A Propensity Score Matched Analysis of Long-term Mortality Outcomes in Patients Aged 50 to 70 Years After Isolated Mechanical Versus Bioprosthetic Aortic Valve Replacement in Newfoundland and Labrador

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A thesis submitted to the School of Graduate Studies in partial fulfillment of the

requirements for the degree of Master of Science in Medicine

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October 2020

St. John's, Newfoundland and Labrador

Abstract

OBJECTIVE: Compare long-term mortality of patients after mechanical versus bioprosthetic aortic valve replacement in Newfoundland and Labrador

METHODS: Retrospective cohort analysis of patients aged 50 to 70 years who underwent aortic valve replacement in Newfoundland and Labrador between 2006 and 2014. A logistic regression propensity score generated a subset of 52 matched patients. The long-term outcome of survival was assessed.

RESULTS: Of 189 patients included, 135 (71%) received mechanical valves, while 54 (29%) received bioprosthetic valves. The mean age in the matched group was 63 (mechanical) and 64 years (bioprosthetic) (P = 0.64). Mean follow-up was 8.1 (maximum 13.8) years. Survival at 30 days, 1, 5, and 10 years was: 100%, 96%, 85%, and 81% (mechanical) versus 100%, 96%, 89%, and 67% (bioprosthetic). The hazard ratio for mortality between mechanical and bioprosthetic valves was 0.64 (95% CI 0.18-2.3, P = 0.491). Secondary outcomes revealed that the most common cause of death to be cardiovascular in etiology (39%), followed by malignancies (27%).

CONCLUSIONS: We found no statistically significant difference in long-term survival in patients aged 50 to 70 years after mechanical versus bioprosthetic aortic valve replacement.

Lay Summary

The aortic valve is one of four valves in the heart and is subject to several diseases that can significantly impact one's life, including causing death. The most common of these diseases of the aortic valve is aortic stenosis - where the valve becomes partially blocked. To address this, surgeons can remove a patient's valve and replace it with a new one in a procedure called aortic valve replacement. There are two general types of valves that surgeons can use: mechanical and bioprosthetic valves. We set out to determine which valve type was associated with longer survival after aortic valve replacement. We included patients from Newfoundland and Labrador, and those who were between 50 and 70 years of age. We found that there was no statistically significant difference in long-term survival between mechanical and bioprosthetic aortic valve replacement. We also highlighted a potential increase in congenital heart disease as a cause for aortic valve disease in NL. The most common cause of death was cardiovascular. These results agree with other published studies and are beneficial in the planning and delivery of future heart surgeries in Newfoundland and Labrador based on our patient population.

Acknowledgements

I would like to thank my two co-supervisors, Dr. Kathleen Hodgkinson and Dr. Corey Adams, for providing the opportunity and motivation to take on this thesis, and for their ongoing support and guidance throughout all aspects of my Masters. Despite moving to another province and starting a new job, Dr. Adams continued to remain devoted, as the content expert, towards aiding me to complete this thesis while also providing frequent in-depth and insightful comments. I would also like to thank my committee member, Dr. Sean Connors, who provided excellent support and practical advice throughout this project. Finally, I would like to acknowledge the Heart and Stroke Foundation for their support through a scholarship associated with this project.

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List of Abbreviations and Symbols

ACC	American College of Cardiology
AHA	American Heart Association
AF	Atrial Fibrillation
APPROACH	Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease
AR	Aortic Regurgitation
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
CABG	Coronary Artery Bypass Grafting
CCS	Canadian Cardiovascular Society
CI	Confidence Interval
CVA	Cerebrovascular Accident
CVICU	Cardiovascular Intensive Care Unit
DOAC	Direct Oral Anticoagulant
DVT	Deep vein thrombosis
ESC	European Society of Cardiology
ESRD	End-stage renal disease
HF	Heart failure
HR	Hazard Ratio
HREB	Health Research Ethics Board
IE	Infective Endocarditis
INR	International Normalized Ratio
LOS	Length of stay
LVEF	Left ventricular ejection fraction
mmHg	Millimeters of mercury
NB	New Brunswick
NL	Newfoundland and Labrador
NLCHI	Newfoundland and Labrador Centre for Health Information
NS	Nova Scotia
PPM	Permanent pacemaker
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation
SJM	St. Jude Medical
SVD	Structural Valve Deterioration
TAVI	Transcatheter Aortic Valve Implantation
TIA	Transient Ischemic Attack
VTE	Venous Thromboembolism

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Chapter 1: Background

1.1 Aortic Valve Pathologies

The aortic valve is one of four valves in the normal human heart and divides the heart from the rest of the body. As such it is the last structure that blood travels through before leaving the heart. Its function is to ensure antegrade flow of blood away from the left ventricle towards the systemic circulatory system. It normally has three cusps that open and close in unison in response to changes in blood pressure in the left ventricular outflow tract and the aorta. The aortic valve is subject to a number of pathologies, this most common etiologies being: aortic stenosis (AS), aortic regurgitation (AR), and infective endocarditis (IE) [1]. Importantly, these pathologies often co-exist and may result in significant morbidity and mortality for patients.

Among adults, there are three principle etiologies of AS: degenerative calcification of a normal trileaflet valve, calcification of a congenitally bicuspid or unicuspid aortic valve, and rheumatic aortic valve disease [1, 2]. Although rheumatic aortic valve disease is often considered the most common cause of AS worldwide, it is uncommon in North America and Europe [2]. Aortic valve disease in North America and Europe is most commonly due to calcification of a native trileaflet valve or congenitally bicuspid valve. The prevalence of AS increases with age [3]. The prevalence among adults aged 70 to 79 years is approximately 3.9 percent, and becomes 9.8 percent at ages 80 to 89 years. Bicuspid aortic valves are thought to be present in 1 to 2 percent of the

population with men affected more commonly than women [1]. Patients with AS due to calcification of a bicuspid aortic valve tend to become symptomatic approximately one decade earlier than the degenerative type of AS. The natural history of AS involves a prolonged asymptomatic period. Adults tend to become symptomatic once the stenosis is considered severe as defined by an aortic valve area of less than or equal to 1.0 centimeters squared, a jet velocity of 4 meters per second or more, and a mean transvalvular gradient of 40 or more millimeters of mercury (mmHg). The signs and symptoms of AS are non-specific and commonly include angina, syncope, heart failure, and atrial fibrillation (AF). Upon the onset of these symptoms there is a marked increase in mortality as shown in Figure 1.1. Sudden cardiac death has also been a recognized complication of AS and is of particular concern. Sudden death in patients with AS who are asymptomatic occurs at a rate of less than 1% per year [85]. The incidence of sudden death among patients with symptomatic AS is markedly increased with some reports of a mortality of 26% at one year after symptom onset [86].

AR is usually the result of pathology of the aortic valve leaflets themselves (e.g. valvular AR) or secondary to dilatation of the aortic root around the aortic valve.. There are three principle etiologies of valvular AR: bicuspid aortic valve, IE, and rheumatic aortic valve disease [1, 4, 5]. AR as a result of aortic root dilatation occurs when the aortic annulus dilates to the point that there is separation of the leaflets. AR can present as either an acute or chronic process and often results in heart failure, conferring significant morbidity and mortality.

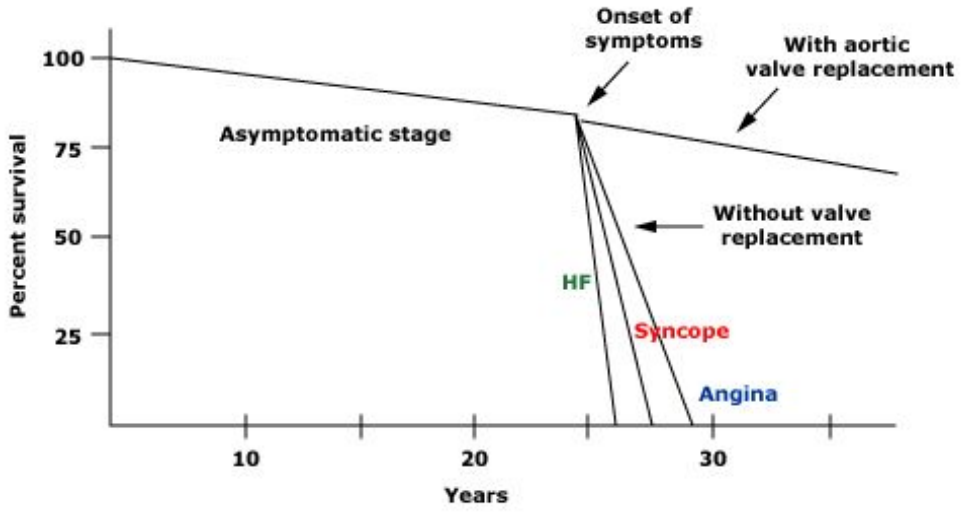


Figure 1.1: The natural history of aortic stenosis [2] Copyright UpToDate 2020 - used with permission.

Symptomatic AS and AR account for the most commonly diagnosed valvular heart diseases in adults and are associated with increased morbidity and mortality if they remain untreated [6]. There is a need to address these pathologies. Medical treatments exist for complications of AS and AR such as heart failure. However, surgical interventions are required to address the underlying pathologies and have become the standard of care for severe, symptomatic AS and AR [7]. Surgical aortic valve replacement (SAVR) significantly improves survival, symptoms, and quality of life [1-4].

It is expected that demand for aortic valve interventions will increase in the future. In a 2019 published randomized controlled trial, Duk-Hyun Kang et al. demonstrated that patients with asymptomatic severe AS who underwent aortic valve interventions had improved mortality outcomes when compared to usual care [8]. Further, it has been noted that 30% to 40% of patients with severe AS or AR are deemed

to be unsuitable for SAVR due to their comorbidities and high predicted surgical mortality [6, 9]. Many of these patients are considered elderly and frail [10]. As the interventions mature and operator-experience increases, it is expected that patients previously considered too high risk may become candidates for surgical intervention [11]. These recent advancements suggest that aortic valve interventions may become more prevalent in the future with a broader set of patients becoming candidates for AVR. With the potential for increasing demand on aortic valve interventions, and their demonstrated benefit, there is a need for improved understanding of the relative benefits and disadvantages of the various aortic valve replacement (AVR) options available to patients.

1.2 History of Aortic Valve Replacement

1.2.1 Development of Mechanical Valves

The development of prosthetic valves for human valve replacement began in the 1950's and culminated with the first successful AVR in 1960 by Dwight Harken [12]. This initial valve employed a "double-caged ball" design and was implanted in five patients of which one patient survived the perioperative period leading the innovators of this intervention to conclude that aortic valve pathologies are "beyond surgical correction". Despite the poor outcomes of this initial case series, interest in this procedure grew and a further 117 AVRs were performed between 1961 and 1964 [13]. The first study evaluating the characteristics and outcomes of a cohort of AVR patients was

published in 1965 [13]. This study commented that there were "uniformly unfavourable results" after aortic valve repair, and heralded the era of prosthetic AVR after outlining the superiority with a ball-valve prosthesis despite high operative mortality [14]. By the late 1960's improved mechanical valve designs emerged using a tilting-disc prosthesis. The Björk-Shiley valve was designed with a central disk rotating on an axis and was the first valve of this design to be widely implanted [15]. Due to excessive thromboembolism, this design was eventually terminated [15]. These initial efforts to develop an effective aortic valve prosthesis identified five major problems with mechanical valves: hemodynamic performance, safety and durability, thromboembolism, prosthesis-induced hemolysis, and IE [16]. Nicoloff et al. recognized dissatisfaction with existing prostheses at that time and developed the bileaflet St. Jude Medical (SJM) prosthesis [16]. Nicoloff and his team implanted the first SJM prosthesis in October 1977 and presented encouraging results in 1981 after completing 22 surgical AVR (SAVR) procedures [16]. The SJM prosthesis became the most widely used aortic valve prosthesis by the end of the 1980s [17].

1.2.2 Development of Bioprosthetic Valves

Interest in bioprosthetic designs existed after promising results in animal studies [18]. Donald Ross performed the first AVR using a bioprosthetic design in July 1962, and by 1969 he reviewed outcomes after his group inserted more than 350 such valves [18, 19]. At these early stages the advantages of bioprosthetic valves were identified including

the ability to implant valves that more closely matched normal human aortic valve design and hemodynamics. Further benefits of bioprosthetic valves that Ross identified included a reduction in thromboembolic complications, hemolysis, and IE [19]. The disadvantages noted were of a more complicated surgical procedure, and valve failure and degeneration. These initial bioprosthetic valves used cadaveric homografts which were difficult to collect and preserve [14]. Subsequent generations of bioprosthetic valves used xenografts - valves collected from animals. The first successful AVR with a xenograft was carried out in September 1965 [20]. These xenografts were examined after the initial implantations and were found to suffer from degeneration and immunological incompatibility [21]. Efforts were made to develop methods of preparing porcine valves while preventing inflammatory reactions in the human body [22]. Carpentier introduced the use of glutaraldehyde to make the tissue immunologically inactive thus preserving the xenografts and improving their durability - a chemical still used today [21]. In 1971 Marian Ionescu created and implanted an aortic valve using bovine pericardium attached to a support frame [23]. Production of this "Ionescu-Shiley Pericardial Xenograft" began in 1976 and has since undergone several modifications. As bioprosthetic valves gained wider use the issue of patient-prosthesis mismatch became clear [24]. It was recognized that there was a reduction in effective orifice size after SAVR with these first and second generation valve prostheses, which was associated with increased mortality and structural valve deterioration (SVD) [24].

1.2.3 Beyond Mechanical and Bioprosthetic Valves

Due to limitations with bioprosthetic and mechanical valves cardiothoracic surgeons explored innovative options to address aortic valve pathologies beyond implantation of an isolated aortic valve. A unique approach involved the creation of a new left ventricular outflow tract. This aorto-apical conduit was first implanted in humans in 1963 by Templeton [25]. After the initial success in the 1960's this procedure became more widely adopted in the 1970s and 1980s and a high incidence of prosthesis dysfunction became clear leading to the procedure becoming mostly discontinued [26]. In 1962 Donald Ross proposed the Ross Procedure whereby a pathological aortic valve is replaced with the patients pulmonary valve, and bioprosthetic pulmonary prosthesis was implanted [19]. He and Magdi Yacoub first carried out this procedure in 1967. Advantages of the procedure included a reduction in thromboembolism and the ability of the valve to grow with the patient; however, it addressed a single-valve pathology by disrupting two valves leading to increased long-term difficulties. This procedure has remained popular among children, but remains limited in use for adults [27]. Stentless valves were then introduced in 1988 [28] and became popular in the following decade due to their reduced size and improved hemodynamics [14]. These stentless valves were used in complete root replacement surgeries. Long-term studies of these stentless valves failed to find an improvement in survival and noted a significant increase in SVD after a medium period of time [29, 30]. Due to their smaller size, stentless valves allowed for the next generation of sutureless design which remain in trials today.

1.2.4 Minimally Invasive Approaches

An alternative minimally-invasive approach to AVR was introduced in 1996 by Delos Cosgrove. This technique avoided the need for a full median sternotomy and central cardiopulmonary bypass and allowed for intervention in the more frail and elderly populations [10]. Current techniques for minimally invasive SAVR include upper hemi-sternotomy and right anterior thoracotomy that is video assisted. Improved catheter-based technology led to the advent of transcatheter aortic valve implantation (TAVI). The first such procedure was carried out in 2002 by Cribier and utilized a balloon-expandable stent with 3 bovine pericardial leaflets [31]. This successful percutaneously implanted aortic valve led to the further evolution of bioprosthetic valves and the development of various delivery designs. In 2005, Paniagua et al, reported the first TAVI implanted through a retrograde approach [32]. Following these two initial case reports Cribier et al. reported on 36 patients who were deemed to not be candidates for SAVR and underwent TAVI [33, 34]. They concluded that this intervention was feasible and led to hemodynamic and clinical improvement. TAVI has matured since these initial experiences and has transformed the management of severe aortic stenosis [11]. Several issues have been identified with the TAVI approach including vascular complications such as cerebrovascular accidents (CVAs), atrioventricular conduction block, and paravalvular leakage. A major advantage of TAVI is the opportunity to provide AVR for the 30-40% of patients with severe, symptomatic AS who otherwise are deemed

unsuitable for surgical interventions due to their comorbidities and high predicted surgical mortality [35]. The current generation of TAVI have resulted in significant improvements in the aforementioned issues, and this technique is becoming first line treatment for many patients with AS that require a bioprosthetic valve.

