The Impact of Patient Prosthesis Mismatch on Outcome and Quality of Life following Aortic Valve Replacement

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Doctor of Philosophy

By

Rajdeep Bilkhu, MBChB, MRCS(Ed)

Institute of Molecular and Clinical Sciences
St. George's University of London
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Dedication

I dedicate this work to my beloved mother and father, Malvinder and Gurmukh Bilkhu who have always given me the encouragement to achieve the best that I can and for teaching me the importance of hard work and persistence.

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1. Preface

1.1 Abstract

Background

The clinical impact of patient prosthesis mismatch (PPM) following aortic valve replacement (AVR) has been debated. Furthermore, the impact of PPM on quality of life (QOL) is not well established. The aim of this study was to investigate the impact of PPM on outcome and QOL.

Methods

Demographic and operative data for patients undergoing AVR ± coronary artery bypass graft surgery (CABG) over a 2-year period was prospectively collected. Data on complications and outcomes were recorded during the hospital stay, at 3, 6 and 12 months. QOL assessment was performed using SF-36® questionnaires preoperatively and 6 and 12 months following discharge. PPM was diagnosed from the first postoperative echocardiogram. Patients who were in extremis and unable to participate were excluded.

Results

Over a two-year period, 173 consecutive patients underwent isolated AVR or AVR + CABG. Median age was 75 years and 64.2% were male. Twenty-six (15%) had PPM of which 11 (42.3%) had severe PPM and the remainder had moderate PPM. The incidence of stroke was 7.7% and 5.4% in those with and without PPM respectively, p=0.81. In hospital mortality was 7.7% and 6.2% in those with and without PPM, p=0.44. There was a significant reduction in LV mass following surgery, except in those with severe PPM, p=0.07. At one year, there was no difference in mortality between those with and without PPM, p=0.2. No patients required reintervention for PPM. In those with severe PPM, there was a significant reduction in QOL mental component scores (p=0.01) and no improvement in QOL physical component score in those with severe PPM, p=0.38.

Conclusions

In patients undergoing AVR, PPM does not impact early postoperative outcomes, regardless of the degree of PPM. There is no significant impact on mortality or reintervention up to one year follow up. In those with severe PPM, QOL scores were lower during follow up.

1.2 Statement of Originality and Contributions

I declare that this research is the product of my own work. I am responsible for the concept, design, regulatory approval, patients' recruitment, data collection, data processing, analysis and interpretation of the results. Any ideas, quotations or data from the work of others, published or otherwise, are fully acknowledged in accordance with standard referencing practice.

Mr. Mohammad Diab (Research fellow, St. George's University of London) trained me in using QOL assessments and questionnaires. He assisted me in following up patients during the study period.

Ms. Nicole Radford (Academic Assistant, St. George's NHS Trust) assisted me in organising follow-up dates for patients, to ensure study completion in a timely fashion.

I had assistance with statistical analysis by Dr Oswaldo Valencia (St George's Hospital, London).

Finally, my academic supervisor, Professor Jahangiri (Professor of Cardiac Surgery, St. George's Hospital) provided overall intellectual and technical supervision on all aspects of the thesis, and assisted in preparation of manuscripts from the results of the thesis for publication in peer reviewed journals.

1.3 Clinical Relevance of Thesis

This study has demonstrated that there is no significant impact on early postoperative outcomes in patients with PPM following AVR. There was also no significant difference in outcomes at follow up in those with PPM. However, I identified that in those with severe PPM, QOL scores were significant lower than those with no PPM or those with moderate PPM. Those with only moderate PPM had similar QOL outcomes to those with no PPM.

Therefore, PPM as a whole, whilst it may not have a significant impact on outcome or QOL at follow up, severe PPM should be avoided as QOL outcome has been shown to be worse than those with moderate or no PPM.

Avoiding severe PPM can be achieved by calculating a predicted postoperative EOA and selecting the appropriate valve size and model. If a conventional surgical valve may result in severe PPM, then the surgeon may consider using a valve with a higher predicted postoperative EOA such as a sutureless or stentless bioprosthetic valve or consider either a complete aortic root replacement or root enlargement procedure. These interventions, based on the results of this study, would not be indicated if no, mild or moderate PPM is predicted.

1.4 Acknowledgements

This work has taken place at St George's University of London and the Department of Cardiothoracic Surgery at St George's Hospital, whilst I have continued my clinical training in Cardiothoracic Surgery.

Although it has taken me longer to reach the end of this journey due to personal and family difficulties, I am indebted to the outstanding individuals who have supported and assisted me in completing the project. This work would not have been possible without the help of the following.

Professor Marjan Jahangiri – I would like to thank my supervisor Professor Jahangiri for giving me the confidence to embark on this project. I have been fortunate to receive guidance and support from Prof over the years, not only relating to this project and research but also relating to my clinical, operative and professional development and for this I am truly grateful.

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Mr Mohammad Diab – Mr Diab helped follow up the study cohort. He also taught me the use of quality of life assessment tools and their interpretation.

Ms. Nicole Radford – Ms Radford was a key member in organising and arranging follow-up appointments. She also helped ensure I met my deadlines.

St. George's Charitable Foundation, Professor Marjan Jahangiri's Research Fund, for funding the project.

I would also like to thank my wonderful family. I would never have had the opportunity of embarking on a project like this or indeed reaching this stage in my career if it had not for my wonderful mother and late father. Thank you for always encouraging me to achieve my goals and for instilling in me the importance of hard work, the same way you worked hard to help me get where I am today.

To my beautiful wife and best friend Nashi; thank you for always being by my side. You continue to encourage me to achieve the best that I can and I appreciate it immensely. And finally, to my delightful son Jaival, you are the reminder of why I must continue to work hard each and every day.

1.5 Presentations and Publications Relevant to Thesis

Publications

- **Bilkhu R**, Jahangiri M

  Should we be worried about patient-prosthesis mismatch?

  Ann Thorac Surg. 2020 Sep 19:S0003-4975(20)31504-6. Doi: 10.1016/j.athoracsur.2020.06.131

- **Bilkhu R,** Jahangiri M

  Should the Ross procedure be considered in infective aortic valve endocarditis?

  Ann Thorac Surg. 2020 Sep;110(3):861-862.

- **Bilkhu R,** Jahangiri M, Otto C

  Patient-prosthesis mismatch following aortic valve replacement

  Heart. 2019 Mar;105(Suppl 2):s28-s33.

- **Bilkhu R,** Borger M, Briffa N, Jahangiri M

  Sutureless aortic valve prostheses

  Heart. 2019 Mar;105(Suppl 2):s16-s20.

- Diab M, **Bilkhu R,** Soppa G, Edsell M, Fletcher N, Heiberg J, Royse C, Jahangiri M

  The influence of prolonged intensive care stay on quality of life, recovery and clinical outcomes following cardiac surgery: prospective cohort study

  J Thorac Cardiovasc Surg. 2018 Nov;156(5):1906-1915.

- Diab M, **Bilkhu R**, Soppa G, McGale N, Hirani SP, Newman SP, Jahangiri M.
  Quality of Life in Relation to Length of Intensive Care Unit Stay After Cardiac Surgery.
  J Cardiothorac Vasc Anesth. 2016:21.pii: S1053-0770(16)30227-0

Presentations

- **Bilkhu R,** Diab M, Soppa G, Edsell M, Jahangiri M
  Quality of Life Outcomes in Patients Undergoing Thoracic Aortic Surgery: A Prospective Study
  AATS Aortic Symposium, New York, April 2018

- Diab M, **Bilkhu R,** Soppa G, Valencia O, Heiberg J, Royse C, Jahangiri M
  The Impact of Prolonged Intensive Care Unit Stay on Quality of Life, Recovery and Clinical Outcomes: A Prospective Study
  American Association for Thoracic Surgery Annual Meeting, New York, May 2017

- Diab M, **Bilkhu R**, Thomson R, Soppa G, Heiberg J, Royse C, Jahangiri M
  The Impact of Prolonged Intensive Care Stay on Quality of Life, Recovery and Clinical Outcomes
  The Society for Cardiothoracic Surgery in Great Britain and Ireland, Belfast, March 2017.

- Diab M, **Bilkhu R**, Thomson R, Soppa G, Heiberg J, Royse C, Jahangiri M
  Does acute kidney injury following cardiac surgery impact quality of life and rate of recovery? A prospective study
  The Society for Cardiothoracic Surgery in Great Britain and Ireland, Belfast, March 2017.

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1.8 List of Abbreviations

(iEOA)	Indexed effective orifice area
ACE	Angiotensin converting enzyme
ACT	Activated clotting time
AF	Atrial fibrillation
ANOVA	Analysis of variance
AR	Aortic regurgitation
AS	Aortic stenosis
AU	Agaston Units
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass graft surgery
CCT	Cross clamp time
CMRI	Cardiac magnetic resonance imaging
CPB	Cardiopulmonary bypass
CT	Computer tomography
CT-AVC	Computer tomography aortic valve scaning
CTICU	Cardiothoracic Intensive Care Unit
EOA	Effective orifice area
ICU	Intensive Care Unit
IQR	Interquartile range
IVSd	Interventricular septal diameter

KCCQ	Kansas City Cardiomyopathy Questionnaire
LMS	Left main stem coronary artery
LV	Left ventricle/ventricular
LVEDd	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MCS	Mental component summary
MI	Myocardial infarction
NYHA	New York Heart Association
PCS	Physical component summary
PPM	Patient prosthesis mismatch
PWD	Posterior wall thickness at end diastole
QOL	Quality of life
QALY	Quality adjusted life year
R&D	Research and development
SAVR	Surgical aortic valve replacement
SF-36	Short Form-36
STS PROM	Society of Thoracic Surgeons Predictor of Mortality
TAVI	Transcatheter aortic valve implantation
TOE	Transoesophageal echocardiography
VARC	Valve Academic Research Consortium
WHO	World Health Organisation

2. Introduction

2 Introduction

Aortic stenosis (AS) is the most common valvular heart disease in the developed world, with a prevalence in Europe of 1-3% (Zakkar *et al.*, 2016). The mainstay of treatment is replacement of the aortic valve. Patient-prosthesis mismatch (PPM) occurs when an implanted prosthetic valve is too small for the patient. Its clinical significance has been debated since it was described in 1978 (Rahimtoola, 1978).

Surgical AVR (SAVR) remains the gold standard treatment for patients with aortic valve pathology (Nishimura *et al.*, 2014). However, treatment modalities for aortic valve disease have seen a change. There has been an increase in the number of transcatheter aortic valve implantations (TAVI) worldwide (Leon *et al.*, 2016). TAVI has widely been adopted as the therapy of choice in the management of AS in patients who may be considered unfit for conventional AVR, particularly the elderly and those considered frail (Leon *et al.*, 2010). Although, more recently, there has been some evidence to suggest that this may be performed in patients of lower surgical risk, despite a lack of long term evidence (Makkar *et al.*, 2020). AVR has also seen a shift towards more minimally invasive techniques, with AVR being performed through an upper hemi sternotomy or through a right anterior thoracotomy (Semsroth *et al.*, 2017).

There have been marked improvements in mortality following cardiac surgery and as a result, focus is now being placed on other outcomes of surgery. An example of this is quality of life (QOL) (Bridgewater *et al.*, 2008; Deschka *et al.*, 2013). Indeed, in the American College of Cardiology and American Heart Association guideline for coronary artery bypass graft surgery, quality of life is considered to be an important outcome measure (Eagle *et al.*, 2004). There have been studies that have assessed the impact of surgical AVR on QOL and have also related

this to age, looking particularly at patients over the age of 80, where surgical AVR has been shown to significantly improve QOL (Sundt *et al.*, 2000; Klomp *et al.*, 2016).

There are however few studies which have assessed postoperative AV gradient and its impact on QOL in patients who have undergone surgical AVR. In PPM, where an implanted aortic valve prosthesis has an orifice area which is less than that of the native aortic valve, results in a gradient across the left ventricular outflow tract (Rahimtoola, 1978). PPM is defined by the indexed effective orifice area (EOA), i.e. EOA of the prosthetic valve divided by the body surface area.

The clinical impact of PPM has been debated (David, 2005). There is however a recognised association between severity of PPM and operative mortality in patients undergoing AVR, particularly in those with impaired left ventricular function (David, 2005; Head *et al.*, 2012). Therefore, the avoidance of implanting a small prosthesis in relation to the patient's body surface area is routine practice. There are several methods of avoiding implantation of a valve that is too small for a patient, and these will be described later in this chapter.

PPM will result in worse postoperative haemodynamic measurements. It has also been shown to have a negative impact on regression of left ventricular hypertrophy (Pibarot *et al.*, 2000). Some groups have suggested that PPM may have little clinical impact on outcomes, except in those with severe PPM (Dayan *et al.*, 2016; Bilkhu *et al.*, 2019).

Other than its effect on clinical outcomes, the impact of postoperative aortic valve gradient and PPM on QOL compared to preoperative reported QOL is not well established.

This aim of this research project was to investigate the clinical outcomes of patients undergoing surgical AVR and the impact of postoperative aortic valve gradient on morbidity, mortality and QOL.

To understand this, we must first understand the normal function of the aortic valve, the way it functions in disease and the treatment of aortic valve disease.

2.1 The Aortic Valve Anatomy and Function

The earliest records and drawings of the aortic valve come from drawings and descriptions by Leonardo da Vinci. In his drawings of the aortic valve, he described his appreciation of the structure of the valve and the aortic sinuses and demonstrating the tri-leaflet nature of the aortic valve and the vortical flow characteristics of blood within the aortic sinuses, which are bulges of the aortic wall (Sterpetti, 2016).

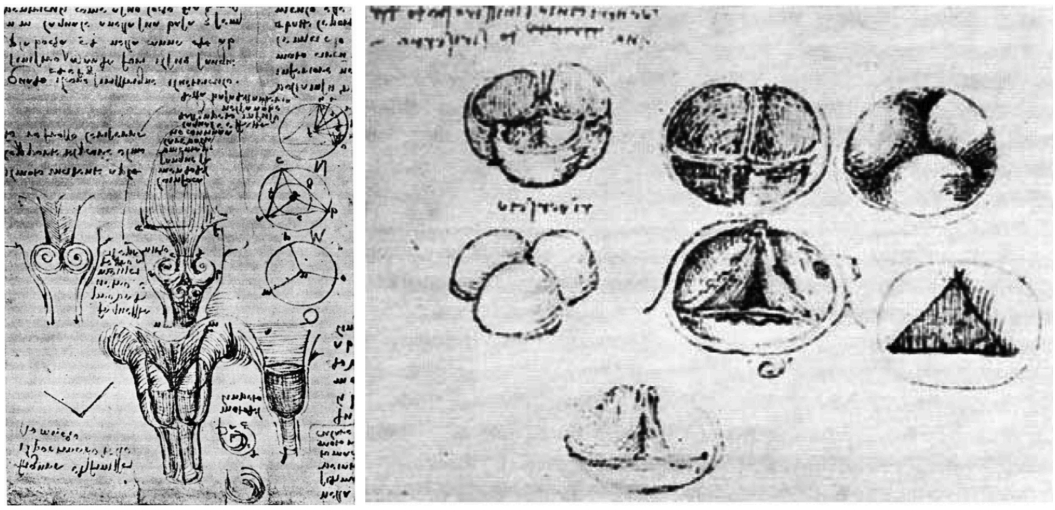


Figure 1: Da Vinci's drawings depicting blood flow in the aortic root and structure of the aortic valve (Sterpetti, 2016).

The aortic valve is commonly considered the “centre-piece” of the heart, given its proximity to other structures within the heart (De Paulis *et al.*, 2019)

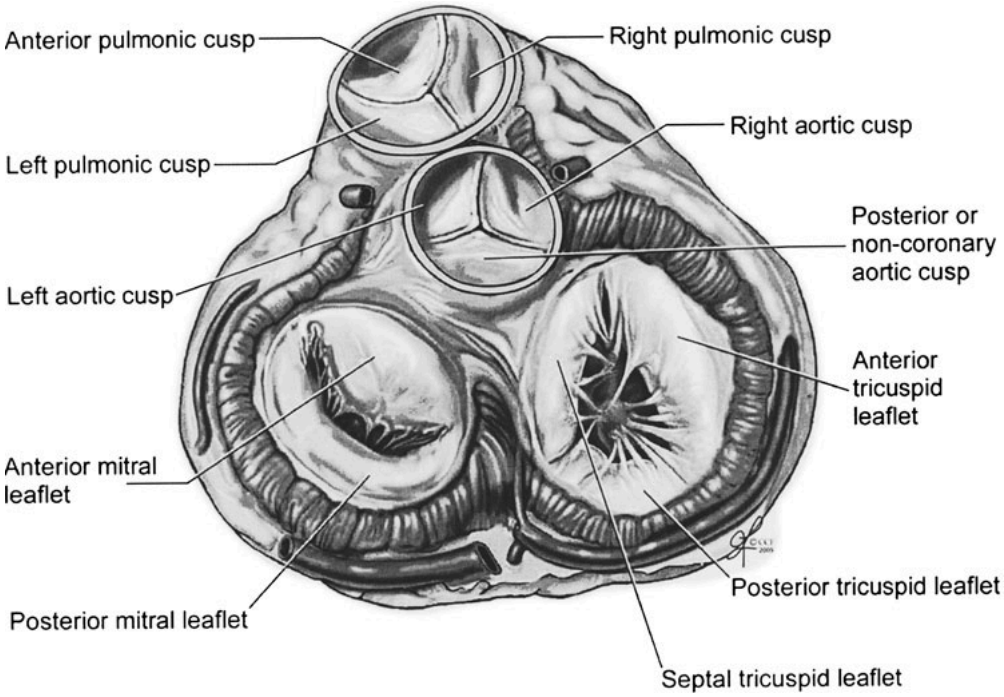


Figure 2: Demonstration of the relationship of the “central” aortic valve and its relationship to other structures in the heart, (Tomislav, 2008).

2.1.1 The Aortic Root

The aortic valve, along with the sinuses of Valsalva as well as the ventriculo-aortic junction, or aortic annulus, form the aortic root. The left and right coronary arteries, supplying the myocardium, arise from the left and right aortic sinuses respectively. The annulus is not a rigid structure, rather, it is formed of a fibrous and muscular component. It therefore changes in diameter during the cardiac cycle.

2.1.2 Aortic Valve Leaflets

The aortic valve leaflets form the one-way valve which prevents blood flowing backwards into the left ventricle during diastole. These normally thin and mobile leaflets allow for the valve to fully open into the aortic sinuses to allow the smooth, unobstructed laminar flow of blood through the valve. The valve is formed of 3 leaflets. Approximately 0.5-2% of the population will have a bicuspid aortic valve (BAV) (Masri *et al.*, 2017), of which they are a number of different morphological types, which is relevant in the development of aortic stenosis in these patients.

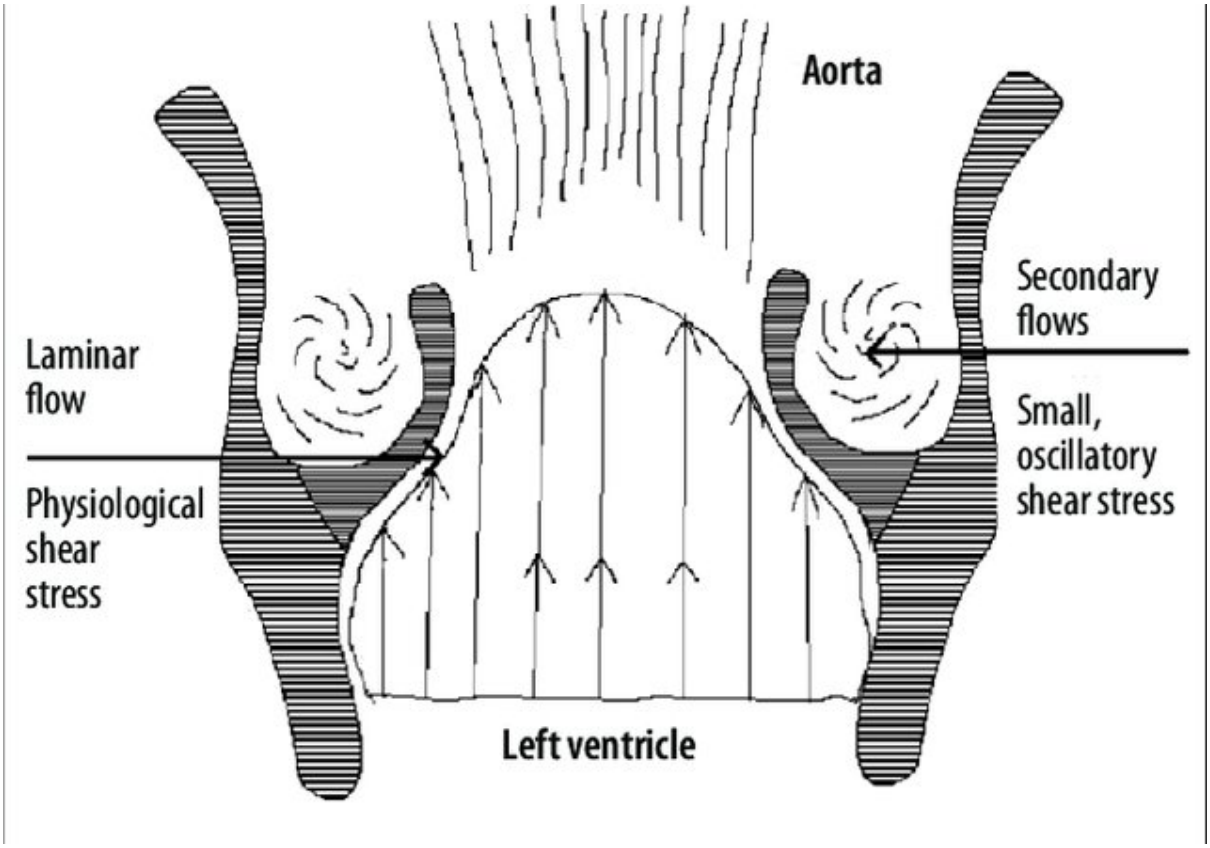


Figure 3: Laminar flow of blood from the left ventricle into the aorta (Wasilewski *et al.*, 2012).

2.2 Aortic Valve Disease

Disease of the aortic valve have an impact on the passage of blood from the left ventricle into the aorta. Commonly this is due to aortic stenosis (AS). Regurgitation of blood from the aorta back into the left ventricle during diastole occurs in aortic regurgitation (AR). The management of aortic stenosis and aortic regurgitation are somewhat similar but have some differences. In both disease states, where there is either severe stenosis or severe regurgitation, this commonly necessitates replacement of the aortic valve. The management of these two conditions is described in the following pages.

2.2.1 Aortic Stenosis

Aortic stenosis is a progressive, degenerative disease which leads to obstruction of the left ventricular outflow tract (Otto *et al.*, 2014). It has a prevalence in Europe of about 1-3% (Zakkar *et al.*, 2016). Its prevalence increases with increasing age, with only 0.2% of adults below the age of 60 being affected (Otto *et al.*, 2014).

It is caused by the progressive calcification of the aortic valve leaflets. There are a number of patients who are at risk and these include those with BAV in addition to patients with hypertension, hyperlipidaemia, diabetes or metabolic syndrome, smoking, renal dysfunction and those with increased serum phosphate. These risk factors, over time, lead to increased sheer stress on the leaflets (as is the case in BAV) or inflammation, lipid infiltration and differentiation in myofibroblasts. As the disease progresses with advancing age, there is oxidative stress on the leaflets and pro-calcific stimuli which lead to increasing calcification of the valve leaflet by the formation of hydroxyapatite nodules (Otto *et al.*, 2014). It is this progressive calcification of the aortic valve, which leads to progressive obstruction.

AS commonly presents with symptoms of dyspnoea on exertion as one of its earlier symptoms. As the disease progressed, the patient may experience angina, syncope and eventually, the symptoms of cardiac failure. Whilst the patient may have the clinical signs of a classical ejection systolic murmur, the diagnosis is made by echocardiography. Its severity is then graded by the velocity of blood flow through the valve (peak velocity), aortic valve gradient (mean gradient) and aortic valve area, as is shown in Table 1.

Echocardiography Parameters	**Peak Velocity (metres/second)**	**Mean Gradient (mmHg)**	**Valve Area (cm^2)**
Mild	2.5-3	<20	≥1.5
Moderate	3-4	20-40	1-1.5
Severe	>4	>40	<1

Table 1: Echocardiographic parameters and grading of severity of aortic stenosis.

In addition to echocardiographic assessment of the aortic valve, increasingly, computer tomography (CT) scanning has been used to assess the degree of calcification of the stenosed aortic valve, so called CT aortic valve scanning or CT-AVC (Pawade *et al.*, 2018). This has also led to CT calcium scoring being included in guidelines for management of valvular heart disease (Baumgartner *et al.*, 2017). The calcium score is reported in Agaston units (AU), with a score of >2065 AU in men and >1274 AU in women, being considered indicative of severe AS (Pawade *et al.*, 2018).

The prognosis of AS requires important consideration. It has been demonstrated that in patients who do not undergo intervention, the risk of sudden cardiac death is 1% per annum in patients

with severe AS and no symptoms. In those with symptoms, it can be as high as 12% at 6 months and a 5 year mortality of 67% in those with severe AS (Everett *et al.*, 2018; Strange *et al.*, 2019). It is therefore not a benign condition.

2.2.1.1 AS and its impact on the Myocardium

To understand why there is such a significant mortality in AS, one must consider the pathophysiological effects on the heart and the changes that occur in AS.

As the severity of the valve stenosis increases, there is increasing pressure inside the left ventricle (LV). As a result of this, the ventricle begins to hypertrophy. As the disease progresses, this leads to the ventricular wall becoming stiff and less compliant and therefore there is impaired relaxation of the ventricle and thereby, there is increase in the LV filling pressure. This leads to diastolic dysfunction. As this process continues, there is progressive ischaemia of the left ventricle given the increase in demand due to the increasing LV mass. There is consequent infiltration of the myocardium with myofibroblasts and expansion of the extracellular matrix. This leads to diffuse myocardial fibrosis. If obstruction is relieved, this process may be reversible, for example, after AVR. However, if the process continues, such as in those who do not undergo timely intervention for AS, there will be so called replacement fibrosis of the myocardium which is an irreversible state and this can lead to cardiac failure (Bing *et al.*, 2019). Myocardial fibrosis in severe AS has been demonstrated to be independently associated with mortality and therefore, when considering treatment for these patients, this should be performed at an appropriate time point to avoid progression to an irreversible state of replacement myocardial fibrosis (Musa *et al.*, 2018). It can be detected on cardiac magnetic resonance imaging (CMRI), by using the late gadolinium enhancement

method, as has been described by the Society for Cardiovascular Magnetic Resonance (Wellcome Trust, 2013).

2.2.1.2 Treatment of Aortic Stenosis

Treatment of AS centres around replacement of the aortic valve. Whilst the symptoms of aortic stenosis may be managed temporarily with medication such as diuretics and use of angiotensin converting enzyme (ACE) inhibitors, it is only relief of valvular obstruction that will improve symptoms and improve long term outcomes. There is therefore no effective medical treatment for AS.

The gold standard treatment for AS is surgical AVR. It is indicated in patients with severe, symptomatic AS (Nishimura *et al.*, 2014; Baumgartner *et al.*, 2017). The valve is replaced with a mechanical prosthetic valve or a biological/bioprosthetic valve. The variations of these will be described later in this chapter.

The alternative to surgical AVR is transcatheter aortic valve implantation (TAVI). This is now being performed increasingly commonly in patients who have isolated aortic valve stenosis (Leon *et al.*, 2016). It has been widely adopted as the treatment of choice in patients who are considered to be at high risk for conventional surgery, although there has been a drive to perform TAVI in patients with lower surgical risk. The most recent results from the Placement of Aortic Transcatheter Valves (PARTNER) 2 trial has been reported to show no significant difference in the incidence of death or disabling stroke in patients who underwent TAVI compared to those who underwent surgery and in whom the risk of surgery was considered intermediate (Makkar *et al.*, 2020). Long term data on outcomes of patients undergoing TAVI is still awaited. Current concerns include the durability of TAVI valves and the higher

incidence of complications, including higher incidence of post procedural conduction problems and pacemaker insertion as well as the incidence of paravalvular leak. TAVI will be described later in this chapter.

2.2.2 Aortic Regurgitation

Aortic regurgitation (AR) is the retrograde flow of blood from the aorta back into the LV. It occurs when the leaflets of the aortic valve do not co-apt and it may occur acutely, such as in aortic valve endocarditis or acute aortic dissection, but more commonly is a chronic condition.

In the developing world, rheumatic disease is the most common cause of AR. In developed countries, this is not the case and is generally related to congenital disease, such as BAV, or degenerative disease such as annuloaortic ectasia, such as that seen in patients with connective tissue disorders such as Marfan Syndrome or Loeys-Dietz Syndrome (Enriquez-Sarano *et al.*, 2004). The disease tends to evolve slowly.

The prevalence of AR varies with age. For mild AR, the prevalence is 3.7, 12.1, and 12.2 percent in men at ages 50 to 59, 60 to 69, and 70 to 83, respectively. The comparable values in women were 1.9, 6.0, and 14.6 percent (Singh *et al.*, 1999). With regard to moderate to severe AR, the prevalence is 0.5, 0.6, and 2.2 percent in men at ages 50 to 59, 60 to 69, and 70 to 83, respectively. The comparable values in women were 0.2, 0.8, and 2.3 percent. This is from data from the Framingham study (Singh *et al.*, 1999).

The pathophysiological process of AR is related to volume overload of the LV. Whilst this may be well tolerated in the early stages of the disease, with the heart dilating, over time there is increasing LV size and declining function of the ventricle (Luis *et al.*, 2019). The ventricle will

adapt with compensatory eccentric hypertrophy, which is different to the hypertrophy seen in AS, which is concentric (UpToDate, 2019). This can again, as in AS, lead to the development of myocardial fibrosis which can ultimately lead to cardiac failure (Borer *et al.*, 2002).

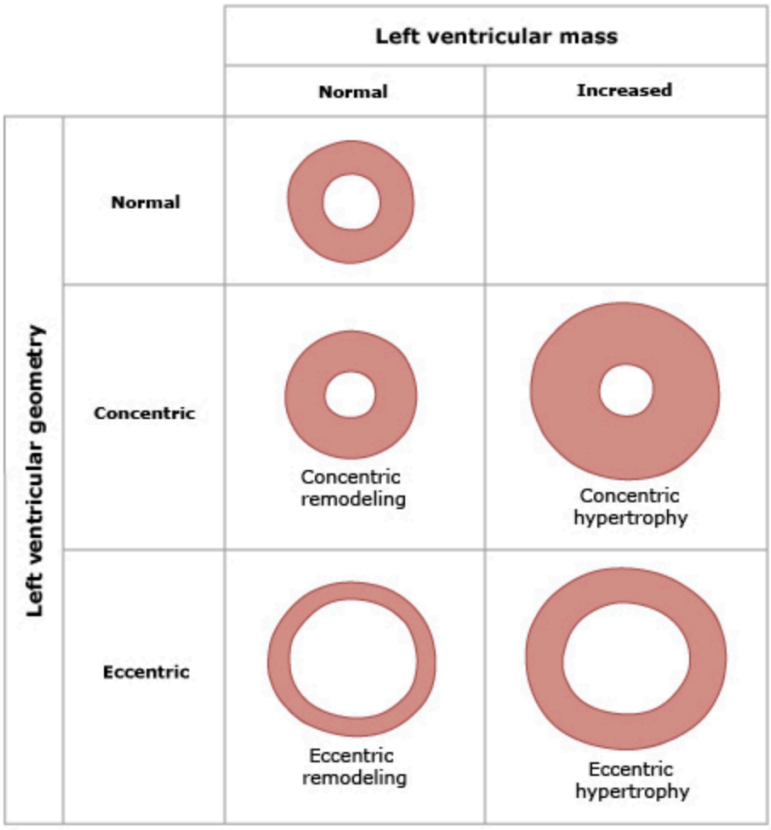


Figure 4: With concentric hypertrophy, LV end diastolic volume is normal or reduced, LV mass is increased, as opposed to eccentric hypertrophy, where the LV end diastolic volume is increased and LV mass is increased (UpToDate, 2019).

As a result of the insidious disease course, it may take a number of years for the patient to become symptomatic.

The diagnosis of AR, as in AS, is made by echocardiography. This can demonstrate whether the valve leaflets are normal, if the valve is bicuspid, whether the aortic sinuses and annulus are dilated and whether there are signs of ventricular overload, i.e. assessment of the LV dimensions.

