as the loop diuretic frusemide are often used to reduce symptoms of acute or chronic dyspnoea. The evidence for their use in RHD is limited with no evidence from formal trials (15) but recommendation only for symptom relief from pulmonary congestion or pulmonary oedema with mitral stenosis or heart failure with tricuspid regurgitation or stenosis (2, 15, 16).

Left ventricular dysfunction

In RHD, left ventricular (LV) dysfunction may relate to LV dilation or hypertrophy with or without a reduction in systolic function. Angiotensin blockade is often recommended for both these issues. LV dilation tends to occur earlier in the setting of relative volume overload associated with regurgitant lesions of the aortic or mitral valve (2). While there is no evidence of the effectiveness of angiotensin blockage in RHD-related aortic regurgitation (AR), evidence for its use in non-RHD AR would indicate no significant effect on LV size or function or delay in the need for aortic valve replacement (17, 18). In patients with RHD-related mitral regurgitation (MR), ACE inhibitors have been shown to significantly reduce LV size and MR volume (19) although this was not universally shown to be the case (20, 21) and there is no evidence to suggest their use delays the eventual need for surgery.

In the setting of RHD-related MR and associated LV dysfunction, beta blockers have also been shown to reduce LV size and end-systolic stress as compared with placebo (22).

Heart rate lowering

In mitral stenosis (MS) impaired LV filling and elevated left atrial pressure are both exacerbated by a rapid heart rate. In this setting a reduction in heart rate, even in patients in sinus rhythm (SR), may reduce symptoms. Classically this has been achieved by using beta blockers which have demonstrated an association with significantly improved symptoms (23). Ivabradine, a newer agent used in heart failure that targets the lowering of the resting heart rate through its effect on the cardiac pacemaker I_f current inhibitor (24), has demonstrated similar efficacy to metoprolol in MS with an improvement in haemodynamics, exercise performance and dyspnoea (25). As such, ivabradine may be a useful adjunct in symptom management of MS, particularly when beta blockers are contra-indicated or not tolerated or where an adequate reduction in heart rate cannot be achieved with beta blockers alone.

In summary all these agents may reduce symptoms while awaiting other interventions, but there is no evidence to suggest they alter the natural history of disease or need for surgery. Nonetheless, in a patient in whom other interventions are refused or contraindicated or where resources are not available there is evidence in RHD-related AR, MR and MS that the tailored use of diuretics, angiotensin blockade, beta blockers and I_f inhibitors may be useful for symptom control.

Atrial Fibrillation

Atrial fibrillation (AF) is both common and its management challenging in the setting of RHD. The incidence of the onset of new AF in RHD is 3.5%/year overall and 6.0%/year in patients with an enlarged left atrium (LA) (≥47 mm) (26). Its prevalence is particularly high in patients with advanced valvular disease (10, 27) with 40% of RHD patients undergoing valve surgery having AF compared to only 17% of non-RHD patients (28). This is further added to by one third of the remaining 60% of RHD patients developing AF following surgery (29, 30).

Medical management of AF targets one of two elements: either rate control with a focus on reducing ventricular rate in the setting of continuing AF or rhythm control with an emphasis on reversion to SR. Existing international guidelines outlining recommendations for the management of AF provide limited assistance when deciding how to manage AF in the setting of RHD. While such guidelines highlight that all trials that have compared rhythm control and rate control to rate control alone have resulted in a lack of evidence regarding superiority of one approach over another, it should be remembered such guidelines have focused on non-RHD related AF (31, 32). The evidence supporting equivalence of outcome in rate versus rhythm control for AF may therefore not necessarily apply in RHD. Indeed in a prospective double-blind trial of AF in RHD patients comparing rate control with rhythm control with electrical cardioversion +/- amiodarone, patients who achieved persisting reversion to SR at one year (52%) had improved exercise tolerance, symptoms, quality-of-life and possibly survival (33). While a discussion regarding the utility of pulmonary vein isolation via ablation is outside this discussion of medical management there is evidence that would suggest this can be a superior form of rhythm control in non-valvular AF.

Rate control

Despite poorer outcomes associated with persisting AF in RHD patients there will remain a need for rate control with beta blockers, digoxin or calcium channel blockers (34, 35) in patients in whom reversion to SR cannot be achieved. This may be particularly the case in patients with a long-standing persistent AF, severe MS, and significant LA enlargement (36). Whilst all these agents are effective in reducing ventricular response beta blockers may, if tolerated, be preferred in the setting of LV dysfunction or MS where beta blockers may provide benefit in addition to their rate control effects.

Rhythm control

The non-invasive medical management of rhythm control can involve medication, electrical cardioversion or a combination of both. Whilst a range of medications can be used for rhythm control of AF, specific evidence in RHD has largely focused on amiodarone. In studies of Indian and South African RHD patients, amiodarone taken for 9 months (37) to 17 months (38) resulted in reversion to SR in 55% (38) to 87% (37) of patients. In the unstable patient or those resistant to medical cardioversion, electrical cardioversion (with preceding anticoagulation and/or transoesophageal echocardiography to assess for LA thrombus) associated with the ongoing use of amiodarone can be an additional management option (39). When reversion to SR cannot be achieved by electrical cardioversion, further attempts at three months, even in the setting of co-administered amiodarone, do not provide additional benefit (40).

Perioperative AF

Treating RHD-related AF in the perioperative period can also be associated with successful reversion to SR with a single dose of intraoperative intravenous amiodarone and intra-operative electrical cardioversion being superior to electrical cardioversion alone (41). Even in post-operative patients with persisting AF, reversion to SR is possible with ongoing amiodarone and delayed electrical cardioversion for those in persisting AF at three months. While a longer duration of AF (more than two years) and an LA diameter greater than 60mm reduces the possibility of reversion to SR even in these patients more than 60% achieved reversion to SR (40). The co-administration of irbesartan with amiodarone is associated with an even greater chance of successful maintenance of SR (42).

Prevention of the development of new AF in association with cardiac surgery has also been investigated in non-RHD related valve disease. Studies from Finland (43) and Jordan (44) have found corticosteroid administered in association with surgery lowered the incidence of new AF (24% (44) to 30% (43)) compared with placebo (46% (44) to 48% (43)). Similar evidence for RHD is however currently lacking.

In summary, the emphasis of medical management of AF in the setting of RHD should be rhythm control with a focus on achieving and maintaining SR with appropriate anticoagulation (see below). In the acute setting or when rhythm control has been unsuccessful, rate control can be considered with a beta blocker providing potentially additional benefit in RHD patients with LV dysfunction and MS. Where feasible, a plan for

achieving and maintaining SR with a combination of amiodarone and electrical conversion should be considered. This must nonetheless be balanced against the potential side-effects associated with long-term amiodarone use, with at least 10% of patients being unable to tolerate this (45-47). The onset of AF should also prompt reassessment regarding the need for more invasive interventions for valve disease management. If surgery is undertaken in the setting of persisting AF, the use of intra-operative intravenous amiodarone and electrical conversion should be undertaken and, if not successful, this should be followed by ongoing amiodarone and a further attempt at electrical conversion at three months if AF persists. Where SR is achieved, the co-administration of irbesartan reduces the risk of reversion to AF (48). While it may be possible to prevent the development of AF in association with surgery with corticosteroid therapy, the evidence for RHD-related valve disease specifically is currently lacking.

Anticoagulation

Anticoagulation can be a key intervention in patients with RHD-related valvular disease to reduce the risk of cardioembolic events, most particularly stroke. Nonetheless, anticoagulation can be difficult to provide in the remote and LMIC settings where many people living with RHD reside. RHD is associated with a significant risk of stroke, particularly in people with associated MS. The risk of cardioembolic complications is even higher when RHD-related valvular disease is associated with AF. In addition, anticoagulation is often used in the perioperative period following bioprosthetic valve replacement and valve repair and routinely required in patients who have a mechanical valve replacement.

In the medical management of RHD key clinical questions are therefore when to consider anticoagulation, which agent to use and issues relating to monitoring and safety. The evidence informing each of these issues will be outlined below.

Indications for anticoagulation

In general, patients with RHD are at an increased risk of stroke. It is reasonable to assume that any RHD patient with a history of stroke or another cardioembolic complication (e.g. limb ischaemia due to arterial obstruction) will be at elevated risk of further episodes and should be anticoagulated. In addition RHD patients with evidence of LA low-velocity blood flow or AF, irrespective of their underlying thromboembolism risk score (49), should also be

anticoagulated. This is supported by a case control study of Indian RHD patients that demonstrated a significant independent association between stroke and evidence of left atrial spontaneous contrast on echocardiography (odds ratio (OR) = 39.9) or AF (OR 3.2) (50).

Anticoagulation is also utilised either as short or longer term management following interventions for RHD especially in the perioperative period following bioprosthetic valve replacement and valve repair and in the long term management of mechanical valve replacements. Following mechanical valve replacement, warfarin remains the therapy of choice to prevent valve thrombosis and thromboembolic complications. A single randomised open label study comparing the non-Vitamin K antagonist oral anticoagulant (NOAC, also described as direct oral anticoagulant or DOAC) dabigatran with warfarin following mechanical valve replacement was prematurely terminated at median follow-up of six months due to a higher risk of thromboembolic complications in patients allocated to dabigatran (5%) compared to those receiving warfarin (0%) (51).

Patients with RHD will often proceed to surgery with either valve replacement with a mechanical or bioprosthetic valve or mitral valve repair. While short term anticoagulation or antiplatelet therapy is often recommended following bioprosthetic valve replacement, the evidence to support this is limited. An observational study of post-operative warfarin use following bioprosthetic aortic valve replacement in 861 patients in SR (133 warfarin and 728 no anticoagulation with 53% in both groups receiving concomitant aspirin) demonstrated no overall difference in the early 90-day risk of thromboembolism, with this occurring in 5% of both those who received and did not receive warfarin. Multivariate analysis did however demonstrate concomitant use of warfarin or aspirin was associated with a reduced risk of thromboembolism in women, those with small prosthetic aortic valves (19mm) and if significant symptoms were present (New York Heart Association III/IV).(52) Another observational study of aspirin versus no aspirin following aortic valve bioprosthesis in 288 patients in SR without any other need for aspirin, all of whom received low molecular weight (LMW) heparin for 14 days following surgery, showed no difference in mortality or stroke risk at one year. (53) An open label randomised controlled trial of warfarin versus aspirin in 370 patients following aortic valve bioprosthesis without coronary artery grafting also demonstrated no difference in thromboembolic complications or mortality at 90 days following surgery, but with a higher risk of major bleeding in those receiving warfarin. (54)

Given the higher risk of thromboembolism associated with mitral valve disease and surgery, there is typically a greater concern and preference for the use of anticoagulation following mitral bioprosthesis or valve repair surgery. In patients in SR following mitral valve bioprothesis insertion, the evidence to support any particular anticoagulation strategy in the early post-operative period is largely lacking. An observational study of 99 patients receiving warfarin, aspirin or no treatment demonstrated no significant difference in stroke or bleeding risk, but the number of participants was small (55). In a 19 centre observational study of 1882 patients following mitral valve repair, no difference was seen in thromboembolic or bleeding risk at six months between patients receiving warfarin or aspirin, but this did not include any patient who did not receive either agent (56).

A summary of indications where anticoagulation for RHD may be warranted is listed in the box below.

- history of cardioembolic complications including ischaemic stroke
- atrial fibrillation
- left atrial spontaneous contrast or left atrial thrombus on echocardiography
- mechanical valve replacement
- short-term following post-operative valve repair or bioprosthetic replacement in selected patients

Choice of agent

Anticoagulation/antiplatelet options in the setting of RHD include those outlined in the box below.

- vitamin K antagonists (usually warfarin).
- antiplatelet agents (e.g. aspirin)
- non-vitamin K antagonist oral anticoagulants (NOACs)
- unfractionated and low molecular weight heparin

Key considerations regarding which agent to choose encompass efficacy, risk/safety (particularly of bleeding), reversibility and suitability for use in pregnancy, an important consideration when managing RHD patients who are more likely to be young and female. In general the mainstay of anticoagulation in RHD remains warfarin, relating mainly to limited evidence of equivalent efficacy of the other agents listed above. In the post-operative setting

following valve prosthesis or mitral valve repair surgery in the patient in SR it has been highlighted already that the evidence to support the use of any anticoagulant is limited. The evidence that is available would suggest that if an anticoagulant is used, aspirin may be a reasonable alternative to warfarin.

The availability of NOACs has prompted their consideration as an alternate agent to warfarin in valvular heart disease in general and RHD specifically. This relates in part to not requiring regular monitoring to determine adequate dosing as in the case with warfarin. This might make these agents specifically useful for patients in marginalised areas where the infrastructure for warfarin monitoring does not exist. Nonetheless, such agents remain more expensive than warfarin. While recommendations relating to NOACs and AF have been largely limited to non-valvular AF, it should be highlighted this definition originally related to excluding patients with MS and has subsequently been expanded to include prosthetic heart valves and mitral valve repair (57). The similar efficacy of NOACs in reducing thromboembolic events in patients with other forms of native valvular heart disease has been demonstrated by sub-group analyses of many clinical trials of NOACs including the RE-LY (dabigatran) (58), ROCKET AF (rivaroxaban) (59), and ARISTOTLE (apixaban) (60) studies. Nonetheless, in the ROCKET AF (59) study there was a greater risk of bleeding in patients with native valvular heart disease and associated AF receiving a NOAC compared with warfarin.

Further insight can be gained from a large retrospective study of administrative clinical data in the US of 20 158 non-vitamin K antagonist oral anticoagulant (NOAC)-treated patients with valvular heart disease (including a smaller number of patients with RHD (n=74) and non-RHD related (n=654) mitral stenosis, bioprosthetic valve replacement (n=24) and mitral valve repair (n=55)) and AF (61). While the sample sizes were limited, no patients with prior valve repair or bioprosthetic heart valves on NOACs were documented to have thromboembolic complications and in patients with mitral stenosis, either RHD or non- RHD related, there were no differences in the rates of stroke or bleeding. In the far greater number of patients with aortic stenosis, AR or MR, the risks of thromboembolism and bleeding were both significantly lower with NOACs compared to warfarin.

Thus, while the use of NOACs in valvular heart disease should be approached with caution, it would appear that they have equivalent efficacy to warfarin in preventing thromboembolic complications associated with AF in aortic stenosis, AR and MR. The evidence supporting their use in MS is limited, but would suggest they may be an alternative in patients in whom

warfarin is not a safe option. Their use following bioprosthetic valve replacement or mitral valve repair should be tempered by the limited evidence that any agent is of benefit in these settings. The use of NOACs in valvular heart disease in general and RHD specifically should also take account of local licencing restrictions which may limit their use in some settings.

The use of unfractionated (UF) or low molecular weight (LMW) heparin is largely restricted to patients who require anticoagulation in pregnancy or when rapid reversibility may be needed in the perioperative period or the setting of bleeding. Whilst this review does not specifically aim to outline the evidence regarding management of RHD in pregnancy, the evidence relating to anticoagulation management that is available is limited and restricted to observational studies. Nonetheless, available data support the efficacy and safety of LMW heparin with anti-Xa level monitoring (62, 63). Whilst warfarin has been associated to embryopathy, this tends to be particularly at doses greater than 5 mg per day and warfarin use may be considered following the first-trimester and ceased prior to expected delivery with bridging heparin therapy (64). In the operative setting an observational study of UF versus LMW heparin in 901 patients demonstrated similar bleeding and thromboembolic risk with the risk of bleeding largely related to type of surgery and the presence of patient comorbidities as demonstrated by a Charlson comorbidity score greater than one.

Monitoring and safety

Warfarin remains the mainstay of anticoagulation following mechanical valve replacements and is still often preferred in RHD-related valve disease associated with AF or a history of thromboembolism. The difficulty of achieving safe and adequate INR monitoring in RHD patients receiving warfarin should not be understated. Two large multi-national studies of warfarin in RHD patients found less than half (44%) participants were in the therapeutic range over the first 12 weeks of therapy (65) and only 8% of the patients were fully compliant with one third taking less than 80% of doses (66). An Indian study similarly found only 30% of INRs were within the target range and 37% of patients did not monitor INRs regularly (67), highlighting the additional challenges in LMIC settings. In remote settings in high income countries adequate and safe anticoagulation can be even harder to achieve (68-70). While point of care (POC) monitoring in patients receiving warfarin is often assumed to improve control, this has not been clearly demonstrated and indeed in a rural and predominantly non-Indigenous Australian setting a randomised trial of such POC monitoring was not associated with an improvement in control (71).

DISCUSSION

This review has outlined the existing evidence regarding the medical management of RHD-related valvular disease with a specific focus on symptoms, LV dysfunction, rate control in MS, AF and anticoagulation. It has highlighted that the tailored use of diuretics, angiotensin blockade, beta blockers and I_f inhibitors may all be useful for symptom control, LV dysfunction and rate control in MS. In contrast to non-valvular AF, there is limited evidence to suggest AF in RHD may benefit from a focus on rhythm control. Nonetheless, in many RHD patients with AF it may not be possible to achieve or maintain SR and the most frequently studied pharmacotherapy, amiodarone, is not tolerated long-term in a significant proportion of patients. In such patients beta blockers may, where tolerated, be preferred especially in the setting of concomitant LV dysfunction or MS.

Anticoagulation remains a difficult issue for RHD patients. All patients with a history of cardioembolism, AF, spontaneous LA contrast and mechanical prosthetic heart valves should be anticoagulated. While warfarin remains the agent of choice in the setting of a mechanical valve replacement, there is increasing evidence that NOACs may have a role in RHD patients with AF, particularly AR and MR and possibly in MS. Nonetheless, this must be balanced against some evidence to suggest a higher risk of bleeding associated with NOACs in some patient groups and their greater cost, key factors particularly in remote and LMIC settings. Available evidence would suggest anticoagulation following bioprosthetic valve replacement or mitral valve repair may not be required and if necessary aspirin alone is sufficient. Nonetheless, this and the efficacy of NOACs in RHD-related AF should be a focus of future research. The lack of agreement and limited evidence regarding the optimal timing of surgery in asymptomatic patients with RHD also suggests the importance of studying early intervention to prevent atrial and ventricular remodelling in RHD leading to heart failure and AF.

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Chapter 3

Valve surgery for rheumatic heart disease in Australia

There have been no Australian multi-centre studies of RHD valve surgery published and limited data available, regarding factors that might affect the choice of surgery in patients with RHD. This chapter provides an introduction to RHD surgery in Australia by first examining the Australian patient population requiring valve surgery and reviews the pre-operative factors that are associated with surgical choice.

This chapter includes the following peer-reviewed and published report:
Russell EA, Tran L, Baker RA, Bennetts JS, Brown A, Reid CM, Tam R, Walsh WF, Maguire GP. A review of valve surgery for rheumatic heart disease in Australia. *BMC Cardiovasc. Disord.* 2014 Oct 2;14:134. doi: 10.1186/1471-2261-14-134.

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RESEARCH ARTICLE Open Access

A review of valve surgery for rheumatic heart disease in Australia

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Abstract

Background: Globally, rheumatic heart disease (RHD) remains an important cause of heart disease. In Australia it particularly affects older non-Indigenous Australians and Aboriginal Australians and/or Torres Strait Islander peoples. Factors associated with the choice of treatment for advanced RHD remain variable and poorly understood.

Methods: The Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database was analysed. Demographics, co-morbidities, pre-operative status and valve(s) affected were collated and associations with management assessed.

Results: Surgical management of 1384 RHD and 15843 non-RHD valve procedures was analysed. RHD patients were younger, more likely to be female and Indigenous Australian, to have atrial fibrillation (AF) and previous percutaneous balloon valvuloplasty (PBV). Surgery was performed on one valve in 64.5%, two valves in 30.0% and three valves in 5.5%. Factors associated with receipt of mechanical valves in RHD were AF (OR 2.69) and previous PBV (OR 1.98) and valve surgery (OR 3.12). Predictors of valve repair included being Indigenous (OR 3.84) and having fewer valves requiring surgery (OR 0.10). Overall there was a significant increase in the use of mitral bioprosthetic valves over time.

Conclusions: RHD valve surgery is more common in young, female and Indigenous patients. The use of bioprosthetic valves in RHD is increasing. Given many patients are female and younger, the choice of valve surgery and need for anticoagulation has implications for future management of RHD and related morbidity, pregnancy and lifestyle plans.

Keywords: Rheumatic heart disease, Rheumatic valve surgery, Indigenous health, Valve choice

Background

Rheumatic heart disease (RHD) is a condition of global health importance. It is estimated 15.6 - 19.6 million people are living with RHD, with almost 80% of those residing in low and middle-income countries [1,2]. Whilst RHD is now rare in high income countries [3], it remains an important cause of preventable heart disease in some Indigenous populations in these countries. This is likely to be explained by a combination of educational, economic and environmental disadvantage and reduced access to primary and specialist health care [4]. In 2010 the prevalence of RHD amongst Australia's Aboriginal and Torres Strait Islander Indigenous peoples was 6.45 per 1000 or 26 times that of non-Indigenous Australians [5]. A recent echocardiographic screening study of Indigenous Australian children aged 5–14 years, found a prevalence of definite RHD [6] of 8.6 per 1000 (95% CI 6.0-12.0) with none detected in a comparably aged non-Indigenous cohort [7].

In some populations at risk of RHD, such as Aboriginal Australians and Torres Strait Islanders, outcomes following cardiac surgery can be inferior [8,9] despite being of younger age at time of surgery [8]. This is likely to be related to factors including comorbidities [4,8,9], barriers to primary and specialist health care and the ability to achieve safe anticoagulation during long-term follow-up [10].

The most common heart valves affected by RHD and non-RHD causes are the mitral and aortic valves, less

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commonly the tricuspid and rarely the pulmonary valve. Rheumatic valve disease most commonly leads to regurgitation [6,11] and less commonly to valve stenosis or mixed regurgitation and stenosis [12]. Although the majority of rheumatic valve disease cases are only mildly affected, [1] a minority progress to more severe disease requiring valve surgery [13].

The options for surgical management of rheumatic valve disease are valve repair or replacement with either a bioprosthetic or mechanical prosthesis. In patients with mitral stenosis an additional option is non-surgical percutaneous mitral balloon valvuloplasty [12,14]. There are limited data available about factors which might affect the choice of surgery in patients with rheumatic valve disease. This decision is likely to be influenced by patient geography, medication access and use, timing and venue of referral, gender and access to ongoing care and follow-up. There have been no Australian multicentre studies of rheumatic valve surgery published with most published data pertaining to small single centre series.

The aim of this study was thus to examine the Australian patient population having valve surgery for RHD and review the pre-operative factors associated with the choice of surgical management of RHD in Australia.

Methods

The database

The Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database is an Australia-wide database for the collection and analysis of cardiac surgical procedures, established to enable benchmarking and comparison with international standards [15]. The database definition set was developed by the ANZSCTS for all participating cardiac surgery units. There is an opt-out Patient Information Sheet which has the approval of each site's Human Research Ethics Committee. At present 19 of 25 Australian public hospital cardiac surgical units enter data relating to cardiac surgical procedures that identify whether patients are Aboriginal Australians and/or Torres Strait Islanders.

The database collects patient demographics, co-morbidities, pre-operative status, previous interventions, haemodynamic data, surgery type and surgical and post-operative outcome data. Only de-identified data is abstracted and utilised for analysis.

Analysis

The aim of the analysis was to describe patients having valve surgery for rheumatic valve disease, to compare Aboriginal and Torres Strait Islander RHD patients with non-Indigenous Australians and to describe and identify factors associated with treatment choice. Demographic data included age, gender, Indigenous status, concomitant coronary artery bypass grafting (CABG) and rurality by Remoteness Area (RA) category as defined by the Australian Statistical Geography Standard [16]. Co-morbidities assessed included chronic kidney disease (defined as pre-operative estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation and stratified to stages 3 (30 - 59 mL/min/1.73 m^2), 4 (15 - 29 mL/min/1.73 m^2), and 5 (<15 mL/min/1.73 m^2) [17], elevated (200 μmol/L or more) pre-surgery serum creatinine, a pre-existing clinician diagnosis of diabetes mellitus and hypertension and smoking status.

The pre-operative status relating to underlying heart disease included symptomatic status based on the New York Heart Association (NYHA) classes I to IV [18], pre-operative atrial fibrillation, echocardiographic assessment of left ventricular ejection fraction (LVEF) (stratified to more than 45%, 30% - 45% and less than 30%), previous valve surgery and percutaneous balloon valvuloplasty (PBV). Valvular lesions were analysed according to the valve(s) affected, the valvular lesion (regurgitation, stenosis or mixed), the number of valves affected, and the year of surgery. Valve-related surgical procedure data included valve repair or replacement and in the case of replacement, whether this was a mechanical or bioprosthetic valve.

Statistical analysis

Data were analysed using IBM SPSS Statistics 20 (IBM, New York, USA) and Stata 13 (StataCorp LP, Texas, USA). Descriptive data were summarised using standard univariate techniques and reported as percentages with 95% confidence intervals (95% CI), means with standard deviation (SD) or medians with interquartile range (IQR) depending on the data format and distribution. Comparisons between groups were undertaken using χ^2 for categorical data and Student's t-Test or Mann–Whitney U test for continuous Normally distributed or non-Normally distributed data respectively. A p valve less than 0.05 was taken to indicate statistical significance and all tests were two-sided.

Logistic regression models were developed to identify independent factors associated with the type of valve surgical procedure utilised. These were developed using a backwards stepwise approach including in the first model all factors associated with a particular management choice using bivariate analysis with a p value <0.1. Factors with a p value > =0.05 were progressively removed from the models starting with the variable with an odds ratio (OR) closest to 1. Interactions between predictive factors were explored and final models were limited to predictive factors with significant coefficients ($p < 0.05$).

Approval for this project was granted by the Monash University Human Research Ethics Committee (CF13/2737 – 2013001472).

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Results

Data in relation to 62 707 cardiac surgical procedures performed between 1 August 2001 and 31 December 2012 were analysed. A breakdown of those procedures is summarized in Figure 1.

A subset of 17 227 surgical valve procedures with or without coronary artery bypass grafting (CABG) was included for analysis. Contributing surgical centres have increased from five in 2001 with 33 RHD valve surgeries to 26 in 2012 and 203 RHD valve surgeries (Figure 2).

Descriptive characteristics of these valve surgery patients are outlined in Table 1. RHD valve surgery patients were, compared with non-RHD valve surgery patients, younger, more likely to be female and Aboriginal and/or Torres Strait Islander and were less likely to have concomitant CABG, severely impaired left ventricular systolic function (LVEF <30%) or associated diabetes or hypertension. RHD patients were also more likely to have associated atrial fibrillation (AF), be current smokers or have a past history of valve surgery and/or PBV.