1.2.5 The Influence of Valve-in-Valve Procedures

As TAVI becomes mainstream for patients with AS, the question of durability remains. Younger patients, those less than 70 years of age, who have a TAVI are at risk of the valve undergoing SVD. Therefore, they may require a sternotomy to allow for explant of the valve. However, more recently, TAVI provides an unconventional opportunity through "valve-in-valve" procedures to avoid the need for redo SAVR. The first such procedure was described by Peter Wenaweser in 2007 and demonstrated feasibility and success of the approach [36]. Several case series and registries of valve-in-valve procedures have since been published [37-40]. These valve-in-valve procedures address the major disadvantage of bioprosthetic SAVR by providing an opportunity to safely manage SVD. The advent of valve-in-valve TAVI has the opportunity to transform the indications of mechanical versus bioprosthetic SAVR - long-term results of valve-in-valve TAVI will eventually shed light on and influence future trends in AVR. However, there is anecdotal evidence that some surgeons are no longer implanting mechanical valves in younger patients given the presumed impact of life-long anticoagulation and the potential benefit of a TAVI valve-in-valve procedure.

This novel procedure is attractive as a less invasive option for patients; however, it is not without risk as it carries a high perioperative mortality [82, 83], among other safety concerns [84]. Due to the design and method of implantation there are risks of serious consequences such as obstruction of the coronary arteries, compression of the cardiac conduction system, malposition or migration of the valve, high post-procedural gradients across the new valve, and vascular complications at the access site (usually the femoral artery). Overall, there have been continuous advancements in the development of both mechanical, and bioprosthetic valves; and our understanding of their relative advantages and limitations. Nowadays, conventional, minimally invasive, and catheter-based approaches are performed internationally, with ever-improving clinical results. Consequently, AVR is the mainstay of treatment for severe AS and AR [41, 42]. Conventional surgeries continue to be the gold-standard approach [43], whereas minimally invasive approaches are reserved for patients with high surgical risk.

1.3 Relative Advantages and Disadvantages of Mechanical and Bioprosthetic Valves

AVR remains the only effective treatment option for AS and AR. Despite significant technological advances over the decades, the procedure continues to be associated with significant risks of morbidity in patients who receive these operations. AVR is largely divided into two surgical options: mechanical and bioprosthetic prostheses. Recommendations for which valve design to use are based upon known differences in the natural history and associated complications of these valves.

The major risks associated with mechanical valves relate to the materials being used. The metallic components result in high shear stress on blood flow that damages cells and proteins in the blood. This can activate coagulation pathways and results in increased thromboembolic events [1]. Patients who receive mechanical valves require lifelong anticoagulation - usually with warfarin - which itself introduces morbidity [1, 41, 42]. Although appropriate use of anticoagulation reduces the risk of thromboembolism, it can be difficult to maintain the international normalized ratio (INR) within the targeted 2.0-3.0 for mechanical aortic valves [41]. The long-term use of anticoagulation introduces the risk of spontaneous and trauma-related bleeding and is a major contributor to morbidity and mortality after SAVR [88]. Reported rates of bleeding with warfarin depend on known risk factors for bleeding including age and comorbidities. Rates of bleeding in patients anticoagulated with warfarin for mechanical valves have been reported to be as high as 22.2% per patient-year [89]. The majority of these bleeding events are considered minor. In recent studies, the incidence of major bleeding events has varied from 0.34% to 1.4% per patient-year [89-92]. The major advantage of a mechanical valve is that SVD is rare, reducing the need for reoperation. There are non-structural causes of deterioration in mechanical valves including pannus growth, endocarditis, and valve thrombosis but these complications rarely result in need for reoperation [44].

Bioprosthetic valves, on the other hand, are generally produced with bovine or equine pericardium or from porcine aortic valves. These bioprosthetic valves are associated with a higher risk of reoperation because of SVD from wear-and-tear [23, 24, 45]. Well recognized risk factors for SVD include young patient age, renal failure, abnormal calcium metabolism, and patient-prosthesis mismatch [93, 94]. Accelerated SVD in younger patients are thought to be related to increased immunological response and calcification of the prosthetic valve as compared to elderly patients [46-48]. The average lifespan of a bioprosthetic AVR has been reported to range from 10 to 15 years [23, 24, 45] upon which there is a need for reoperation. Traditionally, reoperation involved a second sternotomy and exposed the patient to the associated morbidity and mortality. More recently, valve-in-valve TAVI has addressed this shortcoming and offers an alternative treatment option in patients who suffer SVD. Naturally, elderly patients have a shorter life expectancy than younger patients, and are thus at reduced risk of suffering the complications of a deteriorated bioprosthetic valve. Risk of non-SVD also exists in bioprosthetic valves, as in mechanical valves. However, it tends to be equally low to that of mechanical prostheses.

A particular risk with both bioprosthetic and mechanical valves is the risk of prosthetic valve endocarditis. Although the prevalence of endocarditis is similar among both valve types, it can be a devastating complication often requiring prolonged use of broad-spectrum antibiotics and the need for reoperation [106]. Prosthetic valve

endocarditis occurs in approximately 1 to 6% of all patients with valve prostheses, with an annual incidence of 0.3 to 1.2% [107].

1.4 Short and Long-term Survival After Aortic Valve Replacement

Historically severe AS and AR were associated with a poor prognosis. With the onset of symptoms in severe AS the prognosis ranges from 2 to 5 years without intervention, as seen in Figure 1.1. Intervention with AVR on severe AS has been shown by numerous studies to improve survival [49-51]. As early as 1982, patients with severe AS were found to have significantly improved survival compared to matched patients that went unoperated [95]. This improved survival has also been demonstrated in patients with low-gradient AS and severe left ventricular dysfunction [96-98]. Importantly, patients undergoing AVR have reduced survival compared with an age- and gender-matched general population, including among younger patients [99].

The influence of valve-type on survival is less clear, particularly in the 50 to 70 years age range. A meta-analysis of three randomized clinical trials published in 2000 by Kassai et al. found that the valve-type does not significantly influence long-term survival [52]. A subsequent systematic review of 4 randomized controlled trials published in 2018 by Kiyose et al. reevaluated the long-term mortality outcomes after bioprosthetic and mechanical prostheses [53]. They too found no statistically significant difference in the rate of mortality after bioprosthetic and mechanical valves. The relative risk of mortality between bioprosthetic and mechanical SAVR was 1.07 (95% CI 0.99-1.15). They did

note, however, that most of the confidence intervals (CIs) favoured mechanical valves. The relative risk of mortality with bioprosthetic versus mechanical valves reported in this systematic review was 1.07 with a 95% CI of 0.99 to 1.15. A number of more recent prospective studies have evaluated the long-term mortality outcomes after AVR and are discussed in Chapter 2.

Short-term mortality outcomes are generally reported at 30 days post-operatively. Two recent studies reported on short-term mortality after AVR using population-based nationwide databases. The first of these by Dunning et al included 41,227 patients after AVR in Great Britain and Ireland and found an overall short-term mortality of 4.1% [54]. Bioprosthetic valves were associated with a 4.5% short-term mortality, which was not significantly higher than that of mechanical valves. This short-term mortality increased to 8.1% for patients over the age of 80 years. A study by Goldstone et al. in 2017 looked at 9,942 patients in a Californian state registry [55]. They reported no significant difference in mortality at 30 days. The rates of 30-day mortality were 2.4% (bioprosthetic) versus 1.6% (mechanical) for patients aged 45 to 54 years, and 1.6% (bioprosthetic) versus 1.7% (mechanical) for patients aged 55 to 64 years. The p-values associated with these comparisons were 0.15, and 0.93, respectively.

Based on these and other studies, the European Society of Cardiology (ESC) guidelines for the management of valvular heart disease published in 2017 stated that

there are no significant differences in survival between mechanical and bioprosthetic prostheses [56].

1.5 International Guidelines

Both the ESC and the American Heart Association (AHA) and American College of Cardiology (ACC) have produced guidelines to summarize and evaluate available evidence with the intent to provide recommendations to healthcare professionals managing valvular heart disease. The most recent ESC guidelines on valvular heart disease were published in 2017 [56], while the latest AHA/ACC guidelines are from 2014 with a focused update in 2017 [41, 42].

1.5.1 Indications for Intervention

Both the ESC and AHA/ACC agree in their recommendations that aortic valve interventions should be performed in centres with both departments of cardiology and cardiac surgery on site and with structured collaboration between the two, including a Heart Team. The choice of intervention must be based on careful individual evaluation of technical suitability and with consideration to the risks and benefits of each modality. Overall, SAVR is recommended in patients at low surgical risk, while TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team. In patients who are at increased surgical risk, the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics, with TAVI being favoured in elderly patients suitable for transfemoral access. Both

organizations recommend that intervention should not be performed in patients with severe comorbidities when the intervention is unlikely to improve quality of life or survival. On the other hand, SAVR is indicated in patients with severe AS if they are undergoing sternotomy for another purpose, and this can be considered if the patient has moderate AS.

The ACC/AHA and ESC strongly recommend that all symptomatic patients with severe AS undergo early intervention due to the associated poor prognosis. The only exception to this being patients with severe comorbidities that otherwise carry a less than one year survival. The decision to intervene becomes more complicated if there is low-gradient AS (i.e. a mean gradient of <40 mmHg). In patients with a low-gradient, intervention is indicated if there is a reduced ejection fraction and pseudosevere AS is excluded. Similarly, intervention is indicated if CT calcium scoring confirms the presence of severe AS. The ESC also makes recommendations on when to intervene for asymptomatic patients with severe AS. Indications include when systolic left ventricular dysfunction is present and not due to another cause, when the patient has an abnormal exercise test showing symptoms or a drop in blood pressure related to AS.

1.5.2 Choice of Intervention

Aspects to be considered when deciding between SAVR and TAVI in patients at increased surgical risk are complicated and currently in flux. The latest guidelines are

outlined in the corresponding ESC, AHA/ACC, and Canadian Cardiovascular Society (CCS) guidelines [41, 42, 56, 57].

Upon the decision to proceed with SAVR, the next major decision is between opting for a mechanical or bioprosthetic prosthesis. Every valve prosthesis is associated with its own challenges. Mechanical valves are associated with higher rates of bleeding, while bioprosthetic valves have higher rates of reintervention as discussed in Chapter 1.3. Ultimately, the decision is a shared-decision between the informed patient and their Heart Team.

A mechanical prosthesis is recommended by the ESC if the patient is at risk of accelerated SVD such as from hyperparathyroidism, or if they are already on long-term anticoagulation (Grade 2A). A mechanical aortic valve prosthesis is recommended in patients less than 60 years of age (Grade 2A). However, a bioprosthetic valve is recommended if life-long anticoagulation is contra-indicated, if there is a low likelihood of future redo valve surgery, and if the patient is greater than 65 years of age (Grade 2A). Both valve types are considered acceptable options in the 60 to 65 years age range. These age ranges differ markedly from the 2017 AHA/ACC updated recommendations. They recommend AVR with a mechanical prosthesis in patients less than 50 years of age who do not have a contraindication to anticoagulation (Grade 2A). Whereas a bioprosthetic valve is considered reasonable in patients more than 70 years of age (Grade 2A). Both options are considered acceptable in patients between 50 and 70 years of age (Grade 2A).

Notably, the AHA/ACC made an update to their recommendations for the 50 to 70 year age group between 2014 and 2017. Previously, in 2014, they considered both mechanical and bioprosthetic valves reasonable options for patients aged 60 to 70. Their 2017 focused update expanded this range to 50 to 70 years, reflecting increasing use of bioprosthetic AVR in younger patients.

1.5.3 Choice of Intervention in Special Populations

It is well recognized that patients who use recreational intravenous drugs are at increased risk of IE and may develop associated valvular complications necessitating intervention. The Infectious Diseases Society of America (IDSA) has published guidelines addressing IE in this patient population [100]. For patients with IE who undergo valve surgery, they recommend an individualized choice of prosthesis by the surgeon (Grade 2A), and recommend avoidance of surgery when possible (Grade 2A). IE in this patient population predominantly affects right-sided valves (i.e. tricuspid and pulmonary valves). There are no recommendations specifically for IE of the aortic valve. Notably, IE of the left-side of the heart is associated with a severe clinical presentation and often requires surgery with an active infection [101]. A major difficulty in this patient population is that they have a high recurrence rate of IE. Thus the choice of prosthetic valve type must take into account the usual patient factors plus the known risk of re-infection. Generally, intravenous drug users (IVDU) tend to be younger and would otherwise benefit from mechanical valve prosthesis. Rates of endocarditis recurrence tend

to be similar among mechanical and bioprosthetic valves as was shown in a recent large retrospective study [102]. These results support the IDSA guidelines recommending an individualized choice for prosthetic valve type in this patient population.

End-stage renal disease (ESRD) is a known risk factor for the development of AS as discussed in Chapter 1.1. Choice of mechanical versus bioprosthetic AVR is complicated in patients with ESRD. In general, these patients have a poorer prognosis at baseline [103]. Further, ESRD is a well recognized risk factor for bleeding and an etiology of abnormal calcium metabolism. As a result, some surgeons prefer to implant bioprosthetic valves in patients with ESRD to avoid the need for lifelong anticoagulation [104]. While other surgeons prefer to implant mechanical valves to avoid the risk of SVD related to abnormal calcium metabolism [104]. A recent study from Japan that retrospectively evaluated outcomes after AVR in dialysis patients observed that most patients received mechanical valves, regardless of their age [105]. They concluded that assessing overall operative risk of a dialysis patient is more important than the actual choice of valve prosthesis. The guidelines do not specifically address this patient population, and there are no randomized controlled trials to guide decision making. Ultimately, the choice of valve prosthesis in patients with ESRD is a shared-decision between the patient and surgeon and must take into account the additional risks in this population.

1.6 Trends in Mechanical and Bioprosthetic Valve Use

Despite the recommendations of the AHA/ACC and ESC, the use of bioprosthetic valves has steadily increased in recent decades in North America and Europe [54, 55, 58, 59]. Dunning et al. noted marked increases in the annual volume of AVR and those receiving bioprosthetic valves increased from 65% to 78% after analyzing 41,227 AVR operations in Great Britain and Ireland between 2004 and 2009 [54]. Notably, there was a 7% increase from 18% to 25% in the use of bioprosthetic AVR in patients under 55 years. Other population-based studies have also noted increasing use of bioprosthetic over mechanical valves, with a trend towards increased use in younger patients. Goldstone et al. noted a substantial increase in the use of bioprosthetic prostheses from 12% to 52% from 1996 to 2013 in California [55]. Other studies from the Netherlands and Sweden national databases also showed an increase in bioprosthetic valve use, including among younger patients [60, 61]. The increasing use of bioprosthetic valves in younger patients has been challenged [45, 54, 55]. Stuart Head notes that it is well recognized that SVD is accelerated in younger patients, and remarks that life expectancy trends are increasing worldwide - potentially exposing patients who receive bioprosthetic valves to unnecessary risk of reoperation [45].

The reasons for increased use of bioprosthetic valves have been discussed [62]. Applegate et al. noted that current literature indicates that most patients who undergo bioprosthetic AVR do not have a reoperation [62]. They note that the average

life-expectancy after AVR is 12 years. Since most bioprosthetic valves are free from deterioration in that time frame, patients are expected to die from other etiologies before their valves degenerate. Ultimately, implantation of a mechanical versus bioprosthetic valve is a shared-decision between the patient and surgeon. Surgeons have noted that patients are increasingly wary of the life-long anticoagulation required with mechanical valves [54] and therefore opt for bioprosthetic AVR, even at younger ages. The advent of valve-in-valve TAVI and other novel procedures adds a new dimension to the decision of implanting a bioprosthetic valve in a younger patient.

Another explanation for the increasing use of bioprosthetic valves is related to the natural history of their degeneration. SVD is rarely an acute process, whereas the complications associated with mechanical valves - including hemorrhage - are often an acute emergency with guarded prognosis. Similarly, the negative impact of mechanical prostheses on the livelihoods of young active patients is significant [62].

There are developments that may favour the future use of mechanical or bioprosthetic valves. Lifelong anticoagulation with mechanical valves is widely recognized as their major disadvantage. The use of non-vitamin K antagonist anticoagulation with mechanical valves has been explored. Most notably, the RE-ALIGN trial evaluated the use of dabigatran - a direct oral anticoagulant (DOAC) - compared to warfarin in patients with mechanical prostheses. They noted that patients receiving dabigatran had more thromboembolic events and bleeding as compared to warfarin [63].

