Review of Current Practices for the Assessment of Patients with Severe Aortic Stenosis and Predicting Poor Symptom Recovery After Aortic Valve Intervention

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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Summary

Review of Current Practices for the Assessment of Patients with Severe Aortic Stenosis and Predicting Poor Symptom Recovery After Aortic Valve Intervention

The work presented in this thesis explores the perioperative evaluation and management of patients with severe symptomatic aortic stenosis (AS), an increasing common calcific degenerative cardiac valvular disease, and further investigates novel mechanisms of residual symptoms of dyspnoea post-intervention.

The first three research chapters used a retrospective design to examine current practices. We first examined the effect of the introduction of a structural heart program with an accompanying multidisciplinary team on mortality in a tertiary hospital. We found that although no differences in mortality existed between the existing surgical valve replacement and the new transcatheter valve replacement, there was a significant mortality benefit in the AS population, attributed to the expansion of services and the use of multidisciplinary care.

We then analysed the use of balloon aortic valvuloplasty (BAV) as a temporizing measure in patients with severe AS. While BAV had previously fallen out of favour due to a lack of benefit long-term, we found a significant short to medium term mortality benefit, which may allow rapid relief of valvular obstruction, time for further investigation of comorbidities, improvement in cardiac function and safer subsequent procedures.

We then sought to clarify timing of intervention in patients with a discordant number of severe AS criteria. We found that patients with an increasing number of criteria had increased

mortality without intervention, and that those with fewer criteria had a delay in intervention. Despite this, we found that the effect of intervention was similar for all groups, indicating that earlier intervention may be beneficial.

The last three research chapters used a prospective design to examine residual dyspnoea in patients who had undergone intervention. We examined left ventricular strain in severe AS and found that patients with severe AS had reduced strain, indicating a degree of remodeling had already occurred. After intervention, patients who had an improvement in strain had a significantly greater improvement in symptoms than those who did not improve or worsened, implicating this as a cause of residual symptoms.

We then used a non-invasive bedside tool to measure the augmentation index, a marker of arterial stiffness. Since the valvuloarterial impedance is the combined obstruction to flow from the left ventricle due to both valvular disease and reduced systemic compliance, we measured the arterial stiffness after the valvular obstruction had been relieved, finding that those with a higher degree of arterial stiffness were more likely to suffer from residual dyspnoea, likely due to increased myocardial work.

Lastly, we examined the use of a commonly used frailty assessment and found that after intervention frailty improves significantly after intervention, indicating that frailty, as currently measured, may be more a symptom than a comorbidity.

Our research supports that careful consideration, but early action, may prevent irreversible cardiovascular injury leading to residual symptoms, despite intervention.

Declaration

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text. All non-original figures are permitted for reproduction under the licensing agreements of the journals in question.

Dr Dylan Jones, BSc, BMBS, FRACP

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Finally, this would not have been possible without the incredible support of my wife, Carrie, and my two children, Evelyn and Ethan, for providing love and support, and a reason to always strive for more, and my parents, for providing the education upon which this is built.

Abbreviations

6MWT – Six-Minute Walk Test

A_A – Ascending Aortic Area

ABS – Australian Bureau of Statistics

ACS – Acute Coronary Syndrome

AF – Atrial Fibrillation

AIx – Augmentation Index

AMP – Adenosine Monophosphate

ARF – Acute Rheumatic Fever

AS – Aortic Stenosis

AT – Applanation Tonometry

ATP – Adenosine Triphosphate

ATTR – Transthyretin Amyloidosis

AU – Agatston Units

AV – Aortic Valve

AVA – Aortic Valve Area

AVR – Aortic Valve Replacement

BAV – Balloon Aortic Valvuloplasty

BDM – Births, Death and Marriages

BMI – Body Mass Index

BMP-2 - Bone Morphogenic Protein 2

BNP – B-type Natriuretic Peptide

BP – Blood Pressure

CABG – Coronary Artery Bypass Grafting

CAD – Coronary Artery Disease

CAVD – Calcific Aortic Valve Disease

CCI – Charlson Comorbidity Index

CI – Confidence Interval

COPD – Chronic Obstructive Pulmonary Disease

CRP – C-reactive Protein

CRR - Clinical Reporting Repository

CT – Computed Tomography

CTS – Cardiothoracic Surgery

CVA – Cerebrovascular Accident

DM – Diabetes Mellitus

DPI – Dimensionless Performance Index

DSE – Dobutamine Stress Echo

ECG - Electrocardiogram

EDV – End-diastolic Volume

EF – Ejection Fraction

ELCo – Energy Loss Coefficient

eNOS – Endothelial Nitric Oxide Synthase

ENPP1 - Ectonucleotide Pyrophosphatase/Phosphodiesterase 1

EOA – Effective Orifice Area

ESV – End-systolic Volume

ETT – Exercise Treadmill Test

FFS – Fried Frailty Scale

GFR – Glomerular Filtration Rate

GLPS – Global Longitudinal Peak Strain

GLS – Global Longitudinal Strain

HF – Heart Failure

HFA – Hopkins Frailty Assessment

HR – Hazard Ratio

Hs-TNT – High Sensitivity Troponin T

HTN - Hypertension

iAVA – Indexed Aortic Valve Area

ICD-10AM - International Classification of Diseases 10th Revision, Australian Modified

ICU – Intensive Care Unit

IHD – Ischaemic Heart Disease

IL – Interleukin

IPW – Inverse Probability Weighted

ISAAC - Integrated South Australian Activity Collection

KCCQ – Kansas City Cardiomyopathy Questionnaire

KCCQ-OS – Kansas City Cardiomyopathy Questionnaire Overall Score

LAA – Left Atrial Area

LAS – Left Atrial Strain

LAV – Left Atrial Volume

LC – Left Coronary Cusp

LCA – Left Coronary Artery

LDL – Low Density Lipoprotein

LDLc – Low Density Lipoprotein Cholesterol

LFLG – Low Flow/Low Gradient

Lp(a) – Lipoprotein (a)

LV – Left Ventricle

LVEF – Left Ventricular Ejection Fraction

LVH – Left Ventricular Hypertrophy

LVOT – Left Ventricular Outflow Tract

LysoPC – Lysophosphatidylcholine

LVSP – Left Ventricular Systolic Pressure

MAP – Mean Arterial Pressure

MAPSE – Mitral Annular Plane Systolic Excursion

MDRD - Modification of Diet for Renal Disease

MD – Mechanical Dispersion

MDT – Multidisciplinary Team

MG – Mean Gradient

MI – Myocardial Infarction

MRI – Magnetic Resonance Imaging

NC – Non-coronary Cusp

NYHA – New York Heart Association

Ox-LDL – Oxidized Low Density Lipoprotein

Ox-PL – Oxidized Phospholipid

PICF – Patient Information and Consent Form

PP – Pulse Pressure

PPi – Pyrophosphate

PPM – Permanent Pacemaker

PVR – Paravalvular Regurgitation

PWA – Pulse Wave Analysis

QOL – Quality of Life

RAAS – Renin-Angiotensin-Aldosterone System

RANKL - Receptor Activator of Nuclear Factor Kappa B

RC – Right Coronary Cusp

RCA – Right Coronary Artery

RCT – Randomised Controlled Trial

RHD – Rheumatic Heart Disease

ROS – Reactive Oxygen Species

Runx2 - Runt-related Transcription Factor 2

SA – South Australia

SAC – Systemic Arterial Compliance

SAHMRI – South Australian Health and Medical Research Institute

SALHN – Southern Adelaide Local Health Network

SAP – Systolic Arterial Pressure

SAVR – Surgical Aortic Valve Replacement

SD – Standard Deviation

SEVR – Subendocardial Viability Ratio

STS – Society of Thoracic Surgeons

SV – Stroke Volume

SVi – Stroke Volume Index

TAVI – Transcatheter Aortic Valve Implantation

TAVR – Transcatheter Aortic Valve Replacement

TGF – Transforming Growth Factor

TNF – Tumour Necrosis Factor

TTP – Regional Strain Time to Peak

TVT – Transcatheter Valve Therapy

VEC – Valvular Endothelial Cell

VIC – Valvular Interstitial Cell

VARC - Valve Academic Research Consortium

Vmax – Peak Velocity

VTI – Velocity Time Integral

Wnt – Wingless and Int-1

Zva – Valvuloarterial Impedance

CHAPTER 1

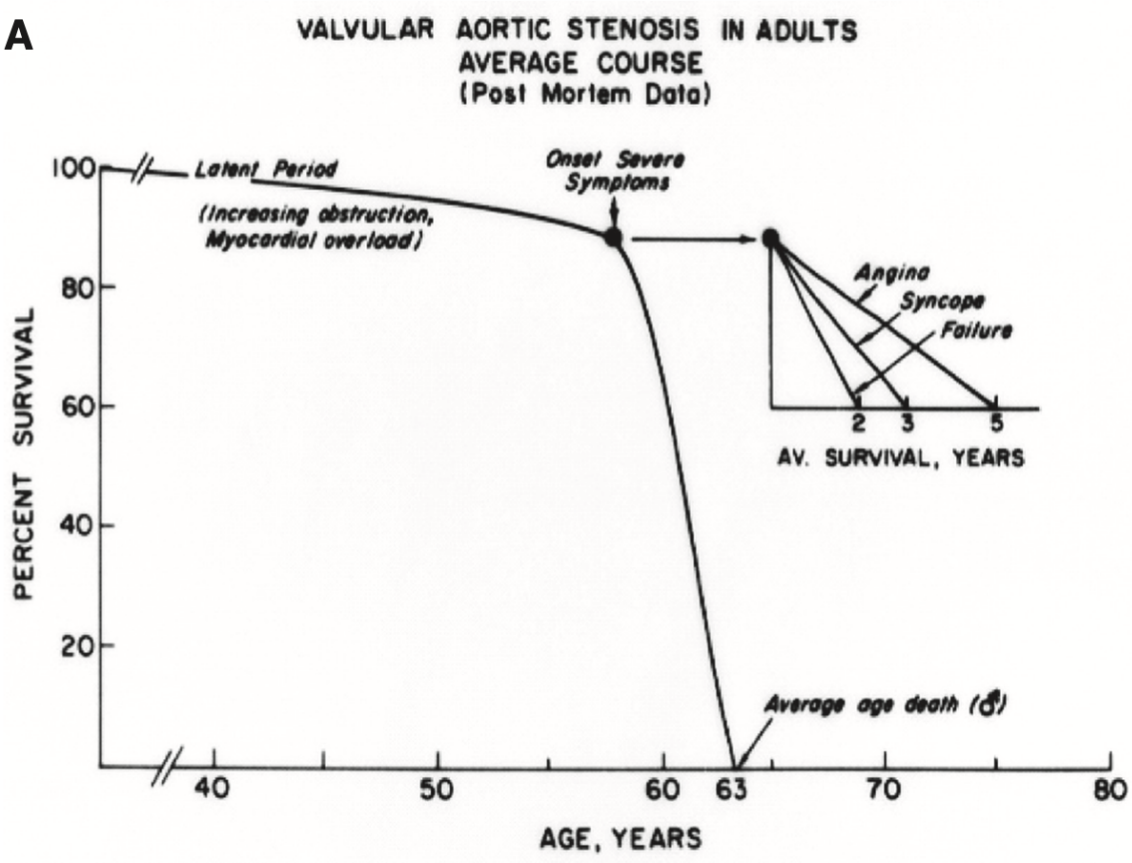
GENERAL OVERVIEW AND INTRODUCTION

1.1 General Overview and Introduction

Aortic stenosis (AS) is the most common degenerative valvular disorder worldwide, characterised by calcification and restriction of the aortic valve (AV) leaflets, typically in the elderly. It affects 2-4% of the population over 75 years of age, and the incidence is rising as the population ages[1, 2]. Calcific AS is now the most common form of the disease, overtaking rheumatic valvular disease and congenital bicuspid aortic stenosis due to the improvements in medical therapy in developed nations over the last 5 decades[1, 3].

Traditionally, it has been taught that AS is associated with a long latent period followed by a symptomatic period associated with a precipitous increase in mortality, as demonstrated by Ross and Braunwald in 1968 (Figure 1.1)[4]. Without aortic valve replacement (AVR), the natural history of severe symptomatic AS is bleak, with a 2-year mortality of ~50%[5].

Figure 1.1. Survival of aortic stenosis (AS) patients according to symptomatic status in the middle of the 20th century

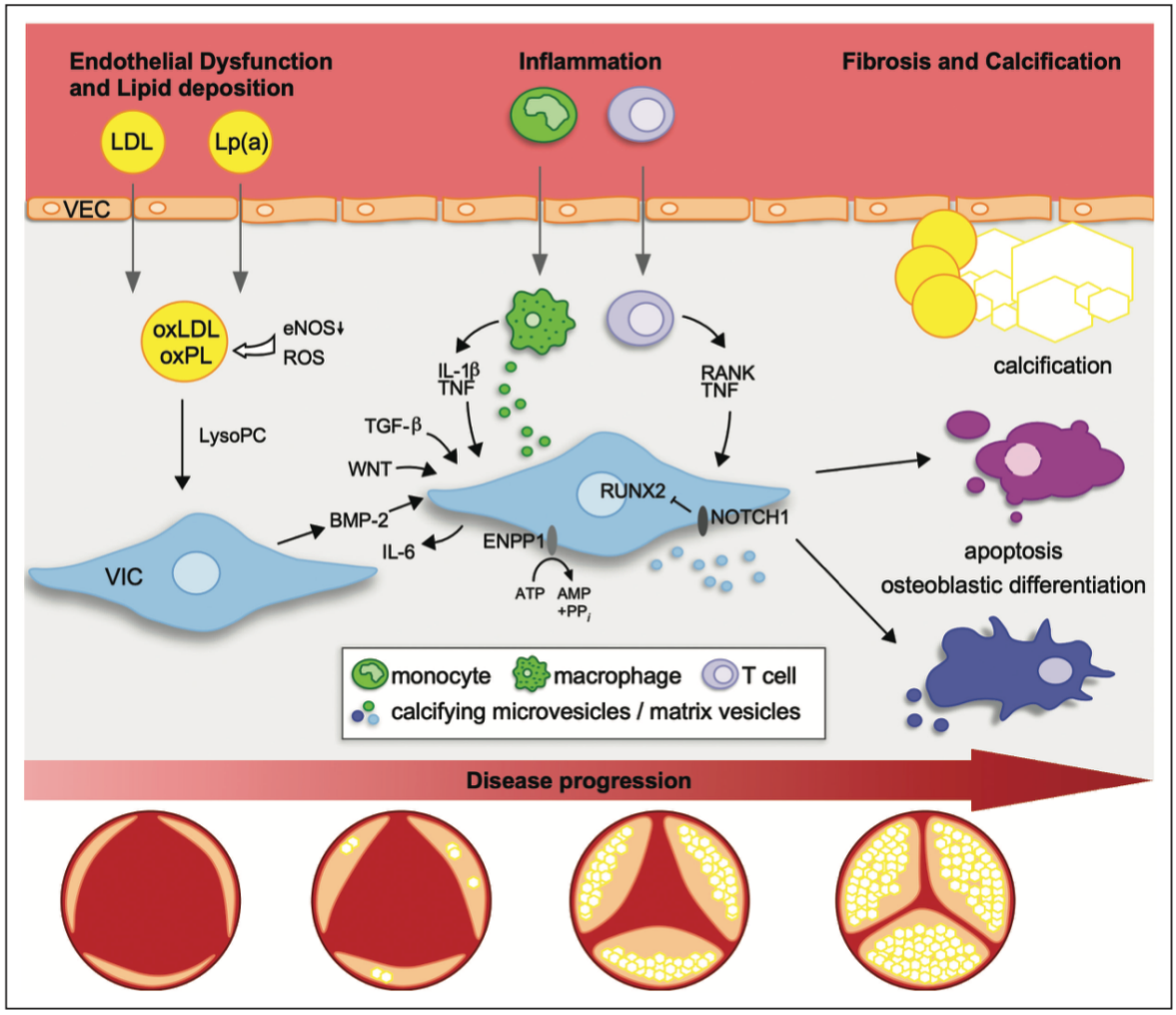


In the modern era, the onset of the disorder is much later, and therefore the likelihood of competing age-related comorbidities is greater, complicating the decision to undergo invasive therapies. In this chapter, we will discuss the pathobiology of AS, the mechanisms and importance of symptoms, the available treatments for AS and finally outline novel considerations for the assessment of AS and investigations for residual symptom states.

1.2 Pathophysiology of Aortic Stenosis

The pathogenesis of AS occurs in several phases. In the initial phase, valvular endothelial injury occurs, allowing immune cells to infiltrate, leading to the propagation phase, characterized by myofibroblastic/osteoblastic differentiation of valvular interstitial cells, and subsequent calcification of the valve leaflets. An overview of this process has been elegantly demonstrated by Goody et al in Figure 1.2[5].

Figure 1.2. Phases of calcific aortic valve disease (CAVD).



AMP=Adenosine Monophosphate, ATP=Adenosine Triphosphate, BMP-2=Bone Morphogenic Protein 2, CAVD=Calcific Aortic Valve Disease, ENPP1=Ectonucleotide Pyrophosphatase/Phosphodiesterase 1, IL=Interleukin, LDL=Low Density Lipoprotein, Lp(a)=Lipoprotein (a), LysoPC=Lysophosphatidylcholine, Ox-LDL=Oxidized Low Density Lipoprotein, Ox-PL=Oxidized Phospholipid, PPi=Pyrophosphate, RANKL=Receptor Activator of Nuclear Factor Kappa B, ROS=Reactive Oxygen Species, Runx2=Runt-related Transcription Factor 2l TGF=Transforming Growth Factor, TNF=Tumour Necrosis Factor, VEC=Valvular Endothelial Cell, VIC=Valvular Interstitial Cell, Wnt=Wingless and Int-1

To summarise in brief, the initial phase begins with a stimulus such as mechanical or shear stress, causing dysfunction of the valvular endothelial cells (VECs). This allows the infiltration of lipoproteins, such as low-density lipoproteins (LDL) and lipoprotein (a) (Lp(a)), and immune cells to reach the interstitium. Reactive oxygen species oxidate lipids and promote apoptosis of valvular interstitial cells (VICs), leading to diffuse calcification. VICs are then stimulated by macrophages and T cells to differentiate into osteoblasts promoting further calcification[5].

1.2.1 Epidemiology

The prevalence of AS differs according to the population studied due to differences in the aetiology of aortic stenosis between the developed and developing populations. In Western society, the prevalence of AS increases exponentially with age, with an estimated prevalence in the Norwegian population of 0.2% in the age 50-59 cohort, 1.3% aged 60-69, 3.9% aged 70-79, and 9.8% in the 80-89 cohort. There were no differences between genders[6].

In Australia, there is a second distinct population of valvular heart disease due to the unfortunate prevalence of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in the indigenous population. Between 2013 and 2017 the incidence of ARF among indigenous Australians was 85 per 100,000 compared with 4 per 100,000 overall. This leads to an incidence of RHD in Australia of 50 per 100,000, 87% of whom are indigenous Australians[7].

1.2.2 Risk Factors

Although the incidence of aortic stenosis is associated with age, age is not the only risk factor for aortic valve calcification. The process of endothelial injury, lipid deposition and inflammation and osteogenic infiltration of interstitial cells is remarkably similar to coronary atherosclerosis. Stewart at al. found that many risk factors associated with coronary disease were also associated with AV calcification (Figure 1.3). Risk factors implicated in aortic sclerosis include smoking, hypertension, dyslipidaemia, diabetes and Lp(a) levels[8-12].

Figure 1.3. Clinical Factors Associated with Aortic Stenosis or Sclerosis by Stepwise Multiple Logistic Regression

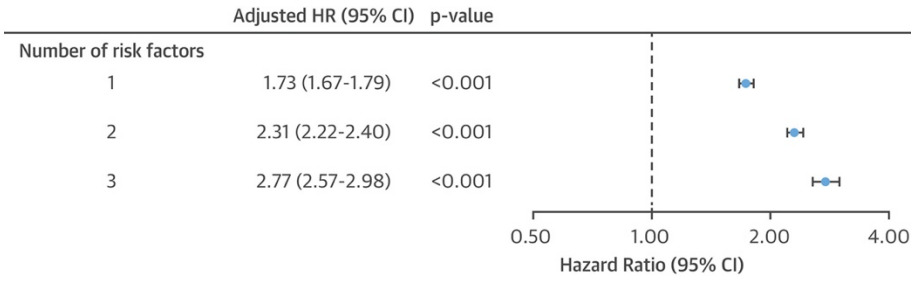
Variable	p Value	Odds Ratio	95% Confidence Limits
Age	<0.001	2.18*	2.15, 2.20
Male gender	<0.001	2.03	1.7, 2.5
Lp(a)	<0.001	1.23†	1.14, 1.32
Height (cm)	0.001	0.84‡	0.75, 0.93
History of hypertension	0.002	1.23	1.1, 1.4
Present smoking	0.006	1.35	1.1, 1.7
LDLc (mg/dl)	0.008	1.12†	1.03, 1.23

*± 75th vs. 25th percentile. †± 10-year increase. ‡± 10-unit increase. LDLc = low density lipoprotein cholesterol; Lp(a) = lipoprotein(a).

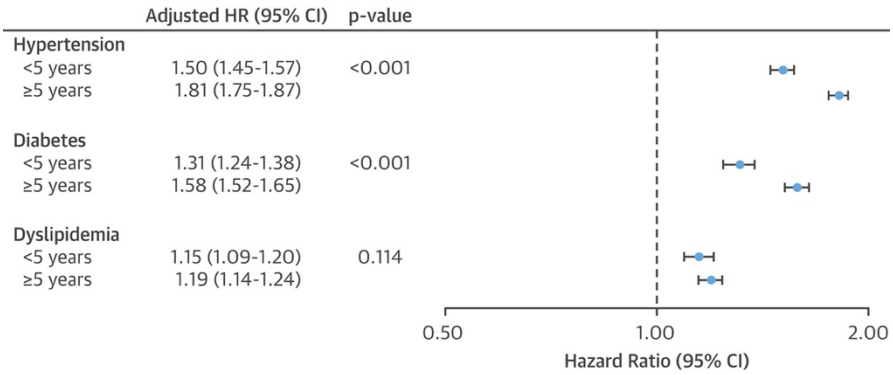
Additionally, Yan et al. used a “big data” approach in a database of 1.1 million Canadian residents over the age of 65 and found a positive dose-response of developing aortic stenosis over 13 years with comorbidities of hypertension, dyslipidaemia and diabetes, as well as a duration-response relationship (Figure 1.4)[13].

Figure 1.4. a) The Relationship Between Number of Cardiac Risk Factors and Aortic Stenosis, b) The Relationship Between Duration of Cardiac Risk Factors and Aortic Stenosis

a)



b)



1.2.4 Haemodynamic and Physiologic Mechanisms

Although typically considered a valvular disorder, AS is often associated with abnormalities of the myocardium and the systemic vascular system as well. Left ventricular (LV) dysfunction can lead to reduced flow velocities and pressures across the aortic valve, leading to difficulties in the assessment of severity of AS and clinical decision-making regarding intervention. Reduced systemic arterial compliance (SAC) can also have an impact on the pathophysiology and clinical outcomes, which could indicate why some patients develop symptoms when the aortic gradients would not typically be considered severe and why others

with clearly severe AS remain asymptomatic[14]. When assessing a patient with AS, all of these factors must be considered as a connected system.

1.2.4.a Aortic Valve Stenosis

AS severity is classically determined by measuring the mean pressure difference across the stenosed valve (the mean gradient or MG, in mmHg), the velocity of the jet caused by the contraction and acceleration of flow through the narrowed orifice (the peak velocity or Vmax, in m/s), the effective orifical valve area at the vena contracta, the smallest point of the flow jet (the aortic valve area or AVA, in cm^2), both in absolute terms and indexed to body surface area (iAVA, in cm^2/m^2), and using a dimensionless performance or severity index (DPI), which gives a unitless ratio of LV outflow tract (LVOT) velocity or velocity time integral (VTI) to AV velocity or VTI, which attempts to remove confounding due to low flow states due to LV dysfunction[2, 14, 15].

The values considered severe in the above measures in the guidelines for aortic stenosis evaluation were established using catheter measurement data and then extended to echocardiographic data on the assumption that these values were equivalent, when in reality, these can vary by up to 50%[14]. Echocardiographic measurements tend to be made at the level of the vena contracta using the continuity equation[16, 17],

$$AVA = (LVOT\ VTI \times Peak\ LVOT\ Velocity)/Peak\ (AV)\ Velocity$$

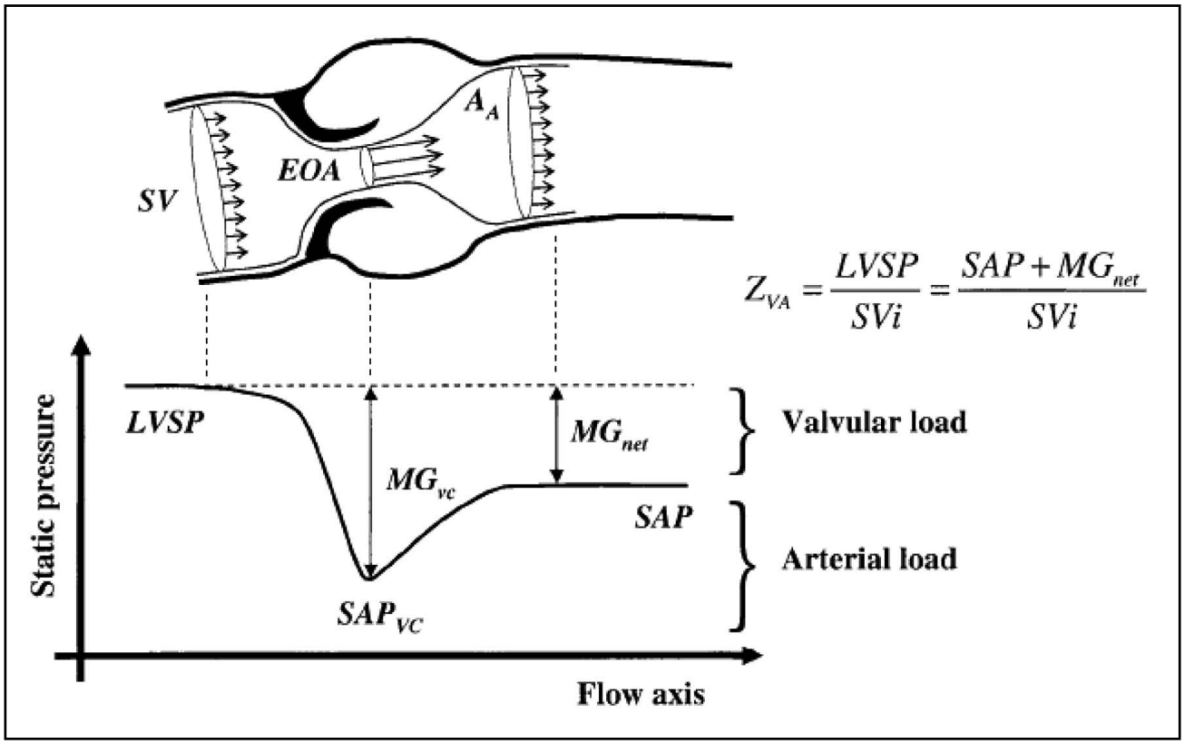
whereas catheter measurements tend to be taken a few centimetres downstream using the Gorlin formula[17, 18].

$$AVA = Cardiac\ Output/(Systolic\ Ejection\ Period \times Heart\ Rate \times 44.3 \times \sqrt{Pressure\ Gradient})$$

The differences observed can be explained by the concept of the pressure recovery phenomenon (Figure 1.5)[14, 19]. When flow passes through the vena contracta, some of the potential energy (a representation of pressure) is converted into kinetic energy (a representation of velocity). After passing through the stenotic valve, the flow jet expands, resulting in turbulent flow. This causes some energy loss in the form of heat, but much of the kinetic energy is converted back into potential energy, resulting in slower velocities, but higher pressures. Therefore, the difference in pressure from the LVOT may be greater at the level of the vena contracta, compared with the aortic root, and catheter measurements may be lower than the echocardiographic measurements. An energy loss coefficient (ELCo) can be used with echocardiographic measurement of the AVA and the ascending Aortic Area (A_A) to resolve this discrepancy.

$$ELCo = (AVA \times AA)/(AA\text{-}AVA)$$

Figure 1.5. Schematic representation of the flow and static pressure across the left ventricular outflow tract, aortic valve and ascending aorta during systole.



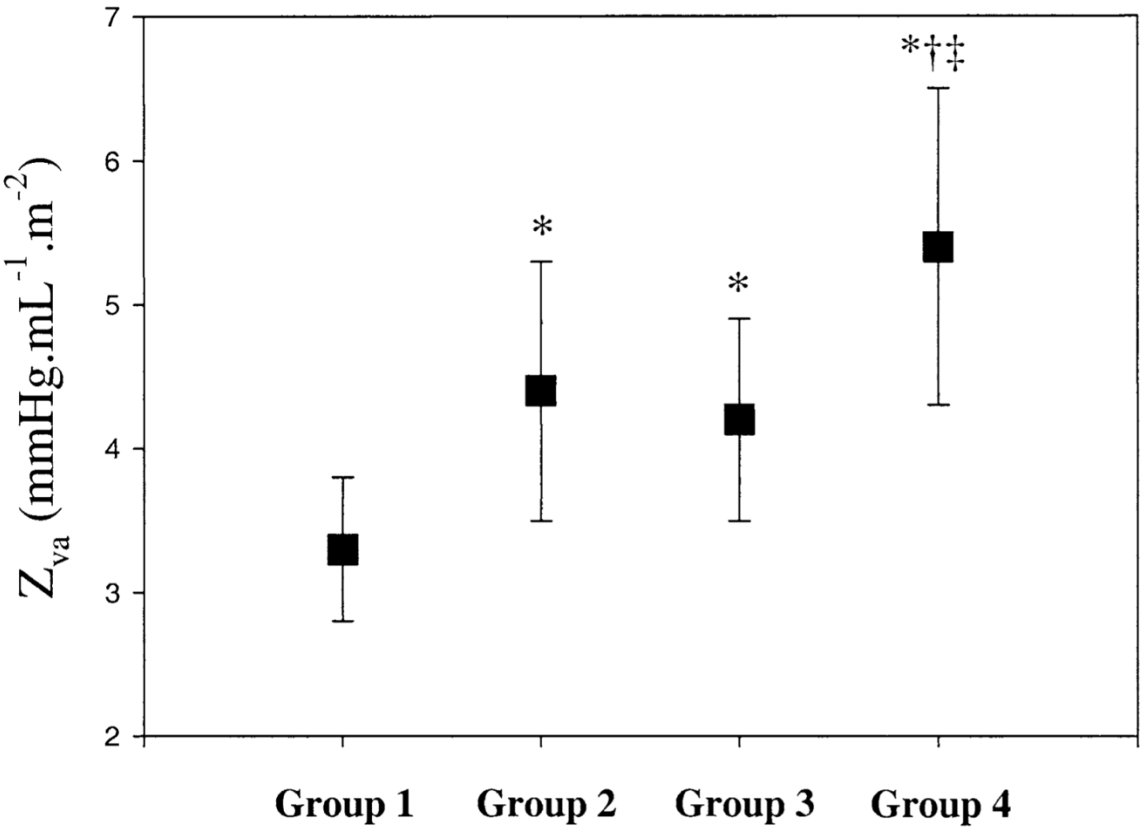
A_A=Aortic Cross-sectional Area, EOA=Effective Orifice Area, LVSP=Left Ventricular Systolic Pressure, MG_{net}=Net Mean Gradient, MG_{vc}=Mean Gradient at the Vena Contracta, SAP=Systolic Aortic Pressure, SAP_{vc}=Systolic Aortic Pressure at the Vena Contracta, SV=Stroke volume, SVi=Stroke Volume Index, Z_{va}= Valvuloarterial Impedance

1.2.4.b Arterial Stiffness

Figure 1.5 also introduces the topic of the Valvuloarterial impedance (Zva), which is the combined haemodynamic myocardial load due to the summation of both the valvular obstruction and the pressure afterload of the systemic vasculature. Focusing on the valvular obstruction alone is to ignore a significant variable contributing to increased myocardial work.

Hypertension, diabetes, dyslipidaemia and atherosclerosis can lead to increased reduced systemic arterial compliance, which limits the ability of the systemic vasculature to buffer increases in phasic pressure[20-23]. Reduced SAC can lead to further hypertension, contributing to myocardial oxygen demand, and leading to worse symptoms[19]. Additionally, reduced SAC has been linked to the development of LV dysfunction and poor outcomes, including in the AS population[19, 24]. The degree of myocardial work contributed to by reduced arterial compliance can be very similar to that of severe AS, as shown by Briand et al in Figure 1.6, and therefore must be considered[19].

Figure 1.6. Comparison of the Valvuloarterial Impedance (Z_{va}) in Patients with Varying Degrees of AS and reduced SAC.

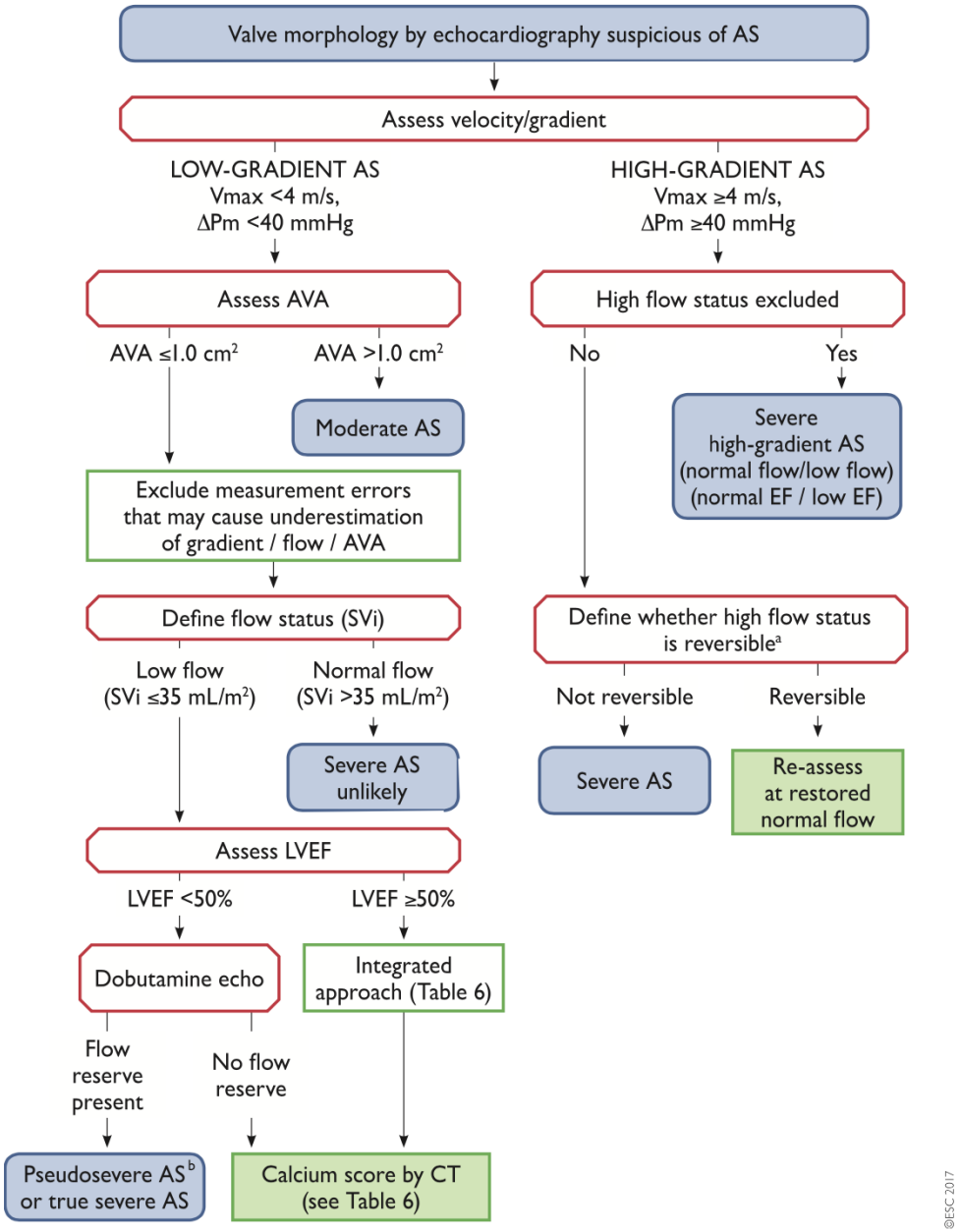


Group 1 - patients with moderate aortic stenosis (AS) and normal systemic arterial compliance (SAC), Group 2 - patients with moderate AS and reduced SAC, Group 3 - patients with severe AS and normal SAC, and Group 4 - patients with severe AS and reduced SAC. *Significant difference versus group 1; †significant difference versus group 2; ‡significant difference versus group 3.

1.2.4.c Left Ventricular Dysfunction

The presence of ventricular dysfunction can alter the haemodynamics of blood flow through the aortic valve, and lead to an underestimation of AS severity. Relative to a normal ventricle, a dysfunctional ventricle often cannot generate sufficient force to drive the potential and kinetic energies to generate the AV Vmax or MG stipulated as classically severe in the guidelines, despite a similar AVA. Low Flow/Low Gradient (LFLG) aortic stenosis is associated with significant mortality despite the relatively lower gradients, and mortality is significantly improved with AVR[25-27]. When evaluating for severe AS, the flow to the valve must be considered in addition to the flow through the valve, by accounting for stroke volume of the LV. As previously stated, DPI attempts to overcome this by measuring AV flow relative to LVOT flow, thereby accounting for lower haemodynamic energy prior to reaching the valvular obstruction. The guidelines account for these discrepancies using the following algorithm (Figure 1.7)[2].

Figure 1.7. Stepwise Integrated Approach for the Assessment of Aortic Stenosis Severity.



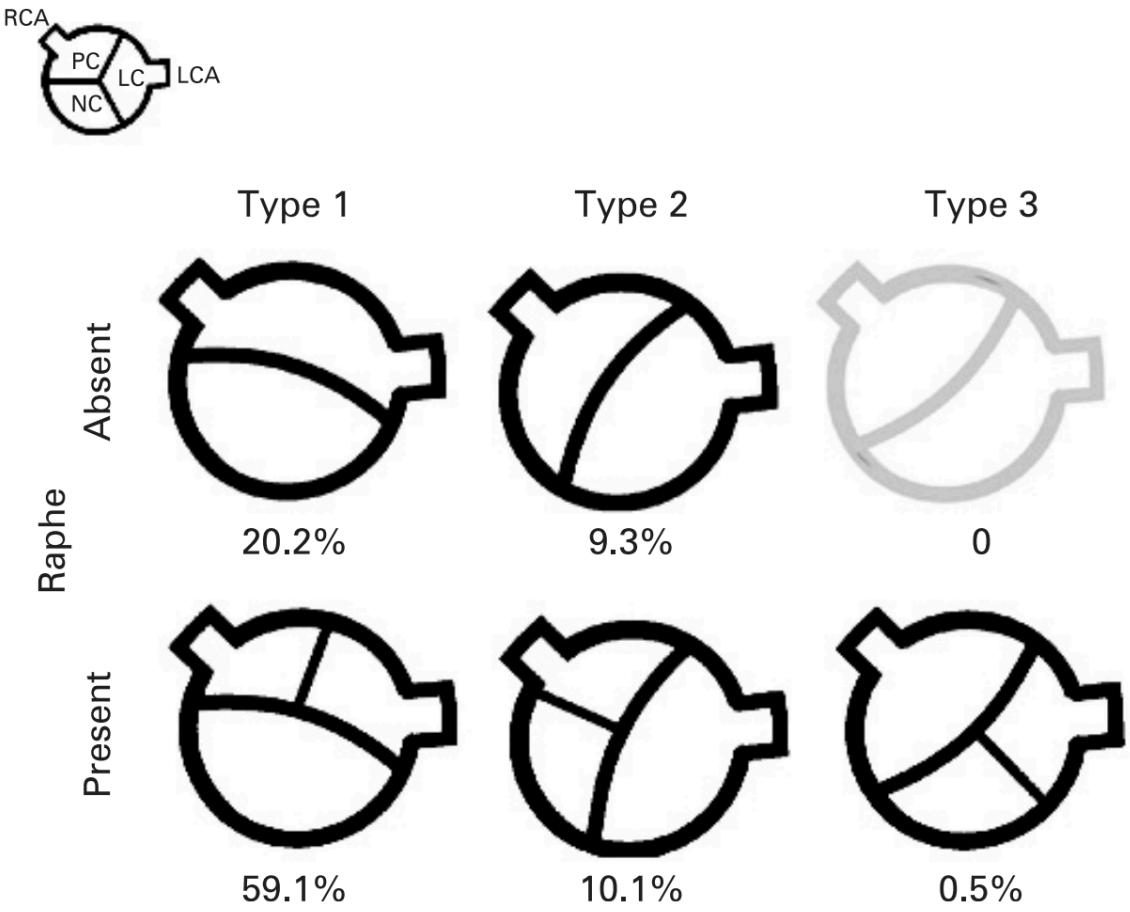
[a]High flow may be reversible in settings such as anaemia, hyperthyroidism, arteriovenous shunts. [b]Pseudosevere AS is defined by an increase to an AVA >1.0cm^2 with flow normalization. ΔPm=Mean Transvalvular Pressure Gradient, AS=Aortic Stenosis, AVA=Aortic Valve Area, CT=Computed Tomography, EF=Ejection Fraction, LVEF=Left Ventricular Ejection Fraction, SVi=Stroke Volume Index, Vmax=Peak Velocity.

1.2.5 Types of Non-Calcific Aortic Stenosis

While calcific AS is the most common form of AS in the elderly and the developed world, rheumatic heart disease is the most common acquired valvular disease in children and young adults in the developing world, and is linked to poor access to healthcare and exposure to rheumatic fever from group A streptococcus infections[28-30]. Acute rheumatic fever can affect all parts of the heart (pericardium, myocardium or valves) and can lead to chronic valvular disease, often affecting multiple valves. Due to the significant differences in aetiology, disease pathology and population from calcified AS, RHD will not be explored further in this document.

Bicuspid AS results from a congenital abnormality in which a patient is either missing an aortic valve leaflet, or two or three leaflets are fused together (Figure 1.8). It is relatively common, with a prevalence of 0.5-2% in the general population, more commonly in males, and can be hereditary in 10-30% of families[31, 32]. As well as the increased wall stress from increased turbulent flow through the abnormal aortic valve, there is also often a genetic abnormality of wall elasticity, leading to increased rates of aortic dissection and aneurysm[33-36]. Bicuspid AVs are prone to early degeneration at a mean age of 55, leading to stenosis, regurgitation or both, but the histopathological features of the bicuspid valve are similar to that of trileaflet AS[37-39]. Further discussion of the treatment of bicuspid and tricuspid aortic stenosis will be made in a subsequent section.