In multivariate modeling, patients undergoing RHD-related surgery were younger (OR 0.99/additional year, 95% CI 0.97 – 1.00), more likely to be female (OR 4.15, 95% CI 3.00 – 5.75), Aboriginal and/or Torres Strait Islander (OR 5.10, 95% CI 2.67 – 9.80), have associated AF (OR 3.85, 95% CI 2.72 – 5.44), a history of PBV (OR 5.71, 95% CI 3.37 – 9.71) or prior valve surgery (OR 1.81, 95% CI 1.26 – 2.60), and were less likely to have hypertension (OR 0.67, 95% CI 0.46 – 1.00) or severe left ventricular dysfunction (OR 0.17, 95% CI 0.05 – 0.58). Details regarding RHD valve surgery patients, stratified by Indigenous status, are outlined in Table 2. In bivariate analyses Aboriginal Australian and/or Torres Strait Islander RHD valve surgery patients were, compared with non- Indigenous Australian patients, younger and less likely to have concomitant CABG, associated chronic kidney disease, hypertension or AF. They were also more likely to be previous or current smokers and to be living in remote Australia. In multivariate logistic regression modeling, Indigenous Australian patients were younger (OR 0.89/additional year, 95% CI 0.87 – 0.91), current smokers (OR 2.52, 95% CI 1.40 – 4.51), residents of remote Australia (OR 15.39, 95% CI 7.81 – 30.30) and, in contrast to bivariate analysis, were more likely to have associated hypertension (OR 1.87, 95% CI 1.04 – 3.39), chronic kidney disease (OR 2.22, 95% CI 1.07 – 4.59) and AF (OR 2.09, 95% CI 1.17 – 3.71) once age was controlled for. There were no significant independent interactions between these factors.

Of patients having RHD valve surgery, 64.5% (95% CI 61.91 – 67.02) required surgery on one valve only, 30.0% (95% CI 27.60 – 32.50) on two valves and 5.5% (95% CI 4.35 – 6.83) on three valves. The details of the valves involved and the associations between different valvular involvement is outlined in Table 3. RHD pulmonary valve

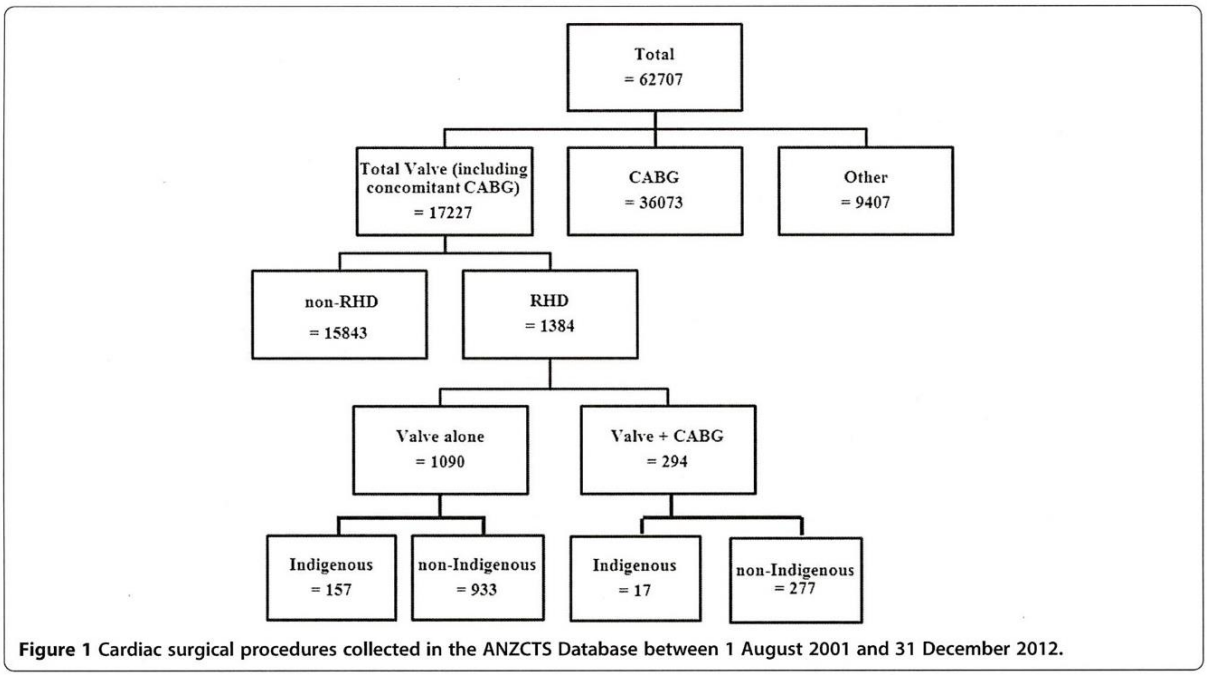

Figure 1 Cardiac surgical procedures collected in the ANZCTS Database between 1 August 2001 and 31 December 2012.

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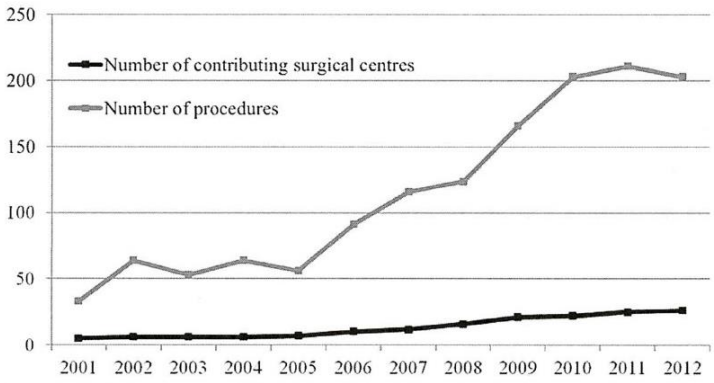

Figure 2 Number of contributing surgical centres and RHD valve procedures over time.

only surgery accounted for only 0.3% (95% CI: 0.08 – 0.60) of procedures and combined RHD aortic, mitral and pulmonary valve surgery, 0.1% (95% CI: 0.02 – 0.52).

The choice of surgical valve procedure for aortic, mitral and tricuspid valve disease overall and stratified by Indigenous status is outlined in Table 4. In bivariate analyses, Indigenous patients were less likely to have mechanical mitral valve replacement, more likely to have mitral valve repair and less likely to have bioprosthetic aortic valve replacement.

Multivariate logistic regression modeling was undertaken to identify independent predictors of mechanical versus bioprosthetic valve replacement and valve replacement versus repair. In patients having an RHD-related valve replacement, mechanical valves, compared with only using bioprosthetic valves, were more likely to be used in those with associated AF (OR 2.69, 95% CI 1.64 – 4.43), when more than one valve required surgery (OR 1.61 for each additional valve, 95% CI 1.03 – 2.49) and if there was a history of previous PBV (OR 3.12, 95% CI 1.87 – 5.21) or other valve surgery (OR 3.12, 95% CI 1.87 – 5.21). Mechanical valves were less likely to be used in those with diabetes (OR 0.51, 95% CI 0.29 – 0.89) or chronic kidney disease (OR 0.50, 95% CI 0.30 – 0.83). Whilst the median age of those receiving mechanical valves was significantly lower (57.1 years, IQR (50.0 – 67.1)) than for those receiving bioprosthetic valves (65.8 years, (61.2 – 77.0), p = <0.001), this was not significant after adjusting for these other covariates. Indigenous status and remoteness of residence were not significant predictors of valve type choice.

In multivariate modelling, patients having isolated valve repair, compared with any valve replacement, were more likely to be Aboriginal and Torres Strait Islander (OR 5.50, 95% CI 3.24 – 9.35), to have fewer valves requiring surgery (OR 0.10 for each additional valve, 95% CI 0.04 – 0.28) and were less likely to have hypertension (OR 0.53, 95% CI 0.32 – 0.89) or a history of smoking (OR 0.59, 95% CI 0.37 – 0.96). Whilst patients having isolated valve repair, compared with any valve replacement were more likely to be younger, reside in a remote area and less likely to have associated AF or concomitant CABG, these were not significant predictors after adjusting for other significant covariates.

Temporal trends in the surgical management of RHD-related mitral and aortic valve disease are outlined in Figures 3 and 4. Overall there was no significant change in aortic valve surgery type over this time. Mitral valve procedures demonstrated a significant increase in bioprosthetic valve replacements (1.8% increase as a proportion of all mitral valve procedures/year, 95% CI 1.0 – 2.6) and a corresponding fall in mechanical valve replacements (1.8% decrease/year, 95% CI 1.0 – 2.6). Whilst mitral valve repairs decreased (1.0% decrease/year, 95% CI –0.5 – 1.7) this was not statistically significant. Given major centres undertaking valve surgery for Aboriginal and Torres Strait Islander peoples only began submitting data from 2006, analysis of temporal trends in the choice of valve surgery stratified by Indigenous status was restricted to 2006 – 2012. Analysis of mitral procedures over time revealed mitral valve repairs declined (Spearman rank r = –0.786, p = 0.036) in Aboriginal and Torres Strait Islander patients from 2006–2012. Aortic valve procedures in non-Indigenous Australian patients over the same time demonstrated an increase in the use of bioprosthetic valves (Spearman rank r = 0.857, p = 0.014) and a decrease in mechanical valves (Spearman rank r = –0.929, p = 0.003). The surgical management of mitral valve disease in non-Indigenous Australians and aortic valve disease in Aboriginal and Torres Strait Islander peoples did not alter significantly over this time.

The nature of the underlying RHD-related mitral and aortic valve lesions stratified by Indigenous status are outlined in Table 5. Aboriginal and Tosses Strait Islander people were, compared with non-Indigenous Australians, more likely to have only mitral stenosis and

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Table 1 Descriptive characteristics of valve surgery patients stratified by causation

	All	RHD-related	Non-RHD	P value
	N = 17227	N = 1384	N = 15843	
Age (years)	71.3	59.7	71.9	<0.001
(Median (IQR))	(61.2 – 78.3)	(50.9 – 71.4)	(62.3 – 78.6)	
Sex (% female)	37.3	64.5	35.0	<0.001
(95% CI)	(36.6 – 38.1)	(61.9 – 67.0)	(34.2 – 35.7)	
Indigenous status	1.9	12.6	1.0	<0.001
(% Aboriginal and Torres Strait Islander people) (95% CI)	(1.7 – 2.1)	(10.9 – 14.4)	(0.8 – 1.2)	
Concomitant CABG	39.1	21.2	40.7	<0.001
(%, 95% CI)	(38.4 – 39.8)	(19.1 – 23.5)	(39.9 – 41.4)	
Pre-operative comorbidities				
Diabetes	23.2	20.3	23.4	0.009
(%, 95% CI)	(22.5 – 23.8)	(18.2 – 22.5)	(22.8 – 24.1)	
Elevated Creatinine	3.4	2.8	3.5	0.436
(% Cr > =200 μmol/L, 95% CI)	(3.1 – 3.7)	(2.0 – 03.8)	(3.2 – 03.8)	
Chronic kidney disease	36.7	31.2	37.2	0.814
(% eGFR < 60 mL/min/1.73 m^2) (95% CI)	(36.0 – 37.5)	(28.8 – 33.7)	(36.5 – 38.0)	
Hypertension	67.0	53.0	68.2	<0.001
(%, 95% CI)	(66.3 – 67.7)	(50.3 – 55.7)	(67.5 – 68.9)	
Previous smoking	53.1	52.7	53.1	0.955
(%, 95% CI)	(52.3 -53.8)	(50.0 - 55.3)	(52.3 - 53.9)	
Current smoking	16.0	25.1	15.2	<0.001
(%, 95% CI)	(15.2 - 16.7)	(22.0 - 28.4)	(14.5 - 16.0)	
Pre-operative status				
NYHA classes III & IV	43.7	53.7	42.8	0.351
(%, 95% CI)	(42.9 – 44.4)	(51.0 – 56.4)	(42.0 – 43.6)	
Atrial fibrillation	19.3	40.5	17.4	<0.001
(%, 95% CI)	(18.7 – 19.9)	(37.9 – 43.2)	(16.8 – 18.0)	
LVEF >45%	81.2	84.6	80.9	0.001
(%, 95% CI)	(80.6 – 81.8)	(82.6 – 86.5)	(80.3 – 81.5)	
LVEF 45 – 60%	12.1	10.9	12.2	0.154
(%, 95% CI)	(11.6 – 12.6)	(9.3 – 12.7)	(11.7 – 12.7)	
LVEF <30%	4.3	2.2	4.5	<0.001
(%, 95% CI)	(4.0 – 4.6)	(1.5 – 3.2)	(4.2 – 4.8)	
Previous procedures				
Valve surgery	6.4	13.5	5.8	<0.001
(%, 95% CI)	(6.1 – 6.8)	(11.8 – 15.4)	(5.4 – 6.2)	
PBV	4.9	20.7	3.3	<0.001
(%, 95% CI)	(4.3 – 5.6)	(16.7 – 25.2)	(2.8 – 4.0)	

regurgitation as well as mixed mitral disease and, whilst more likely to have isolated aortic regurgitation, were less likely to have aortic stenosis only or mixed aortic disease.

The utilisation of mitral or aortic valve repair as compared with valve replacement stratified by the underlying valve lesion is presented in Table 6. Mitral valve repair was more likely to be undertaken in isolated regurgitation

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Table 2 Descriptive characteristics of RHD valve surgery patients stratified by Indigenous status

	Aboriginal and/or Torres Strait Islander	Non-Indigenous Australian	P value
	N = 174	N = 1210	
Age (years)	37.4	65.1	<0.001
(Median (IQR))	(26.9 – 49.1)	(55.5 – 72.8)	
Sex (% female)	67.2	64.0	0.411
(95% CI)	(59.7 – 74.2)	(61.3 – 66.8)	
Concomitant CABG	9.8	22.9	<0.001
(%, 95% CI)	(5.8 – 15.2)	(20.6 – 25.4)	
Area of residence			
Remote and very remote	54.1	1.6	<0.001
(% RA category 3 & 4, 95% CI)	(46.3 – 61.7)	(1.0 – 2.4)	
Inner and outer regional	39.5	33.3	0.108
(% RA category 1 & 2, 95% CI)	(32.2 – 47.3)	(30.7 – 36.1)	
Major city	6.4	65.1	<0.001
(%, 95% CI)	(3.2 – 11.2)	(62.3 – 67.8)	
Pre-surgery comorbidities			
Diabetes	24.3	19.8	0.167
(%, 95% CI)	(18.1 – 31.4)	(17.5 – 22.1)	
Elevated Creatinine	2.9	2.7	0.912
(% Cr > =200 μmol/L) (95% CI)	(0.9 – 6.6)	(1.9 – 3.8)	
Chronic kidney disease (% eGFR < 60 mL/min/1.73 m^2)	14.4	33.5	<0.001
(95% CI)	(9.5 – 20.5)	(30.8 – 36.2)	
Hypertension	37.0	55.3	<0.001
(%, 95% CI)	(29.8 – 44.7)	(52.4 – 58.1)	
Previous smoking	64.2	51.0	<0.001
(%, 95% CI)	(56.5 – 71.3)	(48.2 – 53.9)	
Current smoking	55.4	19.7	<0.001
(%, 95% CI)	(45.7 – 64.8)	(16.7 – 23.1)	
Pre-operative status			
NYHA classes III & IV	47.1	53.1	0.138
(%, 95% CI)	(39.5 – 54.8)	(50.3 – 56.0)	
Atrial fibrillation	33.3	41.6	0.039
(%, 95% CI)	(26.4 – 40.9)	(38.8 – 44.4)	
LVEF >45%	83.9	84.7	0.784
(%, 95% CI)	(77.6 – 89.0)	(82.6 – 86.7)	
LVEF 30 – 45%	11.5	10.8	0.792
(%, 95% CI)	(7.2 – 17.2)	(9.1 – 12.7)	
LVEF <30%	3.4	2.1	0.249
(%, 95% CI)	(1.3 – 7.4)	(1.3 – 3.1)	
Previous procedures			
Valve surgery	16.1	13.1	0.287
(%, 95% CI)	(11.0 – 22.4)	(11.3 – 15.2)	
PBV	29.5	19.5	0.124
(%, 95% CI)	(16.8 – 45.2)	(15.3 – 24.3)	

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Table 3 Association between different RHD-related valve disease requiring surgical management

% (95% CI)		
1 valve		
Mitral valve only	40.3	(37.7 – 42.9)
Aortic valve only	22.9	(20.7 – 25.2)
Tricuspid valve only	1.2	(0.7 – 2.0)
2 valves		
Mitral and aortic valves	20.6	(18.5 – 22.8)
Mitral and tricuspid valves	8.5	(7.1 – 10.1)
Aortic and tricuspid valves	0.7	(0.3 – 1.3)
3 valves		
Mitral, aortic and tricuspid valves	5.4	(4.2 – 6.7)

and mixed disease and aortic valve repair in those with mixed disease.

Discussion

This study is the first to provide a detailed description of Australian RHD valve surgery. It analysed 17227 patients in Australia who had surgical valve procedures performed between 2001 and 2012 including 1384 RHD valve procedures. The high burden of RHD among Aboriginal and Torres Strait Islander people was reflected in the relatively high percentage of Indigenous Australians requiring RHD surgery (12.6%) compared with their representation in the overall Australian population (2.5%) [19]. Advanced RHD affects people at a younger age compared with non-RHD-related valve disease [20,21]. Australians in general and Aboriginal Australian and/or Torres Strait Islander in particular required RHD valve surgery at a younger age, a finding reflected in several earlier studies [9,22].

The finding that RHD surgery patients were both younger and more likely to be female has implications for treatment choice, particularly given the potential hazards of anticoagulation associated with future pregnancies [23]. It is also of relevance for other younger people who often participate in activities associated with an increased risk of trauma (e.g. contact sports). AF was more common in those having RHD-related compared to non-RHD-related valve surgery. Undertaking RHD mitral valve surgery prior to the onset of AF would appear to provide greater therapeutic choice as both bioprosthetic valve replacement and valve repair do not typically require ongoing anticoagulation in the presence

Table 4 Surgical management of RHD valve disease stratified by Indigenous status (There were only five pulmonary procedures performed; all on non-Indigenous patients)

% (95% CI)	Total RHD	Aboriginal and/or Torres Strait Islander	Non-Indigenous Australian	P value
	N = 1384	N = 174	N = 1210	
Mitral		N = 153	N = 882	
Mechanical valve	65.5	51.6	67.9	<0.001
	(62.5 – 68.4)	(43.4 – 59.8)	(64.7 – 71.0)	
Bioprosthetic valve	24.5	26.8	24.1	0.482
	(21.9 – 27.3)	(20.0 – 34.5)	(21.4 – 27.1)	
Valve Repair	10	21.6	7.9	<0.001
	(6.4 – 14.8)	(15.3 – 28.9)	(6.2 – 9.9)	
Aortic		N = 62	N = 628	
Mechanical valve	53.6	64.5	52.5	0.071
	(49.8 – 57. 4)	(51.3 – 76.3)	(48.6 – 56.5)	
Bioprosthetic valve	44.2	32.3	45.4	0.047
	(40.5 – 48.0)	(20.9 – 45.3)	(41.4 – 49.4)	
Valve Repair	2.2	3.2	2.1	0.552
	(1.22 – 3.56)	(0.4 – 11.2)	(1.1 – 3.5)	
Tricuspid		N = 31	N = 188	
Mechanical valve	10	3.2	11.2	0.173
	(8.2 – 11.9)	(0.1 – 16.7)	(7.0 – 16.6)	
Bioprosthetic valve	3.7	6.5	3.2	0.370
	(1.6 – 7.1)	(0.8 – 21.4)	(1.2 – 6.8)	
Valve Repair	86.3	90.3	85.6	0.482
	(81.0 – 90.6)	(74.2 – 98.0)	(79.8 – 90.3)	

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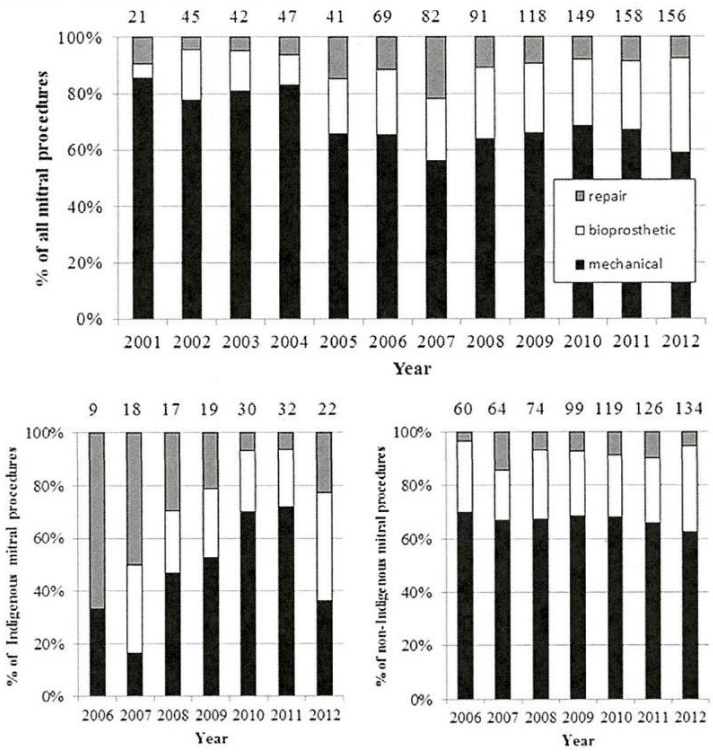

Figure 3 Changes in RHD mitral valve surgery over time, total and stratified by Indigenous status. (Numbers at the top of each column refer to the total number of procedures for that year).

of sinus rhythm and no embolic history. This can be particularly useful when managing younger and female patients for the reasons outlined above and for Indigenous Australian patients who are more likely to reside in remote communities where anticoagulation monitoring and ongoing specialist review can be difficult. Nonetheless the associated increased risk of surgical re-operation in valve repair and bioprosthetic valve replacement must also be considered in the decision-making process.

There was an independent association between RHD valve surgery and previous PBV for mitral stenosis. This is not surprising given PBV can often provide temporary relief of mitral stenosis with restenosis being reported in a number of studies, ranging from 40% of patients at six years [24], 34% at 10 years [25] and 21% at 15 years [26,27]. Despite this risk of restenosis, PBV can provide a non-invasive approach to mitral stenosis management that does not necessarily require ongoing anticoagulation and which has excellent overall survival rates ranging from 96.5% at three years [24] to 99.2% at 16 years [26].

Aboriginal Australian and/or Torres Strait Islander people were less likely to have concomitant CABG when having RHD-related valve surgery. This is surprising given Indigenous Australians are hospitalised 1.9 times more than non-Indigenous Australians for coronary heart disease [28]. Nonetheless this may, at least in part, be explained by the younger age of Indigenous Australian RHD patients who had a median age nearly 30 years less than that of non-Indigenous patients.

We also found Indigenous Australian RHD patients were less likely to have associated kidney disease. This is also perhaps unexpected given the well-documented epidemic of kidney disease in Aboriginal and Torres Strait Islander people [29]. Nonetheless this finding did not persist in multivariate analysis, suggesting the older age of non-Indigenous Australian RHD patients had a greater effect on chronic kidney disease risk compared with younger Aboriginal and Torres Strait Islander patients. This finding is not universal and Indigenous Australian cardiac surgical patients have reported to have an increased burden of kidney disease pre-operatively [7,8]. These reports are likely to have represented Aboriginal and Torres Strait Islander populations which may have been at greater risk of chronic kidney disease due to the high proportion of patients residing in remote centres where the risk of kidney disease has also been shown to be greater [29,30]. Such disparity between these earlier single centre studies and our larger multicenter review reinforces the benefits of national data collection systems such as that used here.

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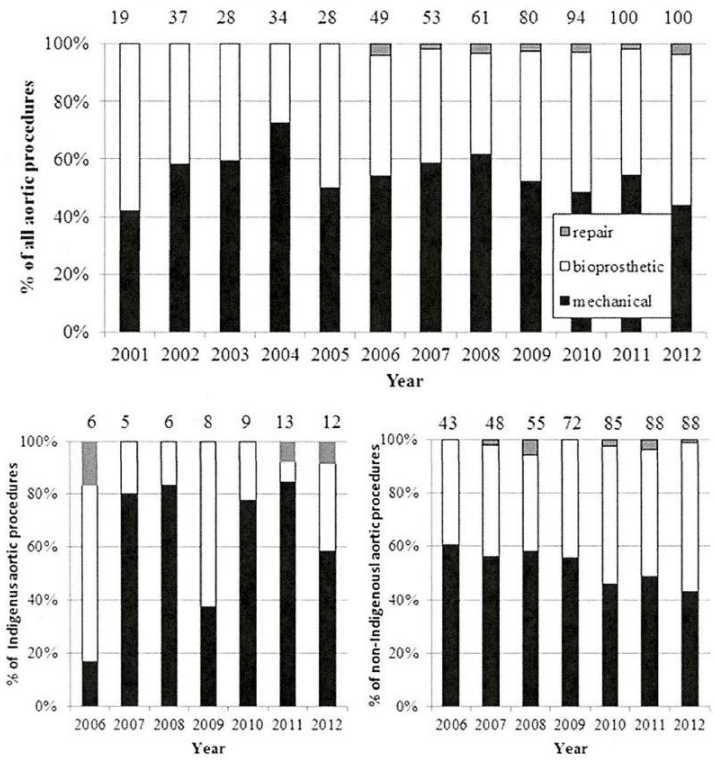

Figure 4 Changes in RHD aortic valve surgery over time, total and stratified by Indigenous status. (Numbers in each column refer to the total valve surgeries for that year).

Table 5 RHD Mitral and aortic valve lesions types stratified by Indigenous status

% (95% CI)	Total RHD	Aboriginal and/or Torres Strait Islander	Non-Indigenous Australian	P value
	N = 1384	N = 174	N = 1210	
Mitral		n = 152	n = 882	
Stenosis only	5.3	12.1	4.3	<0.001
(95% CI)	(4.2 – 6.6)	(7.6 – 17.9)	(3.2 – 5.6)	
Regurgitation only	21	31.0	19.5	<0.001
(95% CI)	(18.8 – 23.2)	(24.3 – 38.5)	(17.3 – 21.9)	
Combined regurgitation and stenosis	28.8	36.2	27.8	0.022
(95% CI)	(26.5 – 31.3)	(29.1 – 43.8)	(25.3 – 30.4)	
Aortic valve		n = 62	n = 628	
Stenosis only	4.9	1.1	5.5	0.014
(95% CI)	(3.8 – 6.2)	(0.1 – 4.1)	(4.2 – 6.9)	
Regurgitation only	12.1	21.8	10.7	<0.001
(95% CI)	(10.4 – 13.9)	(15.9 – 28.7)	(9.0 – 12.5)	
Combined regurgitation and stenosis	17.1	12.1	17.8	0.052
(95% CI)	(15.1 – 19.1)	(7.6 – 17.9)	(15.7 – 20.0)	

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Table 6 RHD Mitral and aortic valve lesions types stratified by isolated repair or replacement

% all valve procedures (95% CI)	Isolated valve repair N = 74	Any valve replacement N = 1297	P value repair versus replacements
Mitral			
Stenosis only	6.8	5.2	0.573
(95% CI)	(2.2 – 15.1)	(4.1 – 6.6)	
Regurgitation only	54.1	19.0	<0.001
(95% CI)	(42.165.7)	(16.9 – 21.2)	
Combined regurgitation and stenosis	14.9	29.8	0.006
(95% CI)	(7.7 – 25.0)	(27.3 – 32.3)	
Aortic valve			
Stenosis only	1.4	5.2	0.142
(95% CI)	(0.03 – 7.3)	(04.0 – 6.5)	
Regurgitation only	9.5	12.3	0.462
(95% CI)	(3.9 – 18.5)	(10.6 – 14.3)	
Combined regurgitation and stenosis	5.4	17.8	0.006
(95% CI)	(1.5 – 13.3)	(15.7 – 20.0)	

The valves involved in RHD valve surgery were in line with earlier studies, most commonly the mitral and aortic valves, less commonly the tricuspid and rarely the pulmonary valve. Isolated RHD-related tricuspid valve disease is relatively uncommon [31] and represented only 1.2% of Australian patients having RHD valve surgery. Thirty percent of patients having RHD-related surgery required management of multiple valves, highlighting the increased complexity of surgery in RHD-related valve disease.