Despite this initial setback, others have studied the opportunity to target lower INR targets in mechanical valves with promising results [64, 65]. Future studies may further shed light on the extent to which INR targets can be reduced in an effort to reduce bleeding complications while also preventing thromboembolism. Home monitoring systems to better regulate daily INR levels are becoming more widely used, allowing for improved quality of life for patients who have received mechanical valves. Concurrently, there is interest in developing mechanical valves using materials that are less thrombogenic [64, 66]. The potential benefits of these modern designs is yet to be established. Although bioprosthetic valves have benefited from not requiring lifelong anticoagulation, the guidelines do recommend low-dose aspirin for the first 3 months after bioprosthetic SAVR, aspirin monotherapy after TAVI [57], and state that consideration can be made for oral anticoagulation for the first 3 months post-operatively (particularly if post-operative AF is documented) [56]. Recent investigators have analyzed the incidence of bioprosthetic valve thrombosis [67]. Two recent studies have demonstrated improved outcomes with lifelong warfarin [68, 69]. These studies are currently interpreted with caution, particularly because the Danish study [69] showed a reduction in the rate of bleeding associated with warfarin use - a counterintuitive conclusion. Historically, patients who already had an indication for anticoagulation with warfarin (i.e. AF, VTE) received mechanical valves. However, with the advent of DOAC's this is being reconsidered and may partially explain increasing use of bioprosthetic valves [70].

1.7 Recent Literature Assessing Long-term Mortality After AVR

Five studies were critically appraised that all analyzed long-term mortality outcomes in patients between 50 and 70 years of age after mechanical versus bioprosthetic AVR. An in-depth appraisal of these publications can be found in Appendices A through C. A summary of these fives studies can be found in Tables 1.1 and 1.2. Four of the five publications reported no discernable difference in long-term mortality outcomes between the valve types as shown in Table 1.2. While, a study from Sweden reported significantly less mortality with mechanical AVR in this age group. However, limitations in the generalizability of their findings was a consistent issue as discussed in the Appendices.

Table 1.1: Summary of five studies appraised

Study author	Year published	Years included	Patient ages (years)	# of patients (# matched)	Hospital/Region included
McClure et al.	2014	1992 - 2001	<65	1701 (722)	Brigham and Women's hospital, Boston
Chiang et al.	2014	1997 - 2004	50 - 69	4253 (2002)	New York State (all hospitals)
Glaser et al.	2015	1997 - 2013	50 - 69	4545 (2198)	Sweden (all hospitals)
Goldstone et al.	2017	1996 - 2013	All; stratified: 45 - 54, and 55 - 64	9942 (N/A)	California (all hospitals)
Caulo et al.	2019	2000 - 2015	50 - 65	1443 (763)	Andalusia, Spain (7 hospitals)

Table 1.2: Summary of primary outcome results and conclusions of five studies appraised

Study	Follow-up time: mean (max)	Long-term survival (bioprosthetic)	Long-term survival (mechanical)	Significance of difference in long-term survival, P-value	Conclusions
McClure et al.	8 (18) years	60% at 18 years	51% at 18 years	0.75	Choice of valve type does not affect survival in patients <65 years
Chiang et al.	10.8 (16.9) years	61% at 15 years	62% at 15 years	0.74	Either valve type reasonable in patients aged 50 to 69 years
Glaser et al.	7.3 (17.2) years	50% at 15 years	59% at 15 years	0.006	Improved survival after mechanical AVR in patients 50 to 69 years
Goldstone et al.	5 - 8.2 (not defined) years	69% at 15 years	74% at 15 years	0.03	Improved survival after mechanical AVR in patients 45 to 54 years
		64% at 15 years	68% at 15 years	0.60	Either valve type reasonable in patients aged 55 to 64 years
Caulo et al.	8.1 (17) years	73% at 15 years	76% at 15 years	0.159	Either valve type reasonable in patients older than 55 years

1.8 Aortic Valve Replacement in Newfoundland and Labrador

All cardiovascular surgeries in the province of Newfoundland and Labrador (NL) are performed at the Health Sciences Centre in St. John's. There is limited published literature reflecting the epidemiology of these surgeries.

Hassan et al. summarized use of valve surgery in Canada from 1994 to 2000 in a publication to the Canadian Journal of Cardiology in 2004 [71]. They reported on age- and sex-adjusted rates of valve surgery per 100,000 people. In NL the rate of SAVR was 6.5 per 100,000 from 1994 to 2000. This was the lowest rate among all 10 provinces in

Canada. More recently, in 2018, McGuire et al reported on regional differences in AVR in Atlantic Canada [87]. Age- and sex-adjusted rates of AVR increased in NL during their study period (2010 to 2014), peaking at 26.4 per 100 000 in 2014. This incidence rate was significantly lower than Nova Scotia (peak of 48.8/100 000) and NB (peak of 38.6/100 000). NL was found to have the highest proportional use of mechanical valves in isolated SAVR (49.0%), as compared to Nova Scotia (2.5%) and New Brunswick (15.8%). Although the reasons for these marked differences were unclear, it is noted that they "*represent variations in practice that are unique to the philosophy and interpretation of the evidence by the clinician group practising at each institution*". The authors speculate that observed differences "*suggest potentially important differences in access, practice patterns and/or patient characteristics*".

Similar to other regions, the decision to proceed with SAVR and the type of prosthetic valve to implant (e.g. bioprosthetic or mechanical) was made by the local cardiovascular heart team. This team consists of local cardiologists, cardiovascular surgeons, intensivists and corresponding allied health and meets on a weekly basis to review individual patient charts. After a discussion of the patient's anatomy, comorbidities and other aspects a joint decision is made regarding the optimal procedure to undertake.

There is no formally published data available for the TAVI program in NL; however, some details of the program were available to the authors of this thesis through

unpublished data and discussion with individuals involved. The program started in 2016 and performs approximately 20 procedures per year. Prior to 2016, approximately 5 to 10 patients were transferred out-of-province for TAVI starting in 2014. The TAVI program in NL is likely to evolve over time and has the potential to change SAVR practices in the province, particularly when considering the possibilities of valve-in-valve procedures with TAVI, as outlined in Chapter 1.2.5.

Based on the limited literature evaluating the epidemiology of AVR in Newfoundland and Labrador there is evidence that cardiovascular surgery practices in NL do not mirror that of other regions in Canada. As a result, it is not clear whether the outcomes observed in other regions necessarily apply to the intervention and population of NL.

1.9 Study Question

Considering the updated guidelines, the trend towards increased use of bioprosthetic valves in younger patients, and unique aspects of the patient population undergoing AVR in NL the following clinical question was established.

In patients between 50 to 70 years of age receiving AVR in NL, are there differences in long-term mortality between those patients who receive mechanical compared to bioprosthetic valve replacements?

1.9.1 Hypothesis

Hypothesis: Mechanical valves result in improved mortality outcomes as compared to bioprosthetic valves in patients aged 50 to 70 years who undergo AVR.

Null Hypothesis: There is no difference in mortality outcomes after mechanical versus bioprosthetic AVR in patients aged 50 to 70 years.

1.9.2 Secondary Outcomes

Several secondary clinical objectives will be addressed beyond the primary outcome of interest of long-term survival as outlined below.

- Describe the population undergoing AVR in NL, including their ages, preoperative comorbidities, and etiology of aortic valve pathology - including rates of congenital bicuspid aortic valve disease
- Perform a secondary assessment of survival differences in an age-stratified sub-group of patients aged 61 to 70 years
- Describe the intraoperative and postoperative characteristics including: frequency of each mechanical and bioprosthetic valve type, cardiopulmonary bypass and cross clamp times, and postoperative complications prior to discharge from hospital
- Determine the duration of follow-up and etiology of death of patients included

Chapter 2: Methods

2.1 Sample Size Calculation

The sample size calculation for survival analysis is based on a study design with a power of at least 85% (i.e. $\beta = 0.15$), a significance level of 0.05 (i.e. $\alpha = 0.05$), and to detect a between-group HR of 1.15 for analysis of mortality at 5 years. It is assumed that the proportion of patients in each treatment group will be equal (i.e. $\boldsymbol{\pi}_1$ and $\boldsymbol{\pi}_2$ equal 0.5). These assumptions are consistent with the literature in this field [6-10]. The survival analysis follows the log-rank test to test the null hypothesis of no difference between implantation of a mechanical or bioprosthetic valve. The required number of events follows the equation:

$$events = \frac{(z_{\alpha/2}+z_{\beta})^2}{\pi_1\pi_2(logHR)^2} = \frac{(1.96+1.04)^2}{0.5*0.5*(log1.15)^2} = 1843$$

The number of patients (i.e. sample size, n) required to achieve 1843 events follows the equation:

$$n = \frac{events}{Pr\{event\}} \text{ , where } Pr\{event\} = 1 - [\pi_1 S_1(T) + \pi_2 S_2(T)]$$

Assuming exponential survival times, we can calculate $S_1(T)$ and $S_2(T)$ using the following equation:

$$S_1(T) = S_2(T) = e^{-\lambda t}$$

$S_1(T)$ and $S_2(T)$ are functions of survival time for the mechanical and bioprosthetic groups, respectively. These can be assumed to be equal based on the null

hypothesis that both interventions are equal. Note that this calculation of event probability ignores patients lost to follow-up. Accounting for patients lost to follow-up would require a higher sample size.

Based on recent studies in this field, it is expected that approximately 70% of patients will survive at the 5-year period [6-10]. Thus,

$S(T) = e^{-0.3} = 0.741$, where 0.3 is the 5-year mortality rate.

$Pr\{event\} = 1 - [\pi_1 S_1(T) + \pi_2 S_2(T)] = 1 - [0.5 * 0.741 + 0.5 * 0.741] = 0.259$

$n = \frac{events}{Pr\{event\}} = \frac{1843}{0.259} = 7116$

Based on the above calculations, the sample size needed to detect a HR of 1.15, with an alpha of 0.05 and power of 85% is 7116 patients at 5-year follow-up. Repeating the calculations at 15-year follow-up, assuming a survival of 60%, yields a sample size of 5590. This sample size was not achieved in any of the studies appraised in Chapter 2, and unrealistic in an exclusively NL population. Thus, it was not anticipated that there would be a statistically significant difference in mortality outcomes between patients who received mechanical versus bioprosthetic AVR. The primary intention is to determine and present the outcomes of patients in NL, and compare these results with those of other regions while providing information to assist in the planning and delivery of future cardiovascular practices in NL based on our patient population.

2.2 Study Design and Population

We analyzed data from patients who underwent isolated AVR in NL between 2006 and 2014 to evaluate long-term survival. The Health Research Ethics Board and the Newfoundland and Labrador Centre for Health Information (NLCHI) approved the study protocol in June 2018 and November 2019, respectively. Data was acquired through a prospectively collected database (Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease - APPROACH) and individualized chart-reviews.

Patients were included in the study if they were 50 to 70 years of age and had undergone isolated AVR in NL between 2006 and 2014. Exclusion criteria included out-of-province residency, concomitant coronary artery bypass grafting, other valve replacement or repair, and thoracic aortic surgery.

Unless therapeutic anticoagulation was indicated for another reason (e.g. AF, VTE), patients who received a bioprosthetic AVR were managed with 3 months of aspirin post-operatively. Some patients who had documented postoperative AF were anticoagulated with warfarin for 3 months. Whereas patients who received a mechanical valve were anticoagulated with lifelong warfarin. The target INR with warfarin was between 2.0 and 3.0, as per the corresponding AHA/ACC guidelines. The decision to implant a bioprosthetic or mechanical valve was a shared-decision between the patient and the Heart Team at the time of surgery.

2.3 Data Collection

Patient characteristics, laboratory values, and in-hospital outcomes were collected in the prospectively-managed APPROACH database. Variables not available in the APPROACH database were collected retrospectively through individualized chart-reviews and from discharge summaries from the hospital admission associated with the index surgery. Cause and date of death were obtained from the APPROACH database which is linked to the Statistics Canada database responsible for tracking mortality statistics across Canada. This data was cross-checked through individualized chart reviews and no discrepancies on date of death were found. All charts were reviewed during a two-week time period in late March 2020. Complete follow-up was achieved, aside from one patient from St. Pierre and Miquelon who was operated on in St. John's.

2.4 Outcomes

The primary outcome was all-cause mortality. This was measured in days and counted from the date of the index surgery until the date of death or the last documented encounter with the healthcare system (such as last blood work, imaging or clinic note). Related secondary outcomes calculated include: perioperative mortality (≤30 days after surgery), and death at 1, 5 and 10 years. Further, etiology of death will be determined through individualized chart reviews and from death certificates if available in the chart. Etiology of death was divided into one of five categories: cardiovascular, malignancy,

bleeding, unknown causes, and other. Sudden, unexplained death was considered a cardiovascular related event.

A number of secondary outcomes related to procedural and post-operative complications will be evaluated. There are several designs of mechanical and bioprosthetic valves and selection was made by the operating surgeon. The type of mechanical and bioprosthetic valve implanted will be presented. Intraoperative statistics including cardiopulmonary bypass and cross clamp times will be analyzed. Postoperative complications including deep vein thrombosis (DVT), CVA, bleeding, AF, HF, delirium, re-exploratory sternotomy, need for permanent pacemaker (PPM) implantation, and length of stay (LOS) will all be presented and compared between the mechanical and bioprosthetic valve cohorts. AF was defined as any occurrence of rapid AF lasting longer than one hour and requiring intervention with either cardioversion or additional medications beyond the patient's preoperative medications. CVA includes both stroke and TIA's as documented in the chart.

2.5 Statistical Analysis

Patient baseline characteristics are presented as mean and standard deviations for continuous variables, while categorical variables are presented as frequencies and percentages. Differences between patients receiving mechanical or bioprosthetic valves were evaluated through the Student's t-test for continuous variables and Pearson's chi-squared test for categorical variables.

To adjust for confounding variables between groups in terms of baseline preoperative characteristics, propensity score matching was performed. A logistic regression was applied to all baseline characteristics in Table 3.1 to create a propensity score model. The primary outcome of interest was all-cause mortality. The predictive model produced by the logistic regression was robust, with an area under the receiver operator characteristic curve of 0.836. A nearest neighbour matching algorithm, without replacement, was performed with a ratio of 1:1 using a maximum calibration of 0.2 (standard deviation) of the logistic regression-based propensity scores. The mechanical valve cohort was the reference intervention in all analyses. Analyses were performed on the entire group and the propensity score matched group. Age-stratification was also carried out to further analyze and determine survival outcomes of patients aged 61 to 70 years.

The crude incidence of mortality at 10 years was calculated with 95% CIs. Cumulative survival was calculated and displayed using the Kaplan-Meier method. These were computed for the actuarial, propensity score matched, and age-stratified groups. A Cox proportional hazards regression model was used to estimate the risk of all-cause mortality according to type of prosthesis. This was expressed as a HR with 95% CIs. A forward stepwise regression analysis was conducted for the independent variables seen in Table 4.1. Any variable that had a significant effect on the outcome in the cox proportional hazards model based on a $P \leq 0.15$ was entered into the final model. The

final model consisted of 8 variables: age, sex, diabetes, hypertension, CVA, pulmonary disease, dialysis, and LVEF, and valve type.

All tests were 2-tailed, and an alpha level of 0.05 was considered statistically significant. Data management and statistical analyses were performed using SPSS Statistics V26 for MacOS (IBM Corp, Armonk, NY, USA) and the R Software environment version 3.6.3 for MacOS (R Foundation, Vienna, Austria).

Chapter 3: Results

3.1 Study Population

A total of 1035 patients received AVR in NL between 2006 and 2014. Of these, 528 were between the ages of 50 to 70 years. After further inclusion and exclusion criteria were applied, a total of 189 patients remained and were included in the study as shown in Figure 3.1. Of these 189 patients, 135 (71%) received mechanical valves and 54 (29%) received bioprosthetic valves. The total number of surgeries completed per year ranged from 8 (2006) to 31 (2011), as seen in Figure 3.2. There was a trend towards increased use of bioprosthetic valves observed throughout the study period. Patients who received bioprosthetic valves tended to be older as shown in Figure 3.3. The mean age of the cohort who received mechanical valves was 59.2 ± 5 (range 50 to 70) years and for the bioprosthetic group was 65.7 ± 4 (range 50 to 70) years ($P < 0.001$). The mode of the ages in each cohort were 62 (mechanical) and 67 (bioprosthetic). The mean and maximum follow-up times were 8.1 ± 3.1 and 13.8 years for both cohorts, 8.4 ± 3.2 and 13.8 years for the mechanical valve cohort, and 7.2 ± 2.8 and 13.2 years for the bioprosthetic valve cohort.