The severity of AR is based upon assessment of the jet of AR, flow reversal of blood in the descending aorta and the volume of regurgitant blood. This is summarised in Table 2.

Echocardiography Parameters	**Vena Contracta Width (mm)**	**Ratio of width of AR jet to LVOT (%)**	**Regurgitant fraction (%)**	**Regurgitant Volume (ml/beat)**	**Effective regurgitant orifice (mm^2)**
Mild	<3.0	<25	<30	<30	<10
Moderate	3.0-5.9	25-64	30-49	30-59	10-29
Severe	≥6.0	≥65	≥50	≥60	≥30

Table 2: Severity of aortic regurgitation. Vena contracta refers to the flow at the orifice of the aortic valve in diastole on colour-flow imaging (Enriquez-Sarano *et al.*, 2004; Cardiology, 2016).

In patients where echocardiographic assessment is not optimal, CMRI scanning can be useful in quantifying the severity of AR as well as giving an accurate assessment of LV dimensions as well assessment of the myocardium for the presence of fibrosis.

Similar to AS, there is a limited role for medical management and AVR is indicated for severe AR when the patient becomes symptomatic. Other indications for surgery in this cohort include

impairment of LV function (<50% ejection fraction), LV dilatation (LV end diastolic diameter of >70mm or end systolic diameter of >50mm (Baumgartner *et al.*, 2017). In patients with dilated aortic root or ascending aorta, repair or replacement of the aortic valve can be performed.

Whilst AVR is the gold standard treatment for AR, there are an increasing number of aortic valve repairs being performed worldwide. That is to say, repair of the aortic valve without replacement of the aortic root or ascending aorta. This includes repair of bicuspid aortic valves where there is severe regurgitation. This can only be performed where the aortic valve leaflets are overall normal and are not be thickened or calcified. It is a specialised technique and should performed in centres with high volume and experience (Nishimura *et al.*, 2014).

TAVI is not performed in AR as there is a risk of valve migration due to the fact that in AR, the annulus is likely to be dilated and also not calcified, which will mean there would be insufficient anchoring of the TAVI prosthesis. There is also a significant risk of leaving significant regurgitation if the valve is not anchored suitably (Roy *et al.*, 2013).

2.3 Aortic Valve Replacement and Surgery for Aortic Valve Disease

The world's first surgical AVR was performed in 1960 by Harken, and involved the implantation of a ball and cage valve, as shown below (HARKEN *et al.*, 1960).

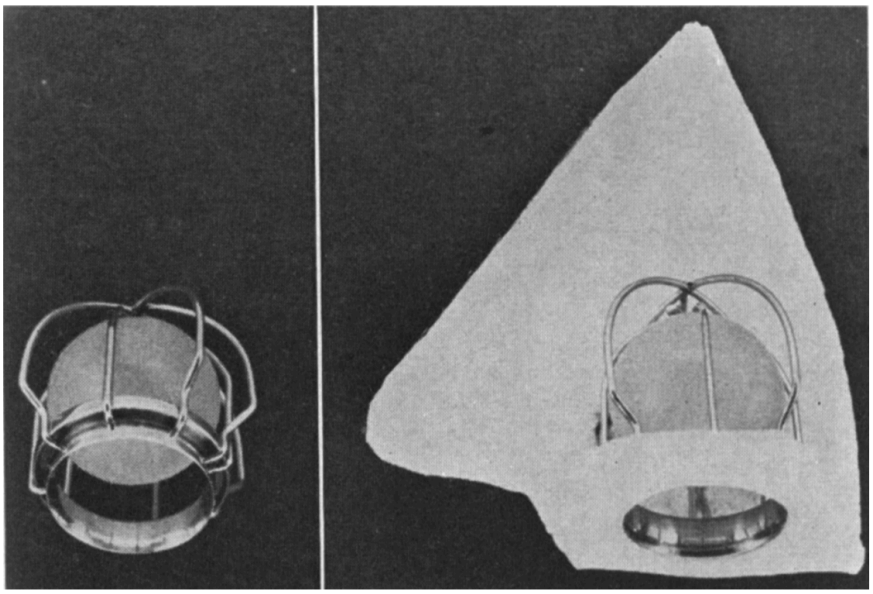


Figure 5: The ball and cage valve that was implanted by Harken in 1960 (HARKEN et al., 1960).

Following this, there have been a number of advances in the development of aortic valve prostheses and surgical approaches, which will be discussed.

2.3.1 Surgical approaches for AVR

Traditionally, AVR has been performed via median sternotomy. Whilst this provides a highly reproducible and safe approach, other surgical approaches to the aortic valve have developed with the aim of trying to reduce the invasiveness of surgical AVR. These include upper hemi-sternotomy or 'mini-sternotomy' as well as right anterior mini-thoracotomy and are demonstrated below.

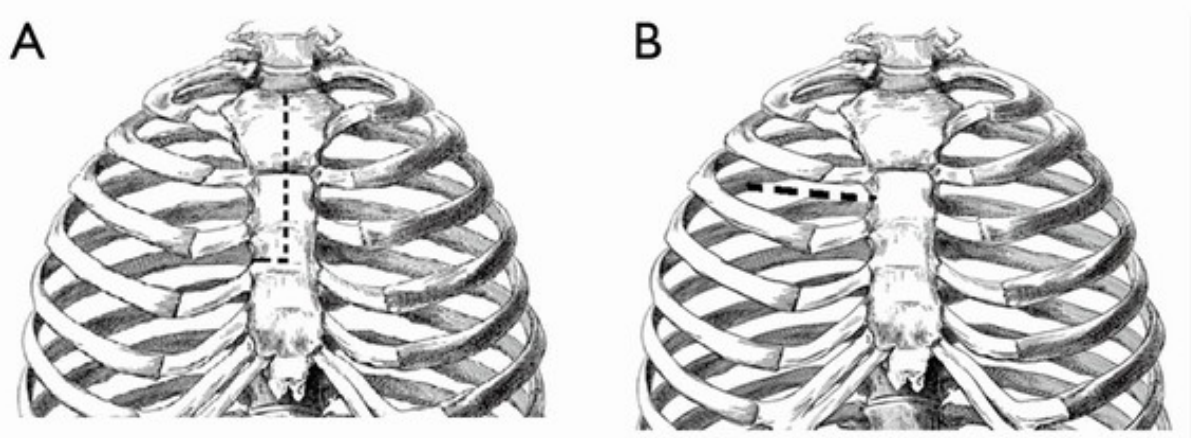


Figure 6: A: upper hemi-sternotomy or 'mini sternotomy'; B: right anterior thoracotomy (Glauber et al., 2015).

The advantages of minimally invasive AVR include improvement in postoperative respiratory function due to preservation of sternal integrity, less wound infection, reduction in postoperative pain, reduction in blood loss and improved cosmesis (Glauber *et al.*, 2015; Semsroth *et al.*, 2017).

The mini sternotomy approach is performed more frequently than the right anterior thoracotomy. It has the advantage of being highly reproducible, with low incidence of complications (Soppa *et al.*, 2015). Whilst right anterior thoracotomy can be performed safely, the incidence of complications may be slightly greater given the technical demand of the procedure. In addition, right anterior thoracotomy can only be performed if CT imaging suggests this is feasible, i.e. is the aorta positioned towards the right border of the sternum and if the depth of the ascending aorta from the sternum does not exceed 10cm and provided the plane of the aortic valve is facing the second intercostal space (Glauber *et al.*, 2015).

2.3.2 Surgical considerations when performing AVR

Regardless of which surgical approach is taken, AVR is performed on cardiopulmonary bypass (CPB). The valve is excised and in the case of aortic stenosis, the aortic annulus is debrided of calcium. The aortic annulus is sized, using a valve sizer, specific to each brand and model of prosthetic valve. This can only be done once the aortic annulus has been completely debrided and ensures that the most appropriately sized valve is implanted. The valve can be implanted using different techniques; either sutured using an interrupted or semi-continuous method or by using suture-less valves. The advantages and disadvantages of each method will be discussed later.

2.3.3 Choice of Prosthesis in Surgical AVR

Surgical AVR is generally performed with either mechanical or biological prostheses. In addition, aortic valve homograft may be used. The Ross procedure, where the pulmonary valve is used as an autograft to replace the aortic valve and where an aortic homograft is used to replace the pulmonary valve, may be used with excellent outcomes, but this is performed in specific settings and where there is a significant expertise and experience in performing the procedure (Martin *et al.*, 2017).

2.3.3.1 Mechanical Aortic Valve Prostheses

Mechanical aortic valve prostheses have evolved from the original ball and cage valves. The Starr Edwards ball and cage valve was initially designed and utilised in the mitral valve position. Whilst there was initial concern about valve durability, there have been cases of patients surviving over 30-40 years after implant (Hirji *et al.*, 2018). Following the Starr Edwards valve, single tilting disc valves were utilised from the late 1970s with excellent valve function and few mechanical failures (Gott *et al.*, 2003). By far, the most implanted mechanical

valves have been those of the bileaflet design, as were introduced by St Jude Medical in 1977 and by Carbo-Medics in 1986 (Gott *et al.*, 2003). Bileaflet valves are now the only implanted mechanical valves. A number of variations exist and all require the patient to be anticoagulated with warfarin.

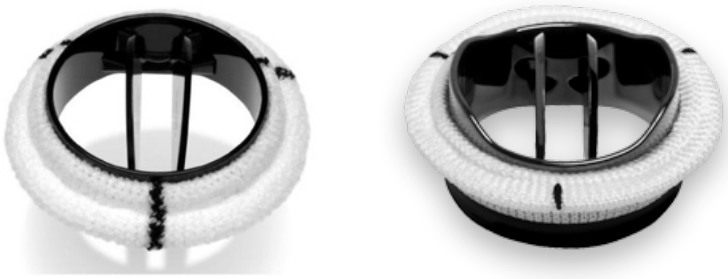


Figure 7: Mechanical aortic valve prostheses, both with slightly different design. Left: ATS bileaflet valve; Right: On-X aortic valve prosthesis

Newer generation valves allow the level of anticoagulation to be lower than that previously required. For example, the On-X aortic valve prosthesis (above), allows the patient to maintain an INR of 1.5-2 as opposed to 2-3 (Puskas *et al.*, 2018). Trileaflet mechanical aortic valve prostheses are being investigated, given the perceived benefit of 3 mechanical leaflets mimicking native aortic valve motion and therefore requiring less or no anticoagulation. These are still being tested in vitro (Schubert *et al.*, 2019).

2.3.3.2 Bioprostheses

Similarly, bioprosthetic valves have also evolved. The first bioprosthetic AVR was performed in Paris in 1965 using a porcine xenograft (Manji *et al.*, 2015). Porcine valves are still used in

the present day, however pericardial bioprosthetic valves are now used more commonly. Porcine valves are mounted onto a stent, although there are some which are not, so called stentless valves.

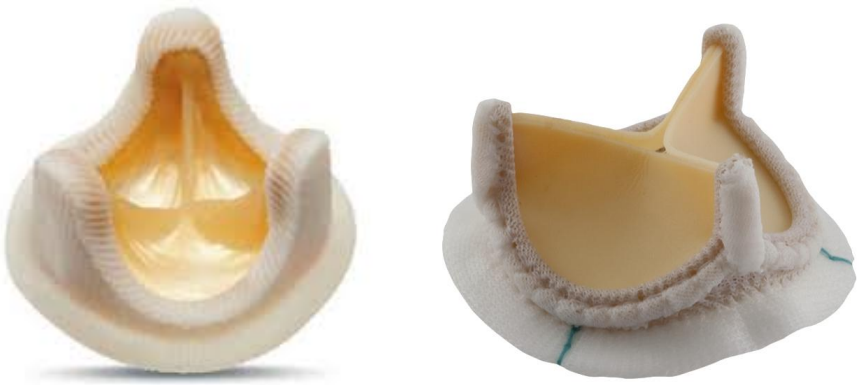


Figure 8: Bioprosthetic aortic valves. Left: porcine valve; Right: pericardial valve

These are formed from flat sheets of bovine pericardium (above) and fashioned into a valve with 3 leaflets, with different manufacturers employing slightly different valve designs and configurations. This valve is then mounted onto a stent. Both porcine and bioprosthetic valves have similar problems in terms of durability. Bioprosthetic valves deteriorate with time and develop calcification over time, secondary to immune reactions. Glutaraldehyde cross linking decreases the immune response, however bioprosthetic valves express the Gal (galactose-α1,3-galactose) antigen. In humans, anti-Gal antibodies are present and it is thought that this drives the immune response to bioprosthetic valves and their subsequent deterioration (Manji *et al.*, 2015). Manufacturers of bioprosthetic valves have developed new ways of treating the tissue used to form the valve. For example, Edwards Lifesciences have developed a bioprosthetic pericardial valve which has been treated using a novel preservation technique which blocks

aldehyde groups from binding to calcium leading to reduced or slowed degeneration of the valve. Long term data is awaited, however initial data demonstrate the safety and efficacy of the prosthesis (Puskas *et al.*, 2017).

Whilst not a prosthesis per se, homograft aortic valve from a cadaveric donor can be considered and has the advantages of excellent haemodynamics and is particularly useful in patients with aortic valve endocarditis and especially in cases of aortic root involvement.

The number of bioprosthetic valve implantations has increased over time and indeed, the number of mechanical valve implantations in young patients has declined (Tam *et al.*, 2020). This may reflect patient choice and the desire of avoiding anticoagulation. Of note, the decline in the number of mechanical valves pre-dates the use of TAVI valves (which are bioprosthetic valves) (Tam *et al.*, 2020).

2.3.3.3 TAVI

TAVI is being used increasingly in the management of patients with AS (Makkar *et al.*, 2020). TAVI valves are mounted and crimped onto a catheter which is constructed of a metal alloy frame, with leaflets formed from animal, typically bovine, pericardium.

These valves can be implanted either by transfemoral or transthoracic approaches, however the majority are performed by transfemoral approach (Leon *et al.*, 2016; Makkar *et al.*, 2020). Transthoracic approaches are considered where it is not possible to perform using an alternative route, for example, due to peripheral vascular disease. It is also important to note that outcomes of TAVI in patient requiring transthoracic access are worse than those undergoing TAVI with

transfemoral access and, importantly, that outcomes of patients undergoing TAVI with transthoracic access are inferior to those undergoing surgical AVR (Makkar *et al.*, 2020).

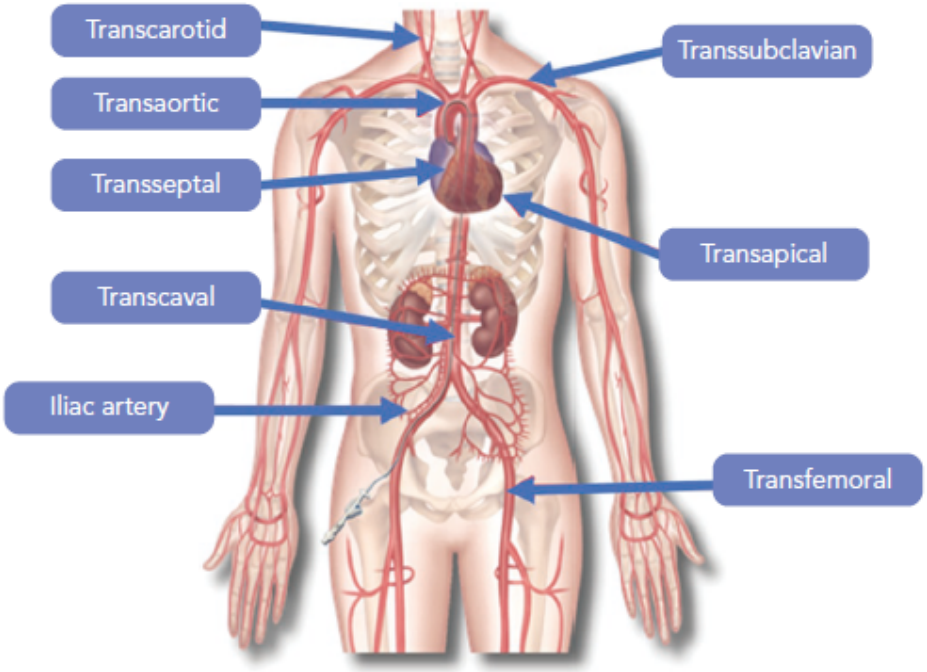


Figure 9: Routes of implantation for TAVI valves.

Whilst TAVI may be performed with less surgical trauma and potentially reduced hospital stay, there are a number of recognised complications of TAVI. These include the incidence of important complications of paravalvular leak, conduction disturbance requiring pacemaker implantation and valve thrombosis, which are higher compared to SAVR (Clayton *et al.*, 2014; Leon *et al.*, 2016; Siontis *et al.*, 2019). One of the post hoc findings of the Placement of Aortic Transcatheter Valves (PARTNER) trial was the lower incidence of patient prosthesis mismatch (PPM) after TAVI compared to surgical AVR (Leon *et al.*, 2016).

TAVI has, to date, largely been considered a treatment in patients who may be unfit for SAVR. Trials studying the outcomes of TAVI have been based on surgical risk stratification. Initially, TAVI was performed in patients with high risk of surgery. There is however increasing interest in performing TAVI in lower risk and perhaps younger patients (Uva, 2019). There are however a number of important points when considering TAVI in younger patients.

One of the most important considerations when valve replacement is required is durability of the valve. To date, the mean age of patients in the PARTNER and SURTAVI trials has been >80 years and as a result of this, it has not been possible to test the durability of these valves. Although there is inadequate data on durability of TAVI valves, however, at best they would resemble the latest generation tissue valves used in SAVR, where there is ample evidence on its durability. There is a large amount of data available which have documented the durability of both mechanical and bioprosthetic aortic valves (Foroutan *et al.*, 2016; Head *et al.*, 2017). The durability of a tissue valve is inversely related to the patients age, such that the 10 year freedom from structural valve deterioration in a patient of 70 years is 90% as opposed to 75% in a patient of 50 years (Fatima *et al.*, 2019). Given the lack of long-term durability data available for TAVI valves, patients should be consented and counselled appropriately at the time of discussion for valve replacement.

The advantage of bioprosthetic valves is the avoidance of anticoagulation, which is a particularly important consideration in older patients. Subclinical leaflet thrombosis has been noted in both bioprosthetic and TAVI valves (Chakravarty *et al.*, 2017). This is noted to be higher in TAVI valves. It is not clear whether this may contribute to valve durability, however, has led to the consideration of anticoagulation in patients with TAVI valves, arguably something that would be desirable to avoid in this older cohort.

2.4 Patient Prosthesis Mismatch (PPM)

The benefit of a prosthetic aortic valve depends on effective relief of left ventricular (LV) outflow obstruction as well as being competent so as not to cause AR. Unfortunately, all prosthetic valves have suboptimal haemodynamics when compared to a normal native valve, with the prosthetic valve orifice area and transvalvular gradient dependent on factors both intrinsic to the prosthesis (such as design and size) and specific to each patient (such as body surface area).

2.4.1 Definition and Incidence of PPM

PPM occurs when an implanted aortic valve prosthesis has an orifice area which is less than that of the native aortic valve, thereby producing a gradient across the left ventricular outflow tract. It was described initially in 1978 by Rahimtoola and colleagues (Rahimtoola, 1978). PPM is defined by the indexed effective orifice area (iEOA) of the aortic valve prosthesis, i.e. EOA divided by the body surface area. This is then graded as mild (>0.85 cm^2/m^2), moderate (0.65-0.85 cm^2/m^2) or severe (<0.65 cm^2/m^2) (Pibarot *et al.*, 2000). In simplistic terms, the prosthetic valve is too small for the patient's body size.

Severity of PPM	Indexed Effective Orifice Area (iEOA) cm^2/m
Mild	>0.85 cm^2/m^2
Moderate	0.65-0.85 cm^2/m^2
Severe	<0.65 cm^2/m^2

Table 3: Grading of PPM based on indexed effective orifice area, calculated from echocardiograpghy.

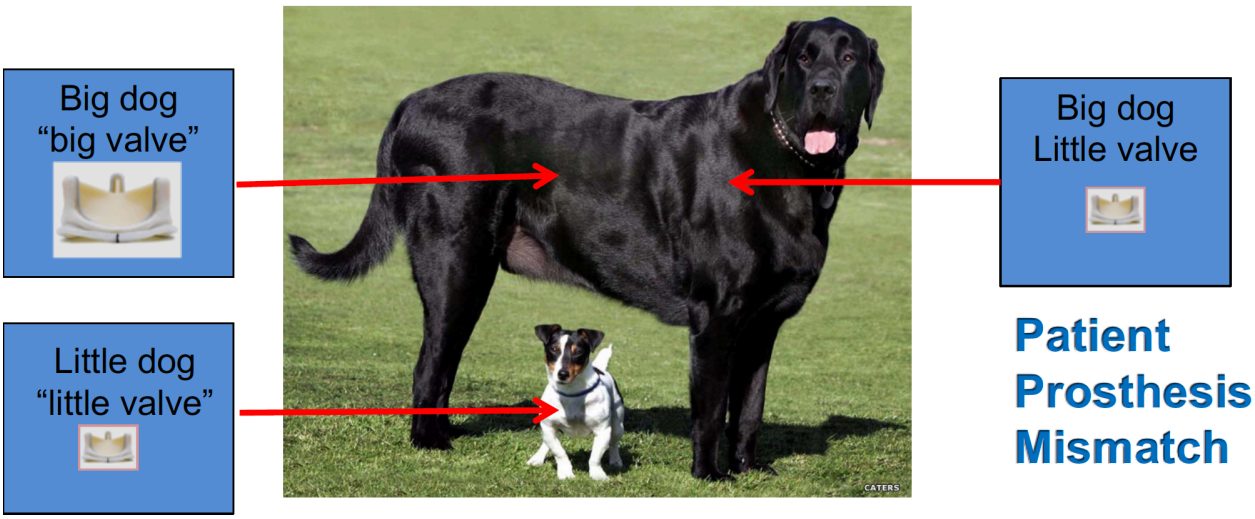


Figure 10: Illustration of why PPM occurs, i.e. where a valve that is too small for the size of the patient

The incidence of PPM after surgical AVR is unclear, with prevalence ranging from about 8 to almost 80% in individual studies, with an estimated overall prevalence of 44% based on a meta-analysis of 34 observational studies that included a total of 27,186 patients (Head *et al.*, 2012). The prevalence of severe PPM ranges from only 0.5% to as high as 62% with moderate PPM in 11% to 90% (Bilkhu, *et al.*, 2019). Despite this, the incidence of PPM appears to be reducing in more recent years, as evidenced in a recent study (Fallon *et al.*, 2018).

The prevalence of PPM and severe PPM is shown in Table 4. The reasons behind the wide variation in the prevalence of PPM may be related to differences in baseline characteristics of patients, for example, it may be reported more commonly in younger patients (Mannacio *et al.*, 2016). Also, there may be variability in the diagnosis of PPM as many people despite having a transvalvular gradient may not present with symptoms. This variation in prevalence adds further question to the clinical impact of PPM.

Study	N	Mean/Median Age PPM Group	Mean/Median Age No PPM	% Male	Prevalence of any degree of PPM (%)	Prevalence of Severe PPM (%)
Yap *et al.*, 2007	701	70.7±10.3		61.5	NR	46 (6.6%)
Nozohoor *et al.*, 2010	230	68.6 ± 11	56.5 ± 13	NR	51 (22.2%)	6/51 (2.2%)
Hernández-Vaquero *et al.*, 2012	199	61 (56-66)	64 (57-68)	45.5 PPM 70.5 no PPM	61 (30.7%)	6/61 (9.8%)
Tully *et al.*, 2013	1060	NR	NR		532 (50.2%)	92/532 (8.7%)
Kaminishi *et al.*, 2013	3609	70 ± 10	68 ± 12	49 PPM 54.4 no PPM	306 (8.5%)	NR
Hong *et al.*, 2013	351	NR	56 ± 11.7	61.2 no PPM	127/351 (36.2%)	36/127 (28.3%)
Price *et al.*, 2014	707	NR	NR		299 (42.3%)	66/707 (9.3%)
Dayan *et al.*, 2015	2023	72.3 ± 8.2	61.6 ± 12.6	35.1 PPM, 65.9 no PPM	715 (64.6%)	57/715 (61.8%)
Mannacio *et al.*, 2016	3082	66.8 ± 12.3	66.6 ± 11.4		2404 (78.5%)	239/2404 (11%)
Swinkels *et al.*, 2016	673	64.0 ± 10.9	68.3 ± 9.6	42.9 PPM, 61.8 no PPM	163 (24.2%)	NR
Sportelli *et al.*, 2016	152	79.9 ± 0.36	81.4 ± 0.39	15 PPM, 28% no PPM	78 (53.8%)	17/78 (11.7%)
Kindo *et al.*, 2017	183	76 ± 6.7	71.7 ± 11.0	39.2 PPM, 59.8 no PPM	51 (27.9%)	1.6%
Guo *et al.*, 2017	869	64 (55-69)	56 (47-62)	41 PPM, 54 no PPM	138 (15.9%)	4/138 (0.5%)
Mannacio *et al.*, 2017	376	66.8 ± 7.8	64.4 ± 8.4	All male	295/376 (78.5%)	35/295 (9.3%)
Fallon *et al.*, 2018	59,779	77 moderate 75 severe	77	51.5% overall	38,726 (64.8%)	6483/38,726 (16.7%)

PPM, patient prosthesis mismatch; NR, not reported

Table 4: Prevalence of PPM in published series

2.4.2 Diagnosis of PPM

The diagnosis of PPM is based on echocardiographic findings. Echocardiography is recommended early after AVR as this provides important baseline valve haemodynamics at a time when valve deterioration has not yet occurred and to which later echocardiographic assessments can be compared.

PPM is diagnosed by calculation of the iEOA, with the standard definitions of its severity as described in the previous section. This is derived from the continuity equation:

AVA = LVOT CSA x LVOT VTI/AV VTI

AVA=aortic valve area, or effective orifice area; LVOT =left ventricular outflow tract; CSA=cross sectional area; VTI=velocity time integral

Whilst this is the most commonly reported measurement in the literature relating to PPM, some have argued that this may not be the most accurate in defining the true orifice area of the valve, as the LVOT diameter may influence the derived valve area (Amorim *et al.*, 2020). The following diagram demonstrates how the EOA of a prosthetic valve, derived using the continuity equation, may be influenced by the LVOT diameter.

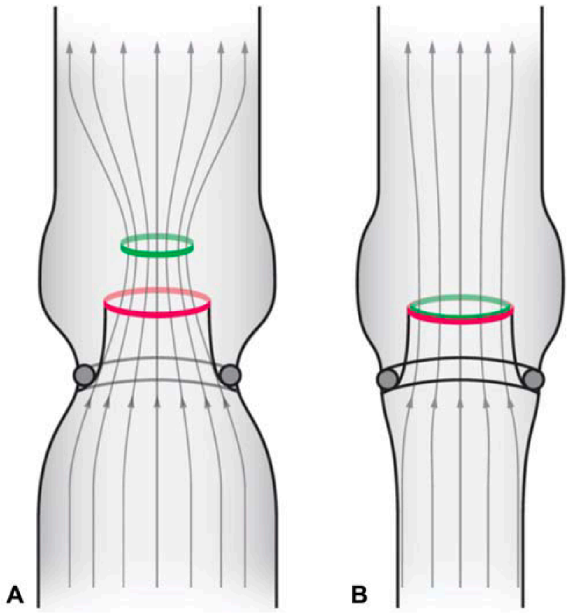


Figure 11: Two identical bioprosthetic valves implanted into two anatomically different aortic roots. The EOA (red circle) is smaller than the geometric opening area, (green circle) in panel (A) and equal to the GOA in panel (B) (Amorim et al., 2020).

The above figure demonstrates that whilst the prosthetic valve orifice area may be the same, differences in the LVOT would alter the LVOT component of the continuity component and as such produce a different derived EOA.

Other methods of assessing the prosthetic aortic valve include fluoroscopy, but also cardiac MRI and multidimensional (4D) CT (Suchá *et al.*, 2015). A limitation of the assessment of the prosthetic aortic valve with standard transthoracic echo is that there is suboptimal visualisation of the valve leaflets, which may be related to acoustic shadowing from the valve structure. However, for the diagnosis of PPM to be accurately made, accurate assessment of the valve leaflets is important given that in patients with PPM, the leaflet morphology and the leaflet motion are usually normal (Pibarot *et al.*, 2019). Multidimensional CT is emerging as a clinically useful tool in the assessment of prosthetic valve function as it has the advantage of

being able to assess the leaflet mobility in either mechanical or bioprosthetic valves; can help exclude other causes of high transvalvular gradient such as pannus or thrombosis and is also able to detect calcification of a bioprosthesis (Cianciulli *et al.*, 2005; Chakravarty *et al.*, 2017; Pibarot *et al.*, 2019).

Regardless of imaging modality used to make the diagnosis of PPM, it should be considered in patients with persistent symptoms after AVR. This is particularly true if there is a high gradient and small iEOA on the early post-operative study, however it is important to note that it is possible this can be over-diagnosed in the post-operative period. A high transaortic velocity and transvalvular gradient may be present without PPM in patients with a high cardiac output; for example, in patients with anaemia, which is relatively common following cardiac surgery. High velocities may also be seen with bileaflet mechanical valves due to local flow acceleration in the narrow central slit-like orifice (Mahjoub H, Dahou A, 2017).

Diagnosis of PPM can be somewhat more challenging in patients presenting with symptoms months or years after AVR because a high gradient and small orifice area may be due to valve thrombosis, fibrosis, calcification, subaortic membrane or pannus formation, rather than to PPM. The first step in evaluation is comparison of the latest echo study to the early post-operative one to determine if there has been any deterioration in valve function over time. As the symptoms of PPM are non-specific, it is important to search for other causes of symptoms, including coronary artery disease, because symptoms of PPM are non-specific, and most patients have multiple comorbidities.

2.4.3 The Clinical Impact of PPM

The clinical impact of PPM is unclear (David, 2005). A number of recent studies have demonstrated no significant difference in early postoperative complications between those with and without PPM (Yap *et al.*, 2007; Hong *et al.*, 2013; Tully *et al.*, 2013; Guo *et al.*, 2017; Kindo *et al.*, 2017). However, some groups report a higher incidence of perioperative stroke in those with any degree of PPM, with one study showing an incidence of peri-operative stroke in those with versus without PPM (3.9% vs 2.4%, p=0.02) (Dayan *et al.*, 2015). A higher incidence of renal failure in patients with PPM has also been reported (Nozohoor *et al.*, 2010; Dayan *et al.*, 2015; Dahou *et al.*, 2016). One study (Kaminishi *et al.*, 2013) has reported a longer ventilation time and ICU stay in patients with PPM. Inotrope requirement was noted to be higher in those with PPM in one study (Nozohoor *et al.*, 2010). Patients with AS undergoing AVR tend to be older and have multiple comorbidities and those likely to have PPM often have a smaller body size. Thus, it remains unclear whether the possible higher rate of postoperative complications is due to PPM itself or is simply a surrogate marker of co-morbidity and a more complex patient.

In terms of late outcomes, physiologically, there is concern that the degree of residual LV outflow obstruction after AVR in patients with PPM will result in persistent LV hypertrophy, which might result in clinical symptoms due to diastolic or systolic dysfunction over time and myocardial fibrosis. A number of studies have shown less regression of LV mass in those with PPM (Bilkhu, *et al.*, 2019). The effect of PPM on LV mass regression seems to show a dose-response relationship – greater degrees of PPM are associated with greater persistence of LV hypertrophy. Although, LV mass regression is predictive of improved long term survival, particularly when mass regression is greater than 150g (Ali *et al.*, 2011), further studies are needed to determine if LV mass regression independently predicts prognosis or if it is a marker

of more severe co-morbidities. Whether the lack of LV mass regression has an impact on myocardial fibrosis also has not been investigated.

Early mortality after AVR does not appear to be related to the presence of PPM but there may be some effect on long-term mortality The data on PPM and late mortality is only convincing for patients younger than the age of 70, those with a smaller body size (< 30 kg/m2) or those with a lower ejection fraction (<50%) (Dayan *et al.*, 2016; Bilkhu, *et al.*, 2019). In a study by Mannacio and colleagues, they found no significant difference in early mortality in those with and those without severe PPM, however at follow up at 5 and 10 years, mortality was greater in those with severe PPM (Mannacio *et al.*, 2016). In a recent meta-analysis of 58 reports, any degree of PPM, up to moderate degree was associated with a one and a half times increased risk of early mortality and in patients with severe PPM, mortality was increased two and a half times (Dayan *et al.*, 2016). The trend towards lower survival was noted to continue during follow up, with late mortality being higher in those with severe PPM.