The choice of valve procedure is likely to be informed by a combination of patient, health practitioner choice, demographic and disease factors. A mechanical valve has long term durability providing therapeutic anticoagulation can be achieved compared to a bioprosthetic valve which is likely to degenerate over time [1,23,32,33]. Mechanical valves may therefore be preferred in younger patients so as to avoid later re-operation. Nonetheless this must be balanced against the inconvenience and risk of anticoagulation in a younger patient who may wish to become pregnant or to participate in recreational or employment activities that entail a greater risk of trauma. The balancing of these factors means there is no universally correct approach to treatment choice in the individual patient. Our data would suggest that mechanical valves are preferred in younger patients irrespective of whether they are Indigenous or not. This is particularly the case when there is co-existent AF (and therefore an additional indication for anticoagulation) and the patient has represented following earlier PBV or past valve surgery. Whilst such an approach can be argued as potentially reasonable for patients living in remote Australia, it would suggest that decisions regarding the use of mechanical valves, particularly in younger Aboriginal and Torres Strait Islander people should be undertaken cautiously and in association with the patient, their family, community and local health care providers. The difficulty of maintaining long-term anticoagulation, particularly in a remote setting, should not be underestimated. In a review of RHD patients prescribed warfarin, 37% had inadequate monitoring and 65% of INR results were outside the recommended range [34]. Our findings support an increasing preference for bioprosthetic over mechanical valve replacement for mitral valve disease and may reflect a greater appreciation of the factors outlined above. Variability in local management practices including the timing of surgical referral and surgical centre practices and expertise are also likely to influence the timing and type of surgery performed. Earlier referral to a surgical centre with a specific interest in valve repair is thus likely to increase the possibility of repair.

Mitral valve repairs as a proportion of all mitral valve procedures decreased (1.0% decrease/year, 95% CI −0.5 - 1.7) but this was not statistically significant. Mitral valve repair compared to replacement has previously been associated with higher survival rates [35-37] in young RHD patients, with Remenyi et al. [35] reporting actuarial survival at 10 and 14 years for patients with mitral replacement of 79% and 44%, compared to 90% and 90% for those who underwent mitral repair. Similarly Wang et al. [37] in a systematic review of mitral valve repair and replacement found a survival benefit associated with mitral repair over replacement.

Not all valves, however, are suitable for repair [38] and repaired valves have an increased risk of early reoperation [38,39]. A key factor in increasing the chance of successful mitral valve repair is likely to be earlier referral prior to the onset of valvular fibrosis and calcification which may reduce the chance of successful repair [40]

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and concentrating RHD surgical management in centres with greater experience in this area.

Whilst the proportion of mitral valve procedures that were repairs rather than replacements had not significantly altered over time it was noted that for all mitral valve lesions, not just mitral regurgitation, that mitral valve repair was more likely in Indigenous patients. This is likely to reflect an understanding of the difficulties associated with anticoagulation. Non-Indigenous patients are more likely to reside in metropolitan Australia and to be more likely to be able to achieve safe anticoagulant use and monitoring. In such a setting mechanical valve replacement with attendant long-term anticoagulation is likely to be preferable. The utilization of mitral valve repair in mitral stenosis and mixed mitral valve disease demonstrates the diversity of valvular lesions that are encountered and dealt with by surgeons when dealing with RHD and the broad scope of expertise required.

Limitations of the study

The main limitation of this study is that it is restricted to Australian surgical practice and does not reflect management in other countries. Nonetheless overall this sample is likely to provide an accurate representation of surgical management of RHD in Australia. Whilst the ANZSCTS database receives data from 19 Australian public hospitals there are six public hospitals in Australia which perform cardiac surgery but do not provide data. It is unlikely the inclusion of these centres would have significantly altered our findings. Of particular note is the inclusion of data from the major Australian centres performing RHD-related valve surgery in Aboriginal Australian and Torres Strait Islander patients. The multiple data collection sites may have led to variable data coding. This was however minimised by each site employing its own data manager who was supported with training and standard data definitions, the use of standardised data entry systems and centralised auditing of site-specific data.

Conclusions

This study is one of the largest reviews of patients undergoing RHD valve surgery. Mitral and aortic valve disease remains the focus of most surgery but tricuspid valve procedures are not uncommon. A range of factors have been identified which are associated with particular surgical procedures. Whilst many of these reflect the underlying nature of disease, the role of AF in predicting treatment choice would suggest that earlier surgery, prior to the onset of AF, and more aggressive management of AF if it does occur, may allow a broader choice of intervention and, correspondingly, less requirement for life-long anticoagulation. Whilst mechanical valves were more likely to be used in younger patients, this needs to be balanced against fertility, lifestyle planning and the safety of anticoagulant use particularly in younger, remote and Aboriginal and Torres Strait Islander patients. The greater use of bioprosthetic valves, valve repair and PBV, whilst having a greater risk of reoperation, may be more suitable in such patients. Earlier referral and surgical management of such patients to centres with expertise in managing RHD valve disease is likely to provide greater opportunity for valve repair and PBV.

Abbreviations

RHD: Rheumatic heart disease; AF: Atrial fibrillation; PBV: Percutaneous balloon valvuloplasty; ANZSCTS: Australia and New Zealand Society of Cardiac and Thoracic Surgeons; CABG: Coronary artery bypass grafting; eGFR: Estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; CI: Confidence interval; SD: Standard deviation; IQR: Interquartile range; OR: Odds ratio.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EAR performed the statistical analysis and drafted the manuscript. LT assisted with acquisition of data and analysis. RAB and helped with revision of the manuscript. JSB and helped with revision of the manuscript. AB conceived of the study and participated in its design and coordination and helped helped with revision of the manuscript. CMR assisted with acquisition of data and helped helped with revision of the manuscript. RT helped helped with revision of the manuscript. WW helped with revision of the manuscript. GPM conceived of the study participated in the design of the study, assisted with the statistical analysis and interpretation and helped to draft the manuscript. All authors read and approved the final manuscript.

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Chapter 4

Outcome following valve surgery for rheumatic heart disease in Australia

This chapter expands on the areas highlighted in Chapter 3 and extends this to an examination of the factors associated with RHD and non-RHD surgery outcome. Significant independent predictors of short or long term outcome overall and for Indigenous Australians specifically are addressed, both alone and in association with procedure type.

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RESEARCH ARTICLE Open Access

A review of outcome following valve surgery for rheumatic heart disease in Australia

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Abstract

Background: Globally, rheumatic heart disease (RHD) remains an important cause of heart disease. In Australia it particularly affects younger Indigenous and older non-Indigenous Australians. Despite its impact there is limited understanding of the factors influencing outcome following surgery for RHD.

Methods: The Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database was analysed to assess outcomes following surgical procedures for RHD and non-RHD valvular disease. The association with demographics, co-morbidities, pre-operative status, valve(s) affected and operative procedure was evaluated.

Results: Outcome of 1384 RHD and 15843 non-RHD valve procedures was analysed. RHD patients had longer ventilation, experienced fewer strokes and had more readmissions to hospital and anticoagulant complications. Mortality following RHD surgery at 30 days was 3.1 % (95 % CI 2.2 – 4.3), 5 years 15.3 % (11.7 – 19.5) and 10 years 25.0 % (10.7 – 44.9). Mortality following non-RHD surgery at 30 days was 4.3 % (95 % CI 3.9 - 4.6), 5 years 17.6 % (16.4 - 18.9) and 10 years 39.4 % (33.0 - 46.1). Factors independently associated with poorer longer term survival following RHD surgery included older age (OR1.03/additional year, 95 % CI 1.01 – 1.05), concomitant diabetes (OR 1.7, 95 % CI 1.1 – 2.5) and chronic kidney disease (1.9, 1.2 – 2.9), longer invasive ventilation time (OR 1.7 if greater than median value, 1.1– 2.9) and prolonged stay in hospital (1.02/additional day, 1.01 – 1.03). Survival in Indigenous Australians was comparable to that seen in non-Indigenous Australians.

Conclusion: In a large prospective cohort study we have demonstrated survival following RHD valve surgery in Australia is comparable to earlier studies. Patients with diabetes and chronic kidney disease, were at particular risk of poorer long-term survival. Unlike earlier studies we did not find pre-existing atrial fibrillation, being an Indigenous Australian or the nature of the underlying valve lesion were independent predictors of survival.

Keywords: Indigenous health, Rheumatic heart disease, Rheumatic valve surgery, Outcome indicators

Background

Rheumatic heart disease (RHD) is a condition of global health importance. It is estimated 15.6 to 19.6 million people are living with RHD, with almost 80 % of these residing in low and middle-income countries [1, 2], with an estimated population prevalence in those countries of 2.5 to 3.2 cases per 1000 [1]. Approximately 1 to 5 % of people with RHD die each year accounting for 233 000 to 294 000 RHD-related deaths per year, 95 % of these occurring in low- and middle income countries [1] with limited facilities to treat advanced disease requiring valve surgery.

Whilst RHD is now rare in high income countries [3], except for migrant and older residents, it remains an important and ongoing cause of preventable heart disease in Indigenous populations [4]. A recent echocardiographic screening study of Indigenous Australian (Aboriginal and Torres Strait Islander) children aged 5–14 years, found a prevalence of RHD [5] of 8.6 per 1000 (95 % CI 6.0 – 12.0) with none detected in a comparably aged non-Indigenous cohort [6].

Surgical intervention remains an important treatment modality for those with more severe forms of RHD, yet disparities exist in access to and outcomes following RHD

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surgery [7]. Factors which have been identified as being associated with outcomes following valve surgery in patients with RHD-related valve disease include age [8–11], pre-operative clinical status [8–10, 12–15], pre-existing atrial fibrillation (AF) [13, 16, 17], left ventricular function [12–14, 18, 19] and the nature of the underlying valve lesion [10, 12, 13, 20].

Increasing age has been associated with lower overall event-free survival [8–11, 21] and operative mortality [16]. Younger patients are, presumably due to longer overall survival, nonetheless subject to a higher risk of eventual deterioration of bioprosthetic valves, with an attendant need for reoperation [19, 22–25]. Other factors which have been reported as being associated with outcome following RHD-related valve surgery include poorer pre-operative clinical status, as assessed by New York Heart Association (NYHA) functional class [26–28] and impaired pre-operative left ventricular function (left ventricular ejection fraction (LVEF) <45 %) [9, 10, 19]. Pre-operative AF has also been found to predict later mortality [16, 26, 29]. Finally the valve involved and the nature of the valve lesion (regurgitation versus stenosis) has been shown to influence outcome with the best long-term outcome seen in those with isolated mitral regurgitation [29].

It has been suggested Indigenous Australians (Aboriginal Australians and Torres Strait Islander peoples) may have poorer survival following RHD valve surgery compared with non-Indigenous Australian patients [16, 25, 26]. Nonetheless previous studies have tended to suffer from a lack of power, have usually been restricted to single site and often failed to control for other factors which may influence survival. Despite tending to be younger at time of surgery, Indigenous Australians have previously been found to have poorer survival within the first 30 days following valve surgery [16, 26] and at five years [16, 26, 30]. Where disparities have been noted they have been attributed to a range of factors including comorbidities [16, 25, 26], barriers to primary and specialist health care and access, compliance and monitoring of anticoagulation during long-term follow-up [23].

Whilst existing national Australian guidelines [25] for RHD management acknowledge that outcomes may be affected by treatment choice, prosthetic valve type and timing of referral for intervention, there remains limited information regarding how these factors interact and how they might be anticipated to influence outcomes and treatment recommendations.

We therefore aimed to identify factors associated with RHD surgery outcome by analysing data from a large multi-site cardiac surgery enhanced surveillance register, The Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database.

Methods

The Database

The Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database is an Australia-wide voluntary database for the prospective collection and analysis of the results of cardiac surgery. It collects data from 25 Australian hospitals on patients who have undergone cardiac surgery, the types of surgery performed and early (30 day) complications [31–33] and links this with long-term survival data.

Analysis

Demographic data including age, gender, location and Indigenous status were assessed. The remoteness of the usual place of residence was classified based on the Australian Statistical Geography Standard [34] as Remote (Remoteness Area (RA) categories 3 or 4) or non-Remote. Co-morbidities assessed included chronic kidney disease (defined as pre-operative estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation [35] and stratified to stages 3 (30 – 59 mL/min/1.73 m^2), 4 (15 – 29 mL/min/1.73 m^2), and 5 (<15 mL/min/1.73 m^2) [37], previous and current smoking status, concomitant coronary artery bypass grafting (CABG) and a pre-existing clinician diagnosis of diabetes mellitus and hypertension. The pre-operative status relating to underlying heart disease included New York Heart Association (NYHA) classes I to IV [37], pre-operative atrial fibrillation (AF), echocardiographic assessment of LVEF stratified to more than 45 %, 30 to 45 % or less than 30 % and previous percutaneous balloon valvuloplasty (PBV) or valve surgery.

Valvular lesions were analysed according to the type and number of valve(s) affected. Valve-related surgical procedure data included valve repair or replacement and in the case of replacement, whether this was a mechanical or bioprosthetic valve.

Outcomes associated with the immediate post- operative course included length of time of invasive ventilatory support and length of intensive care stay (expressed as dichotomous variables based on median values), hospital length of stay in days and the need for re-operation during the initial admission. Early outcomes within the 30 days following surgery included mortality, stratified as cardiac and non-cardiac, readmission and other complications (valve dysfunction, acute kidney injury, new atrial fibrillation, stroke/TIA, deep sternal wound infection, septicaemia, anticoagulation (bleeding, and/or embolic) complications and heart failure). Finally longer-term survival beyond 30 days was determined from the National Death Index (NDI), a database, housed at the Australian

Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980 [38].

Statistical analysis

Data were analysed using IBM SPSS Statistics 20 (IBM, New York, USA) and STATA Release 13 (StataCorp LP, Texas, USA). Descriptive data were summarised using standard univariate techniques and reported as percentages with 95 % confidence intervals (95 % CI), means with standard deviation (SD) or medians with interquartile range (IQR) depending on the data format and distribution. Comparisons between groups were undertaken using χ^2 for categorical data and Student's *t*-Test or Mann–Whitney *U* test for continuous Normally distributed or non-Normally distributed data respectively. A p valve less than 0.05 was taken to indicate statistical significance and all tests were two-sided.

Survival analysis for mortality was presented with Kaplan- Meier curves and analysed using the log rank test to compare survival in RHD and non-RHD surgery and Indigenous and non-Indigenous Australian RHD patients.

Multivariable linear, logistic and Cox proportional hazard models were developed to identify independent factors associated with outcome measures. These used a backwards stepwise approach including in the first model all factors associated with a particular outcome variable using bivariate analysis with a p value <0.1. Factors with a p value > =0.05 were progressively removed from the models starting with those variables with a regression co-efficient closest to 0 or an odds (OR) or hazard (HR) ratio closest to 1. Final models were limited to predictive factors with significant coefficients ($p < 0.05$).

Approval for this project was granted by the Monash University Human Research Ethics Committee (CF13/2737 – 2013001472).

Results

Data in relation to 62 707 cardiac surgical procedures were collated by the ANZCTS database between 1 June 2001 and 31 December 2012. Details regarding the breakdown of patients included in this database have been outlined elsewhere [33]. A subset of 17 227 surgical valve procedures (with or without coronary artery bypass grafting (CABG)) was included for analysis. Demographic and comorbidity data relating to these patients are outlined in Table 1. RHD was a significantly more common indication for valve surgery in Indigenous (52.4 %, 95 % CI 46.9 – 57.9) as compared with non-Indigenous Australians (7.2 %, 95 % CI 6.8 – 7.6 %) (p <0.001).

Table 1 Descriptive characteristics of valve surgery patients stratified by whether indication for surgery was RHD or non-RHD related [33]

	All	RHD-related	Non-RHD	*P* value
	N = 17227	*N* = 1384	*N* = 15843	
Age (years) (median (IQR[a])	71.3(61.2 – 78.3)	59.7(50.9 – 71.4)	71.9(62.3 – 78.6)	<0.001
Sex (% female) (95 % CI[#])	37.3(36.6 – 38.1)	64.5(61.9 – 67.0)	35.0(34.2 – 35.7)	<0.001
Indigenous status (% Aboriginal and Torres Strait Islander people) (95 % CI)	1.9(1.7 – 2.1)	12.6(10.9 – 14.4)	1.0(0.8 – 1.2)	<0.001
Concomitant CABG (%, 95 % CI)	39.1(38.4 – 39.8)	21.2(19.1 – 23.5)	40.7(39.9 – 41.4)	<0.001
Pre-operative comorbidities				
Diabetes (%, 95 % CI)	23.2(22.5 – 23.8)	20.3(18.2 – 22.5)	23.4(22.8 – 24.1)	0.009
Chronic kidney disease (% eGFR < 60 mL/min/1.73 m^2) (95 % CI))	36.7(36.0 – 37.5)	31.2(28.8 – 33.7)	37.2(36.5 – 38.0)	0.814
Hypertension (%, 95 % CI)	67.0(66.3 – 67.7)	53.0(50.3 – 55.7)	68.2(67.5 – 68.9)	<0.001
Previous smoking (%, 95 % CI)	53.1(52.3 – 53.8)	52.7(50.0 – 55.3)	53.1(52.3 – 53.9)	0.955
Current smoking (%, 95 % CI)	16.0(15.2 – 16.7)	25.1(22.0 – 28.4)	15.2(14.5 – 16.0)	<0.001
Pre-operative status				
NYHA classes III & IV (%, 95 % CI)	43.7(42.9 – 44.4)	53.7(51.0 – 56.4)	42.8(42.0 – 43.6)	0.351
Atrial fibrillation (%, 95 % CI)	19.3(18.7 – 19.9)	40.5(37.9 – 43.2)	17.4(16.8 – 18.0)	<0.001
LVEF >45 % (%, 95 % CI)	81.2(80.6 – 81.8)	84.6(82.6 – 86.5)	80.9(80.3 – 81.5)	0.001
LVEF 30 – 45 % (%, 95 % CI)	12.1(11.6 – 12.6)	10.9(9.3 – 12.7)	12.2(11.7 – 12.7)	0.154
LVEF <30 % (%, 95 % CI)	4.3(4.0 – 4.6)	2.2(1.5 – 3.2)	4.5(4.2 – 4.8)	<0.001
Previous procedures				
Valve surgery (%, 95 % CI)	6.4(6.1 – 6.8)	13.5(11.8 – 15.4)	5.8(5.4 – 6.2)	<0.001
Percutaneous balloon valvuloplasty (PBV) (%, 95 % CI)	4.9(4.3 – 5.6)	20.7(16.7 – 25.2)	3.3(2.8 – 4.0)	<0.001

[a]IQR – interquartile range, [#]95 % CI – 95 % confidence intervals

Over a maximum period of follow-up of 10.5 years there were 2089 deaths reported, 157 in RHD patients (11.3 %) and 1932 in non-RHD patients (12.2 %). Data regarding crude 30 day, 5 year and 10 year survival stratified by RHD or non-RHD valve surgery are presented in Table 2.

30 day outcomes

Outcomes within 30 days following surgery are outlined in Table 3. RHD patients, compared with non-RHD patients, had a longer period of invasive ventilation and a higher rate of readmission to hospital but no difference in 30 day survival. RHD patients were less likely to have a stroke but were more likely to have an anticoagulant complication.

Factors independently associated with 30 day mortality following valve surgery using logistic regression modelling are listed in Table 4.

Long term survival

Kaplan-Meier curves comparing mortality in RHD and non-RHD-related valve surgery are shown in Fig. 1. Log rank testing of mortality in RHD and non-RHD patients demonstrated a small, but statistically, significant difference in survival out to 10 years with superior survival in RHD valve surgery patients.

Factors independently associated with longer term mortality following valve surgery using Cox proportional modelling are outlined in Table 5.

Of note was, once these factors were controlled for, the superior longer term survival associated with RHD was no longer present. In addition, being Indigenous Australian, the nature of the valve lesion and the presence of poorer preoperative LVEF were not independently associated with longer-term survival in RHD patients after controlling for the factors highlighted in Table 5.

Outcome in Indigenous Australians

Indigenous RHD patients, compared with non-Indigenous RHD patients had a shorter post procedural length of hospital stay (7 days (95 % CI 6.0 – 10.0) compared to 8 days (95 % CI 7.0 – 12.0)) and were less likely to develop acute kidney injury (2.9 % (95 % CI 1.0 – 6.7) compared to 6.8 % (95 % CI 5.4 – 8.4)) or AF postoperatively (13.8 % (95 % CI 8.1 – 21.4) compared to 36.5 % (95 % CI 32.9 – 40.2)).

Thirty day mortality following RHD valve surgery in Indigenous Australians was comparable to that seen in non-Indigenous Australians (2.9 % compared with 3.1 %, $p = 0.895$). On logistic regression modelling restricted to Indigenous Australians only two factors were independently associated with 30 day mortality in those having RHD valve surgery: chronic kidney disease (OR 14.1, 95 % CI 1.0 – 200.0) and readmission (OR 20.8, 95 % CI 1.5 – 333.3).

Longer term mortality following RHD surgery was also comparable in Indigenous and non-Indigenous patients (10.3 % compared with 11.5 %, $p = 0.657$). Three factors were independently associated with longer term mortality in Indigenous Australians using Cox proportional modelling: LVEF <30 % (HR 31.3, 95 % CI 7.0 – 142.9), a longer period of ventilation (1.04/additional hour, 95 % CI 1.01 – 1.07), and a shorter initial stay in hospital (0.5/additional day, 95 % CI 0.3 – 0.8).

Remote location was not a significant predictor of either short or long term outcome either alone or in association with procedure type (log rank test, $p = 0.594$) in Indigenous Australians, who were more likely to reside in such locations.

Outcome and procedure type

The relationship between the type of surgical procedure for RHD-related disease and survival was analysed over a maximum period of follow-up of 10.5 years. There were 33 (11.8 %, 95 % CI 8.3 – 16.2, $p = 0.775$) deaths reported following RHD-related valve repair (five for isolated repair without associated other valve surgery), 65 (14.1 %, 95 % CI 11.0 – 17.6, $p = 0.024$) following RHD-related bioprosthetic valve replacement (58 for isolated bioprosthetic valve replacement) and 84 (10.1 %, 95 % CI 8.2 – 12.4, $p = 0.082$) (76 for isolated mechanical valve replacement) following RHD-related mechanical valve replacement. A Kaplan-Meier curve comparing mortality in RHD-related valve repair, bioprosthetic valve and mechanical valve surgery is shown in Fig. 2 and demonstrated a significant difference in survival between operative groups. This difference specifically related to poorer survival following bioprosthetic replacement (HR 1.5 (95 % CI 1.1 – 2.0). Multivariate survival analysis for these RHD patients (see Table 5) demonstrated this difference in survival persisted after controlling for co-existent diabetes and chronic kidney

Table 2 Unadjusted mortality at 30 days, 5 years and 10 years stratified by RHD or non-RHD valve surgery

Mortality number (%, 95 % CI)	All valve surgery	RHD valve surgery	Non-RHD valve surgery	RR* (95 % CI) (*p* value)
30 day	576/13866(4.2, 3.8 – 4.5)	35/1137(3.1, 2.2 – 4.3)	541/12729(4.3, 3.9 – 4.6)	1.38 (0.99 – 1.93)(0.058)
5 year	665/3821(17.4, 16.2 – 18.6)	54/353(15.3, 11.7 – 19.5)	611/3468(17.6, 16.4 – 18.9)	1.15 (0.89 – 1.49)(0.273)
10 year	96/254(37.8, 31.8 – 44.1)	7/28(25.0, 10.7 – 44.9)	89/226(39.4, 33.0 – 46.1)	1.58 (0.81 – 3.05)(0.139)

*RR - Relative risk in RHD-related valve surgery patients compared with non-RHD surgery

Table 3 Outcome of valve surgery within 30 days

	All N = 17227	RHD-related N = 1384	Non-RHD N = 15843	P value
Initial admission				
Ventilation (hours) (median (IQR))	11.0(6.8 – 19.0)	12.0(7.0 – 19.0)	11.0(6.7 – 19.0)	0.009
Intensive care unit (ICU) stay (hours) (median (IQR))	43.3(23.0 – 72.3)	42.0(23.0 – 70.8)	43.5(23.0 – 72.5)	0.350
Post procedure length of stay (days) (median (IQR))	8.0(7.0 – 13.0)	8.0(7.0 – 13.0)	8.0(7.0 – 13.0)	0.648
Re-operation for valve dysfunction (%, 95 % CI)	0.2(0.1 – 0.3)	0.4(0.1 – 0.8)	0.2(0.1 – 0.3)	0.152
Re-operation not related to valve dysfunction (%, 95 % CI)	7.0(6.6 – 7.4)	7.3(6.0 – 8.8)	7.0(6.6 – 7.4)	0.652
Mortality				
All cause (%, 95 % CI)	4.2(3.8 – 4.5)	3.1(2.2 – 4.3)	4.3(3.9 – 4.6)	0.058
Cardiac cause (%, 95 % CI)	1.5(1.3 – 1.8)	1.5(0.9 – 2.4)	1.5(1.3 – 1.8)	0.122
Non-cardiac cause (%, 95 % CI)	2.7(2.4 – 2.9)	1.6(1.0 – 2.6)	2.8(2.5 – 3.0)	0.907
Readmission (%, 95 % CI)	11.2(10.7 – 11.7)	13.8(12.0 – 15.7)	11.0(10.5 – 11.5)	0.002
Other complications				
Readmission for valve dysfunction (%, 95 % CI)	0.2(0.1 – 0.4)	0	0.2(0.1 – 0.4)	0.205
Acute kidney injury (%, 95 % CI)	6.3(5.9 – 6.7)	6.3(5.1 – 7.7)	6.3(5.9 – 6.7)	0.971
New AF (% without prior AF, 95 % CI)	34.2(33.4 – 35.1)	33.3(30.1 – 36.6)	34.3(33.5 – 35.1)	0.564
Stroke/ TIA (%, 95 % CI)	2.4(2.2 – 2.6)	1.6(1.0 – 2.4)	2.5(2.2 – 2.7)	0.044
Deep sternal wound infection (%, 95 % CI)	0.9(0.8 – 1.1)	1.2(0.7 – 1.0)	0.9(0.8 – 1.1)	0.247
Anticoagulant complication (bleeding or embolization) (%, 95 % CI)	1.7(1.5 – 1.9)	2.8(2.0 – 3.7)	1.6(1.4 – 1.8)	0.002
Heart failure (%, 95 % CI)	1.9(1.5 – 2.2)	2.4(1.4 – 3.9)	1.8(1.5 – 2.1)	0.274
Septicaemia (positive blood culture with signs of infection)(%, 95 % CI)	1.6(1.4 – 1.8)	0.4(0.8 – 2.1)	0.6(1.4 – 1.8)	0.476

disease, performance status, ventilation time, hospital length of stay and early septicaemia.