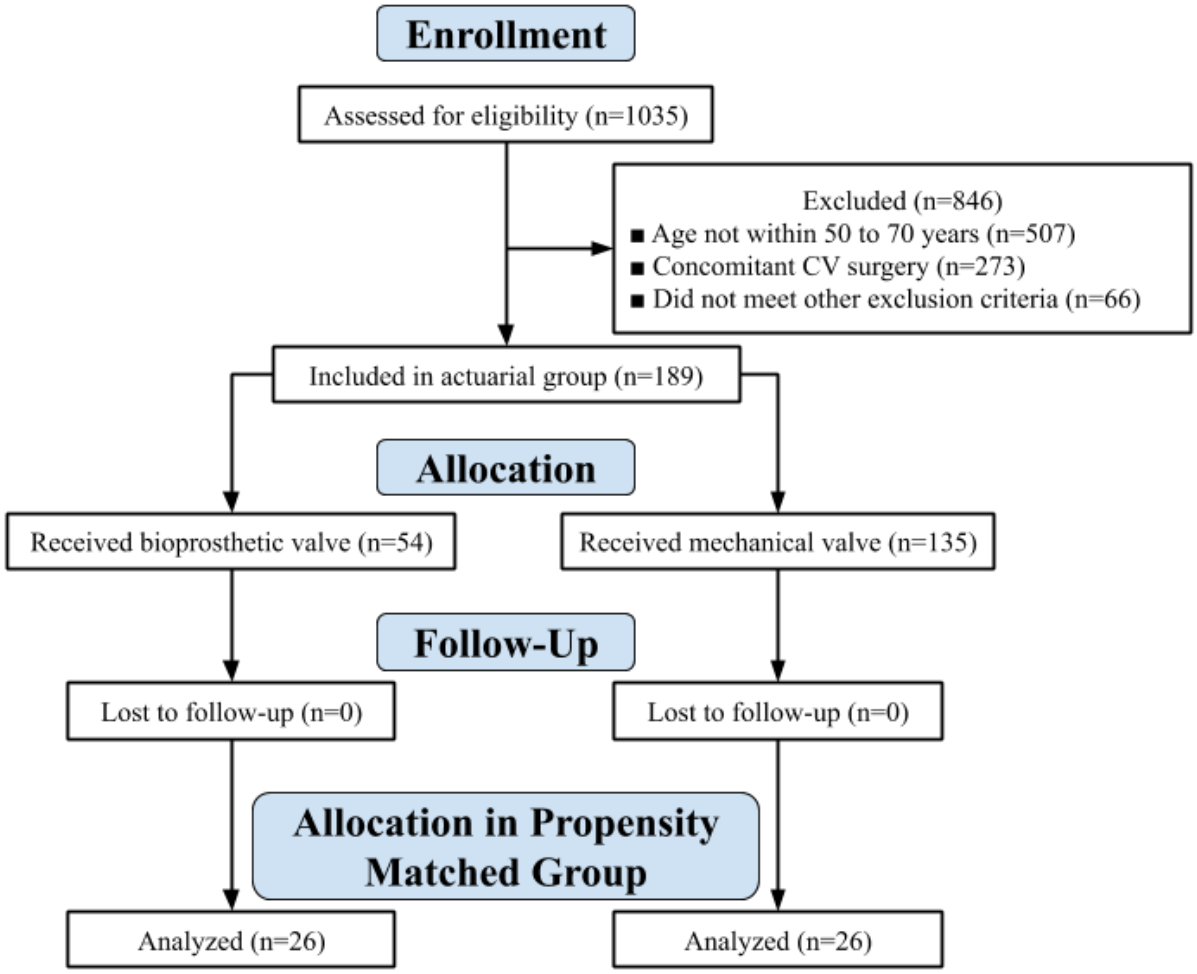


Figure 3.1: CONSORT Flow Diagram of Patients Included in Study

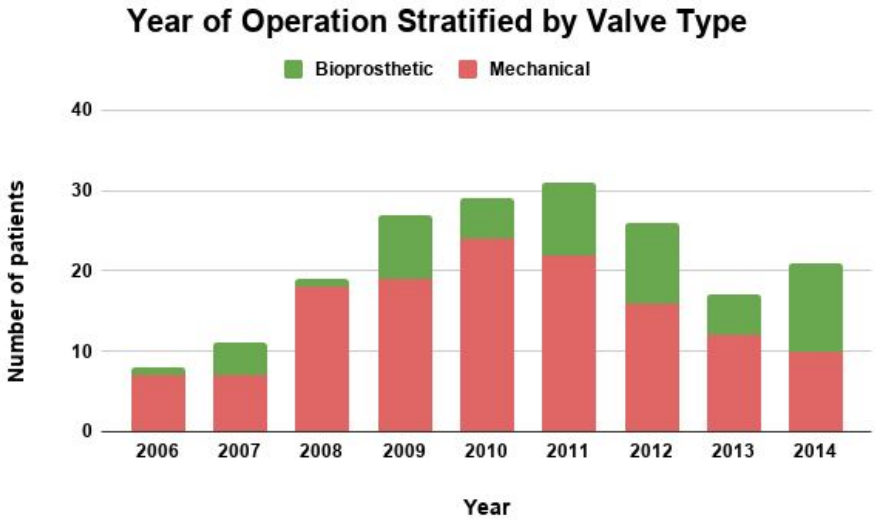


Figure 3.2: Number of patients who underwent isolated AVR with mechanical (red) and bioprosthetic (green) valves in NL from 2006 to 2014

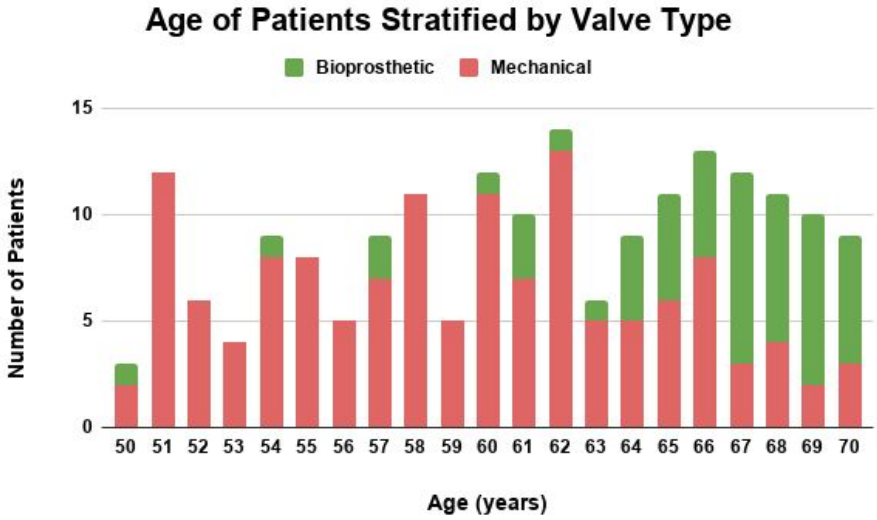


Figure 3.3: Ages of patients who underwent AVR with mechanical (red) and bioprosthetic (green) valves

3.2 Patient Baseline Characteristics

The baseline characteristics in the actuarial cohort are shown in Table 3.1. Other than the variable of age, there were no statistically significant differences in the baseline

characteristics between the two cohorts. After propensity score matching there were no statistically significant differences in age and all other baseline characteristics, as shown in Table 3.2. As discussed in Chapter 2, all variables listed in Table 3.1 were used in the development of the logistic regression model.

Table 3.1: Baseline characteristics in the overall cohort

	All patients (n = 189)	Mechanical prosthesis (n = 135)	Bioprosthetic prosthesis (n = 54)	p-value
Age, years (SD)	61.0 (5.8)	59.2 (5.3)	65.7 (4.2)	<0.001
Female sex	53 (28%)	40 (30%)	13 (24%)	0.434
Comorbidities				
Diabetes mellitus	50 (26%)	38 (28%)	12 (22%)	0.393
Atrial fibrillation	5 (2%)	4 (3%)	1 (2%)	0.639
Hypertension	130 (69%)	91 (67%)	39 (72%)	0.515
Dyslipidemia	141 (75%)	101 (75%)	40 (74%)	0.917
History of TIA/stroke	16 (8%)	11 (8%)	5 (9%)	0.819
Peripheral vascular disease	9 (5%)	4 (3%)	5 (9%)	0.142
Pulmonary disease	42 (22%)	29 (21%)	13 (24%)	0.706
Coronary artery disease				
Prior MI	11 (6%)	8 (6%)	3 (6%)	0.922
Prior PCI	7 (4%)	4 (3%)	3 (6%)	0.457
Alcoholism	3 (2%)	1 (1%)	2 (4%)	0.146
Liver disease	4 (2%)	3 (2%)	1 (2%)	0.869
Cancer	2 (1%)	0 (0%)	2 (4%)	0.159
On hemodialysis	3 (2%)	3 (2%)	0 (0%)	0.083
Perioperative creatinine, umol/L (SD)	92.9 (37.6)	92.1 (40.7)	95.0 (28.4)	0.575
Heart failure	26 (14%)	15 (11%)	11 (20%)	0.137
LVEF, % (SD)	59.8 (10.2)	60.1 (10.2)	59.0 (10.1)	0.531
Infective endocarditis	5 (2%)	2 (1%)	3 (6%)	0.224

Table 3.2: Baseline characteristics after propensity score matching

	All patients (n = 52)	Mechanical prosthesis (n = 26)	Bioprosthetic prosthesis (n = 26)	p-value
Age, years (SD)	63.3 (4.7)	63.0 (4.6)	63.7 (4.8)	0.642
Female sex	13 (25%)	5 (19%)	8 (31%)	0.347
Comorbidities				
Diabetes mellitus	13 (25%)	7 (27%)	6 (23%)	0.755
Atrial fibrillation	3 (6%)	2 (8%)	1 (4%)	0.561
Hypertension	34 (65%)	16 (62%)	18 (69%)	0.569
Dyslipidemia	34 (65%)	17 (65%)	17 (65%)	1
History of TIA/stroke	4 (8%)	2 (8%)	2 (8%)	1
Peripheral vascular disease	4 (8%)	2 (8%)	2 (8%)	1
Pulmonary disease	7 (13%)	4 (15%)	3 (12%)	0.692
Coronary artery disease				
Prior MI	5 (10%)	2 (8%)	3 (12%)	0.646
Prior PCI	1 (2%)	0 (0%)	1 (4%)	0.327
Alcoholism	1 (2%)	1 (4%)	0 (0%)	0.327
Liver disease	0 (0%)	0 (0%)	0 (0%)	N/A
On hemodialysis	0 (0%)	0 (0%)	0 (0%)	N/A
Perioperative creatinine, umol/L (SD)	95.2 (26.5)	92.4 (18.8)	98.0 (32.6)	0.455
Heart failure	9 (17%)	4 (15%)	5 (19%)	0.720
LVEF, % (SD)	59.1 (11.4)	61.1 (10.8)	57.0 (11.8)	0.204
Infective endocarditis	1 (2%)	0 (0%)	1 (4%)	0.327

As shown in Figure 3.7, of the patients who received bioprosthetic valves, the only mortality events occurred in patients between the ages of 61 and 70. This observation prompted an age-stratified sub-analysis of patients aged 61 to 70 years. Of the 189 patients analyzed in the actuarial group, 105 (56%) were aged 61 to 70. The baseline characteristics of this subset of patients are shown in Table 3.3. Patients who received mechanical prosthesis tended to be younger (mean, 64.4 ± 2.7 vs. 66.7 ± 2.5

years, P = 0.009). All other baseline characteristics were balanced between the two cohorts in this age-stratified sub-analysis.

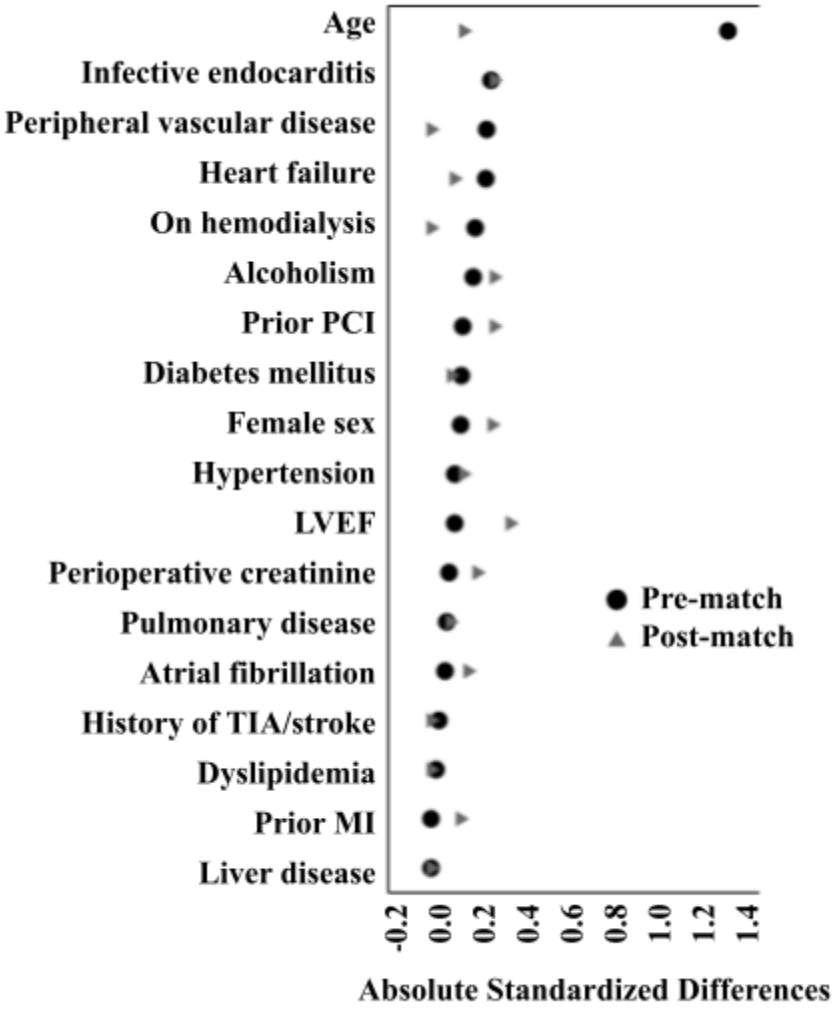


Figure 3.4: Absolute standardized differences between the covariates pre and post propensity matching

Table 3.3: Baseline characteristics of all patients aged 61 to 70 years

	Patients Aged 61-70 (n = 105)	Mechanical prosthesis (n = 56)	Bioprosthetic prosthesis (n = 49)	p-value
Age, years (SD)	65.5 (2.8)	64.4 (2.7)	66.7 (2.5)	0.009
Female sex	29 (28%)	16 (29%)	13 (27%)	0.817
Comorbidities				
Diabetes mellitus	33 (31%)	21 (38%)	12 (24%)	0.152
Atrial fibrillation	5 (5%)	4 (7%)	1 (2%)	0.209
Hypertension	77 (73%)	39 (70%)	38 (78%)	0.362
Dyslipidemia	78 (74%)	40 (71%)	38 (78%)	0.476
History of TIA/stroke	12 (11%)	7 (13%)	5 (10%)	0.714
Peripheral vascular disease	9 (9%)	4 (7%)	5 (10%)	0.585
Pulmonary disease	23 (22%)	10 (18%)	13 (27%)	0.293
Coronary artery disease				
Prior MI	8 (8%)	5 (9%)	3 (6%)	0.589
Prior PCI	7 (7%)	4 (7%)	3 (6%)	0.836
Alcoholism	2 (2%)	0 (0%)	2 (4%)	0.103
Liver disease	3 (3%)	2 (4%)	1 (2%)	0.637
Cancer	2 (2%)	0 (0%)	2 (4%)	0.159
On hemodialysis	3 (3%)	3 (5%)	0 (0%)	0.083
Perioperative creatinine, umol/L (SD)	98.7 (46.0)	102.6 (56.9)	94.3 (29.2)	0.342
Heart failure	24 (23%)	13 (23%)	11 (22%)	0.927
LVEF, % (SD)	58.2 (11.3)	57.9 (12.0)	58.5 (10.5)	0.793
Infective endocarditis	2 (2%)	1 (2%)	1 (2%)	0.925

The etiology of underlying aortic valve pathology was most commonly calcific aortic disease (65%), followed by congenital bicuspid aortic stenosis (20%), as shown in Table 3.4. Of all patients who underwent AVR, 85% had severe AS on preoperative echocardiogram, while 16% had severe AI. There were no statistically significant differences in etiology of aortic valve pathology between the mechanical and bioprosthetic valve cohorts.

Two patients in this study period had redo AVR for a previously implanted valve. One was a St. Jude Mechanical (SJM) valve implanted in 1992 and required debridement in 2005 for leaflet dysfunction resulting from pannus formation. This patient then went on to have redo AVR in 2009, due to further pannus growth, with a bioprosthetic AVR. The other patient had a bioprosthetic valve implanted in 2006 (with concomitant CABG) that underwent SVD. This patient had significant comorbidities including prior liver transplantation, immunosuppressive therapy with cyclosporine, and ESRD requiring intermittent hemodialysis. This patient went on to have redo AVR with a mechanical valve in August 2010.