Figure 1.8. Bicuspid Aortic Valve Leaflet Morphology.



Schematic of bicuspid AV phenotypes as seen from a parasternal short axis view on echocardiography. Small inset top left depicts a normal aortic valve in the same orientation with right coronary cusp (RC), left coronary cusp (LC), non-coronary cusp (NC), right coronary artery (RCA) and left coronary artery (LCA). Valve phenotypes and their frequencies are shown: type 1, ‘‘fusion’’ between right and left coronary cusp; type 2, ‘‘fusion’’ between right and non-coronary cusp; type 3, ‘‘fusion’’ between left and non-coronary cusp. Top row, without a raphe; bottom row with raphe. Type 3 without a raphe was not seen in our study group. Numbers indicate the observed frequency in our cohort.

1.3 Symptoms in Aortic Stenosis

50 years of research into AS management has been predicated on the notion that there is a safe latent period, even when AS is severe, if the patient is asymptomatic, as demonstrated by Ross and Braunwald[4]. This seminal paper was written in the early days of aortic valve surgery, when operative mortality was high, 5-15%, even in the relatively younger and healthier, predominantly rheumatic aortic stenosis seen at that time. There was an understandably difficult balance to reach between treating AS before the onset of irreversible cardiac damage and avoiding the high risk of surgery. Braunwald himself, on the 50th anniversary of the original paper, marvels at the changes and advances seen since, including the change in the patient demographic, the earlier detection via echocardiography, the significant decline in surgical risk and the development of less invasive transcatheter methods of intervention[40]. Despite these advances in detection and intervention, it is still guideline directed that symptoms be present prior to intervention in most cases, despite mounting evidence that asymptomatic AS is not benign and intervention is beneficial[2, 15, 41, 42].

The classic symptoms associated with AS include angina, dyspnoea and syncope. In a general sense, angina occurs when the myocardial oxygen demand exceeds the myocardial oxygen supply. In ischaemic heart disease (IHD), angina is related to coronary luminal obstruction, whereby the abnormal feature is the reduced blood supply to the myocardium via a fixed coronary stenosis. In AS, oxygen demand is increased due to increased wall stress and LV hypertrophy, and concurrently, coronary flow reserve may be limited by more than 50% due to reduction in autoregulation mechanisms and increased LV diastolic pressures limiting endocardial flow[3, 43-45].

Syncope is a reversible loss of consciousness occurring due to temporary reduction in blood flow to the brain. In AS, this typically occurs during exertion. Since blood pressure is a product of cardiac output and peripheral resistance, it is thought that the reduction in peripheral resistance during exercise cannot be compensated for by a cardiac output which has a fixed limit due to the valvular obstruction, and temporary cerebral hypotension occurs, leading to syncope[3, 46]. This can be compounded by a strong vasodepressor effect caused by elevated LV pressures, or a reduction in appropriate vasoconstriction mechanisms[46, 47].

Dyspnoea is not a feature of a single abnormality in AS, but rather a combination of several mechanisms. Constant pressure overload leads to LV remodeling and hypertrophy, which gradually cause diastolic and then systolic dysfunction[48]. Concentric hypertrophy leads to prolonged relaxation and shortened filling time, and greater filling pressures required in passive filling[3, 49]. Systolic dysfunction can then occur due to myocardiocyte dysfunction and/or afterload mismatch, leading to a reduced cardiac output[43, 50].

The exact mechanisms and severity of symptoms in the AS population can be difficult to predict, and do not seem to be related to the degree of valvular stenosis, but rather to left ventricular myocardial factors, such as abnormal global longitudinal strain (GLS) and reduced ejection fraction (EF), raised biomarkers for pressure overload such as b-type natriuretic peptide (BNP), abnormal flow/pressure haemodynamics (E/e`, stroke volume and left atrial pressure) and arterial factors, such as Zva, despite no difference in AVA or MG between symptom groups, as demonstrated by Spampinato et al (Figure 1.9)[48].

Figure 1.9. Laboratory and echocardiographic indices associated with NYHA class

	Total ($n=118$)	NYHA I–II ($n=84$)	NYHA III–IV ($n=34$)	p-Value
Echocardiographic indices				
EF, %	58 ± 10.2	60 ± 8.3	52 ± 12.4	**<0.001**
E/e′	16 ± 6.3	14.2 ± 5	20.6 ± 6.7	**<0.001**
MAPSE, mm	14.4 ± 3.4	15.1 ± 3.2	12.6 ± 3.4	**<0.001**
GLPS, %	−15.4 ± 3.8	−16.4 ± 3	−13 ± 4	**<0.001**
Stroke volume index, ml/m^2	36.9 ± 10	39.2 ± 9.7	31.5 ± 8.9	**<0.001**
EDVi, ml/m^2	43.3 ± 17.5	41.7 ± 16	47 ± 20.3	0.17
ESVi, ml/m^2	18.7 ± 11.8	17 ± 9.8	22 ± 15.1	**0.04**
LAVi, ml/m^2	45 ± 14.6	42.5 ± 13	51.2 ± 17	**0.003**
LAAi, cm^2/m^2	12.3 ± 2.8	11.8 ± 2.6	13.6 ± 2.9	**0.001**
Aortic valve area, cm^2	0.7 ± 0.16	0.7 ± 0.16	0.66 ± 0.17	0.15
Aortic valve area index, cm^2/m^2	0.37 ± 0.09	0.37 ± 0.09	0.35 ± 0.08	0.22
Peak aortic velocity, m/s	4.3 ± 0.7	4.35 ± 0.6	4.05 ± 0.9	**0.045**
Mean aortic pressure gradient, mmHg	50.2 ± 16	51 ± 13.5	47.4 ± 21	0.23
Trans-tricuspidal gradient, mmHg	34.5 ± 11	31.3 ± 6.6	41 ± 14.7	**<0.001**
Mass index, g/m^2	145 ± 42.7	143 ± 38	148 ± 50	0.52
Posterior wall diastolic thickness, mm	13 ± 2	12.8 ± 2	13.4 ± 2.4	0.15
Zva, mmHg/ml m^2	5.9 ± 1.7	5.6 ± 1.4	6.5 ± 2.2	**0.01**
Laboratory parameters				
BNP, ng/L, median (IQR)	559 (278–1654)	399 (215–1074)	1512 (677–6179)	**<0.001**
Activated BNP, n (%)	81 (68.6)	52 (61.9)	29 (85.3)	**0.016**
hs-TNT, ng/L, median (IQR)	12 (9–18)	11 (8–16)	20 (10–59.5)	**<0.001**
Positive hs-TNT, n (%)	49 (41.5)	29 (34.5)	20 (58.8)	**0.02**
CRP, mg/dl, median (IQR)	0.2 (0.1–0.3)	0.2 (0.1–0.2)	0.35 (0.18–0.9)	**0.001**
Creatinine, mg/dl	1.0 ± 0.34	0.95 ± 0.3	1.14 ± 0.4	**0.003**
Glucose, mg/dl	119 ± 39	117 ± 33	124 ± 51	0.36

NYHA, New York Heart Association functional class; EF, left ventricular ejection fraction; E/e′, E/e′ ratio from the medial mitral annulus; MAPSE, mitral annular plane systolic excursion; GLPS, global longitudinal peak systolic strain; EDVi, LV end-diastolic volume index; ESVi, LV end-systolic volume index; LAVi, left atrial volume index; LAAi, left atrial area index; Zva, valvulo-arterial impedance; BNP, pro-B-type natriuretic peptide; Activated BNP, BNP ratio >1; hs-TNT, high-sensitive troponin T; Positive hs-TNT, TNT >14 ng/L; CRP, C-reactive protein. Unless otherwise specified, values are expressed as mean ± SD.
Bold values identify a p.

1.3.1 Importance of Symptoms

Symptom states are very important to determine accurately in AS. Not only does the presence and severity of symptoms correlate with outcomes[51-54], but symptom relief is often more important than prognosis in the typically elderly patient cohort[55-57]. For this reason, it was important to develop accurate and reproducible tools for the measurement of symptom burden, including subjective factors such as health status and quality of life and objective factors such as mobility and strength.

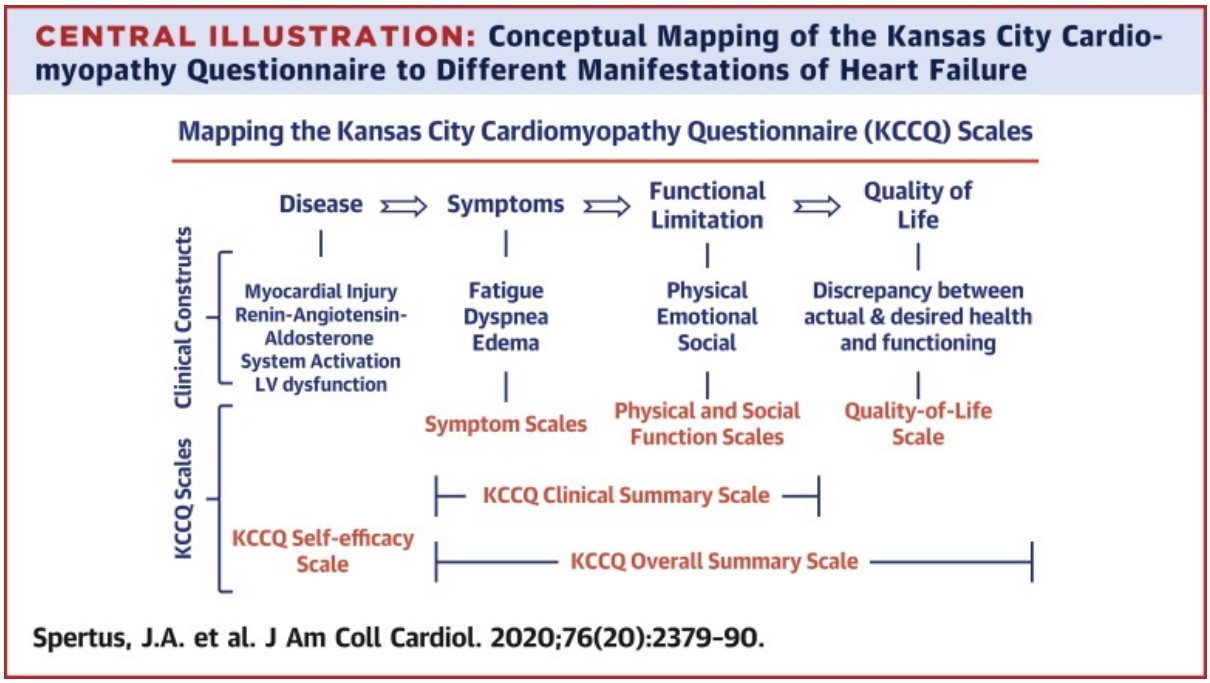
1.3.2 Measuring symptoms

In order to be effective tools for clinical use and research, symptom measures need to be easy to administer, reproducible, and address appropriate criteria. In this thesis and in many trials, a combination of subjective and objective tools were used in order to fully capture all aspects of symptomatology and changes after intervention.

1.3.2.a The Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was originally designed as a tool to monitor symptoms in the heart failure population, but has been validated extensively in the AS population, and used in the landmark PARTNER trials[55, 58-61]. The KCCQ is a 23-item questionnaire that addresses the domains typically affected by symptoms of heart failure: physical limitation, symptoms, quality of life, social limitation, symptom stability and self-efficacy[62]. There are multiple variations of the KCCQ score, focusing on different aspects of symptoms, as demonstrated in Figure 1.10[63]. For the purposes of this thesis, the KCCQ score used will be the KCCQ Overall Summary Score (KCCQ-OS). Not only is the KCCQ a reliable and reproducible symptoms metric, but the results correlate with long-term mortality in the transcatheter aortic valve replacement (TAVR) treated population[51].

Figure 1.10. Conceptual Mapping of the KCCQ to Different Manifestations of Heart Failure



KCCQ=Kansas City Cardiomyopathy Questionnaire

1.3.2.b The New York Heart Association Functional Class

The New York Heart Association (NYHA) Class is a simple, commonly used tool to measure the degree of functional limitations due to symptoms, again developed for heart failure patients in 1964. It uses a four-stage classification system: NYHA I – No limitation due to dyspnoea, NYHA II – Limitation due to dyspnoea with significant effort, NYHA III – Limitation due to dyspnoea with mild effort and NYHA IV – Limitation at rest due to dyspnoea[64]. Because of its ease of use, it has been routinely used in many outcome trials in AS, with significant improvements post intervention[65], although its simplicity makes stratifying patients with milder variations in symptom level difficult.

1.3.2.c The Six-Minute Walk Test

The Six-Minute Walk Test (6MWT) is a standardized methods of determining walking distance over a moderate distance. Patients are instructed to walk as far as possible over a flat track for 6 minutes, with the outcome variable being the distance reached measured in metres[66]. This can often be accompanied by a shorter assessment of gait speed over 4 or 5m, measured in m/s. The 6MWT has been shown to be comparable to cardiopulmonary testing in the heart failure population, can be used as a measure of frailty and correlates with long-term outcomes in the TAVR population, and improves with intervention[52, 53, 67-69]. The NYHA and KCCQ are questionnaire driven and rely on the patient's own interpretations of their symptoms, which although of high importance, can be influenced by other factors such as depression[70]. The 6MWT provides an objective, quantifiable measure of symptoms to be used as a complement to the subjective symptom scores.

1.3.3 Determining the Cause of Symptoms in Patients with Severe Aortic Stenosis and Competing Medical Conditions

In nearly every trial measuring symptoms before and after AV intervention for severe AS, symptoms scores have improved dramatically, when measuring the cohort as a whole. At an individual level, the degree of symptom recovery can be quite variable, and the causes of residual symptoms can be varied. When investigating a patient for residual breathlessness post intervention, it can be useful to try to differentiate between cardiac and non-cardiac causes of dyspnoea based on clinical history, examination, and investigations. This next segment will focus on outlining common causes for residual dyspnoea, and subsequent chapters will outline novel potential causes for ongoing symptoms post intervention.

1.3.3.a Valvular Cardiac Disease

The success rate of AVR is quite high in the modern era, but after intervention, there can still be some cause of dyspnoea related to valvular disease. Post-procedurally, rare but well-known complications of the replaced or implanted valve can lead to residual symptoms, including paravalvular and valvular regurgitation, valve restenosis, and leaflet thrombosis and should be considered if ongoing symptoms[71, 72].

Degenerative aortic valve disease can often be accompanied by disease in other valves, particular in the RHD population. Multiple and mixed valvular heart disease is quite common, with up to 20% of patients with one moderate valvular disorder having at least one other valvular abnormality of moderate severity according to the Euro Heart Survey, and 11% of valve operation in the US between 2003 and 2007 being double valve operations[73].

1.3.3.b Non-Valvular Cardiac Disease

The natural history of AS, as described above, consists of an asymptomatic period of gradually increasing intracardiac pressures, leading to cardiac remodeling and hypertrophy to compensate for the increased workload caused by the valvular obstruction. Since intervention typically occurs once symptoms have developed, in many cases significant cardiac changes to have already occurred, driving these symptoms as described in section 1.3. These changes, indirectly related to valvular obstruction, include LV hypertrophy (LVH), leading to ventricular stiffness and diastolic dysfunction, increased left atrial pressure, post-capillary pulmonary hypertension, and in later stages significant systolic dysfunction or "valvulomyopathy", which can often be reversed by intervention[27, 74, 75].

There are several other non-valvular conditions which can occur in conjunction with aortic stenosis which can also lead to dyspnoea. As previously stated, the risk factors and pathogenesis of AS is remarkably similar to that of coronary artery disease (CAD), and the presence of coronary disease is a common finding during the workup for aortic valve intervention. Patients with severe AS have been shown to have a higher prevalence of coronary risk factors, a higher prevalence of coronary artery disease and a higher likelihood of coronary events[76]. This can present similarly to the symptoms of aortic stenosis, with exertional dyspnoea and angina, and so should be considered if symptoms persist. This can be evaluated using exercise or dobutamine stress testing if coronary angiography has not been recently assessed.

Non-valvular and non-ischaemic cardiomyopathies can also be considered, and particular attention should be made to cardiac amyloidosis. Both amyloidosis and calcific AS tend to occur in older patients and wild-type transthyretin (ATTR) cardiac amyloidosis has been seen in 6% of patients in one series, and led to a significantly worse outcome[77]. Until recent advances in cardiac magnetic resonance imaging (MRI) imaging, amyloidosis was diagnosed with myocardial biopsy, and so was often missed. The LVH noted in cardiac amyloidosis can also often be mistaken for the adaptive hypertrophic remodeling seen in AS. Characteristic strain patterns seen using echocardiography with apical sparing can be a useful tool to aid in the diagnosis[78].

Electrophysiological conduction disease, such as AV node dysfunction can also lead to dyspnoea, and the risk of this increases after aortic valve intervention, particular with TAVR

and with the presence of existing conduction disease such as a right bundle branch block (RBBB). The position of the valve can compress the left bundle branch on implantation, leading to complete heart block[79]. This can be evaluated by 12-lead electrocardiogram (ECG) or Holter monitoring and treated easily with a permanent pacemaker (PPM).

1.3.3.c Non-Cardiac Disease

In reality, dyspnoea is commonly multifactorial and consists of both cardiac and non-cardiac causes. In our own retrospective dataset, the prevalence of prior chronic obstruction pulmonary disease (COPD) among 3,399 patients with severe AS was 10.2%[80]. In other series, this can be closer to 30% and is associated with higher mortality and worse symptomatic outcomes[81].

Aortic stenosis can be frequently associated with anaemia. This can be due to age and frailty, or due to an association with angiodysplastic gastric bleeding, which can be reversible with intervention[82]. In one series, anaemia was present in up to 32% of patients with AS and was associated with increased mortality[83].

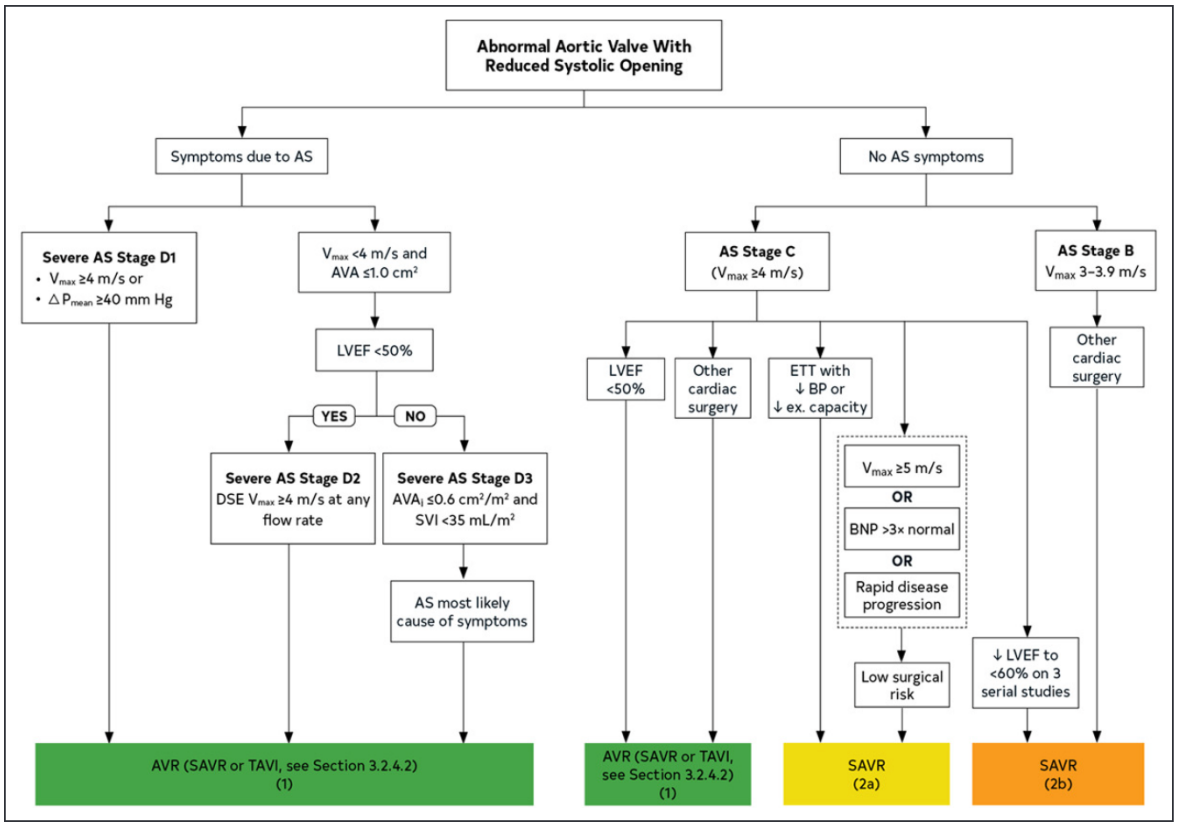
Other factors that can contribute to dyspnoea commonly include obesity and subsequent obstructive sleep apnoea, and physical frailty and deconditioning. These factors are associated with reduced exercise tolerance and a sedentary lifestyle, which can be as a consequence of limited mobility due to AS. With intervention, the valvular obstruction is relieved immediately, but it can take much longer to recover from deconditioning and regain muscle mass. Even 6 months after intervention, treated patients with prior severe AS have reduced exercise tolerance using the 6MWT, likely due to frailty and deconditioning[84].

While obesity can have a paradoxically protective effect after TAVR, likely due to less frailty in the overweight group, obesity and overweight status is associated with breathlessness[85, 86].

1.4 Assessment of Aortic Stenosis Severity and Risk

Assessing the severity of aortic stenosis can have challenges, with no single criterion being used to define severity. According to major guidelines, severity is primarily based on echocardiographic features, as discussed in section 1.2.4, and the presence or absence of symptoms. If the severity is not clear with these initial measures, other factors can be considered, including exercise and dobutamine stress testing, CT assessment of valvular calcium, invasive haemodynamic measurement, and biomarkers (Figure 1.11)[72].

Figure 1.11. Timing of Intervention for AS.



Arrows show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic (Stage C) and symptomatic (Stage D) AS and those with low-gradient AS (Stage D2 or D3) who do not meet the criteria for intervention. AS=Aortic Stenosis AVA=Aortic Valve Area, AVAi=Aortic Valve Area Index, AVR=Aortic Valve Replacement, BNP=B-type Natriuretic Peptide, BP=Blood Pressure, DSE=Dobutamine Stress Echocardiography, ETT=Exercise Treadmill Test, LVEF=Left Ventricular Ejection Fraction, ΔP_{mean}=Mean Systolic Pressure Gradient, SAVR=Surgical Aortic Valve Replacement, SVI=Stroke Volume Index, TAVI=Transcatheter Aortic Valve Implantation, V_{max}=Peak Velocity.

1.4.1 Imaging

The first step in the assessment for any patient being suspected of severe aortic stenosis is echocardiography. At least 2 measurements need to be made, one flow dependent such as MG or Vmax, and another flow independent, such as AVA/iAVA or DPI. Using these in combination can help to differentiate between normal severe AS with normal transvalvular flows (≥40mmHg MG and ≥4.0m/s Vmax in conjunction with AVA ≤1.0cm^2 or iAVA ≤0.6cm^2/m^2) and LFLG severe AS (≤40mmHg MG and/or ≤4.0m/s Vmax, but AVA ≤1.0cm^2 or iAVA ≤0.6cm^2/m^2)[87, 88]. LFLG AS can be further subdivided into true severe AS or pseudosevere AS, wherein the aortic stenosis is overestimated due to reduced LV function with an inability to fully open a moderately stenotic valve[25, 88]. This difference is important, since pseudosevere AS has improved mortality compared with true severe AS, and therefore intervention is unlikely to be beneficial[89]. It is important to note that normal transvalvular flow is not the same as a normal echocardiographic ejection fraction, since the two are not equivalent. While a low EF can reduce flow, patients can have a high transvalvular gradient in the presence of a reduced EF, and conversely, can have low transvalvular gradients with a normal EF, often due to concentric LV remodeling causing a small LV cavity, and impaired diastolic filling, reducing the stroke volume and the LV ejection duration. Atrial fibrillation (AF) can further worsen these parameters[88, 90, 91].

Since symptoms are a major determinant of prognosis, it is important to be clear about the symptom status of the patient. Most of the time, this will be evident, since the symptoms were the driver behind investigation in the first place. Greater than 20% of patients with severe AS may claim to be asymptomatic initially, but have significant exercise limitation on functional testing, and a worse prognosis[92-96]. This can often go unnoticed by patients due

to baseline reduced mobility due to age, frailty and comorbidities, or due to the gradual insidious nature of AS progression. Exercise stress echocardiography can be a useful tool to help clarify symptoms and stratify risk. Guidelines already recommend intervention in previously asymptomatic patients with severe AS who develop exercise-limiting symptoms, complex arrhythmias, or significant hypotension with exercise testing[2]. Additionally, an increase in the transvalvular gradient of >20mmHg in pre-operative severe AS patients has significant prognostic implications, with a 3.8-fold increase in death or need for AVR[92].

When it is unclear whether a patient has LFLG AS or pseudosevere AS, dobutamine stress echocardiography (DSE) can be a useful tool to help differentiate these conditions. DSE uses a continuous infusion of an inotropic and chronotropic medication to increase the rate and contractility of the myocardium, simulating exercise. Stroke volume, transvalvular gradient and AVA are calculated at baseline and with each progressive dose. AS is considered truly severe if at any stage, the MG increases to ≥40mmHg with an AVA remaining <1.0cm^2, whereas pseudosevere AS is characterized by a MG <40mmHg and an AVA >1.0cm^2[88]. Occasionally, the myocardium is unable to be recruited pharmacologically, making this differentiation unclear. In this situation, computed tomography (CT) assessment can be helpful.

CT has become an invaluable tool in the pre-operative assessment for TAVR. Initially used to confirm adequate peripheral access, CT has expanded to allow accurate measurement of the valve annulus for sizing in TAVR, determination of risk of annular rupture due to calcification, assessment of annulus to coronary ostia heights to avoid coronary occlusion during the implantation, and even to determine in advance the ideal fluoroscopic plane for valve implant visualization[97]. For surgically implanted aortic valve surgery, CT is also

very useful, but likely underused. It can be used to assess for a porcelain aorta, which precludes open cardiac surgery due to the inability to cross-clamp the aorta, and can be used in a similar way as in TAVR for valve sizing, resulting in larger implanted valves than intraoperatively measured valves and better flow profiles[98]. While differentiating between LFLG severe AS and pseudosevere AS, CT can often be a useful tool when the DSE is inconclusive. Using a modified Agatston method, a calcium scoring system, the degree of calcification can be measured with values of >1200 Agatston units (AU) in women and >2000AU in men associated with true severe AS[88, 99-101]. CT is also the ideal method of assessing for leaflet thrombosis post-intervention[97, 102].

Direct invasive measurements of valvular gradients can also be made in the catheter laboratory, while assessing for coronary artery disease. This is ideally done using simultaneous aortic and LV pressure transducers or by pullback gradient measurement of a single catheter, but the invasive nature can lead to complications. Measurement of the AVA can also be made using thermodilution cardiac output measurement[72].

1.4.2 Frailty

Frailty is common in the typically elderly severe AS population, and depending on the scale used, the prevalence in the AS population can range from 26% to 68%[103]. Frailty has been shown to have an impact on outcomes after both surgical and transcatheter AVR, including disability and mortality[103-106]. Frailty assessment is now a standard consideration in most AS multidisciplinary team meetings[2, 15], with geriatricians often a key contributor to the pre-operative assessment. Frailty will be discussed further in a subsequent chapter.

1.4.3 Multidisciplinary Teams

Multidisciplinary teams (MDTs) are becoming increasingly commonplace in many specialties to make complex decisions that often require a varied panel of experts. For valvular heart disease, the MDT has been an established feature since the introduction of TAVR and is formally endorsed by all major societies with a class 1 recommendation[2, 72]. In Australia, this goes one step further, with funding for TAVR requiring the involvement of an MDT.

The MDT typically consists of interventional and imaging cardiologists, cardiothoracic surgeons, general physicians or geriatricians, as well as nursing, anaesthetics and intensivists. The MDT is used to review patient comorbidities, imaging data, symptoms and risks to determine the optimal plan for intervention with all factors considered.

1.5 Traditional and Emerging Therapies for Aortic Stenosis

The principles of aortic valve therapy, the replacement of an obstructed valve with an artificial valve, have remained similar over the last 60 years, but the technology, techniques and patient population has altered drastically. When Ross and Braunwald's seminal paper on AS was published, the patients were much younger, with fewer comorbidities and predominantly rheumatic valves. Surgical mortality was relatively high, and so surgery was used as a last resort. Unfortunately, medical therapy has failed to provide any relief from the requirement of surgical or procedural intervention. Fortunately, surgical mortality has dramatically improved, and new catheter-based interventions are available to allow intervention in those previously deemed inoperable.

1.5.1 Medical Therapy

Medical therapy for AS has been disappointing. Several therapies have been investigated in an attempt to slow the progression of AS, but none have proven successful in reducing mortality[107].

Since aortic valve calcification followed a similar mechanism to coronary atheroma, it was hypothesized that statin therapy may limit the progression of valvular degeneration. Statins were shown to reduced osteoblast activity and cholesterol deposition in valve leaflet, and some observational data was promising, but randomized controlled trials (RCTs) found no benefit[108-112].

Antihypertensive therapies were traditionally contraindicated amongst fears that the reduction in afterload would cause diastolic hypotension and reduced myocardial perfusion. In reality,

systemic hypertension adds to the acceleration of LV remodeling and increases myocardial workload and valvuloarterial impedance, both of which are associated with poor outcomes[19, 113, 114]. Renin-angiotensin-aldosterone system (RAAS) inhibition has also had some success, with enalapril improving the 6MWT distance and ramipril reversing LV hypertrophy[115, 116]. For this reason, antihypertensive therapy in patients with AS and hypertension is currently guideline recommended[2, 72].

1.5.2 Balloon Aortic Valvuloplasty

Balloon aortic valvuloplasty (BAV) is the dilatation of a stenotic aortic valve using a balloon via femoral access. It was devised in 1985 as an alternative to surgical aortic valve replacement (SAVR) in high risk patients[117], but quickly fell out of favour due to a high risk of complications and poor long-term durability[118-121]. In the modern era, however, the procedural risk associated with BAV has been greatly reduced by the improved technology developed in conjunction with TAVR, and continues to improve with devices of smaller profile and more experienced operators[122]. This has resulted in a resurgent interest in BAV in certain clinical scenarios[123], however, the use of BAV in most centres has been limited by ongoing concerns over the procedural risks, which are similar to the risks of TAVR alone[124]. BAV will be discussed further in a subsequent chapter.

1.5.3 Surgical Aortic Valve Replacement

The first surgical aortic valve replacement was performed in 1960, but remains a valid option today, despite the development of less invasive therapies. Surgical implantation allows the

use of mechanical valves, which being rigid are unable to pass through a minimally invasive catheter. Although the use of a mechanical valve requires anticoagulation with warfarin to reduce the risk of leaflet thrombosis, they have the benefit of durability, whereas bioprosthetic valves tend to degenerate over time. Mechanical valves can therefore be useful in younger patients who wish to avoid a second procedure. Current guidelines recommend mechanical AVR in patients <50 and bioprosthetic AVR in patients >65, with individualized patient-centered decisions in those 50-65[72].

Due to uncertainties regarding TAVR valve durability, with bench testing results simulating 25 years of use similar to surgical valves[125], but in vivo durability data only up to 8 years[126], and limited trial data in younger patients, SAVR is currently recommended for those undergoing AVR with a bioprosthetic valve under the age of 65 with a life expectancy >20 years, whereas TAVR is recommended above the age of 80, with shared decision making between 65-80[72]. There is some evidence for SAVR in asymptomatic patients with very severe AS with or without rapid progression, and raised BNP[42]. SAVR is also commonly considered in suitable patients requiring non-aortic cardiac surgery, such as mitral valve surgery or coronary artery bypass grafting.

1.5.4 Transcatheter Aortic Valve Replacement

The first TAVR was performed in 2002 using a large femoral venous sheath and a trans-septal puncture[127]. The technology quickly developed, with smaller sheaths and valves, arterial retrograde implantation, technology to reduce paravalvular regurgitation and simpler delivery systems. TAVR came into focus with the first PARTNER trial, showing superiority to medical therapy in inoperable patients[58]. Comparisons to SAVR followed quickly with

the subsequent PARTNER trials, each at lower surgical risk[59, 60, 128]. A recent meta-analysis across all risk groups found that at 2 years TAVR was associated with lower mortality and stroke rates than SAVR, as well as major bleeding, AF, shorter hospital length of stay, and less pain[129]. SAVR on the other hand, is associated with a lower risk of paravalvular regurgitation (PVR), less need for reintervention and less need for PPM insertion. While bicuspid aortic valves were excluded from most RCTs, subsequent studies have found that TAVR in bicuspid valves has a similar prognosis to tricuspid valves, and similar procedural success when using the newer generation transcatheter valves[130, 131].

1.6 Future Directions in Aortic Stenosis Research

With the rapid development over the past decade in transcatheter technology, the intervention population has rapidly expanded, and more interventions are being performed now than ever before. The annual rate of increase of TAVR between 2009 and 2015 was 14.5%, and TAVR procedures now outnumber SAVR[132, 133]. Significant research has already been done in this space, but many questions remain. We will explore two major themes on the topic of aortic stenosis management. First, we wished to review elements of the current practice in pre-operative assessment of patients with severe AS. Second, we wished to address the difficult clinical scenario of post-intervention dyspnoea, and attempt to determine novel factors which could be contributing.

1.6.1 Review Current Practices for the Pre-Operative Assessment of Aortic Stenosis Patients and Timing of Intervention

1.6.1.a Evidence for the Benefit of the MDT

The multidisciplinary team is being used with increasing frequency in many medical disciplines, with varying impacts on outcomes[134-140]. AS is an ideal condition to utilise the variety of expertise inherent in an MDT due to the increased age and comorbidity of these patients and has a class 1 recommendation from the American and European cardiac societies[2, 141]. An MDT involves the coordination of many different specialists and despite the organisational difficulty and high costs involved in such a requirement, the evidence for a clinical benefit of the MDT in AS is lacking[142, 143].

We analysed the effect of the introduction of a TAVR Program, defined as the combination of the minimally invasive transcatheter therapy as well as the accompanying AS MDT, on 5-year survival in a population of patients with severe AS. We hypothesised that despite an older and more complex patient cohort, the implementation of the TAVR Program would result in an overall reduction in mortality in the severe AS population. It was also hypothesised that the MDT itself may reduce mortality independently of the expanded access to intervention, providing evidence for its use in the severe AS population. This data has been published in Open Heart, a peer-reviewed journal[144].

1.6.1.b Utility of Balloon Aortic Valvuloplasty in the Modern Era

BAV fell out of favour due to a high risk of complications and poor long-term durability[118-121], and is currently reserved for the more unwell, highly comorbid patients, often as a measure to retrieve the rapidly deteriorating patient with cardiogenic shock. However, the procedural risk associated with BAV has been greatly reduced by the improved technology developed in conjunction with TAVR, and continues to improve with devices of smaller profile and more experienced operators[122]. BAV can also be used to aid clinical decision making as to whether intervention would offer a substantial benefit in highly comorbid patients, or patients with poor cardiac function[145-150]. We sought to evaluate the characteristics and outcomes of patients undergoing BAV by way of long-term observational analysis. We hypothesized that BAV would be associated with a transient, but significant, mortality benefit over medical therapy, without a significant increase in short term risk in this highly comorbid population, allowing the clinicians to gauge the response to therapy, and relieve cardiac dysfunction due to pressure overload. It was also suspected that patients undergoing treatment with BAV prior to SAVR or TAVR would be higher risk in the modern

era, but BAV itself would not translate to poorer outcomes compared with definitive therapy alone. This data has been published in Heart, Lung and Circulation, a peer reviewed journal[151].

1.6.1.c Timing of Intervention with Discordant Severity Criteria

The timing of intervention is a common source of debate, with different Structural Heart Teams having varying thresholds before recommending intervention, particularly when the severity of AS is unclear, for example when the traditional AS markers are mixed in severity. The current guidelines recommend intervention when AS is deemed severe, and there is evidence for symptoms indicating cardiac decompensation [2, 15], however, there can often be a lag between the onset of myocardial dysfunction and symptoms, and cardiac imaging and biomarkers are being used to detect early phases of asymptomatic dysfunction[152]. A 2016 study showed that in patients with AS and discordant AS severity markers, intervention with SAVR improved mortality with moderate-range MG and Vmax coupled with severe AVA[153], but this has not been investigated in the TAVR or mixed intervention populations. The purpose of this analysis is to inform decision-making by determining whether having a low number or discordant severity of AS indicators was associated with a difference in mortality risk and therefore whether a threshold existed whereby intervention should be considered or deferred. This data has been submitted for publication and is currently under peer review.

1.6.2 Identify Novel Criteria Predisposing Severe Aortic Stenosis Patients to Residual Dyspnoea Post-Intervention

1.6.2.a Impact of Abnormal Global Longitudinal Strain on Residual Symptoms

Strain analysis is a method of quantifying LV muscle fibre dysfunction earlier than EF measurement[154, 155]. Abnormal pre-procedural GLS has been linked to increased mortality, symptoms, and worse procedural outcomes in the severe AS population[48, 156-158]. Post-procedural strain analysis and residual symptoms has not, to our knowledge, been investigated previously. The purpose of this analysis was to measure baseline pre-operative strain and symptoms prior to intervention with SAVR or TAVR, quantify the change in symptoms and strain post-intervention and determine whether a relationship exists between residual symptom burden and abnormal LV strain. This data is being prepared for peer-reviewed submission.

1.6.2.b Impact of Reduced Systemic Arterial Compliance and the Valvuloarterial Impedance on Residual Symptoms

There is a strong association between the presence of aortic stenosis and reduced SAC as both are a manifestation of the degenerative atherosclerotic process common in advanced age[3]. One mechanism by which patients may remain symptomatic is that despite a reduction in the valvular gradient after the procedure, excess LV afterload remains due to ongoing arterial stiffness[19, 159]. Therefore, the symptom complex in these patients is likely due to a combination of exposure of the LV to both the valvular load caused by the aortic transvalvular gradient and the arterial load caused by reduced SAC. The purpose of this

analysis was to determine the relationship between baseline Zva and Augmentation Index (AIx), a measure of arterial stiffness, and symptoms after aortic valve intervention as measured by the KCCQ, NYHA Class and 6MWT. This data has been published in the peer-reviewed International Journal of Cardiology: Heart and Vasculature[160].

1.6.2.c Impact of Frailty on Symptom States

Frailty has been shown to have an impact on outcomes after both SAVR and TAVR, including disability and mortality[103-106]. While the impact of frailty on outcomes has been clearly defined, the impact of intervention on frailty is less clear. Prior work has focused on the pre-intervention frailty state and has not assessed frailty post intervention. Many frailty tools use subjective indicators, such as exhaustion and low activity[51, 103, 161], or objective indicators such as the ability to walk or stand quickly[103, 162-164], which may be impacted on by the disorder itself, and may therefore improve with treatment. We sought to clarify the prevalence of frailty in the modern AS intervention population, as well as by the intervention used, and to determine the impact of intervention, as well as the type of intervention, on a commonly used frailty tool. This data has been submitted for publication and is currently under peer review.

CHAPTER 2

EXPERIMENTAL METHODS

2.1 Methods Overview

As there were two distinct themes for this thesis, there were also two distinct sets of methodologies. Reviewing the past and current practices regarding the perioperative assessment of patients with severe AS required a retrospective, database-driven approach to data collection to gather large amounts of existing outcome data for the variable in question. Assessing patients for novel causes of dyspnoea required prospective, patient-level interaction and assessment, with subsequent follow up assessment to determine if the novel study variables were associated with a predefined outcome. In this chapter, the methods common to each theme will be outlined initially, with the methods specific to each research chapter outlined separately.

2.2 Retrospective Review of Perioperative Assessment and Practices in Severe Aortic Stenosis

Patient Population

A retrospective, observational cohort study of the echocardiography database for the Southern Adelaide Local Health Network (SALHN) in South Australia (SA) was designed to review all consecutive patients undergoing transthoracic echocardiography in a high-volume echocardiography department between January 1, 2006, and December 31, 2016. TAVR was introduced at SALHN in late 2008. Dedicated sonographers obtained the echocardiographic images, using doppler evaluation in all available windows to determine the peak signals indicating severe AS. The cardiothoracic surgery (CTS) database and the Structural Heart Disease database were then reviewed over the same time period to determine whether an intervention in this population had occurred. All patients included in this analysis who underwent intervention had echocardiography data in the database.

Definition of Severe Aortic Stenosis and Echocardiographic Parameters

A patient population was identified as having severe AS if any of the following echocardiographic criteria were achieved: AV MG $\geq$ 40mmHg; AV Vmax $\geq$ 4.0m/s; AVA $\leq$ 1.0 cm^2; or DPI $\leq$ 0.25, as per the criteria outlined in the joint statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[87]. The year of the first echocardiogram demonstrating at least one marker of severe AS was taken as the time of diagnosis of AS, since clinic diagnosis data was not available.

Baseline Demographics, Comorbidities and Outcomes

Baseline demographics, comorbidities and outcomes for this population were determined using the International Classification of Diseases 10th Revision, Australian Modified (ICD-10 AM) diagnostic classification codes in the Integrated South Australian Activity Collection (ISAAC) database as well as from the department of Births, Deaths and Marriages (BDM) and the Clinical Reporting Repository (CRR) databases. Renal function was recorded using biochemistry results in the ISAAC database and was estimated using the Modification of Diet for Renal Disease (MDRD) formula for the glomerular filtration rate (GFR). Body mass index (BMI) was calculated using height and weight data in the echocardiography database. All comorbidity data, including renal function, were defined as having a prior diagnosis of the comorbidity in question using ICD-10 AM codes from the time of the inclusion echocardiogram, to exclude comorbidities which developed after the echocardiographic diagnosis of AS. Data linkage was performed between these, the surgical/procedural databases and the echocardiographic database in a de-identified and confidential manner by an experienced data manager. Patients were excluded from the analysis if they had no linkable outcome data.

The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/17/SAC/79), and all aspects comply with the Declaration of Helsinki.

Statistical Analysis

Continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequencies and proportions. Baseline characteristics were compared using Pearson's chi^2 test for categorical variables and analysis of variance or Mann-Whitney-Wilcoxon for continuous variables, where appropriate. Given the age and comorbidity of the cohort, the outcome of interest for this analysis was time to death from any cause from the date of the first echocardiographic diagnosis of AS.

Mortality was reviewed in our cohort of patients with severe AS. A comparison Kaplan-Meier curve for the general population was derived using age and sex specific life expectancies from the Australian Bureau of Statistics (ABS) Life Table Data and the application of these data to our population in order to determine an expected time of death.