Discussion

This is the largest published study of short and longer-term outcome following RHD valve surgery in Australia. Whilst rheumatic valve surgery was relatively uncommon, representing only 8 % of all valve surgery procedures performed during the study period, it represented a significant proportion (>50 %) of valve procedures in Indigenous Australians. Such findings highlight the higher burden of RHD in Indigenous Australians. Nonetheless the finding that 7.2 % of valve procedures in non-Indigenous Australians were for RHD-related valve disease also demonstrates the remaining importance of residual, and particularly advanced, RHD in non-Indigenous Australians who accounted for the greatest overall number of patients. Much of this RHD in non-Indigenous Australians was presumably associated with residents who had immigrated to Australia from countries where RHD remained endemic or who had acquired RHD decades before, at a time when acute rheumatic fever (ARF) remained an issue for all Australians, rather than predominantly Indigenous Australians as is the case now [6].

Whilst RHD is a relatively common indication for valve surgery, it is not a major contributor to overall mortality in Australia. Nationally, between 2007 and 2009, there were only 897 deaths registered with RHD as the primary cause of death. This accounted for 0.6 % of cardiovascular and 0.2 % of all deaths [40]. National data nonetheless do not highlight the particular impact RHD has on Indigenous Australians. Whilst between 2004 and 2007 there were only 63 deaths from RHD among Indigenous Australians (5.8 per 100,000 population) this rate was 5.2 times greater than that for non-Indigenous Australians (1.1 per 100,000 population) [39].

Our study highlights that survival following valve surgery in the short (30 days) and longer term is equivalent in RHD and non-RHD patients. This concurs with Ribeiro et al's recent review of 352 Brazilian patients who underwent mitral valve replacement. In their study RHD was an indication in 43.5 % of patients and, in similar multivariate analysis, they demonstrated no significant difference in long-term survival for RHD-related surgery [40]. Dillon et al's Malaysian study of mitral valve repair in RHD and non-RHD patients [41] also demonstrated no difference in short and long term survival between these groups. Our Australian valve surgery patients also had short and

Table 4 Factors independently associated with 30 day mortality following valve surgery in logistic regression modelling and variance explained by the model

Odds Ratio (95 % CI)	All	RHD-related	Non-RHD
Age (/additional year)	1.01 (1.00 – 1.02)	-	-
Female sex	-	-	1.4 (1.1 – 1.8)
Pre-operative comorbidities			
Chronic kidney disease	2.4 (1.8 – 3.2)	4.3 (2.0 – 9.2)	2.6 (2.0 – 3.3)
Pre-operative status			
NYHA III & IV	1.7 (1.3 – 2.1)	-	1.7 (1.3 – 2.2)
LVEF 30 – 45 %	2.4 (1.8 – 3.2)	-	2.4 (1.8 – 3.3)
LVEF <30 %	3.5 (2.4 – 5.1)	-	3.6 (2.5 – 5.3)
Mitral valve regurgitation	1.2 (1.1 – 1.3)	-	1.2 (1.1 – 1.2)
Mitral valve stenosis	0.9 (0.8 – 0.9)	-	0.9 (0.8 – 0.9)
Previous procedures			
Valve surgery	2.4 (1.6 – 3.4)	2.5 (1.1 – 5.8)	2.4 (1.6 – 3.5)
Initial admission			
ICU stay (>43 h)	0.7 (0.6 – 0.9)	0.3 (0.1 – 0.7)	-
Post procedure LOS (/additional day)	0.97 (0.96 – 0.98)	-	0.96 (0.95 – 0.97)
Complications within 30 days			
Readmission	0.4 (0.3 – 0.7)	-	0.4 (0.2 – 0.6)
Re-operation for valve dysfunction	-	27.5 (2.2 – 338.9)	-
Re-operation not related to valve dysfunction	2.7 (2.0 – 3.8)	3.3 (1.3 – 8.4)	2.8 (2.2 – 3.9)
Acute kidney injury	7.3 (5.5 – 9.8)	7.3 (2.9 – 17.9)	6.9 (5.1 – 9.3)
Stroke/ TIA	4.6 (2.9 – 7.2)	-	4.6 (2.8 – 7.4)
Anticoagulant complication	2.9 (1.7 – 5.1)	-	2.8 (1.5 – 5.1)
Septicaemia	9.5 (6.1 – 15.27)	9.0 (2.5 – 32.3)	10.2 (6.3 – 16.4)
Explained variance			
(Nagelkerke R Square statistic [68])	24.6 %	24.7 %	25.1 %

long-term survival that was equivalent to earlier cohorts studies of aortic and mitral valve replacement and repair. Chiang et al's US study of survival following aortic valve replacement [42] found an equivalent 30 day mortality of 3 % and Dillon et al's Malaysian study of mitral valve repair [41] a comparable mortality of 4.3 % in RHD patients and 2.0 % in non-RHD patients. The long-term (10 year) survival found in our study (88.7 %) was at the upper limit reported by other studies including Chiang (76 %) [42], Dillon (83-89 %) [41] and Ribeiro (71-74 %) [40]. Neither short nor long term survival was significantly related to Indigenous status as has been suggested in a previous study [26].

A range of other factors had also been identified as being associated with outcome following surgery for advanced RHD [22–24, 43]. These encompassed factors associated with the underlying severity of valve disease [10, 12, 13, 20, 29, 44–48], the procedure undertaken [8–10, 18, 25, 49–57], social and environmental factors that may have increased the risk of ARF/RHD and the risk of complications (e.g. social and environmental disadvantage including access to initial surgical and ongoing primary and specialist health care review) and patient factors that were independent of RHD (e.g. age and comorbidities) [8–11, 16, 21, 25, 46, 47, 49, 58–60]. In contrast our study found that many of these factors were not significant predictors of subsequent short and long term survival in this large cohort using multivariable analysis.

In our study, RHD valve surgery patients, compared to those having valve surgery for non-RHD indications, were more than twice as likely to have pre-operative AF. This has previously been found to significantly increase the risk of late death [13, 16, 29, 46] especially from cardioembolic complications [17]. This greater level of AF in RHD patients has been reported in previous studies including in Dillon et al's review of RHD and non-RHD related valve repair in Malaysia which found 36 % of RHD patients undergoing mitral valve repair had pre-operative AF compared with 25 % of

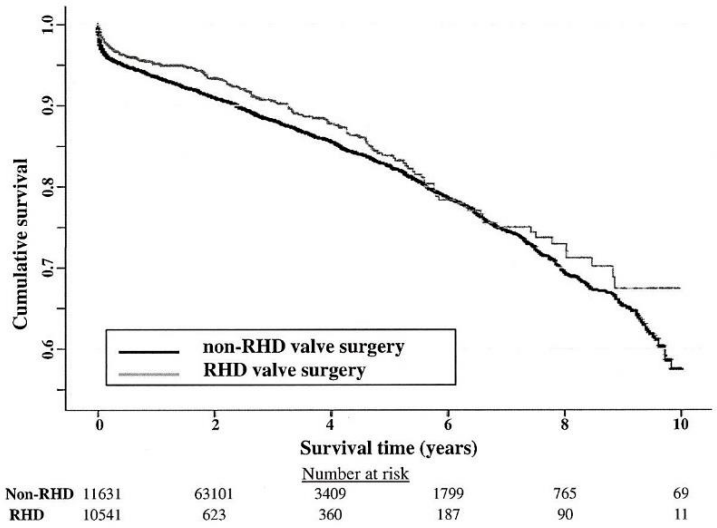

Fig. 1 Cumulative survival following RHD and non-RHD-related valve surgery (log rank test, significant $p = 0.047$)

Table 5 Factors independently associated with long term mortality following valve surgery in Cox proportional hazard modelling and the significance of the relationship of the model

Hazard Ratio (95 % CI)	All	RHD-related	Non-RHD
Age (/additional year)	1.03 (1.02 – 1.04)	1.03 (1.01 – 1.05)	1.03 (1.02 – 1.04)
Pre-operative comorbidities			
Diabetes	1.4 (1.2 – 1.6)	1.7 (1.1 – 2.5)	1.4 (1.2 – 1.6)
Chronic kidney disease	1.5 (1.3 – 1.7)	1.9 (1.2 – 2.9)	1.4 (1.3 – 1.6)
Pre-operative status			
NYHA III & IV	1.3 (1.1 – 1.4)	-	1.3 (1.1 – 1.4)
Atrial fibrillation	1.4 (1.2 – 1.6)	-	1.5 (1.3 – 1.7)
LVEF >45 %	0.7 (0.6 – 0.8)	-	0.7 (0.6 – 0.8)
Operative procedure			
Mechanical valve	0.8 (0.7 – 0.9)	-	0.8 (0.7 – 0.9)
Valve repair only	0.8 (0.6 – 0.9)	-	0.8 (0.6 – 0.9)
Multiple valve surgery	-	-	1.4 (1.1 – 1.7)
Initial admission			
ICU stay (>43 h)	1.2 (1.1 – 1.4)	-	1.3 (1.1 – 1.4)
Ventilation time (>11 h)	-	1.7 (1.1 – 2.9)	-
Post procedure LOS (/additional day)	1.01 (1.00 – 1.01)	1.02 (1.01 – 1.03)	1.00 (1.00 – 1.01)
Complications within 30 days			
Readmission	1.4 (1.2 – 1.6)	-	1.4 (1.2 – 1.7)
Acute kidney injury	1.9 (1.6 – 2.3)	-	1.9 (1.6 – 2.3)
Stroke/ TIA	1.6 (1.2 – 2.1)	-	1.7 (1.3 – 2.2)
Septicaemia	2.1 (1.6 – 2.8)	-	2.2 (1.6 – 2.9)
Significance of model (based on −2 Log Likelihood)	<0.001	<0.001	<0.001

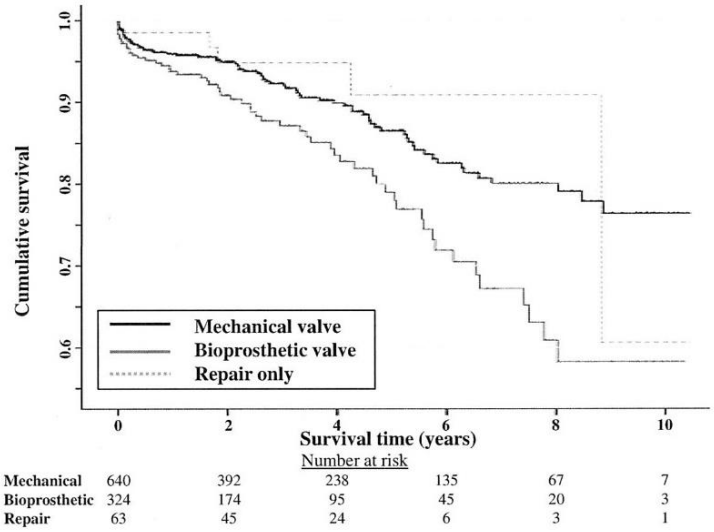

Fig. 2 Cumulative survival following RHD-related valve surgery stratified by procedure type (log rank test, $p = 0.001$)

non-RHD patients [41]. Whilst we demonstrated similar levels of preoperative and post-operative AF, unlike previous studies, neither prior nor new post post-operative AF was an independent predictor of survival. Although this difference may relate to superior long-term anticoagulation in our setting it was not possible to confirm this based on the lack of long-term post-operative anticoagulation results in our cohort.

The greater risk of pre-operative AF in our patients with advanced RHD would nonetheless suggest there may be differences in the atria between RHD and non-RHD patients at the time of surgery. Whether this relates to more advanced valvular dysfunction with attendant increased left atrial volume [61] or other influences on atrial conduction [62] remains to be seen. Irrespective of its underlying aetiology and influence on overall survival, this increased burden of pre-operative AF, will necessarily translate to an attendant greater need, risk and inconvenience of anticoagulation in some patients and has been shown to be associated with surgical choice [33].

Under and over anticoagulation following valve surgery is common [22, 43, 49, 63] and has been associated with thromboembolism, bleeding [1, 30] and poorer survival [12]. In general, anticoagulation can be suboptimal in all patient groups, and RHD valve surgery patients in this study were more likely, compared with non- RHD patients, to develop an anticoagulant complication. This appeared to be particularly related to bleeding rather than the cardioembolic complications of stroke or TIA. This lesser risk of stroke and greater risk of other anticoagulant complications would suggest monitoring and titration of anticoagulation, rather than medication adherence, is a more important contributor to early post-operative complications in our RHD patients. More detailed understanding of the adequacy of early post-operative anticoagulation monitoring and treatment titration in RHD valve surgery patients will be required to understand and potentially minimize this increased risk.

Increasing age has been shown, in previous studies, to be associated with poorer survival [9–11, 21, 47, 58] and an increased need for reoperation [59]. The greater burden of RHD in younger Indigenous patients has been highlighted and whilst a younger age at the time of RHD surgery did have an independent effect on survival following surgery, Indigenous status did not. Such younger patients are likely to be eventually at risk of structural valve deterioration with an attendant greater need for reoperation [29].

Whilst we could not report on the eventual need for reoperation in our cohort it is reassuring that in other studies this risk is relatively small, being required at 10 years in 1.6 % of RHD patients having mitral valve repair [41], 7.3 % of RHD and non-RHD patients with mechanical mitral valve replacement [40] and 13.6 % of RHD and non-RHD patients with bioprosthetic mitral valve replacement [40]. In a setting where late reoperation might be expected to be required in up to 15 % of often younger Indigenous RHD patients it was noted that such reoperation was associated with increased perioperative mortality but equivalent longer term survival.

In earlier studies objective (LVEF) and functional (NYHA) measures of cardiac function have both been associated with outcome following valve surgery [13, 14, 19]. In this study the adverse impact of poorer LVEF and

NYHA on short-term survival was demonstrated when the outcome of all valve surgery was analysed but not when this was restricted to RHD patients alone. The failure to demonstrate such an influence in RHD-related surgery may have been related to our use of multivariate survival analysis. Poorer LVEF was nonetheless found to adversely impact longer term survival when analysis was restricted to Indigenous Australian patients, perhaps highlighting how communication and accurate assessment of performance status may be difficult in a setting of cultural and linguistic diversity.

The importance of NYHA functional class as an independent predictor of survival in the short (perioperative) [12–14, 27, 28] and longer term [8–10, 14, 47] has been demonstrated by numerous studies. Our finding that poorer preoperative clinical status, based on NYHA class, was not independently associated with longer term mortality may suggest other cardiac and non-cardiac factors that influence NYHA-measured function, such as unreported or identified pulmonary hypertension or undiagnosed coronary heart disease, may have had an independent effect on survival. Functional assessment prior to surgery would therefore appear to have an important ongoing role in predicting outcome of surgery in addition to other investigations.

Following discharge, RHD valve surgery patients were more likely to be readmitted to hospital compared with non-RHD valve surgery patients. Although not explicitly recorded, persistent or recurrent rheumatic carditis may have been important in this setting as both are significant factors associated with valve replacement [19] and repair failure [12]. This in part provides the rationale for the recommendation for long-term secondary antibiotic prophylaxis following surgery even if the risk of recurrent ARF is deemed to be low [22, 25, 64].

Chronic diseases were frequent co-morbidities in patients having RHD and non-RHD surgery. Nonetheless it was only chronic kidney disease that was associated with 30 day mortality in both RHD and non-RHD patients and more specifically, Indigenous Australians. Chronic kidney disease and diabetes were both associated with poor longer term survival in RHD and non-RHD patients. The adverse effect of kidney disease on post-operative survival [46, 58] is well described. In Australia between 2007 and 2009 19 % of people dying from RHD had kidney disease as a contributing factor [39]. The association between co-existent diabetes and kidney disease, conditions commonly seen in Aboriginal and Torres Strait Islander patients and older Australians, and outcome following valve surgery highlights how changing disease profiles in an ageing Australian population may influence trends in valve surgery outcomes.

Limitations of the study

The multicenter nature of this study poses potential limitations. We have shown a number of differences between RHD and non-RHD valve surgery patients and factors associated with short and longer-term outcome following surgery. The differentiation between a RHD and non-RHD aetiology for valve disease nonetheless relied on the opinion of the individual surgical centre and was not confirmed by independent sources nor benchmarked against agreed echocardiographic [5] or pathologic criteria. It is therefore possible that the stratification of RHD and non-RHD aetiology may not have always been accurate. Nevertheless the majority of patients came from a relatively small number of high volume centres which have considerable experience in managing patients with RHD and thus, it would be assumed, significant skill in differentiating RHD and non-RHD related valve disease.

The relatively small number of Indigenous Australian patients in this study is also a limitation when undertaking comparisons with non-Indigenous Australians. This reflects the relatively small size of the Indigenous Australian population, the residual burden of RHD in older non-Indigenous Australians and the fact the database began with only a few centres and has only gradually increased over time [33]. During the early years the sample was likely to have not been representative of surgical experience in RHD in Indigenous patients and therefore surveillance of longer term survival in this group of patients will be required.

The ANZSCTS Database does not collect information regarding pulmonary pressures and particularly the presence of pulmonary hypertension. Pulmonary hypertension has been associated with poorer early post-operative mortality in patients having surgery for mitral regurgitation both in those with and without left ventricular functional impairment [65]. In addition, even in patients with mitral valve disease and no overt pulmonary hypertension detected on echocardiography, it has been shown that in many pulmonary hypertension can be revealed by exercise and this in turn is associated with poorer outcome [66, 67]. Thus our inability to include resting and exercise-related pulmonary hypertension in our analyses may in part explain the lack of importance of NYHA functional class and reduced LVEF, as a predictors of long-term survival.

Conclusion

We have presented short and long term outcome data relating to 17 227 surgical procedures required for the management of patients with advanced RHD and non-RHD related valve disease. RHD valve surgery patients, compared with non-RHD patients, had a longer period of invasive ventilation, were more likely to be readmitted to hospital, develop an anticoagulant complication and

less likely to have a stroke. Independent predictors of short term mortality following RHD-related valve surgery were co-existent chronic kidney disease, length of stay in ICU following surgery, acute kidney injury, anticoagulant complication and requiring re-operation for valve dysfunction. Longer term survival in RHD patients, out to 10 years, was at the upper end of that reported in earlier studies and was poorer in those with co-existent chronic kidney disease and diabetes, and those who required a longer period of ventilation and stay in hospital following surgery. Of note, being an Aboriginal Australian and/or Torres Strait Islander, co-existent chronic disease, pre-existing AF, a greater functional impairment as assessed by NYHA functional class and poorer pre-operative LVEF were not independently associated with outcome.

Thus this large cohort of valve surgery patients demonstrates that short and long term outcomes in Australia are comparable to other countries. Whilst the choice of procedure undertaken for the management of advanced RHD is likely to be best informed by patient preference, the ability to maintain safe anticoagulation and the underlying nature of the valve lesion, we have demonstrated poorer long term survival in those having bioprosthetic valve replacements. This may possibly relate to other factors which we have not assessed or controlled for. Ongoing surveillance of valve surgery in this setting should consider incorporating long-term assessment of the adequacy of anticoagulation, measures of baseline exercise tolerance and detailed measurement of resting and exercise-related pulmonary hypertension. These may provide additional insight into why AF is not an independent predictor of outcome, how neither poorer NYHA class nor LVEF influences survival and why bioprosthetic valves may be associated with poorer long term survival. Together they may better inform how best to manage AF and the timing and nature of surgery for advanced RHD.

Abbreviations

RHD: Rheumatic heart disease; OR: Odds ratio; CI: Confidence interval; AF: Atrial fibrillation; NYHA: New York Heart Association functional class; LVEF: Left ventricular ejection fraction; ANZSCTS: Australia and New Zealand Society of Cardiac and Thoracic Surgeons; RA: Remoteness area; eGFR: Estimated glomerular filtration rate; MDRD: Modification of diet in renal disease; CABG: Coronary artery bypass grafting; PBV: Percutaneous balloon valvuloplasty; TIA: Transient ischaemic attack; NDI: National death index; SD: Standard deviation; IQR: Interquartile range; HR: Hazard ratio; ARF: Acute rheumatic fever.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EAR performed the statistical analysis and drafted the manuscript. LT assisted with acquisition of data and analysis. RAB and helped with revision of the manuscript. JSB and helped with revision of the manuscript. AB conceived of the study and participated in its design and coordination and helped with revision of the manuscript. CMR assisted with acquisition of data and helped with revision of the manuscript. RT helped with revision of the manuscript. WW helped with revision of the manuscript. GPM conceived of the study participated in the design of the study, assisted with the statistical analysis and interpretation and helped to draft the manuscript. All authors read and approved the final manuscript.

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Chapter 5

Outcomes after mitral valve surgery for rheumatic heart disease

The most common heart valve affected by rheumatic heart disease (RHD) is the mitral valve. Mitral valve replacement is generally associated with poorer survival compared with mitral repair. This chapter examines the Australian patient population having mitral valve surgery for RHD and non-RHD related valve disease and reviews the factors associated with the choice of surgical management and with short and long-term outcome following valve surgery.

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Original research

Outcomes after mitral valve surgery for rheumatic heart disease

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ABSTRACT

Objective To further the understanding of the factors influencing outcome following rheumatic heart disease (RHD) related mitral valve surgery, which globally remains an important cause of heart disease and a particular problem in Indigenous Australians.

Methods The Australian Cardiac Surgery Database was utilised to assess outcomes following mitral valve repair and replacement for RHD and non-RHD valve disease. The association with aetiology, demographics, comorbidities, preoperative status and operative procedure was evaluated.

Results Mitral valve repairs and replacements undertaken in Australia were analysed from 119 and 1078 RHD surgical procedures and 3279 and 2400 non-RHD procedures, respectively. RHD mitral valve repair, compared with replacement, resulted in a slightly shorter hospital stay and more reoperation for valve dysfunction, but no difference in 30-day survival. In unadjusted survival analysis to 5 years, RHD mitral valve repair and replacement were no different (HR 0.86, 95% CI 0.4 to 1.7), non-RHD repair was superior to replacement (HR 1.7, 95% CI 1.4 to 2.0), RHD and non-RHD repair were no different (HR 0.9, 95% CI 0.5 to 1.7), and RHD replacement was superior to non-RHD (HR 1.5, 95% CI 1.2 to 1.9). None of these differences persisted in adjusted analyses and there was no difference in long-term survival for Indigenous Australians.

Conclusion In this large prospective cohort study we have demonstrated that adjusted long-term survival following RHD mitral valve repair surgery in Australia is no different to replacement and no different to non-RHD. Interpretation of valve surgery outcome requires careful consideration of patient factors that may also influence survival.

INTRODUCTION

The most common heart valve affected by rheumatic heart disease (RHD) is the mitral valve. Management of advanced RHD involves one or a combination of medical management and surgical and non-surgical interventions, with surgical procedures being valve repair, open valvuloplasty or replacement. Replaced valves can be mechanical (entirely synthetic) or bioprosthetic (typically a combination of synthetic and animal or human derived material).

Despite its global impact there remains limited evidence to indicate the most appropriate timing and choice of intervention for RHD-related mitral valve disease.[1 2]

Factors that may influence the type of surgical management for RHD-related valve disease include age, gender and potential future pregnancies, adherence to other medications, availability of local primary and specialist follow-up and social circumstances,[3–5] co-existent atrial fibrillation (where anticoagulation may be indicated irrespective of the procedure undertaken), the number of valves involved, preoperative left ventricular size and function, and co-existent pulmonary hypertension.[4]

RHD-related mitral valve repair has been associated with a reduced risk of complications from infection and anticoagulation compared with valve replacement[6–8] and tends to be associated with superior overall short- and intermediate-term outcomes.[8–10] However, not all valves are suitable for repair[10] and repaired valves may be associated with an increased need for early reoperation.[10] In part this relates to repaired valves remaining susceptible to further episodes of rheumatic fever and RHD progression.[11]

Despite evidence of superior outcome with mitral valve repair, we have previously reported[12 13] that for RHD-related valve disease in Australia repairs are less commonly performed (5.3% of all RHD-related valve procedures) compared with replacements (47.8%). For Aboriginal Australian and Torres Strait Islander peoples (Indigenous Australians), a group of Australians at particular risk of RHD, of those valves requiring replacement or repair, 48.8% were mitral valve replacement and 13.4% mitral valve repair.[12]

The aim of this study was therefore to examine the Australian patient population that has had mitral valve surgery for RHD and non-RHD related valve disease and to describe short- and long-term outcome by analysing data from a large Australian multisite cardiac surgery registry. Given the greater burden of RHD-related valve disease in Indigenous Australians, who are also more likely to reside in remote locations,[12] this study also aimed to examine specifically whether the management and outcome of RHD-related mitral valve disease was different in this particular group.

METHODS

The database

The Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database is an Australia-wide voluntary registry for the prospective collection and analysis of the results of adult cardiac surgery. The nature and breadth of this registry has been reported elsewhere.[12] Briefly, it collects data from 25 Australian hospitals regarding patients who have undergone cardiac surgery, the types of surgery

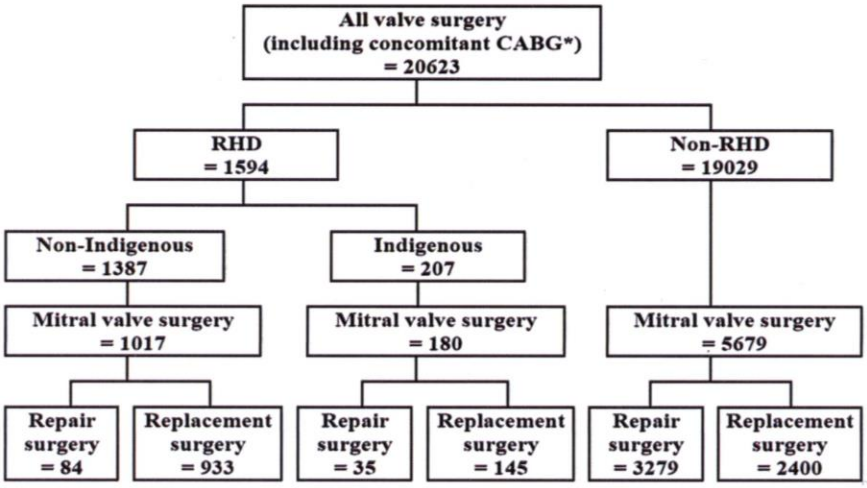

Figure 1 Flow diagram: rheumatic heart disease (RHD) and non-RHD related mitral valve procedures. CABG, coronary artery bypass grafting.

performed and early (30 day) complications,[12 14 15] and links this with long-term survival data.

Selection criteria

Participants were patients who had been registered on the database and who had undergone RHD or non-RHD-related mitral valve repair or replacement surgery with or without coronary artery bypass grafting (CABG) surgery.