Another outcome to consider is re-intervention for PPM. However, this relies on the diagnosis of PPM being made correctly in the first instance. Also, using reintervention as an outcome measure can be counter-intuitive as patients may be too high risk for or refuse a second aortic valve procedure. There is therefore no clear data to suggest whether there is a higher incidence of reintervention in patients with PPM. There are very few reported series of patients undergoing re-operation purely for PPM. One group have reported on 21 patients who have undergone reoperation for PPM (Girard *et al.*, 2001). Whilst they have demonstrated excellent results with no mortality, cardiac re-operation is not without risk. In addition, 8 of the patients who underwent reoperation required concomitant surgery and so it may be that this cohort did

not include patients with PPM only and the indication for surgery may have been something else such as coronary artery disease.

2.4.4 Prevention is better than cure

To prevent PPM, it is of course important to recognise those who are at risk. Female sex is a strong clinical predictor of PPM after AVR, likely reflecting the smaller annulus area in women, making implantation of an adequately sized valve challenging. In addition, older age, hypertension, diabetes, renal failure and a higher surgical risk score predict likelihood of PPM. The association of PPM with adverse clinical outcomes is most evident in younger patients and in those with LV systolic dysfunction (Tully *et al.*, 2013).

The effective orifice size of a prosthetic valve is smaller than the sewing ring size due to the valve design and normal tapering of the flow stream as it passes through a prosthetic valve orifice (Mahjoub H, Dahou A, 2017). Effective orifice area for a given valve type and size can be calculated, and then indexed for patient body surface area, using data provided by the valve manufacturer. Calculation of the expected orifice area before implantation accurately identifies patients at risk of PPM and offers an opportunity to consider alternate approaches to prevent PPM (Pibarot *et al.*, 2001).

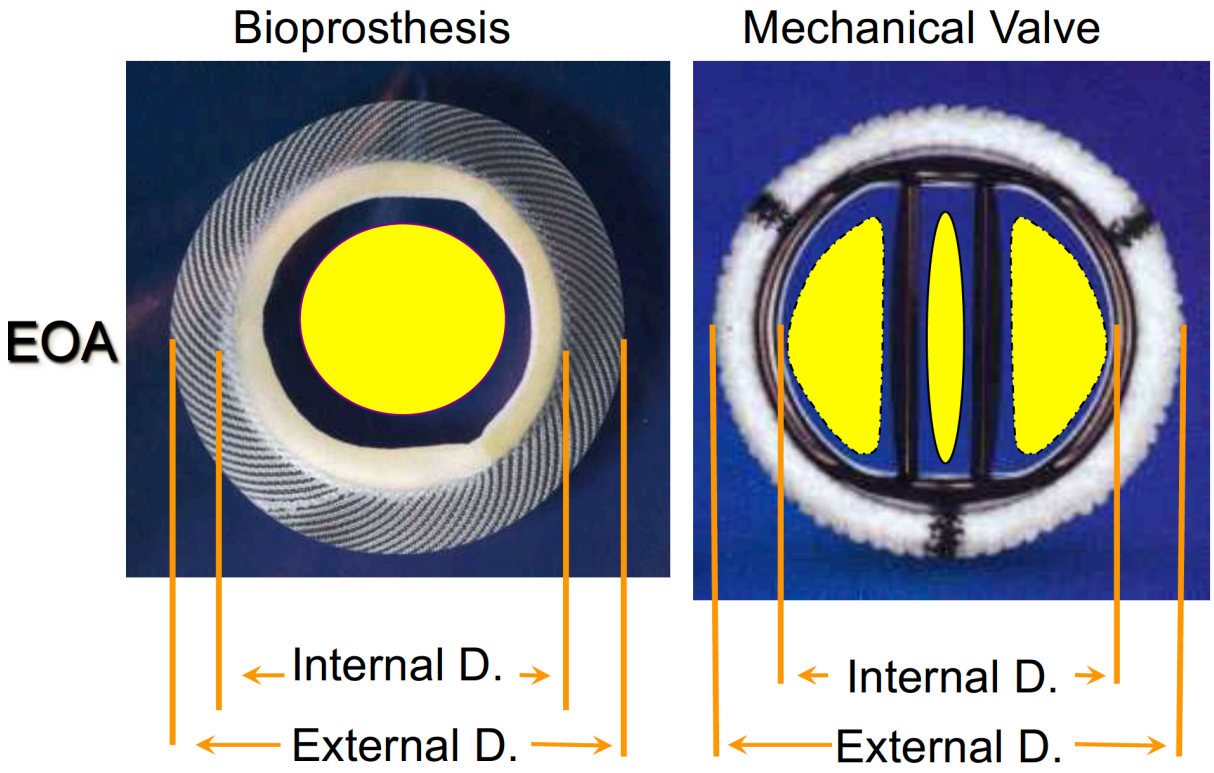


Figure 12: Geometric orifice area (external diameter) of prosthetic valve versus the effective orifice area (internal diameter) (Pibarot et al., 2006).

The following tables detail the internal and external diameters of commonly use prostheses as well as the effective orifice area of each valve and demonstrates that not all valves

Valve Type	Internal/External Diameter by Valve Size (mm)				
	19	21	23	25	27
Bioprosthetic (Stented)					
Edwards Magna Ease	18/24	20/26	22/28	24/30	26/32
Edwards Perimount	18/26	20/26	22/31	24/32	26/35
St Jude Trifecta	19/24	21/26	23/28	25/31	27/33
Medtronic Mosaic (porcine)	17.5/25	18.5/27	20.5/30	22.5/33	24/36
St Jude Epic (porcine)	19/25	19/25	21/27	23/29	25/31
Bioprosthetic (Stentless)					
Medtronic Freestyle	19±0.5/19	21±0.5/21	23±0.5/23	25±0.5/25	27±0.5/27
Bioprosthetic (Rapid Deployment/Sutureless)					
Edwards Intuity	18/24	20/26	22/28	24/30	26/32
LivaNova Perceval	NP	NP	NP	NP	NP
Mechanical					
Medtronic ATS	14.8/19.5	16.8/21.5	18.8/23.5	20.8/25.5	22.8/27.5
CryoLife On-X	17.4/27	19.4/30	21.4/33	23.4/34	23.4/36
St Jude Master	14.8/	16.7/	18.6/	20.4/	22.5/

Table 5: Effective orifice area by valve size, based on data available from valve manufacturers. NP; data not provided by manufacturer

Valve Type	Effective Orifice Area (cm^2) by Valve Size (mm)				
	19	21	23	25	27
Bioprosthetic					
Edwards Magna Ease	1.58	1.90	2.07	2.33	-
Edwards Perimount	1.3	1.3	1.6	1.6	-
Medtronic Mosaic	NP	1.4	1.5	1.8	-
St Jude Trifecta	1.75	NP	NP	3.4	-
Medtronic Freestyle	1.1	1.4	1.7	2.1	2.5
Mechanical					
Medtronic ATS	1.1	1.4	1.7	2.1	2.5
CryoLife On-X	2.28	2.84	3.44	4.11	4.11
St Jude Master	1.63	2.06	2.55	3.09	3.67

Table 6: Internal and external diameters of aortic valve prostheses by manufacturer and model. NP; data not provided by manufacturer

A smartphone application (Cardio Valve, Digimednet™) is available which allows the user to calculate the predicted indexed effective orifice area of individual prosthetic valves and identify the minimum size of prosthesis required to avoid PPM.

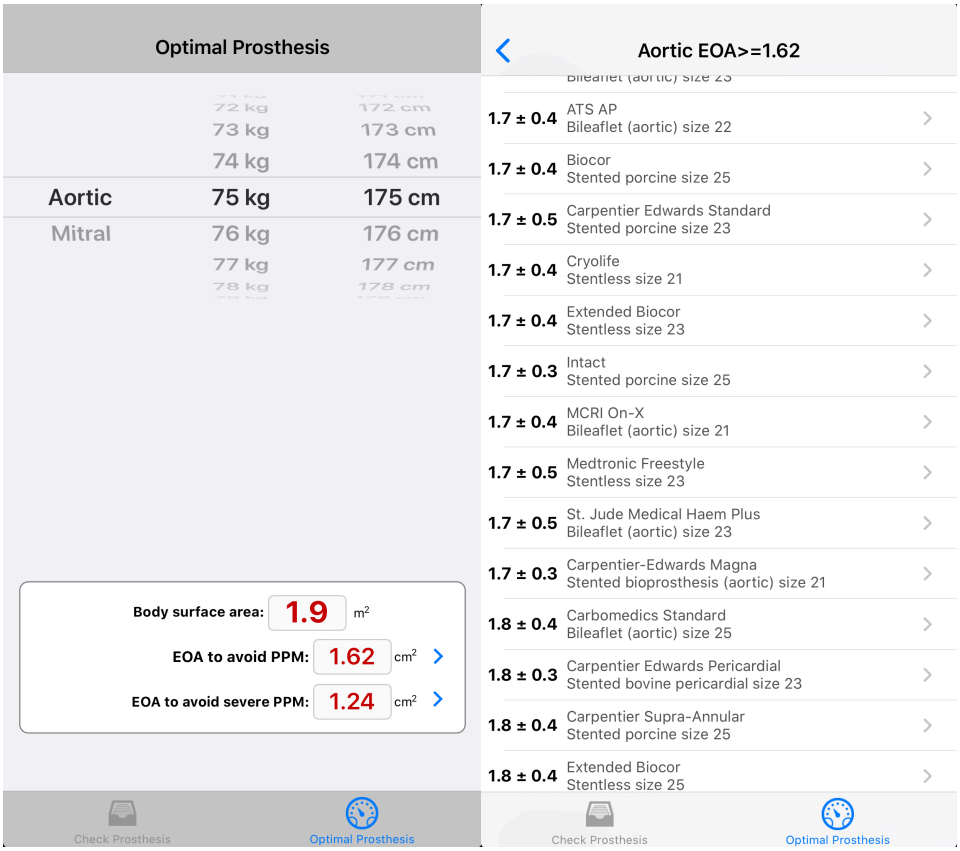


Figure 13: Calculation of predicted iEOA and suggestion of prosthesis to avoid PPM using Cardio Valve Smartphone App.

Given the availability of data from valve manufacturers, and the ease with which PPM can be predicted, the routine prediction of iEOA would seem appropriate, particularly in those patients who are identified to be at risk of PPM and especially severe PPM.

2.4.5.1 Surgical options for prevention of PPM

Modern pericardial bioprosthetic valves have been modified in their design to allow for placement of a larger bioprosthesis and avoid a high gradient across the valve (Botzenhardt *et al.*, 2005). Some bioprosthetic valves are now designed with a lower profile to sit in a supra-annular position, which allows a larger valve size to be implanted. These valves have demonstrated good outcomes with low incidence of PPM during follow up with no patients with severe PPM (Kume *et al.*, 2017). In addition to lower profile supra-annular valves, stentless valves have also been proposed as a means of reducing the incidence of PPM, particularly in those with small aortic roots (Wollersheim *et al.*, 2016).

Recently, the use of sutureless valves has gained popularity, mainly for the advantages of marginal reductions in operative time, and for use in patients with small aortic roots. Some advocate sutureless valves in patients with a small aortic root to allow the placement of a larger bioprosthesis and therefore avoid PPM (Meco *et al.*, 2018). By avoiding the placement of sutures, and sutures with pledgets in the annulus it is postulated that a larger valve size relative to the aortic root size may be implanted. However, there is concern that sutureless valves may be associated with more conduction disorders and paravalvular leaks (Meco *et al.*, 2018; Bilkhu *et al.*, 2019).

Regardless of the type of valve used and how it is implanted, the simplest method of preventing PPM is to choose the right valve and place as large a prosthesis as possible, in relation to the aortic annulus. This should mean that in the case of AS, the valve should only be sized once the annulus has been carefully and thoroughly debrided of calcium so as to ensure as large a valve as possible is implanted. The incidence of PPM has been shown to be lower in those with aortic insufficiency as the primary pathology as opposed to those with aortic stenosis or mixed

aortic valve disease, and this may be related to the limited amount of debridement of the annulus that is required in patients with AR only (Price *et al.*, 2009).

Care should be taken so as not to oversize the valve in order to avoid PPM. A study which looked at placing an oversized bioprosthesis in an in vitro model demonstrated reduced haemodynamic valve performance (Cleveland *et al.*, 2016), possibly related to abnormal stresses around the hinge point of each leaflet, causing the hinge point to be shifted inwards and reducing the EOA of the valve.

Another approach in the prevention of PPM is enlargement of the aortic root to allow the placement of a larger prosthesis, of which there are a number of different surgical techniques. Unfortunately, annular enlarging procedures add extra operative time and in particular, longer cardiopulmonary bypass and aortic cross clamp times, which may negatively impact outcomes following surgery (Salis *et al.*, 2008). They also add to the complexity of the procedure, although some groups have reported that aortic root enlargement can be performed with low operative risk (Kulik *et al.*, 2008). The same group however noted that enlargement of the aortic root does not appear to translate into improved long-term clinical outcomes.

The Ross Procedure, which has been described earlier in this chapter, may be considered, particularly in younger patients as risk of PPM, because the native pulmonic valve has excellent haemodynamics when it has been placed in the aortic position. A recent meta-analysis supports superior haemodynamics of the pulmonic autograft procedure over conventional AVR (Um *et al.*, 2018). However, the advantages of excellent haemodynamics and avoidance of anticoagulation, may be outweighed by the complexity of the operation with 2 valve replacements and the long-term risk of deterioration of the pulmonic valve homograft in

addition to the pulmonic autograft in the aortic position (Vojáček *et al.*, 2017). In addition, the neo-aortic root is at risk of progressive dilation, requiring re-intervention in a subset of patients given the fact the pulmonary valve is normally exposed to a lower pressure system.

2.4.5.2 TAVI to prevent PPM

In older adults, it has been suggested that TAVI may be considered to avoid PPM (Bilkhu, *et al.*, 2019). In a meta-analysis, which included 4000 patients, rates of PPM appeared to be lower in patients undergoing TAVI compared to surgical AVR (Pibarot *et al.*, 2014; Takagi *et al.*, 2016), with the authors concluding that the incidence of severe PPM following TAVI in only about 8% (Takagi *et al.*, 2016). Although this review did not show an impact of PPM on long term survival, this may be due to the patients undergoing TAVI being generally older and more frail. Of course, the disadvantages of TAVI, such as paravalvular regurgitation that has been mentioned already, might offset any beneficial effect of less PPM on LV mass regression and survival (Pibarot *et al.*, 2014). In addition, we have robust data on TAVI durability only up to 5 years (Foroutan *et al.*, 2017), so it is premature to advocate the use of TAVI to prevent PPM, particularly in younger patients given the durability of modern surgical bioprosthetic valves (Foroutan *et al.*, 2016).

Overall, the prevention of PPM can be summarised in the following algorithm (Figure 8).

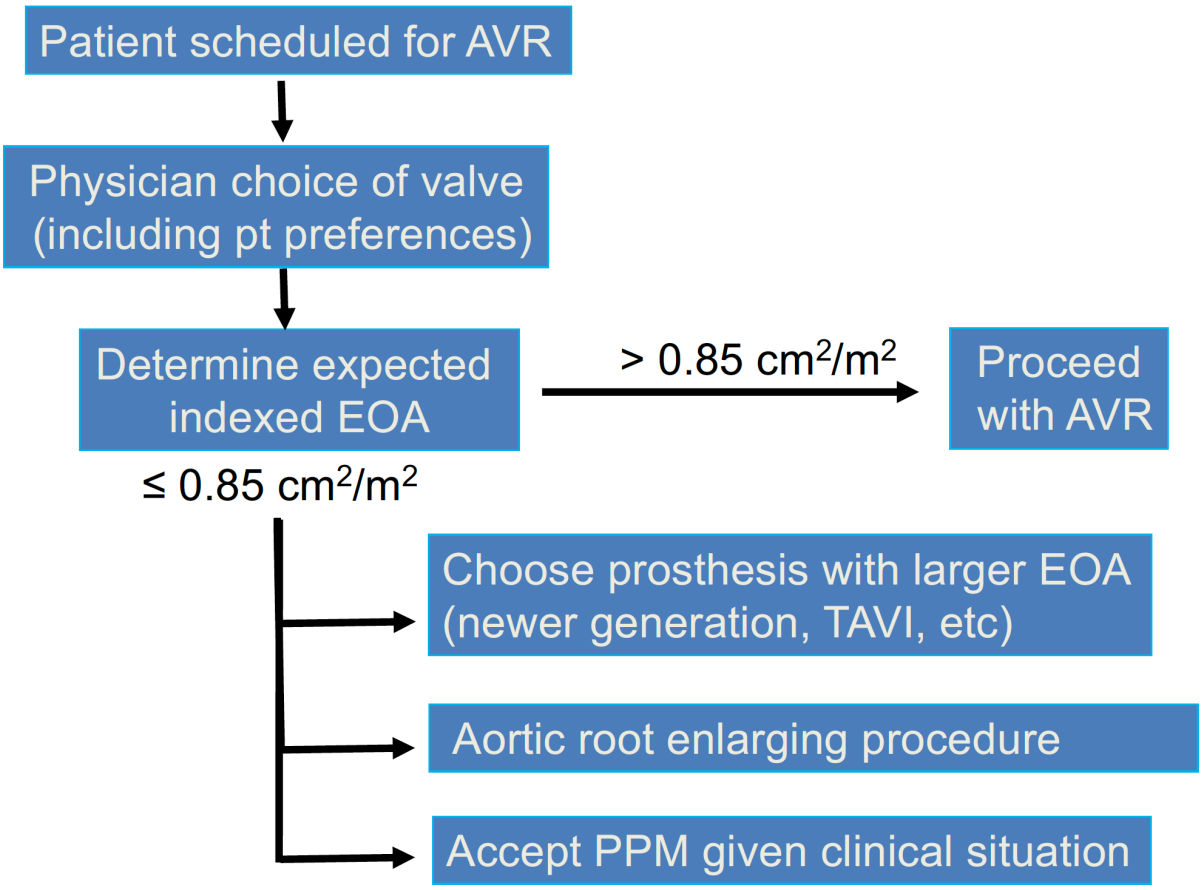


Figure 14: Prevention of PPM when planning AVR.

In general, the impact of postoperative aortic valve gradient and PPM on patient quality of life (QOL) compared to preoperative QOL is not well established, nor is its impact on recovery following surgery. It may be that placement of an appropriately sized prosthesis for the patient's body surface area, without performing additional procedures on the aortic root to insert a prosthesis as large as possible, has no significant impact on outcomes and QOL, even if there is a residual gradient following valve implantation. Patients with AS, even with aortic

valve gradient >40mmHg may not have symptoms until late in the disease. Therefore, even if the patient is reported to have a high post-operative gradient, this may not necessarily translate into symptoms, however, PPM may be considered when a postoperative patient presents with symptoms but only when other causes of symptoms have been excluded, such as symptoms related to anaemia or lung disease for example.

With this in mind, it may be that replacement of the aortic valve and reduction in the gradient may be all that is required for the patient to have a good QOL outcome following surgery.

2.5 Quality of Life following Cardiac Surgery and PPM

The number of patients with higher risks undergoing major cardiac surgery in UK has increased by approximately 5-18% in the last 5 years (The Society for Cardiothoracic Surgery in Great Britain & Ireland, 2018). Changing population demographics, for example, an increase in incidence and impact of obesity, and patient's expectations of better QOL with greater access to treatment are factors influencing management of cardiac conditions. Presence of significant co-morbidities and advanced age at surgery, increase risk of morbidity and mortality.

The World Health Organisation (WHO) has defined health as being "not only the absence of disease and infirmity but also the presence of physical, mental, and social well-being". To capture this concept, QOL has become an increasingly important concept in health care, because it reflects not only objective clinical or physiologic status, but the patients' subjective perception about the impact of a clinical condition on their lives (Perrotti *et al.*, 2019). As such, the assessment of QOL after medical interventions has largely been based on the use of questionnaires.

A number of assessment tools and questionnaires exist. Each of these contain questions divided into groups or domains and are designed to assess specific problems that may have an impact on health and wellbeing. The World Health Organization Quality of Life Assessment (WHOQOL), Medical Outcomes Study 36-Item Short Form (SF-36), and 12-Item Short-Form Health Survey (SF-12) are among the most widely used instruments for assessing QOL (Pequeno *et al.*, 2020).

The WHOQOL assesses individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a 100-question assessment that currently exists indirectly comparable forms in 29 language versions. It yields a multi-dimensional profile of scores across domains and sub-domains (facets) of quality of life (Nakane *et al.*, 1999). This questionnaire is predominantly used in non physical conditions and not used after surgical or cardiac interventions.

Given that QOL is a complex concept, which is interpreted and defined in different ways between different specialties in medicine, many different instruments are now used to assess QOL (Haraldstad *et al.*, 2019). SF-36 and SF-12 both have the advantages of being easy to use and can also be completed quickly. As a result, they are commonly used in studies where there are large study groups, as has been demonstrated in a systematic review by Pequeno and colleagues (Pequeno *et al.*, 2020). They have also been used widely in cardiovascular research (Ware *et al.*, 1992). The use of SF-36 in the current study will be detailed in the methodology section.

There have been marked improvements in mortality following cardiac surgery and as a result, focus is now being placed on other outcomes of surgery. An example of this is QOL (Bridgewater *et al.*, 2008; Deschka *et al.*, 2013). Indeed, in the American College of Cardiology and American Heart Association guideline for coronary artery bypass graft surgery, QOL is considered to be an important outcome measure (Eagle *et al.*, 2004). With increasing age and comorbidity of patients undergoing cardiac surgery, this increased focus is justified.

Whilst there have been a number of studies assessing QOL following cardiac surgery, there have been limited studies assessing QOL at baseline and then prospectively. The methods of assessing QOL also vary between previously published studies (Ryomoto *et al.*, 2008; Sportelli *et al.*, 2016; Swinkels *et al.*, 2016; Reskovic Luksic *et al.*, 2017).

Additionally, there have been limited studies assessing the impact of PPM on QOL. The impact of PPM on QOL is challenging to study in elderly patients who have undergone AVR and have multiple causes of symptoms. However, studies to date have shown no statistically significant different in QOL between those with and without PPM, using various methods to measure QOL (Ryomoto *et al.*, 2008; Sportelli *et al.*, 2016; Swinkels *et al.*, 2016; Reskovic Luksic *et al.*, 2017). However, none of these have assessed QOL at baseline and compared this to QOL at follow up and whether or not this varies with degree of PPM or post operative valve gradient.

3. Aims and Hypotheses

Primary Aims

1. To assess QOL outcomes following SAVR.

2. To assess the impact of patient prosthesis mismatch (PPM) on QOL.

Secondary Aims

1. To assess the clinical outcomes of patients undergoing surgical AVR and the impact of PPM on morbidity and mortality.

Hypothesis

In patients undergoing surgical AVR:

- There are improved reported QOL outcomes, in both physical and mental domains
- PPM is not associated with patient reported QOL, unless it is severe
- Clinical outcomes are not related to PPM except in those patients with poor preoperative left ventricular function
- Patients above the age of 75 achieve a good postoperative QOL

4. Methodology

4 Methodology

4.1 Research Group

The research group was comprised of myself, another research fellow (Mr Mohammad Diab, MD), 1 research assistant and 2 internal supervisors (Professor Marjan Jahangiri and Mr Justin Nowell, St George's University of London). Advice and guidance relating to cardiac imaging and echocardiography was provided by Dr Rajan Sharma, Consultant Cardiologist and Lead Cardiac Imaging Consultant, St George's Hopsital, London).

4.2 Study Design

This is a longitudinal, prospective, observational case-control study of outcomes in patients undergoing surgical AVR and its impact on QOL, with particular reference to the impact of PPM on QOL.

4.3 Study Population

Over a 2 year period (2013-2015), consecutive patients undergoing surgical AVR ± CABG at St George's Hospital were included. Patients undergoing AVR and any other concomitant procedure were excluded.

Patients were targeted mainly from South West London and the surrounding areas. Patients who were undergoing surgery at St George's Hospital were approached upon admission and therefore this means that all patients referred for the surgery detailed above were invited to participate in the study.

4.4 Ethical considerations

National Ethical (REC Reference: 12/SW/0283) and local R&D (JRO Reference: 12.0159) approvals were obtained for the assessment of QOL following cardiac surgery. Patients received a full explanation of the study, their involvement, and were given an information sheet in relation to the assessment of quality of life following cardiac surgery. Written informed consent was obtained.

All data have been handled in accordance with the Data Protection Act 1998. To maintain confidentiality, all patients were given a unique study participation number on their agreement to take part in the study. This number was detailed on the consent form form and also used on the electronic database.

All the preoperative assessments and completion of questionnaires were performed in a quiet and relaxed area within the cardiac surgical ward. Follow up appointments took place in a designated, confidential, clinical room within the University campus, at a time convenient for the patient.

4.5.1 Inclusion Criteria

Both male and female patients undergoing surgical AVR ± CABG during the study period were recruited. All prospective participants were over the age of eighteen at the time of invitation to the study. There was no upper age limit. Those who might have had problems filling in the questionnaires were aided in completing the questionnaires if they wished to participate.

Conscious patients undergoing elective, urgent (in patient, during the same hospital admission) and emergency (within 24 hours of admission, where the patient is not in extremis) surgery were invited to participate.

4.5.2 Exclusion Criteria

Patients who refused to participate, those who were unable to consent, patients who were in extremis and unable to participate, and those who were found to have a language barrier were excluded from the study. In addition, those who underwent concomitant surgery in addition to CABG were not included.

4.6 Data Collection

Demographic and operative data for all included patients was prospectively collected from the St. George's Hospital electronic database, clinical notes and directly from the patients at the time of admission to hospital, prior to surgery.

Data on complications and clinical outcomes was recorded during the hospital stay, at 3, 6 and 12 months following surgery and will be detailed later in the chapter. Specific data definitions used are in accordance with the Valve Academic Research Consortium (VARC) definitions (Kappetein *et al.*, 2012). Index hospital stay and all readmissions were also recorded.

The following describes all pre and postoperative data which was collected. Thereafter follows a description of the specific tools used to assess QOL after surgery.

4.6.1 Patient Related and Demographic Factors at Baseline

The following demographic and patient related factors were collected at baseline: gender (% of female patients); age (% of patients above 75 years of age); body mass index; ethnicity; smoking history; pulmonary disease; extracardiac arteriopathy; neurological dysfunction; previous cardiac surgery; previous primary coronary intervention; previous myocardial infarction (MI) and duration of time since MI prior to surgery; the presence of left main stem coronary artery disease; left ventricular ejection fraction; aortic valve pathology (stenosis, regurgitation or mixed); New York Heart Association (NYHA) score renal dysfunction (in the form of chronic kidney disease and stage of chronic kidney disease); history of diabetes mellitus; history of peripheral vascular disease and pulmonary hypertension.

Table 7: Patient demographics and baseline clinical characteristics

Gender (% of female patients)	Left ventricular ejection fraction (LVEF)
Age (% of patients above 75 years of age)	Good (LVEF >50%)
Body mass index	Moderate (LVEF 31-50%)
Body surface area	Poor (LVEF 21-30%)
Ethnicity	Very Poor (LVEF <20%)
Smoking history	Aortic valve disease
Pulmonary disease	Stenosis
Extracardiac arteriopathy	Regurgitation
Neurological dysfunction	Mixed
Previous cardiac surgery	New York Heart Association (NYHA) score
Previous primary coronary intervention	I
Previous myocardial infarction (MI)	II
Time since MI prior to surgery	III
Left main stem coronary artery disease	IV
Renal dysfunction	
Diabetes Mellitus	

4.6.2 Specific Baseline Echocardiographic Data

Pre-operative 2D echocardiographic data was prospectively collected on all patients. This included left ventricular function; the predominant aortic valve disease (AS, AR or mixed); aortic valve area; mean and peak aortic valve gradient; left ventricular outflow tract diameter; left ventricular end diastolic diameter (LVEDd); interventricular septal diameter at diastole (IVSd); posterior wall thickness at end diastole (PWD).

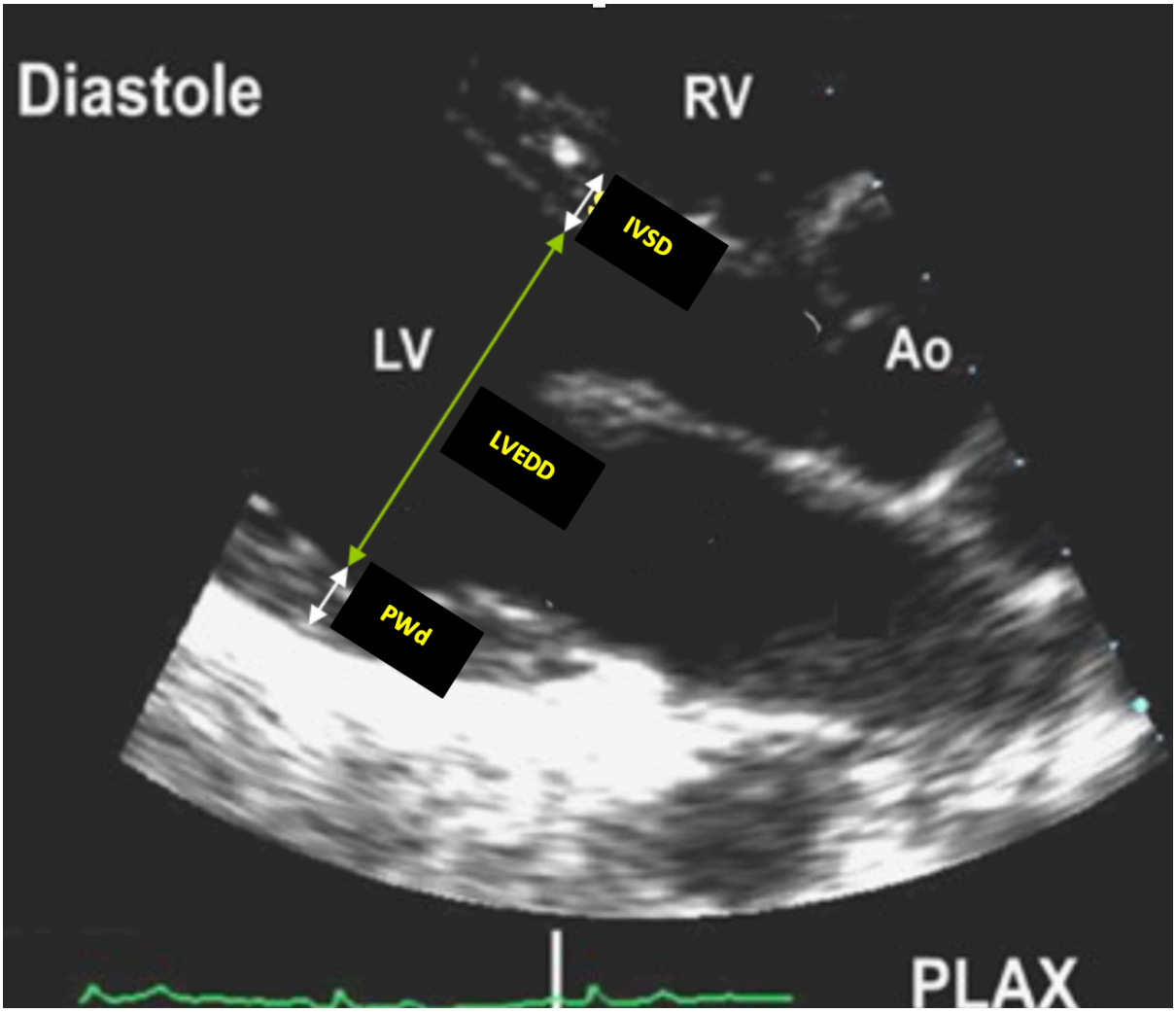


Figure 15: Measurement of LVEDd, IVSd, PWd from 2D echocardiography.

From these measurements of the LV cavity, the LV mass was estimated using the Devereux equation (Devereux *et al.*, 1986). The calculation for LV mass (g) is as follows:

$$\textbf{LV mass} = 0.8((1.04([\textbf{LVEDd} + \textbf{IVSd} + \textbf{PWd}]^3 - \textbf{LVEDd}^3)) + 0.6$$

The calculated LV mass is then indexed to body surface area and adjusted for gender. Whilst this may not be the most accurate measurement of LV mass, it is the most commonly used method in the literature and in clinical practice. This is mainly due to the ease of calculation

from transthoracic echocardiography. It has also been demonstrated to correlate with post mortem assessment of LV mass (Devereux *et al.*, 1986).