All reported P-values were 2-sided, and statistical significance was set at $P<0.05$. Statistical analysis was undertaken using STATA MP 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

2.2.1 Effect of the Introduction of a Multidisciplinary Structural Heart Team Program on Mortality in Patients with Severe Aortic Stenosis

The TAVR Program

The TAVR Program itself is defined as an MDT discussion with the availability of TAVR as an intervention option. The MDT at SALHN was introduced with TAVR in late 2008 to

provide a streamlined process for the selection and peri-procedural investigation of potential TAVR candidates.

Patient Population

Patients are referred to the MDT by a structural heart disease specialist who, in turn, takes referrals from both cardiac and non-cardiac medical practitioners and reviews initial results and organises subsequent investigations. The MDT consists of 1-2 operating structural heart specialists trained in TAVR, 1-2 cardiothoracic surgeons, 1-2 non-interventional cardiologists specialising in heart failure/imaging/cardiogeriatrics, 1-2 vascular surgeons, a radiologist specialising in structural cardiac imaging, 1-2 cardiac anaesthetists, fellows, and nursing staff. While not every patient with severe AS will be discussed at the MDT, all TAVR and most complex SAVR cases are included. Cases that are for continued medical management due to being asymptomatic or extreme risk as well as patients considered low risk for SAVR are often not discussed as the added expertise of the MDT is not considered to be required. Cases are discussed bi-weekly with a review of the relevant history, comorbidities, and investigations. A consensus is sought regarding the appropriateness of intervention, the intervention modality, the access site and the time frame. A decision can also be made to continue medical management and observe, or to seek additional information.

Statistical Analysis

The patient population of interest was initially determined as per section 2.2. Since we aimed to determine the effect of the availability of the TAVR Program at the time of diagnosis on outcomes, rather than the effect of the intervention itself, this time was used to define the era

to which the patient was classified, including the Pre and Post TAVR Program era, as well as the sensitivity analysis subgroups. Comparison was made between groups in the time period prior to the introduction of the TAVR Program in late 2008 and the Post TAVR Program era. The Pre TAVR Program era was therefore defined as prior to Jan 1, 2009, and the Post TAVR Program era was defined as after Jan 1, 2009. Differences in the baseline characteristics were examined between the Pre and Post TAVR Program eras, including age, sex, BMI, LV dysfunction, renal dysfunction, liver dysfunction, diabetes mellitus (DM), hypertension (HTN), COPD, prior history of heart failure (HF), acute coronary syndrome (ACS), cerebrovascular accident (CVA), cancer, dementia and prior coronary artery bypass grafting (CABG). Differences in severity of AS using the echocardiographic markers of AS were also compared, as well as the number of qualifying markers of severe AS.

These clinical and echocardiographic variables were then used to develop and validate the inverse probability weighted (IPW) cohorts based on the probability of "presenting" in either of the eras. Specifically, using baseline clinical and echocardiographic characteristics, the propensity for AS diagnosis within the Pre or Post TAVR Program era was modelled in a logistic regression model and the cohort was weighted for the inverse of the probability for being diagnosed within the specific eras. Assessment of the balance of these two populations by key clinical variables associated with survival were assessed by standardized errors. This reweighted population was used to assess survival. Unadjusted Kaplan-Meier estimates of 5-year survival demonstrated a non-proportional difference in the survival differences related to the era of care, and therefore a flexible parametric approach was used, where the relative hazards for the TAVR Program era were allowed to vary over time. To further ensure adjustment for the key prognostic variables of age, gender, LV function, GFR, and prior

histories of HF, HTN, ACS, CVA, dementia, COPD, DM, liver disease, cancer and CABG, these were also entered together with the era in the final model using the IPW cohort.
We then adjusted for the presence of intervention to account for the effect of the expansion of intervention by TAVR to include patients previously considered too high-risk for SAVR. We were then able to determine if between-era differences other than intervention and comorbidities led to a difference in survival. Any remaining difference in outcome between eras is presumed to be related to the MDT itself, which is the only other significant management change between eras.

As a sensitivity analysis, to explore the impact of the evolving MDT and operator proficiency, a transition period was defined as all diagnoses of AS made in 2009. Furthermore, two subgroups of the Post TAVR Program era, the early and late sub-eras were defined as between Jan 1, 2010, and Dec 31, 2013, and Jan 1, 2014, and Dec 31, 2016, respectively. To explore whether evolving MDT proficiency impacted the outcomes, the transition period was excluded. Furthermore, comparison was made between the subgroups of the Post TAVR Program era, to determine whether improvements in operator experience or technology continued to improve outcomes after the introduction of the TAVR Program.

2.2.2 Effect of Balloon Aortic Valvuloplasty on Mortality in Patients with Severe Aortic Stenosis

Balloon Aortic Valvuloplasty

BAV was performed by a single operator in the catheter laboratory of Flinders Medical Centre, a division of SALHN. Balloons were sized using standard echocardiographic

measurement of the LVOT. Access was gained via the femoral artery, and a balloon was placed retrogradely over a wire crossing the aortic valve. A temporary pacing wire was also placed via a femoral vein into the right ventricle. This was used for rapid pacing of the heart during balloon inflation to ensure low cardiac pressures. The balloon is briefly inflated at high pressures for a few seconds, ensuring the valve opens visually. Invasive pressure measurements are taken, and transthoracic echocardiography is performed afterwards to ensure a reduction in the transvalvular gradient and to assess for aortic regurgitation and annular rupture.

Patient Population

The patient population of interest was initially determined as per section 2.2. To make appropriate comparisons between groups who could be considered candidates for BAV, patients were excluded from the medical management group who were under the age of 75 and had a Charlson Comorbidity Index (CCI) of 0. These patients were likely robust, well patients who would likely proceed directly to intervention, if indicated, and would not be subject to indecision regarding management that would necessitate an initial strategy of BAV, and therefore they were removed to allow a fair between-group comparison. The outcome of interest for this analysis was time to death from any cause. Deaths were defined and dated using combined data from the ISAAC, BDM and CRR databases to maximize data completion.

Statistical Analysis

Differences in patient characteristics were explored between patients according to three initial treatment strategies: Initial BAV prior to a decision regarding medical therapy or intervention, medical management only and initial TAVR or SAVR without prior BAV. The initial strategy was used rather than the final strategy, since the goal of the analysis was to determine outcomes when BAV is used as a triage strategy, rather than a definitive therapy, and the ultimate therapy will depend on the short-term response to BAV as an initial strategy. Comorbidities adjusted for in the analysis included age, sex, BMI, LV dysfunction, renal dysfunction, liver dysfunction, DM, HTN, COPD, prior history of HF, ACS, CVA, cancer, dementia, and prior CABG.

Unadjusted survival was reported in the overall population over 5 years, stratified according to the initial treatment strategy. Due to the time varying effect of the initial treatment strategy, flexible parametric models were used. The single centre mortality difference between TAVR and SAVR was investigated using an age and comorbidity adjusted Cox analysis showing no demonstrable difference in mortality between intervention modalities, therefore SAVR and TAVR patients were grouped into the intervention strategy cohort. We then sought to determine the associated effect of treatment with initial BAV prior to medical or invasive intervention. For this we used an IPW analysis using the above comorbidities, as well as the severity of the qualifying factors which defined severe AS and the likelihood of being treated using one of the three initial treatment strategies. After developing the IPW model, flexible parametric models were used for the comparisons of outcome for an initial BAV strategy against the medical therapy only and intervention

groups. Unfortunately, no specific procedural data was available regarding balloon types, gradients pre and post BAV or number of inflations in our deidentified database.

In the first analysis, to appropriately compare the duration of effect of an initial strategy of BAV against medical therapy alone, we calculated the time from diagnosis of aortic stenosis to either death or intervention, since any outcome subsequent to this could not be influenced by the effect of BAV. Outcomes between the groups defined by an initial treatment strategy of BAV were then compared using an adjusted flexible parametric model and a time varying hazard was reported.

In the subsequent analysis comparing an initial strategy of BAV to intervention alone, we wished to determine outcomes between groups who had an initial strategy of BAV, regardless of further intervention to those who had an intervention without prior BAV. Since the subsequent post-BAV strategy was likely determined by the response to BAV, it was felt that the outcomes would match the treatment modality decision, i.e., those deemed unsuitable for intervention post BAV would have a poor outcome and those deemed suitable would have an improved outcome by definition. We calculated the time from BAV or intervention to death and analysed outcomes using an adjusted flexible parametric analysis within the IPW model. To then confirm the impact of prior BAV on perioperative mortality in the population of patients who ultimately underwent definitive therapy, we compared outcomes between these groups from the time of intervention until death.

2.2.3 Assessing Benefit of Intervention for Aortic Stenosis in Patients with Discordant Severity Criteria

Patient Population

The patient population of interest was initially determined as per section 2.2. Since all participants in this study had at least one criterion of significant AS, in addition to documenting the values of each criterion, the number of severe-range criteria were also summed with each criterion valued equally to provide a score between 1-4 for each patient, to determine the level of discordance in AS severity criteria. The outcome of interest for this analysis was time to death from any cause. Deaths were defined and dated using combined data from the ISAAC, BDM and CRR databases to maximize data completion.

Statistical Analysis

Differences in baseline comorbidities were explored according to the number of severe-range AS criteria and by the presence or absence of intervention. The characteristics of each individual AS severity criterion was also analysed, to determine if any differences existed between groups. Comorbidities adjusted for in the analysis included age, sex, BMI, LV dysfunction, renal dysfunction, liver dysfunction, DM, HTN, COPD, prior history of HF, ACS, CVA, cancer, dementia and prior CABG.

Unadjusted survival was reported in the overall population over 5 years, stratified according to the number of criteria for AS in the severe range. This was then adjusted for age and

comorbidities. Due to the time varying effect of the intervention strategy, flexible parametric models were used.

We then analysed mortality in the intervention cohort from both the time of diagnosis and the time of intervention. The single centre mortality difference between TAVR and SAVR was first investigated using an age and comorbidity adjusted Cox analysis showing no demonstrable difference in mortality between intervention modalities, therefore SAVR and TAVR patients were grouped into a single indicator of intervention and used to explore possible differential treatment effects associated with the number of severe-range AS characteristics. Unadjusted and adjusted survival were then reported by number of severe AS criteria as an interaction between intervention or medical management and differences in survival for the number of AS criteria were noted.

Lastly, we determined the differences in timing of intervention by AS criteria group. We measured the time interval in days between first date of qualifying echocardiogram and first intervention with BAV, TAVR or SAVR and compared time to intervention between AS criteria groups. BAV was included in this analysis, as it was felt that it was acting as a temporising measure in those with other comorbidities, uncertain severity or critical illness allowing time for definitive intervention. We then measured mortality by AS criteria group from diagnosis to first intervention, comparing intervention with conservative therapy within each AS criteria group, to determine if any group had a greater benefit from earlier or deferred intervention, and the interaction of intervention by AS criteria group, to determine if the effect of intervention was more significant at a certain number of AS criteria.

A subgroup analysis was performed excluding patients with an AV MG <40mmHg and AV Vmax < 4.0m/s, an AVA <1.0cm2, and an LVOT VTI of >18cm to try to reduce confounding by patients with suspected pseudosevere AS.

Furthermore, we had concerns that any delay in intervention in the lower AS criteria subgroups may represent a lag period within which the AS severity increased, with intervention occurring once the criteria were more traditionally severe. To account for this, we performed another subgroup analysis excluding patients with a time to intervention from first echocardiographic diagnosis to the first procedure more than 6 months, which we felt was within the window of acting on the initial echocardiogram, once initial clinic review, investigations, MDT discussion and procedural waiting lists are considered.

2.3 Identifying Novel Criteria Predisposing Patients with Severe Aortic Stenosis to Residual Dyspnoea Post-Intervention

Patient Population

A prospective, observational cohort study was designed including patients in SALHN in South Australia being assessed for aortic valve intervention due to severe, symptomatic AS. Both surgical and transcatheter intervention candidates were included. Patients were recruited consecutively from the Structural Cardiology outpatient clinic or the Cardiothoracic Surgery Preoperative Assessment clinic between December 2016 and April 2018. The vast majority of publicly or privately insured patients undergoing TAVR or SAVR at SALHN would attend one of these clinics prior to aortic valve intervention.

The patient population was identified as having severe AS if any of the following echocardiographic criteria were achieved: AV MG $\geq$ 40mmHg; AV Vmax $\geq$ 4.0m/s; AVA $\leq$ 1.0 cm^2; or DPI $\leq$ 0.25, as per the criteria outlined in the joint statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[87].

Patients were approached when attending for clinic reviews or pre-procedural investigations and the project explained in clear, concise language to the patients and any family members or supports present. A copy of the Patient Information and Consent Form (PICF) was provided to each patient to review and take with them. This is provided as Supplement 1.1. After an appropriate amount of time was provided to review the PICF and discuss with supports, an opportunity was provided to discuss the study further with the principal investigator and ask questions. Contact information for the principal investigator was

provided on the PICF in case participants had further questions, concerns or wished to withdraw from the study.

Patients were excluded if they did not proceed to intervention within 6 months of the study end date but were otherwise unselected to avoid bias. Background data and collected data were stored in a purpose-built database using secure REDCap software (Vanderbilt University, version 9.3.1) licenced by the South Australian Health and Medical Research Institute (SAHMRI). Background medical data were collected using patient medical records, clinic letters, by patient history and examination and from cardiovascular imaging databases. The data entry form used is provided in Supplement 1.2.

Baseline Demographics and Patient Assessment

Patients were assessed pre-procedurally, at early review, 4-6 weeks post-procedurally, and at late review, 6-12 months post-procedurally, as determined by the patient's treating cardiologist.

At the initial assessment, demographic details were recorded as per the data entry template. Pre-procedural symptoms were recorded using the NYHA Classes of Heart Failure[165] and the KCCQ[62], as validated in this population by Arnold et al[55]. These symptom tools were repeated at early and late review to determine degree and timing of symptomatic recovery. Objective symptoms were also recorded at all 3 visits, when patient mobility allowed, using a 6MWT[166], and gait speed over 4 metres was also recorded in the first two 25 metre laps. Frailty was assessed using the Fried Frailty Scale (FFS), also known as the

Hopkins Frailty Assessment (HFA), pre-procedurally and at the late review[161]. These data are also included in the data entry template in Supplement 1.2.

The KCCQ Overall Summary (KCCQ-OS) score is scored from 0 to 100, with higher numbers indicating a lower symptom burden. The KCCQ-OS score is often subdivided into 4 classes, roughly analogous to the NYHA classes, with class 1 being the least symptomatic and having a score >75, class 2 between 60 and 75, class 3 between 45 and 60 and class 4 being the most symptomatic and having a score of less than 45. Symptomatic recovery was measured as a continuous variable using change in baseline KCCQ-OS score to final score, and also using the Relative Change in KCCQ-OS, defined as the change in the KCCQ-OS score divided by the baseline KCCQ-OS score, allowing a higher weighting for patients who changed more significantly from a very symptomatic baseline relative to those who had little symptomatic change from an already high baseline KCCQ-OS score. The NYHA is scored as the current symptomatic class. The 6MWT is measured as the distance travelled on a pre-defined track in exactly 6 minutes. Gait speed is measured as walking speed in m/s by measuring the time in seconds taken to walk exactly 4 metres on two occasions and averaging the result and dividing 4 by this value.

After intervention, procedural information was recorded including type of AV intervention (SAVR or TAVR, including which access approach), the date of the procedure, the Society of Thoracic Surgeons (STS) risk scores[167, 168] at the time of procedure, including the Mortality and the Mortality and Morbidity scores, and the Transcatheter Valve Therapy (TVT) TAVR[169] in-hospital mortality score. Deaths, intensive care unit (ICU) admissions, and any perioperative complications including myocardial infarction (MI), CVA, conduction

disease requiring a PPM and bleeding, as defined by the Valve Academic Research Consortium (VARC)[170] were documented.

Statistical Analysis

Continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequencies and proportions. Analysis of differences between the same variable over time were reported as probabilities of the variable being obtained by chance and undertaken using the Wilcoxon signed-rank test and relationships between categorical variables were assessed using the Pearson chi^2 test. Correlations between variables were determined using Spearman's rho test, or the Kruskal-Wallis equality-of-populations rank test and adjustment for comorbidities was undertaken using a linear regression model. Statistical analysis was undertaken in Stata MP 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). Given the observational nature of this study, no adjustments were made for multiple testing and a p-value of 0.05 was considered statistically significant.

The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/16/SAC/168), and all aspects comply with the Declaration of Helsinki.

2.3.1 Assessing Symptom Recovery Using Global Longitudinal Strain After Intervention for Severe Aortic Stenosis

Strain Analysis

The patient population of interest was initially determined as per section 2.3 and assessed for symptoms. Using TomTec strain analysis software (2D cardiac performance analysis, Unterschleissheim, Germany) retrospectively on existing echocardiographic images, echocardiograms were analysed pre-procedurally, at early follow up, and at late follow up. Measurements were performed by a single researcher and included GLS, regional strain time to peak (TTP), mechanical dispersion (MD) and left atrial strain (LAS). Strain is a measure of tissue deformation defined as the degree of lengthening of muscle fibres, and measures 16 myocardial segments in 3 echocardiographic planes. Since with muscle contraction, these fibres shorten, peak strain is measured as a negative percentage of deformation from baseline. Fibres shorten in the longitudinal, and circumferential planes, and lengthen in the radial plane, and can be measured for all 16 segments of myocardium or averaged for a global measurement. Peak GLS has been the focus of most strain-based cardiac research and has applications in the characterisation of cardiomyopathies, assessment of cardiac resynchronization therapy, assessment of myocardial load in valvular heart disease, and prediction of mortality or adverse outcomes[155, 171]. TTP is the time, in milliseconds, within which peak strain is reached from baseline. MD is calculated as the standard deviation of the TTP for all 16 segments, and heterogeneity between myocardial segments has been shown to predict arrhythmias, since it reflects myocardial scarring[172]. LAS is an averaged biplane measurement of atrial deformation, and is associated with adverse outcomes in the AS population[173].

Statistical Analysis

Statistical comparisons were then undertaken between the variables outlined in the strain analysis and the symptom measures outlined in 2.3. We first compared baseline demographics between the intervention groups to determine if any significant differences existed. We also compared differences in echocardiographic severity, strain analysis results and symptom scores. We then sought to determine if any relationships existed between symptoms and strain analysis measures, using both an unadjusted analysis and adjusted for age, gender, COPD and LV function severity.

We then demonstrated the change in symptoms and strain features seen between the pre-intervention period and the late post-intervention review period and compared the change in symptoms with the change in strain to determine if a relationship existed. As a sub-analysis, we dichotomised our group into two populations, those who had an improvement in GLS by >10% and those who did not, and compared the change in symptoms between these two groups.

Lastly, we compared final symptom scores with final strain analysis to determine if those with residual symptoms also had residual strain abnormalities.

2.3.2 Impact of Increased Augmentation Index and Valvuloarterial Impedance on Symptom Recovery After Intervention for Severe Aortic Stenosis

Applanation Tonometry

The patient population of interest was initially determined as per section 2.3 and assessed for symptoms. Pulse Wave Analysis (PWA) using the Applanation Tonometry (AT) method was performed at all 3 reviews using the Sphygmocor AT device using a standardised protocol via the radial artery (Figure 2.1)[174]. Heart rate and systolic and diastolic blood pressure were recorded allowing calculation of mean arterial pressure (MAP) and pulse pressure (PP). Using the Sphygmocor device, record was made of Central Aortic Pressure, Central Aortic Pulse Pressure and Central Augmentation Pressure in mmHg, as well as Central Augmentation Index standardized to a heart rate of 75 bpm (%), Ejection Duration (ms) and Subendocardial Viability Ratio (SEVR) (%).

Figure 2.1. The Sphygmocor Applanation Tonometry Device

https://atcormedical.com/wp-content/uploads/2019/09/XCEL_System.jpg

For this analysis, outcomes were compared between symptomatic recovery as measured by the KCCQ-OS Score and haemodynamic assessment using PWA. The primary haemodynamic assessment used was the AIx, measuring the degree to which the peak of a measured pressure wave is over and above the peak of the incident pressure wave due to the addition of the reflected pressure wave. The AIx is dependent on the timing and magnitude of the reflected waveform and is influenced by the compliance and structure of vessels distal to the site of measurement[174], and is therefore used as a marker of arterial stiffness.

The AIx can vary depending on several factors, including age, gender and height, therefore an augmentation index reference value was used to standardise our patients and the variance between the calculated AIx and the reference AIx was used. The formula for the augmentation reference index used was $AIx = 79.20 + 0.63\ (age) - 0.002\ (age^2) - 0.28\ (heart\ rate) - 0.39\ (height)$ for men and $AIx = 56.28 + 0.90\ (age) - 0.005\ (age^2) - 0.34\ (heart\ rate) - 0.24\ (height)$ for women, according to the analysis by Janner et al[175].

We also analysed differences in blood pressure, heart rate, ejection duration, SEVR, defined as the diastolic to systolic pressure-time integral ratio, a measure of the balance between coronary perfusion and arterial load, and Zva, which is the measured impediment to blood ejection due to the combined resistive forces of both the valvular obstruction and the reduced arterial compliance.

Statistical comparisons were then undertaken between the variables outlined in the AT analysis and the symptom measures outlined in 2.3 at pre-intervention, early assessment and late assessment and relationships were sought between symptoms and the AT values at each

time period in an unadjusted manner and adjusted for age, gender and COPD, as well as the change in symptoms and the change in AT variables between time periods. We also compared initial AT variables with final symptoms to determine if residual symptoms could be predicted prior to intervention.

We also performed a subgroup analysis with just the TAVR population due to concerns regarding heterogeneity of the population and determined at which value for AIx a statistical difference in final symptoms could be seen.

2.3.4 Impact of Surgical and Transcatheter Aortic Valve Replacement on Frailty

The Fried Frailty Scale

The patient population of interest was initially determined as per section 2.3 and assessed for symptoms. Frailty was assessed using the FFS, which is a validated frailty phenotypic assessment that allows standardization and scoring of multiple key domains of abnormalities commonly associated with frailty[161]. It has been extensively validated in many populations, including severe aortic stenosis[103] and parallel the criteria used in the PARTNER trials[104]. Using the FFS, physical frailty is defined using measures of five phenotypic criteria: unintentional weight loss, exhaustion, low energy expenditure, low grip strength, and/or slowed waking speed. A single score out of 5 is then given which categorises the patient in frailty classes; frail (score 3-5), pre-frail (score 1 or 2) or robust (score 0). The frailty class analysis was expressed using frequencies of the population within each class.

The FFS assessment was administered by a single researcher for every patient pre-procedurally and at 6-12 months post-intervention. The results were entered into the official FFS scoring calculator and the total results were documented, as well as the results for each individual frailty domain. Weight loss was determined by direct weight measurement at clinic review, and by interviewing the patient regarding historical weight over the previous year and was defined as a loss of ≥4.5kg in the past year. Exhaustion and low energy expenditure were determined as per the FFS protocol via questionnaire. Grip strength was determined using a hand grip dynamometer using the dominant hand, and walking speed was determined by measuring the walking time over a 4m segment during the first two 25m laps of the 6MWT, with an adequate lead time to achieve full walking speed. This is outlined in Supplement 1.2.

Patients were then reviewed at early review, between 4-6 weeks post procedure, according to Structural Cardiology Clinic Protocol. At this visit, medications, ECG and echocardiographic changes were noted and symptoms were reassessed using the NYHA and KCCQ tools and the 6MWT and gait speed. These were again repeated at late review, 6-12 months, in addition to a repeat frailty assessment.

Some patients were unable or unwilling to attend or perform one or both frailty assessments. Patients with a single frailty assessment were included in the analyses to determine the proportions of frailty in the population at a given timeframe but were excluded from the analysis to determine change in the frailty score and domains. This typically occurred due to living remotely and being unable to attend in-person review. KCCQ-OS scores were still obtained via telephone at 6 months.

The primary outcome for this analysis was change in frailty score and frailty class between pre-procedural and late post-intervention assessment. Secondary outcomes were to determine which domains of frailty were more likely to be influenced by intervention and to stratify these results into transcatheter and surgical cohorts. We also correlated these results with the subjective and objective symptom measurements of the KCCQ and 6MWT since some frailty domains can be influenced by the traditional symptoms of aortic stenosis. Statistical comparisons were then undertaken between the variables outlined in the frailty analysis and the symptom measures outlined in 2.3.

CHAPTER 3

EFFECT OF THE INTRODUCTION OF A MULTIDISCIPLINARY STRUCTURAL HEART TEAM PROGRAM ON MORTALITY IN AORTIC STENOSIS

3.1 Introduction

Severe AS has long been known to increase mortality[4, 176-181], but the development of effective new transcatheter-based interventions for elderly or comorbid patients with AS has reignited interest in the field of valvular heart disease. Despite increases in age and comorbidity in this population, both SAVR and TAVR remain superior to medical therapy in symptomatic, severe AS[58, 182-184].

The MDT is being used with increased frequency in many medical disciplines, with varying impacts on outcomes[134-140]. Many cardiac trials and therapies are now mandating the involvement of an MDT, primarily based upon the methodologies and outcomes of the SYNTAX and PARTNER trials[58, 134, 185, 186]. AS is an ideal condition to utilise the variety of expertise inherent in an MDT due to the increased age and comorbidity of these patients and has a class 1 recommendation from the American and European cardiac societies[2, 141]. An MDT review involving a structural heart specialist, a cardiothoracic surgeon and a non-interventional physician prior to TAVR is required for Commonwealth Medical Benefits Scheme funding in Australia[186]. In reality, many more practitioners are often involved, including radiologists, vascular surgeons, geriatricians and nursing staff. Despite the organisational difficulty and high costs involved in such a requirement, the evidence for a clinical benefit of the MDT in AS is lacking[142, 143].

We analysed the effect of the introduction of a TAVR Program, defined as the combination of the minimally invasive transcatheter therapy as well as the accompanying AS MDT, on 5-year survival in a population of patients with echocardiographically defined severe AS, from the first echocardiogram demonstrating AS. We hypothesised that despite an older and more

complex patient cohort, the implementation of the TAVR Program would result in an overall reduction in mortality in the severe AS population. It was also hypothesised that the MDT itself may reduce mortality independently of the expanded access to intervention, providing evidence for its use in the severe AS population.

3.2 Methods

Patient Population

A retrospective, observational cohort study of the echocardiography database for SALHN in South Australia was designed to review all consecutive patients undergoing transthoracic echocardiography in a high-volume echocardiography department between January 1, 2006, and December 31, 2016. From this population, patients were included in the analysis if they had at least one severe criterion to define AS.

Definition of Severe Aortic Stenosis and Echocardiographic Parameters

A patient population was identified as having severe AS if any of the following echocardiographic criteria were achieved: AV MG ≥ 40mmHg; AV Vmax ≥ 4.0 m/s; AVA ≤ 1.0 cm^2; or DPI ≤ 0.25, as per the criteria outlined in the joint statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[87]. The year of the first echocardiogram demonstrating at least one marker of severe AS was taken as the time of diagnosis of AS, since clinic diagnosis data was not available. Since we aimed to determine the effect of the availability of the TAVR Program at the time of diagnosis on outcomes, rather than the effect of the intervention itself, this time was then used to define the era to which the patient was classified, including the Pre and Post TAVR Program era, as well as the sensitivity analysis subgroups.

The CTS database and the Structural Heart Disease database were then reviewed over the same time period to determine whether an intervention in this population had occurred. All

patients included in this analysis who underwent intervention had echocardiography data in the database.

Baseline Demographics, Comorbidities and Outcomes

Baseline demographics, comorbidities and outcomes for this population were determined using the ICD-10 AM diagnostic classification codes in the ISAAC database as well as from the department of BDM and the CRR databases. Renal function was recorded using biochemistry results in the ISAAC database and was estimated using the MDRD formula for the GFR. BMI was calculated using height and weight data in the echocardiography database. All comorbidity data, including renal function, were defined as having a prior diagnosis of the comorbidity in question using ICD-10 AM codes from the time of the inclusion echocardiogram, to exclude comorbidities which developed after the echocardiographic diagnosis of AS. Data linkage was performed between these and the echocardiographic database in a de-identified and confidential manner by an experienced data manager. Patients were excluded from the analysis if they had no SA Health data for linkage to the echocardiography database. The Human Research Ethics Committee of the SA Department of Health approved this study (approval number: HREC/17/SAC/79), and all aspects comply with the Declaration of Helsinki.

The TAVR Program

The TAVR Program is defined as an MDT discussion with the availability of TAVR as an intervention option. The MDT at SAHLN was introduced with TAVR in late 2008 to provide a streamlined process for the selection and peri-procedural investigation of potential TAVR

candidates. Patients are referred to the MDT by a structural heart disease specialist who, in turn, takes referrals from both cardiac and non-cardiac medical practitioners and reviews initial results and organises subsequent investigations. The MDT consists of 1-2 operating structural heart specialists trained in TAVR, 1-2 cardiothoracic surgeons, 1-2 non-interventional cardiologists specialising in heart failure/imaging/cardiogeriatrics, 1-2 vascular surgeons, a radiologist specialising in structural cardiac imaging, 1-2 cardiac anaesthetists, fellows, and nursing staff. While not every patient with severe AS will be discussed at the MDT, all TAVR and most complex SAVR cases are included. Cases that are clearly for continued medical management due to no symptoms or extreme risk as well as patients considered low risk for SAVR are often not discussed as the added expertise of the MDT is not required. Cases are discussed bi-weekly with a review of the relevant history, comorbidities, and investigations. A consensus is sought regarding the appropriateness of intervention, the intervention modality, the access site and the time frame. A decision can also be made to continue medical management and observe, or to seek additional information.

Analysis

Continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequencies and proportions. Baseline characteristics were compared using Pearson's chi^2 test for categorical variables and analysis of variance or Mann-Whitney-Wilcoxon for continuous variables, where appropriate. Given the age and comorbidity of the cohort, the outcome of interest for this analysis was time to death from any cause from the date of the first echocardiographic diagnosis of AS.

Mortality was reviewed in our cohort of patients with severe AS. A comparison Kaplan-Meier curve for the general population was derived using age and sex specific life expectancies from the ABS Life Table Data and the application of these data to our population in order to determine an expected time of death.

Comparison was then made between groups in the time period prior to the introduction of the TAVR Program in late 2008 and the Post TAVR Program era. The Pre TAVR Program era was therefore defined as prior to Jan 1, 2009, and the Post TAVR Program era was defined as after Jan 1, 2009. Differences in the baseline characteristics were examined between the Pre and Post TAVR Program eras, including age, sex, BMI, LV, renal dysfunction, liver dysfunction, DM, HTN, COPD, prior history of HF, ACS, CVA, cancer, dementia and prior CABG. Differences in severity of AS using the echocardiographic markers of AS were also compared, as well as the number of qualifying markers of severe AS.

These clinical and echocardiographic variables were then used to develop and validate the IPW cohorts based on the probability of "presenting" in either of the eras. Specifically, using baseline clinical and echocardiographic characteristics, the propensity for AS diagnosis within the Pre or Post TAVR Program era was modelled in a logistic regression model and the cohort was weighted for the inverse of the probability for being diagnosed within the specific eras. Assessment of the balance of these two populations by key clinical variables associated with survival were assessed by standardized errors. This reweighted population was used to assess survival. Unadjusted Kaplan-Meier estimates of 5-year survival demonstrates a non-proportional difference in the survival differences related to the era of care, and therefore a flexible parametric approach was used, where the relative hazards for the TAVR Program era were allowed to vary over time. To further ensure adjustment for the

key prognostic variables of age, gender, LV function, GFR, and prior histories of HF, HTN, ACS, CVA, dementia, COPD, diabetes, liver disease, cancer and CABG, these were also entered together with the era in the final model using the IPW cohort.

We then adjusted for the presence of intervention to account for the effect of the expansion of intervention by TAVR to include patients previously considered too high-risk for SAVR. We were then able to determine if between-era differences other than intervention and comorbidities led to a difference in survival. Any remaining difference in outcome between eras is presumed to be related to the MDT itself, which is the only other significant management change between eras.

As a sensitivity analysis, to explore the impact of the evolving MDT and operator proficiency, a transition period was defined as all diagnoses of AS made in 2009. Furthermore, two subgroups of the Post TAVR Program era, the early and late sub-eras were defined as between Jan 1, 2010, and Dec 31, 2013, and Jan 1, 2014, and Dec 31, 2016, respectively. To explore whether or not evolving MDT proficiency impacted the outcomes, the transition period was excluded. Furthermore, comparison was made between the subgroups of the Post TAVR Program era, to determine whether improvements in operator experience or technology continued to improve outcomes after the introduction of the TAVR Program.

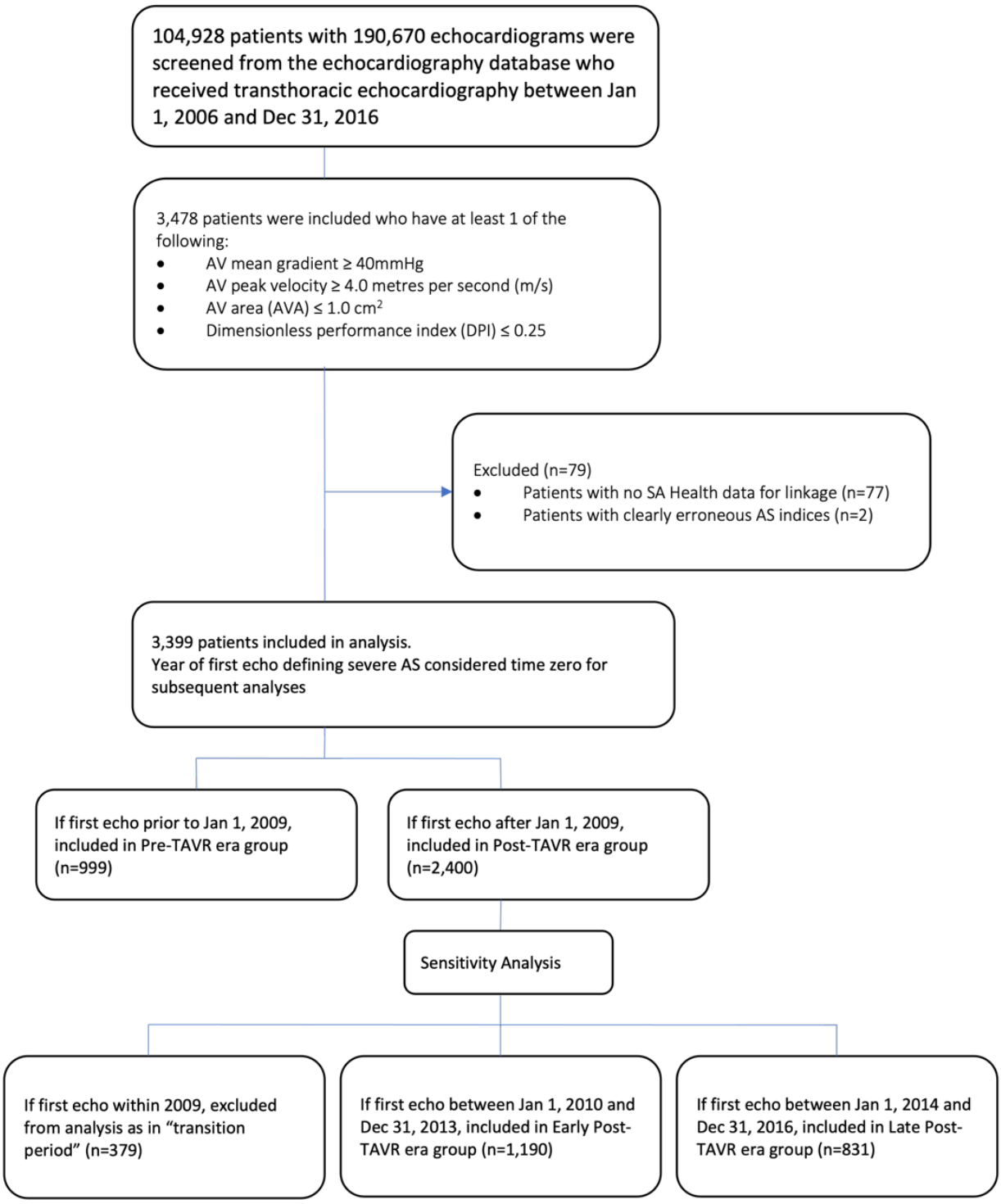
All reported P-values were 2-sided, and statistical significance was set at $P<0.05$. Statistical analysis was undertaken using STATA MP 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

3.3 Results

Patient Characteristics

Within the study period, 104,928 patients had 190,670 echocardiograms. In total, 3,478 patients were identified as having severe AS using the above criteria. 77 observations were removed due to having no SA Health data available for linkage. Two patients were excluded due to not meeting probable severe AS criteria after removing clearly erroneous data. After exclusions, there were 3,399 patients available for analysis (Figure 3.1).

Figure 3.1. Flow Chart for Patient Selection, Exclusion and Grouping



The median number of severe-range AS criteria was 2 in both the intervention and medical groups, with a mean of 2.49 (SD=1.14) in the intervention group and 1.85 (SD=1.00) in the medically managed group (P<0.001). The median time from diagnosis to TAVR was 238 days, and to SAVR was 127 days. The population baseline characteristics, including number of AS criteria, are included in Table 3.1.

Table 3.1. Baseline Characteristics of Patients with Severe Aortic Stenosis, with Comparisons of Characteristics Prior and Subsequent to the Era Defined by the Multidisciplinary Team.

	Overall (N=3,399)	**Pre TAVR Era (N=999)**	**Post TAVR Era (N=2,400)**	**p-value**
Demography				
Age, median (IQR)	81.6 (73.4, 87.2)	81 (73.2, 86.6)	81.8 (73.4, 87.6)	**0.019**
Female Gender, N (%)	1683 (49.5%)	525 (52.6%)	1158 (48.2%)	**0.022**
BMI, median (IQR)	27 (23.8, 31.2)	26.8 (24.2, 29.4)	27 (23.8, 31.4)	0.70
eGFR (mL/min/1.73m^2), median (IQR)	63.2 (45.6, 80.6)	61.2 (43.8, 80.4)	64 (46.6, 80.6)	**0.006**
Echocardiographic Parameters				
AV MG (mmHg), median (IQR)	30.2 (19.6, 41.8)	28.8 (17.4, 41)	30.8 (20.2, 42)	**<0.001**
AV Area (cm2), median (IQR)	0.8 (0.6, 1)	0.8 (0.6, 1)	0.8 (0.8, 1)	**<0.001**
AV Vmax (m/s), median (IQR)	3.6 (3, 4.2)	3.6 (2.8, 4.2)	3.6 (3, 4.2)	**0.006**
DPI, median (IQR)	0.25 (0.20, 0.30)	0.25 (0.20, 0.31)	0.24 (0.20, 0.29)	0.33
Severe AV MG, N (%)	1093 (32.2%)	319 (31.9%)	774 (32.2%)	0.86
Severe AV Vmax, N (%)	1360 (40.0%)	351 (35.1%)	1009 (42.0%)	**<0.001**
Severe AV Area, N (%)	2525 (74.3%)	686 (68.7%)	1839 (76.6%)	**<0.001**
Severe DPI, N (%)	1753 (51.6%)	494 (49.4%)	1259 (52.5%)	0.11
1 Severe AS Criterion, N (%)	1465 (43.1%)	487 (48.7%)	978 (40.8%)	**<0.001**
2 Severe AS Criteria, N (%)	1024 (30.1%)	277 (27.7%)	747 (31.1%)	**0.049**
3 Severe AS Criteria, N (%)	418 (12.3%)	131 (13.1%)	287 (12.0%)	0.35
4 Severe AS Criteria, N (%)	491 (14.4%)	104 (10.4%)	387 (16.1%)	**<0.001**

EF (%), median (IQR)	61.2 (46.8, 73)	65.4 (49.4, 77.6)	60 (45.6, 70.4)	**<0.001**
Normal LV, N (%)	2311 (68.0%)	688 (68.9%)	1623 (67.6%)	0.48
Mild LV Dysfunction, N (%)	425 (12.5%)	134 (13.4%)	291 (12.1%)	0.30
Moderate LV Dysfunction, N (%)	334 (9.8%)	78 (7.8%)	256 (10.7%)	**0.011**
Severe LV Dysfunction, N (%)	279 (8.2%)	98 (9.8%)	181 (7.5%)	**0.028**
Comorbidities				
Prior HF, N (%)	715 (21.0%)	239 (23.9%)	476 (19.8%)	**0.008**
Prior HTN, N (%)	1292 (38.0%)	370 (37.0%)	922 (38.4%)	0.45
Prior ACS, N (%)	895 (26.3%)	294 (29.4%)	601 (25.0%)	**0.008**
Prior CVA, N (%)	122 (3.6%)	27 (2.7%)	95 (4.0%)	0.073
Prior COPD, N (%)	347 (10.2%)	120 (12.0%)	227 (9.5%)	**0.025**
Prior Liver Disease, N (%)	89 (2.6%)	27 (2.7%)	62 (2.6%)	0.84
Prior Dementia, N (%)	75 (2.2%)	29 (2.9%)	46 (1.9%)	0.075
Prior Diabetes, N (%)	662 (19.5%)	189 (18.9%)	473 (19.7%)	0.60
Prior Cancer, N (%)	628 (18.5%)	180 (18.0%)	448 (18.7%)	0.66
Prior CABG, N (%)	128 (3.8%)	31 (3.1%)	97 (4.0%)	0.19

IQR=Interquartile Range, BMI=Body Mass Index, eGFR=Estimated Glomerular Filtration Rate, MG=Mean Gradient, Vmax=Peak Velocity, AV=Aortic Valve, DPI= Dimensionless Performance Index, EF=Ejection Fraction, AS=Aortic Stenosis, LV=Left Ventricular, HF=Heart Failure, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

Survival of AS Population Relative to General Population

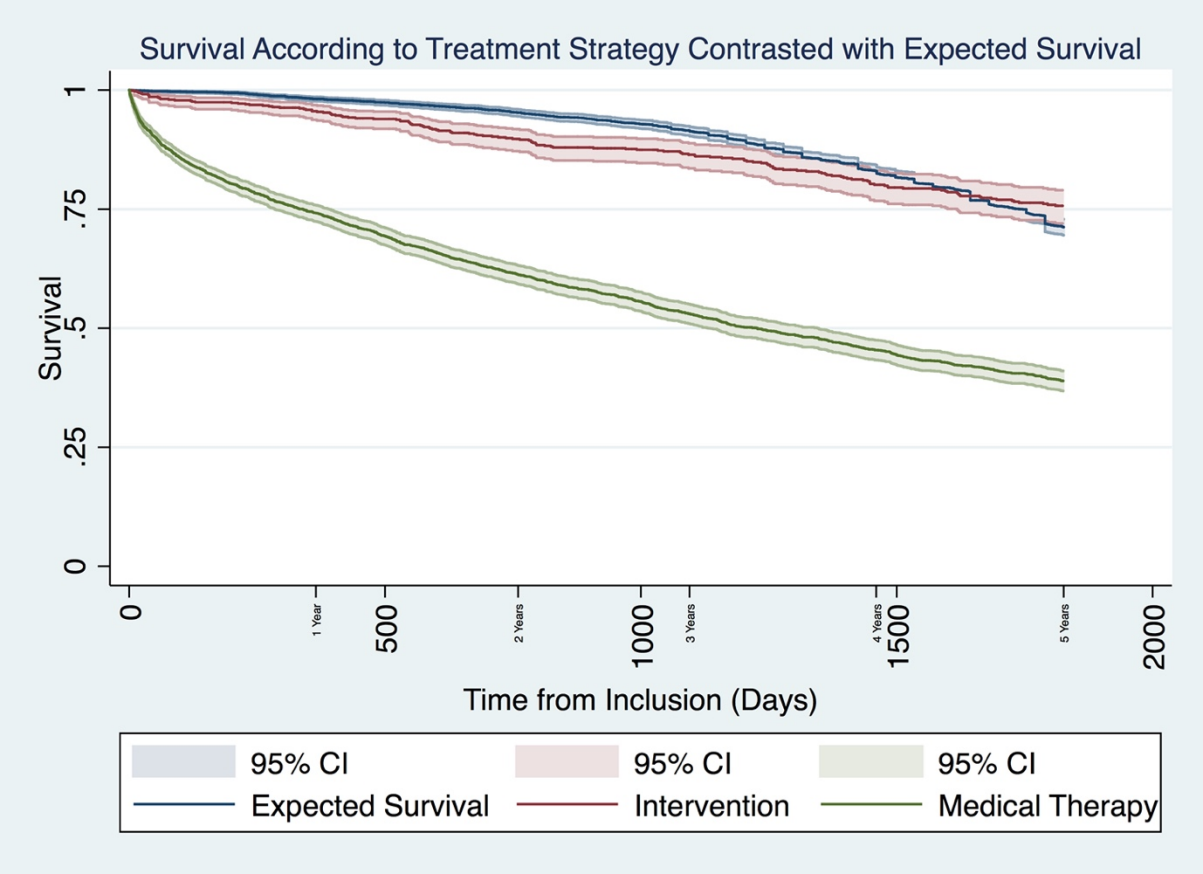
Long-term observed mortality in our population was high. Of the 3,399 patients, there were 210 deaths (6.2%) at 30 days, and 511 deaths (15.0%) at 6 months. By 1 and 5-year follow up, 722 (21.2%) and 1,614 (47.5%) were deceased. The overall survival data, as well as survival data according to management strategy are presented in Table 3.2.