Table 3.4: Etiology of underlying aortic valve pathology

	All patients (n = 189)	Mechanical prosthesis (n = 135)	Bioprosthetic prosthesis (n = 54)	p-value
Severe AS	160 (85%)	119 (88%)	41 (76%)	0.064
Calcific	123 (65%)	86 (64%)	37 (69%)	0.529
Congenital	38 (20%)	32 (24%)	6 (11%)	0.028
Severe AI	30 (16%)	18 (13%)	12 (22%)	0.170
Unknown	11 (6%)	7 (5%)	4 (7%)	0.587
Dilated	5 (3%)	4 (3%)	1 (2%)	0.639
Rheumatic	3 (2%)	2 (1%)	1 (2%)	0.862
Endocarditis	5 (3%)	2 (1%)	3 (6%)	0.224
Prolapse - Posterior	1 (1%)	1 (1%)	0 (0%)	0.319
Prosthetic Valve Dysfunction	2 (1%)	1 (1%)	1 (2%)	0.579
Myxomatous Degeneration	1 (1%)	0 (0%)	1 (2%)	0.322

3.3 Procedural Characteristics and Post-operative Complications

All patients in the mechanical and bioprosthetic valve cohorts underwent full sternotomy with standard cardiopulmonary bypass techniques. During the study period a

total of six cardiovascular surgeons performed all cases. The frequency of each mechanical and bioprosthetic valve design implanted is shown in Tables 3.5 and 3.6. As discussed in Chapter 2.2, patients who received concomitant cardiovascular surgeries, including CABG, were excluded from this study. Intra-operative cardiopulmonary bypass and cross clamp times are shown in Table 3.7. There were no statistically significant differences in cross clamp or cardiopulmonary bypass times when comparing the mechanical valve cohort versus the bioprosthetic valve cohorts.

Table 3.5: Frequency of use of each mechanical valve type

Mechanical Valve Type	Frequency (n = 135)
SJM Heart Valve	60 (44%)
CarboMedics Mech	42 (31%)
CarboMed TopHat-SA	17 (13%)
SJM Masters Series	9 (7%)
SJM Regent Valve	6 (4%)
Björk-Shil Monostrut	1 (1%)

Table 3.6: Frequency of use of each bioprosthetic valve type

Bioprosthetic Valve Type	Frequency (n = 54)
CE/EL Pericardial Magna	43 (80%)
CE/EL Peri-mount/cardial	6 (11%)
SJM Trifecta	3 (6%)
SJM-Bioimplant Porcine	2 (4%)

Table 3.7: Intraoperative cardiopulmonary bypass and cross clamp times

	All patients (n = 189)	Mechanical prosthesis (n = 135)	Bioprosthetic prosthesis (n = 54)	p-value
Cardiopulmonary bypass time (mins)	125.3 (31.6)	125.4 (32.0)	124.9 (31.0)	0.928
Cross clamp time (mins)	91.0 (19.4)	91.2 (19.8)	90.5 (18.5)	0.820

All patients were monitored in the CVICU immediately after surgery and then transferred to the cardiovascular ward and eventual discharge from hospital. Post-operative complications, rates of PPM implantation, and LOS after the index surgery are listed in Table 3.8. There were no statistically significant differences in the post-operative complications between the mechanical and bioprosthetic cohorts.

Table 3.8: Postoperative complications and length of stay

	All patients (n = 189)	Mechanical prosthesis (n = 135)	Bioprosthetic prosthesis (n = 54)	p-value
Post-op DVT	3 (2%)	3 (2%)	0 (0%)	0.083
Post-op AF	53 (28%)	36 (19%)	17 (31%)	0.519
Post-op delirium	22 (12%)	16 (8%)	6 (11%)	0.886
Post-op PPM	7 (4%)	6 (3%)	1 (2%)	0.315
Post-op CVA	5 (3%)	1 (1%)	4 (7%)	0.075
Post-op bleeding	18 (10%)	15 (8%)	3 (6%)	0.184
Post-op HF	10 (5%)	9 (5%)	1 (2%)	0.092
Re-exploratory sternotomy	6 (3%)	5 (3%)	1 (2%)	0.454
Post-op LOS	6	7	6	0.398

3.4 Survival

No statistically significant difference in long-term survival was observed in the propensity score matched group between the mechanical and bioprosthetic valve cohorts (P = 0.491) at a mean follow-up of 8.1 ± 3.1 years. Figures 3.4, 3.5, and 3.6 display the Kaplan-Meier survival curves for the following groups: actuarial, propensity score

matched, and patients aged 61 to 70 years, respectively. The HR for mortality for mechanical versus bioprosthetic valves in the actuarial group was 1.35 (95% CI 0.61-3.00, P = 0.46). The HR for mortality for mechanical versus bioprosthetic valves in the propensity score matched group was 0.638 (95% CI 0.18-2.3, P = 0.491. The HR for mortality for mechanical versus bioprosthetic valves in the patients aged 61 to 70 years was 1.321 (95% CI 0.576-3.03, P = 0.511). There were 30 deaths in the actuarial mechanical group and 14 in the bioprosthetic group during a maximum follow-up of 13.8 years. The actuarial 30-day perioperative mortality was 2% and 0% for the mechanical and bioprosthetic cohorts, respectively. Actuarial 10-year survival was 80% in the mechanical group compared to 66% in the bioprosthetic group, as shown in Table 3.9. Survival at various time-points in the propensity matched group is shown in Table 3.10.

A total of 44 deaths were observed in this study after long-term follow-up. Of 135 patients in the mechanical cohort, there were 30 (22%) mortality events. In the 54 patients who received bioprosthetic valves, there were 14 (26%) mortality events. The age at time of index surgery, of all patients who had an observed mortality event is shown in Figure 3.7. All of the mortality events observed in the bioprosthetic group occurred in patients who were in the 61 to 70 year age range at the time of index surgery.

The etiology of deaths were similar across the two cohorts. The most common cause of death was cardiovascular, followed by malignancy accounting for 39% and 27% of all deaths observed, as shown in Table 3.11. Cardiovascular etiologies accounted for

47% and 21% of observed deaths in the mechanical and bioprosthetic cohorts, respectively. This difference may be influenced by the 16% of deaths where an etiology was not determined. A history of DM (P = 0.009), hypertension (P = 0.002) and pulmonary disease (P = 0.018) were measured comorbidities observed to have a statistically significant influence on the outcome of survival based on the logistic regression.

Three patients in this study were on hemodialysis prior to SAVR. Each received a mechanical valve. None of these patients were included in the propensity-matched sub-analysis as they had no neighbours in the bioprosthetic cohort that were within the pre-defined calibration (0.2 SD's) of the logistic regression-based propensity scores. All three patients suffered mortality during the study period. The first died at 1 year post-operatively due to heart failure, the second passed two days post-operatively, and the third passed within two years of the operation due to heart failure.

Five patients received SAVR due to complications of infective endocarditis. Two received mechanical valves and three received bioprosthetic valves. None of these patients had an observed mortality event. The patients in the mechanical cohort survived a minimum of 9.7, and 10.0 years. While those in the bioprosthetic group survived a minimum of 4.9, 5.7, and 11.0 years.

The freedom from SVD, prosthetic-valve endocarditis and prosthetic-valve thrombosis requiring redo AVR or TAVI was 100% for all 189 patients included in this study. The two patients discussed in Chapter 3.2 who had redo AVR for a previously implanted AVR had observed mortality events at 8.9 and 1.1 years.

Table 3.9: Survival at various time-points, stratified by valve type, in the actuarial group

	Actuarial group	
	Mechanical (n=135)	Bioprosthetic (n=54)
30-day	97.8% (95.3 - 100)	98.1% (94.6 - 100)
1 year	95.6% (92.1 - 99.1)	98.1% (94.6 - 100)
5 years	88.9% (83.7 - 94.4)	83.2% (73.8 - 93.9)
10 years	79.7% (72.5 - 87.6)	65.9% (51.3 - 84.7)

Table 3.10: Survival at various time-points, stratified by valve type, in the propensity matched group

	Propensity matched group	
	Mechanical (n=26)	Bioprosthetic (n=26)
30-day	100%	100%
1 year	96.2% (89.0 - 100)	96.2% (89.0 - 100)
5 years	84.6% (71.8 - 99.7)	88.5% (77.0 - 100)
10 years	80.6% (66.7 - 97.4)	67.2% (46.2 - 97.7)

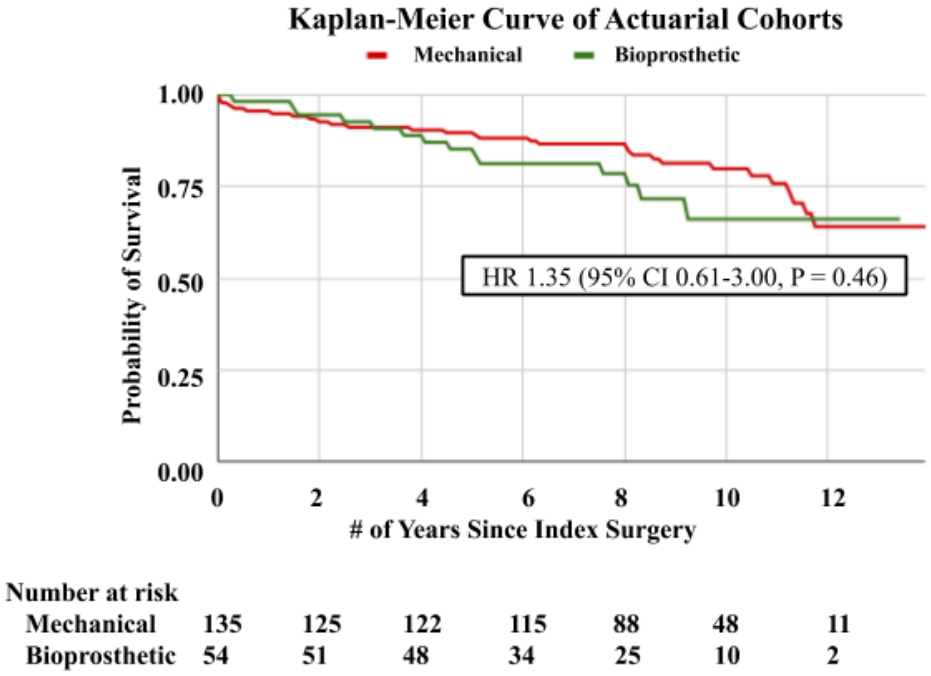


Figure 3.5: Survival after AVR for all patients, stratified by mechanical (red) versus bioprosthetic (green) valves

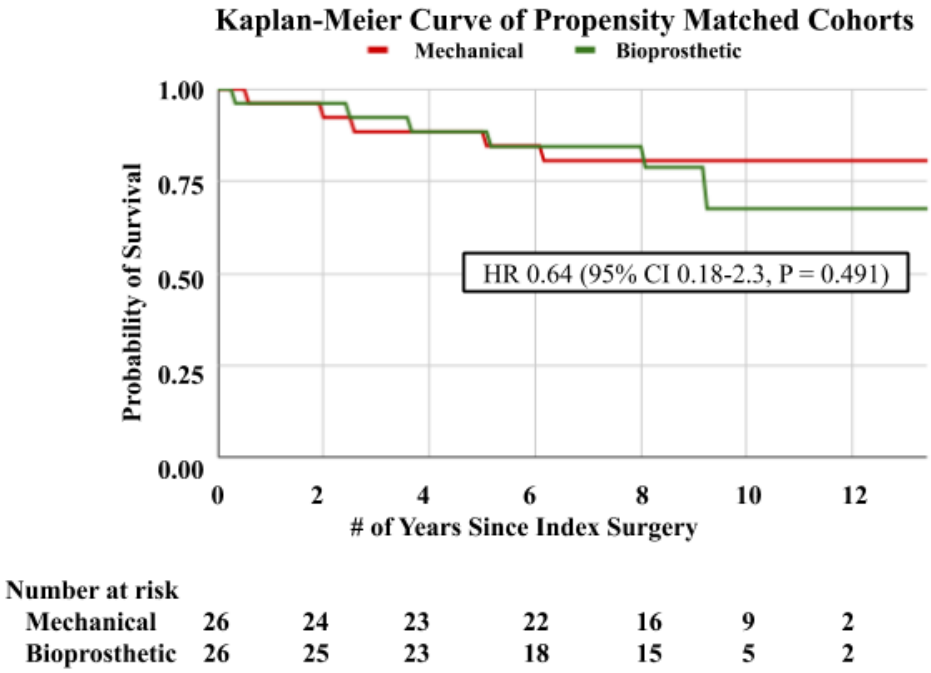
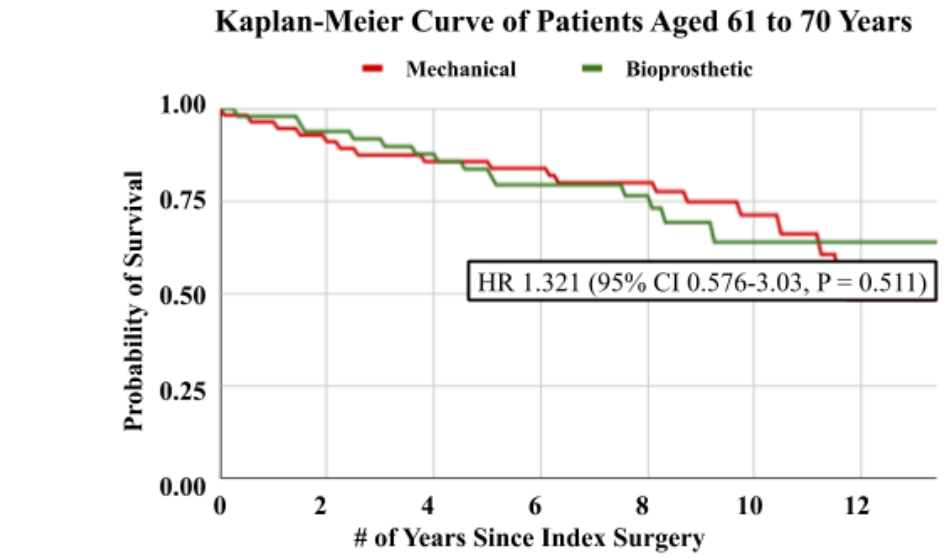


Figure 3.6: Survival after AVR for the propensity score matched patients, stratified by mechanical (red) versus bioprosthetic (green) valves.



Number at risk							
Mechanical	56	51	48	44	33	18	5
Bioprosthetic	49	46	43	31	23	10	2

Figure 3.7: Survival after AVR for patients aged 61 to 70 years, stratified by mechanical (red) versus bioprosthetic (green) valves

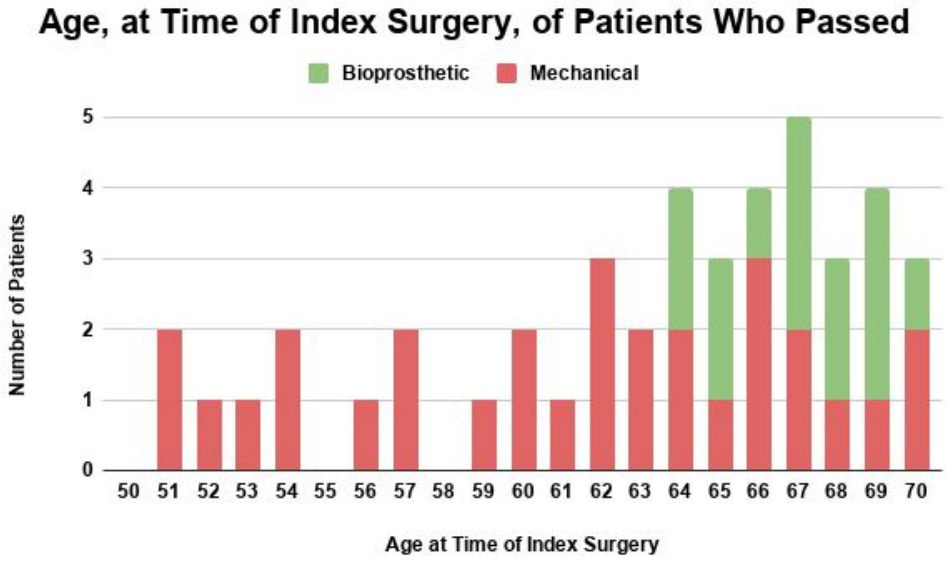


Figure 3.8: Age, at time of index surgery, of all patients who had an observed mortality event

Table 3.11: Frequency and etiology of mortality events observed in all patients

	All (n = 44)	Mechanical (n=30)	Bioprosthetic (n=14)
Cardiovascular	17 (39%)	14 (47%)	3 (21%)
Malignancy	12 (27%)	7 (23%)	5 (36%)
Bleeding	3 (7%)	2 (7%)	1 (7%)
Unknown	7 (16%)	4 (13%)	3 (21%)
Other	5 (11%)	3 (10%)	2 (14%)

Chapter 4: Discussion

This study analyzed mortality outcomes of patients aged 50 to 70 years who underwent isolated mechanical or bioprosthetic AVR in NL from 2006 to 2014. In total, 189 patients satisfied the inclusion and exclusion criteria and their outcomes were presented after a mean follow-up of 8.1 years. The primary finding of this study is that there was no statistically significant difference in long-term mortality for this group. A separate subgroup analysis was performed on a propensity score matched group of 52 patients and also demonstrated no statistically significant difference in survival. A further subgroup analysis of all patients aged 61 to 70 years was performed and also demonstrated no statistically significant difference in survival.