The dimensions required from echocardiography in order to calculate LV mass can be obtained using either M-mode or 2D echo. The advantage of M mode in the assessment of LV mass is the better endocardial border definition, which may result in less inter-observer variability, which may result in inaccuracies in the final calculated LV mass (Foppa *et al.*, 2005).

Cardiac MRI provides the most accurate measurement of LV mass (Myerson *et al.*, 2002; Armstrong *et al.*, 2012). Previously, echocardiography was the prime imaging modality for assessing LV mass, however, has the disadvantage of being operator dependent. Cardiac MRI however can provide a high resolution 3D model of the LV and provides highly accurate assessment of LV mass in both long and short axes (Armstrong *et al.*, 2012). The most commonly used method of assessing LV mass using MRI involves using a set of slices in short axis acquired from cine sequence. Whilst there is a high correlation between measurement of LV mass with cardiac MRI to measurement of LV mass using echocardiographic methods, there is a degree of difference in terms of the absolute valves of LV mass obtained between the two methods (Armstrong *et al.*, 2012). The use of echocardiography, as already mentioned, has been demonstrated to correlate well with necropsy findings of LV mass and given its availability compared to MRI, the practicality of performing echocardiography versus MRI as well as cost, I felt that echocardiography is an appropriate method for the assessment of LV mass regression in the current study.

Other methods include radioisotope gated myocardial perfusion scanning with technetium and CT scanning, the latter having demonstrated good correlation with LV mass necropsy findings (Foppa *et al.*, 2005).

As mentioned in the introduction, one of the sequelae of PPM is thought to be the impairment of LV mass regression and therefore baseline assessment of LV mass is vital to understanding of the effect of AVR on the myocardium.

4.6.3 Operative Details

Operative data was collected. This included the urgency of the operation, based on the definitions described earlier in the chapter, and the type of operation (AVR + CABG or AVR alone). Data collected also included cardiopulmonary bypass (CPB) and cross clamp time (CCT).

Specific data relating to the operation of AVR were also collected and this included the type of prosthesis (mechanical or biological), size of the prosthesis and manufacturer and model of the prosthesis. In addition, the suturing type used to implant the valve was recorded, i.e. whether or not pledgeted sutures were used. There is some suggestion that the use of suture pledgets may reduce the diameter of the left ventricular outflow tract (LVOT) and therefore result in a higher post-operative transvalvular gradient (Kim *et al.*, 2020).

Table 8: Operative details

Date of surgery
Timing of surgery
Elective or urgent
Level of primary operator
Cross clamp time (CCT)
Cardiopulmonary bypass time (CPB)
Degree of hypothermia
CABG (performed or not)
Number of vessels grafted
Size of valve implanted

4.6.4 In Hospital Complications

In addition to perioperative mortality, the following in hospital postoperative data was collected relating to morbidity and complications: new neurological events (transient ischaemic attack or stroke); total ventilation time; total time requiring inotropes; the requirement for haemofiltration; resternotomy for bleeding; laparotomy; peripheral vascular complications; respiratory failure; post-operative new atrial fibrillation (AF); requirement for insertion of permanent pacemaker and sternal wound infection.

Complications were grouped as follows:

- **Respiratory:** postoperative mechanical ventilation for more than 24 hours or pneumonia (defined by the presence of pulmonary infiltrates with positive microbial culture)

- **Cardiac:** arrhythmia requiring cardioversion, either chemical or electrical; new conduction disturbance such as heart block; pulmonary oedema; myocardial infarction (defined by elevated cardiac biomarkers within 72 hours of the index procedure – 15 times the upper limit of normal for cardiac troponin or 5 times the upper limit of normal for creatine kinase MB) (Kappetein *et al.*, 2012)

- **Renal:** acute renal failure, defined by the KDIGO criteria:
  - ***Stage 1:*** serum creatinine 1.5-1.9 times baseline or (26.5 μmol/l) increase or urine output of <0.5 ml/kg/hour for more than 12 hours
  - ***Stage 2:*** serum creatinine 2.0-2.9 times baseline or urine output <0.5 ml/kg/hr for 12 hours or more
  - ***Stage 3:*** serum creatinine 3.0 times baseline or increase in creatinine of >353.6 μmol/l or initiation of renal replacement therapy or urine output <0.3 ml/kg/hr for 24 hours or more or anuria for 12 hours or more

- **Sepsis:** infection with positive microbial culture other than pneumonia

- **Neurological:** defined as a new central neurological deficit.
  - ***Stroke**:* a prolonged (>24 hour) permanent neurological deficit usually associated with abnormal imaging results on MRI or CT scans
  - ***Transient ischaemic attack:*** fully reversible symptoms of a short duration (<24hours), often with normal brain imaging.

- **Gastrointestinal:** occurrence of a postoperative gastrointestinal event such as bleeding, pancreatitis, ileus, bowel obstruction, mesenteric ischaemia or hepatic failure.

Table 9: In-Hospital Complications

New neurological events (transient ischaemic attack or stroke)
Total ventilation time (hours)
Total time requiring inotropes (hours)
Need for haemofiltration
Resternotomy for bleeding
Laparotomy
Peripheral vascular complications
Respiratory failure requiring prolonged ventilation/tracheostomy
Postoperative new atrial fibrillation
Requirement for insertion of permanent pacemaker
Deep sternal wound infection

4.6.5 Mortality

Mortality is a broad term and its definition has been revised and adapted to clinical studies. All-cause mortality has become the most commonly used definition in clinical studies. This is mainly related to the advantage that reporting of all-cause mortality reduces the risk of introducing bias. However, equally, as would be the case in this study, would result in the reporting of mortality which may not be related to cardiac or cardiovascular causes.

Therefore, mortality in this study was divided into cardiovascular and non-cardiovascular mortality, as per VARC criteria (Kappetein *et al.*, 2012):

- ***Cardiovascular mortality:***

  - Death due to a cardiac cause such as myocardial infarction, pericardial tamponade or cardiac failure
  - Death caused by non coronary vascular conditions such as stroke, pulmonary embolism, rupture of aortic aneurysm, aortic dissection
  - All cardiac procedure related deaths
  - Valve related deaths – structural (e.g. aortic stenosis) or non structural (e.g. infective endocarditis)
  - Sudden or unwitnessed death
  - Unknown cause of death

- ***Non-cardiovascular mortality:***

  - Death where the primary cause of death is related to other pathology, e.g. cancer.

4.7 Assessment of Quality of Life (QOL) using SF-36®

QOL was assessed using the SF-36 questionnaire.

The Short Form-36 (SF-36) questionnaire was introduced in 1990 and was revised in 1996. It has been validated for the assessment of health related QOL in the context of cardiovascular disease (Ware *et al.*, 1992). It is one of the most widely used generic measures of health-related QOL (Ware *et al.*, 1992). It has been shown to discriminate between subjects with different chronic conditions and between subjects with different severity levels of the same disease.

SF-36 consists of 36 questions covering 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health).

The 8 domains are as follows:

- **Physical functioning**: limitations in lifting, climbing, bending, kneeling, walking or running

- **Role physical**: degree of physical health to perform activities typical to the specific age and social responsibility, such as a job or community activities

- **Bodily pain**: relating to instensity of the pain and it's duration and limitations as a result of pain

- **General health**: the beliefs and evaluations of overall health

- **Vitality**: feelings of energy, fatigue and tiredness

- **Social functioning**: the ability to develop and maintain social relationships (family, friends, spouse)

- **Role emotional**: personal feelings about for example job performance or other daily activities

- **Mental health**: emotional, cognitive and intellectual status

Using bespoke software, the scores generated from these 8 domains are then summarised as physical and mental component summary scores (PCS and MCS respectively).

The population mean score for healthy UK population for the PCS and MCS is 50. The scores range from 0 to 100, with a higher score indicating a better QOL.

Whilst the SF-36 is a generic measure of health related QOL, it has been validated for QOL assessment in cardiovascular disease (Ware *et al.*, 1992).

The SF-36 questionnaire was given to the participants prior to surgery and at 6 and 12 months following discharge after surgery. The form takes approximately 10 minutes to complete and is available in multiple languages.

The SF-36 questionnaire that was administered to participants for completion is appended below.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

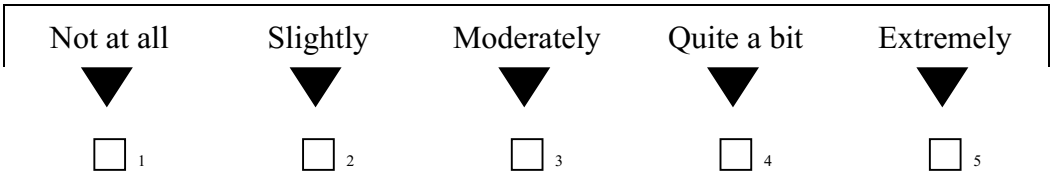
4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

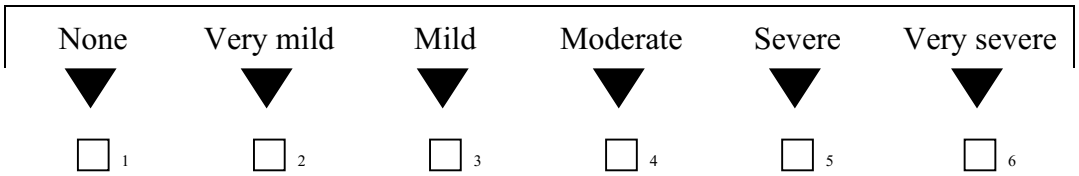
5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

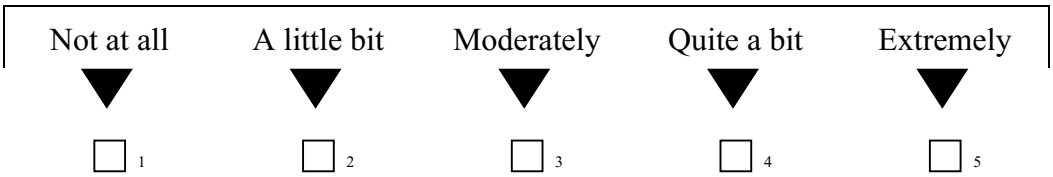
6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?



8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

4.8 Data Handling and Analysis

All data was stored using Microsoft Excel®. Anonymised data was imported to SPSS® (Statistical Package for Social Sciences, IBM, USA) version 26 for Mac and statistical analysis was performed using the same.

4.8 Operative Management

4.9.1 Anaesthesia

Premedication was administered with morphine and hyoscine. All patients had a central venous line and radial or femoral arterial line inserted prior to surgery. Anaesthesia was induced with either fentanyl, propofol and vecuronium or alfentanyl, propofol and pancuronium. Maintenance anaesthesia was provided with isoflourane and propofol.

Transoesophageal echocardiography (TOE) was performed for all cases. The specific utility of TOE in these cases was to guide the efficacy of de-airing procedures and to assess valvular and ventricular function following discontinuation from CPB.

4.9.2 Operative Technique

Surgical access was via median sternotomy or upper hemi sternotomy (mini sternotomy) into the right 4^{th} intercostal space in certain cases of isolated AVR. CPB was established after cannulating the ascending aorta and right atrium at 28-35^0C, dependent on surgical preference.

CPB was performed using a Medtronic Affinity NT® (Medtronic, Minneapolis, MN, USA) oxygenator, a LivaNova S5 Heart-Lung Machine® (LivaNova, London, UK) and a Medtronic

Affinity® arterial line filter (Medtronic, Minneapolis, MN, USA). Priming of the bypass circuit was performed using 1 litre of Hartmann's solution, 500mls of Ringer's lactate solution and 500mls of 10% Mannitol. Heparin was administered at an appropriate time after opening the chest to achieve and activated clotting time (ACT) of >450 seconds whilst on bypass. A haemoglobin level of >7g/dL was maintained whilst on bypass and non-pulsatile perfusion was provided with a mean arterial pressure of 50-80mmHg using metaraminol or noradrenaline as required.

The aorta was cross clamped and antegrade ± retrograde blood based cardioplegic solution was infused to arrest the heart. In certain cases of redo surgery, peripheral cannulation was performed by cannulating the femoral artery with or without cannulation of the femoral vein.

Patients requiring coronary artery bypass graft surgery (CABG) underwent the same setting up using the left internal mammary artery ± the right internal mammary artery ± reversed long saphenous vein ± radial artery as conduits.

Following aortotomy, the aortic valve was excised and decalcification of the annulus was performed as required. The valve was then sized and replaced with an appropriately sized prosthetic valve. The valve was implanted using interrupted everting mattress 2-0 Ticron sutures, with or without pledgets. The decision to use pledgeted sutures was made based on whether the annulus was weakened after valvectomy and decalcification or surgical preference. The aortotomy was then closed.

Prior to weaning off bypass, transoesophageal echocardiography (TOE) was performed in all patients to assess for the presence of intracardiac air, valve function and ventricular function

after weaning from CPB. In patients undergoing AVR via mini sternotomy, TOE was also used to help identify the presence of pericardial effusion.

Standard drainage and closure techniques were performed in each patient.

4.9.3 Immediate Postoperative Care

All subjects participating in the study had their care managed according to criteria-driven protocols. Patients were nursed in the immediate postoperative period in either the recovery unit, as a "fast track" case or in the Cardiothoracic Intensive Care Unit (CTICU).

Standardised criteria for fast track were used to dictate which patients were suitable. These patients were extubated in the cardiac recovery area and transferred to the cardiac surgical ward after pre-defined criteria were satisfied. Patients who did not satisfy these criteria were transferred to CTICU.

Protocols in the ICU detailed post-operative analgesia, medications, requirement for blood and blood product transfusion, indications for haemofiltration, laboratory and radiological examinations, extubation and discharge planning. Each patient had to meet specific criteria to be extubated, and each patient was extubated as soon as these criteria were met. Patients were transferred to the cardiac surgical ward once they were extubated and did not require any inotropic or organ support.

4.10 Postoperative Care on the Cardiac Surgical Ward

Following discharge from CTICU, patients were reviewed daily by a senior doctor. Patients were mobilised early following ICU discharge on day 1 following surgery. Regular diuretics were prescribed in the postoperative period until the patient reached their pre-operative body weight. In patients with mechanical prostheses only, warfarin and therapeutic dose low molecular weight heparin was commenced on day 1 following surgery. Patients undergoing CABG were commenced on aspirin 75mg once daily. If a patient was on anticoagulation prior to surgery, this was commenced on day 2 following surgery.

Temporary epicardial pacing wires were removed on day 3 following surgery, as per protocol. If there was conduction disturbance (heart block) beyond 1 week, the patient was referred to the cardiac electrophysiology team for consideration of insertion of a permanent pacemaker.

Patients were routinely discharged on day 5 following surgery, providing the INR was therapeutic, in those with mechanical valve, and providing there was no ongoing medical concern.

A transthoracic echo was performed prior to discharge on day 4 or day 5 following surgery to document postoperative valvular function, LV function, the presence of pericardial effusion and to document postoperative transvalvular gradient and valve EOA. This data was documented prospectively and was used to determine whether the patient had PPM or not.

Specific in hospital outcome data was collected as described in section 4.5.4.

4.11 Follow Up

Each patient was followed up in the cardiac surgical clinic at 6-8 weeks following surgery as routine and then referred for ongoing follow up at their local cardiology clinic for annual valve assessment.

For the purposes of the study, patients were followed up to 1 year following surgery. Patients received a telephone call from the research team at day 14 and at 3 months following surgery and the following data was collected: re-admission to hospital and reason for readmission.

As already described, patients were also reviewed in the research clinic at 6 and 12 months following surgery, where QOL assessment using the previously mentioned tools was performed. The patients' NYHA score was also recorded at these time points as well as the following data: new stroke; sternal wound infection; respiratory illness; admission to hospital for cardiac related illness; new atrial fibrillation and the requirement for insertion of permanent pacemaker. If there were any clinical concerns at these follow up assessments, the clinical team responsible for the patients were informed for further management. Mortality during follow-up to one year was recorded. Patients requiring cardiac surgical re-intervention was recorded.

4.11.1 Follow up Echocardiography

Patients underwent transthoracic echocardiography at 1 year following surgery, providing there was no clinical concern raised on the initial postoperative echocardiogram which would necessitate earlier re-imaging.

The following data was collected on follow up echocardiogram: LVEDd; IVSd; PWd, from which LV mass was calculated, using the Devereux equation, as already described (section

4.5.2), to assess for LV mass regression. Any paravalvular leak or prosthetic dysfunction was also recorded up to 1 year.

4.12 Sample Size

Based on a prevalence of 20% of PPM in published literature and based on power of 80%, it was calculated that 32 AVR patients would need to be recruited.

Sample size calculations were performed to balance requirements for both multiple regression and repeated measures analyses (baseline, 6 & 12 months) and based on assessments of QOL using the SF36 Physical Component Score (PCS) in a cohort of cardiac surgical patients. A difference of 5 points on the SF36 - Physical Component Summary, over the course of the study was considered a clinically important difference.

4.13 Statistical Analysis

Baseline, operative and postoperative outcomes were compared using Chi-squared test and continuous data were compared using the independent *t* test or Mann-Whitney test, as appropriate.

Patients were divided into 2 groups: one group with patients with no PPM (No PPM) and a group with patients with PPM (PPM). Binary data were compared using Chi-squared test and continuous data were checked for normality using histograms and QQ-plots and were compared using independent t tests or Mann-Whitney tests, as appropriate. Differences in QOL were assessed using repeated analyses of variance.

Statistical analyses were performed using SPSS (IBM-SPSS Inc, Armonk, NY) version 26.

5. Results

5 Results

5.1.1 Study Population

Between October 2013 and October 2015, 176 patients fulfilled the inclusion criteria. Of these, 2 patients declined to participate and 1 patient underwent alternative treatment (TAVI). The remaining 173 patients were included in the final analysis.

5.1.2 Baseline clinical characteristics

Demographic data and baseline clinical characteristics were collected prospectively and are detailed in Table 10. Data is shown with either mean or median values, dependant on the distribution of the data.

The median age was 75 years (range 34 – 89 years, interquartile range 11 years). One hundred and eleven (64.2%) were male. Mean EuroSCORE II was 3.7.

Based on postoperative transthoracic echocardiography, 26 (15%) included patients had any degree of PPM. Of these, 15 (57.7%) had moderate PPM (indexed EOA of 0.65 – 0.85 cm^2) and 11 (42.3%) had severe PPM (indexed EOA <0.65 cm^2). Therefore, I have divided the cohort to reflect this, as shown in Table 1. A total of 18 patients did not have baseline postoperative echocardiography, either due to in hospital mortality or the patient being transferred to a different hospital. This accounts for the difference in the total number of patients in each group.

Table 10: Baseline characteristics of all patients

Baseline Variable	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Age (years)	75 (34 – 89, IQR 11)	77.5 (58-87, IQR 11)	75 (58-84, IQR 19)	79 (68-87, IQR 10)	74 (34-89, IQR 12.5)	0.09
Male	111 (64.2%)	22 (84.6%)	10 (90.9%)	12 (80%)	79 (61.2%)	0.06
BMI (kg/m^2)	28 (16.4 – 41.2, IQR 6.1)	27 (21 – 38, IQR 5)	25.7 (21-30, IQR 3)	28 (21 – 38.1, IQR 5)	28 (16.4-31.2, IQR 7)	0.178
BSA (m^2)	1.93 ± 0.8	1.86 ± 0.23	1.73 ± 0.2	1.94 ± 0.2	1.96 ± 0.9	0.695
LMS coronary disease	15 (8.7%)	0	0	0	13 (10.1%)	0.239
Pulmonary hypertension	33 (19.1%)		4 (36.4%)	4 (26.7%)	18 (14%)	0.09
Hypertension	118 (68.2%)	20 (76.9%)	8 (72.7%)	12 (80%)	87 (67.4)	0.587

Table 10: Baseline characteristics of all patients

Baseline Variable	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Diabetes Mellitus	33 (19.1%)	3 (11.5%)	0	3 (20%)	36 (27.9%)	0.109
Requiring insulin	7 (21.2%)		NA	0	1 (2.8%)	
Previous stroke	12 (6.9%)	3 (11.5%)	1 (9.1%)	2 (13.3%)	6 (4.7%)	0.226
Chronic kidney disease	20 (11.6%)	3 (11.5%)	1 (9.1%)	2 (13.3%)	15 (11.6%)	0.946
Dialysis	1 (5%)	0	0	0	1 (0.8%)	
Peripheral vascular disease	10 (5.8%)	2 (7.7%)	0	2 (14.3%)	7 (5.4%)	0.322
Smoker (current or ex)	72 (41.6%)	12 (75%)	5 (45.5%)	7 (46.7%)	54 (41.9%)	0.854
Atrial fibrillation	29 (16.8%)	2	2 (18.2%)	4 (26.7%)	21 (16.3%)	0.992

Table 10: Baseline characteristics of all patients

Baseline Variable	**All, (n=173) (%)**	**Any degree PPM (n=26) (%)**	**Severe PPM (n=11) (%)**	**Moderate PPM (n=15) (%)**	**No PPM (n=129) (%)**	**p Value**
Left ventricular function (%)	57.4 ± 11.1	55.9 ± 9.8	54.2 ± 9.2	57.1 ± 10.4	57.9 ± 11.4	0.571
Good (>50%)	140 (80.9%)	21 (80.8%)	8 (72.7%)	13 (86.7%)	109 (84.5%)	
Moderate (31 – 50%)	23 (13.3%)	3 (11.5%)	3 (27.3%)	1 (7.7%)	15 (11.6%)	
Poor (<30%)	10 (5.8%)	1 (3.8%)	0	1 (7.7%)	5 (3.9%)	
Aortic Stenosis	101 (58.4%)	16 (61.5%)	5 (45.5%)	11 (73.3%)	77 (59.7%)	<0.0001
Aortic Regurgitation	32 (18.5%)	4 (15.4%)	4 (36.4%)	0	24 (18.6%)	<0.0001

Table 10: Baseline characteristics of all patients

Baseline Variable	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Mixed aortic valve disease	40 (23.1%)	6 (23.1%)	2 (18.2%)	4 (26.7%)	17 (20.9%)	<0.0001
NYHA III/IV	58 (33.5%)	8 (30.7%)	2 (18.2%)	6 (40%)	42 (32.5%)	0.622
Logistic EuroSCORE (%)	10.1 ± 9	12.7 ± 10.3	12.1 ± 10.2	13.2 ± 10.7	9.5 ± 9	0.264
EuroSCORE II (%)	3.7 ± 3.8	3.2 ± 2	3.2 ± 2.4	3.2 ± 1.7	3.8 ± 4.2	0.755
STS PROM (%)	2.6 ± 1.7	2.4 ± 1.1	2.4 ± 1.5	2.4 ± 0.9	2.5 ± 1.6	0.948

Values are median (range, interquartile range), %, or mean ± SD.

PPM, patient prosthesis mismatch; BMI, body mass index; BSA, body surface area; LMS, left main stem; PA, pulmonary artery; NYHA, New York Heart Association Classification; STS PROM, Society of Thoracic Surgeons Predictor of Mortality

There was no significant difference between patients who were found to have PPM on their first postoperative echocardiogram in terms of age, BMI, BSA, LV function or EuroSCORE (II and Logistic) or STS PROM score.

5.1.3 Baseline echocardiographic data

Baseline echocardiographic data is shown in Table 11. As well as showing the data for the overall series, I have separated this into the type of aortic valve disease (stenosis, regurgitation or mixed valve disease).

The majority of included patients had AS. There was no significant difference in left ventricular function (p=0.9) between the groups. Forty patients had mixed AS and AR, however when looking at the preoperative mean and peak aortic valve gradients, as well as there being a significant difference between all these groups, the mixed group had higher preoperative valve gradients than the AR group, suggesting that the predominant pathology in this group is AS.

Preoperative LV mass was highest in the mixed group. However, LV end diastolic diameter was largest in the AR group, as would be expected from the disease process. Whilst the LVOT diameter is largest in the AR group, overall, the mean LVOT diameter is 2.2 cm.

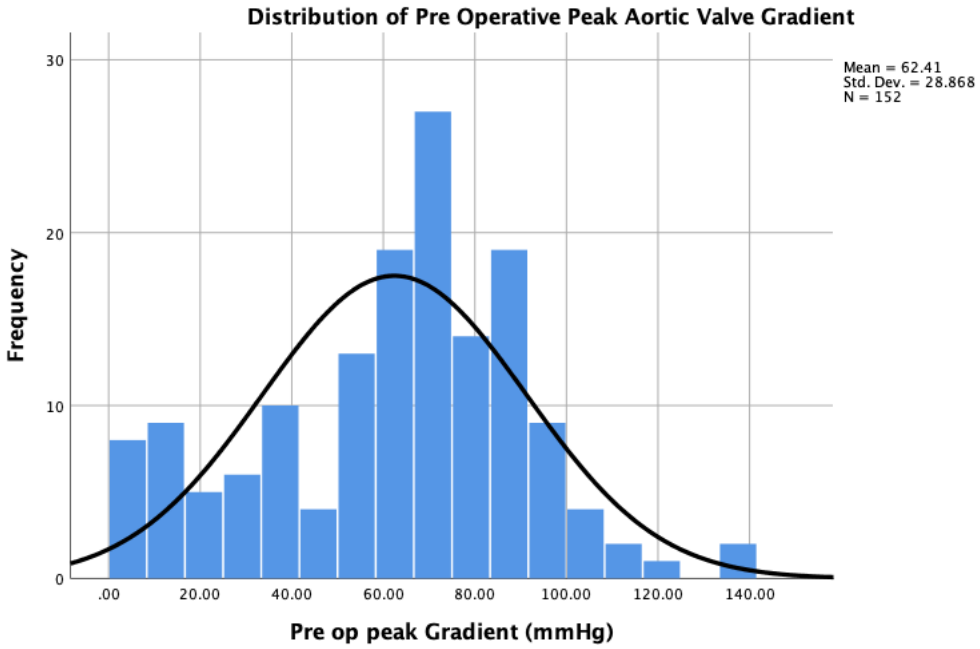


Figure 16: Distribution of peak aortic valve gradient

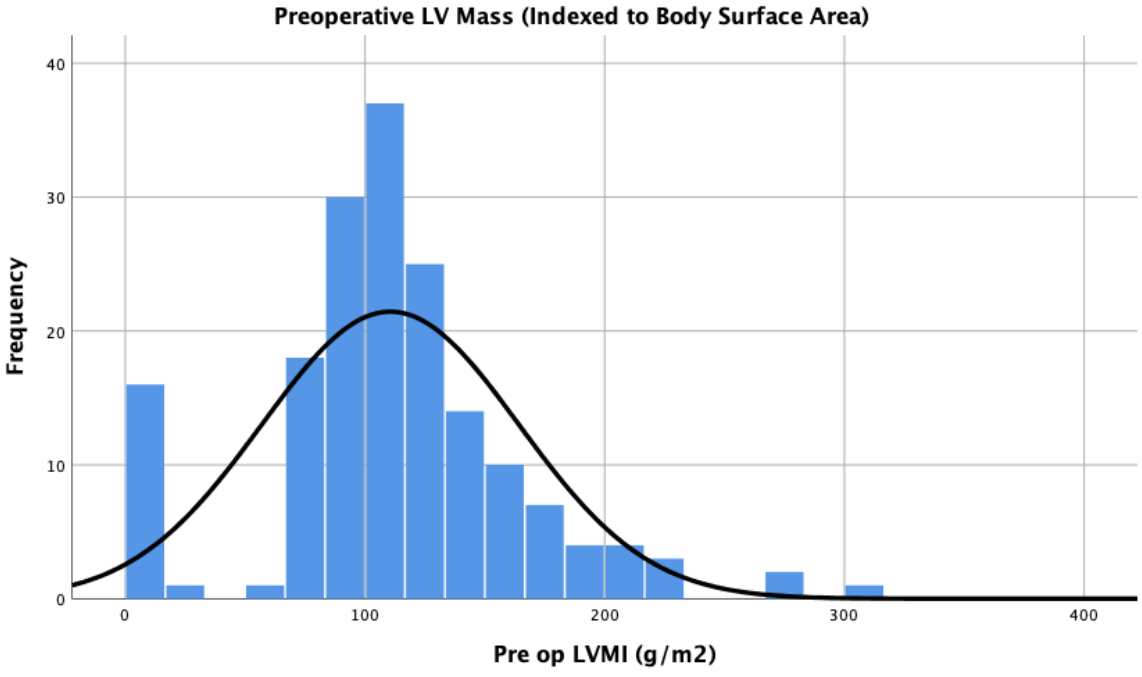


Figure 17: Preoperative LV mass indexed to body surface area.

Table 11: Preoperative echocardiographic data by valve pathology

Baseline Variable	All (n=173)	AS (n=101)	AR (n=32)	Mixed (n=40)	p Value
LV function (%)	57.4 ± 11.1	57.4 ± 10.9	57.4 ± 11.4	57.4 ± 11.3	0.9
Degree of valve disease					
Mild	-	3 (3%)	3 (9.4%)	-	-
Moderate	-	5 (4.9%)	8 (25%)	-	-
Severe	-	93 (92.1%)	21 (65.6%)	-	-
Mean gradient (mmHg)	38.7 ± 15.8	41.4 ± 12.5	23.7 ± 16.8	39.4 ± 18.9	<0.0001
Peak gradient (mmHg)	62.4 ± 28.9	71.4 ± 19	30.1 ± 17.7	66.9 ± 31.6	<0.0001
Valve area (cm^2)	0.86 ± 0.36	0.75 ± 0.23	1.4 ± 0.4	0.96 ± 0.5	<0.0001
Peak velocity (m/s)	3.9 ± 4.16	4.1 ± 0.8	3 ± 1.2	4.1 ± 1	<0.0001
LVEDD (mm)	48.9 ± 7.9	47.1 ± 6.2	53.4 ± 8.9	50.3 ± 8.8	0.01
LV mass (g)	209 ± 104	205 ± 70.1	217 ± 89	223 ± 131	0.02
LVMI (g/m^2)	110 ± 53.6	108 ± 36.5	116 ± 46.1	121 ± 71.4	0.1
LVOT diameter (cm)	2.2 ± 1.5	2.0 ± 0.2	3.4 ± 4.7	2.1 ± 0.26	0.17

Values are mean ± SD. AS, aortic stenosis; AR, aortic regurgitation; LV, left ventricular, SD, standard deviation; LVEDD, left ventricular end diastolic diameter; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract

5.2 Operative Data

Operative data is shown in Table 12 for each of the groups, as per Table 10.

The majority of cases were performed electively. Isolated AVR was performed in 57.2% of the whole cohort and 13 (7.5%) patients underwent redo surgery. Minimal access surgery via mini sternotomy, as described in the methods chapter, was performed in 13 (7.5%) of patients and none of these patients had PPM. Median cross clamp and cardiopulmonary bypass times did not vary significantly across all groups.

Table 12: Operative details

Operative detail	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Urgency						
Elective	124 (71.7%)	22 (84.6%)	11 (100%)	11 (73.3%)	90 (69.8%)	0.334
Urgent	49 (28.3%)	2 (15.4%)	0	4 (26.7%)	39 (30.2%)	
Operation						
Isolated AVR	99 (57.2%)	15 (57.7%)	8 (72.7%)	7 (46.7%)	71 (55%)	0.847
AVR + CABG	74 (42.8%)	11 (42.3%)	3 (27.3%)	8 (53.3%)	58 (45%)	0.847
Redo Surgery	13 (7.5%)	2 (7.7%)	2 (18.2%)	0	8 (6.2%)	
Mini-sternotomy AVR	13 (7.5%)	0	0	0	13 (10.1%)	
Cross Clamp Time (mins)	89 (37-257, IQR 52)	92 (51-161, IQR 64)	83 (65-96, IQR 67)	93 (51-158, IQR 79)	87 (37-257, IQR 46)	0.521
Isolated AVR	79 (39-257, IQR 41)	77 (52-158, IQR 56)	83 (65-96, IQR 67)	66 (52-158, IQR 55)	79 (39-257, IQR 40)	0.696

Table 12: Operative details

Operative detail	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Bypass Time (mins)	112 (47-389, IQR 72)	114 (64-197, IQR 79)	120 (76-197, IQR 86)	110 (64-190, IQR 62)	111 (47-389, IQR 64)	0.575
Same as above comment						
Isolated AVR	104 (49-389, IQR 51)	104 (75-183, IQR 43)	120 (76-197, IQR 86)	100 (75-176, IQR 28)	100 (49-389, IQR 37)	0.182
Valve size (mm)	23 (19-27, IQR 2)	23 (19-25, IQR 0)	23 (19-27, IQR 1.5)	23 (21-25, IQR 0.5)	21 (19-27, IQR 2)	0.906

Values are median (range, interquartile range) or mean ± standard deviation

PPM, patient prosthesis mismatch; IQR, interquartile range; AVR, aortic valve replacement; CABG, coronary artery bypass graft surgery

5.3 In-Hospital Outcomes

Complications and mortality in the entire cohort of patients was collected prospectively, as described in the methods chapter. The complications were then grouped accordingly as described in methodology (page 77, section 4.6.4).