Analysis

Data were analysed using IBM SPSS Statistics 20 (IBM, New York, USA) and STATA Release 14 (StataCorp LP, Texas, USA). Descriptive data (demographic, comorbidity data and surgery type) comparing RHD and non-RHD related mitral valve surgery type (repair or replacement) were summarised using standard univariate techniques and reported as percentages with 95% CI, means with SD, or medians with IQR depending on the data format and distribution. Comparisons between groups were undertaken using χ^2 for categorical data, Student's t-test and analysis of variance (ANOVA) for continuous normally distributed data, and Mann-Whitney U and Kruskal-Wallis rank test for non-normally distributed data. A value of $p<0.05$ was taken to indicate statistical significance and all tests were two-sided.

Early (<30 days) outcomes and complications included postoperative invasive ventilation time, number of hours spent in the intensive care unit (ICU), post-procedural length of stay, need for reoperation for valve or non-valve dysfunction, acute kidney injury, stroke or transient ischaemic attack (TIA), any anticoagulant complication (bleeding or embolisation), heart failure or septicaemia (positive blood culture with signs of infection), and readmission. Survival analysis encompassed 30-day mortality and longer-term survival was analysed out to 5 years.

The association between these outcomes and mitral valve surgery type (including when restricted to Indigenous Australians with RHD) was first assessed using standard bivariate techniques. Survival analysis for mortality was presented with Kaplan-Meier curves and analysed using the log rank test to compare survival in RHD and non-RHD mitral valve repair and replacement surgery, and then restricted to Indigenous and non-Indigenous Australians with RHD.

Multivariable logistic and Cox proportional hazard models were then developed to assess the independent association between surgery type and outcome measures controlling for demographic and comorbidity data where necessary. These models were developed using methods and predictors of survival identified from our previous studies.[12 13 16] Factors independently associated with long-term mortality following RHD valve surgery were age, diabetes, chronic kidney disease, prolonged ventilation time, and prolonged post-procedural length of hospital stay. This cohort study has been reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[17]

Approval for this project was granted by the Monash University Human Research Ethics Committee (CF13/2737 - 2013001472).

RESULTS

Data in relation to 1197 RHD mitral valve surgical procedures including those of 180 Aboriginal and/or Torres Strait Islander people and 5679 non-RHD mitral valve procedures collated by the ANZCTS database between 1 June 2001 and 31 December 2013 were included for analysis (figure 1).

Demographic and comorbidity data relating to these patients are outlined in table 1. RHD-related mitral valve repair surgery was, compared with replacement surgery, more common in younger, male Indigenous patients with moderate or severe mitral valve regurgitation, and less common in those with concomitant preoperative comorbidities of chronic kidney disease, poorer preoperative performance, atrial fibrillation, mitral valve stenosis, and a history of smoking or previous intervention. In contrast, non-RHD mitral valve repair surgery compared with replacement surgery was significantly more common in female, non-Indigenous patients having concomitant CABG surgery and with normal left ventricular ejection fraction (LVEF).

30-day outcomes

Outcomes within 30 days of surgery comparing mitral valve repair and replacement for RHD and non-RHD valve disease are outlined in table 2. In unadjusted analyses RHD mitral valve repair was associated with a slightly shorter length of hospital stay and a higher rate of reoperation for valve dysfunction. Patients having non-RHD mitral valve repair surgery, compared with replacement, had a shorter period of ventilation and stay

Table 1 Descriptive characteristics of mitral valve surgery patients stratified by aetiology and surgery type

	RHD		Non-RHD	
	Repair surgery n=119	Replacement surgery n=1078	Repair surgery n=3279	Replacement surgery n=2400
Age (years)	57.3	62.0*	67.0†	69.3 *†
(median, IQR)	(35.5 to 69.2)	(50.3 to 71.0)	(57.6 to 75.2)	(58.3 to 77.0)
Sex	58.0	71.3*	30.3†	38.3*‡
(% female, 95% CI)	(48.6 to 67.0)	(68.5 to 74.0)	(28.7 to 31.9)	(36.4 to 40.3)
Indigenous status	29.4	13.5*	1.1†	2.7*‡
(% Indigenous Australian, 95% CI)	(21.6 to 38.8)	(11.5 to 15.6)	(0.8 to 1.6)	(2.1 to 3.4)
Concomitant CABG	20.2	18.6	36.5†	30.2*†
(%, 95% CI)	(13.4 to 28.5)	(16.4 to 21.1)	(34.9 to 38.2)	(28.3 to 32.0)
Preoperative comorbidities				
Diabetes	14.3	21.1	14.5	16.5*†
(%, 95% CI)	(8.5 to 21.9)	(18.7 to 23.6)	(13.3 to 15.8)	(15.1 to 18.1)
Chronic kidney disease	21.0	31.0*	30.8†	44.2*†
(% eGFR <60 mL/min/1.73 m^2, 95% CI)	(14.1 to 29.4)	(28.2 to 33.8)	(29.3 to 32.4)	(42.2 to 46.2)
Hypertension	41.2	49.6	56.8†	61.1*†
(%, 95% CI)	(32.2 to 50.6)	(46.6 to 52.6)	(55.1 to 58.5)	(59.1 to 63.0)
Previous smoking	44.5	54.4*	48.6	50.7
(%, 95% CI)	(35.4 to 53.9)	(51.3 to 57.4)	(46.9 to 50.4)	(48.7 to 52.7)
Current smoking	37.5	25.9	17.3†	19.9
(%, 95% CI)	(24.9 to 51.5)	(22.4 to 29.7)	(15.5 to 19.2)	(17.7 to 22.3)
Preoperative status				
NYHA classes III and IV	42.9	58.4*	38.8	53.0*†
(%, 95% CI)	(33.8 to 52.3)	(55.4 to 61.4)	(37.2 to 40.5)	(51.0 to 55.1)
Atrial fibrillation	26.1	48.9*	20.7	33.6*†
(%, 95% CI)	(18.4 to 34.9)	(45.9 to 51.9)	(19.3 to 22.1)	(31.7 to 35.6)
LVEF >45%	79.0	85.7	79.1	75.7*†
(%, 95% CI)	(70.6 to 85.9)	(83.5 to 87.7)	(77.6 to 80.5)	(73.9 to 77.4)
LVEF 30–45%	15.1	10.5	13.3	17.5*†
(%, 95% CI)	(9.2 to 22.8)	(8.7 to 12.5)	(12.1 to 14.5)	(16.0 to 19.1)
LVEF <30%	4.2	1.9	6.2	4.3*†
(%, 95% CI)	(1.4 to 9.5)	(1.2 to 3.0)	(5.4 to 7.0)	(3.5 to 5.1)
Moderate or severe mitral valve regurgitation	81.5	63.9*	91.4†	86.8*†
(%, 95% CI)	(73.4 to 88.0)	(60.9 to 66.8)	(90.4 to 92.4)	(85.4 to 88.2)
Mitral valve stenosis	25.2	75.3*	8.2 †	18.9*†
(%, 95% CI)	(17.7 to 34.0)	(72.6 to 77.8)	(7.2 to 9.1)	(17.4 to 20.6)
Previous procedures				
Valve surgery	1.7	13.5*	2.2	16.4*†
(%, 95% CI)	(0.2 to 5.9)	(11.6 to 15.7)	(1.7 to 2.8)	(15.0 to 18.0)
Percutaneous balloon valvuloplasty	7.7	28.6	0.6†	2.1*†
(%, 95% CI)	(0.2 to 36.0)	(23.4 to 34.1)	(0.1 to 1.7)	(1.2 to 3.4)

*Comparing repair and replacement, p<0.05.
†Comparing RHD and non-RHD repair, p<0.05.
‡Comparing RHD and non-RHD replacement, p<0.05.
CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; NYHA, New York Hearth Association; RHD, rheumatic heart disease.

in ICU and hospital, were less likely to be readmitted for any reason, require further surgery for non-valve related reasons, or have acute kidney injury, stroke or TIA, anticoagulant complications, heart failure or septicaemia.

The only difference in short-term outcome for Indigenous Australians undergoing RHD mitral valve repair was a shorter length of hospital stay (mean 11.9 days, SD 17.7, compared with 9.5 days, SD 10.2, p=0.025). There were no reoperations for valve dysfunction reported in this group of patients within 30 days, for those undergoing either mitral repair or replacement.

Unadjusted analysis of 30-day survival demonstrated no difference in RHD mitral valve repair surgery compared with replacement (95.8% vs 96.2%, p=0.830). In contrast, unadjusted non-RHD mitral valve surgery 30-day survival following repair surgery was superior to that seen with replacement (96.5% compared with 92.6%, p<0.001). In addition 30-day survival following replacement surgery was superior for RHD compared with non-RHD replacement surgery (p<0.001), but was no different for repair (p=0.701). Short-term survival was comparable for Indigenous Australians requiring RHD mitral valve surgery at 96.7% and did not differ between repair and replacement (97.1% vs 96.6%, p=0.861).

There remained no significant difference in short-term survival following RHD mitral valve repair versus replacement (relative to replacement) overall (OR 0.5, 95% CI 0.1 to 2.0) and for Indigenous Australians specifically (OR 0.9, 95% CI 0.1

Table 2 Outcome following RHD-related mitral valve surgery within 30 days, stratified by aetiology and surgery type

	RHD		Non-RHD	
	Repair surgery n=119	Replacement surgery n=1078	Repair surgery n=3279	Replacement surgery n=2400
Initial admission				
Ventilation (hours)	11.3	13.5	8.0	10.0*†
(median IQR)	(6.6 to 21.8)	(8.0 to 21.0)	(6.0 to 12.0)	(7.0 to 17.0)
ICU stay	46.8	46.7	47.1	68.2*†
(hours) (median, IQR)	(25.8 to 96.0)	(24.0 to 91.6)	(24.7 to 88.5)	(36.6 to 122.8)
Post-procedure length of stay	11.7	12.2*	11.4	16.7*†
(days) (mean, SD)	(11.8)	(13.4)	(11.8)	(76.6)
Reoperation for valve dysfunction	1.7	0.3*	0.5	0.3
(%, 95% CI)	(0.2 to 5.9)	(0.06 to 0.8)	(0.3 to 0.8)	(0.1 to 0.7)
Reoperation not related to valve dysfunction	7.6	7.3	6.3	10.9*†
(%, 95% CI)	(3.5 to 13.9)	(5.8 to 9.0)	(5.4 to 7.1)	(9.7 to 12.2)
Mortality (all cause)	4.2	3.8	3.5	7.4*†
(%, 95% CI)	(1.4 to 9.5)	(2.7 to 5.1)	(2.9 to 4.2)	(6.4 to 8.5)
Readmission	9.7	15.6	9.9	13.1*†
(%, 95% CI)	(5.0 to 16. 8)	(13.5 to 18.0)	(8.9 to 11.0)	(11.7 to 14.5)
Other complications				
Readmission for valve dysfunction	0	0	0.6	0.6
(%, 95% CI)			(0.3 to 1.3)	(0.2 to 1.3)
Acute kidney injury	4.3	6.7	5.4	9.7*†
(%, 95% CI)	(1.4 to 9.7)	(5.3 to 8.4)	(4.6 to 6.2)	(8.6 to 11.0)
New AF	15.1	17.2	24.3	23.4
(% without prior AF, 95% CI)	(15.0 to 19.5)	(9.2 to 22.8)	(22.8 to 25.8)	(21.7 to 25.1)
Stroke/TIA	1.7	1.7	2.1	3.8*†
(%, 95% CI)	(0.2 to 5.9)	(1.0 to 2.6)	(1.6 to 2.7)	(3.0 to 4.6)
Deep sternal wound infection	0.8	1.5	0.8	0.8
(%, 95% CI)	(0.0 to 4.6)	(0.9 to 2.4)	(0.5 to 1.2)	(0.5 to 1.3)
Anticoagulant complication (bleeding or embolisation)	4.2	2.7	1.6‡	3.1*
(%, 95% CI)	(1.4 to 9.5)	(1.8 to 3.8)	(1.1 to 1.9)	(2.5 to 3.9)
Heart failure	1.7	3.4	0.9	3.8*
(%, 95% CI)	(0.0 to 9.1)	(2.0 to 5.5)	(0.4 to 1.7)	(2.6 to 5.3)
Septicaemia (positive blood culture with signs of infection)	1.7	1.5	1.4	3.1*†
(%, 95% CI)	(0.2 to 6.0)	(0.9 to 2.4)	(1.1 to 1.9)	(2.5 to 3.9)

*Comparing repair and replacement, p<0.05.
†Comparing RHD and non-RHD replacement, p<0.05.
‡Comparing RHD and non-RHD repair, p<0.05.
AF, atrial fibrillation; ICU, intensive care unit; RHD, rhuematic heart disease; TIA, transient ischaemic attack.

to 11.5) after controlling for previously identified covariates (LVEF <30%, a longer period of ventilation, and a shorter initial stay in hospital) in logistic regression modelling.[13]

The superior unadjusted short-term survival seen with non-RHD mitral valve repair did not persist after controlling for other previously identified factors (chronic kidney disease, previous valve surgery, prolonged stay in ICU, reoperation, acute kidney injury, septicaemia) associated with 30-day survival (OR 1.1, 95% CI 0.6 to 2.0).[12]

Long-term survival

Survival to 5 years following RHD-related mitral valve surgery was 84.0% (95% CI 80.2% to 87.3%), with mitral valve repair 82.4% (95% CI 69.1% to 91.6%) and replacement 84.2% (95% CI 80.2% to 87.7%). For non-RHD mitral valve surgery, survival to 5 years was 83.6% (95% CI 81.7% to 85.3%) overall, with repair 86.7% (95% CI 84.4% to 88.7%) and replacement 79.5% (95% CI 76.4% to 82.4%). For Indigenous Australians, survival to 5 years following RHD-related mitral valve surgery was comparable with 83.3% (95% CI 69.8% to 92.5%) overall, repair 85.0% (95% CI 62.1% to 96.8%) and replacement 82.1% (95% CI 63.1% to 93.9%).

Kaplan-Meier curves comparing survival in RHD and non-RHD mitral valve repair and replacement valve surgery are shown in figures 2 and 3. Log rank testing demonstrated no difference in unadjusted survival between RHD-related mitral valve repair and replacement (HR 0.86, 95% CI 0.4 to 1.7) or in Indigenous Australians with RHD specifically. For non-RHD mitral valve surgery, survival following repair was superior to replacement (HR 1.7, 95% CI 1.4 to 2.0), RHD and non-RHD repair no different (HR 0.9, 95% CI 0.5 to 1.7) and survival following RHD-related mitral valve replacement was superior to that seen with non-RHD replacement (HR 1.5, 95% CI 1.2 to 1.9).

When other factors associated with long-term survival were controlled for in Cox proportional modelling (age, diabetes, chronic kidney disease, prolonged ventilation time and prolonged post-procedural length of hospital stay),[12 13 16] there remained no significant difference in survival between repair and replacement following RHD-related surgery (HR 0.7, 95%

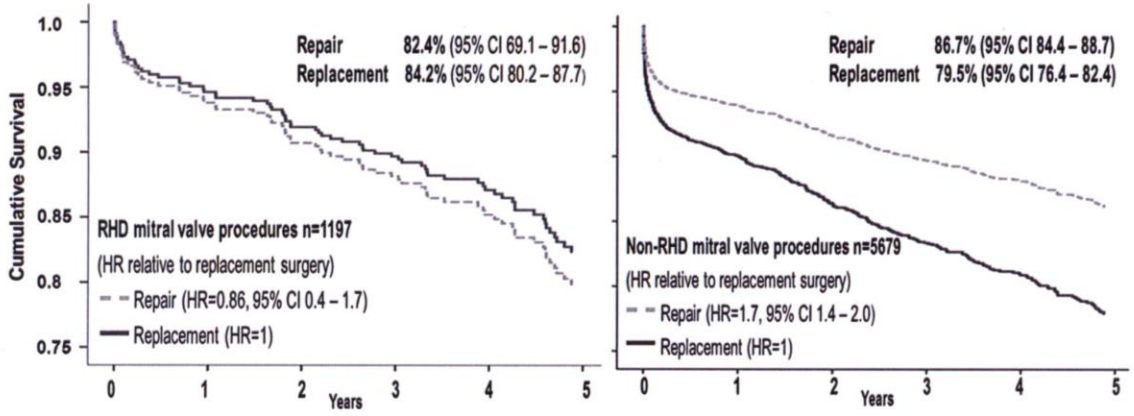

Figure 2 Cumulative survival following rheumatic heart disease (RHD) and non-RHD related mitral valve procedures.

CI 0.4 to 1.6), and the differences seen in unadjusted non-RHD repair and replacement (HR 1.4, 95% CI 0.9 to 2.0) were no longer present.

In addition, there remained no difference in survival on Cox proportional modelling between RHD and non-RHD mitral valve repair patients (HR 1.3, 95% CI 0.2 to 10.4), and the unadjusted differences seen in mitral valve replacement in RHD and non-RHD patients (HR 1.3, 95% CI 0.8 to 2.1) were no longer present.

DISCUSSION

In this large Australian cohort study we have demonstrated that for RHD-related mitral valve disease both short-term and longer-term unadjusted and adjusted survival for valve repair and replacement are no different. While non-RHD related mitral valve disease repair is associated with superior unadjusted survival this is also no different once controlling for covariates.

Patients undergoing mitral repair surgery, either RHD or non-RHD, were younger and predominantly male. For RHD-related mitral repair surgery, patients were more likely to be Indigenous Australian. With specific reference to RHD-related mitral valve disease this would suggest young male patients were referred either at a sufficiently early phase of their disease, when their valve was more amenable to surgical repair, and/or were referred to a surgical centre with a greater interest and capacity to undertake mitral valve repair. This would appear to favour a reduced need for postoperative anticoagulation in younger men, giving them options for physical occupations and contact sport unavailable after a mechanical valve replacement with attendant long-term anticoagulation. Nonetheless, a male predominance would also highlight that young women, in whom the issue of anticoagulation and pregnancy can be a particular issue, may have been relatively overlooked. This may in part be related to a preference in this group to instead use a bioprosthetic mitral valve replacement to obviate the need for ongoing anticoagulation.

RHD-related mitral valve repair surgery was also significantly more common in patients with moderate or severe mitral valve regurgitation rather than stenosis. Given mitral stenosis is likely to reflect more advanced RHD-related mitral valve disease, such an association would highlight the importance of early referral for assessment for suitability for repair. In this case it could be argued that optimising the opportunity for successful mitral repair may require surgery at a time that would be earlier than that which may be required for replacement.

The broader issue of making management recommendations for RHD-related mitral valve disease based on evidence gleaned from the management of non-RHD valve disease, and particularly myxomatous degeneration, is also important. Our findings highlight that such generalisation should be undertaken cautiously given differing pathologic processes and the greater role of fibrosis and calcification in RHD mitral valve disease that can involve both valve leaflets and chordae tendonae.[18]

Whether the possibility of successful mitral valve repair increases with site and surgeon experience remains debatable. Some studies investigating case load and mitral valve repair have specifically suggested the development of centres of excellence for mitral valve repair,[19–22] with minimum

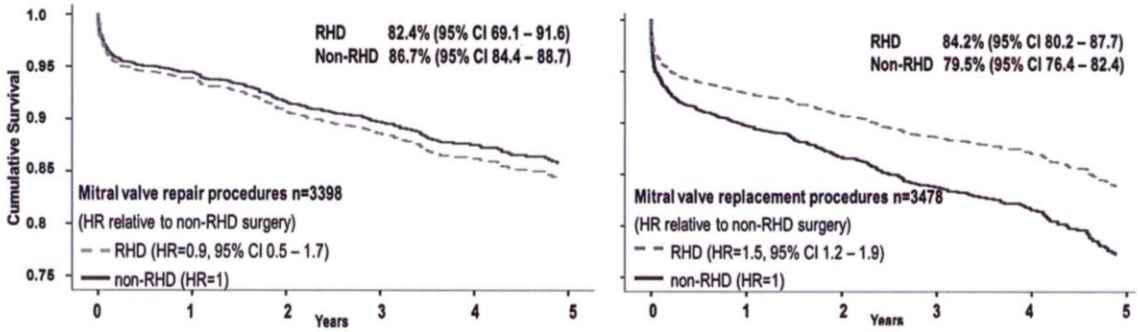

Figure 3 Cumulative survival following mitral valve repair and replacement procedures. RHD, rheumatic heart disease.

standards suggested for such centres.[23] This is supported by our earlier Australian study where we found RHD mitral valve repair was more common in higher volume centres ($p<0.001$ for increasing site case load strata) and for higher volume surgeons ($p=0.001$ for increasing surgeon case load group).[16] Nonetheless it should be highlighted that this did not in turn confer improved long-term outcome.

Mitral valve repair was less common in patients with concomitant preoperative comorbidities, including New York Heart Association (NYHA) functional classes III and IV, chronic kidney disease and atrial fibrillation (AF), which have all previously been found to be predictors of subsequent mortality following RHD mitral valve surgery.[24–29] This is consistent with these patients having more advanced mitral RHD which are therefore less amenable to repair. The prevalence of preoperative AF is particularly high in patients with valvular disease due to RHD,[12] with its occurrence most common in mitral stenosis.[30] Undertaking RHD mitral valve surgery before the onset of AF could provide greater therapeutic choice and optimise the opportunity for repair being undertaken.

We found no difference in adjusted short- or long-term survival following RHD mitral valve repair surgery, compared with replacement. Our level of survival and this lack of difference between surgical type was in line with many earlier studies of mitral valve repair and replacement for RHD related[31 32] and non-RHD related valve disease.[33–35] Such findings have not been seen in all studies with repair particularly associated with superior survival in younger patients.[36–38] Remenyi *et al*'s New Zealand and Pacific island study[36] reported survival at 10 and 14 years following mitral valve surgery to be 79% and 44% for replacement compared with 90% and 90% for repair. While half of these patients were from remote Pacific island nations (where the outcome of mitral valve replacement might be anticipated to be poorer), when analysis was restricted to New Zealand residents, this difference, while less, persisted.

LIMITATIONS

The main limitation of this study is that it is restricted to Australian surgical practice and may not reflect management in other countries. Nonetheless, overall this sample is likely to provide an accurate representation of surgical management of valve disease in Australia that is referable to practice in other high income countries. Multiple data collection sites and personnel may have led to variable data coding. This was, however, minimised by each site being supported with training and standard data definitions, the use of standardised data entry systems, and centralised auditing of site-specific data. The data were from the Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database, an Australia-wide voluntary registry for the prospective collection and analysis of the results of cardiac surgery. The database does not currently collect all known risk factors or quality-of-life data and these could not be included for analysis. While our overall numbers were high, subgroup and multivariate analysis may also have potentially reduced our power to identify differences in outcomes. Long-term outcome was only possible for 5 years which may not reflect the need for late reoperation with its associated morbidity and mortality, especially in the mitral valve repair group. Finally longer-term morbidity including heart failure, endocarditis, bleeding and cardioembolic complications have not been investigated.

CONCLUSION

In this large prospective cohort study we have demonstrated survival following RHD mitral valve repair surgery in Australia is no different to replacement surgery in line with some,[31 32] but not all, earlier studies.[8 29] While unadjusted survival for non-RHD valve repair out to 5 years appeared superior to replacement, this did not persist when adjusting for other factors associated with early mortality. This study highlights the importance of adjusting for patient factors when assessing the outcome of valve surgery and the benefit of determining surgical choice based on a combination of valve disease aetiology, valve morphology and patient demographics and comorbidities. Whether mitral repair compared with replacement is associated with a difference in non-lethal complications, including long-term morbidity, healthcare utilisation and cost should remain a priority for future research.

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Contributors EAR performed the statistical analysis and drafted the manuscript. LT assisted with acquisition of data and analysis. RAB, JSB, AB and RT helped with revision of the manuscript. CMR assisted with acquisition of data and helped with revision of the manuscript. WW conceived of the study and participated in its design and coordination and helped with revision of the manuscript. GPM conceived of the study, participated in the design of the study, assisted with the statistical analysis and interpretation, and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Opt-out consent was given at the time of surgery for data collection for a national database with the explanation that the data were to collate the activities and outcomes of participating units and give an overview of the

Key messages

What is already known about this subject?
Previous international studies, while identifying factors that may influence the type of surgical management for RHD related valve disease, have provided limited evidence to indicate the most appropriate timing and choice of intervention. Many previous international studies concluded RHD related mitral valve repair was associated with superior overall short- and intermediate-term outcomes but with an increased need for early reoperation.

What does this study add?
This study demonstrateds that in a high-income country such as Australia, adjusted long-term survival following valve repair in comparison with valve- replacement for RHD and non-RHD related mitral valve disease is no different.

How might this impact on clinical practice?
In high-income countries such as Australia the evaluation of long-term survival following mitral valve surgery, irrespective of cause, should take account of patient factors beyond surgical choice alone. The lack of any difference in outcome is likely to reflect a combination of patient environmental factors and access to ongoing primary and specialist care following surgery.

patients who underwent surgery, the types of surgery performed, complications and other details relating to risk and the outcomes of cardiac surgery. This de-identified database was used for this research.

Ethics approval Monash University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data were from Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database, an Australia-wide voluntary registry for the prospective collection and analysis of the results of cardiac surgery. Access to this data is via written application to the administrators at Monash University, Melbourne Australia with ethical approval.

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Chapter 6

The burden and implications of preoperative atrial fibrillation in Australian heart valve surgery patients

Atrial fibrillation (AF) is the most common preoperative cardiac surgery arrhythmia and, as highlighted in Chapter 2, particularly prevalent in patients with valvular disease due to RHD. In the setting of RHD AF often requires consideration of anticoagulation, a treatment that can be particularly difficult to provide in a remote Indigenous Australian setting. This chapter describes the burden and assesses the impact of AF on valve surgery, early post-operative complications and short and long term survival, overall and with particular reference to RHD and Indigenous Australians.

This chapter includes the following peer-reviewed and published report:
Russell EA, Walsh WF, Tran L, Tam R, Reid CM, Brown A, Bennetts JS, Baker RA, Maguire GP. The burden and implications of preoperative atrial fibrillation in Australian heart valve surgery patients. *Int. J. Cardiol.* 2017;227:100-105. doi: 10.1016/j.ijcard.2016.11.070.

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The burden and implications of preoperative atrial fibrillation in Australian heart valve surgery patients

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common preoperative arrhythmia in heart valve surgery patients and its prevalence is rising. This study aims to investigate the impact of AF on valve surgery early complications and survival and on valve disease of different aetiologies and populations with particular reference to Indigenous Australians with rheumatic heart disease (RHD).
Methods: The Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database was analysed to determine the association between preoperative AF and valve surgery outcome. Its association with demographics, co-morbidities, preoperative status and short and long term outcome was assessed.
Results: Outcome of 1594 RHD and 19,029 non-RHD-related surgical procedures was analysed. Patients with preoperative AF were more likely to be older, female, Indigenous, to have RHD and to bear a greater burden of co-morbidities. Patients with RHD and preoperative AF had a longer hospital stay and were more likely to require reoperation. Adjusted short (OR 1.4, 95% CI 1.2–1.7) and long term (HR 1.5, 95% CI 1.3–1.7) survival was inferior for patients with non-RHD preoperative AF but was no different for Indigenous and non-Indigenous Australians with RHD.
Conclusions: In this prospective Australian study, patients with valve disease and preoperative AF had inferior short and long term survival. This was particularly the case for patients with non-RHD valve disease. Earlier intervention or more aggressive AF management should be investigated as mechanisms for enhancing postoperative outcomes. This may influence treatment choice and the need for ongoing anticoagulation.