While mechanical valves tend to benefit from longer durability compared with bioprosthetic valves, they impose a higher risk of thromboembolic events on patients and thus require lifelong anticoagulation. The choice of prosthesis for individual patients is a shared-decision made by weighing the risks and benefits of each valve type while considering the patients individual comorbidities. Generally clinicians recommend that younger patients receive mechanical valves and older patients receive bioprosthetic valves. This practice is supported by the ACC/AHA and ESC guidelines. However, intermediate-aged patients (50 to 70 years) remain an age-group without clear guidelines, varying practice trends, and equivocal results across various studies [81]. Increasingly, surgeons have opted to implant bioprosthetic valves in this age group [54, 55, 58, 59].

Recent advancements in both mechanical and bioprosthetic valve designs, and expanding use of TAVI add complexity to this field.

Despite limited literature describing the epidemiology and results after SAVR in NL, there is evidence that the study population of NL and the cardiovascular surgery practices in NL have several unique features [71, 87]. Further, a founder effect has been observed in NL for many Mendelian disorders, and thus there is a possibility of increased congenital or genetic cardiac disorders such as bicuspid aortic valve. As a result, it is not clear whether the outcomes observed in other regions necessarily apply to the intervention and population of NL. These differences and limited understanding of the epidemiology after SAVR in NL motivated this study.

4.1 Primary Outcome of Interest

Five studies with similar methodology to this study were published since 2014 from distinct regions in Europe and North America. In a retrospective study by McClure et al. of 1701 matched patients, choice of valve type was found to not affect survival in patients less than 65 years of age [72]. Chiang et al. reported similar results in 4253 matched patients aged 50 to 69 years [73]. A retrospective study from California by Goldstone et al. performed an age-stratified analysis that showed improved survival after mechanical AVR in patients 45 to 54 years, but no difference in outcomes in patients aged 55 to 64 [55]. In Caulos et al. retrospective study of 1443 matched patients there was no difference in survival after a mean follow-up of 8.1 years [70]. In contrast, a

Swedish study demonstrated, in a retrospective fashion, overall improved survival after mechanical AVR in patients aged 50 to 69 years [61]. Our overall results corroborate the results of four of these five recent studies, as they also failed to find a statistically significant difference in mortality after AVR with mechanical versus bioprosthetic valves. The patients in this study, from NL, had similar baseline characteristics, including age, to all of these studies and those appraised in Chapter 2.

The observed 10-year survival of 80% ± 8% and 66% ± 16% for mechanical and bioprosthetic valves, respectively, in the actuarial group was comparable to other studies. McClure et al. reported survival estimates at 10 years to be 79% ± 3% and 78% ± 3%, while Glaser reported survival at 10 years to be 79% and 75%. Caulo et al. reported the highest 10-year survival of all studies appraised: 86% and 82% for mechanical and bioprosthetic valves. The 10-year survival was not reported in the two other studies appraised. As shown in Figures 4.3 and 4.5, and Table 4.9 and 4.10 there is a notable difference in survival at 10 years (81% versus 67%) for the mechanical and bioprosthetic valve cohorts. This difference was not evident earlier in the follow-up period, and did not persist to the end of the study period. Although differences in overall survival were not statistically significant, this difference at 10 years raises questions of whether there is a clinically significant difference in mortality at 10 years. Certainly, a 14% difference in mortality may be considered clinically significant; however, the interpretation of this is

difficult due to the very wide CI's, and the observation that this difference disappears beyond the 10-year mark.

When looking at the Kaplan-Meier curves in Figures 4.3 and 4.5 (actuarial and age-stratified groups), there is a near linear rate of death for the mechanical cohort before an increase in mortality after 10 years. This pattern is not apparent in the propensity matched sub-analysis. This suggests that some of the comorbidities limit survival in the mechanical cohort beyond 10 years. This influence on survival may have been captured by the propensity scores, potentially explaining why the same pattern in increased mortality beyond 10 years was not observed in the propensity matched sub-analysis. This raises the question of which comorbidities may have influenced mortality in the mechanical valve cohort beyond 10 years. In the actuarial group, there was a higher frequency of diabetes mellitus in the mechanical valve cohort versus that of the bioprosthetic valves (28% versus 22%, P = 0.393). This was the comorbidity that was noted to have the highest association with the mechanical cohort versus the bioprosthetic group. Although this difference was not statistically significant, it is interesting to note that diabetes was one of the few comorbidities that had a statistically significant influence on survival in the logistic regression model (P = 0.009). The other comorbidities found to have a significant influence on survival in the logistic regression model (hypertension and pulmonary disease) had more similar frequencies in the mechanical and bioprosthetic cohorts (P = 0.515, and P = 0.706, respectively). Perhaps DM, a chronic progressive

disease with significant macrovascular and microvascular involvement, limits the survival of patients who receive AVR beyond 10 years from index surgery.

It is worth noting that patients with symptomatic severe AS have a poor prognosis without intervention [2, 86]. It is commonly estimated that there is a 50% mortality at 5 years after symptom onset without surgical intervention [2]. Similarly, patients with aortic regurgitation have a poor prognosis [4]. Upon the development of symptomatic heart failure, patients with AR have a mortality rate of 25% per year. Considering the similar trajectory in the natural history of severe AS and severe AR, and the fact that these pathologies often co-exist, it is not surprising that the five studies appraised grouped patients with these pathologies together in their analyses. Further, none of the five studies appraised noted a difference in survival outcomes after SAVR in patients who had AS versus AR. Considering the limited sample size and low mortality event rate in this study, it is also not surprising that we did not show any difference in mortality between these patient groups. Since the advent of AVR, the survival of patients with symptomatic AS and AR has improved. Our study reports a 5-year survival of 89% (mechanical cohort) and 83% (bioprosthetic cohort). The reasons for the improved survival after surgery compared to those who do not receive surgery are manifold. Primarily, the underlying aortic valve pathology has been removed whether it be calcification, bicuspid aortic valve or endocarditis. These conditions are inherently progressive in nature - AVR resets or removes this timeline of a progressive disease.

Additionally, AS and AR are associated with concentric and eccentric remodeling of the heart, respectively. The heart has the ability to reverse this remodelling after removal of the aortic valve pathology and implantation of a prosthetic valve with near-normal function and hemodynamics. Although AVR offers improved outcomes with long-term survival, the overall survival is still reduced from age-matched individuals with no aortic valve pathologies. It may be possible that intervening on aortic valve pathologies before they become overly symptomatic can result in improved outcomes. In a 2019 published randomized controlled trial, Duk-Hyun Kang et al. demonstrated that patients with asymptomatic severe AS who underwent aortic valve interventions had improved mortality outcomes when compared to usual care [8]. These results may influence the future delivery of AVR towards earlier intervention in asymptomatic patients in an effort to improve overall survival.

A total of 44 deaths were observed in this study. Although the etiology of deaths were similar across the two cohorts it is difficult to draw any conclusions due to the small event rate, and the 16% of deaths where an etiology was unknown. As expected, cardiovascular disease was implicated in the highest percentage of deaths. It is notable that malignancy resulted in 27% of all deaths observed in this study, accounting for 6.3% of the entire study population at a mean follow-up of 8.1 years. This percentage of deaths is in-keeping with the most recent studies summarized by the Canadian Cancer Society where they found that malignancy is the leading cause of death in Canada and is

responsible for 30% of all deaths [108]. However, the observed 6% incidence of cancer-related mortality in this study (at mean follow-up of 8.1 years) is higher than the expected incidence for Canadians, which is 0.2% per year [109]. NL is known to have the highest incidence of cancer in Canada at 551 per 100,000 [108]; however, this does not account for the 6% incidence of mortality seen in this group. Patients who have valvular heart disease and undergo AVR certainly have increased rates of comorbidities than the general population, such as hypertension and DM. Perhaps the comorbidities that contribute to the development of aortic valve disease also increase risk of malignancy. This would suggest that these patients should at minimum undergo age-appropriate cancer-screening prior to consideration for cardiovascular surgery when possible. Appropriate and thorough screening for malignancies would likely result in improved understanding of a patient's overall survival prognosis with or without SAVR. Furthermore, discovery of a malignancy may influence the type of valve implanted depending on the risk of bleeding, thrombosis and survival of that patient and corresponding malignancy. A malignancy that confers a high bleeding risk may influence the heart team's decision towards implanting a bioprosthetic valve as they do not require lifelong anticoagulation and thus may be a safer option.

Bleeding as an etiology of death would be expected to be higher in the mechanical valve cohort as these patients are on lifelong anticoagulation, usually with warfarin. However, the observed frequency of bleeding as an etiology of death was 7% for both

cohorts in this study. This may be skewed due to the high percentage of patients who had an unknown etiology of death (16%) and a reflection of the low number (44) of mortality events included in this study. Etiology of death was collected through individualized chart reviews and was often available from hospital discharge summaries and patient death certificates. Clinicians may have over-attributed deaths to cardiovascular or a patient's malignancy rather than bleeding due to biases in clinical judgement.

ESRD is associated with limited survival, and is a known risk factor for the development of AS. All three patients in our study who were on hemodialysis prior to surgery received mechanical valves. No patients on hemodialysis received bioprosthetic valves in NL, a reflection of local surgical practices. There was 100% mortality observed during the study period for these patients. Etiology of death was noted to be cardiovascular in nature for all hemodialysis patients, and the maximum survival was less than 2 years. These observations are in-keeping with the known increased risk of mortality for patients with ESRD who receive SAVR; however a 100% mortality at two years is notable.

4.2 Secondary Outcomes and Other Observations

The statistically significantly higher frequency of patients with congenital aortic valve disease in the mechanical cohort (24% versus 11%, P = 0.028) is likely a reflection of the younger age of these patients. Bicuspid aortic valves are the most common congenital cardiac pathology in humans and increase the individual's risk for calcification

of the aortic valve and thus AS [1]. These patients tend to develop signs of severe AS a decade earlier than patients with trileaflet aortic valves [1]. Since they tend to present at younger ages, they are more likely to receive mechanical valves. Although there were no other statistically significant differences in the underlying etiology of aortic valve pathology between the two cohorts, there was a lower frequency of patients with severe AI in the mechanical cohort versus the bioprosthetic cohort (13% versus 22%, P = 0.170). Importantly, the presence of AI did not have a significant influence on the outcome of death (P = 0.796). In terms of therapeutic interventions, patients with severe AS are generally limited to the options of SAVR or TAVI. However, patients with severe AI have the added options of aortic valve sparing procedures (e.g. aortic valve repair). It is possible that the patients in this study who had severe AI and received SAVR were a subset of patients with different comorbidities and surgical risk profile, in effect introducing a selection bias to the primary outcome results.

The post-operative complications presented in Table 4.8 were all derived from patient charts and discharge summaries. The rates of post-operative complications are likely an under-estimate of the true rates experienced by patients in this study. There were no statistically significant differences in post-operative complications between the two cohorts. There was a lower frequency of CVA's observed in the mechanical cohort versus the bioprosthetic cohort (1% versus 7%, P = 0.075). Patients who received mechanical valves received therapeutic anticoagulation within 24 to 48 hours of the index

surgery to reduce the risk of thromboembolism from their new mechanical valves. Bioprosthetic valves do not introduce as high of a risk of thromboembolism and were not empirically anticoagulated post-operatively unless the patient had another indication for anticoagulation (e.g. AF). The observed increase in CVA rates in patients who received bioprosthetic valves highlights the coagulopathy associated with cardiovascular surgeries and proposes a potential benefit for anticoagulation in the postoperative period to reduce the risk of CVA for patients who receive either mechanical or bioprosthetic valves. This potential benefit would have to be balanced by the increased risk of bleeding introduced by anticoagulation. It is important to note that the increased rate of CVA in the bioprosthetic valve cohort may be a reflection of their older age of these patients and increased comorbidities and thus may not be a reflection of the natural history of bioprosthetic valves.

A significant postoperative complication evaluated in other studies is the rate of SVD and need for re-operation. Although the secondary outcome of long-term SVD was not available in the databases accessed by this study, there were no patients who had an index AVR between 2006 and 2014 in NL who went on to have reoperation prior to March 2020. All five studies appraised in Chapter 2 reported significantly higher rates of reoperation in the bioprosthetic valve versus mechanical valve cohorts. Their rates of reoperation for the bioprosthetic cohorts were: 19% at 18 years (McClure et al.), 12.1% at 15 years (Chiang et al.), 5.2% at 17.2 years (Glaser et al.), 6.6% at 15 years (Caulo et al.)

and 17.2% at 15 years (Goldstone et al.) It is unclear why patients in NL did not have any observed reoperation. Perhaps the follow-up time was too short. Alternatively, patients who received reoperation for SVD, in the five studies discussed, tended to be younger at time of index surgery - this study involved only five patients who were aged 60 years or younger and received bioprosthetic valves. These patients would be at highest risk of eventual reoperation. This may be a reflection of increased use of mechanical valves in younger patients in the NL practice, as reported by McGuire et al. [87]. Echocardiography provides an opportunity to screen and monitor for the development of SVD post bioprosthetic valve implantation. As SVD develops, early findings could be detected on echocardiogram long before the need for reoperation, potentially increasing the sensitivity of detecting this serious and long-term complication. Although most patients receive regular echocardiograms this was not consistent across our patient population and the corresponding data was not available for this study.

4.3 Differences in Study Design

There are important differences in study design between our study and the five studies described in detail in Chapter 2. All patients in our study underwent SAVR at a single centre; whereas, four of the five studies drew patients from multiple centres. Other differences in study design are also important when interpreting and comparing the results of this study to others. We chose to include patients with etiologies of aortic valve disease including AS, AR, and IE. Caulo et al. designed their study population to be

exclusive to those patients who had an aortic valve dysfunction due to severe AS, while the studies by Chiang and Goldstone did not have access to the reason for intervention in their patients. As a result, we were able to include these important baseline characteristics in our logistic regression that produced the propensity scores. Although etiology of aortic valve pathology did not significantly influence the primary outcome of mortality, this conclusion is limited by the small numbers of patients who had AR or IE in our study.

Similar to the other studies discussed, there was a trend towards increased use of bioprosthetic valves in NL throughout the study period. This trend towards increased use of bioprosthetic valves has been widely described in the literature and is thought to be the result of safer and more durable outcomes after bioprosthetic implantation. However, the overall use of SAVR peaked in the middle of our study period (31 operations in 2011) before declining which contrasts with the other studies discussed. It is unclear why the rates of SAVR in NL declined after 2011 for patients aged 50 to 70 years. The mean and maximum follow-up times of 8.1 and 13.8 years for our patients was comparable to other studies as seen in Table 2.2.

4.4 Limitations

This study was retrospective in nature and thus is subject to selection bias. This was addressed through propensity score matching based on a logistic regression analysis. However, these methods can only take into account known and recorded patient characteristics. There may be unknown or unmeasured variables that confound the

results, and were unable to be controlled for in the logistic regression. Since much of the data comes from the APPROACH administrative database it is subject to input errors and a number of variables were lacking (e.g. history of bleeding, medications, frailty, smoking status, left ventricular diameter, urgency of surgery, etc). Malignancy was found to be a significant cause of mortality in this patient population (27%) - known risk factors for malignancy were not collected by the APPROACH database or studied in this paper. Other studies evaluating this subject considered the performing-surgeon and number of AVR's performed by each surgeon a covariate in their analysis, this data was not available for our patient group. Further, there may be different practices and outcomes associated with specific surgeons, while some surgeons may have recorded their postoperative complications differently on their discharge summaries. These differences were not captured by the databases used in this study. Although echocardiographic data was available through the APPROACH database and cross-checked by chart reviews, it may not equally reflect perioperative hemodynamics as the timing of pre-operative echocardiogram was variable ranging from one day to seven months prior to procedure date. These limitations all relate to the baseline characteristics of patients in our study. Missing and imprecise baseline characteristics existed in all studies reviewed by us and have an unknown effect on the primary outcome of mortality.