In-hospital outcomes are shown in Table 4. These outcomes were also examined during follow up and these will be detailed in the next section of this chapter.

In hospital mortality did not vary between the groups. Overall mortality was 5.8% in the entire cohort. Mortality in patients undergoing first time, isolated aortic valve replacement was 1.2%.

There was no significant difference in stroke, resternotomy for bleeding, tracheostomy or GI complications.

Although the incidence of postoperative AF was proportionately higher in the PPM group (53.8%), this did not reach statistical significance, p=0.06. Of note, no patients with PPM required permanent pacemaker insertion in the early postoperative period.

Table 13: In-Hospital Outcomes

Operative detail	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Mortality	10 (5.8%)	2 (7.7%)	1 (9.1%)	1 (6.7%)	8 (6.2%)	0.436
Isolated AVR	1 (1.2%)	0	0	0	1	
Stroke	9 (5.2%)	2 (7.7%)	0	2 (13.3%)	7 (5.4%)	0.814
Resternotomy for bleeding	9 (5.2%)	1 (3.8%)	0	1 (6.7%)	8 (6.2%)	0.709
Haemofiltration	13 (7.5%)	1 (3.8%)	1 (9.1%)	0	12 (9.3%)	0.506
Tracheostomy	2 (1.2%)	0	0	0	2 (1.5%)	0.834
Laparotomy	2 (1.2%)	1	1 (9.1%)	0	1 (0.8%)	0.607
Peripheral vascular complications	3 (1.7%)	0	0	1 (6.7%)	2 (1.5%)	0.291
AF	60 (34.7%)	14 (53.8%)	5 (45.4%)	9 (60%)	46 (35.6%)	0.062
Permanent pacemaker insertion	4 (2.3%)	0	0	0	4 (3.1%)	0.7
Sternal wound infection	7 (4%)	2 (7.7%)	0	2 (13.3%)	5 (3.9%)	0.066

Table 13: In-Hospital Outcomes

Operative detail	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Postoperative length of stay (days)	8 (2-170)	10.5 (5-36)	6 (5-17)	12 (5-36)	8 (2-170)	0.225

PPM, patient prosthesis mismatch; AVR, aortic valve replacement; AF, atrial fibrillation

5.4 Postoperative Echocardiographic Data

All included patients underwent postoperative transthoracic echocardiogram prior to discharge. Those who suffered operative mortality or were transferred to a referring local hospital did not receive an early postoperative transthoracic echocardiogram prior to discharge.

Postoperative echocardiographic data is shown in Table 14.

Postoperative mean aortic valve gradient for all patients is shown in Figure 17.

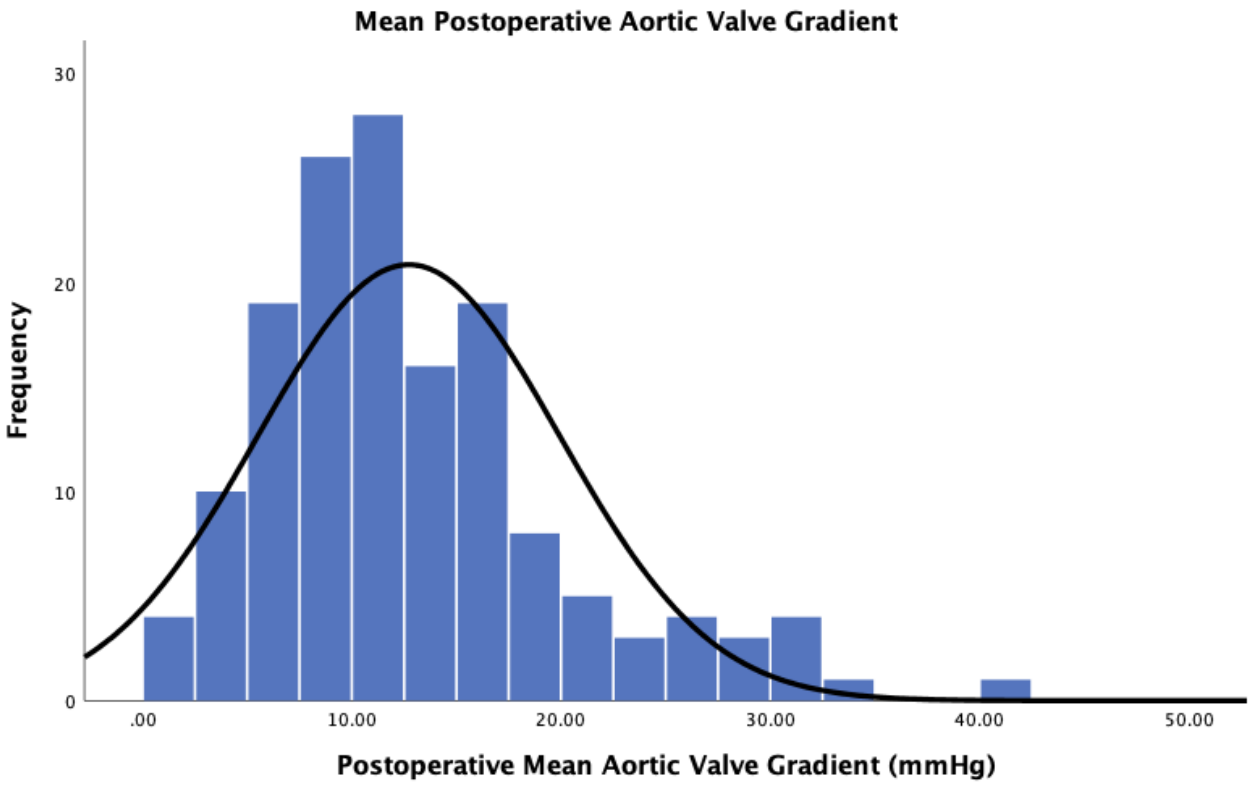


Figure 18: Postoperative aortic valve gradient across entire cohort

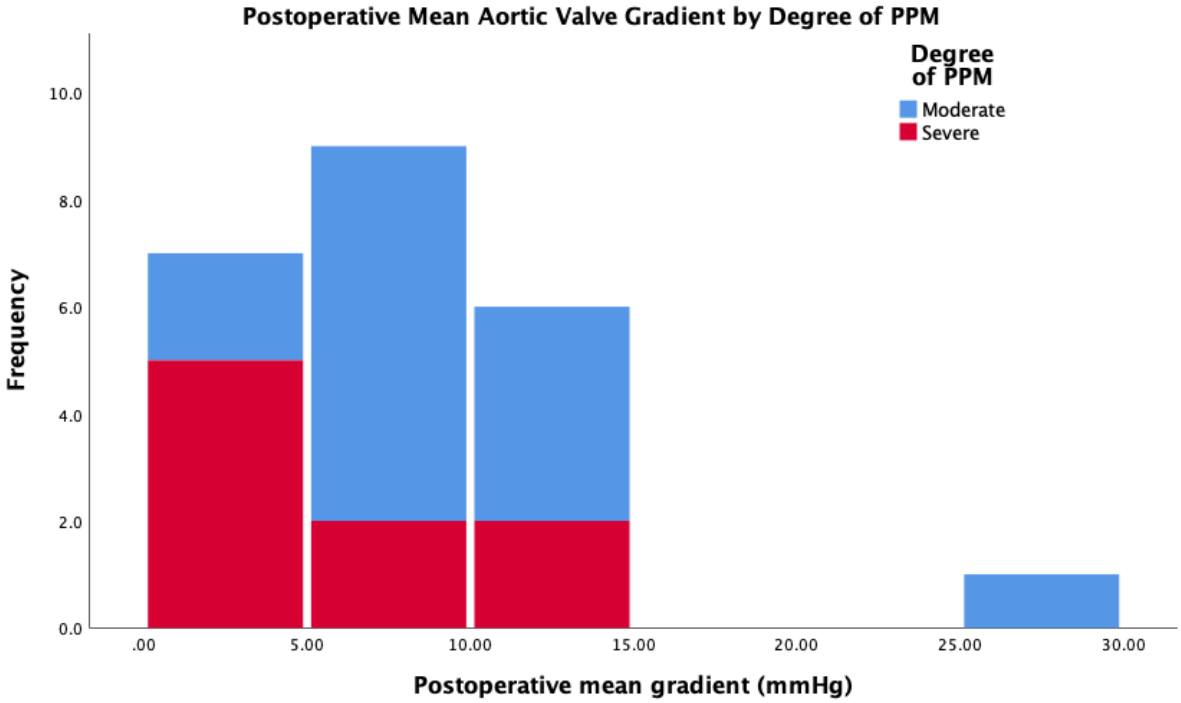


Figure 19: Postoperative aortic valve gradient by degree of PPM.

Table 14: Postoperative echocardiographic data

Operative detail	All, (n=173) (%)	Any degree PPM (n=26) (%)	Severe PPM (n=11) (%)	Moderate PPM (n=15) (%)	No PPM (n=129) (%)	p Value
Peak gradient (mmHg)	23.4 ± 12.3	15.3 ± 6.9	12.3 ± 12.3	17.6 ± 6.7	24.5 ± 12.2	0.04
Mean gradient (mmHg)	12.8 ± 7.3	8 ± 5.4	5.6 ± 3.5	9.9 ± 5.9	13.3 ± 7.1	0.04
Peak velocity (m/s)	2.4 ± 0.6	1.9 ± 0.5	1.7 ± 0.5	2 ± 0.4	2.4 ± 0.6	0.119
EOA (cm^2)	1.7 ± 0.6	2.7 ± 0.7	3 ± 0.9	2.5 ± 0.3	1.5 ± 0.4	0.05
Indexed EOA (cm^2/m^2)	1.3 ± 0.6	0.7 ± 0.13	0.6 ± 0.13	0.78 ± 0.05	1.4 ± 0.5	<0.0001
LV Mass (g)	197 ± 74	213 ± 117	154 ± 83	259 ± 123	179 ± 82	0.02
LVMI (g/m^2)	104 ± 34	115 ± 61	91 ± 48	134 ± 65	94 ± 38	0.08

Values are mean ± standard deviation.

PPM, patient prosthesis mismatch; EOA, effective orifice area; LV, left ventricular; LVMI, left ventricular mass index

There was a significant difference between the groups with all but 2 parameters (EOA and peak velocity. Of note, PPM patients had lower peak and mean postoperative valve gradients. However, when the valve EOA is indexed to body surface area, iEOA is significantly lower in the PPM groups. This suggests that gradient alone may not be indicative of PPM.

Patients with PPM had significantly higher LV mass and this remained the same when indexed to body surface area.

5.4.1 LV Mass Regression

LV mass was calculated from 2D transthoracic echocardiography. Postoperative LV mass was compared to preoperative LV mass to assess for mass regression. When comparing pre and postoperative LV mass, without indexing to body surface area, there was a significant reduction in LV mass at follow up ($p<0.0001$).

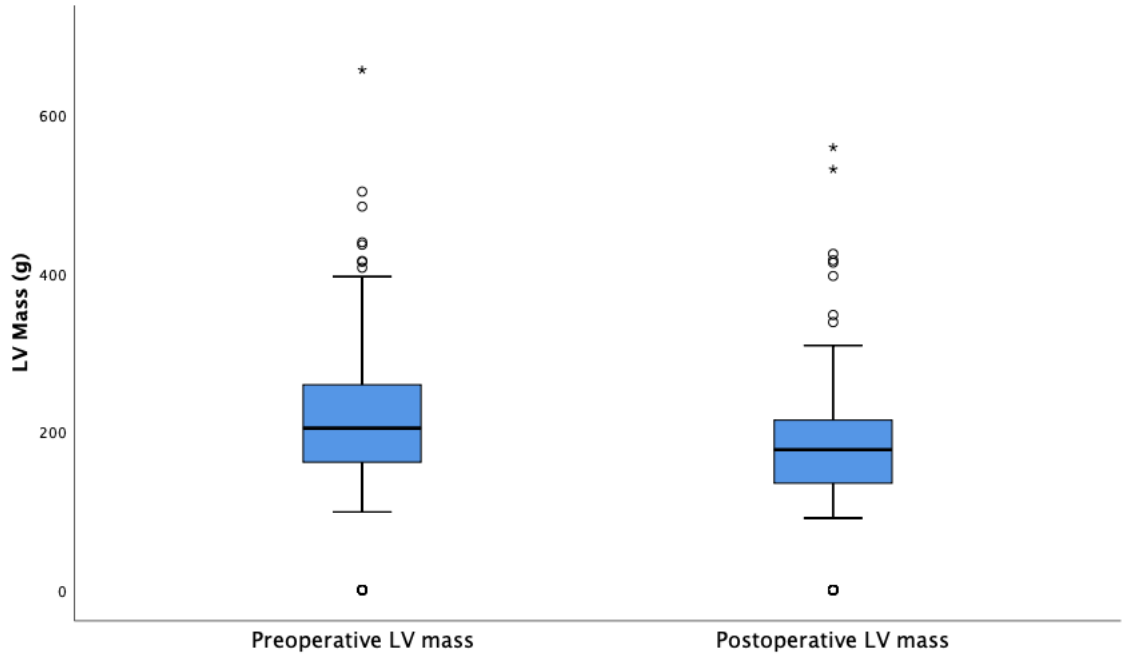


Figure 20: Pre and postoperative LV mass, based on most recent transthoracic echo following surgery.

This was also the case when LV mass was indexed to body surface area, $p<0.0001$.

LV mass regression was also assessed based on whether or not there was PPM, as shown in Table 15.

Table 15: LV mass regression with and without PPM

Degree of PPM (n)	Pre op LVMI	Post op LVMI	% change	p Value
None (129)	107 ± 52	94 ± 38	-12.2%	0.001
Moderate (15)	135 ± 54	132 ± 63	-2.2%	0.002
Severe (11)	126 ± 47	91 ± 48	-27.8%	0.068

Values are mean ± SD. PPM, patient prosthesis mismatch; LVMI, left ventricular mass index

Despite the severe PPM group having the greatest reduction in LV mass index, this did not reach statistical significance. The results were similar when examining the effect of PPM on LV mass, without indexing to BSA.

5.5 Mortality during follow up

Overall, 6 patients died during follow up. The Kaplan Meier curve is shown in Figure 6.

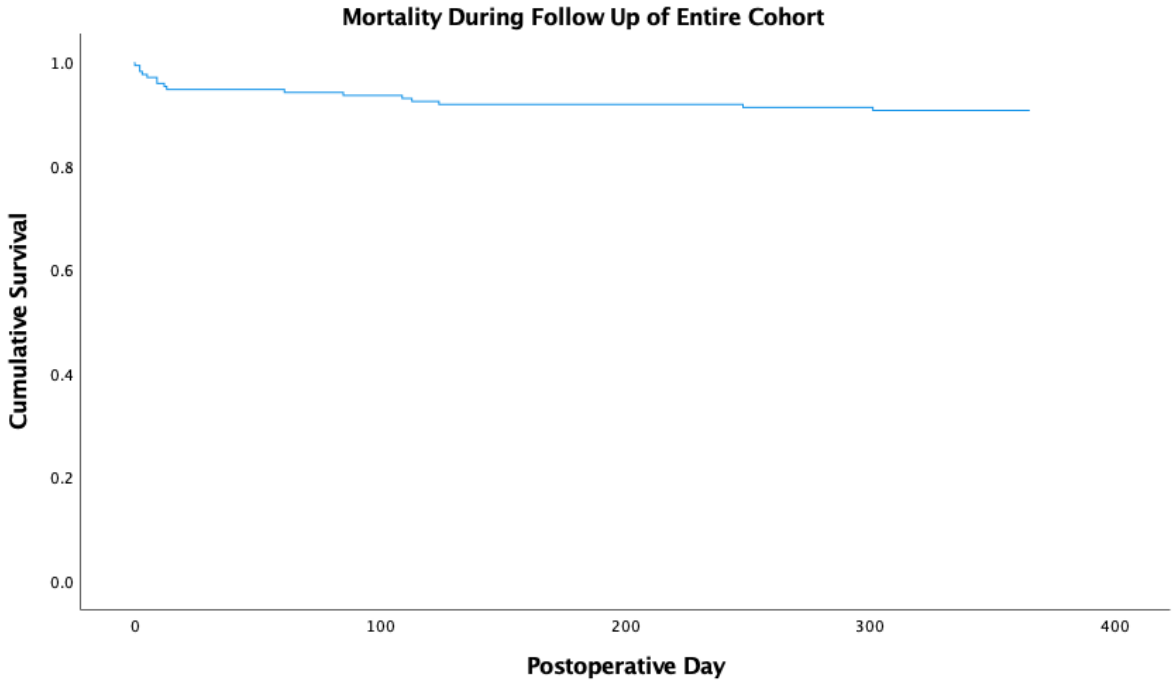


Figure 21: Kaplan-Meier curve demonstrating mortality during follow up of Entire Cohort

I then compared mortality during follow up between the groups. There were 2 mortalities in the PPM groups, one in the severe group and one in the moderate group. Both of these deaths were in hospital mortality and occurred at day 5 and day 12 respectively.

There was no significant difference in mortality during follow up between the groups, Log Rank p=0.45.

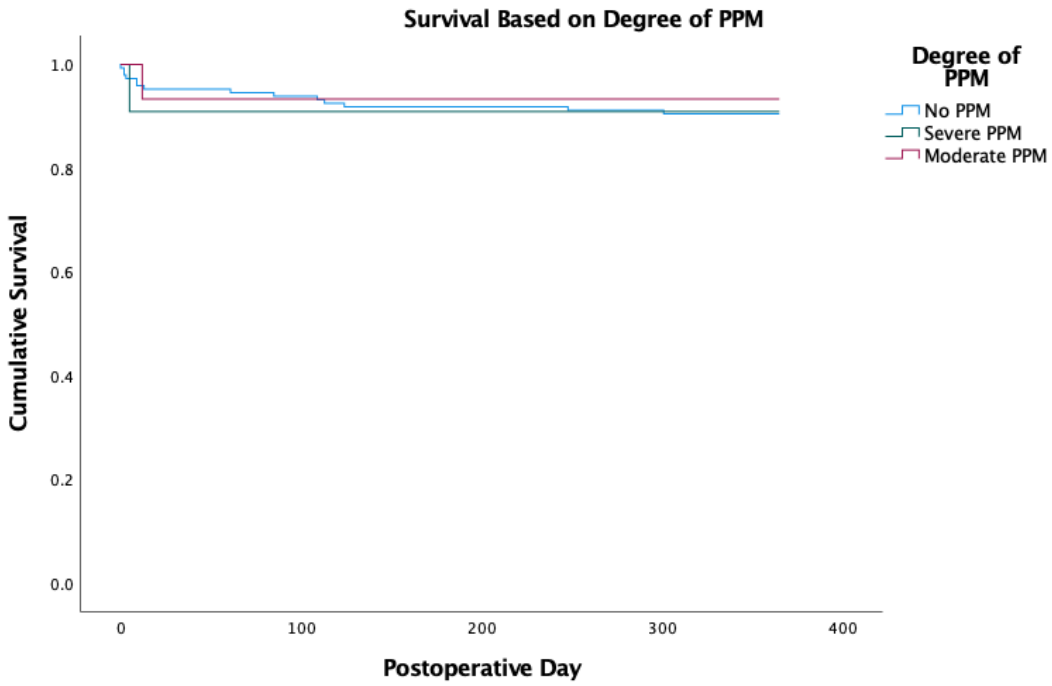


Figure 22: Survival based on degree of PPM

I have also compared survival between the groups up to the present day (Figure 23), and this has demonstrated that there remains no significant difference in mortality during longer term follow up (Log-Rank, p=0.2).

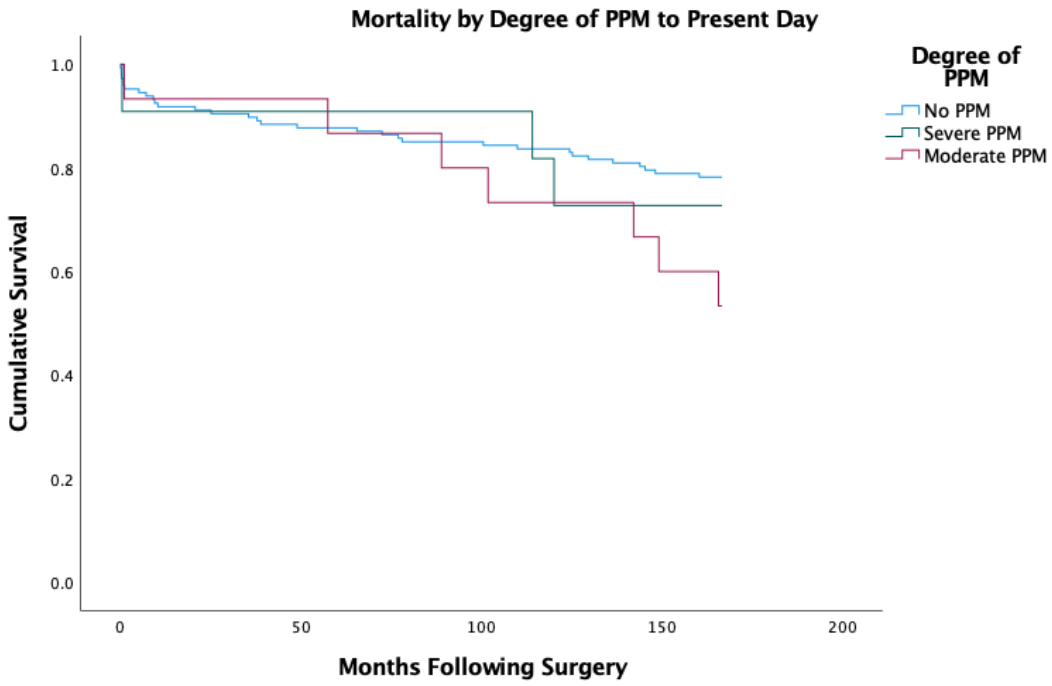


Figure 23: Mortality by degree of PPM to present day.

5.6 Reintervention during follow up

Of the entire cohort, one patient required reintervention during follow up. This patient had prosthetic aortic valve endocarditis and required redo sternotomy and aortic root replacement. The patient did not have PPM following either their initial operation or after redo surgery.

5.7 Quality of Life

SF-36 scores were calculated based on each of the separate components of the questionnaire to produce physical and mental component summary scores. This was analysed using repeated measures ANOVA, based on a standard distribution of data at each time point.

5.7.1 Physical Component Summary Score (PCS)

PCS was assessed at baseline, at 6 and at 12 months following surgery.

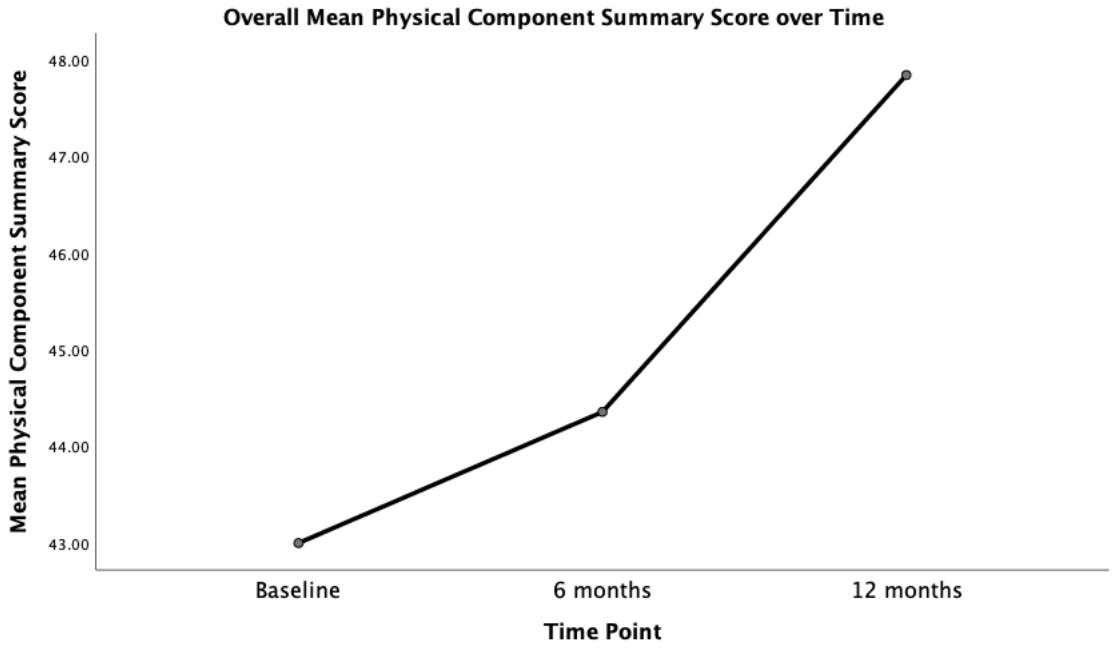


Figure 24: Change in mean PCS scores during follow up.

During follow up, there was a significant improvement from baseline in PCS scores for the entire cohort, p=0.001.

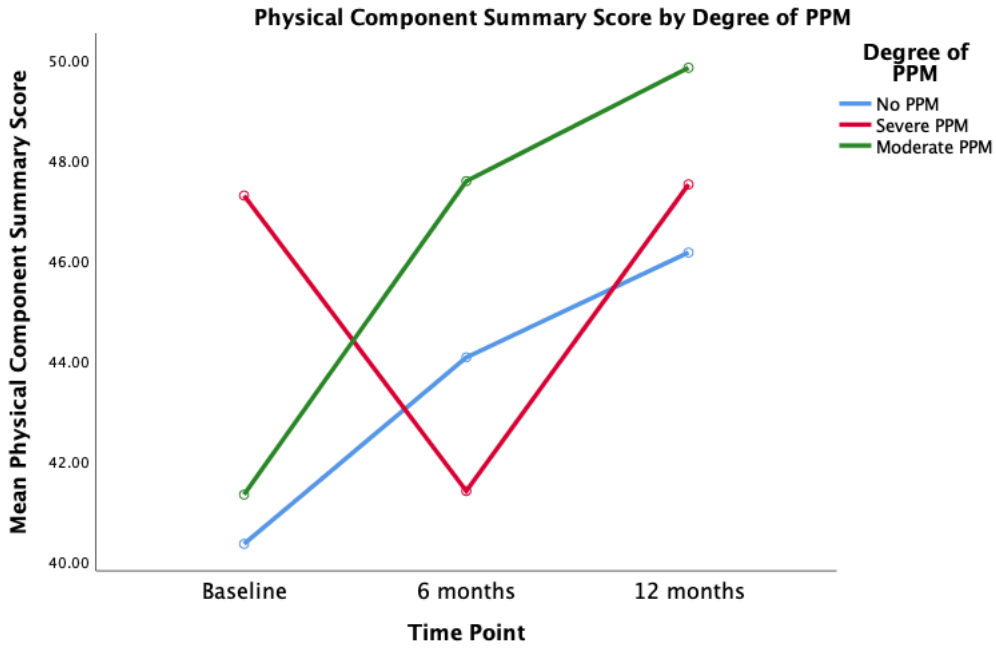


Figure 25: Change in PCS scores based on presence and degree of PPM

Although the severe PPM group had a lower PCS score at 6 months, this improved back to baseline value but did not increase above baseline as in the moderate PPM and no PPM groups, however, this did not reach statistical significance, p=0.38.

I then examined the change in each of the SF-36 component scores, which individually make up the summary scores. These are detailed in the following pages.

General Health:

For the overall cohort, despite there being a drop in mean score in this domain, there was a significant increase from baseline score, p=0.05, at 12 months follow up.

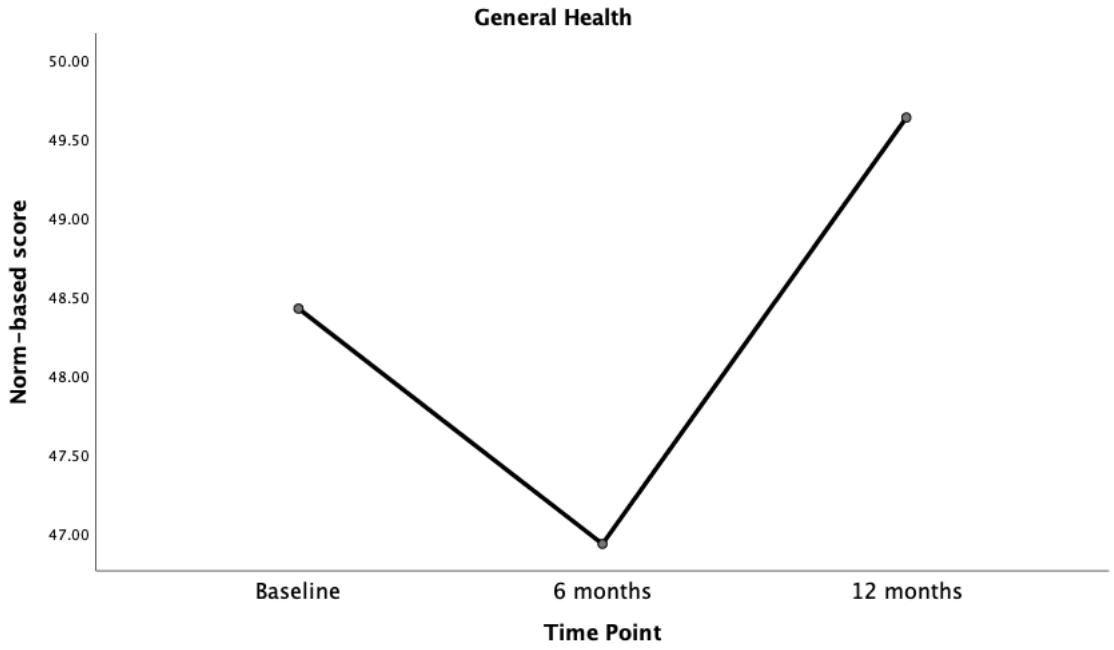


Figure 26: Trend in scores in the general health component of PCS

When dividing the cohort based on the presence and degree of PPM, the severe PPM group had a higher mean baseline score and was the only group to have a reduction in general health score. These differences were statistically significant, p=0.04.

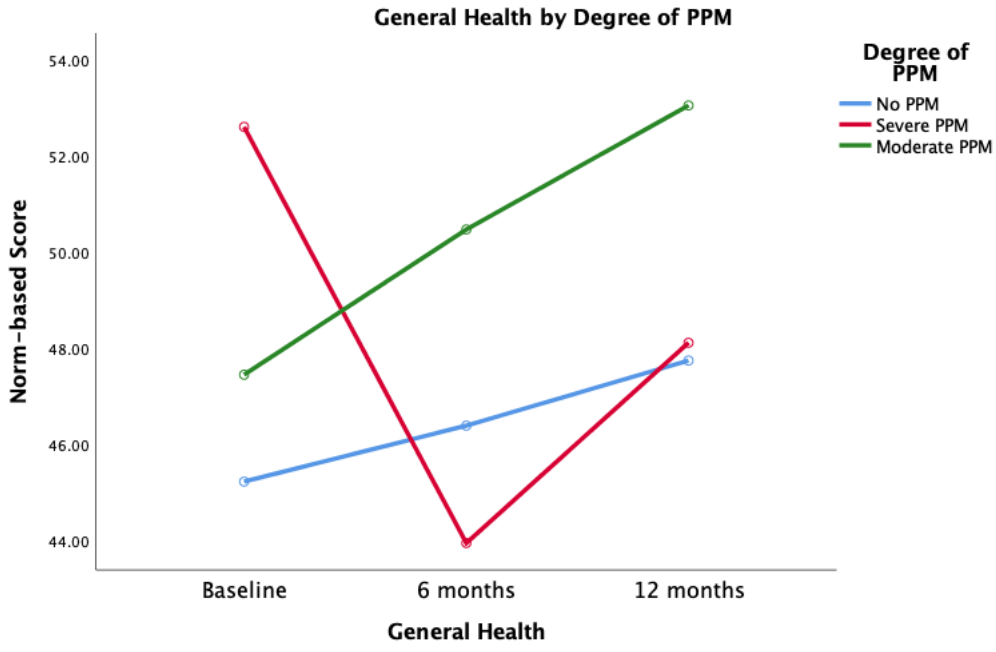


Figure 27: General Health score by degree of PPM.