1. Introduction

Atrial fibrillation (AF) is a significant and increasingly important health issue. In Australia, AF affects between one and 2 % of the general population [1] with hospitalisations for AF more than doubling over the last 15 years [2]. Its burden in patients undergoing heart valve surgery is even greater, with AF being the most common preoperative cardiac surgery arrhythmia [3,4] with an associated rising prevalence [1,5–8]. Heart surgery patients with preoperative AF are typically older [3,8–14], have higher operative risk scores (independent of AF) [9,10], greater functional impairment [9,11,14] and a greater burden of comorbidities (including heart failure [3,8–11,14], renal failure [3,9,10], chronic obstructive pulmonary disease [3,9] and stroke [3,9]). Given the association between AF and these other factors, it can be difficult to determine the independent contribution of AF to surgical outcome. In turn, it remains unclear whether, in patients with valvular heart disease, earlier definitive management whilst patients remain in

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sinus rhythm or more aggressive preoperative treatment of AF to achieve and maintain sinus rhythm can influence postoperative outcome.

The prevalence of preoperative AF is particularly high in patients with valvular disease due to rheumatic heart disease (RHD) [15,16] with its occurrence most common in mitral stenosis [17]. This is particularly important in Australia where RHD remains endemic in Indigenous Australians (Aboriginal Australian and/or Torres Strait Islander peoples) who are in turn more likely to require surgery for RHD related valve disease [15]. The presence of AF associated with valvular disease also requires consideration of anticoagulation, a treatment that can be difficult to provide in a remote Indigenous Australian setting.

In the period following heart valve surgery, patients with preoperative AF have been found to have a longer intensive care unit (ICU) and hospital stay [3,9] and higher rates of postoperative complications [3,9,12]. Preoperative AF has also been shown to be associated with an increase in the risk of early [3,9] and late death [12,14,18,19] especially from cardio-embolic events [20–22] and to be a predictor of outcome following valve surgery, irrespective of cause [23,24]. Nonetheless existing studies have often failed to control for potential confounders, have tended to be limited to short term outcomes and have not included significant populations with RHD.

The aim of this study was therefore to describe the burden and assess the impact of preoperative AF on valve surgery, early postoperative complications and short and long term survival. This included preoperative AF overall and, given the nature of valve surgery in Australia, with particular reference to RHD and Indigenous Australians.

2. Methods

2.1. The database

The Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database was utilised. The details of the Database have been outlined elsewhere [15]. Briefly it is an Australia-wide database for the collection and analysis of the results of cardiac surgery that collates data from Australian hospitals regarding patients who have undergone cardiac surgery, the type of surgery performed, early complications and 30-day mortality. In addition the Database is linked to the Australian National Death Index [25] to assess longer term survival. The Database commenced in 2001 with six surgical centres and currently encompasses 28 Australian sites. All sites were included in this analysis.

2.2. Selection criteria

Participants were patients who had been registered on the Database and who had undergone valve surgery with or without CABG surgery.

2.3. Analysis plan

Descriptive data (demographic, comorbidity data and surgery type) comparing patients with and without preoperative AF (including paroxysmal and persistent AF) were summarised using standard univariate techniques and reported as percentages with 95% confidence intervals (95% CI), means with standard deviation (SD) or medians with interquartile range (IQR) depending on the data format and distribution. Comparisons between groups were undertaken using χ^2 for categorical data, Student's t-Test and ANOVA for continuous normally distributed data, and Mann–Whitney U and Kruskal–Wallis rank test for non-normally distributed data. A p valve less than 0.05 was taken to indicate statistical significance and all tests were two-sided.

Early (less than 30-day) outcomes and complications included postoperative invasive ventilation time, number of hours spent in the intensive care unit (ICU), post procedural length of stay, need for re-operation for valve or non-valve dysfunction, acute kidney injury, stroke or TIA, any anticoagulant complication (bleeding or embolization), heart failure or septicaemia (positive blood culture with signs of infection) and readmission. Survival analysis encompassed 30-day cardiac and all-cause mortality and longer term survival was analysed out to ten years.

The association between these outcomes and preoperative AF (including when restricted to RHD-related valve disease and Indigenous Australians with RHD) was first assessed using standard bivariate techniques. Multivariable logistic and Cox proportional hazard models were then developed to assess the independent association between preoperative AF and outcome measures controlling for demographic and comorbidity data where necessary. These models were developed using predictors for survival identified from our previous studies [15,26]. In separate analysis, the influence of case load on 30-day mortality was also adjusted to take account of the 30-day cardiac mortality risk score developed by Billah and others [27].

Approval for this project was granted by the Monash University Human Research Ethics Committee (CF13/2737 – 2013001472).

3. Results

Data in relation to 1594 RHD-related and 19,029 non-RHD-related valve procedures performed in 28 Australian sites between 1 August 2001 and 31 December 2013 were extracted from the ANZSCTS database for analysis.

AF status was not documented in 0.01% of procedures, 0.02% of non-RHD-related and 0% of RHD-related valve procedures. Preoperative AF was documented in 3992 cases (19.4%, 95% CI 18.8–19.9). Of patients with preoperative AF and valve disease, 648 were RHD-related. This represented 40.7% (95% CI 38.2–43.1) of all RHD-related valve surgeries. There were 67 Indigenous Australian patients with preoperative AF and RHD-related valve disease, representing 32.4% (95% CI 26.0–39.2) of all Indigenous Australian RHD-related valve surgery. This is summarised in Fig. 1.

Descriptive characteristics of valve surgery patients stratified by preoperative AF status (Table 1) demonstrated patients with preoperative AF were more likely to be older, female, carried a greater baseline burden of comorbidities, in particular diabetes, chronic kidney disease, hypertension, poorer preoperative performance status (NYHA class III or IV), lower left ventricular ejection fraction (LVEF) and a previous procedure and were more likely to have RHD-related valve disease and be Indigenous Australian.

In multivariable logistic regression modelling, independent predictors of preoperative AF included older age (OR 1.03/additional year, 95% CI 1.03–1.04), female sex (OR 1.3, 95% CI 1.1–1.5), RHD-related valve disease (OR 2.9, 95% CI 2.3–3.7), poorer preoperative performance status (NYHA classes III or IV) (OR 1.8, 95% CI 1.6–2.1), previous valve surgery (OR 2.2, 95% CI 1.9–2.6) or balloon valvuloplasty (OR 1.9, 95% CI 1.4–2.6) and LVEF less than 45% (OR 0.7, 95% CI 0.6–0.9).

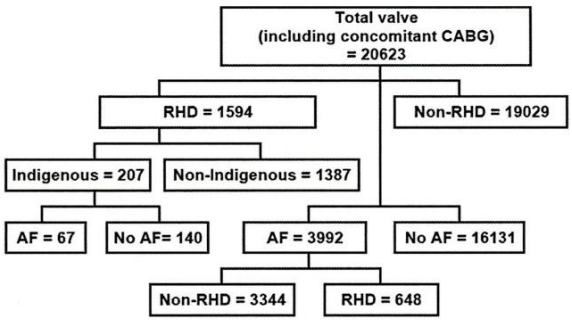

Fig. 1. Flow diagram: valve procedures and documented AF.

Table 1
Descriptive characteristics of valve surgery patients stratified by preoperative AF status.

	All valve surgery N = 20,623	Preoperative AF N = 3992	No preoperative AF N = 16,628	P value
Age (years)	71.4	74.0	70.6	<0.001
(median (IQR)	(61.3–78.4)	(65.6–79.9)	(60.5–77.9)	
Sex (% female)	37.0	41.7	35.8	<0.001
(95% CI)	(36.3–37.6)	(40.2–43.3)	(35.1–36.6)	
RHD related valve disease	7.7	16.2	5.7	<0.001
(95% CI)	(7.4–8.1)	(15.1–17.4)	(5.3–6.1)	
Indigenous status (% Aboriginal Australian and/or Torres Strait Islander)	2.0	2.5	1.9	0.008
(95% CI)	(1.0–2.2)	(2.0–3.0)	1.7–2.1)	
Concomitant CABG	38.4	34.3	39.5	<0.001
(%, 95% CI)	(37.9–39.1)	(32.8–35.8)	(38.7–40.2)	
Preoperative comorbidities				
Diabetes	23.4	24.8	23.1	0.020
(%, 95% CI)	(22.8–24.0)	(23.5–26.2)	(22.4–23.7)	
Chronic kidney disease	36.3	47.4	33.6	<0.001
(% eGFR < 60 mL/min/1.73m^2) (95% CI))	(35.6–36.9)	(45.8–48.9)	(32.9–34.3)	
Hypertension	67.4	70.7	66.6	<0.001
(%, 95% CI)	(66.7–68.0)	(69.2–72.1)	(65.9–67.3)	
Previous smoking	52.6	51.4	52.9	0.121
(%, 95% CI)	(52.0–53.3)	(49.9–53.0)	(52.2–53.7)	
Current smoking	16.1	11.4	17.2	<0.001
(%, 95% CI)	(15.4–16.8)	(10.0–12.8)	(16.4–18.0)	
Preoperative status				
NYHA classes III & IV	42.0	56.2	38.6	<0.001
(%, 95% CI)	(41.3–42.7)	(54.6–57.7)	(37.8–39.3)	
LVEF ≥ 45%	81.6	77.1	82.7	<0.001
(%, 95% CI)	(81.0–82.1)	(75.7–78.4)	(82.1–83.2)	
LVEF 30%–45%	11.9	15.6	11.1	<0.001
(%, 95% CI)	(11.5–12.4)	(14.5–16.7)	(10.6–11.5)	
LVEF ≤ 30%	4.1	5.2	3.9	<0.001
(%, 95% CI)	(3.9–4.4)	(4.5–5.9)	(3.6–4.2)	
Previous procedures				
Valve surgery	6.5	11.5	5.3	<0.001
(%, 95% CI)	(6.2–6.9)	(10.5–12.6)	(5.0–5.7)	
PBV*	5.2	8.4	4.1	<0.001
(%, 95% CI)	(4.6–5.9)	(6.9–10.1)	(3.5–4.8)	

* PBV — percutaneous balloon valvuloplasty.

3.1. Early postoperative outcomes and complications

Outcomes within 30 days following RHD and non-RHD related valve surgery are summarised in Table 2. Patients with RHD and preoperative AF, compared with those without preoperative AF were more likely to stay longer in hospital and had almost double the requirement for re-operation not related to valve dysfunction. Patients with non-RHD related valve disease and preoperative AF had prolonged ventilation (greater

Table 2
Outcome of RHD and non-RHD valve surgery within 30 days stratified by preoperative AF.

	RHD		Non-RHD	
	Preoperative AF N = 648	No preoperative AF N = 946	Preoperative AF N = 3344	No preoperative AF N = 15,682
Initial admission				
Prolonged ventilation	3.9	4.3	6.2	3.4*
(%, 95% CI)	(2.5–5.7)	(3.1–5.7)	(5.4–7.1)	(3.2–3.7)
Prolonged intensive care unit (ICU) stay	47.1	45.1	58.3	46.2*
(%, 95% CI)	(43.2–51.1)	(41.8–48.3)	(53.6–60.0)	(45.5–47.9)
Post procedure LOS	9.0	8.0*	10.0	8.0*
(days) (median (IQR))	(7.0–13.0)	(6.0–11.0)	(7.0–14.0)	(6.0–14.0)
Re-operation (unrelated to valve dysfunction)	9.4	5.4*	8.0	6.6*
(%, 95% CI)	(7.3–11.9)	(4.0–7.0)	(7.1–9.0)	(6.2–7.0)
Other complications				
Acute kidney injury	6.5	6.3	9.1	5.7*
(%, 95% CI)	(4.7–8.7)	(4.8–8.0)	(8.1–10.1)	(5.3–6.0)
Stroke or TIA	1.2	1.7	2.9	2.3
(%, 95% CI)	(0.5–2.4)	(1.0–2.7)	(2.3–3.5)	(2.1–2.6)
Anticoagulant complication (bleeding or embolization)	2.0	3.0	2.0	1.4*
(%, 95% CI)	(1.1–3.4)	(2.0–4.2)	(1.6–2.5)	(1.2–1.6)
Heart failure	4.1	1.9	3.6	1.7*
(%, 95% CI)	(2.1–7.3)	(0.8–3.7)	(2.6–4.9)	(1.4–2.1)
Septicaemia (positive blood culture with signs of infection)	0.8	1.6	2.4	1.3*
(%, 95% CI)	(0.3–1.8)	(0.9–2.6)	(1.9–3.0)	(1.2–1.5)

* Comparing AF and non-AF, $p < 0.05$.

than median of 11 h), ICU (greater than median of 45 h) and overall hospital length of stay, a greater requirement for reoperation not related to valve dysfunction, and higher levels of post-operative acute kidney injury, anticoagulant complications, heart failure and septicaemia. When analysis was restricted to Indigenous Australian patients with RHD the only factor associated with preoperative AF was a longer stay in hospital (median 8.0 days (IQR 6.8–16.0) compared with 7.0 days (IQR 6.0–10.0) ($p = 0.004$)).

3.2. 30-Day mortality

Early (30-day) all-cause mortality was equivalent in RHD patients with preoperative AF (3.4%, 95% CI 2.1–5.1) compared to those without (3.1%, 95% CI 2.1–4.4) (relative risk (RR) 1.1, 95% CI 0.6–1.9). Cardiac-related 30-day mortality was also similar (0.9% (95% CI 0.3–2.0) for pre-operative AF compared to 1.6% (95% CI 0.9–2.6) for those without (RR 0.6, 95% CI 0.2–1.5)).

In Indigenous Australian RHD patients with preoperative AF, 30-day all-cause mortality appeared to differ (6.0% (95% CI 1.7–14.6) with AF compared to 1.4% (95% CI 0.2–5.1) without AF) but this was not statistically significant (RR 4.2, 95% CI 0.8–22.3).

For non-RHD related valve surgery patients, early (30-day) all-cause mortality was worse if preoperative AF was present (6.7%, 95% CI 5.9–7.6) compared to when it was not (3.4%, 95% CI 3.1–3.7) ($p < 0.001$) (RR 2.0, 95% CI 1.7–2.3). Cardiac-related 30-day mortality was similarly worse in AF patients (2.5%, 95% CI 2.0–3.1 compared to 1.2%, 95% CI 1.0–1.3) ($p < 0.001$) (RR 2.1, 95% CI 1.7–2.8).

These differences, for both RHD and non-RHD related valve surgery, did not persist when other contributors to all cause and cardiac-related 30-day mortality that we had identified in earlier analysis [26] were controlled for. When 30-day mortality was controlled for using the 30-day cardiac mortality risk score, there was a persisting association with non-RHD preoperative AF (OR 1.4, 95% CI 1.2–1.7) but not for RHD-related.

3.3. Longer term survival

Mean follow-up (± SD) was 4.5 ± 3.3 years for RHD patients with preoperative AF and 4.6 ± 3.3 years for patients with no preoperative AF with a maximum period of follow-up of 12.5 years for both. For non-RHD patients with preoperative AF, mean follow-up was 4.0 ± 3.1 years and for patients with no preoperative AF, 4.2 ± 3.2 years with a maximum period of follow-up of 12.6 years. There was no difference in survival out to 10 years attributable to the presence or absence of preoperative AF for RHD-related valve disease, both when unadjusted and when survival was adjusted for other factors independently associated with RHD-related valve disease survival that we had identified in earlier analysis [26]. Unadjusted and adjusted Kaplan–Meier curves comparing survival stratified by preoperative AF status for RHD-related valve surgery are shown in Fig. 2.

Unadjusted and adjusted Kaplan–Meier curves comparing survival stratified by preoperative AF status for Indigenous Australians with RHD-related valve disease are shown in Fig. 3. Over a maximum period of follow-up of 5 years there were 19 deaths reported, 9 in Indigenous Australians with RHD-related valve disease with pre-operative AF (13.4%) and 10 in Indigenous Australians with RHD-related valve disease without pre-operative AF (7.1%). Whilst unadjusted survival was superior in Indigenous Australians with RHD-related valve disease without pre-operative AF, Cox proportional modelling controlling for other predictors of long term mortality showed comparable survival out to five years.

Unadjusted and adjusted Kaplan–Meier curves comparing mortality in non-RHD patients with and without preoperative AF are shown in Fig. 4. There was a difference in survival out to 10 years with superior survival in those without preoperative AF. When other factors

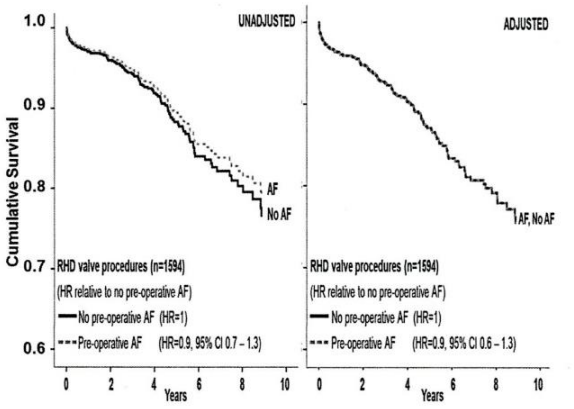

Fig. 2. Unadjusted and adjusted cumulative survival following RHD valve surgery stratified by preoperative AF.

associated with survival that we had identified in earlier analysis [26] were controlled for using Cox proportional modelling this association persisted.

4. Discussion

This study provides important insights into the role of AF in post-surgical outcomes for RHD and non-RHD-related valve disease, including Indigenous Australians. As with previous studies patients with preoperative AF were found to be older [3,9–12,28–32] and carried a greater baseline burden of comorbidities, including RHD [14,30,31], chronic kidney disease [3,9,10,29] and NYHA classes III & IV [9–11,14,29,33]. This greater level of AF in RHD patients has been reported in previous studies including in Dillon et al.'s review of RHD and non-RHD related valve repair in Malaysia which found 36% of RHD patients undergoing mitral valve repair had preoperative AF compared with 25% of non-RHD patients [34]. We also found both RHD and non-RHD patients with preoperative AF more likely to be female as in some [9,16] but not all previous studies [3,11,14,30].

Patients with non-RHD related valve disease and preoperative AF had increased short term complications in line with previous studies. Notably length of ventilation, time in ICU and in hospital [3,9], acute kidney injury [3,9], anticoagulant complications [33], heart failure [31,33], septicaemia [3] and all-cause 30 day mortality [9,10,29,31,35] have all

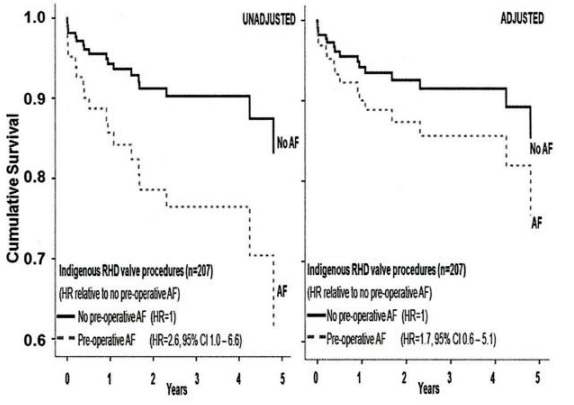

Fig. 3. Unadjusted and adjusted cumulative survival following RHD valve surgery for Indigenous Australians stratified by preprocedure AF status.

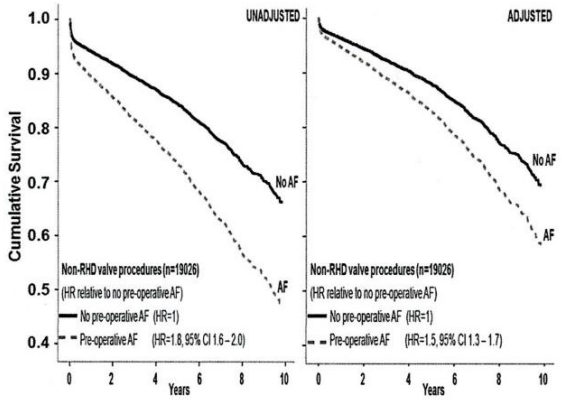

Fig. 4. Unadjusted and adjusted cumulative survival following non-RHD valve surgery stratified by preoperative AF status.

been shown to be worse when AF is present. In our study, stroke was not significantly associated with preoperative AF which was not in keeping with some prior studies [14,29,31,33,35–37]. Our analyses could not control for other factors which may alter the risk of stroke in the setting of AF associated with valvular heart disease. This included a lack of data relating to pre-surgery anticoagulation that may have been higher in this setting compared to that seen in previous studies when stroke risk and AF were related.

For patients with RHD-related valve disease the influence of preoperative AF on short term complications was less marked compared with non-RHD valve disease. In RHD patients with AF only postprocedure length of hospital stay and reoperation for non-valve dysfunction were worse. This may in part be related to the amplifying effect of AF on other factors that contribute to outcome in valve surgery patients. We have previously shown in multivariate modelling that RHD-related valve surgery is independently associated with younger, female and Aboriginal and/or Torres Strait Islander patients with a lower burden of hypertension and severe left ventricular dysfunction [15]. It is therefore possible the influence of AF on non-RHD short term complications seen in this study is explained by effect modification which occurs between AF and hypertension and/or severe left ventricular dysfunction.

Unadjusted 30-day mortality was similarly worse in non-RHD valve disease patients with AF but not in RHD patients. Nonetheless when other factors we had previously reported as being associated with 30-day mortality were controlled for this difference, even for non-RHD patients, did not persist [26]. It was interesting to note that adjusting the risk of 30-day mortality using the 30-day cardiac mortality risk score of Billah et al. [27] revealed a persisting contribution of AF in non-RHD patients. Given this score relates to all adults having cardiac surgery in an Australia cohort, and not just those requiring valve surgery, it is perhaps not surprising that it may not accurately predict survival in this sub-set of patients. It should be noted that the score is higher (and therefore attributes a great risk of 30-day mortality) in patients having valve-related surgery but not atrial fibrillation. This would suggest the cohort upon which this score was determined, based on 14 Australian centres, may not have been generalizable to the 28 Australian sites used here.

Preoperative AF has previously been found to significantly increase the risk of late death [3,14,31,33,36,38,39]. This was also the case in this study, with adjusted mortality up to 10 years following non-RHD cardiac surgery being 15% worse in those with preoperative AF. Adjusted survival was not different in the presence or absence of preoperative AF in patients with RHD-related valve disease. This differing effect of AF in non-RHD versus RHD patients may have again been explained by a greater burden of hypertension and severe left ventricular dysfunction in non-RHD valve surgery patients and associated effect modification.

5. Study limitations

The main limitation of this study is that it is restricted to Australian surgical practice and does not reflect management in other countries. Nonetheless, overall this sample is likely to provide an accurate representation of surgical management of valve disease in Australia that is generalizable to practice in other high income countries. Multiple data collection sites and personnel may have led to variable data coding. This was however minimised by each site being supported with training and standard data definitions, the use of standardised data entry systems and centralised auditing of site-specific data. Finally not all potential factors influencing the risk between AF and poorer outcome may have been collected and therefore available for analysis. These include detailed measures of left atrial size and co-existent long term preoperative anticoagulation.

6. Conclusion

AF is a common arrhythmia in RHD and non-RHD patients requiring valve surgery. In this prospective Australian study, patients with valve disease and preoperative AF carried a higher burden of comorbidities. Whilst adjusted 30-day survival was no different in patients with AF, short term complication were greater especially in those with non-RHD related valve disease. Adjusted long term survival was inferior in patients with non-RHD valve disease and AF but not RHD-related disease in general or, it appears, for Indigenous Australian with RHD specifically. Earlier intervention (prior to the onset of AF) or more aggressive management of AF to facilitate reversion to sinus rhythm should be investigated as mechanisms for enhancing postoperative outcomes in non-RHD valve surgery patients. In addition greater understanding of the differential effect of AF in RHD and non-RHD surgical outcome may identify further targets for intervention.

Conflict of interest

Nil.

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Chapter 7

Valve surgery outcome and case load in Australia

In Australia there are a significant number of centres that undertake valve surgery and it has been suggested that heart valve surgery in general and that for RHD specifically, should be consolidated in a small number of higher volume centres as a mechanism for enhancing treatment choice and short and longer term outcome. Whilst multiple cardiac surgical units may be argued to enhance access (particularly for residents of regional and remote centres) and reduce waiting times, for more specialised valve surgery, including for RHD, a smaller number of specialised units may be preferable. This chapter examines the independent association between site and/ or surgeon-specific average annual case load and short and long-term outcome following valve surgery.

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Case load and valve surgery outcome in Australia

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ABSTRACT

Background: In Australia it has been suggested that heart valve surgery, particularly for rheumatic heart disease (RHD), should be consolidated in higher volume centres. International studies of cardiac surgery suggest large volume centres have superior outcomes. However the effect of site and surgeon case load on longer term outcomes for valve surgery has not been investigated.
Methods: The Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database was analysed. The adjusted association between both average annual site and surgeon case load on short term complications and short and long-term survival was determined.
Results: Outcomes associated with 20,116 valve procedures at 25 surgical sites and by 93 surgeons were analysed. Overall adjusted analysis showed increasing site and surgeon case load was associated with longer ventilation, less reoperation and more anticoagulant complications. Increasing surgeon case load was also associated with less acute kidney injury. Adjusted 30-day mortality was not associated with site or surgeon case load. There was no consistent relationship between increasing site case load and long term survival. The association between surgeon case load and outcome demonstrated poorer adjusted survival in the highest volume surgeon group.
Conclusions: In this Australian study, the adjusted association between surgeon and site case load was not simple or consistent. Overall larger volume sites or surgeons did not have superior outcomes. Mandating a particular site case load level for valve surgery or a minimum number of procedures for individual surgeons, in an Australian context, cannot be supported by these findings.

1. Introduction

Valvular heart disease is an important contributor to cardiovascular morbidity and mortality. In Australia in 2012–13, 9040 heart valve repairs or replacements were performed [1]. The impact of valvular heart disease in some Australian populations, including older Australians and Aboriginal Australian and Torres Strait Islander peoples (Indigenous Australians) is particularly important and is, in part, related to a higher burden of degenerative and/or rheumatic heart disease (RHD)-related valve disease in these populations [2,3]. It has been

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suggested in Australia that heart valve surgery in general and that for RHD specifically, should be consolidated in a small number of higher volume centres [4] as a mechanism for enhancing short and longer term outcome.

In Australia there are a significant number of centres that undertake valve surgery. There are 58 units (2013 figures) spread across seven Australian jurisdictions [5] (Fig. 1) with most of Australia's state capitals hosting at least two, and often multiple, cardiac surgical units. In addition whilst Australia is a highly urbanised country [6] its numerous regional centres and the distances between these centres and capital cities has also encouraged the development of a smaller but significant number of cardiac surgical units in larger regional centres.

International data show the number of cardiac surgical centres at a national level varies greatly. In Australia the average population per cardiac surgical centre (based on the 2013 population [7]) was 0.4 million residents/centre. This compared to California in the US which had 132 centres documented in 2012 [8], 0.3 million/centre [9] or one third greater than Australia. In contrast the United Kingdom had 51 cardiac surgical centres in 2014 [10] or 1.3 million/centre [11], a level one third of that in Australia.