As shown in Chapter 2.1, the sample size necessary to detect a HR of 1.15, with an alpha of 0.05 and power of 85% at 5-year follow-up would be 5590 patients. This

study included only 189 patients. As a result, our study was under-powered for the primary outcome of interest. This also led to relatively wide CIs and may have failed to detect true differences in outcomes after mechanical versus bioprosthetic SAVR. The sample size could be improved by extending the time period of the study beyond 2006 to 2014, determining patient outcomes at a later date, or collaborating with groups in the Maritime provinces of Canada to combine data and outcomes. Notably, all studies published in the past decade that compare mortality outcomes after bioprosthetic and mechanical AVR have been underpowered. This may explain why the majority of these studies have failed to find a significant difference in outcomes. This demonstrates a need for meta-analyses of existing studies to integrate the results of valid studies into a clear signal of mortality outcomes in patients less than 60 years of age who receive mechanical versus bioprosthetic AVR.

Unfortunately, important secondary outcomes such as bleeding, stroke, and readmission were not collected by the databases accessible for this study. As a result, analysis of long-term rates of these secondary morbidity outcomes was not possible. These secondary outcomes inherently influence the primary outcome of mortality. Other studies were able to carry out a competing risk analysis, providing a marginal probability for cause-specific events. These would have allowed for a more detailed understanding of the etiology of death of patients in our study.

There is a single cardiac surgery centre in NL allowing for 100% surgical and outcome follow-up and the long-term use of a standardized cardiac database (APPROACH). Despite complete follow-up of the patients involved in this study, the average follow-up time after index SAVR was 8 years. Longer follow-up, particularly beyond 10 years, has the potential to delineate differences in mortality and other secondary outcomes in the mechanical versus bioprosthetic cohorts. A longer follow-up is particularly applicable to this study population as patients who undergo bioprosthetic SAVR tend to suffer from SVD, and the associated complications, beyond 10 years. A longer follow-up period would be more likely to reflect the natural history of SVD observed in bioprosthetic valves. The single-centre nature of cardiovascular care in NL means that the decision to implant mechanical versus bioprosthetic valves is influenced not only by traditional considerations published in the corresponding guidelines, but also by local practice preferences. For example, all patients who received dialysis received mechanical valves in NL - this is not the case for other regions in the world. This reduces generalizability of our results to other sites; however, the single-centre nature of this patient group increases the internal validity of the results providing an improved understanding of outcomes after AVR in NL.

4.5 Conclusions

In summary, this NL study demonstrated no statistically significant differences in long-term survival at a mean follow-up of 8.1 years, in patients aged 50 to 70 years who

underwent mechanical versus bioprosthetic AVR in NL from 2006 to 2014. The most common cause of death in this group was cardiovascular (39%) followed by malignancy (27%). These results corroborate the results of four recent studies that also failed to find a statistically significant difference in mortality after AVR with mechanical versus bioprosthetic valves. Our study, and all studies appraised were underpowered to detect a difference in mortality. A meta-analysis combining the results of this and other studies may address this limitation.

The results of this study provide epidemiological insight into the prevalence of aortic valve disease, the utilization of AVR, and the outcomes after AVR in NL. It is intended that the information presented will assist in the planning and delivery of future cardiovascular practices in NL based on our patient population.

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APPENDICES

Appendix A: Methodology of Literature Review and Appraisal

Search Strategy and Sources

A review of the literature surrounding the question of mortality following mechanical versus bioprosthetic AVR began with studying the most recent guidelines used to direct decision making in the management of patients who are candidates for AVR. The most prominent of these are the 2014 AHA/ACC guidelines, the ensuing 2017 focused update, and the 2017 ESC guidelines [41, 42, 56]. These guidelines provide a thorough review of current practices in the field of AVR surgery. The corresponding guideline-shaping publications that were cited in these guidelines, a total of 35 citations, provided the foundation for the initial literature review in preparation for this article.

The PubMed, EMBASE, and Cochrane Library databases were searched initially in November 2017 and updated in May 2020 to find relevant literature on the topic of outcomes after aortic valve replacement. Key search words included the following: *valvular heart disease, aortic stenosis, aortic regurgitation, bicuspid aortic valve, endocarditis, aortic valve replacement, mechanical, bioprosthetic, prostheses, cardiac surgery, transcatheter aortic valve replacement,* and *mortality and morbidity*. In total, 2,112 citations were revealed through this search. All of the 35 citations referenced in the guidelines were included in this list of 2,112 citations, validating the broad search. 2,092 articles remained after duplicates were removed. 2,031 citations were found to not be applicable based on their titles and abstracts leaving 61 full-text references that were

retrieved. Six additional references were found through review of bibliographies, ensuring an exhaustive literature review was completed.

Study Selection

A total of 67 articles were reviewed for inclusion and exclusion criteria. Articles were included for appraisal if they were relevant to the topic, published in peer reviewed journals, and relied on or were themselves studies that analyzed outcomes associated with bioprosthetic and mechanical AVR. Studies published prior to 2014 were excluded as a systematic review by Kiyose et al. included all studies prior to this date [53]. AVR is inherently an outcome-based intervention and generally randomization of patients is unrealistic [51], as a result randomized controlled trials are rare and was not an inclusion criterion. Studies were excluded if randomization or, at minimum, comparison of matched cohorts did not occur. Studies were considered eligible if they presented data on AVR in adults, and documented postoperative long-term mortality. Studies with inadequate follow-up (i.e. less than 5 years) were removed from the review. Additionally, studies that involved TAVI were excluded. Age-related data was an important criterion - we limited selection to studies involving adults aged 50 to 70 years of age. Only full publications in English were included. In cases where serial reporting of a patient cohort occurred only the most recent publication was included. Of the 67 articles reviewed for inclusion and exclusion criteria, 62 were removed leaving 5 articles that satisfied the overall criteria.

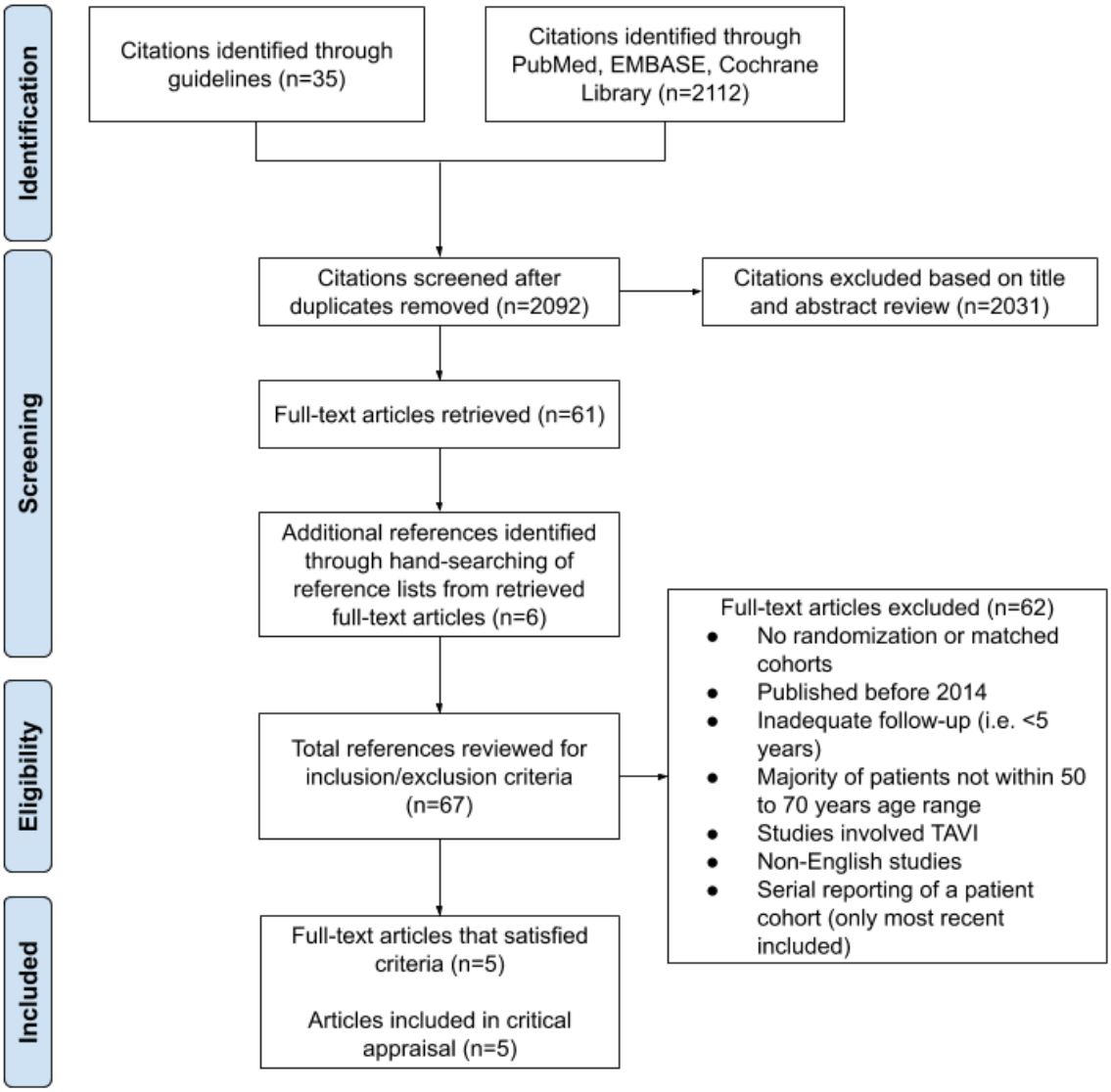

Figure: PRISMA Flowchart of search strategy for literature review and study selection for critical appraisal

Appendix B: Critical Appraisal of Five Recent Studies

In total, five publications met the inclusion and exclusion criteria (see PRISMA FLowchart) and were appraised. These included a prospective study out of the Brigham and Women's Hospital [72], a retrospective study of patients in New York State [73], a Swedish population-based cohort study [61], a retrospective study from California [55], and the ANDALVALVE study of patients in Spain [70]. These studies are briefly summarized in Tables 2.1 and 2.2.

McClure et al. (Harvard study) [72]

McClure et al. published an observational study relying on data collected both prospectively and retrospectively that compared long-term mortality after bioprosthetic and mechanical AVR in patients less than 65 years of age. The authors recognized that guidelines at that time removed age as an absolute indication for valve-type, and remarked on the paucity of data and conflicting conclusions in the literature at that time to support those guidelines. As a result, the authors proceeded with this study with the objective to determine if trends towards implanting bioprosthetic patients in younger patients was justifiable. They included all patients less than 65 years old who underwent isolated AVR at Brigham and Women's Hospital, in Boston, Massachusetts from January 1992 to 2011. Measured covariates that had a P-value of ≤ 0.15 in a stepwise regression were included in their final model. This model guided the propensity score matching

process and had an area under the receiver operating curve of 0.81. Long-term secondary outcomes were determined through voluntary mail-in questionnaires.

The authors identified 6794 patients who underwent AVR during their study period, 1701 of these met the inclusion criteria of which 769 (45%) received a bioprosthetic valve, while 932 (55%) underwent mechanical AVR. Patients who received a bioprosthetic valve tended to be older, and had higher rates of hypertension and dyslipidemia. While patients who underwent mechanical AVR were more likely to have a history of stroke, endocarditis, cardiac surgery, and had a lower ejection fraction. There were no significant differences in the propensity matched cohorts. The authors did not identify a difference in the primary outcome of survival after 18 years of follow-up in the matched cohort. Their reported 18-year survival was 60% ± 6%, and 51% ± 14% (P = 0.752) for the bioprosthetic versus mechanical cohorts, respectively.

This study is limited in its generalizability due to the retrospective, single-center observational design. As with any retrospective study, there is always potential for confounding from unmeasured and unknown covariates. Several secondary outcomes were collected through mail-in questionnaires leading to a risk of responder bias. It is difficult to compare the results of this study with others as their patient population had a mean age of 53.5 years, and was thus several years younger than the mean age of patients in two randomized controlled trials that preceded their study and the other studies appraised here. There was no age stratified analysis presented despite the relatively large patient population and wide-range of ages studied. The authors' final conclusion that

choice of valve prosthesis does not affect survival for any patient less than 65 years may not be valid as they did not perform an age-stratified analysis. They have extrapolated their results that came from patients that were largely between 50 to 65 years, to all patients less than 65 years. The authors opted to exclude patients who had any concomitant surgery which reduces the generalizability of their results, while maintaining internal validity of their results. The strengths of this study include a matched cohort that was the largest of its size for that date. Excellent follow-up out to 18 years post index surgery that was 99% complete is remarkable considering the follow-up relied on mail-in questionnaires.

Chiang et al. (New York State study) [73]

Chiang et al. analyzed a statewide New York database to determine the differences in long-term survival, and secondary outcomes, after AVR. In an effort to improve the internal validity of their results they only included patients between the ages of 50 to 69. Similar to all five studies appraised here, this study was retrospective in design and compared outcomes in patients who received isolated AVR from January 1997 and December 2004. Patients who underwent any concomitant cardiovascular surgery were excluded. Propensity score matching was carried out and was based on a logistic regression that utilized all measured covariates regardless of their influence on the primary outcome of mortality. Their model had an area under the receiver operating curve of 0.83.

A total of 10981 patients aged 50 to 69 who underwent AVR were identified. Of these 4253 patients satisfied their exclusion criteria, of these, 1466 (34.5%) received bioprosthetic valves and 2787 (65.5%) received mechanical valves. Overall mean follow-up was 10.8 years. Patients who received bioprosthetic valves tended to be older, and were more likely to have a history of diabetes mellitus (DM), cerebrovascular disease, liver disease, and cancer. All baseline characteristics were balanced in their propensity matched cohorts which included 1001 patients in each cohort. This study detected no difference in long-term survival and reported a 15-year survival of 60.6% (95% CI, 56.3%-64.9%) for the bioprosthetic group and 62.1% (95% CI, 58.2%-66.0%) in the mechanical group.

The authors of this study concluded that either bioprosthetic or mechanical prosthesis is a reasonable choice in patients aged 60 to 69 years. Their results were based on an administrative database that didn't include a number of possible confounding variables that have previously been shown to significantly influence the outcome of mortality, including frailty, etiology of aortic valve disease, and left ventricular ejection fraction (LVEF). A strength of this study was that it involved patients across an entire state which improves the generalizability of their results compared to the study by McClure et al. Another strength is that their study included a high number of patients all within the same age group and they had a relatively long follow-up period. Their results help delineate differences in outcomes in this age group, where practices are in flux and guidelines are undecided.

Glaser et al. (Swedish study) [61]

A population-based cohort study of all patients aged 50-69 years who had undergone primary AVR in Sweden between 1997 and 2012 was completed by Dr. Glaser and colleagues at the Karolinska University Hospital, Stockholm [58]. The impetus for this investigation came from previous studies that challenged existing guidelines as they demonstrated similar long-term survival in patients aged 50-60 years with either mechanical or bioprosthetic AVR [6, 24]. The primary objective of this Swedish study was to investigate the long-term all-cause mortality in patients receiving mechanical and bioprosthetic AVR. This observational, nationwide, population-based, cohort study examined the Swedish National Patient Register and similar databases. The follow-up period ended on December 31, 2012. To reduce selection bias, logistic regression using 35 variables as covariates was used to calculate a propensity score for each patient. A separate analysis was performed in propensity score-matched patients aged 50 to 59 years and 60 to 69 years of age. Patients who had undergone prior cardiac surgery or a concomitant procedure were excluded.

A total of 4545 patients were included in the study. Of these, 2713 (60%) and 1832 (40%) received bioprosthetic and mechanical valves, respectively. The mean follow-up times were 5.0 and 8.8 years in the bioprosthetic and mechanical valve cohorts, respectively. Complete follow-up was made possible by the comprehensive nature of the Swedish patient databases. Patients who received bioprosthetic valves were on average

63.7 years, whereas those who received a mechanical valve were on average 59.9 years. In the propensity score-matched cohort, all baseline characteristics were well balanced. The 15-year survival in the propensity score-matched cohorts were 59% in the mechanical valve group, and 50% in the bioprosthetic valve group. These results were consistent with the overall cohorts. The long-term survival was significantly greater in the mechanical valve than the bioprosthetic valve group. The unadjusted analysis demonstrated a HR HR of 1.67 (95% CI 1.44-1.94) and in the propensity score-matched cohort the HR was 1.34 (95% CI 1.09 - 1.66; p = 0.006). HRs for the two stratified groups were 1.67 (95% CI 1.06 - 2.61; p = 0.026) for patients 50 to 59 years of age, and 1.08 (95% CI 0.85 - 1.36; p = 0.539) for patients 60 to 69 years of age. This study demonstrated significantly higher long-term survival for patients aged 50 to 59 years who received mechanical AVR, as compared to those who received bioprosthetic AVR.