Physical Functioning

For the overall cohort, there was a significant increase from from baseline score, p=0.002, at 12 months follow up.

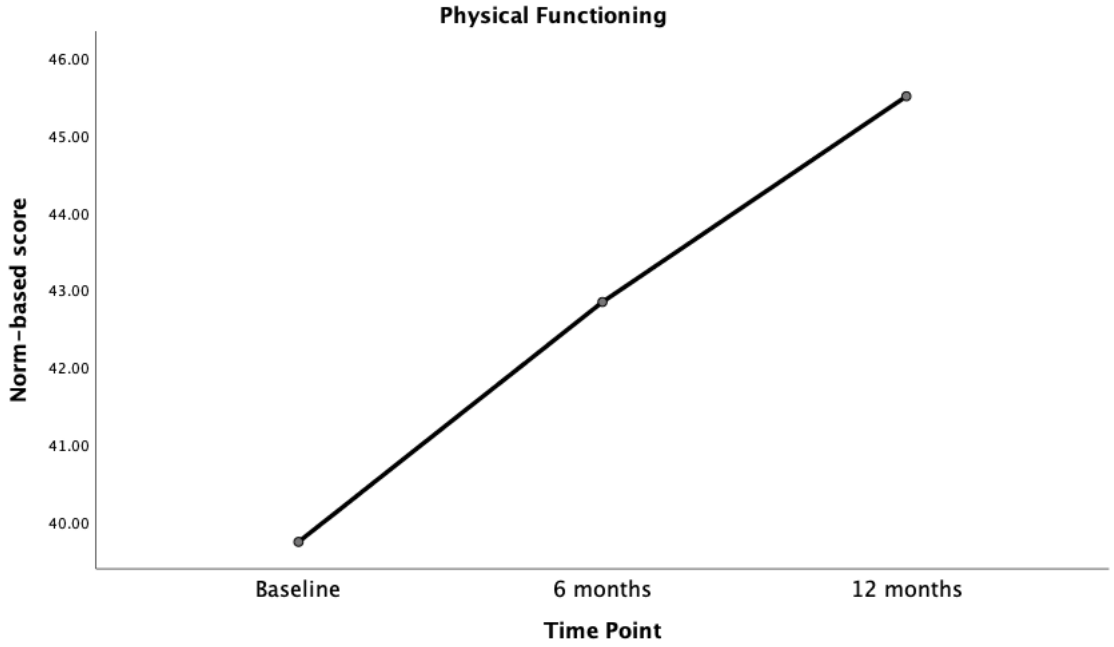


Figure 28: Trend in scores for overall cohort in the physical functioning component of PCS, ***p=0.002.***

In the severe PPM group however, there was initially a lower physical functioning score at 6 months, but this was higher than baseline at 12 months.

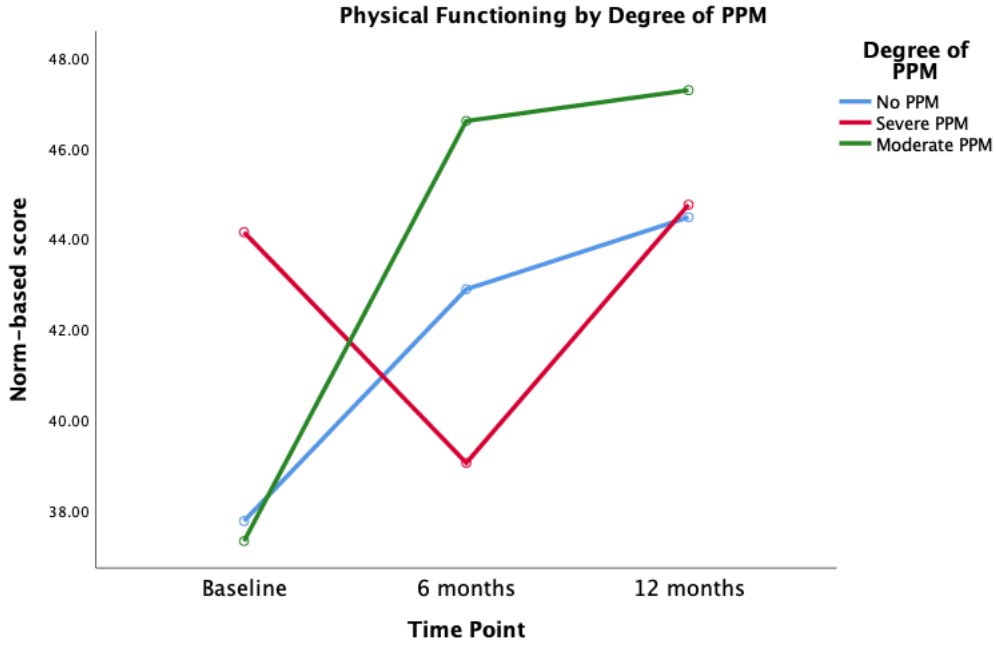


Figure 29: Physical functioning score by degree of PPM, ***p=0.02****.*

Role Physical

As similar trend is seen in the Role Physical domain.

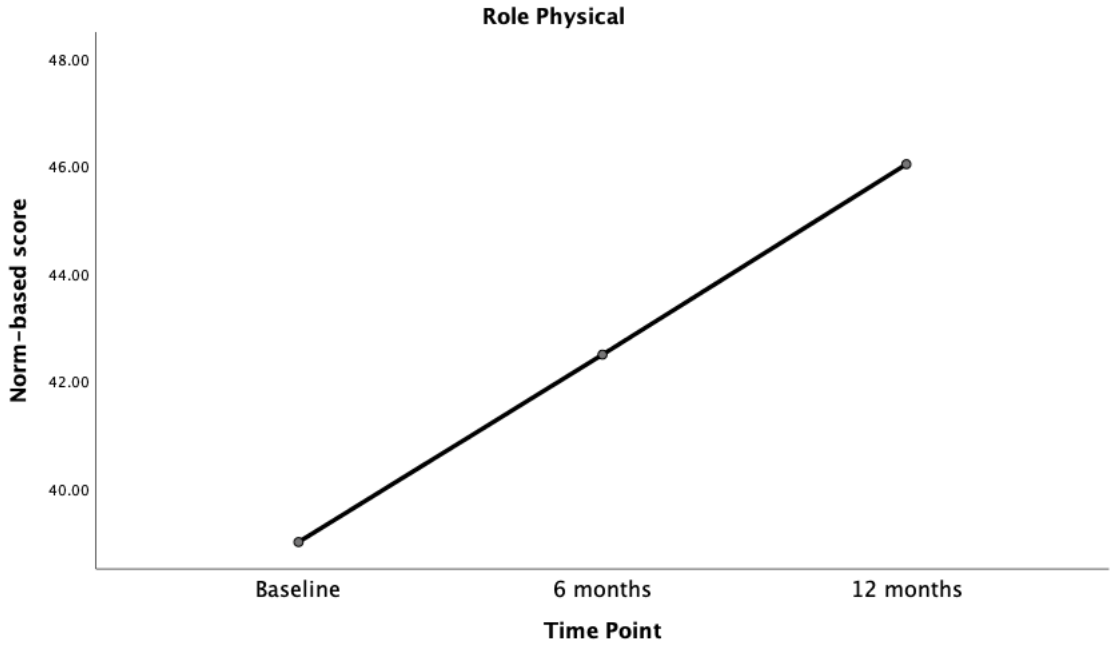


Figure 30: Trend in scores for overall cohort in the role physical component of PCS, ***p=0.001***

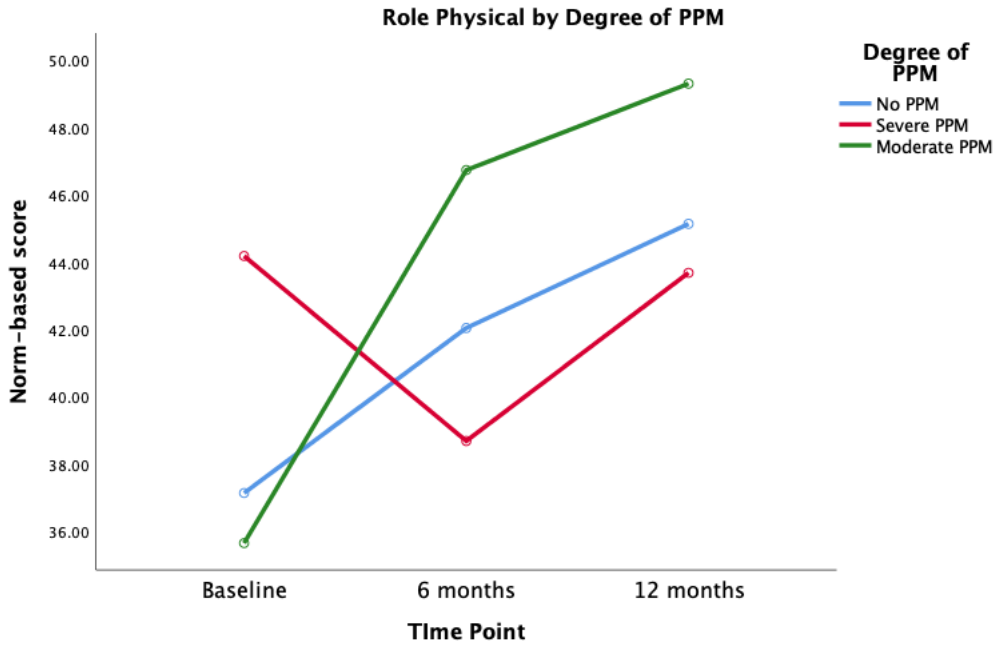


Figure 31: Role physical score by degree of PPM, ***p=0.04****.*

Bodily Pain

There was a significant improvement in Bodily Pain score from baseline in the overall cohort, however, the scores were lower in the severe PPM group.

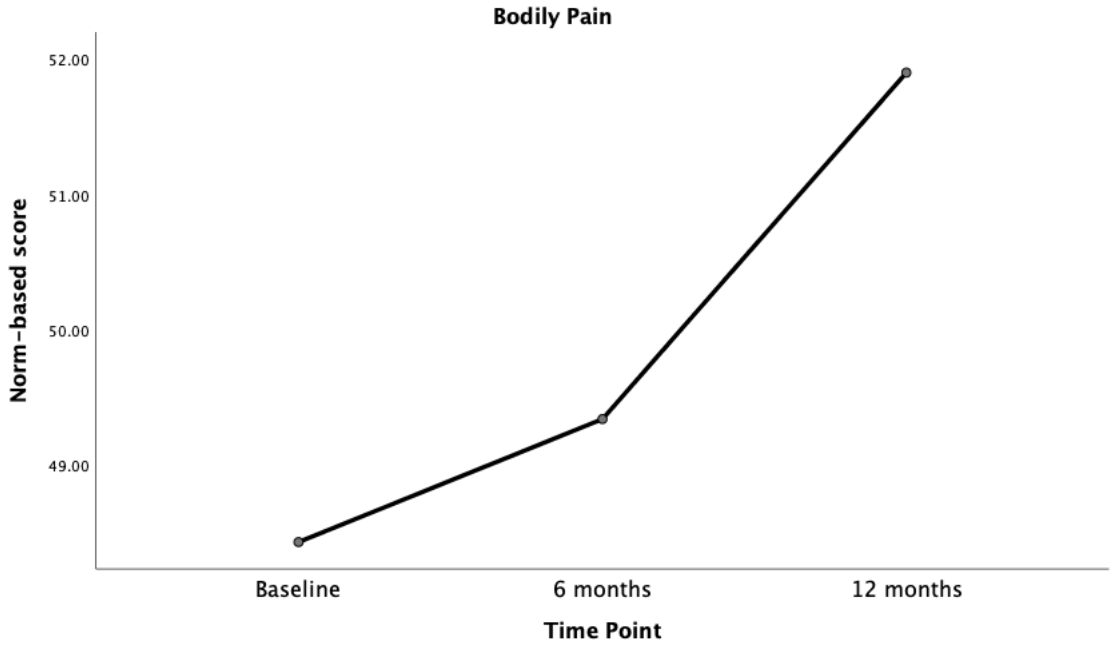


Figure 32: Trend in scores for overall cohort in the bodily pain component of PCS, ***p=0.07***

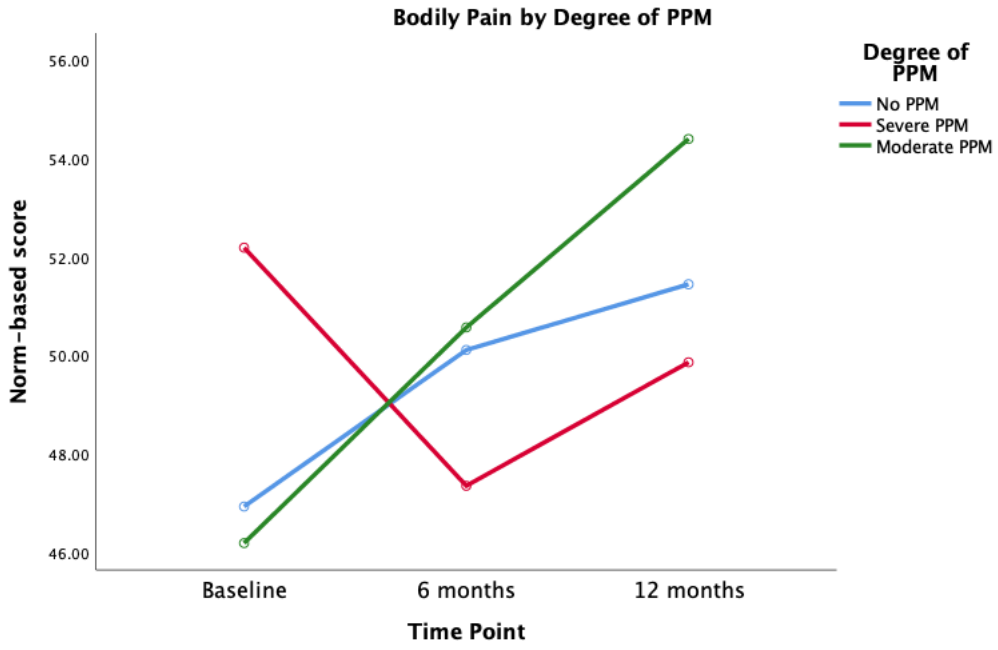


Figure 33: Bodily pain score by degree of PPM, ***p=0.24****.*

5.7.2 Mental Component Summary Scores (MCS)

As with PCS, MCS was calculated at baseline, 6 and 12 months following surgery.

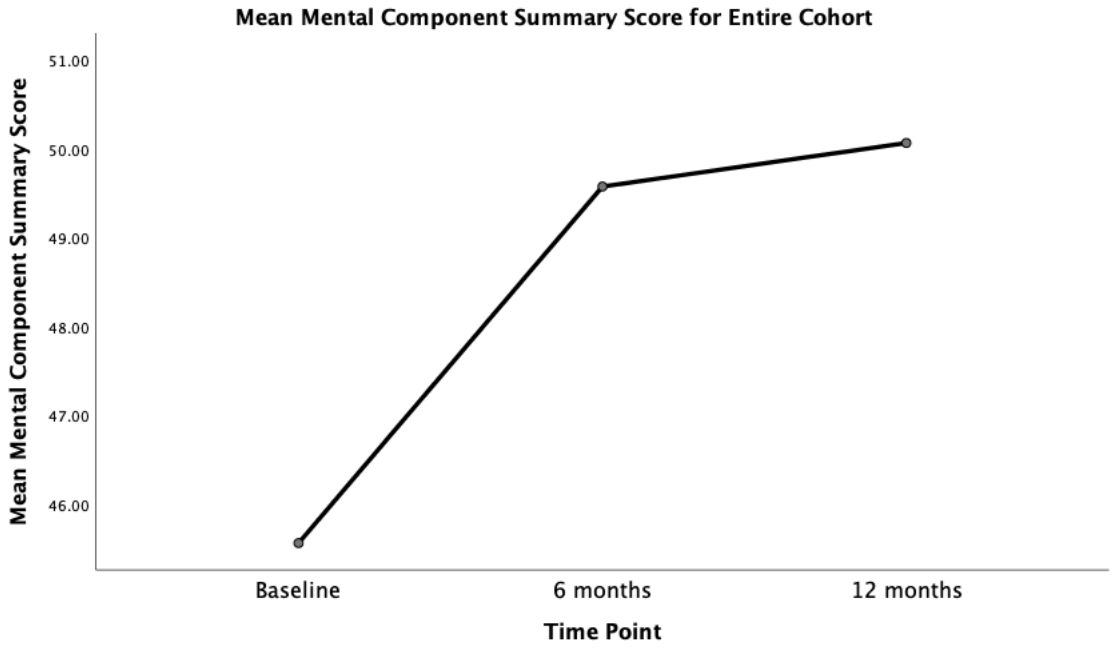


Figure 34: Change in mean MCS scores during follow up.

Overall, there was a significant improvement in MCS score during follow up, p=0.005.

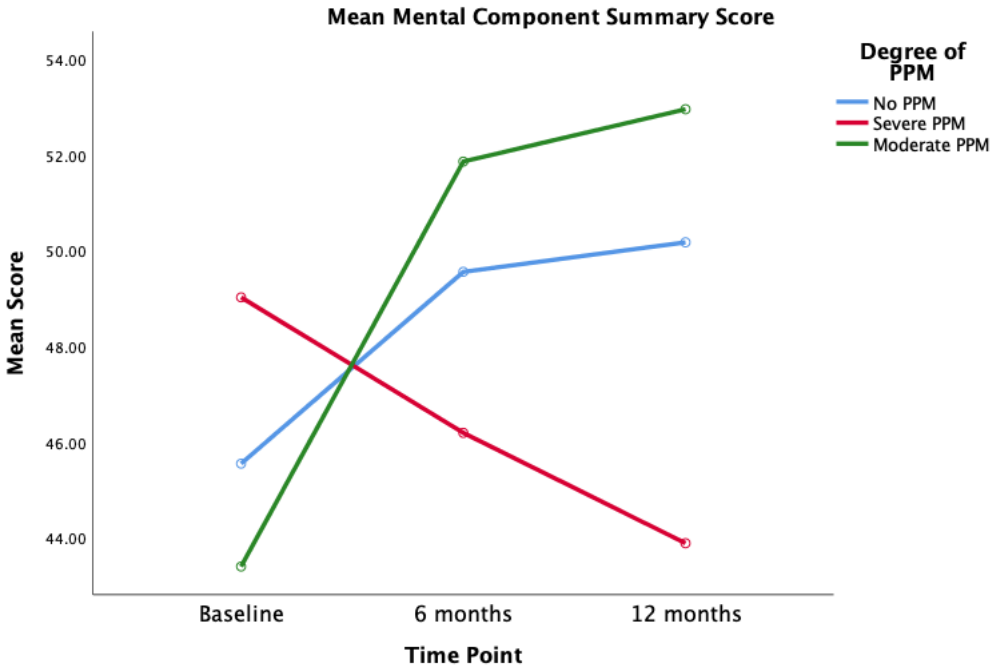


Figure 35: Mean MCS score over time.

The MCS score in those with severe PPM was significantly lower than those in the moderate PPM group and the no PPM group, p=0.01.

I also grouped the PPM sub groups into one "PPM" group and compared these to patients with no PPM. When looking at the PPM group as a whole, there was no significant difference between those with and without PPM (p=0.86), suggesting that only those with severe PPM had a significant reduction in MCS scores (Figure 35).

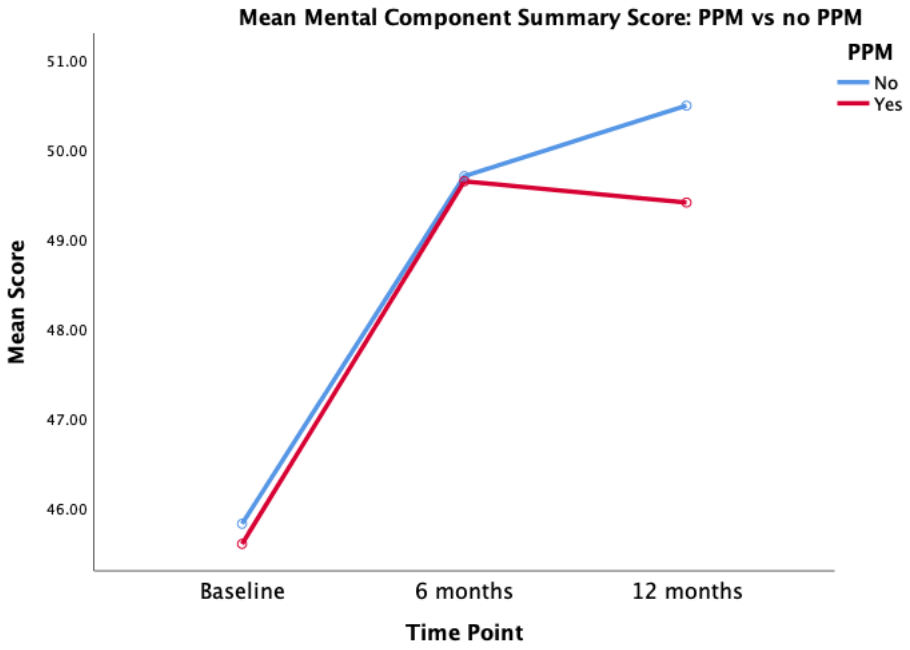


Figure 36: Mean MCS score over time: PPM vs no PPM.

As for PCS, I then looked at each individual component of the mental component summary, as follows.

Vitality

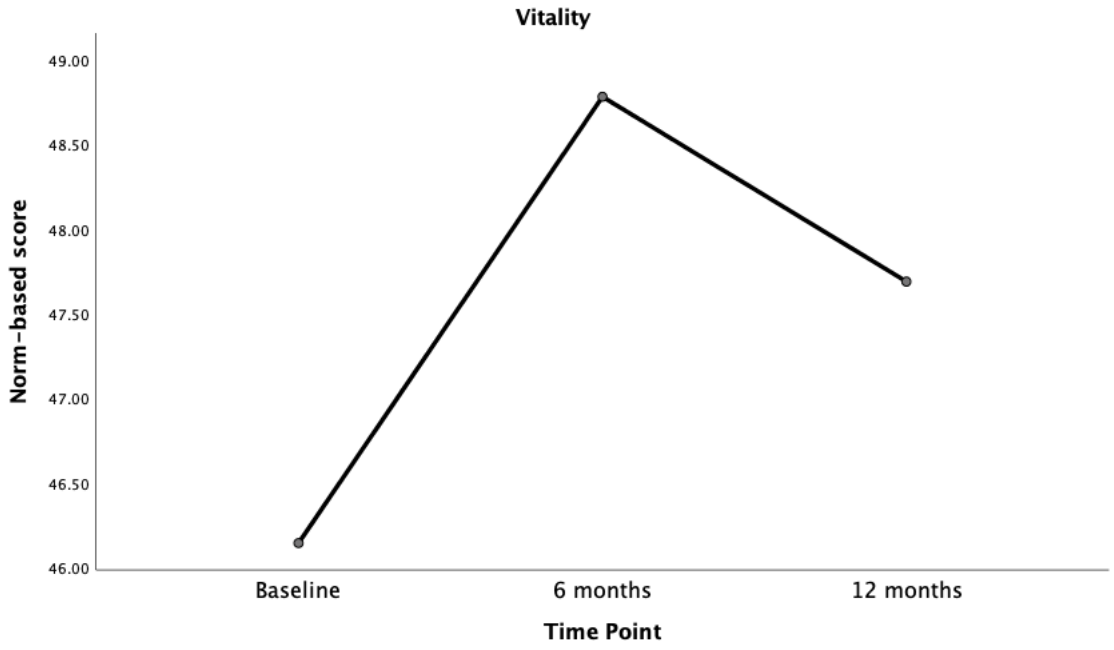


Figure 37: Trend in scores for overall cohort in the vitality component of MCS, ***p=0.21***

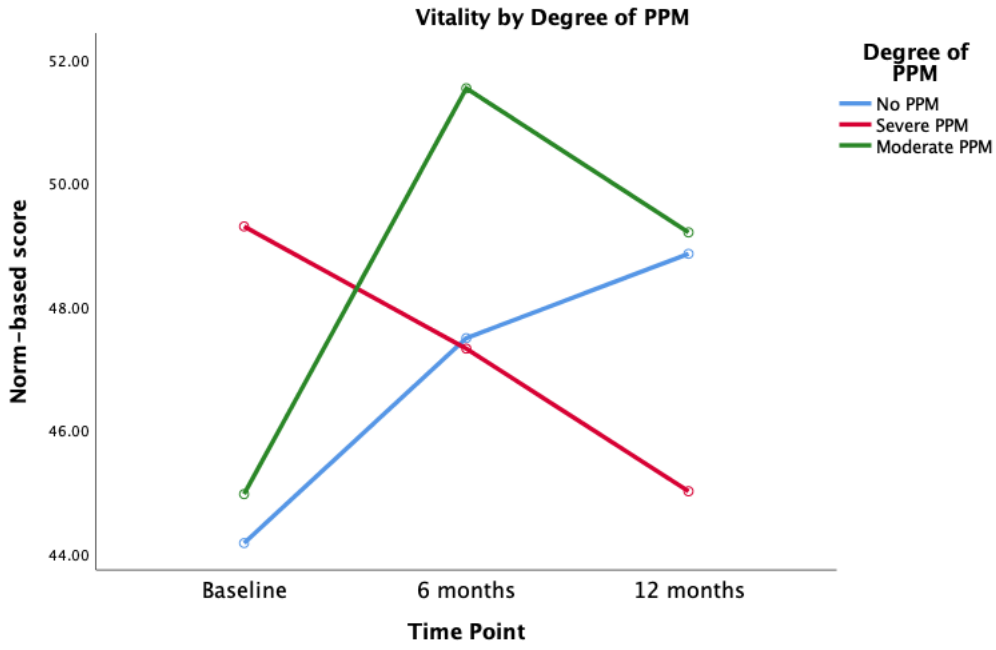


Figure 38: Vitality score by degree of PPM, ***p=0.11****.*

Social Functioning

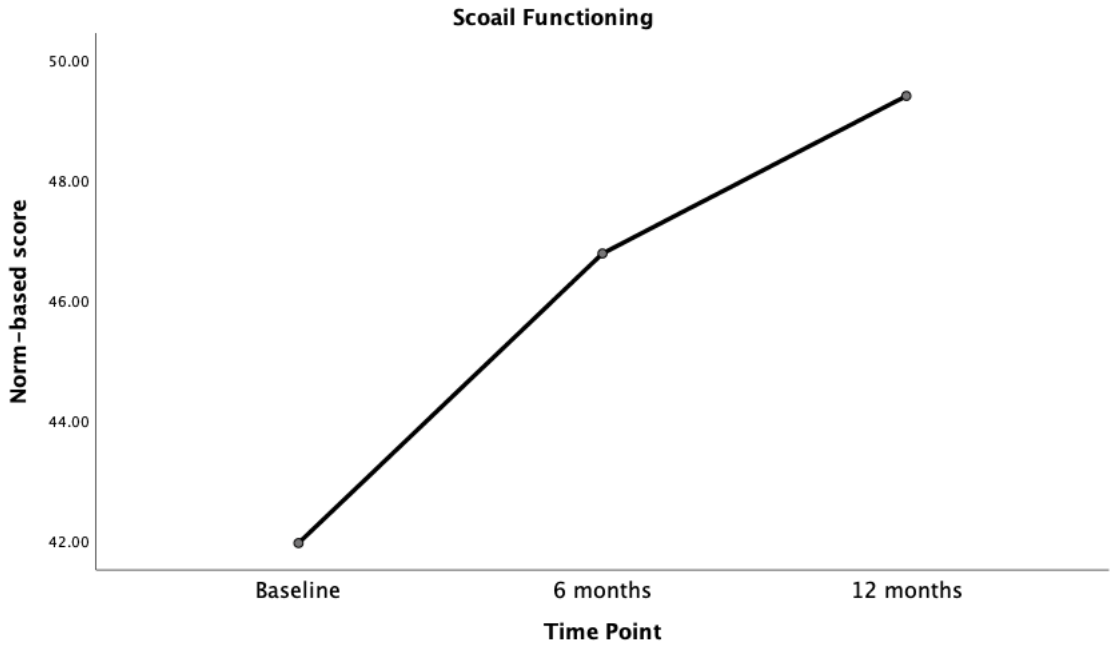


Figure 39: Trend in scores for overall cohort in the vitality component of MCS, ***p=0.0005***

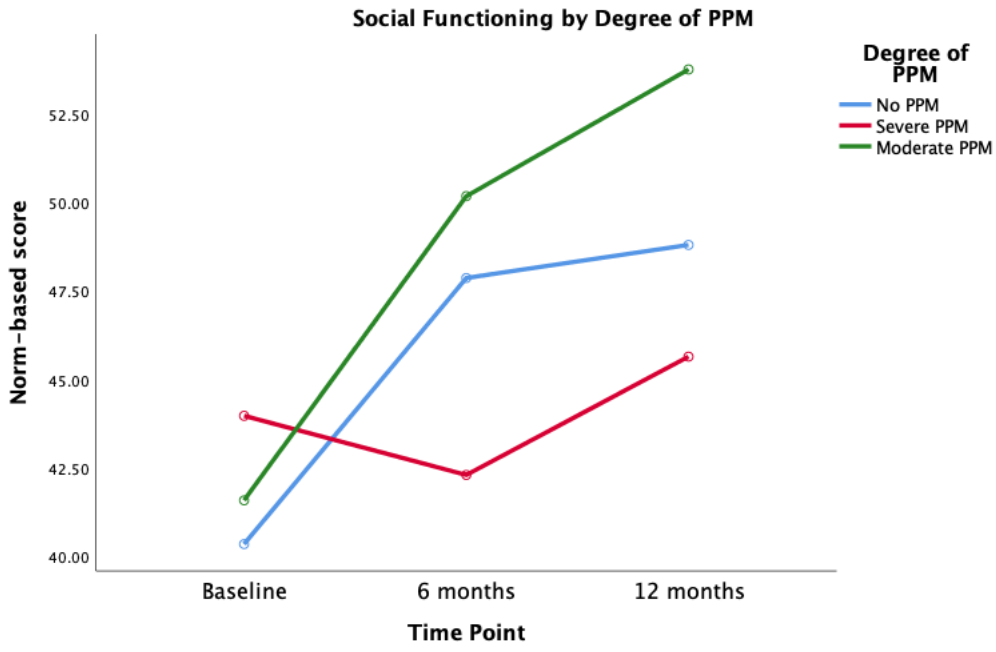


Figure 40: Social functioning score by degree of PPM, ***p=0.2****.*

Role Emotional

Figure 41: Trend in scores for overall cohort in the role emotional component of MCS, ***p=0.23.***