Table 3.2. Unadjusted Mortality in a Population of Patients with Severe Aortic Stenosis Stratified by Intervention Strategy

Deaths	**All (N=3,399)**	**Medical (N=2,694)**	**Intervention (N=705)**
30 Days, N (%)	210 (6.18)	204 (7.57)	6 (0.85)
6 Months, N (%)	511 (15.03)	493 (18.3)	18 (2.55)
1 Year, N (%)	722 (21.24)	691 (25.65)	31 (4.4)
3 Years, N (%)	1,280 (37.66)	1,191 (44.21)	89 (12.62)
5 Years, N (%)	1,614 (47.48)	1,468 (54.49)	146 (20.71)

In order to explore mortality in the AS population in the modern era, we contrasted our population with severe AS with expected survival in an age and gender matched general population in South Australia. It was observed that the population with severe AS appeared to die prematurely. Patients receiving intervention with SAVR or TAVR were much more likely to survive than those treated with medical therapy (Figure 3.2).

Figure 3.2. Observed 5-year Survival in the Population with Aortic Stenosis Stratified by Treatment Strategy Contrasted with the Expected 5-year Survival of an Age and Gender Matched General Population.



Population Characteristics by Era

There were 999 patients diagnosed with AS in the Pre TAVR Program era and 2,400 in the Post TAVR Program era. Significant differences are noted between eras (Table 3.1). Patients diagnosed with severe AS after the introduction of the TAVR Program were older, more likely to be male, and had a higher GFR. Although a lower proportion of patients had severe LV dysfunction in the Post TAVR Program era, overall ejection fraction was lower. AS

severity was worse in the Post TAVR Program era, but patients were less likely to have a previous diagnosis of HF, ACS, and COPD.

Among the 705 patients undergoing intervention between 2006 and 2016 inclusive, those in the Post TAVR Program era were older, with a lower ejection fraction and more severe AS. There were no significant differences in the rates of analysed comorbidities (Table 3.3).

Table 3.3. Baseline Characteristics Between Eras in Patients Undergoing Intervention for Severe Aortic Stenosis

	All Intervention (N=705)	**Intervention Pre TAVR Era (N=191)**	**Intervention Post TAVR Era (N=514)**	**p-value**
Demography				
Age, median (IQR)	76.4 (67.6, 82.2)	74 (65.8, 79.6)	77 (68.8, 83.4)	**<0.001**
Gender, N (%)	289 (41.0%)	77 (40.3%)	212 (41.2%)	0.82
BMI, median (IQR)	28 (24.4, 34.6)	27 (24.4, 33.2)	28 (24.5, 34.7)	0.45
eGFR (mL/min/1.73m^2), median (IQR)	72 (53.8, 86.2)	75.2 (54, 85.8)	69.4 (53.6, 86.6)	0.17
Echocardiographic Parameters				
AV MG (mmHg), median (IQR)	40 (30, 48.2)	38.4 (28.9, 47.9)	40 (31, 48.2)	0.19
AV Area (cm2), median (IQR)	0.8 (0.6, 1)	0.8 (0.6, 1)	0.8 (0.6, 1)	0.13
AV Vmax (m/s), median (IQR)	4 (3.6, 4.4)	4 (3.6, 4.5)	4 (3.6, 4.4)	0.19
DPI, median (IQR)	0.23 (0.19, 0.26)	0.23 (0.19, 0.27)	0.23 (0.19, 0.26)	0.19
Severe AV MG, N (%)	358 (50.8%)	92 (48.2%)	266 (51.8%)	0.40
Severe AV Vmax, N (%)	425 (60.3%)	100 (52.4%)	325 (63.2%)	**0.009**
Severe AV Area, N (%)	521 (73.9%)	117 (61.3%)	404 (78.6%)	**<0.001**
Severe DPI, N (%)	448 (63.5%)	113 (59.2%)	335 (65.2%)	0.14
1 Severe AS Criterion, N (%)	177 (25.1%)	63 (33.0%)	114 (22.2%)	**0.003**
2 Severe AS Criteria, N (%)	196 (27.8%)	57 (29.8%)	139 (27.0%)	0.46
3 Severe AS Criteria, N (%)	141 (20.0%)	39 (20.4%)	102 (19.8%)	0.87
4 Severe AS Criteria, N (%)	190 (27.0%)	32 (16.8%)	158 (30.7%)	**<0.001**

EF (%), median (IQR)	64.4 (51.8, 75.6)	73.4 (58.4, 80)	62 (49.8, 71.4)	**<0.001**
Normal LV, N (%)	504 (71.5%)	151 (79.1%)	353 (68.7%)	**0.007**
Mild LV Dysfunction, N (%)	76 (10.8%)	21 (11.0%)	55 (10.7%)	0.91
Moderate LV Dysfunction, N (%)	64 (9.1%)	10 (5.2%)	54 (10.5%)	**0.030**
Severe LV Dysfunction, N (%)	38 (5.4%)	8 (4.2%)	30 (5.8%)	0.39
Comorbidities				
Prior Heart Failure, N (%)	101 (14.3%)	26 (13.6%)	75 (14.6%)	0.74
Prior HTN, N (%)	251 (35.6%)	62 (32.5%)	189 (36.8%)	0.29
Prior ACS, N (%)	183 (26.0%)	51 (26.7%)	132 (25.7%)	0.78
Prior CVA, N (%)	20 (2.8%)	5 (2.6%)	15 (2.9%)	0.83
Prior COPD, N (%)	45 (6.4%)	16 (8.4%)	29 (5.6%)	0.19
Prior Liver Disease, N (%)	13 (1.8%)	2 (1.0%)	11 (2.1%)	0.34
Prior Dementia, N (%)	3 (0.4%)	1 (0.5%)	2 (0.4%)	0.81
Prior Diabetes, N (%)	149 (21.1%)	42 (22.0%)	107 (20.8%)	0.73
Prior Cancer, N (%)	116 (16.5%)	26 (13.6%)	90 (17.5%)	0.21
Prior CABG, N (%)	31 (4.4%)	5 (2.6%)	26 (5.1%)	0.16

TAVR=Transcatheter Aortic Valve Replacement, IQR=Interquartile Range, BMI=Body Mass Index, eGFR=Estimated Glomerular Filtration Rate, MG=Mean Gradient, Vmax=Peak Velocity, AV=Aortic Valve, DPI=Dimensionless Performance Index, AS=Aortic Stenosis, EF=Ejection Fraction, LV=Left Ventricular, HF=Heart Failure, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

The number of patients identified with severe AS by echocardiography per year is outlined in Table 3.4. The number of patients diagnosed within a given year who are eventually treated with intervention is also included, rather than the year of intervention itself, to better model the outcomes related to presenting in a specific era. The total number of interventions per year were not significantly different, but there was a notable shift in intervention modality from SAVR to TAVR over time.

Table 3.4. Rate of Diagnosis of Aortic Stenosis Per Year, Stratified by Intervention

Year	Diagnosis	Intervention	SAVR	TAVR
2006, N (%)	311 (9.15)	71 (10.07)	64 (13.17)	7 (3.18)
2007, N (%)	310 (9.12)	55 (7.80)	45 (9.26)	10 (4.55)
2008, N (%)	378 (11.12)	65 (9.22)	51 (10.49)	14 (6.36)
2009, N (%)	379 (11.15)	90 (12.77)	63 (12.96)	27 (12.27)
2010, N (%)	337 (9.91)	80 (11.35)	54 (11.11)	27 (12.27)
2011, N (%)	259 (7.62)	60 (8.51)	37 (7.61)	23 (10.45)
2012, N (%)	317 (9.33)	76 (10.78)	52 (10.70)	24 (10.91)
2013, N (%)	277 (8.15)	61 (8.65)	36 (7.41)	25 (11.36)
2014, N (%)	252 (7.41)	52 (7.38)	33 (6.79)	19 (8.64)
2015, N (%)	274 (8.06)	46 (6.52)	25 (5.14)	21 (9.55)
2016, N (%)	305 (8.97)	49 (6.95)	26 (5.35)	23 (10.45)
Total, N (%)	3,399 (100)	705 (100)	486 (100)	220 (100)

*One patient diagnosed in 2010 received both SAVR and TAVR

Effect of the Post TAVR Program Era

The unadjusted mortality in patients prior and subsequent to the introduction of the TAVR Program was not significantly different at 5 years although an early separation in the mortality curves was noted (Figure 3.3). After IPW, the eras were balanced on key clinical characteristics (Table 3.5). Using this flexible parametric model, a significant benefit was noted with the post TAVR Program era (HR=0.86, 95% CI 0.77-0.97, p=0.015). With age, comorbidities and AS severity in the model, this association was more prominent (HR=0.82, 95% CI 0.73-0.92, p=0.001).

Figure 3.3. Observed 5-year Survival in the Population with Aortic Stenosis Stratified by Era of Presentation

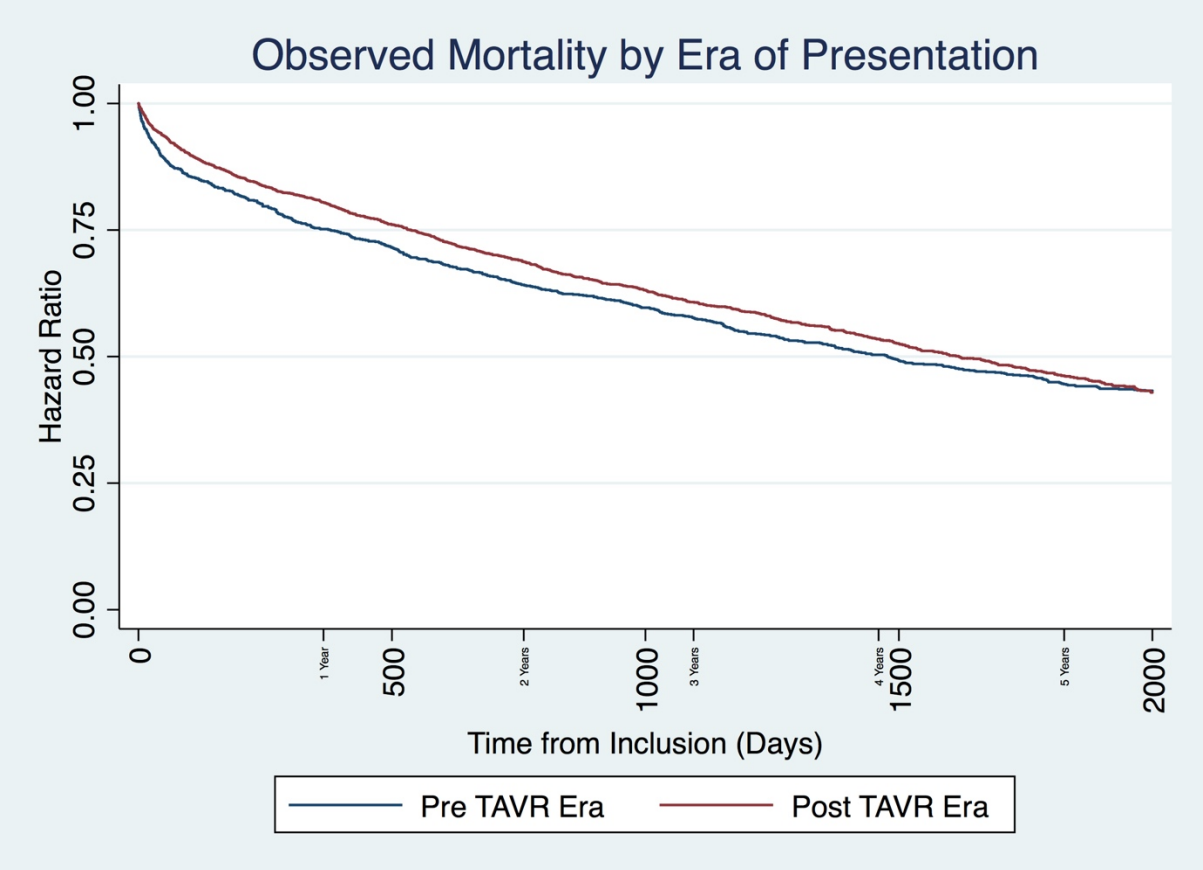


Table 3.5. Inverse Probability Weighting Model and Standardised Differences

	Mean Value or Probability (Treated)	**Mean Value or Probability (Untreated)**	**Standardised Difference**
Demography			
Age	78.63	78.28	0.027
Gender	0.49	0.5	-0.009
eGFR	64.55	64.79	-0.009
Echocardiographic Parameters			
Abnormal LV	0.3	0.3	0.006
Comorbidities			
Prior HF	0.21	0.21	0.006
Prior HTN	0.38	0.37	0.013
Prior ACS	0.26	0.26	0.004
Prior CVA	0.04	0.03	0.023
Prior COPD	0.1	0.11	-0.037
Prior Liver Disease	0.03	0.03	-0.004
Prior Dementia	0.02	0.02	0.001
Prior Diabetes	0.19	0.19	0.005
Prior Cancer	0.18	0.19	-0.015
Prior CABG	0.04	0.04	0.012

eGFR=Estimated Glomerular Filtration Rate, LV=Left Ventricular, HF=Heart Failure, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

When the provision of AV intervention, by SAVR or TAVR, in addition to age, comorbidities and valve severity, was included in the model, the era-associated benefit persisted (HR=0.84, 95% CI 0.75-0.95, p=0.004). No significant mortality difference was noted between SAVR and TAVR treated patients (HR=1.43, 95% CI 0.89-2.30, p=0.141).

Sensitivity Analyses

For the sensitivity analyses, a further 379 patients were excluded from the survival analysis due to presenting in the TAVR Transition era, defined as a diagnosis within the first year of the program, 2009. Excluding the transition period yielded virtually identical results, and therefore this period was included in the main analysis. The early and late Post TAVR Program subgroups were similar in baseline characteristics, and no differences in outcomes were found between groups in a similarly adjusted IPW analysis (HR=1.09, 95% CI 0.93-1.28, p=0.276) and when adjusting for the presence of intervention (HR=1.09, 95% CI 0.93-1.27, p=0.305).

3.4 Discussion

Improvement in Outcomes

Our results suggest that the availability of a TAVR Program significantly impacts mortality in a population of patients with severe AS, independently of the increased access to AV intervention using TAVR or SAVR.

Although patients diagnosed with severe AS after the implementation of the TAVR Program were generally less comorbid, the patient population treated by intervention was older with significantly poorer cardiac function, which suggests that the less invasive nature of TAVR led to an expansion in the treatment population to include those patients previously considered inoperable or high risk for a SAVR. It is well documented, including with our own results, that treatment of severe AS leads to a significant mortality benefit in this population[58], and that improvements in technology which expand the treated population lead to an overall benefit in the severe AS population as a whole. In line with the PARTNER data[58], when adjusting for age and comorbidities, our population had no significant difference in mortality between SAVR and TAVR, indicating the noted difference in mortality between eras cannot be attributed to the implementation of a novel therapy with regional patterns of outcomes better than the published data.

Benefit of the MDT and Potential Mechanisms

Although the implementation of the TAVR Program led to a population-wide benefit, at least partially due to the expansion of access to intervention, there remained a significant mortality

benefit in the Post TAVR Program era, even when adjusting for the expansion of intervention. We propose this may be due to the MDT itself.

Potential mechanisms for this benefit include an improvement in patient selection for intervention, the improved use of diagnostic tools, reduced loss of follow up, improved procedure, device and access modality selection, and reduced access complications or other potential peri-procedural hazards. While not every patient with severe AS needs to be discussed in the MDT, the availability of the MDT since the implementation of TAVR is potentially a powerful tool at the disposal of the treating cardiologist, and we propose that potentially it is the availability of such an expert panel when required, rather than the review itself which could improve survival outcomes.

There are likely additional benefits of MDT involvement apart from improving procedural outcomes, such as improving timelines and consistency of therapy, more complete therapies, and improvements in patient knowledge and satisfaction[134].

Improvement in Technology and Experience over Time

We considered that the improvement in outcomes could be related to improved operator experience or improved device technology. At SALHN, there was a single operator for the entire study period, so no inter-operator differences were contributory. We performed a subgroup analysis splitting the Post TAVR Era subgroup into roughly equal early and late TAVR period groups, with the late TAVR Era group the recipients of a more experienced operator and the latest valve technology. We found that the mortality benefit seen after the implementation of the TAVR Program occurred at the time of this implementation and then

remained relatively static, with no continued improvement in mortality seen between the Post TAVR subgroups, suggesting that operator experience or improvements in technology were unlikely to contribute significantly.

Limitations

While our observational data cannot directly attribute the demonstrated improved survival to the MDT in a causal manner, we were unable to offer many other significant inter-era alterations in the protocol as an explanation for these results, although unmeasured confounders may exist. It is certainly plausible that the involvement of a TAVR coordinator could play a significant role in the pre- and post-TAVR care of patients, improving outcomes. The novel nature of TAVR also led to a greater focus on the determination and documentation of outcomes with higher scrutiny and outcomes registries, which may have altered future practices. The limitations of our data did not allow accurate comment on changing periprocedural complication rates over time, in particular due to improvements in operator experience or device technology, and so only mortality data was reported. Surgical risk scores such as the STS Score or the EuroScore were also unavailable for our population. While a formal MDT may not have existed prior to TAVR, informal collegial discussion between cardiologists and cardiothoracic surgeons have been present for decades, although without the additional medical and surgical specialties of the current program. There was also a relatively short duration of the Pre TAVR Program era included in the analysis due to the limitations of electronic data capture in the echocardiography database.

3.5 Conclusions

The involvement of an MDT in a TAVR Program is a class 1C recommendation from both American and European societies as a central concept of aortic stenosis management, but as far as we are aware, no prior data exist supporting its efficacy[143]. Our data suggest that the addition of TAVR to the longstanding surgical program for the management of AS along with a functional MDT is associated with a mortality benefit in the severe aortic stenosis population. Even when adjusting for the expansion of the intervention population, a significant mortality benefit remains, possibly due to the MDT itself, supporting the use of this collaborative method despite the increased organisational difficulty and cost.

CHAPTER 4

EFFECT OF BALLOON AORTIC VALVULOPLASTY ON MORTALITY IN PATIENTS WITH SEVERE AORTIC STENOSIS

4.1 Introduction

Severe aortic stenosis is a debilitating condition associated with substantial morbidity and mortality[55, 187]. Calcific, degenerative AS typically affects the elderly, who are more likely to have significant comorbidities which may preclude treatment with surgical aortic valve replacement[58]. Left untreated, octogenarians medically managed for severe AS have a survival rate of 65.8% at 1 year and 41.8% at 2 years, regardless of symptoms[188]. The development of TAVR has allowed successful treatment for patients who were previously deemed too high risk for SAVR[58].

Balloon aortic valvuloplasty was devised in 1985 as an alternative to SAVR in high risk patients[117], but quickly fell out of favour due to a high risk of complications and poor long-term durability[118-121]. In the modern era, however, the procedural risk associated with BAV has been greatly reduced by the improved technology developed in conjunction with TAVR, and continues to improve with devices of smaller profile and more experienced operators[122]. This has resulted in a renewed interest in BAV in certain clinical scenarios[123], however, the use of BAV in most centres has been limited by concerns over the procedural risks, which are similar to the risks of TAVR alone[124].

We sought to evaluate the characteristics and outcomes of patients undergoing BAV by way of long-term observational analysis. We hypothesized that BAV would be associated with a transient, but significant, mortality benefit over medical therapy, without a significant increase in short term risk, allowing the clinicians to gauge the response to therapy, and relieve cardiac dysfunction due to pressure overload. It was also suspected that patients undergoing treatment with BAV prior to SAVR or TAVR would be higher risk in the modern

era, but BAV itself would not translate to poorer outcomes compared with definitive therapy alone.

4.2 Methods

Patient Population

A retrospective, observational cohort study of the echocardiography database for SALHN in South Australia was designed to review all consecutive patients undergoing transthoracic echocardiography in a high-volume echocardiography department between January 1, 2006, and December 31, 2017. The CTS database and the Structural Heart Disease database were also reviewed over the same time period to capture procedural information. TAVR was introduced at SALHN in late 2008. Baseline demographics, comorbidities and outcomes for this population were determined using the ICD-10 AM diagnostic classification codes in the ISAAC database as well as from the department of BDM and the CRR databases. Renal function was recorded using biochemistry results in the CRR database and was estimated using the MDRD formula for the GFR. BMI was calculated using height and weight data in the echocardiography database. Data linkage was performed deterministically between these and the echocardiographic database in a confidential manner and de-identified in the analysis dataset. Patients were excluded from analysis if they had no linkable outcome data available within the SA Health data systems. The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/17/SAC/79), and all aspects comply with the Declaration of Helsinki.

Definition of Severe AS and Echocardiographic Parameters

A patient population was identified as having severe AS if any of the following echocardiographic criteria were achieved: AV MG ≥ 40mmHg; AV Vmax ≥ 4.0m/s; AVA ≤ 1.0 cm^2; or DPI ≤ 0.25, as per the criteria outlined in the joint statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[87].

Excluding Patients with Low Likelihood of Receiving BAV

In order to make appropriate comparisons between groups who could be considered candidates for BAV, patients were excluded from the medical management group who were under the age of 75 and had a CCI of 0. These patients were likely robust, well patients who would likely proceed directly to intervention, if indicated, and would not be subject to indecision regarding management that would necessitate an initial strategy of BAV, and therefore they were removed to allow a fair between group comparison.

Outcomes

The outcome of interest for this analysis was time to death from any cause. Deaths were defined and dated using combined data from the ISAAC, BDM and CRR databases to maximize data completion.

Analysis

Differences in patient characteristics were explored between patients according to three initial treatment strategies: Initial BAV prior to a decision regarding medical therapy or intervention, medical management only and initial TAVR or SAVR without prior BAV. The initial strategy was used rather than the final strategy since the goal of the analysis was to determine outcomes when BAV is used as a triage strategy, rather than a definitive therapy, and the ultimate therapy will depend on the short-term response to BAV as an initial strategy. Comorbidities adjusted for in the analysis included age, sex, BMI, LV dysfunction, renal dysfunction, liver dysfunction, DM, HTN, COPD, prior history of HF, ACS, CVA, cancer, dementia and prior CABG. Unadjusted survival was reported in the overall population over 5 years, stratified according to the initial treatment strategy.

Due to the time varying effect of the initial treatment strategy, flexible parametric models were used. The single centre mortality difference between TAVR and SAVR was investigated using an age and comorbidity adjusted Cox analysis showing no demonstrable difference in mortality between intervention modalities, therefore SAVR and TAVR patients were grouped into the intervention strategy cohort.

We then sought to determine the associated effect of treatment with initial BAV prior to medical or invasive intervention. For this we used an IPW analysis using the above comorbidities, as well as the severity of the qualifying factors which defined severe AS and the likelihood of being treated using one of the three initial treatment strategies. After developing the IPW model, flexible parametric models were used for the comparisons of outcome for an initial BAV strategy against the medical therapy only and intervention

groups. Unfortunately, no specific procedural data was available regarding balloon types, gradients pre and post BAV or number of inflations in our deidentified database.

In the first analysis, to appropriately compare the duration of effect of an initial strategy of BAV against medical therapy alone, we calculated the time from diagnosis of aortic stenosis to either death or intervention, since any outcome subsequent to this could not be influenced by the effect of BAV. Outcomes between the groups defined by an initial treatment strategy of BAV were then compared using an adjusted flexible parametric model and a time varying hazard was reported.

In the subsequent analysis comparing an initial strategy of BAV to intervention alone, we wished to determine outcomes between groups who had an initial strategy of BAV, regardless of further intervention to those who had an intervention without prior BAV. The median time from BAV to intervention, in those receiving intervention, was 123 days, however, since the subsequent post-BAV strategy was likely determined by the response to BAV, it was felt that the outcomes would match the initial treatment modality decision, i.e., those deemed unsuitable for intervention post BAV would have a poor outcome and those deemed suitable would have an improved outcome. We calculated the time from BAV or intervention to death and analysed outcomes using an adjusted flexible parametric analysis within the IPW model. To then confirm the impact of prior BAV on perioperative mortality in the population of patients who ultimately underwent definitive therapy, we compared outcomes between these groups from the time of intervention until death. Statistical analysis was undertaken by an using de-identified data in Stata MP 15 software (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

4.3 Results

In total 3,478 patients were identified for analysis. 77 observations were removed due to having no SA Health data available for linkage. 2 patients were excluded due to not meeting probable severe AS criteria after removing clearly erroneous data and not having had a prior intervention. 257 patients were excluded due to being under 75 years of age and having a CCI of 0. After exclusions, there were 3,142 patients available for analysis. The initial BAV group contained 223 patients, the initial intervention group contained 630 patients and the remaining medical therapy group contained 2,289 patients. 75 BAV patients proceeded to intervention, and 148 were medically managed. In the intervention group, there were 705 patients in total, with 220 patients treated with TAVR, and 486 patients treated with SAVR. 1 patient underwent both procedures.

Population Characteristics

The population baseline characteristics, including comorbidities, aortic stenosis severity indices and the number of AS factors, are included in Table 4.1.

Table 4.1. Baseline Characteristics of the Severe Aortic Stenosis Population

	Overall (N=3,142)
Demographics	
Age, median (IQR)	82.6 (75.8, 87.6)
Female Gender, N (%)	1572 (50.0%)
BMI, median (IQR)	26.8 (23.6, 31.2)
eGFR (mL/min/1.73m^2), median (IQR)	61.8 (44.6, 79.2)
Echocardiographic Parameters	
AV MG (mmHg), median (IQR)	30.2 (19.8, 42)
AV Area (cm2), median (IQR)	0.8 (0.6, 1)
AV Vmax (m/s), median (IQR)	3.6 (3, 4.2)
DPI, median (IQR)	0.24 (0.20, 0.29)
Severe AV MG, N (%)	1013 (32.2%)
Severe AV Vmax, N (%)	1250 (39.8%)
Severe AV Area, N (%)	2379 (75.7%)
Severe DPI, N (%)	1650 (52.5%)
1 Severe AS Criterion, N (%)	1330 (42.3%)
2 Severe AS Criteria, N (%)	943 (30.0%)
3 Severe AS Criteria, N (%)	396 (12.6%)
4 Severe AS Criteria, N (%)	472 (15.0%)
EF (%), median (IQR)	61.2 (46.2, 73)
Normal LV, N (%)	2106 (67.0%)
Mild LV Dysfunction, N (%)	402 (12.8%)

Moderate LV Dysfunction, N (%)	325 (10.3%)
Severe LV Dysfunction, N (%)	260 (8.3%)
Comorbidities	
Prior HF, N (%)	701 (22.3%)
Prior HTN, N (%)	1255 (39.9%)
Prior ACS, N (%)	858 (27.3%)
Prior CVA, N (%)	122 (3.9%)
Prior COPD, N (%)	345 (11.0%)
Prior Liver Disease, N (%)	88 (2.8%)
Prior Dementia, N (%)	75 (2.4%)
Prior Diabetes, N (%)	662 (21.1%)
Prior Cancer, N (%)	606 (19.3%)
Prior CABG, N (%)	123 (3.9%)

IQR=Interquartile Range, BMI=Body Mass Index, eGFR=Estimated Glomerular Filtration Rate, MG=Mean Gradient, Vmax=Peak Velocity, AV=Aortic Valve, DPI=Dimensionless Performance Index, AS=Aortic Stenosis, EF=Ejection Fraction, LV=Left Ventricular, HF=Heart Failure, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

Differences in Baseline Characteristics According to Initial Treatment Strategy

There were significant differences between the populations that were managed conservatively, those who were treated initially with BAV and those who were treated invasively with SAVR or TAVR (Table 4.2).

Table 4.2. Baseline Characteristics According to Initial Treatment Strategy

	Medical Therapy (N=2,289)	**Initial BAV (N=223)**	**Intervention (N=630)**	**p-value**
Demographics				
Age, median (IQR)	84.2 (77.8, 88.4)	85 (79.6, 88.6)	75.8 (66.8, 81.6)	**<0.001**
Female Gender, N (%)	1202 (52.5%)	106 (47.5%)	264 (41.9%)	**<0.001**
BMI, median (IQR)	26.6 (23.4, 30.2)	26.6 (23.4, 31.2)	28.1 (24.7, 34.6)	**<0.001**
eGFR (mL/min/1.73m^2), median (IQR)	59.8 (42, 77)	60.8 (41.2, 74.2)	72.3 (54.8, 86.4)	**<0.001**
Echocardiographic Parameters				
AV MG (mmHg), median (IQR)	26.8 (17, 39.2)	32.7 (25.1, 43.9)	40 (31, 48.4)	**<0.001**
AV Area (cm2), median (IQR)	0.8 (0.8, 1)	0.8 (0.6, 0.8)	0.8 (0.6, 1)	**<0.001**
AV Vmax (m/s), median (IQR)	3.4 (2.8, 4)	3.8 (3.2, 4.2)	4 (3.6, 4.4)	**<0.001**
DPI, median (IQR)	0.25 (0.21, 0.31)	0.22 (0.17, 0.25)	0.23 (0.19, 0.26)	**<0.001**
Severe AV MG, N (%)	605 (26.4%)	78 (35.0%)	330 (52.4%)	**<0.001**
Severe AV Vmax, N (%)	767 (33.5%)	93 (41.7%)	390 (61.9%)	**<0.001**
Severe AV Area, N (%)	1726 (75.4%)	195 (87.4%)	458 (72.7%)	**<0.001**
Severe DPI, N (%)	1091 (47.7%)	164 (73.5%)	395 (62.7%)	**<0.001**
1 Severe AS Criterion, N (%)	1122 (49.0%)	53 (23.8%)	155 (24.6%)	**<0.001**
2 Severe AS Criteria, N (%)	683 (29.8%)	84 (37.7%)	176 (27.9%)	**0.023**
3 Severe AS Criteria, N (%)	235 (10.3%)	35 (15.7%)	126 (20.0%)	**<0.001**
4 Severe AS Criteria, N (%)	249 (10.9%)	51 (22.9%)	172 (27.3%)	**<0.001**
EF (%), median (IQR)	60.5 (45.2, 72.6)	52.6 (41.8, 69.2)	64.6 (52.6, 75.8)	**<0.001**
Normal LV, N (%)	1531 (66.9%)	111 (49.8%)	464 (73.7%)	**<0.001**

Mild LV Dysfunction, N (%)	303 (13.2%)	34 (15.2%)	65 (10.3%)	0.079
Moderate LV Dysfunction, N (%)	242 (10.6%)	33 (14.8%)	50 (7.9%)	**0.012**
Severe LV Dysfunction, N (%)	204 (8.9%)	19 (8.5%)	37 (5.9%)	**0.049**
Comorbidities				
Prior HF, N (%)	569 (24.9%)	50 (22.4%)	82 (13.0%)	**<0.001**
Prior HTN, N (%)	951 (41.5%)	85 (38.1%)	219 (34.8%)	**0.007**
Prior ACS, N (%)	635 (27.7%)	65 (29.1%)	158 (25.1%)	0.34
Prior CVA, N (%)	98 (4.3%)	9 (4.0%)	15 (2.4%)	0.091
Prior COPD, N (%)	289 (12.6%)	19 (8.5%)	37 (5.9%)	**<0.001**
Prior Liver Disease, N (%)	71 (3.1%)	7 (3.1%)	10 (1.6%)	0.12
Prior Dementia, N (%)	70 (3.1%)	3 (1.3%)	2 (0.3%)	**<0.001**
Prior Diabetes, N (%)	486 (21.2%)	49 (22.0%)	127 (20.2%)	0.79
Prior Cancer, N (%)	456 (19.9%)	48 (21.5%)	102 (16.2%)	**0.075**
Prior CABG, N (%)	84 (3.7%)	12 (5.4%)	27 (4.3%)	0.39

BAV=Balloon Aortic Valvuloplasty, IQR=Interquartile Range, BMI=Body Mass Index, eGFR=Estimated Glomerular Filtration Rate, MG=Mean Gradient, Vmax=Peak Velocity, AV=Aortic Valve, DPI=Dimensionless Performance Index, AS=Aortic Stenosis, EF=Ejection Fraction, LV=Left Ventricular, HF=Heart Failure, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

Patients being treated with an initial BAV strategy compared with medical therapy alone were similarly aged but had a significantly lower ejection fraction and a lower proportion had normal LV function. Patients in the initial BAV strategy arm had a higher severity of aortic stenosis. There were no differences in renal function or the rates of the analysed comorbidities.

Patients being treated with an initial BAV strategy compared with intervention only were older, with worse renal function. They had a significantly poorer cardiac function. The initial BAV group were significantly less likely to have a severe classification for AV mean gradient and AV peak velocity, which are LV dependent, but were more likely to have a severe AV area and DPI, indicating a higher proportion of LFLG severe AS. Rates of comorbidities were similar, but the initial BAV group were more likely to have a history of heart failure.

Survival and Early Hazard

Long-term observed mortality in our population was high. Of the 3,142 patients, there were 207 deaths (6.6%) at 30 days, and 496 deaths (15.8%) at 6 months. By 1 and 5 year follow up, 703 (22.4%) and 1,568 (49.9%) were deceased.

Mortality was significantly different according to initial treatment strategy, with medical therapy having the highest risk at all time points, and intervention having the lowest risk at all time points. The early hazard for a BAV strategy was low, with a 30-day mortality of 2.7%, compared to 8.5% with medical therapy, but approached the risk of medical therapy by 5 years. These data are presented in Table 4.3.

Table 4.3. Unadjusted Survival in the Aortic Stenosis Population, and Stratified by Initial Treatment Strategy

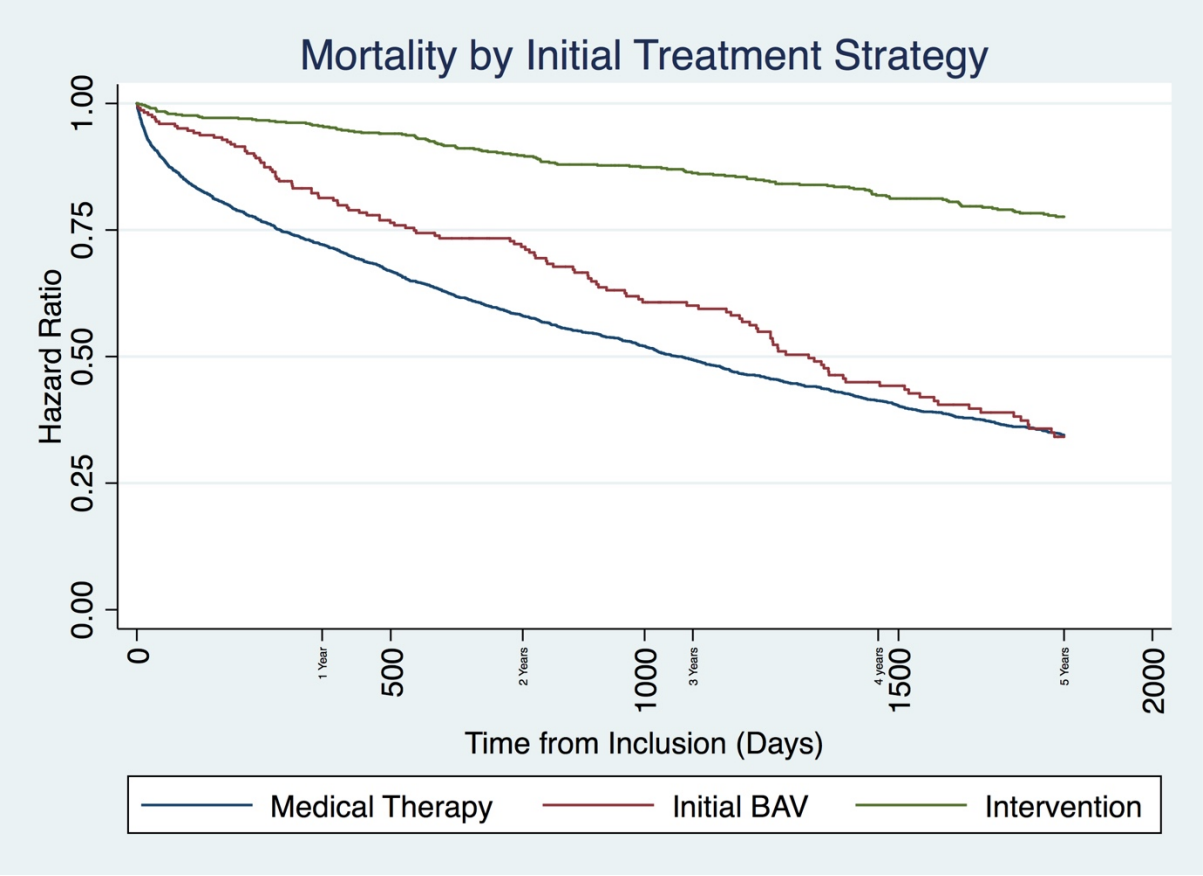
Death	Overall (N=3,142)	Medical Only (N=2,289)	Initial BAV (N=223)	Intervention (N=630)	p-value
30 Days, N (%)	207 (6.59%)	195 (8.52%)	6 (2.69%)	6 (0.95%)	**<0.001**
6 Months, N (%)	496 (15.79%)	461 (20.14%)	17 (7.62%)	18 (2.86%)	**<0.001**
1 Year, N (%)	703 (22.37%)	634 (27.70%)	41 (18.39%)	28 (4.44%)	**<0.001**
3 Years, N (%)	1,246 (39.66%)	1,085 (47.40%)	80 (35.87%)	81 (12.86%)	**<0.001**
5 Years, N (%)	1,568 (49.90%)	1,329 (58.06%)	117 (52.47%)	122 (19.37%)	**<0.001**

BAV=Balloon Aortic Valvuloplasty

Long-term Benefit by Initial Treatment Strategy

In order to determine the duration of benefit, if any, from employing an initial BAV strategy, a Kaplan-Meier Plot was used to review the 5 year mortality with each of the 3 strategies and is displayed in Figure 4.1. Using an IPW matched time-varying hazard model with an age, comorbidity and AS severity matched population, BAV had an initial HR of 0.47 (95% CI 0.37-0.61, p<0.001) and intervention had an initial HR of 0.29 (95% CI 0.24-0.36, p<0.001) when compared with medical management. If we then matched for the receipt of definitive intervention with SAVR or TAVR, the benefit attributed to BAV is attenuated, but remains significant, with an initial HR of 0.62 (95% CI 0.47-0.82 p=0.001).

Figure 4.1. Mortality According to Initial Treatment Strategy

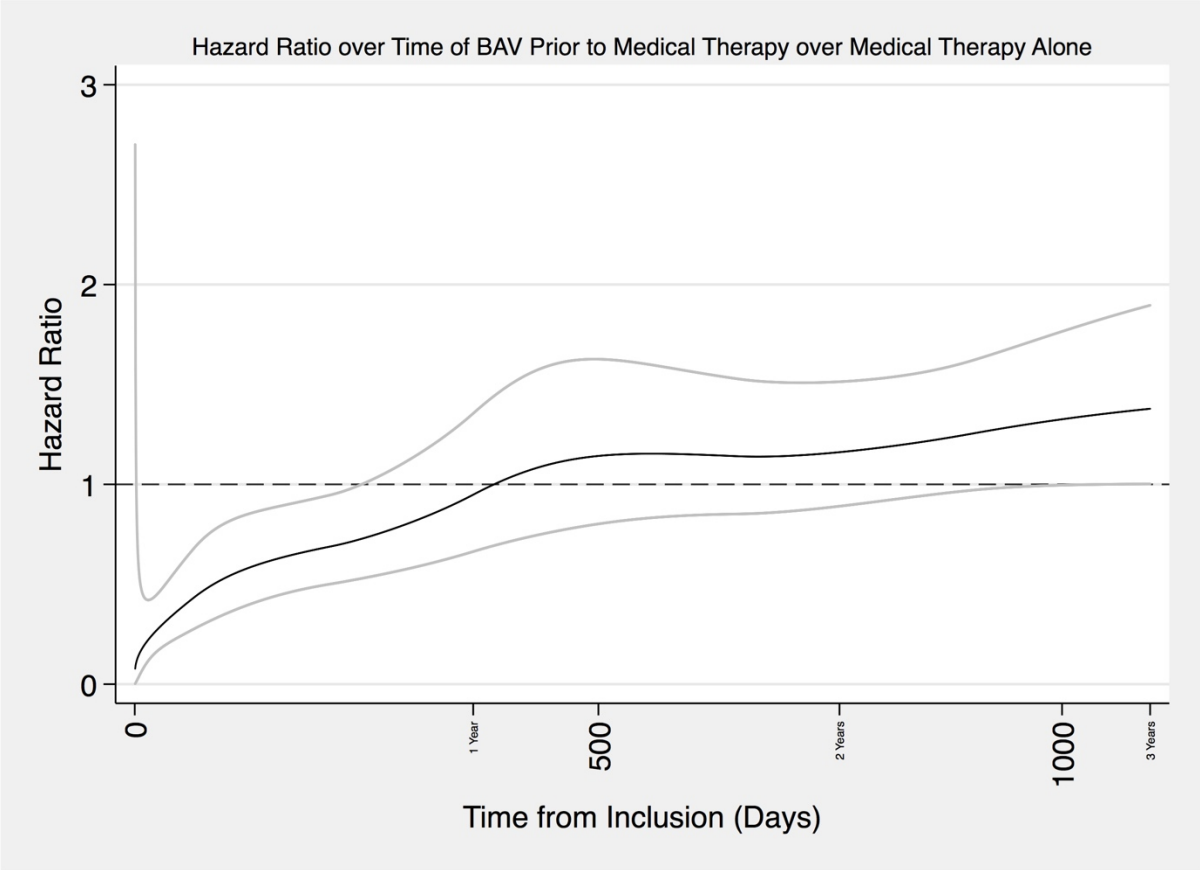


BAV=Balloon Aortic Valvuloplasty

In order to compare BAV to medical therapy alone, we then removed patients from the analysis who only received intervention with SAVR and TAVR directly and compared survival time from diagnosis to intervention or death.