Whilst multiple cardiac surgical units may be argued to enhance access (particularly for residents of regional and remote centres) and reduce waiting times, it is unclear if an attendant smaller annual case load associated with multiple centres influences short and longer term outcomes following valve surgery. In addition for more specialised valve surgery, including for RHD, it is also unclear whether a smaller number of specialised units may be preferable [4].

There have been a number of studies in the USA [12–22], Europe [23], the Caribbean [24], Asia [25] and Australia [26] over the last twenty years that have analysed outcomes following cardiac surgery in large as compared with small volume centres. These studies have varied greatly in the number of surgical sites evaluated and the type of cardiac surgical procedures performed. In addition, many were restricted to short-term and in-hospital mortality. Whilst many concluded that outcomes were superior in large volume centres [12–19,21] this finding was not universal and typically referred to all cardiac surgery rather than valve surgery alone.

Some studies concluded that it was the expertise of the staff that was more important rather than the overall site case load [24–26]. Indeed it was suggested that highly skilled staff with superior outcomes may have attracted more patients [23]. Thus it was hypothesised that superior outcomes may drive an increase in centre activity rather than the other way round. Conversely it was also argued that a lack of association with site case load and outcome may be because experienced or inexperienced surgeons may operate in both high and low volume centres [24].

The lack of superior outcome seen with larger volume sites in some studies may also have been confounded by the finding that such sites attracted complex and higher risk patients [22,27]. Whilst earlier studies analysed mortality following cardiac surgical procedures in low as compared with high volume centres, the definition of high and low volume also differed markedly between studies [12–15,18,19, 21–23,25,27]. Using these differing definitions, low volume site case load was defined as less than 10 [27] to less than 200 [14] cases per year and high from over 75 [17] to at least 500 [14].

The importance of the experience of individual surgeons, as distinct from the total volume of surgery performed at the surgical site, was highlighted by a recent Australian study by Ch'ng and others [26]. They noted that surgeons with a greater number of valve-specific procedures had superior short-term outcomes even after controlling for the complexity of surgery and patient comorbidities. Nonetheless this association was not seen for total (valve and non-valve) cardiac surgery suggesting that valve surgery may be a particular area where individual surgeon experience may be important.

Fig. 1. Cardiac surgical units in Australia [5].

Such findings may support an argument for valve surgical specialisation in individual cardiac surgeons. Nonetheless it remains unclear whether such specialisation translates to superior long-term outcomes, whether it should be at the level of particular types of valve disease (e.g. valve repair) or aetiology (e.g. RHD) and the relative contribution of surgeon-specific specialisation versus centre-specific specialisation and case load. Some studies investigating case load and mitral valve repair have specifically suggested the development of centres of excellence for mitral valve repair [28–31] with minimum standards suggested for such centres [32].

The objective of this study was therefore to determine if site and/or surgeon-specific average annual case load was associated with short and long-term outcome following valve surgery by analysing data from a large Australian multi-site cardiac surgery enhanced surveillance register. Given the impact of RHD-related valve disease, particularly for Indigenous Australians who are more likely to reside in remote locations [2], it also aimed to specifically examine these associations in patients with RHD-related disease and in regard to rheumatic mitral valve repair.

2. Methods

2.1. The database

The Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database was utilised. A detailed description of this database can be found elsewhere [2]. Briefly, it is an Australia-wide database for the collection and analysis of the results of cardiac surgery that collates data from Australian hospitals regarding patients who have undergone cardiac surgery, the type of surgery performed, early complications and 30-day mortality. In addition the database is regularly linked to the Australian National Death Index [33] to assess longer term survival. The database commenced in 2001 with six surgical centres and currently encompasses 28 Australian sites.

2.2. Selection criteria

Participants were patients 18 years and older who had been registered on the Database and who had undergone valve surgery with or without CABG surgery. Three sites had contributed data for less than two full years and were therefore excluded from annual case load comparisons leaving 25 sites for analysis.

2.3. Theory

Despite a lack of a consistent association between site and surgeon case load and outcome, recommendations have been developed regarding the requisite case load a centre should seek to maintain. Thus the American College of Cardiology and American Heart Association guidelines for coronary artery bypass graft (CABG) surgery recommend a minimum volume of 125 cases per year and that centres with caseloads under this number be affiliated with high-volume tertiary centres [34]. Similarly the European Guidelines for cardiac surgery recommend CABG be performed in centres that perform at least 200 cases per year [35]. The Australian and New Zealand Society of Cardiac and Thoracic Surgeons has adopted guidelines for cardiac surgery in general (CABG and valve surgery) with recommendations for at least 100 cases per year per surgeon and site case loads of at least 200 cases per year [36].

Recommendations regarding adequate site-specific case load for valve surgery in particular remain less prescriptive. Whilst the American College of Cardiology and American Heart Association has supported the development of "Heart Valve Centers of Excellence" [37] these are defined by a combination of experience, expertise, management choices, registry participation, guidelines adherence and outcome transparency and do not advocate for a minimum valve procedure specific case load for such centres.

2.4. Calculation

Data were analysed using IBM SPSS Statistics 22 (IBM, New York, USA) and Stata 13 (StataCorp LP, Texas, USA). Descriptive (demographic, comorbidity data and surgery type) and outcome data were summarised using standard univariate techniques and reported as percentages with 95% confidence intervals (95% CI), means with standard deviation (SD) or medians with interquartile range (IQR) depending on the data format and distribution.

Short-term (less than 30-day) outcomes included post-operative invasive ventilation time, number of hours spent in the intensive care unit (ICU), post procedural length of stay, need for re-operation for valve or non-valve dysfunction, acute kidney injury, new atrial fibrillation (AF), stroke or TIA, deep sternal wound infection, any anticoagulant complication (bleeding or embolization), heart failure or septicaemia (positive blood culture with signs of infection), readmission and cardiac and all-cause mortality. Long-term survival was analysed out to five years using the log rank test and presented with Kaplan–Meier curves. A p valve less than 0.05 was taken to indicate statistical significance and all tests were two-sided.

Average site case load was determined for each site using the arithmetic mean number of valve procedures performed each year (including all valve surgery and RHD-related valve surgery) over the period of observation. Based on this calculated average annual case load, sites were ranked in order of increasing total average annual case load and then divided into four equal size groups. As each of the surgical sites varied in the proportion of RHD-related procedures, average site case load group allocation was determined for each site separately for all and RHD-related surgery. In the same manner, average surgeon annual caseload was determined. Due to the smaller number of Indigenous Australian patients, total average annual site and surgeon case load was divided into three equal size groups.

The association between outcome and site and surgeon case load was first assessed using standard bivariate techniques based on the distribution and format of the data as outlined above. Multivariable logistic and Cox proportional hazard models were then developed to assess the independent association between site and surgeon case load and outcome measures controlling for demographic and comorbidity data where necessary. These models were developed using predictors for survival identified from our previous studies [2,3]. In separate analysis the influence of case load on 30-day mortality was also adjusted to take account of the 30-day cardiac risk score developed by Billah and others [38].

Approval for this project was granted by the Monash University Human Research Ethics Committee (CF13/2737 – 2013001472).

3. Results

Data in relation to 20,116 valve procedures (1560 RHD and 18,556 non-RHD) performed in 25 sites and by 93 surgeons between 1 August 2001 and 31 December 2013 were analysed. Patient demographic data for all valve surgery patients and stratified by whether the underlying disease was RHD or non-RHD related is outlined in Table 1.

Median site-specific average annual total valve surgery case load was 93.4/year (range 35–214) and for RHD-related 6.8/year (range 1.8–17.8). The median average annual number of all valve procedures performed by surgeons at one or more sites was 20.2/year (range 1–71) and for RHD related surgery this was 1.9/year (range 0.1–6.9). There were between one and seventeen surgeons at each site who had performed surgery over the preceding 12 years, 53 operating at only one site, 24 at two sites, 14 at three and two at four sites.

3.1. Valve surgical procedures

The choice of valve surgical procedure varied between sites of differing case load strata but not in a consistent fashion. Thus from the lowest to highest site case load strata mechanical valve replacements represented 20.8%, 23.5%, 21.0 and 21.9% respectively of all valve procedures ($p < 0.001$), bioprosthetic 67.9%. 55.7%, 59.1% and 60.0% ($p < 0.001$) and valve repair 9.7%, 16.5%, 13.9% and 16.9% ($p < 0.001$). The choice of valve surgical procedure also varied inconsistently between differing surgeon case load groups. For mechanical valve replacements this was 25.0%, 22.4%, 19.3 and 21.8% respectively ($p < 0.001$) for increasing surgeon case load, 61.2%. 59.6%, 62.8% and 56.7% ($p < 0.001$) for bioprosthetic valve replacements and 12.7%, 15.7%, 15.3% and 15.3% ($p < 0.001$) for valve repair.

The use of mechanical or bioprosthetic valve replacement for RHD-related disease did not vary by site or surgeon case load (data not shown). In contrast mitral valve repair was more common in higher volume centres (7.3%, 8.0%, 9.4% and 15.7% ($p < 0.001$) for increasing site case load strata) and for higher volume surgeons (6.2%, 7.0%, 11.3% and 15.0% ($p = 0.001$) for increasing surgeon case load group).

3.2. Short-term complications

The associations between unadjusted short-term complications for all and RHD-related valve surgery and site and surgeon case load are presented in Table 2. Overall a range of short-term outcomes were associated with increasing site case load strata including a shorter period of ventilation and stay in ICU and reduced need for reoperation in high volume centres with greater levels of acute kidney injury and new atrial fibrillation (AF). For Indigenous Australian RHD-related

Table 1
Patient demographics for valve surgical procedures stratified by aetiology.

	Number (% total)	Age (median, IQR)	Sex (% female, 95% CI)	Indigenous Australian (%, 95% CI)
All	20,116 (100)	71.4 (61.5–78.4)	37.0 (36.3–37.7)	1.9 (1.8–2.1)
RHD-related	1560 (7.8)	62.8 (51.1–71.7)	64.9 (62.5–67.3)	12.7 (11.1–14.4)
Non-RHD-related	18,556 (92.2)	72.1 (62.5–78.7)	34.7 (34.0–35.4)	1.0 (0.9–1.2)
P valve (RHD vs non-RHD)	–	<0.001	<0.001	<0.001

valve surgery, a shorter period of ventilation (OR 0.7, 95% CI 0.5–0.9) and stay in ICU (OR 0.7, 95% CI 0.5–0.8) was associated with increasing site case load.

Unadjusted short-term outcomes associated with increasing surgeon case load included a longer period of ventilation and stay in ICU and more early heart failure and anticoagulation complications. Despite this, there was also a shorter length of hospital stay, reduced need for re-operation and lower levels of acute kidney injury, new atrial fibrillation (AF) and septicaemia. For Indigenous Australian RHD-related valve surgery less septicaemia (OR 0.3, 95% CI 0.1–0.9) was the only factor associated with increasing surgeon case load.

The association between short-term outcomes and average site and surgeon case-load after adjusting for significant covariates, identified from our previous studies [3], is presented in Table 3. In general, increasing site case load for all valve procedures demonstrated an adjusted association with longer than median period of ventilation (although it was shorter for RHD-related valve surgery), less re-operation for a non-valve dysfunction indication and a greater level of anti-coagulation complications. As the average site case load strata was separately determined for all and RHD-related surgery, it was possible for higher case load to be associated with longer ventilation overall and to be protective of longer ventilation in the RHD sub-group. Increasing case load for Indigenous Australians demonstrated an adjusted association with shorter than median period of ventilation (OR 0.6, 95% CI 0.5–0.8) and stay in ICU (OR 0.6, 95% CI 0.5–0.8).

Increasing surgeon case load for all valve surgery demonstrated an adjusted association with a longer period of ventilation, greater level of anticoagulation complications, less re-operation for a non-valve dysfunction indication and less acute kidney injury. Increasing surgeon case load for RHD-related valve surgery demonstrated an adjusted association with a longer stay in ICU and greater level of anticoagulation complications. Indigenous Australian RHD-related valve surgery demonstrated no adjusted associations with increasing surgeon case load.

3.3. Thirty day mortality

Average annual site case load was not significantly related to 30-day mortality for all valve procedures in unadjusted analysis but was for RHD valve surgery (OR 0.76, 95% CI 0.60–0.96), although not for RHD mitral valve repair specifically. This association did not persist when other factors previously found [2] to be independently associated with 30-day mortality following valve surgery were controlled for in logistic regression modelling.

When 30-day mortality was adjusted with the Australian 30-day cardiac mortality risk score [38], the association between site case load and RHD valve surgery persisted (OR 0.73, 95% CI 0.57–0.93). There was no similar significant adjusted association between case load and 30-day mortality for all valve surgery or for RHD valve surgery for Indigenous Australians.

Average annual surgeon case load was not significantly related to 30-day mortality for all valve procedures in unadjusted or adjusted analysis or for RHD valve surgery, for RHD valve surgery for Indigenous Australians or RHD mitral valve repair. There were also no significant adjusted associations between surgeon case load and 30-day mortality when the Australian 30-day cardiac mortality risk score was used [38].

3.4. Long-term survival

Long-term survival analysis was limited to a maximum of five years following surgery. Although the database had collected data since 2001, until 2006 valve surgery was only collected from seven sites and it was not until 2009 that at least 23 of the 25 sites provided valve surgery data.

Overall five year mortality related to 1099 deaths (16.2%, 95% CI 15.3–17.1) following all valve surgery procedures. For RHD-related valve surgery five year mortality was reported as 89 deaths (14.8%, 95% CI 12.1–17.9) and for non-RHD procedures 1010 (16.3%, 95% CI 15.4–17.3).

Unadjusted and adjusted Kaplan–Meier curves comparing survival for all valve surgery stratified by site case load strata are shown in Fig. 2. There was no significant unadjusted association between site case load strata and survival. A significant association between site case load and survival was demonstrated when this was adjusted for surgeon case load and other factors associated with survival [3] However this did not demonstrate a consistent relationship with superior survival seen in the lowest case load strata and inferior survival in the middle strata (strata 2) when compared with the highest case load (strata 4).

Unadjusted and adjusted Kaplan–Meier curves comparing survival for all valve surgery stratified by surgeon case load group are shown in Fig. 3. These demonstrated no significant difference in survival for unadjusted analysis by surgeon case load group but a significant difference in survival when adjusted for site case load and other significant

Table 2
Unadjusted associations between site-specific case load strata and surgeon-specific case load group (1 lowest to 4 highest) and short-term outcomes.

	Increasing site case load		Increasing surgeon case load	
OR (95% CI)	All	RHD-related	All	RHD-related
Ventilation (% > median)	–	0.84 (0.75–0.94)	1.07 (1.01–1.13)	–
ICU stay (% > median)	0.96 (0.93–0.98)	–	1.08 (1.06–1.11)	–
Post procedure length of stay	–	–	–	0.91 (0.84–0.98)
Readmission (any reason)	1.08 (1.03–0.12)	–	–	–
Re-operation (non-valve)	0.92 (0.87–0.96)	–	0.93 (0.89–0.97)	–
Acute kidney injury	1.07 (0.02–0.13)	–	0.92 (0.88–0.96)	–
New AF	1.07 (1.04–1.10)	–	0.96 (0.93–0.98)	–
Anticoagulant complication (bleeding or embolization)	–	–	–	1.6 (1.1–2.3)
Heart Failure	–	–	1.3 (1.1–1.4)	–
Septicaemia (positive blood culture with signs of infection)	–	–	0.89 (0.82–0.97)	–

Table 3
Adjusted associations between site-specific case load strata and surgeon-specific case load group (1 lowest to 4 highest) and short-term outcomes.

	Increasing site case load		Increasing surgeon case load	
OR (95% CI)	All	RHD-related	All	RHD-related
Ventilation (% > median)	1.2 (1.0–1.5)	0.8 (0.8–0.9)	1.6 (1.1–2.2)	–
ICU (% > median)	–	–	–	1.1 (1.0–1.3)
Re-operation (non-valve)	0.91 (0.87–0.96)	0.8 (0.7–0.9)	0.9 (0.8–0.9)	–
Anticoagulant complication	1.3 (1.1–1.6)	–	1.3 (1.1–1.5)	2.9 (1.1–7.7)
Acute kidney injury	–	–	0.9 (0.8–0.9)	–

contributors to survival [3]. In this adjusted analysis superior survival was demonstrated for the three lower surgeon case load groups when compared with the highest case load group.

No significant differences in survival between site case load strata or surgeon case load group were seen for RHD-related valve surgery overall, for RHD mitral valve repair surgery or for Indigenous Australians specifically in unadjusted or adjusted analysis.

4. Discussion

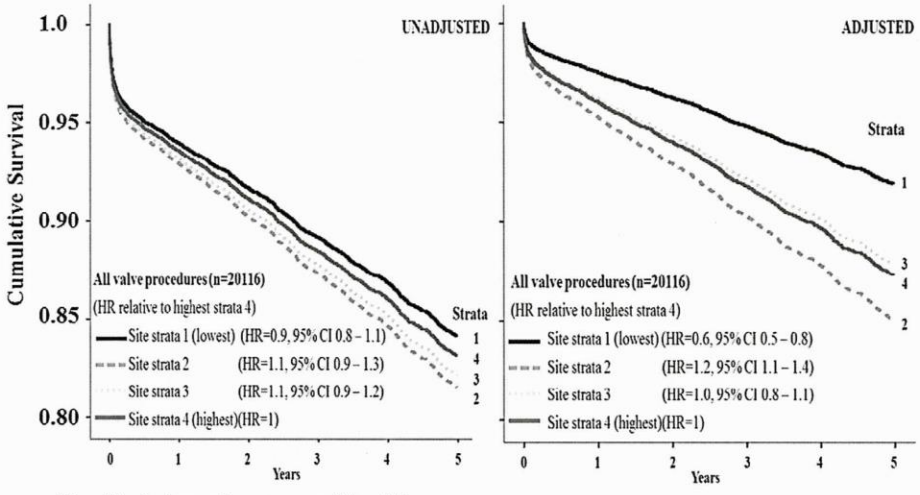
This study provides the first combined assessment of the influence of site and surgeon specific case load on short and long-term outcomes associated with valve surgery in Australia. Using a large national data set incorporating patient and procedural data from 20,116 valve surgical procedures we have demonstrated that high volume centres or surgeons did not have consistently better short or long term outcomes.

It is likely higher volume centres or surgeons undertake more complicated cases with an associated greater risk of early post-operative complications. Nonetheless even after adjusting for other factors associated with short-term complications we found increasing site and surgeon case load was associated with a longer period of ventilation and more anticoagulation complications. In contrast higher volume centres and surgeons had an associated lower need for reoperation due to non-valve indications.

The association between case load and short-term complications varied by the underlying cause of valve disease. Whilst the lack of similar associations for RHD-specific valve surgery may have in part been related to reduced numbers and power it was noted that increasing site case load was associated with a shorter period of ventilation for these patients (compared with longer for all valve surgery). This highlights that the cause of valve disease can influence post-surgical outcomes. In turn, the characteristics of the catchment population and their risk of particular causes of valve disease (e.g. Indigenous Australians and RHD) should be taken into account when assessing outcomes at individual cardiac surgical sites.

Despite these relatively minor differences in short term complications it was reassuring that adjusted thirty-day survival was not related to site or surgeon case load. Thus in this Australian study restricted to valve surgery patients we have not seen the same associations between site case load and short term outcome as have been demonstrated in some studies in other settings. Nonetheless our findings support Papachristofi et al. [39] who found no significant association between site case load and surgeon case load for in-hospital deaths after cardiac surgery in general.

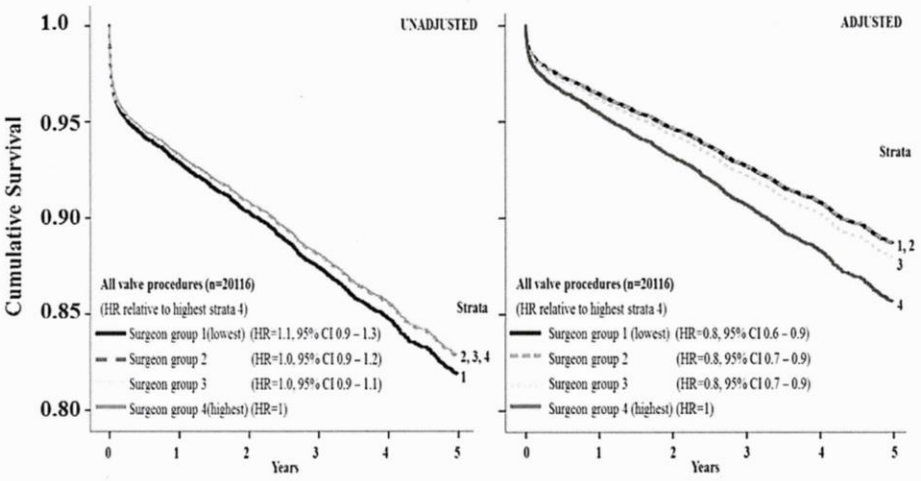
Our findings reflect some but not all findings of Ch'ng et al.'s Australian study of cardiac surgeon case load and outcome [26]. In line with this study we found an association between surgeon case load and short term complications. However we did not demonstrate a



Unadjusted number exposed to risk

Year	0	1	2	3	4	5
Strata 1	1111	714	431	241	133	48
Strata 2	2352	1752	1323	960	701	297
Strata 3	2830	1903	1271	834	581	242
Strata 4	4912	3750	2993	2318	1753	727

Fig. 2. Unadjusted and adjusted Kaplan–Meier curves for survival following all valve procedures stratified by average annual site case load strata.



Unadjusted number exposed to risk

Year	0	1	2	3	4	5
Strata 1	1266	943	732	579	458	191
Strata 2	2652	1948	1497	1131	845	354
Strata 3	4019	3011	2257	1594	1147	482
Strata 4	3268	2216	1532	1049	718	287

Fig. 3. Unadjusted and adjusted Kaplan–Meier survival curves following all valve procedures stratified by average annual surgeon case load group.

similar association with 30-day mortality. This difference may be explained by this earlier study utilising a broader range of variables for adjustment rather than only those we had previously shown to influence outcome. In addition they did not adjust for site case load in their analysis.

Whilst similarities may exist between cardiac surgical practices in high income countries the presence of disparate findings between countries should not be surprising. It should nonetheless caution basing local health service policy on evidence from other settings without due regard for differences in the structure and nature of health services and patients.

We have already highlighted that the population catchment of cardiac surgical centres in other high income settings such as the UK and USA vary markedly compared with Australia. In addition whilst all high income countries are faced with an ageing valve surgery population with associated chronic disease comorbidities, Australia is relatively unique in also providing care to a significant group of patients with RHD including younger and often remote residing Indigenous Australians [3].

A particular strength of this study is its ability to examine long term survival. Long-term survival is likely to be influenced by factors in addition to those of the cardiac surgical unit and surgeon. Issues associated with health care follow-up, including primary and specialist health care access and quality, and the adequacy of anticoagulation and monitoring are all likely to be contributors to survival. In our study we have not shown that higher valve surgery volume sites or surgeons have patients with superior long term survival. This is despite controlling for other factors associated with survival to take account of differing patient populations and the complexity of surgery. Indeed we have shown that higher volume surgeons have associated poorer survival and it was the lowest volume sites that demonstrated the best long-term survival. In light of such finding it could be argued that in Australia there is a need to focus on the nature and adequacy of long term follow-up after valve surgery provided by higher volume sites or surgeons.

Better understanding of long term survival following valve surgery will require more comprehensive follow-up of patients with incorporation of not only survival but also cardiac and anticoagulation-related morbidity and capture of long-term health care access and quality. In the interim, the influence of site and surgeon case load on long-term valve surgery survival should not be viewed in isolation. In turn, recommendations regarding the size or structure of cardiac valve surgical centres should also incorporate an understanding of, and requirements for, long term community-based care and follow-up.

How these differing site case load levels influence the efficiency and cost-effectiveness of surgical centres was beyond the scope of this project but it might be assumed the greater contribution of fixed costs as a proportion of total costs in smaller case load centres may contribute to such centres being less cost-effective than larger ones. The issue of direct financial cost must nonetheless be balanced against the potential benefits smaller and particularly regional cardiac surgical centres have in enhancing access to valve surgery. This has particular implications for residents of regional and remote Australia, including for Indigenous Australians who bear a disproportionate and well-described burden of RHD [3]. Although RHD-related valve disease represented a relatively small proportion of valve surgery it was reassuring that in this group, and particularly in Indigenous Australians with RHD, there was no difference in complications nor adjusted short or long-term survival between low and high volume sites and surgeons.

Whilst these findings related to a large number of Australian centres they were limited by the relatively small case loads of many centres. The nature of Australia's large geographic area and relatively small population means many centres had relatively low case loads compared with earlier international studies. Whether our findings would be replicated in sites with far larger case loads than those seen in Australia remains to be seen. Nonetheless our findings have clear relevance to surgical practice in Australia and other countries with similar geography and health service structures.

The nature of valve procedures and patient populations in high income countries is also undergoing rapid change as new non-surgical

approaches to valve disease expand and become more common and as the age and level of chronic disease comorbidities in the patient population increases. In the future, concentrating only on the surgical management of valve disease is unlikely to capture all valve procedures and future systems for prospective surveillance will need to include surgical and non-surgical/transcatheter approaches for valve disease management. An ageing population with increasing comorbidities is also likely to place far greater reliance on non-operative aspects of care and in such a setting the importance of patient selection and pre and post-operative care provided by multidisciplinary teams is likely to become even more important.

Our findings provide an important addition to the many studies over the last twenty years where most, but not all, have found short-term outcomes were superior in large volume centres [12–19,21]. We have shown that whilst rates of short-term complications may vary that this does not influence short-term outcomes between sites and surgeons of differing case loads. The current study is one of few to examine long-term survival and we have shown there is not a simple or consistent relationship between site or surgeon case load and survival.

A persuasive case can be made for centralising expertise and care in across many areas of health care [40]. Nonetheless, whilst such centralisation may be argued to reduce cost and possibly enhance outcome it may also reduce patient access, particularly in a country such as Australia. The fact that lower volume sites had superior long-term outcomes is encouraging and is likely to reflect the importance, quality and access to ongoing primary and specialist management in such patients in Australia. Supporting such community based care through standardised systems for primary and specialist management and optimising health service access, including regional and outreach specialist services, will remain key if the high quality of Australian valve surgery management and long-term outcome is to be sustained and enhanced.

5. Study limitations

The main limitation of this study is that it is restricted to Australian surgical practice and does not reflect management or the broader health care system in other countries. Nonetheless overall this sample is likely to provide an accurate representation of surgical management of valve disease in Australia that is referable to practice in other comparable high income countries. Multiple data collection sites and personnel may have led to variable data coding. This was however minimised by each site being supported with training and standard data definitions, the use of standardised data entry systems and centralised auditing of site-specific data. Finally, long term outcome was limited to survival alone. A greater understanding of morbidity, health care utilisation and access to and quality of follow-up care would be required to gain a more accurate picture of long term outcome.