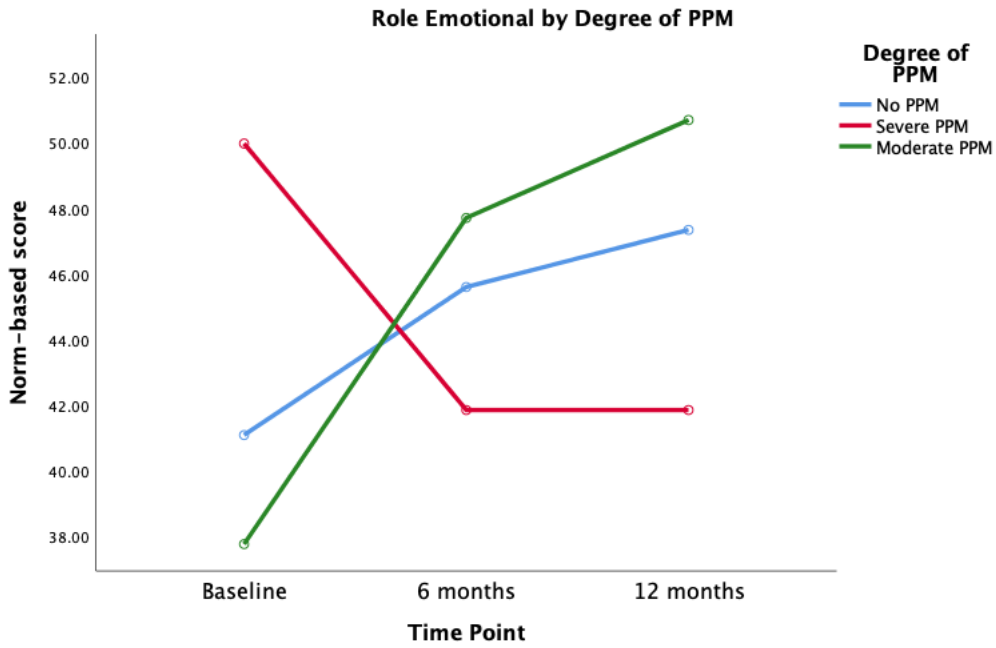


Figure 42: Social functioning score by degree of PPM, ***p=0.02****.*

Mental Health

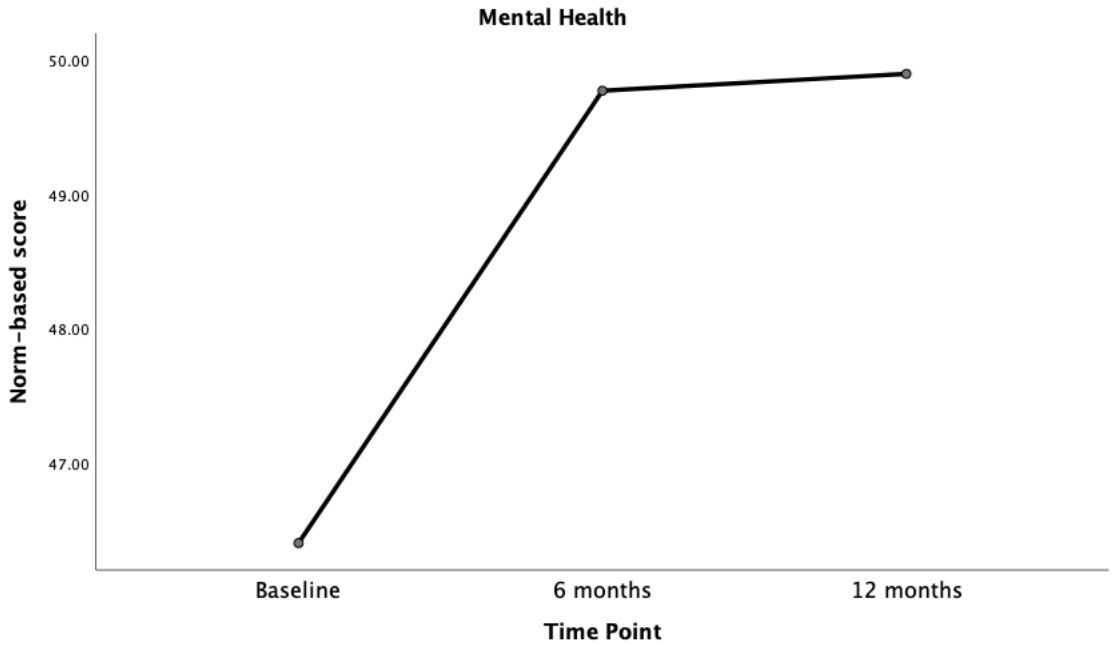


Figure 43: Trend in scores for overall cohort in the mental health component of MCS, ***p=0.06.***

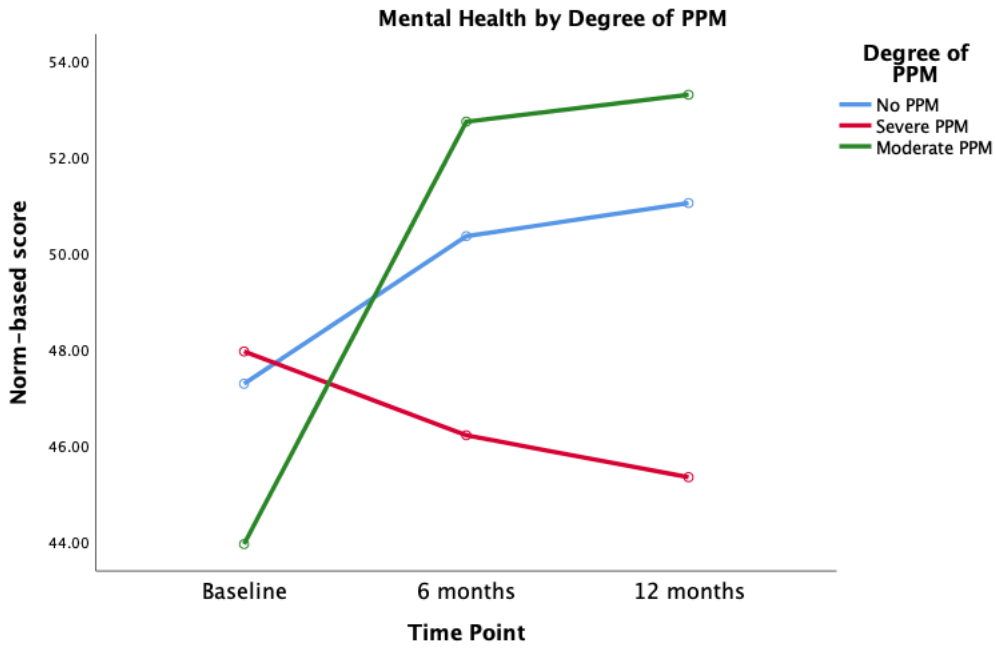


Figure 44: Mental health score by degree of PPM, ***p=0.11****.*

Patients with severe PPM reported the lowest scores in each of the components of the MCS, although not all of these reached statistical significance. This likely reflects the small number of patients in the cohort with severe PPM.

5.8 Predictors of PPM

From the literature, female sex, older age, hypertension, diabetes, renal failure and high surgical risk scores have been shown to be predictive of PPM.

I therefore hypothesised that older age, higher body surface area, smaller valve size and higher surgical risk score (EuroSCORE II), as well as smaller LVOT diameter would be predictive of PPM.

On univariate analysis, none of these were predictive of PPM.

On multivariate logistic regression analysis, the only predictor of PPM in this cohort was valve size (p=0.001, OR 2.45, CI 1.43 – 4.2), with smaller valve sizes being predictive of PPM.

6. Discussion

6 Discussion

6.1 Overview

The main aim of this study was to assess the outcomes of aortic valve replacement and the impact of postoperative valve gradient or patient prosthesis mismatch on postoperative outcomes and in particular, QOL. This study was performed following a larger QOL study on the outcomes of patients who had undergone cardiac surgery in the same unit. Patients who underwent AVR ± CABG were included and their outcomes analysed.

The novelty of this study is the fact that whilst there remains considerable debate about the impact of PPM on outcomes in those who have undergone AVR, there is a significant knowledge gap about its impact on patient reported QOL that our group has reported earlier (Bilkhu *et al.*, 2019). Multiple studies have demonstrated conflicting outcomes with some demonstrating no significant impact on outcome in those who have PPM following AVR, however, the vast majority of these studies have not assessed the impact of PPM on QOL.

This study has demonstrated that there is no significant impact on clinical outcomes in those with PPM following AVR, regardless of the degree of PPM. Whilst PPM does not impact the physical components of QOL, there is however a significantly lower score in the mental components of QOL.

6.2 Early outcomes of AVR

One of the principle aims of this study was to assess the outcomes of AVR. This was however a small cohort of patients and I studied patients who had undergone either AVR or AVR + CABG. The mortality for isolated AVR in the current series was 1.2%, which is similar to

international registry data (Thourani *et al.*, 2015; Tokuda *et al.*, 2020). In the UK there is no contemporary published data on the outcomes of AVR.

When looking at the entire cohort, including those who underwent AVR+CABG, the mortality was 5.8%. This may be due to possible higher predicted mortality in those who require CABG in addition to AVR but may also be as a result of the relatively small sample size. Despite this, there was no significant difference in mortality when comparing those with and without PPM.

The incidence of new stroke in this cohort was 5.2%. This is higher than the figures reported in the current literature, however this includes all patients and patients who underwent CABG in addition to AVR. This study demonstrated no difference in the incidence of stroke regardless of the presence of PPM. A number of groups however have reported a higher incidence of perioperative stroke in those with any degree of PPM (Hernández-Vaquero *et al.*, 2012; Dayan *et al.*, 2016; Swinkels *et al.*, 2016) with one study showing an incidence of peri-operative stroke in those with versus without PPM (3.9% vs 2.4% , p=0.02) (Dayan *et al.*, 2015).

Similarly, in terms of patients requiring renal replacement therapy, 7.5% in the current study required haemofiltration following AVR. This did not differ significantly across the groups, with only one patient in the PPM group requiring renal replacement therapy. In the literature, some groups have reported a higher incidence of renal failure and the requirement for renal replacement therapy in patients with PPM (Nozohoor *et al.*, 2010; Dayan *et al.*, 2015; Dahou *et al.*, 2016). These studies have studied patients who have undergone both isolated AVR and AVR+CABG. In one of the studies (Nozohoor *et al.*, 2010), the incidence of preoperative renal failure was higher in those with PPM. Therefore, whether PPM itself results in a higher

incidence of complications is not clear and as such, PPM may simply be a surrogate marker of comorbidity.

In the current study, the requirement for permanent pacemaker was 2.3%. The incidence after AVR is reported between 2 and 7%, which is relevant in the current era with the increase in the use of TAVI, which is reported to have a higher incidence of permanent pacemaker implantation of up to 34% (Mehaffey *et al.*, 2018; Mack *et al.*, 2019; Moskowitz *et al.*, 2019; Popma *et al.*, 2019).

6.2.1 Mortality during follow up

In the current study, 6 patients died during follow up. Two of these mortalities were early following surgery (5 and 12 days). The remaining 4 died during follow up. There was no significant difference between those with and without PPM.

This is consistent with the reported literature, whereby early mortality does not appear to be related to the presence of PPM (Bilkhu *et al.*, 2019). However, mortality at 5 to 10 years has been demonstrated to be higher in those with PPM (Mannacio *et al.*, 2017), despite being similar earlier mortality.

Whilst the current study did not identify any difference in mortality between the PPM and non PPM groups, it may be that a difference could emerge with longer follow-up.

6.3 Patient Prosthesis Mismatch

In the current study, the incidence of PPM was 15%, of which 42.3% had severe PPM. However, of the total cohort, only 6.4% had severe PPM. This is consistent with the reported literature (Pibarot *et al.*, 2019). The incidence of PPM varies in prevalence from 8-80% (Head *et al.*, 2012), with the incidence of severe PPM ranging between 6 and 62% (Bilkhu *et al.*, 2019).

The impact of PPM has been debated extensively. One of the arguments in patients who undergo TAVI is that there is a reduced incidence of PPM. One of the post hoc findings of the Placement of Aortic Transcatheter Valves (PARTNER) trial was the lower incidence of PPM after TAVI compared to surgical AVR, however, its incidence and impact on outcome has been reported varyingly (Bilkhu *et al.*, 2019).

PPM is fundamentally an echocardiographic diagnosis, and as such, may not necessarily manifest itself following surgery with specific symptoms, however it's diagnosis should be considered in those who present following surgery with symptoms such as breathlessness, after excluding other causes. It also relies on the identification of PPM at an early stage in the patient's postoperative recovery, so that it's diagnosis can be excluded if a patient re-presents with symptoms. Diagnosis of PPM can be somewhat more challenging in patients presenting with symptoms months or years after AVR because a high gradient and small orifice area may be due to structural valve deterioration rather than to PPM. In the current study, the majority of patients underwent early postoperative echocardiography upon which the diagnosis of PPM was made.

The current study has demonstrated no significant difference between patients who were found to have PPM on their first postoperative echocardiogram in terms of age, BMI, BSA, LV function or EuroSCORE (II and Logistic) or STS PROM score. In a meta-analysis by Dayan and colleagues, they demonstrated that in addition to larger BMI and BSA, diabetes, hypertension, renal failure and implantation of a bioprosthesis were predictive of PPM (Dayan *et al.*, 2015).

As would be expected, there was no significant difference in the operative characteristics of each of the groups in the current study. Of note, there was no significant difference in the size of the aortic valve prosthesis that was implanted at the time of surgery, with the overall median valve size being 23mm. It is thought that a small valve size results in a higher velocity and gradient across the valve and in mismatch (Medalion, 2000), however the results of the current study would not suggest that this is the case.

Indeed, when looking at the postoperative echocardiographic data, peak transvalvular velocity and EOA did not vary significantly across all groups. This reiterates the importance of ensuring indexed postoperative valve area to the body surface area are used to assess valve haemodynamics.

The current study has shown that in those with severe PPM, there are almost equal numbers of people with aortic regurgitation and aortic stenosis. Previous studies have demonstrated that PPM is more likely to occur in those with aortic stenosis (Pibarot *et al.*, 2000). This reflects the potentially smaller aortic annulus in patients with aortic stenosis, which may be related to calcification of the annulus. The incidence of severe PPM in patients with aortic regurgitation in the current study may simply reflect the small number of patients with PPM.

6.3.1 LV Mass Regression

An important parameter to assess is the reduction in LV mass or LV mass regression following AVR. This has important implications for LV function as failure of regression of myocardial mass will result in myocardial fibrosis and consequently impaired ventricular function in the long term (Minamino-Muta *et al.*, 2017; Puls *et al.*, 2020).

The results of the current study have demonstrated a significant reduction in LV mass index following AVR. Of note in the cohort of patients I studied, whilst there was a 27.8% reduction in LV mass in those with severe PPM, this did not reach statistical significance.

The data for LV mass regression was calculated on the most recent follow up echocardiogram available for that patient. In some, the only follow up scan available was performed prior to discharge from hospital. It was interesting to note that even on early postoperative echocardiography, there was reduction in the LV mass. This is similar to the findings of a study of 57 patients by Christakis and colleagues where they noted that on the echocardiogram performed just prior to discharge, there was a significant reduction in LV mass (Christakis *et al.*, 1996), leading them to conclude that LV mass regression begins in the early postoperative period. Recent data, albeit in patients who have undergone TAVI, shows that in patients who have greater regression of LV mass at one year, there is lower mortality and lower hospitalisation up to 5 years following valve replacement (Chau *et al.*, 2020).

The pathophysiology which can lead to this, in cases of severe PPM, results from failure of reduction in LV afterload. As a result, there is increased fibroblast infiltration of the myocardium and resultant expansion of the extracellular membrane which ultimately lead to myocyte death (Bing *et al.*, 2019). This is summarised below.

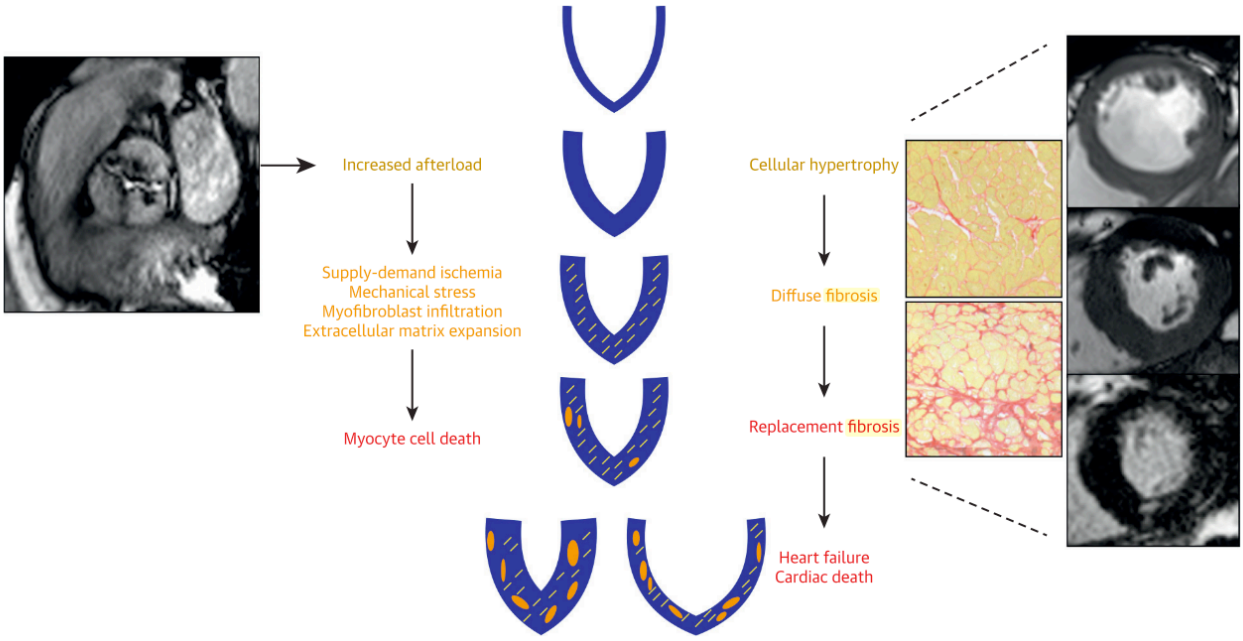


Figure 45: Mechanism of left ventricular decompensation in aortic stenosis (Bing *et al.*, 2019).

Therefore, although this study has identified that there is a significant reduction in LV mass after AVR, this is less significant in those with severe PPM. As a result, avoidance of severe PPM is important to ensure adequate recovery of the myocardium and to prevent the sequelae of myocardial fibrosis which would ultimately lead to cardiac failure and death.

6.3.2 Reintervention for PPM and Structural Valve Deterioration

During follow up, none of the patients required reintervention for PPM. Only one patient required re-operation and this was a patient who had prosthetic valve endocarditis.

In day to day practice, it is uncommon for a patient to undergo redo surgery for pure PPM. Patients may however require surgery for structural valve deterioration. In the majority of series reported in the literature in those with PPM, the reasons for reintervention which have been reported are most often due to structural valve deterioration and prosthetic valve endocarditis as opposed to PPM per se. In a recent report from the Finn-Valve registry which included 1874 patients with PPM, none of the patients underwent surgery for the diagnosis of PPM alone (Dahlbacka *et al.*, 2020).

There are limited reports of reintervention for PPM. However, a recent study by Keeling and colleagues assessed outcomes of patients who underwent surgery for the sole diagnosis of PPM (Keeling *et al.*, 2020). Over a 14-year period, they re-operated on 60 patients (4 patients per year) for the sole diagnosis of PPM. The patients either underwent aortic root replacement or a subcoronary stentless valve, with an operative mortality of 5%. They demonstrated a significant increase in the postoperative aortic valve area and reduction in the peak and mean gradients. None of the patients underwent aortic root enlargement procedures. This is relevant to prevention of PPM, which I will discuss later in the chapter.

6.4 QOL after Cardiac Surgery

There is greater emphasis being placed on outcomes such as QOL, given the marked improvements in mortality and major morbidity following cardiac surgery as this gives a more accurate measure of the impact of surgery on functional status (Noyez *et al.*, 2011; Tully, 2013).

There have been studies that have assessed the impact of AVR on QOL and have also related this to age, looking particularly at patients over the age of 80, where surgical AVR has been shown to significantly improve QOL (Sundt *et al.*, 2000; Klomp *et al.*, 2016).

The majority of studies which have assessed QOL in patients after cardiac surgery have mainly been limited to those without any preoperative QOL assessment. Our group previously studied the impact of prolonged intensive care unit stay on QOL in patients undergoing cardiac surgery. This demonstrated that even in patients who had a prolonged intensive care unit stay, there was improvement in QOL following surgery, albeit scores in the prolonged intensive care unit stay group being lower than those without (Diab *et al.*, 2018). All the patients had QOL assessment at baseline and were followed up for one year, similar to the current study.

The assessment of QOL may previously have been seen as a 'soft' end point, compared to others such as operative mortality. Therefore, the literature on QOL following cardiac surgery is somewhat limited. The majority of reports of QOL after cardiac surgery are mainly those where a QOL score has been used to compare one treatment to another, without necessarily having preoperative data (Noyez *et al.*, 2011). In addition, there is variability in the methods of QOL assessment used in the reported literature. One example would be the recent PARTNER 3 trial, where QOL outcomes of low risk patients who underwent TAVI were

compared to AVR, in which the method of assessment of QOL was using the NYHA classification, 6-minute walk test and the KCCQ (Kansas City Cardiomyopathy Questionnaire) (Mack *et al.*, 2019). These scores, aside from the 6-minute walk test, are disease specific and may not reflect the patients' overall wellbeing.

Therefore, to assess the overall wellbeing of the patient, using a tool which assesses QOL more generically is likely to give a more accurate picture of the patients' perceived health and wellbeing.

In the current study, SF-36 was used as the questionnaire to assess QOL. It is one of the most widely used generic measures of health-related QOL (Ware *et al.*, 1992). It has been shown to discriminate between subjects with different chronic conditions and between subjects with different severity levels of the same disease. It does not require a long time to complete and as a result, I was able to obtain >90% follow up QOL data.

Whilst not assessed in this study, quality adjusted life years or QALYs have been used in health economics to combine quantity and quality of life into a single metric. QALY assumes that a year of life lived in perfect health is worth 1 QALY (1 Year of Life × 1 Utility = 1 QALY). If the individual has lived a year of life lived in a state of less than perfect health then the QALY is worth less than 1. In order to determine the exact QALY value, the utility value associated with a given state of health is multiplied by the years lived in that state. QALYs are therefore expressed in terms of "years lived in perfect health" e.g. half a year lived in perfect health is equivalent to 0.5 QALYs ((Prieto *et al.*, 2003). It has the advantage of being easily calculated. However, there are a number of criticisms of the use of QALYs, including the concern that QALYs may discriminate on the basis of age and disability by favouring those healthier

populations who have a greater potential QALYs to gain. Another critcism is that QALYs are not patient focused, for example QALYs may not reflect certain individual priorities patients may have in treatment decisions, such as their effect on family circumstances. QALYs were not assessed in the current study given that patients were followed up for one year only and the QOL assessment methods which were used in the study provided a more comprehensive understanding of patients' perceptions of their health.

When looking at the whole of the cohort which I studied, there was a significant improvement in both physical and mental components of QOL during follow up. I then assessed the cohort based on the presence or absence of PPM.

6.5 QOL and PPM

In this study, I chose to assess QOL in relation to PPM. The reason for this was that given the conflicting data regarding PPM and its impact on outcome following surgery, it was important to see if PPM has any impact on what the patient experiences and reports following surgery. Is replacement of a stenotic aortic valve with a prosthetic valve of a lower gradient and with a larger valve area, and even where there may be a degree of PPM, enough to relieve symptoms and lead to improved QOL?

A number of groups have reported a lower incidence of PPM in patients who undergo TAVI. In a meta-analysis, which included 4000 patients, rates of PPM appeared to be lower in patients undergoing TAVI compared to surgical AVR (Pibarot *et al.*, 2014; Takagi *et al.*, 2016). This is now being considered an advantage of TAVI over surgical AVR, however, the benefit of TAVI in terms of PPM and its impact on QOL is unclear.

The majority of studies relating to PPM have focused on the impact on outcomes and mortality, either early following intervention or mortality during follow up. There are only a limited number of studies which have assessed the impact of PPM on QOL. They have shown no statistically significant difference in QOL between those with and without PPM (Ryomoto *et al.*, 2008; Sportelli *et al.*, 2016; Swinkels *et al.*, 2016; Reskovic Luksic *et al.*, 2017). Most of these studies do not assess QOL at baseline and only assess QOL in the follow up period.

6.5.1 Physical Component Summary Score of QOL

There was an overall improvement in the PCS score of SF-36, however, in those with severe PPM, there was no improvement in score from baseline. Both moderate PPM and no PPM groups had improved PCS scores from baseline.

Patients with severe PPM in the current series were noted to have a reduction in the PCS score of QOL at 6 months, however at 12 months, this had improved, but it did not go above baseline. When compared to those with PPM and moderate PPM, there was no significant difference, but both these groups did have improvement in PCS from baseline.

One explanation is that in these patients, despite there being no significant difference in hospital or operative outcomes, the fundamental issue is the small aortic valve area. Therefore, despite undergoing AVR, they may be experiencing the symptoms of aortic stenosis, with consequent impact on their QOL score.

When I looked at the individual components of the PCS, I noted that those with severe PPM, there was a significantly lower score in the general health domain, whilst those with no or

moderate PPM both had improvements in this score. Furthermore, there was a significant difference between those without or with moderate PPM and with severe PPM in the physical functioning and role physical domains but not in the bodily pain domain. Does not read well. Therefore, whilst there was an overall significant improvement in PCS scores for the whole cohort, analysis of the individual components of the PCS has demonstrated that patients with severe PPM have lower physical scores than those with no or moderate PPM. This may be related to the lack of improvement in the aortic valve orifice area despite AVR, meaning the patient may be limited by symptoms which may be similar to those of aortic stenosis which they presented with. It may also be related to regression of LV mass, which occurs to a much lesser degree in those with severe PPM.

6.5.2 Mental Component Summary Score of QOL

MCS score in the cohort was similar to PCS. Whilst there was an overall improvement in MCS score, in patients with severe PPM the score deteriorated when assessing the individual components of the MCS.

Scores in the vitality, role emotional and mental health components were lower in those with severe PPM. However, social functioning score, which was lower than those with no or moderate PPM showed improvement during follow up.

The differences between the groups may be accounted for by the small aortic valve orifice area relative to the patient's BSA, despite having undergone AVR, meaning the patient may be limited by symptoms which may be similar to those of aortic stenosis which they presented with, similar to the lower PCS scores.

If a patient reports lower PCS, this may mean that they are not able to return to their normal level of physical activity which may have a consequential impact on the patients' mental state. It is unlikely that PPM would directly have an impact on the patients mental state.

Whilst it may seem simplistic to associate mental state with physical mobility or ability, this has been studied. Ostir and colleagues assessed women aged above the age of 65 and demonstrated that with an increase in physical activity, there was an associated increase in social participation and reduction in depressive symptoms (Ostir *et al.*, 2007).

The impact of PPM on mental health has not been studied. However, there have been studies assessing the impact of aortic stenosis on an individual's mental health. Baz and colleagues reported on 140 patients with aortic stenosis and demonstrated that there was improvement in anxiety/depression scores following TAVI (Bäz *et al.*, 2020). The study population however were all above the age of 70.

6.6 Clinical Implications

Whilst this study has identified that there is no significant difference in early outcomes in those with PPM following AVR, regardless of the degree of PPM, it may have an impact on QOL during follow up and in particular, in those with severe PPM. However this difference appears to be subtle.

The question therefore arises whether PPM is an outcome that is important to avoid? Certainly, it would seem illogical to implant a valve that is not sufficient in size and matched for the patient. There are methods, based on data supplied from valve manufacturers, which can be used to predict postoperative iEOA and as such help to prevent PPM. However, there remains

little evidence that these methods of prediction are accurate. Vriesendorp and colleagues assessed 996 patients who had predicted iEOA, as opposed to iEOA calculated based on postoperative aortic valve area, and therefore predicted whether they would have PPM post op. Using iEOA charts, they incorrectly predicted PPM in 30% of the patients and severe PPM in 22% (Vriesendorp *et al.*, 2020). They concluded that studies relating to PPM should be based on actual measured EOA values and not on iEOA. This is a major criticism of another recent paper which assessed 4100 patients who underwent AVR and in whom they reported an incidence of PPM of 46% (Dahlbacka *et al.*, 2020). Their study was limited by the use of projected indexed effective orifice area (iEOA), and post procedural echocardiographic data were not available. This is therefore unlikely to be an accurate reflection of the number of patients with PPM in their cohort. The incidence in the current study of any degree of PPM was 15%.

6.6.1 Preventing PPM

Aside from predicting PPM, there are a number of methods or considerations to avoid PPM. The simplest method is to choose the right valve and place as large a prosthesis as possible, in relation to the aortic annulus. To ensure this happens, thorough removal of all native leaflets and thorough decalcification of the annulus would ensure as large a prosthesis as possible is implanted. Additionally, the use of pledgeted sutures, where possible, may be avoided in order to reduce the incidence of PPM. Kim and colleagues demonstrated in a series of 439 patients that the group of patients who underwent AVR with non pledgeted sutures had lower incidence of PPM (Kim *et al.*, 2020). However, the use of pledgeted sutures may be required for example where there is concern regarding the integrity and strength of the aortic annulus and if there is concern regarding paravalvular leakage.

Whilst it is important to ensure an adequately size prosthesis is implanted, it is equally important to ensure an oversized prosthesis is not implanted. An in vitro model study examined the effects of placing an oversized bioprosthetic valve and showed that there was reduced haemodynamic valve performance (Cleveland *et al.*, 2016), possibly related to abnormal stresses around the hinge point of each leaflet, causing the hinge point to be shifted inwards and reducing the EOA of the valve.

Whilst none of the patients in the current study did not undergo reintervention for valve deterioration during follow up, there is some evidence to suggest that structural valve deterioration may be accelerated in the context of PPM (Flameng *et al.*, 2010). Flameng and colleagues concluded that stenotic valve deterioration in the context of structural valve deterioration was typical of those with PPM whereas those with regurgitant type valve deterioration were mostly not related to PPM. In another study by Urso and colleagues, they reported that patients with PPM had a higher reoperation rate for structural valve deterioration (Urso *et al.*, 2014). This paper is difficult to interpret, given that estimated iEOA values were used to assess PPM as opposed to early postoperative echocardiographic data.

Another approach to prevention of PPM is enlargement of the aortic root to allow the placement of a larger prosthesis, of which there are a number of different surgical techniques. None of the included patients in the current study underwent an aortic root enlargement procedure.

Annular enlarging procedures add extra operative time and in particular, longer cardiopulmonary bypass and aortic cross clamp times, which may negatively impact outcomes following surgery (Salis *et al.*, 2008). They also add to the complexity of the procedure,

although some groups have reported that aortic root enlargement can be performed with low operative risk (Kulik *et al.*, 2008). The same group however noted that enlargement of the aortic root does not appear to translate into improved long-term clinical outcomes. In a recent propensity matched study by Tam and colleagues, they demonstrated that the addition of aortic root enlargement did not have an impact on early mortality, even with the addition of CABG; although the AVR + CABG and aortic root enlargement group did have a significantly higher requirement for resternotomy for bleeding (Tam *et al.*, 2019). Even at up to 8 years follow up, there was no difference in late mortality. A criticism of this study is that the authors have not defined which techniques of aortic root enlargement was used. Some groups have reported aortic root enlargement whereby the aortic annulus is not crossed and they have simply performed "root enlargement" by extending the aortotomy into the non-coronary sinus, without crossing the aortic annulus, and enlarging the sinus, such that a larger valve can be placed tilted, in a supra-annular position (Dhareshwar *et al.*, 2007). The originally described 'Nick's' and 'Manougian' techniques of aortic root enlargement involved crossing the aortic annulus and onto the anterior leaflet of the mitral valve (Grubb, 2015). One could argue that performing "root enlargement" without disrupting the annulus is technically more straight forward and therefore, it is important to understand which method of aortic root enlargement has been used when reporting this.

Some advocate the use of sutureless aortic valves in patients with a small aortic root and who may be at risk of PPM because of the improved haemodynamic performance (Borger *et al.*, 2016; Meco *et al.*, 2018). None of the patients in the current study had a sutureless valve implanted. Such a strategy would avoid additional procedures that increase CCT and CPB times, such as aortic root enlargement techniques. Shalabi and colleagues reported that in patients undergoing sutureless AVR there was a significantly lower postoperative transvalvular

gradient as well as greater left ventricular mass regression than those undergoing conventional biological AVR (Shalabi *et al.*, 2016). In addition, Borger et al demonstrated in a randomised controlled trial that sutureless AVR with the Intuity valve was associated with lower gradients and a lower incidence of PPM than conventional stented bioprostheses (Borger *et al.*, 2016).

Others have reported the contrary. Ghoneim and colleagues studied the outcomes of various biological valve options, including stentless valves, stented valves and sutureless variety and reported similar postoperative transvalvular gradient in the sutureless group compared to the stented group (Ghoneim *et al.*, 2016). The similarity in postoperative transvalvular gradient between sutureless and conventional biological valves was also reported in a meta-analysis by Sohn and colleagues (Sohn *et al.*, 2018).