In a population of 2,511 patients, using a similar IPW weighted analysis adjusting for comorbidities and AS severity, mortality with BAV was again superior to medical therapy with an initial HR of 0.62 (95% CI 0.48-0.80, $p<0.001$). This mortality benefit was significant to 245 days (Figure 4.2).

Figure 4.2. Hazard Ratio Over Time of an Initial Balloon Aortic Valvuloplasty Strategy Prior to Medical Therapy Over Medical Therapy Alone



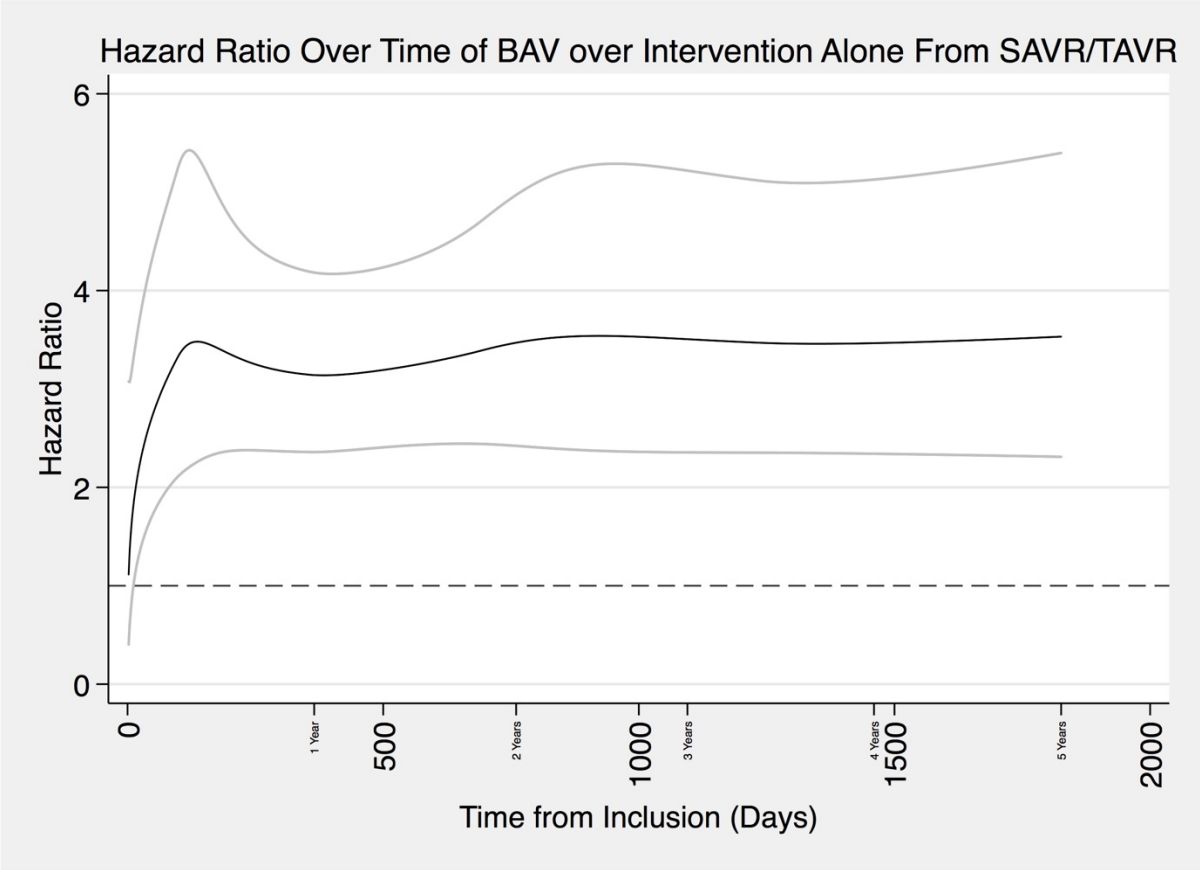
BAV=Balloon Aortic Valvuloplasty

We then compared mortality in the groups employing an initial strategy of BAV regardless of subsequent intervention compared with intervention with SAVR or TAVR without a prior BAV, from the time of the initial intervention of BAV, SAVR or TAVR to death, to determine if a preceding BAV had a beneficial or detrimental effect on long-term outcomes, and the duration of this effect.

In 853 patients over 5 years, the initial BAV strategy group had a significantly higher mortality compared with intervention alone at all time points. The net hazard associated with the initial BAV strategy group compared with the intervention alone group in the IPW

analysis was significant (HR=2.76, 95% CI 2.07-3.66, p<0.001). This is presented in Figure 4.3.

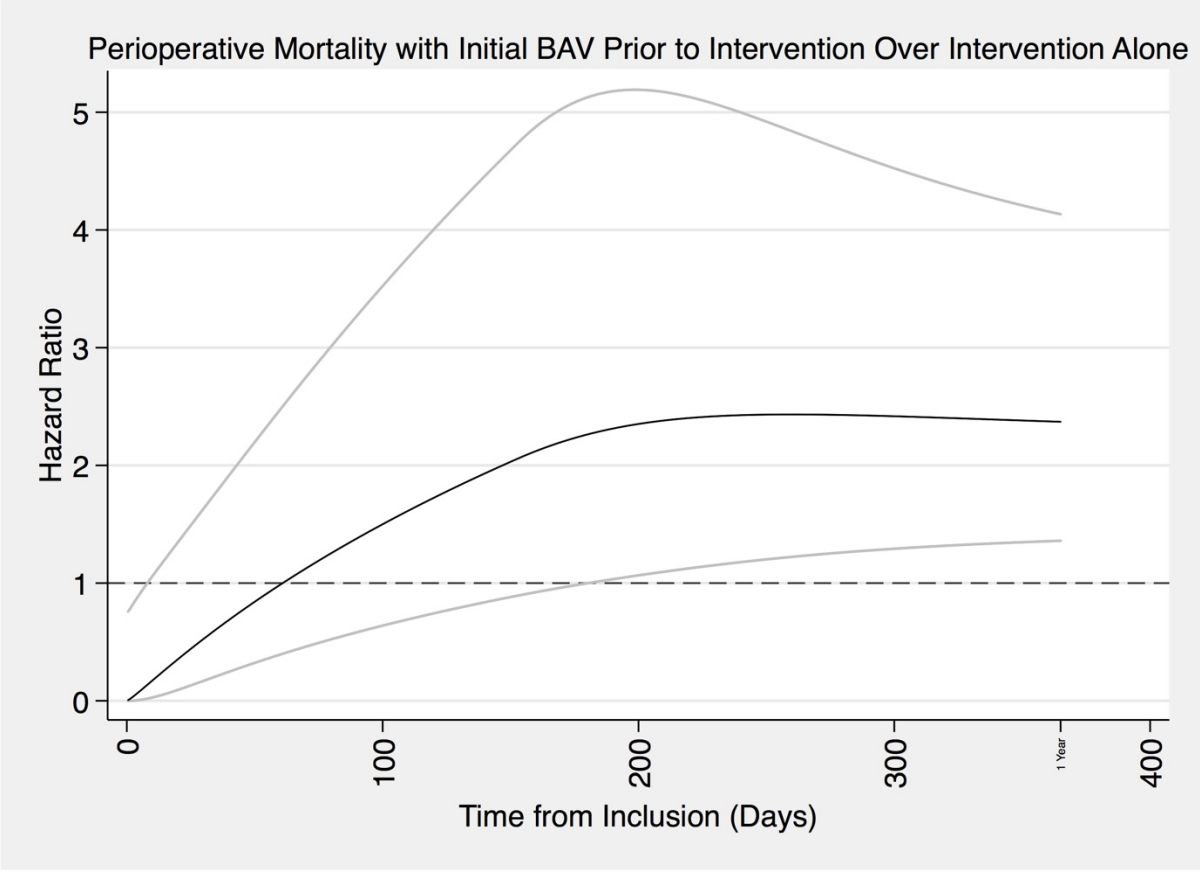
Figure 4.3. Hazard Ratio Over Time of an Initial Balloon Aortic Valvuloplasty Strategy, Regardless of Subsequent Intervention, Over Intervention Alone From the Initial Intervention to Death



BAV=Balloon Aortic Valvuloplasty, SAVR=Surgical Aortic Valve Replacement, TAVR=Transcatheter Aortic Valve Replacement

To confirm the role of BAV itself on perioperative mortality, relative to the differences in the character of the population and the timing of intervention, we then analysed mortality in the group who underwent definitive intervention, from intervention with SAVR or TAVR to 1 year, comparing the groups who did and did not receive a prior BAV. In 705 patients who underwent intervention, the net hazard associated with a prior BAV over 5 years was 1.45 (95% CI 0.91-2.31, p=0.117) with a significant mortality benefit in the first 17 days post intervention, and a significant hazard in this population after 180 days (Figure 4.4).

Figure 4.4. Hazard Ratio Over Time of Patients Undergoing Balloon Aortic Valvuloplasty Prior to Intervention Compared With Those Receiving Intervention Alone from Intervention to Death



BAV=Balloon Aortic Valvuloplasty

Outcomes Between All Four Treatment Options

As a sensitivity analysis, we further subdivided our group into all four treatment modalities options; 1) Medical therapy alone, 2) BAV then medical therapy, 3) BAV then intervention and 4) Intervention alone and measured unadjusted mortality to 5 years.

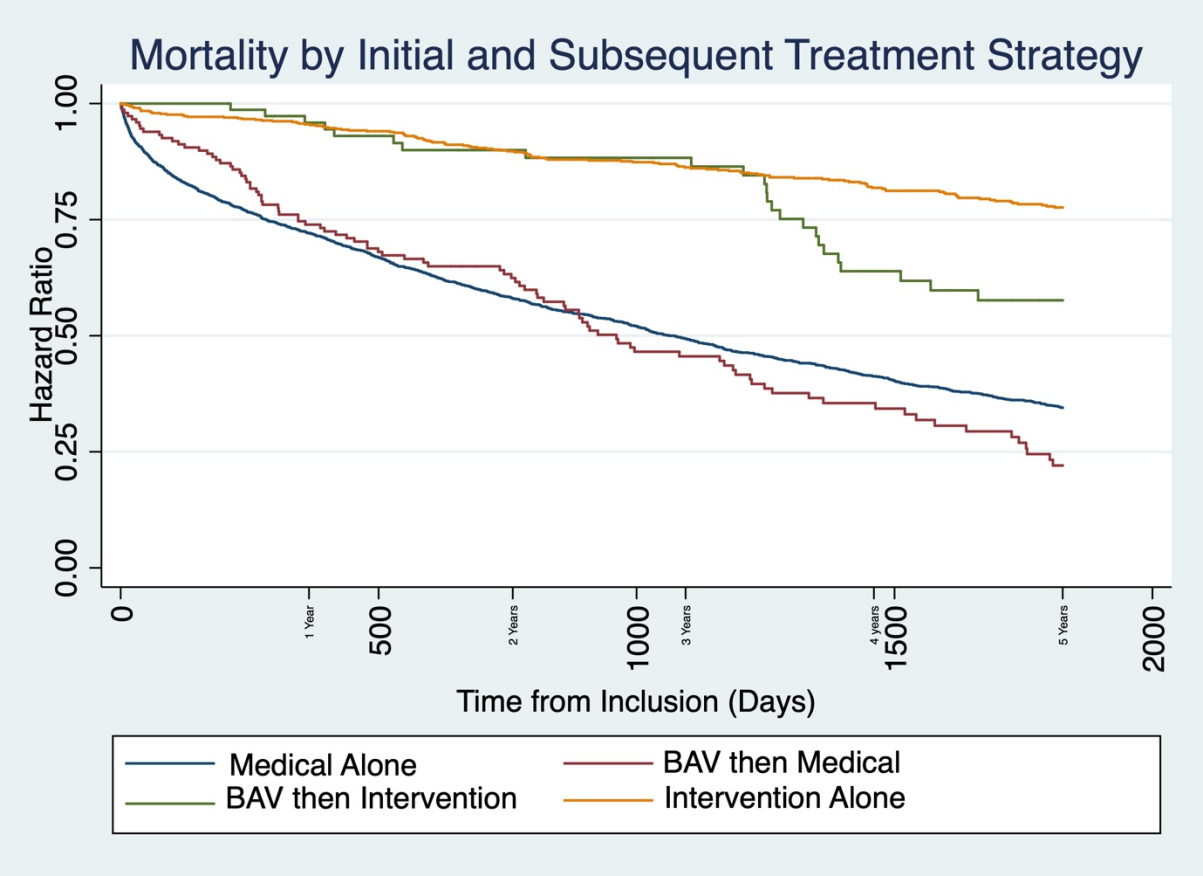
Table 4.4 and Figure 4.5 demonstrate the short- and long-term outcomes when further subdividing the BAV group according to their subsequent intervention strategy, confirming a very early separation in mortality risk between the BAV then intervention group and the BAV then medical group, a medium-term outcome with BAV then intervention similar to intervention alone and an early mortality benefit with BAV prior to medical therapy over medical therapy alone before a similar long-term outcome.

Table 4.4. Unadjusted Survival in the Aortic Stenosis Population, and Stratified by Initial and Subsequent Treatment Strategy

Death	Overall (N=3,142)	Medical Only (N=2,289)	BAV then Medical (N=148)	BAV then Intervention (N=75)	Intervention Alone (N=630)	p-value
30 Days, N (%)	207 (6.59%)	195 (8.52%)	6 (2.69%)	0 (0.00%)	6 (0.95%)	**<0.001**
6 Months, N (%)	496 (15.79%)	461 (20.14%)	17 (7.62%)	0 (0.00%)	18 (2.86%)	**<0.001**
1 Year, N (%)	703 (22.37%)	634 (27.70%)	38 (25.63%)	3 (4.00%)	28 (4.44%)	**<0.001**
3 Years, N (%)	1,246 (39.66%)	1,085 (47.40%)	72 (48.65%)	8 (10.67%)	81 (12.86%)	**<0.001**
5 Years, N (%)	1,568 (49.90%)	1,329 (58.06%)	93 (62.84%)	24 (32.00%)	122 (19.37%)	**<0.001**

BAV=Balloon Aortic Valvuloplasty

Figure 4.5. Mortality According to Initial and Subsequent Treatment Strategy



BAV=Balloon Aortic Valvuloplasty

4.4 Discussion

Our analysis intended to provide further data on the outcomes of BAV as an initial strategy in patients with severe AS. Our results indicate that in selected patients, BAV may improve short-term mortality over medical therapy, with little early hazard, and its use may be an appropriate consideration in certain populations to appropriately triage patients to subsequent therapeutic strategies.

It is clear from the population characteristics that an initial strategy of BAV is currently reserved for the more unwell, highly comorbid patients, often as a measure to retrieve the rapidly deteriorating patient with cardiogenic shock, but it is also used to aid clinical decision making as to whether or not intervention would offer a substantial benefit in highly comorbid patients, or patients with poor cardiac function[145-150]. The rationale behind the decisions to proceed to balloon aortic valvuloplasty rather than direct to urgent TAVR are varied and highly individual to each case. Reasons often include cost, since there may be a reluctance to spend resources funding a valve in a rapidly deteriorating patient, or efficacy, since it may be felt that demonstrating an improvement in left or right ventricular function may be beneficial prior to implanting a valve, or to allow time for proper perioperative assessment and investigations in a deteriorating patient.

In the TAVR era, with more experienced operators and lower profile devices, an initial strategy of BAV incurs less risk than previously documented[122]. In our population, early mortality in the BAV population was lower than in the medical therapy population, despite being older, with poorer LV function and a worse severity of AS, indicating that the procedure itself does not increase risk. In fact, in our unadjusted sensitivity analysis, the

group with the lowest mortality at all time points up to 3 years was the BAV then intervention group, with results not significantly different from the comparatively robust direct intervention patients (Table 4.4).

The early benefit attributed to BAV alone is not permanent, however, with similar long-term mortality rates between BAV then medical therapy to medical therapy alone. It is also worth noting that intervention alone is associated with the lowest mortality at 5 years, as the BAV then intervention group eventually succumbs to their age and comorbidities, with a late separation in the mortality curves noted after 3 years.

The demonstrated mortality benefit of BAV over medical therapy of 245 days, however, could be crucial for certain populations in whom immediate intervention may not be an ideal option. There are many scenarios in which a temporary relief of cardiac pressure overload may benefit a patient long term, in addition to rapid relief of cardiogenic shock, such as patients with a left or right ventricular “valvulomyopathy”, severe pulmonary hypertension, or significant non-cardiac competing risks, such as a requirement for the removal of a malignant tumour, all of which would be preferable to ameliorate prior to definitive valvular intervention. The ability of BAV to triage patients according to future risk can be achieved relatively rapidly, with an early separation of the unadjusted mortality curve and a trend towards a mortality difference between the BAV then medical and BAV then intervention groups by 30 days ($p=0.08$). This indicates that the path forward becomes clear relatively early, and a significant mortality difference is evident at 6 months, indicating a final intervention has been performed successfully in suitable candidates.

While we have clearly shown that BAV is at least transiently superior to medical therapy, our results indicated that patients in whom an initial strategy of BAV was employed were of higher risk and therefore had a higher mortality over the next 5 years compared with patients deemed suitable for immediate intervention. It is important to note that the long-term strategy following the BAV in the initial BAV group was not restricted in our primary analysis and included ultimately medically management patients, which likely worsened the late outcomes. This was done to limit survivor bias by avoiding the exclusion of patients who had poor outcomes following the BAV.

Despite poorer long-term outcomes in the initial BAV strategy group, when analysing perioperative mortality at the time of TAVR or SAVR in those surviving to intervention, mortality was similar or lower when adjusting for echocardiographic parameters and comorbidities in the immediate perioperative period. Since any hazard associated with BAV should be concentrated to the periprocedural time frame, this lends further support to our conclusion that BAV itself does not cause significant harm. The improved periprocedural mortality associated with prior BAV may be as a result of improved LV or RV function at the time of definitive intervention, reduced pulmonary pressures, improved patient selection, or may just be a statistical anomaly due to unmeasured confounders. The late mortality seen in the initial BAV strategy group (including the BAV then intervention sensitivity analysis group) is likely due to a much more comorbid population, with poorer cardiac function, which we were unable to fully adjust for in this analysis.

Limitations of this study include its observational, retrospective design, the single centre patient population and potential unmeasured confounders, such as frailty. Also due to the retrospective, observational nature of the study, we were unable to accurately comment on

specific factors that may have led to a decision to undertake BAV as a primary treatment modality apart from age and general comorbidity, as well as which specific patients benefited most from BAV. A future prospective analysis may be able to clarify this further. There may also be selection biases due to patient and physician preference. We attempted to overcome these limitations using the IPW analysis. Also, the intervention numbers are relatively low, although they are reasonable compared with the currently published literature and the event rates were relatively high. A prospective, randomised study would be required to determine the true utility of BAV in this population.

4.5 Conclusions

Untreated, aortic stenosis is associated with a very high mortality. While there is no doubt that definitive intervention remains the gold standard in improving mortality in severe AS, BAV has been shown to significantly improve mortality over medical therapy, up to 245 days. This time frame is longer than previously believed and provides a significant opportunity to allow the appropriate periprocedural workup involved in such a significant subsequent intervention.

Additionally, in the population who received BAV prior to intervention, there was a small, but significant mortality benefit in the immediate perioperative period, indicating that perhaps a prior BAV lessens the operative risk of TAVR or SAVR when adjusting for comorbidities.

Our results indicate that the early hazard associated with BAV is low, despite the population receiving BAV being at much higher risk, and BAV is likely able to rapidly and accurately triage patients into those who would and would not benefit from subsequent intervention. BAV remains a clinically valuable treatment modality and is likely underused.

CHAPTER 5

ASSESSING BENEFIT OF INTERVENTION FOR AORTIC STENOSIS IN PATIENTS WITH DISCORDANT SEVERITY CRITERIA

5.1 Introduction

Aortic stenosis is a common and debilitating condition associated with substantial morbidity and mortality[55, 58, 189]. It is well established that aortic valve replacement for severe, symptomatic AS is associated with a significant reduction in mortality, and the development of TAVR has enabled intervention options in those previously deemed untreatable[58-60, 128].

The timing of intervention is a common source of debate in the AS MDT meeting. Different teams may have varying thresholds before recommending intervention, particularly when the severity of AS is unclear, for example when the traditional AS markers are mixed in severity. The current guidelines recommend intervention when AS is deemed severe (MG >40mmHg, Vmax >4.0m/s, or MG <40mmHg and Vmax <4.0m/s with AVA <1.0cm^2 and LV impairment) and there is evidence for symptoms indicating cardiac decompensation [2, 15], however, there can often be a lag between the onset of myocardial dysfunction and symptoms, and cardiac imaging and biomarkers are being used to detect early phases of asymptomatic dysfunction[152]. A 2016 study showed that in patients with AS and discordant AS severity markers, intervention with SAVR improved mortality with moderate-range MG and Vmax coupled with severe AVA[153]. Furthermore, a recent trial showed that early intervention was beneficial in surgically managed patients with asymptomatic very severe AS[42], challenging the dogma that "aortic valve replacement is the most common cause of death in patients with asymptomatic severe aortic stenosis"[152]. On the other end of the spectrum of severity, it is likely that the risk associated with AS rises continuously with severity rather than reaching a "tipping-point" once the echocardiographic parameters reach the severe threshold, despite this being used as a common threshold for intervention.

The purpose of this analysis is to inform AS MDT decision-making by determining whether having a low number of, or discordant severity of AS indicators was associated with difference in mortality risk and therefore whether a threshold existed whereby intervention should be considered or deferred.

5.2 Methods

Patient Population

A retrospective, observational cohort study of the echocardiography database for the SALHN in South Australia was designed to review all consecutive patients undergoing transthoracic echocardiography in a high-volume echocardiography department between January 1, 2006, and December 31, 2016. Dedicated sonographers obtained the echocardiographic images, using doppler evaluation in all available windows to determine the peak signals indicating severe AS. The CTS database and the Structural Heart Disease database were also reviewed over the same time frame to link with procedural information. TAVR was introduced at SALHN in late 2008. Baseline demographics, comorbidities and outcomes for this population were determined using the ICD-10 AM diagnostic classification codes in the ISAAC database as well as from the department of BDM and the CRR databases. Renal function was recorded from biochemistry results in the CRR database and was estimated using the MDRD formula for the GFR. BMI was calculated using height and weight data in the echocardiography database. Data linkage was performed in a confidential manner and de-identified for the analysis. Patients were excluded from analysis if they had no linkable outcome data. The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/17/SAC/79), and all aspects comply with the Declaration of Helsinki.

Definition of AS and Echocardiographic Parameters

A patient population was identified as having significant AS if any of the following echocardiographic criteria were achieved: AV MG ≥ 40mmHg; AV Vmax ≥ 4.0m/s; AVA ≤ 1.0 cm^2; or DPI ≤ 0.25, as per the criteria outlined in the joint statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[87]. Some overlap and redundancy exist in the measurement of these values, but we chose not to omit any of the widely used variables since they are present in the clinical guidelines and are therefore clinically relevant. Since all participants in this study had at least one characteristic of significant AS, these were summed with each characteristic valued equally to provide a score between 1-4 for each patient.

Outcomes

The outcome of interest for this analysis was time to death from any cause. Deaths were defined and dated using combined data from the ISAAC, BDM and CRR databases to maximize data completion.

Analysis

Differences in baseline comorbidities were explored according to the number of severe-range AS measurements and by the presence or absence of intervention. The characteristics of each individual AS severity criterion was also analysed, to determine if any differences existed between groups. Comorbidities adjusted for in the analysis included age, sex, BMI, LV

dysfunction, renal dysfunction, liver dysfunction, DM, HTN, COPD, prior history of HF, ACS, CVA, cancer, dementia and prior CABG.

Unadjusted survival was reported in the overall population over 5 years, stratified according to the number of criteria for AS in the severe range. This was then adjusted for age and comorbidities. Due to the time varying effect of the intervention strategy, flexible parametric models were used.

We then analysed mortality in the intervention cohort from both the time of diagnosis and the time of intervention. The single centre mortality difference between TAVR and SAVR was first investigated using an age and comorbidity adjusted Cox analysis showing no demonstrable difference in mortality between intervention modalities, therefore SAVR and TAVR patients were grouped into a single indicator of intervention and used to explore possible differential treatment effects associated with the number of severe-range AS characteristics. Unadjusted and adjusted survival were then reported by number of severe AS criteria as an interaction between intervention or medical management and differences in survival for the number of AS criteria were noted.

Lastly, we determined the differences in timing of intervention by AS criteria group. We measured the time interval in days between first date of qualifying echocardiogram and first intervention with BAV, TAVR or SAVR and compared time to intervention between AS criteria groups. BAV was included in this analysis, as it was felt that it was acting as a temporising measure in those with other comorbidities, uncertain severity or critical illness allowing time for definitive intervention. We then measured mortality by AS criteria group from diagnosis to first intervention, comparing intervention with conservative therapy within

each AS criteria group, to determine if any group had a greater benefit from earlier or deferred intervention, and the interaction of intervention by AS criteria group, to determine if the effect of intervention was more significant at a certain number of AS criteria.

A subgroup analysis was performed excluding patients with an AV MG <40mmHg and AV Vmax < 4.0m/s, an AVA <1.0cm2, and an LVOT VTI of >18cm to try to reduce confounding by patients with suspected pseudosevere AS.

Finally, we had concerns that any delay in intervention in the lower AS criteria subgroups may represent a lag period within which the AS severity increased, with intervention occurring once the criteria were more traditionally severe. To account for this, we performed another subgroup analysis excluding patients with a time to intervention from first echocardiographic diagnosis to the first procedure more than 6 months, which we felt was within the window of acting on the initial echocardiogram, once initial clinic review, investigations, MDT discussion and procedural waiting lists are considered.

Statistical analysis was undertaken by an using de-identified data in Stata MP 15 software (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

5.3 Results

In total, 3,478 patients were identified for analysis by having at least one marker in the severe range for aortic stenosis. Seventy-seven patients without SA Health data available for linkage were excluded. Three patients were removed due to having no significant AS criteria, despite undergoing an intervention. After exclusions there were 3,398 patients available for analysis. There were 2,546 patients treated with medical therapy alone, with 148 more receiving BAV prior to conservative therapy, for a total of 2,694 within the time period of 2006-2017. The intervention group included 485 patients who underwent SAVR, with 12 receiving BAV prior, and 219 who underwent TAVR with 63 receiving BAV prior, combining to form total cohort of 704 patients, and a BAV subgroup of 223. An adjusted mortality analysis found that the hazard ratio for TAVR was not significantly different to SAVR (HR 0.957, 95% CI 0.644-1.423, p=0.829).

Population Characteristics

The baseline population characteristics, as well as by the number of qualifying severe AS criteria are demonstrated in Table 5.1. Patients with more AS criteria were older, but there was no difference in BMI to indicate frailty. As expected, with increasing numbers of severe AS criteria, there was a significant increase in the median severity of each of the individual criteria. Also, as predicted the LVEF and the LVOT VTI, which can be used as a surrogate for stroke volume index[190], were lower in the 1-2 AS criteria group than the 3-4 AS criteria group, accounting for the LFLG severe AS group with LV impairment, who cannot generate sufficient ventricular pressures to drive the pressure gradient and ejection velocity. AVA was the most commonly seen single AS criterion, with MG and Vmax increasing

together sharply in the 3 AS criteria group, again due to the previously attenuated LFLG group. Renal function was worse in the low AS criteria group, and a history of HF, HTN, ACS, CVA, COPD and prior CABG were all more common in the lower AS criteria groups.

Table 5.1. Baseline Characteristics of the Total Population, and by Number of AS Criteria

Demographics and Comorbidities	Total (N=3398)	1 AS Criterion (N=1465)	2 AS Criteria (N=1024)	3 AS Criteria (N=418)	4 AS Criteria (N=491)	p-value
Age, median (IQR)	81.6 (73.4, 87.2)	80.8 (72.6, 86.8)	81.8 (73.3, 87.4)	82 (74.8, 87)	82.8 (74, 88)	**0.016**
Female Gender (N, %)	1683 (49.5%)	777 (53.0%)	446 (43.6%)	216 (51.7%)	244 (49.7%)	**<0.001**
BMI, median (IQR)	27 (23.8, 31.2)	26.8 (23.8, 31.2)	27 (23.4, 31.6)	27.5 (24.8, 31.6)	26.6 (23.6, 31.2)	0.57
eGFR (mL/min/1.73m^2), median (IQR)	63.2 (45.6, 80.6)	62.8 (44.6, 80.2)	62 (43.1, 79.6)	65.2 (50.6, 82.4)	65.8 (49.8, 82)	**0.001**
AV MG (mmHg), median (IQR)	30.2 (19.7, 41.9)	21.3 (14.6, 29)	31.2 (22.4, 39.8)	42.8 (38.6, 50.2)	49.7 (45, 60)	**<0.001**
AVA (cm^2), median (IQR)	0.8 (0.6, 1)	1 (0.8, 1)	0.8 (0.6, 1)	0.8 (0.6, 1)	0.6 (0.6, 0.8)	**<0.001**
AV Vmax (m/s), median (IQR)	3.6 (3, 4.2)	3 (2.6, 3.6)	3.6 (3.2, 4)	4.4 (4, 4.6)	4.6 (4.2, 5)	**<0.001**
DPI, median (IQR)	0.23 (0.19, 0.27)	0.26 (0.23, 0.31)	0.23 (0.19, 0.27)	0.22 (0.18, 0.27)	0.18 (0.16, 0.21)	**<0.001**
EF (%), median (IQR)	61.2 (46.8, 73)	61.7 (46.8, 74)	59.4 (43.4, 72.4)	64.9 (52, 74.6)	62 (49.8, 72)	**<0.001**
Normal LV Function (N,%)	2310 (68.0%)	1030 (70.3%)	629 (61.4%)	303 (72.5%)	348 (70.9%)	**<0.001**
Mild LV Dysfunction (N,%)	425 (12.5%)	167 (11.4%)	158 (15.4%)	42 (10.0%)	58 (11.8%)	**0.007**

Moderate LV Dysfunction (N,%)	334 (9.8%)	131 (8.9%)	116 (11.3%)	41 (9.8%)	46 (9.4%)	0.26
Severe LV Dysfunction (N,%)	279 (8.2%)	126 (8.6%)	103 (10.1%)	21 (5.0%)	29 (5.9%)	**0.003**
LVOT VTI, median (IQR)	19.0 (14.8, 23.4)	19.0 (14.8, 23)	17.1 (13.4, 22.9)	21.3 (16.9, 23.2)	20.2 (16.9, 23.3)	**<0.001**
Severe MG (N,%)	1093 (32.2%)	16 (1.1%)	282 (27.5%)	304 (72.7%)	491 (100.0%)	**<0.001**
Severe AVA (N,%)	2525 (74.3%)	981 (67.0%)	739 (72.2%)	314 (75.1%)	491 (100.0%)	**<0.001**
Severe Vmax (N,%)	1360 (40.0%)	102 (7.0%)	382 (37.3%)	385 (92.1%)	491 (100.0%)	**<0.001**
Severe DPI (N,%)	1753 (51.6%)	366 (25.0%)	645 (63.0%)	251 (60.0%)	491 (100.0%)	**<0.001**
Prior HF (N,%)	715 (21.0%)	324 (22.1%)	230 (22.5%)	85 (20.3%)	76 (15.5%)	**0.009**
Prior HTN (N,%)	1291 (38.0%)	579 (39.5%)	391 (38.2%)	165 (39.5%)	156 (31.8%)	**0.019**
Prior ACS (N,%)	894 (26.3%)	424 (28.9%)	275 (26.9%)	96 (23.0%)	99 (20.2%)	**<0.001**
Prior CVA (N,%)	122 (3.6%)	51 (3.5%)	49 (4.8%)	11 (2.6%)	11 (2.2%)	**0.047**
Prior COPD (N,%)	347 (10.2%)	168 (11.5%)	112 (10.9%)	30 (7.2%)	37 (7.5%)	**0.011**
Prior Liver Disease (N,%)	89 (2.6%)	32 (2.2%)	36 (3.5%)	7 (1.7%)	14 (2.9%)	0.12
Prior Dementia (N,%)	75 (2.2%)	30 (2.0%)	29 (2.8%)	7 (1.7%)	9 (1.8%)	0.41
Prior Diabetes (N,%)	662 (19.5%)	294 (20.1%)	207 (20.2%)	74 (17.7%)	87 (17.7%)	0.48

Prior Cancer (N,%)	628 (18.5%)	270 (18.4%)	191 (18.7%)	75 (17.9%)	92 (18.7%)	0.99
Prior CABG (N,%)	128 (3.8%)	71 (4.8%)	39 (3.8%)	7 (1.7%)	11 (2.2%)	**0.005**
Intervention (N,%)	704 (20.3%)	177 (11.8%)	196 (18.8%)	141 (33.0%)	190 (38.0%)	**<0.001**

AS=Aortic Stenosis, BMI=Body Mass Index, EF=Ejection Fraction, AV=Aortic Valve, MG=Mean Gradient, AVA=Aortic Valve Area, Vmax=Peak Velocity, DPI=Dimensionless Performance Indicator, HF=Heart Failure, eGFR=Estimated Glomerular Filtration Rate, LV=Left Ventricle, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

Population characteristics according to the presence or absence of intervention are demonstrated in Table 5.2. Patients undergoing intervention were significantly younger, with a higher BMI, eGFR, EF and LVOT VTI, and a lower prior history of HF, COPD and dementia. These differences were adjusted for in the mortality analysis. The AS criteria MG, Vmax and DPI were more consistently in the severe range, whilst AVA was not significantly different.

Table 5.2. Baseline Characteristics by Presence or Absence of Intervention

Demographics and Comorbidities	**No Intervention (N=2694)**	**Intervention (N=704)**	**p-value**
Age, median (IQR)	83 (75.2, 88)	76.4 (67.6, 82.2)	**<0.001**
Female Gender (N, %)	1394 (51.7%)	289 (41.1%)	**<0.001**
BMI, median (IQR)	26.6 (23.6, 30.8)	28 (24.4, 34.6)	**<0.001**
eGFR (mL/min/1.73m^2), median (IQR)	61 (43.8, 78.8)	72 (53.8, 86.3)	**<0.001**
AV MG (mmHg), median (IQR)	27.6 (17.8, 39.9)	40 (30, 48.2)	**<0.001**
AVA (cm^2), median (IQR)	0.8 (0.8, 1)	0.8 (0.6, 1)	**<0.001**
AV Vmax (m/s), median (IQR)	3.4 (2.8, 4)	4 (3.6, 4.4)	**<0.001**
DPI, median (IQR)	0.23 (0.19, 0.28)	0.21 (0.18, 0.25)	**<0.001**
EF (%), median (IQR)	60.8 (46, 72.4)	64.3 (51.4, 75.5)	**<0.001**
Normal LV Function (N,%)	1807 (67.1%)	503 (71.4%)	**0.027**
Mild LV Dysfunction (N,%)	349 (13.0%)	76 (10.8%)	0.12
Moderate LV Dysfunction (N,%)	270 (10.0%)	64 (9.1%)	0.46
Severe LV Dysfunction (N,%)	241 (8.9%)	38 (5.4%)	**0.002**
LVOT VTI, median (IQR)	18.5 (14.3, 23)	20.37 (17, 24.8)	**<0.001**
Severe MG (N,%)	735 (27.3%)	358 (50.9%)	**<0.001**
Severe Vmax (N,%)	935 (34.7%)	425 (60.4%)	**<0.001**
Severe AVA (N,%)	2004 (74.4%)	521 (74.0%)	0.84
Severe DPI (N,%)	1305 (48.4%)	448 (63.6%)	**<0.001**
1 AS Criterion (N, %)	1288 (47.8%)	177 (25.1%)	**<0.001**
2 AS Criteria (N, %)	828 (30.7%)	196 (27.8%)	0.14
3 AS Criteria (N, %)	277 (10.3%)	141 (20.0%)	**<0.001**

4 AS Criteria (N, %)	301 (11.2%)	190 (27.0%)	**<0.001**
Prior HF (N,%)	614 (22.8%)	101 (14.3%)	**<0.001**
Prior HTN (N,%)	1041 (38.6%)	250 (35.5%)	0.13
Prior ACS (N,%)	712 (26.4%)	182 (25.9%)	0.76
Prior CVA (N,%)	102 (3.8%)	20 (2.8%)	0.23
Prior COPD (N,%)	302 (11.2%)	45 (6.4%)	**<0.001**
Prior Liver Disease (N,%)	76 (2.8%)	13 (1.8%)	0.15
Prior Dementia (N,%)	72 (2.7%)	3 (0.4%)	**<0.001**
Prior Diabetes (N,%)	513 (19.0%)	149 (21.2%)	0.21
Prior Cancer (N,%)	512 (19.0%)	116 (16.5%)	0.12
Prior CABG (N,%)	97 (3.6%)	31 (4.4%)	0.32

AS=Aortic Stenosis, BMI=Body Mass Index, EF=Ejection Fraction, AV=Aortic Valve, MG=Mean Gradient, AVA=Aortic Valve Area, Vmax=Peak Velocity, DPI=Dimensionless Performance Indicator, eGFR=Estimated Glomerular Filtration Rate, LV=Left Ventricle, HF=Heart Failure, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

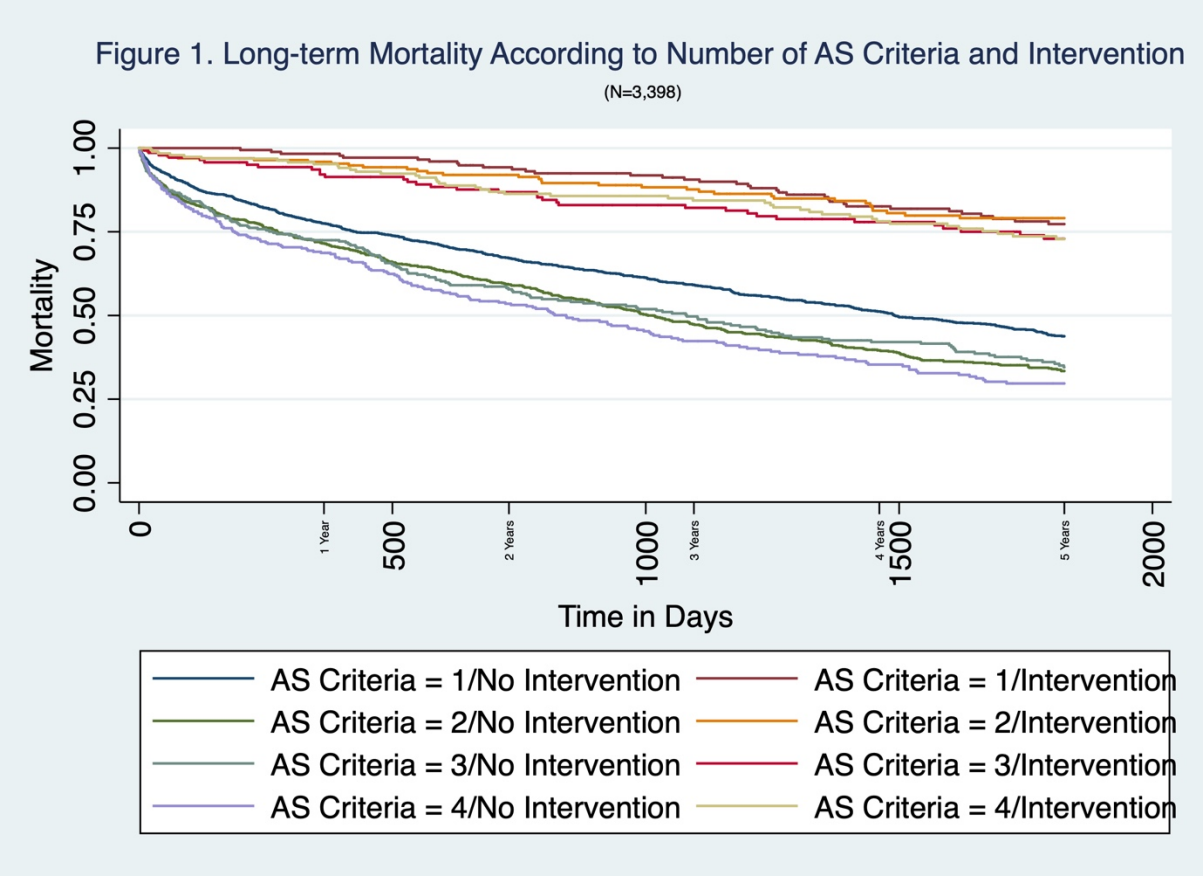
Mortality According to AS Criteria

Long-term observed mortality in our group varied significantly according to whether intervention occurred. In the conservatively treated group, 30-day, 1-year and 5-year mortality was 7.6%, 25.6%, and 54.5% respectively. The adjusted hazard ratio for mortality in the conservatively managed group relative to having 1 AS criteria was 1.23 for 2 AS

criteria (95% CI 1.09-1.39, p=0.001), 1.37 for 3 AS criteria (95% CI 1.15-1.63, p<0.001) and 1.46 for 4 AS criteria (95% CI 1.24-1.73, p<0.001). In the intervention group, the 30-day, 1-year and 5-year mortality was 0.8%, 4.4% and 20.7% respectively. The unadjusted HR for mortality in the intervention group was 0.27 (95% CI 0.23-0.32, P<0.001) compared with the conservatively managed group and adjusting for comorbidities was 0.36 (95% CI 0.30-0.43, p<0.001).