6. Conclusion

In this prospective Australian study of valve surgery outcome we have shown short-term survival following valve surgery in Australia is not related to site or surgeon case load. In contrast long-term survival appears to be superior in lower volume sites and surgeons. This suggests long-term outcome may be more related to the broader community-based health care environment to which patients return or that higher volume sites may be faced with a potential diseconomy of scale particularly for surgeons who undertake the highest average annual number of valve surgical procedures. Mandating a particular site case load level for valve surgery or a minimum number of procedures for individual surgeons cannot be supported by these findings either overall or for RHD specifically.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Chapter 8

Outcome following valve surgery in Australia: development of an enhanced database module

The seventh and final paper presented in this thesis outlines a protocol for a study that will further inform the management of advanced RHD. This study will involve the development of a multicentre, enhanced baseline assessment and data linkage surveillance system to better understand short and longer term non-lethal outcomes associated with surgical management of RHD. It will collect and incorporate more detailed information regarding pre and postoperative factors at four Australian cardiothoracic surgical sites caring for patients with both RHD and non-RHD related valvular heart disease and link this to hospital separation and other registry data sources

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STUDY PROTOCOL Open Access

Outcome following valve surgery in Australia: development of an enhanced database module

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Abstract

Background: Valvular heart disease, including rheumatic heart disease (RHD), is an important cause of heart disease globally. Management of advanced disease can include surgery and other interventions to repair or replace affected valves. This article summarises the methodology of a study that will incorporate enhanced data collection systems to provide additional insights into treatment choice and outcome for advanced valvular disease including that due to RHD.

Methods: An enhanced data collection system will be developed linking an existing Australian cardiac surgery registry to more detailed baseline co-morbidity, medication, echocardiographic and hospital separation data to identify predictors of morbidity and mortality outcome following valve surgery.

Discussion: This project aims to collect and incorporate more detailed information regarding pre and postoperative factors and subsequent morbidity. We will use this to provide additional insights into treatment choice and outcome.

Keyword: Indigenous health, Rheumatic heart disease, Valve surgery, Surgery timing, Outcome indicators

Background

Valvular heart disease can be congenital or acquired. Acquired disease can be either a result of aging or due to a disease process that damages valves. Management of valvular heart disease can involve a combination of medication, surgical repair or valve replacement with a mechanical or bioprosthetic valve. There were 9,276 heart valve repair or replacement procedures reported in Australia in the year 2013–14 [1]. From a clinician and patient perspective, the aim is to intervene at a time and in a way that ensures the lowest possible operative complications and mortality with the best short and long-term outcome.

A particular cause of acquired valvular heart disease is rheumatic heart disease (RHD). Whilst now rare in high income countries [2, 3], it remains a condition of global health importance and an important cause of preventable heart disease. In Australia RHD particularly affects Aboriginal and/or Torres Strait Islander peoples (Indigenous Australians) and older non-Indigenous Australians [4, 5].

We have previously analysed data [6] from the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database [7] and have identified differences in surgical management for RHD and nonRHD valve disease and for Aboriginal and/or Torres Strait Islander and nonIndigenous Australian patients [5]. In addition we have been able to identify factors associated with outcomes following valve surgery for RHD and nonRHD related valve disease [5, 6, 8].

The details of the Database have been outlined elsewhere [5]. Briefly it is an Australia-wide database for the collection and analysis of the results of cardiac surgery that collates data from Australian hospitals regarding patients who have undergone cardiac surgery, the type of surgery performed, early complications and 30 day mortality. In addition the Database is linked to the Australian National Death Index [9] to assess longer term survival. The Database commenced in 2001 with six surgical centres and currently encompasses 28 Australian sites.

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Table 1 Enhanced peri-operative data collection

Pre-operative history	ICD 10 code [29]
Cerebrovascular diseases	I60-I69
Haemorrhagic	I60-I62
Ischaemic	I63
Transitory ischaemic attack (TIA)	I65-I66
Bleeding	Eye: H21.00, H35.6
	Digestive system: K22.11, K22.8, K25.4, K29.00, K29.01, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K62.5, K92.0, K92.1, K92.2
	Circulatory system: I85.00, I85.01, I85.11, N93.0, N92.3, N93.9, N95.0, R04.0, R04.1
	Genitourinary system: R04.89, R19.5, R58
	Haemorrhagic disorder due to circulating anticoagulants: D68.3
	I50.9, I50.0, I50.1, I51.5, I11.0, I11.9, I13.0, I13.2
Heart failure	O74.2, O75.4, I97.1, I97.8, I25.5, O29.1, O89.1, I09.81, I27.89
Endocarditis	B33.21, I01.1, I09.1, I33, I38, I39, I42.9
Cardiac surgery (including type)	CABG: 0210 – 0213;
	Valve repair: aortic 02QF, mitral 02QG, pulmonary 02QH, tricuspid 02QJ
	Valve replacement: aortic 02RF, mitral 02RG, pulmonary 02RH, tricuspid 02RJ
	Percutaneous/trans-catheter valve replacement: 623, 628, 637, 634
	Percutaneous valvuloplasty: 38270-01, 38270-02
Arrhythmia	I44.0-9, I45.0-9, I480-9, I49.0-9, I97.8, I47.0, J84.1, M62.8
	Pacemaker and/or defibrillator (insertion but not replacement, removal or adjustment): 38256-00/01 38368-00, 38390-00/01/02, 38350-00, 90202-00/01/02, 38473-00/01, 38470-00/01, 38654-00/03, 38353-00, 38393-00
Pre-operative and discharge	
Medication	Time period
Beta blocker	Pre-operative, on discharge
ACE Inhibitors	Pre-operative, on discharge
Angiotensin Receptor Blocker	Pre-operative, on discharge
Diuretic	Pre-operative, on discharge
Digoxin	Pre-operative, on discharge
Warfarin	Pre-operative, on discharge
NOAC (new oral anticoagulants)	Pre-operative, on discharge
Aspirin	Pre-operative, on discharge
Clopidogrel/Prasugrel/Ticagrelor	Pre-operative, on discharge

Clinical registries such as this provide a minimum dataset related to the patient, the procedure and outcome. As such they are a valuable resource for informing clinical care, quality assurance activities and for research hypothesis generation. While the Database collects a range of pre-operative patient demographic, co-morbidity and outcome data it does not include prior medication use, detailed echocardiography measurements and non-lethal complications beyond 30 days post-procedure.

The medical management of advanced valvular disease can include anti-platelet and anti-coagulant medication, diuretics, angiotensin-converting enzyme (ACE) inhibitors [10], and beta blockers but it is unclear if these agents can influence early and longer term outcomes following surgery. In addition while valvular disease can be complicated by cardioembolism (e.g., stroke) [10] the influence of such a history prior to surgery on outcome, and how this may influence surgical choice, remains unclear.

Existing studies highlight the importance of echocardiographic assessment of the severity of valve disease and preoperative valve and heart function. Such data is currently not collected by the existing Database, in particular, left ventricular endsystolic (LVESD) and enddiastolic (LVEDD) diameter and pulmonary arterial systolic pressure (PASP).

Valve morphology has also been shown to predict outcome for those undergoing RHD-related mitral valve repair including the absence of deformity of the mitral valves leaflets and mitral valve prolapse [11] and maintenance of anterior mitral leaflet mobility [12].

Whilst longer-term survival beyond 30 days for the Database is determined from the National Death Index (NDI) [9], other outcomes are currently captured only to 30 days following surgery and only for the surgical site. Non-lethal longer term outcomes relevant to valve surgery include bleeding and thromboembolic complications, heart failure, endocarditis and reoperation.

Thromboembolic events reported in previous studies for follow-up to 7 years following surgery has ranged from none [13] to 5.9% [14] and for up to 10 years, 6% [14] to 24.7% [15] of mechanical valve replacement recipients and 7% [16] to 25% [17] of bioprosthetic valve recipients. Bleeding events have been reported as between 8.8% [17] and 52.6% [18]. The long term risk and burden of heart failure following valve surgery is poorly defined and earlier studies have demonstrated a significant risk of subsequent endocarditis [19] .

Reporting of re-operation varies greatly. After a repaired mitral valve, this has ranged from none at 2 years [20] to 90% at 30 years [21], from 1% [22] at 9 years for all mitral valve replacements, 3.4% [14] at 5 years to 12.6% [23] at 25 years for mechanical valve replacement and 3.6% at 5 years [14] to 63% at 25 years [23] for bioprosthetic valve replacements.

This multicentre, enhanced surveillance system therefore aims to collect short and longer term outcome data to assist in predicting outcomes and providing evidence to inform the development of guidelines to facilitate consistent practice. Utilizing an enhanced data collection system it will collect and incorporate more detailed information regarding pre and postoperative factors at Australian sites that undertake both non-RHD and RHD-related surgery. It will use these more detailed data to provide additional insights into treatment choice and outcome for valve surgery in general and RHD specifically.

Information demonstrated to be important and relevant will be considered for future inclusion in the existing ANZSCTS national cardiac surgery database to assist in predicting outcomes and providing evidence to inform the development of guidelines to facilitate consistent and evidencebased practice in the management of valve disease including for that relating to RHD [10].

Methods

Population and method of sampling

Four Australian cardiothoracic surgical sites with significant RHD and non-RHD surgical caseloads representing cases from two different Australian jurisdictions will be included. A random subset of patients having procedures over the preceding ten years, will be chosen from the existing Database.

Sample size

The sample size will be based on the number required to detect a difference in major adverse prosthesis-related events (MAPE) between bioprosthetic and mechanical valve replacements. MAPE will be defined as a composite outcome of any reoperation, major bleeding, thromboembolic event, or endocarditis during late follow-up [24]. A sample size of 600 patients will be recruited based on an anticipated rate of MAPE over ten years of follow-up of 50% for mechanical valve replacements and 35% for bioprosthetic valve replacement [24], a ratio of mechanical to bioprosthetic mitral valve replacements of 2:1 [5], two-sided alpha of 0.05 and power of 80%.

Instrumentation

An enhanced baseline dataset with identical definitions for all data points has been created to standardize data collection. Field names and coding have been defined in line with the existing Database data definitions. The enhanced baseline dataset consists of data shown in Table 1. Pre-operative history will be based on linkage with hospital separation data and with reference to the Massive Transfusion Registry (MTR) [25]. Medication and echocardiography data will be ascertained from the index hospital admission for valve surgery including admission history for pre-operative medication, discharge medication and linkage with imaging reporting systems.

Table 1 Enhanced peri-operative data collection *(Continued)*

Pre-operative echocardiography	Measurement
Left Ventricular End-Systolic Diameter	mm
Left Ventricular End-Diastolic Diameter	mm
Left Atrial Diameter	mm
Left Atrial Area	cm^2
Pulmonary Artery Pressure (maximal tricuspid regurgitant pressure + estimated right atrial pressure)	mmHg
Valve data	
Mean Gradient	Aortic and mitral valve (mmHg)
Peak Gradient	Aortic valve (mmHg)
Area	Aortic and mitral valve (cm^2)
Pressure half time	Aortic and mitral valve (ms)
Area Planimetery	Mitral valve (cm^2)
Jet Area	Mitral valve (cm^2)
Valve morphology	Aortic and mitral valve
Valve abnormality	Tricuspid and pulmonary valve

In addition to enhanced baseline data collection the project will identify late (more than 30 day) complications potentially associated with valve surgery. In line with pre-surgery morbidity this will be undertaken by using jurisdiction hospital separation data linkage for all hospitalizations and the conditions outlined in Table 1 as well as with reference to the MTR [25]. Outcomes will be recorded and reported according to the *Guidelines for reporting mortality and morbidity after cardiac valve interventions* [24] with comparisons of major morbidity between mechanical and bioprosthetic valves made using MAPE [26].

Once ethics committee approval is obtained for all sites for the data collection, data will be obtained from surgeon and hospital records for the initial admission and entered onto data collection forms. Permission to access the MTR will be sought to identify all valve surgery patients (≥18 years old) who have received at least 5 units of red blood cells (RBCs) within any 4 h time period.

Analysis plan

The data collected will be analysed using multivariable, logistic and Cox proportional hazard models to identify independent factors associated with the outcome previously analysed [5, 6] and short and long term outcome. This will be undertaken using IBM SPSS Statistics 20 (IBM, New York, USA) and STATA Release 14 (StataCorp LP, Texas,

USA). Missing data will be noted and assessed for potential bias. Possible missing data could be specific echocardiographic measurements not performed, which would be missing at random and readmission occurring outside the jurisdiction, which may be not missing at random if they are patients from remote areas. Where the patient's residential address is determined to be outside the jurisdiction of the surgical site access to local hospital separation data will be sought. Echocardiographic continuous variables will be stratified as necessary for analysis, using acknowledged cut off values (e.g., mild, mod, severe). The analysis will be assessed to determine if the new data is useful for future incorporation in the national ANZSCTS database for ongoing prospective collection.

This study has been reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [27].

Discussion

The development of this multicentre, enhanced surveillance systems to collect enhanced baseline and longer term morbidity data will aim to assist in predicting outcomes and providing evidence to inform the development of guidelines to facilitate consistent practice. Added to the existing national cardiac surgery database (Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS)) these data may assist in deciding the most appropriate choice and timing of surgery.

Our analysis of the current database [6] has challenged the findings of earlier studies of surgical outcome in other settings. The finding that neither prior nor new post-operative AF was found to be an independent predictor of survival in RHD versus non-RHD valve surgery highlights the importance of considering these conditions as separate entities in the setting of valve surgery [28]. Our earlier finding that poorer preoperative clinical status, based on NYHA class, was also not independently associated with longer term survival requires further investigation with the addition of other cardiac and non-cardiac factors that influence NYHA-measured function to assess an independent effect on survival [6]. The addition of medications, echocardiography results and longer-term follow-up will also assist in strengthening the understanding regarding how pre-operative comorbidities and medication use influence outcome with the ultimate aim of enhance the timing and management of patient with advanced valvular heart disease.

Conclusion

This article summarises the methodology of a project that aims to collect and incorporate more detailed information regarding pre and postoperative factors and non-lethal outcomes at Australian sites that undertake a significant proportion of RHD and non-RHD surgery. We will use these more detailed data to provide additional insights into treatment choice, timing and outcome.

Information demonstrated to be important and relevant will be considered for future inclusion in an ongoing Australia cardiac surgery registry to assist in predicting outcomes and providing evidence to inform the development of guidelines to facilitate consistent and evidencebased practice in the surgical management of valve disease.

Such data will also be integral to informing future national and international guidelines for the management of advanced valvular heart disease including for RHD as part of the Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease [10].

Abbreviations

ACE: Angiotensin-converting enzyme inhibitors; ANZSCTS: Australian and New Zealand Society of Cardiac and Thoracic Surgeons; LVEDD: Left ventricular enddiastolic diameter; LVESD: Left ventricular endsystolic diameter; MAPE: Major adverse prosthesis-related events; MUHREC: Monash University Human Research Ethics Committee; NDI: National Death Index; PASP: Pulmonary arterial systolic pressure; RBC: Red blood cell; RHD: Rheumatic heart disease; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Availability of data and materials

The data that support the findings of this study are available from Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database, Monash Centre of Cardiovascular Research and Education in Therapeutics School of Public Health and Preventive Medicine, Monash University but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of ANZSCTS Research Committee.

Authors' contributions

EAR drafted the manuscript and will collect the data and perform the statistical analysis. AB helped with revision of the manuscript. CMR helped with revision of the manuscript and will assist with acquisition of data. WW helped with revision of the manuscript. GPM conceived of the study participated in the design of the study, helped to draft the manuscript and will assist with the statistical analysis and interpretation. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication
Permission was obtained from the ANZSCTS National Cardiac Surgery Database Program, managed by The School of Public Health and Preventive Medicine, to use and analyse the data included in the surveillance system.

Ethics approval and consent to participate
Approval to undertake this study has been provided by the Monash University Human Research Ethics Committee (MUHREC) (CF13/2737 – 2013001472), Central Adelaide Local Health Network Human Research Ethics Committee (CALHNHREC) (R20161023 HREC/16/RAH/435) and Sir Charles Gairdner Hospital Human Research Ethics Committee (SCGHHREC) (HREC Ref: 2016-165).

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Chapter 9

Discussion

This is the first detailed description of Australian RHD valve surgery and includes analyses of short and longer-term outcome, the burden and implications of preoperative atrial fibrillation and the relationship between outcome and case load. There has been limited evidence and consistency in the timing and choice of interventions for the management of advanced RHD, with management based largely on clinician preferences and experience.

We found RHD valve surgery patients were younger and more likely to be female and Indigenous Australian than non-RHD valve surgery patients. This has implications for treatment choice, particularly given the potential difficulty in ensuring safe and effective anticoagulation in association with mechanical valve replacements and its implications for future pregnancies and activities associated with an increased risk of trauma. AF was also more common in those having RHD-related compared to non-RHD-related valve surgery. Given AF is frequently, in itself, an indication for anticoagulation, RHD mitral valve surgery prior to the onset of AF would appear to provide greater therapeutic choice, as both bioprosthetic valve replacement and valve repair do not typically require ongoing anticoagulation in the absence of AF. Mechanical valves which have longer term durability providing therapeutic anticoagulation can be achieved, were preferred in younger patients irrespective of whether they were Indigenous or not.

Survival following valve surgery in the short (30 days) and longer term was equivalent in RHD and non-RHD patients and, in contrast to some earlier studies, neither short nor long term survival was significantly related to Indigenous status. Although RHD valve surgery patients, compared to those having non-RHD valve surgery, were more than twice as likely to have pre-operative AF, this was not an independent predictor of survival. It was not possible to confirm if this related to achievement of therapeutic anticoagulation as information regarding the adequacy of long-term post-operative anticoagulation was not available for this cohort. RHD valve surgery patients were however more likely, compared with non-RHD patients, to develop an anticoagulant complication, in particular bleeding complications which suggest monitoring and titration of anticoagulation, rather than medication adherence, was a more important contributor to early post-operative complications in our RHD patients.

For RHD-related mitral valve disease both short term and longer term unadjusted and adjusted survival for mitral valve repair is equivalent to mitral valve replacement. While non-RHD-related mitral valve disease repair is associated with superior unadjusted survival, this is also equivalent once controlling for covariates. Patients undergoing both RHD and non-RHD mitral repair surgery were younger and male, suggesting young male patients were referred either at a sufficiently early phase of their disease and/or to a surgical centre with a greater interest and capacity to undertake mitral valve repair reducing their need for post-operative anticoagulation.

There were more short term complications in patients with non-RHD related valve disease and preoperative AF than with RHD related valve disease and preoperative AF, although these did not include stroke. This may be due to the absence of data relating to pre-surgery anticoagulation which may alter the risk of stroke in the setting of AF associated with valvular heart disease. Only post-procedure length of hospital stay and reoperation for non-valve dysfunction were worse in patients with RHD related valve disease and preoperative AF, perhaps related to the amplifying effect of AF on other factors that contribute to outcome in valve surgery patients. Unadjusted 30-day mortality was worse in non-RHD valve disease patients with AF than without AF but not in RHD patients, although this difference did not persist when adjusted. Longer term (up to 10 years) mortality was significantly related to preoperative AF following non-RHD but not RHD-related cardiac surgery, which may have been explained by a shared association between AF and other drivers of poorer outcome, including a greater burden of hypertension and severe left ventricular dysfunction.

Increasing site and surgeon case load was associated with a longer period of ventilation (shorter for RHD-specific valve surgery patients) and more anticoagulation complications. In contrast, higher volume centres and surgeons had an associated lower need for reoperation due to non-valve indications. Adjusted 30-day survival was not related to site or surgeon case load and it was the lowest volume sites that demonstrated the best long-term survival. In the RHD-related valve disease and particularly in Indigenous Australians with RHD, there was no difference in adjusted short or long-term survival between low and high volume sites and surgeons. Long-term survival is likely to be influenced by issues associated with health care follow-up, including primary and specialist health care access and quality and the adequacy of anticoagulation and monitoring, in addition to those of the cardiac surgical unit and surgeon.

The characteristics of the catchment population and their risk of particular causes of valve disease (e.g. Indigenous Australians and RHD) should be taken into account when assessing outcomes at individual cardiac surgical sites. Whilst similarities may exist between cardiac surgical practices in high income countries, Australia also provides care to a significant group of patients with RHD including younger and often remote residing Indigenous Australians. The fact that lower volume sites had superior long-term outcomes is encouraging and is likely to reflect the importance, quality and access to ongoing primary and specialist management in such patients in Australia. While centralisation may potentially reduce cost, it does not appear to enhance outcome and may also reduce patient access, particularly in a geographically large country such as Australia.

Better understanding of long term outcomes following valve surgery will require more comprehensive follow-up of patients with incorporation of not only survival, but also cardiac and anticoagulation-related morbidity and capture of long-term health care access and quality. The development of a multicentre, enhanced surveillance system to collect short and longer term outcome data will assist in predicting outcomes and providing further evidence to inform the development of guidelines to facilitate consistent and optimal practice. Added to the existing national cardiac surgery database (Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS)) these data will provide further assistance in deciding the most appropriate choice and timing of surgery. The addition of medications, echocardiography results and monitoring of longer-term non-lethal complications will strengthen the understanding of long term outcomes beyond survival alone and it is hoped will improve patient outcomes.

Chapter 10

Conclusion

This thesis has outlined findings relating to one of the largest prospective cohort studies of patients undergoing valve surgery for RHD. Short and long term outcome data relating to 20 623 surgical procedures required for the management of patients with advanced RHD and non-RHD related valve disease were presented.

Our Australian valve surgery patients had short and long-term survival that was comparable to international cohort studies, although longer term survival in RHD patients, out to 10 years, was at the upper end of that reported in earlier studies. Survival, equivalent in RHD and non-RHD patients, was also found in studies from Malaysia and the USA. Nonetheless longer term survival reported in our study was also at the upper limit reported by studies from Brazil, Malaysia and the USA. The lack of difference between surgical type and outcome seen here was in line with earlier studies from South Korea and Taiwan. Independent predictors of longer term mortality following RHD-related valve surgery were co-existent diabetes and chronic kidney disease and length of ventilation and hospital stay following surgery. Of note being an Aboriginal Australian and/or Torres Strait Island person, pre-existing AF, a greater functional impairment as assessed by NYHA functional class and poorer pre-operative LVEF were not independently associated with outcome. Mechanical valves were more likely to be used in younger patients, but a greater use of bioprosthetic valves and valve repair, whilst having a greater risk of reoperation, may be more suitable in such patients, particularly in younger, remote and Aboriginal and Torres Strait Islander peoples. Whilst we demonstrated that those having bioprosthetic valve replacements had poorer long term survival, this was possibly related to factors for which we have not assessed or controlled.

Survival following RHD mitral valve repair surgery in Australia was demonstrated to be equivalent to replacement surgery in line with some but not all earlier studies. Unadjusted survival for non-RHD valve disease out to five years appeared superior to replacement, but this did not persist when adjusting for other factors associated with early mortality. Whether mitral repair compared with replacement is associated with a difference in non-lethal complications including long term morbidity, health care utilisation and cost should remain a priority for future research.

AF is a common arrhythmia in RHD and non-RHD patients requiring valve surgery and patients with valve disease and preoperative AF were found to carry a higher burden of comorbidities. Whilst adjusted 30-day survival was no different in patients with AF, short term complications were greater especially in those with non-RHD related valve disease.

Adjusted long term survival was inferior in patients with non-RHD valve disease and AF but not RHD-related disease in general or for Indigenous Australian with RHD specifically.

Earlier intervention (prior to the onset of AF) or more aggressive management of AF to facilitate reversion to sinus rhythm should be investigated as mechanisms for enhancing postoperative outcomes in non-RHD valve surgery patients. In addition greater understanding of the differential effect of AF in RHD and non-RHD surgical outcome may identify further targets for intervention.

Short-term survival following valve surgery in Australia was not related to site or surgeon case load. We did not demonstrate the same associations between site case load and short term outcome as have been seen in some American studies where short-term outcomes were superior in larger volume centres. Nonetheless our findings support those from Britain where there was no significant association found between site or surgeon case load for in-hospital deaths after cardiac surgery in general. In this Australian study, long-term survival appeared to be superior in lower volume sites and surgeons. This suggests long-term outcome may be more related to the broader community-based health care environment to which patients return or that higher volume sites may be faced with a potential diseconomy of scale particularly for surgeons who undertake the highest average annual number of valve surgical procedures. Our study is one of few to examine long-term survival and the population catchment of cardiac surgical centres in other high income settings such as the UK and USA vary markedly compared with Australia's large geographic area and relatively small population associated with relatively small case loads. Whether our findings would be replicated in sites with far larger case loads than those seen in Australia remains to be seen. Nonetheless our findings have clear relevance to surgical practice in Australia and other countries with similar geography and health service structures. Mandating a particular site case load level for valve surgery or a minimum number of procedures for individual surgeons in Australia cannot be supported by these findings either overall or for RHD specifically.

The methodology of a future project that aims to collect and incorporate more detailed information regarding pre and postoperative factors at four Australian sites that undertake a

significant proportion of RHD and non-RHD surgery completes this project. Information demonstrated to be important and relevant has been included in this ANZSCTS Database enhanced surveillance module to assist in predicting outcomes and providing evidence to inform the development of national and international guidelines to facilitate consistent and evidence-based practice in the management of RHD. These more detailed data will be used to provide additional insights into treatment choice, timing and outcome and be used to inform on-going development of existing jurisdictional ARF/RHD register and recall systems.

This project began with the ambitious aim of attempting to reduce the health disparity between Aboriginal and Torres Strait Islander peoples and non-Indigenous Australians and facilitating 'Closing the Gap' in life expectancy. It intended to do this by informing the on-going development of rational and evidence-based recommendations for the management of advanced RHD in Aboriginal and Torres Strait Islander peoples that reflect the realities of patients' lives, especially those resident in remote Australia. Existing national guidelines for RHD management acknowledge that outcomes may be affected by timing of referral for intervention, treatment choice, prosthetic valve type, need and adequacy of monitoring of anticoagulation therapy and access to ongoing specialist follow-up and echocardiography monitoring. Nonetheless existing evidence regarding the relative role of factors that are important in determining such timing of treatment and treatment choice remained limited.

The studies and papers presented in this thesis provide an important addition to existing knowledge in this area. It is now possible to better identify those patients who are at risk of complications and poorer survival and to accordingly counsel them and their families prior to surgery. In addition, reassurance has been provided regarding the comparable outcome following valve surgery in Indigenous versus non-Indigenous Australians and in mitral valve replacement in comparison with repair. Important differences between RHD and non-RHD valve disease including the far greater burden of AF in the former provides a tantalising focus for future research to better understand both the underlying pathophysiology and management of this condition as it relates specifically to RHD. Finally, while there have been a number of position statements and advocacy to develop national centres for RHD management specifically and valve surgery more generally, it has been demonstrated there is little evidence in Australia to support such an approach.

The findings from this project will not only inform the management and health service response to RHD in Australia. This is a global health issue whose impact is felt most in low and middle-income countries. The evidence we have been so fortunate to summarise in

Australia, thanks to a well-developed surgical registry, will also provide the opportunity to inform advanced RHD management in other settings including in our region of Oceania and in other populations faced with similar social and environmental factors and an increased burden of RHD.

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