The results of this study were compared to two similarly designed studies that found no difference in 15-year survival between the two groups [72, 73]. The quality of anticoagulation control in Sweden has repeatedly been shown to be exceptional [75, 76] and is attributed to universal access to health insurance coverage. The authors state that this may have favorably affected clinical outcomes among patients who received mechanical valves who require lifelong anticoagulation. However, they did not publish data on INR trends for this patient cohort.

This study demonstrates significant improvement in survival for patients less than 60 years of age who received mechanical AVR. However, it was an observational study

which has associated limitations. It is prone to input errors into the national databases that were used, there is a risk of selection bias among physicians who followed patients after AVR, and it is not possible to compare baseline characteristics that were unmeasured in the two cohorts. In addition, some patients may have died outside of Sweden which may have led to underestimation of mortality as their deaths may have not been recorded in the national databases. The particular strengths of this study include a large population, and relatively long and complete follow-up. Although their findings differ from similarly designed studies, the authors believe that higher quality follow-up, and specifically anticoagulation, explains the improved outcomes seen after mechanical AVR in Sweden. They highlighted the importance of close monitoring of anticoagulation in patients who receive mechanical valves. An age-stratified analysis may have helped delineate differences in outcomes in younger versus older patients in the 60 to 69 year age range. In summary, this study demonstrates improved mortality outcomes with mechanical AVR in patients less aged 50 to 69 years assuming close monitoring of anticoagulation is feasible. Considering that Canada also benefits from universal guaranteed healthcare, and has similar quality of anticoagulation [77], it is reasonable to believe that these results are applicable here.

Goldstone et al. (Californian study) [55]

In November of 2017 a retrospective study was published that evaluated outcomes in patients who underwent AVR at 142 nonfederal hospitals in California. The motivation for this study came from an awareness of increasing use of biologic over

mechanical AVR despite limited evidence to support this practice. The goal was to compare the long-term benefits and risks of mechanical and biologic prostheses for AVR in California. Data was examined from patients who underwent primary AVR at 142 nonfederal hospitals in California between 1996 and 2013. Of note, this study did not exclusively analyze outcomes of individual valve designs, instead all designs were included. Patients who received prior cardiac surgery or had concomitant cardiac surgery of any kind, were excluded. Patients were stratified according to age, the categories were: 45 to 54 years, and 55 to 64 years. Clinical follow-up was obtained through the California electronic medical record system and state death records. Patients who were not documented as having died were censored on December 31, 2013.

Of 45,639 patients who received AVR during the study period, 9942 were eligible for inclusion in the study. Analysis of baseline characteristics revealed that recipients of biologic prostheses were older and had a higher incidence of coexisting conditions than recipients of mechanical AVR. Inverse probability weighting was used to balance baseline characteristics in each age group. The median follow-up time was 5 and 8 years for biologic and mechanical prosthesis, respectively. In the 45 to 54 years age group, long-term mortality was statistically significantly higher among recipients of a bioprosthetic AVR than among patients who received mechanical AVR (30.6% versus 26.4% at 15 years; $p = 0.03$). The difference was not as significant for the 55 to 64 years age group (36.1% versus 32.1% at 15 years; $p = 0.60$). These relationships were unaffected by multivariable adjustment or incorporation of individual hospitals as a

random effect. When age at time of surgery was analyzed as a continuous variable, the mortality benefit with mechanical AVR persisted until 53 years of age, and a HR of 1.0 occurred at approximately 63 years of age. The final conclusion was that the benefit of mechanical AVR disappeared by 55 years of age.

Similar to most studies in this field, it is a retrospective design and as such has inherent limitations. The study's exclusion criteria meant that only 9942 of 45,639 patients who underwent AVR during the study period were eligible. This relatively strict inclusion criteria limits the generalizability of the results. An administrative database was used rather than a clinical database. Therefore, it was subject to input errors and lacked important clinical details such as the etiology of valvular disease. A limitation of this study is that the median follow-up time was 5 years among patients receiving biological prosthesis and 8 years for those who received mechanical prosthesis. This may have limited the ability to discern differences in long-term outcomes for the patients in the 55 to 64 age category. The rate of AVR involving biological prosthesis increased from 11.5% in 1996 to 53.7% in 2013. No explanation for this trend was offered. This study stands out for a number of reasons: it involves a relatively high number of patients, data was collected from a wide variety of hospitals (142), and the study largely involves the use of modern prosthetic valve designs. However, the long study duration (1996 to 2013) introduces concern regarding changes in practice. Only patients undergoing isolated AVR were included in this study which improves the internal validity of the outcomes, whereas other studies discussed here included patients who underwent concomitant surgeries of

the other valves or cardiac operations. In summary, this study demonstrates improved mortality outcomes associated with mechanical AVR in younger patients and adds evidence to already existing studies that demonstrate improved outcomes with mechanical prosthesis in patients less than 60 years of age.

Caulo et al. (ANDALVALVE study) [70]

The most recent study appraised was published in 2019 by Rodriguez-Caulo et al. They performed a multicentre observational retrospective study that included all patients aged 50 to 65 years who received isolated AVR from 7 hospitals in Southern Spain between 2000 and 2015. They recognized that the decision between bioprosthetic and mechanical AVR remained controversial in this age group and hadn't been studied in a Mediterranean population. Their primary objective was to determine long-term survival. They included patients with documented severe AS and excluded patients who had any concomitant surgery or previous cardiac surgery. Their data was sourced from a regional database and direct telephoning was carried out to address missing data. A 2:1 propensity matching was conducted to adjust for differences in baseline characteristics between the two groups.

A total of 1443 patients met their inclusion and exclusion criteria, and follow-up was completed in 1392 (96%) of these patients. In total, 1171 (81.2%) received mechanical valves while 272 (18.8%) received bioprosthetic valves. The propensity matched cohorts included 506 patients who received mechanical valves, and 257 who received bioprosthetic valves. Their mean follow-up time was 8.1 years with a maximum

of 17 years. The use of bioprosthetic valves increased from 12% at the beginning of their study period to 26% towards the end. Patients who received bioprosthetic valves were on average older, and were more likely to have pulmonary disease, a history of stroke, myocardial infarction, and peripheral arterial disease. Whereas patients who received mechanical valves were more likely to have a history of AF. All baseline characteristics were balanced in the propensity matched cohorts. After propensity matching their reported 15-year survival was 73% and 76% (P=0.159) for the bioprosthetic and mechanical valve cohorts, respectively.

The main limitation of this study is the retrospective design and thus it is subject to confounding from unknown and unmeasured variables. Further, Caulo et al. reported the highest percentage use of mechanical valves (81.2%) compared to the other studies appraised. To address these a 2:1 propensity matched analysis was performed. Thus twice as many patients who received mechanical valves were included in the final analysis. As a result, the patients who received bioprosthetic valves in this group had an undue influence on the final results. No explanation was offered to directly explain the high rates of mechanical AVR in Andalusia; however, the authors do point out that their patients tend to have smaller body surface areas and sizes [Caulo-16]. This may explain the increased use of mechanical valves and reduces the generalizability of their results. Of the five studies appraised, this was the only one that strictly included patients with severe AS - other studies included patients with AR, and IE. This improves the internal validity of their results, but may have contributed to their smaller sample size. Overall,

the study was under-powered to discern differences in survival between bioprosthetic and mechanical valves in the 50 to 65 years age group.

Appendix C: Key Biases and Limitations of Studies Appraised

Due to the nature of the intervention being studied there are a number of potential sources of bias that affect all five studies appraised. Predominantly, they were all retrospective studies and are therefore subject to selection bias as patients were not randomized to intervention. In the Swiss study, 81% of patients already had a clear preference concerning valve choice prior to their AVR surgery as determined by a postoperative questionnaire [74]. To reduce selection bias all studies compared the two cohorts according to a list of measured baseline characteristics and generally reported cohorts that were similar. All studies compared the two cohorts based on their baseline patient characteristics for both the actuarial and propensity matched groups. The patient characteristics included varied across the studies depending on available data. Further, it is impossible to know if there are unknown characteristics that may have led to an influence on the results.

Strict exclusion criteria by some studies resulted in a loss of a high proportion of patients identified. For example, the Californian study excluded 78% of patients. Reason for AVR beyond severe AS was listed as an exclusion criteria by some studies. Although these improve the internal validity of the results, it reduces generalizability. Certainly, the majority of patients undergoing AVR will have AS; however, there is a need to study the outcomes for patients who undergo AVR for other etiologies, particularly AR and IE.

Data custodians and researchers who collected outcome data (i.e. mortality, etiology of death, stroke, etc) were likely aware of the type of prosthesis implanted. This

may have introduced a biased evaluation from individuals inputting these data points. For example, a patient with a mechanical valve who presents with vague symptoms of a CVA may have been more likely to be labelled as having a stroke or transient ischemic attack (TIA) if the observer is aware of the patient's prosthesis type and the associated increased risk of thromboembolism. One study used mail-in questionnaires and another used a telephone survey to determine their outcomes of interest. These methods rely on patients, and family, to recall events in the past. This method of data collection is subject to responder bias.

The age groups analyzed in the appraised studies were different. This makes it difficult to directly compare and contrast results. Although age-stratification was carried out by Glaser et al. and Goldstone et al., it was not performed in the other three studies. The McClure et al. study included all patients less than 65 years of age. Their youngest patient was less than 40 years old. Including such a wide age-range of patients reduces the validity of their results to the age-group of interest: 50 to 70 years. The younger patients in their analysis may have had an undue influence on the outcome of survival.

Patients who receive mechanical valves require lifelong anticoagulation and thus regular follow-up to manage their INR with warfarin. This introduces a significant confounder as there is a distinction in treatment between the groups after the intervention. Conceivably, measurement bias may occur due to closer follow-up for patients who undergo mechanical AVR resulting in increased detection of complications or other medical issues. All 5 studies reported longer follow-up times in their mechanical cohorts,

potentially due to the closer follow-up of these patients. Similarly, blinding of intervention is impossible as the surgeon is aware of which prosthesis is being implanted, and the patient and physician can hear an implanted mechanical valve. This may introduce detection and observer biases.

There are limitations from all studies with respect to their follow-up of patients. The Californian study had the lowest median follow-up time at five and eight years for bioprosthetic and mechanical valve cohorts, respectively. This may have limited their ability to discern true differences in outcomes over the long-term, particularly for patients in the 55 to 64 years age-range. Follow-up was limited in all studies as they relied on data from their individual regions. Any patients that moved outside the regions of study will have been lost to follow-up. It is assumed this out-migration will have equally affected both the mechanical and bioprosthetic cohorts equally.

Ultimately, none of the five studies appraised had a sample size large enough to detect differences in outcomes. Based on calculations carried out in similar studies [49, 55, 73, 78-80], and in Chapter 3.1 of this paper, a sample size of over 7,000 patients is needed. The largest propensity matched group involved 2,198 patients in the Glaser et al. study. The study by Goldstone et al. avoided the loss of patients in propensity matching by performing a weighted analysis of their 9942 patients. The sum of their weights was not presented and as such it is unclear if they were able to appropriately address this limitation.

All studies noted changes in practices in their respective regions. The rates of bioprosthetic valve implantation increased throughout all study periods. The reasons for these changes in practice are varied, but reflect evolution in valve design, experience of surgeons, and clinical practice. Notably, the study by Caulo et al. reported a very high percentage of mechanical valves, reflecting differences in practice across the regions. These differences limit the generalizability of the results to global modern day practices.

Appendix D: Ethics Application

Included here is the most recent application for amendment to the Health Research Ethics Board (HREB) of NL. The initial application was made on 19 January 2018, and this amendment was made 28 August 2019.

HREB - Amendment Form

Project Info

File No: 20181608
PI: Buckley Alvan(Faculty of Medicine\FOM)
Project Title: Single center experience with medium-term morbidity and mortality outcomes of mechanical and bioprosthetic aortic and mitral valve replacement.
Submitted: Wednesday, August 28, 2019
Submitted by: Alvan Buckley

Event Info

Event No: 20181608-466460
Notes:
Approval Letter Generated?: Not Yet Set

Common Questions

1. Amendment Form

#	Question	Answer
1.1	Amendment date:	2019/08/29
1.2	Version # (if applicable):	
1.3	Is a 'Letter of No Objection' (NOL) from Health Canada required for this amendment?	No
1.4	If you responded 'Yes' to question 1.3, please enter the date of the NOL.	

2. Amendment Details

#	Question	Answer
2.1	List ALL documents, including version dates, to be approved. Please upload these documents under the 'Attachments' tab.	Data Request Letter APPROACH (28 Aug 2019)
2.2	Will there be any increase in risk, discomfort or inconvenience to the participants?	Yes
2.3	Please specify.	See below

2.4	Are there changes to inclusion or exclusion criteria?	No
2.5	Please specify.	
2.6	Are participants enrolled in the study at this site?	Yes
2.7	Is a modification to the consent form required?	No
2.8	Is a consent addendum required?	No

2.9	Please summarize the changes and provide the rationale for the significant changes being requested.	I am requesting access to patient IDENTIFIABLE data from the APPROACH database. More specifically, I am seeking MCP and DOB for all patients who have received AVR/MVR in Newfoundland during the study period.I intend to perform chart reviews of each patient using meditech and healtheNL.The reason I require access to patient charts is to more accurately determine several secondary outcomes. Namely, I am interested in determining the following post-operative outcomes:- rates of readmission (including etiology of admission)- rates of major bleed- rates of cerebrovascular accidents- rates of reoperation and rates of subsequent transcatheter aortic valve replacementAlthough some of these secondary outcomes are recorded by the APPROACH and NLCHI databases (which I already have access to), those that are available are largely incomplete, and/or inaccurate.This will result in increased risk to patients in that patient identifiable data will be released to the study team. However, this is balanced by the unique opportunity to acquire very thorough post-operative outcomes in our province. Since all AVR/MVR surgeries are performed at one site (HSC) and all patients are accessible through the provinces electronic medical record we have a unique opportunity to publish very thorough follow-up outcomes on this patient cohort.Current literature in the field consistently reports on the secondary outcomes listed above. To achieve this standard I will have to perform chart reviews on individual patients.This will benefit future patients because their operative risk will be quantifiable not only in terms of mortality, but also expected rates of significant morbidity. Ultimately, this results in improved education for future

		patients such that they can make a more informed choice on their care.
2.10	If applicable, please describe how the information will be disseminated to participants enrolled in the study.	N/A

Attachments

Doc / Agreement	Version Date	File Name	Description
Letter (Other)	2019/09/13	DataRequest_Letter_APPROACH_Sept2019.pdf	Data request letter for APPROACH
List of Variables	2019/09/05	List of Variables_Sep2019.pdf	List of variables updated to reflect variables I intend to gather from electronic medical records.
List of Variables	2019/12/06	Data Custodian Variable List Alvan Buckley 2019-12-06.docx.pdf	Data Custodian Variable List (signed by NLCHI, and Eastern Health representatives)

Appendix E: Ethics Approval (HREB)

Included here is confirmation of approval of the most recent application to HREB related to this study (see Appendix D for the application).

amendment approved 466460

administrator@hrea.ca <administrator@hrea.ca> 13 December 2019 at 09:22
To: "Buckley Alvan(Principal Investigator)" <adb605@mun.ca>
Cc: "Hodgkinson Kathleen(Supervisor)" <KHODGKIN@mun.ca>, administrator@hrea.ca

Researcher Portal File #: 20181608

Dear Dr. Alvan Buckley:

This e-mail is to inform you that your amendment event – Event No. 466460 - for study HREB # 2018.015 – Single center experience with medium-term morbidity and mortality outcomes of mechanical and bioprosthetic aortic and mitral valve replacement. - was reviewed by the Chair and has been approved and/or acknowledged (as indicated in the Researcher Portal).
You may view this decision by logging into the Researcher Portal.

It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

Thank you,

Research Ethics Office

(e) info@hrea.ca
(t) 709-777-6974
(f) 709-777-8776
(w) www.hrea.ca
Office Hours: 8:30 a.m. – 4:30 p.m. (NL TIME) Monday-Friday

Appendix F: Ethics Approval (NLCHI)

Included here is confirmation of approval for access to the list of variables from NLCHI. For privacy reasons, the signature is concealed.

Data Custodian Variable List for Record-Level Information Request

To be completed by the data custodian/representative prior to HREB submission

Notes about the data requested:

Custodian Acknowledgment(s):

Organization: NL Centre for Health Information
Title: VP Data & Information Services
Name: Dr. Dan MacDonald
Signature: [redacted]
Date: Dec 6th, 2019

Organization: _____
Title: _____
Name: _____
Signature: _____
Date: _____

Organization: _____
Title: _____
Name: _____
Signature: _____
Date: _____

Organization: _____
Title: _____
Name: _____
Signature: _____
Date: _____

** Please note that this letter of acknowledgement does not represent permission to access the above data, it is only a confirmation that the above organization(s) is a/are custodian(s) of this data.