In the total population of 3,398 observations, with 1 AS criterion as a baseline, having 2, 3, and 4 AS criteria was associated with an increased adjusted hazard for mortality of 1.24 (95% CI 1.10-1.40, p=0.001), 1.37 (95% CI 1.15-1.63, p<0.001), and 1.48 (95% CI 1.25-1.74, p<0.001) respectively. The interaction between intervention and number of AS criteria was not significant for any number of AS criteria, demonstrating that intervention with any number of severe AS criteria was equally beneficial (Figure 5.1).

Figure 5.1. Long-term Mortality in Aortic Stenosis According to Number of Accumulated Aortic Stenosis Criteria and the Presence or Absence of Intervention



AS=Aortic Stenosis

In order to further account for confounding by potentially overestimated severity due to suspected pseudosevere aortic stenosis, we then repeated the analysis excluding 889 patients with a severe AVA, but a non-severe MG and Vmax, but a normal LVOT VTI, defined as >18cm. Baseline characteristics stratified by AS criteria and by intervention for this cohort are demonstrated in Tables 5.3 and 5.4. The increase in risk of mortality with accumulating AS criteria was similar. In 2,509 observations, with 1 AS criterion as a baseline, having 2, 3, and 4 AS criteria was associated with an increased hazard for mortality of 1.19 (95% CI 1.04-1.38, p=0.014), 1.23 (95% CI 1.01-1.49, p=0.037), and 1.33 (95% CI 1.12-1.59, p=0.002), when adjusting for age, gender and comorbidities. The adjusted benefit of intervention was

again significant with a HR for mortality of 0.43, (95% CI 0.27-0.69, $p<0.001$) and the interaction between intervention and accumulated AS criteria was again not significantly different between groups. This is demonstrated in Figure 5.2.

Table 5.3. Baseline Characteristics by Aortic Stenosis Criteria, Excluding Patients with Low Gradients and Normal Left Ventricular Outflow Tract Velocity Time Integral

Demographics and Comorbidities	**Overall (N=2,509)**	**1 AS Criterion (N=852)**	**2 AS Criteria (N=800)**	**3 AS Criteria (N=366)**	**4 AS Criteria (N=491)**	**p-value**
Age, median (IQR)	81.6 (72.6, 87.2)	80.2 (71, 86.4)	81.8 (72.6, 87.4)	81.8 (74.6, 87.2)	82.8 (74, 88)	**<0.001**
Female Gender (N, %)	1114 (44.4%)	347 (40.7%)	332 (41.5%)	191 (52.2%)	244 (49.7%)	**<0.001**
BMI, median (IQR)	27.2 (23.8, 31.8)	27.2 (24.2, 31.8)	27.2 (23.4, 32)	27.6 (24.4, 31.2)	26.6 (23.6, 31.2)	0.74
eGFR (mL/min/1.73m^2), median (IQR)	63.8 (46.6, 80.8)	63.7 (44.4, 79.9)	61.7 (43.2, 79.8)	65.7 (51.2, 82.4)	65.8 (49.8, 82)	**0.003**
AV MG (mmHg), median (IQR)	34.2 (19.8, 45.6)	19.4 (12.4, 29.4)	30.4 (21, 41.4)	44 (40.6, 51.4)	49.7 (45, 60)	**<0.001**
AVA (cm^2), median (IQR)	0.8 (0.6, 1)	1 (0.8, 1)	0.8 (0.6, 1)	0.8 (0.6, 1)	0.6 (0.6, 0.8)	**<0.001**
AV Vmax (m/s), median (IQR)	3.8 (3, 4.4)	3 (2.4, 3.6)	3.6 (3, 4.2)	4.4 (4.2, 4.6)	4.6 (4.2, 5)	**<0.001**
DPI, median (IQR)	0.23 (0.19, 0.27)	0.26 (0.23, 0.31)	0.23 (0.19, 0.27)	0.22 (0.18, 0.27)	0.18 (0.16, 0.21)	**<0.001**
EF (%), median (IQR)	60 (43, 72)	57.7 (39.6, 70.5)	55.8 (40, 71)	66 (53, 75)	62 (49.8, 72)	**<0.001**
Normal LV Function (N,%)	1595 (63.6%)	517 (60.7%)	460 (57.5%)	270 (73.8%)	348 (70.9%)	**<0.001**
Mild LV Dysfunction (N,%)	323 (12.9%)	107 (12.6%)	122 (15.2%)	36 (9.8%)	58 (11.8%)	0.055
Moderate LV Dysfunction (N,%)	297 (11.8%)	110 (12.9%)	109 (13.6%)	32 (8.7%)	46 (9.4%)	**0.022**

Severe LV Dysfunction (N,%)	259 (10.3%)	113 (13.3%)	98 (12.2%)	19 (5.2%)	29 (5.9%)	**<0.001**
LVOT VTI, median (IQR)	16.86 (13.6, 22.5)	15.5 (12.9, 17.9)	15.3 (12.4, 21.0)	21.6 (15.6, 26.9)	20.2 (16.9, 23.3)	**<0.001**
Severe MG (N,%)	1093 (43.6%)	16 (1.9%)	282 (35.2%)	304 (83.1%)	491 (100.0%)	**<0.001**
Severe Peak Velocity (N,%)	1636 (65.2%)	368 (43.2%)	515 (64.4%)	262 (71.6%)	491 (100.0%)	**<0.001**
Severe AVA (N,%)	1225 (48.8%)	102 (12.0%)	299 (37.4%)	333 (91.0%)	491 (100.0%)	**<0.001**
Severe DPI (N,%)	1560 (62.2%)	366 (43.0%)	504 (63.0%)	199 (54.4%)	491 (100.0%)	**<0.001**
Prior Heart Failure (N,%)	551 (22.0%)	210 (24.6%)	190 (23.8%)	75 (20.5%)	76 (15.5%)	**<0.001**
Prior HTN (N,%)	943 (37.6%)	346 (40.6%)	298 (37.2%)	143 (39.1%)	156 (31.8%)	**0.013**
Prior ACS (N,%)	654 (26.1%)	259 (30.4%)	210 (26.2%)	86 (23.5%)	99 (20.2%)	**<0.001**
Prior CVA (N,%)	91 (3.6%)	31 (3.6%)	39 (4.9%)	10 (2.7%)	11 (2.2%)	0.069
Prior COPD (N,%)	259 (10.3%)	105 (12.3%)	91 (11.4%)	26 (7.1%)	37 (7.5%)	**0.005**
Prior Liver Disease (N,%)	72 (2.9%)	20 (2.3%)	32 (4.0%)	6 (1.6%)	14 (2.9%)	0.090
Prior Dementia (N,%)	54 (2.2%)	16 (1.9%)	23 (2.9%)	6 (1.6%)	9 (1.8%)	0.39
Prior Diabetes (N,%)	483 (19.3%)	173 (20.3%)	160 (20.0%)	63 (17.2%)	87 (17.7%)	0.45
Prior Cancer (N,%)	456 (18.2%)	154 (18.1%)	147 (18.4%)	63 (17.2%)	92 (18.7%)	0.95
Prior CABG (N,%)	91 (3.6%)	44 (5.2%)	29 (3.6%)	7 (1.9%)	11 (2.2%)	**0.009**

AS=Aortic Stenosis, BMI=Body Mass Index, EF=Ejection Fraction, AV=Aortic Valve, MG=Mean Gradient, AVA=Aortic Valve Area, Vmax=Peak Velocity, DPI=Dimensionless Performance Indicator, eGFR=Estimated Glomerular Filtration Rate, LV=Left Ventricle, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

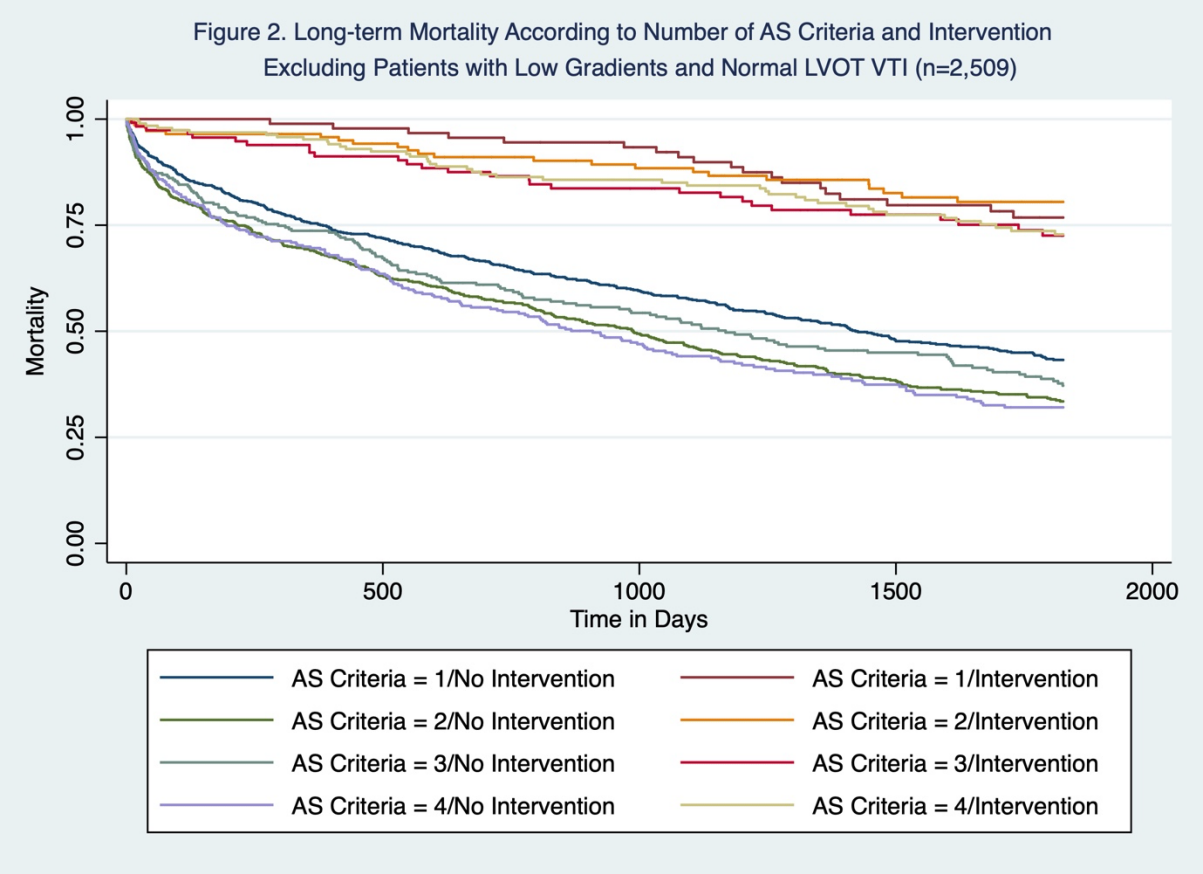
Table 5.4. Baseline Characteristics by Intervention, Excluding Patients with Low Gradients and Normal Left Ventricular Outflow Tract Velocity Time Integral

Demographics and Comorbidities	**No Intervention (N=1971)**	**Intervention (N=538)**	**p-value**
Age, median (IQR)	83 (74.6, 88)	76.1 (67, 82)	**<0.001**
Female Gender (N, %)	905 (45.9%)	209 (38.8%)	**0.003**
BMI, median (IQR)	26.8 (23.8, 31.2)	28.3 (24.4, 34.6)	**<0.001**
eGFR (mL/min/1.73m^2), median (IQR)	61.4 (43.8, 78.6)	72.3 (54.4, 88.4)	**<0.001**
AV MG (mmHg), median (IQR)	30 (17.8, 43)	43.1 (34, 51.2)	**<0.001**
AVA (cm^2), median (IQR)	0.8 (0.6, 1)	0.8 (0.6, 1)	**<0.001**
AV Vmax (m/s), median (IQR)	3.6 (2.8, 4.2)	4.2 (3.8, 4.6)	**<0.001**
DPI, median (IQR)	0.23 (0.19, 0.28)	0.21 (0.18, 0.25)	**<0.001**
EF (%), median (IQR)	58.4 (41, 71)	63.7 (51.8, 75)	**<0.001**
Normal LV Function (N,%)	1212 (61.5%)	383 (71.2%)	**<0.001**
Mild LV Dysfunction (N,%)	268 (13.6%)	55 (10.2%)	**0.038**
Moderate LV Dysfunction (N,%)	246 (12.5%)	51 (9.5%)	0.056
Severe LV Dysfunction (N,%)	225 (11.4%)	34 (6.3%)	**<0.001**
LVOT VTI, median (IQR)	16.2 (13.1, 21.5)	19.6 (16.0, 24.7)	**<0.001**
Severe MG (N,%)	735 (37.3%)	358 (66.5%)	**<0.001**
Severe Vmax (N,%)	1281 (65.0%)	355 (66.0%)	0.67
Severe AVA (N,%)	844 (42.8%)	381 (70.8%)	**<0.001**
Severe DPI (N,%)	1174 (59.6%)	386 (71.7%)	**<0.001**
1 AS Criterion (N, %)	761 (38.6%)	91 (16.9%)	**<0.001**
2 AS Criteria (N, %)	658 (33.4%)	142 (26.4%)	**0.002**

3 AS Criteria (N, %)	251 (12.7%)	115 (21.4%)	**<0.001**
4 AS Criteria (N, %)	301 (15.3%)	190 (35.3%)	**<0.001**
Prior Heart Failure (N,%)	479 (24.3%)	72 (13.4%)	**<0.001**
Prior HTN (N,%)	755 (38.3%)	188 (34.9%)	0.15
Prior ACS (N,%)	521 (26.4%)	133 (24.7%)	0.42
Prior CVA (N,%)	75 (3.8%)	16 (3.0%)	0.36
Prior COPD (N,%)	227 (11.5%)	32 (5.9%)	**<0.001**
Prior Liver Disease (N,%)	62 (3.1%)	10 (1.9%)	0.11
Prior Dementia (N,%)	52 (2.6%)	2 (0.4%)	**0.001**
Prior Diabetes (N,%)	372 (18.9%)	111 (20.6%)	0.36
Prior Cancer (N,%)	375 (19.0%)	81 (15.1%)	**0.034**
Prior CABG (N,%)	69 (3.5%)	22 (4.1%)	0.52

AS=Aortic Stenosis, BMI=Body Mass Index, EF=Ejection Fraction, AV=Aortic Valve, MG=Mean Gradient, AVA=Aortic Valve Area, Vmax=Peak Velocity, DPI=Dimensionless Performance Indicator, eGFR=Estimated Glomerular Filtration Rate, LV=Left Ventricle, HTN=Hypertension, ACS=Acute Coronary Syndrome, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, CABG=Coronary Artery Bypass Grafting

Figure 5.2. Long-term Mortality According to Number of Accumulated Aortic Stenosis Criteria and the Presence or Absence of Intervention Excluding Patients with Low Gradients and Normal Left Ventricular Outflow Tract Velocity Time Integral



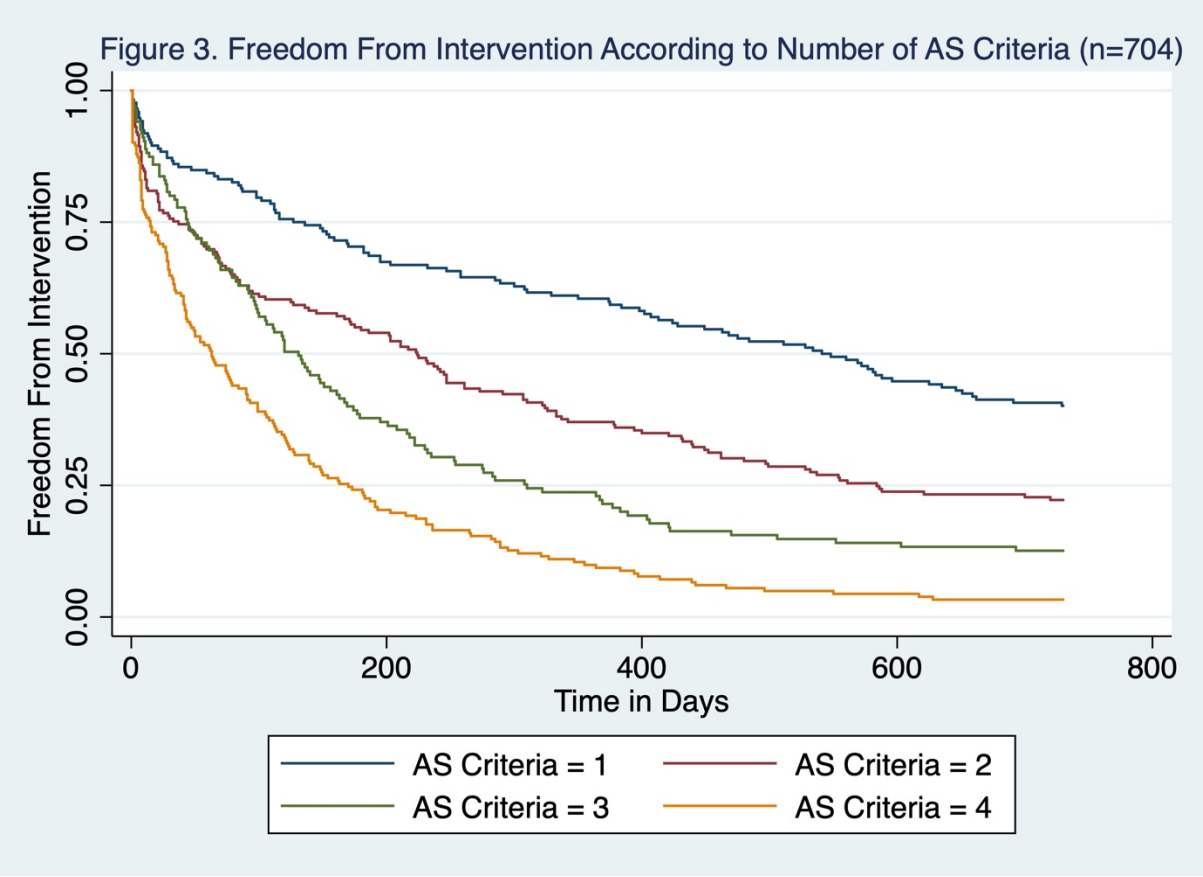
AS=Aortic Stenosis, LVOT=Left Ventricular Outflow Tract, VTI=Velocity Time Integral

Time to Intervention According to AS Criteria

Although all patients included had a least one marker of severe aortic stenosis, and therefore may have qualified for intervention, the time to therapy varied significantly between groups, indicating indecision regarding the severity of aortic stenosis by the treating team. Patients receiving their first intervention with BAV, TAVR or SAVR had a median time between first echocardiogram documenting possible severe AS and intervention of 528 days for 1 criterion,

211 days for 2 criteria, 120 days for 3 criteria and 55.5 days for 4 criteria (Figure 5.3). The difference in time to intervention between groups was statistically significant ($p<0.001$). Median time to intervention was not significantly altered in the low gradient, normal LVOT VTI subgroup, with respective times to intervention for each incremental increase in AS Criteria of 541, 173.5, 119, and 55.5 days ($p<0.001$).

Figure 5.3. Time to Intervention According to Number of Aortic Stenosis Criteria



AS=Aortic Stenosis

Effect of Timing of Intervention on Mortality

Although the time to intervention was significantly different between AS criteria groups, the mortality curves within the intervention population were not significantly different. The adjusted hazard ratio for mortality from the diagnostic echocardiogram in the intervention group according to number of AS criteria relative to 1 AS criteria was 0.90 for 2 AS criteria (95% CI 0.56-1.45, p=0.662), 1.11 for 3 AS criteria (95% CI 0.68-1.79, p=0.683), and 1.17 for 4 AS criteria (95% CI 0.74-1.84, p=0.496), as depicted in Figure 5.1. We also compared mortality from the time of intervention in the intervention group according to number of AS criteria and similarly found no significant difference.

We then excluded patients with a significantly delayed procedure from the time of initial qualifying echocardiogram of more than 6 months. This method excluded 373 patients and found similar results. In 3,025 observations, with 1 AS criterion as a baseline, having 2, 3, and 4 AS criteria was associated with an increased hazard for mortality of 1.25 (95% CI 1.11-1.41, p<0.001), 1.36 (95% CI 1.14-1.62, p=0.001), and 1.44 (95% CI 1.22-1.70, p<0.001), when adjusting for age, gender and comorbidities. The adjusted benefit of intervention trended, but was no longer significant overall (HR 0.66, 95% CI 0.41-1.02, p=0.062) but the interaction between AS criteria and intervention was significant in the 2 and 4 AS criteria groups (HR=0.47, p=0.028 and HR=0.42, p=0.004 respectively) and not in the 3 AS criteria group (HR=0.64, p=0.156).

Overall, within the entire group there was an adjusted daily HR of 0.9988 (p<0.001) with intervention over medical therapy. This equates to a 30-day HR of 0.96, or a 1-year HR of 0.64 with earlier intervention.

5.4 Discussion

In this study, we analysed mortality according to the accumulated number of the typical AS severity criteria, as well as the effect of intervention in each group to determine if an optimal timing of intervention could be determined in patients with discordant severe AS criteria. We found that mortality increased with an increasing number of AS severity criteria, and that intervention was beneficial with all groups, and that this benefit of intervention did not differ between groups, despite intervention being deferred in the fewer AS criteria cohorts.

Having lower numbers of echocardiographic AS high-risk criteria has often led to varying diagnoses of moderate AS, moderate+ AS, moderate to severe AS or moderately severe AS, which has been presumed to have inherently lower risk and therefore intervention could be deferred or delayed. This philosophy is demonstrated in our cohort by the significant differences in time from diagnosis to first intervention. This analysis counters the notion that delaying intervention is safe in those with lower numbers of severe AS criteria, by showing that even a single criterion indicating severe AS is associated with significant hazard, with the hazard increasing as AS criteria accumulate. Furthermore, our data suggest that intervention at any point in the AS criteria spectrum is significantly beneficial and that this does not vary depending on the number of criteria involved. In all AS criteria groups in our analysis, earlier intervention led to a continuous improvement in mortality. This observation suggests that there is no benefit in waiting for AS criteria to accumulate further before intervention.

Additionally, a recent analysis from the National Echo Database Australia by Strange et al. found that patients with moderate AS had a significantly elevated 5-year mortality, greater

than 50%[191], further suggesting early intervention may be beneficial as soon as significant AS is suspected rather than waiting for potentially irreversible myocardial damage or dysfunction and poor outcome. This challenges the study design of several ongoing trials examining intervention in asymptomatic severe AS patients, such as EARLY TAVR[192], EASY-AS[193] and EVoLVeD[194].

There can be varying reasons for the discordance of AS criteria, including, but not limited to, reduced cardiac output leading to a reduction in the traditional severe gradients, i.e., true but low flow/low gradient AS, or a falsely reduced AVA with moderate gradients and velocities with normal cardiac function, i.e., pseudosevere AS. We attempted to overcome this by excluding the population most likely to represent pseudosevere AS and found similar outcomes.

This analysis has the benefit of large numbers, with a long period of follow up and mortality as a hard endpoint. However, limitations to this study include the single centre, retrospective, observational nature of the data collection, and potential bias inherent in this. We attempted to match for comorbidities to the best capability of our dataset, but some differences may still exist. The decisions surrounding continuing medical therapy rather than intervention for the large cohort of conservatively managed patients is largely unknown, but the database included several years prior to the advent of TAVR and several years for which TAVR was still used with hesitation in only the highest risk patients, and so perhaps patients were not considered surgical candidates who would be considered for TAVR in the current era. Also, the symptom status of our cohort is unknown and so it is feasible that many patients were conservatively managed or deferred for intervention in the absence of symptoms, but with the recent challenges to the requirement for significant symptoms to exist, at least in the high

severity AS group, this may prove less relevant with time. Certainly, our data, which is symptom agnostic, suggests a potential mortality benefit in all AS criteria subgroups, regardless of symptoms.

Although mortality was numerically lower with fewer AS criteria despite a delay in intervention, the motives for the delay are unclear and so we believe it is inaccurate to conclude that deferral of intervention is safe, due to the demonstrated similar benefit of intervention in all groups. Hence, whilst the optimal timing for AS intervention in still under investigation, our study results lend further credence to the growing evidence that early aortic valve intervention may be beneficial. The historical teaching that the risk of AV intervention may be worse than this disease itself should be reconsidered.

5.5 Conclusions

Discordant severity of echocardiographic aortic stenosis criteria has led to indecision regarding the timing of AS intervention. Our analysis suggests that intervention at any number of AS criteria is beneficial. Moreover, the strength of this benefit is independent of the number of accumulated AS criteria. Additionally, earlier intervention for AS may lead to improved mortality, independent of the number of accumulated AS criteria. This supports the growing position that early intervention is beneficial, particularly as the risk inherent in AS intervention decreases. This data should be confirmed with larger studies, and potentially a randomised controlled trial of intervention versus conservative management in patients with 1-2 AS criteria compared with 3-4 AS criteria.

CHAPTER 6

ASSESSING SYMPTOM RECOVERY USING GLOBAL LONGITUDINAL STRAIN AFTER INTERVENTION FOR SEVERE AORTIC STENOSIS

6.1 Introduction

Aortic stenosis is an increasingly common degenerative valvular disorder which leads to increased mortality and a significant symptom burden, typically causing dyspnoea, angina and, as it progresses, presyncope and syncope[195]. Symptoms are difficult to manage with medical therapy, with AVR the only definitive method of improving symptoms and mortality[15]. Traditionally, this involved open heart surgery with SAVR, but the last decade has seen a sharp increase in the use of TAVR, first for inoperable patients, but as the technology advanced, later including increasingly lower surgical-risk patients[58-60, 127, 128, 196].

In the often-elderly AS population, patients are often less focused on longevity, and more concerned with prompt symptomatic improvement, with symptoms typically the trigger for intervention[15]. The landmark PARTNER trials included symptom scores in the analysis to ensure symptomatic improvement as a therapeutic priority in addition to mortality outcomes[55, 197]. Additionally, higher pre-operative symptom scores have been linked to worse outcomes in SAVR-treated patients[198]. The KCCQ, the NYHA heart failure classes and the 6MWT have all been used to assess symptom burden in the heart failure population for decades and have been validated in the AS population as well[55, 165, 166]. Since symptoms are such an important outcome measure in aortic intervention, particularly to patients, lack of symptomatic improvement post-intervention is an outcome which warrants significant research.

Strain analysis is a method of quantifying LV muscle fibre dysfunction earlier than EF measurement[154, 155]. Abnormal pre-procedural GLS has been linked to increased

mortality, symptoms, and worse procedural outcomes in the severe AS population[48, 156-158]. Post-procedural strain analysis and residual symptoms has not, to our knowledge, been investigated previously. The purpose of this analysis was to measure baseline pre-operative strain and symptoms prior to intervention with SAVR or TAVR, quantify the improvement in symptoms and strain post-intervention and determine whether a relationship exists between residual symptom burden and abnormal LV strain.

6.2 Methods

Study Population

A prospective, observational cohort study was designed including patients in SALHN in South Australia being assessed for aortic valve intervention due to severe, symptomatic aortic stenosis. Both surgical and transcatheter intervention candidates were included. Patients were recruited consecutively from the Structural Cardiology outpatient clinic or the Cardiothoracic Surgery Preoperative Assessment clinic between December 2016 and April 2018. Demographic and clinical data including medication histories, biochemistry, and ECG results, and preprocedural echocardiographic data were recorded. Patients were excluded if they did not proceed to intervention within 6 months of the study end date but were otherwise unselected to avoid bias.

Symptoms

After obtaining consent, patients were assessed for symptoms subjectively, using both the NYHA classification and the KCCQ, and objectively, using the 6MWT and gait speed, if physically able. The KCCQ-OS is scored out of 100, with a lower score indicating a higher degree of symptoms. The KCCQ-OS scores are often subdivided into 4 classes, roughly analogous to the NYHA classes, with class 1 being the least symptomatic and having a score >75, class 2 between 60 and 75, class 3 between 45 and 60 and class 4 being the most symptomatic and having a score of less than 45. Symptoms were again recorded at early follow up, typically 4-6 weeks, and late follow up, between 6-12 months.

Strain Analysis

Using TomTec strain analysis software (2D cardiac performance analysis, Unterschleissheim, Germany) retrospectively on existing echocardiographic images, echocardiograms were analysed pre-procedurally, at early follow up, and at late follow up. Measurements were performed by a single researcher and included GLS, TTP, MD and LAS. Strain is a measure of tissue deformation defined as the degree of lengthening of muscle fibres, and measures 16 myocardial segments in 3 echocardiographic planes. Since with muscle contraction, these fibres shorten, peak strain is measured as a negative percentage of deformation from baseline. Fibres shorten in the longitudinal, and circumferential planes, and lengthen in the radial plane, and can be measured for all 16 segments of myocardium or averaged for a global measurement. Peak GLS has been the focus of most strain-based cardiac research and has applications in the characterisation of cardiomyopathies, assessment of cardiac resynchronization therapy, assessment of myocardial load in valvular heart disease, and prediction of mortality or adverse outcomes[155, 171]. TTP is the time, in milliseconds, within which peak strain is reached from baseline. MD is calculated as the standard deviation of the TTP for all 16 segments, and heterogeneity between myocardial segments has been shown to predict arrhythmias, since it reflects myocardial scarring[172]. LAS is an averaged biplane measurement of atrial deformation, and is associated with adverse outcomes in the AS population[173].

Analysis

Data were collected and aggregated by a single researcher by way of patient interview and assessment, SALHN medical records, private clinician letters, and investigations with consent from all parties involved. Results were stored in the online REDCap database from Vanderbilt University, version 9.3.1 licensed by the South Australia Health and Medical Research Institute (SAHMRI).

Correlations between variables were determined using the Wilcoxon signed-rank test, Spearman's correlations test, the Kruskal-Wallis equality-of-populations rank test or linear regression, and statistical analysis was undertaken in Stata MP 15 software (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). Given the observational nature of this study, no adjustments were made for multiple testing and a p-value of 0.05 was considered statistically significant.

The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/16/SAC/168), and all aspects comply with the Declaration of Helsinki.

6.3 Results

In total, 158 patients with severe aortic stenosis were screened, but 67 of these were excluded due to not receiving their final intervention within 6 months of the study end date. Of the 91 remaining patients, 3 had BAV only and were excluded, therefore 88 patients contributed data to the population. Thirteen patients were missing at least one out of the initial or final strain analysis, usually due to poor image quality, or the final KCCQ assessment and so were excluded from the change in variable analysis. Seven of 23 SAVR-treated patients underwent concomitant coronary grafting, but since the only significant difference in baseline demographics between those who did and did not receive grafting was the EF, and the median values were both >=50%, they were grouped for the remainder of the analysis. Additionally, no significant differences in initial or final KCCQ-OS or GLS were noted between the SAVR-treated groups with or without grafting. Baseline characteristics of the entire cohort and by procedure are described in Table 6.1.

Table 6.1. Baseline Demographics

	Overall (N=88)	**TAVR (N=65)**	**SAVR (N=23)**	**p-value**
Demographics				
Age, median (IQR)	87 (81.5, 90)	88 (85, 91)	74 (68, 86)	**<0.001**
Female, N (%)	33 (38%)	26 (40%)	7 (30%)	0.42
BMI, median (IQR)	27.4 (24.6, 30.6)	27.3 (24.3, 29.3)	28.8 (24.8, 34.0)	0.15
FFS, median (IQR)	1 (1, 3)	2 (1, 3)	1 (1, 3)	0.42
STS Score, median (IQR)	2.7 (2.0, 4.0)	3.0 (2.4, 4.4)	1.9 (0.9, 2.6)	**<0.001**
Echocardiography				
EF (%), median (IQR)	59 (49, 63.7)	58 (48, 63.7)	60 (50, 64)	0.75
AV MG (mmHg), median (IQR)	45.2 (39.1, 52.2)	43.4 (38.8, 51)	47.2 (40.7, 57.2)	0.19
AVA (cm^2), median (IQR)	0.8 (0.63, 0.94)	0.75 (0.61, 0.91)	0.9 (0.72, 1)	**0.029**
AV Vmax (m/s), median (IQR)	4.4 (4.1, 4.7)	4.4 (4, 4.65)	4.5 (4.1, 4.9)	0.32
DPI, median (IQR)	0.23 (0.18, 0.27)	0.23 (0.17, 0.27)	0.23 (0.2, 0.28)	0.62
Comorbidities				
eGFR (mL/min/1.73m^2), median (IQR)	64 (50.5, 74.5)	60 (48, 69)	71 (61, 83)	**<0.001**
NT-proBNP (ng/L), median (IQR)	1307 (680, 3142)	1568 (748, 5214)	492 (295, 2299)	0.099
Prior HF, N (%)	10 (11%)	7 (11%)	3 (13%)	0.77
Prior HTN, N (%)	70 (80%)	54 (83%)	16 (70%)	0.17
Prior IHD, N (%)	46 (52%)	35 (54%)	11 (48%)	0.62
Prior CVA, N (%)	21 (24%)	15 (23%)	6 (26%)	0.77
Prior COPD, N (%)	10 (11%)	8 (12%)	2 (9%)	0.64
Prior PVD, N (%)	16 (18%)	14 (22%)	2 (9%)	0.17

Moderate+ MR, N (%)	4 (5%)	4 (6%)	0 (0%)	0.22
Prior Diabetes, N (%)	23 (26%)	17 (26%)	6 (26%)	0.99
Prior AF, N (%)	30 (34%)	24 (37%)	6 (26%)	0.35
Prior CABG, N (%)	18 (20%)	14 (22%)	4 (17%)	0.67
Strain				
GLS (%), median (IQR)	-14.2 (-16.8, -11.2)	-13.9 (-16.5, -12.0)	-14.8 (-18.3, -9.8)	0.67
TTP (ms), median (IQR)	405.5 (375.5, 454)	408 (372.1, 459.3)	391 (378, 440)	0.45
MD (ms), median (IQR)	69 (53, 89.5)	72 (60, 93)	60 (49, 76)	**0.028**
LAS (%), median (IQR)	18.8 (10.8, 25.8)	18.3 (9.8, 24.5)	18.9 (12.6, 26.3)	0.33
Symptoms				
KCCQ-OS, median (IQR)	60.2 (40.8, 76.7)	55.9 (39.1, 70.4)	69.9 (49.2, 85.4)	0.085
NYHA, median (IQR)	3 (2, 3)	3 (2, 3)	2 (2, 3)	0.19
6MWT Distance (m), median (IQR)	384 (284, 432)	335.75 (270, 403.5)	420.5 (394.5, 480)	**0.002**

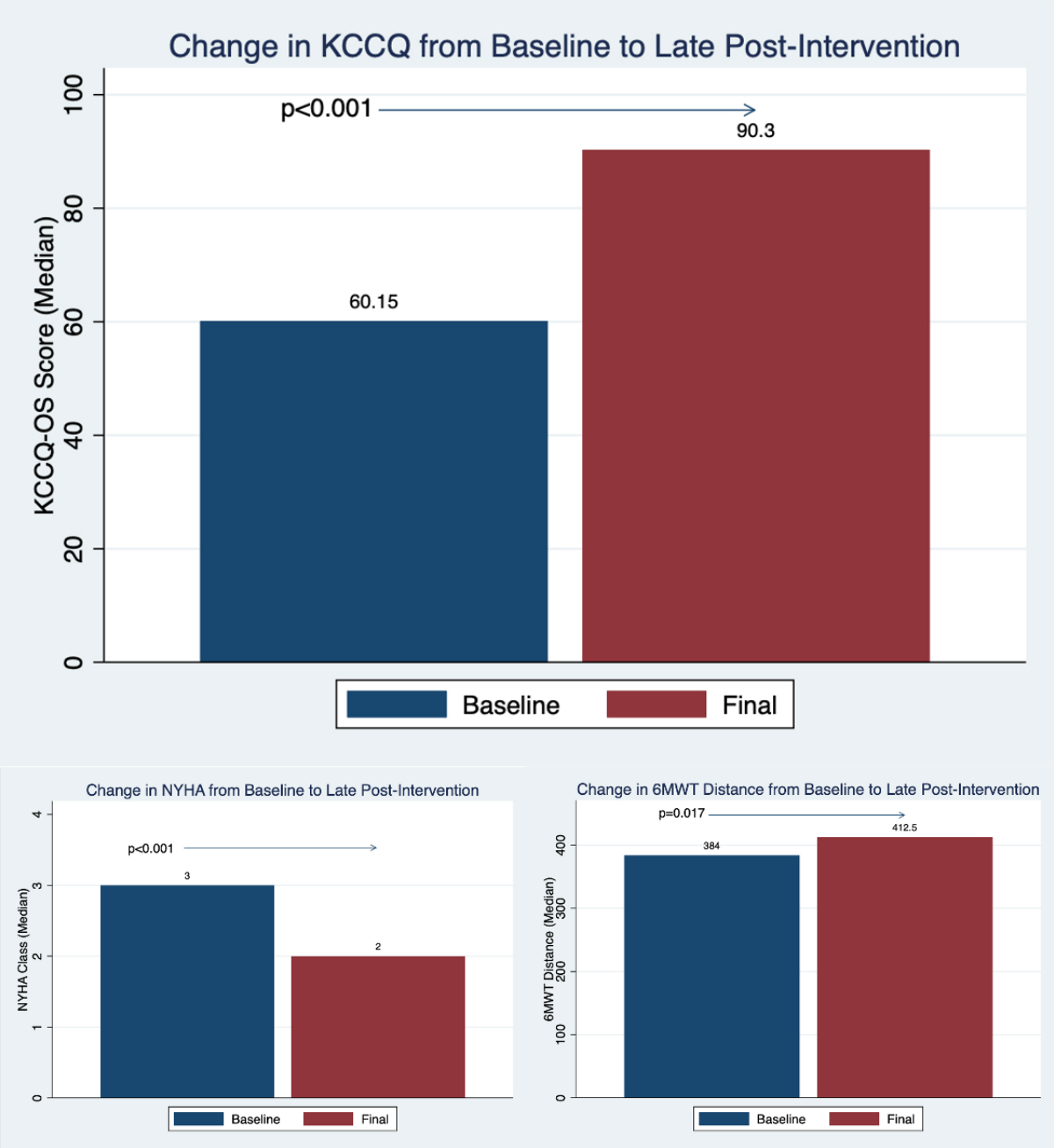
TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement, IQR=Interquartile Range, BMI=Body Mass Index, FFS=Fried Frailty Scale, STS=Society of Thoracic Surgeons, EF=Ejection Fraction, MG=Mean Gradient, AVA=Aortic Valve Area, DPI=Dimensionless Performance Index, eGFR=Estimated Glomerular Filtration Rate, NT-proBNP=N-terminal proB-type Natriuretic Peptide, HF=Heart Failure, HTN=Hypertension, IHD=Ischaemic Heart Disease, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, PVD=Peripheral Vascular Disease, MR=Mitral Regurgitation, AF=Atrial Fibrillation, CABG=Coronary Artery Bypass Grafting, GLS=Global Longitudinal Strain, TTP=Time to Peak, MD=Mechanical Dispersion, LAS=Left Atrial Strain, KCCQ=Kansas City Cardiomyopathy Questionnaire - Overall Summary Score, NYHA=New York Heart Association, 6MWT=6-minute Walk Test

Analysis

Baseline GLS was reduced, with a median GLS of -14.2% in the population prior to intervention (normal range <18%). Median TTP was 405.5ms, with mean MD of 69ms. LAS was also abnormal, with a median value of 18.8% (normal range >40%). When comparing transcatheter and surgical cohorts, both groups had a similar baseline GLS (-13.9% for TAVR and -14.8% for SAVR, p=0.666, and final GLS (-14.4% for TAVR and -15.8% for SAVR, p=0.310).

Baseline symptom burden was also high, with a median initial KCCQ-OS of 60.2, NYHA class of 3 and 6MWT distance of 384m. The symptom scores improved significantly between the initial assessment and the late post-intervention assessment. The KCCQ-OS improved from 60.2 to 90.3 (P<0.001), the NYHA class from 3 to 2 (P<0.001) and 6MWT distance from 384 to 412.5m (P=0.017). This is shown in Figure 6.1.

Figure 6.1. Change in Symptom Scores from Baseline to Late Post-Intervention Assessment



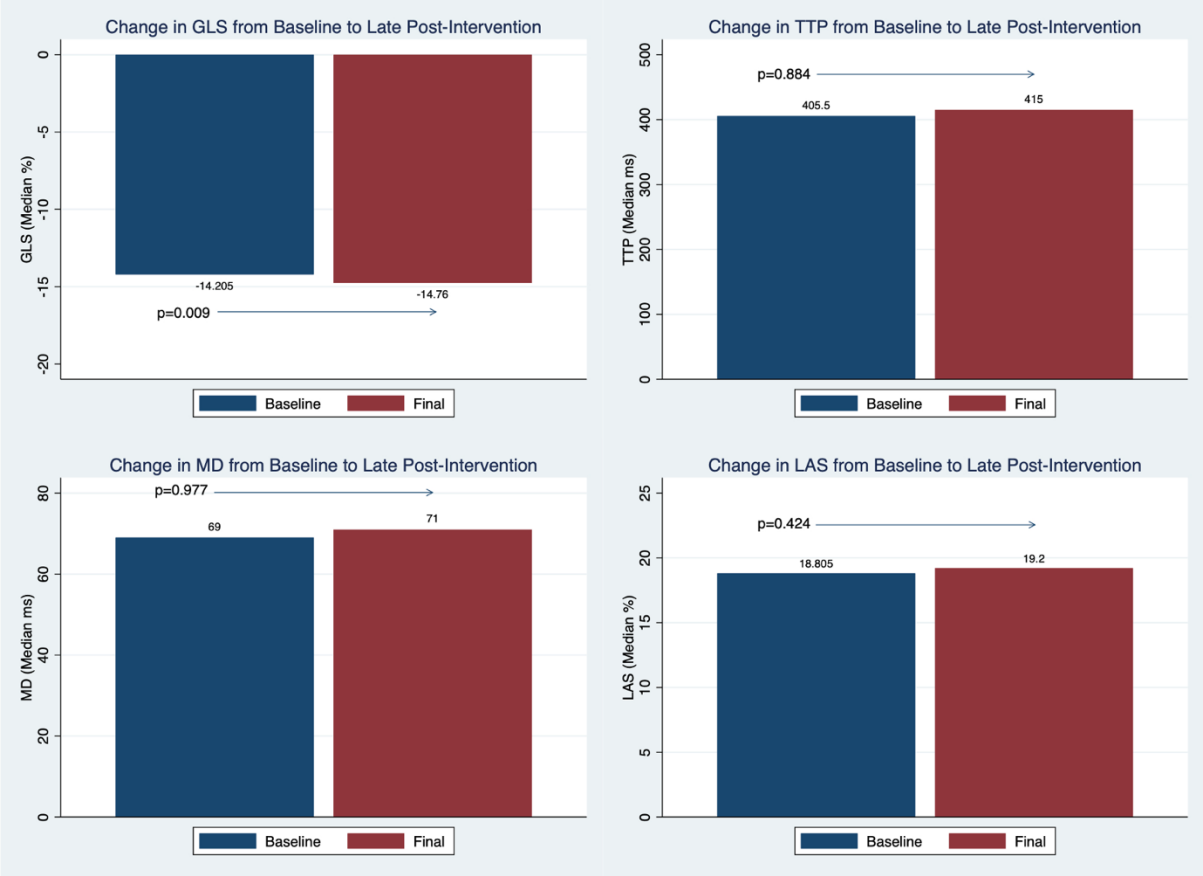
KCCQ-OS=Kansas City Cardiomyopathy Questionnaire – Overall Score, NYHA=New York Heart Association, 6MWT=Six Minute Walk Test

None of the unadjusted initial symptom scores correlated significantly with any of the initial strain indices except for the 6MWT distance with LAS (rho 0.294, p=0.031). When adjusting for age, gender, prior COPD, and echocardiographic LV function (subdivided into normal,

mild, moderate, or severely impaired), no symptom scores correlated significantly with any of the strain indices.