Modern pericardial bioprosthetic valves have been modified in their design to allow for placement of a larger bioprosthesis and avoid a high gradient across the valve (Botzenhardt *et al.*, 2005). Some bioprosthetic valves are designed with a lower profile to sit in a supra-annular position, which allows a larger valve size to be implanted, without having to perform root enlargement procedures. These valves have demonstrated good outcomes with low incidence of PPM during follow up with no patients with severe PPM (Kume *et al.*, 2017). In addition stentless valves have also been proposed as a means of reducing the incidence of PPM, particularly in those with small aortic roots (Wollersheim *et al.*, 2016). The majority of patients in the current study received a stented bioprosthetic valve.

6.6.2 Implications of Placing a Large Prosthesis

Whilst the current study has not demonstrated any difference in early postoperative outcomes in those with PPM, patients with PPM by definition have a small valve relative to their BSA.

Multivariate analysis in the current study demonstrated that smaller valve sizes were predictive of PPM.

Ensuring a larger prosthesis will not only mean a larger EOA and less risk of PPM, however there may now be another reason to consider a larger prosthesis. There has been a trend of increased use of tissue valves and a decrease in the use of mechanical valves in recent years (Tam *et al.*, 2020). This may be due to the evolution of TAVI whereby younger patients can have a TAVI valve in the future when the tissue valve has deteriorated, so called valve-in-valve TAVI (Simonato *et al.*, 2019; Landes *et al.*, 2020). However, for this to be performed with good result and without residual high transvalvular gradient, a large enough surgical prosthesis needs to be in situ. For example, a TAVI valve placed inside a 19mm surgical prosthesis may produce a high transvalvular gradient (Azadani *et al.*, 2011).

Whilst valve in valve TAVI is a possibility that may be considered in the failing bioprosthesis, the outcomes of redo aortic valve replacement, even in those above the age of 80 are good (Onorati *et al.*, 2014).

6.7 Limitations of this study

This study has the advantage of prospective data collection, baseline and early postoperative echocardiographic data and baseline QOL assessment. The limitations include the relatively small number of patients. In addition, whilst it has not demonstrated any significant differences in those with PPM in terms of in hospital outcomes and mortality or mortality and mortality during follow up, the follow up period is relatively short. In addition, echocardiography in all patients was not necessarily performed by the same sonographer and so may have introduced

observer variability. This study was powered to assess QOL in patients with PPM and it was limited by not being powered to assess the secondary outcomes of various categories of PPM.

The study lacked the assessment of myocardial fibrosis which may have been possible with MRI assessment. However, due to nature of MRI scanning and the time required for each patient, I decided that measuring change in LV mass would be the main outcome for assessing myocardial remodelling, particularly given evidence demonstrating that LV mass regression is associated with improved outcomes following AVR (Ali *et al.*, 2011).

6.8 Future work

Potential areas for further study into PPM should include more detailed assessment of the effect of PPM on the myocardium. Whilst this study assessed the effect on LV mass, there was no quantification of the extent of myocardial fibrosis. It would be important to assess whether or not there is increasing myocardial fibrosis in those with PPM during follow up. To undertake this accurately, cardiac MRI scanning would be required.

Other potential assessment on the effect of PPM on the myocardium may include measurement of BNP and assessment of cardiac failure during follow up. In progressive aortic stenosis, the natural history would end in cardiac failure and as such, if the afterload on the left ventricle is not relieved sufficiently, as in severe PPM, BNP may rise.

6.9 Conclusions

This study has demonstrated that PPM following surgical AVR does not impact early postoperative outcomes, regardless of the degree of PPM. It has also demonstrated that there is no significant impact on mortality or reintervention up to one year follow up. Quality of life

was noted to improve over time following surgery in those with no or moderate PPM, however in those with severe PPM, QOL scores were lower during follow up. Valve implant size was identified as the main predictor of PPM.

In order to prevent PPM, aside from placing the largest size prosthesis, choice of valve implant type, method of implant type, additional procedures such as aortic root enlargement may be considered. The addition of extra surgical procedures increase the complexity and operative time, which may have an impact on outcome. The prediction of PPM is possible, and whilst this may not be completely accurate, would guide the surgeon with regard the optimal size prosthesis to be implanted and to plan surgical approach and technique accordingly.

Further long term studies, which utilise baseline and early postoperative echocardiographic data to define PPM should be considered.

References

References

Ali, A, Patel, A, Ali, Z, *et al.* (2011) Enhanced left ventricular mass regression after aortic valve replacement in patients with aortic stenosis is associated with improved long-term survival. *J. Thorac. Cardiovasc. Surg.* 142(2):285–291.

Amorim, PA, Diab, M, Walther, M, *et al.* (2020) Limitations in the Assessment of Prosthesis-Patient Mismatch. *Thorac. Cardiovasc. Surg.* 68(7):550–556.

Armstrong, AC, Gidding, S, Gjesdal, O, *et al.* (2012) LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. *JACC Cardiovasc. Imaging*. 5(8):837–848.

Azadani, AN and Tseng, EE (2011) Transcatheter heart valves for failing bioprostheses: State-of-the-art review of valve-in-valve implantation. *Circ. Cardiovasc. Interv.* 4(6):621–628.

Baumgartner, H, Falk, V and Bax, J et al. (2017) 2017 ESC / EACTS Guidelines for the management of valvular heart disease The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European. *Eur. Heart J.* 38(September):2739–2786.

Bäz, L, Wiesel, M, Möbius-Winkler, S, *et al.* (2020) Depression and anxiety in elderly patients with severe symptomatic aortic stenosis persistently improves after transcatheter aortic valve replacement (TAVR). *Int. J. Cardiol.* 30948–54.

Bilkhu, Rajdeep, Borger, MA, Briffa, NP, *et al.* (2019) Sutureless aortic valve prostheses. *Heart*. 105:s16–S20.

Bilkhu, Rajdeep, Jahangiri, M and Otto, CM (2019) Patient-prosthesis mismatch following aortic valve replacement. *Heart*. 105(Suppl 2):s28–s33.

Bing, R, Cavalcante, JL, Everett, RJ, *et al.* (2019) Imaging and Impact of Myocardial Fibrosis in Aortic Stenosis. *JACC Cardiovasc. Imaging*. 12(2):283–296.

Borer, JS, Truter, S, Herrold, EM, *et al.* (2002) Myocardial Fibrosis in Chronic Aortic Regurgitation. *Circulation*. 105(15):1837–1842.

Borger, MA, Dohmen, PM, Knosalla, C, *et al.* (2016) Haemodynamic benefits of rapid deployment aortic valve replacement via a minimally invasive approach: 1-year results of a prospective multicentre randomized controlled trial. *Eur. J. Cardiothorac. Surg.* 50(4):713-720.

Botzenhardt, F, Eichinger, WB, Bleiziffer, S, *et al.* (2005) Hemodynamic comparison of bioprostheses for complete supra-annular position in patients with small aortic annulus. *J. Am. Coll. Cardiol.* 45(12):2054–2060.

Bridgewater, B, Keogh, B, Kinsman, R, *et al.* (2008) *The Society for Cardiothoracic Surgery in Great Britain & Ireland Sixth National Adult Cardiac Surgical Database Report: Demonstrating quality*.

Cardiology, BJ of (2016) *Heart valve disease module 4: diagnosis - The British Journal of Cardiology*. Available at: https://bjcardio.co.uk/2016/03/heart-valve-disease-module-4-diagnosis-2/4/ (Accessed: 13 April 2020).

Chakravarty, T, Søndergaard, L, Friedman, J, *et al.* (2017) Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 389(10087):2383–2392.

Chau, KH, Douglas, PS, Pibarot, P, *et al.* (2020) Regression of Left Ventricular Mass After Transcatheter Aortic Valve Replacement: The PARTNER Trials and Registries. *J. Am. Coll. Cardiol.* 75(19):2446–2458.

Christakis, GT, Joyner, CD, Morgan, CD, *et al.* (1996) Left ventricular mass regression early after aortic valve replacement. *Ann. Thorac. Surg.* 62(4):1084–1089.

Cianciulli, TE, Lax, JA, Beck, MA, *et al.* (2005) Cinefluoroscopic assessment of mechanical disc prostheses: its value as a complementary method to echocardiography. *J. Heart Valve Dis.* 14(5):664-73.

Clayton, B, Morgan-Hughes, G and Roobottom, C (2014) Transcatheter aortic valve insertion (TAVI): A review. *Br. J. Radiol.* 87(1033).

Cleveland, JD, Bowdish, ME, Eberhardt, CE, *et al.* (2016) Evaluation of Hemodynamic Performance of Aortic Valve Bioprostheses in a Model of Oversizing. *Ann. Thorac. Surg.* 103(6):1866-1876.

Dahlbacka, S, Laakso, T, Kinnunen, E-M, *et al.* (2020) Patient-Prosthesis Mismatch Worsens Long-term Survival – Insights From The FinnValve Registry. *Ann. Thorac. Surg.* 111(4):1284-1290.

Dahou, A, Mahjoub, H and Pibarot, P (2016) Prosthesis-patient mismatch after aortic valve replacement. *Curr. Treat. Options Cardiovasc. Med.* 18(11):67.

David, TE (2005) Is prosthesis-patient mismatch a clinically relevant entity? *Circulation*. 111(24):3186–3187.

Dayan, V, Soca, G, Stanham, R, *et al.* (2015) Is patient-prosthesis mismatch a predictor of survival or a surrogate marker of co-morbidities in cardiac surgery? *Int. J. Cardiol.* 190389–392.

Dayan, V, Vignolo, G, Soca, G, *et al.* (2016) Predictors and Outcomes of Prosthesis-Patient Mismatch After Aortic Valve Replacement. *JACC Cardiovasc. Imaging*. 9(8):924–933.

Deschka, H, Schreier, R, El-Ayoubi, L, *et al.* (2013) Survival, functional capacity, and quality of life after cardiac surgery followed by long-term intensive care stay. *Thorac. Cardiovasc. Surg.* 61(8):696–700.

Devereux, RB, Alonso, DR, Lutas, EM, *et al.* (1986) Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am. J. Cardiol.* 57(6):450–458.

Dhareshwar, J, Sundt, TM, Dearani, JA, *et al.* (2007) Aortic root enlargement: What are the

operative risks? *J. Thorac. Cardiovasc. Surg.* 134(4):916–924.

Diab, MS, Bilkhu, R, Soppa, G, *et al.* (2018) The impact of prolonged intensive care stay on quality of life, recovery and clinical outcomes following cardiac surgery: prospective cohort study. *J. Thorac. Cardiovasc. Surg.* 156(5):1906-1915.e3.

Eagle, KA, Guyton, RA, Davidoff, R, *et al.* (2004) ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery. *Circulation*. 110(9):1168-76.

Enriquez-Sarano, M and Tajik, AJ (2004) Aortic regurgitation. *Aortic Regurgitation*. 351(15):1539–1546.

Everett, RJ, Clavel, MA, Pibarot, P, *et al.* (2018) Timing of intervention in aortic stenosis: A review of current and future strategies. *Heart*. 104(24):2067–2076.

Fallon, JM, DeSimone, JP, Brennan, JM, *et al.* (2018) The Incidence and Consequence of Prosthesis-Patient Mismatch After Surgical Aortic Valve Replacement. *Ann. Thorac. Surg.* 106(1):14–22.

Fatima, B, Mohananey, D, Khan, FW, *et al.* (2019) Durability Data for Bioprosthetic Surgical Aortic Valve: A Systematic Review. *JAMA Cardiol.* 4(1):71–80.

Flameng, W, Herregods, MC, Vercalsteren, M, *et al.* (2010) Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. *Circulation*. 121(19):2123–2129.

Foppa, M, Duncan, BB and Rohde, LEP (2005) Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? *Cardiovasc. Ultrasound*. 31–13.

Foroutan, F, Guyatt, GH, O'Brien, K, *et al.* (2016) Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: Systematic review of observational studies. *BMJ*. 3541–9.

Foroutan, F, Guyatt, GH, Otto, CM, *et al.* (2017) Structural valve deterioration after transcatheter aortic valve implantation. *Heart*. 103(23):1899–1905.

Ghoneim, A, Bouhout, I, Demers, P, *et al.* (2016) Management of small aortic annulus in the era of sutureless valves: A comparative study among different biological options. *J. Thorac. Cardiovasc. Surg.* 152(4):1019–1028.

Girard, SE, Miller, FA, Montgomery, S, *et al.* (2001) Outcome of reoperation for aortic valve prosthesis-patient mismatch. *Am. J. Cardiol.* 87(1):111–114.

Glauber, M, Ferrarini, M and Miceli, A (2015) Minimally invasive aortic valve surgery: state of the art and future directions. *Ann. Cardiothorac. Surg.* 4(1):26–32.

Gott, VL, Alejo, DE and Cameron, DE (2003) Mechanical Heart Valves: 50 Years of Evolution. in *Ann. Thorac. Surg.* S2230–S2239.

Grubb, KJ (2015) Aortic Root Enlargement During Aortic Valve Replacement: Nicks and Manouguian Techniques. *Oper. Tech. Thorac. Cardiovasc. Surg.* 20(3):206–218.

Guo, L, Zheng, J, Chen, L, *et al.* (2017) Impact of prosthesis–patient mismatch on short-term outcomes after aortic valve replacement: a retrospective analysis in East China. *J. Cardiothorac. Surg.* 12(1):42.

Haraldstad, K, Wahl, A, Andenæs, R, *et al.* (2019) A systematic review of quality of life research in medicine and health sciences. *Qual. Life Res.* 28(10):2641–2650.

HARKEN, DE, SOROFF, HS, TAYLOR, WJ, *et al.* (1960) Partial and complete prostheses in aortic insufficiency. *J. Thorac. Cardiovasc. Surg.* 40(6):744–762.

Head, SJ, Mokhles, MM, Osnabrugge, RLJ, *et al.* (2012) The impact of prosthesispatient mismatch on long-term survival after aortic valve replacement: A systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur. Heart J.* 33(12):1518–1529.

Head, SJ, Çelik, M and Kappetein, AP (2017) Mechanical versus bioprosthetic aortic valve replacement. *Eur. Heart J.* 38(28):2183–2191.

Hernández-Vaquero, D, Llosa, JC, Díaz, R, *et al.* (2012) Impact of patient-prosthesis mismatch on 30-day outcomes in young and middle-aged patients undergoing aortic valve replacement. *J. Cardiothorac. Surg.* 7:46.

Hirji, SA, Kaneko, T and Aranki, S (2018) The revolution and evolution of mechanical valves: The ball has left the cage. *J. Thorac. Cardiovasc. Surg.* e149–e150.

Hong, S, Yi, G, Youn, Y-N, *et al.* (2013) Effect of the prosthesis-patient mismatch on long-term clinical outcomes after isolated aortic valve replacement for aortic stenosis: a prospective observational study. *J. Thorac. Cardiovasc. Surg.* 146(5):1098–104.

Kaminishi, Y, Misawa, Y, Kobayashi, J, *et al.* (2013) Patient-prosthesis mismatch in patients with aortic valve replacement. *Gen. Thorac. Cardiovasc. Surg.* 61(5):274–279.

Keeling, B, Beckerman, Z, Wei, J, *et al.* (2020) Benchmarking Outcomes: Reoperation for Aortic Valve Patient Prosthesis Mismatch. *Ann. Thorac. Surg.* 111(5):1472-1477.

Kim, HH, Lee, S, Joo, HC, *et al.* (2020) Impact of Suture Techniques for Aortic Valve Replacement on Prosthesis-Patient Mismatch. *Ann. Thorac. Surg.* 109(3):661–667.

Kindo, M, Minh, TH, Perrier, S, *et al.* (2017) Impact of prosthesis-patient mismatch on early haemodynamic status after aortic valve replacement. *Interact. Cardiovasc. Thorac. Surg.* 24(1):48–54.

Klomp, WWJ, Nierich, AP, Peelen, LM, *et al.* (2016) Survival and quality of life after surgical aortic valve replacement in octogenarians. *J. Cardiothorac. Surg.* 11:38.

Kulik, A, Al-Saigh, M, Chan, V, *et al.* (2008) Enlargement of the Small Aortic Root During Aortic Valve Replacement: Is There a Benefit? *Ann. Thorac. Surg.* 85(1):94–100.

Kume, Y, Fujita, T, Fukushima, S, *et al.* (2017) Reducing Prosthesis-Patient Mismatch With Edwards Magna Prosthesis for Aortic Valve Replacement. *Circ. J.* 81(4):468–475.

Landes, U, Webb, JG, De Backer, O, *et al.* (2020) Repeat Transcatheter Aortic Valve Replacement for Transcatheter Prosthesis Dysfunction. *J. Am. Coll. Cardiol.* 75(16):1882–1893.

Leon, MB, Smith, CR, Mack, M, *et al.* (2010) Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. *N. Engl. J. Med.* 363(17):1597–1607.

Leon, MB, Smith, CR, Mack, MJ, *et al.* (2016) Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N. Engl. J. Med.* 374(17):1609–1620.

Luis, SA, Padang, R and Murphy, JG (2019) Isolated Aortic Regurgitation: A Tale of Two Disorders. *Mayo Clin. Proc.* 1131–1134.

Mack, MJ, Leon, MB, Thourani, VH, *et al.* (2019) Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N. Engl. J. Med.* 380(18):1695–1705.

Mahjoub H, Dahou A, DJ and PP (2017) *Echocardiographic recognition and quantiation of prosthetic valve dysfunction*. 5th Ed. Edited by C. M. Otto.

Makkar, RR, Thourani, VH, Mack, MJ, *et al.* (2020) Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. *N. Engl. J. Med.* 382(9):799–809.

Manji, RA, Lee, W and Cooper, DKC (2015) Xenograft bioprosthetic heart valves: Past,

present and future. *Int. J. Surg.* 280–284.

Mannacio, V, Mannacio, L, Mango, E, *et al.* (2016) Severe prosthesis-patient mismatch after aortic valve replacement for aortic stenosis: Analysis of risk factors for early and long-term mortality. *J Cardiol*. 69(1):333–339.

Mannacio, VA, Mannacio, L, Antignano, A, *et al.* (2017) Impact of different values of prosthesis-patient mismatch on outcome in male patients with aortic valve replacement. *J. Cardiovasc. Med.* 18(5):366-373.

Martin, E, Mohammadi, S, Jacques, F, *et al.* (2017) Clinical Outcomes Following the Ross Procedure in Adults: A 25-Year Longitudinal Study. *J. Am. Coll. Cardiol.* 70(15):1890–1899.

Masri, A, Svensson, LG, Griffin, BP, *et al.* (2017) Contemporary natural history of bicuspid aortic valve disease: A systematic review. *Heart*. 103(17):1323–1330.

Meco, M, Montisci, A, Miceli, A, *et al.* (2018) Sutureless perceval aortic valve versus conventional stented bioprostheses: Meta-analysis of postoperative and midterm results in isolated aortic valve replacement. *J. Am. Heart Assoc.* 7(4):

Medalion, B (2000) Aortic valve replacement: Is valve size important? *J. Thorac. Cardiovasc. Surg.* 119(5):963–974.

Mehaffey, JH, Haywood, NS, Hawkins, RB, *et al.* (2018) Need for Permanent Pacemaker After Surgical Aortic Valve Replacement Reduces Long-Term Survival. *Ann. Thorac. Surg.*

106(2):460–465.

Minamino-Muta, E, Kato, T, Morimoto, T, *et al.* (2017) Impact of the left ventricular mass index on the outcomes of severe aortic stenosis. *Heart*. 103(24):1992–1999.

Moskowitz, G, Hong, KN, Giustino, G, *et al.* (2019) Incidence and Risk Factors for Permanent Pacemaker Implantation Following Mitral or Aortic Valve Surgery. *J. Am. Coll. Cardiol.* 74(21):2607–2620.

Musa, TA, Treibel, TA, Vassiliou, VS, *et al.* (2018) Myocardial Scar and Mortality in Severe Aortic Stenosis: Data from the BSCMR Valve Consortium. *Circulation*. CIRCULATIONAHA.117.032839.

Myerson, SG, Bellenger, NG and Pennell, DJ (2002) Assessment of Left Ventricular Mass by Cardiovascular Magnetic Resonance. *Hypertension*. 39750–755.

Nakane, Y, Tazaki, M and Miyaoka, E (1999) Whoqol. *Iryo To Shakai*. 9(1):123–131.

Nishimura, RA, Otto, CM, Bonow, RO, *et al.* (2014) *2014 AHA / ACC Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines*. *Circulation*. 63(22):e57-185.

Noyez, L, de Jager, MJ and Markou, ALP (2011) Quality of life after cardiac surgery:Underresearched research. *Interact. Cardiovasc. Thorac. Surg.* 13(5):511–515.

Nozohoor, S, Nilsson, J, Lührs, C, *et al.* (2010) Influence of prosthesis-patient mismatch on left ventricular remodelling in severe aortic insufficiency. *Eur. J. Cardiothorac. Surg.* 37(1):133–138.

Onorati, F, Biancari, F, De Feo, M, *et al.* (2014) Outcome of redo surgical aortic valve replacement in patients 80 years and older: Results from the multicenter RECORD initiative. *Ann. Thorac. Surg.* 97(2):537–543.

Ostir, G, Ottenbacher, K, Fried, L, *et al.* (2007) The Effect of Depressive Symptoms on the Association Between Functional Status and Social Participation. *Soc Indic Res.* 80(2):379–392.

Otto, CM and Prendergast, B (2014) Aortic-valve stenosis - From patients at risk to severe valve obstruction. *N. Engl. J. Med.* 371(8):744–756.

De Paulis, R and Salica, A (2019) Surgical anatomy of the aortic valve and root-implications for valve repair. *Ann. Cardiothorac. Surg.* 8(3):313–321.

Pawade, T, Clavel, MA, Tribouilloy, C, *et al.* (2018) Computed Tomography Aortic Valve Calcium Scoring in Patients with Aortic Stenosis. *Circ. Cardiovasc. Imaging*. 11(3):1–11.

Pequeno, NPF, Pequeno, NPF, Cabral, NL de A, *et al.* (2020) Quality of life assessment instruments for adults: a systematic review of population-based studies. *Health Qual. Life Outcomes*. 18(1):1–13.

Perrotti, A, Ecarnot, F, Monaco, F, *et al.* (2019) Quality of life 10 years after cardiac surgery

in adults: A long-term follow-up study. *Health Qual. Life Outcomes*. 17(1):88.

Pibarot, P, Dumesnil, JG, Cartier, PC, *et al.* (2001) Patient-prosthesis mismatch can be predicted at the time of operation. *Ann. Thorac. Surg.* 71(5 SUPPL.):0–3.

Pibarot, P, Weissman, NJ, Stewart, WJ, *et al.* (2014) Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: A PARTNER trial cohort-a analysis. *J. Am. Coll. Cardiol.* 64(13):1323–1334.

Pibarot, P, Magne, J, Leipsic, J, *et al.* (2019) Imaging for Predicting and Assessing Prosthesis-Patient Mismatch After Aortic Valve Replacement. *JACC Cardiovasc. Imaging*. 12(1):149–162.

Pibarot, P and Dumesnil, JG (2000) Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. *J. Am. Coll. Cardiol.* 1131–1141.

Pibarot, P and Dumesnil, JG (2006) Prosthesis-patient mismatch: Definition, clinical impact, and prevention. *Heart*. 92(8):1022–1029.

Pieter Kappetein, A, Head, SJ, Généreux, P, *et al.* (2012) Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. *EuroIntervention*. 8(7):782–795.

Popma, JJ, Michael Deeb, G, Yakubov, SJ, *et al.* (2019) Transcatheter aortic-valve replacement

with a self-expanding valve in low-risk patients. *N. Engl. J. Med.* 380(18):1706–1715.

Price, J, Lapierre, H, Ressler, L, *et al.* (2009) Prosthesis-patient mismatch is less frequent and more clinically indolent in patients operated for aortic insufficiency. *J. Thorac. Cardiovasc. Surg.* 138(3):639–645.

Price, J, Toeg, H, Lam, B-K, *et al.* (2014) The impact of prosthesis-patient mismatch after aortic valve replacement varies according to age at operation. *Heart*. 100(14):1099-106.

Prieto, L and Sacristán, JA (2003) Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual. Life Outcomes*. 11–8.

Puls, M, Beuthner, BE, Topci, R, *et al.* (2020) Impact of myocardial fibrosis on left ventricular remodelling, recovery, and outcome after transcatheter aortic valve implantation in different haemodynamic subtypes of severe aortic stenosis. *Eur. Heart J.* 41(20):1903–1914.

Puskas, JD, Bavaria, JE, Svensson, LG, *et al.* (2017) The COMMENCE trial: 2-year outcomes with an aortic bioprosthesis with RESILIA tissue. *Eur. J. Cardiothorac. Surg.* 52(3):432–439.

Puskas, JD, Gerdisch, M, Nichols, D, *et al.* (2018) Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement. *J. Am. Coll. Cardiol.* 71(24):2717–2726.

Rahimtoola, SH (1978) The Problem of Valve Prosthesis-Patient Mismatch. *Circu*. 58(1):20–25.

Reskovic Luksic, V, Dosen, D, Pasalic, M, *et al.* (2017) Impact of mild patient prosthesis mismatch on quality of life in patients with preserved ejection fraction after isolated aortic valve replacement for aortic stenosis. *Int. J. Cardiol.* 227225–228.

Roy, DA, Schaefer, U, Guetta, V, *et al.* (2013) Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J. Am. Coll. Cardiol.* 61(15):1577–84.

Ryomoto, M, Mitsuno, M, Yamamura, M, *et al.* (2008) Patient-prosthesis mismatch after aortic valve replacement in the elderly. *Gen. Thorac. Cardiovasc. Surg.* 56(7):330–334.

Salis, S, Mazzanti, V V., Merli, G, *et al.* (2008) Cardiopulmonary Bypass Duration Is an Independent Predictor of Morbidity and Mortality After Cardiac Surgery. *J. Cardiothorac. Vasc. Anesth.* 22(6):814–822.

Schubert, K, Schaller, T, Stojenthin, E, *et al.* (2019) A novel trileaflet mechanical heart valve: first in vitro results. *Interact. Cardiovasc. Thorac. Surg.* 28(5):689–694.

Semsroth, S, Matteucci Gothe, R, Raith, YR, *et al.* (2017) Comparison of Two Minimally Invasive Techniques and Median Sternotomy in Aortic Valve Replacement. *Ann. Thorac. Surg.* 104(3):877–883.

Shalabi, A, Spiegelstein, D, Sternik, L, *et al.* (2016) Sutureless Versus Stented Valve in Aortic Valve Replacement in Patients with Small Annulus. *Ann. Thorac. Surg.* 102(1):118–123.

Simonato, M and Dvir, D (2019) Transcatheter aortic valve replacement in failed surgical

valves. *Heart*. 105:S38–S43.

Singh, JP, Evans, JC, Levy, D, *et al.* (1999) Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). *Am. J. Cardiol.* 83(6):897.

Siontis, GCM, Overtchouk, P, Cahill, TJ, *et al.* (2019) Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: An updated meta-analysis. *Eur. Heart J.* 40(38):3143–3153.

Sohn, SH, Jang, M jin, Hwang, HY, *et al.* (2018) Rapid deployment or sutureless versus conventional bioprosthetic aortic valve replacement: A meta-analysis. *J. Thorac. Cardiovasc. Surg.* 155(6):2402-2412.e5.

Soppa, G, Yates, M, Viviano, A, *et al.* (2015) Trainees can learn minimally invasive aortic valve replacement without compromising safety. *Interact. Cardiovasc. Thorac. Surg.* 20(4):458–462.

Sportelli, E, Regesta, T, Salsano, A, *et al.* (2016) Does patient–prosthesis mismatch after aortic valve replacement affect survival and quality of life in elderly patients? *J. Cardiovasc. Med.* 17(2):137–143.

Sterpetti, A V. (2016) Anatomy and physiology by Leonardo: The hidden revolution? *Surg. (United States)*. 159(3):675–687.

Strange, G, Stewart, S, Celermajer, D, *et al.* (2019) Poor Long-Term Survival in Patients With Moderate Aortic Stenosis. *J. Am. Coll. Cardiol.* 74(15):1851–1863.

Suchá, D, Symersky, P, Tanis, W, *et al.* (2015) Multimodality Imaging Assessment of Prosthetic Heart Valves. *Circ. Cardiovasc. Imaging*. 8(9).

Sundt, TM, Bailey, MS, Moon, MR, *et al.* (2000) Quality of life after aortic valve replacement at the age of >80 years. *Circulation*. 102(19 Suppl 3):III70-4.

Swinkels, BM, de Mol, BA, Kelder, JC, *et al.* (2016) Prosthesis–Patient Mismatch After Aortic Valve Replacement: Effect on Long-Term Survival. *Ann. Thorac. Surg.* 101(4):1388–1394.

Takagi, H and Umemoto, T (2016) Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Implantation. *Ann. Thorac. Surg.* 101(3):872–880.

Tam, DY, Dharma, C, Rocha, R V., *et al.* (2019) Early and late outcomes following aortic root enlargement: A multicenter propensity score–matched cohort analysis. *J. Thorac. Cardiovasc. Surg.* 160(4):908-919.e15.

Tam, DY, Rocha, R V., Wijeysundera, HC, *et al.* (2020) Surgical valve selection in the era of transcatheter aortic valve replacement in the Society of Thoracic Surgeons Database. *J. Thorac. Cardiovasc. Surg.* 159(2):416–427.

The Society for Cardiothoracic Surgery in Great Britain & Ireland (2018) *Blue Book Online*.

Thourani, VH, Suri, RM, Gunter, RL, *et al.* (2015) Contemporary real-world outcomes of

surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. *Ann. Thorac. Surg.* 99(1):55–61.

Tokuda, Y, Yamamoto, H, Miyata, H, *et al.* (2020) Contemporary outcomes of surgical aortic valve replacement in Japan. *Circ. J.* 84(2):277–282.

Tomislav, MMRSSCSSP (2008) Valvular Heart Disease (Aortic). in Cohn, L. (ed.) *Card. Surg. Adult*. 826–827.

Tully, PJ, Aty, W, Rice, GD, *et al.* (2013) Aortic valve prosthesis-patient mismatch and long-term outcomes: 19-year single-center experience. *Ann. Thorac. Surg.* 96(3):844–850.

Tully, PJ (2013) Quality-of-life measures for cardiac surgery practice and research: A review and primer. *J. Extra. Corpor. Technol.* 45(1):8–15.

Um, KJ, McClure, GR, Belley-Cote, EP, *et al.* (2018) Hemodynamic outcomes of the ross procedure versus other aortic valve replacement: A systematic review and meta-analysis. *J. Cardiovasc. Surg. (Torino).* 59(3):462–470.

UpToDate (2019) *Clinical manifestations and diagnosis of chronic aortic regurgitation in adults - UpToDate*. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-aortic-regurgitation-in-adults?search=aortic regurgitation&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2358779662 (Accessed: 13 April 2020).

Urso, S, Calderõn, P, Sadaba, R, *et al.* (2014) Patient-prosthesis mismatch in patients undergoing bioprosthetic aortic valve implantation increases risk of reoperation for structural valve deterioration. *J. Card. Surg.* 29(4):439–444.

Uva, MS (2019) Transcatheter aortic valve implantation in low-risk patients: Is it too early? *Heart*. 105S51–S56.

Vojáček, J, El-Hamamsy, I, Ondrášek, J, *et al.* (2017) Current status of the Ross procedure in aortic valve surgery. *Cor Vasa*. 59(1):e71–e76.

Vriesendorp, MD, Van Wijngaarden, RAFDL, Head, SJ, *et al.* (2020) The fallacy of indexed effective orifice area charts to predict prosthesis–patient mismatch after prosthesis implantation. *Eur. Hear. J. - Cardiovasc. Imaging*. 311116–1122.

Ware, JJ and Sherbourne, C (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med. Care*. 30(6):473–483.

Wasilewski, J, Mirota, K, Wilczek, K, *et al.* (2012) Calcific aortic valve damage as a risk factor for cardiovascular events. *Polish J. Radiol.* 77(4):30–34.

Wellcome Trust (2013) Position Statement on Open Access. *J. Cardiovasc. Magn. Reson.* 1–19.

Wollersheim, LW, Li, WW, Kaya, A, *et al.* (2016) Stentless vs Stented Aortic Valve Bioprostheses in the Small Aortic Root. *Semin. Thorac. Cardiovasc. Surg.* 28(2):390–397.

Yap, C-H, Mohajeri, M and Yii, M (2007) Prosthesis-Patient Mismatch is Associated with Higher Operative Mortality Following Aortic Valve Replacement. *Hear. Lung Circ.* 16(4):260–264.

Zakkar, M, Bryan, AJ and Angelini, GD (2016) Aortic stenosis: diagnosis and management. *BMJ*. 355:1–9.