GLS changed significantly between initial and final strain analysis (-14.2% v -14.8%, p=0.009). TTP, MD and LAS did not change significantly within the same period (Figure 6.2). When comparing the change in symptom scores and strain indices between the initial assessment and the final assessment, excluding patients with missing data, the change in GLS correlated significantly with the change in KCCQ (rho -0.292, p=0.011), and the NYHA class change (rho 0.306, p=0.008).

Figure 6.2. Change in Strain Indices from Baseline to Late Post-Intervention Assessment



GLS=Global Longitudinal Strain, TTP=Time to Peak Strain, MD=Mechanical Dispersion, LAS=Left Atrial Strain

Although the change in GLS was statistically significant, the absolute median change was relatively small. We then dichotomised patients into 2 groups; those who had an improvement in GLS by at least 10%, and those who remained unchanged or worsened. Forty-six patients had improved GLS after intervention (responders) and 42 patients did not respond (non-responders). Responders had a median final KCCQ-OS of 95.8, and non-responders had a median final KCCQ-OS of 88 (p=0.012). After adjusting for age, gender, prior COPD and echocardiographic LV function, this remained significant (Coeff 7.98, p=0.048)

Lastly, comparing final symptoms scores with the final strain analysis revealed multiple significant correlations between strain and symptoms. In the unadjusted analysis, the final KCCQ-OS trended towards, but did not quite reach significance with GLS, but NYHA class and 6MWT distance did correlate significantly with GLS. In addition, further significant correlations existed between final NYHA class and TTP, and LAS correlated significantly with all 3 symptom measures. These data are demonstrated in table 6.2.

Table 6.2. Unadjusted and Adjusted Correlations between Final Strain and Final Symptoms

	KCCQ (N=79)	NYHA (N=82)	6MWT (N=35)
Unadjusted			
GLS, rho (p)	-0.219 (0.052)	**0.242 (0.028)**	**-0.601 (<0.001)**
TTP, rho (p)	0.198 (0.080)	**-0.314 (0.004)**	0.046 (0.794)
MD, rho (p)	-0.072 (0.527)	0.026 (0.817)	-0.236 (0.172)
LAS, rho (p)	**0.262 (0.020)**	**-0.246 (0.026)**	**0.470 (0.004)**
Adjusted for Age, Gender, Prior COPD and LV Function			
GLS, Coeff (p)	**-1.175 (0.042)**	0.032 (0.081)	**-16.489 (<0.001)**
TTP, Coeff (p)	**0.107 (0.006)**	**-0.004 (0.002)**	-0.135 (0.715)
MD, Coeff (p)	-0.109 (0.132)	0.001 (0.519)	-0.910 (0.330)
LAS, Coeff (p)	0.296 (0.167)	-0.010 (0.129)	2.993 (0.054)

KCCQ=Kansas City Cardiomyopathy Questionnaire, NYHA=New York Heart Association, 6MWT=Six Minute Walk Test, GLS=Global Longitudinal Strain, TTP=Time to Peak, MD=Mechanical Dispersion, LAS=Left Atrial Strain, COPD=Chronic obstructive pulmonary disease, LV=Left Ventricle

In the regression analysis, when adjusted for age, gender, prior COPD, and final echo LV function these correlations persisted. The KCCQ-OS now correlated significantly with GLS and TTP, the NYHA class correlated with TTP, and trended towards correlation with GLS, and the 6MWT distance correlated with GLS. This is also demonstrated in table 6.2. The post-procedural pacemaker implantation rate was 6 (9%) in the TAVR group and 0 (0%) in the SAVR group. Due to the small population this did not reach statistical significance ($p=0.13$) and did not significantly impact final symptom scores or strain variables.

6.4 Discussion

The clinical dilemma of residual dyspnoea post intervention for aortic stenosis can be frustrating for patients and clinicians alike, especially in the elderly patients for whom symptomatic improvement is often the main driver behind intervention, rather than prolonging life. This analysis intended to help clarify potential causes of residual dyspnoea to help guide ongoing medical therapy.

It has been well established, in this study and many others, that symptoms improve with intervention, but the degree of symptomatic improvement can be variable. GLS and LAS are often abnormal prior to intervention, potentially because of the valvular disease itself. Interestingly, prior to AV intervention, none of the adjusted strain indices correlated with any of the symptom scores, likely since in the severe AS population, the valvular obstruction and resulting myocardial wall stress is the clear defining factor leading to poor symptoms.

With intervention, relief of the valvular obstruction leads to a clear and dramatic improvement in symptoms, but also a small but significant improvement in GLS. The per-patient degree of change in GLS correlated significantly with the degree of change in KCCQ-OS and NYHA class, indicating that greater improvements in GLS can lead to a more robust symptomatic improvement, and when dichotomising patients into responders and non-responders, there was a clearly significant difference in median KCCQ-OS in patients in whom the GLS improved, even adjusting for age, gender, prior COPD and LV function, the latter two being the most likely causes for residual symptoms in this population. Additionally, in the late post-intervention assessment, after adjustment, it was found that GLS correlated significantly with the KCCQ-OS and 6MWT distance, and there was a trend towards a

correlation with the NYHA class. This indicates that patients with abnormal strain post-intervention are significantly more likely to have a higher residual symptom burden than those without, even when adjusting for LV dysfunction.

Limitations to this study include the small sample size, and the heterogenous intervention population, although every attempt was made to demonstrate the heterogeneity in intervention did not lead to any significant variability in the measures of interest. Echocardiographic imaging was done predominantly in one centre, by different, but similarly trained, dedicated sonographers, with few outliers depending on the referring centre. Strain analysis was done retrospectively on existing echocardiographic imaging, therefore images were not acquired with strain analysis in mind, however, the vast majority of patients had suitable imaging for analysis.

Strengths of this study include the prospective design of the analysis, and an attempt to limit inter-operator variability by all symptom measurements and strain analyses being done by a single researcher.

6.5 Conclusions

While we were previously aware that abnormal GLS could result in poor outcomes and increased mortality, the relationship between abnormal strain and symptoms was previously unclear. This analysis serves to demonstrate a novel potential cause for residual symptoms in the post-intervention severe AS population, by demonstrating that less improvement from abnormal baseline strain, and abnormal late GLS may be associated with more symptoms. Further confirmatory research in larger populations is warranted to demonstrate potential targets for intervention in future studies.

CHAPTER 7

IMPACT OF INCREASED AUGMENTATION INDEX AND VALVULOARTERIAL IMPEDANCE ON SYMPTOM RECOVERY AFTER INTERVENTION FOR SEVERE AORTIC STENOSIS

7.1 Introduction

Severe aortic stenosis is a common valvular heart condition in elderly patients and is associated with significant symptoms and poor prognosis if left untreated. Symptoms are largely a manifestation of increased LV afterload, resulting in increased myocardial wall stress, and myocardial oxygen demand[3] as well as increased left sided filling pressures, leading to heart failure. Aortic valve replacement reduces the valvular gradient in patients with severe aortic stenosis and therefore decreases afterload and myocardial wall stress, and results in improved symptoms, quality of life (QOL) and survival[58-60, 127, 128]. However, not all patients achieve the same symptomatic or QOL benefit from AVR. As symptoms and QOL scores gain increased relative importance in advanced age, determining who is likely to achieve the greatest symptomatic benefit from this procedure is of importance.

There is a strong association between the presence of AS and reduced systemic arterial compliance as both are a manifestation of the degenerative atherosclerotic process common in advanced age[3]. One mechanism by which patients may remain symptomatic is that despite a reduction in the valvular gradient after the procedure, excess LV afterload remains due to ongoing arterial stiffness[19, 159]. Therefore, the symptom complex in these patients is likely due to a combination of exposure of the LV to both the valvular load caused by the aortic transvalvular gradient and the arterial load caused by reduced SAC.

The central augmentation index is a measure of arterial stiffness derived by measuring the augmented pressure waveform in the ascending aorta divided by pulse pressure[199]. This reflection wave returns during diastole in healthy individuals, resulting in an insignificant elevation in peak central arterial pressure, but in a stiffer arterial system, the systolic pressure

wave is rapidly reflected within a less compliant vascular system, and augments the late systolic pressure, increasing the peak central arterial pressure[200] and therefore systolic myocardial afterload. This component of LV afterload is theoretically less dependent on the transaortic gradient and may potentially predict an ongoing symptomatic state after the aortic valve gradient is reduced by either surgical or transcatheter AVR. The correlation between baseline AIx and symptoms following AVR has not been described.

An estimate of combined LV haemodynamic load is provided by the valvuloarterial impedance, which takes into account both the valvular and vascular afterload[19]. This parameter has previously been shown to be associated with mortality after TAVR[159], but its relationship with symptom improvement is unclear.

The purpose of this analysis was to determine the relationship between baseline AIx and Zva and symptoms after aortic valve intervention as measured by the KCCQ, NYHA Class and 6MWT.

7.2 Methods

Patient Population

Patients with severe, symptomatic AS expected to undergo treatment with TAVR or SAVR were prospectively enrolled after informed consent on presentation to the Structural Heart Disease Clinic or the CTS Pre-Operative Assessment Clinic at SALHN between September 2016 and April 2018. Further follow up continued until December 2018.

Definition of Severe AS and Echocardiographic Parameters

The patient population was identified as having severe AS if any of the following echocardiographic criteria were achieved: AV MG ≥ 40mmHg; AV Vmax ≥ 4.0m/s; AVA ≤ 1.0 cm^2; or DPI ≤ 0.25, as per the criteria outlined in the joint statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[87].

Baseline Demographics and Patient Assessment

Patients were assessed pre-procedurally, at early review, 4-6 weeks post-procedurally, and at late review, 6-12 months post-procedurally, as determined by the patient's treating cardiologist.

At the initial assessment, demographic details were recorded, as well as height and weight, and relevant clinical history. A medication history and any ECG abnormalities were taken at all 3 visits. Relevant pathology including haematology, biochemistry and Troponin T and

BNP, if available, were documented at the first and final visit. The pre-procedural echocardiogram was also documented, and haemodynamic information was recorded, as well as at the early and late reviews.

Pre-procedural symptoms were recorded using the NYHA Classes of Heart Failure[165] and the KCCQ[62], as validated in this population by Arnold et al[55]. These symptom tools were repeated at early and late review to determine degree and timing of symptomatic recovery. Objective symptoms were also recorded at all 3 visits, when patient mobility allowed, using a 6MWT[166]. Gait speed over 4 metres was also recorded in the first two 25 metre laps. Frailty was assessed using the Fried Frailty Scale[161] pre-procedurally and at the late review.

Lastly, PWA using the Applanation Tonometry method was performed at all 3 reviews using the Sphygmocor AT device using a standardised protocol via the radial artery[174]. Heart rate and systolic and diastolic blood pressure were recorded allowing calculation of MAP and PP. Using the Sphygmocor device, record was made of Central Aortic Pressure, Central Aortic Pulse Pressure and Central Augmentation Pressure in mmHg, as well as Central AIx, which is standardized to a heart rate of 75 bpm (%), Ejection Duration (ms) and SEVR (%).

Procedural information was recorded including type of AV intervention (SAVR or TAVR, including which access approach), the date of the procedure, the STS risk scores[167, 168] at the time of procedure, including the Mortality and the Mortality and Morbidity scores, and the TVT-TAVR[169] in-hospital mortality score. Deaths, ICU admissions, and any perioperative complications including MI, CVA, conduction disease requiring a PPM and bleeding, as defined by VARC[170] were documented.

Outcomes

For this analysis, outcomes were compared between symptomatic recovery and PWA as measured by the KCCQ-OS Score and haemodynamic assessment using AT.

KCCQ-OS is scored from 0 to 100, with higher numbers indicating a lower symptom burden. Recovery was measured as a continuous variable by change in baseline KCCQ-OS score to final score, and also using Relative Change in KCCQ, defined as the change in the KCCQ-OS Score divided by the baseline KCCQ-OS Score, allowing a higher weighting for patients who changed more significantly from a very symptomatic baseline relative to those who had little symptomatic change from an already high baseline KCCQ-OS Score.

The primary haemodynamic assessment used was the AIx, measuring the degree to which the peak of a measured pressure wave is over and above the peak of the incident pressure wave due to the addition of the reflected pressure wave. The AIx is dependent on the timing and magnitude of the reflected waveform and is influenced by the compliance and structure of vessels distal to the site of measurement[174], and so is used as a marker of arterial stiffness.

AIx can vary depending on several factors, including age, gender and height, therefore an AIx reference value was used to standardise our patients and the variance between the calculated AIx and the reference AIx was used. The formula for the augmentation reference index used was $AIx = 79.20 + 0.63\ (age) - 0.002\ (age^2) - 0.28\ (heart\ rate) - 0.39\ (height)$ for men and $AIx = 56.28 + 0.90\ (age) - 0.005\ (age^2) - 0.34\ (heart\ rate) - 0.24\ (height)$ for women, according to the analysis by Janner et al[175].

We also analysed differences in blood pressure, heart rate, ejection duration, SEVR, defined as diastolic to systolic pressure-time integral ratio, a measure of the balance between coronary perfusion and arterial load, and Zva, which is the measured impediment to blood ejection due to the combined resistive forces of both the valvular obstruction and the reduced arterial compliance.

Study data were collected and managed using REDCap electronic data capture tools (Vanderbilt University, version 9.3.1) hosted at the South Australian Health and Medical Research Institute (SAHMRI)[201, 202].

The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/16/SAC/168), and all aspects comply with the Declaration of Helsinki.

Statistical Analysis

Continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequencies and proportions. Correlations between two difference variables were reported as probabilities of the variable being obtained by chance and undertaken using Spearman's rho test. Adjustment for comorbidities was undertaken using a linear regression model. Analysis of differences between the same variable over time were reported as probabilities of the variable being obtained by changes and undertaken using the Wilcoxon signed-rank test.

All reported P-values were 2-sided, and statistical significance was set at $P<0.05$. Statistical analysis, and the production of tables and figures were undertaken using STATA IC 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

7.3 Results

Patient Characteristics

Within the study period, 158 patients were prospectively enrolled for potential inclusion. Of these, 91 patients proceeded to aortic valve intervention within the study period with 65 patients treated with TAVR, 23 patients treated with SAVR (including 7 with concomitant coronary artery bypass grafting) and 3 patients with BAV alone. BAV only patients were excluded from the analysis, and the SAVR and SAVR with grafts groups were combined.

Patients undergoing TAVR were significantly older, with worse renal function, lower aortic valve areas and higher STS scores but were otherwise similar. AT data were then analysed, and the groups were compared. There were no significant differences between groups but a trend towards a lower AIx reference value in the SAVR group, which is age dependent. The variance from the AIx reference value was not different between groups. Baseline symptoms were also assessed to determine if any differences existed between groups. There was a non-significant trend towards a higher baseline symptom burden with TAVR compared with SAVR, and a significantly lower unadjusted 6MWT distance. Baseline patient data are summarised in Table 7.1.

Table 7.1. Baseline Patient Characteristics, Echocardiographic Data, Applanation Tonometry Values and Symptom Scores by Procedure

	Overall (N=88)	**TAVR (N=65)**	**SAVR (N=23)**	**p-value**
Demographics and Comorbidities				
Age, median (IQR)	84 (79, 87)	86 (82, 88)	72 (65, 83)	**<0.001**
Female Gender, N (%)	33 (38%)	26 (40%)	7 (30%)	0.42
BMI, median (IQR)	27.4 (24.6, 30.6)	27.3 (24.3, 29.3)	28.8 (24.8, 34.0)	0.15
NT-proBNP (ng/mL), median (IQR)	1307 (680, 3142)	1568 (748, 5214)	492 (295, 2299)	0.099
eGFR (mL/min/1.73m^2), median (IQR)	64 (50.5, 74.5)	60 (48, 69)	71 (61, 83)	**<0.001**
Prior HF, N (%)	10 (11%)	7 (11%)	3 (13%)	0.77
Prior HTN, N (%)	70 (80%)	54 (83%)	16 (70%)	0.17
Prior IHD, N (%)	46 (52%)	35 (54%)	11 (48%)	0.62
Prior CVA, N (%)	21 (24%)	15 (23%)	6 (26%)	0.77
Prior COPD, N (%)	10 (11%)	8 (12%)	2 (9%)	0.64
Prior PVD, N (%)	16 (18%)	14 (22%)	2 (9%)	0.17
Mitral Valve Disease – Mod+, N (%)	4 (5%)	4 (6%)	0 (0%)	0.22
Prior Diabetes, N (%)	23 (26%)	17 (26%)	6 (26%)	0.99
Prior AF/Flutter, N (%)	30 (34%)	24 (37%)	6 (26%)	0.35
Prior CABG, N (%)	18 (20%)	14 (22%)	4 (17%)	0.67
FFS Score, median (IQR)	1 (1, 3)	2 (1, 3)	1 (1, 3)	0.42
STS Score (%), median (IQR)	2.7 (2.0, 4.0)	3.0 (2.4, 4.4)	1.9 (0.9, 2.6)	**<0.001**
Echocardiographic Data				
EF (%), median (IQR)	59 (49, 63.7)	58 (48, 63.7)	60 (50, 64)	0.75

AV MG (mmHg), median (IQR)	45.25 (39.1, 52.2)	43.4 (38.8, 51)	47.2 (40.7, 57.2)	0.19
AV Area (cm^2), median (IQR)	0.8 (0.63, 0.94)	0.75 (0.61, 0.91)	0.9 (0.72, 1)	**0.029**
AV Vmax (m/s), median (IQR)	4.40 (4.10, 4.70)	4.38 (4.00, 4.65)	4.50 (4.10, 4.90)	0.32
DPI, median (IQR)	0.23 (0.18, 0.27)	0.23 (0.17, 0.27)	0.225 (0.2, 0.28)	0.62
E/e', median (IQR)	15.2 (12.0, 20.9)	16 (12.0, 20.9)	14 (13.0, 18.5)	0.66
Left Atrial Area (cm^2), median (IQR)	25.3 (22.0, 28.1)	25.4 (22.0, 28.0)	25.2 (21.0, 28.3)	0.87
Applanation Tonometry Data				
Systolic BP (mmHg), median (IQR)	152 (136, 166)	153 (135, 167)	150 (143, 160)	0.60
Diastolic BP (mmHg), median (IQR)	81 (70, 87)	79 (70, 87)	84 (75, 86)	0.48
MAP (mmHg), median (IQR)	104 (95, 112)	103 (94, 111)	104 (100, 112)	0.73
Pulse Pressure (mmHg), median (IQR)	70 (60, 83)	76 (61, 85)	66 (56, 75)	0.21
Heart Rate (bpm), median (IQR)	68 (60, 80)	68 (60, 80)	66 (59, 78)	0.71
Central Arterial Pressure (mmHg), median (IQR)	142 (127, 157)	142 (127, 158)	139 (133, 152)	0.84
Central Pulse Pressure (mmHg), median (IQR)	59 (48, 72)	60 (50, 73)	55 (46, 61)	0.13
Augmentation Pressure (mmHg), median (IQR)	22 (15, 29)	22 (16, 30)	21 (12, 25)	0.3
AIx (%), median (IQR)	36 (26, 42)	36 (28, 42)	34 (23, 43)	0.85
Ejection Duration (ms), median (IQR)	37 (33, 41)	38 (34, 42)	36 (33, 41)	0.61
SEVR (%), median (IQR)	132 (113, 154)	130 (111, 152)	144 (120, 158)	0.19
Zva, median (IQR)	4.3 (3.8, 5.4)	4.4 (3.9, 5.6)	3.9 (3.6, 4.3)	0.1
AIx Reference Value (%), median (IQR)	31.9 (27.6, 36.1)	32.8 (29.2, 36.7)	30.1 (23.8, 35.9)	0.053

AIx Variance, median (IQR)	2.98 (-6.28, 10.12)	3.22 (-6.80, 9.45)	0.18 (-2.86, 10.27)	0.51
Symptom Scores				
KCCQ-OS, median (IQR)	60.2 (40.8, 76.7)	55.9 (39.1, 70.4)	69.9 (49.2, 85.4)	0.085
NYHA Class, median (IQR)	3 (2, 3)	3 (2, 3)	2 (2, 3)	0.19
6MWT Distance (m), median (IQR)	384 (284, 432)	336 (270, 404)	420 (394, 480)	**0.002**

TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement, IQR=Interquartile Range, BMI=Body Mass Index, NT-proBNP=N-Terminal proB-type Natriuretic Peptide, eGFR=Estimated Glomerular Filtration Rate, HF=Heart Failure, HTN=Hypertension, IHD=Ischaemic Heart Disease, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, PVD=Peripheral Vascular Disease, AF=Atrial Fibrillation, CABG=Coronary Artery Bypass Grafting, FFS=Fried Frailty Scale, EF=Ejection Fraction, AV=Aortic Valve, MG=Mean Gradient, Vmax=Peak Velocity, DPI=Dimensionless Performance Index, BP=Blood Pressure, MAP=Mean Arterial Pressure, AIx=Augmentation Index, SEVR=Subendocardial Viability Ratio, Zva=Valvuloarterial Impedance, KCCQ-OS=Kansas City Cardiomyopathy Questionnaire – Overall Summary, NYHA=New York Heart Association, 6MWT=Six Minute Walk Test

Applanation Tonometry and Symptoms

Since the procedural groups were similar, they were then combined for the primary analysis. Due to concerns regarding heterogeneity between TAVR and SAVR groups, a subgroup excluding surgically managed patients was also analysed. We first determined whether aortic stenosis significantly altered the augmentation pressures by comparing the augmentation index of our group prior to intervention with the augmentation reference value. There was no

significant difference between groups (35.5% v 32.0%, p=0.134 for the entire cohort and 34.3% v 32.6%, p=0.303 for the TAVR only subgroup), indicating that aortic stenosis does not significantly alter AIx.

Next, we determined whether the AT variables analysed correlated significantly with patient symptoms at baseline, as measured by the KCCQ, the NYHA class or the 6MWT using Spearman's rho test. The baseline KCCQ-OS only correlated significantly with diastolic blood pressure, but the NYHA class correlated significantly with heart rate, AIx, and the ejection duration. The 6MWT distance did not correlate significantly with any of the AT variables at baseline.

A regression analysis was performed to adjust for age, gender and prior COPD, the comorbidity most likely to contribute to non-cardiac dyspnoea. The results were similar, with significant correlations between NYHA class and heart rate, ejection duration and AIx, and the addition of SEVR. The KCCQ-OS no longer correlated with any variables, but the 6MWT now significantly correlated with the pulse pressure. These correlations are summarised in Table 7.2.

Table 7.2. Unadjusted and Adjusted Correlation between Baseline Haemodynamic Parameters and Baseline Symptom Scores

Factor	KCCQ-OS	NYHA Class	6MWT Distance
Unadjusted			
Systolic BP, median (Rho, (p))	-0.065, (0.56)	0.112, (0.32)	0.074, (0.60)
Diastolic BP, median (Rho, (p))	0.249, **(0.02)**	-0.018, (0.87)	-0.017, (0.90)
MAP, median (Rho, (p))	0.099, (0.38)	0.087, (0.44)	0.017, (0.90)
PP, median (Rho, (p))	-0.145, (0.09)	0.091, (0.42)	0.084, (0.55)
Heart Rate, median (Rho, (p))	-0.120, (0.28)	0.234, **(0.03)**	-0.077, (0.58)
Central Arterial Pressure, median (Rho, (p))	-0.043, (0.70)	0.098, (0.38)	0.055, (0.69)
Central Pulse Pressure, median (Rho, (p))	-0.188, (0.09)	0.121, (0.28)	-0.012, (0.93)
Augmentation Pressure, median (Rho, (p))	-0.137, (0.22)	0.108, (0.33)	-0.022, (0.87)
AIx, median (Rho, (p))	-0.167, (0.13)	0.243, **(0.03)**	-0.082, (0.55)
Ejection Duration, median (Rho, (p))	-0.061, (0.58)	0.221, **(0.046)**	-0.048, (0.73)
SEVR, median (Rho, (p))	0.122, (0.27)	-0.201, (0.07)	0.066, (0.64)
Zva, median (Rho, (p))	-0.011, (0.92)	0.148, (0.18)	0.118, (0.40)
Adjusted for Age, Gender and COPD			
Systolic BP, median (Coeff, (p))	0.086, (0.41)	-0.001, (0.75)	0.939, (0.09)
Diastolic BP, median (Coeff, (p))	0.298, (0.10)	0.002, (0.73)	-0.211, (0.83)
MAP, median (Coeff, (p))	0.235, (0.16)	<0.001, (0.97)	0.630, (0.47)
Pulse Pressure, median (Coeff, (p))	-0.015, (0.91)	-0.002, (0.54)	1.561, **(0.02)**
Heart Rate, median (Coeff, (p))	-0.223, (0.25)	0.014, **(0.02)**	-0.360, (0.72)
Central Arterial Pressure, median (Coeff, (p))	0.097, (0.36)	-0.002, (0.61)	0.811, (0.15)

Central Pulse Pressure, median (Coeff, (p))	-0.071, (0.61)	-0.001, (0.83)	1.427, (0.06)
Augmentation Pressure, median (Coeff, (p))	-0.176, (0.40)	0.002, (0.73)	1.86, (0.11)
AIx, median (Coeff, (p))	-0.261, (0.18)	0.014, **(0.02)**	1.382, (0.23)
Ejection Duration, median (Coeff, (p))	-0.290, (0.51)	0.030, **(0.02)**	1.451, (0.53)
SEVR, median (Coeff, (p))	0.090, (0.23)	-0.005, **(0.03)**	-0.404, (0.34)
Zva, median (Coeff, (p))	-1.098, (0.49)	0.051, (0.29)	11.183, (0.23)

KCCQ-OS=Kansas City Cardiomyopathy Questionnaire – Overall Summary, NYHA=New York Heart Association, 6MWT=Six Minute Walk Test, BP=Blood Pressure, MAP=Mean Arterial Pressure, PP=Pulse Pressure, AIx=Augmentation Index, SEVR=Subendocardial Viability Ratio, Zva=Valvuloarterial Impedance

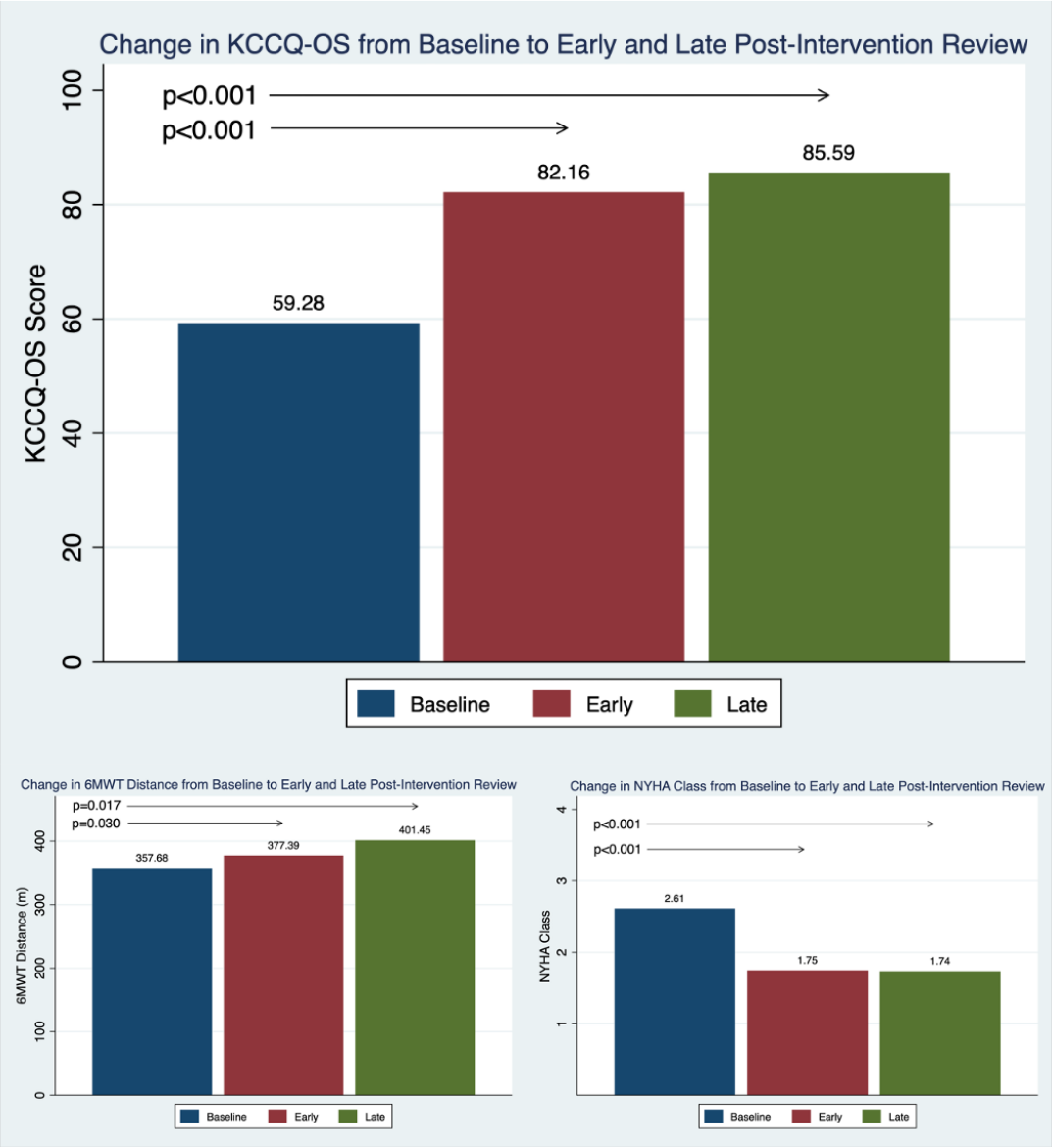
In the TAVR only subgroup, with the adjusted analysis the results were similar, with baseline NYHA class correlating with heart rate (Coeff. 0.014, p=0.041), AIx (Coeff. 0.018, p=0.012), ejection duration (Coeff. 0.036, p=0.024) and SEVR (Coeff. -0.006, p=0.032), and the 6MWT now correlated with Zva (Coeff. 21.48, p=0.047). No other correlations reached significance.

Symptoms After AV Intervention

Symptoms were then compared over time, between baseline, the early post-intervention period and the late post-intervention period. Symptoms significantly improved for all groups. This is demonstrated in Figure 7.1. We were concerned that further intervention group heterogeneity could be present due to differences in symptomatic recovery time between

TAVR and SAVR, so we compared median KCCQ-OS scores at early review and found no significant difference between TAVR and SAVR (87.5 v 83.6, p=0.809).

Figure 7.1. Change in Symptom Status from Baseline to Early and Late Post-intervention with TAVR or SAVR



AVR=Aortic Valve Replacement, KCCQ(-OS)=Kansas City Cardiomyopathy Questionnaire – Overall Summary, NYHA=New York Heart Association, 6MWT=Six-Minute walk test

Additionally, using a Wilcoxon signed-rank test, no significant differences were noted between baseline and late review for E/e' ($z=0.57$, $p=0.57$) or BNP ($z=0.14$, $p=0.89$), but LAA was larger ($z=2.28$, $p=0.02$).

Applanation Tonometry After Aortic Valve Intervention

AT values were then compared between baseline, early post-intervention and late post-intervention. The AIx reduced significantly, as did the ejection duration and the Zva, as expected due to the valvular improvement. The SEVR increased significantly. This is demonstrated in Table 7.3. AIx and ejection duration correlated strongly with each other (rho 0.378, $p=0.002$).

Table 7.3. Change in Applanation Tonometry Values at Baseline and Early and Late Post Intervention

Factor	**Baseline**	**Early Review**	**Late Review**	**p-value**
Systolic BP (mmHg), median (IQR)	152 (136, 166)	150 (134, 165)	150 (133, 164)	0.64
Diastolic BP (mmHg), median (IQR)	80 (70, 87)	74 (64, 82)	81 (73, 86)	0.41
MAP (mmHg), median (IQR)	104 (95, 112)	100 (88, 110)	102 (94, 111)	0.50
Pulse Pressure (mmHg), median (IQR)	70 (60, 83)	76 (62, 88)	72 (55, 86)	0.94
Heart Rate (bpm), median (IQR)	68 (60, 80)	66 (62, 82)	69 (61, 79)	0.54
Central Arterial Pressure (mmHg), median (IQR)	141 (127, 157)	134 (121, 156)	136 (119, 152)	0.27
Central Pulse Pressure (mmHg), median (IQR)	59 (48, 71	60 (48, 73)	59 (41, 71)	0.46
Augmentation Pressure (mmHg), median (IQR)	22 (14, 30)	16 (11, 27)	20 (10, 26)	0.08
AIx (%), median (IQR)	35.5 (26.5, 42.5)	27.5 (19, 34)	31 (23, 37)	**0.048**
Ejection Duration (ms), median (IQR)	37 (33, 42)	34 (31, 37)	35 (32, 39)	**0.01**
SEVR (%), median (IQR)	133 (113, 156)	144 (123, 167)	144 (125, 159)	**0.01**
Zva, median (IQR)	4.3 (3.8, 5.6)	3.6 (2.8, 4.7)	3.7 (3.2, 4.5)	**<0.001**
AIx Variance	3.0 (-6.3, 10.1)	-5.6 (-12.3, 0.4)	-0.9 (-9.3, 7.7)	0.08

BP=Blood Pressure, MAP=Mean Arterial Pressure, AIx=Augmentation Index, SEVR=Subendocardial Viability Ratio, Zva=Valvuloarterial Impedance

In the TAVR only subgroup, the AIx reduction trended towards, but did not reach, significance (z=1.513, p=0.13). The ejection duration (z=2.984, p=0.003), and the Zva (z=2.592, p=0.010) reduced significantly, and the SEVR increased significantly (z=-2.662, p=0.008), as with the entire cohort.

Predicting Symptoms Based on Initial AT

We then did an analysis to investigate whether final symptoms using the KCCQ-OS score, NYHA Class, 6MWT Distance and the Relative KCCQ, could be predicted based on initial AT values. The only significant correlation was between initial diastolic BP and the Relative KCCQ (rho=-0.28, p=0.04). This correlation strengthened slightly when adjusting for age, gender and prior COPD (Coeff.=-0.02, p=0.02). Additionally, with adjustment the final KCCQ-OS correlated with initial HR (Coeff.=-0.34, p=0.03), AIx (Coeff.=-0.38, p=0.02) and Zva (Coeff.=-3.22, p=0.01). NYHA Class also correlated with the initial AIx (Coeff.=0.01, p=0.02). Baseline AIx, however, did not correlate with the relative change of KCCQ-OS at late assessment.

In the TAVR only subgroup, when adjusted, the initial diastolic BP again correlated with the relative KCCQ (Coeff.=-0.017, p=0.015), and the initial Zva correlated with the final KCCQ-OS (Coeff.=-3.767, p=0.005). The correlations between baseline AIx, and final KCCQ-OS and NYHA Class were lost (p=0.162 and p=0.111, respectively).

We then wished to determine whether the final AT and the final symptoms correlated with each other and found that when adjusted for age, gender and prior COPD, only Zva significantly correlated with the final 6MWT distance, but the AIx trended towards

significance for the final Relative KCCQ, designed to be weighted towards those with the largest change from the lowest baseline. These data are demonstrated in Table 7.4.

Table 7.4. Adjusted Correlation Between Baseline and Final Applanation Tonometry and Final Symptoms

	Final KCCQ	Final NYHA	Final 6MWT	Final Relative KCCQ
Baseline AT				
Systolic BP, median (Coeff., (p))	-0.032, (0.72)	-0.001, (0.80)	0.646, (0.45)	-0.003, (0.46)
Diastolic BP, median (Coeff., (p))	-0.045, (0.77)	-0.002, (0.68)	0.749, (0.52)	-0.015, **(0.01)**
MAP, median (Coeff., (p))	-0.052, (0.72)	-0.002, (0.70)	0.875, (0.44)	-0.010, (0.05)
Pulse Pressure, median (Coeff., (p))	-0.024, (0.83)	<-0.001, (0.98)	0.385, (0.72)	0.003, (0.40)
Heart Rate, median (Coeff., (p))	-0.342, **(0.03)**	0.006, (0.26)	0.745, (0.54)	<0.001, (0.99)
Central Arterial Pressure, median (Coeff., (p))	-0.024, (0.79)	-0.001, (0.80)	0.161, (0.85)	-0.004, (0.30)
Central Pulse Pressure, median (Coeff., (p))	-0.028, (0.82)	<0.001, (0.96)	0.128, (0.91)	0.004, (0.34)
Augmentation Pressure, median (Coeff., (p))	-0.160, (0.37)	0.007, (0.23)	-0.398, (0.80)	0.001, (0.92)
AIx, median (Coeff., (p))	-0.383, **(0.02)**	0.012, **(0.03)**	-0.205, (0.88)	-0.004, (0.48)
Ejection Duration, median (Coeff., (p))	-0.481, (0.18)	0.001, (0.92)	2.001, (0.44)	-0.001, (0.92)
SEVR, median (Coeff., (p))	0.086, (0.17)	-0.001, (0.66)	-0.131, (0.77)	-0.002, (0.52)
Zva, median (Coeff., (p))	-3.219, **(0.01)**	0.016, (0.71)	8.808, (0.44)	-0.038, (0.45)
Final AT				
Systolic BP, median (Coeff, (p))	0.088, (0.40)	<0.001, (0.93)	0.404, (0.58)	-0.001, (0.77)
Diastolic BP, median (Coeff, (p))	-0.216, (0.28)	0.011, (0.10)	0.403, (0.79)	-0.011, (0.15)
MAP, median (Coeff, (p))	-0.027, (0.88)	0.006, (0.31)	0.649, (0.63)	-0.007, (0.31)
Pulse Pressure, median (Coeff, (p))	0.185, (0.11)	-0.003, (0.39)	0.371, (0.65)	0.002, (0.62)
Heart Rate, median (Coeff, (p))	-0.135, (0.37)	0.002, (0.70)	0.467, (0.73)	0.002, (0.66)

Central Arterial Pressure, median (Coeff, (p))	0.089, (0.41)	<0.001, (0.90)	0.341, (0.66)	-0.004, (0.38)
Central Pulse Pressure, median (Coeff, (p))	0.208, (0.10)	-0.004, (0.38)	0.288, (0.74)	>-0.001, (0.88)
Augmentation Pressure, median (Coeff, (p))	0.443, (0.06)	-0.006, (0.44)	1.549, (0.33)	-0.012, (0.16)
AIx, median (Coeff, (p))	0.143, (0.53)	0.003, (0.71)	1.295, (0.40)	-0.016, (0.06)
Ejection Duration, median (Coeff, (p))	-0.144, (0.72)	<0.001, (0.94)	0.460, (0.89)	-0.012, (0.43)
SEVR, median (Coeff, (p))	-0.023, (0.69)	<0.001, (0.86)	0.094, (0.81)	<0.001, (0.75)
Zva, median (Coeff, (p))	-3.556, (0.15)	0.073, (0.36)	-38.509, **(0.04)**	0.035, (0.70)

KCCQ=Kansas City Cardiomyopathy Questionnaire – Overall Summary, NYHA=New York Heart Association, 6MWT=Six Minute Walk Test, BP=Blood Pressure, MAP=Mean Arterial Pressure, AIx=Augmentation Index, SEVR=Subendocardial Viability Ratio, Zva=Valvuloarterial Impedance

Lastly, we wished to determine whether a specific initial AIx value could be found which resulted in a significant reduction in symptomatic recovery. We tested the median and the highest quartile of initial AIx against the final KCCQ-OS.

Using the median AIx of 35.5%, there was no significant difference in the KCCQ-OS at late review between patients with a value above and below this mark (94.95 v 87.5, p=0.290). However, using the highest quartile of AIx in our population of 42%, we found a significant difference in the final KCCQ-OS (95.1 v 85.2, p=0.046).

If including only TAVR treated patients, the final KCCQ-OS scores were similar (95.1 v 87.2), but this did not reach significance with the reduced power (p=0.118).

7.4 Discussion

Predicting symptomatic outcomes can be difficult, especially in the elderly population who may have competing causes for dyspnoea. This ability would be especially useful in the elderly severe aortic stenosis population for whom symptomatic benefit is often the main driver behind intervention, rather than prolonging life. This analysis intended to examine whether a simple, inexpensive, non-invasive bedside investigation could assist in making this determination.

As has been previously reported, symptoms improved with intervention for aortic stenosis, by both surgical and transcatheter approaches. The timing of symptomatic recovery was also relatively similar, with no difference in symptom scores noted between groups at early assessment. Zva also significantly improved, since it is a composite variable representing both valvular and arterial resistance. Although the valvular obstruction has been relieved, the reduced SAC component remains, which can also be represented by AIx, a measure of arterial stiffness leading to increased arterial pressure during systolic contraction, and therefore myocardial workload and symptoms. Additionally, the NYHA class, but not the KCCQ-OS score or the 6MWT distance was shown to correlate at baseline with the AIx, but not Zva. The AIx was also one of the few AT variables shown to significantly decrease with intervention. Other variables that significantly changed included the ejection duration, the SEVR and the Zva, which all can be explained mechanistically by relief of the valvular obstruction and improved transvalvular flow. One hypothesis is that it is the reduced ejection duration post intervention which leads to a modification and hence reduction in the peak reflected pressure wave which causes the increased augmentation pressure as demonstrated by the strong statistical correlation between the AIx and ejection duration. This, in addition to

the increased coronary perfusion time as demonstrated by the SEVR, could both, in theory, improve symptoms.

The baseline AIx, prior to intervention, also significantly correlated with the final adjusted KCCQ and NYHA scores, indicating that a higher AIx could potentially predict the final symptomatic outcome, although the relative change in KCCQ did not correlate.

Interestingly, it was found that a baseline AIx value of 42% and higher correlated with a significantly worse symptomatic benefit as measured by the final KCCQ-OS, indicating it is patients in the top quartile of AIx who are most at risk of a poor outcome.

In a subgroup analysis including only TAVR treated patients, performed due to concerns regarding differences in baseline demographics, there were no differences between the AIx and the age, gender and body size predicted reference values, as with the entire cohort. The correlations between baseline symptoms and AT values were also similar to the entire cohort. The changes in AT values after intervention were again similar, except the AIx reduction now trended towards, but did not reach, significance, likely due to reduced power. The significant correlations seen in the entire group between baseline AIx, and Final KCCQ-OS and NYHA Class were also lost in the TAVR only subgroup, although a trend existed, again likely due to a reduction in power, as well as the significant difference in symptoms at the highest AIx quartile.

Potential limitations to this analysis include the relatively small sample size and the heterogenous intervention population. This was exacerbated for the TAVR only subgroup, making definitive correlations difficult, however, we were able to show that the intervention

groups were similar and that the major differences in the intervention groups were accounted for by the adjustments made in the AIx calculation, namely age. The AIx can also vary between different body types and genders, which we attempted to overcome by comparing with validated reference values. Also due to the small population it was difficult to adjust for many comorbidities, and so it was decided to focus on COPD, which is most likely to contribute to persistent symptoms post intervention.

7.5 Conclusions

Applanation tonometry may be useful in predicting a poor symptomatic response to aortic valve intervention, particularly for the top quartile of AIx. This warrants further investigation in a larger dataset as it could potentially be a very simple but useful tool to assist in assessing expected symptomatic benefit post severe aortic stenosis intervention in the elderly.

CHAPTER 8

IMPACT OF SURGICAL AND TRANSCATHETER AORTIC VALVE REPLACEMENT ON FRAILTY

8.1 Introduction

Aortic stenosis is increasing in incidence, particularly as the population ages[195, 203]. Additionally, treatment of aortic stenosis has become more frequent, even at advanced ages, with the development of transcatheter aortic valve replacement technology over the last 2 decades[2, 15, 58, 127, 195] expanding the available intervention options. Frailty is also common in the symptomatic AS population[103]. Afilalo et al reported that among the elderly cohort of 907 patients with AS undergoing TAVR or SAVR, the incidence of frailty ranged from 26% to 68%, depending on the scale used to measure frailty.

Frailty has been shown to have an impact on outcomes after both surgical and transcatheter AVR, including disability and mortality[103-106]. Frailty assessment is now a standard consideration in most AS MDT meetings[2, 15]. This can impact the perceived suitability of a patient to undergo intervention, with the frailest patients often excluded from intervention.

While the impact of frailty on outcomes has been clearly defined, the impact of intervention on frailty is less clear. Prior work has focused on the pre-intervention frailty state and have not assessed frailty post-intervention. Many frailty tools use subjective indicators, such as exhaustion and low activity[51, 103, 161], or objective indicators such as the ability to walk or stand quickly[103, 162-164], which may be impacted on by the disorder itself, and may therefore improve with treatment. As frailty can be a determinant in excluding a patient from intervention, it is important to consider what impact intervention has on these measures.

This prospective, observational, patient focused study aims to clarify the prevalence of frailty in the modern AS intervention population, as well as by the intervention used. It is also

designed to determine the impact of intervention, as well as the type of intervention, on a commonly used frailty tool. Lastly, it correlates the changes in the frailty markers with changes in both subjective and objective symptom scores.

8.2 Methods

Patient Population and Procedural Data

A prospective, observational cohort study was designed to include patients in SALHN in South Australia who were being assessed for aortic valve intervention due to suspected or confirmed severe, symptomatic aortic stenosis, either by TAVR or sAVR. Patients were recruited from the Structural Cardiology outpatient clinic or the CTS Preoperative Assessment clinic between December 2016 and April 2018. Demographic data, clinical and medication histories, biochemistry and ECG results, and pre-procedural echocardiographic data were recorded from the patient's medical records, or from the patient themselves. Patients were only excluded if they did not undergo intervention within 6 months of the study end date but were otherwise unselected to avoid bias.

At the time of the procedure, the procedure type was documented, along with the STS score, the TVT-TAVR Risk Score, and the occurrence of any procedural complications.

The Human Research Ethics Committee of the South Australian Department of Health approved this study (approval number: HREC/16/SAC/168), and all aspects comply with the Declaration of Helsinki.

Symptoms

At or near the time of recruitment, following consent, patients were assessed for symptoms subjectively, using both the NYHA classification and the KCCQ, and objectively, using a

6MWT and gait speed. The KCCQ was originally developed to measure symptoms in heart failure patients but has been validated in the AS population[55] and has been used as the symptom score of choice in the PARTNER trials. The KCCQ-OS gives an absolute score out of 100, with a higher score indicating a lower degree of symptoms. The KCCQ-OS scores are often subdivided into 4 classes, roughly analogous to the NYHA classes, with class 1 being the least symptomatic and having a score >75, class 2 between 60 and 75, class 3 between 45 and 60 and class 4 being the most symptomatic and having a score of less than 45.

The Fried Frailty Scale

Frailty was assessed using the Fried Frailty Scale (FFS), which is a validated frailty phenotypic assessment that allows standardization and scoring of multiple key domains of abnormalities commonly associated with frailty[161]. It has been extensively validated in many populations, including severe aortic stenosis[103] and parallel the criteria used in the PARTNER trials[104]. Using the FFS, physical frailty is defined using measures of five phenotypic criteria: unintentional weight loss, exhaustion, low energy expenditure, low grip strength, and/or slowed waking speed. A single score out of 5 is then given which categorises the patient into frailty classes; frail (score 3-5), pre-frail (score 1 or 2) or robust (score 0). The frailty class analysis was expressed using frequencies of the population within each class.

The FFS assessment was administered by a single researcher for every patient pre-procedurally and at late review, 6-12 months post-intervention. The results were entered into the official FFS scoring calculator and the total results were documented, as well as the results for each individual frailty domain. Weight loss was determined by direct weight measurement at clinic review, and by interviewing the patient regarding historical weight

over the previous year and was defined as a loss of ≥4.5kg in the past year. Exhaustion and low energy expenditure were determined as per the FFS protocol via questionnaire. Grip strength was determined using a hand grip dynamometer using the dominant hand, and walking speed was determined by measuring the walking time over a 4m segment during the first two 25m laps of the 6MWT, with an adequate lead time to achieve full walking speed. This protocol is available in Supplement 1.2.

Follow Up and Outcomes

Patients were then reviewed at the early post-intervention review, between 4-6 weeks post procedure, according to Structural Cardiology Clinic protocol. At this visit, medications, ECG and echocardiographic changes were noted and symptoms were reassessed using the NYHA and KCCQ classifications and the 6MWT and 4m walk speed. These were again repeated at late review, in addition to a repeat frailty assessment.

The primary outcome for this analysis was change in frailty score and frailty class between pre-procedural and late post-intervention assessment. Secondary outcomes were to determine which domains of frailty were more likely to be influenced by intervention and to stratify these results into transcatheter and surgical cohorts. We also correlated these results with the subjective and objective symptom measurements of the KCCQ and 6MWT since some frailty domains can be influenced by the traditional symptoms of aortic stenosis.

Analysis

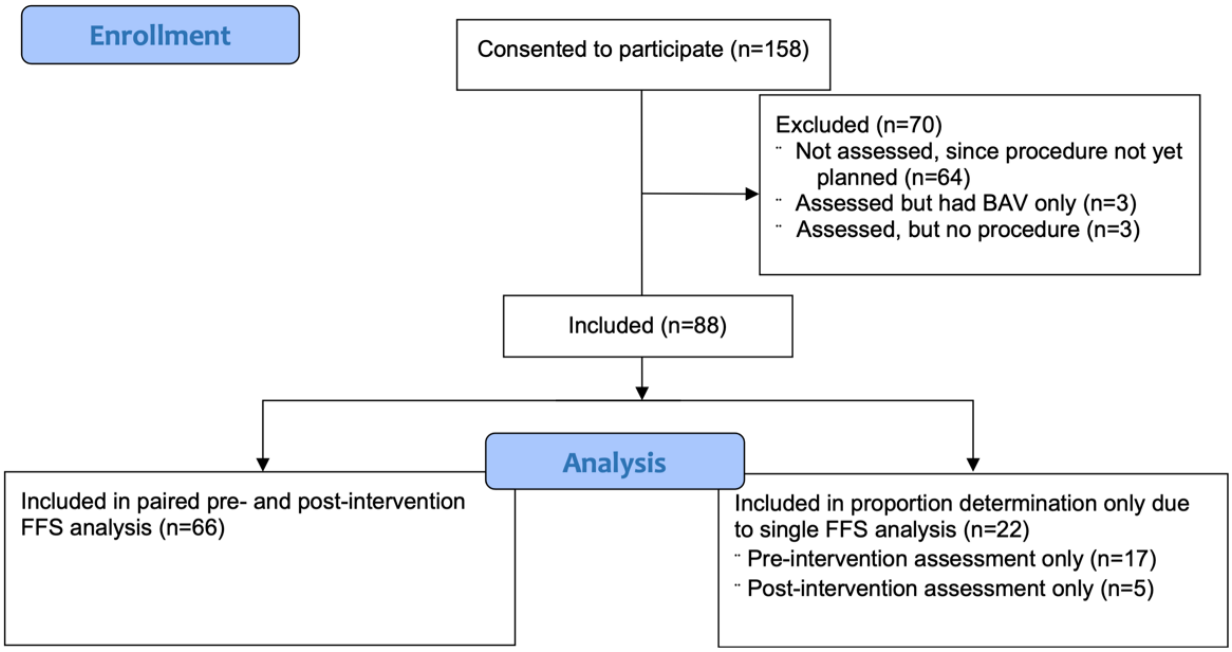
Data were collected and aggregated by a single researcher by way of patient interview and assessment, SALHN medical records, private clinician letters, and investigations with consent from all parties involved. Results were stored in the online REDCap database from Vanderbilt University, version 9.3.1 licensed by the South Australia Health and Medical Research Institute (SAHMRI).

Correlations between variables were determined using the Wilcoxon signed-rank test, the Kruskal-Wallis equality-of-populations rank test or the Pearson chi^2 test, and statistical analysis was undertaken in Stata MP 15 software (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). Patients with a single frailty assessment were included in the analyses to determine the proportions of frailty in the population at a given timeframe but were excluded from the analysis to determine change in the frailty score and domains. This typically occurred due to living remotely and being unable to attend in-person review. KCCQ scores were still obtained via telephone at 6-12 months. Given the observational nature of this study, no adjustments were made for multiple testing and a p-value of 0.05 was considered statistically significant.

8.3 Results

In total, 158 patients were screened, but 64 patients did not receive their intervention within 6 months prior to the study end date, therefore 94 patients were ultimately assessed (Figure 8.1). Of these, three underwent BAV only and three did not undergo any procedure and were hence excluded. Five patients did not have a frailty assessment prior to intervention but did undergo late assessment. The median time from frailty assessment to procedure was 4 days, and 24% of cases were assessed the morning of the procedure. Seventeen patients were initially assessed but did not have late FFS assessment. Therefore 88 patients contributed data to the population and 66 patients completed both pre-intervention and late post intervention reviews to allow inclusion in the full frailty analysis. Seven of 23 SAVR-treated patients underwent concomitant coronary grafting, but since the only significant difference in baseline demographics between those who did and did not receive grafting was the EF, and the median values were both >=50%, they were grouped for the remainder of the analysis. Additionally, no differences in change in frailty score or change in KCCQ-OS were noted between the SAVR-treated groups with or without grafting. Baseline characteristics of the entire cohort are described in Table 8.1.

Figure 8.1. CONSORT Diagram



BAV=Balloon Aortic Valvuloplasty, FFS=Fried Frailty Scale

Table 8.1. Baseline Patient Characteristics for Demographics and Comorbidities and Echocardiographic Criteria

Characteristic	**Overall (N=88)**	**TAVR (N=65)**	**SAVR (N=23)**	**p-value**
Demographics and Comorbidities				
Age, median (IQR)	84 (79, 87.5)	86 (82, 88)	72 (65, 83)	**<0.001**
Female Gender, N (%)	33 (38%)	26 (40%)	7 (30%)	0.42
BMI, median (IQR)	27.4 (24.6, 30.6)	27.3 (24.3, 29.3)	28.8 (24.8, 34.0)	0.15
NT-proBNP, median (IQR)	1307 (680, 3142)	1568 (748, 5214)	492 (295, 2299)	0.099
eGFR (mL/min/1.73m^2), median (IQR)	64 (50.5, 74.5)	60 (48, 69)	71 (61, 83)	**<0.001**
FFS Score, median (IQR)	1 (1, 3)	2 (1, 3)	1 (1, 3)	0.42
STS Score, median (IQR)	2.68 (2.03, 4.01)	2.98 (2.35, 4.40)	1.92 (0.85, 2.58)	**<0.001**
Prior HF, N (%)	10 (11%)	7 (11%)	3 (13%)	0.77
Prior HTN, N (%)	70 (80%)	54 (83%)	16 (70%)	0.17
Prior IHD, N (%)	46 (52%)	35 (54%)	11 (48%)	0.62
Prior CVA, N (%)	21 (24%)	15 (23%)	6 (26%)	0.77
Prior COPD, N (%)	10 (11%)	8 (12%)	2 (9%)	0.64
Prior PVD, N (%)	16 (18%)	14 (22%)	2 (9%)	0.17
Mitral Valve Disease – Mod+, N (%)	4 (5%)	4 (6%)	0 (0%)	0.22
Prior Diabetes, N (%)	23 (26%)	17 (26%)	6 (26%)	0.99
Prior AF/flutter, N (%)	30 (34%)	24 (37%)	6 (26%)	0.35
Prior CABG, N (%)	18 (20%)	14 (22%)	4 (17%)	0.67
Procedural Outcomes				
Perioperative CVA/TIA, N (%)	3 (3%)	3 (5%)	0 (0%)	0.29

Death at 6 months, N (%)	1 (1%)	1 (2%)	0 (0%)	0.55
Echocardiographic Criteria				
EF (%), median (IQR)	59 (49, 63.7)	58 (48, 63.7)	60 (50, 64)	0.75
AV MG (mmHg), median (IQR)	45.25 (39.1, 52.2)	43.4 (38.8, 51)	47.2 (40.7, 57.2)	0.19
AV Area (cm^2), median (IQR)	0.8 (0.62, 0.94)	0.75 (0.61, 0.91)	0.9 (0.72, 1)	**0.029**
AV Vmax (m/s), median (IQR)	4.4 (4.1, 4.7)	4.38 (4, 4.65)	4.5 (4.1, 4.9)	0.32
DPI, median (IQR)	0.23 (0.18, 0.27)	0.23 (0.17, 0.27)	0.22 (0.2, 0.28)	0.62

TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement, IQR=Interquartile Range, BMI=Body Mass Index, NT-proBNP=N-Terminal B-type Natriuretic Peptide, eGFR=Estimated Glomerular Filtration Rate, FFS=Fried Frailty Scale, STS=Society of Thoracic Surgeons, HF=Heart Failure, HTN=Hypertension, IHD=Ischaemic Heart Disease, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, PVD=Peripheral Vascular Disease, AF=Atrial Fibrillation, CABG=Coronary Artery Bypass Grafting, TIA=Transient Ischaemic Attack, EF=Ejection Fraction, AV=Aortic Valve, MG=Mean Gradient, Vmax=Peak Velocity, DPI=Dimensionless Performance Index

Frailty

Within the entire study population, the mean FFS score was significantly lower at late review relative to pre-procedure (1.18 v. 1.73, P=0.002). The mean change in FFS score at late review was -0.45.

When comparing the transcatheter and surgical cohorts, the groups had a similar baseline mean frailty score (1.79 for TAVR v 1.59 for SAVR, p=0.424). At late review, the mean FFS of both groups decreased significantly, the TAVR group to 1.33 (p=0.030) and the SAVR group to 0.8 (p=0.015). Although the final mean FFS score was significantly lower in the surgical group, there was no significant difference in the degree of improvement between interventions (p=0.517) (Table 8.2). The change in FFS values pre- and post-intervention overall, as well as stratified by intervention type, are demonstrated in Figure 8.2. This demonstrates in improvement in frailty score by ≥1 point in 51.5% of patients overall, with 46.8% in the TAVR group and 63.2% in the SAVR group.

Table 8.2. Mean Frailty Score Overall and by Aortic Valve Intervention and Change in Mean Frailty Score Post Intervention

FFS Score	**Overall (*N^1)**	**TAVR (*N^2)**	**SAVR (*N^3)**	**p-value**
Baseline, mean	1.73	1.79	1.59	0.424
Final, mean	1.18	1.33	0.80	**0.022**
Change, mean, (%)	-0.455 (-26.3%)	-0.404 (-22.6%)	-0.579 (-36.4%)	0.517
p-value	**0.002**	**0.030**	**0.015**	

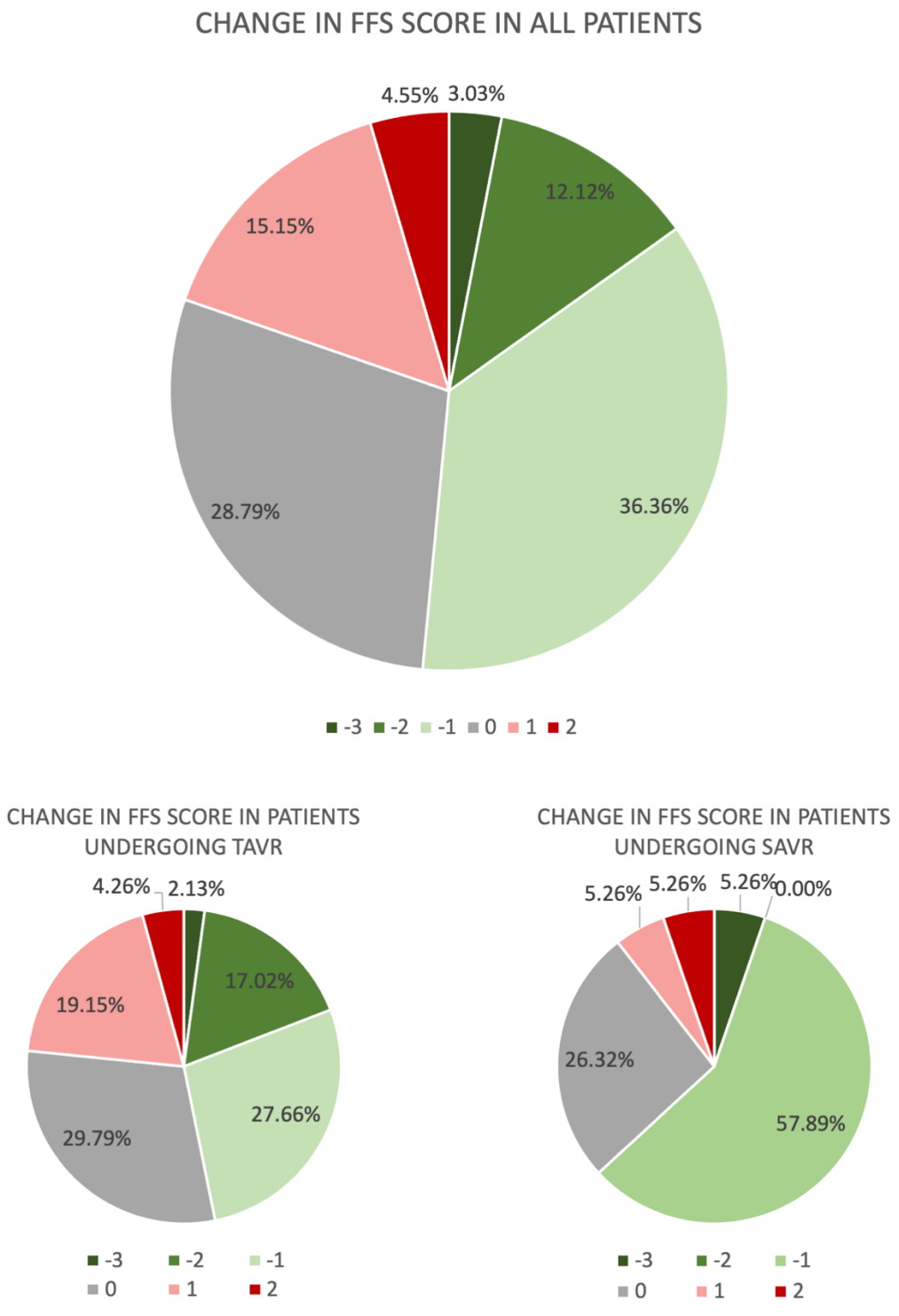
FFS=Fried Frailty Scale, TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement.

*N^1=83 at Baseline, N^1=71 at Final, and N^1=66 for Change

*N^2=61 at Baseline, N^2=51 at Final and N^2=47 for Change

*N^3=22 at Baseline, N^3=20 at Final and N^3=19 for Change

Figure 8.2. Change in Overall Frailty Score After Intervention and By Intervention Type

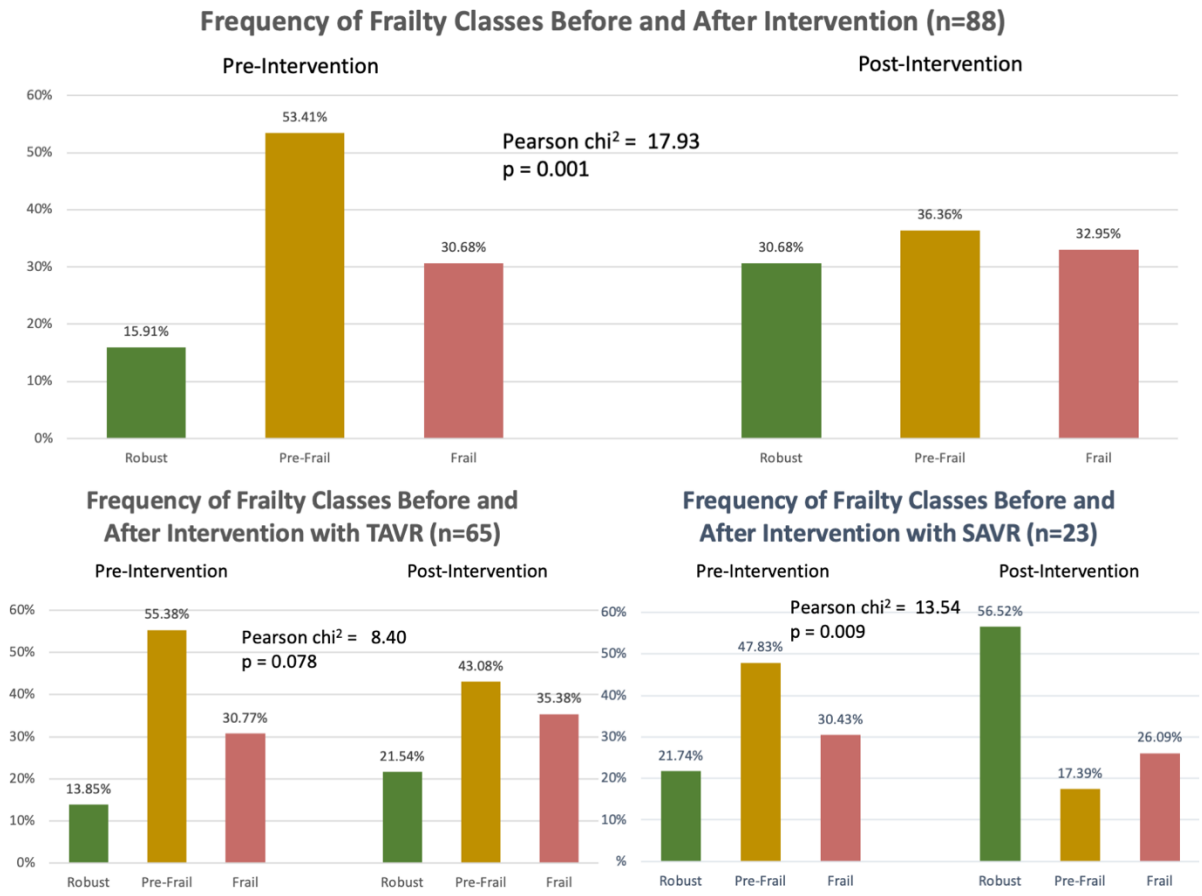


FFS=Fried Frailty Scale, TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement.

*A) N=66 B) N=47 C) N=19

When grouping cohorts into the frailty classes outlined by Fried et al[161], we found that the majority of our population was considered frail (30.7%) or pre-frail (53.4%) prior to intervention, whereas only 15.9% of patients were considered robust. At late review post-intervention, 30.7% of patients were considered robust, and the proportion of patients considered pre-frail reduced to 36.4%. The number of patients considered frail remained similar at 32.9%. When grouping patients into their frailty class, rather than by their frailty score we note that overall and within the SAVR treated group, the frequencies within each frailty class change significantly ($p=0.001$ and $p=0.009$ respectively), but the frequencies within the TAVR treated group trended towards, but did not reach, significance ($p=0.078$) (Figure 8.3).

Figure 8.3. Mean Frailty Class Before and After Intervention



TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement.

To determine whether certain domains of frailty were more likely to improve, the relative proportions of abnormality within each domain was compared. At the final frailty assessment, exhaustion and low activity were found to be significantly improved. Between treatment groups, the frequencies of frailty domain abnormalities were similar for all except the post-intervention weakness domain, which had a significantly lower frequency in the SAVR treated group relative to the TAVR group (Table 8.3).

Table 8.3. Differences in Abnormal Frailty Subdomain Frequencies by Aortic Valve Intervention at Baseline and Late Review and the Change in Frequencies

Subdomain	**Overall (*N[1])**	**TAVR (*N[2])**	**SAVR (*N[3])**	**p-value**
Weight Loss (Baseline)	18.0%	19.7%	13.6%	0.531
Weight Loss (Final)	19.7%	23.5%	10.0%	0.201
Change in Weight Loss	1.5%	4.3%	-5.3%	0.488
p-value	0.808	0.593	0.564	
Weakness (Baseline)	56.6%	62.3%	40.9%	0.085
Weakness (Final)	50.7%	60.8%	25.0%	**0.007**
Change in Weakness, (% change)	-1.5%	0%	-5.3%	0.487
p-value	0.655	1.000	0.317	
Slowness (Baseline)	21.7%	21.3%	22.7%	0.891
Slowness (Final)	12.7%	13.7%	10.0%	0.674
Change in Slowness, (% change)	-6.1%	-6.4%	-5.3%	0.950
p-value	0.248	0.257	0.655	
Exhaustion (Baseline)	50.6%	49.2%	54.5%	0.668
Exhaustion (Final)	22.5%	23.5%	20.0%	0.750
Change in Exhaustion, (% change)	-27.3%	-23.4%	-36.8%	0.406
p-value	**<0.001**	**0.008**	**0.008**	

Low Activity (Baseline)	26.5%	26.2%	27.3%	0.925
Low Activity (Final)	14.1%	13.7%	15.0%	0.890
Change in Low Activity, (% change)	-10.6%	-12.8%	-5.3%	0.498
p-value	**0.035**	**0.034**	0.564	

TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement

*N^1=83 at Baseline, N^1=71 at Final, and N^1=66 for Change

*N^2=61 at Baseline, N^2=51 at Final and N^2=66 for Change

*N^3=22 at Baseline, N^3=20 at Final and N^3=66 for Change

Symptoms

In total, 88 patients had a preintervention KCCQ-OS documented, with 57 having an early review KCCQ-OS and 85 having a late review KCCQ-OS.

Within the entire cohort, the median KCCQ-OS improved significantly with intervention, from 60.2 to 91.1 ($p<0.001$), and the median NYHA class improved from 3 to 2 ($p<0.001$). There was a significant difference in the degree of change in KCCQ-OS between intervention groups in favour of TAVR (Table 8.4).

Table 8.4. Mean KCCQ Overall Summary Score, Overall and by Aortic Valve Intervention at Baseline, and Early and Final Review

KCCQ Overall Score	**Overall (*N^1)**	**TAVR (*N^2)**	**SAVR (*N^3)**	**p-value**
Baseline	59.3	57.0	65.8	0.085
Early Review (1 Month)	82.2	81.7	84.8	0.809
Final Review (6 Months)	85.6	86.0	84.6	0.714
p-value	**<0.001**	**<0.001**	**<0.001**	
Change in KCCQ-OS Score, median (IQR)	20 (11.1, 37.2)	22.6 (12.5, 45.3)	16.1 (6.4, 28.6)	**0.049**

KCCQ-OS=Kansas City Cardiomyopathy Questionnaire - Overall Summary Score, TAVR=Transcatheter Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement

*N^1=88 at Baseline, N^1=57 at Early Review, N^1=81 at Final Review/Change

*N^2=65 at Baseline, N^2=49 at Early Review, N^2=59 at Final Review/Change

*N^3=23 at Baseline, N^3=8 at Early Review, N^3=22 at Final Review/Change

The degree of change in the KCCQ-OS score correlated significantly with the degree of change in the FFS score, both in the entire cohort ($z=6.602$, $p<0.001$) and within intervention groups (TAVR $z=5.693$, $p<0.001$, SAVR $z=3.280$, $p=0.001$). No difference existed in the final KCCQ-OS score between those who did and did not complete a final frailty assessment ($p=0.730$).

The 6MWT had a median distance for the cohort of 384m at baseline and 412.5m at late review ($p=0.017$). The median baseline and final distances for the TAVR group (335.8m and

380m, respectively) were significantly lower than the SAVR group (420.5m and 504m, respectively), and both interventions had a trend toward improvement with intervention, but likely due to reduced power did not reach statistical significance individually (TAVR p=0.075, SAVR p=0.093).

8.4 Discussion

In our cohort, the mean frailty score significantly improved after intervention with either TAVR or SAVR. Additionally, there was a significant improvement in the frailty class overall and within the SAVR treated group, with a trend towards significance in the TAVR group. No significant differences in the magnitude of improvement in the frailty score existed between interventions, indicating that both procedures improve the frailty score to a similar degree, however, likely since the SAVR group was younger and more robust, there was a trend towards a lower baseline frailty score which enabled the SAVR group to reach the tipping point between pre-frail and frail more frequently. This improvement was particularly evident with the symptom driven frailty subdomains, exhaustion and low activity, demonstrating that AV intervention is able to reduce the frailty score largely as a symptom focused syndrome, according to a commonly used measure of frailty.

Additionally, symptoms as measured by the KCCQ improved post intervention as expected, and the degree of symptomatic improvement correlated strongly with the degree of frailty improvement, lending further support to the argument that perhaps what had previously been defined as frailty among patients with severe AS, is in truth more reflective of the symptom burden of AS. Many of the domains used to assess frailty overlap with the domains used to assess symptoms. For instance, the KCCQ assesses physical limitation, symptom burden and frequency, self-efficacy, quality of life and social limitation, and the FFS assesses weight loss, grip strength, walking speed, symptoms of exhaustion and low activity. It is quite easy to link these domains in the daily life of a patient with severe symptomatic AS. The burden and frequency of the symptoms of severe aortic stenosis, and their limitations on daily life, as measured by the KCCQ, lead to an increase in symptoms of exhaustion and therefore reduced

activity levels, as scored by the FFS. This is further supported by previous work by Arsalan et al, which showed that BAV improves independence in activities of daily living 30 days post-procedure[204].

It is clear from previous studies that aortic valve intervention by either available intervention improves both mortality and symptoms, and, while it is known that high frailty scores are associated with worse outcomes, as far as the authors are aware no studies to date have examined the reverse; the impact of intervention on frailty. Clinical trials are, however, underway to determine whether home-based exercise and nutritional supplementation in frail patients prior to TAVR impact frailty scores post TAVR[205]. Whether or not AV intervention truly reduces "frailty", or whether "frailty" as it is currently defined by the FFS is, at least in part, overestimated due to significant overlap with the classic symptoms of aortic stenosis is unclear. For this reason, although patients defined as frail may have relatively poorer outcomes it is important to note that this is not necessarily a static variable. Intervention should still be considered carefully in the patient classed as frail, since this can improve significantly.

Limitations of this study include the relatively small sample size of the cohort. We sought to avoid selection bias by attempting to include all patients undergoing intervention, but it is conceivable that the most symptomatic or frail patients would decline to consent to further questioning and assessment. There was an absence of baseline FFS in five patients and a loss of frailty assessment follow up for 17 patients reducing this number further. The early omissions were typically due to time pressure prior to intervention, and the late omissions were typically due to geographic limitations to presenting for follow up in person. The KCCQ was still assessed via telephone, and there was no significant difference in final

KCCQ between those who did or did not receive a final frailty assessment, so it is unlikely that these patients were too sick or unwell to attend follow up.

Expanding this study with a larger population or registry, if the late frailty score has been measured is warranted. It would also be worth repeating with multiple and varied frailty scores further delineate whether this result is generalisable across all proposed frailty scales, or whether the FFS is particularly prone to measure symptoms over frailty. Lastly a larger cohort with longer term outcome data would be beneficial to determine whether patients with a frailty score which improved more significantly had better long-term outcomes.

8.5 Conclusions

Frailty as it is currently defined has now been shown to improve post aortic valve intervention with both TAVR and SAVR to a similar degree, and the degree of improvement in frailty correlates strongly with the degree of improvement in symptoms. Our study counters the general conception that frailty is a degenerative or fixed state that is independent of a particular disease process. Frailty, as it is often scored, including in the landmark PARTNER trials, may be more of a reflection of symptom burden rather than a true representation of a fixed and degenerative state, and for this reason frailty scores alone should not be considered an exclusion criterion for intervention, and conversely, the potential for improvement in frailty should therefore be potentially considered as an indication for intervention.

CHAPTER 9

SUMMARY AND CONCLUSIONS

9.1 Summary of Findings and Future Research

9.1.1 Principal Findings

The work presented in this thesis explores the perioperative evaluation and management of patients with severe symptomatic AS, and further investigates novel mechanisms of residual symptoms of dyspnoea post-intervention. Within these two themes, this thesis provides a greater understanding of our current practices and provides promising potential targets for future research and medical therapy with a series of patient-centric and quality of life focused studies.

The MDT is widely considered to be a key feature of AS management, so much so that it has received a level 1 recommendation from the major cardiac societies and is mandated for funding in Australia. Despite this, to date there has been no strong evidence that it provides a significant benefit to the patients. Our analysis demonstrated that the introduction of a TAVR program, with an associated MDT, led to improvement in mortality in a population of patients with severe AS, despite expanding intervention to older patients with poorer cardiac function. In our population, we found no significant difference in mortality between SAVR and TAVR, indicating that the novel procedure itself was not the cause of this improvement. We also considered operator experience as a mechanism, but there was no significant difference between the early TAVR period and the late TAVR period, indicating that it was the transition itself that led to a benefit. We propose that better consideration of patient comorbidities and better patient selection along with improved and more frequently utilised diagnostic imaging, leading to fewer access site complications and better bioprosthetic valve

sizing have all contributed. These mechanisms are all coincident with the more careful discussion enabled by the MDT.

Balloon aortic valvuloplasty allows for rapid, but non-durable, alleviation of AV obstruction without the need for full TAVR assessment and valve sizing. BAV had fallen out of favour in recent years due to long-term data showing no mortality benefit with similar procedural risks to TAVR, but can be crucial in cases where severe LV dysfunction has insidiously occurred, and the patient requires urgent treatment. BAV can also be used as a diagnostic tool to assess improvement in symptoms or LV function prior to committing to a potentially futile procedure. While we agree from our data that long-term mortality with BAV is similar to medical therapy, we found that in selected patients, BAV can offer a short-term mortality benefit, for up to 245 days, with little procedural risk, likely due to the recent advances in transcatheter technologies. This may allow treatment of urgent comorbidities, provide rapid myocardial relief from pressure overload, and predict symptomatic response to more permanent interventions. BAV may also potentially allow for safer subsequent intervention with similar mortality outcomes to the direct intervention group despite having significantly higher baseline risk.

The timing of aortic valve intervention remains a contentious point of discussion in many TAVR MDTs despite the growing evidence that a mortality benefit is present in certain scenarios in which the traditional criteria may not be severe, that symptoms are not always required, and that potentially irreversible myocardial dysfunction occurs in the background prior to the development of symptoms. Discordance in the severity of the traditional AS criteria often leads to a conclusion that AS is moderate and therefore should be conservatively managed. Our analysis counters this notion. We analysed mortality stratified

by the number of severe-range criteria using the traditional 4 AS severity criteria and found that although a stepwise increase in mortality existed with increasing criteria, intervention reduced mortality similarly in all groups, despite intervention being deferred with fewer criteria. These data support a strategy of early intervention once a single severe AS criterion is achieved.

The clinical dilemma of residual breathlessness post intervention warrants significant investigation. Global longitudinal strain allows for earlier detection of sub-clinical myocardial dysfunction, and pre-procedural abnormal GLS has been associated with symptoms, mortality and worse procedural outcomes in the AS population. Our study sought to determine the relationship between GLS and residual dyspnoea in the post-intervention period. We found that both symptoms and GLS improved with intervention, and that the degree of improvement in GLS correlated with degree of improvement in symptoms, by multiple symptom scales, even when adjusting for LVEF. When stratifying patients according to those responded with a 10% improvement in GLS and those that did not respond, there was a significantly greater symptomatic improvement in those with a GLS improvement, indicating that abnormal GLS can be a sensitive marker for residual symptoms not detected by LVEF.

Another measure that has been associated with increased symptoms and mortality in the AS population is the valvuloarterial impedance, which measures the combined valvular and systemic arterial impediment to LV ejection, increasing myocardial workload. AS is often associated with reduced systemic arterial compliance as both are manifestations of a degenerative atherosclerotic process, although our AIx values were not significantly different to an age and gender matched reference value. Since Zva has two components, and only one

of these is address by AVR, we sought to determine the effect of the remaining component, arterial stiffness, as measured by AIx, on residual symptoms post intervention. We found, using simple, non-invasive AT, that baseline abnormalities in AIx correlated with the final KCCQ-OS and NYHA class, indicating that AIx could in fact predict the risk of residual dyspnoea pre-procedurally. Patients in the top quartile of AIx, with an augmentation of 42%, had a significantly worse symptomatic outcome relative to the bottom three quartiles.

Lastly, we wished to clarify the link between symptoms and frailty. Frailty is common in the elderly AS population and frail patients have worse outcomes after intervention. For this reason, frail patients are often not considered for surgical or transcatheter AVR. While the impact of frailty on outcomes has been studied previously, the impact of intervention on frailty had not, to our knowledge, been assessed. We considered that many frailty tools use subjective indicators, such as exhaustion and fatigue, or objective indicators such as walking speed, which could in fact be hindered by symptoms of severe AS, thereby overestimating the degree of frailty. We found that a commonly used frailty score improved significantly after AV intervention, and the degree of symptomatic improvement, as measured by the KCCQ, correlated with the degree of improvement in frailty, suggesting a link between symptoms and frailty. Whether or not frailty truly improves, or the FFS is simply more a symptom scale than a frailty scale in this population is undetermined, but it is clear that the potential for improvement in frailty should be taken into consideration at the AS MDT.

9.1.2 Future Directions

Our retrospective analyses discovered interesting potential directions for future research. While an RCT regarding the benefit of the AS MDT is difficult given the clear advantage to the careful consideration of each patient by a panel of specialists involved in their care, it is reassuring to have evidence of a mortality benefit supporting its use. It is also useful to have stronger evidence for an additional tool in the catheter laboratory for the emergency management of AS related cardiogenic shock and rapid deterioration. BAV has been shown in our population to be a relatively safe procedure, providing a medium-term mortality benefit in the sickest patients, and warrants further investigation with an RCT examining BAV then early, but controlled, intervention versus immediate intervention in patients with critical AS and shock. Further RCT data is also warranted to confirm our findings with regards to discordant AS criteria, in addition to currently ongoing trials on moderate and asymptomatic, but severe AS. A randomized trial of early intervention or conservative management in asymptomatic patients with 1-2 AS criteria compared with 3-4 criteria could yield interesting results.

Our exploratory analyses investigating causes of residual dyspnoea and poor symptom recovery also warrant further investigation. A major limitation of these trials was the small recruitment due to the limited funding and manpower of a single researcher study. Despite these limitations, some interesting findings were noted which warrant larger confirmatory trials. A larger study of the impact of GLS on residual dyspnoea would be useful to confirm our findings, and given the significantly reduced baseline GLS, a study investigating the effect of early intervention based on GLS abnormalities compared with standard care on mortality and residual symptom burden prior to the development of strain abnormalities

could further support early intervention. Larger confirmatory studies on AIx are also needed to clarify the role of SAC on residual dyspnoea, and a trial of standard versus aggressive HTN management on symptoms post-intervention could prove interesting. Lastly, it needs to be determined whether frailty truly improves after AVR, or whether the FFS is a frailty tool ill-suited to this population, despite its use in the PARTNER trials. If invalid, this throws into question much of the preceding frailty data in existence, perhaps indicating that rather than the most frail, it is the most symptomatic who have the worst outcomes, potentially further implicating subclinical LV dysfunction or increased myocardial work.

Lastly, it may be beneficial to unify some of these findings. In particular, it may prove interesting to determine if differences in the augmentation index, strain or frailty, could help stratify those with discordant severity criteria in order to better assist with clinical decision making.

9.2 Conclusions

Although research in this field has expanded enormously in the last decade, there is still much to discover. Interventional techniques have developed rapidly, but the underlying mechanism of the disease remains incomplete, and targets for medical therapy remain elusive. There may come a day when calcific AS can be reversed medically, but AVR will remain the cornerstone of therapy for the foreseeable future. We now know how to intervene, but there is still much to be determined regarding when to intervene. A common conclusion of the studies in this thesis is that careful consideration, but early action, may prevent irreversible cardiovascular injury leading to residual symptoms, despite intervention. As technologies improve and procedural risks decline, we may find that the original doctrines of Ross and Braunwald no longer apply in the modern era.

Appendix: Publications Associated With This Thesis

1. Jones, D.R., et al., *Multidisciplinary transcatheter aortic valve replacement heart team programme improves mortality in aortic stenosis.* Open Heart, 2019. **6**(2): p. e000983.
    - Oral presentation at EuroPCR 2018

2. Jones, D.R., et al., *Effect of Balloon Aortic Valvuloplasty on Mortality in Patients With Severe Aortic Stenosis Prior to Conservative Treatment and Surgical or Transcatheter Aortic Valve Replacement.* Heart Lung Circ, 2020. **29**(5): p. 719-728.
    - Oral presentation at EuroPCR, 2018

3. Jones, D.R., et al., *Impact of increased augmentation index and valvuloarterial impedance on symptom recovery after aortic valve replacement for severe aortic stenosis.* Int J Cardiol Heart Vasc, 2021. **32**: p. 100705.

4. Jones, D.R., et al., *Impact of Surgical and Transcatheter Aortic Valve Replacement on Frailty Score*. Heart Lung Circ, 2021, https://doi.org/10.1016/j.hlc.2021.09.014.
    - Presentated as Finalist for the Early Career Research Award, CSANZ, 2021
    - Presented at the Flinders University Emerging Leaders Showcase, 2021

Supplements

1.1 Patient Information and Consent Form

1.2 REDCap Database Data Entry Template

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